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Searching for the genetic underpinnings of schizophrenia and bipolar disorder: Functional neuroimaging markers as potential endophenotypes

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ABBREVIATIONS

avPFC	anteroventral prefrontal cortex
BOLD	blood oxygen level-dependent
DC	desire context
DRD	desire-reason dilemma
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPI	echo-planar imaging
FEF	frontal eye field
fMRI	functional magnetic resonance imaging
FOV	field of view
FPN	fronto-parietal network
GWAS	genome-wide association study
HRC	Haplotype Reference Consortium
HRF	hemodynamic response function
ICA	independent component analysis
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th revision
IFJ	inferior frontal junction
LD	linkage disequilibrium
MAF	minor allele frequency
MFG	middle frontal gyrus
MNI	Montreal Neurological Institute
MPRAGE	magnetization-prepared rapid gradient-echo
NAcc	nucleus accumbens
OFC	orbitofrontal cortex
PC	principal component
PFC	prefrontal cortex
QC	quality control
QQ plot	quantile-quantile plot
RC	reason context
RDoC	Research Domain Criteria
RelBD	unaffected first-degree relatives of patients with bipolar disorder
RelSZ	unaffected first-degree relatives of patients with schizophrenia
rsFC	resting-state functional connectivity
SMG	supramarginal gyrus
SNP	single nucleotide polymorphism
SPM	statistical parametric mapping
TE	echo time
TR	repetition time
vStr	ventral striatum
VTA	ventral tegmental area

1. INTRODUCTION

Recent years have seen a profound discourse about our understanding of psychopathology. Our current model of psychiatric classification, as established in our contemporary diagnostic systems (American Psychiatric Association 2013; World Health Organization 1992), assumes a clear distinction of nosologic entities from normality and between disease categories (Anderzhanova et al. 2017; Lilienfeld 2014). This categorical assignment of illness clearly has its benefits, as it enables reliability and ease of diagnosis across a variety of contexts (Anderzhanova et al. 2017; Nusslock and Alloy 2017). However, certain shortcomings have been determined in recent years (Insel et al. 2010). In particular, diagnostic categories based on clinical manifestations and subjectively-reported symptoms may lack to (a) reflect current findings from psychological research, neuroscience and genetics, (b) be predictive for treatment response, and (c) capture the mechanisms underlying disease (Insel et al. 2010; Nusslock and Alloy 2017). Because of this, disease classification has often been perceived as insufficient for research as well as in clinical diagnostic practice (Anderzhanova et al. 2017; Gruber 2011, 2014; Lilienfeld 2014; Maj 2015).

To overcome these limitations, the framework of Research Domain Criteria (RDoC) has been proposed (Insel et al. 2010). The aim of RDoC is to pave the way to future reliable and valid classification systems that will improve early diagnosis, facilitate prediction of outcome and enable personalized psychiatric treatment (Schmitt et al. 2016). RDoC conceptualizes mental illnesses as disorders of brain circuits (Insel and Cuthbert 2015). These brain dysfunctions are assumed to be measurable, among others, with functional neuroimaging. Genomics and neuroscience are supposed to inform about underlying disease mechanisms by identifying biosignatures (Insel et al. 2010; Insel and Cuthbert 2015).

The concept that comes most proximate to the goal of the RDoC is the concept of ‘endophenotype’ (Lenzenweger 2013; Young 2014). The use of endophenotypes has turned out to be particularly promising in the search for the genetic underpinnings of mental disorders in the last decades (Schmitt et al. 2016; Yamada et al. 2020). Two examples for clinically relevant models of circuitry-behavior relationships that may constitute potential endophenotypes are the mesolimbic reward system (Insel et al. 2010; Nusslock and Alloy 2017) and resting-state functional networks (Fu et al. 2015). This doctoral thesis aims to (a) underline the relevance of the mesolimbic reward system as potential endophenotype by examining its function in unaffected first-degree relatives of patients with schizophrenia (RelSZ) and bipolar disorder (RelBD), and (b) identify genetic markers that are associated with an (previously identified) endophenotype of resting-state functional connectivity (rsFC) between the left fronto-parietal network (FPN) and Heschl’s gyrus.

In this introduction, I will first give an overview over the phenotypic characterization of schizophrenia and bipolar disorder, as well as their quantitative and molecular genetic underpinnings. Then, I will introduce the concept of endophenotypes to bridge the gap between genetic variation and complex disease phenotype. As the targeted investigation of pathomechanisms in the brain plays a fundamental role to moving forward in understanding mental disorders, the imaging genetics approach using functional neuroimaging is introduced. The last and main part of this introduction will describe the potential functional magnetic resonance imaging (fMRI) endophenotypes that are examined in this thesis.

1.1 Schizophrenia and bipolar disorder

Schizophrenia and bipolar disorder are severe neurodevelopmental disorders, associated with enormous personal and societal burdens (Charlson et al. 2018; Collins et al. 2011; Ferrari et al. 2016; Rehm and Shield 2019). In their etiology, genetic and environmental factors play a role. There is converging evidence for overlap in phenomenology, familial patterns and genetics between schizophrenia and bipolar disorder (Keshavan et al. 2011; Yamada et al. 2020).

1.1.1 Clinical phenotypes

Schizophrenia and bipolar disorder share many clinical characteristics (Yamada et al. 2020) and have been escribed as two extremes of a spectrum between prototypic schizophrenia or bipolar disorder by a dimensional approach (Keshavan et al. 2011). According to the contemporary diagnostic systems (American Psychiatric Association 2013; World Health Organization 1992), they are defined as distinct diagnostic entities. In schizophrenia, a heterogeneous composition of psychopathological symptoms may appear during the course of the disorder: so called ‘positive’ symptoms including delusions, hallucinations, disorganized speech, distortions of thinking and perception, ‘negative’ symptoms including affective flattening and cognitive deficits, as well as psychomotor abnormalities (van Os and Kapur 2009). Bipolar disorder is characterized by disturbance of mood and activity level (elevated/increased) as core symptoms, but also possibly includes delusions, hallucinations and anxiety (American Psychiatric Association 2013; Schmitt et al. 2016; World Health Organization 1992). The co-occurrence of symptoms of both disorders during one and the same episode is defined as the discrete entity of ‘schizoaffective disorder’ in the current diagnostic systems, but it has been supposed to reflect a diagnosis along a continuum between schizophrenia and bipolar disorder (Keshavan et al. 2011; Parker 2019).

1.1.2 Epidemiology and quantitative genetics

Schizophrenia and bipolar disorder display considerable overlap in epidemiologic features (Bramon and Sham 2001). Evidence from family, twin and adoption studies implicate a strong genetic component of both schizophrenia (Cardno and Gottesman 2000; Sullivan et al. 2003) and bipolar disorder (Cardno and Owen 2014; Craddock and Sklar 2013; Wray and Gottesman 2012). The risk of developing schizophrenia or bipolar disorder is the higher the closer the genetic relatedness to an individual with the respective disorder is. In comparison to a prevalence of about 1% for schizophrenia (Jablensky 1997; McGrath et al. 2008) and bipolar disorder (Craddock and Jones 1999), respectively, in the general population, first-degree relatives show an increased risk of between 5-10% for schizophrenia (Lichtenstein et al. 2009) and bipolar disorder (Craddock and Jones 1999). Twin studies show concordances of around 0-10% in dizygotic and 40-80% in monozygotic twin pairs for SZ (Cardno and Gottesman 2000; Sullivan et al. 2003) and bipolar disorder (Kieseppä et al. 2004; McGuffin et al. 2003).

Moreover, family studies have reported substantial familial co-aggregation between schizophrenia and bipolar disorder (Bramon and Sham 2001; van Snellenberg and Candia 2009), indicating an at least partial sharing of genetic influences.

1.1.3 Molecular genetics

As phenotypic characteristics of schizophrenia and bipolar disorder are heterogeneous, it is assumed that mode of inheritance is complex (Cardno and Owen 2014; Kendler 2015). For both schizophrenia (Sullivan et al. 2003) and bipolar disorder (Craddock and Sklar 2013) the neurogenetic risk architecture is assumed to be polygenic, i.e., to involve thousands of common single nucleotide polymorphisms (SNPs), each contributing with small effect to disease risk (Purcell et al. 2009).

Genome-wide association studies (GWAS) have so far been the most successful strategy for identifying genetic variants associated with brain disorders (Anttila et al. 2018) like schizophrenia (Arslan 2018) and bipolar disorder (Gordovez and McMahon 2020). In GWAS large numbers of genetic markers across the whole genome are tested for association with a trait. Evidence from GWAS strongly support the contribution of a large number of common alleles to the heritability of schizophrenia (Li et al. 2017; Ripke et al. 2014) and bipolar disorder (Stahl et al. 2019). The largest GWAS for schizophrenia, by the Psychiatric Genomics Consortium (PGC), based on ~ 37 K cases and ~113 K controls, has detected 125 genetic loci associated with disease phenotype of which 108 are independent (Ripke et al. 2014). For bipolar disorder, almost 20 GWAS have been published, as summarized in a

recent review by Gordovez and McMahon (2020). The most recent GWAS that included ~20 K cases and ~30 K controls has identified 30 genome-wide significant loci (Stahl et al. 2019). However, most of the lead SNPs are noncoding, and effect sizes are small (for reviews see Gordovez and McMahon 2020; Jacobs and Voineskos 2020).

Recent GWAS identified significant SNP associations with bipolar disorder and schizophrenia for the calcium signaling gene CACNA1C and ANK3, a protein which plays a role in axonal myelination and is expressed in multiple tissues (Gordovez and McMahon 2020; Jacobs and Voineskos 2020). Further genes for which GWAS support a role in schizophrenia include DRD2, which is related to the dopaminergic system, the glutamatergic transmission genes GRM3 and GRIN2A, and NRG1, which is also involved in calcium signaling, and further genes of interest like ZNF804A, among others (Jacobs and Voineskos 2020). For bipolar disorder convergent data additionally point to TRANK1, which encodes a large, mostly uncharacterized protein with high expression in multiple tissues, especially brain, that may play a role in maintenance of the blood–brain barrier (Gordovez and McMahon 2020). However, more studies increasing the data base on functional genomics are needed to draw reliable conclusions about specific risk genes and pathways (Gordovez and McMahon 2020).

1.1.4 Shared genetic influences

On a molecular genetic basis, converging evidence from GWA studies indicates that liability for schizophrenia and bipolar disorder is substantially shared (Cardno and Owen 2014; Purcell et al. 2009). Heritability-based methods (Solovieff et al. 2013) allow the exploration of the extent of shared common variant genetic influences (Anttila et al. 2018). The shared genetic liability (genetic correlation) between schizophrenia and bipolar disorder has been quantified to be about 65% (Anttila et al. 2018; Lee et al. 2013; Lichtenstein et al. 2009; Zwarte et al. 2019). A recent review of all available GWAS data (Prata et al. 2019) found evidence common genetic basis for schizophrenia and bipolar disorder. The genes that were most strongly implicated in both disorders were ANK3 (see 1.1.3), NDST3, which is abundantly expressed in the brain involved in neuronal processes, and PLXNA2 which encodes a neurodevelopmental-mediating receptor (Prata et al. 2019).

1.2 The endophenotype concept: from genetic variation to risk for neuropsychiatric disorders

However recent years have been successful in identifying genetic risk variants for schizophrenia and bipolar disorder (see 1.1.3), it is still largely unknown how exactly these

genetic risk variants contribute to the development of the disease. To bridge the gap between distal genotype and complex disease phenotype, the concept of 'endophenotypes' has been introduced in psychiatric research (Gottesman and Shields 1973). In this view, neurobiological correlates of disease have been assumed to underlie a less complex genetic determination than the disease phenotype, resulting in a higher statistical power in the search of genetic variants than behavioral phenotypes (Ching et al. 2020; Meyer-Lindenberg and Weinberger 2006).

For the concept of endophenotypes, there exist various definitions (Cannon and Keller 2006; Gottesman and Gould 2003; Preston and Weinberger 2005; see Kendler and Neale 2010 for a review). The core criteria are that endophenotypes are to be associated with disease and to be heritable traits. For that, the investigation of unaffected first-degree relatives has been a common strategy (Cao et al. 2016; Ching et al. 2020; Miskowiak et al. 2017) as they constitute a group of persons that is at increased risk of developing the disorders and shares an enriched set of risk genes, but does not manifest clinical symptoms and is free of confounds like psychotropic medication (Craddock and Jones 1999; Lichtenstein et al. 2009).

Two models have been proposed for the concept of 'endophenotype', namely the mediational model and the liability index model (Kendler and Neale 2010). According to the traditional mediational model, the static genome unidirectionally impacts neural endophenotypes, such as brain structure and function, and in turn causes behavior (i.e., the disease phenotype). This description, as a causal pathway, provides a mechanistic understanding of disease risk. In contrast, according to the liability index model, a risk allele influences both brain structure and risk for a neuropsychiatric disorder via pleiotropic effects (Kendler and Neale 2010). To make matters even more complex, there is converging evidence from modern genetics that the etiology of psychiatric disorders is multifactorial, thus involving environmental and genetic factors in an interactive manner (Bogdan et al. 2017; Uher and Zwicker 2017). This doctoral thesis will refer to the traditional conceptualization in which (multiple) endophenotypes lie along a mechanistic pathway from genetic variation to disease risk.

1.3 Imaging genetics

Brain structure and function as measured with magnetic resonance imaging (MRI) have been assumed to constitute excellent endophenotypes (Bigos and Weinberger 2010; Le and Stein 2019). During the past decades, psychiatric research has witnessed intensive efforts to identify potential neuroimaging endophenotypes for schizophrenia and bipolar disorder (Miskowiak et al. 2017; Schmitt et al. 2016). The field of imaging genetics – combining the use of neuroimaging and molecular genetics - has become an increasingly important

approach to examine the molecular and genetic architecture of neural phenotypes and mechanisms underlying psychopathology (Arslan 2015, 2018; Bogdan et al. 2017; Carter et al. 2017; Dima and Breen 2015; Jacobs and Voineskos 2020).

1.3.1 Genome-wide association studies using endophenotypes

In the last decade, worldwide consortia have formed to combine enormous samples of imaging and genetics data in meta-analyses. One of the largest has been the ENIGMA consortium (Enhancing NeuroImaging Genetics through Meta Analysis), which has been initiated with the aim to identify common variants underlying variation in brain structure function and connectivity (Thompson et al. 2020). Large-scale studies driven by ENIGMA based on the assumption of a causal mechanistic 'endophenotype' model have proven successful in identifying risk variants and in some cases also enabled the identification of risk pathways for neuropsychiatric disorders (Le and Stein 2019; Thompson et al. 2020). Existing studies have almost exclusively focused on structural MRI, such as brain morphometric variation or white matter microstructure (Thompson et al. 2020). Despite large effort, and contrary to expectations (see 1.2), individual genetic variants have been shown to only yield small effect sizes (<1%) on brain structural endophenotypes (Ching et al. 2020; Franke et al. 2016; Jacobs and Voineskos 2020).

The state-of-the-art about large-scale neuroimaging and genetics has been reviewed by Jacobs and Voineskos (2020) for schizophrenia and by Ching an colleagues (2020) for bipolar disorder. Although large-scale cooperative studies have been successful in improving our knowledge about the genetic architecture of mental disorders, they are also subject to several limitations. One disadvantage lies in grouping together large samples across study centers and international borders. The included samples are heterogeneous with regards to subject inclusion criteria (including diagnostic characteristics), study protocols, recruitment location and scanners (Ching et al. 2020; Jacobs and Voineskos 2020). As a consequence, by addressing sample heterogeneity with sample size, signals from relevant risk factors that affect subgroups of cases might be drowned out (Ching et al. 2020; Jacobs and Voineskos 2020). To specifically investigate aspects of pathophysiological mechanisms, studies using smaller, but homogeneous samples may play an important role (Jacobs and Voineskos 2020). Moreover, success in identifying genetic associations with brain structural imaging (endo-)phenotypes may have been limited due to the fact that the phenotypes under investigation have been too simplistic to depict the relationship between polygenic genetic variation and clinically complex diseases like schizophrenia and bipolar disorder (Jacobs and Voineskos 2020). Under these assumptions, the investigation of functional brain networks might constitute a more promising approach (Jacobs and Voineskos 2020). This is also in

congruence with the claim made by RDoC, according to which research on psychopathology would have to involve systems or dimensions that have both cognitive and biological validity and cross current diagnostic boundaries (Goodkind et al. 2015; Insel et al. 2010; Lee et al. 2013).

Taken together, growing knowledge suggests that a wide range of genetic variation and altered biological mechanisms can lead to development of one and the same mental disorder (like schizophrenia or bipolar disorder, respectively) (Jacobs and Voineskos 2020; Jiang et al. 2019). Instead of studying the disorder as a whole, the targeted investigation of functional brain networks in homogeneous samples may play an important role in improving our understanding of disease. Within this, brain functional neuroimaging markers may play an important role (Gruber 2011).

1.3.2 Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging has emerged the method of choice for exploring brain function in humans. It measures brain activity indirectly by detecting changes in regional blood flow (for detailed reviews about the principles of fMRI see Buxton 2009; Norris 2006). Active neurons require more oxygen. The brain vasculature, in turn, responds to neural activity by increasing blood flow in active regions. The blood oxygen level-dependent (BOLD) contrast represents differences in blood oxygenation and constitutes the basis of fMRI (Kwong et al. 1992; Ogawa et al. 1992).

In more detail, fMRI takes advantage of the fact that deoxyhemoglobin (hemoglobin that has donated its oxygen) has different magnetic properties, and therefore a different magnetic resonance, than oxyhemoglobin (the oxygenated form of hemoglobin in the blood), of which magnetic properties are similar to the surrounding brain tissue (Stöcker and Shah 2013). Oxygen is transported via hemoglobin in blood. Hemoglobin contains an iron atom which determines the magnetic properties in binding oxygen. Magnetic field homogeneity is generally measured using a T2*-weighted MRI sequence, most commonly by means of the echo-planar imaging (EPI) method (Mansfield 1977; Norris 2006). Deoxyhemoglobin is paramagnetic, decreasing transverse relaxation time T2*. An increase in the amount of deoxyhemoglobin leads to a local reduction in main field homogeneity and thus local MR signal. When oxygen is consumed by active neurons, the brain overcompensates this consumption with an increased blood flow, which leads to an increased concentration of local oxyhemoglobin. Like this, almost paradoxically, increased neural activity leads to an increase in BOLD signal as measured by T2*-weighted imaging (Ogawa et al. 1990).

Blood oxygenation peaks with a delay of about 4 seconds from neuronal activity (Stöcker and Shah 2013). Then, the MR signal returns to baseline, followed by a short phase of deactivation before equilibrium between oxygenated and deoxygenated hemoglobin is re-established. This is commonly referred to as the canonical hemodynamic response function (HRF) (Monti 2011; Roy and Sherrington 1890; Stöcker and Shah 2013).

BOLD response can be modeled using a linear time invariant system (Lindquist 2008; Poldrack et al. 2011). Under the assumption of linearity, a general linear model can be applied for the statistical analysis of fMRI data (Friston et al. 1994). This approach, allows the analysis of activation in each voxel over time. A stimulus function is convolved with a canonical HRF in order to obtain a predicted BOLD response for each experimental condition (Lindquist 2008). Subsequently, activation differences in voxels between the experimental conditions of interest can be analyzed statistically. A detailed description of fMRI data analysis can be found elsewhere (Lindquist 2008; Poldrack et al. 2011).

1.4 Potential fMRI endophenotypes for schizophrenia and bipolar disorder

There exist two main approaches for the investigation of brain activations using fMRI: a) the targeted activation of brain networks using task-based study designs and b) the investigation of brain network activity at rest using resting-state fMRI. Consistent with the RDoC framework (Cuthbert and Insel 2013), it appears that the dopaminergic reward system (Nusslock and Alloy 2017), as well as resting-state fMRI connectivity with the FPN (Cole et al. 2014) represent potential endophenotypic markers for mental disease.

This doctoral thesis will concentrate on two potential fMRI endophenotypes: a) reward processing as measured with task-based fMRI, and b) resting-state activation within an auditory system endophenotypic cluster spanning left FPN and Heschl's gyrus.

1.4.1 The dopaminergic reward system and its prefrontal control

In the human body, rewards serve many different functions, such as to produce learning, motivate to approach behavior and decision-making and elicit positive emotions. In an evolutionary sense, rewards drive us to survive and reproduce. For establishing testable hypothesis for experiments, behavioral theories are of specific significance (Schultz 2015). With regards to reward learning, the most prominent theories are classical 'Pavlovian' (Pavlov 1927) and (Skinner's) operant conditioning. As for the biological basis of reward processing, rewards and reward-associated events are coded in the mesolimbic reward system and its major dopaminergic input in the brain (Haber and Knutson 2010; Schultz

2015). Rewards produce measurable synaptic potentials that can be detected, for example, by fMRI BOLD signals (Schultz 2015; Wang et al. 2016).

While proximal reward can be well described as immediate behavioral reactions to stimuli, distal reward seeking plays an important role in evolutionary fitness (Schultz 2015). To be able to engage in long-term goals, it is assumed that humans possess the ability to restrain the behavioral bias toward immediate reward ('desire') through a cognitive mechanism mediating self-control ('reason') (Diekhof and Gruber 2010; Freud 1927; Hume 1740). This conflict may be conceptualized as a 'desire-reason dilemma' (DRD) in an operant conditioning, monetary incentive paradigm (see 2.1.2) (Diekhof and Gruber 2010).

1.4.1.1 Brain regions of the mesocorticolimbic reward network

The brain's reward system was first described by Olds and Milner (1954), who demonstrated in electrophysiological experiments in rats that electrical stimulation of certain brain regions elicited rewarding experience and positive reinforcement. Since then, extensive knowledge has been collected about the brain regions and pathways involved in reward processing and learning, e.g. by Pavlovian or operant conditioning (for reviews see Arias-Carrión et al. 2010; Cox and Witten 2019; Haber and Knutson 2010; Sesack and Grace 2010). The mesocorticolimbic reward network involves the mesolimbic reward system at its core and regulation by the fronto-striatal network. Dopaminergic signals originate in the ventral tegmental area (VTA) and project to the prefrontal cortex (PFC) via the ventral and dorsal striatum. In this, projections from the VTA to the nucleus accumbens (NAcc), which is part of the ventral striatum (vStr), play the central role (Cox and Witten 2019; Hikosaka et al. 2008; Kelley and Berridge 2002; Rolls 2000; Schultz 2000; Schultz et al. 2000; Stefani and Moghaddam 2006; Wise 2002). Activity in the VTA and the NAcc is, in turn, modulated by prefrontal cortical regions via the fronto-striatal circuit to enable behavioral flexibility and promote goal-directed behavior (Diekhof and Gruber 2010; Haber and Knutson 2010; Sesack and Grace 2010).

In more detail, the neurotransmitter dopamine is released from cells in the midbrain structures VTA and substantia nigra, an area that has widespread projections to brain areas involved in reward processing and initiating goal-directed behavior (Arias-Carrión et al. 2010; Cox and Witten 2019; Grace et al. 2007; Sesack and Grace 2010; Wise 2004). Neurons of the VTA and the substantia nigra, especially at their border, project to the NAcc (Sesack and Grace 2010). Besides, dopaminergic neurons in the VTA also project to several other regions including the medial and lateral PFC, amygdala, hippocampus and the caudate and putamen in the dorsal striatum (Russo and Nestler 2013; Sesack and Grace 2010). Dopamine and its projections to the vStr play an important role in approach behaviors and incentive learning

(Ikemoto 2007; Redgrave et al. 2008; Schultz 2007; Sesack and Grace 2010; Wise 2004). Dopamine neurons respond to novel rewards and conditioned stimuli that predict reward (Sesack and Grace 2010).

