A Systems Neuroscience Perspective on Treatment Resistant Schizophrenia
The Role of Cognitive Control, Reinforcement Learning, and Myelination

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A Systems Neuroscience Perspective on Treatment Resistant Schizophrenia: The Role of Cognitive Control, Reinforcement Learning, and Myelination

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Contents

Abstract

Approximately a third of patients with schizophrenia do not respond to antipsychotic treatment targeting the dopamine system, suggesting that a separable neural dysfunction may drive psychosis in these patients. This thesis aims to probe the mechanisms underlying treatment response by investigating two cognitive processes which have been implicated in schizophrenia – cognitive control and reinforcement learning – as well as brain myelination. The key hypotheses are that 1) treatment resistant schizophrenia emerges due to a failure to exert cognitive control, characterised by prefrontal hypoactivation and functional dysconnectivity, 2) treatment responsive schizophrenia is selectively associated with a subcortical dopaminergic dysfunction, evident in an abnormal neural signature of reward prediction error (RPE) during reinforcement learning, and 3) treatment resistant schizophrenia is characterised by exacerbated structural dysconnectivity as indexed by myelin content. To dissect these mechanisms, performance and neural activation during a cognitive control task and a reinforcement learning task, as well as myelin water fraction (MWF) were compared between 22 treatment resistant patients, 21 treatment responsive patients, and 24 healthy controls. Treatment resistant and responsive patients showed similarly impaired performance on both tasks compared to controls. During the cognitive control task, resistant patients showed an inverse correlation between frontal activation and psychotic symptoms as well as reduced functional fronto-thalamic connectivity compared to controls. During the reinforcement learning task, responsive patients showed reduced cortical and subcortical RPE related activation compared to controls and treatment resistant patients. MWF was reduced in patients compared to controls in several white matter regions but did not differ between the two patient groups. The findings support distinct neural mechanisms underlying treatment resistant and responsive schizophrenia despite similar behaviour. Functional dysconnectivity within the cognitive control network and a deterioration of frontal activation as a function of symptom severity may perpetuate psychosis despite dopaminergic treatment in treatment resistant schizophrenia, although this is not reflected in an exacerbated myelin dysfunction. The results highlight the importance of stratifying patient samples by treatment response status in future research.

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List of Abbreviations

ACC	Anterior cingulate cortex
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AVH	Auditory verbal hallucinations
BOLD	Blood oxygenation level dependent
BPRS	Brief Psychiatric Rating Scale
CSF	Cerebral spinal fluid
CSTC	Cortico-striatal-thalamic-cortical
CT	Computed tomography
DLPFC	Dorsolateral prefrontal cortex
DTI	Diffusion tensor imaging
EPS	Extrapyramidal symptoms
FA	Fractional anisotropy
FEP	First episode psychosis
fMRI	Functional magnetic resonance imaging
FWHM	Full width at half maximum
GABA	Gamma amino butyric acid

GLM	General linear model
HC	Healthy control
HRF	Hemodynamic response function
ICM	Intracortical myelin
MRI	Magnetic resonance imaging
MWF	Myelin water fraction
NTR	Non-treatment resistant schizophrenia
OFC	Orbitofrontal cortex
PANSS	Positive and Negative Symptom Scale
PET	Positron emission tomography
PPI	Psychophysiological interaction
RL	Reinforcement learning
ROI	Region of interest
RPE	Reward prediction error
RT	Reaction time
SMA	Supplementary motor area
SNR	Signal to noise ratio
SPM	Statistical parametric map
TFCE	Threshold-free cluster enhancement
TPJ	Temporal parietal junction
TRS	Treatment resistant schizophrenia
UHR	Ultra-high risk
WCST	Wisconsin Card Sorting Test

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Chapter 1

Introduction

1.1 Overview

Schizophrenia is a severe mental disorder which affects approximately 1% of the population worldwide (Jablensky, 2000). It is characterised by positive (psychotic) symptoms, negative symptoms, as well as cognitive impairments. Symptoms of psychosis include delusions, hallucinations, and thought disorder, resulting in an often distressing distortion of reality. Negative symptoms consist of an absence of normal functioning due to factors such as flattened affect, anhedonia, social withdrawal, and diminished expression, constituting a major cause of disability in schizophrenia. The introduction of antipsychotic medications in the 1950s revolutionised the treatment of this devastating illness and drastically improved the average prognosis for affected individuals. However, a large proportion of patients – variably estimated to be as large as 40% – do not respond adequately to antipsychotic medication (Lindenmayer, 2000; Mortimer, Singh, Shepherd & Puthiryackal, 2010). These patients continue to experience symptoms of schizophrenia and their debilitating effects on every-day life despite optimal treatment. This form of "treatment resistant" schizophrenia (TRS) continues to be one of the most significant areas of unmet need in psychiatry, as to date our understanding of the mechanisms underlying antipsychotic treatment resistance remains incomplete.

All currently licensed antipsychotics exert their therapeutic effect via blockade of dopamine D2 receptors (Kapur & Seeman, 2001; Seeman & Lee, 1975; Seeman, Lee, Chau-Wong & Wong, 1976), leading to the prevailing theory of subcortical

hyperdopaminergia in schizophrenia (Kapur, Mizrahi & Li, 2005; Howes & Kapur, 2009). Research has suggested that TRS may not fit into the classic dopamine model of schizophrenia (Coppens et al., 1991; Wolkin et al., 1989; Demjaha, Murray, McGuire, Kapur & Howes, 2012; Demjaha et al., 2014; Mouchlianitis et al., 2015) and may constitute a neurobiologically discrete subtype of the illness. However there is a distinct lack of research explicitly contrasting TRS with treatment responsive schizophrenia which could lead to a more effective tailoring of treatment (Mouchlianitis, McCutcheon & Howes, 2016; Nakajima et al., 2015). Although there has been an increase in in-vivo structural neuroimaging studies in recent years, the underlying function of the brain in the context of cognition and decision making has not been thoroughly explored.

Dysfunctional cognitive processing has long been regarded as a core feature of schizophrenia (Keefe & Harvey, 2012) and is likely to play an important role in symptom formation and maintenance (Freeman, Garety, Kuipers, Fowler & Bebbington, 2002; Garety, Kuipers, Fowler, Freeman & Bebbington, 2001). In this regard schizophrenia is frequently described in terms of a dysconnection syndrome, with symptoms of psychosis emerging as a result of a dysfunctional integration of different cognitive functions subserved by distributed networks in the brain (Cannon, 2015; Friston, Brown, Siemerkus & Stephan, 2016; Friston & Frith, 1995; Stephan, Friston & Frith, 2009). In particular, it has been suggested that impairments in distinct regions of cortico-subcortical networks may be involved in distinguishable aspects of symptom formation in psychosis. For example, striatal hyperdopaminergia is thought to cause errors in attributing salience to reward-predicting stimuli, while dysfunctions of the prefrontal cortex associated with hypodopaminergia may be involved in delusion formation (Heinz & Schlagenhauf, 2010). As a result, treatment may target abnormalities in one, but not another, node of a relevant network. Thus, while antipsychotics attenuate striatal hyperdopaminergia, symptoms may persist despite treatment in the absence of a normative response from prefrontal cortex.

Intact integration of prefrontally modulated control processes with dopamine driven reward signals is particularly important during reinforcement learning, which is known to be impaired in schizophrenia (Gold, Waltz, Prentice, Morris & Heerey, 2008; Deserno, Schlagenhauf & Heinz, 2016). In this thesis, I will explore the hypothesis that TRS is characterised by an exacerbated dysfunction of pre-

frontal cognitive control, particularly in the context of feedback learning. Within this framework, I will first utilise functional magnetic resonance imaging (fMRI) in order to compare both the behaviour and underlying neural mechanisms of treatment resistant and treatment responsive patients with schizophrenia, as well as healthy control subjects, on a standard measure of cognitive control, the Stroop task (Stroop, 1935). Following on from this, cognitive control in the context of feedback learning will be assessed in an fMRI study using a reinforcement learning task which is known to elicit a cognitive bias (Averbeck & Duchaine, 2009). In order to perform well on this task, cognitive control has to be exerted so as to overcome the bias and learn adequately from ongoing feedback. Finally, since abnormal cognitive integration is likely to be modulated by underlying structural dysconnectivity, I will assess myelin content in the brain using a novel imaging technique (mcDESPOT; Deoni, Rutt, Arun, Pierpaoli & Jones, 2008) in order to determine whether more severe white matter changes in TRS can account for the lack of response to antipsychotic treatment. The following introductory sections will provide an overview of antipsychotic treatment and treatment resistance, as well as an outline of the relevant existing literature on cognitive control, reinforcement learning, and white matter changes in schizophrenia.

1.2 Treatment resistant schizophrenia (TRS)

1.2.1 Pharmacological treatment of schizophrenia

The serendipitous nature of the discovery of antipsychotic medication rarely goes unmentioned in historical accounts of treatment for schizophrenia (e.g., Kapur & Mamo, 2003, Carpenter & Davis, 2012). The observation in the 1950s that chlorpromazine exerts a therapeutic effect on symptoms of psychosis was not borne out of scientific experimentation following a mechanistic understanding of psychotic illnesses. Rather, the compound, which had been developed as an antihistamine for use in general anaesthesia (Charpentier, Gailliot, Jacob, Gaudechon & Buisson, 1952), was trialled in psychiatric populations after its "neuroleptic" effects on the central nervous system were discovered (Delay, Deniker & Harl, 1952; Laborit, Huguenard & Alluaume, 1952). In the decades that followed, a neuroscientific understanding of psychosis was built predominantly in the course of studying

how chlorpromazine and similar pharmacological agents exert their effects on the brain. The recognition throughout the 1960s and 1970s that dopamine receptor antagonism was one of the main mechanisms of action of these drugs (Carlsson & Lindqvist, 1963), and particularly the findings that the extent of D2 receptor affinity was closely coupled with their antipsychotic effect, have shaped the prevailing understanding of psychosis as a state of subcortical hyperdopaminergia to this day (Seeman & Lee, 1975; Seeman et al., 1976; Creese, Burt & Snyder, 1976; Kapur & Seeman, 2001; Howes & Kapur, 2009).

Antipsychotics are clustered into typical (chlorpromazine being the earliest of this first generation) and atypical (or second generation) antipsychotics, although the defining criteria of atypicality are not clearly delineated. Clozapine, the prototype of atypical antipsychotics, was hailed as showing greater antipsychotic efficacy as compared with typical antipsychotics chlorpromazine and haloperidol, as well as a reduced tendency to evoke extrapyramidal side effects (EPS) (Kane, Honigfeld, Singer & Meltzer, 1988). Thus, atypical antipsychotics are generally classed as such if they show a therapeutic effect in the absence of significant EPS (Kinon & Lieberman, 1996). However all antipsychotic medications have in common, to varying extents, an antagonistic action at the dopamine D2 receptor site (Creese et al., 1976). D2 receptors are mostly expressed subcortically in the striatum, thus leading to the dominant aetiological theory of increased striatal dopamine in schizophrenia (Carlsson, 1988; Kapur, 2003; Abi-Dargham, 2004). Recent developments in the field of neuroimaging have allowed for explicit tests of this theory in vivo, overwhelmingly converging on the finding of increased striatal dopaminergic neurotransmission in schizophrenia (Hietala et al., 1995; Abi-Dargham et al., 1998; Lindström et al., 1999; Abi-Dargham et al., 2000; Meyer-Lindenberg et al., 2002). However, despite these breakthrough developments in the treatment and neurobiological understanding of schizophrenia, a number of contradictions and obscurities remain. One is that atypical antipsychotics can have somewhat lower affinity to D2 receptors, yet have showed at least equivalent efficacy to typical antipsychotics. Reduced blockade of D2 receptors is likely the cause for an improvement in EPS, which could in turn ameliorate concomitant negative and cognitive symptoms. However, it is more difficult to explain the at least equal, if not increased, efficacy in treating positive symptoms. The second, and related issue, is that only few antipsychotic drugs are selective dopamine D2 ant-

agonists, and most exert effects on a wide range of receptors, including other dopaminergic (D1, D3, D4), serotonergic, muscarinic cholinergic, and histamine receptors. The extent to which action at other receptor sites increases the therapeutic effects of antipsychotics remains elusive, although atypical antipsychotics have been suggested to improve symptoms as a function of their 5HT2/D2 affinity ratio (Meltzer, Matsubara & Lee, 1989). A further, crucial point is that schizophrenia is characterised not only by psychotic symptoms, but also debilitating negative and cognitive symptoms, impacting on individuals' affective, social, volitional, and motivational lives. Currently licensed antipsychotic medications have very limited efficacy in treating these symptoms. Lastly, antipsychotic medication proves ineffective in treating symptoms in a large remaining proportion of patients with schizophrenia despite adequate dopamine D2 receptor binding (Wolkin et al., 1989; Coppens et al., 1991).

Taken together, a dopamine dysfunction is unlikely to be the primary or sole neurobiological aetiological factor in the development of schizophrenia. Research into the development of new antipsychotic drugs has focused on other neurobiological targets including the glutamate, gamma amino butyric acid (GABA), serotonin, and acetylcholine systems, as well as inflammation and oxidative stress (Keshavan, Lawler, Nasrallah & Tandon, 2017). However to date, these approaches have not been successful in clinical trials and dopamine antagonism remains the main mechanism of action of all currently approved antipsychotic drugs.

1.2.2 Definitions and course of TRS

Approximately 30-40% of patients with a diagnosis of schizophrenia are considered to be treatment resistant (Lindenmayer, 2000; Mortimer et al., 2010). Conceptually, TRS is characterised by a lack of symptomatic response to antipsychotic medication at adequate dose and duration. In practice, however, the precise definition of "adequacy" in terms of medication dose and duration has varied throughout the literature, as has the extent of symptomatic change required to constitute response (Suzuki et al., 2012). A widely adopted approach to operationalising TRS with respect to these issues was first offered by Kane et al. (1988), who proposed the following criteria for treatment resistance:

- at least three previous periods of treatment with antipsychotics at dosages

of ≥1000 mg per day of chlorpromazine (or equivalent) for a period of at least six weeks without symptomatic relief

- no period of good functioning in the preceding five years.
- score of ≥45 on the Brief Psychiatric Rating Scale (BPRS)
- severity score ≥4 on two or more BPRS psychotic symptom items

However, these criteria have been modified by several groups in recent years to reflect a more inclusive definition of TRS. Since it has become increasingly clear that patients who failed to respond to two antipsychotic treatment trials are highly unlikely to respond to a third (Kinon, Kane, Perovish, Ismi & Koreen, 1992), there is a general consensus that two failed treatment periods are just as predictive as three to establish treatment resistance (Conley & Kelly, 2001). Similarly, recent operationalisations of TRS require previous treatments to have been administered at 400 mg (Conley & Kelly, 2001) or 600 mg (Suzuki et al., 2012) chlorpromazine equivalent per day. The Maudsley Prescribing Guidelines in Psychiatry (D. M. Taylor, Paton & Kapur, 2015) in fact recommends a consideration of patients as treatment resistant if they have failed to respond to at least two previous mediations at at least minimum effective dosage. Criteria for psychopathological severity differ depending on whether studies are cross-sectional, therefore requiring an absolute threshold of symptom severity, or prospective, allowing for a direct assessment of symptom reduction post-treatment. In the latter case, good response to treatment is typically defined as a >20% symptom reduction on the BPRS or Positive and Negative Symptom Scale (PANSS; Kay, Flszbein & Opfer, 1987) compared to baseline (Kane et al., 1988; Elkis, 2007; Suzuki et al., 2012). Cross-sectional studies typically retain Kane et al.'s (1988) criterion of a score of 4 (moderate severity) or more on at least two positive symptom items of the BPRS or PANSS. In 2016, the Treatment Response and Resistance in Psychosis (TRRIP) working group was formed to review and revise consensus guidelines for defining treatment resistant schizophrenia in clinical trials. The minimum requirement for TRS agreed upon by this group includes symptoms of at least moderate severity for 12 weeks or more; two or more past adequate treatment episodes with different antipsychotic drugs for 6 weeks or more at an equivalent dosage of 600mg chlorpromazine a day; and medication adherence of at least 80% of the prescribed doses (Howes et al., 2016).

In their seminal study, Kane et al. (1988) established the superior efficacy of clozapine in treating patients who meet criteria for TRS. Around 50% of treatment resistant patients are thought to respond to clozapine (Chakos, Lieberman, Hoffman, Bradford & Sheitman, 2001). Clozapine remains, to this day, the mainstay treatment for TRS; however, due to the potentially severe adverse effects associated with the drug (J. Nielsen, Correll, Manu & Kane, 2013), notably the increased risk for agranulocytosis, it remains underprescribed. Once prescribed, it requires ongoing haematological and physiological monitoring (Beck et al., 2014), but side effects can generally be well managed with the relevant expertise (D. D. Miller, 2000). Despite this, clozapine prescribing is delayed in the UK, with an average of 4 to 5 years delay before clozapine initiation (D. M. Taylor, Young & Paton, 2003; Howes et al., 2012). In 2001, patients in southeast London experienced an average of 9.2 medication prescription trials prior to clozapine (D. M. Taylor et al., 2003), in contrast to the recommended two. This period of inadequately treated TRS is likely to increase the burden both on the affected individuals and the health care system (Aitchison & Kerwin, 1997; Essock, Frisman, Covell & Hargreaves, 2000; Hayhurst, Brown & Lewis, 2002).

TRS is associated with a large number of adverse consequences. Treatment resistant patients require more frequent and longer hospitalisations compared to the average schizophrenia population (Lindenmayer, 2000). As a result, TRS takes up a disproportionate volume of the total cost for treating schizophrenia, with a recent estimation lying at approximately 60-70% of total costs (Kennedy, Altar, Taylor, Degtiar & Hornberger, 2014). The burden associated with TRS is further evidenced in a significant decrement in quality of life, as well as an increase in suicide risk, violence, and comorbidity rates (Kennedy et al., 2014; Conley & Kelly, 2001). There is consistent evidence that persistent symptoms despite treatment result in significant cognitive and functional decline (Strassnig & Harvey, 2014; Harvey & Rosenthal, 2016). Several recent studies have shown that treatment refractory patients exhibit greater cognitive impairment as well as negative symptoms compared to treatment responsive patients (de Bartolomeis et al., 2013; Frydecka, Beszlej, Goscimski, Kiejna & Misiak, 2016), and are more impaired in their everyday functioning (Iasevoli et al., 2016). Importantly, TRS becomes more difficult to treat as the illness progresses, with time to remission increasing with each consecutive relapse (Lindenmayer, 2000). The importance of identifying

TRS early on in the illness was highlighted by two recent studies showing that 70-80% of TRS patients are in fact treatment resistant from illness onset, but still experience long delays to clozapine initiation (Lally et al., 2016; Demjaha et al., 2017). In terms of risk factors for developing TRS, demographic and clinical correlates include male gender, early age at illness onset, poor premorbid functioning, history of substance abuse, and a family history of schizophrenia (Huber, Gross, Schüttler & Linz, 1980; Lieberman et al., 1993; Meltzer, Rabinowitz, Lee, Cola et al., 1997; Lindenmayer, 2000; Lally et al., 2016).

Despite the fact that treatment resistance has been a consistent phenomenon since the advent of antipsychotic medication, the pathophysiology of treatment refractoriness remains unclear. Although it is widely accepted that clozapine has a higher efficacy than conventional antipsychotic treatment in TRS, the mechanisms by which its superiority takes effect are incompletely understood. There is a great need for a more comprehensive understanding of the neural mechanisms underlying TRS. This could lead to early identification of refractoriness through predictive biomarkers and subsequent acceleration of clozapine initiation, as well as to the informed development of research strategies into potential new avenues for treatment of TRS.

1.2.3 Neuroimaging evidence in TRS

1.2.3.1 Structural imaging findings

One of the earliest observations of structural brain differences between remitted and non-remitted patients with schizophrenia was made by K. L. Davis et al. (1998), who reported increased ventricle size in poor-outcome patients using computed tomography (CT), with a progressive course of further ventricular increase over a 4 year span. The subsequent advances in neuroimaging techniques, notably MRI, have lead to a proliferation of studies investigating brain structure in schizophrenia as well as TRS specifically. Volumetric studies have shown decreases in frontal and occipital grey matter volume in TRS patients compared to healthy controls (Molina et al., 2008), as well as in widespread regions – particularly frontal and temporal structures – compared to treatment responsive patients (Lawrie et al., 1995; Quarantelli et al., 2014; Anderson, Goldstein, Kydd & Russell, 2015).

These findings are in line with research showing that cortical grey matter volume in first episode psychosis (FEP) is correlated with subsequent treatment response (Zipursky, Zhang-Wong, Lambe, Bean & Beiser, 1998). Interestingly, grey matter volume reductions in medial frontal, insular, and bilateral temporal cortical regions have been specifically linked to treatment resistant auditory verbal hallucinations, suggesting a direct association between cortical volume and persistent symptoms (Kubera et al., 2014). More widespread reductions in cortical thickness have also been observed in TRS patients than in responsive patients compared to healthy controls (Zugman et al., 2013; Ahmed et al., 2015), and response to clozapine is associated with less cortical thinning over the course of treatment (Ahmed et al., 2015).

In terms of white matter, a number of studies have observed reduced white matter volume in TRS patients compared to healthy controls (Maller et al., 2012; Ahmed et al., 2015; Anderson et al., 2015). In contrast, Molina et al. (2008) reported that increased occipital and temporal white matter volume was predictive of treatment resistance. In studying white matter integrity with diffusion weighted imaging, Holleran et al. (2014) found widespread reductions of fractional anisotropy in the corpus callosum and temporal lobe in clozapine-naive TRS patients compared to healthy controls.

1.2.3.2 Functional imaging findings

A number of studies have focused on resting-state functional connectivity in TRS compared to either healthy controls or treatment responsive patients. Two groups specifically studied treatment-resistant auditory verbal hallucinations (AVH) in relation to functional connectivity (Vercammen, Knegtering, den Boer, Liemburg & Aleman, 2010; Alonso-Solís et al., 2015). Alonso-Solís et al. (2015) found that patients with treatment resistant AVH showed increased functional connectivity between the dorso-medial prefrontal cortex and bilateral precentral gyri, opercular, and insular cortices, but decreased functional connectivity between ventromedial prefrontal cortex and dorsal anterior cingulate cortex (ACC) compared to non-hallucinating treatment responsive patients. Vercammen et al. (2010) reported that in comparison to healthy controls, patients with treatment resistant AVH had reduced functional connectivity between the temporal parietal junction (TPJ) and Broca's area, cortical regions associated with speech perception and

language production, respectively. In addition, connectivity between the TPJ and ACC was negatively correlated with the severity of AVH.

In two elegant studies assessing striatal functional connectivity, Sarpal and colleagues showed that striatal connectivity with frontal and limbic regions increased after 12 weeks of treatment with aripiprazole or risperidone, with treatment response correlating with the degree of striato-parietal connectivity increase (Sarpal, Robinson et al., 2015), and that baseline striatal connectivity can potentially be used as a prognostic biomarker for treatment response (Sarpal, Argyelan et al., 2015). In a further recent study, T. P. White et al. (2016) compared chronic treatment resistant and responsive patients in terms of striatal connectivity patterns. TRS patients showed reduced connectivity between ventral striatum and substantia nigra, as well as between dorsal-caudal putamen and thalamus compared to treatment responders. In contrast, there was increased functional connectivity between the dorsal caudate and medial/superior prefrontal cortex in TRS patients, suggesting that striatal systems selectively differ as a function of treatment response status.

There has been an increased effort in recent years to elucidate metabolic processes in the brain in TRS. Demjaha et al. (2012) used F-DOPA Positron Emission Tomography (PET) imaging to assess striatal dopamine synthesis capacity in treatment resistant and treatment responsive patients as well as healthy controls. They found that patients who had responded well to treatment exhibited higher dopamine synthesis capacity than both TRS patients and healthy controls, providing the first evidence that TRS may not be characterised by the same dopamine dysfunction typically associated with schizophrenia. In the same year, Egerton et al. (2012) reported that FEP patients who were still symptomatic after at least one course of antipsychotic treatment showed elevated glutamate levels in the ACC compared to FEP patients who were in remission. This finding was supported by subsequent studies showing elevated ACC glutamate in chronic TRS patients compared to healthy controls (Demjaha et al., 2014) and treatment responders (Mouchlianitis et al., 2015).

1.2.3.3 Summary

Taken together, the available neuroimaging evidence suggests that treatment resistant and treatment responsive schizophrenia may be characterised by divergent neuropathophysiologies. TRS is associated with greater abnormalities in cortical structure as well as functional connectivity patterns, which may result in the failure of conventional antipsychotics, targeting primarily the dopamine system, to exert a therapeutic effect. Crucially, there is mounting evidence that TRS may not exhibit a dopaminergic dysfunction at all or to the same extent as treatment responsive schizophrenia. However, despite the proliferation of neuroimaging studies in TRS, only few of these studies directly compare treatment resistant and treatment responsive patients, particularly prior to clozapine initiation. Due to the differential effects of clozapine on the brain compared to conventional antipsychotics (Navari & Dazzan, 2009), clozapine exposure remains a potential confounder in many studies. Furthermore, stringency of definitions of TRS varies widely throughout the literature and a number of studies do not include a sample of treatment responsive patients. While a pattern of exacerbated functional dysconnectivity in TRS is emerging, functional neuroimaging studies overwhelmingly utilise resting-state fMRI without taking into account task-related activation patterns. Given the availability of a vast array of cognitive behavioural paradigms which have been widely implemented in schizophrenia research, explicit comparisons of patient subgroups in terms of both behaviour and task-related brain function may provide valuable insights into the neural mechanisms underlying treatment response in psychosis.

