Aus dem Zentrum für Psychosoziale Medizin der Universität Heidelberg
(Geschäftsführende Direktorin: Prof. Dr. med. Sabine C. Herpertz)
Klinik für Allgemeine Psychiatrie
(Ärztliche Direktorin: Prof. Dr. med. Sabine C. Herpertz)

Examinations of pathomechanisms in schizophrenic and bipolar disorders –

results from two functional magnetic resonance imaging studies

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Lisa Rauer

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Dekan: Herr Professor Dr. med. Hans-Georg Kräusslich

Doktorvater: Herr Professor Dr. med. Oliver Gruber

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ABBREVIATIONS

AA R	Atypical antipsychotic responders
AA NR	Atypical antipsychotic non-responders
AP R	Aripiprazole responders
AP NR	Aripiprazole non-responders
avPFC	Anteroventral prefrontal cortex
BD	Bipolar disorder
BOLD	Blood oxygen level dependent
CBT	Cognitive behavioral therapy
CGI	Clinical Global Impression Scale
D1R	D_1 dopamine receptor
D2R	D_2 dopamine receptor
DA	Dopamine
DAT	Dopamine transporter
DC	Desire context
DRD	Desire-reason-dilemma
DTI	Diffusion tensor imaging
EPI	Echoplanar imaging
ERP	Event-related potential
FDA	Food and Drug Administration
FEF	Frontal eye field
FN	False negative
FP	False positive
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
FWHM	Full width at half maximum
GABA	*gamma*-Aminobutyric acid
GLM	General linear model
GWAS	Genome-wide association studies
HC	Healthy controls
HRF	Hemodynamic response function
HPA	Hypothalamic–pituitary–adrenal
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10
IFS	Inferior frontal sulcus
IGT	Iowa Gambling Task
IP	Intraparietal cortex
LCD	Liquid crystal display
LSD	Lysergic acid diethylamide
MADRS	Montgomery-Asperg Depression Scale
MFG	Middle frontal gyrus
MMN	Mismatch negativity
MNI	Montreal Neurological Institute
MSN	Medium spiny neurons

MTG	Middle temporal gyrus
NAc	Nucleus accumbens
NMDA	*N*-methyl-D-aspartate
NMR	Nuclear magnetic resonance
OFC	Orbitofrontal cortex
PANSS	Positive and Negative Symptom Scale
PET	Positron emission tomography
PFC	Prefrontal cortex
pgACC	Pregenual anterior cingulate cortex
RC	Reason context
RDoC	Research Domain Criteria
ROI	Region of interest
RPE	Reward prediction error
SCZ	Schizophrenia
SD	Standard deviation
SPM	Statistical Parametric Mapping
SVM	Support vector machine
TA R	Typical antipsychotic responders
TA NR	Typical antipsychotic non-responders
TN	True negative
TP	True positive
TPJ	Temporoparietal junction
TR	Time of repetition
VMAT	Vesicular monoamine transporter protein
VTA	Ventral tegmental area
VFC	Ventral frontal cortex
YMRS	Young Mania Rating Scale

1 INTRODUCTION

The two studies of this thesis ought to gain a deeper understanding of the pathomechanisms underlying schizophrenia and bipolar disorder. Even though a great amount of research revealed structural or functional alterations in both disorders, none of the previous results has matured into a clinically applicable biomarker, yet. This is due to the fact that most psychiatric disorders have complex and diverse origins as well as individual forms of progression. This thesis was driven by the possibility of finding specific neurobiological markers that might reliably be ascribed to the disorders or subgroups. Furthermore, the ability to predict treatment response or improve the status quo of current treatment through analyses of neuroimaging data would have great advances on the course of the diseases.

1.1 Overview disorders

The first chapter is supposed to give a summary of the two psychiatric disorders involved in the two different studies of this thesis. The manifestation and hypotheses around the development of schizophrenia and bipolar disorder will be shortly described to better understand the subsequent description of impairments and deficits involved in the reward and attention networks of both disorders.

1.1.1 Schizophrenia

1.1.1.1 Symptoms & diagnosis

Schizophrenia is characterized by impaired perception and thought disorder. Core symptoms listed in the International Statistical Classification of Diseases and Related Health Problems (ICD-10) are thought echo, thought insertion, delusions and hallucinations. Furthermore, so called negative symptoms can derogate the individual's cognitive function temporarily, but also continue during euthymic phases. These include for example a lack of motivation, anhedonia and social withdrawal. In addition, schizophrenia patients suffer from cognitive impairment, such as shorter attention spans, longer reaction times and poorer performance during memory tasks (reviewed in Bowie and Harvey, 2005; reviewed in Heinrichs and Zakzanis, 1998; reviewed in Mesholam-Gately *et al.*, 2009). Whereas the positive symptoms can be treated very well, cognitive dysfunctions often continue during remitted phases (Caldiroli *et al.*, 2016; Kumar *et al.*, 2016; Trivedi *et al.*, 2007). Cognitive decline has sometimes also been defined as a hallmark of the disorder as it often appears many years before the actual onset of psychosis (Fuller *et al.*, 2002; Reichenberg *et al.*, 2010; van Oel *et al.*, 2002). Kraepelin (1893) already described intellectual and cognitive disturbances more in-depth than positive symptoms such as hallucinations, delusions etc. (reviewed in van Os and Kapur, 2009). Moreover, schizophrenia was originally named *dementia praecox* (Bleuler, 1950; Morel, 1860, p.565-566). This underlines the early understanding and nowadays importance of cognitive underperformance

in schizophrenia. Overall, schizophrenia is a severe psychiatric disorder with numerous symptoms of different dimensions that need to be addressed. This thesis will focus especially on potential deficits of schizophrenia patients in reward and cognitive control processes.

1.1.1.2 Epidemiology & risk factors

In general, the median lifetime prevalence of schizophrenia is stated with 0.4-0.87% and an incidence rate of 15 persons per 100'000 per year (reviewed in Kahn *et al.*, 2015; reviewed in McGrath *et al.*, 2008; reviewed in McGrath *et al.*, 2004; reviewed in Saha *et al.*, 2005). Taking related psychotic disorders such as e.g. schizoaffective disorders, delusional disorder etc. into account the prevalence rises to over three percent (Perala *et al.*, 2007). Women and men are equally often affected; however, the incidence rate ratio median of men is higher than in women (1.4:1) (reviewed in Kahn *et al.*, 2015; reviewed in McGrath *et al.*, 2004). The disease onset is in the early adolescence, i.e. 16-30 years (reviewed in Owen *et al.*, 2016). A systematic review of studies regarding clinical outcome and social recovery criteria found that the median recovery estimates of schizophrenia patients was only 13.5% (reviewed in Jääskeläinen *et al.*, 2013; reviewed in Kahn *et al.*, 2015). Even worse, people suffering from schizophrenia have a significantly decreased life expectancy, i.e. 20 years below the general population and an increased excess mortality with 13.9% accounting for suicide (Charlson *et al.*, 2015; reviewed in Laursen *et al.*, 2014; Laursen *et al.*, 2013; Lawrence *et al.*, 2013). Moreover, early death is also caused by cardiovascular diseases which in many cases result from widespread cigarette abuse, a higher probability of living an unhealthy lifestyle or adverse effects of antipsychotic drugs leading to obesity (Bobes *et al.*, 2010; Daumit *et al.*, 2008; Jerrell *et al.*, 2010; Kahn *et al.*, 2008; reviewed in Kahn *et al.*, 2015; reviewed in Laursen *et al.*, 2014).

A lot of studies have been conducted to find causes of or risk factors for the development of schizophrenia. Pre-/ perinatal complications (reviewed in Cannon *et al.*, 2002), life events (reviewed in Beards *et al.*, 2013; Raune *et al.*, 2009; reviewed in Varese *et al.*, 2012), paternal age (Malaspina *et al.*, 2001; Petersen *et al.*, 2011), sex (reviewed in Aleman *et al.*, 2003), urbanicity (Kirkbride *et al.*, 2007; Pedersen and Mortensen, 2001) and migration (Hutchinson *et al.*, 1996) have been described as possible risk factors for the onset of schizophrenia (reviewed in Kahn *et al.*, 2015; reviewed in Owen *et al.*, 2016). In addition, over the last 50 years the impact of genetics on the development of schizophrenia has also been examined. So far, the influence of genetics on schizophrenia has been found to be highly polygenic and pleiotropic making it impossible to predict its genesis (Gottesman and Shields, 1972; Lee *et al.*, 2013; reviewed in Owen *et al.*, 2016). In sum, most likely a combination of environmental and genetic factors will lead to the actual outbreak of psychotic disorders.

1.1.1.3 Pathology

For many years a lot of approaches in understanding the causes for schizophrenia have been ensued. Thereby, hypotheses which were developed on the basis of post-mortem studies, genetic factors, neurodevelopmental influences and structural or functional imaging, have tried to fathom the core pathophysiology of schizophrenia (reviewed in Kahn *et al.*, 2015). Experiments examining the brain tissue of deceased schizophrenia patients have found multiple cellular abnormalities regarding receptors involved in dopaminergic, glutamatergic and *gamma*-Aminobutyric acid (GABA) transmission. Kestler *et al.* conducted a meta-analysis and reported increased dopamine receptor density in schizophrenia patients (reviewed in Kestler *et al.*, 2001). Furthermore, morphological variations of glutamatergic neuron dendrites were reviewed by Hu *et al.* (2015). Consistently, hypofunction of GABAergic transmission resulting from plausible molecular and cellular alterations was reported (reviewed in Curley and Lewis, 2012; Guillozet-Bongaarts *et al.*, 2014). Moreover, relative and twin studies as well as genome wide association studies have shed some light on genetic factors and risk loci that seem to be involved in the development of schizophrenia (reviewed in Cardno and Gottesman, 2000; Ripke *et al.*, 2014). However, their molecular implications have not been completely understood, yet. Further experiments tried to link neurodevelopmental factors to the genesis of schizophrenia and found repeatedly associated genes that are mostly expressed during fetal brain development (Birnbaum *et al.*, 2014; Gulsuner *et al.*, 2013; Jaffe *et al.*, 2015). Although a broad spectrum of hypotheses with several approaches has been tested so far, it can be concluded that multiple factors influence the genesis, course and outcome of schizophrenia.

The most accepted and wide-spread theory regarding the psychopathology of schizophrenia is the dopamine hypothesis (reviewed in Baumeister and Francis, 2002; reviewed in Grace, 2016; reviewed in McCutcheon *et al.*, 2019). It describes a strong involvement of dopamine dysfunctions due to excess or deficiencies at dopamine receptors sites. The dopamine hypothesis evolved when clinical studies reported a link between the administration of dopaminergic agonists or stimulants and the development of psychotic conditions in healthy individuals (Angrist and Gershon, 1970; Connell, 1957). Another great advance was 1975, when Seeman and Lee discovered that there was a direct relation between clinically potent dosages of antipsychotic drugs and the release of dopamine (Seeman and Lee, 1975). Soon after, post-mortem studies elaborated enhanced levels of dopaminergic receptors in the striatum of schizophrenia patients (Lee and Seeman, 1980). Later, the development of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) enabled *in vivo* examinations of the molecular underpinnings of the dopaminergic system in schizophrenia individuals (reviewed in McCutcheon *et al.*, 2019). Experiments in the subsequent years revealed various factors such as elevated presynaptic dopaminergic function or the correlation between striatal dopaminergic release and its baseline levels which supported the hypothesis

that abnormalities in the dopaminergic system might contribute to psychotic conditions (Abi-Dargham *et al.*, 2009; Howes *et al.*, 2013). The role of dopamine was extended to the aberrant salience hypothesis. It claims that an enhanced dopamine distribution leads to aberrant attribution of salience to external and internal stimuli before the actual outbreak of psychotic symtpoms (reviewed in Kapur, 2003). Over the years, however, conflicting results (among other things from genome-wide association studies) led to growing doubts concerning the dopamine hypothesis or, more precisely, the exclusive role of dopamine in the development of schizophrenia (Edwards *et al.*, 2016; reviewed in Kambeitz *et al.*, 2014). These concerns began to leave room for alternative hypotheses such as the exploration of neurodevelopmental factors or the involvement of other neurotransmitters (Sørensen *et al.*, 2010; reviewed in Stahl, 2018).

Other neurotransmitters that have been associated with schizophrenia are serotonin and glutamate (reviewed in Stahl, 2018). As lysergic acid diethylamide (LSD) and psilocybin can induce hallucinations by acting as serotonin agonists, serotonin was thought to be involved in eliciting psychotic symptoms (Hoch *et al.*, 1952; Hyde *et al.*, 1978; Shaw and Woolley, 1956; Vollenweider *et al.*, 1998). The association between serotonergic neurotransmission and positive symptoms had a strong impact on the following development of new psychopharmacological treatments, i.e. atypical antipsychotics (reviewed in Lally and MacCabe, 2015; reviewed in Lieberman, 2004). As they act as partial agonists on dopaminergic and serotonergic receptors, they do not exclusively affect the dopaminergic system (Bymaster *et al.*, 1996; Leysen *et al.*, 1988; Saller and Salama, 1993).

The findings of decreased glutamate levels in the cerebrospinal fluid of schizophrenia and the occurrence of psychotic symptoms after administration of *N*-methyl-D-aspartate (NMDA) receptor antagonists suggests that glutamate might be implicated in the development or continuity of schizophrenia (Fine and Finestone, 1973; reviewed in Hu *et al.*, 2015; Kim *et al.*, 1980; Perel and Davidson, 1976). Glutamate is the key player in excitatory neurotransmission and binds to the NMDA receptor, which is important for learning and memory. The discovery of NMDA receptor alterations or abnormal expression supports the idea of dysfunctional glutamatergic neurotransmission (reviewed in Gao *et al.*, 2000; Meador-Woodruff and Healy, 2000). As potential treatment target, glutamate modulation might hence improve negative and cognitive symptoms in schizophrenia patients.

Taken together it is not yet clear to which extent the different neurotransmitters contribute to the development and dimension of schizophrenia. Therefore, it is of great interest to better understand the underlying pathophysiology and mechanisms of psychotic conditions.

1.1.2 Bipolar disorder

1.1.2.1 Symptoms

According to the ICD-10, bipolar affective disorder is defined as a disorder consisting of at least two episodes of drastically altered mood in two opposite directions. On the one hand, states of mania or hypomania, i.e. severely enhanced energy and activity, and on the other hand, conditions of depression, i.e. strongly reduced levels of energy and activity, have to appear. Hypomanic or manic phases are often characterized by elevated mood, volubility, productivity and performance as well as decreased need for sleep. In more severe cases patients may present sexual disinhibition, irritability and importunity up to megalomania, delusions and hallucinations. During depressive episodes patients show a lack of energy, joy, concentration and appetite as well as rumination and feelings of guilt and worthlessness. In worse cases, patients vegetate and suffer from emotional numbness and suicidal thoughts. One or more manic episodes are the key criterion for meeting the diagnosis bipolar disorder II or I, respectively (reviewed in Vieta *et al.*, 2018).

Another major factor affecting bipolar patients is a decrease in cognitive performance (Basso *et al.*, 2002; reviewed in Bora and Pantelis, 2015; reviewed in Cipriani *et al.*, 2017; Martinez-Aran *et al.*, 2004). An integral amount of patients suffer from mild to severe disturbances in executive function, attention, reaction time and verbal as well as visual memory- not just during acute phases, but also in remission (reviewed in Altshuler *et al.*, 2004; Cavanagh *et al.*, 2002; Cullen *et al.*, 2016; Daban *et al.*, 2012; Eric *et al.*, 2013; Mur *et al.*, 2007; Sparding *et al.*, 2015). Potential impairments in the cognitive control of attentional processes and its underlying neural networks will be investigated in this thesis.

1.1.2.2 Epidemiology & risk factors

In a broad study, Merikangas *et al.* (2011) conducted structured psychiatric diagnostic interviews (World Health Organization Composite International Diagnostic Interview) with more than 60’000 adults from America, Europe and Asia. They concluded a lifetime prevalence for bipolar I disorder of 0.6% and bipolar II disorder of 0.4%. In comparison, the epidemiological study by Blanco *et al.* (2017) with over 30’000 US-only adults reported a lifetime prevalence of 2.1% in bipolar I disorder. A strict determination of age of onset is quite difficult; however, literature suggests a main age of onset in late adolescence up to the early forties (Merikangas *et al.*, 2007). Approximately one-half to one-third of the bipolar patients will attempt suicide in their life leading to the highest suicide rate among affective disorders (Chen and Dilsaver, 1996; Valtonen *et al.*, 2005).

Over the years it has been discovered that bipolar disorder has a high heritability, i.e. 58-85% (Johansson *et al.*, 2019; McGuffin *et al.*, 2003; Song *et al.*, 2015). However, also environmental

factors have been named to be associated with a greater risk of developing bipolar disorder (reviewed in Vieta *et al.*, 2018). Reported influences have been caesarean section delivery (Chudal *et al.*, 2014), smoking during pregnancy (Chudal *et al.*, 2015; Talati *et al.*, 2013), high paternal age (Frans *et al.*, 2008) and adverse events in the childhood (reviewed in Bortolato *et al.*, 2017; Jimenez *et al.*, 2017).

1.1.2.3 Pathology

A multifactorial model consisting of a strong interdependency between environmental and genetic factors is the most convincing hypothesis regarding the pathology of bipolar disorder so far. Even if the heritability of bipolar disorder is reported to be up to 85% (McGuffin *et al.*, 2003), there is no single bipolar disorder-specific gene responsible for an outbreak of the disease (reviewed in Craddock and Sklar, 2013; reviewed in Vieta *et al.*, 2018). In the recent years, genome-wide association studies (GWAS) proposed common variants, which partly have also been associated with schizophrenia (Hamshere *et al.*, 2013; Sklar *et al.*, 2011).

It is anticipated that the interplay of different neurotransmitter systems, rather than a single one, is involved in the genesis of bipolar disorder. Beside the serotonergic and noradrenergic neurotransmitter systems, there are indications that a dysfunction or imbalance in the dopaminergic system might have a particular influence on this mood disorder (reviewed in Vieta *et al.*, 2018). Around 40-50 years ago the dopamine hypothesis in bipolar disorder emerged within psychiatric research (reviewed in Ashok *et al.*, 2017). It resulted from observations reporting similarities between manic behavior and the behavior after amphetamine consumption as well as findings of attenuating effects of anti-dopaminergic medication on mania (Jacobs and Silverstone, 1986; Nolen, 1983; Post *et al.*, 1980). Initially, manic-like conditions were induced in rodents, e.g. hyperlocomotion, through different techniques such as amphetamine administration, dopamine transporter (DAT) knock-out, DAT blockers, dopamine receptor stimulation, etc. (Perry *et al.*, 2009; Young *et al.*, 2010). Results from these studies argue for an involvement of dopamine in bipolar disorder's pathophysiology. More specifically, the results propose that hyperdopaminergia might induce manic-like behavior. Rodent studies showing a reversal of manic-like conditions through administration of mood stabilizers further support this hypothesis (Berggren *et al.*, 1978; Gould *et al.*, 2001; Shaldubina *et al.*, 2002). Furthermore, a potential connection between hypodopaminergia and the initiation of depressive-like symptoms was shown by Winter *et al.* who described depressive-like behavior following lesions in dopaminergic regions, such as ventral tegmental area (VTA) and substantia nigra (Winter *et al.*, 2007). However, the transition to human research discloses a more complex relationship between dopamine and bipolar disorder.

Whereas animal studies propose a quite straight-forward mechanism of hyperdopaminergia being responsible for manic symptoms and hypodopaminergia causing depressive symptoms, human (neuro-) imaging and post-mortem studies suffer from stringent and consistent explanations of bipolar disorder symptomatology. This is due to the fact that, on the one hand, a lot of studies report contradicting results and, on the other hand, most of the studies have not been replicated (reviewed in Ashok *et al.*, 2017; Kaalund *et al.*, 2014; Pantazopoulos *et al.*, 2004). Therefore, the current literature yields indications of abnormalities of reward-related activity in bipolar disorder but cannot clearly propose the underlying molecular pathways. Many results showed an increase or upregulation of dopamine receptors and transporters or vesicular monoamine transporter protein (VMAT-2), which is involved in the storage of dopamine (Kaalund *et al.*, 2014; Pearlson *et al.*, 1995; Wong *et al.*, 1997; Zhan *et al.*, 2011; Zubieta *et al.*, 2000). Neuroimaging data suggests abnormal reward-related activity in the nucleus accumbens (NAc), striatum and frontal cortex (Bermpohl *et al.*, 2010; Mason *et al.*, 2014; Nusslock *et al.*, 2012; Trost *et al.*, 2014).

In addition to potential imbalances of neurotransmitter systems, factors such as altered endocrine function (in particular regarding the hypothalamic–pituitary–adrenal (HPA) axis) and modulation of synaptic plasticity as well as alterations in cellular and molecular connectivity have been discussed (Grande *et al.*, 2010; reviewed in Vieta *et al.*, 2018; Vieta *et al.*, 1999). In the last years, a lot of research focused on parameters such as neurotrophic molecules, dendritic spines, which have a huge impact on synaptic and neural plasticity, oxidative stress, mitochondria and inflammation (Andreazza *et al.*, 2009; Cunha *et al.*, 2006; Grande *et al.*, 2014; Konopaske *et al.*, 2014; Rao *et al.*, 2010). Taken together, intertwined influences of various pathomechanisms seem to affect the phenotype of bipolar disorder and further experiments need to validate the current hypotheses.

1.1.3 Treatment

1.1.3.1 Psychopharmacology

The most commonly applied psychopharmacological treatment of schizophrenia is the administration of atypical antipsychotics, such as olanzapine, risperidone, quetiapine etc. (Toto *et al.*, 2019). Although most bipolar patients received lithium or anticonvulsant compounds as treatment of choice, since the beginning of the 21st century atypical antipsychotics have also gained ground in the treatment of mania. When multiple studies reported their antimanic effects, the USA Food and Drug Administration (FDA) approved several atypical antipsychotics as psychopharmacological treatment option for bipolar disorder (Keck *et al.*, 2003a; Keck *et al.*, 2003b; Tohen *et al.*, 2000). Second-generation antipsychotics share their mode of action, i.e. they influence dopaminergic as well as serotonergic receptors (Bymaster *et al.*, 1996; Leysen *et al.*, 1988; Saller and Salama, 1993). So-called first-generation, or typical, antipsychotics only

affect dopaminergic receptors (Seeman *et al.*, 1975). Their oftentimes strong side effects, in particular extrapyramidal symptoms which cause motor malfunction, led to the development of atypical antipsychotics (reviewed in Lally and MacCabe, 2015).

One special atypical antipsychotic is aripiprazole, also called third-generation antipsychotic. Its mechanism of action differs from the second-generation antipsychotics by acting as partial agonist at the dopamine D2 receptor and serotonin (5-HT(1A)) receptors (Burris *et al.*, 2002; Jordan *et al.*, 2002). Its unique profile has been shown to achieve as high clinical efficacy as other atypical antipsychotics, while at the same time demonstrating very low side effects (Kane *et al.*, 2002; reviewed in Leucht *et al.*, 2013). Partial agonists act as functional agonists in surroundings where no dopamine is present and thereby initiate a, however attenuated, response (Momiyama *et al.*, 1996). In addition, aripiprazole can also operate as functional antagonists in the presence of dopamine (Inoue *et al.*, 1996; Kikuchi *et al.*, 1995; Semba *et al.*, 1995). In this case it prevents dopaminergic binding and decreases the overall effect. Third-generation antipsychotics seem to offer a great mode of action, as increased dopaminergic transmission in the mesolimbic pathway might be responsible for positive symptoms and decreased distribution in the mesocortical pathway might be associated with negative symptoms and cognitive impairment (reviewed in McCutcheon *et al.*, 2019; reviewed in Patel *et al.*, 2014). Due to their balancing effects they can fulfill both requirements.

