Section of Neurodiagnostic Applications
at the Clinic for Psychiatry and Psychotherapy
of the Ludwig-Maximilians-Universität München

Elucidating the Efficacy and Response to Social Cognitive Training in Recent-onset Psychosis

Dissertation
zum Erwerb des Doctor of Philosophy (Ph.D.)
an der Medizinischen Fakultät der
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Abstract

Neurocognitive deficits are one of the core features of psychosis spectrum disorders (PSD), and they are predictive of poor functional outcome and negative symptoms many years later (Green, Kern, Braff, & Mintz, 2000). Neurocognitive interventions (NCIs) have emerged in the last two decades as a strong potential supplementary treatment option to improve cognitive deficits and drop in functioning affecting patients with PSD. Social cognitive training (SCT) involving e.g., facial stimuli has gained considerably more attention in recent studies than computerized NCIs, that use basic visual or auditory stimuli. This is due to the complex character of social cognition (SC) that draws on multiple brain structures involved in behaviors and perception beyond default cognitive function. SC is also tightly interlinked with psychosocial functioning.

Although they are cost-effective and quite independent of clinical staff, such technological approaches as SCT are currently not integrated into routine clinical practice. Recent studies have mapped the effects of SCT in task-based studies on multiple brain regions such as the amygdala, putamen, medial prefrontal cortex, and postcentral gyrus (Ramsay & MacDonald III, 2015). Yet, the degree to which alterations in brain function are associated with response to such interventions is still poorly understood. Importantly, resting-state functional connectivity (rsFC) may be a viable neuromarker as it has shown greater sensitivity in distinguishing patients from healthy controls (HC) across neuroimaging studies, and is relatively easy to administer especially in patients with acute symptoms (Kambeitz et al., 2015).

In this dissertation, we employed 1) a univariate statistical approach to elucidate the efficacy of a 10-hour SCT in improving cognition, symptoms, functioning and the restoration of rsFC in patients undergoing SCT as compared to the treatment as usual (TAU) group, and 2) multivariate methods. In particular, we used a Support Vector Machine (SVM) approach to neuromonitor the recovery of rsFC in the SCT group compared to TAU. We also investigated the potential utility of rsFC as a baseline (T0) neuromarker viable of predicting role functioning approximately 2 months later.

First, current findings suggest a 10-hour SCT has the capability of improving role functioning in recent-onset psychosis (ROP) patients. Second, we have shown intervention-specific rsFC changes within parts of default mode and social cognitive network. Moreover, patients with worse SC performance at T0 showed greater rsFC changes following the intervention, suggestive of a greater degree of rsFC restoration potential in patients with worse social cognitive deficits. Third, when referring to neuromonitoring results, it is important to state that only greater transition from ROP to "HC-like" SVM decision scores, based on the resting-state modality, was paralleled by intervention specific significantly greater improvement in global cognition and attention. Finally, we were able to show the early prediction of good versus poor role functioning is feasible at the individual subject level using a rsFC-based linear SVM classifier with a Balanced Accuracy (BAC) of 74 %.

This dissertation sheds light on the effects and feasibility of a relatively short computerized SCT, and the potential utility of multivariate pattern analysis (MVPA) for better clinical stratification of predicted treatment response based on rsFC neuromarkers.

To my father and my mother

—you have shaped me into the person I am today.

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Contents

Acronyms

AMAP	Adaptive Maximum A Posteriori
ANOVA	Analysis of Variance
Attn	attention
BAC	Balanced Accuracy
BOLD	Blood Oxygenation Level Dependent
CAT12	Computational Anatomy Toolbox
CCT	computerized cognitive training
CSF	cerebrospinal fluid
CV	cross-validation
DANVA-2	Diagnostic Analysis of Nonverbal Accuracy-2
DARTEL	Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra
dlPFC	dorsolateral prefrontal cortex
DMN	default mode network
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EF	executive functioning
FD	framewise displacement
FDR	False Discovery Rate
FEP	first-episode psychosis
fMRI	functional Magnetic Resonance Imaging
FU	follow-up
GAF	Global Assessment of Functioning

GC	global cognition
GF-R	Global Functioning - Role
GF-S	Global Functioning - Social
HC	healthy controls
LOOCV	leave-one-out cross-validation
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MNI	Montreal Neurological Institute
mPFC	medial prefrontal cortex
MVPA	multivariate pattern analysis
NCIs	neurocognitive interventions
OOCV	out-of-sample cross-validation
PANSS	Positive and Negative Syndrome Scale
PC	Principal Components
PCA	Principal Component Analysis
PCC	posterior cingulate cortex
PSD	psychosis spectrum disorders
RAVLT	Rey Auditory Verbal Learning Test
ROIs	regions of interest
ROP	recent-onset psychosis
rsFC	resting-state functional connectivity
rsfMRI	resting-state functional Magnetic Resonance Imaging
SC	social cognition
SCID	Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
SCIT	Social Cognition and Interaction Training
SCT	social cognitive training
sMRI	structural Magnetic Resonance Imaging
SoP	speed of processing
SOPT	Self-Ordered Pointing Task
SPM12	Statistical Parametric Mapping, version 12
SVC	Support Vector Classification

SVM	Support Vector Machine
T0	baseline
TAU	treatment as usual
TE	echo time
TR	repetition time
VL	verbal learning
WM	working memory

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1 Introduction

It's not what you look at that matters, it's what you see.

— Henry David Thoreau

1.1 Context of the Study

1.1.1 Psychosis: a disorder of cognition

Psychosis is a severe mental disorder affecting nearly 1 % of the world's population (McGrath, Saha, Chant, & Welham, 2008). It is characterized by the presence of hallucinations (perceptual experiences in the absence of external stimuli) and delusions (fixed false beliefs) without insight, and/or disorganized thinking (American Psychiatric Association, 2000). Currently, diagnostic tools such as the International Classification of Diseases and Related Health Problems, 10th edition (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) are widely used to assess symptoms in a clinical setting (American Psychiatric Association, 2013; WHO, 2004). Psychosis is common to a number of psychiatric disorders and differences between diagnostic criteria of various psychosis spectrum disorders (PSD) depends on the duration, number, severity, type, and complexity of symptoms patients present with. Among the various forms, schizophrenia is one of the most debilitating and severe.

While schizophrenia is characterized by the same *positive* symptoms that encompass psychosis such as hallucinations, delusions, and disorganized speech and behavior, it is also often accompanied by *negative* symptoms, which includes reduced motivation and marked deficits in cognitive, social and emotional domains (Barbato, 1998). Although

schizophrenia has a relatively low lifetime prevalence (4.0 per 1000) (Saha, Chant, Welham, & McGrath, 2005), it is one of the most expensive brain-related disorders due to decreased self-care and quality of life, reduced social and occupational functioning, and greater cost of lifetime disability (Barbato, 1998; Häfner, Löffler, Maurer, Hambrecht, & an der Heiden, 1999). In fact, while some patients will generally improve after a first-episode psychosis (FEP), the majority experience subsequent episodes, and few are able to regain premorbid levels of functioning (Robinson, Woerner, McMeniman, Mendelowitz, & Bilder, 2004). Both the onset of the disorder (which often occurs between adolescence and early adulthood) and persistent or fluctuating symptoms throughout life (despite treatment) has led to greater emphasis towards developing early interventions in the hopes of (1) preventing the onset or (2) improving outcomes in patients who develop PSD (Birchwood, Todd, & Jackson, 1998; McGorry, Purcell, Goldstone, & Amminger, 2011). This results from studies showing improvement not only in clinical symptoms, employment conditions and lower overall costs of treatment following the implementation of intensive early intervention programs (Cullberg et al., 2006; Hastrup et al., 2013; Mihalopoulos, Harris, Henry, Harrigan, & McGorry, 2009), but also improvement in global levels of psychosocial functioning (Stafford, Jackson, Mayo-Wilson, Morrison, & Kendall, 2013).

Although diagnostically, schizophrenia is mainly defined by its psychotic features, there has been a reemergence of the notion that psychosis is a cognitive illness (Green & Nuechterlein, 1999; Kahn & Keefe, 2013). This idea was already popularized over a century ago by the German psychiatrist, Emil Kraepelin. The term *dementia praecox*, or "premature dementia" placed greater emphasis on the early onset of progressive cognitive decline in patients with psychotic disorders (Kraepelin, Barclay, & Robertson, 1919). Similarly, Eugen Bleuler, who coined the term "schizophrenia", regarded delusions and hallucinations as *accessory* symptoms, while the cognitive deficits along with disturbances in affect, social interaction, and volition represented *fundamental* symptoms of the disorder (Bleuler, 1950). Years later, the emphasis on the importance of treating cognition in psychosis is as prominent as ever.

Widespread neurocognitive deficits in the domains of executive function, verbal fluency, attention, visual and verbal memory, working memory (WM), general intelligence and social cognition are core features of psychosis that are already present at illness onset (Jahshan, Heaton, Golshan, & Cadenhead, 2010; McCleery et al., 2014). Such deficits

have also been shown to precede the onset of psychotic symptoms in individuals at high-risk for psychosis with attenuated psychotic symptoms, with greater impairment in verbal fluency, WM and visual and verbal memory in individuals who later transition to psychosis (Fusar-Poli et al., 2012; Seidman et al., 2010). While some studies have shown relative stability of cognitive deficits after illness onset without evidence for cognitive decline (Addington, Saeedi, & Addington, 2005; Bora & Murray, 2014), other studies have reported a worsening of cognitive impairments over time (Corigliano et al., 2014; Kenney et al., 2015). These studies emphasize the need for treatment strategies that specifically target cognitive skills that may be impaired already at the early stages of the disorder (1) as antipsychotic medication has limited effects on cognition or outcome and (2) in order to prevent further decline in cognitive abilities (R. S. Keefe et al., 2007; Leucht et al., 2009; Nielsen, Le Quach, Emborg, Foldager, & Correll, 2010). Despite mixed findings with respect to the course of cognitive deficits following FEP, there is an overall consensus that the degree and severity of cognitive deficits that patients bear at onset correlates with poor functioning, resumption of work, social and occupational outcome, and negative symptoms years later (Bowie & Harvey, 2006; K. H. Nuechterlein et al., 2011; Rodríguez-Sánchez et al., 2013).

1.1.2 Shifting the Focus to Social Cognition

Recently, researchers have turned from broad cognitive deficits to social cognitive deficits as the degree of impairment in social cognition (SC) has been shown to better predict everyday functional ability than both neurocognitive abilities and the severity of positive symptoms (Fett, Viechtbauer, Penn, van Os, & Krabbendam, 2011; Horan, Green, et al., 2011). Moreover, evidence suggests SC mediates the relationship between neurocognition and outcome (Brekke, Kay, Lee, & Green, 2005; Couture, Penn, & Roberts, 2006; Couture, Granholm, & Fish, 2011). SC also overlaps substantially with cognitive processes engaged in non-social tasks, such as WM and perception (Green, Horan, & Lee, 2015). Despite such overlaps, other studies still suggest distinctions exist in SC when looking at both the behavioral and neural level (Adolphs, 2001; Green et al., 2015).

SC encompasses cognitive functions utilized in socially relevant situations— mental processes by which humans perceive and think about themselves and how they interpret

and respond to the behavior of others (Green et al., 2015). Social cognitive deficits include impairments in five major domains: facial affect recognition (the ability to recognize feelings from the facial expressions or vocal inflections of others), social cue perception (the ability to judge rules within social situations), theory of mind or mentalizing (the ability to infer the beliefs, emotions, and intentions of others), attributional style (the attribution of the cause of events to oneself or others) and empathy (the ability to understand and similarly experience the emotional states of others) (Adolphs, 2009; Pinkham et al., 2014). It is well established that patients with PSD experience deficits in all of these domains (Green et al., 2015; Healey, Bartholomeusz, & Penn, 2016). Similar to the pattern of general cognitive deficits described above, social cognitive deficits are present at the early stages of the illness (Healey et al., 2016), have been shown to precede the onset of psychosis (Addington, Penn, Woods, Addington, & Perkins, 2008; Pinkham, Penn, Perkins, Graham, & Siegel, 2007), and persist in schizophrenia (Green, 2007). Moreover, similar to general cognition, the use of pharmacological interventions for the treatment of psychosis has shown limited effects on SC (Sergi, Green, et al., 2007). As social cognitive deficits affect daily living factors such as occupational status (Kee, Green, Mintz, & Brekke, 2003), community functioning (Fett et al., 2011), independent living skills (Kee et al., 2003), interpersonal skills (Pinkham & Penn, 2006) and quality of life (Fett et al., 2011) in patients with PSD, developing treatment strategies that target SC deficits directly may thereby result in greater improvement in widespread areas of cognition, symptoms and functioning.

1.1.3 The Emergence of Cognitive Interventions

Neurocognitive interventions (NCIs) have received great attention in recent years as a potential supplementary treatment option to improve cognitive deficits affecting a number of psychiatric disorders including psychosis. There are two predominant types of NCIs: top-down *strategy-based* and bottom-up *restorative* or *"drill-and-practice"* approaches. Within top-down programs, higher cognitive functions, such as executive functions, are the target of intervention. Therapists work together with patients by providing greater support initially in learning specific cognitive strategies such as cognitive flexibility, WM, and planning (Kurtz, 2012). Over time, clinicians gradually reduce their support so that patients may develop skills that can be transferable to

the real world. However, the treatment used across these strategy-based intervention programs is limited by long treatment durations, the need for trained clinicians, and in some cases the organization of patients into groups for program delivery.

These limitations have been overcome with the recent development of computerized cognitive training (CCT) programs that utilize a bottom-up restorative approach. These "drill-and-practice" programs have been designed to drive the brain in the direction of healthy functioning. They work by targeting low-level perceptual processing that then extends to higher-level working-memory, attention, and executive and motor processes (Vinogradov, Fisher, & de Villers-Sidani, 2012). All exercises are both adaptive and progressive, adjusting their difficulty based on the performance of the individual completing the exercises to ensure success while also remaining challenging. Such CCT programs are delivered via computers or tablets, have low costs compared with other treatments, and do not necessarily require the presence of a medical professional.

Unfortunately, to date, such technological approaches have not yet become the norm for practitioners and have not been translated into routine clinical practice (Barbui et al., 2014). This is especially problematic due to the wide array of available cognitive training programs on the market with varying mechanisms, durations of treatment, various modalities targeted, and effects that result from the training. Moreover, some researchers have refuted the effects of cognitive interventions based on unprecedented claims made by some companies on the effects of their training program (Harvey, McGurk, Mahncke, & Wykes, 2018; Simons et al., 2016). Such faulty claims could be detrimental to potential progress in this relatively young field, especially since evidence suggests positive effects in a number of domains for particular patient groups including patients with PSD and older adults (Harvey et al., 2018).

Several reviews and meta-analyses have attempted to synthesize evidence supporting the benefits of both bottom-up and top-down NCIs. Across studies, there is an overall consensus that NCIs generally lead to gains in cognition (Harvey et al., 2018; McGurk, Mueser, Feldman, Wolfe, & Pascaris, 2007; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). The effects on cognition are robust regardless of the specific therapy characteristics such as the mechanism (top-down versus bottom-up), duration, or delivery (Wykes et al., 2011). However, improvements in psychosocial functioning have shown greater success in improving functioning when using combined "drill-and-strategy" approaches

i.e., supplementing CCT with higher-level psychiatric rehabilitation strategies such as social skills training or vocational support (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007; Wykes et al., 2011). When focusing solely on patients with a FEP, effect sizes of NCIs tend to be smaller across cognition, symptoms, and functioning (Revell, Neill, Harte, Khan, & Drake, 2015). This may, however, largely be due to the relatively small number of studies that have thus far investigated the effects of NCIs in the earlier stages of PSD. Although CCT alone is not as successful in improving functioning, they have led to decreases in global costs associated with acute clinical care (Garrido et al., 2017). Patients who received CCT were admitted for psychiatric care less often and for shorter durations post-therapy than patients in control conditions (Garrido et al., 2017; Vita et al., 2016). The possibility of completing interventions such as CCT both in the clinic and from home has clinical implications for providing treatment to a greater number of patients. Thus further research in this field is warranted.

A greater emphasis has been placed on the need for interventions that target work recovery. Patients with schizophrenia have low employment rates ranging from 20 to 28 % at intake into the clinic (Marwaha et al., 2007). Following the clinical intervention, Ventura et al. (2011) showed lower rates of work recovery (38 %), as compared with social recovery (60 %) within the first year after a FEP. The authors explain that the lack of work outcome improvement is what generally prevents patients from meeting recovery criteria. Several studies to date have shown the benefits of supplementing CCT with work support (M. D. Bell, Bryson, Greig, Fiszdon, & Wexler, 2005; M. D. Bell, Zito, Greig, & Wexler, 2008; McGurk et al., 2007). Patients who received combined interventions showed significant improvements in occupational outcome—working a significantly greater number of hours and maintaining higher rates of employment on average in a follow-up (FU) post-intervention period (M. D. Bell et al., 2005, 2008). Similarly, McGurk et al. (2007) showed patients who received supported employment together with CCT were more likely to work, held more jobs, worked more hours, and earned more wages than patients receiving supported employment alone. Thus, research seems to indicate greater benefits from including targeted CCT approaches as opposed to targeting specific skills such as employment support alone.

Despite the vast array of cognitive interventions on the market, a particularly promising approach is that of the neuroplasticity-based CCT offered from Posit Science, Inc.[1] A

[1] https://www.brainhq.com/

computerized set of "drill-and-practice" exercises trains low-level cognitive-perceptual domains in order to improve higher-order cognitive functioning in the domains of WM, attention and processing speed (Nahum, Lee, & Merzenich, 2013). The repetitive tasks are designed to induce lasting neural changes through neuronal tuning and cortical expansion, resulting in better detection and processing of sensory stimuli (Merzenich, Van Vleet, & Nahum, 2014; Nahum et al., 2013; Vinogradov et al., 2012). These neuroplasticity-based programs have shown their restorative potential by improving global cognition (GC) and verbal learning and memory (Fisher, Holland, Merzenich, & Vinogradov, 2009), while also showing durability of the effects post-intervention (Fisher, Holland, Subramaniam, & Vinogradov, 2010; Subramaniam et al., 2014). These changes have also been associated with improvement in functioning (Fisher et al., 2010). Such interventions have successfully been implemented to improve cognition and outcome measures in individuals at high-risk for psychosis (Hooker et al., 2014), patients with recent-onset psychosis (ROP) (Fisher et al., 2015) and those with chronic schizophrenia (Fisher et al., 2009, 2010, 2017; Sacks et al., 2013).

Researchers have recently turned their focus to social cognitive training (SCT) which is meant to improve impairments in the domains of SC. By targeting SC deficits, widespread improvement may result not only in general cognition but also in SC and functioning based on their strong association as we mentioned above. One particular intervention recently developed by Posit Science is the computer-based SCT ("SocialVille"). This SCT implements learning-based neuroplasticity principles based on brain areas that underlie SC and function (Nahum et al., 2014). Similar to other CCT, discrimination of socially relevant stimuli become progressively more complex, while driving improvements in processing speed, WM, and attention control (Nahum et al., 2014). These exercises are used to improve the speed and accuracy of social and emotional information processing while engaging attention and reward systems (Nahum et al., 2014). Such targeted exercises activate neuromodulatory systems such as dopamine, norepinephrine, and acetylcholine (Merzenich et al., 2014). As these systems support synaptic plasticity, improved neural integrity as a result of such interventions might elicit the behavioral effects (Merzenich et al., 2014; Nahum et al., 2014; Vinogradov et al., 2012).

A pilot study investigating the effects of SCT in patients with schizophrenia has shown significant gains on standard measures of SC (Cohen's d = 0.60-0.73), social func-

tioning (Cohen's d = 0.40), and motivation (Cohen's d = 0.28) (Nahum et al., 2014). Bartholomeusz et al. (2013) showed small-to-moderate improvements in two measures of functioning following a 10-hour intervention utilizing a similar SCT called Social Cognition and Interaction Training (SCIT): social and occupational functioning assessment scale, d = 0.19; the role sub-scale of the global functioning scales, d = 0.32. Additionally, a number of studies have used SCT in conjunction with auditory CCT. Sacks et al. (2013) showed small-to-moderate effect sizes in various measures of social cognition (Cohen's d = 0.33-0.53), plus a significant decrease in positive symptoms (Cohen's d = 0.41). When comparing the effects of supplementing visual and auditory CCT with SCT, while both groups showed improvements in multiple cognitive domains and functional capacity, only those who received combined CCT and SCT showed additional improvements in both prosody identification and reward processing (Fisher et al., 2017). Other studies utilizing SCT in chronic patients have also shown gains in emotion perception and management, as well as social functioning (Hooker et al., 2012, 2013; Sacks et al., 2013).