The NAcc is the key region for the integration of extensive inhibitory and modulatory afferents from the cerebral cortex, limbic regions and brainstem, under the modulatory influence of dopamine, but also involving glutamatergic and GABAergic signaling (Cox and Witten 2019; Sesack and Grace 2010; Treadway and Zald 2011). An illustration of the mesocorticolimbic reward circuitry is given in Figure 1. Cortical neurons are assumed to promote goal-directed behaviors. The PFC provides executive control, including task switching and response inhibition (Sesack and Grace 2010). The hippocampus supplies spatial and contextual information to the NAcc, and the amygdala communicates information regarding emotion and conditioned affective associations (Ambroggi et al. 2008; Gruber et al. 2009; Ito et al. 2008; Moore et al. 1999; Sesack and Grace 2010). Moreover, the NAcc plays a key role in integrating incoming motivations derived from the limbic system with motor control network to regulate appropriate goal-directed behavior (Sesack and Grace 2010). Consecutively, the NAcc and many of its inputs, directly or indirectly regulate dopamine neuron activity states in the VTA (Sesack and Grace 2010). There is evidence that the midbrain and striatal regions involved in reward are not anatomically restricted to VTA and NAcc, also including the entire vStr (Haber and Knutson 2010). Therefore I will refer to these regions with ‘midbrain/VTA’ and ‘vStr’ in the following.

Further brain regions involved in reward include the supplementary motor area in the frontal lobe, the orbitofrontal cortex (OFC), cingulate and perirhinal cortex, the septum, the ventral pallidum, the thalamus and the hypothalamus (Arias-Carrión et al. 2010; Dichter et al. 2012; Kringelbach and Rolls 2004; Sesack and Grace 2010). All of these ‘brain reward regions’ are inter-connected in many complex ways. A critical role comes to the PFC which regulates the interaction of cognitive with affective processes that support optimal goal-directed behavior (Sesack and Grace 2010). It is assumed that pathological changes in many possible ways would lead to a destabilization in these circuits with functional relevance, therefore contributing to a number of neurologic and mental conditions (Arias-Carrión et al. 2010; Grace 2016; Sesack and Grace 2010).

In the following parts of study 1 frontal and parietal brain regions associated with the regulation of reward response will be referred to with “extended FPN”. This is, however, not to be confused with the language-associated left FPN as defined by Chahine and colleagues (2017), which is examined in study 2 of this thesis.

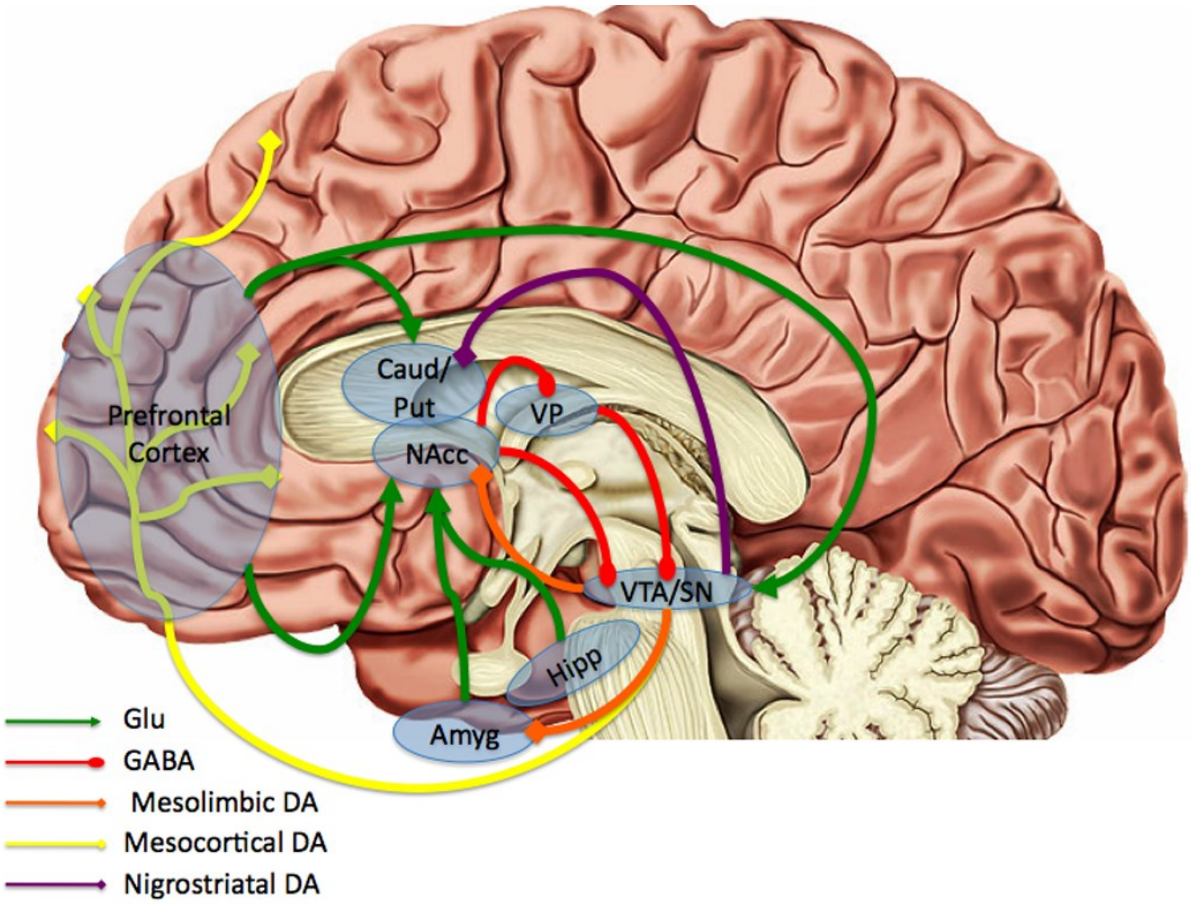

Figure 1. Mesocorticolimbic reward circuitry and its glutamatergic, GABAergic and dopaminergic projections in the brain. Cells in the VTA/SN project to the NAcc most strongly. Furthermore, it innervates the prefrontal cortex, the amygdala, hippocampus and the dorsal striatum (caudate and putamen). Excitatory projections from prefrontal cortex, amygdala and hippocampus converge on ventral striatum, including the NAcc. The NAcc, in turn, regulates DA neuron activity states in the VTA by GABAergic projections. Note: Placement of structure labels is approximate. Abbreviations: Amyg = amygdala; Caud = caudate; DA = dopamine; GABA = GABAergic projections; Glu = glutamatergic projections; Hipp = hippocampus; NAcc = nucleus accumbens; Put = putamen; SN = substantia nigra; VP = ventral pallidum; VTA = ventral tegmental area. Figure and legend adapted with permission from Treadway and Zald (2011).

1.4.1.2 Reward circuitry dysfunction in patients with schizophrenia and bipolar disorder and unaffected first-degree relatives

Converging evidence suggests that reward processing is disturbed in major psychiatric disorders, such as bipolar disorder and schizophrenia, pointing to a cross-diagnostic dysfunction (for a review see Whitton et al. 2015). In more detail, reward-related striatal signaling appears to be decreased as related to negative symptoms, in particular anhedonia, in schizophrenia (Gold et al. 2008; Gold et al. 2013; Treadway and Zald 2013), misallocated in the positive symptoms of psychosis (Barch et al. 2014) and elevated (Caseras et al. 2013) in bipolar (hypo)mania (Whitton et al. 2015). To be precise, the term ‘reward processing’

subsumes a set of aspects like approach motivation, salience, anticipation, pleasure and satiety (Whitton et al. 2015). If viewing reward sensitivity and affective symptoms from an RDoC perspective, reward hyposensitivity has been proposed to be linked to motivational anhedonia, while reward hypersensitivity to approach-related (hypo)manic symptoms, thereby constituting extreme and opposite profiles of a reward processing continuum (Nusslock and Alloy 2017). Results consistently support the role of an abnormal striatal dopamine signaling and deficits in reinforcement learning, reward-related goal-directed behavior and allocation of attention to reward-predictive cues (Whitton et al. 2015).

It has been proposed that hedonics per se are relatively intact, while impairment might rather be due to aberrant PFC function not enabling patients to use reward information to modulate cognitive control (Barch and Dowd 2010). There is strong evidence for prefrontal regulation during reward being disturbed in schizophrenia (Gold et al. 2008; Grace et al. 2007; Richter et al. 2015; Shukla et al. 2019) and bipolar disorder (Macoveanu et al. 2020; Mason et al. 2014; Trost et al. 2014). However, it is still unclear whether abnormal reward processing across the two disorders is due to shared or distinct pathophysiological mechanisms (Whitton et al. 2015).

A recent meta-analysis investigating reward processing across patterns of hyper- or hyporeactivity and a broad range of psychiatric disorders including schizophrenia and bipolar disorder, could confirm these dysfunctions of the mesocorticolimbic reward network. Abnormal activation was identified in the amygdala, the hippocampus, the thalamus, and the fusiform gyri, as well as the medial and lateral dorsal and ventral prefrontal regions (McTeague et al. 2020).

The investigation of unaffected first-degree relatives can shed light on the effect of familial risk for mental disorders because they share degrees of genetic vulnerability, but are free of confounds like medication (i.e., dopamine receptor D2 blocking effects of antipsychotic medication), psychopathology or illness chronicity and hospitalization (Hanssen et al. 2015; Zwarte et al. 2019). Studies in these populations may therefore lead to the identification of the most consistent biological pathways (Miskowiak et al. 2017). There exist only a limited number of studies investigating reward processing in unaffected relatives so far. For schizophrenia, two studies reported blunted vStr activation in siblings (De Leeuw et al. 2015) and other first-degree relatives (Grimm et al. 2014), while a third study, in siblings, could not confirm this disruption, but described differences in widespread areas of the brain associated with the default mode network (Hanssen et al. 2015). Still, disturbed activation was reported in the insula (De Leeuw et al. 2015; Hanssen et al. 2015), posterior cingulate cortex (Hanssen et al. 2015), middle frontal gyrus (MFG) (Hanssen et al. 2015) and supplementary motor area (De Leeuw et al. 2015; Hanssen et al. 2015). In two studies on first-degree

relatives of patients with bipolar disorder, no disturbances have been found in vStr activation (Kollmann et al. 2017; Linke et al. 2012). However, an aberrant activation in the OFC was reported (Linke et al. 2012). None of the studies found any significant difference in task behavioral performance between relatives and controls. Generally speaking, studies in relatives seem to produce less uniform evidence for changes in neurocognitive function compared with patients (Johnsen et al. 2020; Miskowiak et al. 2017).

Taken together, despite the less consistent findings, aberrant responses in widespread areas associated with the dopaminergic reward system to different types of reward stimuli have been reported in first-degree relatives of patients with schizophrenia and bipolar disorder. Therefore, reward processing is assumed to constitute a putative endophenotype for these disorders. The aforementioned studies, however, primarily investigate responses to immediate rewards.

1.4.1.3 Disturbed anterior prefrontal control of the mesolimbic reward system as potential endophenotype for schizophrenia and bipolar disorder

In a ‘desire-reason dilemma’ situation, when actions promoting a superordinate (long-term) goal preclude exploitation of an immediately available reward option, the human brain has to mediate the balance between proximal reward desiring and a long-term goal (Diekhof and Gruber 2010). Thus, experimentally induced behavior that favors a long-term goal but counteracts immediate reward desiring during action control, allows the targeted investigation of a negative functional coupling between anteroventral prefrontal cortex (avPFC) and the mesolimbic reward system (i.e., vStr and midbrain/VTA) (Diekhof and Gruber 2010). The experimental paradigm is described in detail in 2.1.2. By conditioning of specific color stimuli with reward feedback activation in dopaminergic brain regions, i.e., the midbrain/VTA, as well as dopaminergic innervated areas such as the vStr, is elicited. The downregulation of activation in the vStr and midbrain/VTA as well as in an extended fronto-parietal cortical network is assessed in a DRD situation. The paradigm has proven reliable for both effects across samples (Diekhof et al. 2012a; Diekhof et al. 2012b; Diekhof and Gruber 2010; Richter et al. 2015; Trost et al. 2014).

Preceding studies have shown that this control mechanism is disturbed in patients with schizophrenia (Richter et al. 2015) and bipolar disorder (Trost et al. 2014). For schizophrenia, a significant hyperactivation of the left vStr in response to conditioned reward stimuli has been reported. In addition, several frontal and parietal regions showed hyperactivation, while for the avPFC, a hypoactivation has been reported (Richter et al. 2015). Top-down regulation (suppression) of activation in the mesolimbic reward system in the dilemma situation (i.e., while having to reject the immediate reward to pursue the

superordinate task-goal) was significantly weaker in patients with schizophrenia than controls in the right dorsal striatum, as well as in regions of an extended FPN associated with the regulation of reward response (Richter et al. 2015). Patients with bipolar disorder showed reduced neural responses of the bilateral vStr and several prefrontal cortical regions when exploiting a reward stimulus. Prefrontal top-down regulation of the reward-related activation of the mesolimbic reward system in the DRD situation was significantly weaker as well as in an extended FPN (Trost et al. 2014). For both patients with schizophrenia (Richter et al. 2015) and bipolar disorder (Trost et al. 2014) behavioral performance was lower as compared with controls.

Two doctoral theses, of which data is included in this thesis, investigated reward-related brain activation in RelSZ and RelBD, respectively using the DRD paradigm. RelSZ showed a hyperactivation as compared with controls without a family history of psychiatric disorder in bilateral midbrain/VTA in response to conditioned reward stimuli, as well as for regions of an extended FPN. No mesocorticolimbic-system-specific (see 1.4.1.1) differences were identified for top-down regulation in the dilemma situation, but a significantly stronger suppression for the primary visual cortex (Fanelli 2013). For RelBD compared with controls, (Jakob 2013) could not confirm a reduced suppression of vStr or midbrain/VTA activation during the DRD situation, but reported that suppression was significantly reduced in pregenual anterior cingulate cortex, right posterior cingulate cortex, right posterior inferior temporal gyrus and right thalamus. For task performance, a significant difference has been found between RelSZ and controls in correctly accepted reward stimuli (Fanelli 2013), while there were no differences between RelBD and controls (Jakob 2013) However, sample size of these doctoral theses was small. The first part of this thesis examined reward-associated brain activations during a ‘desire-reason dilemma’ in an extended sample of RelSZ and RelBD to investigate the genetic vulnerability for dysregulations in the reward-system.

1.4.2 Disruptions in left fronto-parietal network (FPN) connectivity

Schizophrenia has been conceptualized as a syndrome of brain functional disconnection (Friston and Frith 1995; Weinberger 1993). This means that the disorder is caused by a deficient integration of information between brain regions, i.e., impairment in neural circuit functions (Cao et al. 2016). In recent years, functional connectivity has been proposed in the investigation of potential endophenotypes for schizophrenia for use in imaging genetics studies (Tost et al. 2012). So far, the majority of functional connectivity-based phenotype studies have focused on the analysis of resting-state data (Cao et al. 2016).

1.4.2.1 Resting-state functional connectivity changes in schizophrenia

Resting-state fMRI is a method, in which brain activation is recorded in a task-free, thus resting, state, and regional interactions are evaluated. This has, especially for patient cohorts, the advantages that task demands are low, task-related behavioral confounds are (presumably) absent (Cao et al. 2016). Furthermore, reliability of the derived connectivity measures is high (Cao et al. 2014; Shehzad et al. 2009). Resting state networks are believed to reflect the intrinsic functional connectivity of brain regions (Alderson-Day et al. 2015). In its simplest form, 'functional connectivity' in neuroimaging quantifies the temporal covariance of BOLD signals between spatially distant brain regions (Cao et al. 2016; Friston 2011).

Analysis of human cerebral cortical activity at rest has revealed an organization in functionally meaningful spatiotemporal networks (Damoiseaux et al. 2006; Engel et al. 2013; Fox et al. 2005; Friston 2005; Yeo et al. 2011). A recent review lists rsFC networks in an overview as follows: the salience network, auditory network, basal ganglia network, higher visual network, visuospatial network, default mode network, language network, executive control network, precuneus network, primary visual network and sensory motor network, among others (Smitha et al. 2017). However, depending on the respective statistical approach, segregation and terminology vary in literature (e.g. Cole et al. 2014). For that reason, a need for a common taxonomy that can be referred to across research groups has recently been stated (Uddin et al. 2019).

Comparing schizophrenia patients with controls, a vast variety of rsFC changes has been reported in literature (Cao et al. 2016). Among them, the default mode network, the salience network and the fronto-parietal executive network are assumed to be promising candidate endophenotypes (Brandl et al. 2019; Cao et al. 2016; Dong et al. 2018; Yamada et al. 2020; Yu et al. 2012).

1.4.2.2 The fronto-parietal control network and its role in mental disorders

Extensive evidence suggests that there exists a cortical 'control' system that enacts cognitive control (for reviews see Cole et al. 2014; Marek and Dosenbach 2018). The FPN is highly interconnected with many other brain regions, constituting a so called functional 'hub'. This is true both on the level of functional connectivity between brain regions (Cole et al. 2010; Power et al. 2013), but also on a brain network level, as it interacts with other control and processing networks (Marek and Dosenbach 2018) like the cingulo-opercular and the dorsal attention network (Cole et al. 2014; Corbetta and Shulman 2002; Dosenbach et al. 2007). Connectivity patterns between the systems are adjusted in dependence of the current task demands (Cole et al. 2013b). By implementing task-dependent biases (Cole et al. 2013b;

Cole et al. 2013a; Marek et al. 2015; Power et al. 2013), the FPN can regulate other systems in order to promote goal-directed behavior (Cole et al. 2013b; Marek and Dosenbach 2018). Like this, it is central to adaptive task control (Cole et al. 2013b; Dosenbach et al. 2007). The FPN includes many regions that are known to play a role in cognitive control and decision-making processes, for example, lateral PFC, anterior cingulate cortex, and inferior parietal lobule (Dosenbach et al. 2007; Vincent et al. 2008). However, the precise anatomy of the FPN is subject to strong individual variation (Marek and Dosenbach 2018).

According to this theoretical concept, disruptions of flexible cognitive control, i.e., dysregulations in brain systems, may constitute one core feature in psychopathology (Cuthbert and Insel 2013; Marek and Dosenbach 2018) resulting in mental disease (Cole et al. 2014).

1.4.2.3 Resting-state functional connectivity between the left FPN and Heschl's gyrus as potential endophenotype for schizophrenia

In line with theory, there is evidence that FPN connectivity is disrupted in mental disease. Most consistent results of altered brain-wide connectivity have been reported in schizophrenia (Anticevic et al. 2012; Barch and Ceaser 2012; Cole et al. 2011), though similar results have also been identified for bipolar disorder (Anticevic et al. 2014) and many other mental disorders (Cole et al. 2014). Consistent with relatively low levels of cognitive control (Heinrichs and Zakzanis 1998; Marek and Dosenbach 2018), patients with schizophrenia have been shown to exhibit reduced BOLD connectivity within and between regions of the FPN across many cognitive tasks (Cole et al. 2011; Marek and Dosenbach 2018; Sheffield et al. 2015). There is evidence that rsFC is heritable, implying that alterations in this networks in schizophrenia may be due to genetic risk (Fu et al. 2015; Glahn et al. 2010).

In a recent study in schizophrenia patients, a significantly increased rsFC with the left FPN was observed in a cluster that stretches from the Heschl's gyrus medially to the middle and superior temporal gyri and Brodmann Area 40 in the supramarginal gyrus (SMG), with peak activation in the Heschl's gyrus (Chahine et al. 2017). This is of particular interest as there is extensive evidence that disruptions in rsFC of the auditory cortex, in the left temporal lobe, especially in the left superior temporal gyrus, are associated with positive symptoms in schizophrenia (Alderson-Day et al. 2015). Furthermore, a higher functional integrity of left Heschl's gyrus and left fronto-parietal regions involved in language and speech processing has been reported in schizophrenia patients with auditory verbal hallucinations (Shinn et al. 2013). Further evidence shows a link between the SMG and positive symptoms (Bhojraj et al. 2009; Jeong and Kubicki 2010; Kubota et al. 2011; Zhang et al. 2017). The strength of

positive symptoms has been reported to covary with functional connectivity between the FPN and the auditory network (Rotarska-Jagiela et al. 2010).

As first-degree relatives shared this hyperconnectivity, in particular in the SMG, this finding is assumed to constitute a potential endophenotype for schizophrenia (Chahine et al. 2017). To investigate the genetic underpinnings of healthy rsFC between the left FPN and Heschl's gyrus, the second part of this doctoral thesis uses a hypothesis-free genome-wide approach to identify common variants associated with variation in fMRI BOLD activity in a homogeneous sample of young healthy adults.

1.5 Goals and hypotheses

As summarized in the previous sections, recent years have shown huge progress in the investigation of the underpinnings of schizophrenia and bipolar disorder on a genetic and neurocircuit level. However, exact pathways from genetics to neuropsychiatric phenotype are largely unknown.

The aim of the present thesis was to contribute to the identification of biosignatures on a neuroimaging and molecular genetic level for schizophrenia and bipolar disorder by using functional neuroimaging endophenotypes and an imaging genetics approach. For this, two studies were conducted. As they focus on two different research questions, details on methods, results and discussion are reported separately in the respective section.

Study 1 aimed to examine the neurofunctional correlates of reward processing in RelSZ and RelBD, respectively, using the DRD paradigm (Diekhof and Gruber 2010). Insights into the neurofunction in relatives would shed light into the familial vulnerability of the disorders, potentially underlining the relevance of the mesocorticolimbic reward circuitry as endophenotype for schizophrenia and bipolar disorder. Brain activation in relatives was measured with fMRI. Because of the differential patterns of aberrant brain activation between schizophrenia (Richter et al. 2015) and bipolar disorder (Trost et al. 2014), this doctoral thesis examined schizophrenia and bipolar disorder as two distinct groups. Brain activation in RelSZ and RelBD, respectively, was contrasted with a matched control group of healthy subjects without family history of psychiatric disorders. I hypothesized that, (a) there would be no differences between groups in task performance, and (b) similar to patients, relatives would show altered mesolimbic reward system activation in vStr and midbrain/VTA as response to the reward stimuli, as well as disturbed top-down control by prefrontal regions due to a DRD situation.

The purpose of study 2 was to identify genetic markers that are associated with an endophenotypic marker of resting-state fMRI connectivity between the left FPN and a cluster

spanning left temporal and parietal auditory regions including Heschl's gyrus in a homogeneous sample of young healthy adults. To investigate the genetic underpinnings of healthy rsFC between the left FPN and Heschl's gyrus, genome-wide association analyses were performed to identify markers on a single-marker, gene and pathway level.

2. METHODS

2.1 Study 1: Activations in the mesolimbic reward network in unaffected first-degree relatives of patients with schizophrenia (RelSZ) and bipolar disorder (RelBD)

2.1.1 Recruitment and sample details

Thirty-six RelSZ and RelBD, respectively, were included in the study. The sample consisted of *n*=20 subjects per relative group (RelSZ and RelBD) from two earlier doctoral theses of the research group, recruited in 2010 and 2011 at the Department of Psychiatry and Psychotherapy, University Medical Center Göttingen. Additionally, I recruited *n*=16 subjects per group as part of the present doctoral thesis. Recruitment was conducted between February 2017 and July 2018 via online sample calls, patient interviews, and sample calls in the Clinic for General Psychiatry at Heidelberg University Hospital and in Heidelberg University. Index patients fulfilled a diagnosis of schizophrenia or bipolar disorder according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10; World Health Organization 1992).

Data for the matched control sample has been acquired as part of the following research projects: ‘Translational neuroimaging studies on genotype-phenotype relationships in the longitudinal course of psychosis”, work package (WP2) of the Clinical Research Group (KFO) 241 ‘Genotype-Phenotype Relationships and Neurobiology’, the ‘Clinical Neuroimaging Göttingen” (CLING) project and the ‘Genomic Imaging Göttingen” (GIG) project, conducted at the University Medical Center Göttingen. Furthermore, *n*=17 healthy control subjects from Project 2 of the PsyCourse (PC2) consortium ‘Translational neuroimaging studies on genotype-phenotype relationships in the longitudinal course of psychosis” recruited via sample calls at the Clinic for General Psychiatry, University Hospital Heidelberg were included.