In one of the two studies conducted in this thesis, patients will be subdivided into response arms of atypical, typical and aripiprazole treatment. It was of interest to investigate if patients (not) responding to the respective treatments show differences in their brain activation during a reward-related paradigm.

1.1.3.2 Treatment response prediction

Multivariate methods, i.e. pattern-classifiers as predictors of variables were developed for the first time for PET data in the beginning of the 1990s (Azari *et al.*, 1993; Clark *et al.*, 1991; Kippenhan *et al.*, 1992; Moeller and Strother, 1991; reviewed in O'Toole *et al.*, 2007).

Classifiers are functions that use various parameters of an example to predict the class of the respective example. Thereby, the classifier learns specific features of the examples from training data. It develops a model of the relationship between features and class, which is then able to predict the classes of new examples from a test set. The most important underlying assumption for this type of analysis is the random splitting of training and test data from an example distribution (reviewed in Pereira *et al.*, 2009).

In the case of small samples, the application of leave-one-out cross-validation offers the opportunity to achieve sufficient classification results. For this purpose, the classifier is trained

with a by one example reduced data set and validated with the remaining data sample n times until every example was left out (reviewed in Pereira *et al.*, 2009).

Up to now, only few studies have used support vector machine (SVM) algorithms on functional magnetic resonance imaging (fMRI) data of psychiatric disorders to predict treatment response of psychopharmacological treatment. However, there is one study by Mansson *et al.* (2015) who applied supervised SVM analyses to predict the long-term outcome of web-based cognitive behavioral therapy (CBT). They included blood oxygen level dependent (BOLD) responses from the dorsal anterior cingulate cortex and amygdala to predict long-term response rates and were able to reach 92% accuracy. Another study from Mechelli *et al.* (2017) tried to predict clinical outcomes and functioning of people at ultra-high risk for psychosis. In this case they used psychopathological information, i.e. scores of different rating scales, to forecast the longitudinal development of their subjects. The prediction of transition to psychosis reached an accuracy of 64.6% and the functioning 62.5%. A study from Fleck *et al.* (2017) used a cascading genetic fuzzy tree design to develop a linguistic machine learning system which should predict the treatment response of bipolar patients to lithium. As inputs they fed the algorithm ^{1}H-MRS and fMRI data. Their machine learning system was able to predict post-treatment symptom reduction with 88% accuracy. Furthermore, in a clinical trial the efficacy of repetitive transcranial magnetic stimulation in schizophrenia patients was predicted with the help of machine learning algorithms. By employing structural magnetic resonance images, they achieved a cross-validated balanced accuracy of 85% for the response prediction (Koutsouleris *et al.*, 2018).

In sum, there is a slowly emerging field of treatment response prediction studies. Due to the very heterogeneous responses to antipsychotic treatment and the lack of prediction parameters, most patients are currently treated according to a trial-and-error principle (reviewed in Lally and MacCabe, 2015). This, in turn, results in longer acute phases of disease and thus suffering of psychiatric patients. Therefore, it is of great relevance and importance to further explore this field and make use of SVM algorithms to potentially predict treatment response in the future.

1.2 Overview brain networks

In the following chapter, the underlying neural networks of reward and attention will be closely examined in general and in the psychopathological context. The two paradigms described in this thesis strongly rely on these networks. Presenting the current state of knowledge about the reward circuit in general and attentional effects will hence help to interpret the results of this thesis.

1.2.1 Reward processing

1.2.1.1 Reward circuit of the human brain

Reward processing comprises many elements such as assessment of reward outcome probability, prediction error, goal-directed behavior and positive reinforcement for learning. Apart from that, primary and secondary rewards can be defined. Primary rewards comprise pleasant tastes, sounds etc., whereas secondary rewards describe monetary gains etc. In addition, reward processing can also be divided into reward anticipation and response to reward outcome (reviewed in Haber and Knutson, 2010).

The brain region most often associated with reward is the ventral striatum, consisting of the NAc, ventral medial caudate and rostroventral putamen. They receive input from the medial prefrontal cortex (PFC), orbitofrontal cortex (OFC), dorsal anterior cingulate cortex, VTA, amygdala and hippocampus. The ventral striatum projects to the ventral pallidum and midbrain which relays further back to the PFC. This interacting network is called the frontostriatal neural circuit. An important feature of this circuit is the massive reciprocal influences of the ventral striatum and midbrain. On the one hand, striatal projections together with projections from the ventral pallidum arrive at the VTA and substantia nigra pars compacta. On the other hand, dopaminergic projections from dopamine neurons of the VTA and substantia nigra pars compacta project back to the ventral striatum (reviewed in Haber and Knutson, 2010). Three major dopaminergic projections define the reward circuit: the mesolimbic (VTA to NAc), mesocortical (VTA to PFC) and nigrostriatal (substantia nigra to putamen and caudate nucleus) (reviewed in Björklund and Dunnett, 2007).

Specific brain regions were attributed to the reward circuit for the first time in a rodent experiment by Milner and Olds (1954). They implanted a number of electrodes in various regions of the rats' brains and prepared a setup in which the rats could reward themselves via button press. The results showed the greatest electrical stimulation in septal regions. Later, electrophysiological experiments in primates demonstrated phasic discharges of action potentials in dopaminergic neurons following unanticipated food reward during an operant condition task (Ljungberg *et al.*, 1992). In the following, the reward prediction error (RPE) hypothesis was proposed, stating that dopaminergic neurons code the difference between anticipated reward and its effective outcome (Montague *et al.*, 1996; reviewed in Schultz *et al.*, 1997). Its plausibility was reviewed in human fMRI studies (D'Ardenne *et al.*, 2008) and multiple electrophysiological experiments and species (Day *et al.*, 2007; Eshel *et al.*, 2015; Fiorillo *et al.*, 2003; Roesch *et al.*, 2007). Moreover, it has been proposed that the RPE signal, i.e. dopaminergic activity acting as a learning signal, plays a vital role in reinforcement learning. Additionally, depending on projections to particular striatal regions, it also facilitates other

types of learning such as Pavlovian, contextual or operant learning (reviewed in Cox and Witten, 2019; Hamid *et al.*, 2016; Saunders *et al.*, 2018; Tsai *et al.*, 2009).

The NAc as key player of the reward circuit consists in large part of GABAergic medium spiny neurons (MSN) (Kemp and Powell, 1971; Preston *et al.*, 1980; Somogyi *et al.*, 1981). Its functional outcome is modulated by GABAergic and cholinergic interneurons and mainly leads to the acknowledgment of reward and the resulting quest for its fulfillment. MSN in the striatum either express D_1 dopamine receptors (D1R) or D_2 dopamine receptors (D2R), which inhibit (direct pathway) or increase (indirect pathway) the basal ganglia output, respectively. By modulating the firing rate of the basal ganglia output nuclei, they regulate and encode action (reviewed in Cox and Witten, 2019). During value-based decision-making, D1R MSN respond with greater activity to reward presentation, whereas D2R MSN react to unexpected reward (Nonomura *et al.*, 2018). Similar effects can be found in Pavlovian learning with a positively correlated increase to reward-predicting cues of D1R MSN and negatively correlated response of D2R MSN (Shin *et al.*, 2018).

The actual processing of reward, i.e. primary and secondary rewards, could be demonstrated by PET and fMRI studies which showed increased activation of striatal areas (Blood and Zatorre, 2001; Delgado *et al.*, 2000; Elliott *et al.*, 2000; Knutson *et al.*, 2000; Menon and Levitin, 2005). In line with the aforementioned description of striatal projections, fMRI studies revealed activation in the OFC during primary reward anticipation as well as reward outcome (O'Doherty *et al.*, 2001; Rolls *et al.*, 2003). Furthermore, the tight connection to the midbrain, or better its involvement in reward processing, has also been examined. FMRI studies revealed enhanced activation of the midbrain during the anticipation of reward and also during the visual presentation of reward-predicting cues (D'Ardenne *et al.*, 2008; O'Doherty *et al.*, 2002; Wittmann *et al.*, 2005).

Taken together, the ventral striatum and its associated mesolimbic and mesocortical networks have repeatedly been defined as key players in reward processing which also influences decision-making. Due to the reliable effects, they provide a great foundation to examine reward processing with fMRI.

1.2.1.2 Alterations in reward processing of bipolar and schizophrenia patients

In chapters 1.1.1.3 and 1.1.2.3, abnormalities in the dopaminergic pathways of bipolar disorder and schizophrenia patients were described which might affect their dopaminergic modulated reward circuit. Therefore, the next paragraphs will summarize the experimental evidence for alterations in the reward processing of the two disorders.

As mentioned in previous chapters, patients with bipolar disorder seem to have abnormally modulated dopaminergic neurotransmission. In great accordance, neuroimaging studies

reported abnormal activation in the ventral striatum and PFC during reward-related paradigms (Abler *et al.*, 2008; Dutra *et al.*, 2015; Yip *et al.*, 2015). A study by Caseras *et al.* (2013) demonstrated atypically increased activation in the ventral striatum of bipolar disorder II patients during reward anticipation compared to healthy controls. In concordance, Mason *et al.* (2014) detected a significant increase in the left ventral striatum for high-probability rewards (relative to low) in bipolar patients but not healthy controls. They proposed that other than in healthy controls, bipolar patients' ventral striatum might have a stronger effect on suboptimal decision making, so that lower-order desires are preferred over long-term goal rewards. This would also imply an alteration of ventromedial PFC activity as it is responsible for the integration and weighting of signals from the dorsolateral PFC (long-term goal representation) and ventral striatum (lower order-preferences). This is in line with a study of Nusslock *et al.* (2012) who described elevated striatal and OFC activity during reward anticipation, suggesting activation in the ventral striatum and OFC as a functional marker for bipolar disorder while at the same time explaining a predisposition to (hypo)mania. In contrast, Trost *et al.* (2014) reported reduced activation in the ventral striatum in bipolar patients compared to healthy controls. However, they argued that compromised top-down regulation of prefrontal areas on the ventral striatum led to this effect. This interpretation could also be supported by their additional findings describing a dysfunctional connectivity pattern between anteroventral prefrontal cortex (avPFC) and ventral striatum. Similarly, studies examining reward anticipation and anticipation-related arousal have identified aberrant activation in the left ventrolateral PFC in bipolar patients (Chase *et al.*, 2013; Dolcos *et al.*, 2004). Furthermore, a PET study from Anand *et al.* (2011) showed that unmedicated bipolar patients seem to have a dysfunction in dopamine transmission due to significantly less dopamine transporter (DAT) availability. They proposed that in consequence, more dopamine might remain in the synaptic cleft leading to the state of hyperdopaminergia. In addition, a translational study revealed that mice with chronic or acute DAT depletion demonstrated impaired decision-making in a rodent version of the Iowa Gambling Task (IGT) (van Enkhuizen *et al.*, 2014). They compared this behavior to bipolar disorder patients also performing the IGT and found the same deficient decision-making profile.

Taken together, the specific effects of abnormal reward processing differ between hyper- and hypoactivation in relevant brain areas of bipolar patients. Characteristic activations could also be linked to differential affective phases, i.e. manic or depressed, medication status, i.e. medication-naïve or low- or high dosage medication, or heterogeneous clinical appearance etc. that have been examined in the various studies. However, it can be concluded that abnormal activation in the ventral striatum and frontal brain areas indicate a dysfunction of dopaminergic modulation in bipolar disorder.

The reward processing system has also been reported to be disturbed in schizophrenia patients. Again, the ventral striatum appears to be a key area associated with aberrant reward modulation (reviewed in Chase *et al.*, 2018). In various experiments involving reward-related tasks, decreased activation in the ventral striatum of schizophrenia patients compared to healthy controls was reported (Esslinger *et al.*, 2012; Juckel *et al.*, 2006b; Schlagenhauf *et al.*, 2009). In contrast, more recent studies presented increased activation in the ventral striatum during paradigms associated with reward processing (Morris *et al.*, 2012; Richter *et al.*, 2015; Tikasz *et al.*, 2019). The study by Richter *et al.* applied the desire-reason-dilemma paradigm, which was also used in this thesis, and detected significantly enhanced brain activation in the ventral striatum in response to conditioned reward stimuli. Furthermore, they showed a disrupted top-down influence of the PFC on the ventral striatum and VTA during reward stimuli presentation. The influence of dopamine on the ventral striatum particularly during reward processing was also confirmed by a study of Wulff *et al.* who examined the fMRI response in a monetary incentive delay task in antipsychotic-naïve schizophrenia patients (Wulff *et al.*, 2019). They found decreased activation in the caudate nucleus of schizophrenia patients compared to healthy individuals. Their follow-up measurement after six weeks of amisulpride exposed that patients responding to the antipsychotic treatment had an enhanced BOLD response in the nucleus caudate. These findings are in line with earlier studies showing that patients treated with atypical antipsychotics had comparable functional responses to reward-indicating cues as healthy controls, but patients treated with typical antipsychotics had reduced activation in the left ventral striatum (Juckel *et al.*, 2006a; Schlagenhauf *et al.*, 2008). In sum, it can be stated that the aforementioned deficits in dopaminergic modulation most likely influence the reported alterations in brain activation during reward processing of schizophrenia patients.

1.2.2 Attentional processing

1.2.2.1 Attention: oddball & incongruence effects

Attention is a cognitive process that entails various subtopics and wide-spread hypotheses. In general, attention is defined as a condition of selectively processing concurrent stimuli (Bear *et al.* 2007, p.644). In this chapter the neural correlates of goal-directed behavior and stimulus-driven attention will be further illuminated. With respect to the paradigm used in this study, it will be focused on the incongruence and oddball effect.

The most famous incongruence task was developed by Stroop in 1935 (Stroop, 1935). He published the results of a study introducing a task which aimed at creating inference in the participants. In this task, the individuals were asked to call the print color of words ignoring the colors named by the words, e.g. the word “green” was printed in red and therefore had to be called “red”. Back then, Stroop demonstrated significantly enhanced reaction times in the inference condition compared to congruent or neutral conditions, in which the individuals had

to name the color of a color patch or neutral stimuli, respectively. He concluded that the processing of the irrelevant task dimension led to an interference with the relevant task. Since then, the reduction of the response speed during incongruent compared to congruent stimuli has been replicated multiple times and has ever since been named "Stroop effect". It could also be detected in nonhuman primates confirming the robustness of the Stroop interference even across species (Allritz *et al.*, 2016; Beran *et al.*, 2007; Washburn, 1994; reviewed in Washburn, 2016). Over the years various tasks and paradigms have been developed, such as Flanker, Simon, Go/No-Go or Stop-Signal test (Eriksen and Eriksen, 1974; Logan and Cowan, 1984; Simon and Small, 1969). Most of them involve a task-relevant and task-irrelevant dimension with the latter conflicting with the appropriate response reaction. They all have in common that the participants fail, on the one hand, to concentrate on the relevant stimulus and, on the other hand, to control the suppression of the information provided by irrelevant stimuli. One possible interpretation for the Stroop phenomenon has been developed by Cohen *et al.* (1990) who established a model which describes a two-route neural network with three layers. One route is responsible for the color identification of the stimulus and the other for its meaning. The three layers reflect the stimulus representation, response activation and interaction between the two routes during processing. Botvinick *et al.* (2001) added a conflict-monitoring model unit and described control as dynamic processes that are elicited by the level of conflict. In the paradigm used here, the incongruence condition comprises a color-shape conflict, where attention to the irrelevant task dimension interferes with the response to be given regarding the relevant task dimension resulting in prolonged reaction times (Gruber *et al.*, 2009).

Another specific cognitive effect which will be part of this study is induced by the oddball stimulus. In tasks involving an oddball stimulus, participants are instructed to distinguish rare target stimuli (oddballs) from a series of frequent standard stimuli. Oddball effects were reported for the first time in event-related potential (ERP) measures, when the response of participants to the oddball stimuli was recorded via electroencephalogram (Squires *et al.*, 1975). ERPs which were elicited specifically after the presentation of the oddball stimulus, were named P300 as they usually occur 300ms after the stimulus presentation (reviewed in Picton, 1992). An ERP comparable to the P300 component could also be detected in nonhuman primates (Arthur and Starr, 1984; Glover *et al.*, 1986). Additionally, auditory-evoked potential P300-responses following the presentation of oddball stimuli have recently been described in rodents (Ahnaou *et al.*, 2018). These animal studies underline the reliability of the oddball effect across species.

The combined oddball-incongruence paradigm used in this study forms a combination of both effects. It has previously been hypothesized that response conflicts and reactions to relevant stimuli might induce similar cognitive processes (Gruber *et al.*, 2010; Gruber *et al.*, 2009). Every time a potentially relevant stimulus is recognized by the "background monitoring" system, the

attention is shifted towards the stimulus (reviewed in Corbetta and Shulman, 2002). In general, humans constantly keep a frail balance between focusing on task-relevant information and at the same time processing potentially threatening or rewarding but task-irrelevant background information. These salient or novel stimuli need to be quickly prioritized in case of an emergency and will thereby disrupt the ongoing behavior. Both, top-down and bottom-up, processes are involved in the regulation of this attention equilibrium. On the one hand, cognitive features such as knowledge, experience, current goals etc. modulate visual attention. On the other hand, sensory stimulation can interfere with it and thereby steer the attention in certain directions. A novel or unexpected stimulus can evoke a rapid switch of attention to a new target dimension (reviewed in Corbetta *et al.*, 2008).

Taken together, the incongruence and oddball effects offer a great possibility to investigate potential differences in specific processes of attention in bipolar and schizophrenia patients.

1.2.2.2 Brain regions associated with the incongruence and oddball effect

This paragraph will describe the underlying brain structures associated with the incongruence and oddball effects. Regions mostly reported to be involved in the processing of incongruence and oddball tasks are part of the frontoparietal network.

A recent large-scale meta-analysis studying the functional neural network of response inhibition processes, found great overlapping in activation of the frontoparietal and ventral attentional systems (reviewed in Zhang *et al.*, 2017). Other meta-analyses support these findings and additionally underline the involvement of the anterior cingulate cortex (reviewed in Cieslik *et al.*, 2015; reviewed in Nee *et al.*, 2007). Frontal brain regions reported to be associated with response inhibition have been the right inferior frontal gyrus, anterior insula and dorsolateral PFC (Durston *et al.*, 2003). In addition, parietal brain regions such as the intraparietal cortex and superior parietal cortex were described to be involved in attentional conflicts. Another study demonstrated significant activations in the anterior cingulate and left PFC in three different conflict tasks (Fan *et al.*, 2003). However, they also found varying activation localizations in the different tasks. A study by Zysset *et al.* used the Stroop paradigm to examine interference and found the lateral PFC, intraparietal cortex and occipitotemporal gyrus to be activated in the incongruent versus neutral condition (Zysset *et al.*, 2001). They argued that activation in the anterior cingulate cortex which is often reported in conjunction with incongruence effects does not reflect interference but rather a degree of conflict. All in all, frontoparietal regions as well as the anterior cingulate cortex have reliably been shown to activate during interference tasks.

Nonhuman primate studies investigating the underlying brain regions involved in the processing of oddball effects reported consistently the involvement of the frontal eye field (FEF)

(Schall *et al.*, 1995; Thompson *et al.*, 1996). Furthermore, single-cell recordings revealed that bottom-up processing of salient stimuli was located in the lateral intraparietal area (Arcizet *et al.*, 2011; Constantinidis and Steinmetz, 2005). This is in line with human fMRI experiments which repeatedly demonstrated activation of the frontoparietal network during oddball tasks. They mostly reported activation patterns in the PFC, temporoparietal junction and superior parietal cortex (Bledowski *et al.*, 2004; Huettel *et al.*, 2002; Milham *et al.*, 2003). A study by Bledowski *et al.* (2004) emphasized the common influence of the temporoparietal junction and right PFC on target and distractor processing. They concluded that subsystems are recruited for the modulation of specific tasks associated with memory and attention. Amongst others, Kiehl *et al.* and Braver *et al.* both discussed the engagement of the anterior cingulate cortex in target detection (Braver *et al.*, 2001; Kiehl *et al.*, 2001). A recent combined ERP-fMRI oddball study showed activations in the inferior frontal gyrus, anterior insula, extrastriate occipital and supplementary motor area as well as close to the anterior intraparietal cortex (Ragazzoni *et al.*, 2019). Similar results have been found in earlier ERP-fMRI studies by Rusiniak *et al.* (2013) and Strobel *et al.* (2008) who examined a modified oddball paradigm.

A review from almost twenty years ago used over 250 studies to investigate the functional neuroanatomy of various cognitive tasks, inter alia attention. They found consistent activations in parietal and prefrontal regions during various tasks associated with cognitive control (reviewed in Cabeza and Nyberg, 2000). One specific frontal region that has been reported to be involved in cognitive control processes in different meta-analyses is the inferior frontal junction (reviewed in Derrfuss *et al.*, 2005; reviewed in Neumann *et al.*, 2005). These more general results overlap with brain areas that were reported independently during the incongruence and oddball tasks and therefore strongly indicate a shared underlying attention processing network.

The general model of cognitive control involves bottom-up attention processes that are supposed to derive from the visual cortex and project via the ventral or dorsal pathway to the PFC (reviewed in Corbetta and Shulman, 2002). In contrast to the automatically initiated stimulus-driven processes, top-down attention is voluntary, directing one's attention to a specific feature of the stimulus (see figure 1).

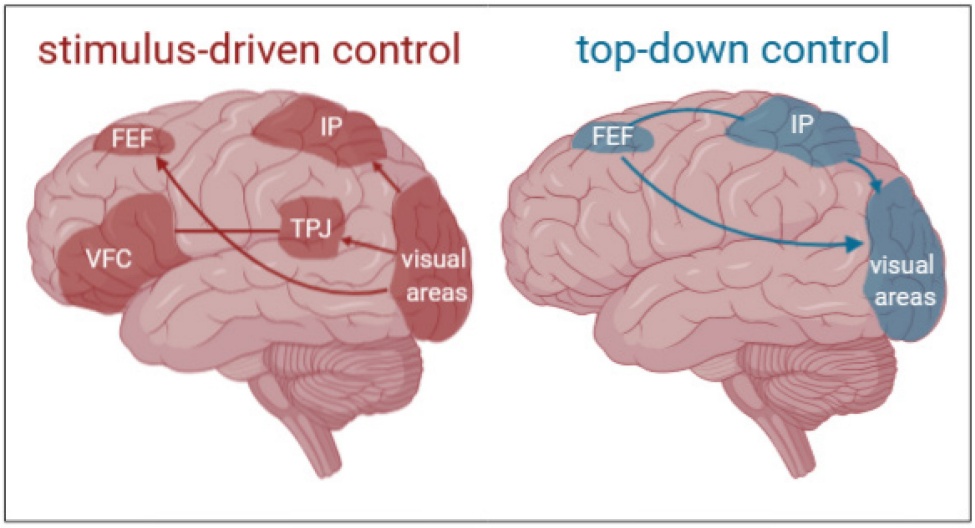


FIGURE 1 Hypothetical model of key projections of the visual attention circuit from Corbetta and Shulman (reviewed in Corbetta and Shulman, 2002). In the bottom-up attention processing, visual areas transmit visual information to the frontal eye field (FEF) and intraparietal cortex (IP) as well as via the temporoparietal junction (TPJ) to the ventral frontal cortex (VFC). The FEF is involved in the top-down integration of experiences, motivation etc. into the processing of visual stimuli, and projects to the IP and visual cortex. Illustration created in BioRender.com.