In one meta-analysis integrating results from 19 studies employing various SCT programs in patients with schizophrenia, the authors showed improvements in social cognitive functions (Cohen's d as high as 1.01), total symptoms (Cohen's d = 0.68), and psychosocial functioning (Cohen's d = 0.78) (Kurtz & Richardson, 2011). These authors critiqued their work due to the heterogeneity of interventions they included: brief proof-of-concept social cognitive interventions, combined social cognitive interventions with psychosocial treatment, as well as comprehensive SCT programs targeting multiple SC domains (Kurtz, Gagen, Rocha, Machado, & Penn, 2016). Thus, in an updated meta-analysis, the authors included only studies utilizing comprehensive SCT. Here, improvements were seen in all domains of social cognition (Cohen's d ranging from 0.30-1.29), as well as small-to-moderate effects for negative (Cohen's d = 0.32) and general symptoms (Cohen's d = 0.40). While social cognitive interventions showed a small negative effect on overall cognition (Cohen's d = -0.31), measures of functioning were unfortunately not reported within this meta-analysis.

Taken together, these results show that improving SC and social skills using a single-user, computer-based intervention is both feasible and beneficial. Specifically targeting SC deficits may prove to have greater positive effects not only on cognition and social functioning as training mechanisms work on targeting the same underlying processes,

but also factors related to daily living including community functioning, work status, self-care and independence, a reduction in relapse rates, and quality of life (Addington, Saeedi, & Addington, 2006b; M. Bell, Tsang, Greig, & Bryson, 2009; Couture et al., 2006; Fett et al., 2011; Horan, Green, et al., 2011; Merzenich et al., 2014; Sergi, Rassovsky, et al., 2007; Vauth, Rüsch, Wirtz, & Corrigan, 2004). The mechanism underlying the behavioral and cognitive gains that result from interventions such as SCT might result from a restoration of impaired neural systems that have previously often been implicated in the pathophysiology of PSD (Dodell-Feder, Tully, & Hooker, 2015; Fisher, Loewy, Hardy, Schlosser, & Vinogradov, 2013; Isaac & Januel, 2016).

1.1.4 Neural Effects of CCT

Neuroplasticity is an ongoing state of neural reorganization resulting from both physiological and environmental changes (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). Changes occur in widespread regions of the brain throughout normal development. One's environment can also affect neuroplasticity, for example through stress, pressure, learning, and experiences throughout life (Pascual-Leone et al., 2005). Widespread neural impairments have been reported across stages in patients with PSD (Friston & Frith, 1995; T. Li et al., 2017). Moreover, these neural deficits are accompanied by impairments in perceptual, cognitive, social, and motor control. CCT are designed to elicit behavioral effects by inducing learning-based neuroplastic changes in the brain (Merzenich et al., 2014). The training programs developed by Posit Science, Inc., target specific modalities, such as auditory, visual, or social modalities. They function by improving low-level perceptual processing through the repetitive engagement of attention and reward systems in the brain (Vinogradov et al., 2012). As we mentioned above, CCT leads to cholinergic, dopaminergic, and noradrenergic neuromodulation that helps to improve the impaired higher-level processes including WM, attention, and executive and motor control (Merzenich et al., 2014).

The majority of studies that have investigated the effects of CCT on neurobiology have used task-based functional designs with patients undergoing WM and executive tasks while being scanned. Patients with PSD who undergo the active CCT consistently have shown baseline (T0) to FU increases in activation mainly in prefrontal regions while performing a variety of WM and executive tasks in the scanner (refer to Penadés et al.

for a recent review from 2017). Moreover, the increases in brain activation correlates with improvements in various measures of cognition measured outside of the scanner (Isaac & Januel, 2016) as well as the quality of life six months later (Subramaniam et al., 2014). Such studies show support for the neuroplastic effects of CCT on the brain.

A number of reviews have attempted to consolidate the research on the neural effects of NCIs in schizophrenia (Isaac & Januel, 2016; Penadés et al., 2017; Thorsen, Johansson, & Loberg, 2014). In a recent review, Penadés et al. (2017) found predominantly frontal and thalamic alterations following NCIs. The predominance of frontal changes from cognitive interventions seems to support the hypofrontality hypothesis, which posits reductions in prefrontal cortex utility might be the core mechanism underlying cognitive impairments in PSD (Andreasen et al., 1997). Improvements in cognition through the use of CCT in patients with PSD may thereby result from modifications of underlying prefrontal neural integrity. As the prefrontal cortex has been shown to modulate sensory information processed by the thalamus (E. K. Miller & Cohen, 2001) and is highly connected with the rest of the brain (Zhou, Fan, Qiu, & Jiang, 2015), targeting processes associated with the prefrontal cortex may lead to wide-ranging effects.

Still, a number of other brain regions have changed following NCIs. Thorsen et al. (2014) reported improvements in the structure and function of prefrontal, parietal, and limbic areas, while Isaac and Januel (2016) reported increased brain activation in prefrontal, occipital, and anterior cingulate regions during WM and executive tasks. Two meta-analyses similarly showed increased activations across both studies in widespread frontal and parietal regions (Ramsay & MacDonald III, 2015; Wei et al., 2016). Ramsay and MacDonald III (2015) showed additional activation changes resulting from cognitive interventions in the insula, caudate, and thalamus, whereas Wei et al. (2016) found distinct alterations in the postcentral gyrus. When they compared brain regions altered following NCIs with regions impaired when performing WM and executive functioning tasks in patients with PSD, Ramsay and MacDonald III showed only a subset of brain regions that overlapped. This suggests both compensatory and restorative mechanisms following NCIs (Ramsay & MacDonald III, 2015).

1.1.5 Neural Effects of SCT

To date, there have been only two reviews that have examined the neural effects of various SCT programs in patients with schizophrenia (Campos et al., 2016; Dodell-Feder et al., 2015). Impairments in SC networks and other widespread neural systems have consistently been reported in PSD, and these neural alterations may influence the clinical and cognitive deficits seen in such disorders (Adolphs, 2009; Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011; Pinkham, Penn, Perkins, & Lieberman, 2003). Using a variety of neuroimaging measures, evidence suggests SCT paradigms are capable of modifying networks underlying SC, and these improvements transfer to enhanced social cognitive performance (Campos et al., 2016; Dodell-Feder et al., 2015).

When combining auditory CCT with SCT, two studies reported greater pre-to-post activation increases in the postcentral gyrus and superior temporal gyrus (Hooker et al., 2012), as well as in bilateral amygdala (Hooker et al., 2013) during emotion recognition tasks. Hooker et al. (2013) additionally showed the neural activity increases in these regions across participants also predicted improvement on an independent emotion perception test done outside of the scanner. This suggests improved neural systems in these regions support social-cognition skills. Similarly, in two other studies that measured neural activation while performing experimental tasks in the scanner, patients with schizophrenia that underwent combined CCT and SCT showed increases in medial prefrontal cortex (mPFC) activity during a reality monitoring task, and inferior and middle frontal gyrus increases during a WM task (n-back) (Subramaniam et al., 2012, 2014). While these studies and other studies show support for the neuroplastic effects such interventions have on the brain, it is difficult to tease apart the effects arising from SCT compared with the effects from CCT that focus on either auditory or visual modalities when combined. Relatively few studies that target multiple domains of SC have investigated the neural effects of comprehensive SCT paradigms alone (Campos et al., 2016; Kurtz et al., 2016).

SC draws on many of the same brain structures critically involved in perception, cognition, and behavior (Adolphs, 2009). Specialized social cognitive skills have been associated with brain connectivity and activity in (1) the amygdala, somatosensory cortex, ventral striatum, and medial orbitofrontal cortex during emotion processing;

(2) lateral prefrontal cortex, anterior cingulate cortex, and superior parietal lobe for cognitive control important during self-regulatory processes; (3) superior temporal sulcus, temporoparietal junction, posterior cingulate, and mPFC during mentalizing tasks (Dodell-Feder et al., 2015). Moreover, with respect to general processing of social information, the mPFC, fusiform gyrus, superior temporal sulcus, temporoparietal junction, and amygdala are involved (Adolphs, 2009; Green et al., 2015). Researchers have recently turned their focus to task-absent resting-state functional Magnetic Resonance Imaging (rsfMRI), as greater activation in particular brain regions does not necessarily translate to better cognitive functioning. In some brain regions, decreased activation correlates with high performance in cognitive tasks (Callicott et al., 2003). Therefore, while task-based studies provide insight into brain regions critical for particular mental processes, it may be noteworthy to instead focus on functional connectivity changes induced by SCT.

Functional connectivity is acquired through rsfMRI scans and measures similar patterns of activation between regionally distinct brain areas (Fox et al., 2005; Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001). rsfMRI studies are easy to administer and are done in the absence of any tasks. This is an advantage over task-based studies where the tasks may be too difficult for some patients, especially those with severe and acute symptoms. Research supports the notion of widespread impairments of functional connectivity both between and within the majority of networks in the brain (Dong, Wang, Chang, Luo, & Yao, 2018; Friston & Frith, 1995; Sharma et al., 2018). As SC has strong ties with functioning (as described above), strengthening neural circuits within SC networks may result in greater improvement in social functioning and social skills that are critical for real-world functioning in patients with PSD.

The mPFC and amygdala are two regions often impaired in patients with PSD. They also play a central role in specialized social cognitive processes. For example, the mPFC is a key region of the default mode network (DMN), which is activated during self-reflection (Green et al., 2015). The DMN includes a set of functionally related regions that are intrinsically active in the absence of any task (Biswal, Yetkin, Haughton, & Hyde, 1995; Fox et al., 2005; Greicius et al., 2003; Raichle et al., 2001). In addition to the mPFC, the DMN is comprised of the posterior cingulate cortex (PCC) and precuneus, medial temporal lobe, and lateral temporo-parietal areas (Raichle et al., 2001). Similarly, the amygdala is involved in a number of social cognitive tasks such as detecting threat,

recognizing emotions (especially negative emotion) and faces, and making complex social judgments (Adolphs, 2001). Studies generally show an underactivation of the amygdala in patients with schizophrenia while performing emotion processing tasks in the scanner, such as while judging the trustworthiness of faces (Mukherjee et al., 2014), or during negative emotion processing tasks (Adolphs, 2003). However, a recent meta-analysis revealed the latter only to be true when the negative emotion processing task is contrasted with neutral stimuli (Anticevic et al., 2010). Thus, the decreased activation may actually result from overactivation of the amygdala to neutral faces (Pinkham et al., 2003).

At the level of functional connectivity, the amygdala has been shown to exhibit widespread dysconnectivity between networks. Reductions in connectivity are often seen between the amygdala and frontal regions in patients with PSD (Anticevic et al., 2014; Mamah, Barch, & Repovš, 2013; Mukherjee et al., 2016). While making social judgments about the approachability of individuals based on facial images, patients with schizophrenia showed: 1) hyperconnectivity of the amygdala with the middle frontal gyrus, superior frontal gyrus, and precuneus, and 2) hypoconnectivity between the amygdala and insula when compared to healthy controls (HC) (Mukherjee et al., 2014). An overcompensation of impaired neural systems within the hypoconnections and activations in the brain might result in the hyperactivation and connectivity reported. Such neural deficits additionally relate back to symptoms and functioning. Patients with reduced amygdala-mPFC connectivity relate to worse performance on emotion processing tasks, greater symptom severity, and unemployment (Mukherjee et al., 2016).

To date, only two other studies that have investigated the effects of NCIs on resting-state functional connectivity (rsFC) in early-course schizophrenia (Eack, Newhill, & Keshavan, 2016; Ramsay, Nienow, & MacDonald, 2017). The first implemented cognitive enhancement therapy in patients with a FEP (Eack et al., 2016). This intervention is delivered over two years with a total of 60 hours of CCT as well as 45 additional 1.5-hour SCT group sessions. This study provided support for the neuroprotective effects of their intervention with preserved rsFC between the PCC and dorsolateral prefrontal cortex (dlPFC) in those who underwent the intervention, along with intervention-specific increases in rsFC between the PCC and right insula (Eack et al., 2016). Impairments in these regions have been associated with impairments in executive function, emotion processing, and emotion regulation (Su et al., 2013; Taylor et al., 2012). However, the

relatively high attrition rates (50 % in patients in the control condition and 32 % in patients undergoing the NCIs) calls into question the feasibility of such an intervention in a clinical setting (Eack et al., 2016; Matsuda et al., 2018). Additionally, social-cognitive group sessions took place once per week in the clinic, which may not be feasible for some patients.

Ramsay, Nienow, and MacDonald (2017) utilized a 48-hour "drill-and-practice" working memory CCT that spanned verbal, visual and spatial modalities in patients with schizophrenia. They found significant intervention-specific rsFC increases between the thalamus and 1) right middle frontal gyrus and 2) anterior cingulate cortex. Moreover, the degree of increases in connectivity between the thalamus and middle frontal gyrus for the intervention group was positively correlated with improvements in global cognition. The results show evidence for a relationship between plasticity-based improvements and training-specific improvements in cognition (Ramsay, Nienow, & MacDonald, 2017). While the authors showed positive results, they did not mention their attrition rates. In addition, similar to the study by Eack et al. mentioned above, this particular NCIs has a relatively long duration.

Nevertheless, these findings support the idea that neural alterations may be induced through SCT in patients at chronic, but also early stages of the disorder. As we mentioned above, we now have the capability of overcoming previous limitations in cognitive intervention studies, including the long treatment duration, the need for trained clinicians, and in some cases the need for group delivery of programs through the advent of CCT. Moreover, studies utilizing SCT have shown improved neural integrity in regions implicated in SC. Improvements in neural networks implicated in SC might thereby lead not only to better cognition but also show a potential for transfer to real-world functioning.

1.1.6 Utilizing Multivariate Methods to Measure Individual Response

Despite evidence supporting improvements in cognition, social skills, and altered neural activity in regions involved in SC, there is still substantial heterogeneity of individual response to CCT. multivariate pattern analysis (MVPA) is a promising tool with the

capability of making inferences at the single-subject level and thus may highlight specific markers predictive of response to SCT. Whereas univariate methods focus on group characteristics (with a substantial overlap of measures between groups), MVPA is able to find a boundary that best separates two groups based on a particular set of features (clinical, cognitive, or biological). This allows for the quantification of diagnostic group membership at the individual level—aiding in the identification of robust, reliable and valid markers (Abi-Dargham & Horga, 2016).

A number of different machine learning algorithms may be used to create predictive classification and regression models. One such algorithm widely used in psychiatry, and also used in the analyses described below, is the Support Vector Machine (SVM) (Dwyer, Falkai, & Koutsouleris, 2018; Orrù, Pettersson-Yeo, Marquand, Sartori, & Mechelli, 2012). SVM is a supervised machine learning technique that uses a margin-based framework to find the optimal function (a hyperplane) to either maximally separate individuals into groups in the case of Support Vector Classification (SVC) or find the optimal linear (or non-linear) fitting function to fit a number of continuous values in the case of Support Vector Regression (Cortes & Vapnik, 1995; Dwyer et al., 2018). The resulting decision boundary is then used to classify new unseen cases.

Support vectors, which consist of the cases closest to the hyperplane that may be the most difficult to discriminate, help to determine the optimal decision boundary. They are most informative for the classification as they determine how large the margin (the distance to the support vectors perpendicular to the hyperplane separating the two groups) will be. The margin can be optimized by allowing a certain degree of error (SVM regularization parameter: *C* parameter). A larger margin (small C) may be problematic if outliers appear in the sample or too many cases are misclassified. On the other hand, having too many correctly classified cases (large C, smaller margin) in the training data, makes the model less generalizable to new data (Zarogianni, Moorhead, & Lawrie, 2013). Different values for the regularization parameter can be tested within the training data, thereby optimizing the C parameter. For a review please refer to Mwangi, Tian, and Soares (2013).

Data is separated into training and test sets in the SVC and regularities in the data are used to predict specific outcome measures (Orrù et al., 2012). The SVM thus produces a model based on training data, which has the capability of predicting the target values

(labels) of the test data only given the information from data that was input into the model used to make the predictions (features) (Pereira, Mitchell, & Botvinick, 2009). Feature selection is an additional reduction technique used when building the model, in which a subset of relevant features is selected (Guyon & Elisseeff, 2003). Benefits in using various feature selection techniques include enhancing model generalizability, compressing learning time, and improving prediction performance (Dwyer et al., 2018). Moreover, such techniques help to reduce the effects of the curse of dimensionality, where a low number of observations along with a high number of predictors imposes a limit on studies (Guyon & Elisseeff, 2003).

This is the case for studies that have utilized the SVC, where the number of cases (i.e., subjects) is generally low, while the number of predictor variables or features is disproportionately high (i.e., the curse of dimensionality) (Dwyer et al., 2018). Multivariate studies incorporating neuroimaging markers, or "neuromarkers" (Jollans & Whelan, 2018), have an especially high number of features. Even when brain data is parcellated, as in the Dosenbach atlas into the 160 regions of interest (ROIs) (Dosenbach et al., 2010), we are still left with 12 720 features before any further preprocessing steps are implemented (see Figure 2.4). The SVM algorithm is able to deal with high dimensional data and has successfully been used in a large number of previous neuroimaging studies of patients with PSD (Dwyer et al., 2018; Kambeitz et al., 2015; Wolfers, Buitelaar, Beckmann, Franke, & Marquand, 2015).

With the field of psychiatry shifting towards utilizing multivariate methods such as machine learning, researchers are making strides towards answering complex research questions that allow for the quantification of diagnostic group membership at the single-subject level (Lemm, Blankertz, Dickhaus, & Müller, 2011; Pereira et al., 2009) based on neuromarkers (Dwyer et al., 2018; Kambeitz et al., 2015; Wolfers et al., 2015). Two studies have shown the predictive utility of using multivariate methods to predict the outcomes of patients with PSD using T0 characteristics—albeit without integrating any particular interventions. Mourão-Miranda et al. (2012) was able to show separability of patients with different illness courses using T0 structural Magnetic Resonance Imaging (sMRI). Patients with a continuous course of symptoms following a FEP were distinguishable from HC at T0 with an accuracy of 70 %. Additionally, patients with a continuous course were also distinguishable from patients with an episodic course of symptoms using T0 sMRI with an accuracy of 70 %.

Similarly, Koutsouleris, Kambeitz-Ilankovic, et al. (2018) used T0 sMRI and functioning to predict good versus poor social and role outcomes in patients with a recent onset of depression and individuals at clinical high risk for psychosis. Using combined T0 clinical and neuroanatomical features, the authors showed greater prediction accuracies for social functioning (70 % for patients with recent onset depression and 83 % for patients at risk for psychosis) as compared with role functioning (63 % for patients with recent onset depression and 65 % for patients at risk for psychosis). Yet, this study had a naturalistic design and did not implement any interventions outside of standard clinical care.

As we mentioned above, supplementing clinical treatment with a CCT such as SCT may lead to altered trajectories of role functioning. Moreover, as this study used sMRI, it may be that structural abnormalities predictive of role functioning appear somewhat later than abnormalities associated with SC. A recent review investigating structural neuromarkers predictive of poor response to clinical treatment in patients with schizophrenia suggested regions of the medial temporal and prefrontal cortex, along with connections with subcortical structures to be promising Dazzan et al. (2015). In sum, these findings point to a disturbed cortical reorganization at the structural level, especially in frontal and temporal regions, in patients with PSD.

A recent meta-analysis has integrated information from studies that have used MVPA of sMRI and rsfMRI alterations to classify schizophrenia patients and HC. Here, greater sensitivity (the ability to correctly detect the patient group) was found in studies using rsfMRI, whereas specificity (the ability to correctly detect HC) was similar across modalities (Kambeitz et al., 2015). This suggests a focus on functional alterations following a short-term intervention might better gauge the subtle neural changes that might be predictive of response. Moreover, although few studies have investigated the characteristics that could inform treatment response in NCIs studies, when looking at psychopharmacological studies, researchers have been able to show an association between particular T0 characteristics of patients and improvement in symptoms using both traditional univariate statistics (Boter et al., 2009) and predicting response using multivariate methods (Chekroud et al., 2016; Koutsouleris et al., 2016).