1.3 Cognitive control in schizophrenia

1.3.1 Mechanisms of cognitive control

In everyday life we are regularly confronted with a complex set of demands which compete for attention and adequate behavioural responses. The ability to flexibly adapt attention in response to these demands and guide behaviour towards relevant goals, while inhibiting task-irrelevant behaviour, is broadly included in the concept of cognitive control. Cognitive (or executive) control plays an im-

portant role in a wide array of higher cognitive domains, including episodic and working memory, flexible learning, task switching, response inhibition, and emotion regulation (Cohen, Braver & O'Reilly, 1996; Banich et al., 2000; Ochsner & Gross, 2005; Ranganath, Minzenberg & Ragland, 2008; Ragland et al., 2009). As such it requires the intact functioning of a number of sub-processes such as goal representation, update, and maintenance; conflict monitoring; stimulus-response mapping; and response selection (Ridderinkhof, Van Den Wildenberg, Segalowitz & Carter, 2004). Cognitive control thus underlies much of the remarkable ability of humans to adapt flexibly to fluctuating daily challenges. Accordingly, cognitive control is subserved by a widely distributed network in the brain and can be probed with a large variety of behavioural paradigms. Functional abnormalities within distinct components of the underlying network are thought to manifest in dysfunctions in different aspects of control-related behaviour.

Mounting evidence indicates the importance of aspects of the salience network, including the anterior cingulate cortex (ACC) and anterior insula, working in concert with a fronto-parietal network spanning the dorsolateral prefrontal cortex (DLPFC), ACC, and parietal cortex, in order to coordinate flexible adaptation to contextual demands (S. K. Peters, Dunlop & Downar, 2016; McTeague et al., 2017). Recent meta-analytical findings suggest that executive functioning is subserved by a superordinate fronto-parietal cognitive control network (Minzenberg, Laird, Thelen, Carter & Glahn, 2009; Niendam et al., 2012), with variation in additional task-specific recruitment of other cortical and subcortical regions. Connectivity with subcortical nodes of the salience network in the striatum, thalamus, and brainstem forms discrete cortico-striatal-thalamic-cortical (CSTC) loops which are thought to play a key role in cognitive control (S. K. Peters et al., 2016). Abnormalities of cognitive control related networks have been observed across a range of psychiatric illnesses, whereby the exact localisation and severity of the disruption differ between diagnoses (McTeague et al., 2017).

1.3.2 Cognitive control deficits in schizophrenia

Cognitive deficits are a consistent feature of schizophrenia. Many cognitive functions which rely on executive control are impaired in the illness and these impairments are thought to contribute to poor functional outcomes (Green, Kern, Braff

& Mintz, 2000). In addition, symptoms of psychosis can be understood in terms of concepts relevant to cognitive control, namely deficits in the flexible, adaptive control of thoughts and behaviour, as well as a difficulty in separating relevant from irrelevant environmental stimuli.

On a behavioural level, patients with schizophrenia exhibit a failure to exert cognitive control adequately in a number of tasks, such as the Stroop task. The Stroop task is a standard measure of cognitive inhibition, whereby performance relies on the suppression of a prepotent response elicited by stimulus interference. Specifically, the task requires naming of the font colour of a printed colour word, whereby the word and font colour can be congruent (e.g., the word "blue" written in blue) or incongruent (e.g. the word "blue" written in yellow). On incongruent trials, respondents have to overcome the prepotent reading response in favour of the more difficult colour naming task by exerting cognitive control. Patients with schizophrenia typically show a greater interference effect in terms of both reaction time and accuracy, as confirmed by a recent meta-analysis (Westerhausen, Kompus & Hugdahl, 2011), although the presence and extent of the dysfunction appears to depend on the experimental setup of the task (Henik & Salo, 2004).

Behavioural deficits in cognitive control are also commonly observed in schizophrenia on other measures of executive functioning, pointing towards an overarching impairment in control related processes (Minzenberg et al., 2009; Lesh, Niendam, Minzenberg & Carter, 2011). For example on the Wisconsin Card Sorting Test (WCST), a set-shifting task which requires flexible responding in the face of contingency changes, patients with schizophrenia typically display increased perseverative responding and require more trials to reach a performance criterion compared to healthy controls (Berman, Zec & Weinberger, 1986; Weinberger, Berman & Zec, 1986; Braff et al., 1991; Everett, Lavoie, Gagnon & Gosselin, 2001; Prentice, Gold & Buchanan, 2008). Furthermore, schizophrenia has been consistently associated with working memory deficits (Goldman-Rakic, 1994; Glahn et al., 2005; Manoach, 2003). The link between cognitive control and working memory has been extensively reviewed and is evident in the role of executive control in maintaining task-relevant information in working memory and protecting it against sources of interference. Research suggests that working memory deficits in schizophrenia may be due to a failure of active goal maintenance in control-related circuits (Braver, Gray & Burgess, 2007). More classical tasks of cognitive

control and inhibition such as the Go/NoGo task (Weisbrod, Kiefer, Marzinzik & Spitzer, 2000), Eriksen flanker task (Sambataro et al., 2013), and Continuous Performance Test (Chen & Faraone, 2000), are also sensitive to behavioural deficits in patients with schizophrenia. In light of these collective findings, cognitive control has been proposed as a unifying theory for higher cognitive dysfunctions in schizophrenia (Lesh et al., 2011).

1.3.3 Neural correlates of cognitive control deficits in schizophrenia

The observed behavioural effects are mirrored in neural abnormalities in networks relevant to cognitive control in schizophrenia, most commonly reflected in reduced activation of prefrontal cortical areas (Lewis & Anderson, 1995; Glahn et al., 2005). Hypoactivation of the DLPFC during the WCST was reported in an early study by Weinberger et al. (1986), which has since been repeatedly observed during several other cognitive controls tasks (Barch et al., 2001; Perlstein, Carter, Noll & Cohen, 2001; MacDonald et al., 2005; Snitz et al., 2005; Weiss et al., 2007; Yoon et al., 2008). Furthermore, reduced ACC activation in schizophrenia is commonly reported both for the Stroop task (Carter, Mintun, Nichols & Cohen, 1997; Yücel et al., 2002; Kerns et al., 2005; Weiss et al., 2007) as well as other tasks involving error monitoring or response inhibition (Rubia et al., 2001; Carter, MacDonald, Ross & Stenger, 2001; Laurens, Ngan, Bates, Kiehl & Liddle, 2003; Ford et al., 2004; Polli et al., 2007).

Interestingly, a meta-analysis in FEP patients showed reduced ACC activations across a range of cognitive tasks, suggesting that functional abnormalities in this area manifest at an early stage of the illness (Radua et al., 2012). In contrast, unaffected first-degree relatives of patients with schizophrenia showed impaired DLPFC functioning, but an intact ACC response during the Stroop task, pointing towards an illness-specific role for ACC functioning in schizophrenia (Becker, Kerns, MacDonald & Carter, 2008). The DLPFC and ACC are the key frontal nodes involved in exerting active executive control. DLPFC has been suggested to regulate goal representation, maintenance, and updating, while ACC plays a role in conflict detection, conveying this information back to DLPFC, which in turn modulates goal-directed behaviour in a top-down fashion (MacDonald, Co-

hen, Stenger & Carter, 2000). Abnormal recruitment of these areas appears to underlie the observed behavioural deficits and is associated with increased symptom severity in schizophrenia (Goghari, Sponheim & MacDonald, 2010; Edwards, Barch & Braver, 2010; Fornito, Yoon, Zalesky, Bullmore & Carter, 2011). A comprehensive meta-analysis of executive function deficits in schizophrenia confirmed a consistent hypoactivation of DLPFC and ACC, as well as thalamus and posterior temporal and parietal areas (Minzenberg et al., 2009). In addition, there is a consistent pattern of hyperactivation in medial frontal areas subtending midcingulate and presupplementary motor cortices (Minzenberg et al., 2009; McTeague et al., 2017), which may reflect a compensatory response in patients performing at a similar level as healthy controls.

Connectivity within CSTC loops also plays a key role in cognitive control processes and evidence from several lines of research suggests that both structural and functional abnormalities within these circuits contribute to cognitive deficits in schizophrenia (Frith & Done, 1988; Andreasen et al., 1997; Eisenberg & Berman, 2010). Rubia et al. (2001) observed increased activation of the thalamus and putamen during an inhibition task with simultaneous DLPFC hypoactivation, although hyperactivity of the basal ganglia in the context of normal prefrontal functioning has also been reported (Kawasaki et al., 1992). In an influential study, Meyer-Lindenberg et al. (2002) studied striatal presynaptic dopamine synthesis as well as prefrontal activation during the WCST in unmedicated patients and healthy controls. They found exaggerated presynaptic dopaminergic function as well as reduced task-related DLPFC activation in patients compared to healthy controls. These measures were significantly correlated in patients, but not in controls, suggesting that the subcortical dopaminergic dysfunction may arise as a result of prefrontal hypoactivation. This notion converges with formulations of the dopamine hypothesis of schizophrenia, which posits that reduced cortical activation caused by prefrontal hypodopaminergia results in excess dopaminergic transmission in the striatum (K. L. Davis, Kahn et al., 1991). However, importantly, the most recent version of the hypothesis stresses that this is only one of several possible pathways leading to subcortical hyperdopaminergia (Howes & Kapur, 2009), which in turn is thought to result in a state of aberrant salience whereby salience is randomly assigned to irrelevant environmental stimuli. In the context of cognitive control, the basal ganglia have been suggested to provide a gating mechanism, regulating

the flow of relevant information into working memory (Frank, Loughry & O'Reilly, 2001a). As such, elevated subcortical dopamine levels are likely to increase the potential for irrelevant distracting stimuli to "pass" the gate and be processed by prefrontal cortex, which would manifest as a failure of response inhibition or directed attention. In a direct test of this hypothesis, Ceaser and Barch (2015) showed that patients' striatal activity, when incorrectly responding to distracter stimuli during a cognitive control task, was significantly related to aberrant salience symptoms. In this modified match-to-sample task, subjects encoded two abstract symbols and were subsequently presented with a third symbol: either a distracter which was to be ignored, or an update symbol which was to replace one of the previously encoded stimuli. Importantly, prefrontal and striatal activation was increased compared to healthy controls when patients incorrectly encoded a distracter, but decreased when they failed to update a new symbol in working memory. These findings highlight the complex nature of reciprocal fronto-striatal connections involved in cognitive control.

1.3.4 Implications for TRS

Taken together, converging evidence suggests that disturbances in dynamic cortical-subcortical and fronto-parietal networks underlie cognitive control deficits in schizophrenia. Limited evidence suggests that antipsychotic medication may improve neural activation during cognitive tasks; however, the relationship to symptomatic treatment response is unclear (Kani, Shinn, Lewandowski & Öngür, 2017). For example, Snitz et al. (2005) demonstrated improved DLPFC and ACC functioning on an inhibition task after four weeks of antipsychotic treatment, but no association with symptom change was observed. Similarly, DLPFC activation during a working memory task has been shown to increase with antipsychotic treatment (Honey et al., 1999; Schlagenhauf, Wüstenberg et al., 2008), but symptoms did not improve significantly in these studies. Meisenzahl et al. (2006) reported that ventrolateral prefrontal cortex activation increased after 12 weeks of atypical antipsychotic treatment on a 2-back task; this change was accompanied by a significant improvement in symptoms. Symptom change after 6-8 weeks of antipsychotic treatment was furthermore shown to be significantly associated with increased activation in the inferior frontal junction during a Stroop task (Krabbendam et al., 2009). Van Veelen et al. (2011) divided patients into responders and non-

responders after 10 weeks of receiving antipsychotic medication. While there was no change in DLPFC function after treatment on a working memory task, non-responders showed a reduced practice effect over time compared to responders and healthy controls. However, to date no study has explicitly investigated differences in neural activation related to cognitive control tasks in treatment resistant and treatment responsive patients as defined using strict criteria of TRS. It is possible that subtle differences in cortical-subcortical interactions between these patient groups would lead to a differential impact of antipsychotic medication on cognitive and neural function. Given that antipsychotic treatment response is associated with increased resting-state connectivity of the midbrain with ACC and thalamus (Hadley et al., 2014), it seems likely that TRS patients would benefit to a lesser degree from antipsychotic medication in terms of improving cognitive control function.

1.4 Reinforcement learning in schizophrenia

1.4.1 Mechanisms of reinforcement learning

Central to human decision making is the ability to choose actions contingent on the environment which will yield a rewarding outcome. Adaptive functioning in a highly dynamic surrounding relies on ongoing learning processes, whereby the consequences of actions are utilised to inform future behaviour so as to achieve long-term gain. Learning mechanisms are intimately linked with cognitive control mechanisms, both conceptually and neurobiologically (Holroyd & Coles, 2002; Ridderinkhof et al., 2004; Boehler et al., 2011; Collins & Frank, 2013). Just as cognitive control involves distinguishing between relevant and irrelevant stimuli and guiding behaviour toward task-relevant goals, learning from feedback implies separating rewarding from non-rewarding outcomes and reinforcing behaviour that leads to reward. It is therefore unsurprising that feedback learning mechanisms are for a large part underpinned by similar cortical-subcortical circuits which are implicated in cognitive control (Holroyd & Coles, 2002; Botvinick, 2007; Collins & Frank, 2013).

The mesencephalic dopamine system in particular plays an important role in reward processing, the current understanding of which was heavily influenced by

seminal studies conducted by Schultz and colleagues (Romo & Schultz, 1990; Schultz, Apicella, Scarnati & Ljungberg, 1992; Schultz, Apicella & Ljungberg, 1993; Mirenowicz & Schultz, 1994, 1996; Schultz, 1998). Using single cell recording in monkeys, Schultz and colleagues demonstrated that midbrain dopamine neurons show phasic activation in response to rewarding stimuli, and a phasic decrease in activation in response to aversive stimuli. Crucially, however, when the stimulus is preceded by a conditioned predictive cue, dopamine neurons respond to the cue rather than to the reward stimulus itself (Schultz, 1998). Consequently, predictable rewards do not elicit a dopamine response and omission of predicted rewards results in a negative response. The implication is that midbrain dopamine does not, as previously thought (Berridge, 2004), code for primary reward itself, but rather for deviations from predictions about reward, or reward prediction error (RPE) (Schultz & Dickinson, 2000; Bayer & Glimcher, 2005; Maia, 2009). Dopaminergic RPE signalling is thought to act as a learning signal which is fed back to the prefrontal cortex via the basal ganglia in order to adjust behaviour accordingly, increasing *go* behaviour which leads to reward, and suppressing *no-go* behaviour which leads to aversive outcomes (Hikida, Kimura, Wada, Funabiki & Nakanishi, 2010; Maia & Frank, 2011). Computational modelling of reinforcement learning behaviour, in combination with functional neuroimaging, allows for the identification and localisation of neural activation correlating with RPE in humans (Garrison, Erdeniz & Done, 2013). Indeed, RPE-related activation during reinforcement learning tasks is typically observed in the striatal projection targets of dopaminergic neurons, notably the ventral striatum (Pagnoni, Zink, Montague & Berns, 2002; McClure, Berns & Montague, 2003; O'Doherty, Dayan, Friston, Critchley & Dolan, 2003; Pessiglione, Seymour, Flandin, Dolan & Frith, 2006; Bray & O'Doherty, 2007).

Cortical nodes of the reward network, including the orbitofrontal cortex (OFC), DLPFC, and ACC, are thought to represent to varying extents the value of anticipated outcomes. Specifically, OFC has been shown to represent stimulus reward value for both primary (O'Doherty et al., 2003; Small et al., 2003) and secondary (Elliott, Newman, Longe & Deakin, 2003; Hare, O'Doherty, Camerer, Schultz & Rangel, 2008) reward stimuli and is particularly implicated in flexible learning under changing reward contingencies in the environment (John O'Doherty, Kringelbach, Rolls, Hornak & Andrews, 2001; Fellows & Farah, 2003; Clark, Cools &

Robbins, 2004). Thus, OFC dysfunctions are associated with deficits in reversal learning tasks (John O'Doherty et al., 2001; Fellows & Farah, 2003). In line with its role in cognitive control function, DLPFC is thought to regulate executive functions necessary for reinforcement learning, such as attention (Hornak et al., 2004) and working memory (D. Lee & Seo, 2007), although it has also been shown to be involved in reward value representation (Knutson, Taylor, Kaufman, Peterson & Glover, 2005; Seo, Barraclough & Lee, 2007). The conflict-monitoring activity of ACC is implicated in reinforcement learning specifically for *no-go* learning, whereby ACC receives dopaminergic negative reinforcement signals from the midbrain and guides behaviour through avoidance-learning mechanisms (Holroyd & Coles, 2002; Botvinick, 2007). ACC function appears to be most involved in the early stages of learning, when conflict is arguably highest (Bussey, Muir, Everitt & Robbins, 1996; Bush et al., 1998). In addition, RPE signalling has been observed in all of these cortical regions both in animal (Tremblay & Schultz, 2000; Buch, Brasted & Wise, 2006; Matsumoto, Matsumoto, Abe & Tanaka, 2007) and human (Nobre, Coull, Frith & Mesulam, 1999; O'Doherty et al., 2003; Schultz & Dickinson, 2000; Behrens, Woolrich, Walton & Rushworth, 2007) studies, although the interpretation of cortical RPE signalling remains a subject of debate (Niv & Schoenbaum, 2008).

1.4.2 Reinforcement learning deficits in schizophrenia

Learning mechanisms have been central to research on schizophrenia due to the relevance of dopamine both to reward processing and psychosis. Indeed schizophrenia has long been understood to involve reduced or disordered reward-motivated behaviour (Kraepelin, 1921; Bleuler, 1950; Barch, 2008), an observation which has been associated naturally with the prevalence of anhedonia in schizophrenia (Barch & Dowd, 2010). However, research shows that patients with schizophrenia do not show reduced sensitivity to reward itself or a lack of hedonic experiences (Kring, Kerr, Smith & Neale, 1993; Heerey & Gold, 2007; Burbridge & Barch, 2007). Instead, it has become increasingly clear that abnormal reward processing in schizophrenia is associated with a deficit in learning from feedback (Barch & Dowd, 2010; Strauss, Waltz & Gold, 2013). In particular, patients with schizophrenia exhibit impaired learning on probabilistic reinforcement learning tasks (Waltz, Frank, Wiecki & Gold, 2011; Waltz & Gold, 2007). These behavioural

deficits are variably attributed to impairments in representing and updating predicted reward values or impairments in generating reward prediction errors in response to feedback. In a computational modelling approach to tease apart these two mechanisms, Gold et al. (2012) showed that patients with schizophrenia with pronounced negative symptoms showed impairments in learning to obtain gains, but relatively intact learning to avoid losses. Crucially, when asked to choose between a potential gain stimulus and potential loss-avoidance stimulus in a transfer phase, the same patients failed to prefer the stimulus with the overall higher expected value. These findings suggest that negative symptoms are associated with normal generation of prediction errors (since loss-avoidance learning was intact), but an inability to correctly represent the overall reward value of stimuli. Also consistent with abnormal reward value representation are dysfunctions in rapid adjustment to contingency changes, as evidenced in reversal learning tasks (Waltz & Gold, 2007). More recently it has been suggested that the failure to represent reward value may be accounted for by working memory deficits (Collins, Albrecht, Waltz, Gold & Frank, 2017). Support for dysfunctional prediction error generation comes predominantly from the neuroimaging literature, as discussed below.

Overall, there is consistent evidence that patients with schizophrenia are impaired in *go* learning with relatively preserved *no-go* learning. For example, Waltz, Frank, Robinson and Gold (2007) reported impaired reinforcement learning for rewarding stimuli with normal avoidance of the most negative stimuli. Furthermore, by explicitly modelling learning rates for gain-related and loss-related stimuli, Dowd, Frank, Collins, Gold and Barch (2016) demonstrated significantly lower gain learning rates in patients with schizophrenia compared to healthy controls, but similar loss learning rates. These findings are consistent with the notion of increased tonic dopamine activity in the midbrain (known to enhance *no-go* learning) but decreased phasic firing to behaviourally relevant stimuli (necessary for intact *go* learning). Importantly however, not all studies have reported impaired learning behaviour in schizophrenia (Gold, Hahn, Strauss & Waltz, 2009; Graham K Murray, Corlett & Fletcher, 2010), and learning seems to be spared in relatively simple reinforcement learning tasks (Weinberger, Berman & Frith, 1996).

1.4.3 Neural correlates of reinforcement learning deficits in schizophrenia

There is an abundance of neuroimaging studies examining the neural correlates of reinforcement learning in schizophrenia; however, studies vary widely in their tasks, patient sample characteristics, and the specific aspect of reinforcement learning that was the focus of the study. There is relative consistency in the evidence concerning reward anticipation, for which decreased ventral striatal activity has been observed in unmedicated patients with schizophrenia (Juckel, Schlagenhauf, Koslowski, Wüstenberg et al., 2006; M. O. Nielsen, Rostrup, Wulff, Bak, Lublin et al., 2012; Schlagenhauf et al., 2009) and first episode psychosis (Esslinger et al., 2012). A recent meta-analysis of 23 studies confirmed the presence of a strong ventral striatum hypoactivation during reward anticipation in schizophrenia (Radua et al., 2015). Consistent with behavioural findings, the attenuation of striatal reward-related activation is attributed to an overall increase in tonic dopamine activity in combination with decreased phasic reward elicited firing (Heinz & Schlagenhauf, 2010).

In contrast, the literature on feedback processing in schizophrenia is less consistent (Maia & Frank, 2017). Several studies have reported reduced RPE signalling in schizophrenia and FEP patients compared to healthy controls in both subcortical (G. Murray et al., 2008; Schlagenhauf et al., 2009; Waltz et al., 2009; Koch et al., 2010; Gradin et al., 2011; Schlagenhauf et al., 2014) and cortical (Corlett et al., 2007; Koch et al., 2010; G. Murray et al., 2008) structures; whereas other studies have found normal RPE signalling in patients (Dowd et al., 2016; Culbreth, Westbrook, Xu, Barch & Waltz, 2016). It has been suggested that discrepancies may be due to differences in the inclusion of medicated and unmedicated patients into studies and that antipsychotic medication normalises the RPE response in patients (Culbreth et al., 2016). However, this interpretation is at odds with the finding of abnormal RPE activation in medicated patients (Corlett et al., 2007; G. Murray et al., 2008; Waltz et al., 2009; Gradin et al., 2011).

Abnormal RPE signalling in schizophrenia has been shown in several studies to arise as a result of blunted responses to unexpected reward as well as augmented responses to predictable reward (Corlett et al., 2007; Waltz et al., 2009; Morris et al., 2012). Interestingly, there is converging evidence that patients with schizo-

phrenia show intact RPE signalling in response to losses (negative RPEs), but blunted activation in response to wins (positive RPEs), a result which is consistent with behavioural findings of selectively impaired *go*-learning in schizophrenia (Waltz et al., 2009; Koch et al., 2010; Waltz et al., 2010; Simon et al., 2010). Furthermore, blunted responses to reward outcomes has been related to negative symptoms such as anhedonia (Dowd et al., 2016) and avolition (Waltz et al., 2009), as well as positive symptoms (Culbreth et al., 2016; Schlagenhauf et al., 2009; Corlett et al., 2007; Gradin et al., 2011). A meta-analysis of ventral striatal RPE-related activation including 8 studies could only establish hypoactivation in patients at trend level, with no consistent relationship observed with symptom dimensions (Radua et al., 2015). Taken together, there is tentative evidence to suggest that abnormal prediction error signalling may contribute to reinforcement learning deficits as well as symptom formation in schizophrenia, although considerable inconsistencies remain regarding the localisation and extent of the dysfunction.

Besides abnormal generation of RPE signals, reinforcement learning processes may arise due to a failure to update reward value representations on a trial-by-trial basis. This rapid process is underpinned by prefrontal areas, in particular OFC. It has been suggested that OFC dysfunction in schizophrenia may result in impaired representation of reward value, as well as an inability to utilise feedback information to rapidly update this representation (Gold et al., 2008). Behavioural findings of impaired reversal learning (Elliott, McKenna, Robbins & Sahakian, 1995; Pantelis et al., 1999), which is known to be underpinned by OFC functioning (Cools, Clark, Owen & Robbins, 2002; Hornak et al., 2004; Waltz & Gold, 2007), have been interpreted as an indicator of OFC dysfunction in schizophrenia (Waltz & Gold, 2007). More recently neuroimaging studies have indeed reported abnormal frontal activation during probabilistic reversal learning (Waltz et al., 2013; Culbreth et al., 2016).

In summary, converging evidence suggests that patients with schizophrenia show reinforcement learning deficits which are underpinned by dysfunctions of the underlying neural reward network. These are largely attributed to abnormalities in the subcortical dopamine system, with elevated baseline levels of dopamine in combination with attenuated response of dopamine neurons to reward anticipation and receipt resulting in blunted activation patterns in patients as compared

to healthy controls. In addition, prefrontal hypofunction – potentially mediated by reduced dopamine in the prefrontal cortex – results in abnormal processing of reward feedback and representation of stimulus values. This dysfunction is likely to contribute to the development of psychotic symptoms such as delusions, due to a failure to accurately represent and update expectations of the environment, as well as anhedonia and avolition due to the inability to anticipate reward outcomes adequately.

1.4.4 Implications for TRS

Very little is known about how antipsychotic treatment response relates to reinforcement learning deficits and their underlying neural impairments in schizophrenia. However, reinforcement learning tasks may provide a particularly useful tool for elucidating the mechanisms underlying treatment response in psychosis, as they tap into various facets of cognitive processing and neural functioning which could be differentially implicated in patient subgroups.