1.2.2.3 Implications of bipolar disorder and schizophrenia on the incongruence and oddball effect

In general, it is well known that patients with bipolar disorder or schizophrenia suffer from cognitive impairment in many domains of attentional processes (Collier *et al.*, 2014; Mohn and Torgalsboen, 2018; reviewed in Robinson *et al.*, 2006; reviewed in Torres *et al.*, 2007; Wang *et al.*, 2005). Executive control has been extensively researched in both disorders and suggests the idea of gradual dysfunctions. Schizophrenia patients seem to have the greatest deficits, whereas bipolar patients usually show intermediate malfunction (Melcher *et al.*, 2014). In the following, fMRI studies investigating brain regions associated with disturbances of bipolar and schizophrenia patients in cognitive control processes, in particular regarding the incongruence and oddball effect, will be summarized.

Overall, fMRI studies examining inhibitory control effects in bipolar disorder consistently report hypoactivations compared to healthy controls (Altshuler *et al.*, 2005; Blumberg *et al.*, 2003; Kaladjian *et al.*, 2009; Kronhaus *et al.*, 2006; Penfold *et al.*, 2015; Strakowski *et al.*, 2008; Strakowski *et al.*, 2005; Townsend *et al.*, 2012). These reduced activations were found independently of their mood states, i.e. manic, depressed or euthymic, and comprised frontal, temporal and parietal regions, as well as subcortical areas such as the basal ganglia. Hypoactivation in particular in the right inferior frontal gyrus might constitute a trait marker for bipolar disorder (reviewed in Alustiza *et al.*, 2017; reviewed in Hajek *et al.*, 2013). The meta-

analysis by Hajek *et al.* reported thus hyperactivations specific for euthymic bipolar patients compared to healthy controls in cortical brain areas such as the right middle frontal and left superior temporal gyrus (reviewed in Hajek *et al.*, 2013). A more recent meta-analysis found hyperactivation or deficient deactivation in the left precentral, left superior frontal and right superior temporal gyri independent of the patients' mood state (reviewed in Alustiza *et al.*, 2017). In that respect, it is important to note that the meta-analysis included a broad spectrum of cognitive control tasks, including visual emotion regulation tasks etc.

A meta-analysis comparing schizophrenia patients and healthy controls outlined hypoactivations in frontal, cingulate and parietal brain regions as well as the left thalamus linked to cognitive control processes (reviewed in Minzenberg *et al.*, 2009). A more recent meta-analysis identified reduced activations in mainly the same brain structures (reviewed in Alustiza *et al.*, 2017). Overall, deficits in cognitive control of schizophrenia patients seem to reflect in hypoactivations mainly in frontal and cingulate brain areas (Lesh *et al.*, 2013; Wagner *et al.*, 2013). Additionally, the two meta-analyses also reported enhanced activations of schizophrenia patients compared to healthy controls (Alustiza *et al.*, 2017; Minzenberg *et al.*, 2009). However, the hyperactivated brain regions varied strongly between both studies including the rostral pole of the left PFC, left dorsal and ventral premotor areas, dorsal anterior cingulate cortex and subcortical regions (Minzenberg *et al.*, 2009) compared to the right middle occipital gyrus and bilateral precentral gyrus (Alustiza *et al.*, 2017). These results differ from the findings of a study by Wolter *et al.* who described hyperactivations in the intraparietal cortex, left inferior parietal lobule, right middle temporal gyrus (MTG) and left intra-occipital lobe as well as the VTA. They argued that increased activation in the reorienting network and dopaminergic midbrain underline the aberrant salience theory of schizophrenia (Kapur, 2003). It can be concluded that the current literature does not provide a completely homogeneous and clear picture regarding interference dysfunctions of bipolar and schizophrenia patients. This might result from strongly varying tasks (e.g. Stroop, Go/ No-Go, Flanker, etc.) and task presentations (e.g. auditory, visual, multisensory, etc.) as well as in many cases very small sample sizes.

Regarding the oddball effect, Morey *et al.* revealed that schizophrenia patients showed less activation in frontostriatal areas during a visual oddball task in comparison to healthy controls (Morey *et al.*, 2005). Additionally, another study reported hypoactivations in intraparietal areas, the dorsal frontal cortex as well as subcortical regions such as thalamus and basal ganglia during novel stimulus processing (Laurens *et al.*, 2005). Contrary, an oddball paradigm by Gur *et al.* (2007) discovered hyperactivations in occipital-parietal and frontal areas. They only found reduced activation in the visual cortex and right inferior parietal lobule. Another auditory oddball paradigm exhibited hyperactivation in the right temporal cortex, left superior frontal cortex and temporal parietal junction. The authors hypothesized that disorganized thinking of

schizophrenia patients might disturb speech processing leading to a disruptive functional network (Ngan *et al.*, 2003). In addition, Wolter *et al.* (2016) detected significantly enhanced activation of schizophrenia patients in the bilateral intraparietal cortex and VTA. As mentioned before, they associated their results to the aberrant salient network of schizophrenia patients. Taken together, brain activation abnormalities in schizophrenia patients' novelty detection processing differed between the presented studies. Again, the task designs might not be well comparable, and the samples were very heterogeneous. This explanation is supported by a study from Collier *et al.* who found significant differences in the brain activation of schizophrenia patients in the comparison between an auditory and visual oddball paradigm (Collier *et al.*, 2014).

A recent study used a passive auditory oddball paradigm to compare mismatch negativity (MMN) of schizophrenia and bipolar patients with EEG and structural MRI. Both patient groups demonstrated significantly reduced MMN amplitudes in comparison to healthy individuals. In addition, they found an association between MMN decrease and cortical thinning in frontal and temporal regions of the patients' brains (Kim *et al.*, 2019). A combined fMRI-diffusion tensor imaging (DTI) study looked at differences between bipolar and schizophrenia patients during an auditory oddball task. They discovered a similar malfunction of the dorsolateral PFC and thalamus in the two patient groups compared to healthy controls. Furthermore, bipolar and schizophrenia patients could be discriminated on the basis of activation differences in the parahippocampal gyrus and visual cortex (Sui *et al.*, 2011). No further studies examining the oddball effect in bipolar patients with fMRI could be found. Therefore, it is important to provide new insights regarding the manifestation of the oddball effect in bipolar disorder

1.3 Functional magnetic response imaging

In 1946 the basics of magnetic resonance imaging, i.e. nuclear magnetic resonance (NMR) were developed and reported by Bloch (1946) and Purcell *et al.* (1946). Further advancements by Lauterbur (1973) and Mansfield (1977) led eventually to the clinical application of MRI as we know and use it today. Its broad field of application makes MRI a unique and very popular technique. The selection of measuring parameters, i.e. diffusion-, proton density- and relaxation time- weighted images permits the visualization of tissue differences, or contrasts. Every (hydrogen) proton has an intrinsic spin around its own axis caused by thermal energy. When the nuclei are placed in an external magnetic field the spins start precessing around the axis of the field direction. They can either precess parallel or antiparallel to the magnetic field. The parallel formation needs less energy and is therefore called "low energy state", whereas the antiparallel direction is named "high energy state". The longitudinal magnetization is defined by the net magnetization which is parallel to the magnetic field. During the excitation, longitudinal magnetization is converted to transverse magnetization. In the process energy at a resonant frequency is applied to the nuclei, leading to a change from the low to the high

energy state of most nuclei. As soon as the energy is removed from the nuclei, they return to their original low energy state and thereby release the previously absorbed energy. The emitted energy can be detected by the scanner hardware and leads to the recording of MR signals (reception). Changes of these MR signals are called relaxation. There are two types of relaxation: T1 and T2*, describing the recovery of the longitudinal magnetization or decay of the transverse magnetization, respectively (Huettel *et al.*, 2009, pp.57-67).

Less than 20 years later, it became apparent that cerebral blood flow can work as the body's own contrast agent, i.e. blood oxygen level dependency (BOLD). Oxygen is transported via hemoglobin in the blood. The so-called oxygenated hemoglobin contains an iron atom, which binds the oxygen and thus has similar magnetic features as the surrounding brain tissue. Desoxygenated hemoglobin, on the other hand, is paramagnetic. During neural activity local blood flow overcompensates the oxygen consumption with an increase of oxygenated hemoglobin leading to a local increase in T2* relaxation, i.e. an increase of MR signal in T2*-weighted images (Fox and Raichle, 1986; Ogawa *et al.*, 1990). The MR signal peaks four seconds after neuronal activity and is followed by a short phase of deactivation afterwards. Shortly after, an equilibrium between oxygenated and desoxygenated hemoglobin will evolve. This is called the hemodynamic response function (HRF). Under the assumption that neural response and BOLD signals exhibit linear time variant properties, a general linear model can be applied to analyze the activation of each voxel at different time points (Friston *et al.*, 1994). An indicator function with the onsets of the events is convoluted with a canonical HRF resulting in a design matrix, i.e. a predicted HRF for each experimental condition. In the following, statistical tests can be applied to identify significant activation differences between voxels in the respective experimental conditions.

1.4 Aims of the present thesis

As presented in previous chapters, a lot of research has been conducted to better understand the underlying pathophysiologies of bipolar disorder and schizophrenia. Even though many characteristics and properties regarding behavioral, structural and functional abnormalities have been found and described in the respective disorders over the years, there are still remaining pieces to the puzzle. This doctoral thesis aimed to tackle some of these open questions and in particular investigate the underlying neural correlates of attentional processes and reward circuits in bipolar disorder and schizophrenia.

The thesis was divided in two studies throughout the methods, results and discussion section, as they focused on two different research questions. The first study concentrated on diagnosis-specific brain activation differences in attention processing, whereas the second study was interested in the development of reward-related neuroimaging biomarkers for treatment

response prediction. For a better understanding, it is recommended to read the corresponding subchapters of each study separately.

Study A was conducted to explore the neural correlates of attentional processes in bipolar disorder and schizophrenia. As reported in previous chapters, cognitive dysfunctions in particular during cognitive control processes are crucial symptoms of both psychiatric disorders. A better understanding of alterations in their functional responses during inhibitory control and novelty processing might improve the overall comprehension of pathophysiological processes in bipolar disorder and schizophrenia. On the basis of a previous study that reported hyperactivations of schizophrenia patients in the intraparietal cortex during the same combined oddball-incongruence paradigm, it was tried to replicate those findings in a larger schizophrenia sample and additionally investigate potential equally disturbed effects in bipolar disorder. The aim was to compare cortical activations of the individual diagnoses and healthy controls using fMRI. It was hypothesized that previously found frontoparietal activations of healthy individuals as well as hyperactivations in the intraparietal cortex of schizophrenia patients might constitute differences that provide deeper insights into the pathophysiology of the two disorders. Furthermore, performances of the patients and healthy controls were investigated. It was hypothesized that the attentional capacity might be impaired in the patients' groups and that schizophrenia patients might have greater difficulties than bipolar disorder patients.

Study B aimed to further investigate whether differential treatment response might also identify different pathomechanisms. The current psychopharmacological treatment of schizophrenia and bipolar disorder is mostly decided on the basis of clinical appearance and experience of the psychiatrist but does not include neurobiological features or standardized measures. This is owed to the fact that neuroimaging biomarkers found so far in bipolar disorder or schizophrenia, primarily divided between diagnosis groups. Clinicians, however, treat individuals and not groups of patients. To avoid mistakes and give patients the best possible treatment a priori, it would thus be of great interest to identify independent markers that could predict treatment response. SVM methods offer a solution to classify patients on an individual level and additionally are sensitive to small effects in brain activation. Furthermore, the discovery of biomarkers would potentially open up the development of new therapeutics that might target individual symptoms of the patients more specifically. Taking the advantages of treatment prediction into account, study B concentrated on detecting functional differences in the brain activation of responders and non-responders of bipolar and schizophrenia patients within their respective treatment groups, i.e. atypical or typical antipsychotics or aripiprazole. The main goal was to identify specific differences of the individual treatment arms, i.e. subgroup-specific hyperactivations or deactivations during the reward-related desire-reason-dilemma fMRI paradigm. Multiple studies reported disturbed reward processing in bipolar and

schizophrenia patients so far. The underlying alterations of the dopaminergic transmission system are the target of all antipsychotic medication. Therefore, a reward-related paradigm offers a great approach to look for prognostic biomarkers for treatment response. It was hypothesized that regions which might present activation differences would possibly be associated with reward-associated brain structures, such as the ventral striatum or VTA. On the basis of previous studies examining reward processing of bipolar and schizophrenia patients, it was thought that the heterogeneity within both disorders might affect activation in the mesolimbic or prefrontal brain areas so that subgroups demonstrate differential response to antipsychotic treatment. Parameter estimates of brain regions that showed reward-related activation differences between responders and non-responders were applied to SVM algorithms in the following to explore possible predictors for treatment success of the individual neuroleptic treatment. Overall, the aim was to identify (de)activated brain regions that might potentially be able to predict the individual treatment response to specific subgroups of antipsychotic medication of the patients. This is the first time SVM algorithms are applied to neuroimaging data related to reward processing to predict treatment response of specific neuroleptic subclasses.

Taken together, results of the current literature on cognitive control and reward processes of schizophrenia and bipolar disorder urge for a better comprehension of both psychiatric diseases. Understanding the attentional and reward-related pathways and networks could help to develop multimodal biomarkers that might ultimately benefit treating patients more effectively and responsibly.

2 METHODS

2.1 Subjects

This thesis comprises two different studies which differ in the implemented paradigms and sample composition. Patients of both studies and healthy controls were enrolled by Dr. Sarah Trost and Aleksandra Petrovic from the Department of Psychiatry and Psychotherapy, University Medical Center Göttingen. After receiving complete information about the study and being able to ask questions, subjects had to sign a written informed consent. The studies were approved by the Göttingen Ethics Committee and underlay the latest version of the Declaration of Helsinki. As compensation for their participation, all probands received an expense allowance. To avoid undesirable effects of uncontrollable factors, the following exclusion criteria were defined: lifetime diagnoses of substance dependence, substance abuse during the last month, cannabis abuse within the last two weeks, mental retardation, severe somatic diseases, claustrophobia, achondroplasia and neurological diseases.

2.1.1 *Study A*: Executive network dysfunction of bipolar and schizophrenia patients

In study A, 90 subjects were recruited for a combined oddball-incongruence fMRI paradigm. Twenty of the participating patients were diagnosed with bipolar disorder and thirty patients with schizophrenia according to ICD-10 classification standards. In addition, forty healthy controls were recruited and matched with the patients' demographics. Gender, school education, handedness and age of the participants as well as the scores from psychopathological scales such as Montgomery-Asberg Depression Scale (MADRS), Young Mania Rating Scale (YMRS), Positive and Negative Symptom Scale (PANSS) and Clinical Global Impression Scale (CGI) and medication at the time of the investigation can be found in table 1.

TABLE 1 Overview of the demographic and clinical data of bipolar and schizophrenia patients as well as healthy controls included in the combined oddball-incongruence study.

		bipolar disorder		schizophrenia		healthy controls	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Demographic data							
	total	20	-	30	-	40	-
gender	female	12	-	4	-	15	-
	male	8	-	26	-	25	-
school education	< 9 years	2	-	3	-	1	-
	10 years	5	-	6	-	3	-
	> 13 years	13	-	21	-	36	-
handedness	right	20	-	26	-	37	-
	left	0	-	4	-	3	-
age	years	-	39.30 (12.54)	-	29.83 (7.79)	-	33.10 (9.10)
Clinical data							
	age of onset	-	26.25 (10.39)	-	23.29 (5.08)	-	-
	MADRS	-	8.45 (7.56)	-	9.37 (7.03)	-	-
	CGI	-	3.55 (1.23)	-	3.9 (1.12)	-	-
	YMRS	-	3.85 (4.55)	-	-	-	-
	PANSS	-	-	-	49.73 (12.15)	-	-
Medication							
	Atypical antipsychotics	14	-	27	-	-	-
	Typical antipsychotics	7	-	4	-	-	-
	Antidepressants	11	-	11	-	-	-
	Mood stabilizers	4	-	0	-	-	-
	Anticonvulsants	15	-	0	-	-	-

Abbreviations: SD= standard deviation, MADRS= Montgomery-Asberg Depression Scale, CGI: Clinical Global Impression Scale, YMRS= Young Mania Rating Scale, PANSS= Positive and Negative Symptom Scale

2.1.2 *Study B*: Treatment response prediction in bipolar and schizophrenia patients

In study B, 38 patients were recruited from the Department of Psychiatry and Psychotherapy, University Medical Center Göttingen. Twenty-eight of these patients met the criteria of schizophrenia and ten patients of bipolar disorder according to ICD-10 classification standards. Table 2 contains the demographic and clinical data of the patients.

The patients' medical records were retrospectively examined for successful and failed psychopharmacological treatment. Based on this information, patients were divided into groups of responders and non-responders to either atypical, typical antipsychotics or aripiprazole. The classification of those patients was independently of their medication at the time point of their participation in this study and can be viewed in table 2.

TABLE 2 Overview of demographic and clinical data of the patients and healthy individuals from the treatment response prediction study.

		Atypical antipsychotic				Typical antipsychotic				Aripiprazole			
		responders		non-responders		responders		non-responders		responders		non-responders	
		N	mean	N	mean	N	mean	N	mean	N	mean	N	mean
total		15	-	7	-	2	-	4	-	7	-	3	-
gender	female	0	-	4	-	0	-	1	-	5	-	1	-
	male	15	-	3	-	2	-	3	-	2	-	2	-
school education	< 9 years	2	-	1	-	1	-	0	-	0	-	0	-
	10 years	4	-	2	-	1	-	0	-	4	-	0	-
	> 13 years	9	-	4	-	0	-	4	-	3	-	3	-
handedness	right	12	-	6	-	2	-	4	-	6	-	2	-
	left	3	-	1	-	0	-	0	-	1	-	1	-
age	years	-	35.33 (SD: 12.20)	-	38.14 (SD: 11.96)	-	26.50	-	31.75 (SD: 8.38)	-	30.43 (SD: 9.64)	-	26.00 (SD: 4.58)
Clinical data	age of onset	-	27.93 (SD: 13.31)	-	30.86 (SD: 8.03)	-	17	-	21.75 (SD: 5.91)	-	21.29 (SD: 4.72)	-	21.00 (SD: 4.36)
	MADRS	-	7.67 (SD: 6.42)	-	7.71 (SD: 8.44)	-	4.5	-	11.75 (SD: 8.30)	-	9.17 (SD: 6.05)	-	8.00 (SD: 7.55)
	CGI	-	3.73 (SD: 1.28)	-	3.29 (SD: 0.76)	-	3	-	4.00 (SD: 1.63)	-	4.00 (SD: 0.89)	-	4.00 (SD: 1.00)
	YMRS	-	12	-	4.33	-	-	-	2	-	-	-	-
	PANSS	-	47.38 (SD: 14.89)	-	43.00 (SD: 7.35)	-	38.5	-	54.67 (SD: 16.44)	-	-	-	-
Medication at time of investigation	Atypical antipsychotics	13/15	-	6/7	-	2/2	-	3/4	-	5/7	-	3/3	-
	Typical antipsychotics	0/15	-	1/7	-	2/2	-	0/4	-	2/7	-	1/3	-
	Aripiprazole	3/15	-	1/7	-	0/2	-	1/4	-	4/7	-	1/3	-
	Antidepressants	5/15	-	3/7	-	1/2	-	2/4	-	2/7	-	0/3	-
	Mood stabilizer	2/15	-	1/7	-	0/2	-	1/4	-	1/7	-	0/3	-
	Anticonvulsants	2/15	-	1/7	-	0/2	-	1/4	-	3/7	-	0/3	-
	Benzodiazepines	1/15	-	0/7	-	0/2	-	0/4	-	0/7	-	0/3	-

Abbreviations: SD= standard deviation, MADRS= Montgomery-Asberg Depression Scale, CGI: Clinical Global Impression Scale, YMRS= Young Mania Rating Scale, PANSS= Positive and Negative Symptom Scale

2.2 Experimental tasks

2.2.1 *Study A*: Combined oddball-incongruence paradigm

In study A subjects underwent fMRI while performing a combined oddball-incongruence paradigm (Gruber *et al.*, 2009). At the beginning, all subjects were verbally instructed outside the scanner. They were asked to classify geometric objects according to either color or shape as quickly as possible. In a pseudo-random trial-by-trial manner, task cues indicated whether the color or shape should be classified.

The task cue was presented for 500ms, followed by a short 250ms cue-stimulus interval and a 750ms presentation of the relevant stimulus. Within 1000ms, subjects had to respond to the stimulus, i.e. 750ms stimulus display + 250ms stimulus-cue interval. In the shape condition, subjects had to press the left button with their index finger for the slim object and the right button with their middle finger for the broad object. In the color condition, participants had to push the left button for the red object and the right button for the blue object. All participants were instructed to respond with their right hand.

Since all objects consisted of two dimensions, subjects had to differ between relevant and irrelevant dimensions during the task. They had to respond to the relevant dimension, i.e. the condition indicated by the task cue, and ignore the irrelevant dimension. These two dimensions lead to four conditions: color congruent, color incongruent, shape congruent and shape incongruent. In the congruent conditions, response to the stimulus matched the same button, i.e. the red color and slim object or the blue color and broad object. During the incongruent conditions, the responses to the stimulus were mapped on two different buttons, i.e. the red color and broad object or the blue color and slim object. In addition, a fifth condition, the so-called “oddball” was integrated. It was rarely displayed and constituted of a white stimulus (either slim or broad), which should always be allocated regarding its shape. For a visual representation see figure 2.

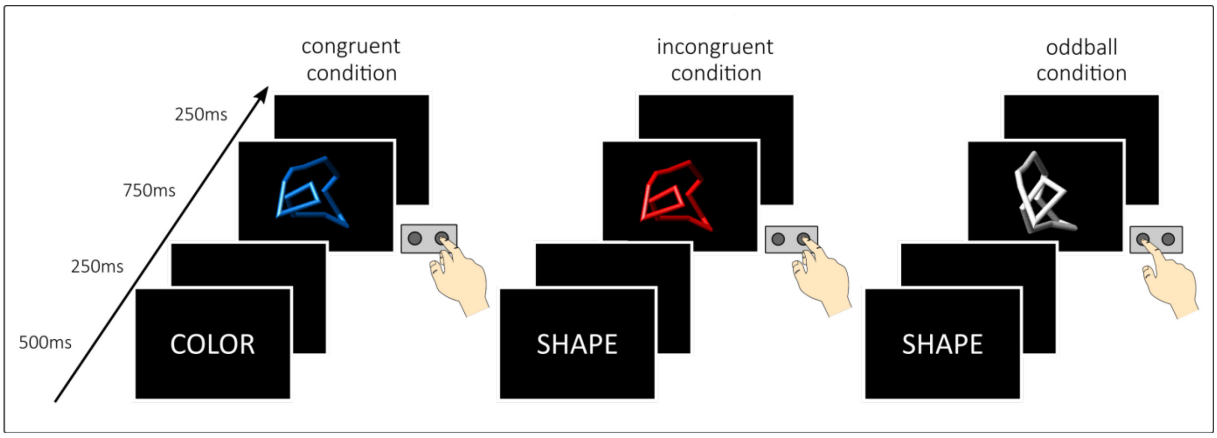


FIGURE 2 Graphical presentation of the combined oddball-incongruence paradigm. Each trial contained a relevant and an irrelevant dimension. During the color condition, the color of the object (red or blue) represented the relevant and its shape the irrelevant dimension. During the shape condition, the shape of the object (slim or broad) depicted the relevant dimension, whereas the color was irrelevant. During the oddball trials participants had to ignore the rare color of the object, i.e. white, and respond only to its shape. Responses "red" and "slim" were mapped on the left button and responses "blue" and "broad" on the right button. Illustration created with Inkscape 0.92.3.