In one example, Chekroud et al. (2016) used a subset of variables (responses to questionnaire items) that were most predictive of treatment outcome to train a machine-learning

algorithm to detect patients with depression that would respond to a specific antidepressant with an accuracy of 64.6 %. Similarly, Koutsouleris et al. (2016) was able to predict poor versus good functioning in patients with FEP based on pre-treatment clinical information with an accuracy 75.0 % after 4-weeks and 73.8 % after 52 weeks. When the authors took a subset of the top ten features used to predict outcome in an independent set of patients, the classification model identified patients' functioning with an accuracy of 71.7 %. Moreover, the choice of antipsychotic medication was shown to be relevant in individuals with poor, rather than good, one-year prognoses (Koutsouleris et al., 2016). These studies implicate the clinical utility of MVPA in predicting treatment response.

As individuals are multidimensional in nature and differ on a large number of features, such as symptoms, structure, and function in the brain, cognitive ability, and demographic background, it can be difficult to determine which characteristics of an individual could best inform treatment response. CCT have been shown to be effective in improving cognitive abilities and overall functioning in patients with chronic schizophrenia (Fisher et al., 2010, 2017) as well as individuals at earlier stages of psychosis (Hooker et al., 2014). Nevertheless, not all patients respond to such interventions. The majority of bottom-up restorative interventions administer standardized exercise programs to all participants, regardless of T0 profiles—potentially compromising effect sizes.

The subset of treated patients that do not respond to NCIs indicates a need for individualized treatment and reliable markers to predict and monitor response, especially at earlier stages of PSD (Medalia, Saperstein, Hansen, & Lee, 2016). Few studies thus far have utilized multivariate methods to determine which characteristics are critical for determining treatment response. In a recent study, Ramsay et al. (2018) investigated which cognitive, demographic, or psychological characteristics are predictive of treatment response following a CCT. They found T0 GC and years of education in patients with early schizophrenia to predict improvement in GC following the intervention. Still, no one has investigated the potential of neuromarkers in predicting response to CCT.

The underlying reason for the large heterogeneity in treatment response seen across CCT could be due to the heterogeneity of the affected neural systems (brain-phenotypes)

and reduced systemic neuroplastic response to environmental (i.e., therapeutic) stimuli in certain patient subgroups. Yet, to date, reliable techniques that have monitored neural response ("neuromonitoring") to NCIs at the individual-level are sparse. Neuromonitoring refers to measurement and monitoring of (potentially subtle) changes in brain function over time (Stocchetti et al., 2013). Through neuromonitoring, we may better identify individuals who show response to NCIs by measuring changes in brain function at varying intervals. Empirical measurements that provide a quantitative measure of changes in the entire brain could help clinicians make informed decisions on the dosage or types of interventions to be used.

Evidence suggests the stratification of individuals based on specific T0 cognitive, psychological, or neurobiological characteristics results in better predictions of treatment response (Medalia et al., 2016). Due to the significant heterogeneity of treatment response shown in the current NCIs literature, the development, validation, and clinical translation of specialized CCT programs (such as SCT) will depend not only on the identification of clinical and cognitive markers, but also brain-based neuromarkers (due to the advantage of the easy and short duration of acquisition) for individualized treatment response prediction. As the field of psychiatry continues to make use of the multivariate methods we have available today, there is ample opportunity to shift our understanding from the descriptive to the predictive, and from the group to the individual: by understanding the factors that may contribute to the successful improvement of outcomes in patients undergoing supplementary treatment therapies such as SCT.

1.2 Aims

The general aim of this dissertation was (1) to assess the effects of a 10-hour SCT in patients with ROP at the cognitive, behavioral and neural levels and (2) determine the potential utility of rsFC as a functional neuromarker for measuring the response to SCT. The following specific aims will be investigated in three studies within this dissertation:

1) This study will first examine the effects of the intervention on the primary outcome measure of cognition. In addition, we will also investigate the effects of SCT as compared to the treatment as usual (TAU) group on secondary outcome

measures: social and role functioning and clinical symptoms. Last, we will measure whether observed changes in the primary outcome measures of cognitive domains are associated with changes in any of the secondary outcome measures. We expect patients who receive SCT to show greater improvements in GC, SC, and functioning.

2) In the second study, we move from the clinical and behavioral to the neural level. This study will investigate the effects of SCT on rsFC in the brain. First, we will focus on the mPFC of the DMN and amygdala. Second, we will examine whether the observed changes associated with SCT relate to changes in cognition, functioning, or symptoms. Last, we will determine whether the T0 measures of cognition, symptoms, or functioning are associated with rsFC changes in patients undergoing SCT. We expect regions that support SC and higher-order cognitive functioning to show changes in the SCT group.

3) In the last study, we move from univariate group statistics to multivariate single-subject prediction in order to determine whether rsFC could be utilized as a viable neuromarker to monitor and measure the response to SCT.

    a) We validated an independent HC-ROP classification model based on whole-brain rsFC on our study sample at two different time-points in order to monitor neural response to SCT. This would allow us to determine whether patients were more likely to shift across the SVM hyperplane according to their rsFC pattern in the "HC-like" direction following SCT as compared to those in a TAU control condition. Additionally, we examined whether there were behavioral or clinical differences between patients who received SCT that shifted in the "HC-like" versus "ROP-like" directions following the intervention. We expected patients who received SCT to show greater shifts in the "HC-like" direction as compared to the TAU condition. Moreover, we expected patients who showed rsFC shifts across the SVM "hyperplane" in the "HC-like" direction following the intervention to show greater gains in the primary (cognition) and secondary (functioning and symptoms) outcome measurements.

    b) We additionally investigated whether T0 whole-brain rsFC could be utilized to predict good versus poor role functioning at FU in patients who

received SCT. We expected T0 rsFC to be a viable marker for predicting role functioning following SCT. Moreover, we expected connections between widespread brain regions including temporal and prefrontal cortical areas to contribute most to the prediction of good versus poor functioning.

2 Methods and Materials

2.1 General Methods

2.1.1 Participants

Study Sample

Our sample consisted of 54 patients (Table 2.2) aged 15-40 years recruited from the Early Detection and Intervention Center at the *Department of Psychiatry and Psychotherapy* of the Ludwig-Maximilians-University (LMU) in Munich, Germany. All participants in this study had a ROP with a duration of illness of fewer than 2 years and the presence of psychotic symptoms within the last 3 months for at least 7 days based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (see Table 2.2). In order to exclude cannabis-induced psychosis as the primary diagnosis, we required the continual presence of symptoms following abstinence for at least one month after symptom onset. If symptoms remitted during the abstinence of cannabis, patients were excluded from the study. Study inclusion and exclusion criteria for all individuals are summarized in Table 2.1.

All participants provided written informed consent prior to study inclusion. The study was approved by the Local Research Ethics Committee of the Ludwig-Maximilian-University. Participants were examined using a series of standardized clinical, neuropsychological and neuroimaging protocols described below. At the time of inclusion, only 2 of the 54 patients had outpatient status—all other patients were being treated on the ward. Of the 54 patients, 27.8 % (N = 15) had neither previously nor currently taken antipsychotic medication (see Table 2.2).

Table 2.1: Inclusion & exclusion criteria for the participation in the intervention study.

GENERAL INCLUSION AND EXCLUSION CRITERIA

Inclusion

1. Age 15 to 40 years
2. Language skills sufficient for participation
3. Sufficient capacity to consent
4. Presence of Psychotic Syndrome:
   a) Any of the Scale of Prodromal Symptoms P1 - P5 scales rated 6 + symptoms occurring daily for more than one week and
   b) Any of the Scale of Prodromal Symptoms P1-P5 Scales scored 6 or ever been + symptoms seriously disorganizing or dangerous
5. Symptoms present within the past 3 months, but no longer than 24 months

Exclusion

1. IQ below 70
2. Hearing is not sufficient for neurocognitive testing
3. Current or past head trauma with loss of consciousness (> 5 minutes)
4. Current or past known neurological disorder of the brain[1]
5. Current or past known somatic disorder potentially affecting the brain[2]
6. Current or past alcohol dependency
7. Current polytoxicomania (poly-dependency) within the past six months
8. MRI incompatibility
9. Antipsychotic medication for >90 days (cumulative number of days) at or above minimum dosage of the '1st episode psychosis' range of Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde e.V. (DGPPN) S3 Guidelines[3]

[1] Refer to Table A.3 in the Appendix.
[2] Refer to Table A.2 in the Appendix.
[3] Refer to Figure A.1 in the Appendix for details.

Table 2.2: Baseline demographic and clinical characteristics for recent onset psychosis (ROP) patients randomly assigned to either social cognitive training (SCT) or treatment as usual (TAU). MRI = Magnetic Resonance Imaging; NOS = not otherwise specified; MDD = Major Depressive Disorder; CPZ = chlorpromazine equivalent; GAF = Global Assessment of Functioning; GF = Global Functioning, PANSS = Positive and Negative Syndrome Scale.

	SCT (N = 27)	TAU (N = 27)	T/ $\chi 2$	P-value
Number female (%)	11 (40.74 %)	11 (40.74 %)	0.000	1.000
Age (SD)	26.98 (6.23)	25.59 (6.22)	0.821	0.415
Years of education (SD)	14.96 (3.71)	13.67 (3.51)	1.319	0.193
Premorbid IQ (SD)	98.52 (14.73)	93.33 (17.87)	1.164	0.250
Number of days between assessments (SD)	49.22 (11.23)	46.67 (17.34)	-0.643	0.523
Number of hours trained (SD)	9.98 (0.71)	-	-	-
Handedness	-	-	5.260	0.072
Right (%)	21	12	-	-
Mixed (%)	2	7	-	-
Left (%)	2	3	-	-
Diagnosis	-	-	10.410	0.170
Schizophrenia (%)	8 (29.63 %)	3 (11.11 %)	-	-
Schizoaffective disorder (%)	1 (3.70 %)	5 (18.52 %)	-	-
Schizophreniform disorder (%)	3 (11.11 %)	6 (22.22 %)	-	-
Brief psychotic disorder (%)	6 (22.22 %)	6 (22.22 %)	-	-
Delusional disorder (%)	4 (14.81 %)	2 (7.41 %)	-	-
Psychotic disorder NOS (%)	1 (3.70 %)	-	-	-
MDD with psychotic symptoms (%)	3 (11.11 %)	1 (3.70 %)	-	-
Substance-induced psychotic disorder (%)	1 (3.70 %)	4 (14.81 %)	-	-
Medication at baseline (N = 39)				
CPZ equivalent (SD)	67.39 (71.82)	71.14 (102.01)	-0.156	0.876
GAF global rating past month	47.44 (14.56)	40.52 (11.84)	1.917	0.061
GF current				
Role (SD)	4.48 (1.48)	4.59 (1.67)	-0.259	0.797
Social (SD)	6.00 (1.11)	5.63 (1.57)	1.000	0.322
PANSS				
Total (SD)	67.48 (16.26)	69.22 (17.76)	-0.376	0.709
Positive (SD)	19.30 (5.88)	21.26 (4.46)	-1.383	0.173
Negative (SD)	14.56 (5.60)	14.85 (6.53)	-0.179	0.859
General (SD)	33.63 (8.79)	33.11 (11.19)	0.189	0.851

2.1.2 Study Design

Of the 54 patients, 27 (mean age = 26.98, *SD* = 6.23, 40.74 % female) were randomly assigned to an active 10-hour SCT group and the other 27 (mean age = 25.59, *SD* = 6.22, 40.74 % female) to the TAU control group. At T0 and FU time-points, all patients received standardized clinical, neuropsychological and neuroimaging assessments (please refer to Figure 2.1 for a summary of the study design). On average, there were 47.94 (*SD* = 14.53) days between T0 and FU assessments with no significant difference (*P* = 0.052) between the two conditions (Table 2.2).

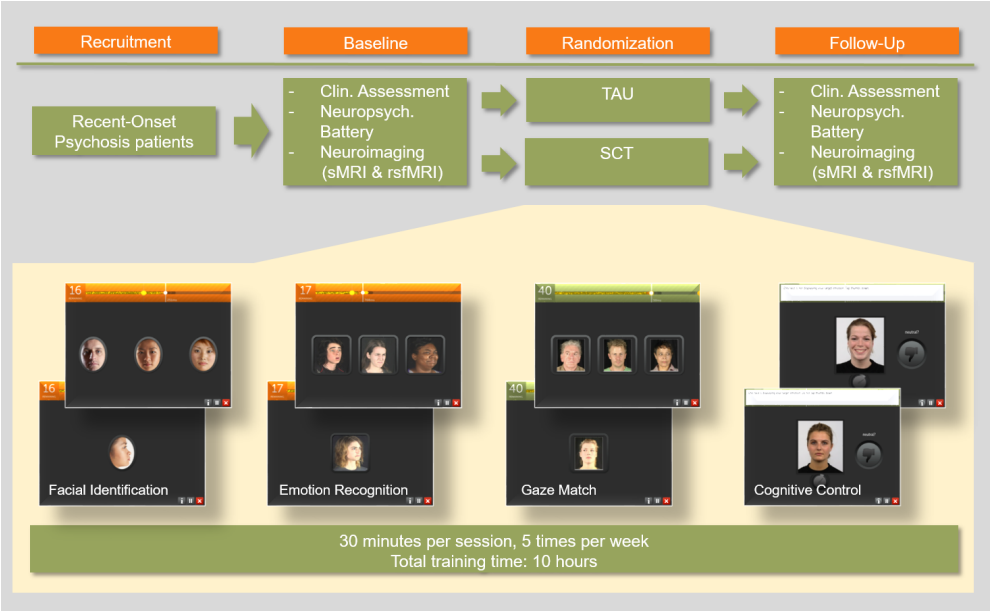

Figure 2.1: A depiction of the study design used in the study. sMRI = structural Magnetic Resonance Imaging, rsfMRI = resting-state functional Magnetic Resonance Imaging, SCT = social cognitive training, TAU = treatment as usual.

Patients in the active intervention group were paid 80 € and those in the passive control group 30 € for participation after the completion of the FU assessments. Assessments included clinical, neuropsychological and neuroimaging. Patients in both the SCT and TAU control condition were receiving additional treatments by clinic personnel not involved in the study. This may have included psychoeducation, psychotherapy, and adjustments in medications as clinically relevant. Demographic characteristics and medication at T0 are presented in Table 2.2.

2.1.3 Training Procedure

The 10-hour SCT was provided by the SocialVille program, an online program developed by Posit Science, Inc. designed to treat SC deficits (Nahum et al., 2014). The exercises were meant to improve accuracy and speed of neural functions associated with processing social information. These exercises target attention, WM, and perception in the social cognitive domains of both vocal and visual affect perception and social cue perception. As the exercises were not available in German at the start of the study, the current study utilized a subset of the exercises pertaining only to the visual domain that did not require English knowledge. Four exercises were included in every training session (see Figure 2.1 for examples of the exercises). Each exercise repeated several iterations until participants completed approximately 7-8 minutes of the exercise, and then the program automatically progressed to the next exercise. Descriptions of the 4 exercises can be found in Table 2.3 and further details regarding the training in Nahum et al. (2014).

Table 2.3: Description of the social cognitive training exercises provided by Posit Science, Inc. (SocialVille) used for the intervention in the order of administration.

Exercise	Trials per iteration[*]	Description	Target
Recognition	20	A speeded face matching task: Select the correct target face from an array of faces	Improve processing of facial features.
Face to Face	20	A speeded facial emotion matching task: Select the face showing the same facial expression as the target face	Improve the ability to make implicit speeded decisions about facial emotion features.
Gaze Match	40	A speeded gaze matching task: Match gaze direction of target face	Improve processing speed for accurate identification eye gaze direction.
Face Poke	60	A CPT task with facial expressions: Withhold response for neutral expressions (10 % of trials), respond quickly to emotional faces (90 %)	Improve the brain's ability to distinguish between emotionally expressive faces and neutral faces.

[*] Each exercise repeated several iterations of each exercise until approximately 7-8 minutes were complete.

Throughout the course of training, each task progressively becomes more difficult based on the individual's performance, with the final blocks being considered the most challenging. Within a training session, adaptive algorithms continually adjust the exercise's difficulty level so that participants maintain 75 to 80 % correct responses. Patients

received direct feedback after each trial and were awarded points and animations for correct trials. If a participant answered incorrectly, they heard a thumping sound and were shown the intended correct response along with the initial stimulus presented.

Participants included in the active intervention group were asked to participate for a total of 10 hours (30 minutes per session, 4-5 days per week, for 5 weeks). The first three training sessions took place at the *Department of Psychiatry and Psychotherapy* of the Ludwig-Maximilians-University (LMU). Training sessions were conducted on iPads in comfortable and quiet rooms that were also used for the clinical assessments. Researchers familiar with the training exercises provided patients with instructions on the exercises and with all necessary information to complete one full training session within individual sessions. After these three sessions, participants had the option of attending group training sessions in the clinic or training from home. Although a majority of patients included in the study were in an acute phase of the illness and in-patient at the time of inclusion into the study, 15 participants in the SCT condition completed training sessions within the clinic whereas 11 trained from home. FU assessments occurred on average 49.22 days (SD = 11.23) after T0 in the SCT group, and on average 46.67 days (SD = 17.34) in the TAU group (P = 0.56, Table A.7).

For patients who completed training in the clinic, the room in which subsequent SCT sessions took place consisted of three seated stations where patients could complete the training. Patients were provided with soundproof over-ear headphones in order to receive auditory feedback for their responses to the training and prevent interference with other patients' training experience. After each training session, training data was automatically uploaded to a secure central database provided by Posit Science, Inc[1], where training progress could be monitored. Both patients who trained from home or in the clinic were contacted if they missed sessions. Trained research personnel set up iPads for participants training in the clinic using standardized procedures. Additionally, the trained staff provided technical support to patients training from home if necessary. Mean training time was 9.98 hours (SD = 0.71).

Although previous studies generally engaged chronic schizophrenia patients in exercises for greater than 40 hours (Fisher et al., 2009, 2010), there are a number of reasons why a shorter training duration in ROP patients was chosen. In the current study, as

[1] https://www.brainhq.com/

patients are at an early and acute phase of the illness, a shorter—albeit intense—training regimen may show benefits after 10 hours of intervention. In line with this reasoning, in a recent meta-analysis investigating the effects of computerized cognitive training programs, Prikken, Konings, Lei, Begemann, and Sommer (2019) found greater effect sizes from studies with shorter duration times. Upon further investigation, however, they found this was not due to the shorter duration. Instead, a higher frequency of training sessions within a shorter overall duration—similar to our study design—resulted in greater effect sizes of improvement in a number of domains. Additionally, by limiting the intervention to 10 hours, the time frame of intervention overlaps with the general duration of treatment patients receive in the clinic. This would provide us with additional information regarding the feasibility of implementing such an intervention in a real-world clinical setting.

2.1.4 Assessment Procedures

Participants included in the study sample were examined at T0 and FU using a series of standardized clinical, neuropsychological and neuroimaging protocols. All T0 assessments were also conducted on participants in an independent sample described in Section 2.4.1 below.

Clinical Assessment Procedures

At study entry, each participant received a standardized clinical and diagnostic evaluation from trained research personnel of the Early Detection and Intervention Center in order to determine eligibility into the study based on the criteria outlined in Table 2.1. Primary diagnosis was determined using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SCID) for Axis I Disorders (First, Williams, Spitzer, & Gibbon, 2007), as well as consultation of the patients' psychiatrist and medical records. All subjects had a diagnosis of a psychotic disorder that was present within the last three months, but no longer than 24 months (see Table 2.2).