Few studies have explicitly studied the effect of antipsychotic medication on reward processing. In examining the differential effect of first and second generation antipsychotics on reward anticipation, Juckel, Schlagenhauf, Koslowski, Filonov et al. (2006) reported that patients currently taking first generation antipsychotics showed an absence of ventral striatal activation, whereas patients taking second generation antipsychotics showed a normal response similar to healthy controls while anticipating reward. Similarly, in a longitudinal study, Schlagenhauf, Juckel et al. (2008) were able to show that the blunted ventral striatal activation in patients on first generation antipsychotics was subsequently normalised after the same patients were switched to second generation antipsychotics. However, it is unclear whether psychotic symptom change was related to this change in activation. Instead, blunted activation in patients on typical antipsychotics was significantly related to negative symptomatology in both studies. In contrast, M. O. Nielsen, Rostrup, Wulff, Bak, Broberg et al. (2012) compared ventral striatal activation during reward anticipation in antipsychotic naive FEP patients before and after 6 weeks of antipsychotic medication and found that an improvement in psychotic symptoms was correlated with a normalisation of the previously blunted neural response. However no data on RPE signalling was presented. Insel et al.

(2014) recently reported that medication dosage correlated negatively with RPE response in patients with schizophrenia; however, it remains unclear how this effect relates to treatment response. Medication dosage was not related to symptom severity in this study, hence it is possible that highly medicated patients included both those who responded well to this high dosage, and those who were resistant to treatment and thus prescribed higher doses, as is typically observed. Notably, in a study reporting relatively intact RPE signalling in medicated patients at the group level (Culbreth et al., 2016), RPE activation was positively correlated with positive symptoms, suggesting that the most unwell patients showed the strongest RPE response despite antipsychotic treatment. This is in line with the notion that treatment resistant schizophrenia may not be characterised by a dopaminergic abnormality to the same extent as treatment responsive schizophrenia.

As such, it is possible that the reported inconsistencies regarding reward feedback in schizophrenia are a result of combining different neurobiological subgroups of the illness within individual studies. Specifically, it is possible that neural signatures related to subcortical dopamine functioning (i.e., RPE signalling) may be more abnormal in patients who respond well to antipsychotic medication, whereas TRS patients may show a non-dopaminergic dysfunction which results in similar behavioural impairments. For example, if prefrontally modulated cognitive control mechanisms are more severely impaired in these patients, this may result in an inability to adequately make use of otherwise intact reward prediction error signals.

1.5 White matter connectivity in schizophrenia

1.5.1 White matter changes in schizophrenia

Ever since the earliest formulations of schizophrenia as a disorder of the brain, there has been a conceptual understanding of the illness as one characterised by a lack of coordination, or integration, of cognitive and perceptual functions (Bleuler, 1950). With an improved understanding of the neurobiology and phenomenology of the illness in recent years, schizophrenia is increasingly described in terms of

a dysconnection syndrome (Friston & Frith, 1995; Stephan et al., 2009; Friston et al., 2016). Neural dysconnectivity leading to impaired communication between distributed cortical, subcortical, and cerebellar regions is thought to play a major role in the formation and maintenance of symptoms of psychosis as well as negative symptoms. The dysfunction likely arises due to dysconnectivity at the level of the synapse (Friston et al., 2016), as well as abnormal structural integrity of the axonal projections connecting these brain regions (K. L. Davis et al., 2003).

Neuronal axons are insulated in lipid sheaths of myelin formed by oligodendroglia, giving axon fibre bundles their brightness in MR images. Myelin increases the conduction velocity of action potentials propagating along the axon, facilitating fast communication within and between distributed neural networks. Although myelination begins prenatally in humans, many major tracts undergo continued myelination throughout childhood and adolescence, reaching their peak in early adulthood (Lenroot & Giedd, 2006). Age-related reductions in myelination are typically not observed until the age of 40 (Bartzokis et al., 2001). Converging evidence from a number of research modalities supports myelin abnormalities as a core pathophysiology of schizophrenia (K. L. Davis et al., 2003).

Neuroimaging research has most commonly assessed white matter using diffusion weighted imaging, applying the diffusion tensor model to determine the directionality of diffusing water molecules in each voxel (Karlsgodt, 2016). Diffusion can be restricted along the axis of structured tissue such as fibre bundles, or occur isotropically in all directions. Accordingly, the typically reported measure in diffusion tensor imaging (DTI) studies is fractional anisotropy (FA), which indicates the extent to which water molecules are anisotropically diffusing along the axis of white matter tracts. FA is thus utilised as a proxy for white matter tract integrity, which may correspond to a number of measures such as myelination, axon membrane integrity, fibre density, axon diameter, or number. Most commonly FA is interpreted in terms of myelination.

There is strong evidence for reduced FA in schizophrenia throughout the brain, although there remains substantial variability in the extent and regional specificity of the disruption (Fitzsimmons, Kubicki & Shenton, 2013). The most frequently reported regions of decreased FA in patients with schizophrenia compared to healthy controls include the frontal and temporal lobes as well as their connecting tracts, such as the superior and inferior longitudinal fasciculi (Hatton

et al., 2014; Caprihan et al., 2011; Sasamoto et al., 2013; Hoptman et al., 2008; Lener et al., 2014), uncinate fasciculus (Maniega et al., 2008; De Weijer et al., 2011; Boos et al., 2013; Sasamoto et al., 2013), arcuate fasciculus (De Weijer et al., 2011; Maniega et al., 2008), and the cingulum bundle (Skelly et al., 2008; Hao et al., 2006). The corpus callosum, connecting the two cerebral hemispheres, as well as the internal capsule and cerebellar peduncles have also been frequently implicated (Schneiderman et al., 2009; Roalf et al., 2013; Lener et al., 2014; Sasamoto et al., 2013; Maniega et al., 2008; Hu Liu, Fan, Xu & Wang, 2011).

While several studies have only found focal differences in a few of these regions, more recent research on larger samples suggests that the disruption may be widespread and affect the majority of white matter tracts throughout the brain (Klauser et al., 2017). Given the heterogeneity of symptom profiles in schizophrenia, it is furthermore likely that different neurobiological subtypes of myelin dysfunction exist. Indeed, two studies have recently demonstrated that different patterns of FA reductions are associated with different symptom subgroups (Arnedo et al., 2015; H. Sun et al., 2015). Interestingly, one of the few studies reporting FA *increases* in schizophrenia found that patients experiencing hallucinations had increased FA in the lateral part of the arcuate fasciculus compared to patients without hallucinations and healthy controls (Hubl et al., 2004). This is particularly interesting given the role of this portion of the arcuate fasciculus in connecting frontal speech production areas with temporal auditory and speech perception areas.

White matter disruptions have also been observed in FEP patients; however there is less consistency of results in these samples. Reduced FA has been observed in FEP in frontal and temporal tracts as well as the corpus callosum (Price et al., 2007; Cheung et al., 2011; Melicher et al., 2015; Q. Wang et al., 2011), whereas other studies have found no difference between FEP patients and healthy controls (T. White et al., 2009; Moriya et al., 2010; Kong et al., 2011; B. D. Peters et al., 2008). However, where FA reductions are reported, the affected regions appear to be subsets of those often implicated in chronic schizophrenia (Di Biase et al., 2017). It has thus been argued that white matter abnormalities begin in part early on in the illness and take a progressive course thereafter. Nevertheless, a remaining confounder in the association of white matter abnormalities with illness progression is antipsychotic medication, which has been found to cause both

increases and decreases in myelin (Bartzokis et al., 2007; Bartzokis et al., 2012; Ho, Andreasen, Ziebell, Pierson & Magnotta, 2011; Q. Wang et al., 2013; Ozcelik-Eroglu et al., 2014). It is unclear to what extent cumulative antipsychotic medication over the lifespan may contribute to white matter abnormalities in chronic schizophrenia; however findings of white matter abnormalities in medication-naive patients lend support for a disease-related deterioration of white matter tracts (X. Liu et al., 2014; Mandl et al., 2013). Fronto-temporal and fronto-limbic abnormalities have also been observed in individuals at ultra-high risk (UHR) for psychosis (Vijayakumar et al., 2016), with the extent of FA reductions showing an association with functional deterioration (Karlsgodt, Niendam, Bearden & Cannon, 2009) and conversion to psychosis (Carletti et al., 2012).

Thus, DTI studies provide overwhelming evidence for widespread white matter disruptions in schizophrenia, which are typically taken as indicators of a myelin-related dysfunction. These findings converge with genetic data showing that oligodendroglial and myelin related genes are associated with schizophrenia risk, as evidenced in numerous candidate gene studies (N. Takahashi, Sakurai, Davis & Buxbaum, 2011) as well as genome wide association studies, albeit to a lesser extent (Roussos & Haroutunian, 2014). In addition, gene expression studies in postmortem brains have found downregulation of genes related to oligodendrocytes and myelin in DLPFC, cingulate cortex, superior temporal gyrus, and hippocampus (Hakak et al., 2001; Aston, Jiang & Sokolov, 2004; Dracheva et al., 2006; Katsel, Davis & Haroutunian, 2005). There is some evidence for an association between neuroinflammation and white matter pathology in schizophrenia (Najjar & Pearlman, 2015); however, the directionality of a potential causal relationship between the two remains unclear. Within neuroimaging research, the importance of moving beyond FA based assessments has been noted (Karlsgodt, 2016). While FA constitutes a sensitive measure of white matter abnormalities, it is not specific to myelin content. As such, there is a need to combine these efforts with more sophisticated myelin imaging techniques, enabling a more detailed understanding of the microstructural changes involved in white matter pathology in schizophrenia.

1.5.2 Implications for TRS

Numerous studies have attempted to elucidate the association between antipsychotic medication, treatment response, and white matter changes in schizophrenia. There is early evidence that white matter abnormalities may serve as a potential biomarker for treatment resistance; however the complexity of the association has resulted in several inconsistent findings.

Research has shown that antipsychotic medication increases intracortical myelin (ICM) and white matter volume in patients with FEP (Bartzokis et al., 2011; Bartzokis et al., 2012), with the extent of increase correlating with response to treatment. In contrast, other studies have found a decrease in FA after 6 or 12 weeks of antipsychotic treatment in FEP patients (Q. Wang et al., 2013; Szeszko et al., 2014) and a reduction of white matter volume (Ho et al., 2011). Interestingly, in a recent study Tishler et al. (2017) investigated the association between antipsychotic exposure duration and ICM in 93 patients with schizophrenia and found that while medication was associated with an increase in ICM within the first year of exposure, there was a decline thereafter.

DTI studies explicitly relating white matter integrity to treatment response status have also procured variable results (Reis Marques et al., 2013; Garver, Holcomb & Christensen, 2008; Luck et al., 2011; Kim et al., 2016; Szeszko et al., 2014). Two longitudinal studies in FEP patients found that FA was reduced in the uncinate, cingulum, and corpus callosum (Reis Marques et al., 2013) as well as superior longitudinal fasciculi (Luck et al., 2011) at medication-free baseline in patients who subsequently showed poor response to antipsychotic treatment. Contrary to these findings, Kim et al. (2016) found that lower FA in similar regions was in fact correlated with better treatment response. A further study reported increased diffusivity, a measure of impaired white matter integrity, in treatment responders at baseline, with subsequent repair during 28 days of antipsychotic treatment (Garver et al., 2008).

Several groups have also studied treatment response and white matter in chronic patient samples, reporting lower FA in treatment resistant patients compared to healthy controls (Holleran et al., 2014) and treatment responsive patients (Mitelman et al., 2006; Mitelman et al., 2009). In a longitudinal design, Mitelman et al. (2009) found that patients with a good outcome had initially higher FA compared

to poor outcome patients, but showed a subsequent stronger decline in FA after four years treated with antipsychotics. Similarly, white matter volume decreased significantly in treatment responsive patients after four weeks of antipsychotic treatment compared to an antipsychotic-free baseline in a further study, whereas an increase was observed in treatment resistant patients (J. D. Christensen, Holcomb & Garver, 2004).

Taken together, the longitudinal white matter changes as a function of antipsychotic exposure appear to differ between patient subgroups and vary with increasing drug exposure and illness duration. It has been argued that myelin integrity is more heavily impacted in treatment resistant patients, such that the limited beneficial effects of antipsychotic medication on myelination are not sufficient to impact symptoms in these patients (Reis Marques et al., 2013). Alternatively, myelin abnormalities may be more severe in treatment responders, who in turn show a stronger effect of medication on white matter microstructure, thus improving neural dysconnectivity and related symptoms. A further possibility is that while antipsychotic medication impacts white matter equally in both good and poor responders, white matter connectivity itself is differentially associated with symptoms in these two groups. Indeed research has found white matter integrity to be correlated negatively with both negative (Knöchel et al., 2012; Wolkin et al., 2003; Asami et al., 2014; Szeszko et al., 2014) and positive (Skelly et al., 2008; Reis Marques et al., 2013; Cooper, Alm, Olson & Ellman, 2016) symptoms in some studies, but positive correlations with certain positive symptom profiles (Hubl et al., 2004) as well as no association with positive symptoms (Asami et al., 2014) have also been reported. These inconsistent findings may be due to the heterogeneity of the samples included in these studies. Further research is necessary to disentangle the relationship between antipsychotic exposure and white matter integrity as a function of treatment response status; particularly with a focus on the relationship between myelination and symptoms as well as cognition in these patient subgroups.

1.6 Aims and hypotheses

The principal aim of the current work is to elucidate the neural mechanisms underlying antipsychotic treatment response in the context of cognitive control

and reinforcement learning. There is a dearth of functional imaging studies explicitly comparing treatment resistant and treatment responsive patients with schizophrenia on cognitive tasks. Hence, this thesis aims to assess whether these patient groups exhibit differential neural signatures of cognitive function which can be related to symptoms of psychosis. In addition, myelin content will be compared between groups as a measure of underlying structural connectivity dysfunction. There is a need for comparisons of treatment resistant and responsive patients with schizophrenia both at an early and chronic stage of the illness. The current work focuses on chronic schizophrenia so as to assess neural dysfunctions at the established stage of treatment resistance and determine how these dysfunctions serve to perpetuate symptoms despite treatment. Both patient groups – patients with treatment resistant schizophrenia (TRS) and non-treatment-resistant schizophrenia (NTR) – will be compared to a third healthy control (HC) group on all measures in this study.

In the first experiment, behavioural performance and neural activation will be assessed using a verbal Stroop task. In short, participants are required to respond to the font colour of congruent or incongruent colour words while undergoing functional MRI scanning. Response conflict arises when the word meaning and font colour are incongruent, and as such this constitutes a standard measure of cognitive control. The expectation is to replicate known behavioural and neural dysfunctions in patients with schizophrenia compared to healthy controls, with deficits being more strongly pronounced in the TRS patient group. Given that antipsychotic medication attenuates dopaminergic function in the striatum of all patients, the expectation is that the key change in the treatment resistant patients would be a greater degree of hypofrontality relative to the NTR patient group; evident both in the between-group comparisons and more specifically as an inverse correlation of frontal activation with the degree of positive symptoms. This correlation should be particularly pronounced in the TRS group. An exploratory analysis would also demonstrate reduced functional connectivity in TRS between frontal cortex and subcortical structures of the cognitive control network, such as the thalamus or striatum, during response conflict in the Stroop task.

In the second experiment, behavioural performance and neural activation will be assessed using a reinforcement learning task. Participants are required to learn the reward contingencies of emotionally valenced faces (emotional condition) and

neutral faces (neutral condition); whereby in the emotional condition, happy faces are known to elicit a response bias over angry faces (Averbeck & Duchaine, 2009). An element of cognitive control is therefore necessary to overcome the bias in order to learn reward contingencies adequately. As such, this task allows for an investigation of neural mechanisms underlying feedback learning as well as the impact of bias on learning mechanisms. Neural activation correlating with reward prediction error (RPE), known to be driven by subcortical dopamine function, will serve as a measure of reward prediction and learning, and is expected to be more impacted in treatment responsive patients; in contrast, the association between bias and neural activation will index the extent to which prefrontal cognitive mechanisms influence learning and is expected to be stronger in treatment resistant patients. Thus the hypotheses for this experiment are that responsive patients would show greater abnormalities in RPE signalling than TRS patients, and emotional bias would differentially modulate the neural response to feedback in TRS patients compared with both responsive patients and controls.

In the final experiment, myelin content will be assessed using multicomponent driven equilibrium single pulse observation of T1 and T2 (mcDESPOT; Deoni et al., 2008). This MRI technique allows for the derivation of a myelin water fraction (MWF) map, which indicates the amount of myelin (relative to intra-/extracellular water and cerebrospinal fluid) at each voxel in the brain. White matter integrity has as yet not been assessed in schizophrenia using mcDESPOT. This experiment therefore serves the purpose of testing the utility of mcDESPOT in detecting differences in myelination between patients with schizophrenia and healthy controls, as well as assessing whether more severe myelin-related dysfunction accounts in part for the lack of response to antipsychotic medication in TRS. In addition, the association between myelin content and cognitive control will be tested and mediation analyses performed so as to determine whether abnormal myelination accounts in part for behavioural differences on the Stroop task.

Chapter 2

General Methods

2.1 Participants

2.1.1 Recruitment

Patients with a diagnosis of schizophrenia were recruited through the South London and Maudsley (SLAM) NHS foundation trust. The "consent for contact" (c4c) scheme within SLAM was used in order to identify eligible patients within the trust who had previously consented to being contacted for research purposes. In line with c4c guidelines, patients' care coordinators were informed before contacting patients directly. In addition, extant databases of patients who had previously taken part in departmental research and consented to being re-contacted were searched for eligible patients. Healthy controls were recruited via advertisements on Gumtree.

In total, 57 patients consented to take part in the study. Of these, 22 met criteria for treatment resistance (TRS group), and 21 met criteria for being treatment responsive (NTR group). One patient was excluded due to non-compliance to antipsychotic medication; two patients did not meet criteria for either patient group; and one patient aborted the scan before data could be acquired. Twenty-four healthy controls (HC group) consented to take part in the study. Ethical approval was provided by the London Camberwell St Giles Research and Ethics Committee. All participants provided informed written consent and were compensated for their time and travel.

2.1.2 Treatment resistant schizophrenia patients

The following modified Kane criteria were used for inclusion of patients into the treatment resistant schizophrenia (TRS) group:

- at least two previous periods of treatment with antipsychotics at adequate dosage for a period of at least four weeks without symptomatic relief
- no period of good functioning in the preceding five years
- severity score ≥ 4 on at least 2 positive symptoms items of the PANSS

The aim was to match treatment resistant and responsive patient groups as closely as possible on key demographic and clinical variables, so as to avoid confounds such as age, gender, illness chronicity, or medication dosage. Therefore criteria did not specify a minimum chlorpromazine equivalent dosage for previous medication trials in TRS patients. Instead, it was ensured that all medications had been prescribed above effective therapeutic dosage (Leucht et al., 2014). In addition, we excluded any patients currently receiving clozapine treatment due to the potential confound that this may entail in terms of brain structure and function. This also avoids the potential introduction of subgroups of patients resistant to clozapine (super-resistant patients). These criteria likely lead to a more liberal inclusion of patients into the TRS group compared to original Kane criteria; however, thorough audits of medical records were conducted besides formal PANSS assessments so as to ensure that TRS patients were experiencing persistent symptoms of at least moderate severity despite several adequate treatment trials. Further exclusion criteria were a history of neurological illness, current major physical illness, and drug dependency over the last six months.

2.1.3 Treatment responsive schizophrenia patients

Patients in the non-treatment-resistant (NTR) group met criteria for being in symptomatic remission (Andreasen et al., 2005), as defined by a score of 3 or less on all items of the PANSS, and these symptoms having been stable for at least 6 months. Exclusion criteria were a history of neurological illness, current major physical illness, and drug dependency over the last six months.

2.1.4 Healthy controls

Healthy controls did not have a history of psychiatric illness or a first-degree relative currently or previously suffering from a psychotic illness. Further exclusion criteria were a history of neurological illness, current major physical illness, and drug dependency over the last six months.

2.2 Study procedures

2.2.1 General procedure

All participants were initially contacted by telephone to complete a brief screening. This screening included questions on MRI safety, (family) psychiatric history, and neurological history. If participants met screening criteria to be included into the study, they were invited to attend a session at the Institute of Psychiatry, Psychology and Neuroscience. Participants received an information sheet and were given an opportunity to ask questions, after which signed consent was given to take part in the research.

Participants then received instructions for the functional tasks to be completed in the scanner (Stroop task and Faces task) and were able to practise each task until the instructions were understood. This was followed by a behavioural assessment session of approximately 1.5 hours duration including short breaks. If participants were not able to complete behavioural assessments before the scanning session, they were asked to return to the institute the following day to complete the assessments. The MRI scan took place at the Centre for Neuroimaging Sciences (CNS) and lasted approximately 1.6 hours.

2.2.2 Assessments

The Positive and Negative Symptom Scale (PANSS) semi-structured interview was administered by myself and, in some cases, a further trained researcher, in order to assess symptom severity in all patients. All participants completed pen-and-paper questionnaires consisting of demographic information, the Aberrant

Salience Inventory, Behavioural inhibition / Behavioural approach system scale, Balanced Inventory of Desirable Responding, Beck Depression Inventory, and Cannabis Experience Questionnaire. Socio-economic status was assessed with parental occupation following the National Statistics Socio-economic Classification (NS-SEC; Rose, Pevalin & O'Reilly, 2005).

Questionnaires were followed by cognitive assessments. These included phonological and semantic verbal fluency, letter-number-sequencing (a measure of working memory), and the two-item subscale of the Wechsler Adult Scale of Intelligence (WASI), consisting of the Vocabulary and Matrix Reasoning subtests (as a measure of intelligence quotient).

Sample characteristics of core demographic and clinical variables can be found in Table 1. Remaining questionnaire and cognitive data can be found in Appendix Table A.7.

2.2.3 MRI procedure and acquisition parameters

MRI data were acquired on a 3T GE Excite II MR scanner (GE Healthcare, USA) with an 8-channel head coil. For the functional tasks, the task screen was viewed via a head-mounted mirror and responses were given via a button box held in the right hand. Throughout the scan, cardiac activity was measured with a pulse oximeter attached to the participant's finger, and respiratory activity was measured with a pressure belt worn around the abdomen. A high-resolution structural image (T1-weighted magnetization-prepared rapid gradient-echo, MP-RAGE) was acquired, followed by T2*-weighted echo planar imaging (EPI) sequences for the two functional tasks (Stroop task and Faces task). For the mcDESPOT protocol, three series of scans were acquired: a spoiled-gradient recalled echo (SPGR), an inversion recovery (IR) prepared SPGR, and a balanced steady-state free procession (bSSFP) sequence. Acquisition parameters of all scans can be found in Table 2. The MRI protocol also included a third functional task, proton magnetic resonance imaging (^{1}H-MRS) of the anterior cingulate cortex, and diffusion weighted imaging, which are not discussed further in this thesis. The duration of the full MRI protocol was approximately 1.6 hours.

Table 1
Means and standard deviations of demographic and clinical variables per group

	HC		NTR		TRS			
	M	*SD*	*M*	*SD*	*M*	*SD*	Group statistics	
							$X^2(2)$	*P*
Female (%)	25.0		13.6		14.2		1.28	.527
Smokers (%)	16.7		66.7		59.1		13.43	.001
							$F(2)$	*P*
Age	38.4	10.0	41.3	10.4	40.8	10.9	0.52	.597
WASI	115.8	11.7	91.9	14.8	97.0	16.4	17.63	$< .001$
NS-SEC	3.1	1.6	3.7	1.9	3.3	1.7	0.67	.515
Onset age (years)			27.7	6.2	25.7	7.6	0.84	.365
Illness duration (years)			14.1	10.1	15.0	8.9	0.08	.781
CPZ equivalents			305.0	182.8	386.5	227.6	1.67	.204
PANSS score								
Positive symptoms			10.7	2.1	20.6	3.0	153.70	$< .001$
Negative symptoms			13.0	5.6	19.6	4.5	18.03	$< .001$
General symptoms			23.6	5.1	35.1	9.1	26.11	$< .001$
Total score			46.9	10.3	76.7	10.5	88.39	$< .001$

HC = Healthy controls
NTR = non-treatment-resistant schizophrenia
TRS = Treatment resistant schizophrenia
WASI = Wechsler Abbreviated Scale of Intelligence
NS-SEC = National Statistics Socio-economic Classification
CPZ = Chlorpromazine
PANSS = Positive and Negative Syndrome Scale

2.3 Functional magnetic resonance imaging (fMRI)

2.3.1 Principals of fMRI physics

Functional magnetic resonance imaging (fMRI) is an imaging technique which provides an indirect measure of brain activity. The utility of fMRI rests primarily on the magnetic properties of haemoglobin molecules as a function of their oxygenation. Specifically, oxyhaemoglobin is diamagnetic and deoxyhaemoglobin is paramagnetic, resulting in small MR signal changes known as the blood oxygena-

Table 2
Scanning acquisition parameters

	Structural	Stroop	Faces	mcDESPOT		
Sequence	MP-RAGE	EPI	EPI	SPGR	IR-SPGR	bSSFP
Volumes	1	153	420	9	1	16
TR (ms)	7300	2000	2000	8	8	~4
TE (ms)	3000	30	35	3.6	3.6	~2
TI (ms)	400			450		
FOV	270	211	75	220	220	220
Voxel size (mm)	1.2	3	3	1.7	2	1.7
Matrix	256×256	64×64	64×64	128×128	220×110	128×128
Flip angle	11°	75°	75°	[2, 3, 4, 5, 6, 7, 9, 13, 18]°	5°	[12, 16, 21, 27, 33, 40, 51, 68]°

tion level dependent (BOLD) effect (Ogawa et al., 1992). In response to neuronal activation in the brain there is an initial small decrease in deoxyhaemoglobin in the active region, whereupon blood flow increases in order to meet the greater demand for oxygen. Indeed, the increase in blood flow exceeds the oxygen metabolism, in effect overcompensating for the oxygen demand and resulting in an MR signal detectable as a BOLD contrast (Buxton, 2013). The BOLD contrast is usually measured using T2*-weighted echo planar imaging. The haemodynamic response function (HRF) is well defined for most brain regions and can thus be modelled in fMRI settings to estimate the evoked response to task-related stimuli.