2.2.2 *Study B*: Desire-reason-dilemma paradigm

In study B the patients underwent the desire-reason-dilemma (DRD) paradigm (Diekhof and Gruber, 2010). At first, the patients were verbally instructed and performed a conditioning task. The stimuli were presented on a screen outside the MRI scanner. In this task, squares in eight different colors were alternately presented on a neutral grey background on the monitor. Subjects were instructed to identify the rewarded and punished colors by trial-and-error via free button press of their right hand. The left button was allocated to collecting a certain color, whereas the right button was allocated to rejecting the color. The software was programmed to display the stimulus on the screen until one of the buttons was pressed. Following the response, participants immediately obtained feedback whether the selected color was associated with a reward (bonus of +10 points, i.e. red and green) or a punishment (-10 points; purple and brown) or if the stimulus color was neutral (0 points; yellow, pink, turquoise, blue). Green and red remained the two rewarded colors throughout the rest of the experiment.

In the second part, patients underwent the actual DRD paradigm. This task was trained first outside the scanner until the patients collected at least 500 points, but not more than three times. The task consisted of two different round types- the bonus (or 'desire context') and the target (or 'reason context') round alternating after two blocks. In both rounds, subjects had to pursue a superordinate long-term goal, i.e. correctly responding to stimuli to collect 50 points. Each block consisted of four or eight trials. At the beginning of the block, two target colors were presented as cues, which had to be accepted throughout the following block. During the target

round, indicated as 'T' (in the German version the letter 'Z' was presented for the German word of target, i.e. 'Ziel'), patients had to collect all target colors and reject all non-target and the bonus colors to receive 50 points at the end of the block. During the bonus round, indicated as 'B', patients were asked to collect target colors and the previously learned bonuses, i.e. rewarded colors. Each collected bonus color added 10 points to the total outcome of each block. Rejecting a bonus cue in the desire condition did not terminate the block. It follows from this design that the subjects had to actively suppress the impulse to accept the bonus colors during the reason context in order to achieve the superordinate long-term goal ('desire-reason dilemma'). After completing a block, they received a total feedback showing the complete amount of points they had collected during the respective block. If the participants reacted too slowly or pressed the wrong button, the block was aborted and an immediate feedback on the screen ("goal not achieved") was shown.

All participants completed 80 blocks over the course of two fMRI runs. Both contexts were equally often presented. The target cue presentation lasted for 1'500ms. Afterwards, each stimulus target was presented for 900ms, leading to a maximum reaction time of 900ms per stimuli. For a visual representation of the paradigm see figure 3.

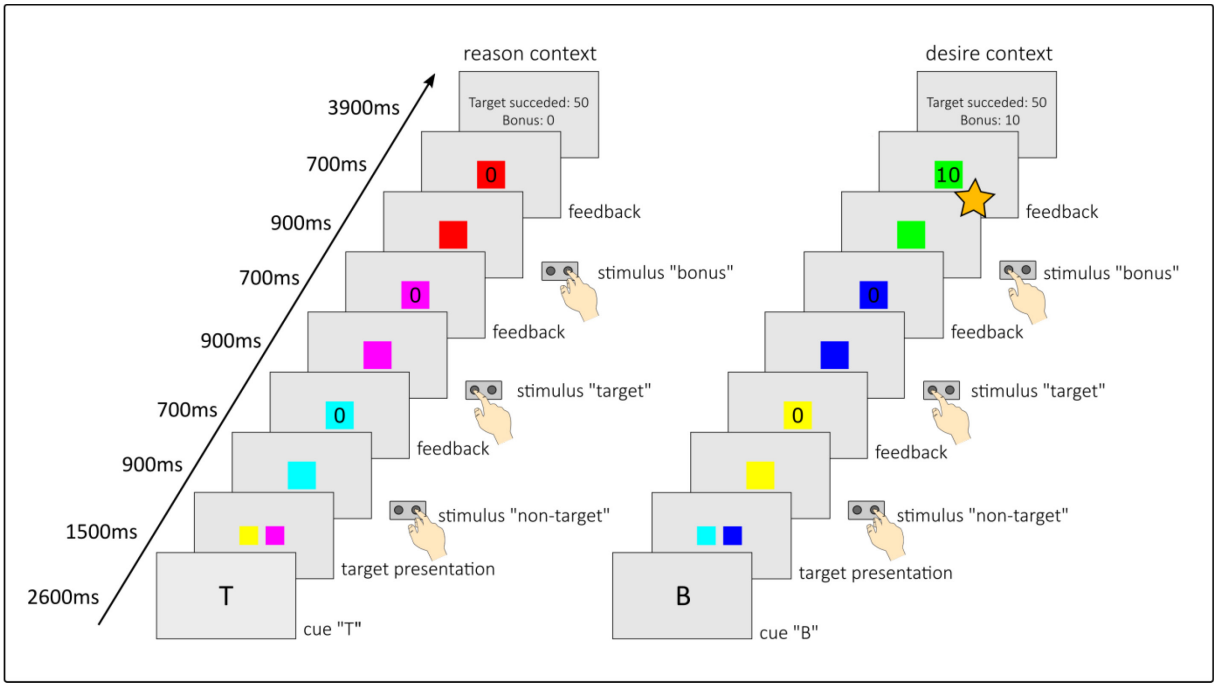


FIGURE 3 Graphical presentation of the desire-reason dilemma (DRD) paradigm. The DRD task consists of two conditions: the desire and reason context. In both contexts the participants were asked to remember two target colors at the beginning of each round, which had to be accepted in the following round. Accepting a stimulus was mapped on the left button, whereas rejecting a stimulus was mapped on the right button. In the reason context, stimuli that had previously been associated with reward (red and green) had to be rejected. During the desire context, bonus and target colors had to be accepted

and all remaining stimuli (non-targets) had to be rejected. A cue at the beginning of each block indicated the upcoming condition, i.e. "T" for the reason context and "B" for the desire context. Successfully finishing the reason context added 50 points to the subjects' points account. During the desire context for each accepted bonus 10 points were additionally added to the points account. Participants received immediate feedback after they pressed their response during the stimulus presentation. The more points the subject collected, the more allowance they received for the experiment. The orange star indicates the bonus condition in the desire context, which was used for the fMRI analysis. Illustration created with Inkscape 0.92.3.

2.3 fMRI data acquisition and analyses

The experiments of both studies took place in a 3 T MRI scanner (Magnetom TrioTim syngo; Siemens Healthcare, Erlangen, Germany) equipped with an eight-channel head coil. For the T1-weighted anatomical dataset one millimeter isotropic resolution was used. In the fMRI experiment, 33 slices in study A and 31 axial slices in study B parallel to the anterior-posterior commissure were obtained in ascending acquisition order with a slice thickness of 3mm and a gap of 20%. A T2*-sensitive echoplanar imaging (EPI) sequence was applied (study A: TR 2000ms, echo time 30ms, flipangle 70, field-of-view 192mm; study B: TR 1900ms, echo time 30ms, flipangle 70, field-of-view 192mm). In study A 251 image volumes were recorded during the experiment. In study B, each run contained 185 images, summing up to 370 image volumes over two functional runs. Both paradigms were presented via MR-compatible liquid crystal display (LCD) goggles. Responses were conducted via a button box and recorded using the Presentation Software (Neurobehavioral Systems, Albany, USA). Generation of stimuli and triggering of visual stimulation was achieved using the Presentation Software.

The analysis of the fMRI data was carried out using the software Statistical Parametric Mapping (SPM) 8 (Wellcome Trust Centre for Neuroimaging, London, UK). MATLAB served as the environment for implementing the toolbox SPM8. Preprocessing steps comprised realignment and unwarping, correction for slice time acquisition difference (reference slice 1), co-registration with the mean EPI image, normalization to Montreal Neurological Institute (MNI) space and spatial smoothing with a Gaussian kernel of 9mm full width at half maximum (FWHM). Head movement of more than 3 mm led to the exclusion of subjects from the analysis. First level analyses were based on a general linear model (GLM) with five regressors (color congruent, color incongruent, shape congruent, shape incongruent, oddball) in study A and six regressors (target, non-target and reward stimuli for both conditions, i.e. DC and RC) and five independent regressors (block and target cues as well as feedback cues in successful and failed blocks) in study B. Considering the delay of the BOLD response, the temporal onsets of stimulus presentation were convolved with a canonical hemodynamic response function. In both studies only correctly performed rounds were included in the analysis.

Linear t-contrasts were defined for the purpose of examining the effects of the different experimental conditions. In study A the single subject contrast images consisted of the oddball and incongruence stimulus versus implicit baseline, respectively. In study B activation of the conditioned reward stimuli in the desire context (see orange star in Figure 3) was compared to implicit baseline.

The second level analyses were carried out with SPM 12 (Wellcome Trust Centre for Neuroimaging, London, UK) to compare group effects. In study A, it consisted of the first-level "oddball" and "incongruence" contrast images, i.e. oddball and incongruence conditions versus implicit baseline. To assess differences between the patient groups and healthy controls the one-way ANOVA was applied. Statistically significant effects were determined at a level of $p<0.05$ family-wise error (FWE) corrected for the whole brain. Small volume corrections were applied for regions with *a priori* hypotheses derived from the literature. The significance threshold for the small volume correction was $p<0.05$ FWE-corrected for small-volume (Worsley *et al.*, 1996). For the small volume correction, the MNI coordinate of the left intraparietal cortex [-36 -60 40] taken from Gruber *et al.* (2009) was used. Furthermore, new findings were reported with a statistical threshold of $p < 0.005$, uncorrected.

In study B, the second level analysis comprised single subject contrast images of the response to the bonus stimuli in the desire context. A one-way ANOVA was used to determine differences between responders versus non-responders in their corresponding psychopharmacological treatment group. The findings were reported with a statistical threshold of $p < 0.001$, uncorrected.

2.4 Behavioral data analyses

For behavioral data analyses the software package SPSS (IBM SPSS statistics 25) was used. Performance was defined as the success rates of the participants. Whether performance and mean reaction times data of the patients' correct trials were normally distributed was checked with the Shapiro-Wilk test.

2.4.1 *Study A*

Behavioral data of study A comprised the oddball, incongruence and congruence conditions. To guarantee comparability, only incongruent and congruent trials of the shape task were considered for the analyses. Table 3 depicts the reaction times and performance of the bipolar, schizophrenia and healthy control group.

The Kruskal-Wallis test was used to identify between-subject differences in performance of bipolar, schizophrenia and healthy individuals. Additionally, the Friedman's ANOVA was applied

to compare differences of performances in the congruent, incongruent and oddball condition within the respective groups. Wilcoxon tests were conducted to follow up the findings.

A one-way ANOVA was used to analyze between-subject effects of mean reaction times of the bipolar, schizophrenia and healthy control groups. Furthermore, individual one-way ANOVAs were applied to identify differences between mean reaction times of the three conditions within the respective diagnostic groups. In addition, Gabriel post hoc t-tests were conducted to assess group differences in the behavioral data.

2.4.2 *Study B*

In study B, the "correctly accepted bonus stimuli in the desire context" was analyzed according to the treatment response division as can be seen in table 4. Patients were organized in atypical antipsychotic responders (AA R), atypical antipsychotic non-responders (AA NR), typical antipsychotic responders (TA R), typical antipsychotic non-responders (TA NR), aripiprazole responders (AP R) and aripiprazole non-responders (AP NR). Success rates and mean reaction times were analyzed using separate one-way ANOVAs with the treatment response groups as between-subject factor. In addition, Gabriel post hoc t-tests were conducted to assess group differences in the behavioral data.

2.5 Support vector machine analyses

Multivariate pattern analyses were performed by Dr. Evgeny Gladilin to further validate the previous univariate analyses of study B. Therefore, a binary SVM classifier separated responders from non-responders. Data analysis was performed with MATLAB 2015a and by using a selection of *a priori* regions of interest (ROIs). 3D whole brain parameter estimates obtained from the bonus trials of the desire context were imported as nifti files using the nii MATLAB toolbox. The coordinates of target regions initially given in mm were transformed into voxel coordinates under consideration of the fMRI voxel resolution and image location. The parameter estimates for the predefined coordinates were subsequently extracted and saved in a 3 x nVoxels matrix for further analysis. Cohort classification tests were performed with raw as well as normalized parameter estimates of the desire versus implicit baseline contrast. Normalization was introduced to account for (1) individual differences in the whole-brain activity (normalization step 1):

$$m(i) = b(i) - \frac{1}{N}\sum_{i=1..N} b(i)$$

Formula 1 Normalization of the parameter estimates step 1.

where *b(i)* is the beta-score value in the *i*-th fMRI voxel, as well as (2) to determine the contrast between local brain activity of a pathological subject with respect to the reference cohort (normalization step 2):

$$z(i) = \frac{m(i) - a(i)}{s(i)}$$

Formula 2 Normalization of the parameter estimates step 2.

where *a(i)* denotes the average beta-score in the *i*-the voxel crossover the reference cohort and *s(i)* the standard deviation of *m(i)* in the reference cohort.

The leave-one-out analysis was conducted to test the classifier. The principle scheme of the leave-one-out test is as follows:

1. Exclude the i-th subject from cohort
2. Train binary SVM classification model for all remaining subjects
3. Predict the group label of the i-the subject (i.e. pathological or healthy group) using the model trained with remaining subjects
4. Iterate over all subjects (i=1..N)
5. Calculate the confusion matrix and its derivatives (accuracy, sensitivity, specificity) from the real group labels and the results of their model prediction.

A confusion matrix (also known as error matrix) is a table used for visualization of the performance of categorical classifiers in terms of correctly or incorrectly estimated subject categories, see an overview in figure 4. Typically, the following performance measures are derived from the confusion matrix: accuracy, sensitivity, specificity. Accuracy is defined as the ratio between the correctly predicted samples divided by all samples. Correctly classified positive samples divided by the sum of correctly classified positive and wrongly negative classified samples are specified as sensitivity. The specificity is defined as correctly predicted negative samples divided by the sum of correctly negative classified samples and correctly predicted negative samples. Additionally, balanced accuracy was calculated to estimate the generalization performance of the classifier (Brodersen *et al.*, 2010). The balanced accuracy is defined as the arithmetic mean between specificity and sensitivity verifying the balance of the dataset. In case of an imbalanced dataset the ordinary accuracy would be oversized whereas the balanced accuracy would fall to 50%. Brodersen *et al.* (2011) stated that in case of imbalanced datasets, balanced accuracy is able to eliminate bias from approximations of generalizability.

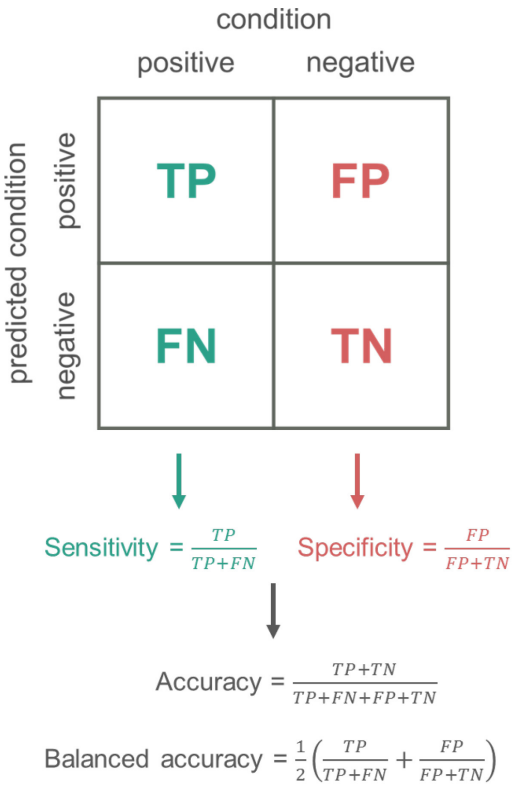


FIGURE 4 Overview of a standard diffusion matrix.

Abbreviations: TP= number of true positives; FN= number of false negatives; TN= number of true negatives; FP= number of false positives

3 RESULTS

3.1 Behavioral Results

3.1.1 *Study A*: Comparison of performance and mean reaction times between patients and healthy individuals in the combined oddball-incongruence paradigm

First, it was examined if performance and mean reaction times within the respective diagnoses (bipolar disorder: BD, schizophrenia: SCZ) and healthy control (HC) groups were normally distributed by applying a Shapiro-Wilk test. Performance deviated in each condition and diagnosis group significantly from normal (oddball: D_{BD} (20)= 0.799, p=0.001; D_{SCZ} (30)= 0.918, p=0.024; D_{HC} (40)= 0.628, p<0.001; incongruence: D_{BD} (20)= 0.882, p=0.019; D_{SCZ} (30)= 0.896, p= 0.007; D_{HC} (40)= 0.833, p<0.001; congruence: D_{BD} (20)= 0.868, p=0.011; D_{SCZ} (30)= 0.855, p= 0.001; D_{HC} (40)= 0.760, p<0.001). Therefore, non-parametric tests were applied for the following group analyses. Mean reaction times in the oddball condition did not show deviations from normal in the three groups (D_{BD}(20)= 0.978, p= 0.905; D_{SCZ}(30)= 0.967, p= 0.469; D_{HC} (40)= 0.976, p= 0.531). In the incongruence condition, mean reaction times were normally distributed in bipolar disorder and healthy controls (D_{BD}(20)= 0.968, p= 0.705; D_{HC} (40)= 0.958, p= 0.141), but not schizophrenia (D_{SCZ}(30)= 0.929, p= 0.047). In the congruence condition, mean reaction times did not deviate significantly from normal in the patients groups, but were not normally distributed in the control group (D_{BD}(20)= 0.982, p= 0.959; D_{SCZ}(30)= 0.958, p= 0.283; D_{HC} (40)= 0.895, p= 0.001). Table 3 shows performance rates and mean reaction times of the patient groups and healthy controls.

TABLE 3 Overview of the task performance and reaction times of the correct responses of bipolar and schizophrenia patients as well as healthy controls

	Bipolar disorder		Schizophrenia		Healthy controls	
	mean	SD	mean	SD	mean	SD
Performance (%)						
congruence	90.96	8.44	92.05	7.21	96.01	5.03
oddball	90.67	7.99	89.00	9.15	94.92	8.34
incongruence	86.53	10.64	84.91	9.31	91.40	9.17
Reaction time (ms)						
congruence	510.44	90.38	518.60	76.14	461.38	63.52
oddball	533.63	100.86	545.34	76.39	477.37	69.55
incongruence	526.12	93.37	530.91	77.35	470.35	62.02

Abbreviations: ms = milliseconds; SD= standard deviation

The Kruskal-Wallis test revealed that performance was significantly affected by diagnosis in the three conditions (oddball: H(2)=14.841, p=0.001; incongruence H(2)=12.247, p=0.002; congruence H(2)=10.800, p=0.005). Follow-up analyses revealed that in the oddball condition the schizophrenia and bipolar disorder group demonstrated a similar amount of correct trials (p=1.00, r=0.047). However, they presented worse performance compared to the healthy

controls (SCZ vs HC: p=0.001, r=-0.422; BD vs HC: p=0.017, r=-0.356). In the incongruent condition, the comparison between bipolar disorder and healthy control groups (p=0.138, r=-0.258) as well as bipolar disorder and schizophrenia patients (p=1.000, r=0.136) demonstrated similar performances, whereas schizophrenia patients performed worse than healthy controls (p=0.002, r=-0.408). There was no significant difference between the schizophrenia and bipolar group in the congruent condition (p=1.000, r=-0.026). However, both patient groups performed significantly worse than healthy controls (SCZ vs. HC: p=0.016, r=-0,331; BD vs HC: p=0.024, r=-0.343).

In the next step, the Friedman's ANOVA was applied to analyze differences between the different task conditions within the respective diagnoses groups (BD: $\chi^2(2)= 7.772$, p= 0.021; SCZ: $\chi^2(2)= 18.200$, $p < 0.001$; HC: $\chi^2(2)= 12.859$, p = 0.002). Follow-up analysis revealed significant differences between the incongruence and congruence condition in the bipolar disorder group (T= 2.763, r= 0.437). Schizophrenia patients performed worse in the incongruence than congruence condition (T= 4.248, r= 0.548). The incongruence versus oddball (T= -3.440, r= -0.385) as well as the incongruence versus congruence (T= 3.548, r= 0.400) conditions showed significant performance differences in the healthy control group. Figure 5 depicts the results of the performance analyses.

In the following, a one-way ANOVA was applied to investigate potential differences between bipolar disorder and schizophrenia as well as healthy controls in their respective mean reaction times. Mean reaction times were significantly affected by diagnosis in each condition (oddball: $F(2, 89)=7.155$, $p=0.001$, r=0.376, $\omega^2=0.120$; incongruence: $F(2, 89)=6.681$, $p=0.002$, r=0.369, $\omega^2=0.115$; congruence: $F(2, 89)=5.928$, $p=0.004$, r=0.346, $\omega^2=0.099$). Pairwise comparisons with adjusted *p*-values showed that there were no significant differences in the response speed between bipolar and schizophrenia patients in the oddball, incongruence and congruence condition. However, the schizophrenia and bipolar disorder groups reacted significantly slower than the healthy controls in all three task conditions (oddball: HC vs BD: $p=0.031$, HC vs SCZ: $p=0.002$; incongruence: HC vs BD: $p=0.021$, HC vs SCZ: $p=0.003$; congruence: HC vs BD: $p=0.048$, HC vs SCZ: $p=0.006$).

Lastly, mean reaction times were compared between the conditions within each participant group by applying a repeated-measure ANOVA. Mauchly's test indicated that the assumption of sphericity were not violated in the three groups (BD: $\chi^2(2)=0.119$, $p= 0.942$; SCZ: $\chi^2(2)=0.647$, $p=0.724$; HC: $\chi^2(2)=3.081$, $p=0.214$). The mean reaction time of the three diagnoses groups varied significantly between the task conditions (BD: $F(1.940, 172.645)=27.379$, $p=0.000$; SCZ: $F(1.955, 56{,}705)=11.030$, $p=0.000$; HC: $F(1.856, 72.365)=7.774$, $p=0.001$). Follow-up analyses

detected that the reaction times of the oddball and congruence (p=0.001) and incongruence and congruence (p=0.017) differed significantly within the bipolar disorder group. Bipolar disorder patients responded fastest to the congruent compared to the incongruent and oddball stimuli. Mean reaction times of the oddball condition in schizophrenia were significantly different from the incongruence (p=0.033) and congruence (p=0.000) conditions. They took longer to react to the oddball stimulus than to the congruent or incongruent stimulus. Pairwise comparison revealed a significant difference between the congruence versus oddball condition (p=0.002) in the healthy individuals' group. Their response to oddball stimuli took longer than to the congruent stimuli. Figure 6 visualizes the results of the mean reaction time analyses.