The presence of psychosis was determined using the Structured Interview for Prodromal Syndromes—a structured diagnostic interview generally used to assess prodromal

symptoms of psychosis, but also has the capability of providing an operational definition for the presence of psychosis (T. J. Miller et al., 2003). Patients should have scored a 6 (most severe possible score) for at least one week in at least one of the following symptoms: (1) unusual thought content/delusional ideas, (2) suspiciousness/persecutory ideas, (3) grandiose ideas, (4) perceptual abnormalities, and (5) disorganized communication. In order to assess clinical status and the presence and severity of symptoms, research personnel administered the Positive and Negative Syndrome Scale (PANSS) (Kay, Flszbein, & Opfer, 1987). The PANSS consists of 30 items meant to gauge the Positive, Negative, and General Psychopathology scales (for a complete list of PANSS items, please refer to Table A.4 in the Appendix). This scale has been shown to be highly reliable and internally consistent (Kay, Opler, & Lindenmayer, 1988).

In order to assess a global rating of disability and impairment, the Global Assessment of Functioning (GAF) Disability and Impairment Scale of the DSM-IV was used (Hall, 1995). Additionally, to better disentangle the effects of SCT on specific domains of functioning, the clinician-rated Global Functioning - Social (GF-S) and Global Functioning - Role (GF-R) Scales were used to assess social and role functioning separately (Cornblatt et al., 2007). These scales have previously been used to predict outcome based on T0 neurobiological information in patients with recent onset depression and individuals at risk for psychosis (Kambeitz-Ilankovic et al., 2015; Koutsouleris, Kambeitz-Ilankovic, et al., 2018). At FU, a semi-structured clinical interview again took place in order to evaluate changes in symptoms and outcomes using the instruments described above.

Cognitive Assessment Procedures

A cross-domain neuropsychological test battery comprising of 9 tests were administered to all subjects at T0 and FU by trained research personnel of the Early Detection and Intervention Center in a fixed order (see Table 2.4 for a list of the 9 neurocognitive tests used). These tests were chosen based on a previous meta-analysis that synthesized tests targeting specific cognitive domains that showed widespread impairment at T0 in patients at risk for psychosis who later went on to develop psychosis (Fusar-Poli et al., 2012). Additionally, these tests have previously been shown to measure neuropsychological functions that are often impaired in patients with PSD (Bilder et al.,

2000; R. S. Keefe et al., 2004). For a complete list of neuropsychological tests conducted, please refer to Table A.1 in the Appendix. We specifically chose a subset of the individual tests administered to closely resemble the cognitive domains based on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)-recommended measures (K. H. Nuechterlein et al., 2008). Please refer to Table 2.4 for detailed descriptions of the tests used for the respective cognitive domains included for further analysis within this dissertation.

Table 2.4: The seven cognitive domains assessed and a description of their respective tests.

Neurocognitive domain	Cognitive test	Description of tests
Social cognition	Diagnostic Analysis of Nonverbal Accuracy-2[1]	A test of social cognition measuring the ability to read nonverbal social information (# correct)
Speed of processing	Trail Making Test (TMT): Part A[2]	A test of visual scanning and visuomotor tracking (time to completion)
	Verbal Fluency: semantic[3]	A verbal index of speed of processing (# correct words)
	Wechsler Adult Intelligence Scale, 3rd ed., digit symbol coding task[4]	A measure of visuomotor speed (# correct)
Working memory	Wechsler Memory Scale, 3rd ed., digit span subtest[4]	A measure of nonverbal working memory (# correct forward and backwards)
Verbal learning	Rey Auditory Verbal Learning Test (RAVLT)[5]	A list of 15 words presented 5 times, which must be recalled from memory (sum correctly recalled)
Attention	Continuous Performance Task - Identical Pairs[6]	A measure of attention and vigilance using the signal detection index (d' = hits - false alarms)
Executive functioning	Trail Making Test (TMT): Part B[2]	A test measuring cognitive flexibility and set shifting ability
	Verbal Fluency: phonetic[3]	A verbal index of executive ability (# correct words)
Global cognition	Composite across all cognitive measures included above	A global measure of cognitive functioning (average z-score)

[1] Nowicki and Duke (1994); [2] Reitan (1992); [3] Strauss, Sherman, and Spreen (2006);
[4] Wechsler (1997); [5] Lezak (1995); Rey (1941);
[6] Cornblatt, Risch, Faris, Friedman, and Erlenmeyer-Kimling (1988);

For the domain of SC, we used the adult version of the Diagnostic Analysis of Nonverbal Accuracy-2 (DANVA-2), meant to gauge nonverbal emotion perception with varying intensities of affective expressions (Nowicki, 2000). For the domain of reasoning and

problem solving, or general executive functioning (EF), we used the Trail Making Test, Part B and phonetic verbal fluency tests, that have previously been used to reflect this specific domain (Koutsouleris et al., 2012). We chose the Rey Auditory Verbal Learning Test (RAVLT) for the domain of verbal learning, consisting of 5 immediate recall repetitions. WM was assessed using the auditory digit span (forward & backwards) (Koutsouleris et al., 2012). The tests used within the domains of speed of processing (SoP) and attention (Attn) overlapped with those used in the MATRICS battery. The raw scores from the tests listed in Table 2.4 at T0 were all converted z scores. FU test scores were converted to z-scores using individual subjects' T0 scores in order to gauge the change between the two time-points while accounting for T0 differences. Composite and domain scores were computed as the average z-score across all measures defining the composite global or cognitive domain score. The measures used to test cognitive ability were meant to assess processes distinct from the exercises trained in the intervention group. Additional post-hoc analyses were conducted using the remaining tests outlined in Table A.1.

Imaging Procedures

Both sMRI and rsfMRI were acquired from all participants on a 3 Tesla Philips Ingenia scanner with a 32 channel radio-frequency coil at the Radiology Department in the university clinic of the Ludwig-Maximilians-University, in Munich, Germany. For the rsfMRI scan, participants were instructed to lie still in the scanner with their eyes open and to allow their mind to wander without focusing on any particular thoughts.

sMRI Acquisition and Preprocessing

Structural images were obtained using a multi-echo MPRAGE sequence with the following parameters: repetition time (TR) = 9.5 ms, echo time (TE) = 5.5 ms, flip angle = 8°, field of view = 250 x 250 mm, matrix size = 256 x 256; 190 contiguous sagittal slices of 1.0 mm thickness and a 1.0 mm gap, voxel size = .97 mm x .97 mm x 1 mm, pixel band width = 650 Hz.

sMRI data were preprocessed using the Computational Anatomy Toolbox (CAT12) toolbox[2] version r1207. First, a denoising step based on Spatially Adaptive Non-Local Means filtering was done to increase the signal-to-noise ratio of the data (Manjón et al., 2008). Next, an Adaptive Maximum A Posteriori (AMAP) segmentation technique was applied—this step achieves homogeneous segmentation across cortical and subcortical structures through modeling of local variations of intensity distributions as slowly varying spatial functions (Rajapakse, Giedd, & Rapoport, 1997). Then a second denoising step incorporating a Markov Random Field approach was applied. This step uses spatial prior information of adjacent voxels for the segmentation estimation generated by AMAP (Rajapakse et al., 1997). Additionally, due to white matter inhomogeneity and varying gray matter intensities caused by the differing iron content in cortical and subcortical structures, images were adjusted using a Local Adaptive Segmentation step. Using a Partial Volume Segmentation algorithm was applied to the gray matter, white matter, and cerebrospinal fluid (CSF), generated by the AMAP technique. Finally, images were registered to a Montreal Neurological Institute (MNI) template[3] using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) algorithm (Ashburner, 2007).

rsMRI Acquisition and Preprocessing

Blood Oxygenation Level Dependent (BOLD) images of the whole brain using an echo planar imaging (EPI) sequence were acquired in 53 ascending slices (TR = 3000 ms, TE = 30 ms, flip angle = 90°, field of view = 230 x 230 mm, 3.0 mm thickness and 3.0 mm gap, matrix size = 80x80, voxel size = 2.875 mm x 2.875 mm x 3 mm) using the intercommissural line (AC-PC) as a reference. rsfMRI scans resulted in 603 s duration (200 volumes) and subjects were instructed to keep their eyes open during the scan, as this is suggested to facilitate network delineation compared to eyes-closed conditions and helps ensure that subjects remain awake.

rsfMRI preprocessing was divided into two main processes: core and denoising steps based on Patel et al. (2014). Refer to Figure 2.2 for an overview of the preprocessing steps used. Core preprocessing consisted of the following and were performed using Statistical

[2] http://www.neuro.uni-jena.de/cat12/

[3] This template was generated from data of 555 HC in the IXI database (http://www.braindevelopment.org).

Parametric Mapping, version 12 (SPM12) (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) version 6685. After initially discarding the first 8 volumes (magnetization equilibrium not reached), the remaining 192 images were slice-time corrected, and then unwarped and realigned to the first volume for head-motion correction. The time course of head motion was obtained by estimating the translations in each direction and the rotations in angular motion about each axis for each volume. Next, framewise displacement (FD), which indexes volume-to-volume changes in head position, was calculated for each subject based on the sum of the absolute values of the derivatives of the translational (X, Y, and Z) and rotational (roll, pitch, and yaw) realignment estimates obtained in the step before (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Rotational estimates were converted from degrees to millimeters by calculating displacement on the surface of a sphere of 50 mm radius. FD for the first volume of a run is by convention zero. Subjects with greater than 38.5 % of volumes with mean FD of > 0.50 mm were excluded from further analyses (Power et al., 2014).

Affine coregistration of images to structural images followed and were then resliced using 4th-degree B-Spline interpolation. The standard CAT12 template was converted from DARTEL space to MNI space using SPM12's population to International Consortium for Brain Mapping 152 registration procedure. The resulting image was used as a deformation field to normalize all coregistered images to MNI space. Next, gray matter, white matter, and CSF masks were created using an image calculator procedure within SPM12 using thresholds of 0.20, 0.20, and 0.50 respectively. Subsequently, Friston 24 motion parameters (Satterthwaite et al., 2013) including 6 motion parameters, 6 temporal derivatives, 6 quadratic terms and 6 quadratic expressions of the derivatives of motion estimates, were derived. Then mean individual signal estimates with variance regressed out from white matter and CSF were generated. Finally, functional volumes were masked using the gray matter mask to limit space and spatial smoothing using a Gaussian kernel of 6 mm full width at half-maximum was applied.

Denoising methods consisted of: motion correction using time series despiking (Wavelet Despike) with the BrainWavelet Toolbox (http://www.brainwavelet.org/) (Patel et al., 2014). The following steps were done using the Resting-State fMRI Data Analysis Toolkit (REST version 1.8; http://www.restfmri.net/) (Song et al., 2011). Confound signal regression of the Friston 24 motion parameters, and residuals of white matter

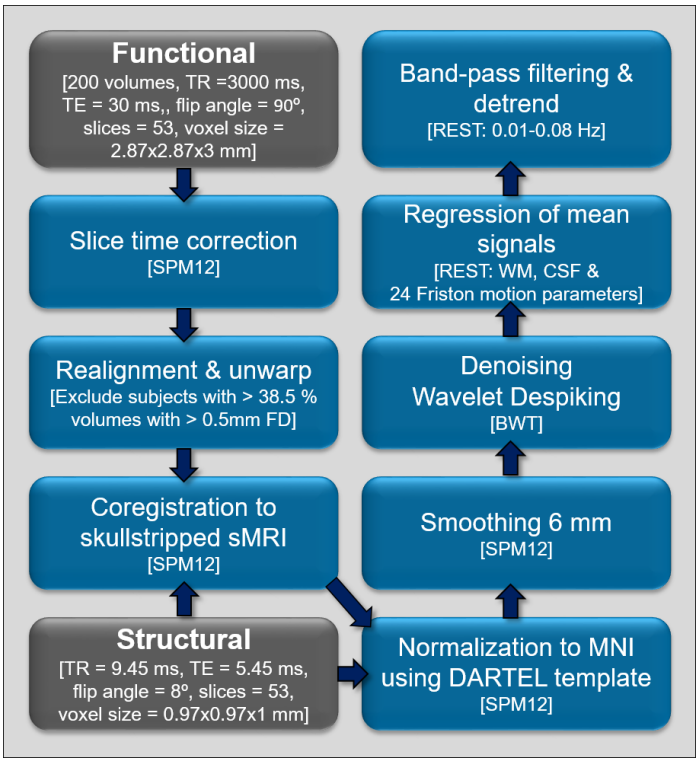

Figure 2.2: Preprocessing pipeline used for resting-state fMRI data. TR = repetition time; TE = echo time; FD = Framewise Displacement; SPM12 = Statistical Parametric Mapping; BWT = Brain Wavelet Toolbox; WM = white matter; CSF = cerebrospinal fluid; REST = Resting-State fMRI Data Analysis Toolkit.

and CSF was applied. Although there currently still is not a consensus regarding the inclusion or exclusion of global signal regression (Murphy & Fox, 2017), we excluded it in order to avoid the potential introduction of anti-correlations between brain regions that otherwise would not be exhibited (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009). Finally, the images underwent background filtering and temporal band-pass filtering (0.01 - 0.08 Hz) was performed to reduce the effects of low-frequency drift and high-frequency noise (Song et al., 2011).

2.2 Study 1 Specific Methods

2.2.1 Statistical Analyses

Power Analysis

A statistical power analysis was performed for sample size estimation, based on data from a comparable published study utilizing SCT from Fisher et al. (2017). The effect size in this study (d = 0.74), was considered to be medium-to-large using Cohen's criteria (Cohen, 2013). With an α= 0.05 and power = 0.80, the projected sample size needed with this effect size (G * Power Version 3.1[4]) is N = 24 per condition for the simplest between group comparison. Thus, our proposed sample size of 27 participants per condition was adequate for the main objective of this study. We expected to recruit approximately 2-3 patients with ROP per month. Based on an expected attrition rate of 10 % within the study, the required sample size of 24 per condition was deemed feasible.

Study Analyses

All variables were screened and normally distributed after winsorizing of outlying values (greater than three standard deviations from the mean). Independent-samples t-tests were used for testing group T0 differences in demographic variables, hours of training, medication, and days between assessments. Fisher's chi-square test tested for group differences in categorical variables (i.e., gender, diagnosis, handedness, and attrition). To determine whether training site had a differential effect on treatment response on the SCT condition, an independent-samples t-test was conducted with baseline demographics, and the change in cognition, symptoms and functioning measures based on site of training (clinic or home).

Behavioral and neuropsychological test performance was calculated using main effects, and a repeated-measures Analysis of Variance (ANOVA) with time (T0 and FU) as the repeated measure and condition (SCT versus TAU) as a between-subjects factor in SPSS version 22. Patients were compared on the changes in the PANSS symptom ratings

[4]http://www.gpower.hhu.de/

(total, positive, negative, and general), functioning (GAF Disability and Impairment rating for the past month, and current social and role functioning using the GF-S and GF-R scales) and cognitive measures (Table 2.4). Significance levels were defined at p = 0.05 with False Discovery Rate (FDR) correction for multiple comparisons (Benjamini & Hochberg, 1995). Pearson's bivariate correlations (two-tailed tests of significance) were conducted to determine the associations between changes in cognition (FU-T0) and differences between T0 and FU in 1) symptoms (PANSS) and 2) functioning (GF-R, GF-S, and GAF). Correlations were conducted between 1) cognitive measures and 2) the GF-R and GF-S current score, GAF Disability and Impairment score within the past month, and 3) PANSS total item score only (i.e., not PANSS sub-scale measures).

2.3 Study 2 Specific Methods

2.3.1 Procedures

Generation of Seed-based rsFC Maps

Following the steps described in Section 2.1.4, a seed-based rsFC analysis was performed to examine the effects of SCT on rsFC with the mPFC and amygdala. Coordinates of interest were taken from previous rsfMRI studies (Fox et al., 2005; Wu et al., 2008). Where coordinates were presented in Talaraich space, they were converted to MNI space using GingerALE 2.3[5] ('Talairach to MNI' transform) (Eickhoff et al., 2009). BOLD time series were first extracted from a 10-millimeter (mm)-radius sphere centered at the coordinates (-1, 47, -4) for the mPFC. Similarly, BOLD time series were also extracted for the amygdala, using a 6-mm-radius sphere centered at (-20, -5, -9). Using the Resting-State fMRI Data Analysis Toolkit (REST version 1.8), a correlation map was produced by computing the Pearson correlation coefficients between the average time course that was extracted for each seed (mPFC and amygdala) and each voxel in the whole brain for every subject (see Figure 2.3). Correlation coefficients were then converted to z-values using Fisher's r-to-z transform to improve normality and allow for parametric testing. The individual z-score maps were obtained for each subject and each seed.

[5] http://brainmap.org/ale/

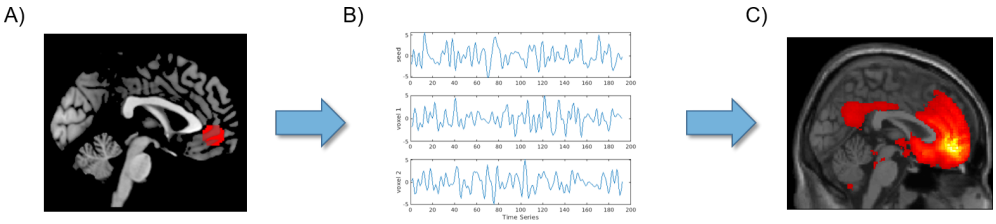

Figure 2.3: Depiction of the generation of seed-based functional connectivity maps in rsfMRI studies. A) Select a brain region of interest (ROI) as the seed. B) Time courses are extracted from the seed and all other brain voxels. An example of two brain voxels and the seed are depicted here. C) After preprocessing a functional connectivity brain map showing standardized z-transformed temporal correlations between the given seed and all other brain voxels is produced. Adapted from (Q. Yu et al., 2012).

2.3.2 Statistical Analyses

T0 demographic differences, as well as behavioral and clinical effects, were calculated using methods described in Section 2.2.1.

Individual z-maps were entered into a random effects one-sample t-test to determine the brain regions that showed significant positive or negative correlation with the seed region within each group. To assess longitudinal effects of SCT, we used a flexible factorial model in SPM12 (version 6685) to measure the interaction between condition (SCT versus TAU) and time (T0 versus FU), taking between-subject variation (e.g. age, medication, and gender) at each time point into account. T0 and FU seed-based functional connectivity maps were entered into the flexible factorial model. Each model also included the mean FD movement parameters and medication as a covariate of no interest. Thus, all condition by time models controlled for potential remaining effects of movement and medication at pre- and post-time points as well as the effects of movement and medication on pre-to-post change in rsFC.

The family-wise error correction (FWE) with a cutoff of $P < 0.05$ was used for the one-sample t-test, and a minimum cluster size of 30 voxels was used in order to obtain the connection maps across groups for each seed region. For the flexible factorial model, statistical significance was set at $p < 0.001$ (uncorrected) and clusters were considered statistically significant using two thresholds. The more stringent of the two was set at a $p < 0.05$ level, FDR at the cluster level, cluster size > 30 mm^3). In addition, we also included results using a less stringent cutoff of $p < 0.001$ (uncorrected, cluster size >

30 mm^3). This was additionally included in order to better understand the potential direction of effects in this small sample. Bar-plots display condition by time analysis results, i.e. average rsFC for each condition and each time point (adjusted for covariates, etc. in the model).

Last, we explored the relationship between rsFC changes and changes in clinical (symptoms and functioning) and behavioral measurements (GC and cognitive domains). First, z-transformed connectivity values were extracted from the global maxima of regions with significant training-related effects (condition by time interaction favoring the SCT group) using Marsbar version 0.44[6] (Brett, Anton, Valabregue, & Poline, 2002). The difference between the T0 and post-test was computed (FU - T0) for the changes. We performed Pearson's correlations between these values and changes in the previously described outcome measures of cognition, functioning, and symptoms from Section 2.2.1. Similarly, we used Pearson's correlations in order to assess associations between T0 measures of cognition, symptoms and functioning and changes in rsFC. We used FDR correction for multiple comparisons.

2.4 Study 3A Specific Methods

2.4.1 Participants

Independent Sample

38 patients with ROP and 56 HC individuals aged 15-40 years were recruited from the *Department of Psychiatry and Psychotherapy* of the Ludwig-Maximilians-University (LMU) in Munich, Germany to be included as an independent sample from the larger PRONIA cohort. As the participants in the main study (the intervention study sample) were recruited solely out of the Munich site, we only included participants in the independent sample from the Munich site. This would help to reduce potential site effects often encountered in multi-site studies (Dansereau et al., 2017). PRONIA[7] is a project funded by the European Union with the goal of developing reliable prognostic

[6] http://marsbar.sourceforge.net/
[7] http://www.pronia.eu/the-project/

tools in order to predict the individualized risk of patients for affective and non-affective psychoses. In pursuance of generating a prognostic system that generalizes well across varying mental health centers worldwide, a large population is necessary from multiple varying sites.