General exclusion criteria comprised any lifetime mental or neurological disorder, mental retardation, somatic disorders that would interfere with the study protocol, past or present substance dependency, substance use within the last month, and cannabis use within the last 2 weeks. Subjects in the relatives sample had at least one first-degree relative (i.e., parent, offspring, and sibling) diagnosed with schizophrenia or bipolar disorder, respectively, according to the ICD-10. Control subjects were required not to have a family history of psychiatric disorders.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics commissions. Written informed consent was obtained from all participants. Subjects received remuneration for participation.

2.1.2 Task procedure: 'desire-reason dilemma' paradigm

Subjects performed the DRD paradigm which assesses bottom-up activation of the subcortical dopaminergic brain regions as well as their top-down modulation by prefrontal subregions within mesocorticolimbic circuits (Diekhof and Gruber 2010). The paradigm in its current version has been described elsewhere (Diekhof et al. 2012a; Richter et al. 2015; Trost et al. 2014).

The day before the fMRI measurement or directly before it, subjects underwent a training session consisting of an operant conditioning task (duration: 5 minutes) and 2 or 3 runs of the main task (6 minutes per run). The training took place at a computer in a separate room. The task was presented on screen. Subject's responses were given via keyboard. For standardization reasons, instructions were given in text format. Prior to each part of the experiment, subjects were asked to read the instructions. Subsequently, a verbal instruction was given and subjects got the opportunity to clarify questions about the task procedure before the task was executed.

In an initial operant conditioning task, subjects were supposed to acquire stimulus-reward-contingencies. Squares in eight different colors were presented in a shuffled mode. Subjects were asked to respond to each of the presented colored squares by accepting (pressing the left button of the keypad with the right index finger) or rejecting (pressing the right button of the keypad with the right middle finger) them. Button choice was free, and subjects were encouraged to explore the response–reward contingencies of the colors to maximize the overall outcome. Squares remained on screen until a button press took place. Immediately after the button press, depending on the subject's response, a feedback was displayed. Two of the colors (red and green) led to an immediate reward of 10 bonus points if they were accepted. Four colors led to neutral outcome (0 points regardless of the decision for or against the color). Two further colors led to an immediate loss of 10 points if they were accepted. The inclusion of the latter (punished) colors should prevent a behavioral preference for the left response button. However, the respective colors were not included in the main task.

The main task consisted of a sequential forced-choice task. The experiment consisted of blocks of four to eight trials. Subjects had to pursue a superordinate long-term goal: to gain 50 points at the end of each block. To reach this goal, subjects had to collect the two target

colors that were presented at the beginning of each block. Additionally, subjects had to follow specific context rules depending on two types of blocks: the ‘desire context’ (DC) and the ‘reason context’ (RC). In the DC, subjects were encouraged to additionally collect the previously conditioned reward colors (free-choice bonuses). If doing so, bonus points were added to the total outcome at the end of each block, if the block was successfully completed. In the RC, in contrast, subjects had to reject all colors (including the reward colors) except for the target stimuli. Because in the RC subjects had to overcome the tendency to acquire immediate reward in order to reach the superordinate long-term goal, this condition constituted a DRD situation (Diekhof and Gruber 2010). The context (DC, RC) always changed after two consecutive task blocks and was indicated by a cue (DC: bonus, ‘B’ for German ‘Bonus”; RC: target, ‘Z’ for German ‘Zielverfolgung”) at the beginning of each block. Failure to execute the task (e.g. falsely rejecting a target or collecting a non-target) or a delayed response led to termination of the current block and the feedback ‘goal not achieved’ appeared on screen. In this case, the overall block rewards, as well as all free-choice bonuses acquired during the block were lost.

Before each block, a fixation cross on grey screen was shown for 7800ms. Then, cues indicating the context (‘Z’ or ‘B’) appeared for 1800ms. Each block started with the presentation of the two target colors for 1500ms duration. Subjects had to make a decision during the presentation of individual squares (900ms) followed by an immediate feedback of 700ms duration and a blank screen interval of 100ms. At the end of each block, a feedback about the actual outcome (‘goal achieved’ and number of points acquired, or ‘goal not achieved’) was presented for 1800ms followed by a blank screen (100ms). Feedback about the overall outcome was given at the end of each run (1800ms). An illustration of the experimental paradigm is given in Figure 2.

In the MR scanner, subjects performed two runs of the task. Each run consisted of 20 blocks (120 trials). In both the DC and the RC, subjects could perform up to 60 target color trials and 30 reward-color trials, depending on the individual task performance.

Per session, a total amount of up to 1150 points could be gained. Overall points acquired over the course of the two sessions were cashed into real money. Subjects could gain up to 20€ bonus remuneration (Supplementary table 1) which was added to the general allowance of 20€.

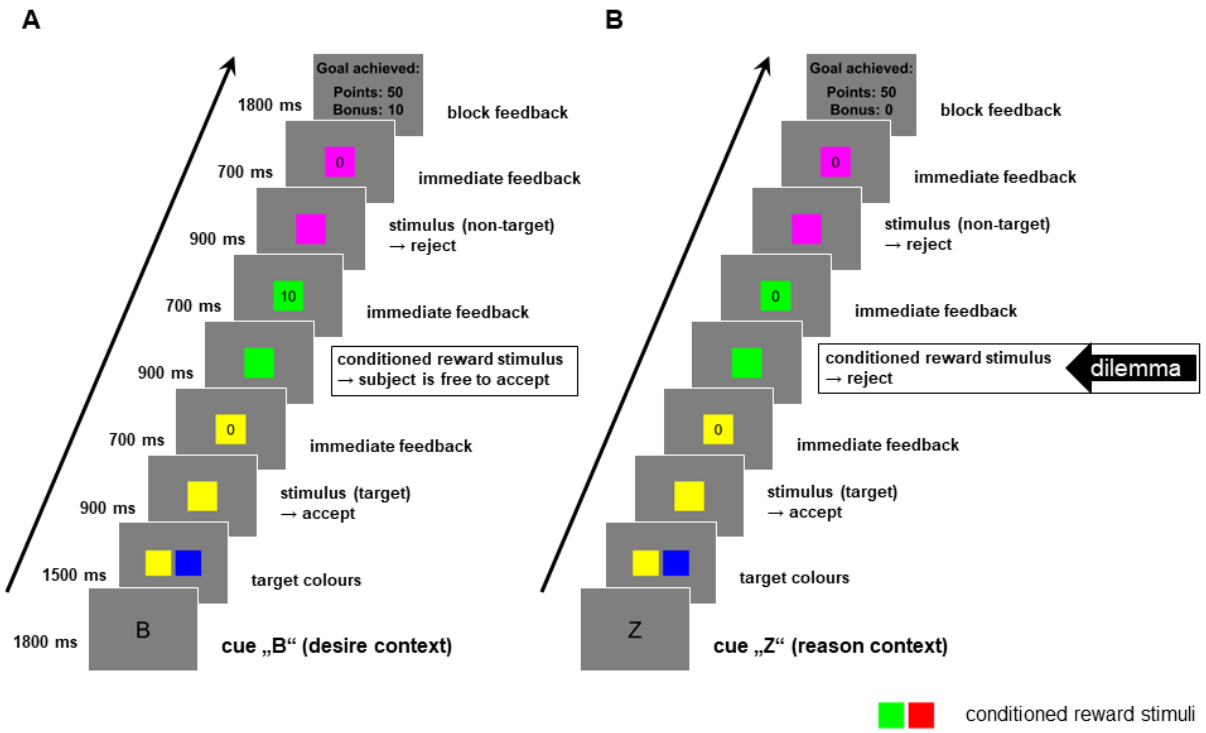

Figure 2. Experimental design of the 'desire-reason dilemma' paradigm. Subjects had to follow specific context rules depending on two types of blocks: A) 'Desire context': subjects were free to collect the conditioned reward stimuli (red and green), which were associated with a reward of +10 points. Furthermore, subjects had to accept the two target stimuli (in this example: yellow and blue) and reject all non-rewarded non-target stimuli to achieve the superordinate long-term goal (50 points at the end of each block). B) 'Reason context': subjects had to accept all target stimuli and reject all non-target stimuli, including the conditioned reward stimuli to achieve the superordinate goal. This led to a 'desire-reason dilemma' situation during which subjects had to overcome their impulsive behavior to optimize their behavioral outcome.

2.1.3 Demographic and behavioral data analysis

Demographic and behavioral data were analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Subjects were excluded from the analysis for insufficient task performance if they had accepted less than 8 out of 30 conditioned bonus stimuli in the DC, if they had less than 70 percent of the target stimuli correctly accepted or more than 30 block terminations due to failure to execute the task or delayed response. Chi^2-tests, Kruskal-Wallis *H* test and a post-hoc Mann-Whitney *U* test were performed to explore differences in demographics and behavioral data between groups.

2.1.4 FMRI data acquisition and analysis

MRI data was acquired using a 3-T scanner (Magnetom TIM Trio; Siemens Healthcare, Erlangen, Germany). Thirty-one axial slices were acquired in ascending order, oriented

parallel to the AC-PC line (slice thickness=3mm; gap=20%). fMRI BOLD images were acquired in a total of 370 scans over the course of two runs (185 scans per run) using a T2*-sensitive EPI sequence (TR=1900ms; TE=30ms; flip angle 70°; FOV 192 mm). For anatomical reference, a high-resolution T1-weighted 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence (voxel size 1×1×1mm) was acquired.

For data collection in Göttingen, stimuli were presented via goggles (Resonance Technology, Northridge, CA, USA). Data collection in Heidelberg was implemented with stimuli presentation on a screen placed behind the scanner that could be seen by the subject through a mirror placed above the subject's face. In both centers, responses were given via button presses on a fiber optic computer response device (Current designs, Philadelphia, PA, USA). Stimuli were generated and visual stimulation was triggered using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA, USA; www.neurobs.com). The head of the subjects was stabilized with small cushions to prevent motion.

FMRI data was preprocessed and analyzed using the SPM12 toolbox (The Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK) in MATLAB R2015a. The study design was event-related. Only correctly answered trials were entered in the analysis. Preprocessing comprised coregistration, correction of movement-related artefacts (realignment and unwarping), corrections for slice-time acquisition differences and low-frequency fluctuations, normalization into standard stereotactic space (skull-stripped EPI template by the Montreal Neurological Institute (MNI)), and spatial smoothing with an isotropic Gaussian kernel filter of 6 mm full-width half-maximum.

Statistical analysis was performed using a general linear model (GLM), which comprised 3 regressors (i.e., goal-relevant targets, neutral non-targets, conditioned reward non-targets), both for the DC and the RC. The cues and the block feedback for either successful goal completion or overall goal failure were also modeled as independent regressors, which resulted in a total of 9 onset regressors. For first-level analysis, a vector representing the temporal onsets of stimulus presentation was convolved with a canonical HRF to produce a predicted hemodynamic response to each experimental condition. Linear *t* contrasts were defined for analyzing the brain activation effects induced by the conditioned reward stimuli in the DC and the RC, respectively. To test for reward-related activation in the absence of a competing superordinate long-term goal, the selection of conditioned reward stimuli was compared with implicit baseline. This condition is referred to as DC. To assess the extent of downregulation (suppression) of reward-related activation during the competition between an immediate reward option and the superordinate long-term goal ('desire-reason dilemma'), the

activation elicited by the conditioned reward stimuli in the DC was contrasted with the effects of the same conditioned reward stimuli when being presented in the RC.

Single-subject contrast images were then taken to the second level to assess group effects with random-effects analyses. A one-way ANOVA and subsequent two-sample *t* tests were calculated to examine group differences in brain activation during DC and during the DRD situation, including sex, age, education and study center as covariates. I used a threshold of $p<0.005$, uncorrected, as the statistical search criterion. Correction for multiple comparisons was performed using family-wise error (FWE) rate at $p<0.05$. Additionally, for brain regions with a specific a priori hypothesis, small volume correction at $p<0.05$ for 6mm spheres around a priori coordinates from Diekhof and Gruber (2010) was used.

2.2 Study 2: Genome-wide association study of resting-state functional connectivity (rsFC) between the left FPN and Heschl's gyrus

2.2.1 Participants

Detailed sample information has been reported elsewhere (Chahine et al. 2017). The current study was conducted in the healthy control ('HC') sample ($n=268$). This represents a homogeneous sample of young healthy adults with an average high level of education. Out of this sample, for $n=258$ subjects both resting-state fMRI and genotype information was available. Exclusion criteria were any diagnosis of the subject or a first-degree relative according to the Diagnostic and Statistical Manual of Mental Disorders 4th revision (DSM-IV; American Psychiatric Association 2000). Data was collected between 2009 and 2011 at the University Medical Center Göttingen. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee in Georg August University Göttingen. Written informed consent was obtained of all subjects prior to study participation. Subjects were paid for participation.

2.2.2 FMRI data acquisition

Resting-state fMRI scans were acquired in a Siemens Magnetom TRIO 3T scanner. The full fMRI acquisition details have been described in Chahine and colleagues (2016). Functional scans of 5.2min duration were obtained. Scanning parameters were: 3×3×3mm^3 voxel size, 33 slices, interscan interval of 2,000ms, 64×64 matrix, 0.6mm spacing, flip angle of 70 degrees, FOV 192mm, TE=30ms and a total of 160 volumes. Additionally, for each subject a high-resolution, T1-weighted 3D anatomical set (MPRAGE sequence, TE=4.42ms,

TR=11.9ms, flip angle 15°, FOV 256×256mm^2, voxel size 1×1×1mm^3, 176 consecutive slices) was acquired. Subjects were asked to leave the eyes open and fixate a white cross presented in the middle of a dark screen. No subject fell asleep during the measurement.

2.2.3 Endophenotype extraction

The endophenotypic marker was derived from independent component analysis (ICA) and a subsequent second-level analysis as described by Chahine and colleagues (2017). Masks were established based on clusters showing significant differences in connectivity with the FPN between schizophrenia patients and a control group, and then applied to the HC sample. The HC sample was independent from the control group of the aforementioned second-level analysis. HC subjects had no family history of psychotic disorders in first-degree relatives. For each subject of the HC sample, the individual effect size of connectivity between the left FPN and the voxels within the mask (mean *t*-value) was extracted and entered as regressor in genome-wide association analyses.

2.2.4 Genotyping

Genetic Material (DNA) was extracted from saliva collected with ORAgene OG-500 (DNA Genotek, Ottawa, ON, Canada) using the Gentra Puregene Blood Kit (Qiagen, Hilden, Germany) with standardized protocols. Genotyping was performed using the HumanOmniExpress-12 BeadChip (Illumina, San Diego, CA, USA).

2.2.5 Genetic quality control and imputation

A detailed description of quality control (QC) and imputation procedures can be found in (Lam et al. 2019). Preimputation QC and imputation was provided by the research group of Prof. Dr. Stephan Ripke in a larger sample, additionally containing cases. Subjects were excluded based on the following criteria: deviation in autosomal heterozygosity rate (|FHet|>0.2), subject missingness >0.02, pedigree sex not matching genetic sex and population outlier status. Criteria for the exclusion of SNPs were: SNP missing rate >0.02, difference in SNP missingness between cases and controls >0.02, SNPs without valid association *p*-value and SNP deviation from Hardy-Weinberg equilibrium $p<10^{-6}$. Genotype imputation was performed using the pre-phasing/imputation stepwise approach in Eagle v2.3.5/Minimac3 using the Haplotype Reference Consortium (HRC) reference panel.

For my analysis, I included best-guess genotypes with genotype call *p*>0.8, SNP missing rate <0.02 and minor allele frequency (MAF) >5%. QC procedures were conducted with PLINK

v1.9 (Purcell et al. 2007). Relatedness testing was conducted based on an LD pruned (r^2>0.01) subset of 62047 SNPs that fulfilled strict quality criteria (genotype call p>0.8; SNP missing rate <0.01; MAF>0.05). In cryptically related subjects (PIhat>0.2), one member of each pair was removed at random. Principal components (PCs) were computed from genotype data (see Supplementary figure 1).

2.2.6 Genome-wide association study

Association of single markers was tested with PLINK under an additive linear regression model adjusting for age, sex and five ancestry PCs. SNP associations were considered significant at $p<5\times10^{-8}$. The 'Functional Mapping and Annotation of Genome-Wide Association Studies' (FUMA) web application v1.3.6 (Watanabe et al. 2017) was used for visualizing and interpreting GWAS results. A Manhattan plot and a quantile-quantile (QQ) plot were generated by R as implemented in FUMA and SNP functional annotations were applied. Functional consequences of SNPs on gene functions were obtained using ANNOVAR (http://annovar.openbioinformatics.org/en/latest/) via FUMA.

2.2.7 Gene-based, gene-set and tissue expression analysis

Gene-based, gene-set and tissue expression analyses were performed using MAGMA v1.07 via the FUMA platform (Leeuw et al. 2015). Both analyses were based on GWAS summary statistics. SNPs were mapped to protein coding genes based on an annotation window of ±20kb. The major histocompatibility complex region was excluded from annotations. A Manhattan plot and a QQ plot were generated by R as implemented in FUMA. Gene-set analyses was performed for curated gene sets and GO terms obtained from MsigDB v6.2 (https://www.gsea-msigdb.org/gsea/index.jsp). MAGMA tissue expression (gene-property) analysis was performed to identify tissue specificity of the phenotype. This analysis tests the relationship between tissue specific gene-expression profiles and phenotype-gene associations. Expression profiles were obtained from GTEx v8 (https://www.gtexportal.org/home/datasets), which contained 53 different tissue types across 30 general tissue types.

2.2.8 Statistical analyses of demographics

Sample characteristics were analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

3. RESULTS

3.1 Study 1: Comparison of activations in the mesolimbic reward network in RelSZ, RelBD and controls

3.1.1 Sample characteristics

Due to QC reasons (insufficient task performance; poor quality of fMRI data) *n*=7 subjects of RelSZ and RelBD, respectively, had to be excluded. The final sample comprised *n*=29 subjects for RelSZ and RelBD, respectively. A control group of *n*=29 healthy subjects without family history of any psychiatric disorders was matched for age, sex, school education and study center. All Heidelberg control subjects fulfilling study and quality criteria (*n*=10) were included. Further subjects were taken from the research group's data pool.

3.1.2 Demographic and behavioral data

Demographics are shown in Table 1. Because of a skewed distribution, for age and task performance variables, non-parametric testing was performed. A Kruskal-Wallis *H* test showed that age differed significantly between groups, $H(2)=3.29$, $p=0.04$. RelSZ (*Mdn*=36.00) had higher age than controls (*Mdn*=30.00) and RelBD (*Mdn*=26.00). Post-hoc Mann-Whitney *U* tests using a Bonferroni-corrected alpha level of 0.02 (0.05/3) were used to compare all pairs of groups. A significant difference between age of RelSZ (*Mdn*=36.00) and RelBD was found (*Mdn*=26.00), $U(N_{RelSZ}=29, N_{RelBD}=29)=260.50$, $z=-2.49$, $p=0.01$. Samples did not differ significantly in sex, education or test center (all *p*s>0.05). A group comparison of family relationship to the index patient is shown in Supplementary table 2. Descriptively, RelSZ were offspring (*n*=7), parents (*n*=10) and siblings (*n*=12) in almost equal shares, while RelBD were mostly offspring (*n*=21) and no parents were included (*n*=0). A Chi^2-test showed that differences in family relationship to the index patient between RelSZ and RelBD were significant, $\chi^2(2, n=58)=17.80$, $p<0.001$). For task performance, there were no significant differences between groups in percentage of correctly accepted rewards and targets in the DC, as well as percentage of correctly rejected rewards and correctly accepted targets in the RC in Kruskal Wallis *H* tests (pss>0.05; for details see Table 2).

Table 1. Sample demographics of study 1.

	RelSZ (*n*=29)		**RelBD** (*n*=29)		**Controls** (*n*=29)				
	mean (SD)	median	mean (SD)	median	mean (SD)	median	Kruskal-Wallis *H*	df	p
Age	36.28 (12.85)	36.00	28.97 (9.92)	26.00	32.24 (9.52)	30.00	3.29	2	0.04*
Range (years)	19-57		19-52		19-57				
	N	%	N	%	N	%	Chi2	df	p
Sex							1.78	2	0.41
male	15	51	10	34	13	45			
female	14	49	19	66	16	55			
Education							7.54	-	0.16 [a]
no degree	1	3	0	0	0	0			
Hauptschule	2	7	1	3	0	0			
Realschule	8	28	7	24	3	10			
Abitur	18	62	21	72	26	90			
Center							0.67	2	0.72
Göttingen	16	55	17	59	19	66			
Heidelberg	13	45	12	41	10	34			
Medication									
L-thyroxine	4	14	2	7	3	10			
Beta blockers	1	3	0	0	0	0			
Relationship									
Father	3	10	0	0					
Mother	7	24	0	0					
Son	6	21	7	24					
Daughter	2	7	13	45					
Brother	5	17	3	10					
Sister	6	21	6	21					

*p<0.05; [a]Fisher's exact test; A post-hoc Mann-Whitney U test revealed a significant difference (p<0.05) in age between RelSZ (Mdn=36) and RelBD (Mdn=26), $U(N_{RelSZ}=29, N_{RelBD}=29)=260.50$, z=-2.49, p=0.01. Abbreviations: RelSZ = unaffected first-degree relatives of patients with schizophrenia, RelBD = unaffected first-degree relatives of patients with bipolar disorder.

Table 2. Task performance during the 'desire-reason dilemma' paradigm (in %).

	RelSZ (n=29)		**RelBD** (n=29)		**Controls** (n=29)				
	mean (SD)	median	mean (SD)	median	mean (SD)	median	Kruskal-Wallis *H*	df	p
Desire context									
Correctly accepted bonus stimuli	79.43 (14.22)	80.00	83.28 (14.75)	87.50	86.32 (14.76)	92.00	4.65	2	0.10
Correctly accepted target stimuli	93.82 (4.63)	93.94	93.98 (4.42)	94.23	94.80 (4.31)	96.23	1.15	2	0.56
Reason context									
Correctly rejected bonus stimuli	90.57 (12.29)	96.00	93.65 (8.08)	96.43	94.46 (5.66)	96.43	1.52	2	0.47
Correctly accepted target stimuli	96.94 (3.55)	98.08	97.49 (8.08)	98.21	98.00 (2.61)	98.25	1.28	2	0.53

Kruskal-Wallis *H* test did not reveal any significant differences between groups. Abbreviations: RelSZ = unaffected first-degree relatives of patients with schizophrenia, RelBD = unaffected first-degree relatives of patients with bipolar disorder.

3.1.3 FMRI data

In the DC, all groups showed reward-related activations in the vStr and midbrain/VTA (p<0.005, uncorrected). Results are shown in Table 3 and Figure 3. Moreover, activations in an extended FPN including prefrontal, orbitofrontal and parietal regions were found in all three groups.

Group comparisons showed a hyperactivation in the right vStr in RelSZ compared with controls and RelBD (p<0.05, small volume corrected; RelSZ > Controls, RelSZ > RelBD). Furthermore, a hyperactivation was found for RelSZ compared with controls and RelBD (p<0.005, uncorrected; RelSZ > Controls, RelSZ > RelBD) in the right avPFC and for RelBD compared with controls in the left avPFC (p<0.005, uncorrected; RelBD > Controls). In addition, hyperactivations were found for RelSZ and RelBD, respectively, compared with controls in several frontal and parietal regions. RelSZ showed hyperactivation in a network with emphasis rather on the right hemisphere, including right MFG, right inferior frontal junction (IFJ), right frontal eye field (FEF), left frontoopercular/insular regions, bilateral intraparietal cortex, and the right lateral occipitotemporal gyrus compared with controls (p<0.005, uncorrected; RelSZ > Controls). For RelBD, hyperactivation was found in right MFG, right IFJ, left FEF, right Pre-SMA/frontomedian cortex compared with controls (p<0.005, uncorrected; RelBD > Controls). Differences were more pronounced for RelSZ than RelBD compared with controls, which could also be confirmed in the direct group comparison where RelSZ showed significantly stronger activation in the right vStr, right avPFC, and several frontal and parietal regions than RelBD (RelSZ > RelBD).