2.3.2 Principals of fMRI processing and analysis

In event-related fMRI designs, activation in response to brief single events can be estimated (Josephs, Turner & Friston, 1997). The assumed underlying neural response to each event is typically modelled as a delta (or "stick") function and then convolved with the HRF. The scaling of the predicted response can then be estimated within the framework of the general linear model (GLM). This operation can thus be performed for the timecourse of each voxel in the brain in order to identify regionally specific neural responses to task stimuli.

Before statistical inference about neural activation can be made effectively within the GLM, fMRI data must undergo a number of preprocessing steps. The first

preprocessing step is typically motion correction, which consists of first realigning all acquired volumes using rigid-body transformations to account for subtle head movement in the scanner, from which movement parameters can be estimated. Due to the fact that head movement can cause statistical artefacts in the MR signal, movement parameters can later be used within the GLM to partial out these effects from the data. In addition, spatial smoothing is usually performed by convolving the data with a Gaussian kernel with a specified full width at half maximum (FWHM). The primary utility of spatial smoothing is an increase in signal to noise ratio (SNR), though it comes at the cost of degraded spatial resolution of the data. Temporal filtering can be performed in order to remove high or low frequency noise, such as scanner drift or physiological noise, which in turn also results in an increase in SNR. In order to be able to compare activation patterns across subjects and groups, data must be normalised to a standard anatomical space. This can be done either before or after first level (i.e. subject level) statistical analyses are performed. Within the Oxford Centre for Functional MRI of the Brain Software Library (FSL), all first level analyses are performed in subject native space, and statistical parametric maps are then transformed into standard space before being subjected to second level (i.e. group level) analysis.

At the first level, a GLM estimating the relative contribution of different task conditions is fit to each voxel's signal timecourse. This results in statistical parametric maps (SPMs) containing a test statistic for each voxel, indicating how closely the model fits each voxel's signal. Contrast images for effects of interest are generated by weighting parameter estimates of model regressors accordingly. At the second level, contrast images from all subjects can be subjected to mixed effects modelling within the GLM in order to make inferences on a group level, again resulting in SPMs containing a test statistic for each voxel. The statistical maps can then be thresholded at a prespecified level (e.g. $p < .05$) in order to indicate voxels where the signal is statistically significantly correlated with certain task conditions. However, this mass univariate approach of estimating a GLM at each individual voxel incurs a multiple comparison problem due to the accumulation of the type I error rate (in this case 5%), which is further complicated by the spatial dependence of proximate voxels (both due to functional similarities and the smoothing applied during preprocessing). Gaussian random field theory (RFT) can be applied to correct for multiple comparisons, controlling the family-wise

error (FWE) rate and simultaneously accounting for spatial correlation of voxels in the brain. Cluster level inference, providing information on groups of voxels which are simultaneously active, can be made by applying a height threshold (i.e. minimum test statistic value) and an extent threshold (i.e. minimum number of adjacent voxels within a cluster) to each statistical map.

2.3.3 fMRI processing protocols

Functional data for both the Stroop task and the Faces task were analysed using the general linear model as implemented in FSL FEAT, (version 5.0;Smith et al., 2004). Functional and structural brain images were extracted from non-brain tissue using FSL's brain extraction tool (BET; Smith, 2002), and EPI images were realigned using MCFLIRT to correct for effects of head motion (Jenkinson, Bannister, Brady & Smith, 2002). A 100-s temporal high-pass filter was applied and data was spatially smoothed using a Gaussian kernel of 5mm FWHM. The statistical models (including motion artefact correction) used for the Stroop and Faces tasks are described in detail in chapters 3 and 4, respectively. Due to group differences in IQ as measured by the WASI, inclusion of WASI scores as a covariate of no interest was considered for each task. Where task performance significantly correlated with IQ within groups, WASI was included into fMRI analyses to control for potential confounding effects. At the group level, significant clusters were determined by a voxelwise z-threshold of 2.3 and a cluster significance threshold of $p = 0.05$ (whole-brain FWE corrected for multiple comparisons).

2.4 Multicomponent driven equilibrium single pulse observation of T1 and T2 (mcDESPOT)

2.4.1 Principals of mcDESPOT

Multicomponent driven equilibrium single pulse observation of T1 and T2 (mcDESPOT) is a magnetic resonance imaging technique which makes use of the differential contributions of different tissue water compartments in the brain to the

longitudinal (T1) and transverse (T2) relaxation signal, thereby allowing for in-vivo volumetric quantification of myelin-associated water in the brain (Deoni et al., 2008). Gleaning information on tissue microstructure from T1 and T2 relaxation has long been relevant both in neurology and psychiatry, however whole-brain mapping of T1 and T2 was not always possible in clinically acceptable scan times. K. Christensen, Grant, Schulman and Walling (1974) first proposed a new rapid method for volumetric T1 mapping which relied on acquiring a series of spoiled gradient recalled-echo (SPGR) images over a range of flip angles, while keeping the relaxation time (TR) constant. This method, later termed DESPOT or DESPOT1 (Homer & Beevers, 1985; Deoni, Rutt & Peters, 2003), provided much faster acquisition and processing times than conventional T1 mapping techniques and was further adapted and developed by other groups (Homer & Beevers, 1985; H. Z. Wang, Riederer & Lee, 1987; Deoni et al., 2003; Deoni, Peters & Rutt, 2005). It was eventually extended by Deoni et al. (2003) to achieve rapid T2 mapping (DESPOT2) by applying the multi-flip angle technique to a steady-state free procession (SSFP) pulse sequence. The combined DESPOT1 and DESPOT2 pulse sequences allowed for T1 and T2 mapping in under 15 minutes at high spatial resolution.

The T1 and T2 signals describe the relaxation time of excited protons when returning to longitudinal and transverse equilibrium, respectively. Tissue contrast arises due to the different relaxation properties of tissue types in the brain. However, the DESPOT mapping technique assumes that the T1 and T2 signal in each voxel originate from a single water compartment despite the high microstructural complexity within each voxel. Indeed, T2 relaxation measures can typically be decomposed into two or three components thought to correspond to separate water compartments. For example, water trapped between the lipid bilayers of myelin sheaths is associated with very fast T2 relaxation; intra- and extracellular water shows intermediate T2 times; and free water in the cerebral spinal fluid (CSF) typically exhibits the slowest relaxation (Kroeker & Henkelman, 1986; Kreis, Fusch, & Boesch, 1992; Whittall et al., 1997). This decomposition of relaxometry data allows for volumetric quantification of microstructural tissue types by comparing the relative contribution of each water compartment to the signal. Each voxel can be characterised by a fraction value for each compartment, with the myelin water fraction (MWF) constituting a widely used and histologically validated

proxy for myelin content (Webb, Munro, Midha, & Stanisz, 2003; Laule et al., 2006). In addition, T1 relaxation measures can be utilised to further improve the signal decomposition using so-called 2D relaxometry (Snaar & Van As, 1992; Does, Beaulieu, Allen, & Snyder, 1998; Does & Gore, 2002). Given the clinically suitable acquisition time of the DESPOT protocol, Deoni et al. (2008) further extended the technique to allow for 2D relaxometric analysis, thus introducing mcDESPOT.

Within the mcDESPOT protocol, a whole-brain T1 map is derived from several SPGR images acquired across a range of flip angles. Due to inevitable flip angle errors caused by inhomogeneities within the B1 (transmit) magnetic field, an inversion recovery (IR) SPGR image is acquired to estimate the B1 field and correct for flip angle artefacts (Deoni, 2007). The T2 map is estimated from several SSFP images, acquired across several flip angles and with two phase cycling patterns (0° and 180°) to correct for (off-resonance) banding artefacts, using the previously estimated T1 and B1 maps. Finally, a stochastic region contraction approach is used (Deoni & Kolind, 2015) to model the SPGR and SSFP signals with a two- or three compartment model (Deoni, Matthews, & Kolind, 2013) to generate compartment specific T1, T2, water residence time, and fraction maps. MWF maps contain the estimated fraction value of the myelin-associated water at each voxel. Voxels within myelin-rich white matter regions typically show MWF values of approximately 25-30%, whereas values within the grey matter are expected to be below 10%.

2.4.2 mcDESPOT processing protocol

Acquisition parameters for the mcDESPOT scanning sequences can be found in Table 2. Each subject's scans were linearly coregistered to each other using the highest flip angle SPGR as the reference volume with FSL FLIRT. Non-brain parenchyma signal was then removed using FSL BET. Myelin water fraction (MWF) maps were derived using in-house mcDESPOT processing software (https://github.com/spinicist/QUIT), which includes the tools qidespot1hifi (for simultaneous calculation of B1 and T1 maps), qidespot2fm (for simultaneous calculation of off-resonance f0 and T2 maps), and qimcdespot (for calculation of MWF maps). A three compartment model was used, assuming signal contribu-

tions from a myelin associated species, an intra- and extracellular water compartment, and a CSF species. MWF maps were then non-linearly registered to the MNI152 2mm isotropic standard brain using FSL FNIRT and smoothed using a Gaussian kernel at 5mm FWHM. Standardised, smoothed MWF were subjected to statistical permutation testing using FSL RANDOMISE as described in detail in Chapter 5.

All neuroimaging results presented in this thesis are shown in radiological convention.

Chapter 3

Experiment 1: Neural mechanisms underlying cognitive control function in treatment resistant and responsive schizophrenia

3.1 Introduction

The ability to overcome cognitive and behavioural interference is integral to efficient and adaptive functioning. Cognitive control broadly represents the element of executive function which enables one to maintain behavioural goals in the face of interference from task-irrelevant information (Melcher & Gruber, 2009). Prefrontal brain regions, in particular both dorsal and rostral aspects of anterior cingulate cortex (ACC) and lateral prefrontal cortex, are thought to play an important role in cognitive control mechanisms (Derrfuss, Brass, Neumann & von Cramon, 2005; Di Pellegrino, Ciaramelli & Ladavas, 2007; Laird et al., 2005; Umemoto & Holroyd, 2016; Van Veen & Carter, 2005).

Deficits in executive functions are a core characteristic of psychotic disorders, with dysfunctions observed in cognitive control, working memory, planning, and cognitive flexibility (Eisenberg & Berman, 2010; Knowles et al., 2015; Minzenberg et al., 2009). These deficits are accompanied by altered cortical activation, most commonly decreased activation of frontal cortical regions. A meta-analysis of executive function imaging studies in schizophrenia identified reduced activation in a network of regions relevant to cognitive control, comprising dorsolateral prefrontal cortex, ACC, and mediodorsal thalamus (Minzenberg et al., 2009). Concurrently, hyperactivations – possibly reflecting compensatory responses – are seen in the

ventrolateral prefrontal cortex and a midline cortical region extending from dorsal ACC to supplementary motor area (SMA).

There is limited evidence for improvement of this cognitive dysfunction in patients with schizophrenia with treatment, yet several lines of research suggest that the prefrontal neural response during cognitive tasks is improved or even normalised as a result of antipsychotic medication (Kani et al., 2017; Schneider et al., 2013; Snitz et al., 2005). Krabbendam et al. (2009) showed that activation in inferior frontal junction during a cognitive inhibition task increased after 6-8 weeks of antipsychotic treatment, and change in activation was related with positive symptom change. However, it is unclear whether patients with schizophrenia who are resistant to antipsychotic treatment are characterised by a distinct functional signature of cognitive performance.

Treatment resistance remains a difficult problem, with up to 40% of diagnosed patients showing inadequate response to optimal antipsychotic treatment (Lindenmayer, 2000; Mortimer et al., 2010). All antipsychotic medication acts by modulating dopamine receptors and treatment resistance occurs despite adequate D2 receptor occupancy by antipsychotic medication (Coppens et al., 1991; Wolkin et al., 1989), indicating that alternative mechanisms to hyperdopaminergia may be driving psychotic symptoms in the refractory patients. Treatment resistant patients show more robust cognitive deficits compared to treatment responders (Frydecka et al., 2016), and stronger cognitive performance is associated with a more favourable clinical outcome (Brissos, Dias, Balanza-Martinez, Carita & Figueira, 2011; Hofer et al., 2011). The neurophysiological underpinnings of this remain unclear.

Schizophrenia has been repeatedly described in terms of a dysconnection syndrome, with frontostriatal interactions in particular postulated to be crucial in symptom formation (Stephan et al., 2009). In this view, decreased input from prefrontal cortex to the midbrain results in disinhibition of dopamine neurons projecting to striatum. The resulting hyperdopaminergia leads to a state of aberrant salience, whereby irrelevant stimuli are imbued with special significance and the individual develops bizarre ideas or delusions in order to explain these experiences of salience (Howes & Kapur, 2009). At the same time, a failure of top-down control signals from prefrontal areas to widespread networks may contribute to the maintenance of psychotic symptoms as integration with bottom-up sensory

information is disrupted (Friston & Frith, 1995).

Following from this view, one might argue that even if the striatal dopaminergic dysfunction is alleviated with antipsychotic medication, this would not necessarily suffice to reduce symptoms once they have been established if fronto-striatal connectivity remains impaired. This model of treatment resistance would suggest that functional integration is more severely impaired in treatment resistant schizophrenia (TRS) compared to non-treatment-resistant (NTR) patients. Consequently, antipsychotic treatment may effectively attenuate the striatal dopaminergic dysfunction, but in the absence of a normative response from prefrontal cortex in TRS, symptoms could be perpetuated despite optimal treatment. In contrast, NTR patients may have sufficient cognitive reserve and frontal functional connectivity such that alleviating the striatal dysfunction is sufficient to reduce symptoms adequately.

Indeed recent research has shown that frontostriatal resting-state connectivity is more disturbed in TRS compared to non-refractory schizophrenia (T. P. White et al., 2016). In addition, Sarpal and colleagues demonstrated that improvement of psychosis after antipsychotic treatment is associated with increased frontostriatal connectivity (Sarpal, Robinson et al., 2015), and that baseline connectivity may in fact be used to predict treatment outcome in first episode psychosis (Sarpal, Argyelan et al., 2015). However task-related functional connectivity in the context of cognitive control mechanisms, which rely more heavily on fronto-thalamic circuits (Wagner et al., 2013), has not yet been explicitly assessed in TRS.

The aim of this experiment was to investigate the neural mechanisms underlying cognitive control as a function of treatment response status in patients with a diagnosis of schizophrenia. The Stroop task, a standard paradigm for tapping into executive control function, was used. Patients with schizophrenia have shown both behavioural and neurofunctional deficits on this task. Improvement on the Stroop task following antipsychotic treatment was recently linked with symptom reductions (Krabbendam et al., 2009), but it is unclear whether treatment responders and non-responders show a differential neural profile at the chronic stage of the illness. The hypotheses for this experiment were that:

1. Patients with schizophrenia will show slower reaction time (RT) and accuracy interference effects (defined as the difference between the congruent and

incongruent conditions) compared to HC

2. Patients with schizophrenia will show reduced frontal activation during response conflict compared to HC

3. TRS patients will show slower RT and accuracy interference effects compared to HC and NTR

4. TRS patients will show reduced frontal activation during response conflict compared to HC and NTR

5. TRS patients will show a negative association between psychotic symptom severity and frontal activation during response conflict

6. TRS patients will show reduced connectivity between frontal and subcortical regions of the cognitive control network compared to HC and NTR.

3.2 Methods

3.2.1 Participants

Stroop data was available for 21 patients fulfilling criteria for treatment resistant schizophrenia (TRS), 21 patients with non-treatment-resistant schizophrenia (NTR), and 23 healthy controls (HC).

3.2.2 Procedure

Subjects performed a verbal Stroop paradigm while undergoing functional magnetic resonance imaging. The screen was viewed via a head-mounted mirror. On each trial, a single colour word was presented on the screen ("BLUE", "RED", "GREEN", or "YELLOW") against a black background. The word was printed in one of four possible font colours (blue, red, green, or yellow). Word meaning and font colour were either congruent or incongruent, and subjects were instructed to respond verbally to the font colour and to ignore the word meaning. In addition, on fixation trials a central white fixation cross was presented in the centre of the screen and no response was required. Thirty-three congruent, 33 incongruent,

and 34 fixation trials were presented in randomised order, each with a duration of 700 ms and inter-stimulus-interval of 2300 ms. Responses were recorded via a microphone mounted inside the scanner in order to assess reaction times. Only responses between 200 and 2700 ms after stimulus presentation were recorded.

3.2.3 Behavioural data analysis

3.2.3.1 Accuracy

All trials were included in the accuracy analysis. The proportion of correct trials was computed for each subject and compared via analysis of variance (ANOVA) with group (HC vs. NTR vs. TRS) as between-subjects factor and condition (congruent vs. incongruent) as within-subjects factor. Significant effects were followed up with pairwise t-tests (Bonferroni corrected for multiple comparisons). The Accuracy Stroop effect, defined as [Proportion correct(incongruent) – Proportion correct(congruent)] was furthermore compared directly between groups using pairwise t-tests.

3.2.3.2 Reaction time

Trials on which an incorrect response was given (2.9% of total trials) were removed from further analysis. Mean reaction times (RTs) were analysed via ANOVA with group (HC vs. NTR vs. TRS) as between-subjects factor and condition (congruent vs. incongruent) as within-subjects factor. Significant effects were followed up with pairwise t-tests (Bonferroni corrected for multiple comparisons). The RT Stroop effect, defined as [RT(incongruent) – RT(congruent)] was furthermore compared directly between groups using pairwise t-tests.

3.2.4 Neuroimaging data analysis

3.2.4.1 First level analysis

For the first level analysis, regressors representing onsets of stimulus presentation for incongruent trials and congruent trials were included into the model.

Each regressor was modelled as a delta function and convolved with a canonical haemodynamic response function. Potentially exacerbated motion artefacts were anticipated due to the verbal nature of responses given during the task; thus comprehensive motion regression was performed. Both standard and extended motion parameters were included as nuisance regressors. Standard motion parameters include 3 rotational and 3 translational movement parameters, and extended parameters consist of the derivatives of the standard parameters, as well as the squares of the standard parameters and their derivatives. In addition, to correct for physiological noise, cardiac and respiratory signals were modelled using FSL's Physiological Noise Modelling (PNM) as described in Brooks et al. (2008). Cardiac and respiratory regressors (principal frequency and first three harmonics) as well as their interactions were created, resulting in a total of 32 regressors which were treated as voxelwise confounds in FEAT.

For each subject, contrasts of interest included the *Stroop* contrast (defined as [Incongruent – Congruent]) and the *Incongruent* contrast. The Stroop contrast is typically used to capture pure interference effects by subtracting the congruent condition, which does not entail a response conflict, from the incongruent interference condition. However, given the randomised order of trial conditions, it is likely that the congruent condition may also contain an element of cognitive control, which may thus be subtracted out in the Stroop contrast. The simple Incongruent condition contrast was therefore also assessed separately.

3.2.4.2 Second level analysis

Mean activation differences The first level contrast images for the *Stroop* and *Incongruent* contrasts, respectively, were subjected to separate mixed effects group level analyses (FLAME1) modelling the effect of group. In a first analysis, contrast images of NTR and TRS patients were pooled into one patient group so as to assess mean activation differences between HC and patients. Due to significant differences between groups on the WASI IQ scores and significant correlations between WASI and the RT Stroop effect both in NTR ($R = $-0.66, $p = .001$) and TRS ($R = $-0.68, $p < .001$), WASI was included as a covariate of no interest. In a second analysis, mean activation differences between NTR and TRS patients were analysed. Chlorpromazine (CPZ) equivalent medication dosage was included as a

covariate of no interest. Where group differences were not significant on a whole-brain level, region of interest (ROI) analyses were performed. Functional ROIs were defined as activation clusters which were significant across all groups (i.e. in the F contrast [1 1] across both groups). Mean parameter estimates were extracted from these clusters for each subject and then specifically compared between groups using one-way ANOVA.

Correlations with psychotic symptoms In order to test for differential correlations between symptoms and brain activation in the two patient groups, further analyses of the *Incongruent* contrast were conducted modelling the effect of group (NTR vs. TRS) and PANSS positive symptom score. A group × symptom score interaction term tested specifically whether the two groups showed differential correlations between neural activation and symptoms. An identical analysis was conducted with PANSS negative symptom scores. CPZ equivalent dosage was included as a covariate of no interest.

Functional connectivity analysis Finally, a psychophysiological interaction (PPI) analysis was conducted to assess differences in functional connectivity during the *Incongruent* condition between the three groups. A cluster in the ACC identified in the previously described symptoms analysis was used as a seed region. An ROI mask consisting of bilateral striatum and thalamus (anatomically defined from the probabilistic Harvard Oxford Subcortical Structural Atlas thresholded at 30%, see Appendix Figure A.1) was used to directly assess connectivity of the ACC with this region.

3.3 Results

3.3.1 Behavioural data

3.3.1.1 Accuracy

The ANOVA on proportion of correct trials revealed a significant main effect of group, $F(2,62) = 5.18$, $p = .008$, a significant main effect of condition, $F(1,62) = 36.71$,

$p < .001$, as well as a significant group × condition interaction, $F(2,62) = 4.58$, $p = .014$ (see Figure 1). Post-hoc comparisons showed that groups performed similarly on congruent trials, all ps $> .05$. In contrast, on incongruent trials, HC had a higher mean proportion of correct trials compared to NTR, $p = .03$, and TRS, $p = .005$ (Bonferroni corrected).

Pairwise comparisons revealed that both TRS ($M = 6.6\%$; $SD = 8.4\%$) and NTR ($M = 7.5\%$; $SD = 7.9\%$) showed a greater accuracy Stroop effect than HC ($M = 1.7\%$; $SD = 3.4\%$), all ps $< .05$ (Bonferroni corrected), with no difference between the two patient groups, $p = .999$.

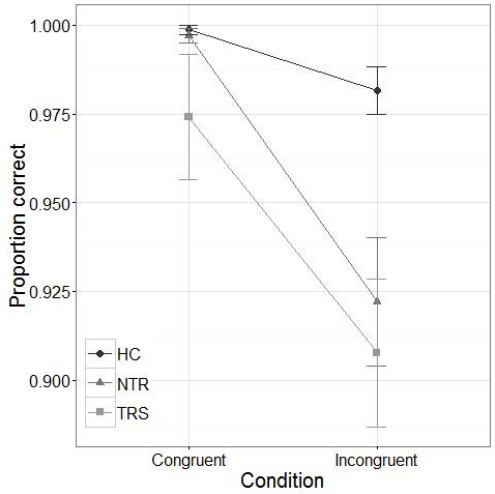

Figure 1. Mean proportion correct by group and condition. Error bars represent the standard error of the mean.

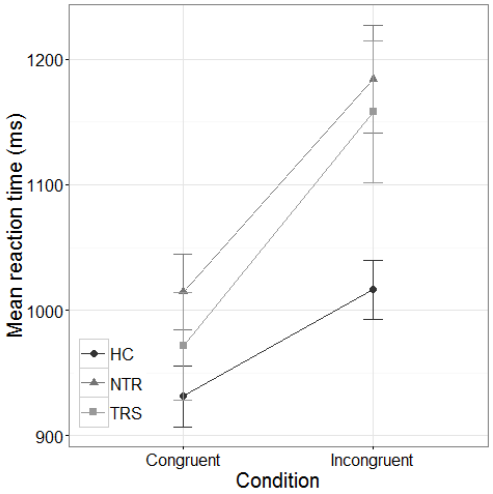

Figure 2. Mean reaction time in ms by group and condition. Error bars represent the standard error of the mean.

3.3.1.2 Reaction time

For the RT data, there was a significant main effect of group, $F(2,62) = 3.35$, $p = .042$, a significant main effect of condition, $F(1,62) = 109.00$, $p < .001$, as well as a significant group × condition interaction, $F(2,62) = 5.23$, $p = .008$ (see Figure 2). Groups did not differ significantly on congruent trials, whereas on incongruent trials HC responded significantly faster compared to NTR, $p = .019$, and marginally compared to TRS, $p = .060$ (Bonferroni corrected).

Pairwise comparisons revealed that both TRS ($M = 186.66$ ms; $SD = 128.26$ ms) and NTR ($M = 169.78$ ms ; $SD = 129.95$ ms) showed a greater RT Stroop effect than HC ($M = 85.14$ ms; $SD = 71.87$), all $ps < .05$ (Bonferroni corrected), with no difference between the two patient groups, $p = .627$.

3.3.2 Neuroimaging data

3.3.2.1 Mean activation differences

HC vs. Patients Across both groups, subjects showed *Stroop*-related BOLD signal in a midline section extending from paracingulate gyrus to supplementary motor area (SMA) as well as bilateral precentral gyri (see Appendix Table A.1). There was no whole-brain group effect at a voxelwise level. However, functional ROI analyses on the three significant activation clusters revealed that patients with schizophrenia showed significantly increased activation compared to HC in the cluster extending from dorsal ACC to SMA (Figure 3).

Across groups on *Incongruent* trials, subjects showed extensive activation of areas classically associated with the Stroop task, including bilateral superior frontal gyri, two large clusters extending from bilateral precentral gyri to the superior temporal lobes, as well as bilateral precuneous cortex and lateral occipital lobes (see Appendix Table A.2). Whole-brain group differences were found in two significant clusters (Table 3), with patients showing attenuated activation compared to HC in left superior parietal cortex extending to lateral occipital cortex as well as in the right insula extending anteriorly to OFC and posteriorly to the hippocampus (Figure 4).