Detailed demographic information of the HC and ROP groups are reported in Table 2.5. Inclusion and exclusion criteria for ROP patients overlapped with those used for the study sample and are listed in Table 2.6. HC were additionally excluded if (1) they have or have had any past DSM-IV Axis-I disorder as measured with the SCID, (2) meet clinical high risk (CHR) criteria as described by Schultze-Lutter, Klosterkötter, and Ruhrmann (2014), (3) have consumed any psycho-pharmacological substances or illegal drugs more than five times per year per substance class, or within the past month, or (4) the presence of any affective or non-affective psychosis or major affective disorder such as major depressive disorder or bipolar disorder in first degree relatives. All procedures performed in this study were in accordance with the ethical standards of the Local Research Ethics Committee of the Ludwig-Maximilian-University and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

This independent sample does not include any patients included in the intervention sample. Moreover, we solely used rsfMRI data from participants in the independent sample for the purposes of generating a multivariate healthy-to-psychosis spectrum model that would be validated in the study sample using out-of-sample cross-validation (OOCV). For this reason, we do not further describe this sample, except for the purposes of describing their demographics. For a full list of assessments conducted within PRONIA, please refer to Table A.5 and Table A.6 in the Appendix.

OOCV Sample

The OOCV sample consists of the same participants in the study sample described in Section 2.1.1.

Table 2.5: Baseline demographic and clinical characteristics for ROP patients and HC individuals included for the generation of a healthy-to-psychosis model based on rsFC. MRI = Magnetic Resonance Imaging; NOS = not otherwise specified; MDD = Major Depressive Disorder; CPZ = chlorpromazine equivalent; GAF = Global Assessment of Functioning; GF = Global Functioning, PANSS = Positive and Negative Syndrome Scale.

	ROP (N= 38)	HC (N= 56)	T/ χ^2	P value
Number of female (%)	14 (36.84 %)	36 (64.29 %)	6.850	0.009
Age (SD)	30.20 (6.09)	30.60 (6.78)	2.801	0.728
Years education (SD)	13.80 (3.41)	15.40 (3.85)	2.015	0.047*
Premorbid IQ (SD)	100 (18.6)	110 (13.2)	2.801	0.006**
Handedness	-	-	0.629	0.730
Right (%)	29	47	-	-
Mixed (%)	2	5	-	-
Left (%)	3	3	-	-
Diagnosis				
No Axis I Diagnosis (%)	0	56	-	-
Schizophrenia (%)	21 (55.26 %)	-	-	-
Schizoaffective disorder (%)	1 (2.63 %)	-	-	-
Schizophreniform disorder (%)	4 (10.53 %)	-	-	-
Delusional disorder (%)	5 (13.16 %)	-	-	-
Psychotic disorder NOS (%)	5 (13.16 %)	-	-	-
Substance-induced psychotic disorder (%)	2 (5.26 %)	-	-	-
GAF global rating past month	41.5 (10.10)	83.7 (5.11)	26.392	<0.001***
GF current				
Role (SD)	5.06 (1.80)	8.29 (0.59)	12.431	<0.001***
Social (SD)	5.63 (1.31)	8.25 (0.69)	12.473	<0.001***
PANSS				
Total (SD)	68.3 (16.0)	-	-	-
Positive (SD)	18.3 (5.66)	-	-	-
Negative (SD)	15.3 (5.98)	-	-	-
General (SD)	34.6 (7.71)	-	-	-

Table 2.6: Inclusion & exclusion criteria for participation in the independent PRONIA sample.

GENERAL INCLUSION CRITERIA

ALL SUBJECTS

1. Age 15 to 40 years
2. Language skills sufficient for participation
3. Sufficient capacity to consent

PATIENT GROUP

1. Presence of Psychotic Syndrome:
    a) Any of the Scale of Prodromal Symptoms P1 - P5 scales rated 6 + symptoms occurring daily for more than one week
    b) Any of the Scale of Prodromal Symptoms P1-P5 Scales scored 6 or ever been + symptoms seriously disorganizing or dangerous
    c) Any of the Scale of Prodromal Symptoms P1-P5 Scales scored 6 or ever been + symptoms occur for at least one hour per day at an average frequency of four days per week over one month
2. Symptoms present within the past 3 months, but no longer than 24 months

GENERAL EXCLUSION CRITERIA

ALL SUBJECTS

1. IQ below 70
2. Hearing is not sufficient for neuro-cognitive testing
3. Current or past head trauma with loss of consciousness (> 5 minutes)
4. Current or past known neurological disorder of the brain
5. Current of past known somatic disorder potentially affecting the brain
6. Current or past alcohol dependency
7. Current polytoxicomania (poly-dependency) within the past six months
8. MRI not possible (medical reasons)

HEALTHY CONTROL GROUP

1. Current or past DSM-IV-TR Axis-I disorder
2. CHR criteria positive (life time)
3. Intake of psychopharmacological substances or illegal drugs:
    a) during the past month prior examination
    b) for more than 5 times per year per substance class
4. Affective or non-affective psychosis or major affective disorder (MDD, Bip. Dis.) of 1° relatives (defined by treatment or diagnosis)

RECENT ONSET PSYCHOSIS PATIENTS

1. Antipsychotic medication for >90 days (cumulative number of days) at or above minimum dosage of the '1st episode psychosis' range of Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde e.V. (DGPPN) S3 Guidelines

2.4.2 Procedures

Generation of rsFC Correlation Matrices

Following the rsfMRI preprocessing steps described in Section 2.1.4, the brain was parcellated into 160 ROIs according to the Dosenbach atlas (Dosenbach et al., 2010). We extracted the mean signal from 10 mm spheres centered at each of 160 ROIs using the MarsBaR Toolbox[8] version 0.42 (Brett et al., 2002). Next, the Pearson's correlation of average time series between pairwise ROIs was calculated within Matlab R2018a using in-house scripts—resulting in 12 720 rsFC for each participant. See Figure 2.4 for a summary of these steps. We derived the 12 720 features by first removing 160 diagonal elements, and then we extracted the upper triangle elements of the functional connectivity matrix as classification features (see Part B in Figure 2.4). The feature space for classification was thus derived by the $(160 \times 159)/2 = 12\,720$ dimensional features. Connectivity matrices were generated for each subject in both the study sample (Section 2.1.1) and independent sample (Section 2.4.1) described above.

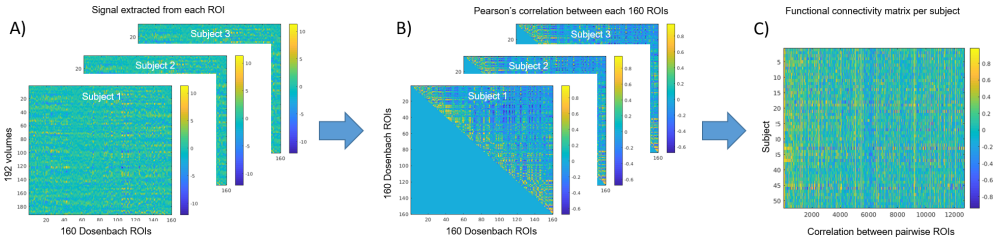

Figure 2.4: Steps describing the generation of functional connectivity maps entered as features in the multivariate model. A) First, signals are extracted from each region of interest (ROI) for every volume and every subject. B) Then, pairwise correlations are calculated between the average mean signal of each ROI resulting in 12 720 correlations (i.e., functional connectivity). C) Finally, the functional connectivity maps for each subject are transformed into one line and concatenated vertically with each line on the y-axis representing the 12 720 functional connectivities for each subject. ROI = region of interest.

Machine Learning Strategies

Within the third aim of this dissertation, we implemented a method of neural monitoring (e.g., neuromonitoring) in order to better understand which patients might

[8] http://marsbar.sourceforge.net/download.html

benefit from this particular 10-hour SCT. Moreover, we wanted to identify possible neuroimaging markers (e.g., neuromarkers) of individual response to SCT. To this end, we used a linear SVC algorithm to develop a healthy-to-recent-onset-psychosis (HC-ROP) rsFC classifier based on the independent sample described in Section 2.4.1. This model (depicted in Figure 2.5) was built to identify disorder-related brain rsFC signatures and depicts a spectrum of "HC-likeness" to "ROP-likeness" based on rsFC. The rsFC matrices generated in Section 2.4.2 from the independent sample were entered into a MVPA to predict group membership (HC or ROP). To measure changes in disorder-related brain signatures as a result of SCT, the HC-ROP classifier was applied using OOCV (i.e., externally validated) to the ROP patients within the study sample described in Section 2.1.1. This would allow us to determine whether patients who received SCT were more likely to shift across the SVM hyperplane according to their rsFC pattern in a particular direction. We expected patients in the SCT condition to show greater shifts in the "HC-like" direction as compared to the TAU control condition. The measured changes in decision scores will verify if the brain trajectory from "ROP-like" to "HC-like" has been altered in the SCT group as compared to TAU.

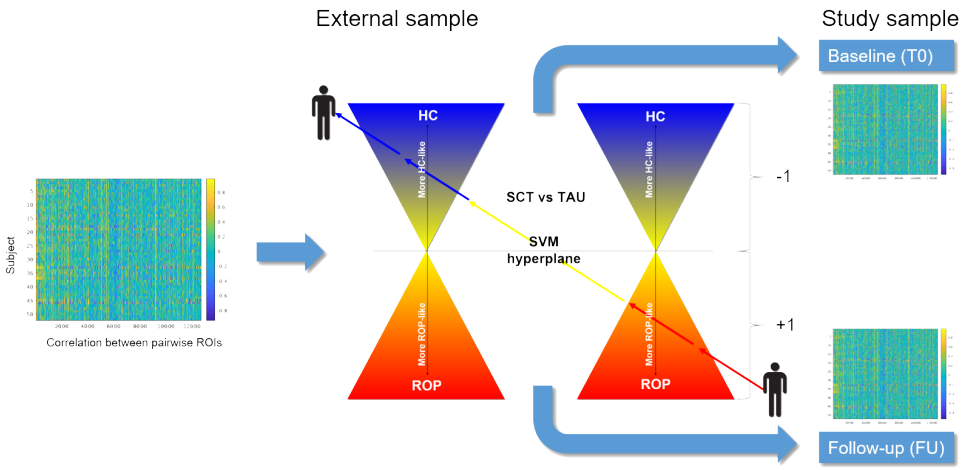

Figure 2.5: Proposed model depicting the application of a "HC-like" to "ROP-like" spectrum that could be used for monitoring treatment response to SCT. rsFC correlation matrices are entered into the classification model to distinguish HC from ROP in an external sample. Using OOCV, the model is validated on patients in the study sample (SCT and TAU) at two time-points. Changes in decision scores are compared at the two time-points in order to measure the direction of shift across the hyperplane based on rsFC.

Machine Learning Pipeline

The classification methodology used was built upon recent methods implemented by Borgwardt et al. (2013), Kambeitz-Ilankovic et al. (2015), and Koutsouleris, Kambeitz-Ilankovic, et al. (2018). The strategies used within this model are summarized in Table 2.7 and described in greater detail below.

Table 2.7: Details of the framework used within the multivariate pattern analyses (MVPA) conducted in this chapter are described here. CV = cross-validation; SVC = support vector classification; SVR = support vector regression; HC = healthy control; ROP = recent onset psychosis; GC = global cognition; GF-R = Global Functioning Scale: Role; T0 = baseline; FU = follow-up; rsFC = resting-state functional connectivity; LOO = leave-one-out.

MVPA	Algorithm	Kernel	Cases per group	Label	Features	CV1		CV2	
						k-folds	N perms.	k-folds	N perms.
SVC: HC-ROP Classifier	LIBSVM 3.1.2 L1-Loss SVC	Linear	HC = 56 / ROP = 38	Categorical: HC vs ROP	rsFC	10	10	10	10
SVC: GF-R treatment response prediction	LIBSVM 3.1.2 L1-Loss SVC	Linear	Good = 9 / Poor = 17	Categorical: Good vs Poor	rsFC	10	5	LOO	

The machine learning platform NeuroMiner[9] version 1.0 (Koutsouleris, Kambeitz-Ilankovic, et al., 2018) was used to set up a machine learning analysis pipeline to extract multivariate decision rules from the rsFC data. We used a linear SVC algorithm (LIBSVM 3.1.2 L1-Loss SVC) to create a predictive model in an independent sample that could separate patients with ROP from HC based on rsFC. The pipeline implemented was built upon methods previously described by (Filzmoser, Liebmann, & Varmuza, 2009). These include implementing a repeated-nested double cross-validation (CV) framework. Such a framework strictly separates the training process from the evaluation of the predictor's generalization capacity into an inner (CV1) and outer (CV2) CV to avoid overfitting and prevent leakage of information (Varma & Simon, 2006).

Within the inner and outer CV, data is split into k a number of folds and each partition provides an estimate of the predictor's performance trained from cases (individual subjects) included in all but one "held-out" fold. In CV1, feature selection and parameter optimization are performed, while the generalization error is estimated from the CV2

[9] https://www.pronia.eu/neurominer/

test samples. This process is iterated based on *N*-permutations, with higher permutations providing robust and reliable results, but requiring greater computational power (Dwyer et al., 2018). Different CV schemes have previously been used, differing based on factors specific to the particular research question or due to sample size restrictions (Dwyer et al., 2018). In the HC-ROP model generated using the independent sample, we used a 10-by-10 CV structure for both CV1 and CV2 based on the modest sample size ($N = 94$). For further details on this methodology, please refer to a recent review from Dwyer et al. (2018)—published from colleagues in our lab.

Within the inner loop (CV1), matrices were first pruned of zero-variance features. We then adjusted for sex effects using partial correlations from the whole sample due to differences between the two groups. Then, a dimensionality reduction procedure was applied through Principal Component Analysis (PCA). Following previous studies, to minimize generalization error, a dimensionality reduction procedure was applied through Principal Component Analysis (PCA) in which the principal components with the highest eigenvalues that cumulatively explained 80 % of the variance were selected and the single subject rsFC matrices were projected into the reduced principal components space (Cabral et al., 2016; Hansen et al., 1999). Principal Components (PC) scores were then scaled between 0 to 1 and a linear SVC was used (Vapnik, 1999) to detect a set of PC that optimally predicted the training and test cases' labels within the CV1 partition. The regularization parameter (*C* parameter) was additionally optimized using 2^x, where x ranged from -6 to 4 in steps of 2 (i.e., from 0.0156 to 16). The analysis chain was then applied to the outer CV cycle (CV2). SVM decision models for brain functional connectivity features were obtained for each *k*-fold and *N*-permutation. Majority voting was used within every individual classifier to determine the subject's classification.

Statistical significance of individual and ensemble classifiers was assessed through permutation testing with $\alpha = 0.05$ and 1000 permutations (Golland & Fischl, 2003; Koutsouleris et al., 2016). For the SVC models, the performance was measured using Sensitivity, Specificity, Balanced Accuracy (BAC), Positive Predictive Value (PPV), Negative Predictive Value (NPV), based on the class membership probability scores generated through majority voting in the outer CV cycle (see Table 2.8 for descriptions of these metrics). To better understand which variables might inform the various predictions at the single-subject level, as well as the direction of the most informative

functional connections (i.e., increased or decreased connectivity strength), we additionally extracted the mean feature weight of each feature within the repeated-nested CV scheme of individual classifiers.

Validation of the HC-ROP rsFC Classifier

Following the steps described above, we subsequently validated the HC-ROP model in the study sample (in SCT and TAU) at the two time-points (T0 and FU) using OOCV. In order to do this, all SVM decision models obtained from our HC-ROP analysis were applied without any in-between retraining steps to the study sample: once for T0 and once for FU. This would provide us with subject-specific linear SVM decision scores at each time-point for every patient.

Table 2.8: Performance metrics used to interpret results and optimize predictions for both classification and regression models. This table was adapted from Dwyer et al. (2018).

Measure	Description
Sensitivity	The proportion of affected cases with a positive test result (true positive) in reference to all affected cases
Specificity	The proportion of nonaffected cases with a negative test result (true negative) in reference to all non-affected cases
Balanced accuracy	The accuracy in terms of true positive and negative cases balanced by the sample size of each positive and negative group; used to optimize models with unbalanced sample sizes
False positive rate	The proportion of all the people who are non-affected who will be identified as affected.
Positive predictive value	The probability that cases with a positive test result are actually positive
Negative predictive value	The probability that cases with a negative test result are actually negative
Diagnostic odds ratio	A ratio of the probability that the test is positive in subjects who are positive for the condition relative to that for negative results
Area under a curve	Area representing the discriminative power of a test between 0.5 (no discrimination) and 1 (perfect discrimination)

2.4.3 Statistical Analyses

Independent Sample

Differences in demographic characteristics between ROP and HC were examined using independent-samples t-tests in SPSS 22.

Validation Sample

T0 demographic differences, as well as behavioral and clinical effects, were calculated using methods described in Section 2.2.1.

Associations of Changes in Decision Scores with Cognition, Symptoms, and Functioning

We extracted the decision scores from the model and used a repeated-measures ANOVA in order assess condition (SCT versus TAU) by time (T0 versus FU) interactions in shifts. This was measured by extracting the difference in decision scores (FU-T0) of patients, which represents the degree to which patients are predicted to be either HC (negative decision scores) or as having a ROP (positive decision scores). Patients with measured differences in decision scores that were negative represent patients who shifted in the "HC-like" direction. Patients with measured differences in decision scores that were positive represent patients who shifted in the "ROP-like" direction. The shifts observed from T0 to FU based on the independent validation of the models in the study sample were correlated with the changes in behavioral measures (cognition, functioning, and symptoms) observed in each condition (SCT and TAU) separately.

This would enable us to determine whether individuals with rsFC changes in the "HC-like" direction relate to clinical and behavioral improvements specific to the intervention. Pearson's bivariate correlations (two-tailed tests of significance) was used to calculate the association between changes in decision scores and changes in symptoms PANSS, cognition (GC and cognitive domains) and functional outcome (GF-R, GF-S, and GAF). Additionally, we were interested in understanding why a subset of patients in the SCT group shifted in a particular direction. Using these differences, we conducted a repeated-measures ANOVA using the direction of shift ("HC-like" or "ROP-like") as

the between-subjects factor and time (T0 and FU) as the within-subjects factor. Tests were done in cognition, symptoms, and functioning.

2.5 Study 3B Specific Methods

2.5.1 Procedures

Generation of rsFC Correlation Matrices

The rsFC correlation matrices were created using the same methods described in Section 2.4.2 under the heading *rsFC correlation matrix*.

Machine Learning Strategies

In the second investigation within Study 3, we generated a multivariate model in order to investigate the association between T0 neurobiological characteristics (rsFC) and treatment response in individuals who received SCT. Here, treatment response was measured based on role functioning—which showed improvement specific to the SCT condition in Study 1. Namely, we investigated the degree to which T0 rsFC could be used to separate good versus poor role functioning (based on the Global Function Scale: Role) at FU. Patients with good role functioning were defined as having a score of 7 or above at FU (7 = mild impairment to 10 = superior functioning); poor role functioning included patients with scores below 7 at FU (ranging from: 1 = not working for extended period and not doing anything role related to 6 = moderate impairment) based on previous studies (Cornblatt et al., 2012). If successful, this analysis would provide us with potential neuromarkers predictive of response to SCT.

Machine Learning Pipeline

The machine learning pipeline used for this model largely overlaps with the one described in Study 2 Section 2.4.2. The strategies used within this model are also summarized in Table 2.7 and described in greater detail below.