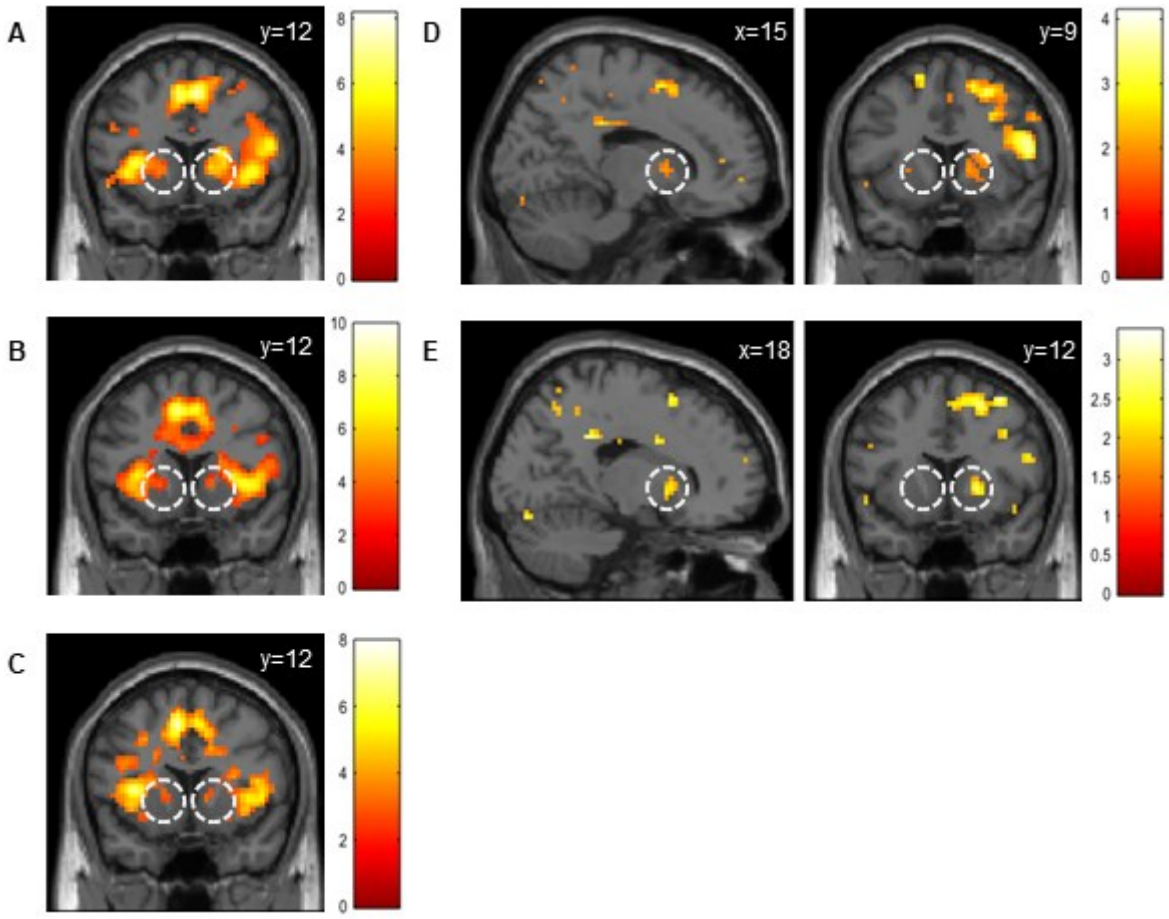

Figure 3. Increased reward responsiveness in the ventral striatum (vStr; white circles) in RelSZ. Bottom-up activation of the vStr during presentation of conditioned reward stimuli is shown for (A) RelSZ (*n*=29), (B) RelBD (*n*=29) and (C) matched controls (*n*=29; *p*<0.005, uncorrected). A hyperresponsivity of the right vStr was found in RelSZ compared with controls (D) and RelBD (E), respectively (*p*<0.05, small volume corrected around a priori coordinates (6mm sphere at 12 12 -3) from Diekhof and Gruber (2010). *T*-values are indicated by color bars. For more details, see Table 3. Abbreviations: RelSZ = unaffected first-degree relatives of patients with schizophrenia, RelBD = unaffected first-degree relatives of patients with bipolar disorder.

Table 3. Group comparison of reward-related regional brain activation during the 'desire context'.

REGION	RelSZ	RelBD	Controls	RelSZ > RelBD	RelSZ > Controls	RelBD > Controls
L ventral/dorsal striatum	-12 6 3 (6.00) **	-15 9 0 (4.09) *	-15 6 6 (5.69) **	n.s.	n.s.	n.s.
R ventral/dorsal striatum	15 6 3 (6.49) **	15 6 3 (6.09) **	14 8 4 (3.57)	18 12 -3 (1.77) +	15 9 0 (1.72) +	n.s.
L midbrain/VTA	-6 -24 -9 (5.29) **	-6 -27 -9 (6.63) **	-6 -21 -15 (5.73) **	n.s.	n.s.	n.s.
R midbrain/VTA	6 -27 -12 (4.52) *	6 -27 -12 (7.57) **	6 -27 -12 (7.09) **	n.s.	n.s.	n.s.
L avPFC	-30 48 9 (3.66) *	-32 48 6 (3.90) *	-30 42 9 (5.77) **	n.s.	n.s.	-27 48 -9 (2.90)
R avPFC	36 39 15 (6.83) **	36 51 6 (4.96) *	33 45 -6 (5.70) **	36 39 15 (3.00)	33 45 18 (2.81)	n.s.
L MFG (middle or anterior third)	-42 33 21 (4.55) *	-39 27 24 (5.64) **	-39 30 18 (5.36) **	n.s.	n.s.	n.s.
R MFG (middle or anterior third)	36 39 15 (6.83) **	42 33 30 (6.99) **	44 34 21 (3.73) *	30 27 33 (3.32)	42 42 21 (3.24)	36 45 27 (2.72)
L IFJ	-48 3 30 (6.75) **	-45 -3 36 (5.84) **	-39 -3 42 (5.99) **	n.s.	n.s.	n.s.
R IFJ	45 6 21 (5.43) **	45 3 27 (5.78) **	42 3 30 (4.29) *	36 9 57 (3.32)	30 6 39 (3.86)	33 6 42 (3.09)
L FEF (MFG posterior third)	-24 -6 48 (5.84) **	-24 -9 48 (6.14) **	-30 -6 45 (3.98) *	n.s.	n.s.	-21 -15 54 (2.85)
R FEF (MFG posterior third)	30 3 51 (5.68) **	30 0 51 (4.92) *	30 0 51 (3.21) *	n.s.	33 3 54 (4.12)	n.s.
L frontoopercular cortex/anterior insular cortex	-30 21 3 (7.75) **	-30 18 0 (7.82) **	-30 24 0 (7.30) **	n.s.	39 30 6 (3.07)	n.s.
R frontoopercular cortex/anterior insular cortex	33 21 -9 (7.95) **	33 21 -9 (9.92) **	36 18 0 (7.37) **	n.s.	n.s.	n.s.
L Pre-SMA/frontomedian cortex	-6 3 57 (6.73) **	-6 12 48 (8.36) **	-6 12 48 (7.52) **	n.s.	n.s.	n.s.
R Pre-SMA/frontomedian cortex	6 12 51 (8.13) **	6 15 45 (7.25) *	12 21 33 (6.61) **	n.s.	n.s.	9 33 30 (3.26)
L intraparietal cortex	-39 -39 45 (7.13) **	-39 -42 39 (7.03) **	-27 -48 45 (6.62) **	-42 -54 21 (2.70)	-42 -57 21 (2.89)	n.s.
R intraparietal cortex	30 -57 48 (5.57) **	33 -57 45 (6.20) **	-48 -36 42 (7.80) **	n.s.	45 -60 51 (2.91)	n.s.
L thalamus	-12 -15 9 (6.04) **	-12 -12 6 (5.51) **	-15 -9 12 (5.69) **	-12 -21 12 (2.88)	n.s.	n.s.
R thalamus	12 -6 6 (4.84) *	12 -9 3 (5.58) **	12 -9 3 (3.80) *	n.s.	n.s.	n.s.
L visual association cortex	-15 -99 -3 (3.23) *	-12 -99 0 (5.78) **	-18 -96 -6 (5.65) **	n.s.	n.s.	n.s.
R visual association cortex	30 -90 6 (5.25) **	27 -93 6 (6.39) **	24 -87 -3 (6.46) **	n.s.	n.s.	n.s.

L inferior temporal/inferior occipital/fusiform gyrus	-48 -51 -12 (5.14)	**	-39 -60 -6 (3.57)	*	-45 -60 -9 (5.11)	**	n.s.		n.s.		n.s.
R inferior temporal/inferior occipital/fusiform gyrus	42 -69 -9 (4.56)	*	45 -72 -12 (4.85)	*	36 -60 -12 (4.58)	*	n.s.		30 -57 -15 (3.00)		n.s.

MNI coordinates (x, y, z) and *t*-values of local maxima are presented at a search criterion of $p<0.005$, uncorrected if not otherwise indicated. *$p<0.001$, **$p<0.05$, FWE-corrected for whole brain; +$p<0.05$, corrected for small volume (6mm sphere) around a priori coordinates from Diekhof and Gruber (2010). Maxima are reported at the respective strictest criterion. Abbreviations: avPFC = anteroventral prefrontal cortex; FEF = frontal eye field; IFJ = inferior frontal junction; L = left; MFG = middle frontal gyrus; n.s. = not significant; R = right; RelBD = unaffected first-degree relatives of patients with bipolar disorder; RelSZ = unaffected first-degree relatives of patients with schizophrenia; SMA = supplementary motor area; VTA = ventral tegmental area.

During the ‘desire-reason dilemma’ (DRD) situation, successful decisions against the conditioned reward stimuli (immediate reward desiring) were associated with a significant suppression of reward-related activation in the vStr in all three groups, while descriptively effects were smaller in RelSZ and RelBD (p<0.05, small volume corrected) compared with controls (p<0.05, FWE-corrected). Results are shown in Table 4. Additionally, RelBD and Controls showed significant suppression effects in midbrain/VTA and avPFC.

Group comparisons exhibited significantly weaker suppression of reward-related activation in RelSZ and RelBD compared with controls (Controls > RelSZ, Controls > RelBD) in the bilateral vStr and right midbrain/VTA, as well as bilateral avPFC. Suppression was also diminished in frontal and parietal regions. For both RelSZ and RelBD compared with controls significantly weaker suppression has been found in bilateral MFG, right inferior frontal gyrus, right frontoopercular/insular regions, middle cingulate gyrus, bilateral hippocampus, intraparietal cortex, thalamus, and ventral visual pathway (p<0.005, uncorrected; Controls > RelSZ, Controls > RelBD). The extent of suppression was even more reduced for RelSZ than RelBD, as was shown in the direct comparison (p<0.005, uncorrected; RelBD > RelSZ) for midbrain/VTA, avPFC and several frontal and parietal brain regions. Conversely, RelBD did not show any significant reduced suppression effects compared with RelSZ.

Table 4. Group comparison of suppression of reward-related activity due to the 'desire-reason dilemma' situation.

REGION	RelSZ	RelBD	Controls	RelBD > RelSZ	Controls > RelSZ	Controls > RelBD
L ventral striatum	-12 9 0 (1.81) +	-12 12 3 (2.96) +	-9 6 -3 (5.26) **	n.s.	-12 21 -6 (3.36)	-12 12 -3 (2.42) +
R ventral striatum	9 9 0 (2.99) +	12 6 -3 (3.44) +	12 18 -3 (5.77) **	n.s.	15 21 -6 (4.45)	18 18 -9 (3.87) *
L midbrain/VTA	n.s.	-6 -33 -18 (4.10) *	-3 -27 -18 (5.32) **	-6 -30 -18 (3.33) *	0 -36 -27 (4.01) *	-12 -27 -6 (3.68) *
R midbrain/VTA	n.s.	6 -30 -15 (6.52) **	6 -30 -18 (6.08) **	6 -33 -21 (3.96) *	6 -33 -27 (4.23) *	n.s.
L dorsal striatum	-12 12 9 (3.65)	-9 6 6 (4.17) *	-12 9 12 (5.36) **	-21 9 18 (3.58) *	-12 21 -6 (3.36 *	-15 -12 21 (2.72)
R dorsal striatum	12 12 12 (3.71) *	12 9 15 (3.85) *	15 -3 18 (5.98) **	n.s.	18 -3 18 (3.94) *	18 21 6 (3.33) *
L avPFC	n.s.	-33 57 9 (3.89) *	-39 48 3 (5.92) **	-39 42 3 (3.48) *	-39 48 -3 (3.12)	-39 51 0 (2.78)
R avPFC	n.s.	39 51 6 (4.74) *	45 48 3 (6.61) **	36 54 6 (2.82)	33 51 3 (2.72)	30 42 0 (2.79)
L MFG (middle or anterior third)	-42 21 48 (2.75)	-42 33 27 (3.61) *	-39 24 36 (5.28) **	-42 27 30 (3.06)	-36 24 33 (4.43) *	-27 18 36 (4.99) *
R MFG (middle or anterior third)	30 30 48 (3.84) *	45 42 18 (5.16) **	39 24 42 (5.48) **	39 39 21 (3.05)	24 24 39 (3.30) *	42 27 42 (2.78)
L IFG (opercular part)	n.s.	-57 15 24 (3.74) *	n.s.	n.s.	n.s.	n.s.
R IFG (opercular part)	n.s.	51 15 15 (5.83) **	51 12 6 (5.85) **	51 15 12 (3.85) *	57 12 6 (3.80) *	54 9 6 (3.69) *
L IFJ	n.s.	-48 3 21 (3.49) *	-38 2 40 (2.72)	-42 -6 36 (3.14)	-30 6 36 (3.32) *	n.s.
R IFJ	45 6 33 (3.10)	45 3 30 (3.38)	42 3 30 (4.32) *	n.s.	n.s.	36 6 30 (2.92)
L frontoopercular cortex/anterior insula	-39 21 -12 (3.61) *	-33 15 -6 (5.83) **	-33 15 0 (5.38) **	-33 18 -6 (3.19)	n.s.	-36 6 6 (3.06)
R frontoopercular cortex/anterior insula	39 30 -15 (4.44) *	30 18 -12 (6.34) **	39 15 -6 (6.32) **	n.s.	39 0 -6 (4.17) *	39 3 -6 (3.75) *
L/R middle cingulate gyrus	3 -3 27 (2.66)	-6 15 24 (4.62) *	0 -27 39 (5.41) **	-9 15 27 (3.53) *	-6 15 30 (3.68) *	-9 3 39 (3.32) *
L hippocampus	n.s.	n.s.	-24 -28 -12 (3.40) *	n.s.	-21 -30 -18 (3.36) *	-21 -30 -15 (3.15)
R hippocampus	n.s.	n.s.	27 -27 -15 (5.26) **	n.s.	36 -12 -21 (3.45) *	24 -27 -15 (3.61) *
L intraparietal cortex	-42 -54 57 (3.57) *	-45 -51 54 (4.86) *	-27 -69 51 (6.54) **	n.s.	-39 -51 42 (3.83) *	-33 -63 33 (2.72)
R intraparietal cortex	48 -54 54 (3.85) *	48 -48 51 (4.88) *	42 -54 60 (6.96) **	n.s.	36 -42 39 (3.31) *	39 -54 60 (3.33)
L thalamus	n.s.	-9 -9 -6 (2.69)	-9 -9 -3 (5.70) **	-9 -9 -6 (2.03)	-21 -21 -3 (3.19)	-6 -12 -3 (3.21)
R thalamus	n.s.	9 -9 0 (3.88) *	3 -12 15 (5.81) **	9 -12 0 (2.17)	18 -21 0 (3.29) *	3 -12 15 (3.10)
L ventral visual pathway	-39 -87 -3 (3.28) *	n.s.	-24 -90 -6 (3.52) *	n.s.	-24 -72 33 (3.66) *	-21 -78 33 (4.35) *

R ventral visual pathway	36 -84 9 (3.65)	*	42 -84 -3 (3.40)	*	33 -78 6 (5.22)	**	n.s.	36 -69 6 (4.03)	*	33 -78 6 (3.91)	*	

MNI coordinates and *t*-values of local maxima are presented at a search criterion of $p<0.005$, uncorrected, if not otherwise indicated. * $p<0.001$, uncorrected; ** $p<0.05$, FWE-corrected for whole brain; + $p<0.05$, corrected for small volume (6mm sphere) around a priori coordinates from Diekhof and Gruber (2010). Maxima are reported at the respective strictest criterion. Abbreviations: avPFC = anteroventral prefrontal cortex; IFG = inferior frontal gyrus; IFJ = inferior frontal junction; L = left; MFG = middle frontal gyrus; n.s. = not significant; R = right; RelBD = unaffected first-degree relatives of patients with bipolar disorder; RelSZ = unaffected first-degree relatives of patients with schizophrenia; VTA = ventral tegmental area.

3.2 Study 2: Genome-wide association study of rsFC between the left FPN and Heschl's gyrus

3.2.1 Sample characteristics

The final dataset after QC comprised 4678346 SNPs and 232 subjects (84 males, 148 females). Mean age was 24.1 years (range: 19–31 years; standard deviation: 2.38). Eleven subjects were left-handed. 229 subjects had higher school education.

3.2.2 Genome-wide association study

One SNP (rs12621273) within one locus near Integrin Subunit Alpha 6 (ITGA6) gene on chromosome 2 reached genome-wide significance at $p<5\times10^{-8}$ ($p=4.58\times10^{-8}$, T allele, beta=0.7477; Figure 4). 114 SNPs reaching a threshold of $p<1\times10^{-5}$ were assumed to show suggestive evidence for association (Supplementary table 3). These SNPs represented 15 independent genomic loci (Table 5; Supplementary table 4; Supplementary figure 2). Among these loci, 4 were intronic, 7 were intergenic, 2 were ncRNA intronic and 2 were exonic. The intronic loci were located within calcium/calmodulin dependent protein kinase II alpha (CAMK2A) gene on chromosome 5 with the lowest *p*-value for rs4958456 ($p=6.64\times10^{-8}$, T allele, *beta*=1.053), vaccinia related kinase 1 (VRK1) gene on chromosome 14 with the lowest *p*-value for rs67957817 ($p=2.63\times10^{-6}$, A allele, *beta*=0.9503), Protein KIAA0556 (synonym: KATNIP) gene on chromosome 16 with the lowest *p*-value for rs916762 ($p=3.79\times10^{-6}$, C allele, *beta*=0.7417), and adenylate cyclase type VII (ADCY7) gene on chromosome 16 with the lowest *p*-value for rs16948353 ($p=9.25\times10^{-6}$, T allele, *beta*=-0.5675), respectively. The gene with the most SNPs (*n*=25) with $p<1\times10^{-5}$ is inner mitochondrial membrane peptidase subunit 2 (IMMP2L) gene on chromosome 7 (for details see Supplementary table 3). The QQ plot of the GWAS is shown in Supplementary figure 3.

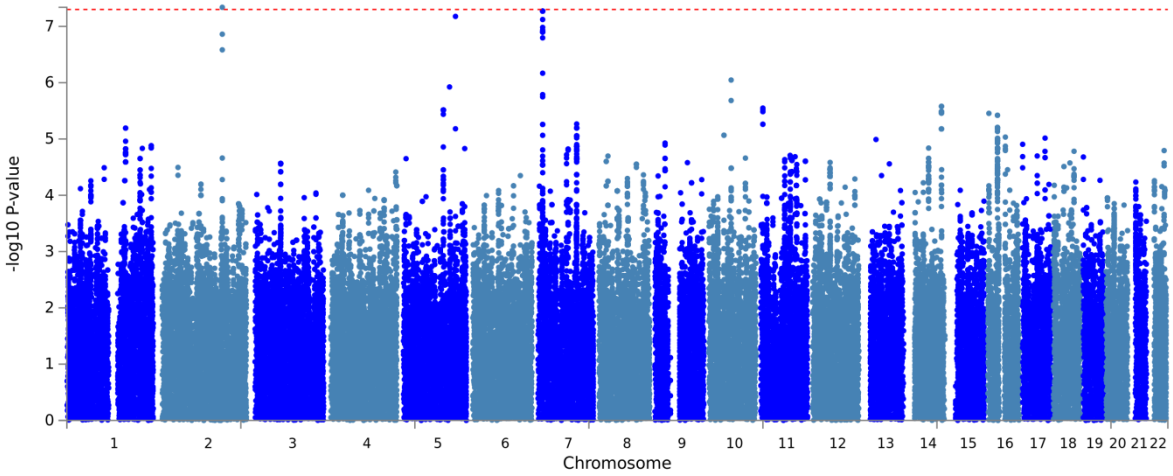

Figure 4. Manhattan plot of genome-wide association analysis (GWAS) results. Single-nucleotide polymorphisms (SNP) are displayed according to their chromosomal position (x-axis). For each SNP, the –log10 association *p*-value is shown on the y-axis. The red dashed line indicates genome-wide significance ($p<5\times10^{-8}$). One SNP (rs12621273) on chromosome 2 reached genome-wide significance ($p=4.58\times10^{-8}$, T allele, *beta*=0.747).

Table 5. Genomic risk loci and lead SNPs.

LOCUS	LEAD SNP	CHR	FUNC	NEAREST GENE	DIST	P	EFFECT ALLELE	MAF	BETA
2	rs12621273	2	intergenic	ITGA6	14298	4.58×10^{-8}	T	0.2962	0.7477
6	rs1432490	7	ncRNA_intronic	AC011288.2	0	5.35×10^{-8}	C	0.2048	0.854
5	rs4958456	5	intronic	CAMK2A	0	6.64×10^{-8}	T	0.1382	1.053
9	rs7096931	10	intergenic	ZNF365	4996	8.97×10^{-7}	A	0.172	0.765
4	rs61741674	5	exonic	FSTL4	0	1.19×10^{-6}	A	0.0507	1.076
11	rs67957817	14	intronic	VRK1	0	2.63×10^{-6}	A	0.1024	0.9503
10	rs4758406	11	intergenic	RP11-304C12.4	6539	2.83×10^{-6}	T	0.1789	0.7749
3	rs10478230	5	intergenic	CTNNAP1	11441	3.06×10^{-6}	T	0.0835	1.184
12	rs2074363	16	exonic	FLYWCH1	0	3.51×10^{-6}	T	0.1143	0.921
13	rs916762	16	intronic	KIAA0556	0	3.79×10^{-6}	C	0.1551	0.7417
7	rs2906623	7	intergenic	IMMP2L	26165	5.41×10^{-6}	G	0.165	0.7494
1	rs1853278	1	ncRNA_intronic	LINC00970	0	6.41×10^{-6}	C	0.1958	0.6688
8	rs2565190	10	intergenic	MIR5100	36941	8.58×10^{-6}	A	0.4374	0.5955
14	rs16948353	16	intronic	ADCY7	0	9.25×10^{-6}	T	0.3837	-0.5675
15	rs150389995	17	intergenic	RP11-401F2.2	23590	9.65×10^{-6}	A	0.1074	0.8669

Summary of the 15 genomic loci associated with the endophenotype of resting-state functional connectivity between the left fronto-parietal network and Heschl's gyrus at $p<1\times10^{-5}$ in the genome-wide association analysis (GWAS). Loci are sorted according to *p*-value. Abbreviations: LOCUS = genomic Locus, LEAD SNP = rsID of the top lead SNP based on dbSNP build 146, CHR = chromosome, FUNC = functional consequence of the SNP on the gene obtained from ANNOVAR, NEAREST GENE = the nearest Gene of the SNP based on ANNOVAR annotations, DIST = distance to the nearest gene, P = GWAS *p*-value of top lead SNP, EFFECT ALLELE = effect/risk allele, MAF = minor allele frequency computed based on 1000G, BETA = GWAS beta.