NTR vs. TRS There were no significant mean activation differences between the NTR and TRS groups for the *Stroop* contrast or the *Incongruent* contrast either at a voxelwise level or within functional ROIs.

3.3.2.2 Correlations with psychotic symptoms

A further analysis in patients only with PANSS positive symptoms as covariate and controlling for medication dosage showed a differential relationship between

Table 3
Significant clusters for the effect of group (Healthy controls vs. patients) on the Incongruent contrast

Region	Side	k	z	MNI		
Insula	R	973	4.31	44	8	-6
Hippocampus	R			34	-30	-6
Hippocampus	R			36	-30	-6
Hippocampus	R			34	-38	4
Orbitofrontal cortex	R			22	8	-14
Hippocampus	R			16	-16	-16
Superior parietal cortex	L	2474	3.97	-6	-60	60
Superior parietal cortex	L			-28	-34	52
Precuneous cortex	L			-12	-50	56
Superior parietal cortex	R			14	-48	58
Postcentral gyrus	L			-16	-48	58
Postcentral gyrus	L			-14	-48	62

positive symptoms and BOLD response in rostral ACC in NTR compared to TRS (Table 4; Figure 5A). As can be seen in Figure 5B, activation in rostral ACC was positively correlated with PANSS positive score in NTR ($R = 0.58$, $p = .007$), but negatively correlated in TRS ($R = $-0.44, $p = .048$).

Table 4
Significant cluster for the positive symptom × group effect on the Incongruent contrast

Region	Side	k	z	MNI		
Anterior cingulate cortex	R	1000	3.46	4	36	6
Anterior cingulate cortex	R			10	40	4
Paracingulate gyrus	R			14	48	2
Paracingulate gyrus	R			-14	42	-4
Paracingulate gyrus	R			12	46	-4
Anterior cingulate cortex	R			-2	36	6

In addition, exploratory correlation analyses of rostral ACC activation and task performance were conducted (Figure 5C). In the TRS group, deactivation of ACC was associated with slower mean RTs in the incongruent condition ($R = $-0.56, $p = .008$). This correlation differed significantly from that in both NTR ($R = $-0.02, $p = .929$) and HC ($R = $ -0.05, $p = .811$), as established with Fisher's R to Z transform (both $z > 2.1$, $ps < .05$).

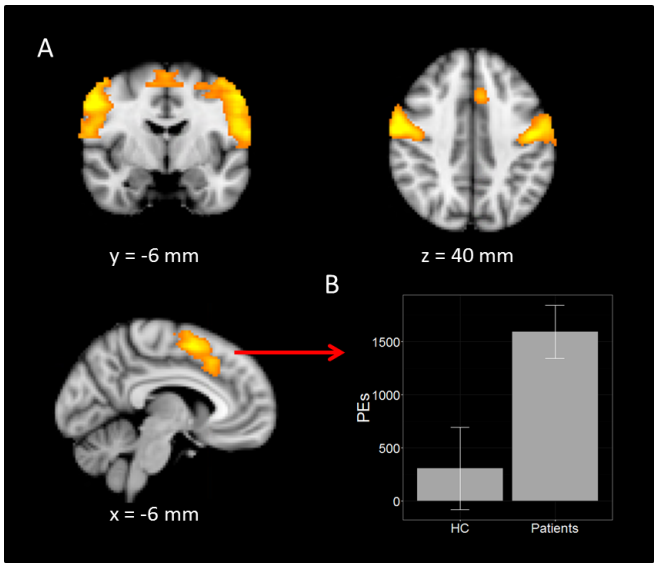

Figure 3. Activation for Stroop contrast across groups (A) and mean parameter estimates (PEs) for supplementary motor area region of interest in healthy controls (HC) and patients (B). Activation maps reflect z-values thresholded at 2.3, corrected p $<$ .05.

The equivalent analysis using PANSS negative symptom score as covariate did not yield any significant group $\times$ symptom effect.

3.3.2.3 Functional connectivity analysis

Finally, a functional connectivity analysis controlling for WASI scores was run using the reported rostral ACC cluster shown in Figure 5A as seed region and a subcortical mask including bilateral thalamus and striatum as ROI. Across the three groups significant connectivity was found with bilateral dorsal thalamus (Table 5; Figure 6A). Mean connectivity parameter estimates for each group can be seen in Figure 6B. Pairwise comparisons on mean parameter estimates revealed a trend towards reduced connectivity between ACC and dorsal thalamus in TRS compared to HC, $p < .063$ (uncorrected), Cohen's $d = 0.63$. There was no significant difference between NTR and HC, or NTR and TRS.

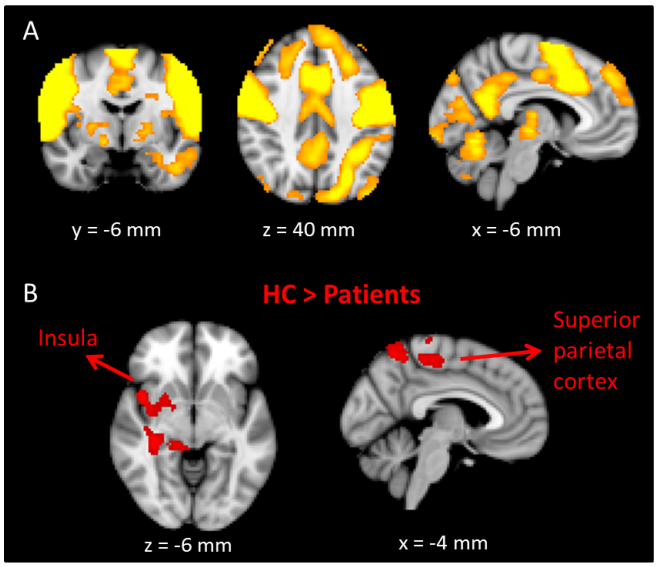

Figure 4. Activation for Incongruent contrast across groups (A) and whole-brain significant clusters of group differences (B). Activation maps reflect z-values thresholded at 2.3, corrected $p < .05$.

3.4 Discussion

The aim of this experiment was to compare cognitive control mechanisms in patients with schizophrenia who were either treatment resistant (TRS) or non-treatment-resistant (NTR) and healthy controls (HC). The focus lay in identifying whether more pronounced cognitive control deficits could account for persistence of psychosis despite optimal treatment in TRS. On a behavioural level, both patient groups showed similarly impaired performance, with increased reaction time interference effects compared to healthy controls and no significant between-patient subgroup differences. In a similar vein, there were no significant differences in overall BOLD response between the two patient groups. Rather, patients showed increased activation of dorsal ACC extending to SMA compared to HC on the interference Stroop contrast, consistent with a compensatory response observed in earlier studies (Johnson et al., 2006; Minzenberg et al., 2009; Tan et al., 2006). On incongruent trials, patients showed attenuated activation compared to HC in superior parietal cortex and left insula extending to orbitofrontal cortex, regions previously implicated in cognitive control deficits in schizophrenia (Minzenberg et al., 2009). In sum, overall behaviour and neural activation in this

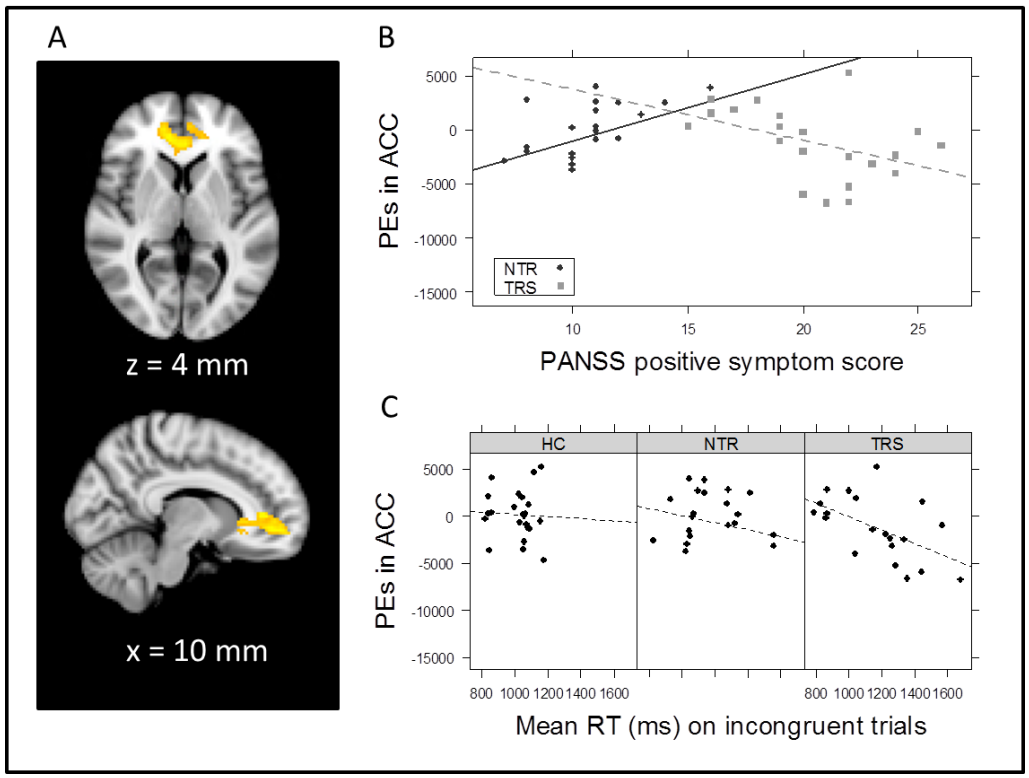

Figure 5. Anterior cingulate cortex (ACC) region showing significant group × positive symptom score interaction (A); correlation between mean parameter estimate in ACC and positive symptom score by group (B); and correlation between mean parameter estimates (PEs) in ACC and mean reaction time on incongruent trials by group (C). Activation maps reflect z-values thresholded at 2.3, corrected $p < .05$.

particular task do not adequately differentiate between the two patient groups.

A further analysis investigated how both positive and negative symptoms modulate neural activation on this task in the two patient subgroups. There was no significant effect for negative symptoms. Intriguingly, there was a differential association between BOLD response in rostral ACC and positive symptom severity in the two patient subgroups. While higher positive symptoms were associated with a higher BOLD response in NTR, increased positive symptoms were associated with ACC deactivation in TRS. This suggests a differential role for ACC functioning in these two groups during cognitive interference: the most unwell TRS patients showed the strongest ACC deactivation, which in turn predicted slower response times on the task. In contrast, the NTR group demonstrated the greatest deactivation in the least symptomatic patients, and this was unrelated to behaviour. Significant dysfunction of the ACC in schizophrenia has been observed in

Table 5
Significant cluster for the functional connectivity analysis with anterior cingulate seed

Region	Side	k	z	MNI		
Thalamus	R	763	3.95	-6	0	4
Thalamus	R			4	-26	4
Caudate	L			-6	6	4
Thalamus	R			4	-20	14
Thalamus	R			4	-4	4
Thalamus	L			-2	-26	4

both structural and functional imaging (Fornito, Yücel, Dean, Wood & Pantelis, 2009; McGuire et al., 1998; Radua et al., 2012), and is associated with executive dysfunction in the illness (Glahn et al., 2005; Kerns et al., 2005; Szeszko et al., 2000). Snitz et al. (2005) showed that ACC functioning is improved after four weeks of antipsychotic treatment. These findings suggest that this may not be the case in the most severe cases of TRS. In light of the involvement of glutamatergic neurotransmission in cognitive control processes (Falkenberg, Westerhausen, Specht & Hugdahl, 2012; Lorenz et al., 2015; van Wageningen, Jorgensen, Specht & Hugdahl, 2009), as well as suggestions that prefrontal glutamate may differentially modulate cognitive control processes in patients with schizophrenia, it is possible that aberrant ACC function and connectivity in the more symptomatic TRS patients may be related to altered ACC glutamate levels previously reported in TRS (Demjaha et al., 2014; Egerton et al., 2012; Mouchlianitis et al., 2015).

Previous neuroimaging studies of the Stroop task have reported involvement of a fronto-striato-thalamic network (Bari & Robbins, 2013; Chambers, Garavan & Bellgrove, 2009) that regulates inhibitory control. The PPI analysis identified a region in the dorsal thalamus which showed significant functional connectivity with ACC on incongruent trials, in line with these reports. The strength of connectivity was indistinguishable in the HC and NTR groups, but there was a tendency towards reduced connectivity in TRS. This reduction was only marginally significant and must thus be interpreted with caution; however the moderate effect size suggests that the effect may be more evident in a larger sample with reduced variability.

Taken together, the results indicate that despite similar overall activation pat-

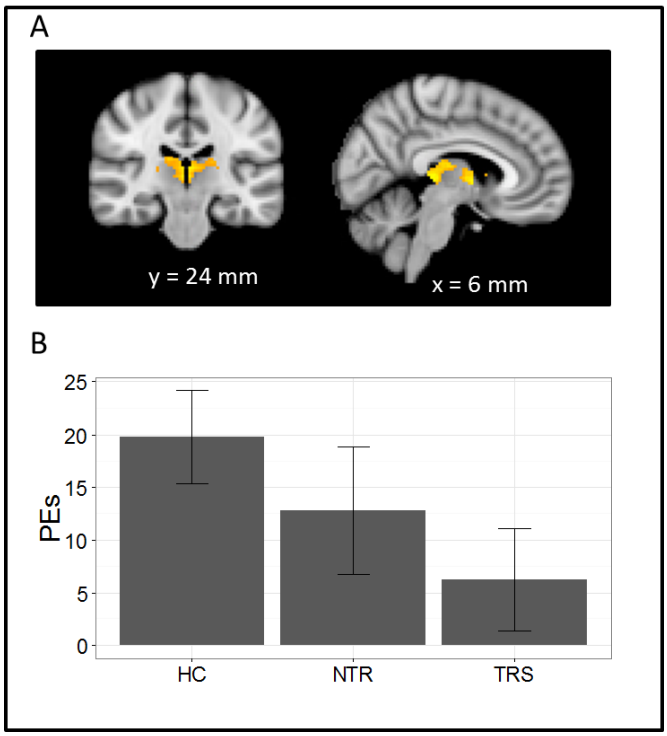

Figure 6. Dorsal thalamus region showing significant functional connectivity with anterior cingulate seed (A); and mean parameter estimates (PEs) within this region by group (B). Activation maps reflect z-values thresholded at 2.3, corrected $p < .05$.

terns on this version of the Stroop task, patients with treatment resistant schizophrenia are differentiated by a unique association of ACC function with symptom severity, accounting in part for the observed behavioural deficits. In addition, though only a preliminary finding which did not survive stringent corrections, the trend towards weakened connectivity of this region with dorsal thalamus, a key region in the cognitive control network, is in line with a lack of functional frontal-midbrain integration which may play a role in perpetuating symptoms despite optimal treatment. While there were no frontal activation differences between the two patient subgroups, the relationship of ACC activation and positive symptoms differed significantly. The positive relationship in NTR and negative relationship in TRS is best conceptualised as an inverse U-shaped curve across the range of positive symptoms: cognitive control as reflected in ACC activation initially increases as symptoms increase, but as symptoms become more severe, the inhibitory process fails. The inverted U-shape is analogous to that seen in frontal and

parietal activation as cognitive load increases during working memory tasks (Callicott et al., 1999; Linden, 2007). One speculation might be that a compensatory neural response is effective in maintaining behavioural performance up to a certain threshold, upon which increased task demands are met with an inversion of the neural response and performance deteriorates. The findings of this experiment support the notion that alleviation of striatal dysfunction by antipsychotics is not sufficient to alleviate symptoms in TRS due to a persistence of frontal dysfunction and functional dysconnectivity.

Chapter 4

Experiment 2: Neural mechanisms underlying reinforcement learning in treatment resistant and responsive schizophrenia

4.1 Introduction

Schizophrenia has frequently been studied within a framework of reinforcement learning given the involvement of dopamine function in reward prediction (Deserno et al., 2016). Reinforcement learning is driven by midbrain dopamine neurons encoding violations of expected reward outcomes (Schultz, 1998), known as reward prediction error (RPE) signals. RPE signalling in the striatum has been shown to be reduced in schizophrenia patients (Schlagenhauf et al., 2014; G. Murray et al., 2008; Waltz et al., 2009), a finding attributed to "drowning" of these phasic signals due to elevated presynaptic dopamine. Dysfunctional RPE signalling has been related to both positive (Corlett et al., 2007; Gradin et al., 2011) and negative (Waltz et al., 2009; Moran, Owen, Crookes, Al-Uzri & Reveley, 2008) symptoms and is intimately linked with the aberrant salience hypothesis of schizophrenia. According to this account, excessive subcortical dopamine activity observed in patients (Howes & Kapur, 2009) would lead to dopamine neurons firing out of context, leading to a perplexing state where environmental stimuli acquire value that cannot be logically explained by the individual without developing unusual ideas, or delusions (Howes & Kapur, 2009; Kapur, 2003; Kapur et al., 2005).

The question of whether a common dopaminergic abnormality underlies both treatment responsive and treatment resistant schizophrenia (TRS) remains cru-

cial. Plausibly, an alternative aberrant mechanism may give rise to symptoms in TRS (Demjaha et al., 2012) and drive reinforcement learning deficits in these patients. Importantly, reinforcement learning relies not only on striatal dopamine function, but also on complex cortico-subcortical interactions regulating related processes such as cognitive control, goal maintenance and planning, as well as action value and effort computations (Barch & Dowd, 2010; Frank, Loughry & O'Reilly, 2001b; Frank & Claus, 2006). As bottom-up learning signals are utilized to update a model of the surrounding environment, it is necessary to exert top-down cognitive control – particularly in the presence of persistent cognitive or behavioral bias – in order to optimise task focused learning. As such, it is possible that even with intact RPE signalling, a lack of cognitive control modulating learning processes could lead to a disruption of reinforcement learning. In particular, while cognitive biases occur in all individuals, the manner in which these interact with subcortical learning processes may be crucial with respect to TRS.

There is a distinct lack of studies investigating the cognitive and neural mechanisms underlying these processes directly in treatment resistant and treatment responsive individuals with schizophrenia. In this experiment, these groups are compared using functional magnetic resonance imaging (fMRI) while investigating 1) neural correlates of RPEs during wins and losses and 2) the influence of cognitive bias on these learning signals. A probabilistic reinforcement learning task was used in which subjects learned reward contingencies of faces with varying emotional expressions (Averbeck & Duchaine, 2009). Both healthy controls and patients with schizophrenia have been shown to exhibit an emotional bias towards happy faces on this task, evident as more frequent choices for happy faces (versus angry faces) even when the reward feedback is equivalent (Evans et al., 2011). The task, therefore, sets up a conflict between reward processing and emotions, as optimal learning would ignore the emotional expressions.

In the current experiment, RPE signalling was examined separately for wins and losses on this task both because dissociable systems have been suggested for prediction error signalling of rewards and losses (Yacubian et al., 2006; Garrison et al., 2013) and due to evidence that reward and loss processing may be differentially impacted in schizophrenia (Chang, Waltz, Gold, Chan & Chen, 2016; Reinen et al., 2016; Waltz et al., 2007; Waltz et al., 2011). In addition it was

anticipated that this would more closely reflect variabilities in prediction errors rather than effects of outcome itself. Based on the theory that treatment responsive schizophrenia, but not TRS, is characterised by an abnormal dopaminergic signature, this experiment tested the hypotheses that:

1. All groups will show an emotional bias towards the happy face
2. Patients with schizophrenia will show impaired learning in both the emotional and neutral condition compared to HC
3. RPE signalling will be attenuated specifically in NTR patients compared to HC and TRS
4. TRS will show a greater impact of bias on neural response to feedback in the emotional condition compared to NTR patients and HC.

4.2 Methods

4.2.1 Participants

Faces task data was available for 21 patients fulfilling criteria for treatment resistant schizophrenia (TRS), 21 patients with non-treatment-resistant schizophrenia (NTR), and 24 healthy controls (HC).

4.2.2 Procedure

Subjects underwent a reward learning paradigm which consisted of choosing between two simultaneously presented faces, learning which of the faces was associated with a higher reward probability over a series of iterative trials. The subjects were asked to maximise the reward achieved in the task. The task consisted of four blocks of 30 trials each. Blocks 1 and 3 were emotional blocks, and blocks 2 and 4 were neutral blocks. In emotional blocks, the two faces had the same identity but one showed a happy expression while the other showed an angry expression. In neutral blocks both faces wore neutral expressions but consisted of two separate identities. In each block one face was associated with a 60% reward

probability and the other with a 40% reward probability. The order in which identities and expressions were associated with the higher reward probability was counterbalanced across subjects. A schematic of a trial sequence is shown in Figure 7.

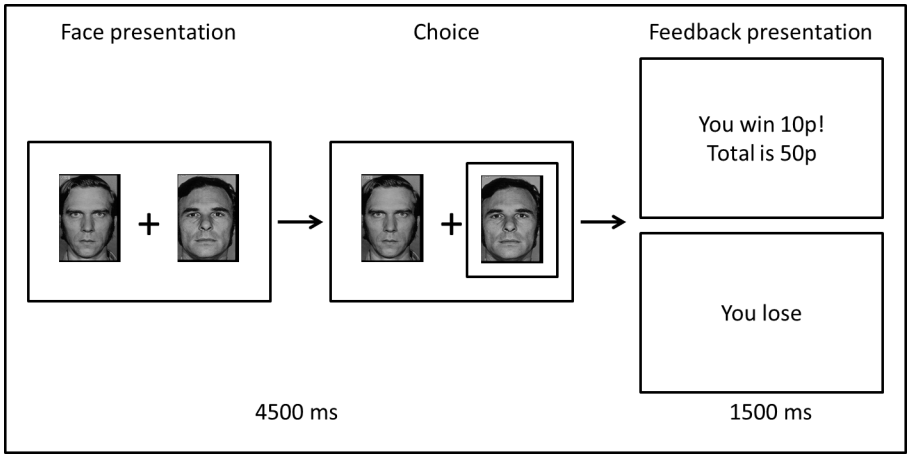

Figure 7. Schematic of task sequence (neutral block). Background and text colours are inverted. The chosen face was highlighted with a yellow box surrounding it.

Each trial began with a period of 1000 ms during which a white central fixation cross was presented against a dark background. This was followed by two faces being presented to the right and left of the fixation cross for 4500 ms. Within this time window subjects were required to select one of the faces by pressing the corresponding button with their right hand. The selected face was highlighted by a yellow square surrounding it. Feedback was then presented on the screen for a duration of 1500 ms. If the correct face was chosen, the words "You win 10 pence. Total is X pence" were presented, with X representing the running total for the task. If the incorrect face was chosen, the words "You lose" were presented. The total did not change after an incorrect choice.

4.2.3 Behavioural data analysis

The behavioural data was modelled using a "double update" reinforcement learning (RL) model (Schlagenhauf et al., 2014). Choice probability for choosing option 1 on trial t was computed on each trial using the softmax function

$$P_1(t) = \frac{exp(\beta \times Q_1(t))}{exp(\beta \times Q_1(t)) + exp(\beta \times Q_2(t))}$$

where the inverse temperature β determines the randomness of the subject's choice, and Q1(t) denotes the action value, or expected reward, for choice 1 on trial t. The action value for the chosen option is updated on a trial-by-trial basis using the reward prediction error, defined as the difference between the expected reward Q and obtained reward R on trial t, scaled by the learning rate parameter α.

$$Q_1(t+1) = Q_1(t) + \alpha(R(t) - Q_1(t))$$

The action value for the unchosen option 2 was additionally updated on each trial, using the inverse reward value $\overline{R}$ (1 if the chosen option lost, and 0 if the chosen option won) and identical learning rate parameter:

$$Q_2(t+1) = Q_2(t) + \alpha(\overline{R}(t) - Q_2(t))$$

This model reflects the symmetry of choice outcomes, whereby feedback associated with a chosen option is also informative of the unchosen option (e.g., if stimulus 1 lost, stimulus 2 would have won).

The two free parameters β and α were estimated for each group separately by minimizing the negative log likelihood of the observed data pooled across all subjects within the group. Action values Q1 and Q2 were both initialised at 0. A hundred optimisations were performed for each group so as to avoid local minima, with starting values for α randomly drawn from a uniform distribution between 0 and 1 and starting values for β randomly drawn from a uniform distribution between 0 and 10.

Choices on each trial were defined as ideal if the action value (computed by the model) of the chosen option was greater than that of the unchosen option. Subjects' proportions of ideal choices were compared between groups (HC vs. NTR vs. TRS) and conditions (emotional vs. neutral) using mixed effects ANOVA.

Emotional bias was defined as the difference between the proportion of choices for the happy face when the angry face would have been an ideal choice, and proportion of choices for the angry face when the happy face would have been

the ideal choice. Emotional bias was compared between groups using one-way ANOVA.

All behavioural analyses were conducted in R (R Core team, 2013).

4.2.4 Imaging data analysis

4.2.4.1 First level analysis

For the first level analysis, the phases of the task (face presentation, choice, win outcome, and loss outcome) were modelled separately for emotional and neutral trials, resulting in eight unmodulated regressors. Additional parametric regressors were included for the win outcome and loss outcome phases, using RPE as modulator, again separately for emotional and neutral trials, resulting in four additional parametrically modulated regressors.