We used a linear SVC algorithm (LIBSVM 3.1.2 L1-Loss SVC) within NeuroMiner version 1.0 to create a predictive model in patients who underwent SCT that could separate patients with good versus poor role functioning based on T0 rsFC. The machine learning pipeline in this study is the same as in Section 2.4.2, with the exception of the CV scheme. Different CV schemes have previously been used based on the specific research question or sample size restraints (Dwyer et al., 2018). For the SVC analysis conducted in SCT to predict treatment response using T0 rsFC, we used a leave-one-out cross-validation (LOOCV) for CV2 and a repeated 10-by-5-fold structure for CV1 based on the reduced sample size (N = 26). In LOOCV, each subject is iteratively held out once from entering CV1 optimization and used as a test of generalization. This allowed us to maximize the data available to the machine learning process (the number of patients that received the intervention within study sample was less than those included in the independent sample) while also generating robust parameter estimates and avoid overfitting. A similar CV scheme has been used in creating an outcome prediction model (Kambeitz-Ilankovic et al., 2015).

Within the inner loop (CV1), matrices were first pruned of zero-variance features. Then, a dimensionality reduction procedure was applied through PCA. PCA models were trained with a limited number of PC in the CV1 training data (15, 20, and 25 PC). PC scores were then scaled from 0 to 1, and a linear SVC was used (Vapnik, 1999) to detect a set of PC that optimally predicted the training and test cases' labels within the CV1 partition. The regularization parameter (C parameter) was optimized using 2^x, where x ranged from -6 to 4 in steps of 2 (i.e., from 0.0156 to 16). The analysis chain was then applied to the outer CV cycle (CV2). SVM decision models for brain rsFC features were obtained for each k-fold and N-permutation. Majority voting was used within every individual classifier to determine the held-out subject's classification.

Additional tests were conducted in order to test model significance, generalizability, and therapeutic specificity. First, we determined whether the observed prediction performances of the role functioning predictor significantly differed from a null distribution of the respective outcome labels by training and cross-validating SVM model on N = 1000 random label permutations (Golland & Fischl, 2003). Model significance was defined at α = 0.05 (Koutsouleris et al., 2016; Koutsouleris, Wobrock, et al., 2018). For the SVC models, the performance was measured using Sensitivity, Specificity, BAC, Positive Predictive Value (PPV), Negative Predictive Value (NPV), based on the class

membership probability scores generated through majority voting in the outer CV cycle (see Table 2.8 for descriptions of these metrics).

Second, we tested the treatment and outcome specificity of the role functioning predictor created in patients that received SCT by measuring its prediction performance when OOCV in patients in the TAU control condition as described in Section 2.4.2 under the heading "Validation of the HC-ROP rsFC Classifier". Following the steps described above, we aimed to build a classification model that could separate good from poor outcome defined by role functioning based on T0 rsFC. This model would provide us with individualized estimates (decision scores) of treatment response (positive values for good and negative values for poor functioning) based on neurobiological information when patients are first admitted in the clinic. The decision scores were extracted for further statistical analyses described below.

2.5.2 Statistical Analyses

Associations of Decision Scores with Cognition, Symptoms, and Social Functioning

To investigate the relationship between the performance of the predictive model generated above and behavioral or clinical phenotypes, we performed Pearson's r correlation analysis between subject-specific linear SVM decision scores and changes in 1) cognition, 2) symptoms, and 3) functioning. For functioning, we only used social functioning as the model was built on separating good versus poor role functioning at FU.

3 Results

3.1 Study 1 Results: Effects of SCT on Cognition, Symptoms, and Functioning

3.1.1 Baseline Demographic, Clinical, and Cognitive Information

At T0, there were no significant differences between the TAU and SCT groups in demographic characteristics, cognitive measures, symptom severity, functioning, number of days between assessments, or antipsychotic medication (see Table 2.2). Three out of 30 (10 %) SCT subjects compared with 1 of 28 (3.6 %) TAU subjects withdrew from the study prior to completion, however the difference was not significant (X^2 = 0.93, P = 0.33, N = 58, df = 1). Of the remaining 54 subjects, two further participants were excluded from further analyses due to outliers of greater than three standard deviations in higher than two neuropsychological tests. There were no significant demographic differences based on training site among patients who received SCT, except in the number of days between T0 and FU (Table A.7). Participants who completed SCT from home were assessed significantly fewer days after T0 than those that trained in the clinic: those training at home were assessed on average after 43.91 days (8.57) versus 53.60 days (11.62) for those training in the clinic (T = -2.33, P = 0.028). This difference does not survive FDR correction for multiple comparisons (corrected P-values = 0.304).

3.1.2 Cognition

There was a main effect of time across groups in the domains of GC (F = 11.43, P = 0.001), SoP (F = 15.16, P < 0.001), WM (F = 9.32, P = 0.004), verbal learning (VL) (F = 7.19, P = 0.01), and EF (F = 12.48, P < 0.001). Across both groups, patients showed a general improvement in all of these domains except for VL (see Table 3.1). Patients in both groups performed worse in VL at FU when compared to T0 (Figure 3.1). Besides the domain of Attn (F = 4.26, P = 0.044), there were no significant condition by time interaction effects (see Table 3.1 and Figure 3.1). Patients who were in the active intervention condition seemed to worsen in their performance, whereas those who received TAU improved (Figure 3.1). The results remained the same with and without covarying for age. The effect of training site (clinic or home) on GC was nonsignificant (F = 1.87, df = 1, N = 26, P = 0.18). With respect to the cognitive domains, there was a significant difference only in the domain of processing speed (T = -2.07, P = 0.050), with those training in the clinic showing greater gains in SoP (mean gain = 1.71, SD = 2.39) than those training at home (mean gain = 0.14, SD = 0.91). This difference does not, however, survive FDR correction for multiple comparisons (P-values = 0.317). See Table A.7 in the Appendix for further information.

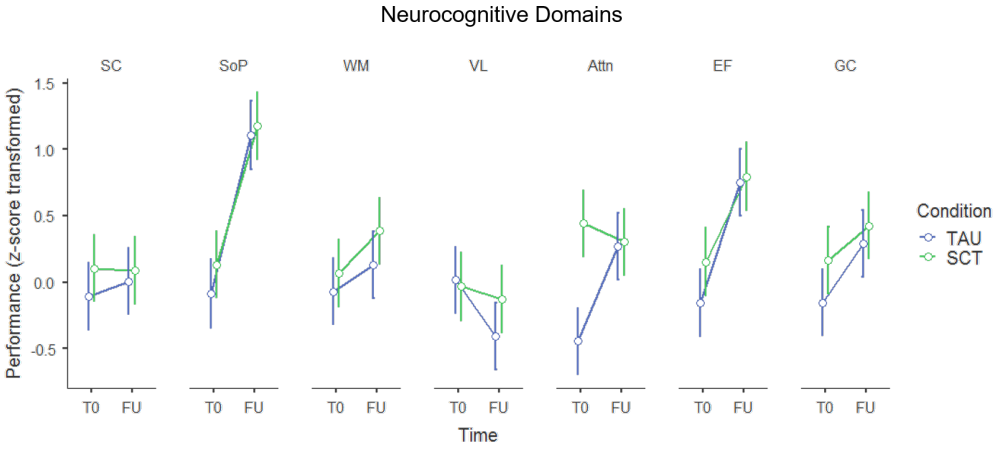

Figure 3.1: Pattern of performance over time and across domains for each condition (mean Z-scores). The bars represent the standard errors. SC = social cognition; SoP = speed of processing; WM = working memory; VL = verbal learning; Attn = attention; EF = executive functioning; GC = global cognition, T0 = baseline; FU = follow-up; TAU = treatment as usual; SCT = social cognitive training.

Table 3.1: Scores on cognitive measures, symptom ratings, and functional outcomes at baseline and follow-up of participants who received SCT or TAU. SCT = social cognitive training; TAU = treatment as usual; T0 = baseline; FU = follow-up; GAF = Global Assessment of Functioning; PANSS = Positive and Negative Syndrome Scale.

	SCT (N = 26)		TAU (N = 26)		Main Effect	Interaction	Effect Size
	To (SD)	FU (SD)	To (SD)	FU (SD)	of Time F (P)	(Condition x Time) F (P)	SCT (Cohen's d)
Cognition							
Global cognition	0.17 (1.06)	0.42 (0.63)	-0.15 (1.16)	0.23 (0.65)	11.430 (0.001)***	0.519 (0.475)	0.37
Social cognition	0.11 (0.68)	0.09 (1.04)	-0.11 (1.25)	0.01 (0.96)	0.102 (0.75)	0.182 (0.671)	-0.02
Speed of processing	0.13 (2.49)	1.18 (0.63)	-0.09 (2.44)	1.07 (0.59)	15.158 (<0.001)***	0.068 (0.796)	0.51
Working memory	0.07 (0.86)	0.39 (0.76)	-0.07 (1.14)	0.13 (0.83)	9.318 (0.004)**	0.485 (-0.49)	0.49
Verbal Learning	0.02 (1.03)	-0.13 (1.08)	-0.02 (0.99)	-0.41 (0.75)	7.19 (0.01)*	2.91 (-0.094)	-0.14
Attention	0.44 (1.34)	0.30 (1.70)	-0.44 (1.87)	0.27 (1.72)	1.93 (-0.171)	4.26 (0.044)*[1]	-0.11
Executive functioning	0.16 (1.58)	0.83 (0.49)	-0.15 (1.98)	0.75 (0.49)	12.48 (<0.001)***	0.369 (-0.546)	0.45
Functional Outcome							
GAF global rating past month	47.69 (14.79)	57.46 (12.62)	40.15 (11.92)	52.27 (14.86)	28.27 (<0.001)***	0.325 (0.571)	0.57
Global Functioning - Role	4.42 (1.47)	5.54 (1.48)	4.65 (1.67)	4.73 (1.73)	13.23 (<0.001)***	8.74 (0.005)**	0.77
Global Functioning - Social	6.00 (1.13)	6.58 (1.14)	5.62 (1.60)	6.12 (1.58)	13.74 (<0.001)***	0.70 (0.792)	0.54
Symptoms							
PANSS total	67.81 (16.49)	44.08 (14.73)	68.73 (17.93)	51.46 (17.53)	47.91 (<0.001)***	1.19 (0.281)	1.11
PANSS positive	19.50 (5.89)	10.38 (3.67)	20.96 (4.27)	12.27 (4.51)	87.33 (<0.001)***	0.05 (0.825)	1.39
PANSS negative	14.54 (5.72)	10.77 (4.56)	14.88 (6.66)	13.42 (6.43)	8.01 (0.007)**	1.56 (0.217)	0.60
PANSS general psychopathology	33.77 (8.93)	22.92 (7.86)	32.88 (11.35)	25.77 (9.37)	31.96 (<0.001)***	1.38 (0.246)	0.95

[1] No longer significant after correcting for multiple comparisons using FDR correction.

Additionally, we investigated the condition by time interactions in performance on individual cognitive tests that were not included within the cognitive domains (Table A.1). Here, we found a significant interaction in the number of errors made with 6 items in the Self-Ordered Pointing Task (SOPT) ($F = 5.64$, $P = 0.021$). Patients who were in the active intervention condition made fewer errors at FU than at T0, whereas those who received TAU made a greater number of errors at FU (refer to Figure 3.2). There was a trend towards a significant interaction in the number of correctly recalled words for the interference list in RAVLT ($F = 3.74$, $P = 0.059$).

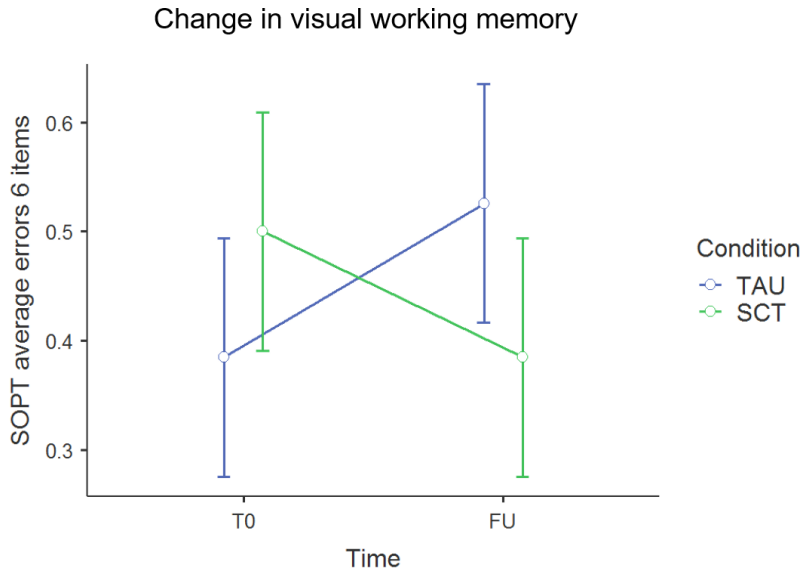

Figure 3.2: Pattern of visual working memory based on the number of errors made in the Spatial Ordered Pointing Task (SOPT) over time. The bars represent the standard errors. TAU = treatment as usual; SCT = social cognitive training.

3.1.3 Functioning

Across both conditions, there was a significant main effect of time in all domains of functioning: GAF ($F = 28.27$, $P < 0.001$), GF-S ($F = 13.74$, $P < 0.001$), and GF-R ($F = 13.23$, $P < 0.001$). Additionally, there was a significant condition by time interaction in role functioning ($F = 8.74$, $P = 0.005$), which can be seen in Figure 3.3. Patients who

underwent the intervention showed greater improvements in GF-R than those that were in the TAU condition (Table 3.1). When looking within the group that received the SCT, patients training from home showed significantly greater gains in GF-S (mean = 1.09, *SD* = 0.94) than those training in the clinic (mean = 0.20, *SD* = 1.01; *T* = 2.28, *P* = 0.032). This difference does not, however, survive FDR correction for multiple comparisons (*P*-values = 0.304). Detail can be found in Table A.7 in the Appendix.

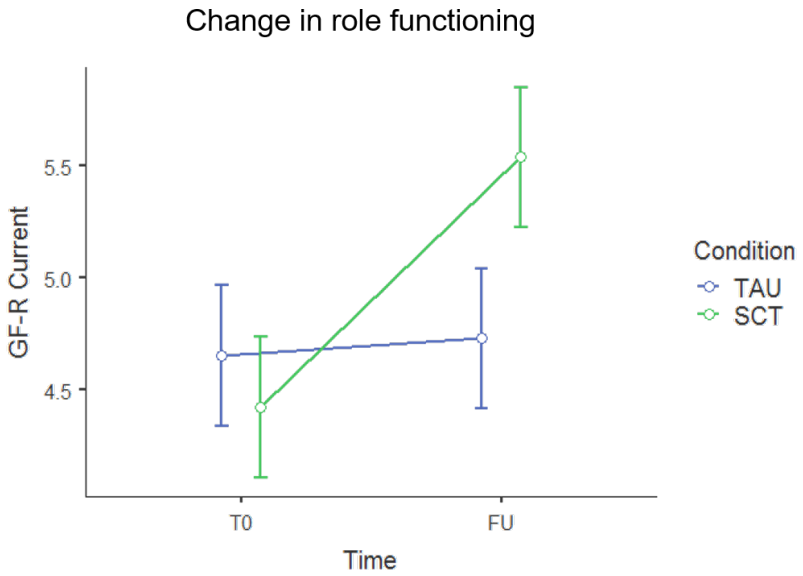

Figure 3.3: Pattern of role functioning (GF-R) in SCT and TAU over time. The bars represent the standard errors. GF-R = Global Functioning-Role; TAU = treatment as usual; SCT = social cognitive training.

3.1.4 Symptoms

Patients showed overall improvement (in this case decrease) across both conditions with respect to all symptom domains. Both groups showed a large decrease in PANSS Total symptoms (Mean Rating Change = −20.50, *SD* = 2.97, *F* = 47.91, df = 1, 50, *P* < 0.001), moderate decreases in PANSS Positive (Mean Rating Change = -8.90, *SD* = 0.94, *F* = 87.33, df = 1, 50, *P* < 0.001), and PANSS General Psychopathology symptoms (Mean Rating Change = -8.98, *SD* = 1.60, *F* = 31.96, df = 1, 50, *P* < 0.001), and a small decrease in PANSS Negative symptoms (Mean Rating Change = −2.62, *SD* = 0.93, *F*

= 8.01, df = 1, 50, *P* = 0.007). The improvements were, however, not specific to the intervention condition as there were no significant condition by time interactions on the PANSS total or subscales (Table 3.1).

3.1.5 Relationship Between Cognition, Functioning and Symptoms

There were no significant associations between changes in GC and changes in functioning or PANSS Total symptoms. There was a significant correlation between changes in VL and changes in both social (r = 0.448, P = 0.025) and role functioning (r = 0.452, P = 0.023) only in the SCT group (see Figure 3.4 and Figure 3.5). Greater improvement in verbal learning relates to greater improvement in social and role functioning. These associations were not significant in the TAU group (changes in verbal learning and social functioning: r = -0.089, P = 0.665; changes in verbal learning and role functioning: r = 0.171, P = 0.404).

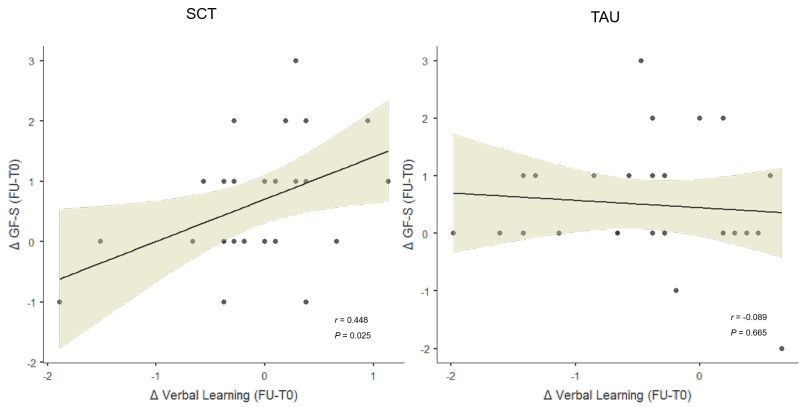

Figure 3.4: The association between changes in verbal learning and changes in social functioning in the SCT and TAU conditions. GF-S = Global Functioning-Social; TAU = treatment as usual; SCT = social cognitive training.

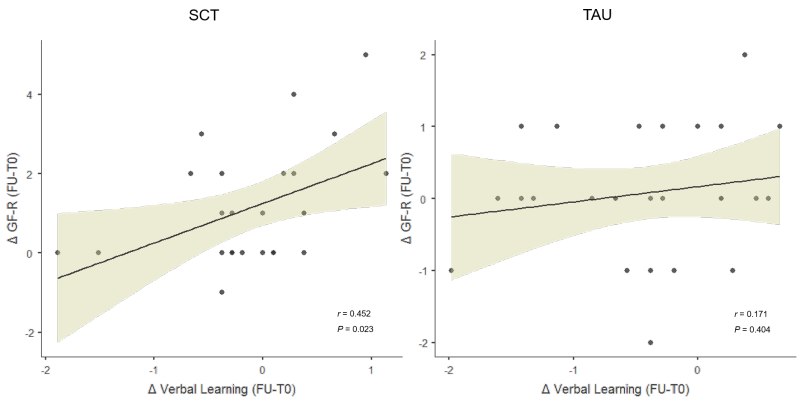

Figure 3.5: The association between changes in verbal learning and changes in role functioning in the SCT and TAU conditions. GF-R = Global Functioning-Role; TAU = treatment as usual; SCT = social cognitive training.

3.2 Study 2 Results: Effects of SCT on rsFC

3.2.1 Effects of SCT on Cognition, Symptoms, and Functioning

T0 differences, along with the effects of the training on SCT versus TAU in cognition, functioning, and symptoms are reported in Section 3.1.

3.2.2 Functional Connectivity Changes

Two networks were constituted by seed-based rsFC analysis, seeding at the mPFC for the DMN and at the right amygdala for the SC network. The one-sample t-test revealed rsFC of the mPFC seed with the PCC/precuneus, ventromedial prefrontal cortex, dorsomedial prefrontal cortex, right inferior parietal lobe, right temporal lobe, bilateral parahippocampus, and cerebellar crus II (Supplementary Figure A.2 part A). The amygdala mainly included rsFC with the right superior temporal sulcus, bilateral middle temporal regions, left superior temporal pole, left caudate, and left cerebellum crus II (Supplementary A.2 part B).