3.2.3 Gene-based, gene-set and tissue expression analysis

Input SNPs were mapped to 19051 genes by MAGMA. Gene-based analysis was performed using the default SNP-wide mean model. No gene reached genome-wide significance on a Bonferroni-corrected level of p=0.05/19051=2.625×10^{-6} (Supplementary figure 4). The QQ plot of the gene-based analysis by MAGMA is shown in Supplementary figure 5. The most significant genes (p<5×10^{-4}) are shown in Table 6. The gene reaching the lowest p-value was protein kinase C delta-binding protein gene (PRKCDBP; synonym: CAVIN3; p=1.34×10^{-5}).

In the MAGMA gene set analysis calculated via FUMA, 10678 gene sets (4761 curated gene sets; 5917 GO terms) were tested in a competitive test model. Nine gene sets reached a p-value <0.0005 (Supplementary table 5). However, no gene set revealed to be reliable after correction for multiple testing (p-value threshold of p=0.05/10678=5×10^{-6}).

To identify tissue specificity of the endophenotype, MAGMA gene-property analysis was run. Two analyses were performed with a) 30 general tissue types (Figure 5; Supplementary table 6) and b) 53 specific tissue types (Figure 6; Supplementary table 7). In the expression analysis of 30 general tissue types, brain tissue reached the lowest p-value (p=3.91×10^{-4}), followed by nerve tissue (p=0.07). In the analysis on 53 specific tissue types, tissues from the brain reached the lowest p-values. Amygdala tissue reached significance at p<0.001.

Table 6. Results of the MAGMA gene-based analysis.

GENE	CHR	START	STOP	NSNPs	NPARAM	N	ZSTAT	P
PRKCDBP	11	6320176	6361877	75	11	231	4.1998	1.34×10^{-5}
KIAA0556	16	27541454	27811690	204	7	231	4.1549	1.63×10^{-5}
IMMP2L	7	110283110	111222573	1118	47	231	4.1431	1.71×10^{-5}
ITGA6	2	173272082	173391181	319	25	232	3.9504	3.90×10^{-5}
GTF3C1	16	27450876	27581234	105	5	232	3.8366	6.24×10^{-5}
CLEC2D	12	9797565	9868413	247	18	231	3.7322	9.49×10^{-5}
HPD	12	122257433	122321502	85	8	232	3.728	9.65×10^{-5}
STARD6	18	51830728	51904334	192	12	232	3.7095	1.04×10^{-4}
KIAA1324L	7	86486222	86709015	351	10	231	3.679	1.17×10^{-4}
MISP	19	731126	784319	23	8	231	3.6575	1.27×10^{-4}
ATF1	12	51137493	51234905	108	7	231	3.6436	1.34×10^{-4}
C17orf104	17	42713762	42787676	86	9	231	3.6054	1.56×10^{-4}
CDC34	19	511714	562097	29	8	230	3.6001	1.59×10^{-4}
TRIM2	4	154053494	154280472	362	39	231	3.5834	1.70×10^{-4}
C18orf54	18	51864287	51931588	191	9	232	3.579	1.72×10^{-4}
GZMM	19	524034	569919	27	7	230	3.5763	1.74×10^{-4}
FMN1	15	33037747	33506897	1274	87	231	3.5357	2.03×10^{-4}
BTG1	12	92516286	92559673	71	13	231	3.511	2.23×10^{-4}
DIP2B	12	50878768	51162450	261	7	232	3.4752	2.55×10^{-4}
MTNR1A	4	187434809	187496721	76	10	231	3.4551	2.75×10^{-4}
CCDC43	17	42730437	42787147	49	9	231	3.4329	2.99×10^{-4}
C19orf43	19	12821454	12865589	3	1	231	3.4039	3.32×10^{-4}
C12orf79	12	92358756	92556690	290	41	231	3.3652	3.82×10^{-4}
ATP5EP2	13	28499343	28539727	75	6	232	3.3451	4.11×10^{-4}
RP11-505K9.4	16	83921738	84005058	187	21	231	3.3319	4.31×10^{-4}
BAK1	6	33520329	33568019	169	15	232	3.3253	4.42×10^{-4}
TMEM256-PLSCR3	17	7273046	7327416	64	15	231	3.3199	4.50×10^{-4}
C17orf61-PLSCR3	17	7273053	7327416	64	15	231	3.3199	4.50×10^{-4}
NCF4	22	37237030	37294057	80	14	231	3.3138	4.60×10^{-4}
DDI1	11	103887308	103929922	68	11	232	3.3026	4.79×10^{-4}

Most significant genes ($p<5\times10^{-4}$) in the gene-based analysis and their chromosomal position are shown. No gene reached genome-wide significance on a Bonferroni-corrected level of $p=0.05/19051=2.625\times10^{-6}$. Loci are sorted according to *p*-value. Abbreviations: GENE = gene symbol, CHR = chromosome, START = start position of the gene (hg19), STOP = end position of the gene (hg19), NSNPs = number of single-nucleotide polymorphism, NPARAM = number of parameters included in the model, N = sample size, ZSTAT = z-value of the gene, P = *p*-value of the gene.

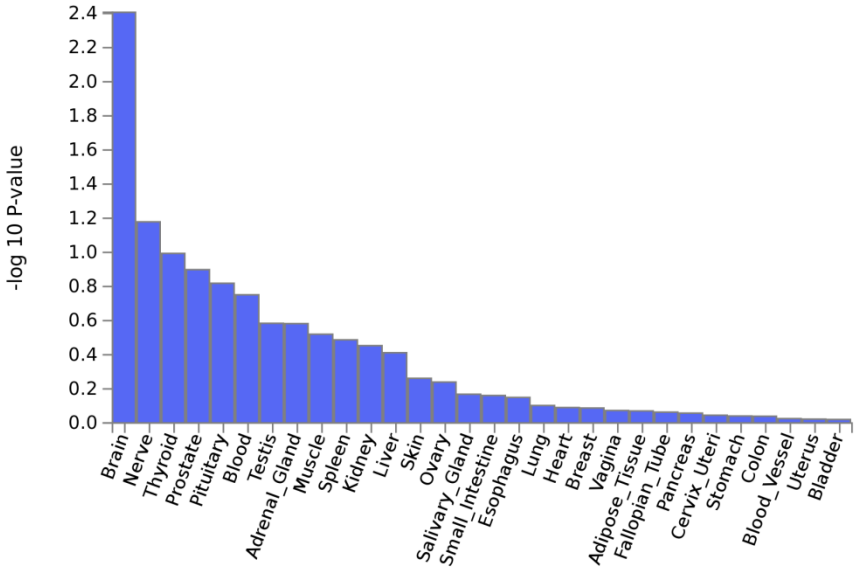

Figure 5. Results of MAGMA tissue expression analysis on 30 general tissue types by GTex. For each tissue-type (x-axis), the association –log10 *p*-value is shown on the y-axis. Tissue types are sorted according to *p*-value. Results were considered significant, if exceeding a significance threshold of $p<0.001$. Significant results are indicated in red, otherwise in blue.

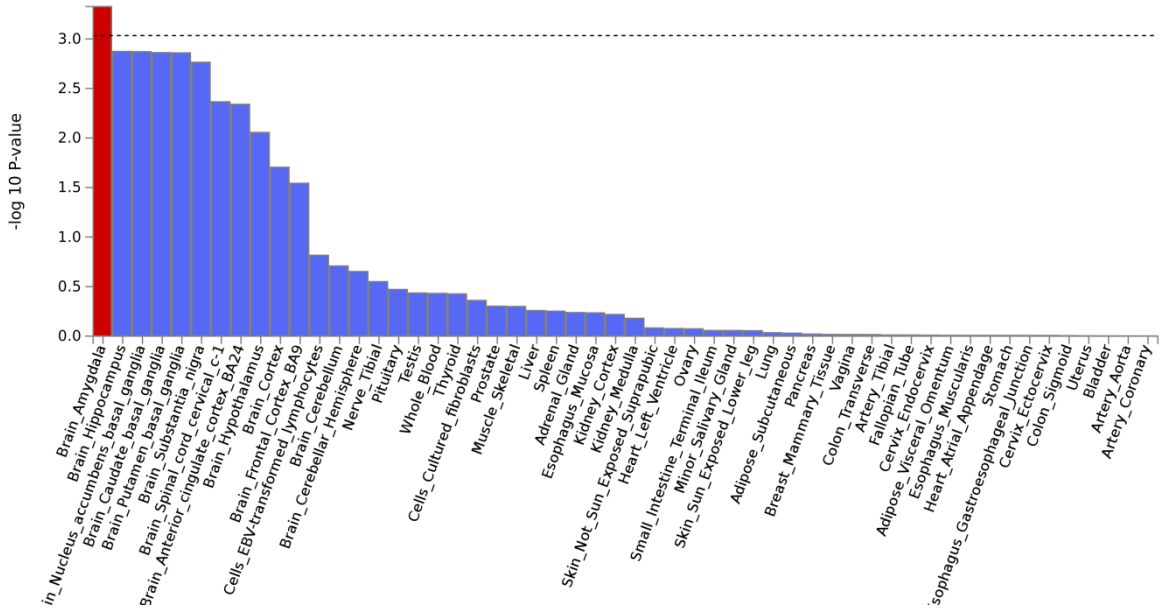

Figure 6. Results of MAGMA tissue expression analysis on 53 specific tissue types by GTex. For each tissue-type (x-axis), the association –log10 *p*-value is shown on the y-axis. Tissue types are sorted according to *p*-value. The dashed line indicates significance at $p<0.001$. Significant results are indicated in red, otherwise in blue.

4. DISCUSSION

This thesis aimed to contribute to the identification of biosignatures for schizophrenia and bipolar disorder on a neuroimaging and molecular genetic level by using functional neuroimaging endophenotypes and an imaging genetics approach. Two studies were conducted. Study 1 examined the neurofunctional correlates of reward processing in unaffected first-degree relatives of patients with schizophrenia and bipolar disorder using the 'desire-reason dilemma' paradigm. Study 2 investigated the genetic underpinnings of healthy resting-state functional connectivity between the left FPN and Heschl's gyrus using a genome-wide association approach. In the following sections, the results of the two studies will separately be discussed in detail, followed by a combined conclusion and further remarks.

4.1 Study 1: Diminished prefrontal control of the mesolimbic reward system in RelSZ and RelBD

The first study examined reward-related brain activations, i.e., the neurofunctional mechanisms underlying the ability to resist immediate reward desiring in favor of a superordinate long-term goal in extended samples of RelSZ and RelBD using fMRI. The aim of this study was to investigate the genetic vulnerability for dysregulations in the reward-system, thereby proving if brain activation elicited by DRD paradigm constitutes a potential endophenotype. First, I confirmed the absence of behavioral differences between RelSZ and RelBD, respectively, compared with controls, which is in line with previous research (De Leeuw et al. 2015; Grimm et al. 2014; Hanssen et al. 2015; Jakob 2013; Kollmann et al. 2017; Linke et al. 2012). As data from (Fanelli 2013), where RelSZ showed significantly poorer performance in correctly accepted bonus stimuli in the DC, is contained in my sample, this difference is still reflected on a descriptive level. Second, I confirmed that the task activated the intended reward-related brain regions during reward-exploitation in the DC and that these regions were downregulated in the 'desire-reason dilemma' in both RelSZ and RelBD. Third, group differences in neurofunction between RelSZ, RelBD and a control group were examined. My main results were that in RelSZ bottom-up neural response of the right vStr and right avPFC to conditioned reward stimuli was significantly increased and top-down regulation of reward-related activity in the bilateral vStr and midbrain/VTA was impaired. RelBD, in contrast, did not show disturbances in activations of the mesolimbic reward system in response to reward stimuli. Though, hyperactivation in the left avPFC in response to reward, and an impaired top-down regulation of reward-related activity in the vStr and left midbrain/VTA was found in RelBD. In sum, this study found aberrant brain activation in relatives in response to reward similar to patients. These study results suggest that aberrant

reward system functioning as well as its disturbed control by an extended fronto-parietal executive network might represent a vulnerability marker for future development of psychopathology.

The hyperactivation observed in the right vStr during reward exploitation in RelSZ is, disregarding laterality, in line with findings in patients with schizophrenia (Richter et al. 2015) and a preceding doctoral thesis that compared RelSZ with controls (Fanelli 2013) (of which data is included in this study). No difference was found in the midbrain/VTA activation between RelSZ and controls. This converges with results contrasting patients with schizophrenia and controls (Richter et al. 2015), indicating that the feedback loop from vStr to midbrain/VTA is intact. Still, this is in contrast with results by Fanelli (2013) who reported a significantly increased response in midbrain/VTA in RelSZ compared with controls. The right avPFC showed significantly increased activation compared with controls. This differs from findings in patients showing a hypoactivation in the right avPFC (Richter et al. 2015) and RelSZ (Fanelli 2013), for whom no significant differences were reported. Moreover, my results showed hyperactivation in frontal and parietal regions with emphasis rather on the right hemisphere. This replicates findings in patients (Richter et al. 2015) and RelSZ (Fanelli 2013), for whom also hyperactivation in an extended FPN has been reported. Correct rejection of immediate reward stimuli in the dilemma situation was associated with a significantly weaker suppression in ventral and dorsal striatum and midbrain/VTA in RelSZ. This is partly consistent with findings in patients (Richter et al. 2015), who reported diminished suppression for the right dorsal striatum. Furthermore, in line with findings in patients (Richter et al. 2015), suppression was diminished in widespread regions of an extended FPN (see Table 4). This finding can most likely be attributed to an impaired top-down control by prefrontal regions on the vStr reward response.

RelBD showed no differences in vStr and midbrain/VTA activation during reward exploitation compared with controls in my study. This is in line with earlier findings in RelBD (Jakob 2013), but differs from findings in patients with bipolar disorder (Trost et al. 2016). A hyperactivation was observed in the left avPFC, which also differs from findings in patients with bipolar disorder (Trost et al. 2014), where a significant hypoactivation in the right avPFC has been reported. Furthermore, RelBD in my study showed hyperactivations in several frontal and parietal regions, which is contradictory to findings in patients (Trost et al. 2014) and previous findings in RelBD (Jakob 2013), where hypoactivations were reported. More importantly, the extent of downregulation of activation due to the DRD situation was significantly weaker in RelBD than in controls in the bilateral vStr and the left midbrain/VTA, as well as in regions of an extended FPN. This is in line with findings in patients (Trost et al. 2014) and the previous doctoral thesis of RelBD (Jakob 2013) and may be interpreted as a diminished top-down control of reward signals in mesolimbic structures by prefrontal regions.

In comparison with results from studies on relatives using different fMRI paradigms, my results might seem contradictory. While in preceding studies, vStr activation has been reported to be significantly reduced in siblings (De Leeuw et al. 2015) and other first-degree relatives (Grimm et al. 2014) during reward anticipation, my findings, in contrast, implicate a significantly increased activation during reward exploitation. The same is true for areas of an extended FPN, where preceding studies described reduced activation in the insula (De Leeuw et al. 2015; Hanssen et al. 2015) and the MFG (Hanssen et al. 2015), among others. In my study, in contrast, activation was significantly increased as compared with controls. For RelBD, my finding of no difference in vStr activation between RelBD and controls is in line with earlier findings (Kollmann et al. 2017; Linke et al. 2012). With regards to prefrontal brain regions, a hyperactivation has been identified in my study for the left avPFC, while a previous study has reported a hyperactivation in the right OFC (Linke et al. 2012). However, directionality of the effects has to be interpreted in light of the respective reward processing phase, in dependence of the respective paradigm (Richter et al. 2015). Despite divergent findings on patterns of hyper- and hypoactivation, this study provides additional evidence for aberrant functioning in the aforementioned brain regions in RelSZ and RelBD.

In general, differences were more pronounced for RelSZ than RelBD compared with controls. This could also be confirmed in the direct comparison, where RelBD showed significantly weaker response to conditioned reward stimuli in the DC in the right vStr and regions of an extended FPN. The extent of downregulation during the DRD situation was significantly weaker in RelSZ compared with RelBD.

The vStr, above all the NAcc, has a crucial role in the reward circuitry (O'Doherty et al. 2004; Schultz et al. 2000). Hyperresponsivity in this region in schizophrenia patients has earlier been interpreted in terms of a general subcortical hyperdopaminergic state (Richter et al. 2015). For schizophrenia patients, abnormalities in dopamine function have been reported, leading to heightened levels of dopamine release and increased D2 receptor binding (Abi-Dargham et al. 2000). The hyperactivation in the right vStr during reward exploitation I observed in my study in RelSZ, comparable to results in patients with schizophrenia (Richter et al. 2015), might thus be interpreted as at least partial sharing of a dopamine malfunction in relatives. Both RelSZ and RelBD showed aberrant activation in an extended fronto-parietal cortical network, which is assumed to be engaged in working memory and executive control functions (Richter 2017; see Gruber and Goschke 2004 for a review). In more detail, both RelSZ and RelBD convergently showed hyperactivation in the right MFG and the right IFJ. In addition, RelSZ showed hyperactivation in the right FEF, left frontoopercular/anterior insular cortex, the bilateral intraparietal cortex and the inferior temporal/occipital cortical regions, while RelBD showed aberrant responses in the left FEF, supplementary motor area/frontomedian. These increased activations might reflect an attempt to regulate

mesolimbic reward responses, which is more successful for RelBD - as net vStr activation does not differ from controls -, than for RelSZ. In sum, aberrant reward system functioning as well as its disturbed control by a fronto-parietal executive network might represent a vulnerability marker for future development of psychopathology.

This study has several strengths. Previous studies have looked for neural correlates of reward processing in first-degree relatives of patients with schizophrenia (De Leeuw et al. 2015; Fanelli 2013; Grimm et al. 2014; Hanssen et al. 2015) and bipolar disorder (Jakob 2013; Kollmann et al. 2017; Linke et al. 2012), respectively. The current study shows an altered activation in regions of the mesocorticolimbic reward circuitry in response to reward as well as impaired top-down control during a DRD situation in an enlarged sample. As this is in line with findings in patients with schizophrenia and bipolar disorder, the results implicate that mesocorticolimbic reward response measured using the DRD paradigm constitutes a potential endophenotypic neuroimaging marker. Moreover, the findings that there are no significant differences on a task performance behavioral level but in neurofunction fits in line with the theoretical assumption of the endophenotype concept.

Studies like this lay groundwork to imaging genetics studies, investigating molecular genetic underpinnings of brain neuroimaging markers. Until now, there are several candidate gene studies and one GWAS on the reward system. Candidate gene studies investigate associations between genetic variation within pre-selected genes of interest, and disease states or other (endo-)phenotypes (Kwon and Goate 2000). In a study using the ‘desire-reason dilemma’ paradigm (Diekhof and Gruber 2010), the effect of an intronic SNP (rs11764590) of MAD1L1 was investigated. A significantly reduced activation in the bilateral vStr, in the midbrain/VTA as well as in frontal and parietal regions was reported in the risk allele carriers in comparison with the homozygous major allele carriers during reward exploitation in the DC. In the dilemma situation, healthy risk allele carriers showed significantly lower neural response in the bilateral frontoopercular/insular cortex and the right intraparietal cortex compared with homozygous major allele carriers (Trost et al. 2016). Grimm and colleagues (2014) studied the effects of a protective missense variant in neuregulin 1 (NRG1; i.e., rs10503929) using a monetary incentive delay paradigm. A significant decrease in vStr activation was reported in homozygous risk-associated T-allele carriers compared with C-allele carriers contrasting the money vs. control condition. Another study reported a positive association between rs322931 genotype - a GWAS-identified variant previously associated with the passive viewing of positive stimuli - and activation within a cluster in the left vStr during receipt of reward compared with punishment during a probabilistic decision-making procedure (Lancaster et al. 2017). One GWAS tested for single marker associations with activation in a node comprising NAcc of the striatum, caudate nucleus, and putamen during reward anticipation using the monetary incentive delay

paradigm (Jia et al. 2016). The authors identified an intronic locus of the vacuolar protein sorting-associated protein 4A (VPS4A) gene (C/T; rs16958736), while the major C allele was associated with reduced neural response in the striatum. Furthermore, the role of VPS4 for hyperactivation was validated in Drosophila (Jia et al. 2016). Comparably to this, GWAS on a DRD-based endophenotypic marker could shed light on the neurobehavioral pathways behind variation in reward-related behaviors during a dilemma situation of immediate reward conflicting with long-term goal pursuit.

The results of this study have to be interpreted in consideration of some limitations. First, I included first-degree relatives without distinguishing in family relationship to the index patient. This means that besides offspring (that shares 50% of genetic variation with the index patient) and siblings (that share 50% of genetic variation with the index patient on average), also parents were included. Despite parents (also) genetically sharing 50% of variation, the included subject is not obligatory also carrier of risk variants as genetic load might be due to the other parent. Furthermore, RelSZ sample differed significantly from RelBD in family relationship to the index patient. This should be taken into account when interpreting the results, especially if comparing the results between the two disorders from this study. Further studies investigating reward-associated mesocorticolimbic activation in offspring of patients with schizophrenia and/or bipolar would be interesting to address the question of heritability more thoroughly. Although my findings of diminished prefrontal control of the mesolimbic reward system in first-degree relatives suggest a genetic vulnerability for schizophrenia or bipolar disorder, respectively, an influence of shared and non-shared environmental factors cannot be ruled out. To actually investigate the genetic determinants (i.e., the effect of genetic loading) of an aberrant reward processing, future studies with monozygotic and dizygotic twins who are discordant for schizophrenia or bipolar disorder, respectively, would be necessary (De Leeuw et al. 2015). Second, FMRI data for the preceding doctoral theses and this study were acquired in two study centers and in two different scanners. Additionally, the first setup used goggles for stimulus presentation, while in my data acquisition stimuli were presented on a screen (viewable through a mirror). Though introducing ‘scanner’ as covariate into the statistical model, this might not be sufficient to address possible effects resulting from magnetic field inhomogeneity between scanners or subject’s psychological reaction due to the different setup. Third, some of the subjects were medicated with l-thyroxine and one RelSZ subject was medicated with beta blockers. There is evidence that thyroid system is linked with dopamine system (Gaum et al. 2019) with thyroxine-concentrations probably playing an important role of thyroxine in the synthesis of dopamine (Hassan et al. 2013b; Hassan et al. 2013a). However numbers of l-thyroxine medicated subjects were tried to keep equal across groups (n=4 in RelSZ, n=2 in RelBD and n=3 in controls), medication effects on activity of the dopaminergic reward system cannot be

completely ruled out. Fourth, the RelSZ sample differs significantly from RelBD in age. There is evidence that sensitivity to the magnitude of reward is age-dependent. In a monetary incentive delay task, age was correlated with diminished reward-related activation in widespread areas of the brain during reward anticipation and with higher response to outcomes of small loss (Dhingra et al. 2020). However, according to internal analyses of the working group using the DRD paradigm, no significant effect of age has been found. This suggests that confounding of changes in regional activation by age in the current study is rather unlikely. Finally, there are some remarks on results presentation, especially in comparison with preceding studies from the working group. For contrasts in which no differences in a priori regions of interest (i.e., vStr, midbrain/VTA and avPFC) have been found, I did not evaluate any further regions. This led to the selection of contrasts as presented in the results section. It must be noted that the preceding studies presented data at different search criteria, limiting comparability of reported results. Above all, studies in patients with schizophrenia (Richter et al. 2015) and bipolar disorder (Trost et al. 2014) applied small-volume correction for a priori regions of interests (i.e., vStr and midbrain/VTA), while doctoral theses on RelSZ (Fanelli 2013) and RelBD (Jakob 2013) applied the same significance threshold for the all brain regions. I chose to present data at a search criterion of $p<0.005$, uncorrected, and $p<0.05$ small volume corrected for a priori regions of interest. However, regarding the lenient *p*-value thresholds used for a priori regions of interest (i.e., vStr and midbrain/VTA) it must be taken in mind that the reported differences are rather gradual in these regions.

In conclusion, this study found disruptions in mesocorticolimbic reward processing in relatives of patients with schizophrenia and bipolar disorder, while differences were more emphasized for schizophrenia. This suggests that reward processing may constitute a potential endophenotype for schizophrenia and bipolar disorder. However, future studies are necessary to dissect genetic from environmental influences.