Each regressor was modelled with a delta function of zero duration and convolved with a canonical hemodynamic response function and its temporal derivative. Six standard motion parameters as well as a motion artefact confound matrix, which identified motion-corrupted volumes, were added as regressors of no interest. Volumes detected as corrupted were calculated by DVARS (Power, Barnes, Snyder, Schlaggar & Petersen, 2012) as implemented by FSL Motion Outliers. The percentage of corrupted volumes did not differ between groups, $F(2,60) = 0.166$, $p > .848$ (HC: $N = 24$; $M = 0.4\%$, $SD = 0.2\%$; NTR: $N = 21$; $M = 0.4\%$, $SD = 0.2\%$; TRS: $N = 18$; $M = 0.4\%$, $SD = 0.3\%$).

Contrasts of interest were created for RPE regressors, either averaging across conditions or contrasting emotional and neutral condition, resulting in the following contrasts of interest: 1) win RPE; 2) loss RPE; 3) win RPE [emotional > neutral]; 4) loss RPE [emotional > neutral].

4.2.4.2 Second level analysis

Mean activation differences At the group level, contrasts were submitted to separate mixed effects analyses (FLAME1), modelling the effect of group (HC, NTR, or TRS) on BOLD signal. Whole-brain activation differences between groups were tested for win RPE and loss RPE. In order to detect subcortical

RPE activation an ROI analysis was conducted using a binary subcortical mask consisting of the bilateral striatum and thalamus (anatomically defined from the probabilistic Harvard Oxford Subcortical Structural Atlas thresholded at 30%, see Appendix Figure A.1).

Correlations with emotional bias In order to assess the differential effect of emotional bias on RPE-related signal, analyses of the win RPE [emotional > neutral] and loss RPE [emotional > neutral] contrasts included emotional bias as a covariate, and group × bias interaction effects were assessed.

4.3 Results

4.3.1 Behavioural results

The proportion of ideal choices differed significantly between the three groups, $F(2,63) = 3.69$, $p = .031$, with HC ($M = 0.63$, $SD = 0.13$) making significantly more ideal choices compared to NTR patients ($M = 0.55$, $SD = 0.13$), $p = .006$, as well as compared to TRS patients ($M = 0.57$, $SD = 0.11$), $p = .048$. There was no significant difference between NTR and TRS patients, $p > .05$ (post-hoc t-tests Bonferroni corrected for all three pairwise comparisons). There was no significant main effect of (emotional vs. neutral) condition, and no group × condition interaction, $ps > .05$.

There was a significant positive emotional bias across subjects ($M = 0.8$, $SD = 0.17$, $p < .001$) indicating a preference for choosing the happy over the angry face. Emotional bias did not differ significantly between groups, $p > .05$ (HC: $M = 0.06$, $SD = 0.13$; NTR: $M = 0.13$, $SD = 0.22$; TRS: $M = 0.04$, $SD = 0.16$).

4.3.2 Neuroimaging results

4.3.2.1 RPE signalling for wins and losses

Figure 8A shows the pattern of RPE-related activation in response to win outcomes in HC, who showed a significant signal in bilateral dorsolateral prefrontal

cortices, parietal cortices and occipital cortex extending to cerebellum (see Appendix Table A.3). TRS patients showed a similar activation pattern (Figure 8B; see Appendix TableA.4). In contrast, NTR patients showed no supra-threshold RPE-related activation. Group comparisons showed that NTR patients had significantly reduced RPE-related activation in precentral gyrus compared to TRS, in angular gyrus compared to HC, as well as in cerebellum compared to both HC and TRS (Table 6; Figure 9). The subcortical ROI analysis revealed a significant effect of group ($p < .05$ uncorrected), with NTR patients showing reduced RPE-related activation in bilateral thalamus and caudate head compared to both HC and TRS (Figure 10).

Table 6
Significant clusters for the effect of group on reward prediction error related activation during wins

Region	Side	k	z	MNI		
HC > NTR						
Angular gyrus	R	690	3.41	50	-66	32
Middle temporal gyrus	R			42	-48	4
Angular gyrus	R			46	-54	18
Angular gyrus	R			34	-50	38
Angular gyrus	R			42	-54	18
Cerebellum	R	1736	3.69	0	-54	-20
Cerebellum	R			2	-74	-14
Occipital fusiform cortex	R			16	-78	-12
Cerebellum	L			-24	-80	-26
Cerebellum	R			16	-64	-18
Occipital pole	R			12	-90	4
TRS > NTR						
Precentral gyrus	R	991	2.66	64	2	26
Precentral gyrus	R			54	-4	28
Supramarginal gyrus	R			62	-28	22
Postcentral gyrus	R			62	-6	36
Precentral gyrus	R			48	-6	30
Precentral gyrus	R			58	0	12
Cerebellum	R	19885		4	-54	-20
Cerebellum	L			-18	-38	-24
Cerebellum	R			16	-46	-22
Cerebellum	L			-10	-44	-22
Cerebellum	R			12	-46	-22

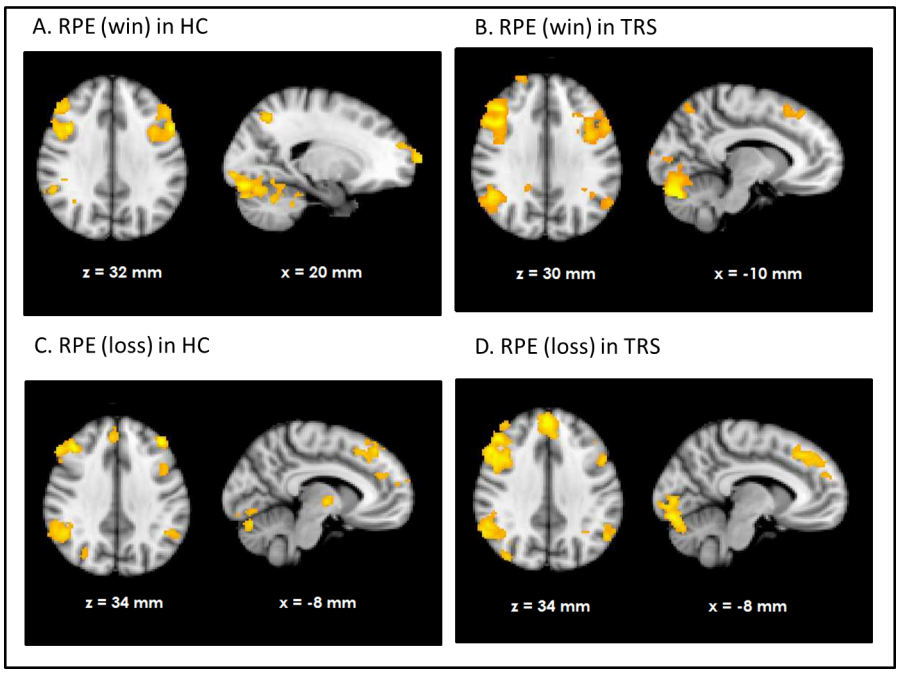

Figure 8. Neural response correlating with reward prediction error (RPE) during wins in healthy controls (A) and treatment resistant schizophrenia (B) as well as during losses in healthy controls (C) and treatment resistant schizophrenia (D). Activation maps reflect z-values thresholded at 2.3, corrected $p < .05$.

Loss-related RPE response was observed in a widespread network in both HC and TRS (see Appendix Tables A.5 and A.6), similar to that during win outcomes (Figures 8C and 8D). Due to the negative sign of loss-related RPE, this signal reflects a negative RPE signal, with greater prediction errors resulting in greater deactivation in these areas. The NTR group showed no significant supra-threshold RPE related signal, but there were no significant group differences at whole-brain level. The subcortical ROI analysis revealed reduced RPE-related signal in bilateral pallidum and caudate in NTR compared to HC ($p < .05$ uncorrected) and no significant difference between TRS and either of the other two groups (Figure 10B).

4.3.2.2 Emotional bias × group interaction on RPE signal

During the emotional (versus neutral) loss trials, the whole-brain analysis showed a significant group × emotional bias interaction on RPE signal in bilateral thal-

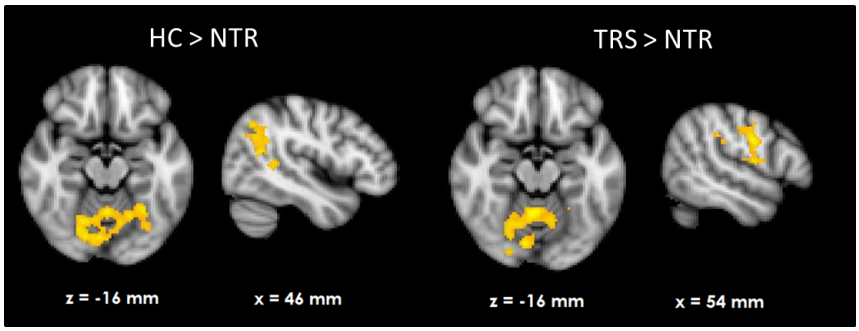

Figure 9. Group differences in neural reward prediction error related activation during wins. Activation maps reflect z-values thresholded at 2.3, corrected p < .05.

amus and caudate nucleus, indicating a differential correlation in TRS and NTR patients (Table 7; Figure 11). In TRS patients, a stronger emotional bias was associated with increased RPE signal in this region ($R = 0.58$, $p = .006$). In contrast, in NTR patients, the opposite was the case ($R = $-0.56, $p = .008$). This negative correlation in NTR was no longer significant after excluding one outlier, however the difference between correlation coefficients in the two groups remained significant (Fisher's R to $Z = 2.69$, two-tailed $p = .007$). Interestingly, RPE signal in this region was significantly correlated with delusion severity in TRS patients, with stronger RPE signalling associated with more severe symptoms of delusions ($R = 0.48$, $p = .027$).

The equivalent analysis on emotional (versus neutral) win trials did not yield a significant group × emotional bias interaction.

Table 7
Significant cluster for the emotional bias × group effect on reward prediction error related activation during emotional (vs. neutral) loss trials

Region	Side	k	z	MNI		
Thalamus	L	593	3.33	-6	-10	14
Caudate	L			-18	-4	16
Caudate	L			-16	0	16
Thalamus	L			-12	-10	16
Caudate	L			-20	-22	18
Thalamus	L			0	-18	16

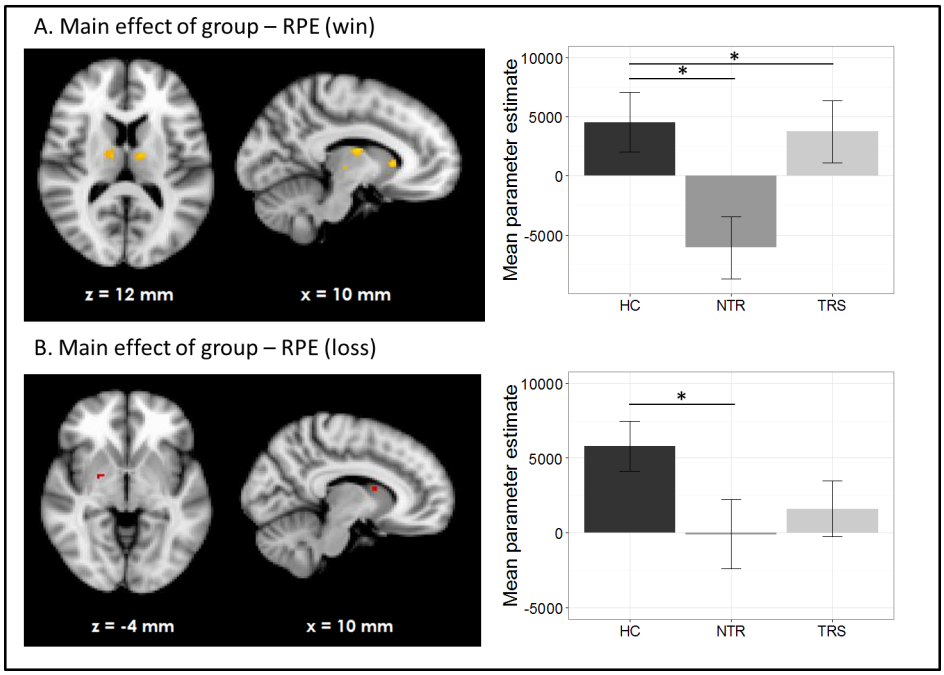

Figure 10. Subcortical region of interest analysis ($p < .05$, uncorrected) of group differences in reward prediction error signal during wins (A) and losses (B). Bar plots represent the mean parameter estimate across the significant voxels.

4.3.2.3 Exploratory correlation analyses

For each of the significant clusters showing group differences in RPE-related activation either during wins or losses, exploratory analyses of correlations between BOLD signal and WASI scores as well as CPZ equivalent medication dosages were conducted within each group. No correlation was significant, all $ps > .05$ (uncorrected for multiple comparisons).

4.4 Discussion

In this experiment, a probabilistic reward learning task was used to assess differences in neural mechanisms underlying reinforcement learning in patients with schizophrenia who were either treatment resistant (TRS) or treatment responsive (NTR), relative to a healthy control (HC) group. The experiment tested the hypothesis that NTR patients would show abnormal prediction error related activation

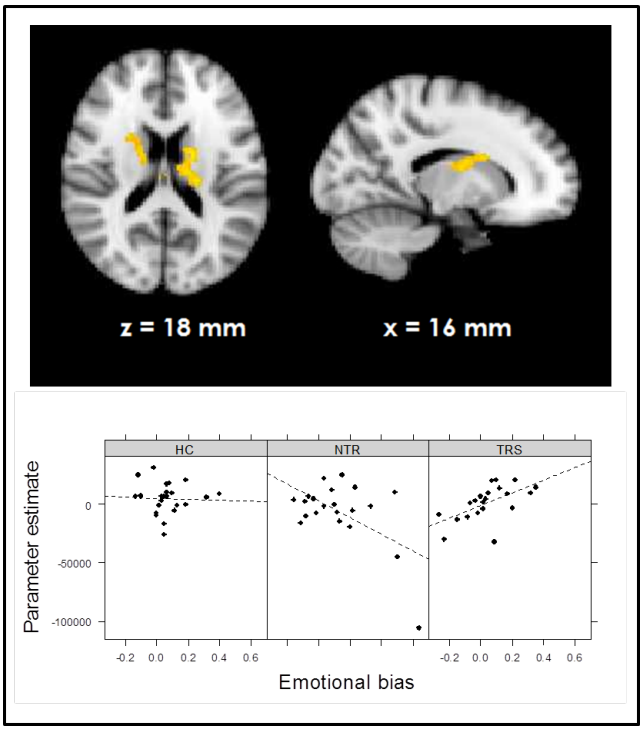

Figure 11. Group × emotional bias interaction in prediction error signal during losses. Activation maps reflect z-values thresholded at 2.3, corrected $p < .05$.

compared to both HC and TRS, based on the theory that the responsive patient group is characterised by a greater disruption of dopaminergic signalling. In addition, the hypothesis was tested that underlying cognitive bias would differentially modulate learning processes in the two patient groups.

The results revealed that HC and TRS patients showed similar patterns of prediction error signalling both during wins and losses. RPE activation was evident in a widespread network in these groups, consistent with the notion that reward processing is almost ubiquitous in the brain (Vickery, Chun & Lee, 2011). In contrast, NTR patients did not exhibit the same activation pattern and showed significant reductions in parietal, occipital and cerebellar regions during wins. Subcortically, an ROI analysis showed hypoactivation in the striatum and thalamus specifically in NTR patients. These findings imply that putatively dopamine-driven mechanisms underlying reinforcement learning in response to reward feedback are disrupted in NTR, while remaining relatively intact in TRS. The data are consistent with the notion that TRS patients do not respond to dopaminergic antipsychotic medication because a dopaminergic abnormality is not the primary cause of symp-

toms in this subgroup (Demjaha et al., 2012).

Interestingly, groups did not differ in terms of their bias towards choosing the happy face over the angry face on emotional trials. However, there was a significant difference between TRS and NTR patients in how this bias was associated with RPE signal in the thalamus and caudate during loss processing. In NTR patients, a strong emotional bias was associated with further attenuation of the RPE signal. By comparison, emotional bias in TRS was associated with an increased RPE signal. In turn, RPE signal in this region was positively related to delusional symptom severity specifically in the TRS group. This is surprising as RPE signalling has previously been reported to be negatively linked with symptom severity in schizophrenia (Corlett et al., 2007; Gradin et al., 2011); in line with the view that hyperdopaminergia – reflected in reduced RPE signal signalling – drives psychosis. The findings suggest that this relationship may be inverted in TRS patients in the thalamus and caudate. Increased RPE signalling specifically on loss trials may reflect less accurate predictions, resulting in greater prediction errors when the outcome is negative. As such, a strong emotional bias in TRS may lead to worse predictions about outcomes but an intact subcortical response to prediction error, which in turn is not adequately utilized to update predictions. In contrast, in NTR the prediction error response itself seems to be impaired, an effect which is further augmented in the presence of cognitive bias.

It is worth noting that the differences in striatal RPE activation between groups were apparent only at a liberal statistical threshold uncorrected for multiple comparisons. However, the consistent pattern of hypoactivation in NTR patients across the network lends support to this finding as a true positive. Subcortical dysfunctions in reward processing in NTR may be particularly hard to detect given that these may be ameliorated in chronic patients after antipsychotic medication (Culbreth et al., 2016).

These data support a model of TRS whereby the central dysfunction lies not in the subcortical dopamine system itself, but in the cognitive mechanisms interacting with this system. The striatum and cortex are interconnected by multiple partially overlapping circuits subserving learning and flexible cognition (Kehagia, Murray & Robbins, 2010). The ability to maintain behavioural goals in the presence of interference, uncertainty, or bias – broadly the definition of cognitive control – is an integral aspect of feedback learning. A breakdown of this system may not

only lead to reinforcement learning deficits, but also psychotic symptoms such as delusions as control processes are not adequately exerted in order to update internal models of the environment (Adams, Stephan, Brown, Frith & Friston, 2013). Control-related regions such as prefrontal cortex, which also shows strong functional connectivity with the striatum (Di Martino et al., 2008), may indeed be involved in delusion formation and maintenance (Heinz & Schlagenhauf, 2010). Arguably, in the absence of an adequate cognitive control mechanism regulating bias, solely targeting subcortical dopamine with antipsychotics may not suffice to alleviate symptoms. In contrast, NTR patients may have sufficient cognitive control such that alleviating the striatal dysfunction is sufficient to reduce symptoms adequately.

This experiment offers the first task-related neuroimaging evidence for differential caudate function in chronic TRS and NTR patients. It has been suggested that metabolic as well as anatomical abnormalities in the basal ganglia including the caudate nucleus are involved in TRS and may also be associated with clozapine response. For example, clozapine responders show hypermetabolism in the thalamus and basal ganglia, which is reduced following successful clozapine treatment (Rodriguez, Andree, Castejon & Garcia, 1996; Rodriguez et al., 1997). A reduction of metabolism specifically in the caudate after clozapine response was observed more recently (Molina, Sanz, Sarramea & Palomo, 2007) and clozapine administration is associated with a reduction of caudate volume (Chakos, Lieberman, Alvir, Bilder & Ashtari, 1995; Frazier et al., 1996; Scheepers, de Wied et al., 2001; Scheepers, Gispen de Wied, Hulshoff Pol & Kahn, 2001). Notably, treatment responsive patients were found to have increased dopamine synthesis capacity compared to TRS (Demjaha et al., 2012), a finding which was most strong in the caudate nucleus. Thus the caudate may constitute an interesting target for further investigation of TRS in studies stratifying patient subgroups by response.

In summary, the data suggest that while the behavioral output during reward learning of patients with treatment resistant and treatment responsive schizophrenia appears to be similar, it is underpinned by different neural systems. The data support the idea that TRS may represent a different disease from treatment responsive schizophrenia; in line with suggestions that TRS does not fit well into the contemporary dopaminergic dysfunction model of schizophrenia.

Chapter 5

Experiment 3: Myelin water fraction and its association with cognitive control in treatment resistant and responsive schizophrenia

5.1 Introduction

Schizophrenia, a debilitating psychotic disorder, has been widely described in terms of a dysconnection syndrome (Friston et al., 2016; Friston & Frith, 1995; Volkow et al., 1988). Symptoms of psychosis, including delusions and hallucinations, are in part suggested to emerge as a result of inadequate integration of neural processes in the brain. Both functional and structural connectivity dysfunctions have been observed in schizophrenia (Pettersson-Yeo, Allen, Benetti, McGuire & Mechelli, 2011) and it is by now widely established that white matter abnormalities are pervasive in the disorder (Klauser et al., 2017). These have been shown to be associated with abnormal functional activation (Marenco et al., 2012) and connectivity (Hu Liu et al., 2011) as well as symptoms (Canu, Agosta & Filippi, 2015). The most consistent findings show white matter changes in frontal and temporal lobes, as well as in the corpus callosum and internal capsule (Kubicki et al., 2007; Samartzis, Dima, Fusar-Poli & Kyriakopoulos, 2014; Wheeler & Voineskos, 2014).

Most imaging studies include medicated patients and there are mixed findings regarding the effects of antipsychotic medication on white matter (Amato, Beasley, Hahn & Vernon, 2016). Tishler et al. (2017) showed that myelination initially increases within the first year of antipsychotic medication treatment, but de-

creases thereafter. It has also been suggested that good treatment response is associated with improved white matter integrity (Garver et al., 2008). Unfortunately symptomatic non-response to treatment remains an area of unmet clinical need, with around 30% of patients with a diagnosis of schizophrenia showing inadequate response despite optimal treatment (Lindenmayer, 2000; Mortimer et al., 2010). It is therefore possible that this form of "treatment-resistant" schizophrenia (TRS) constitutes a separate neurobiological disorder to treatment responsive schizophrenia, such that antipsychotic medication focussed on dopamine receptor blockade is not targeting the underlying cause of psychosis in this patient subgroup. Indeed, one possibility is that the abnormalities in connectivity in TRS are of such severity that it precludes a remission of symptoms despite adequate treatment (T. P. White et al., 2016). Specifically, it is possible that altered frontostriatal interactions result in dysfunctional cognitive control and that treatment resistance arises due to a greater difficulty in integrating bottom-up sensory signals with top-down executive control, rendering dopamine D2 receptor blockade an insufficient mechanism to reduce symptoms of psychosis. This dysconnectivity could be instantiated as a dysfunction of structural integrity of white matter tracts; how these changes, particularly myelination, relate to TRS and cognitive control remains unknown.

Overall there is a large body of evidence suggesting that patients with schizophrenia show widespread decreases in white matter integrity, usually on the basis of diffusion weighted imaging (Wheeler & Voineskos, 2014). The most commonly reported measure is fractional anisotropy (FA), which indexes the degree of directionality of diffusing water molecules. Changes in FA are attributed to changes in the microstructure of white matter tracts; however, these could in effect be indicators of numerous underlying features such as myelination, axon diameter, fibre density, axon number, or axonal membrane integrity. Multicomponent driven equilibrium single pulse observation of T1 and T2 (mcDESPOT) is a recently developed imaging technique which allows for the derivation of a whole-brain myelin water fraction (MWF) map with rapid acquisition times (Deoni et al., 2008). As a metric for the fraction of water trapped between the myelin sheaths around the neuronal axons, MWF has been shown to correlate strongly with histological measures of myelin content (Laule et al., 2006; Webb et al., 2003), and to provide higher specificity to myelin content as compared with diffusion measures (Mädler,

Drabycz, Kolind, Whittall & MacKay, 2008; Vavasour, Laule, Li, Traboulsee & MacKay, 2011). This experiment is the first to report use of mcDESPOT in a sample of patients with a diagnosis of schizophrenia, stratified by treatment response status, and a healthy control sample.

The aims of this experiment were to test the utility of mcDESPOT in detecting differences in myelination between patients with schizophrenia and healthy controls and to investigate whether differences in myelination may account for differences in response to antipsychotic treatment. Specifically, the hypotheses were that:

1. Patients with schizophrenia will show reduced MWF compared to HC in widespread areas of the brain, particularly in frontal white matter tracts
2. TRS patients will show a greater MWF deficit compared to HC, with NTR patients at intermediate levels
3. MWF will serve as a mediator in the association of group and Stroop task performance.

5.2 Methods

5.2.1 Participants

mcDESPOT data was available for 22 patients fulfilling criteria for treatment resistant schizophrenia (TRS), 21 patients with non-treatment-resistant schizophrenia (NTR), and 24 healthy controls (HC).

5.2.2 Statistical analysis

5.2.2.1 Whole-brain group comparisons

Whole-brain normalised MWF maps were subjected to non-parametric permutation tests using FSL's randomise (with 10000 permutations), and significance

values were corrected for multiple comparisons using threshold-free cluster enhancement (TFCE). Clusters were defined with an extent threshold of 50 voxels. The effect of group (HC vs. NTR vs. TRS) was tested, adjusting for effects of age and sex.

5.2.2.2 White matter histogram analysis

In order to analyse the distribution of MWF values within the white matter specifically, MWF maps were overlaid with a white matter mask obtained from the Johns Hopkins University White Matter Atlas. Histogram analyses of white matter MWF were conducted by summing the number of voxels for 100 uniform bins between 0% and 30%, similar to Kolind et al. (2012). Each individual's histogram was normalised with respect to the area of the histogram. For each subject, the mean (first moment), variance (second moment), peak position (mode), and peak height (frequency of voxels in the modal bin) of the histogram were calculated and subsequently compared between groups. Non-parametric Kruskal Wallis tests were used due to non-equal variances.

5.2.2.3 MWF and Stroop effect

The following analysis was conducted for the 23 HC, 21 TRS and 21 NTR patients for whom Stroop data, as presented in Chapter 3, was available. FSL's randomise was used to test for a correlation between whole-brain MWF and the RT Stroop effect across all subjects. For the resulting significant cluster, each subject's mean MWF was extracted and compared between groups. Following this, a mediation analysis was conducted to test whether MWF in this region mediated group differences in the RT Stroop effect. A bootstrap approach proposed by Preacher and Hayes (2004) was used in order to test for significance of the indirect effect of group on RT Stroop effect.