Second-level analyses revealed a number of significant differences between T0 and FU between patients that underwent SCT and TAU controls in the DMN (see Table 3.2). Patients in the SCT condition, showed increases in connectivity between the mPFC and left temporal pole and bilateral middle temporal gyrus. There was one condition by time change in connectivity with the amygdala with increases in the SCT condition—it was, however, not significant ($P = 0.082$, FDR corrected) when using FDR correction (see Table 3.2). Additionally, there was one connection that showed greater increase in the TAU condition between the right precentral gyrus and the mPFC (Table 3.2). There were no significantly greater increases in connectivity in the amygdala in the TAU group as compared to the SCT condition.

Extraction of the z-transformed connectivity values from the global maxima for each seed revealed the condition by time interaction. The SCT group showed increases in connectivity between the mPFC and left temporal pole, whereas the TAU group showed decreases in connectivity between these two regions ($F = 15.39$, $P < 0.001$). This is depicted in part A of Figure 3.6. This was similar with the rsFC between the amygdala and right middle frontal gyrus (see part B of Figure 3.6). Patients who underwent the active intervention showed increases in connectivity, whereas those in the TAU control condition showed decreases between these two regions ($F = 13.60$, $P < 0.001$).

Table 3.2: Regions that show a significant condition (SCT vs. TAU) by time (T0 vs. FU) interaction. (A) Condition by time interactions in the expected direction (i.e. SCT vs TAU showed an increase in connectivity from T0 to FU training). (B) Condition by time interactions in the unexpected direction (i.e. SCT versus TAU showed a decrease in connectivity from T0 to FU). BA = Brodmann area; MNI = Montreal Neurological Institute; SCT = social cognitive training; TAU = treatment as usual; T0 = baseline; FU = follow-up; mPFC = medial prefrontal cortex; AMYG = amygdala; FDR = false discovery rate.

Seed	Brain region	BA	MNI coordinate			Score		Cluster size (mm^3)	FDR Corrected P-value	Uncorrected P-value
			X	*Y*	*Z*	*T*	*Z*			
(A) Condition x Time interaction in the expected direction: SCT vs. TAU showed an increase in connectivity from pre to post										
mPFC	Left temporal pole	38	-46	16	-24	4.47	4.25	150	0.000	0.000
	Left temporal pole	20	-39	9	-44	4.39	4.18	246	0.000	0.000
		20	-56	-3	-42	3.74	3.61			
		20	-38	18	-42	3.64	3.52			
	Left middle temporal gyrus	37	-51	-57	14	4.37	4.17	52	0.005	0.000
	Right middle temporal gyrus	21	-68	-24	-9	3.48	3.37	35	0.024	0.002
AMYG	Right middle frontal gyrus[1]	47	38	45	3	4.25	4.07	35	0.082	0.002
(B) Condition x Time interaction in the unexpected direction: SCT vs. TAU showed an decrease in connectivity from pre to post										
mPFC	Right precentral gyrus	4	14	-26	75	3.92	3.77	37	0.600	0.002
AMYG	No significant findings									

[1] Not significant at level of FDR correction.

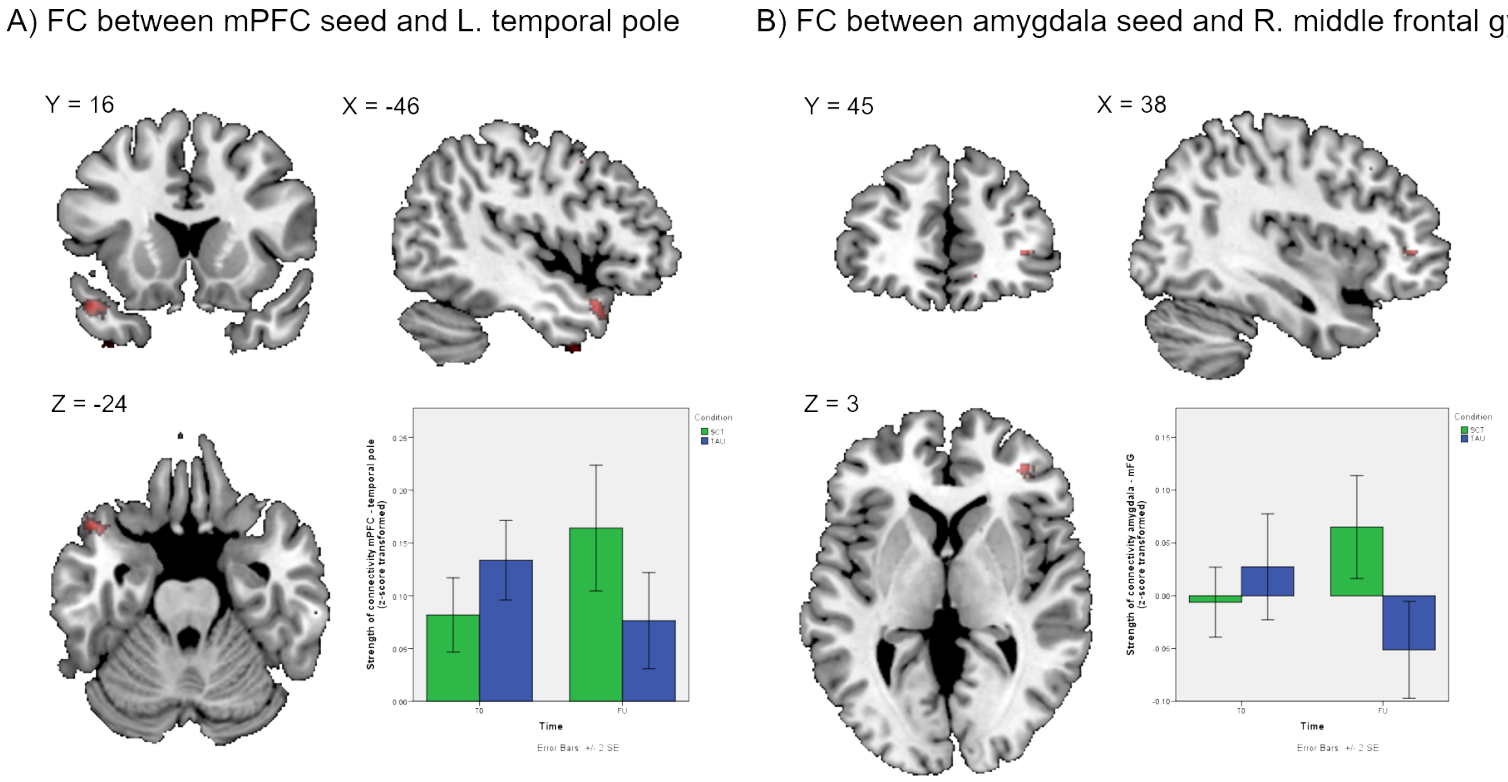

Figure 3.6: Depiction of the functional connectivity changes in the two seed regions and the global maxima. A) Functional connectivity (FC) between medial prefrontal cortex (mPFC) and the left temporal pole (Brodmann area 38). Bars represent the average connectivity between the seed region and the left temporal pole within each condition and time-point. Connectivity values for each subject were calculated as the correlation between the time course from the global maxima of the left temporal pole and the time course from the mPFC seed. B) Functional connectivity between the amygdala and the right middle frontal gyrus (Brodmann area 47). Bars represent the average connectivity between the amygdala seed and the right middle frontal gyrus within each group and time-point. Error bars represent standard errors. Connectivity values for each subject were calculated as the correlation between the time course from the global maxima of the right middle frontal gyrus and the time course from the amygdala seed. Error bars represent standard errors.

3.2.3 Relationship between Neural Alterations and Cognition, Functioning, and Symptoms

There was no significant relationship between changes in functional connectivity in favor of the SCT group, and changes in cognition, functioning, or symptoms. We also examined whether T0 cognition, symptoms or functioning showed an association with changes in rsFC in the SCT group. Figure 3.7 shows a significant negative correlation between T0 SC scores and changes in rsFC between the amygdala seed and the right middle frontal gyrus (R = -0.454, P = 0.020). This correlation does not survive FDR correction (corrected P = 0.14), and was not significant in the TAU group (R = -0.252, P = 0.215). There were no other significant relationships with any T0 measures and changes in rsFC.

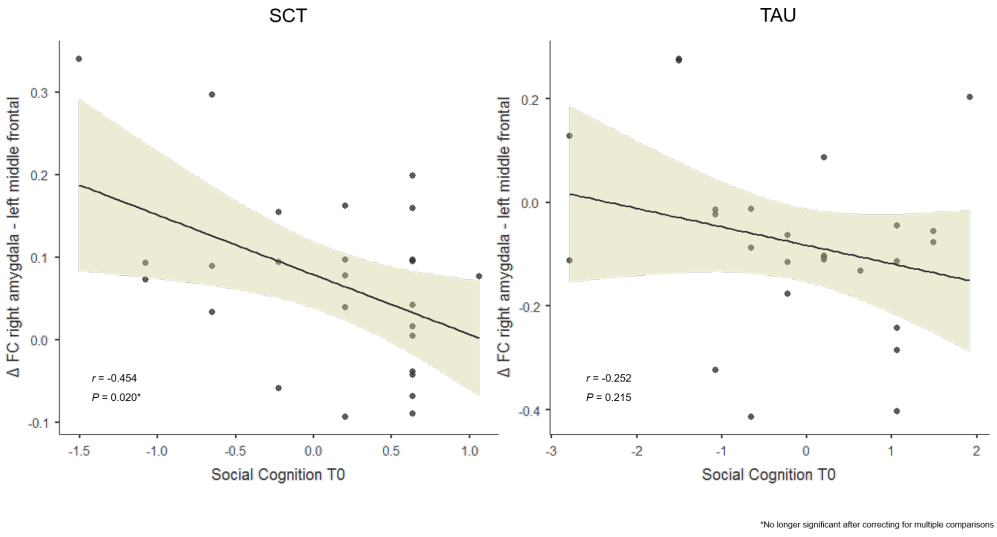

Figure 3.7: The association between baseline social cognition scores and changes in functional connectivity separately for the SCT and TAU conditions. SCT = social cognitive training; TAU = treatment as usual, FC = functional connectivity; T0 = baseline.

3.3 Study 3A Results: rsFC for Monitoring Treatment Response

3.3.1 Independent Sample: Baseline Demographic, Clinical, and Cognitive Information

At T0, there was a significant difference between HC and ROP in the following demographic characteristics: sex ($\chi^2 = 6.85$, $P = 0.009$), years of education ($T = 2.01$, $P = 0.049$), premorbid IQ ($T = 2.80$, $P = 0.006$). There were significantly more females in the HC group (64.29 %) compared to the ROP group (36.84 %). Patients had significantly fewer years of education, and lower premorbid IQ than HC subjects (see Table 2.5). As expected, patients with ROP showed significantly lower levels of functioning in all measures at T0: GAF Disability and Impairment ($T = 26.39$, $P < 0.001$), GF-R ($T = 12.43$, $P < 0.001$), and GF-S ($T = 12.47$, $P < 0.001$). Symptom severity was not assessed in HC individuals. For a summary, refer to Table 2.5).

3.3.2 Study Sample: Baseline Demographic, Clinical, and Cognitive Information

T0 differences, along with the effects of the training on SCT versus TAU in cognition, functioning, and symptoms are reported in Section 3.1.

3.3.3 Performance of Multivariate Classification and OOCV Models

The HC-ROP classifier correctly discriminated patients with ROP from HC with a cross-validated BAC of 70.8 % and was significant at $P < 0.001$ (sensitivity = 71.3 %, specificity = 68.4 %). Detailed statistics of the classification model are reported in Table 3.3. Inspection of the mean feature weights generated within the CV framework revealed that the brain connections mainly driving the classification are comprised of

widespread connectivity networks in which connections between parietal, temporal, occipital, frontal, PCC/precuneus, cerebellum and the thalamus were involved (see Figure 3.9 part A). Figure 3.8 part B shows a visualization of the functional connectivities mapped onto the brain with the BrainNet Viewer Toolbox [1]) (Xia, Wang, & He, 2013).

The connectivity patterns were mainly characterized by a majority of functional connectivities that showed stronger correlations between ROIs for patients with ROP (more red connections in part B of Figure 3.9. In contrast, two fronto-parietal connections showed greater connectivity strength in HC subjects (more blue connections in part B of Figure 3.8). Applying the models generated within the external sample to the study sample revealed a sensitivity of 58.2 % at T0 and 60.0 % at FU. As there were no HC participants in the study sample, we only have a measure of sensitivity when validating the externally-generated HC-ROP model.

Table 3.3: Performance of the independent HC-ROP classification model based on rsFC and validation performance in the study sample at T0 and FU without any in-between re-training.

	TP	TN	FP	FN	Sens [%]	Spec [%]	BAC [%]	FPR [%]	PPV [%]	NPV [%]	DOR
Classification:											
HC versus ROP	26	41	15	12	71.3	68.4	70.8	26.8	63.4	77.4	6.5
Out-of-sample validation:											
T0	32	-	-	23	58.2	-	-	-	100	0	-
FU	33	-	-	22	60.0	-	-	-	100	0	-

3.3.4 Association of Changes in Decision Scores with Changes in Cognition, Functioning, and Symptoms

Patients in both SCT and TAU conditions shifted across the SVM hyperplane according to their rsFC pattern in the "HC-like" direction overall (i.e., a decrease in decision scores from T0 to FU): SCT mean at T0 = 0.17 (SD = 0.41), SCT mean at FU = 0.11 (SD = 0.32); TAU mean at T0 = 0.12 (SD = 0.36), TAU mean at FU = 0.07 (SD = 0.29). There was, however, no significant main-effect of time (F = 0.77, P = 0.38) nor condition by

[1] https://www.nitrc.org/projects/bnv/

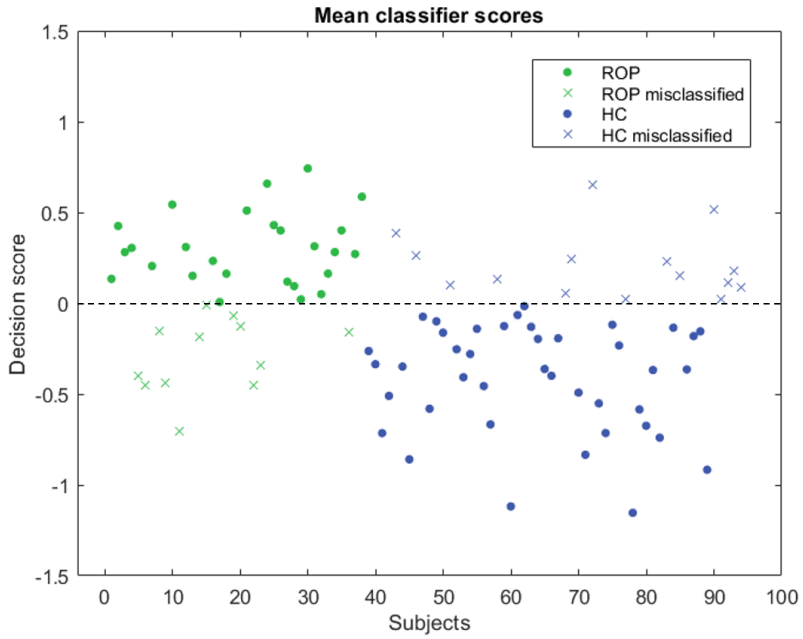

Figure 3.8: Model created using rsFC of 56 HC and 38 ROP from an independent sample. HC = healthy control; ROP = recent-onset psychosis.

time interaction between SCT and TAU (F = 0.01, P = 0.91) in decision score changes over time (see Figure 3.10). Additionally, there were no significant associations between changes in decision scores and changes in cognition, functioning, or symptoms across those who received the intervention.

Within the intervention group, there were significant interactions over time in two cognitive domains between patients who neurally shifted across the SVM hyperplane according to their rsFC pattern in the "HC-like" direction versus those who shifted in the "ROP-like" direction based on rsFC. Direction of shift by time interactions were seen in GC (F = 4.52, P = 0.044, Part A in Figure 3.11) and Attn (F = 7.86, P = 0.010, Part A in Figure 3.12). Patients that shifted in the "HC-like" direction based on rsFC changes following the intervention showed greater improvement in GC from T0 (mean = 0.03, SD = 1.34) to FU (mean = 0.51, SD = 0.70). There was no such significant difference in GC observed in patients that shifted in the "ROP-like" direction following the intervention (Part A, Figure 3.11). Similarly, patients who showed shifts across the SVM hyperplane in the "HC-like" direction, also showed greater improvement in Attn

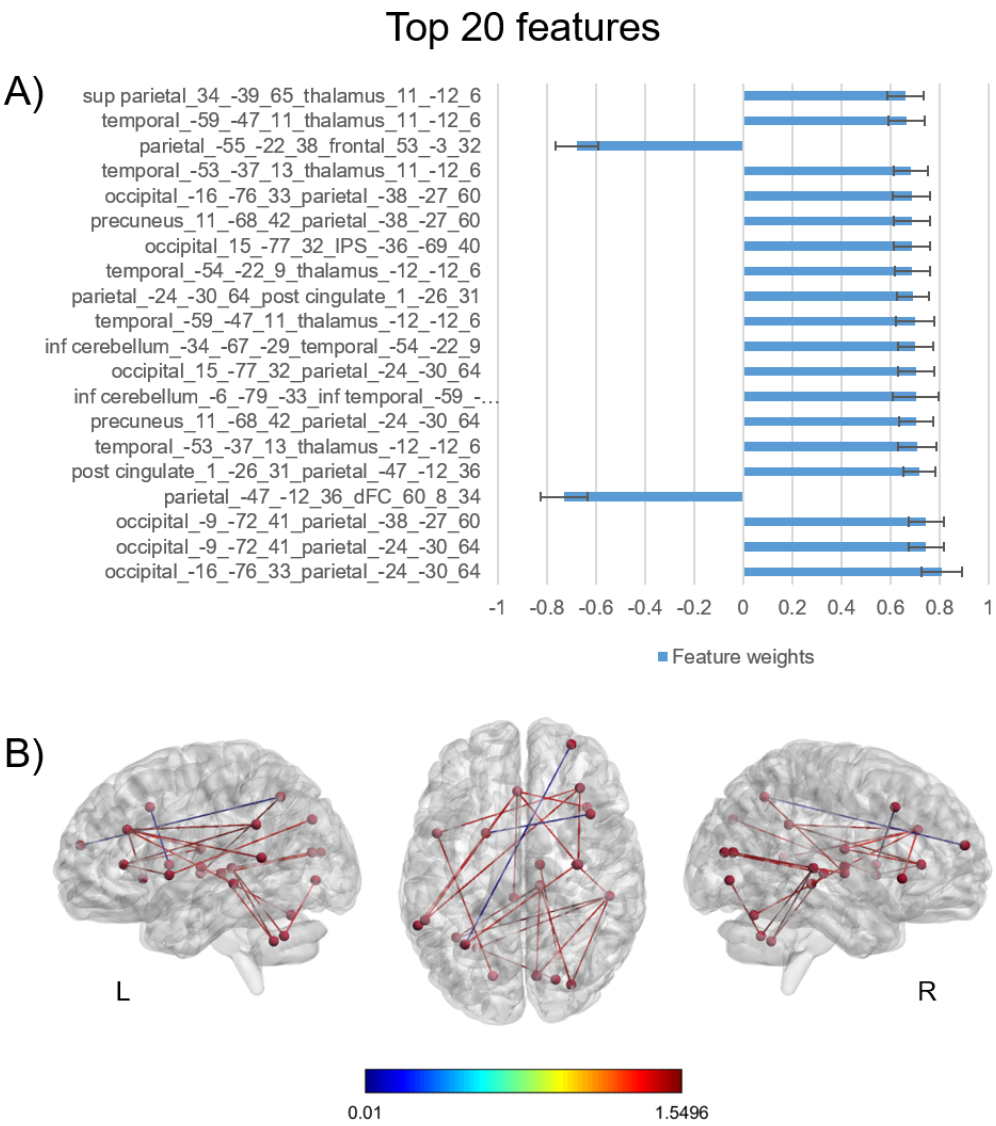

Figure 3.9: Depiction of the Dosenbach-based functional connections with the highest individual feature weight for the healthy (HC) vs. recent-onset psychosis (ROP) classification. A) Shows the top 20 features extracted using a percentile rank of approximately 99.99 %. B) Shows the inter- and intrahemispheric connectivities mapped onto the brain using BrainNet Viewer (Xia et al., 2013). Blue lines indicate higher connectivity in the HC group; red lines indicate greater connectivity in the ROP group.