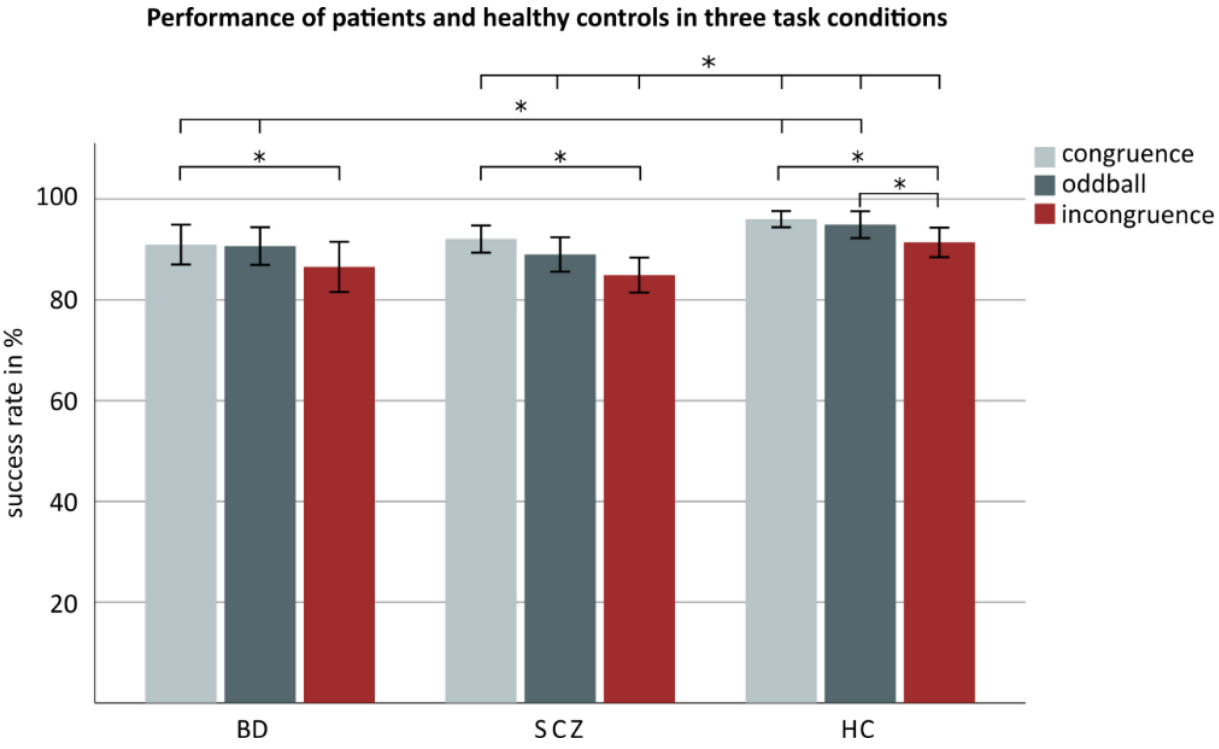


FIGURE 5 Correct trials in percentage of patients and healthy controls during the oddball and incongruence condition. Schizophrenia patients demonstrated significantly worse performance in all three conditions compared to healthy controls. Bipolar patients performed worse in the oddball and congruence conditions compared to healthy individuals. All three groups showed decreased success rates in the incongruence compared to the congruence condition. Healthy controls additionally performed worse in the incongruence compared to the oddball condition. * p<0.05

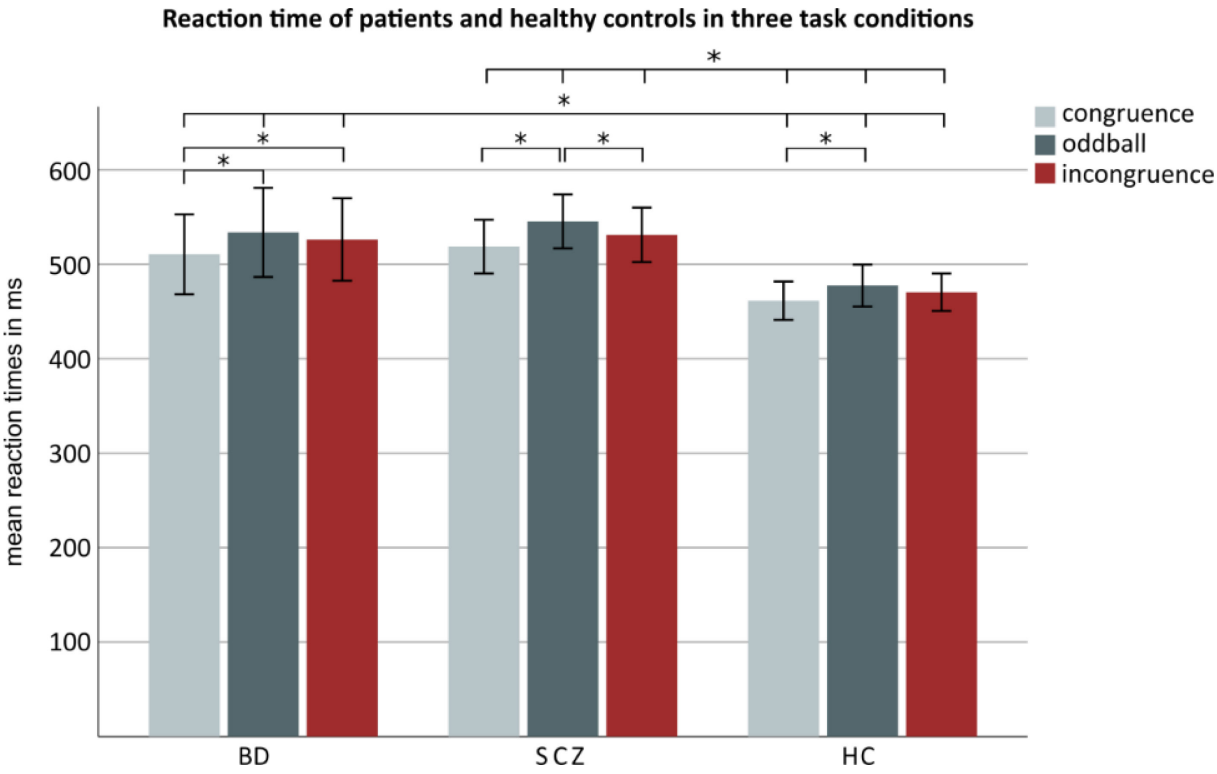


FIGURE 6 Mean reaction times in milliseconds (ms) of patients and healthy controls during the oddball and incongruence condition. Healthy controls responded in all three conditions significantly faster than the patient groups. Bipolar patients showed the fastest mean reaction time in the congruent condition. Within the schizophrenia group the reaction times varied significantly between the congruent and oddball as well as incongruent and oddball condition. Healthy controls demonstrated significantly faster reaction times in the congruent compared to the oddball condition.

3.1.2 *Study B*: Comparison of performance and reaction times between six treatment response groups in the DRD paradigm

In a first step, the Shapiro-Wilk test was used to test if performance data in the "correctly accepted bonus stimuli in the desire context" of the six groups (AA R= atypical antipsychotic responders; AA NR= atypical antipsychotic non-responders; TA R= typical antipsychotic responders; TA NR= typical antipsychotic non-responders; AP R= aripiprazole responders; AP NR= aripiprazole non-responders) was normally distributed. The success rate in this context was normally distributed in all groups (AA R: $D(15)=0.936$, $p=0.337$; AA NR: $D(7)=0.880$, $p=0.227$; TA NR: $D(4)=0.894$, $p=0.402$; AP R: $D(7)=0.915$, $p=0.431$; AP NR: $D(3)=0.956$, $p=0.598$). Secondly, it was tested if the mean reaction times of the six groups varied from the normal distribution. Mean reaction times of the "correctly accepted bonus stimuli in the desire context" were normally distributed in the following groups: AA NR ($D(7)=0.828$, $p=0.076$), TA NR ($D(4)=0.944$, $p=0.677$), AP R ($D(7)=0.836$, $p=0.091$), AP NR ($D(3)=0.864$, $p=0.277$). Non-normally distributed mean reaction times were only found in the AA R group ($D(15)=0.793$, $p=0.003$). It is important to note that the typical antipsychotic responders' performance and

mean reaction times could not be statistically analyzed, as the sample size was too small to gain valid results. Table 4 gives an overview of performance and mean reaction times of the six responder and non-responder groups.

Next, by applying a one-way ANOVA it was examined whether significant differences between the six groups regarding their correct trials data could be found. There was no significant difference between the groups in the "correctly accepted bonus stimuli in the desire context" ($F(5, 37)=0.898$, $p=0.494$, $r=0.35$, $\omega^2=-0.014$). Furthermore, no significant differences between the six groups' reaction times in the "correctly accepted bonus stimuli in the desire context" were detected ($F(5, 37)=1.005$, $p=0.431$, $r=0.368$, $\omega^2=0.001$).

TABLE 4 Task performance and mean reaction times of correct responses of aripiprazole, atypical antipsychotic and typical antipsychotic responders and non-responders.

	Aripiprazole		Atypical antipsychotics		Typical antipsychotics	
	R	NR	R	NR	R	NR
Performance in % (SD)						
Correctly accepted bonus in DC	63.08 (22.01)	40.59 (47.34)	53.75 (29.57)	49.24 (25.68)	62.88 (5.36)	77.67 (15.82)
Reaction time in ms (SD)						
Correctly accepted bonus in DC	560.15 (75.09)	405.21 (354.66)	531.27 (174.96)	621.11 (72.71)	479.63 (7.52)	585.77 (58.43)

Abbreviations: ms = milliseconds, SD= standard deviation, R= responder, NR= non-responder, DC= desire context

3.2 fMRI Results

3.2.1 *Study A*: Hyper- and hypoactivations of bipolar and schizophrenia patients in the combined oddball-incongruence paradigm

In the following the results of the comparison of brain activations between bipolar and schizophrenia patients as well as healthy individuals in the oddball and incongruence condition will be presented.

The analysis of activations in the oddball condition revealed diagnosis-specific hyperactivations of bipolar patients compared to healthy controls and schizophrenia patients in frontal regions such as the left middle frontal gyrus (MFG), precentral gyrus, OFC and avPFC. These results indicate qualitative activation differences between bipolar and schizophrenia patients, i.e. diagnosis-specific differences between the patient groups. Furthermore, hyperactivation in the right intraparietal cortex in both, bipolar and schizophrenia, patient groups compared to healthy individuals was detected. In addition, bipolar patients showed increased activation in the right and left intraparietal cortex in relation to schizophrenia patients. Since both psychiatric disorders demonstrated enhanced activation in the intraparietal cortex in

comparison to healthy individuals it might rather represent a diagnosis-unspecific quantitative difference (see table 5 and figure 7).

TABLE 5 Overview of diagnosis-specific and –unspecific hyperactivations of bipolar and schizophrenia patients compared to healthy controls during the oddball condition.

Region MNI coordinates (t-value)	BD	SCZ	HC	BD> HC	SCZ> HC	BD> SCZ
Diagnosis-specific activation						
L MFG	-36 33 30 (4.04)*	n.s.	[-36 33 30 (1.82)]	[-36 36 30 (2.58)]	n.s.	-36 33 30 (4.28)*
L precentral gyrus	-45 0 51 (4.47)*	-48 -6 54 (3.06)*	-48 -9 54 (7.96)	-45 9 51 (2.90)*	n.s.	-45 6 51 (3.42)*
L OFC	-21 39 -9 (3.88)*	n.s.	n.s.	-18 39 -12 (2.84)*	n.s.	-24 39 -12 (2.87)*
L avPFC	-21 39 15 (3.30)*	n.s.	n.s.	-27 45 15 (2.66)*	n.s.	-21 48 6 (2.81)*
Diagnosis-unspecific activation						
R intraparietal cortex	33 -54 60 (5.37)	27 -54 48 (5.38)	27 -54 51 (7.04)	45 -48 57 (2.95)*	[33 -72 57 (2.38)]	[42 -42 66 (2.05)]
L intraparietal cortex	-30 -51 39 (6.57)	-27 -63 51 (5.38)	-24 -54 54 (8.16)	-36 -54 42 (3.69)*/ -36 -54 39 (3.41)**	[-33 -69 51 (2.36)]	-36 -54 39 (2.67)*/ -36 -51 39 (2.97)*

Abbreviations: L= left, R= right, BD= bipolar disorder patients, SCZ= schizophrenia patients, HC= healthy controls, MFG= middle frontal gyrus, OFC= orbitofrontal cortex, avPFC= anteroventral prefrontal cortex
Activations are reported at p<0.05, corrected for family-wise error rate (FWE); * activation at p<0.005, uncorrected; ** activation at p<0.05, FWE-corrected for small volume (6 mm sphere) around a priori coordinates from Gruber *et al.* (2009); [] activation at p<0.05, uncorrected

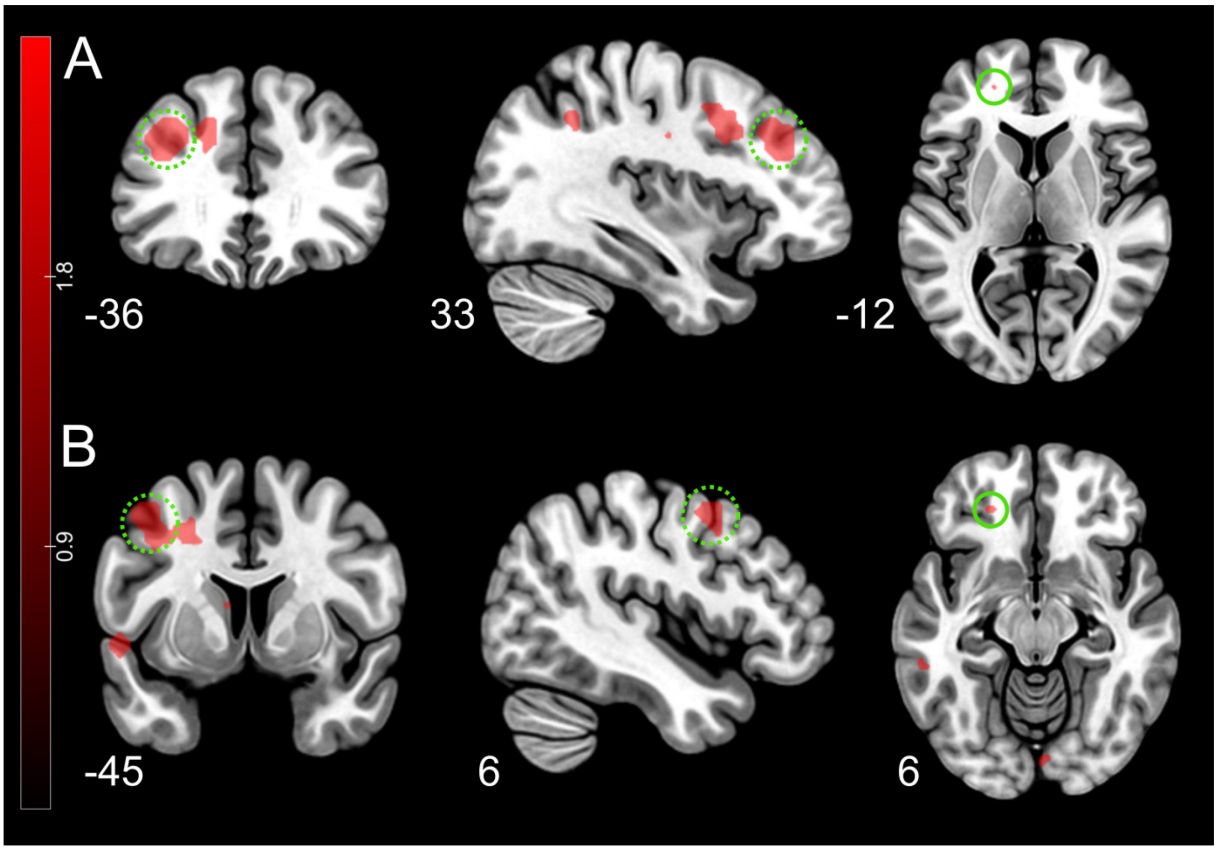


FIGURE 7 Diagnosis-specific hyperactivations of bipolar patients in comparison to schizophrenia patients. Compared to schizophrenia patients, bipolar patients showed hyperactivations in the oddball condition in A) the middle frontal gyrus (MFG) (-36 33 30; p=0.005, uncorrected; dotted line), orbitofrontal cortex (-24 39 -12; p=0.005, uncorrected; solid line) and B) the precentral gyrus (-45 6 51; p=0.005, uncorrected; dotted line) and avPFC (-21 48 6; p=0.005, uncorrected; solid line).

Next, hypoactivations of bipolar and schizophrenia patients were detected in the inferior frontal junctions bilaterally, left ventral pathway and pars triangularis. These decreased activations were independent of the respective diagnosis. Furthermore, increased deactivation of the bipolar patients in the hypothalamus led to significant differences compared to healthy controls and schizophrenia patients (see table 6 and figure 8).

TABLE 6 Overview of diagnosis–unspecific hypoactivations and deactivation and thereof resulting differences of patients and healthy controls during the oddball condition.

Region MNI coordinates (t-value)	BD	SCZ	HC	BD<HC	SCZ<HC	BD<SCZ
Diagnosis-unspecific hypoactivation						
L inferior frontal junction	-42 3 33 (4.01)*	-54 3 42 (3.92)*	-42 0 33 (7.17)	[-48 -3 30 (2.19)]	-39 -9 30 (3.42)*	n.s.
R inferior frontal junction/ precentral gyrus	42 3 27 (3.99)*	48 3 30 (3.51)*	45 3 30 (7.06)	54 0 18 (2.81)*	42 6 27 (3.23)*/57 0 24 (4.24)*	n.s
L posterior inferior temporal cortex/ ventral pathway	-30 -57 -12 (4.24)*	-33 -63 -9 (5.46)	-33 -51 -18 (10.41)/ -36 -69 -6 (10.71)	-33 -66 -3 (3.30)*	-36 -69 9 (4.73)*	n.s.
Pars triangularis/ orbitalis/ R inferior frontal gyrus	n.s.	n.s.	42 36 15 (4.61)*	48 36 6 (2.65)*	42 42 6 (3.68)*	n.s.
Diagnosis-specific deactivation						
Hypothalamus	n.s.	n.s.	n.s.	3 -9 -15 (3.28)*	n.s.	[3 -9 -15 (2.57)]

Abbreviations: L= left, R= right, BD= bipolar disorder patients, SCZ= schizophrenia patients, HC= healthy controls, MFG= middle frontal gyrus, OFC= orbitofrontal cortex, avPFC= anteroventral prefrontal cortex
Activations are reported at p<0.05, corrected for family-wise error rate (FWE); * activation at p<0.005, uncorrected; [] activation at p<0.05, uncorrected

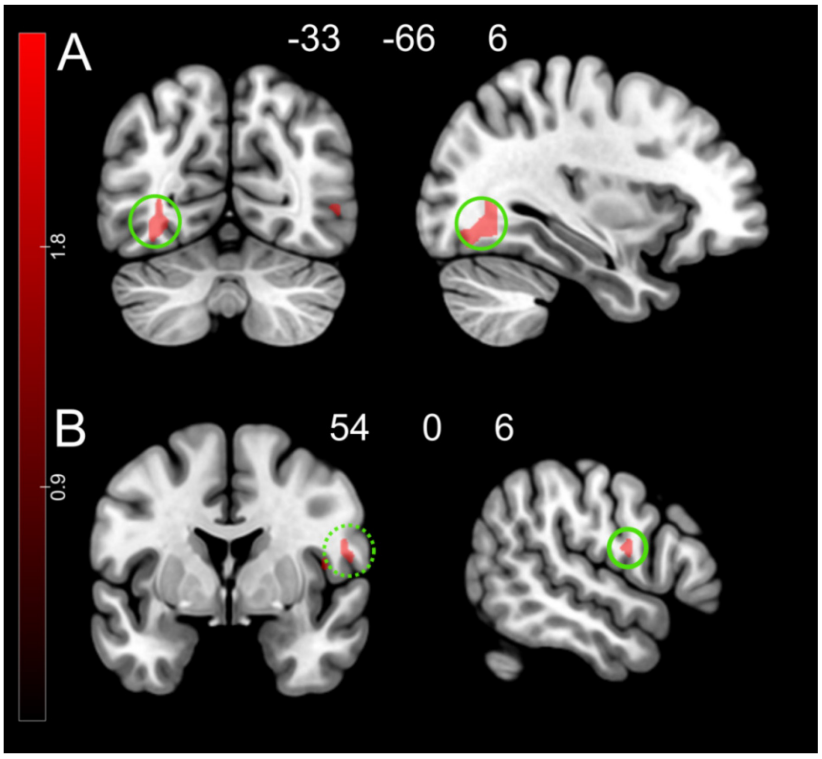


FIGURE 8 Hypoactivations of bipolar patients in comparison to healthy controls. Bipolar patients depicted hypoactivations compared to healthy individuals evoked by the oddball condition in A) the ventral pathway (-33 -66 -3; p=0.005, uncorrected; solid line) and B) the pars triangularis (48 36 6; p=0.005, uncorrected; dotted line) and inferior frontal junction (54 0 18; p=0.005, uncorrected; solid line).

In the incongruence condition, patients revealed hypoactivations in similar brain areas as were found in the oddball condition. These comprise the inferior frontal junction, ventral pathway and pars triangularis. However, brain regions that were hyperactivated in bipolar patients during the oddball condition could not be detected during the incongruence condition. In fact, both patient groups exhibited hypoactivations in brain regions that were hyperactivated in bipolar patients during the oddball condition. Both patient groups exhibited hypoactivations in the intraparietal cortex, left MFG, precentral gyrus and avPFC/ OFC compared to the healthy individuals. Additionally, decreased activation of bipolar and schizophrenia patients was found in the bilateral putamen.

Finally, increased deactivation of the bipolar patients compared to healthy as well as schizophrenia individuals in the hypothalamus/ VTA could be detected (see table 7 and figure 9).

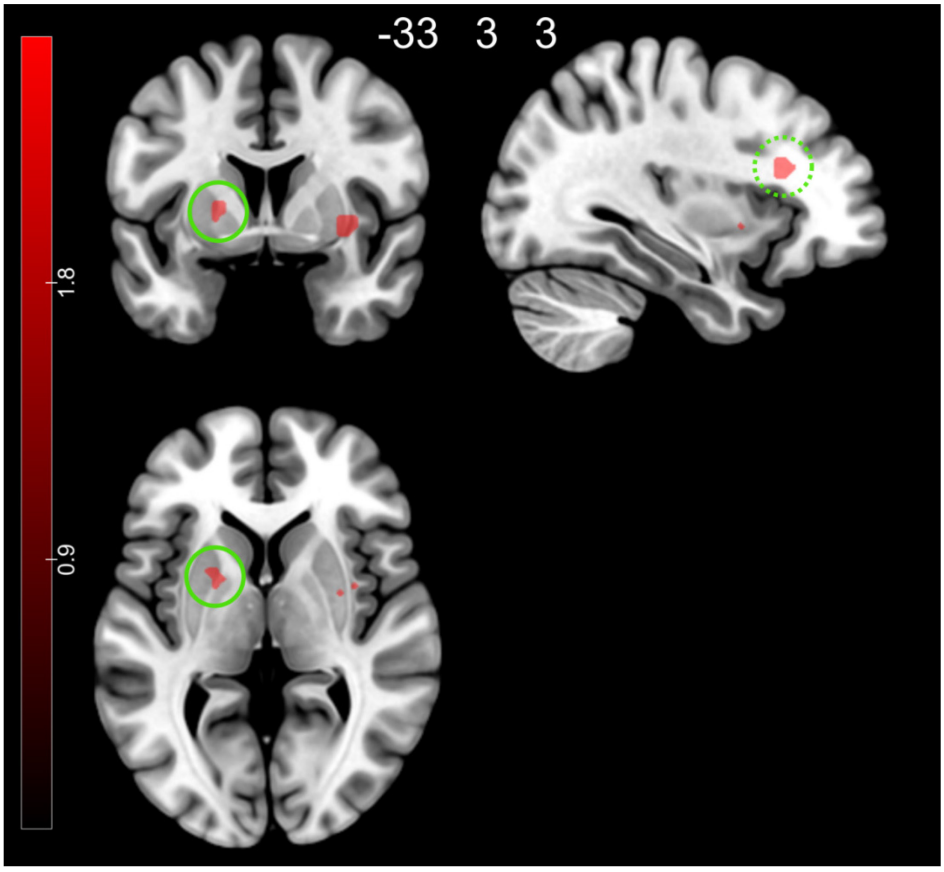


FIGURE 9 Diagnosis-unspecific hypoactivations of bipolar patients in comparison to healthy controls. Bipolar patients demonstrated hypoactivations compared to healthy individuals in the incongruence condition in the putamen (-21 3 3; p=0.005, uncorrected; solid line) and the MFG (-33 24 21; p=0.005, uncorrected; dotted line).