5.3 Results

5.3.1 Whole-brain group comparisons

At whole-brain level, controlling for sex and age, there was a significant effect of group in four clusters (Figure 12): two large clusters covering much of the right and left subcortical white matter including the inferior fronto-occipital fasciculi, particularly in the vicinity of the striatum and extending to the cerebellum, one cluster containing the left putamen, and a small cluster in the right subcallosal cortex (Table 8). In each of these clusters, post-hoc t-tests revealed that both NTR and TRS patients showed reductions compared to HC, all $ps < .05$, with no difference detected between the two patient groups, all $ps > .05$. Mean MWF within these clusters ranged from 6% to 19% – lower than the expected range for white matter – indicating partial voluming effects within the significant voxels.

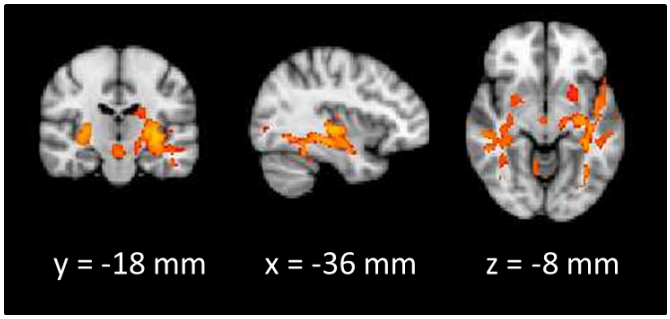

Figure 12. Main effect of group on myelin water fraction. Maps reflect threshold-free cluster enhancement corrected p-values.

5.3.2 White matter histogram analysis

Group histograms (depicted in Figure 13) show that voxel count peaks in the expected range for white matter (25-30%), consistent with previous mcDESPOT reports. Both patient groups show shifts slightly downwards and to the left, suggesting that less voxels within the white matter fall into the normal region of MWF values.

Table 9 shows Kruskal-Wallis test statistics for the effect of group on histogram metrics. Post-hoc Mann-Whitney tests (Bonferroni corrected for multiple compar-

Table 8
Significant clusters of group differences in myelin water fraction

Region	Side	k	*p*	MNI		
Subcallosal cortex	R	52	.026	8	18	-24
Putamen	L	189	.035	-26	6	-6
Putamen	L			-26	14	0
Putamen	L			-20	4	2
Inferior fronto-occipital fasciculus	L	2875	.01	-32	-18	-2
Inferior fronto-occipital fasciculus	L			-34	-28	-12
Internal capsule	L			-24	-18	4
External capsule	L			-32	-6	4
Inferior longitudinal fasciculus	L			-38	-50	-20
Inferior longitudinal fasciculus	L			-34	-50	-12
Cerebellar white matter	R	4278	.016	44	-68	-36
Cerebellar white matter	R			6	-44	-26
Cerebellar white matter	R			30	-18	2
Cerebellar white matter	R			44	-58	-38
Cerebellar white matter	R			46	-74	-36
Cerebellar white matter	R			34	-52	-26

isons) showed that histogram means were significantly lower in TRS compared to HC ($W = 374$, $p = .045$), and marginally lower in NTR compared to HC ($W = 353$, $p = .064$). The variance was greater in both NTR and TRS compared to HC, all ps $< .05$. Peak height was reduced in both patient groups compared to HC, although these tests did not survive corrections for multiple comparisons. There were no differences between NTR and TRS groups on any of the histogram measures.

Table 9
Means and standard deviations of histogram data per group

	HC		NTR		TRS			
	M	*SD*	*M*	*SD*	*M*	*SD*		
							$X^2(2)$	*P*
Mean	24.19	0.98	23.33	1.30	23.31	1.24	7.61	.022
Variance	24.02	4.57	28.93	4.71	27.90	5.00	13.49	.001
Mode (peak position)	27.46	1.18	27.15	1.39	26.89	1.33	2.23	$> .05$
Mode frequency (peak height)	0.17	0.04	0.14	0.03	0.14	0.03	6.98	.031

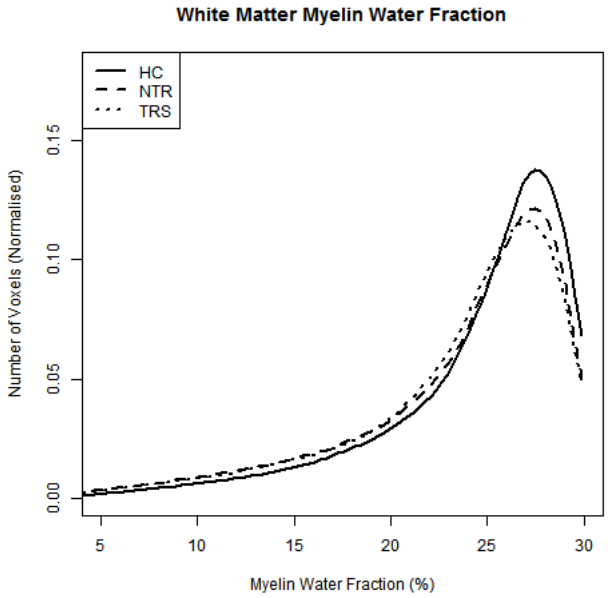

Figure 13. Normalised histograms of white matter myelin water fraction by group. Histograms are graphically smoothed in R (smoothing parameter 0.35)

5.3.3 MWF and Stroop effect

A large cluster consisting of the corpus callosum (genu, body, and splenium) was negatively related with RT Stroop effect across all subjects, such that higher MWF values were associated with a smaller Stroop effect (Figure 14). Mean MWF from within this significant cluster was extracted for each subject for further analyses. The negative correlation was evident within each group separately (HC: $R = $-0.35, $p = .09$; NTR: $R = $-0.50, $p = .021$; TRS: $R = $-0.59, $p = .005$). Pairwise comparisons of mean MWF in the corpus callosum between HC and the two patient subgroups did not survive Bonferroni corrections for multiple comparisons; hence NTR and TRS patients were pooled into a single schizophrenia (SZ) group for the mediation analysis. A mediation analysis tested whether corpus callosum MWF mediated group differences in the Stroop effect according to the Baron and Kenny steps (Baron & Kenny, 1986; Figure 15). Regressing the Stroop effect on group (HC vs. SZ) showed a significant effect of group (path c': $\beta = 93.08$, $SD = 28.93$, $p = .002$). Regressing corpus callosum MWF on group showed a significant effect of group, (path a: $\beta = $-0.01, $SD = 0.01$, $p = .019$), with higher MWF in HC ($M = 0.20$, $SD = 0.1$) compared to SZ ($M = 0.19$, $SD = 0.17$). Finally, regressing

the Stroop effect on both group and corpus callosum MWF revealed a significant effect of MWF (path b: $\beta = $-3534.33, $SD = 765.24$, $p < .001$). The effect of group ($\beta = 60.42$, $SD = 26.13$, $p = .02$), though significant, was reduced compared to the simple model regressing the Stroop effect on group alone. An analysis of the indirect effect (defined as the product between the effect of group on MWF and the effect of MWF on RT Stroop, controlling for group) was performed with non-parametric bootstrapping of the sampling distribution using 5000 bootstrap samples (Preacher & Hayes, 2004). This revealed a significant indirect effect (95% confidence interval [4.69, 67.50]); suggesting that there was a partial mediation of the effect of group on Stroop effect by corpus callosum MWF.

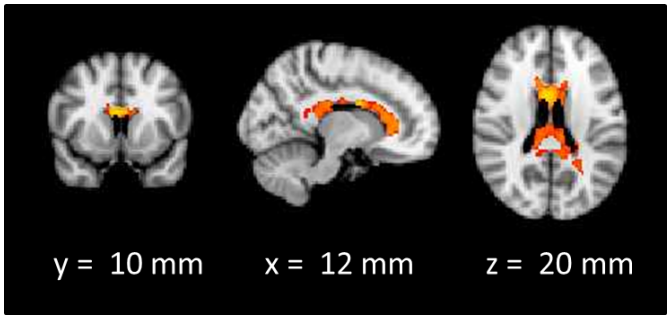

Figure 14. Significant cluster of whole-brain analysis of correlation between Stroop effect and myelin water fraction. Maps reflect threshold-free cluster enhancement corrected p-values.

5.3.4 Relationship with clinical variables

For each of the four significant clusters from the whole-brain MWF group analysis as well as the corpus callosum cluster from the Stroop analysis, an exploratory analysis of MWF was conducted for correlations with PANSS positive symptom score, PANSS negative symptom score, illness duration, and CPZ equivalent medication dosages, both across all patients as well as within the two patient groups separately. No correlation was significant, all $ps > .05$ (uncorrected for multiple comparisons).

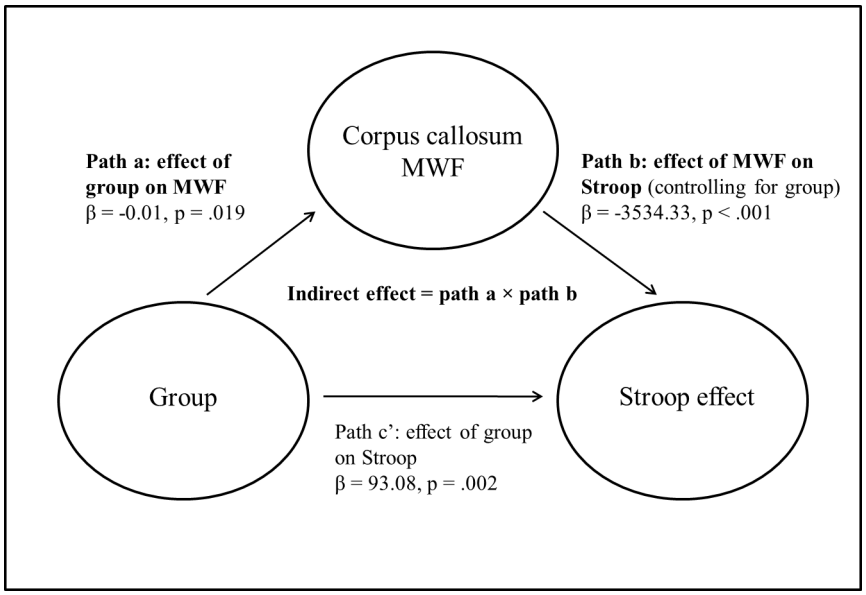

Figure 15. Mediation diagram of the association between group, Stroop effect, and callosal myelin water fraction

5.4 Discussion

In this experiment, mcDESPOT imaging (Deoni et al., 2008) was applied to a sample of patients with a diagnosis of schizophrenia, stratified by treatment response, and healthy controls. The results show that this method is sensitive to reductions in myelin water fraction (MWF) in schizophrenia compared to healthy controls, with the greatest effect evident in areas surrounding bilateral striatum, particularly the inferior fronto-occipital fasciculus, as well as the cerebellum. Reductions in the patient groups were bilateral but with larger clusters observed within the left cerebral hemisphere. The findings of reduced MWF in the inferior fronto-occipital fasciculus is consistent with DTI based results of reduced fractional anisotropy in this tract (S.-H. Lee et al., 2013; X. Liu et al., 2013; Epstein et al., 2014; Ćurčić-Blake et al., 2015). The inferior fronto-occipital fasciculus connects the occipital and temporal lobes with orbitofrontal areas and is an important aspect of both the language and visual networks (Catani, Howard, Pajevic & Jones, 2002). Thus, impaired information flow along the tract due to impaired white matter may be involved in auditory or visual hallucinations and has also been associated with cognitive impairments in schizophrenia (X. Liu et al., 2013). Mean MWF in the areas showing significant reductions in patients

were below the expected range for white matter, thus suggesting that the reductions included both white and grey matter voxels. Histograms of MWF restricted to the white matter tracts allowed for a closer comparison of the distribution of values specifically in the white matter between the three groups, confirming that patients' histograms were shifted towards lower MWF values, with a greater variance compared to healthy controls. MWF did not, however, distinguish between the two patient subgroups, consisting of treatment resistant (TRS) and treatment responsive (NTR) schizophrenia patients. This suggests that underlying abnormal myelination is not a driving force behind antipsychotic treatment resistance at the chronic stage of the illness.

There was a correlation between performance on the Stroop task, a standard measure of executive control, and corpus callosum MWF, whereby greater MWF values were associated with a smaller reaction time interference effect. This association was observable both across all subjects and within all groups separately. A mediation analysis showed that MWF in the corpus callosum partially mediated the group difference on the Stroop task, such that lower MWF in patients accounted in part for the greater interference effects seen in this sample compared to controls.

The finding of reduced MWF in patients with schizophrenia compared to healthy controls is in line with a large body of evidence suggesting impaired white matter integrity in the illness (Fitzsimmons et al., 2013; Kubicki, McCarley & Shenton, 2005; Pettersson-Yeo et al., 2011). The proliferation of diffusion weighted imaging reports in recent years has shed enormous light on disturbances of white matter in psychosis and schizophrenia on a whole-brain basis, yet a remaining disadvantage of the technique is the large number of microstructural factors which could contribute to the signal. Multicomponent relaxation imaging allows for a more myelin-specific quantification of the dysfunction in vivo. The mcDESPOT protocol is such a technique which has recently been validated pre-clinically (Wood et al., 2016), and this is the first report to use this technique in chronic patients with a diagnosis of schizophrenia, with an additional stratification by treatment response status. The mechanisms underlying resistance to antipsychotic medication are as yet not well understood (Mouchlianitis et al., 2016), but the lack of response despite adequate dopamine D2 receptor occupancy in TRS (Coppens et al., 1991; Wolkin et al., 1989) suggests that striatal hyperdopaminergia may not

be the principal aetiology of psychotic symptoms in this patient subgroup. One study investigating white matter microstructure found reduced fractional anisotropy and increased radial diffusivity in the corpus callosum in chronic treatment resistant patients as compared to healthy controls (Holleran et al., 2014); however this study did not include a remitted patient group and as such the specificity of the finding to TRS is unclear. On a functional connectivity level, a recent report by T. P. White et al. (2016) suggested that divergent pathophysiologies of striatal resting-state connectivity are present in treatment resistant and treatment responsive schizophrenia. In addition, Sarpal and colleagues demonstrated that functional striatal resting-state connectivity may be predictive of treatment response in first-episode psychosis patients (Sarpal, Argyelan et al., 2015). The data from the current experiment suggest that these findings of functional connectivity differences are not mirrored by myelin water fraction differences. In this chronic patient sample, the effects of illness chronicity and exposure to medication can by definition not be entirely disentangled from the effects of interest and therefore remain as potential confounds. However, the absence of group difference on these variables as well as the lack of association with myelin water fraction suggest that it is unlikely that these effects are masking true differences in myelination between treatment resistant and responsive patients. Nevertheless, future research could usefully examine these issues by applying the technique to patients at an earlier stage of the illness.

Cognitive deficits are considered a core feature of TRS (Buckley & Shendarkar, 2005). Cognitive control further relies on intact connectivity of the underlying neural network (Cole, Yarkoni, Repovs, Anticevic & Braver, 2012; Hwang, Velanova & Luna, 2010); hence the aim of this experiment was to assess how both cognitive and structural mechanisms relate to treatment response. As described in detail in Chapter 3, there were no differences in reaction time interference on the Stroop task between the two patient groups. Thus on a behavioural level, treatment resistance does not seem to be associated with exacerbated cognitive control deficits at the chronic stage of the illness. However, callosal myelin reductions in schizophrenia patients partially mediated performance differences compared to healthy individuals. Impaired white matter integrity in the corpus callosum reductions have been widely observed in the illness, but this is the first report of a direct link between a measure of callosal myelination and cognitive

control function in schizophrenia.

Despite a growing literature on mcDESPOT and recent pre-clinical validation (Wood et al., 2016), it is a relatively new technique which requires further evaluation by independent groups. It has as yet not been extensively applied to many neuropsychiatric disorders and as such there are limitations to the interpretability of the results in terms of specificity to schizophrenia. However taken together, this experiment suggests that mcDESPOT is a suitable method to detect myelin alterations in schizophrenia, clarifying the nature of the changes reported in earlier DTI studies, and this may be a relevant marker in terms of cognitive control performance in patients. However, this study did not uncover more severe myelin abnormalities in treatment resistant patients compared to treatment responsive patients, suggesting that primary differences in treatment response and functional dysconnectivity are not driven by alterations in myelination.

Chapter 6

General discussion

6.1 Summary of findings and implications

The purpose of this thesis was to examine the neural mechanisms of treatment response in psychosis within a framework of cognitive control. The underlying hypothesis was that an inability to exert cognitive control, particularly in the context of feedback learning, would account for the lack of symptomatic response to antipsychotic medication in patients with treatment resistant schizophrenia (TRS). The expectation was furthermore that this dysfunction would be characterised by exacerbated dysconnectivity both on a functional and structural neural level in TRS patients compared to patients with non-treatment-resistant schizophrenia (NTR) and healthy controls (HC).

6.1.1 Experiment 1

In the first experiment, subjects performed a verbal Stroop task while undergoing functional magnetic resonance imaging (fMRI). On a behavioural level, as expected, both patient groups showed increased interference effects compared to HC. This was evident both in the accuracy and reaction time (RT) data of the task. This finding is consistent with previous evidence for deficits in cognitive control in schizophrenia (Westerhausen et al., 2011). However, contrary to expectations, NTR and TRS patients did not differ with respect to the extent of the dysfunction, exhibiting similar accuracy and RT interference Stroop effects. Thus, on this basic level of cognitive control, TRS patients do not appear to be more severely

impaired compared to remitted patients. The average neural activation during the Stroop task mirrored these behavioural findings, in that NTR and TRS patients did not differ from one another but, as a group, showed some abnormal activation compared to HC. On incongruent (vs. congruent) trials, a contrast which is thought to capture response conflict most potently, patients showed hyperactivation of the supplementary motor cortex (SMA). This finding replicates results from a recent meta-analysis (Minzenberg et al., 2009) reporting increased activation in this region in schizophrenia on tasks of executive function. This hyperactivation may reflect a compensatory response to increased interference, in line with suggestions of inefficient cortical processing. Moreover, hypoactivations were evident in superior parietal cortex as well as the insula during incongruent trials. These regions constitute core nodes of the fronto-parietal and salience networks, respectively, which are thought to jointly coordinate flexible executive control (B. D. Peters et al., 2008). As this dysfunction was evident on the simple contrast of incongruent trials, they may reflect more general control related demands beyond response conflict.

Importantly, this experiment identified a region in rostral ACC which differentiated NTR and TRS groups in terms of how psychotic symptoms related to neural activation. While NTR patients showed increased neural activation with increasing symptoms, potentially also reflecting a compensatory mechanism, TRS patients showed an inverse relationship between activation and symptoms. Crucially, the ensuing hypoactivation in the most symptomatic TRS patients predicted a deterioration in performance as measured by RT. This association establishes a direct link between symptoms, neural activation, and behaviour which is specific to TRS, thus providing evidence for distinct abnormal mechanisms in this patient group. Finally, an exploratory analysis was performed in order to assess whether connectivity of the identified ACC region with subcortical nodes of the cognitive control network was also more impacted in TRS patients. Indeed, there was a tendency towards reduced functional connectivity between ACC and dorsal thalamus in TRS compared to HC, while NTR patients showed normal functional connectivity.

Although the finding of reduced functional connectivity in TRS is only marginally significant, it provides novel insights into potential dysfunctional mechanisms which may drive resistance to antipsychotics. Cortical-subcortical interactions

play an important role in psychotic symptom formation, and structural as well as resting state dysconnectivity have previously been implicated in TRS (Pettersson-Yeo et al., 2011). However, this is the first study to link task-related connectivity to treatment response status, suggesting that dysconnectivity underlying cognitive control deficits may be specifically involved in non-response. Specifically, antipsychotics may normalise subcortical hyperdopaminergia in TRS, but in the absence of normal integrative processes with prefrontal cortical regions symptoms may persist despite treatment. Alternatively, TRS may not present with abnormal subcortical dopamine function (Demjaha et al., 2014), rendering antipsychotics largely ineffective in their primary aim.

6.1.2 Experiment 2

The second experiment aimed to probe a dopamine-dependent cognitive process in TRS, NTR, and HC, while linking this process to cognitive control. In a further fMRI experiment, subjects performed a reward learning task which allowed for computational modelling of their behaviour using a reinforcement learning (RL) model. Similarly to the Stroop task, both patient groups performed more poorly compared to HC, but did not differ from each other. Specifically, patients made fewer ideal choices, as determined by the RL model, compared to HC. This finding is in line with a large literature on impaired feedback learning in schizophrenia. The study further replicated previous findings of an emotional bias toward happy faces over angry faces in this task across patients and controls (Evans et al., 2011). Subjects were, on average, more likely to select a happy face despite feedback evidence being in favour of the angry face than to select an angry face when the evidence is in favour of the happy face. This bias did not differ between groups.

Reward prediction error (RPE) was computed on a trial by trial basis for each subject, and the associated neural activation compared between groups. As hypothesised, NTR patients specifically showed abnormal RPE-related activation compared to HC both cortically and subcortically. In contrast, TRS patients did not differ from HC. Abnormal RPE-related activation has previously been reported in schizophrenia and interpreted as an indicator of dopaminergic dysfunction (Corlett et al., 2007). This finding therefore supports the hypothesis that a dopaminergic abnormality is selectively present in NTR patients, while

TRS patients show normal dopamine function. The results are in line with recent PET imaging data (Demjaha et al., 2014) and provide the first task-related evidence to support this notion.

Since reinforcement learning is underpinned to a large extent by similar neural networks as cognitive control processes, the secondary aim was to assess whether groups differed in how cognitive bias modulated the feedback-related neural response. The premise of this analysis was that in emotional blocks, subjects would have to exert more cognitive control compared to neutral blocks in order to overcome their bias and learn adequately from the reward feedback. Due to the overarching hypothesis of exacerbated cognitive control dysfunction in TRS it was expected that emotional bias would have a larger impact on RPE-related signal in this group. Indeed, a stronger emotional bias in TRS predicted a stronger RPE signal in bilateral thalamus and caudate nucleus in response to losses. In contrast, NTR patients showed an inverse association between bias and RPE signal. Importantly, the correlation differed significantly between the two patient groups. The positive association in TRS specifically on trials on which subjects received negative feedback suggests that subjects were more surprised by this feedback when they had a strong prior bias. Thus, predictions about reward values appear to suffer most in these subjects. In contrast, NTR patients did not show this association. In summary, the results suggest that while in NTR patients the RPE signal itself is impaired, TRS patients show normal RPE signalling but a greater difficulty in making appropriate predictions with stronger emotional bias.

6.1.3 Experiment 3

In the final experiment, subjects underwent multicomponent driven equilibrium single pulse observation of T1 and T2 (mcDESPOT) imaging. The aim was to compare myelin water fraction (MWF) between groups in order to determine whether TRS is characterised by an exacerbated abnormality in myelin content compared to NTR and HC. In addition, the experiment aimed to establish whether differences in MWF would account for deficits in cognitive control as measured by the Stroop task. In line with longstanding evidence for white matter abnormalities in schizophrenia, both patient groups showed extensive MWF reductions compared to HC. However, contrary to expectations, there were no significant

differences in MWF between NTR and TRS patients.

With respect to cognitive control, MWF in the corpus callosum was significantly related to Stroop task performance across and within groups. Since the NTR and TRS patient groups did not differ in terms of MWF or Stroop performance, they were pooled into a single patient group for the subsequent mediation analysis. In line with expectations, callosal MWF partially mediated differences between patients and controls on the Stroop task; providing evidence that cognitive control deficits in schizophrenia are at least partially attributable to white matter abnormalities.

6.2 Methodological considerations

6.2.1 Experimental design

A limitation of this study is its cross-sectional design, restricting the interpretability of the results to some extent. Patients were classified as treatment resistant or treatment responsive based on their current psychotic symptoms and medication history; however, it is unclear how symptomatic patients were at illness onset. Longitudinal study setups allow for an assessment of symptom change which can subsequently be related to change in task performance and activation; however this comes at the risk of problems such as attrition or practice effects. As part of a larger funded project, this study was set up as a cross-sectional design in order to identify potential biomarkers which can be applied to the analysis of data from first episode psychosis (FEP) patients in a longitudinal study setup.

In addition it is possible that the sample size in this study was not sufficient to detect subtle differences between the two patients groups. A sample size of approximately 20 per group is reflective of the typical sample size in many fMRI studies in the field of psychiatry; however, the NTR and TRS groups included in this study are likely to have higher similarity to each other than to healthy controls, thus potentially requiring larger samples in order to differentiate them statistically. The possibility can therefore not be excluded that a lack of difference in mean neural activation or myelin water fraction may be due to a lack of power. However, with respect to the functional tasks, the descriptive behavioural data

does not suggest a clear tendency toward group differences.

An alternative possible explanation for the absence of group differences in task performance lies in the experimental setup of the tasks themselves. The verbal Stroop task is a standard measure of executive function and reflects on a very basic level cognitive control in the context of interference. It is possible that an alternative experimental paradigm of cognitive control may have been more sensitive to potential group differences. For example, a speeded motor response task such as the Eriksen Flanker task may set up a stronger response conflict and therefore differentiate more easily between groups.