4.2 Study 2: Genome-wide markers underpinning rsFC between the left FPN and Heschl's gyrus

The aim of the second study was to identify genetic markers that are associated with an endophenotypic marker of rsFC between the left FPN and a cluster spanning left temporal and parietal auditory regions including Heschl's gyrus (Chahine et al. 2017). Genome-wide association analyses were performed in healthy adults to identify markers on a single-marker, gene and pathway level. In my single-marker analysis, one SNP (rs12621273) within a locus near ITGA6 gene on chromosome 2 reached genome-wide significance, while 114 SNPs showed suggestive evidence for association ($p<1\times10^{-5}$). A gene-based and gene-set

analysis did not reveal genome-wide significant results after correction for multiple testing. In MAGMA gene-property analysis on specific tissue types, amygdala tissue reached significance at $p<0.001$. In general, though not significant, tissues from the brain reached the lowest *p*-values in both the analysis on general and specific tissue types. These study results contribute to the growing knowledge about the genetic underpinnings of brain network connectivity and a potential endophenotype for schizophrenia.

In the single-marker analysis, one SNP that reached genome-wide significance ($p=4.58\times10^{-8}$) was located within an intergenic region near ITGA6 gene on chromosome 2 (rs12621273; distance >10,000 kb). ITGA6 encodes alpha-6 integrin, a member of the integrin alpha chain family of proteins. It is broadly expressed across different tissue types (Fagerberg et al. 2014). ITGA6 has been shown to be linked with epidermolysis bullosa (Georges-Labouesse et al. 1996; Pfendner and Lucky 1993; Varki et al. 2006). However, recently a potential exonic *de novo* variant (rs863223349) of ITGA6 was identified in childhood-onset schizophrenia (Ambalavanan et al. 2016). Only few studies examine the role of ITGA6 in neurons (Fernandez et al. 2019). Evidence from one study suggests that Alpha-6 integrin is involved in neural migration (Yao et al. 2018). Alpha-6, as well as Beta-1 integrins, has been reported to promote axonal regeneration and to mediate of Schwann cell-axon interactions (Chang et al. 2018). Furthermore, Alpha-3 integrin, of the same integrin gene family, has been reported to play a critical role in fetal development of the brain, on the basis of wide range of cellular processes and *de novo* mutations have been reported in patients with schizophrenia (Gulsuner et al. 2013).

Among the loci that showed suggestive evidence for association at $p<1\times10^{-5}$, four were intronic. The first locus (rs4958456; $p=6.64\times10^{-8}$) was located within CAMK2A gene on chromosome 5. This SNP has been associated with urinary free dopamine as metabolite measurement for obesity in Hispanic children (Comuzzie et al. 2012). The gene CAMK2A encodes a protein that belongs to the calcium/calmodulin-dependent protein kinase II (CAMK2) family. CAMK2 is a calcium-activated serine/threonine kinase (for a review see Chia et al. 2018). In humans, there exist four genes that encode distinct CAMK2 iso-enzymes: alpha, beta, gamma, and delta (Chia et al. 2018). CAMK2 expression is prominent in neurons in general, and in the brain (Bennett et al. 1983; Chia et al. 2018). All four iso-enzymes are expressed in the brain (Hanson and Schulman 1992). CAMK2 is highly enriched at synapses, playing a key role in neurotransmitter release, activity-dependent synaptic plasticity and long-term potentiation in glutamatergic synapses that underlie learning and memory (Kandel et al. 2014; Lisman et al. 2002). Among the four protein isoforms, CAMK2A is the most predominant in the brain (Chia et al. 2018; Hanson and Schulman 1992). It has been reported to regulate dendritic spine development (Stephenson et al. 2017) and the migration of developing neurons (Küry et al. 2017). Furthermore, CAMK2A is high-

specifically expressed in brain tissue (Fagerberg et al. 2014). High-level expression of CAMK2A has been demonstrated in hippocampal and cortical neurons (Hanson and Schulman 1992). Mutations in this gene have been reported in association with autosomal recessive 63 and autosomal dominant 53 mental retardation (Akita et al. 2018; Chia et al. 2018; Küry et al. 2017). Taken together, this finding of genetic association with an endophenotype for schizophrenia may be interpreted as in line with earlier studies supporting the role of calcium signaling in schizophrenia (Berridge 2014; Lidow 2003; Mizoguchi et al. 2014).

The second intronic locus (rs67957817; $p=2.63\times10^{-6}$) was located within VRK1 gene on chromosome 14. Its gene product is a member of the vaccinia-related kinase (VRK) family of serine-threonine protein kinases (Martín-Doncel et al. 2019). VRK1 is broadly expressed in human tissues (Fagerberg et al. 2014). Its protein localizes to the nucleus, where it has regulatory function on different nuclear proteins (Martín-Doncel et al. 2019). It is involved in various cellular functions and steps of DNA-damage responses (Martín-Doncel et al. 2019). As a consequence, all of these processes are susceptible to disruption in the case of pathogenic variation. Mutations in genes involved in DNA repair processes often manifest as neurodevelopmental syndromes (Bianchi et al. 2018; Martín-Doncel et al. 2019). In humans, very rare polymorphisms in VRK1 gene have been detected in complex neuromotor phenotypes (Gonzaga-Jauregui et al. 2013; Martín-Doncel et al. 2019; Najmabadi et al. 2011; Renbaum et al. 2009).

The third intronic locus (rs916762; $p=3.79\times10^{-6}$) was located within KIAA0556 gene on chromosome 16. This gene encodes a protein, which is located at the ciliary base and enriched at the ciliary tip. The protein binds to microtubules in vitro and may stabilize them when it is overexpressed (Sanders et al. 2015). It is expressed across all different kinds of tissues with slightly augmented expression in thyroid (Fagerberg et al. 2014). There is evidence that Joubert syndrome is caused by a homozygous null mutation in the KIAA0556 gene (Roosing et al. 2016; Sanders et al. 2015). Joubert syndrome is a rare, autosomal recessive ciliopathy leading to congenital malformation of the brainstem and agenesis or hypoplasia of the cerebellar vermis (Sanders et al. 2015). Phenotypically, it is characterized by abnormal respiratory pattern, nystagmus, hypotonia, ataxia, intellectual disability and global developmental delay (Romani et al. 2013).

The fourth intronic locus (rs16948353; $p=9.25\times10^{-6}$) was located within ADCY7 gene on chromosome 16. This gene encodes adenylyl cyclase (ADCY) that catalyzes the conversion of adenosine-5'-triphosphate (ATP) into 3',5'-adenosine monophosphate (cyclic AMP/cAMP) and can be inhibited by calcium (Devasani and Yao 2022). Expression is tissue-unspecific (Devasani and Yao 2022; Fagerberg et al. 2014) and its function still is largely unknown

(Devasani and Yao 2022). There is evidence that implies a role of ADCY7 in mood regulation and major depressive disorder (Hines et al. 2006; Joeyen-Waldorf et al. 2012).

However, only a small number of SNPs within the previously mentioned genomic regions is also associated with the phenotype, as shown in the Manhattan plot (Figure 4), region plots (Supplementary figure 2) and listed in Supplementary table 4.

The gene with the most SNPs (n=25) with $p<1\times10^{-5}$ is IMMP2L gene on chromosome 7 (Supplementary table 3). The protein encodes a protein of the mitochondrial inner membrane (Vasilyev et al. 2021). Low expression has been observed across tissue types (Fagerberg et al. 2014). The IMMP2L has been suggested as a susceptibility gene for Gilles de la Tourette syndrome (Bertelsen et al. 2014; Bjerregaard et al. 2020; Díaz-Anzaldúa et al. 2004; Pagliaroli et al. 2020; Patel et al. 2011; Petek et al. 2001; Petek et al. 2007). Variants in this gene have been associated with a range of neuropsychiatric conditions such as bipolar disorder, major depression, schizophrenia, autism spectrum disorder, attention deficit-hyperactivity disorder (Elia et al. 2010; Hawi et al. 2018; Petek et al. 2007; Ripke et al. 2014; Warburton et al. 2000).

Interestingly, the most significant gene from the gene-based analysis was PRKCDBP (synonym: CAVIN3; $p=1.34\times10^{-5}$), not ITGA6 where the top SNP is located or IMMP2L, the gene with most SNPs with $p<1\times10^{-5}$ in GWAS. The protein encoded binds protein kinase C, delta (PRKCD). Down-regulation of its expression has been described to be associated with tumorigenesis (Lee et al. 2011). Moreover, PRKCDBP has been associated with circadian rhythm (Kovanen et al. 2015). The most-significant pathway in gene-set analysis was reactome curated gene-set phosphatidylinositol 3-kinase (PI-3K) cascade fibroblast growth factor receptor 4 (FGFR4), while PI-3K FGFR3 and FGFR2 also were among the nine gene-sets with $p<0.005$. There is evidence that PI3K is required for neural cell adhesion molecule (NCAM)-mediated neurite outgrowth from PC12 cells and from cerebellar and dopaminergic neurons through signaling pathways involving the fibroblast growth factor receptor. Furthermore, NCAM-stimulation with caspase-3 ligand is indicated to have a survival-promoting effect on cerebellar and dopaminergic neurons induced to undergo apoptosis, while this effect has also been shown to be dependent on PI3K (Ditlevsen et al. 2003). This suggestive association between PI3K cascade and rsFC between the left FPN and Heschl's gyrus might possibly be interpreted in the light of the dopamine hypothesis in schizophrenia.

In both tissue expression analyses on general and specific tissue types, brain tissues reached the lowest p-values. Amygdala tissue reached significance in the analysis on specific tissue types. For general tissue types, this is in line with my assumption. However, in specific, brain cortical tissue, which would have been expected to show the strongest associations, only showed relatively weak association. Furthermore, contrary to

expectations, Amygdala tissue reached significance, although this brain region does not seem to be involved in the endophenotype under investigation. Additional research is needed to test if genetic associations with the endophenotype of rsFC between the left FPN and Heschl's gyrus and highly expressed genes in specific tissues are linked.

This study has several strengths. To my knowledge, this is the first study to specifically investigate genetic associations with a schizophrenia-associated endophenotype of rsFC between the left FPN and Heschl's gyrus using a genome-wide approach. This endophenotype represents an ICA-based measure that has been shown to be heritable in a previous study (Chahine et al. 2017). Using meaningful dimension reduction by statistical learning approaches, such as ICA or learning sparseness (Hastie et al. 2017), may be a promising way to define and quantify relevant brain variability beyond expert-defined anatomical criteria (Fan et al. 2018). This is especially true for disorders with a strong genetic component, such as schizophrenia, and if the pathological process is relatively homogeneous (Fan et al. 2018). Moreover, I examined a homogeneous sample that consisted exclusively of young, healthy subjects with a high level of education. This selective study design aims at ruling out confounding factors as far as possible and allows the investigation of the genetics of healthy brain function.

This study is also subject to several limitations. First, this study might be criticized for its relatively low sample size, resulting in poor statistical power. However, it can be argued that statistical power in this study is boosted by its very high sample homogeneity. Furthermore, it has recently been shown, in the example of Williams Syndrome, that reducing dimensional representation of neuroimaging measures can lead to an increase of statistical power for association testing (Fan et al. 2017; Fan et al. 2018). Accordingly, statistical power in the current study may be assumed to be relatively high due to the use of dimension reduction in the endophenotype. A second limiting factor may be that left-handed subjects have not been excluded from the final sample. Analysis was repeated under exclusion of left-handed subjects (n=11). There was no relevant difference in top-results in the re-analysis. However, p-values were lower, which might be attributed to the loss of sample size. Against this background and for retaining highest possible sample size, I decided to use the full sample. Finally, the QQ plot suggested that there are residual confounding factors which have not been adjusted for. Those could be substantiated by psychological factors, based on the experimental procedure, or vascular factors.

In sum, this study is a significant contribution to the literature on the genetic underpinnings of endophenotypic markers of schizophrenia. Validity of these findings will have to be tested by replication, using larger and more heterogeneous samples. If replicable, these results may

lay groundwork for the investigation of pathways to neurofunction in neuropsychiatric disorders.

4.3 Conclusion and further remarks

To contribute to the identification of biosignatures for schizophrenia and bipolar disorder on a neuroimaging and molecular genetic level, two studies were conducted for this thesis.

Study 1 suggests that reward processing in relatives of patients with schizophrenia and bipolar disorder is disrupted, possibly relying on dopamine malfunction. As this malfunction is assumed to be associated with the genetic vulnerability to develop schizophrenia or bipolar disorder, disruption in mesocorticolimbic reward processing may constitute a potential endophenotype for schizophrenia and bipolar disorder. Although this data suggests a genetic basis, an influence by environmental factors cannot be ruled out. To specifically address the genetic determinants of disturbed reward processing, future studies in monozygotic and dizygotic twin pairs discordant for schizophrenia and bipolar disorder, respectively, will be necessary.

In Study 2, using a genome-wide association approach, markers associated with functional connectivity between the left FPN and Heschl's gyrus could be identified. Among the top results, an intronic locus (rs4958456) within CAMK2a gene showed suggestive evidence for association. This gene is high-specifically expressed in brain cortical tissue. Its gene product CaM-kinase II plays an important role in neurotransmitter release, long-term potentiation and synaptic plasticity in glutamatergic synapses. This finding is in line with earlier studies supporting the role of calcium signaling in schizophrenia. However, further research in multiple cohorts will be needed to replicate these preliminary findings.

Taken together, in line with the framework of RDoC, these findings contribute to our understanding of the underpinnings of schizophrenia and bipolar disorder on a genomic and brain functional level. Growing knowledge about mechanisms underlying mental disease is expected to provide a basis for improved early diagnosis, precision of psychiatric diagnosis, and holds tremendous opportunities for personalized psychiatric treatment.

5. SUMMARY/ZUSAMMENFASSUNG

5.1 Summary

According to the Research Domain Criteria (RDoC) framework, mental diseases are conceptualized as disorders of brain circuits, which are measurable, and are based on genetic mechanisms. In the search for genetic underpinnings of psychopathology, the use of endophenotypes constitutes a promising approach.

This thesis aimed to contribute to the identification of biosignatures for schizophrenia and bipolar disorder on a neuroimaging and molecular genetic level by using functional neuroimaging endophenotypes and an imaging genetics approach. It comprises two parts: In study 1, neurofunctional correlates of reward processing in unaffected first-degree relatives of patients with schizophrenia and bipolar disorder was examined using the 'desire-reason dilemma' paradigm. Study 2 investigated the genetic underpinnings of resting-state functional connectivity between the left fronto-parietal network and Heschl's gyrus, which constitutes a potential endophenotype for schizophrenia, using a genome-wide association approach in a homogeneous sample of healthy subjects.

Study 1 shows disruptions in mesocorticolimbic reward processing in first-degree relatives of patients with schizophrenia and bipolar disorder. Specifically, the study gives evidence for an enhanced bottom-up activation of the ventral striatum in first-degree relatives of patients with schizophrenia, which is in line with the hypothesis of a general hyperdopaminergic state in schizophrenia. In contrast, in first-degree relatives of patients with bipolar disorder, there was no difference in ventral striatal activation compared with controls, indicating intact bottom-up activation of the ventral striatum. More importantly, study results show a disturbed top-down control of mesolimbic reward signals by prefrontal brain regions in first-degree relatives of patients with schizophrenia and bipolar disorder. These results suggest that disrupted reward processing, possibly relying on dopamine malfunction, may be linked with the genetic vulnerability to develop schizophrenia or bipolar disorder, and thus constitutes a potential endophenotype for schizophrenia and bipolar disorder. Although these data suggests a genetic basis for mesocorticolimbic reward processing, an influence by environmental factors cannot be ruled out. Future studies in monozygotic and dizygotic twin pairs discordant for schizophrenia will be necessary to further investigate the genetic determinants of disturbed reward processing.

Study 2 was able to identify one genome-wide significant variant, as well as four intronic loci with suggestive evidence for association. Among the top hits was an intronic locus (rs4958456) within calcium/calmodulin dependent protein kinase II alpha (CAMK2a) gene,

which is high-specifically expressed in brain cortical tissue. Its gene product CaM-kinase II may function in neurotransmitter release, long-term potentiation and synaptic plasticity in glutamatergic synapses. This finding is in line with earlier studies supporting the role of calcium signaling in schizophrenia. However, replication will be necessary to evaluate these preliminary findings.

Taken together, in line with the framework of RDoC, these findings contribute to the understanding of schizophrenia and bipolar disorder on a genomic and brain functional level.

5.2 Zusammenfassung

Gemäß des Research Domain Criteria (RDoC) Rahmenwerks werden psychische Erkrankungen als Störungen von Gehirnnetzwerken konzeptualisiert, die messbar sind und denen genetische Mechanismen zugrunde liegen. Bei der Suche nach genetischen Grundlagen der Psychopathologie stellt die Untersuchung von ‘Endophänotypen’ einen vielversprechenden Ansatz dar.

Das Ziel der vorliegenden Arbeit war es, durch den Einsatz funktioneller Neuroimaging-Endophänotypen und eines Imaging Genetics Ansatzes einen Beitrag zur Identifizierung von Biosignaturen für Schizophrenie und bipolare Störung auf Bildgebungs- und molekulargenetischer Ebene zu leisten. Sie besteht aus zwei Teilen: In Studie 1 wurden neurofunktionelle Korrelate der Belohnungsverarbeitung bei nicht erkrankten Angehörigen ersten Grades von Patienten mit Schizophrenie und bipolarer Störung mit dem ‚Desire-Reason-Dilemma‘-Paradigma untersucht. Studie 2 untersuchte die genetischen Grundlagen der funktionellen Konnektivität im Ruhezustand zwischen dem linken frontoparietalen Netzwerk und der Heschl‘schen Querwindung, die einen potentiellen Endophänotyp für Schizophrenie darstellt, unter Verwendung eines genomweiten Assoziationsansatzes in einer homogenen Stichprobe gesunder Probanden.

Studie 1 zeigt Störungen der mesokortikolimbischen Belohnungsverarbeitung bei Angehörigen ersten Grades von Patienten mit Schizophrenie und bipolarer Störung. Konkret konnte die Studie eine verstärkte Bottom-up-Aktivierung des ventralen Striatums bei Angehörigen ersten Grades von Patienten mit Schizophrenie identifizieren, was mit der Hypothese eines generellen hyperdopaminergen Zustands bei Schizophrenie übereinstimmt. Im Gegensatz dazu war bei Angehörigen ersten Grades von Patienten mit bipolarer Störung kein Unterschied in der Aktivierung des ventralen Striatums im Vergleich zu den Kontrollen zu finden, was auf eine intakte Bottom-up-Aktivierung des ventralen Striatums hindeutet. Noch bedeutender ist, dass die Studienergebnisse darauf hinweisen, dass die Top-Down-Kontrolle mesolimbischer Belohnungssignale durch präfrontale Hirnregionen bei Angehörigen ersten Grades von Patienten mit Schizophrenie und bipolarer Störung gestört ist. Diese Ergebnisse legen nahe, dass eine gestörte Belohnungsverarbeitung, die möglicherweise auf einer Dopamin-Fehlfunktion beruht, mit der genetischen Vorbelastung für eine Entwicklung von Schizophrenie oder bipolarer Störung in Verbindung gebracht werden kann und somit einen potentiellen Endophänotyp für Schizophrenie und bipolare Störung darstellt. Obwohl diese Daten eine genetische Grundlage für die mesokortikolimbische Belohnungsverarbeitung nahelegen, kann eine Beeinflussung durch Umweltfaktoren nicht ausgeschlossen werden. Zukünftige Studien an eineiigen und zweieiigen Zwillingspaaren,

die für Schizophrenie diskordant sind, werden notwendig sein, um die genetischen Determinanten der gestörten Belohnungsverarbeitung weiter zu untersuchen.

Studie 2 konnte eine genomweit signifikante Variante sowie vier Intron-Loci mit suggestiver Assoziation identifizieren. Unter den Top-Hits war ein Intron-Locus (rs4958456) innerhalb des Calcium/Calmodulin Dependent Protein Kinase II Alpha (CAMK2a) Gens, der hochspezifisch im kortikalen Hirngewebe exprimiert wird. Sein Genprodukt CaM-Kinase II wird mit der Freisetzung von Neurotransmittern, der Langzeitpotenzierung und der synaptischen Plastizität in glutamatergen Synapsen in Verbindung gebracht. Dieses Ergebnis steht in Übereinstimmung mit früheren Studien, die die Rolle des Calciumsignals bei Schizophrenie belegen. Um diese vorläufigen Ergebnisse zu bewerten, ist jedoch eine Replikation erforderlich.

Zusammengenommen tragen diese Ergebnisse, in Übereinstimmung mit dem Rahmenwerk der RDoC zum Verständnis von Schizophrenie und bipolarer Störung auf Gen- und Gehirnfunktionsebene bei.

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7. EIGENANTEIL AN DATENERHEBUNG UND –AUSWERTUNG

Die Erhebung der Daten für Studie 1 dieser Arbeit wurde an das DFG-geförderte Projekt PsyCourse, Projekt 2 (PC2): ‘Translational neuroimaging studies on genotype-phenotype relationships in the longitudinal course of psychosis’ angegliedert. Dieses umfasste die Rekrutierung von Patient*innen mit schizophrenen und affektiven Störungen. Um die Rekrutierung um die Personengruppe der Angehörigen zu erweitern, habe ich ein Amendment zum bestehenden Ethikantrag (Zeichen S-122/2016) gestellt. Die Rekrutierung oblag mir. Neben den in dieser Arbeit ausgewerteten Daten umfasste die Datenerhebung im Rahmen dieser Doktorarbeit drei weitere fMRT-Paradigmen, eine Resting-State Messung der Gehirnaktivität, sowie Blut- und Speichelproben für DNA-Analysen und die Erhebung psychologischer Daten mittels Fragebögen. Insgesamt habe ich Daten von 16 Angehörigen von Patient*innen mit einer bipolaren Störung und 16 Angehörigen von Patient*innen mit Schizophrenie erhoben. Im Falle einzelner Proband*innen vertrat mich meine Projektkollegin Lisa Rauer bei der Datenerhebung. Zusätzlich zu den von mir in Heidelberg erhobenen Daten wurden für Studie 1 Daten zweier früherer Doktorarbeiten (Frau Dr. Anna Fanelli und Frau Dr. Kathrin Jakob) verwendet, die in Göttingen erhoben wurden. Zusätzlich habe ich für das Matching von Kontrollpersonen für diese Studie Daten aus langfristig angelegten Projekten meines Betreuers Herr Prof. Dr. Oliver Gruber (s. unter 2.1.1), insbesondere aus DFG-geförderten Projekten sowie aus parallel laufenden, nicht Drittmittel-geförderten Projekten, verwendet. Die Qualitätskontrolle der Bildgebungsdaten habe ich durchgeführt, wie auch die Planung und Durchführung der Analysen. Die first-level Analyse der Bildgebungsdaten wurde von Herrn Dr. Bernd Krämer bereitgestellt, der mich auch bei den second-level Analysen supervidierte.

Für Studie 2 wurden Daten aus Herrn Prof. Dr. Grubers nicht Drittmittel-geförderten Projekts ‘Genomic Imaging Göttingen (GIG)’ benutzt. Der hier verwendete Konnektivitäts-Phänotyp wurde von Herrn Dr. George Chahine extrahiert. Die Imputation der genetischen Daten, wie auch Teile der genetischen Qualitätskontrolle wurden in der Arbeitsgruppe von Herrn Prof. Dr. Stephan Ripke von Herrn Swapnil Awasthi durchgeführt. Die Finalisierung der Qualitätskontrolle (siehe 2.2.5) und die genomweiten Assoziationsanalysen oblagen mir.

Die Interpretation und Diskussion aller Ergebnisse, sowie deren wissenschaftliche Einordnung habe ich vorgenommen.

Publikation

Martin, J., Richter, A., Brodmann, K., Chahine, G., Papiol, S., Gruber, O. (2017). **Genome-wide association study of resting state endophenotypic markers in schizophrenia**. Poster presented at: WPA XVII World Congress of Psychiatry, Berlin.

APPENDIX: SUPPLEMENTARY DATA

Supplementary table 1. Bonus remuneration in the DRD paradigm.