TABLE 7 Overview of diagnosis-specific and –unspecific hypo- or deactivation and thereof resulting differences of patients and healthy controls during the incongruence condition.

Region MNI coordinates (t-value)	BD	SCZ	HC	BD<HC	SCZ<HC	BD<SCZ
Diagnosis- unspecific hypoactivation						
L inferior frontal junction	[-48 6 36 (2.29)]	-54 6 36 (3.63)* / -48 6 27 (2.54)**	-42 0 33 (7.16)	-45 -3 30 (3.63)*	-42 -3 27 (3.73)*	n.s.
L posterior inferior temporal cortex/ ventral pathway	[-33 -60 -21 (2.53)]	-42 -72 -6 (5.59)	-30 -60 -21 (8.44)/ -36 -72 -6 (9.44)	-24 -60 -21 (3.47)* /-39 -81 3 (3.87)* /-33 -78 -9 (3.52)	-33 -51 -18 (4.15)*/ -39 -72 6 (4.16)*	[-33 -66 -3 (2.30)]
R inferior frontal junction/ precentral gyrus	n.s.	48 3 27 (5.65)	45 3 27 (7.73)	48 0 30 (3.53)*	[51 -6 30 (1.93)]	48 3 24 (2.71)*
L intraparietal cortex	[-33 -54 45 (2.14)]	-30 -54 45 (5.19)	-24 -51 51 (8.39)	-24 -51 51 (3.07)*	-24 -48 54 (3.17)*	n.s.
R intraparietal cortex/ superior parietal lobe	[30 -54 51 (1.78)]	30 -54 48 (5.59)/ 33 -66 54 (4.92)	27 -51 51 (8.10)	30 -42 45 (2.71)*/ 21 -57 48 (2.82)*	21 -54 63 (2.93)*	[33 -69 57 (2.15)] / [24 -57 51 (1.74)]
L precentral gyrus	[-45 -3 51 (1.87)]	-48 -3 54 (4.15)*	-48 -6 54 (8.38)	-51 -6 51 (2.99)*	-48 -9 51 (3.32)*	n.s.
L MFG	[-39 33 30 (1.69)]	-45 30 36 (3.01)*	-27 27 18 (5.87)	-33 24 21 (3.10)*	[-33 33 15 (2.52)]	[-48 27 39 (2.04)]
L avPFC / L OFC	-18 33 6 (3.36)*	-21 33 -3 (3.38)*	-27 39 -3 (6.69)	-30 42 -3 (2.87)*	[-21 39 3 (2.22)]	n.s.
R putamen	n.s.	n.s.	27 12 0 (3.64)*	33 9 0 (2.98)*/ 33 0 -3 (3.20)*	27 3 -9 (2.84)*	n.s.
L putamen	n.s.	n.s.	-24 6 3 (5.30)	-21 3 3 (2.94)*	-24 12 6 (3.42)*	n.s.
Pars triangularis/ orbitalis/ R inferior frontal gyrus	n.s.	n.s.	27 39 0 (4.77)	45 36 6 (4.38)*	36 42 0 (2.69)*	n.s.
Diagnosis-specific deactivation						
Hypothalamus/ VTA	n.s.	n.s.	n.s.	[-9 -12 -12 (3.05)] / [12 -6 -18 (2.54)]	n.s.	-9 -3 -12 (2.81)*/ 6 -6 -18 (2.96)*

Abbreviations: L= left, R= right, BD= bipolar disorder patients, SCZ= schizophrenia patients, HC= healthy controls, IFS= inferior frontal sulcus

Activations are reported at p<0.05, corrected for family-wise error rate (FWE); * activation at p<0.005, uncorrected; ** activation at p<0.05, FWE-corrected for small volume (6 mm sphere) around a priori coordinates from Gruber *et al.* (2009); [] activation at p<0.05, uncorrected

3.2.2 *Study B*: Reward-related (de-)activations of the individual treatment response groups

A univariate ANOVA revealed significant differences in brain activation between treatment responders and non-responders in the desire context of the individual treatment groups. The aripiprazole responders exhibited stronger deactivation of the bilateral MTG (MNI coordinates: -66 -36 0 (L) and 57 -9 -21 (R)), left precuneus (MNI coordinates: -9 -63 42), angular gyrus (MNI coordinates: -48 -66 18), occipital cortex (MNI coordinates: -30 -78 15), superior frontal gyrus (MNI coordinates: -24 12 39) and right hippocampus (MNI coordinates: 21 -24 -12), pregenual anterior cingulate cortex (MNI coordinates: 12 60 15), frontal inferior orbital gyrus (MNI coordinates: 45 39 -9) and amygdala (MNI coordinates: 24 3 -15). Comparisons between atypical antipsychotic responders and non-responders and between typical antipsychotic responders and non-responders only revealed low-threshold differences in brain areas such as the right MTG, hippocampus and left precuneus (MNI coordinates AA R> AA NR: 63 -6 24 (MTG); TA R > TA NR: 24 -33 -12 (hippocampus), 57 -3 -15 (MTG), -9 -51 36 (precuneus)).

In addition, stronger activations of the aripiprazole responders compared to non-responders were found in the right avPFC (MNI coordinates: 39 51 6) and ventral striatum (MNI coordinates: 9 9 -6). As can be seen in table 8, it was differentiated between activation-induced and deactivation-initiated differences. Figure 10 shows activation differences between aripiprazole responders and non-responders. Only low-threshold differences between atypical responders and non-responders and between typical responders and non-responders could be found in the avPFC (MNI coordinates AA R> AA NR: -45 45 -9; TA R > TA NR: -36 45 6 (L), 39 45 6 (R)).

To further validate these findings, an interaction contrast ((AP R – AP NR)- ((AA R | TA R) - (AA NR | TA NR)) was used to examine the results. The interaction contrast supported the effects found in the comparison of aripiprazole responders and non-responders by revealing significant increased activations in the same brain regions, i.e. bilateral avPFC and ventral striatum. Furthermore deactivation-induced differences were consistently found in the precuneus, pregenual anterior cingulate cortex, angular gyrus, subcortical areas, such as the right hippocampus, right amygdala, as well as temporal and parietal brain regions (indicated in more detail in table 8).

TABLE 8 Reward related brain (de-)activation in the desire condition in responders (R) compared to non-responders (NR) of aripiprazole (AP), atypical (AA) and typical (TA) antipsychotic treatment.

Region	AP R > AP NR	AA R > AA NR	TA R > TA NR	(AP R- AP NR)> ((AA R | TA R)-(AA NR | TA NR))
MNI coordinates (t-value)				
Activation				
L avPFC	-42 45 3 (2.56)**	-45 45 -9 (1.93)**	-36 45 6 (1.82)**	-45 51 3 (2.23)**
R avPFC	39 51 6 (3.55)	n.s.	39 45 6 (2.44)**	45 54 0 (3.66)
L ventral striatum	-6 9 -6 (2.92)*	n.s.	n.s.	-6 9 -6 (2.76)*
R ventral striatum	9 9 -6 (4.12)	n.s.	n.s.	9 9 -6 (3.96)
Deactivation				
R hippocampus	21 -24 -12 (3.75)	n.s.	24 -33 -12 (2.09)**	18 -21 -12 (4.24)
L MTG	-66 -36 0 (3.79)	n.s.	n.s.	-66 -36 0 (3.58)
R MTG	57 -9 -21 (3.87)	63 -6 -24 (2.74)*	57 -3 -15 (2.29)**	60 -3 -21 (2.10)**
L precuneus	-9 -63 42 (4.45)	n.s.	-9 -51 36 (1.98)**	-12 -60 39 (3.41)
R pgACC	12 60 15 (4.83)	n.s.	n.s.	12 60 15 (3.87)
L angular gyrus	-48 -66 18 (4.62)	n.s.	n.s.	-45 -66 18 (4.77)
L cuneus	-18 -63 18 (4.82)	n.s.	n.s.	-18 -63 18 (4.81)
L occipital cortex	-30 -78 15 (4.38)	n.s.	n.s.	-30 -78 12 (3.76)
R frontalinferior orbital gyrus	45 39 -9 (4.89)	45 39 -18 (3.03)*	n.s.	45 39 -9 (4.55)
R amygdala	24 3 -15 (4.30)	n.s.	n.s.	24 3 -15 (3.50)
L superior frontal gyrus	-24 12 39 (4.04)	n.s.	n.s.	-24 12 39 (4.36)

Abbreviations: L= left, R= right, AP R= aripiprazole responders, AP NR= aripiprazole non-responders, AA R= atypical antipsychotics responders, AA NR= atypical antipsychotics non-responders, TA R= typical antipsychotics responders, TA NR= typical antipsychotics non-responders, avPFC= anteroventral prefrontal cortex, MTG= middle temporal gyrus, pgACC= pregenual anterior cingulate cortex | Activations are reported at p<0.001, uncorrected; * activation at p<0.005, uncorrected; ** activation at p<0.05, uncorrected

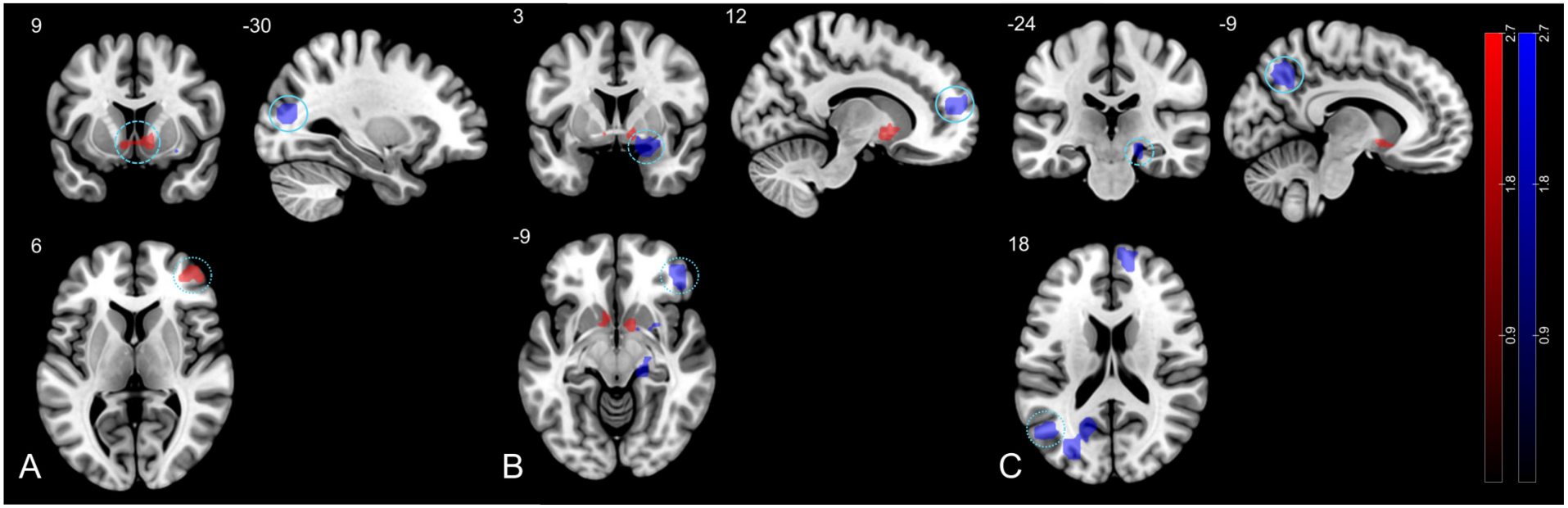


FIGURE 10 Activation differences between aripiprazole responders and non-responders in the DRD paradigm. Aripiprazole responders showed stronger activations (red) compared to the non-responders in A) the ventral striatum (9 9 -6, t= 4.12, dashed line) and anteroventral prefrontal cortex (39 51 6, t= 3.55, dotted line). Non-responders revealed deactivations (blue) in A) the occipital lobe (-30 -78 15, t= 4.38, solid line), B) amygdala (24 3 -15, t= 4.30, dashed line), pregenual anterior cingulate cortex (12 60 15, t= 4.83, solid line), frontalinferior orbital gyrus (45 39 -9, t= 4.89, dotted line), C) hippocampus (21 -24 -12, t= 3.75, dashed line), precuneus (-9 -63 42, t= 4.45, solid line) and angular gyrus (-48 -66 18, t= 4.62, dotted line). Activations are reported at $p<0.001$, uncorrected.

3.3 SVM results

3.3.1 *Study B*: Treatment response prediction using SVM analyses

Bain regions (i.e. fMRI voxels) identified by the univariate analyses of study B (see table 8) were used for the training of a multivariate prediction model of the patients' treatment response to aripiprazole using the linear SVM classifier as described in Section 2.5.

Two SVM analyses were separately performed for two groups of fMRI voxels that demonstrated either elevated or reduced activation during the DRD paradigm in aripiprazole responders in comparison to non-responders, see table 8 (activation vs deactivation).

The first SVM analysis used parameter estimates of stronger activated regions, i.e. the avPFC and ventral striatum (L/R) to predict treatment response of patients being treated with aripiprazole, atypical or typical antipsychotics. For these regions, mean balanced accuracies ranged between 53.33% and 54.17% in the aripiprazole, atypical and typical antipsychotic groups. These accuracy measures led to non-significant results in all three groups ($p>0.05$) indicating no reliable prediction of treatment response.

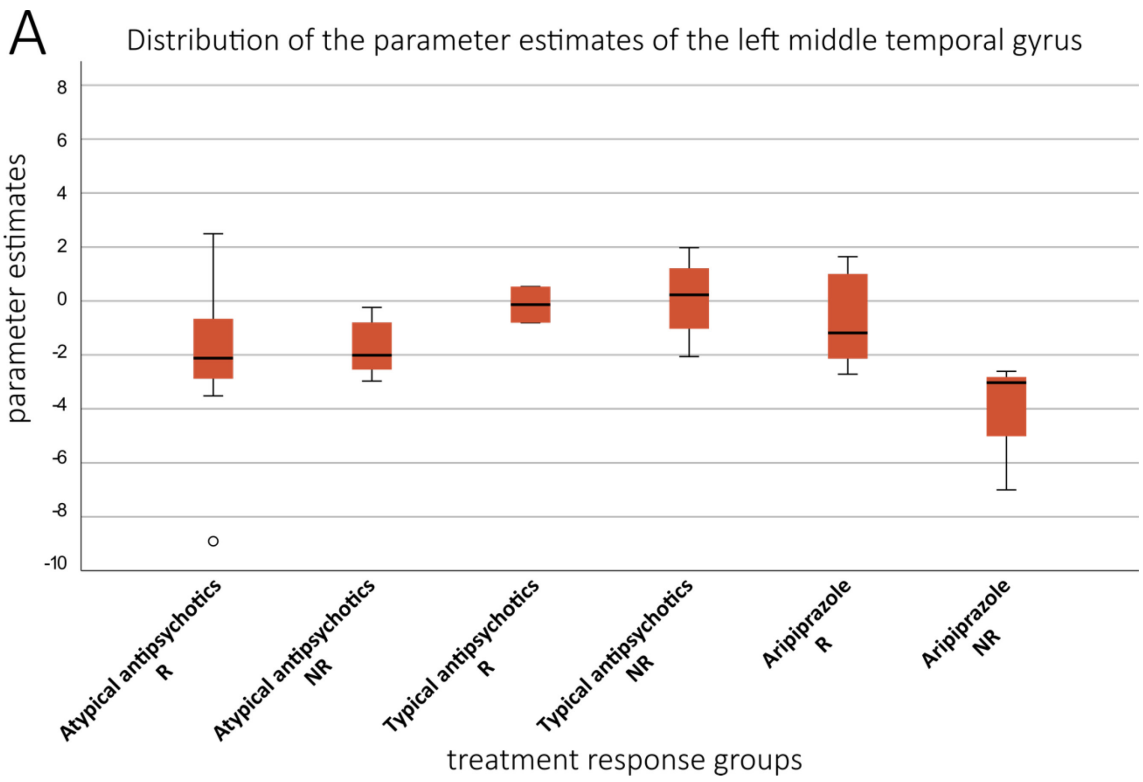
The second model based on parameter estimates of regions found to be stronger deactivated in aripiprazole non-responders, was used to predict treatment response of the patients respectively of their corresponding treatment group. SVM leave-one-out tests revealed that information from the deactivation coordinates enabled significantly more accurate predictions of aripiprazole treatment: accuracy=100%, sensitivity=100%, specificity=100%, balanced accuracy=84.49% (p-value=0.002), see table 9. In contrast, the results of the leave-one-out test for typical and atypical antipsychotics indicated rather poor predictability of the SVM classification model (atypical antipsychotics: 51.63%, $p>0.05$; typical antipsychotics: 37.48%, $p>0.05$).

TABLE 1 Predictions of treatment response after treatment with aripiprazole, atypical and typical antipsychotics.

	Aripiprazole		Atypical antipsychotics		Typical antipsychotics	
	Activation	Deactivation	Activation	Deactivation	Activation	Deactivation
Accuracy	60.00%	100%	63.64%	54.55%	66.67%	33.33%
Sensitivity	33.33%	100%	28.57%	42.86%	100.00%	50.00%
Specificity	33.33%	100%	40.00%	33.33%	66.67%	50.00%
Balanced accuracy*	53.33%	84.49%	54.90%	51.63%	54.17%	37.48%
p value*	0.405	0.002	0.300	0.437	0.373	0.821

*: calculated according to Brodersen *et al.,* 2010

Finally, boxplots of parameter estimates at their local minima and maxima were prepared to visualize the influence of the different brain regions on the SVM algorithm (see figure 11). Three very influential brain regions were selected to outline the great variance between the six groups. This depiction underlines the severe effect of the aripiprazole non-responders' deactivation on the outcome of the machine learning treatment prediction.



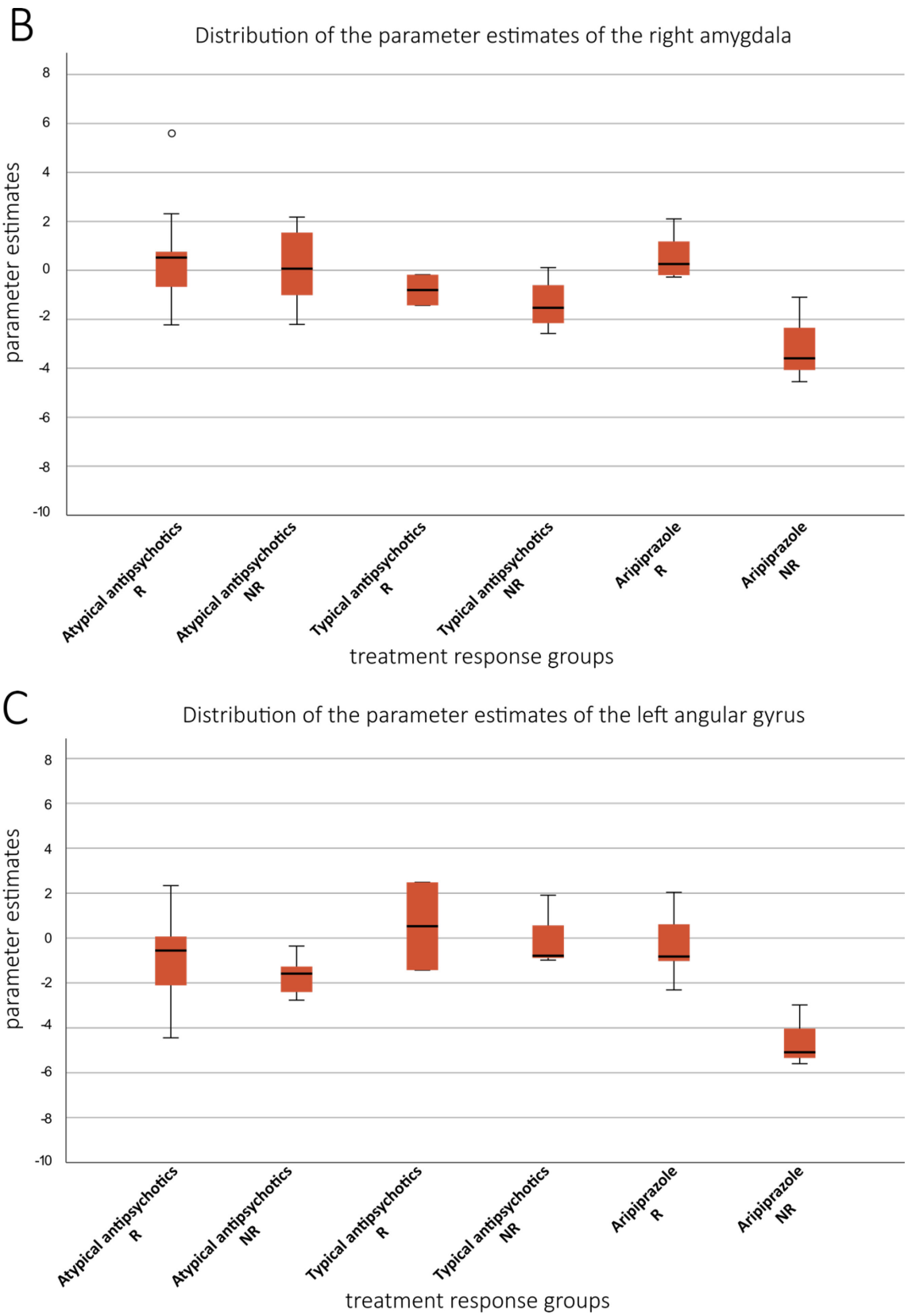


FIGURE 11 Mean parameter estimates distribution of the treatment response groups. In all three brain regions (A: left middle temporal gyrus (MTG), B: right amygdala, C: left angular gyrus) the aripiprazole non-responder group showed the lowest mean parameter estimates indicating strong deactivation. Abbreviations: R= responders, NR= non-responders

4 DISCUSSION

This thesis aimed to investigate pathomechanisms of bipolar and schizophrenia patients. It is commonly observed that these disorders exhibit disturbed processing in various cognitive as well as reward related tasks. To improve diagnosis and treatment of both psychiatric disorders, it is necessary to better understand the functional changes in relevant brain regions. Study A demonstrated diagnosis-(un)specific differences in the frontoparietal attention network of bipolar disorder and schizophrenia patients during a combined oddball-incongruence paradigm. In study B, the application of the DRD paradigm revealed activation abnormalities in frontostriatal brain areas of aripiprazole non-responders compared to aripiprazole responders. Moreover, an SVM algorithm used the parameter estimates of deactivation coordinates from the univariate analysis to predict their treatment response.