Furthermore, a major drawback of the Faces task is the relatively low number of trials per block. This precluded an estimation of RL model parameters (learning rate and inverse temperature) on a single subject level. Parameter estimation on a group level is common in the fMRI literature (Gläscher, Daw, Dayan, & O'Doherty, 2010; Schönberg, Daw, Joel, & O'Doherty, 2007), and allows for an estimation of subject-specific trialwise prediction errors nevertheless, but limits the utility of the estimated parameters themselves for group comparisons. In addition, as the Faces task used reward contingencies of 40% and 60% for the two stimuli, it constitutes a rather difficult task which does not leave a large range within which to perform above chance level. Observable group differences on this task are therefore necessarily relatively small, and as such this task may not allow for enough variation in performance to detect small differences reliably.

6.2.2 Inclusion and exclusion criteria

The definition of TRS criteria has been a point of debate in the literature (Suzuki et al., 2011). The primary aim of recruitment criteria in this study was to identify a group of patients who had not responded to antipsychotic treatment and a group of patients in symptomatic remission, while holding as many potential confounding factors constant as possible. Therefore, patient groups were well matched on illness duration, age of onset, current medication dosage, age, and sex. While this avoids a number of confounds, an argument can be made that TRS criteria were not strict enough to ensure clearly defined groups. Consensus guidelines have more recently been presented (Howes et al., 2016) which include several criteria that were not met in the current study. For example, not all TRS patients were

currently or previously prescribed antipsychotics at dosages equivalent to 600 mg CPZ daily; instead, it was ensured that dosages were above the minimum effective dosage (Leucht et al., 2014). Had patient groups been defined partly on the basis of their medication dosage, they would have likely differed substantially on this variable. This type of pre-existing group difference which is essentially a defining characteristic of group membership cannot be statistically "controlled for" with analysis of covariance (ANCOVA), as has been argued elegantly elsewhere (Suckling, 2011; G. A. Miller & Chapman, 2001), despite a common practice to attempt to do so. The less stringent inclusion criteria used in this study therefore attempted to avoid the potentially confounding effects of medication dosage. In a similar vein, patients currently on clozapine were excluded so as to avoid potentially differential effects of clozapine as compared to other antipsychotics on the brain, as well as to avoid the introduction of sub-groups of patients refractory to clozapine (super-resistant patients). Importantly, these issues highlight a more general difficulty in schizophrenia research stemming from the heterogeneity of the illness. The clinical presentation of schizophrenia varies widely across affected idividuals and therefore subsampling representative groups of patients remains a substantial challenge in this field of research.

The exclusion of clozapine patients raises the question of why the included TRS patients were not prescribed clozapine, if they were indeed treatment resistant. In fact, a number of these patients (n=4) had previously been prescribed clozapine, but treatment had been discontinued at least 2 years before study participation. It is possible that some patients were unwilling to take clozapine or were not offered the opportunity, in line with reports that clozapine is underprescribed in the UK (Howes et al., 2012).

Necessarily this study may entail a selection bias of patients suitable for scanning, who may not be reflective of the overall population of diagnosed schizophrenia patients.

6.2.3 Potential confounds

As described above, patient groups were well matched for a number of clinical variables including illness duration, age of onset, and current medication dosage. However, cumulative lifetime medication exposure was not assessed as historical

records were not available for many patients due to the relatively long illness duration. It is likely that TRS patients would have been exposed to more medications at higher doses over the course of their lifetime, but it is unclear how this may impact on the functional and structural measures assessed in this study. Cumulative medication exposure therefore remains a possible confound.

Due to the nature of TRS and NTR criteria in this study, group membership is inextricably linked with symptoms of psychosis. Indeed the main defining difference between groups was psychosis severity, thus rendering psychotic symptoms a further potential confound. This is of particular relevance in the Stroop fMRI data analysis, which yielded a significantly different effect of psychotic symptoms on ACC activation in the two patient groups. In fact it may be argued that the observed effect arose as a function of psychosis rather than of treatment response status itself. To resolve this issue it would be necessary to assess the relationship between neural activation and psychosis in symptomatic patients who later respond well to treatment; a procedure which is planned in the context of a follow-up study in FEP patients. Nevertheless, given that the identified cortical region in the current study proved to be behaviourally relevant specifically in the TRS group, it seems likely that the finding reflects at least partially an effect of treatment response.

Patients and healthy controls differed significantly in terms of IQ as measured by the WASI. This is reflective of a common observation in studies of schizophrenia. Premorbid IQ score is a known indicator of risk for schizophrenia (Woodberry, Giuliano & Seidman, 2008). Thus, patient and control samples matched for IQ would likely constitute an inaccurate representation of the true population distributions, calling into question the ecological validity of subsequent research outcomes. It is also worth noting that IQ may be underestimated in patients with schizophrenia when using standardised batteries such as the WASI, since effects of motivation or poverty of speech (associated with negative symptoms) are likely to play a role. In this study IQ was not related to neural activation or myelin content in areas identified as relevant to diagnostic or treatment response status, however the possibility of confounding effects cannot be entirely excluded. Nevertheless, it stands to reason that entirely removing effects of IQ in itself may not be a desirable aim given the relevance of cognitive abilities to the clinical presentation of schizophrenia.

Similarly, as can be seen in Table A.7, groups differed significantly in terms of depression as measured by the Beck Depression Inventory (BDI). A confounding effect of depression severity on the current results can therefore not be excluded. It is possible that depression may impact on cognitive performance and therefore be associated with some of the observed behavioual differences in this study. However, it is unlikely to explain the between-patient differences in neural activation related to reward prediction error. Depression has been associated with a blunted RPE response (Kumar et al., 2008), thus if depression were driving group differences one would expect the TRS group (showing the highest BDI score) to exhibit a more blunted RPE signal compared to NTR. However, the inverse was observed, rendering a driving effect of depression unlikely.

6.3 Conclusion

The work presented in this thesis examined treatment resistant schizophrenia in the context of cognitive control, reinforcement learning, and structural connectivity. As such, it provided a systems neuroscience perspective on TRS, taking into account possible dysfunctions on a functional cognitive as well as a neuroanatomical level. The primary question driving the presented research was: is TRS characterised by a categorically distinct neuropathology from treatment responsive schizophrenia; and is this expressed in observable ways on the neural and behavioural level during cognitive tasks? The overarching hypothesis was that an exacerbated cognitive control dysfunction in TRS would lead to inadequate integration of top-down cognitive processes with ongoing incoming information (e.g. reward feedback), resulting in an abnormal representation of the surrounding environment and thus psychotic symptoms such as delusions and hallucinations. This dysfunction was hypothesised to be reflected in task-related hypoactivation particularly of the frontal cortex as well as functional and structural dysconnectivity in TRS compared to treatment responsive schizophrenia. Symptoms of psychosis would thus be perpetuated in these patients despite treatment with antipsychotic medication, which primarily targets the subcortical dopamine system.

While the patient groups included in this study did not show immediate differences in cognitive control related behaviour or neural activation, the results imply a more complex pattern of differences. Rather than simple differences in mean

activation, differences between groups emerge when relating task activation to symptom severity, prediction error, and cognitive bias. This suggests that similar behavioural output may be underpinned by different modulatory mechanisms in the brain. This is consistent with the notion that a similar clinical presentation, resulting in a shared diagnosis of schizophrenia, may be underpinned by different neural abnormalities in treatment resistant and treatment responsive patients. The results presented in this thesis point toward reduced cognitive control related frontal activation in highly symptomatic TRS patients, as well as reduced fronto-thalamic functional connectivity specifically in TRS. However this specificity is not mirrored on a structural level in terms of myelination. A possible explanation for this is that the exacerbated dysconnectivity operates at the level of the synapse rather than in terms of anatomical abnormalities of white matter tracts. It has previously been argued that aberrant synaptic plasticity, rather than structural connectivity changes, are likely to drive symptoms of psychosis (Stephan, Baldeweg & Friston, 2006; Friston et al., 2016). It is thus possible that patients fall on a continuum of synaptic dysconnectivity, with more severe abnormalities leading to treatment resistance. While dysconnectivity may be the result of a dopaminergic dysfunction in some patients, it may arise from abnormalities in alternative neurotransmitter systems in others (e.g. acetylcholine, Stephan et al., 2006). The results presented in this thesis furthermore lend support for the hypothesis that TRS patients do not exhibit the dopamine dysfunction classically associated with schizophrenia.

This work offers the first account of an explicit comparison between two chronic schizophrenia patient groups who differed only in their treatment response status during task-related fMRI as well as mcDESPOT imaging. While these procedures will need to be applied in a longitudinal setting, the findings provide a useful insight into treatment response at the chronic stage of the illness as well as the suitability of the methods in these patient groups. The study also highlights the importance of examining group differences beyond mean activation comparisons, particularly in highly similar clinical samples which may be differentiated by more subtle changes that are not categorical in nature.

6.4 Future directions

First and foremost, it will be crucial to assess neural functioning in the context of cognitive control in patients with FEP in a longitudinal study setup. The project from which data was presented in this thesis is currently in a second phase of recruitment, whereby 100 FEP patients are undergoing the identical imaging protocol. All patients will be followed up at 6 and 12 months, with a second scan conducted during the final visit. This design will allow for the results obtained in the chronic patient sample to be tested prospectively in the FEP patients. Specifically, measures of cognitive control, reinforcement learning, and myelination will be tested for their ability to predict treatment response after one year and beyond, using results from the work presented in this thesis to inform data analyses. Generally speaking, further research could usefully address potential confounds of medication exposure, illness duration and levels of psychosis by studying these measures in a longitudinal setup in FEP patients.

In light of the various effects antipsychotic medication can have on brain function and structure, studying initially antipsychotic naive patients is an important aspect of research into treatment response. The focus should lie in identifying biomarkers of treatment response at an early stage in the illness – after occurrence of a first psychotic episode or even in the prodrome – that will allow for adaptive treatment options, ideally offering a possibility to fast-track a subset of patients to clozapine. However, in order to fully understand the mechanisms underlying treatment response in psychosis, more research on the cognitive mechanisms involved in the development of psychosis in treatment resistant and treatment responsive schizophrenia is necessary. Within a framework of cognitive control, it will be important to incorporate varying levels of complexity in order to establish the most sensitive measures in these highly similar patient groups. For example, the difficulty of speeded response tasks including distractor stimuli may be manipulated by varying the trial durations. The N-back task furthermore offers a useful tool of executive functioning at increasingly difficult levels. Given the potentially differential associations between task performance and neural activation or clinical variables, tasks allowing for a wide performance range (e.g. probabilistic learning tasks with more divergent reward contingencies than those used in the current study) can be utilised. In addition, given the mounting evidence for

a divergent pathology at the neurochemical level (Egerton et al., 2012; Demjaha et al., 2014), future research will need to examine interactions between different neurotransmitter systems (e.g. the glutamate and dopamine system), and assess whether certain neurotransmitters differentially modulate cognitive function in different patient subgroups. Multimodal neuroimaging studies including both MRI and PET are highly useful in this regard.

The predominant challenge for future research will be to establish study designs which are able to detect subtle and complex differences between treatment resistant and treatment responsive schizophrenia. The pattern emerging from the research presented in this thesis is that rather than clear differences in average behaviour or neural activation, these patient groups differ primarily in the modulatory mechanisms acting on the neural circuits relevant to different cognitive domains. In terms of studying modulatory influences on synaptic connectivity with noninvasive neuroimaging, EEG may represent a valuable tool. The mismatch negativity (MMN), a negative potential elicited by deviant stimuli (usually in an auditory oddball paradigm), is a well-established marker of N-methyl-D-aspartate (NMDA) receptor activity and has been extensively studied in schizophrenia, with consistent reductions of the MMN observed in patients compared to healthy controls (Umbricht & Krljes, 2005; M. Lee et al., 2017). Reductions in the MMN are associated with poor functioning in chronic schizophrenia (Light & Braff, 2005b, 2005a). As an indicator of perceptual learning and NMDA-mediated plasticity, the MMN may provide useful insights into the neuromodulatory mechanisms underlying antipsychotic treatment response.

However, neuroimaging techniques are not able to detect schizophrenia-related changes on a cellular or molecular level. A promising tool in this regard is the study of human induced pluripotent stem cells (hiPSC; K. Takahashi & Yamanaka, 2006, K. Takahashi et al., 2007). Recent advances in this domain have allowed for modelling of neural development in neuropsychiatric disorders such as schizophrenia (Ardhanareeswaran, Mariani, Coppola, Abyzov & Vaccarino, 2017), while being able to carefully disentangle genetic and environmental influences. Notably, findings from the first hiPSC model of schizophrenia included reduced neuronal connectivity as well as decreased glutamate receptor expression; abnormalities which were subsequently responsive to treatment with the antipsychotic loxapine (Brennand et al., 2011). The technique may provide an opportunity to

assess cellular changes and trajectories of brain development in treatment resistant and responsive schizophrenia while keeping constant many potential confounding factors such as medication exposure and illness duration. In addition, hiPSC-related methodologies have great potential for informing the discovery and development of drugs for treatment of psychosis (Y. Sun & Dolmetsch, 2016).

Despite extensive research on task-related neural activity in schizophrenia, studies typically do not use stratifiers related to treatment response to reduce the heterogeneity of the sample and are likely combining neurobiologically distinct subtypes of schizophrenia. This not only clouds studies of mechanism, but potentially also of treatment trials; missing effects that are specific to one or the other subset of patients (Joyce, Kehagia, Tracy, Proctor & Shergill, 2017). There is an urgent need for stratification of patients by response; both at the chronic stage of the illness and in patients suffering a first episode of psychosis. The separation of schizophrenia subgroups will allow the development of clearer hypotheses into the neural mechanisms underlying antipsychotic treatment response and potentially move us closer to being able to use these biomarkers to tailor treatment in a more personalized and effective manner.

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Appendix

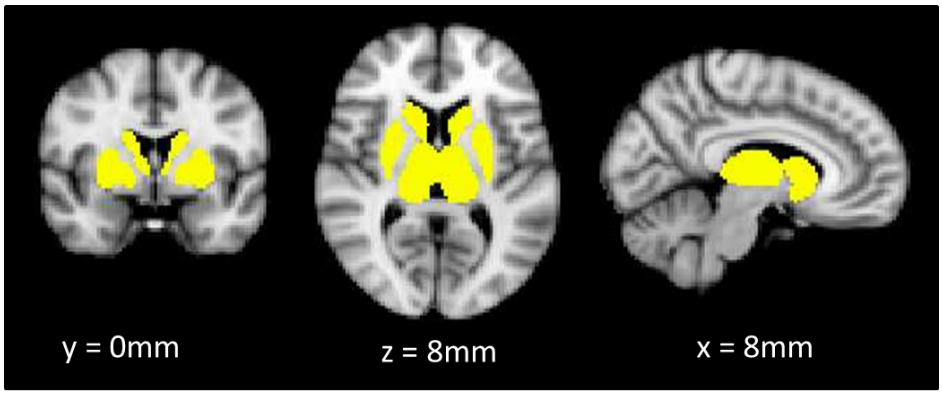

Figure A.1. Subcortical region of interest mask consisting of bilateral thalamus and striatum (nucleus accumbens, caudate nucleus, pallidum, and putamen)

Table A.1
Significant clusters of activation across groups for the Stroop contrast

Region	Side	k	z	MNI		
Supplementary motor area	L	1587	5.23	-6	4	56
Supplementary motor area	R			8	4	58
Supplementary motor area	R			4	0	64
Paracingulate gyrus	L			-6	20	42
Paracingulate gyrus	R			12	20	44
Paracingulate gyrus	R			8	14	46
Precentral gyrus	L	2656	5.43	-48	-12	40
Precentral gyrus	L			-56	-6	48
Precentral gyrus	L			-50	-10	36
Postcentral gyrus	L			-64	-4	18
Postcentral gyrus	L			-54	-8	24
Precentral gyrus	L			-58	-4	20
Precentral gyrus	R	1577	5.5	58	-6	40
Postcentral gyrus	R			62	-6	40
Precentral gyrus	R			58	-4	46
Precentral gyrus	R			62	-2	20
Precentral gyrus	R			50	-4	58
Postcentral gyrus	R			52	-8	60

Table A.2

Significant clusters of activation across groups for the Incongruent contrast

Region	Side	k	z	MNI		
Superior frontal gyrus	L	3163	5.13	-24	-28	44
Middle frontal gyrus	R			26	28	46
Superior frontal gyrus	R			26	28	52
Frontal pole	L			-8	48	42
Middle frontal gyrus	L			-32	26	46
Frontal pole	L			-18	40	42
Postcentral gyrus	L	38972	8.21	-58	-6	16
Postcentral gyrus	L			-42	-14	34
Postcentral gyrus	L			-64	-16	24
Occipital pole	R			24	-98	-8
Superior temporal gyrus	L			-42	-30	12
Superior temporal gyrus	R	14992	8.21	64	-22	4
Precentral gyrus	R			64	0	14
Superior temporal gyrus	R			66	-10	6
Superior temporal gyrus	R			62	-8	8
Supramarginal gyrus	R			38	-30	16
Postcentral gyrus	R			68	-12	12
Precuneus cortex	L	8003	5.72	-8	-58	18
Precuneus cortex	L			-6	-56	22
Precuneus cortex	R			8	-58	22
Lateral occipital cortex	R			48	-76	28
Precuneus cortex	R			6	-56	16
Lateral occipital cortex	R			52	-70	26
Lateral occipital cortex	L	1196	5.57	-42	-76	34
Lateral occipital cortex	L			-42	-80	30
Lateral occipital cortex	L			-44	-72	32
Lateral occipital cortex	L			-42	-72	28
Lateral occipital cortex	L			-48	-70	28
Lateral occipital cortex	L			-54	-78	18

Table A.3
Significant clusters of reward prediction error related activation during wins in healthy controls

Region	Side	k	z	MNI		
Dorsolateral prefrontal cortex	R	4527	4.48	42	28	40
Dorsolateral prefrontal cortex	R			44	32	30
Dorsolateral prefrontal cortex	R			44	18	30
Inferior frontal gyrus	R			52	18	30
Dorsolateral prefrontal cortex	R			40	8	62
Dorsolateral prefrontal cortex	R			32	10	62
Dorsolateral prefrontal cortex	L	1680	3.69	-48	22	40
Dorsolateral prefrontal cortex	L			-46	36	20
Dorsolateral prefrontal cortex	L			-44	8	34
Dorsolateral prefrontal cortex	L			-40	6	32
Dorsolateral prefrontal cortex	L			-32	10	60
Precentral gyrus	L			-38	4	26
Angular gyrus	R	3041	7.22	50	-56	38
Angular gyrus	R			48	-54	52
Lateral occipital cortex	R			38	-68	54
Superior parietal cortex	R			36	-54	52
Angular gyrus	R			50	-56	44
Lateral occipital cortex	R			32	-66	52
Occipital fusiform cortex	L	10048	4.66	-40	-58	-24
Occipital fusiform cortex	L			-10	-80	-24
Occipital fusiform cortex	L			-16	-88	-24
Occipital fusiform cortex	L			-16	-80	-20
Occipital fusiform cortex	R			16	-78	-14
Occipital fusiform cortex	R			40	-66	-14
Lateral occipital cortex	L	2865	4.21	-38	-62	50
Lateral occipital cortex	L			-46	-62	46
Angular gyrus	L			-46	-54	42
Superior parietal cortex	L			-48	-50	58
Angular gyrus	L			-40	-54	36
Angular gyrus	L			-42	-56	40

Table A.4
Significant clusters of reward prediction error related activation during wins in treatment resistant schizophrenia patients

Region	Side	k	z	MNI		
Frontal pole	R	630	3.67	6	74	14
Frontal pole	R			38	62	-2
Frontal pole	R			34	64	-4
Frontal pole	R			20	74	8
Frontal pole	R			4	74	8
Frontal pole	R			28	58	-2
Inferior frontal gyrus	L	1410	3.82	-54	14	30
Dorsolateral prefrontal cortex	L			-44	30	26
Inferior frontal gyrus	L			-50	12	24
Dorsolateral prefrontal cortex	L			-44	14	42
Dorsolateral prefrontal cortex	L			-48	10	38
Inferior frontal gyrus	L			-52	28	22
Dorsolateral prefrontal cortex	R	1507	4.07	42	10	36
Dorsolateral prefrontal cortex	R			48	8	36
Dorsolateral prefrontal cortex	R			40	14	32
Inferior frontal gyrus	R			48	10	22
Dorsolateral prefrontal cortex	R			52	32	22
Dorsolateral prefrontal cortex	R			30	4	54
Lateral occipital cortex	R	1352	3.66	34	-64	42
Superior parietal cortex	R			36	-44	46
Lateral occipital cortex	R			22	-62	48
Lateral occipital cortex	R			18	-66	48
Lateral occipital cortex	R			36	-58	38
Angular gyrus	R			52	-54	40
Occipital fusiform cortex	R	7420	4.35	34	-78	-20
Occipital fusiform cortex	R			10	-80	-16
Cerebellum	L			-34	-56	-26
Occipital fusiform cortex	R			26	-84	-18
Occipital fusiform cortex	L			-24	-82	-18
Occipital fusiform cortex	L			-32	-74	-20

Table A.5
Significant clusters of reward prediction error related activation during losses in healthy controls

Region	Side	k	z	MNI		
Middle frontal gyrus	L	1291	3.92	-40	38	34
Middle frontal gyrus	L			-44	38	28
Middle frontal gyrus	L			-46	34	20
Middle frontal gyrus	L			-42	40	18
Middle frontal gyrus	L			-46	18	48
Middle frontal gyrus	R	2627	3.87	42	34	36
Middle frontal gyrus	R			54	30	36
Middle frontal gyrus	R			50	26	36
Frontal pole	R			28	60	26
Middle frontal gyrus	R			30	16	50
Superior frontal gyrus	L	1310	3.98	0	26	48
Superior frontal gyrus	L			-6	24	48
Paracingulate gyrus	L			-2	50	26
Superior frontal gyrus	L			-8	36	50
Superior frontal gyrus	R			2	42	44
Putamen	L	541	3.39	-24	-2	-8
Pallidum	L			-16	0	0
Thalamus	L			-8	-8	0
Putamen	L			-30	4	-8
Putamen	L			-34	0	-8
Thalamus	R	558	1.44	28	-24	-4
Thalamus	R			26	-28	0
Thalamus	R			28	-24	0
Putamen	R			30	-16	-6
Pallidum	R			18	0	2
Superior parietal cortex	R	2224	4.27	54	-42	46
Superior parietal cortex	R			30	-64	50
Angular gyrus	R			44	-52	48
Lateral occipital cortex	R			34	-66	56
Angular gyrus	R			46	-52	48
Superior parietal cortex	L	1274	3.78	-50	-42	48
Superior parietal cortex	L			-46	-42	46
Superior parietal cortex	L			-38	-56	52
Angular gyrus	L			-44	-56	52
Supramarginal gyrus	L			-52	-46	48
Lateral occipital cortex	R	1432	4.23	42	-90	6
Lateral occipital cortex	R			28	-92	18
Lateral occipital cortex	R			42	-66	-18
Lateral occipital cortex	R			44	-82	-6
Lateral occipital cortex	L	1217	3.94	-36	-90	-8
Lateral occipital cortex	L			-40	-70	-18
Occipital fusiform gyrus	L			-44	-64	-22
Lateral occipital cortex	L			-40	-84	-12

Table A.6

Significant clusters of reward prediction error related activation during losses in treatment resistant schizophrenia patients

Region	Side	k	z	MNI		
Orbitofrontal cortex	L	3028	8.11	-46	40	-6
Dorsolateral prefrontal cortex	L			-40	20	40
Inferior frontal gyrus	L			-50	20	26
Inferior frontal gyrus	L			-50	20	2
Frontal pole	L			-42	48	0
Frontal pole	L			-44	48	-10
Superior frontal gyrus	L	5204	4.19	-2	38	42
Inferior frontal gyrus	R			46	28	20
Frontal pole	R			24	38	50
Dorsolateral prefrontal cortex	R			40	22	24
Superior frontal gyrus	R			6	32	42
Dorsolateral prefrontal cortex	R			54	22	34
Lateral occipital cortex	L	1426	3.83	-28	-62	56
Angular gyrus	L			-42	-56	56
Supramarginal gyrus	L			-50	-50	42
Angular gyrus	L			-52	-56	38
Lateral occipital cortex	L			-54	-64	28
Superior parietal cortex	L			-30	-54	58
Lateral occipital cortex	R	12130	4.46	38	-76	-30
Occipital cortex	R			16	-94	2
Cerebellum	L			-20	-82	-28
Occipital cortex	L			-26	-94	6
Occipital fusiform cortex	R			34	-44	-22
Cerebellum	L			-24	-78	-30

Table A.7

Means and standard deviations of demographic and clinical variables per group

	HC		NTR		TRS			
	M	*SD*	*M*	*SD*	*M*	*SD*	Group statistics	
							$F(2)$	P
Phonological verbal fluency	15.4	5.2	10.1	3.9	11.1	2.8	10.03	$< .001$
Semantic verbal fluency	19.7	4.4	14.3	4.0	14.5	3.4	12.96	$< .001$
Letter number sequencing	11.5	3.0	9.4	2.7	9.0	3.1	4.60	.014
ASI	7.3	7.4	10.8	9.0	18.9	5.9	11.07	$< .001$
BIS/BAS	60.4	11.5	64.5	8.7	70.8	12.6	5.36	.007
BIDR	125.1	17.3	126.5	13.3	120.2	18.1	0.28	.758
BDI	4.4	3.7	12.3	12.2	17.3	10.8	11.13	.001

HC = Healthy controls
NTR = non-treatment-resistant schizophrenia
TRS = Treatment resistant schizophrenia
ASI = Aberrant Salience Inventory
BIS/BAS = Behavioural inhibition / Behavioural approach system scale
BIDR = Balanced Inventory of Desirable Responding
BDI = Beck Depression Inventory