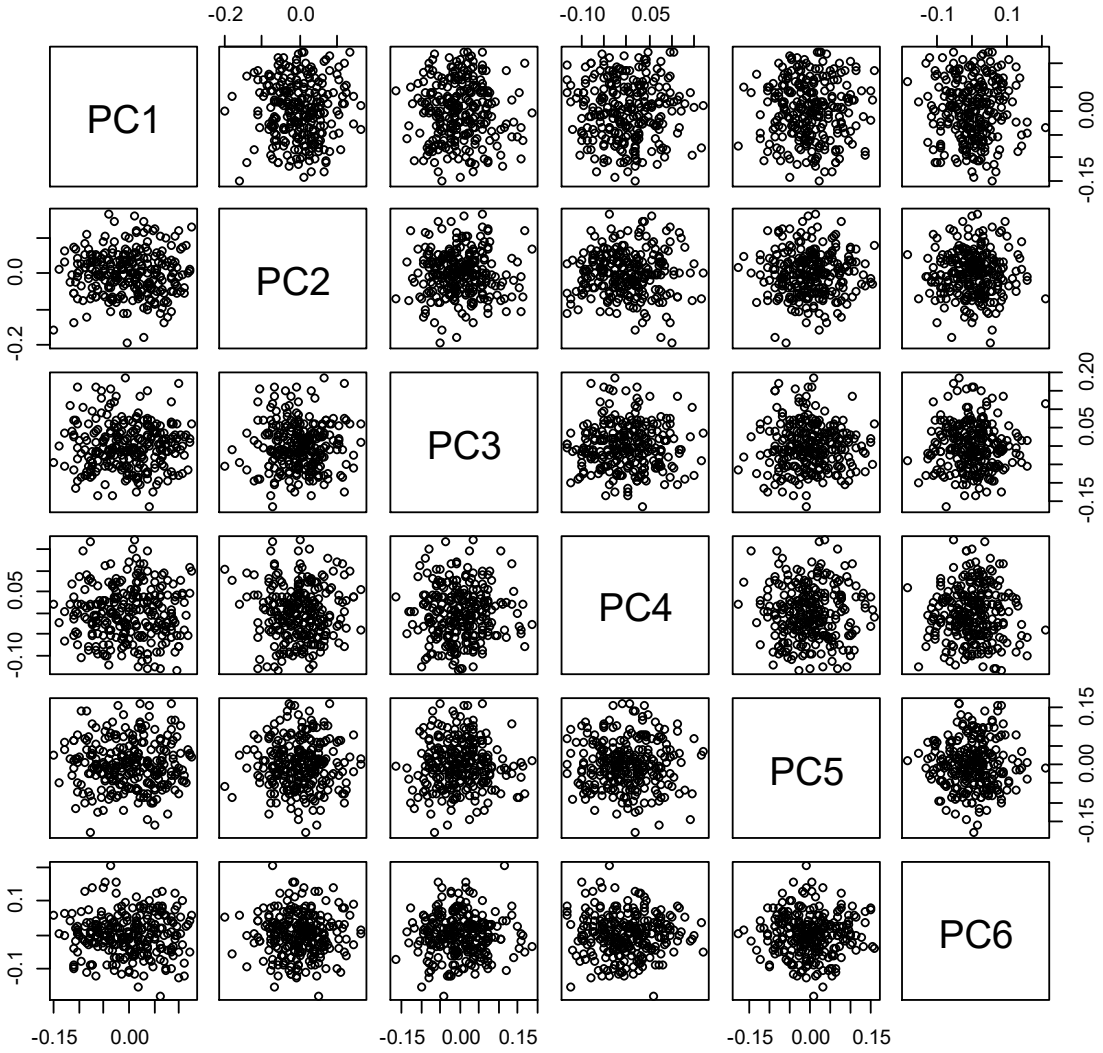
DRD overall score	Bonus remuneration (in Euro)
≥ 2300	20
2200 - 2299	15
2100 - 2199	12
2000 - 2099	9
1500 - 1999	6
0 - 1499	3

Depending on their task performance, i.e., their achieved DRD overall score, subjects gained bonus remuneration. This amount was added to their general allowance of 20 Euro. DRD total score was aggregated across the two runs. Abbreviation: DRD = desire-reason dilemma.

Supplementary table 2. Family relationship to the index patient.

	offspring	parent	sibling
RelSZ	7	10	12
RelBD	21	0	8

Abbreviations: RelSZ = unaffected first-degree relatives of patients with schizophrenia, RelBD = unaffected first-degree relatives of patients with bipolar disorder.



Supplementary figure 1. Scatterplot matrix of principal components (PCs) 1 to 5 of imputed best guess genotypes.

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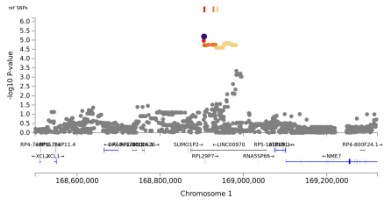

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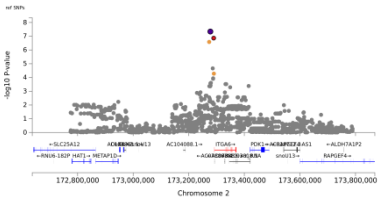

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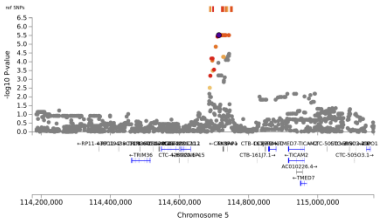

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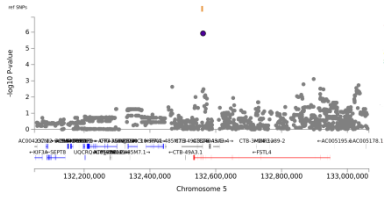

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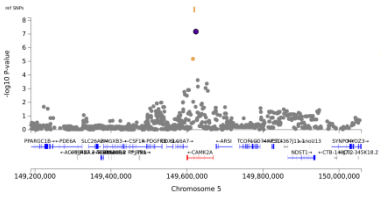

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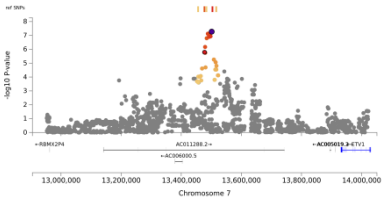

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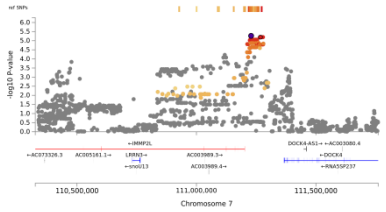

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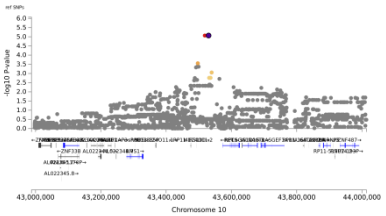

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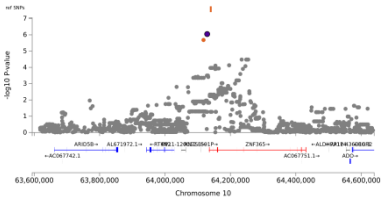

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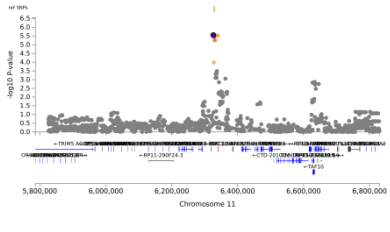

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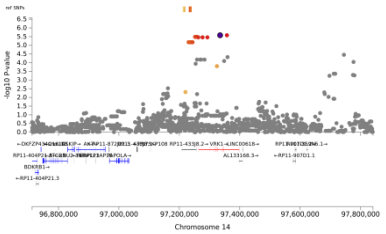

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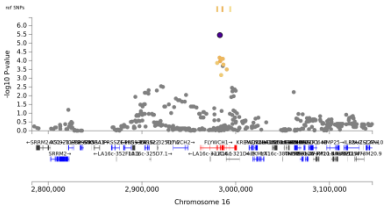

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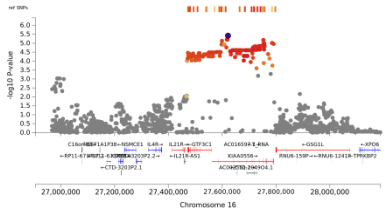

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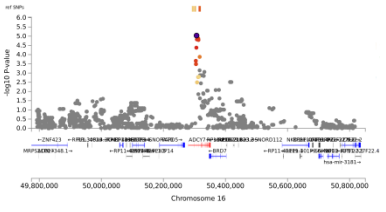

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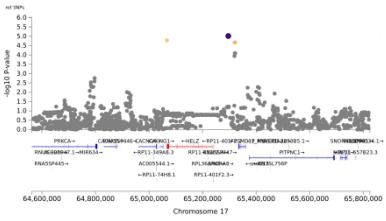
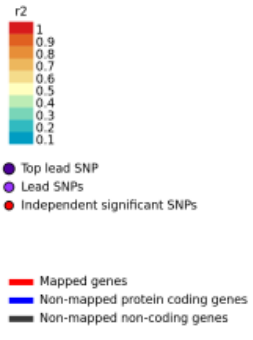
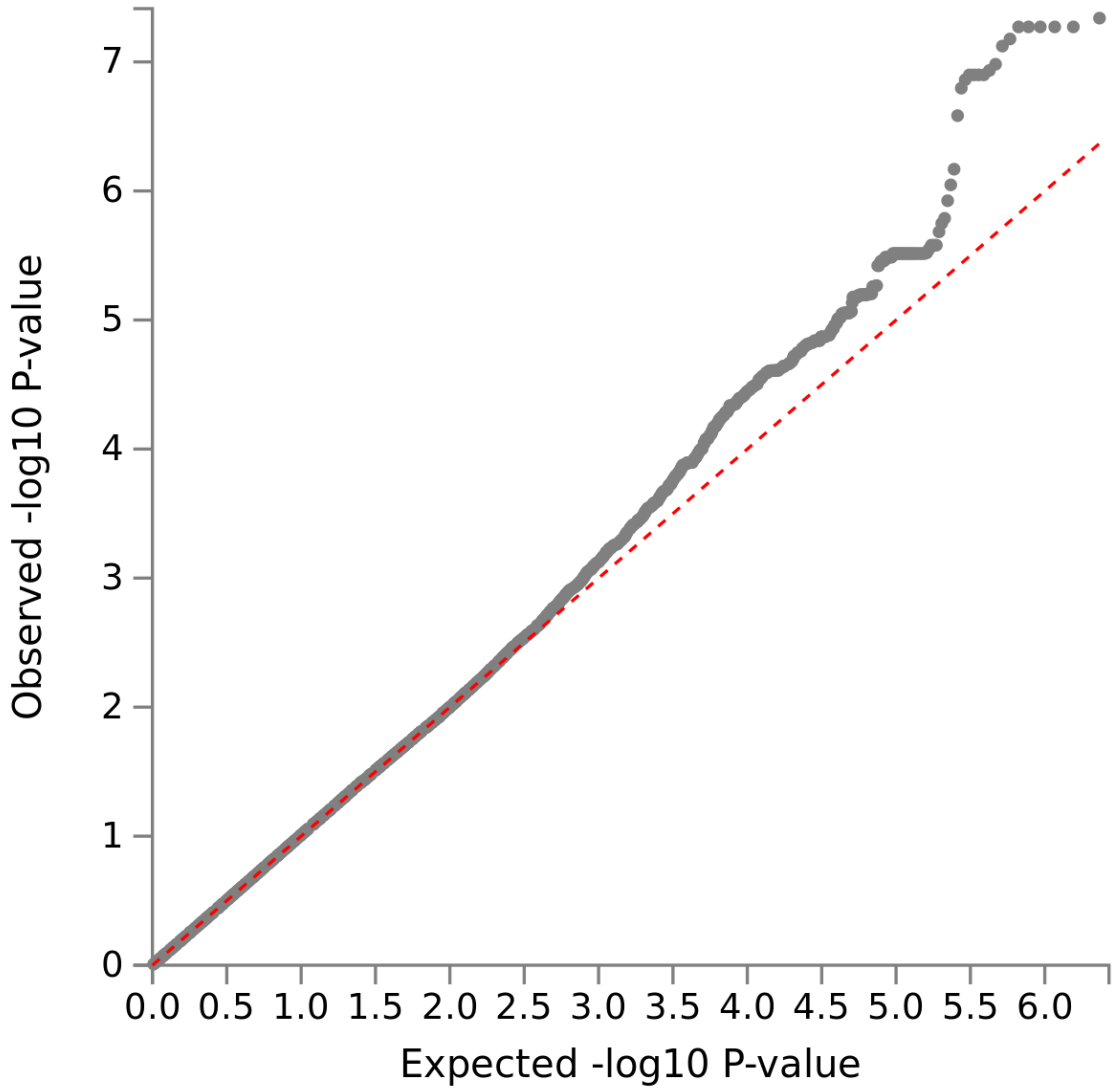




Supplementary figure 2. Region plots of genomic risk loci. Each significant single nucleotide polymorphism (SNP; $p<1x10^{-5}$) is color-coded based on the highest r^2 to one of the independently significant SNPs if $r^2>0.6$. SNPs that are not in linkage disequilibrium (LD) with any of independent significant SNPs ($r^2<0.6$) are colored in grey. The top lead SNPs in genomic risk loci, lead SNPs and individually significant SNPs are circled in black and colored in dark-purple, purple and red, respectively.



Supplementary figure 3. Quantile-quantile (QQ) plot of genome-wide association study (GWAS) summary statistics (filtered for SNPs with $p \geq 1 \times 10^{-5}$). Expected are plotted against observed –log10 *p*-values.

Supplementary table 3. SNP Results from GWAS.

chr	rsID	pos	effect allele	non-effect allele	MAF	P	beta	r2	IndSigSNP	Genomic Locus	nearestGene	dist	func
1	rs1853278	168905326	C	T	0.1958	6.41×10^{-6}	0.6688	1	rs1853278	1	LINC00970	0	ncRNA_intronic
1	rs6427167	168906061	T	A	0.1938	6.41×10^{-6}	0.6688	0.987054	rs1853278	1	LINC00970	0	ncRNA_intronic
2	rs10184828	173273509	C	G	0.337	2.61×10^{-7}	0.6974	0.771134	rs12621273	2	ITGA6	18572	intergenic
2	rs12621273	173277783	T	C	0.2962	4.58×10^{-8}	0.7477	1	rs12621273	2	ITGA6	14298	intergenic
2	rs10930555	173289736	G	A	0.2217	1.38×10^{-7}	0.7706	1	rs10930555	2	ITGA6	2345	intergenic
5	rs10078844	114709970	C	G	0.0835	3.65×10^{-6}	1.177	1	rs10478230	3	CTNNAP1	15369	intergenic
5	rs10478229	114713726	T	C	0.0835	3.06×10^{-6}	1.184	1	rs10478230	3	CTNNAP1	11613	intergenic
5	rs10478230	114713898	T	C	0.0835	3.06×10^{-6}	1.184	1	rs10478230	3	CTNNAP1	11441	intergenic
5	rs10052335	114716602	A	G	0.0825	3.06×10^{-6}	1.184	0.987633	rs10478230	3	CTNNAP1	8737	intergenic
5	rs2004680	114719236	C	T	0.0825	3.06×10^{-6}	1.184	0.987633	rs10478230	3	CTNNAP1	6103	intergenic
5	rs12332367	114721592	T	G	0.0825	3.06×10^{-6}	1.184	0.987633	rs10478230	3	CTNNAP1	3747	intergenic
5	rs1109015	114722966	T	A	0.0835	3.06×10^{-6}	1.184	0.950608	rs10478230	3	CTNNAP1	2373	intergenic
5	rs1109016	114723044	C	G	0.0835	3.06×10^{-6}	1.184	0.950608	rs10478230	3	CTNNAP1	2295	intergenic
5	rs10052230	114723951	G	A	0.08151	3.06×10^{-6}	1.184	0.925934	rs10478230	3	CTNNAP1	1388	intergenic
5	rs10077024	114724609	C	T	0.08151	3.06×10^{-6}	1.184	0.925934	rs10478230	3	CTNNAP1	730	downstream
5	rs10054091	114724610	G	A	0.0825	3.06×10^{-6}	1.184	0.914074	rs10478230	3	CTNNAP1	729	downstream
5	rs79832319	114728285	A	C	0.08052	3.06×10^{-6}	1.184	0.913055	rs10478230	3	CTNNAP1	217	upstream
5	rs9986246	114729857	A	G	0.08052	3.06×10^{-6}	1.184	0.913055	rs10478230	3	CTNNAP1	1789	intergenic
5	rs9986244	114729864	T	C	0.08052	3.06×10^{-6}	1.184	0.913055	rs10478230	3	CTNNAP1	1796	intergenic
5	rs10072589	114731144	A	G	0.08052	3.06×10^{-6}	1.184	0.913055	rs10478230	3	CTNNAP1	3076	intergenic
5	rs2605185	114731199	T	C	0.08052	3.06×10^{-6}	1.184	0.913055	rs10478230	3	CTNNAP1	3131	intergenic
5	rs7713623	114733369	A	C	0.08052	3.06×10^{-6}	1.184	0.913055	rs10478230	3	AK3P4	4707	intergenic
5	rs7713947	114733621	T	A	0.08052	3.06×10^{-6}	1.184	0.913055	rs10478230	3	AK3P4	4455	intergenic

5	rs10036686	114742083	A	G	0.08052	3.06×10^{-6}	1.184	0.913055	rs10478230	3	AK3P4	3423	intergenic
5	rs77635191	114742893	G	A	0.08052	3.06×10^{-6}	1.184	0.913055	rs10478230	3	AK3P4	4233	intergenic
5	rs17137761	114743006	A	G	0.08052	3.06×10^{-6}	1.184	0.913055	rs10478230	3	AK3P4	4346	intergenic
5	rs61741674	132561468	A	C	0.0507	1.19×10^{-6}	1.076	1	rs61741674	4	FSTL4	0	exonic
5	rs10066581	149615681	A	G	0.1392	6.59×10^{-6}	0.8292	0.743946	rs4958456	5	CAMK2A	0	intronic
5	rs4958456	149623365	T	C	0.1382	6.64×10^{-8}	1.053	1	rs4958456	5	CAMK2A	0	intronic
7	rs2723411	13477607	C	T	0.2386	1.63×10^{-6}	0.678	1	rs2723411	6	AC011288.2	0	ncRNA_intronic
7	rs2723412	13479424	G	T	0.2256	6.78×10^{-7}	0.7143	0.933594	rs2723411	6	AC011288.2	0	ncRNA_intronic
7	rs1368209	13479911	C	T	0.2256	1.78×10^{-6}	0.6978	0.933594	rs2723411	6	AC011288.2	0	ncRNA_intronic
7	rs1560612	13484706	T	A	0.2097	1.60×10^{-7}	0.8135	0.912363	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs2568634	13488521	T	A	0.2078	7.54×10^{-8}	0.8355	0.953543	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs878642	13492280	C	T	0.2097	1.26×10^{-7}	0.8233	0.964007	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs878643	13492340	A	C	0.2087	1.26×10^{-7}	0.8233	0.95876	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs1109598	13493211	A	G	0.2087	1.26×10^{-7}	0.8233	0.948533	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs1109599	13493548	C	T	0.2087	1.26×10^{-7}	0.8233	0.95876	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs2466502	13495062	A	G	0.2058	1.04×10^{-7}	0.834	0.942872	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs2723462	13497557	C	A	0.2107	1.17×10^{-7}	0.8244	0.969285	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs2568572	13500476	C	A	0.2058	5.35×10^{-8}	0.854	0.994747	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs2568573	13500596	G	A	0.2058	5.35×10^{-8}	0.854	0.994747	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs2568574	13500618	G	A	0.2058	5.35×10^{-8}	0.854	0.994747	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs1432490	13501318	C	T	0.2048	5.35×10^{-8}	0.854	1	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs1432491	13501337	G	A	0.2048	5.35×10^{-8}	0.854	1	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs12671880	13508497	C	T	0.2058	5.52×10^{-6}	0.7812	0.782231	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs12673834	13508714	G	A	0.2038	5.52×10^{-6}	0.7812	0.771616	rs1432490	6	AC011288.2	0	ncRNA_intronic
7	rs56015937	13514435	T	C	0.2038	8.61×10^{-6}	0.7615	0.781169	rs1432490	6	AC011288.2	0	ncRNA_intronic

7	rs2613593	111223421	G	C	0.161	9.52×10^{-6}	0.7287	0.973482	rs2906623	7	IMMP2L	20847	intergenic
7	rs10280411	111223779	G	T	0.162	9.52×10^{-6}	0.7287	0.980058	rs2906623	7	IMMP2L	21205	intergenic
7	rs2613592	111224355	G	A	0.165	8.97×10^{-6}	0.73	1	rs2906623	7	IMMP2L	21781	intergenic
7	rs2528676	111225408	T	C	0.164	8.93×10^{-6}	0.7351	0.993317	rs2906623	7	IMMP2L	22834	intergenic
7	rs2906623	111228739	G	A	0.165	5.41×10^{-6}	0.7494	1	rs2906623	7	IMMP2L	26165	intergenic
7	rs2969506	111228993	T	C	0.164	8.93×10^{-6}	0.7351	0.993317	rs2906623	7	IMMP2L	26419	intergenic
7	rs2613602	111236503	C	T	0.162	8.83×10^{-6}	0.7363	0.980058	rs2906623	7	IMMP2L	33929	intergenic
7	rs2057973	111243905	A	T	0.162	8.83×10^{-6}	0.7363	0.980058	rs2906623	7	IMMP2L	41331	intergenic
7	rs2969504	111246285	C	T	0.162	8.83×10^{-6}	0.7363	0.980058	rs2906623	7	IMMP2L	43711	intergenic
7	rs2528663	111246791	G	C	0.162	8.83×10^{-6}	0.7363	0.980058	rs2906623	7	IMMP2L	44217	intergenic
7	rs2613611	111246951	C	A	0.163	8.83×10^{-6}	0.7363	0.97337	rs2906623	7	IMMP2L	44377	intergenic
7	rs2613612	111247924	C	A	0.164	8.83×10^{-6}	0.7363	0.979988	rs2906623	7	IMMP2L	45350	intergenic
7	rs2906614	111252799	G	C	0.163	8.80×10^{-6}	0.7407	0.97337	rs2906623	7	IMMP2L	50225	intergenic
7	rs2528667	111253564	A	G	0.162	8.80×10^{-6}	0.7407	0.980058	rs2906623	7	IMMP2L	50990	intergenic
7	rs2528669	111254240	G	A	0.162	8.80×10^{-6}	0.7407	0.980058	rs2906623	7	IMMP2L	51666	intergenic
7	rs2613615	111254357	A	C	0.162	8.80×10^{-6}	0.7407	0.980058	rs2906623	7	IMMP2L	51783	intergenic
7	rs74726413	111265771	T	C	0.09443	6.37×10^{-6}	1.006	0.990188	rs73428366	7	IMMP2L	63197	intergenic
7	rs73428366	111267766	T	C	0.09543	6.37×10^{-6}	1.006	1	rs73428366	7	IMMP2L	65192	intergenic
7	rs73428367	111267895	A	G	0.09543	6.37×10^{-6}	1.006	1	rs73428366	7	IMMP2L	65321	intergenic
7	rs117921364	111269430	A	T	0.09443	6.37×10^{-6}	1.006	0.990188	rs73428366	7	IMMP2L	66856	intergenic
7	rs28742043	111272850	T	C	0.09543	6.37×10^{-6}	1.006	1	rs73428366	7	IMMP2L	70276	intergenic
7	rs61207672	111273054	A	G	0.09543	6.37×10^{-6}	1.006	1	rs73428366	7	IMMP2L	70480	intergenic
7	rs28674043	111275050	T	C	0.09543	6.37×10^{-6}	1.006	1	rs73428366	7	IMMP2L	72476	intergenic
7	rs73428388	111276467	G	C	0.09543	6.37×10^{-6}	1.006	1	rs73428366	7	IMMP2L	73893	intergenic
7	rs74881019	111278386	C	A	0.09443	6.37×10^{-6}	1.006	0.990188	rs73428366	7	IMMP2L	75812	intergenic