The development of biomarkers derived from activation abnormalities within reward- or attention-associated networks offers the chance for individualized and efficient diagnosis and treatment of patients. The results of study A demonstrated diagnosis-specific frontal hyperactivations of bipolar disorder individuals, which brought new insights regarding task difficulty- dependent disturbances within their attention network. The findings suggest bipolar disorder-specific compensation mechanisms that might represent a novel biomarker for diagnosis. In study B, deactivations of aripiprazole non-responders in brain regions such as the hippocampus, amygdala, anterior cingulate cortex etc. during the DRD paradigm indicated that they could potentially be valuable for predicting treatment response. This is the first time that brain deactivation patterns resulting from a reward-related paradigm, were able to classify patients as responders or non-responders of aripiprazole treatment. The investigation of pathomechanisms of bipolar disorder and schizophrenia might hence be useful to further elaborate their predictive potential.

In the following sections, the results of the individual studies will be discussed in detail. Afterwards there will be a combined conclusion of both studies, followed by a discussion of potential limitations and prospective ideas.

4.1 *Study A*: Diagnosis-(un)specific hyper- and hypoactivations of bipolar and schizophrenia patients

Study A compared the functional responses underlying attentional processes induced by oddball and incongruence stimuli in bipolar and schizophrenia patients. New insights were gained with regard to the exertion of cognitive control. The results revealed corresponding brain activation patterns during the presentation of the oddball and incongruence stimuli, however, quantitatively and qualitatively differences were detected between bipolar and

schizophrenia patients as well as healthy controls. The pathophysiological alterations found in the patients' brain activation seem to be associated with the task difficulty.

Diagnosis-specific hyperactivations of bipolar patients compared to schizophrenia and healthy individuals were found in frontal brain regions such as the left avPFC, OFC, precentral gyrus and MFG during the oddball condition. Since these hyperactivations could be specifically assigned to bipolar patients, they seem to represent a qualitative pathophysiological difference between bipolar disorder and schizophrenia. Taking the behavioral results into account, bipolar patients performed significantly worse and slower than healthy controls but not schizophrenia patients in the oddball condition. Therefore, hyperactivations of the bipolar group might reflect a compensation mechanism trying to balance potential deficits. Similar studies that investigated cognitive control processes already reported increased activation in bipolar patients compared to healthy controls. In an experiment by Fleck et al. (2011), greater activation in the frontal cortex of mixed episode bipolar disorder patients compared to healthy controls was shown during a Go/ No-Go task. This is in line with another study, showing enhanced activation in the PFC of bipolar patients in comparison to healthy individuals during a Multi-Source Interference Task (Gruber et al., 2017). The authors of both studies concluded that a lack of cognitive control might lead to abnormal activation patterns while solving cognitive tasks. It was hypothesized that brain regions linked to emotion processing might be hyperactivated in bipolar disorder and hence interfere with efficient processing of novel stimuli. However, it is important to note that the majority of fMRI studies examining cognitive control processes in bipolar disorder demonstrated reduced activation in prefrontal brain structures compared to healthy controls (Frangou et al., 2006; Joshi et al., 2016; Kronhaus et al., 2006; Penfold et al., 2015). A potential explanation for this discrepancy could be the varying cognitive load of the different experimental tasks. Most of the cognitive control experiments might overstrain bipolar patients leading to reduced activation in their prefrontal control network. This assumption will be discussed in more detail in a later paragraph. The oddball condition in this study, however, might be challenging enough to induce behavioral deficits, but not demanding enough to cause hypoactivations. Bipolar patients in this study might compensate for the novelty effect of the oddball stimulus by hyperactivating frontal brain areas.

While bipolar and schizophrenia patients demonstrated comparable performance deficits, i.e. significantly worse performance than healthy controls, their activation in frontal brain regions differed significantly in the oddball condition. Variations in the underlying compensation mechanisms could be a possible cause for the activation differences. Bipolar patients might have recruited frontal brain regions such as the OFC and avPFC to try and maintain the novelty detection processing. Schizophrenia patients, on the other hand, might not activate prefrontal regions to the same extent. A prior study already reported increased activation in bipolar compared to schizophrenia patients during a neurocognitive fMRI task (McIntosh *et al.*, 2008). They found hyperactivation in the OFC during the Hayling Sentence Completion Test. In

addition, hypoactivation of ultra-high-risk schizophrenia individuals during a visual oddball task was reported in the MFG and inferior frontal gyrus (Morey *et al.*, 2005). They linked their results to the deficient dopamine transmission of schizophrenia patients, resulting in dopamine-induced enhanced salience to external stimuli. Therefore, even prodromal schizophrenia individuals would have greater problems with the processing of task-relevant features (Morey *et al.*, 2005).

Another possible reason for differences in cognitive control processing might result from differently impaired cognitive performance levels. Various studies and meta-analyses of cognitive processes in bipolar disorder and schizophrenia ascribe greater cognitive dysfunction to schizophrenia patients and intermediate deficits to bipolar disorder (Altshuler *et al.*, 2004; reviewed in Krabbendam *et al.*, 2005; Lynham *et al.*, 2018; reviewed in Stefanopoulou *et al.*, 2009). Melcher *et al.* (2014) examined the cognitive performance of bipolar and schizophrenia patients in the same combined oddball-incongruence task. They reported an overall greater cognitive impairment in schizophrenia patients in both, the oddball and incongruence, conditions. It can be hypothesized that these cognitive disturbances also affect functional responses. Therefore, compensatory mechanisms might be less pronounced in schizophrenia compared to affective disorders leading to reduced activation in frontal brain areas.

In this study bipolar patients exhibited greater activation in the intraparietal cortex compared to schizophrenia patients and healthy controls. However, schizophrenia individuals also presented increased, but low-threshold, hyperactivation compared to the controls. Bipolar patients might integrate frontal and intraparietal regions and hence compensate for their cognitive deficits whereas schizophrenia patients might only recruit the intraparietal cortex as compensatory support. As a result, bipolar and schizophrenia patients vary in their quantitative level of compensation. This mechanism seems to be consistent, as the hyperactivation of schizophrenia patients in the intraparietal cortex during the same combined oddball-incongruence task was already shown by Wolter *et al.* (2016). The difference in the statistical power might result from greater heterogeneity within the schizophrenia group due to the increased sample size in the current study. It has been shown multiple times that schizophrenia comprises a great spectrum involving multiple symptomatic features (Lewandowski *et al.*, 2014). Therefore, it might not be surprising to find quantitative differences in the functional data.

So far, these results hint at different compensatory strategies and capacities of bipolar and schizophrenia patients. Whereas bipolar patients seemed to use a frontoparietal network to counterbalance deficits in the processing of the oddball stimulus, schizophrenia patients might have deficits in their compensatory mechanisms and only showed low threshold hyperactivation in the intraparietal cortex compared to healthy controls.

In the next section, hypoactivations of the bipolar and schizophrenia group will be examined more closely. Both patient groups exhibited hypoactivations in the frontal areas and the ventral pathway.

The ventral pathway plays a central role in the processing of visual stimuli as it connects the primary visual cortex to temporal brain areas (Mishkin, 1982). Conjunctions of temporal regions with limbic and frontal networks facilitate the integration of emotional or experiential factors in the processing of feature dimensions (Kuypers *et al.*, 1965; reviewed in Mishkin *et al.*, 1983; Turner *et al.*, 1980). In the current study, healthy individuals seem to identify visual objects without difficulties and without interference of other implicit processing networks. Patients, however, might experience more malfunctions due to the influence of parallel processing of other cognitive requirements. Therefore, patients' hypoactivations in the ventral pathway might indicate aberrant processing of visual stimuli. The current literature mostly supports this idea as various studies demonstrated hypoactivations in the visual cortex and temporal areas of schizophrenia patients compared to healthy controls during visual perception tasks (Green *et al.*, 2009; Lee *et al.*, 2019; Sehatpour *et al.*, 2010). In contrast, Silverstein *et al.* presented hyperactivation in the lateral occipital complex of schizophrenia patients in an object recognition task in comparison to healthy controls (Silverstein *et al.*, 2015). Consequently, the pathomechanisms of schizophrenia regarding vison processing seem not be completely understood, yet.

There are only few studies examining visual processing in bipolar disorder. Shaffer *et al*. demonstrated decreased brain activation in visual areas of manic and depressed bipolar patients compared to healthy controls (Shaffer *et al.*, 2018). Since they also found functional differences between mood states, i.e. manic, depressed and euthymic, they assumed visual processing activation to be a state marker for bipolar disorder. Furthermore, fMRI adaptation in the visual cortex seems to be impaired in bipolar patients (Lee *et al.*, 2019). While healthy controls demonstrated reduced functional response to the repeated presentation of the same objects in the visual cortex, bipolar patients did not present this adaptation. Another non-fMRI study revealed deficits of bipolar patients compared to healthy controls only in late stages of visual processing, i.e. higher involvement of perceptual and attentional processes (Jahshan *et al.*, 2014). Schizophrenia patients, on the other hand, demonstrated impairments in all stages of visual processing (Jahshan *et al.*, 2014). This is in line with the aforementioned hypothesis of greater cognitive dysfunction and a lack of compensatory mechanisms of schizophrenia patients compared to bipolar patients. However, in sum, the underlying pathomechanisms responsible for abnormalities in visual processing of bipolar and schizophrenia seem not to be fully resolved, yet.

Diagnosis-unspecific hypoactivations of bipolar and schizophrenia patients compared to healthy controls were further detected in the inferior frontal junction. The inferior frontal junction has been associated with the processing of goal-directed and stimulus-driven attention

(Asplund *et al.*, 2010; Tamber-Rosenau *et al.*, 2018). Tamber-Rosenau *et al.* in particular emphasized its involvement in attention shifting. Consequently, deficits in attention shifting from novel to relevant stimuli might lead to reduced activation. In line with this, various studies reported deficiencies of bipolar and schizophrenia patients in shifting their attention (Bozikas *et al.*, 2014; Di Giorgio Silva *et al.*, 2016; Melcher *et al.*, 2014).

Taken together, results from the oddball condition showed diagnosis-specific hyperactivations of bipolar patients in frontal regions as well as diagnosis-unspecific hyperactivations of bipolar and schizophrenia patients compared to healthy controls in the intraparietal cortex. Furthermore, both patient groups revealed hypoactivations in the inferior frontal junctions and ventral pathway. A possible explanation might be compensatory mechanisms, including the involvement of frontal structures, to balance deficiencies within their cognitive control network. It seems as if this process might be more pronounced in bipolar disorder, as schizophrenia patients only recruited the intraparietal cortex to compensate for their cognitive impairments.

In this next section, brain activation differences between bipolar and schizophrenia as well as healthy individuals in the incongruence condition will be discussed. The incongruence condition has been shown to induce response conflicts and to interfere with executive control (Gruber *et al.*, 2009; Melcher *et al.*, 2014). In the current study, most of the brain areas that were activated in the oddball condition also showed activation in the healthy control group during the incongruence condition. These comprise the inferior frontal junction, ventral stream, intraparietal cortex, precentral gyrus, putamen and superior frontal sulcus. These frontoparietal regions and the ventral pathway have repeatedly been shown to be activated during oddball and incongruence conditions in healthy individuals (Corbetta *et al.*, 2000; Falkenberg *et al.*, 2011; Hopfinger *et al.*, 2000; Rusiniak *et al.*, 2013; Strobel *et al.*, 2008; van Veen and Carter, 2005; Wolter, 2016; Zysset *et al.*, 2001). The results of these studies underline the reliability of oddball and incongruence effects. Therefore, underlying mechanisms such as selective attention, the processing of rare and interference-inducing stimuli seem to be replicable and stable across different tasks.

The comparison between the patient groups and healthy controls revealed hypoactivations in regions that were also hypoactivated during the oddball condition. These comprise the inferior frontal junction, ventral pathway and right pars triangularis. It can be concluded that bipolar and schizophrenia patients share potentially pathophysiological hypoactivations in the processing of the oddball stimulus and the response conflict induced by the incongruence task.

Additional brain areas such as the avPFC, MFG, intraparietal cortex and superior frontal gyrus revealed diagnosis-unspecific hypoactivations of the patient groups during the incongruence condition. As these brain regions were hyperactivated in bipolar patients during the oddball condition it can be hypothesized that the incongruence condition might require more

attentional capacities. Taking the behavioral data into account, it can be observed that healthy controls had greater difficulties in the incongruence condition leading to significant differences in their performance compared to the congruent and oddball condition. Due to the fact that the incongruence condition involves another dimension, i.e. an interference-inducing color dimension, more information needs to be processed, leading to an increased cognitive demand. As a result, enhanced mental load could cause a decrease in their task accuracy. Mean reaction times of the three groups in the oddball condition indicate a slightly delayed response potentially due to the saliency effect of the oddball stimulus. All in all, the mental load of the incongruence condition might expect too many resources of the two patient groups. The compensation mechanism of the frontoparietal network which could be seen in the bipolar patients during the oddball condition might not be sufficient. As a result, the compensatory strategy might collapse resulting in hypoactivations across the relevant brain regions. A possible explanation for this effect was originally proposed for contradictory effects in the working memory load of psychiatric patients. Multiple studies have published data supporting this model (Callicott *et al.*, 1999; Jansma *et al.*, 2004; Karlsgodt *et al.*, 2007; reviewed in Manoach, 2003; Mendrek *et al.*, 2004). It describes a linear correlation between task difficulty and the functional response curve, which is capped at a certain turning point and afterwards leads with further increasing difficulty to a reduction in the neurophysiological response resulting in an inverted U-shaped curve. In psychiatric patients this curve has been shown to be shifted to the left, as they often suffer from cognitive impairment. Consequently, the comparison between patients and healthy controls shows hyperactivations in patients during easier tasks, e.g. the oddball condition, but hypoactivations in tasks that require more mental capacity, e.g. the incongruence condition. In the current study, bipolar patients might have recruited the frontoparietal network to accomplish the oddball condition. However, in the incongruence condition their attention load was exceeded, leading to reduced functional response. Schizophrenia patients demonstrated hyperactivation during the oddball task and hypoactivation during the incongruence task in the intraparietal cortex, suggesting an overall more impaired attention processing system with even greater deficits during the presentation of the incongruent stimuli.

The putamen is another region that presented diagnosis-unspecific hypoactivations in bipolar and schizophrenia. It is part of the striatum which has been shown to be altered in schizophrenia and bipolar disorder multiple times (reviewed in McCutcheon *et al.*, 2019; Trost *et al.*, 2014). A meta-analysis by Minzenberg *et al.* compared brain activations in the cognitive control network of healthy controls and schizophrenia patients and revealed decreased activation in the right putamen of schizophrenia patients (reviewed in Minzenberg *et al.*, 2009). Furthermore, a recent meta-analysis by Tian *et al.* demonstrated a lack of activation in the ventral striatum of bipolar patients during executive functioning tasks (reviewed in Alustiza *et al.*, 2017; reviewed in Tian *et al.*, 2019). In sum, the putamen seems to play a role in executive

functioning and hence might also be involved in pathophysiological processes of bipolar disorder and schizophrenia.

Another finding affecting both, the oddball and incongruence, conditions was a diagnosis-specific deactivation of the bipolar disorder patients in the hypothalamus. Over 80 years ago it was proposed that the limbic system projects to the hypothalamus and thereby possibly initiates emotion expression (MacLean, 1949; Papez, 1937). Later on, also outputs from prefrontal brain regions were discovered to innervate the hypothalamus in primates (Barbas *et al.*, 2003; Öngür *et al.*, 1998). Lesion studies of the human ventromedial PFC confirmed this connection as they found attenuation of basic somatic states in response to emotional stimuli (Damasio *et al.*, 1990). Additionally, anomalies have been found in the hypothalamus of bipolar patients. On the one hand, a decreased overall volume of the hypothalamus was shown in structural MRI studies (Bielau *et al.*, 2005). On the other hand, bipolar disorder has been linked to a dysfunctional HPA axis which is involved in the stress response, somatic processes as well as mood (Watson *et al.*, 2006). Furthermore, the hypothalamic suprachiasmatic nucleus controls the circadian clock via the secretion of melatonin. Taking into account that one major symptom of bipolar disorder is a drastically reduced need to sleep, it is hypothesized that the function of the hypothalamus regulating the day-night-rhythm might be disturbed (Lewy *et al.*, 1985; Zhou *et al.*, 2001). In line with this argumentation, bipolar-specific deactivation in the hypothalamus might be related to an overall disruption in this brain area and might not be specific for the processing of cognitive control.

Taken together, these results revealed activation differences between patients and healthy controls during the processing of the oddball and incongruence effects suggesting differential compensation mechanisms as well as impairment severity in attentional processing of the two psychiatric disorders. Whereas bipolar patients recruited frontoparietal brain areas to compensate for potentially deficits in the oddball task, schizophrenia patients showed hyperactivation exclusively in the intraparietal cortex. However, the incongruence condition seemed to involve greater cognitive load compared to the bipolar disorder resulting in frontoparietal hypoactivations of both patient groups. Consequently, both tasks seem to involve the activation of similar brain regions, though evoke only partially shared responses in the two patients' groups. Future studies will be necessary to further investigate differences in the pathomechanisms of bipolar disorder and schizophrenia regarding cognitive control processes.

4.2 *Study B*: Potential biomarkers to predict treatment response of aripiprazole

The main finding of study B was that an SVM algorithm could predict treatment response to aripiprazole based on task-induced deactivation differences between responders and non-responders. Aripiprazole non-responders demonstrated altered activation patterns in the right hippocampus, pregenual anterior cingulate cortex (pgACC), left precuneus, angular gyrus and

superior frontal gyrus providing the data for a successful prediction. These results indicate that task-induced deactivations in regions linked to the default mode network (DMN) might be reliable markers to predict treatment response for aripiprazole administration.

In general, it might be of interest to give a short overview of the reward-related DRD paradigm applied in this study. The DRD paradigm aims to examine the dopaminergic reward system and networks connected with its processing. By associating a strong bond between specific color stimuli and a reward feedback it provokes activation in dopaminergic brain regions, i.e. the VTA, as well as dopaminergic innervated areas such as the ventral striatum. Its reliability has been proven in various studies which reported consistently activation of the VTA and ventral striatum during the bonus stimuli presentation in the desire context (Diekhof and Gruber, 2010; Diekhof *et al.*, 2012; Richter *et al.*, 2015; Trost *et al.*, 2014). The DRD paradigm was also used to detect differences in the reward processing of psychiatric patients. A recent study applying the DRD paradigm, revealed significant hypoactivation of schizophrenia patients compared to healthy controls in the avPFC as well as hyperactivation in the left ventral striatum (Richter *et al.*, 2015). Another study detected hypoactivation in the ventral striatum of bipolar disorder patients during the DRD paradigm (Trost *et al.*, 2014). Since bipolar disorder and schizophrenia are both linked to dopaminergic dysfunction (reviewed in Ashok *et al.*, 2017; reviewed in McCutcheon *et al.*, 2019), it was of great interest to find out whether the utilization of this paradigm can identify activation differences in reward-related brain areas between responders and non-responders. Indeed, results from this thesis indicated activation anomalies in reward processing associated brain regions such as the ventral striatum of aripiprazole responders and non-responders. However, it was not possible to make predictions about the success of the respective psychopharmacological treatment groups by applying data of these activation anomalies to the SVM algorithm.

In contrast, deactivations of the aripiprazole non-responders were able to predict treatment response. Deactivation of the hippocampus during the DRD paradigm might result from impaired dopaminergic modulation. Due to its dopaminergic input (Gasbarri *et al.*, 1997) the hippocampus is known to mediate reward processing and plays an important role in reinforcement learning (Stevens *et al.*, 1991). Therefore, disruptions of dopaminergic transmission in the hippocampal area, as previously found in schizophrenia (reviewed in Heckers and Konradi, 2010) and affective disorder patients, might result in decreased activations in the hippocampus during reward-related tasks. Furthermore, the administration of rewarding stimuli has been associated with improved memory consolidation (Messier and White, 1984). However, responding to the steady color change does not require long-term memory performance. Conversely, the activation of memory processes might interfere with the participants' reaction to constantly changing cue stimuli. Consequently, deactivation of the hippocampus through dopaminergic modulation might facilitate the execution of the task for patients.

In addition, aripiprazole non-responders revealed deactivations in the right pgACC, left precuneus and angular gyrus in during the desire context of the DRD paradigm. These brain regions have been associated with the DFM. In general, a lot of hypothesis-driven fMRI studies aim to induce activation patterns in brain regions associated with their hypothesis by applying cognitive paradigms which involve specific stimuli that supposedly elicit the hypothesized response. However, it was discovered already in the 1990s that subjects also show task-induced deactivation apart from the expected responses to certain stimuli (Haxby *et al.*, 1994; Kawashima *et al.*, 1995). Back then, these deactivations were thought to present a brain mechanism suppressing unnecessary background activation to enhance performance in brain regions involved in the task's execution (reviewed in Binder, 2012). Shulman *et al.* (1997) demonstrated in a meta-analysis that a lot of the task-induced decreases in blood flow were found in the same regions across various tasks. The most common explanation for this effect proposes that deactivations result from the redistribution of attentional activity from internal processes to task-relevant information. Therefore, these deactivations might be unspecific and overlap across various cognitive tasks as they might not be induced by specific stimuli but rather represent some form of suppression of processes that take place during "resting" or passive states.

Taken together, task-induced deactivations might be a marker for aripiprazole non-response. It is not clear why aripiprazole non-responders deactivated more than aripiprazole responders. As no significant differences in their behavioral data could be detected, it seems as if these differences might be based on specific pathomechanisms linked to DMN processes. Consequently, it could be proposed that corresponding subgroups might not respond very well to the dopamine partial agonist aripiprazole. They might, however, benefit from treatment with first- or second-generation antipsychotics.

Results of this thesis suggest the existence of subgroups within the schizophrenia-bipolar disorder- spectrum that have greater or fewer dysfunctions in the mesolimbic reward system as well as the DMN resulting in activation differences. These subgroups might also respond differently well to antipsychotic medication. Therefore, their subgroup-specific activation patterns might represent biomarkers for individual treatment response. This is in accordance with a study by Bak *et al.* (2017) who tried to identify subgroups within a sample of antipsychotic-naïve first-episode schizophrenia patients. In their study, a Gaussian mixture model with electrophysiological and cognitive data of the patients differentiated two subgroups after six weeks of treatment with amisulpride. Additionally, they investigated the correlation between PANSS scores and the two subgroups by applying SVM analyses. Even though univariate comparisons of demographic or clinical data at baseline did not yield any differences, SVM analyses were able to predict the treatment response with an accuracy of 74.3% (Bak *et al.*, 2017). In their conclusion, they called for multivariate and multimodal approaches to improve treatment on a symptom-based level. Another study conducted an

executive function task to identify subgroups of schizophrenia. The authors detected three clusters of schizophrenia patients that differed in their cognitive capacities (Carruthers *et al.*, 2019). Similar results have also been found in bipolar disorder (Kollmann *et al.*, 2019; Russo *et al.*, 2017). In addition, structural differences in brains of bipolar patients have been found, indicating subtypes within the same disease (Sarrazin *et al.*, 2018). These results underline the heterogeneity within the individual diagnoses, but also across schizophrenia, schizoaffective and bipolar disorder. They seem to form subclusters according to other scales and independent of their specific diagnosis. In addition, as mentioned before, the border between bipolar disorder and schizophrenia is fluent and sometimes bipolar disorder is also referred as a milder version along the schizophrenia spectrum (Argyelan *et al.*, 2014; Costafreda *et al.*, 2011; Crow, 1986; reviewed in De Peri *et al.*, 2012; Hill *et al.*, 2013; Krishnadas *et al.*, 2014). Therefore, it seems not surprising to find differences in the reward and DMN processing between the aripiprazole response groups. Consequently, the heterogeneity across the diagnoses might also affect the response to psychopharmacological treatment. This study demonstrated activation differences in mesolimbic areas and deactivations in DMN-associated brain regions. These results hint at different DMN- or reward-related pathophysiologies of the treatment groups which in consequence urge for differential treatment.