10	rs2419089	43518525	T	C	0.4384	8.58×10^{-6}	0.5955	0.995994	rs2565190	8	MIR5100	25395	intergenic
10	rs2565190	43530071	A	C	0.4374	8.58×10^{-6}	0.5955	1	rs2565190	8	MIR5100	36941	intergenic
10	rs2087625	64117756	T	C	0.1809	2.07×10^{-6}	0.739	0.889551	rs7096931	9	RN7SL591P	7707	intergenic
10	rs7096931	64128954	A	C	0.172	8.97×10^{-7}	0.765	1	rs7096931	9	ZNF365	4996	intergenic
11	rs4758406	6326376	T	C	0.1789	2.83×10^{-6}	0.7749	1	rs4758406	10	RP11-304C12.4	6539	intergenic
11	rs10500666	6327534	T	C	0.1769	3.26×10^{-6}	0.7715	0.986341	rs4758406	10	RP11-304C12.4	7697	intergenic
11	rs10500669	6328472	T	G	0.1769	3.26×10^{-6}	0.7715	0.986341	rs4758406	10	RP11-304C12.4	8635	intergenic
11	rs11040855	6330188	G	C	0.1928	5.47×10^{-6}	0.7408	0.824242	rs4758406	10	PRKCDBP	9987	intergenic
11	rs16911751	6331026	G	T	0.1928	5.47×10^{-6}	0.7408	0.824242	rs4758406	10	PRKCDBP	9149	intergenic
11	rs13377556	6339486	A	G	0.1889	3.01×10^{-6}	0.7675	0.734034	rs4758406	10	PRKCDBP	689	downstream
14	rs67722203	97230827	G	A	0.09841	6.63×10^{-6}	0.9055	0.915529	rs67957817	11	RP11-433J8.2	0	ncRNA_intronic
14	rs10873474	97236360	A	G	0.09841	6.63×10^{-6}	0.9055	0.915529	rs67957817	11	RP11-433J8.2	0	ncRNA_intronic
14	rs61078535	97238647	A	G	0.09841	6.63×10^{-6}	0.9055	0.915529	rs67957817	11	RP11-433J8.2	0	ncRNA_intronic
14	rs17310204	97242600	A	G	0.1004	6.63×10^{-6}	0.9055	0.936855	rs67957817	11	RP11-433J8.2	0	ncRNA_intronic
14	rs10149171	97243961	A	G	0.1004	6.63×10^{-6}	0.9055	0.936855	rs67957817	11	RP11-433J8.2	0	ncRNA_intronic
14	rs10135222	97252301	T	G	0.0994	3.26×10^{-6}	0.9404	0.947242	rs67957817	11	RP11-433J8.2	0	ncRNA_intronic
14	rs10144908	97255242	A	G	0.0994	3.26×10^{-6}	0.9404	0.947242	rs67957817	11	RP11-433J8.2	0	ncRNA_intronic
14	rs10145396	97255679	T	G	0.0994	3.26×10^{-6}	0.9404	0.947242	rs67957817	11	RP11-433J8.2	0	ncRNA_intronic
14	rs10132065	97258798	T	C	0.1004	3.26×10^{-6}	0.9404	0.936855	rs67957817	11	RP11-433J8.2	1847	intergenic
14	rs67804110	97262856	C	T	0.1044	3.47×10^{-6}	0.931	0.979068	rs67957817	11	VRK1	784	upstream
14	rs722869	97277005	G	C	0.1034	3.47×10^{-6}	0.931	0.989727	rs67957817	11	VRK1	0	intronic
14	rs3825576	97292973	T	C	0.1034	3.47×10^{-6}	0.931	0.989727	rs67957817	11	VRK1	0	intronic
14	rs67957817	97335116	A	G	0.1024	2.63×10^{-6}	0.9503	1	rs67957817	11	VRK1	0	intronic
14	rs11160371	97336752	C	G	0.1024	2.63×10^{-6}	0.9503	1	rs67957817	11	VRK1	0	intronic
14	rs12590723	97357702	G	A	0.1024	2.63×10^{-6}	0.9503	1	rs67957817	11	VRK1	0	intronic

16	rs2074363	2983138	T	C	0.1143	3.51×10^{-6}	0.921	1	rs2074363	12	FLYWCH1	0	exonic
16	rs1018885	27599139	T	C	0.1571	7.36×10^{-6}	0.7273	0.953396	rs916762	13	KIAA0556	0	intronic
16	rs1989855	27617287	T	C	0.1561	6.25×10^{-6}	0.7221	0.976537	rs916762	13	KIAA0556	0	intronic
16	rs4787978	27618011	G	A	0.1561	6.25×10^{-6}	0.7221	0.992209	rs916762	13	KIAA0556	0	intronic
16	rs8061334	27618752	C	G	0.1551	6.25×10^{-6}	0.7221	0.984328	rs916762	13	KIAA0556	0	intronic
16	rs4787979	27618982	A	G	0.1551	6.25×10^{-6}	0.7221	0.98439	rs916762	13	KIAA0556	0	intronic
16	rs7192272	27620095	A	G	0.1571	6.25×10^{-6}	0.7221	0.984505	rs916762	13	KIAA0556	0	intronic
16	rs916762	27621697	C	G	0.1551	3.79×10^{-6}	0.7417	1	rs916762	13	KIAA0556	0	intronic
16	rs916763	27621716	T	A	0.1581	3.79×10^{-6}	0.7417	0.977602	rs916762	13	KIAA0556	0	intronic
16	rs12923139	27752807	G	A	0.1571	6.65×10^{-6}	0.7142	0.984505	rs916762	13	KIAA0556	0	intronic
16	rs12928569	27753737	A	G	0.1561	6.65×10^{-6}	0.7142	0.976682	rs916762	13	KIAA0556	0	intronic
16	rs12919220	27784928	A	G	0.1551	9.71×10^{-6}	0.7027	0.953952	rs916762	13	KIAA0556	0	intronic
16	rs8053976	27786145	A	G	0.1551	9.81×10^{-6}	0.7046	0.953952	rs916762	13	KIAA0556	0	intronic
16	rs8054700	27786668	T	C	0.1551	9.76×10^{-6}	0.701	0.953952	rs916762	13	KIAA0556	0	intronic
16	rs16948353	50306914	T	G	0.3837	9.25×10^{-6}	-0.5675	1	rs16948353	14	ADCY7	0	intronic
17	rs150389995	65296058	A	C	0.1074	9.65×10^{-6}	0.8669	1	rs150389995	15	RP11-401F2.2	23590	intergenic

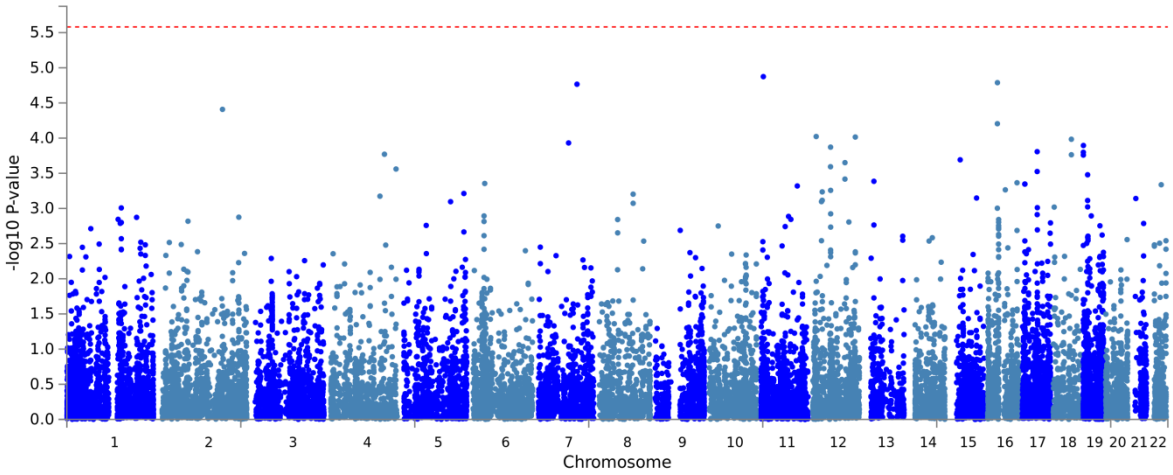
SNPs with $p<1x10^{-5}$ are shown, sorted according to chromosomal position. Abbreviations: SNP = single nucleotide polymorphism; GWAS = genome-wide association study; chr = chromosome, rsID = rsID of the top lead SNP based on dbSNP build 146, pos = position on hg19, effect allele = effect/risk allele, non-effect allele = non-effect/non-risk allele, MAF = minor allele frequency, P = GWAS *p*-value, beta = GWAS *beta*, r2 = the maximum r^2 of the SNP with one of the independent significant SNPs, IndSigSNP = rsID of the independent significant SNP which has the maximum r^2 with the SNP, GenomicLocus = index of the genomic risk loci matching with Supplementary table 4, nearestGene = the nearest Gene of the SNP based on ANNOVAR annotations, dist = distance to the nearest gene, func = functional consequence of the SNP on the gene obtained from ANNOVAR.

Supplementary table 4. Details on genomic risk loci, their lead SNPs and independent significant SNPs from GWAS.

Genomic Locus	chr	start	end	nSNPs PerLocus	nGWASSNPs PerLocus	LeadSNPs	IndSigSNPs	pos	P	nSNPs PerIndSigSNP	nGWASSNPs PerIndSigSNP
1	1	168903257	168981560	43	39	rs1853278	rs1853278	168905326	6.41×10^{-6}	43	39
2	2	173273509	173290395	4	4	rs12621273	rs12621273	173277783	4.58×10^{-8}	2	2
							rs10930555	173289736	1.38×10^{-7}	2	2
3	5	114685700	114748960	51	35	rs10478230	rs10478230	114713898	3.06×10^{-6}	51	35
4	5	132556082	132561468	2	1	rs61741674	rs61741674	132561468	1.19×10^{-6}	2	1
5	5	149615681	149623365	3	2	rs4958456	rs4958456	149623365	6.64×10^{-8}	3	2
6	7	13452449	13522921	49	43	rs1432490	rs2723411	13477607	1.63×10^{-6}	18	14
							rs1432490	13501318	5.35×10^{-8}	35	32
7	7	110838098	111300659	181	148	rs2906623	rs2906623	111228739	5.41×10^{-6}	157	131
							rs73428366	111267766	6.37×10^{-6}	85	70
8	10	43497079	43539481	6	6	rs2565190	rs2565190	43530071	8.58×10^{-6}	6	6
9	10	64117756	64137328	5	2	rs7096931	rs7096931	64128954	8.97×10^{-7}	5	2
10	11	6326376	6339486	8	7	rs4758406	rs4758406	6326376	2.83×10^{-6}	8	7
11	14	97211346	97357702	22	17	rs67957817	rs67957817	97335116	2.63×10^{-6}	22	17
12	16	2979412	2993288	17	12	rs2074363	rs2074363	2983138	3.51×10^{-6}	17	12
13	16	27466978	27794327	218	187	rs916762	rs916762	27621697	3.79×10^{-6}	218	187
14	16	50291951	50317077	22	12	rs16948353	rs16948353	50306914	9.25×10^{-6}	22	12
15	17	65066811	65321351	4	4	rs150389995	rs150389995	65296058	9.65×10^{-6}	4	4

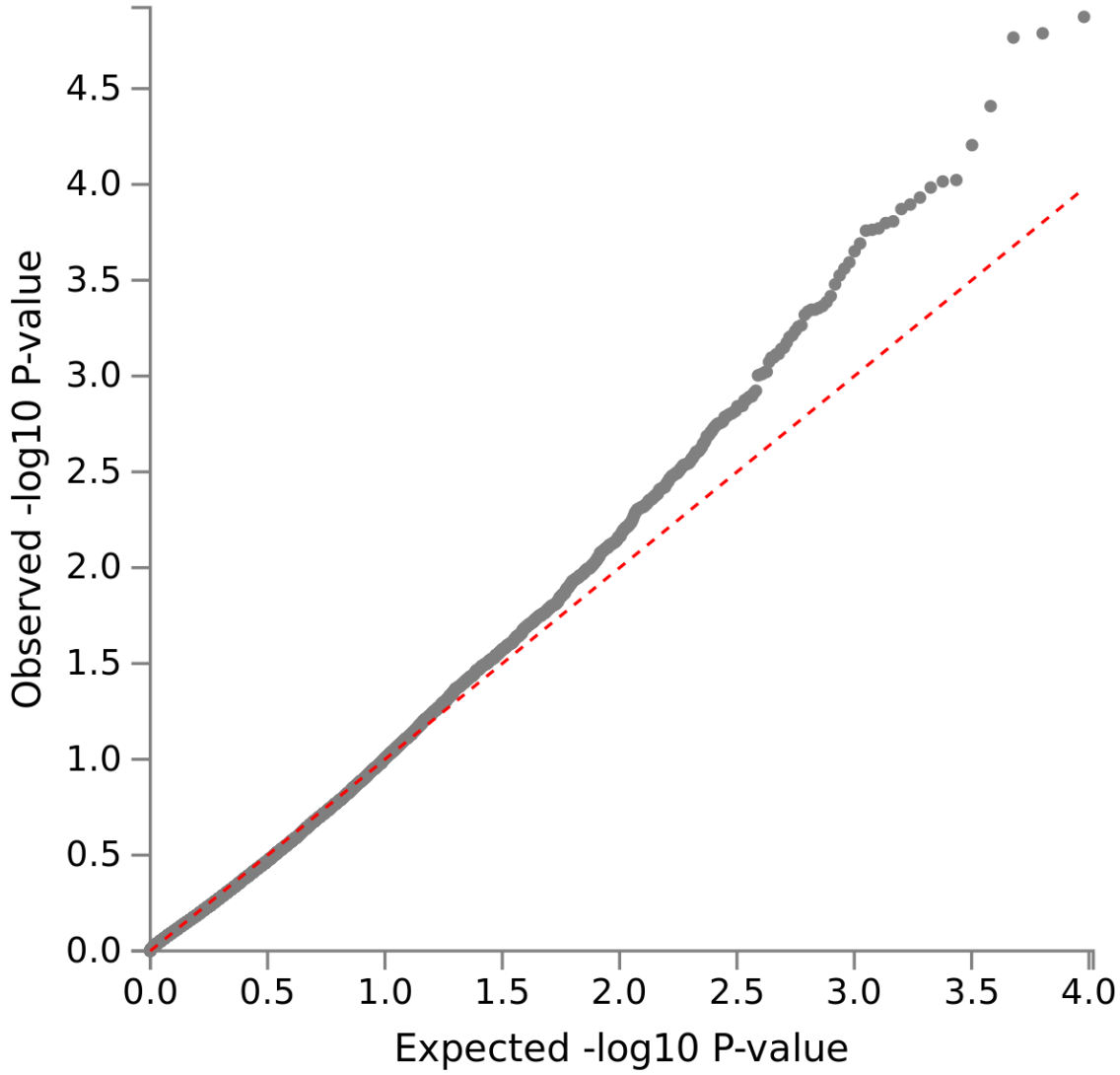
Genomic risk loci with their lead SNPs, IndSigSNPs and their corresponding number of SNPs are shown. Genomic loci are sorted according to chromosomal position. Abbreviations: SNP = single nucleotide polymorphism; GWAS = genome-wide association study; chr = chromosome, start = start position of the locus, end = end position of the locus, nSNPsPerLocus = the number of unique candidate SNPs in the genomic locus, including non-GWAS-tagged SNPs (which are available in the 1000G reference panel). Candidate SNPs are all SNPs that are in linkage disequilibrium (LD) (r^2=0.6) with any of independent significant SNPs at $p<1\text{x}10^{-5}$ or are only available in 1000G. nGWASSNPsPerLocus = the number of unique GWAS-tagged candidate SNPs in the genomic locus which is available in the GWAS summary statistics. This is a subset of 'nSNPsPerLocus', LeadSNPs = rsID of lead SNPs in the genomic locus, IndSigSNPs = rsID of the

independent significant SNPs in the genomic locus, pos = position on hg19, P = GWAS *p*-value, nSNPsPerIndSigSNP = the number of SNPs in LD with the lead SNP given r^2, including non-GWAS-tagged SNPs (which are extracted from 1000G), nGWASSNPsPerIndSigSNP = the number of GWAS-tagged SNPs in LD with the lead SNP given r^2. This is a subset of 'nSNPsPerIndSigSNP'.



Supplementary figure 4. Manhattan plot from MAGMA gene-based analysis. Genes are displayed according to their chromosomal position (x-axis). For each gene, the –log10 *p*-value is shown on the y-axis. The red dashed line indicates genome-wide significance defined at a Bonferroni-corrected level of $p=0.05/19051=2.625\times10^{-6}$.

:



Supplementary figure 5. Quantile-quantile (QQ) plot of MAGMA gene-based analysis. Expected are plotted against observed –log10 *p*-values.

Supplementary table 5. Top 10 gene sets from MAGMA gene-set analysis.

Gene Sets	NGENES	BETA	SE	P
Curated_gene_sets:reactome_pi_3k_cascade:fgfr4	19	0.63386	0.17486	0.00014502
Curated_gene_sets:roeth_tert_targets_dn	9	1.0495	0.29369	0.00017678
GO_bp:go_positive_regulation_of_leukocyte_degranulation	21	0.63043	0.17859	0.00020848
GO_mf:go_bh_domain_binding	10	1.0657	0.30271	0.00021595
GO_cc:go_phagolysosome	5	1.5843	0.45241	0.00023168
Curated_gene_sets:reactome_pi_3k_cascade:fgfr3	17	0.66344	0.19011	0.00024245
Curated_gene_sets:reactome_pi_3k_cascade:fgfr2	22	0.59642	0.17097	0.0002436
GO_bp:go_response_to_l_ascorbic_acid	5	1.2219	0.36202	0.00036974
Curated_gene_sets:reactome_gaba_receptor_activation	52	0.42472	0.12659	0.00039784

Abbreviations: Gene Sets = full names of gene sets, NGENES = number of genes, SE = standard error.

Supplementary table 6. MAGMA tissue expression analysis on 30 general tissue types.

Tissues	BETA	SE	P
Brain	0.018351	0.0068998	0.0039163
Nerve	0.01569	0.010428	0.06622
Thyroid	0.013918	0.010927	0.10139
Prostate	0.015944	0.013932	0.12623
Pituitary	0.0084282	0.0081888	0.15169
Blood	0.0058312	0.0062963	0.1772
Testis	0.0036632	0.0057037	0.26036
Adrenal_Gland	0.0065509	0.010255	0.26147
Muscle	0.0036435	0.0070141	0.30173
Spleen	0.0035656	0.0078789	0.32544
Kidney	0.0035421	0.009322	0.35199
Liver	0.0018872	0.0065889	0.38728
Skin	-0.0011952	0.010107	0.54707
Ovary	-0.0019376	0.0102	0.57533
Salivary_Gland	-0.0050261	0.010864	0.67818
Small_Intestine	-0.0052825	0.010674	0.68966
Esophagus	-0.0094383	0.017227	0.70811
Lung	-0.0084154	0.010458	0.78949
Heart	-0.0086063	0.0097427	0.81147
Breast	-0.014153	0.015658	0.81696
Vagina	-0.012897	0.012719	0.8447
Adipose_Tissue	-0.013728	0.013272	0.8495
Fallopian_Tube	-0.015227	0.0139	0.86334
Pancreas	-0.010308	0.0089573	0.87508
Cervix_Uteri	-0.018346	0.014299	0.90025
Stomach	-0.017953	0.01342	0.9095
Colon	-0.021036	0.015508	0.91251
Blood_Vessel	-0.018554	0.011787	0.94226
Uterus	-0.01972	0.012072	0.9488
Bladder	-0.026955	0.016048	0.95347

Tissue types are sorted according to *p*-value. Number of Genes: 17267. Abbreviation: SE = standard error.

Supplementary table 7. MAGMA tissue expression analysis on 53 specific tissue types.

Tissues	BETA	SE	P
Brain_Amygdala	0.026063	0.0078791	0.00047147
Brain_Hippocampus	0.024047	0.0080074	0.0013386
Brain_Nucleus_accumbens_basal_ganglia	0.022727	0.0075721	0.001346
Brain_Caudate_basal_ganglia	0.023493	0.007845	0.0013765
Brain_Putamen_basal_ganglia	0.023712	0.0079226	0.0013837
Brain_Substantia_nigra	0.024953	0.0085282	0.0017202
Brain_Spinal_cord_cervical_c-1	0.022164	0.0084368	0.0043121
Brain_Anterior_cingulate_cortex_BA24	0.018946	0.0072674	0.0045727
Brain_Hypothalamus	0.019133	0.0080567	0.0087851
Brain_Cortex	0.014705	0.0071394	0.019727
Brain_Frontal_Cortex_BA9	0.013152	0.006917	0.028637
Cells_EBV-transformed_lymphocytes	0.005095	0.0049707	0.15269
Brain_Cerebellum	0.0053756	0.0062758	0.19585
Brain_Cerebellar_Hemisphere	0.0046486	0.0060904	0.22266
Nerve_Tibial	0.0058207	0.010067	0.28158
Pituitary	0.0036978	0.0088425	0.33791
Testis	0.0019419	0.0057024	0.36673
Whole_Blood	0.0018829	0.0056942	0.37045
Thyroid	0.0031043	0.0097272	0.37481
Cells_Cultured_fibroblasts	0.0010592	0.0065729	0.43599
Prostate	0.000051982	0.01211	0.49829
Muscle_Skeletal	-0.000029071	0.0070116	0.50165
Liver	-0.00082683	0.006371	0.55163
Spleen	-0.0010943	0.0073349	0.5593
Adrenal_Gland	-0.0019487	0.0099459	0.57767
Esophagus_Mucosa	-0.0015978	0.0076967	0.58222
Kidney_Cortex	-0.0023366	0.0088367	0.60427
Kidney_Medulla	-0.0038041	0.0091783	0.66073
Skin_Not_Sun_Exposed_Suprapubic	-0.0072873	0.0077537	0.82634
Heart_Left_Ventricle	-0.0091396	0.0092407	0.83867
Ovary	-0.0096781	0.009588	0.8436
Small_Intestine_Terminal_Ileum	-0.011039	0.0095175	0.87693
Minor_Salivary_Gland	-0.011167	0.0096247	0.87702
Skin_Sun_Exposed_Lower_leg	-0.0091863	0.0077831	0.88105
Lung	-0.012844	0.0090357	0.9224
Adipose_Subcutaneous	-0.015882	0.010581	0.9333
Pancreas	-0.014377	0.0085966	0.95277
Breast_Mammary_Tissue	-0.02216	0.012516	0.96166

Vagina	-0.019594	0.011	0.96255
Colon_Transverse	-0.020543	0.011455	0.96353
Artery_Tibial	-0.019111	0.0099373	0.97276
Fallopian_Tube	-0.022895	0.01185	0.97331
Cervix_Endocervix	-0.023361	0.011636	0.97765
Adipose_Visceral_Omentum	-0.022878	0.010999	0.98123
Esophagus_Muscularis	-0.025846	0.012291	0.98225
Heart_Atrial_Appendage	-0.020162	0.0095706	0.98242
Stomach	-0.025111	0.011895	0.98261
Esophagus_Gastroesophageal_Junction	-0.027091	0.012686	0.98363
Cervix_Ectocervix	-0.026095	0.012085	0.98458
Colon_Sigmoid	-0.028124	0.012363	0.98854
Uterus	-0.026493	0.010881	0.99254
Bladder	-0.03207	0.013002	0.99317
Artery_Aorta	-0.025944	0.010046	0.99509
Artery_Coronary	-0.032599	0.011739	0.99725

Tissue types are sorted according to *p*-value. Number of Genes: 17267. Abbreviation: SE = standard error.

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EIDESSTATTLICHE VERSICHERUNG

1. Bei der eingereichten Dissertation zu dem Thema

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handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

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