It is of great interest to understand the neurobiological correlates of the (de)activation differences between aripiprazole responders and non-responders in the reward condition of the desire context. A potential reason might be that the previously discussed functional heterogeneity within schizophrenia and bipolar patients is based on molecular, genetic and structural differences that influence the response to psychopharmacological medication. This is supported by a recent study reporting a subthreshold impact of epigenetic dopamine D2 receptor modifications on the response to aripiprazole treatment (Miura *et al.*, 2018). They hypothesized that epigenetic factors might influence dopaminergic transmission and hence affect treatment response of schizophrenia patients. In line with this, another study found that the genetic polymorphism of a dopamine metabolizing protein influenced the improvement of schizophrenia patients treated with aripiprazole (Kaneko *et al.*, 2018). In consequence, (epi)genetic variations causing alterations in the dopaminergic transmission of schizophrenia or bipolar patients might become visible as functional differences within the reward processing network. In addition, genetic polymorphisms of DAT affected the influence of aripiprazole on cue-elicited ventral striatum activation (Schacht *et al.*, 2018). This further supports the idea that neurobiological alterations of dopamine release in patients might be a predictor for treatment response. As proposed in this thesis, functional response differences might act as reliable biomarkers for individual treatment response prediction. It should be noted that even though the sample sizes are quite small in the aripiprazole groups, there seems to be a valid difference between responders and non-responders. However, due to the study design it is not possible to definitely identify the factors responsible for the discrepancy in the functional responses of the two groups.

In the next step, the SVM algorithm could differentiate between responders and non-responders based on deactivations but not activations. It can be hypothesized that functional changes in the DMN might be associated with different treatment responses. Further experiments will be needed to define the specificity of the deactivations in these brain regions. It is not clear whether these deactivations are reward- related or might appear independently of different context stimuli. Furthermore, regions of the DMN need to be further explored.

The SVM results predicted on the basis of the deactivation DRD parameter estimates with a balanced accuracy of 84.5% the treatment success of aripiprazole. In consequence, a translation of this result into the clinical setting could potentially predict in four out of five patients whether they would benefit from aripiprazole treatment or not. This would offer an enormous advantage over the current approach to drug administration. A look at the recent literature reveals that the rising call for personalized medicine, i.e. individually tailored treatment (Fernandes *et al.*, 2020; Fountoulakis and Stahl, 2020; Lenze *et al.*, 2020), also includes the application of treatment response prediction methods (reviewed in Kang and Cho, 2020; reviewed in Zhang *et al.*, 2020). In recent years clinical data, genetic features and other information such as electrophysiological data has been used to predict the treatment outcome of psychiatric patients. However, only a minority of studies have used neuroimaging results to estimate the success of the individual treatment of schizophrenia and bipolar patients. One of them was a proof-of-principle study using a linguistic machine learning system and fMRI data to predict lithium response of first-episode bipolar patients (Fleck *et al.*, 2017). They were able to reach 80% accuracy in validation of symptom decrease after the treatment (Fleck *et al.*, 2017). Another study tried to predict the response to haloperidol in schizophrenia patients. They could show that striatal D2 occupancy predicted antipsychotic response as well as side effects of haloperidol (Kapur *et al.*, 2000). In major depressive disorder research, neuroimaging has been used more often to find biomarkers that predict treatment response (Kozel *et al.*, 2011; McGrath *et al.*, 2013). One of these studies used structural MRI data and applied an SVM classifier to predict clinical outcome (Gong *et al.*, 2011). Their results demonstrated that grey matter as well as white matter could potentially forecast treatment success (Gong *et al.*, 2011). Additionally, SVM algorithms applied to neuroimaging data have been used to predict response to behavioral therapy of various psychiatric or personality disorders (Ball *et al.*, 2014; Mansson *et al.*, 2015; Schmitgen *et al.*, 2019). However, research of neuroimaging data being used as treatment response predictors is still limited. This was the first time a study used univariate results from a reward paradigm to predict treatment response by applying an SVM algorithm. Questions regarding the underlying pathomechanisms for different brain activation patterns between responders and non-responders still remain open and need to be examined in depth in the future.

Taken together, the use of artificial intelligence, i.e. machine learning, might offer a great opportunity to non-invasively predict the individual outcome of psychopharmacological

treatment. This, in turn, would lead to less trial-and-error drug administration and to a more efficient disease management.

4.3 General discussion

In this thesis, two fMRI studies examined differential pathophysiological processes of bipolar disorder and schizophrenia patients. Whereas in study A both diagnoses were compared categorically, study B used a transnosological approach to investigate the differential treatment responses.

Previous studies reported partly opposing activation abnormalities in bipolar disorder and schizophrenia patients during the DRD paradigm (Richter *et al.*, 2015; Trost *et al.*, 2014). Whereas bipolar disorder patients demonstrated hypoactivations (Trost *et al.*, 2014), schizophrenia patients presented hyperactivations in comparison to healthy controls (Richter *et al.*, 2015). The hypo- and hyperactivations were both located in the same brain area, i.e. the frontal lobe. Therefore, pathophysiologies seem to be located in similar brain regions in schizophrenia and bipolar patients. However, the direction of their activation differed in the two diseases. In addition, a study by Melcher *et al.* (2014) revealed differences in the behavioral data, i.e. performance and reaction times, between the schizophrenia and bipolar disorder spectrum in the combined oddball-incongruence paradigm in an independent sample. These prior results suggested subgroup-specific differences in the pathomechanisms of the two disorders and urged for a closer examination. This thesis aimed to further elaborate these subgroup-specific differences.

Study A found brain regions that were activated to varying degrees by alleged subgroups of the schizophrenia and bipolar disorder spectrum. The results show that specific pathophysiological processes, which can be addressed by the combined oddball-incongruence task, appear significantly more often in bipolar than schizophrenia patients. However, these group differences do not inevitably confirm diagnostic, categorical entities. On single case levels these effects might not be valid. It is important to note that diagnostic entities often limit the assertions of psychiatric studies. Therefore, more and more studies use a transnosological approach. Consequently, in the second part of this thesis a pilot study was conducted to retrospectively examine differential treatment response of bipolar and schizophrenia patients to different treatment arms. The results of study B indicate a biomarker for non-response to the dopaminergic partial agonist aripiprazole. The study revealed deactivations induced by the DRD paradigm, which were able to predict treatment response through the application of SVM algorithms. Additionally, activation in the NAc and avPFC can directly be associated with the DRD paradigm suggesting these brain areas to act as potential biomarkers. However, on a single case level it was not possible to divide responders from non-responders by applying these brain areas to the SVM.

In recent years the strict nosological division between bipolar disorder and schizophrenia once established by Kraepelin, started to soften towards a continuum between the two disorders. Continuously, new findings were published, demonstrating concordance of genetic, biological and phenomenological properties (Chan *et al.*, 2019; reviewed in Craddock *et al.*, 2006; Keshavan *et al.*, 2011; reviewed in Pearlson, 2015; Purcell *et al.*, 2009; Ruocco *et al.*, 2014; Tamminga *et al.*, 2013; reviewed in Whalley *et al.*, 2012). In consequence, a broad field emerged examining overlaps and differences between the two disorders. Various studies investigated cognition (Ancin *et al.*, 2013; reviewed in Bora and Pantelis, 2015; Hill *et al.*, 2013; Krishnadas *et al.*, 2014; Lewandowski *et al.*, 2014; Schretlen *et al.*, 2013; Smith *et al.*, 2009; Van Rheenen *et al.*, 2016; reviewed in Wang *et al.*, 2013), brain structure (Anderson *et al.*, 2013; reviewed in De Peri *et al.*, 2012; Haukvik *et al.*, 2015; Mathew *et al.*, 2014; Molina *et al.*, 2011; Nanda *et al.*, 2014; Rimol *et al.*, 2010; Womer *et al.*, 2014) and function (Costafreda *et al.*, 2011; Lui *et al.*, 2015) in comparative settings to understand the relation and pathophysiology of both disorders. Since some of the studies reported contradictory results, it is important to further examine and strive for a greater understanding of neurobiological pathomechanisms influencing the effects of bipolar disorder and schizophrenia. Future experiments hence ought to follow the idea of the Research Domain Criteria (RDoC) Initiative to perceive psychiatric disorders, in particular schizophrenia and bipolar disorder, as spectrums and preferably work with dimensions of detectable neurobiological and behavioral features (Insel *et al.*, 2010). In study A schizophrenia patients displayed similar, but low-threshold effects compared to bipolar disorders. Therefore, a better approach might be to categorize the groups according to biological or behavioral features rather than solely their respective diagnosis. A multimodal approach of neuroimaging data involving results from tasks eliciting different cognitive or emotional pathways, might improve the understanding of causes for the partly overlapping symptomatology.

The ultimate goal connecting both studies is the importance and relevance to improve the current status quo of psychiatric treatment. A recent study by Wolfers *et al.* (2018) examined a great sample of bipolar and schizophrenia patients' brain structures and concluded that an average patient does not exist. They reported massive interindividual differences and an overlap of more than two percent in only a few brain loci (Wolfers et al., 2018). Therefore, a deeper understanding of the deficits in the reward and attention system as well as alterations in the DMN of bipolar disorder and schizophrenia might eventually make it possible to treat psychiatric disorders more specifically or even individually customized to the respective patients' needs and impairments. Personalized psychiatric treatment would give patients the opportunity to receive the most effective treatment possible and reduce long periods of illness.

4.4 Limitations and Outlook

Study A revealed convincing indications for aberrant activations of the frontoparietal networks of bipolar and schizophrenia patients depending on the difficulty of attentional tasks. However, the study also faced some limitations. First, the sample sizes of the patient groups and healthy individuals varied a lot. In future studies the different groups should consist of similar sample sizes to avoid undesirable influences on the effect size. Furthermore, the patients participating in this study received different psychopharmacological medication. On the one hand, this mirrors a naturalistic setting as both disorders realistically present a very heterogeneous clinical picture with often more than one psychopharmacological drug. On the other hand, to exclude possible effects of medication on the performance and brain activation of the patients, it would be better to include either medication-naïve or monotherapeutically treated patients (preferably with the same psychopharmacological agent). Another limitation of this study might be that the conditions, oddball and incongruence deviate from "typical" oddball and incongruence tasks. As they, in contrast to classical oddball and incongruence experiments, contain two dimensions, it is possible that bottom-up and top-down processes take place concurrently. As a consequence, the cognitive control processes as well as stimulus-driven bottom-up processes would both be depicted in the results and it would not be possible to distinguish them. Lastly, the patients' ages differed, i.e. schizophrenia patients were on average younger than the bipolar patients. This is no surprise as the chance of chronification in schizophrenia patients increases with proceeding age. Bipolar patients, though, commonly keep a quite constant level of cognitive performance over the years. Therefore, oftentimes younger schizophrenia patients are included into studies as they are still able to handle the challenges of the oftentimes demanding study designs. To make sure that age had no impact on the results described in the previous chapters, the univariate fMRI analyses were repeated with the covariate age. The results did not display any major differences compared to the prior results. It can be concluded that even though the mean age differed between the two patient groups, the resulting effects originated from valid psychopathological anomalies.

It is important to note that study B was a small estimated pilot study in order to look for potential effects and does not replace the necessity of a large-scale clinical study. The sample sizes were very small; hence, all results need to be revised carefully. However, even though the sample sizes were very small in the different treatment response groups, significant differences between the responder and non-responder aripiprazole group could be detected. An examination of the raw data revealed that the differences were not attributable to one single outlier, but rather the quite homogeneous non-responder group. This gives a first hint of potential underlying differences in neural networks and processing of this treatment group but must be further elaborated to get to the bottom of this effect. Furthermore, an objective response criterion must be implemented. Other studies have used independent scores of e.g. the PANSS or CGI etc. to define treatment response/ success. An objective response criterion

would give an opportunity to better understand the origin of activation differences. Another important improvement would be to only compare monotherapeutically treated patients. A mix or wide range of antipsychotic, antidepressant etc. administration makes it hard to determine which drug was responsible for the treatment success. However, it is also important to mention that unmedicated schizophrenia and bipolar patients can often not be recruited for clinical studies as the severity of their symptoms would not make it possible to complete the demanding fMRI tasks. Taken together, future studies trying to identify biomarker for treatment response should ideally strive for the following key aspects in their study design:

1) Baseline measurement of clinical state on the basis of objective psychopathological scales such as PANSS, CGI, MADRS etc.
2) Monotherapeutic treatment with either an atypical or typical antipsychotic or aripiprazole
3) Assignment to the responder or non-responder group on the basis of cut-off values of psychopathological scores

However, due to the difficulties of thoroughly implementing such a complex and challenging study design, not many studies developing strategies for treatment prediction have been published, yet. Nevertheless, the realization of a similar but larger study has great potential to identify biomarkers that predict individual treatment response in psychiatric patients.

Taking everything into account, both studies found exclusive results in fields that have not yet been extensively researched. On the one hand, this thesis could provide some interesting novel insights into cognitive control processes of bipolar and schizophrenia patients. The presented results and their interpretation suggest some kind of balanced cognitive control system that destabilizes when too much mental load is expected. Future studies will need to replicate these findings in an independent sample and try to identify the underlying neural correlates in more detail. Treatment response prediction using neuroimaging data, on the other hand, will probably be explored much more in the following years. The technical usage of artificial intelligence, i.e. SVM algorithms, is booming in biotechnological areas and will ultimately also be applied to neuroimaging data. It yields great opportunities for personalized psychiatric treatment and will be useful to treat patients more efficiently, thereby reducing their time of suffering.

5 SUMMARY/ZUSAMMENFASSUNG

5.1 Summary

Psychiatric disorders, in particular schizophrenia and bipolar disorder, affect the patients' lives deeply on many levels and place a heavy burden on the healthcare system. The treatment of these diseases is often complicated and marked by many setbacks. Symptoms that have the strongest consequences for coping with everyday life are the impairments of cognitive performance, for example memory or attention deficits. Therefore, it is of great interest to better understand the underlying pathomechanisms to eventually improve treatment options for those patients. In this thesis two different fMRI studies were used to investigate the functional correlates of patients suffering from schizophrenia or bipolar disorder while performing a combined oddball-incongruence task and a reward associated task.

Study A conducted a categorical comparison between bipolar and schizophrenia patients of the brain activation during an oddball and incongruence task. The results showed pathophysiological differences in the activation intensities between bipolar and schizophrenia patients as well as between the patient groups and healthy individuals. Overall it seems as if the brain activation severely depended on the task difficulty leading to compensatory hyperactivations in frontal brain areas of bipolar patients during the oddball task. Schizophrenia patients demonstrated low threshold hyperactivations in the intraparietal cortex compared to healthy controls. In the cognitively more demanding incongruence condition these compensatory mechanisms seemed to fail leading to hypoactivations in various brain regions such as the middle frontal gyrus or ventral pathway.

Pilot study B searched retrospectively for functional markers which enable support vector machine algorithms predicting specific treatment response to typical and atypical antipsychotics as well as aripiprazole in a transnosological sample consisting of bipolar and schizophrenia patients. Consequently, (de-)activation differences between responders and non-responders in their respective treatment arm resulting from the desire-reason-dilemma paradigm were applied to support vector machine algorithms. The implementation of parameter estimates from deactivations of aripiprazole non-responders in brain regions partially associated with the default mode network, led to a successful treatment response prediction of patients receiving aripiprazole.

Even though in future studies the sample sizes should be increased and monotherapeutical treatment ensured, this thesis already provides important insights on the pathomechanisms of bipolar disorder and schizophrenia patients or more specifically within the spectrum of both diseases. Prospectively, further studies can help to specify potential functional biomarkers which also might be able to predict treatment response and consequently approach personalized precision treatment in psychiatric disorders.

5.2 Zusammenfassung

Psychiatrische Erkrankungen, insbesondere Schizophrenie und bipolare Störung, haben schwerwiegende Auswirkungen auf das Leben der Betroffenen und stellen eine große Belastung für das Gesundheitssystem dar. Die Behandlung dieser Krankheiten ist oftmals kompliziert und von häufigen Rückschlägen geprägt. Symptome, die besonders starke Konsequenzen auf die Bewältigung des Alltags der Erkrankten haben, sind verschiedene Beeinträchtigungen der kognitiven Leistung, wie z.B. des Gedächtnisses und der Aufmerksamkeit. Aus diesem Grund ist es von großem Interesse, die Ursachen der zugrundeliegenden Pathomechanismen genauer zu verstehen, um gegebenenfalls die Behandlungsmöglichkeiten zu verbessern. In dieser Dissertation wurden mittels zwei verschiedener funktioneller Magnetresonanztomographiestudien die funktionellen Korrelate von Patientinnen und Patienten, die an Schizophrenie oder bipolarer Störung erkrankt sind, während sie eine kombinierte Oddball-Inkongruenz-Aufgabe und eine belohnungsassoziierte Aufgabe bearbeiten, genauer untersucht.

In Studie A fand ein kategorischer Vergleich der Gehirnaktivierung zwischen bipolaren und schizophrenen Patientinnen und Patienten, sowie gesunden Kontrollen, während des Oddball- und Inkongruenzeffekts statt. Die Ergebnisse zeigten pathophysiologische Unterschiede in der Intensität der Aktivierungen bei den bipolaren im Vergleich zu den schizophrenen Patientinnen und Patienten, als auch zwischen den Erkrankungsgruppen und der gesunden Kontrollgruppe. Insgesamt scheinen die Gehirnaktivierungen stark von der Aufgabenschwierigkeit abzuhängen, sodass bipolare Patientinnen und Patienten in der leichteren Oddball-Aufgabe potentielle kognitive Defizite mit teils diagnose-spezifischen Hyperaktivierungen im frontalen Bereich kompensieren konnten. Schizophrene Probandinnen und Probanden zeigten hier nur leichte Hyperaktivierungen im intraparietalen Kortex im Vergleich zu den gesunden Kontrollen. In der schwierigeren Inkongruenz-Aufgabe schienen die Kompensationsmechanismen zu versagen, sodass nun diagnose-unspezifische Hypoaktivierungen in zahlreichen, u.a. auch frontalen, Hirnarealen der beiden Erkrankungsgruppen auftraten.

In Studie B wurden pilotierend retrospektiv funktionelle Marker gesucht, mit denen Support Vector Machine-Analysen das differentielle Ansprechen auf typische und atypische Antipsychotika sowie Aripiprazol von schizophrenen und bipolaren Individuen in einer transnosologischen Stichprobe vorhersagen können. Dabei wurden (De-) Aktivierungsunterschiede zwischen Respondern und Nicht-Respondern der jeweiligen Psychopharmakagruppen im Desire-Reason-Dilemma-Paradigma verglichen und für die Auswertung mit Support Vector Machine-Algorithmen genutzt. Unter Verwendung der Intensitätswerte von Deaktivierungen in Hirnarealen der Aripiprazol Non-Responder, die unter anderem mit dem Default Mode Network assoziiert zu sein scheinen, war es möglich den Therapieerfolg von Aripiprazolbehandelten vorherzusagen.

Auch wenn in zukünftigen Studien die Stichprobengröße erhöht und eine monotherapeutische psychopharmakologische Behandlung der Patienten gewährleistet werden sollte, liefert diese Doktorarbeit wichtige Erkenntnisse über die Pathomechanismen in Patienten mit bipolarer Störung oder Schizophrenie – beziehungsweise innerhalb des Spektrums beider Erkrankungen. Zukünftig können weitere Studien helfen, potentielle funktionelle Marker zur Vorhersage des Therapieerfolgs zu präzisieren und der personalisierten Behandlung ein Stück näher zu kommen.

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7 Eigenanteil an Datenerhebung und Datenauswertung und eigene Veröffentlichungen

Im Rahmen meiner Promotion habe ich Verhaltensdaten, sowie Daten aus der funktionellen Magnetresonanztomographie von über 80 Patientinnen und Patienten für die laufenden vom BMBF bzw. der DFG geförderten Projekte BipoLife B2 und Psycourse Teilprojekt 2 Workpackage 1 erhoben und analysiert. Für die Doktorarbeit habe ich auf bereits zuvor von anderen Mitarbeiterinnen (Dr. Sarah Trost und Alexandra Petrovic) erhobene Daten zurückgegriffen, deren Analysen jedoch selbstständig geplant und durchgeführt. Diese Arbeit verwendete für die Auswertung Daten aus langfristig angelegten Projekten von Herrn Professor Grubers Professur in Göttingen, insbesondere aus DFG-geförderten Projekten innerhalb der KFO241 sowie aus parallellaufenden, nicht Drittmittel-geförderten Projekten. Die Auswertungen bezüglich der Differenzierung von Aufmerksamkeitsnetzwerken bipolarer im Vergleich zu schizophrenen Patienten und gesunden Kontrollen während einer kombinierten Oddball-Inkongruenz-Aufgabe wurden vollständig von mir durchgeführt und sind eins der beiden zentralen Ergebnisse dieser Dissertationen. Die univariaten Auswertungen bezüglich der Vorhersage der Therapieprädiktion von bipolaren und schizophrenen Patienten anhand von funktionellen MRT- Aktivierungen induziert durch das DRD Paradigma wurden vollständig von mir durchgeführt und lieferten die Grundlage der folgenden Support Vector Machine-Analysen. Diese wurden von Herrn Dr. Evgeny Gladilin durchgeführt und sind in Kapitel 3.3 zu finden. Die wissenschaftliche Einordnung, Interpretation und Diskussion aller Daten wurden von mir übernommen.

Teilergebnisse der vorliegenden Arbeit wurden in folgendem Aufsatz zur Publikation eingereicht:

Rauer, L., Trost, S., Petrovic, A., Gruber, O. (2020) **Cortical activation abnormalities in bipolar and schizophrenia patients in a combined oddball-incongruence paradigm.** Eur Arch Psychiatry Clin Neurosci, Epub ahead of print, doi: 10.1007/s00406-020-01168-1

Diese Publikation basiert auf den Ergebnissen aus den Dissertationskapiteln 3.1.1 und 3.2.1. Auch die Diskussion der potentiell unterliegenden Pathophysiologien der beiden Patientengruppen während der Aufmerksamkeitsaufgabe wurde in dieser Publikation inhaltlich abgebildet (s. Kapitel 4.1). Mein Eigenanteil an der Publikation erstreckt sich auf die Qualitätskontrolle, Analyse und Auswertung der Daten bezüglich des Oddball- und Inkongruenzeffekts, der Interpretation der Ergebnisse und das Schreiben des Manuskripts, inklusive der Einleitung, des Material- und Methodenteils sowie der Ergebnisse und der Diskussion.

EIDESSTATTLICHE VERSICHERUNG

1. Bei der eingereichten Dissertation zum Thema „Examinations of pathomechanisms in schizophrenic and bipolar disorders – results from two functional magnetic resonance imaging studies“ 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.

3. Die Arbeit oder Teile davon habe ich bislang nicht an einer Hochschule des In- oder Auslands als Bestandteil einer Prüfungs- oder Qualifikationsleistung vorgelegt.

4. Die Richtigkeit der vorstehenden Erklärungen bestätige ich.

5. Die Bedeutung der eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unrichtigen oder unvollständigen eidesstattlichen Versicherung sind mir bekannt. Ich versichere an Eides statt, dass ich nach bestem Wissen die reine Wahrheit erklärt und nichts verschwiegen habe.

Stuttgart, 06.06.2020