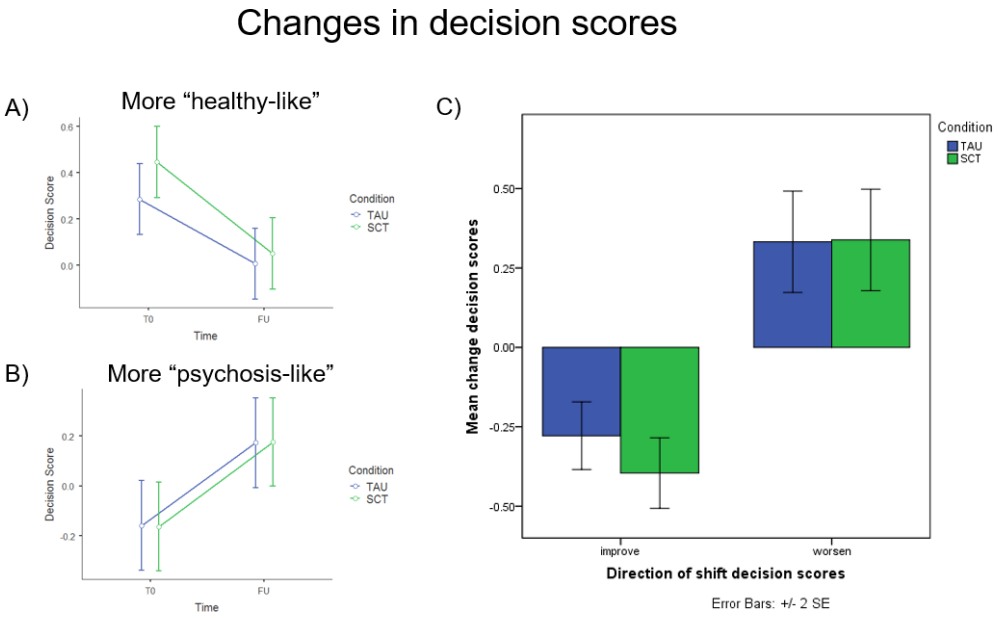

Figure 3.10: Changes in decision scores over time based on condition in A) patients who shifted across the SVM hyperplane based on rsFC in the "HC-like" direction, B) or the "ROP-like" direction, and C) the mean change per group and per direction.

from T0 (mean = 0.51, SD = 1.33) to FU (mean = 0.93, SD = 1.25). In contrast, patients who's decision scores increased showed worse performance in Attn from T0 (mean = 0.36, SD = 1.42) to FU (mean = -0.43, SD = 1.90, Part A Figure 3.12). There were no such significant group by time interactions in GC (F = 0.005, P = 0.95) or Attn (F = 0.41, P = 0.527) in patients in the TAU control condition (see Part B in Figure 3.11 and Figure 3.12).

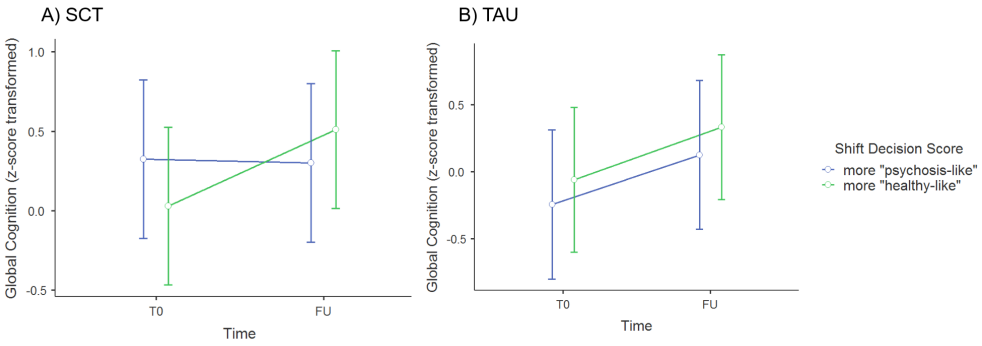

Figure 3.11: Differences in GC over time based on changes in decision scores according to their rsFC pattern in the more "HC-like" direction versus and the more "ROP-like" direction in A) patients who received SCT, and B) patients in the TAU control condition.

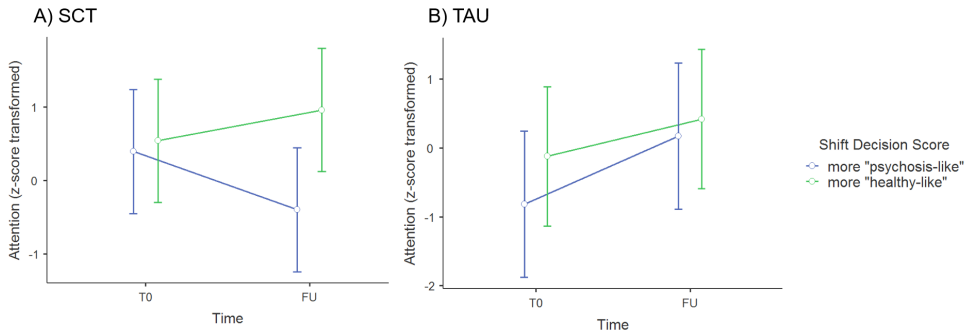

Figure 3.12: Differences in Attn over time based on changes in decision scores according to their rsFC pattern in the more "HC-like" direction versus and the more "ROP-like" direction in A) patients who received SCT, and B) patients in the TAU control condition.

3.4 Study 3B Results: rsFC for Predicting Treatment Response

3.4.1 Performance of Multivariate Classification and OOCV Models

The model predicting role functioning based on rsFC at T0 estimated outcomes in patients who received the SCT intervention with a significant BAC of 74.2 % (sensitivity: 77.8 %; specificity: 70.6 %; P = .009, see Table 3.4 and Figure 3.13). The brain connections mainly driving the classification in this model are comprised of connectivities between regions within frontal and temporal regions as well as long range connections between fronto-parietal and temporo-parietal regions (see Part A in Figure 3.14). Furthermore, these connectivities were characterized by greater strengths of connectivity patterns between some ROIs for patients with good outcomes (more red connections in Part B in Figure 3.14), and other regions for patients with poor outcomes (more blue connections in Part B in Figure 3.14). Finally, the role functioning prediction model validated on the TAU control sample produced a BAC of 58.0 % (sensitivity = 40.9 %, specificity = 75.0 %), which was nonsignificant ($P > 0.05$).

Table 3.4: Validated classification performance of the good versus poor role functioning classifier based on patients in SCT condition and the classification performance of the model applied to the TAU control condition without any in-between re-training.

	TP	TN	FP	FN	Sens [%]	Spec [%]	BAC [%]	FPR [%]	PPV [%]	NPV [%]	DOR
Classification: Good vs Poor role functional outcome											
SCT	7	12	5	2	77.78	70.59	74.18	29.4	58.3	85.7	6.9
Out-of-sample validation:											
TAU	9	3	1	13	40.91	75.00	57.95	25.0	90.0	18.8	2.7

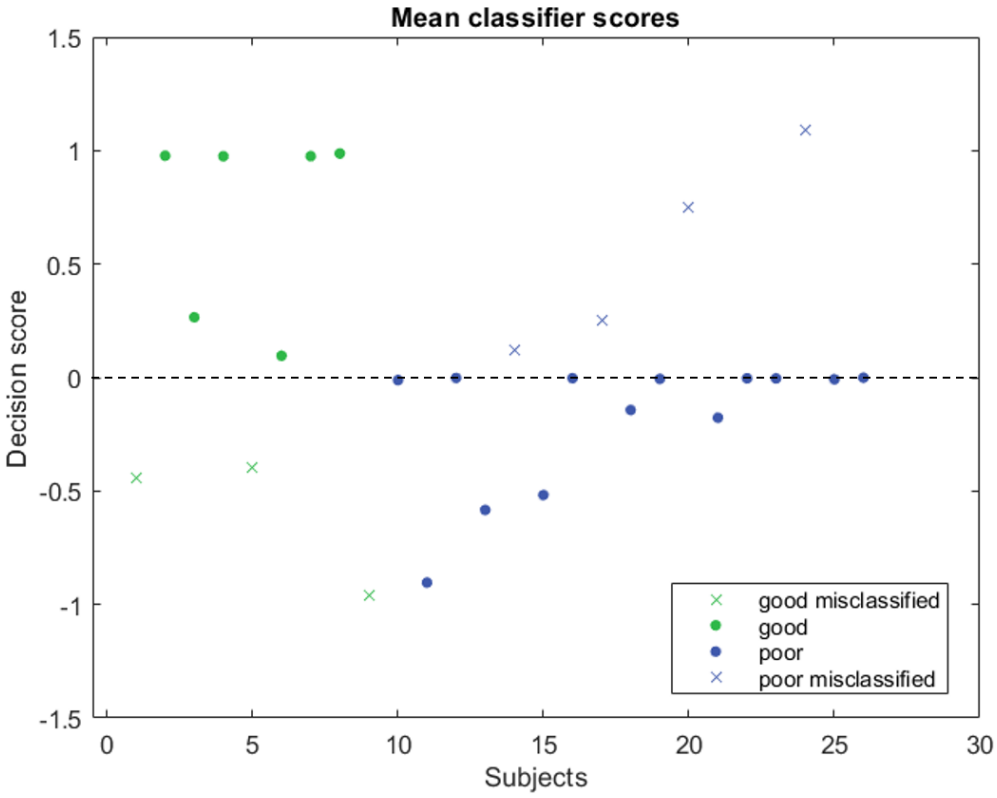

Figure 3.13: Classification performance of the good versus poor role functioning predictor based on T0 rsFC in patients who received the intervention.

3.4.2 Association of Decision Scores with Changes in Cognition, Functioning, and Symptoms

The decision scores extracted from this model in the SCT group were not associated with any changes in cognition, symptoms or functioning (all $P > 0.05$).

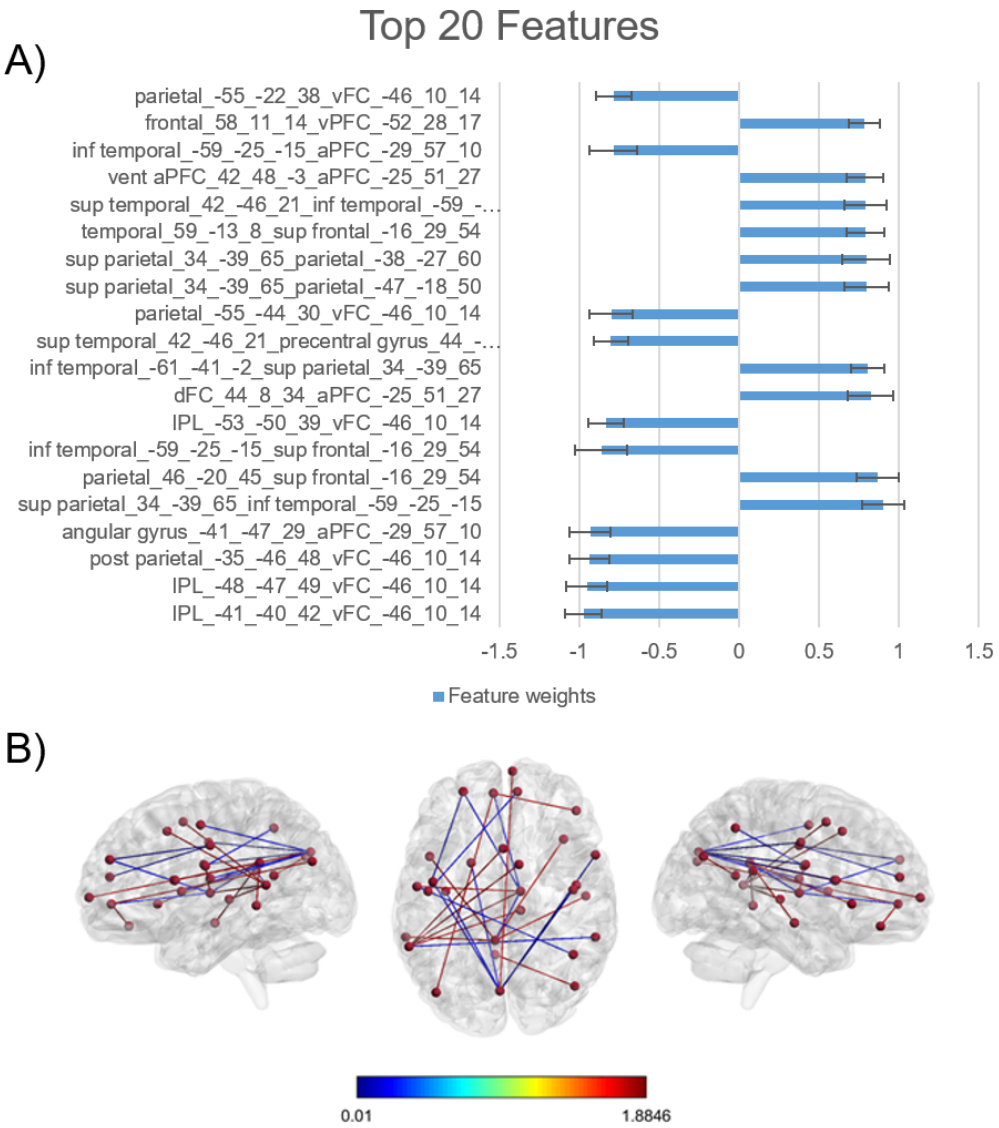

Figure 3.14: Depiction of the Dosenbach-based functional connections with the highest individual feature weight for the good vs. poor role functioning classification. A) Shows the top 20 features extracted using a percentile rank of approximately 99.99 %. B) Shows the inter- and intrahemispheric connectivities mapped onto the brain using BrainNet Viewer (Xia et al., 2013). Blue lines indicate higher connectivity in the poor outcome group; red lines indicate greater connectivity in the good outcome group.

4 Discussion

To the best of our knowledge, this dissertation is the first to use a comprehensive approach of a 10-hour computerized SCT in patients with ROP—moving from group-level statistics assessing behavioral and neural effects to multivariate monitoring and prediction of treatment response at the individual level. Within this dissertation, we have attempted to answer four main questions. First, we investigated the direct effects of SCT on cognition, symptoms, and functioning. Second, we then moved from the behavioral to the neural-level to investigate whether the clinical and/or behavioral effects may have been driven by alterations in rsFC. Additionally, we investigated the association between behavioral, clinical, and neural alterations. Subsequently, we shifted from group-level investigations to the individual with two multivariate questions assessing the potential of using rsFC to gauge treatment response. First, we used a novel method of rsFC neuromonitoring. We validated a rsFC HC-ROP classification model that was generated in an independent sample to patients in both the SCT and TAU conditions. We compared the direction of decision score changes ("HC-like" or "ROP-like shifts across the SVM hyperplane) between the two time-points (T0 and FU). Additionally, we investigated whether changes in behavioral or clinical measures differed between patients who shifted in a particular direction solely in the SCT condition. Finally, we determined whether T0 rsFC could inform outcomes in role functioning response at FU in patients who received SCT.

4.1 Effects of SCT on Cognition, Symptoms, and Functioning

Within the first aim of this dissertation, we investigated the effects of a relatively new, low therapist support, 10-hour computer-based SCT on cognition, symptoms, and functioning in patients with ROP in comparison to patients in a TAU control condition. Specifically, we tested the feasibility and preliminary efficacy of SocialVille, developed by Posit Science, Inc.—a new online training program targeting deficits in processing speed, WM, and attention control by improving speed and accuracy of discrimination of social and emotional information. Moreover, we also investigated whether intervention specific changes in cognition were associated with any changes in symptoms or functioning.

Primary Outcome Variables: Effects on Cognition

With respect to cognition, across all ROP patients, we saw a main-effect of time in SoP, WM, VL, EF, and in the composite score of GC. Within these domains, patients showed improvements from T0 to FU, with the exception of VL. In the domain of VL, performance worsened over time in both SCT and TAU conditions. Contrary to our hypothesis, we did not find improvements in any single or the composite cognitive domain specific to the intervention. There was a significant interaction in the unexpected direction in the domain of attention. Patients who underwent SCT showed significantly worse performance over time, while patients in the TAU condition showed better performance. These results might be suggestive of a regression to the mean, as patients in the SCT group showed better performance at T0 than patients in the control group, albeit nonsignificant. As a result, within this study, we did not see any positive effects of the 10-hour SCT on GC or any other cognitive domains.

Although previous meta-analyses generally have shown greater positive effects in various cognitive domains as a result of NCIs, these meta-analyses have generally focused on patients at chronic stages of schizophrenia and also included studies that combined CCT with cognitive remediation (McGurk et al., 2007; Wykes et al., 2011). Recently, in a meta-analysis investigating the specific effects of 24 CCT studies (without additional psychosocial rehabilitation), Prikken et al. (2019) showed small-to-moderate effects

across studies only in the cognitive domains of attention and WM. Although we did not find positive effects within the SCT condition when looking at the cognitive domains, we found significantly greater improvement in a visual WM task (SOPT) in patients who received the intervention. Still, Prikken et al. also included studies which used a variety of interventions in chronic patients. They showed significant associations between the effects on attention and duration of illness—suggesting patients with more chronic illness benefit more for CCT (Prikken et al., 2019). This might explain why we did not see positive effects in this domain.

To date, there has been only one meta-analysis that examined the effects of cognitive remediation studies at earlier stages of psychosis. Here, Revell et al. (2015) showed much smaller effect sizes than meta-analyses including studies with chronic PSD patients. The authors showed a significant improvement only in the domain of verbal learning and memory across studies. Although we did not see direct effects in this domain when comparing the groups over time, this might be explained due to the fact that we did not counter-balance the versions of the list of words patients learned at T0 and at FU. Both groups worsened over time in their performance specifically in this domain. Although speculative, the word list at FU may have been more difficult than the one at T0, masking any true effects of the intervention on VL that we might have otherwise seen. Future studies should ensure that versions of the neuropsychological tests are counterbalanced across time-points.

Nevertheless, in this study, we found an association between changes VL and changes in both role and social functioning specific to the SCT group. Patients who showed greater improvement in VL also showed greater gains in social and role functioning. There were no such associations was seen in the TAU control condition.

In sum, previous meta-analyses have attempted to synthesize the effects of NCIs on cognition. In comparison to these meta-analyses, the combination of focusing on earlier stages of psychosis along with using a solely computerized form of SCT targeting one modality may have led to the lack of improvements we see in cognition. Nevertheless, there seems to be an association between patients who do show greater improvement in VL and greater gains in social and role functioning in patients that underwent SCT.

There have been two meta-analyses to-date that have investigated the effects of social cognitive interventions. In the first, although the authors showed a moderate-to-large

effect size on psychosocial functioning (0.78) following SCT, they did not report the effects on general cognition (Kurtz & Richardson, 2011). Additionally, the particular SCT used within our study was still under development at the time this meta-analysis was published and therefore does not include results from this particular type of computerized SCT.

In a subsequent meta-analysis by the same authors, they critiqued their own previous work from 2011 due to the heterogeneity of interventions they included: brief proof-of-concept social cognitive interventions, combined social cognitive interventions with psychosocial treatments, and comprehensive SCT programs targeting multiple SC domains (Kurtz et al., 2016). Thus, the authors included only studies utilizing comprehensive social cognitive interventions. Here, Kurtz et al. showed improvements in various subdomains of SC, and both negative and general symptoms. However, in line with our results, such interventions did not show an improvement in cognition. In fact, they found a general worsening of cognition (effect size = -0.31). This seems to suggest that such training programs work by affecting SC directly, and not as a secondary effect through improving general cognition (Kurtz et al., 2016).

In support of this claim, two studies directly compared the effects of social cognitive interventions to general cognitive training (Horan, Kern, et al., 2011; Wölwer et al., 2005). Both studies showed 1) greater improvement in various domains of social cognition in the patients receiving SCT, and 2) no significant differences between conditions on general cognitive performance. As we used an intervention specifically focused on SC, this may explain why we did not find significant improvements in GC or any specific cognitive domain.

Alternatively, it may also be, that we did not see direct effects on cognitive improvement in the group that received SCT because we did not supplement the training with CCT that target other modalities (such as auditory targeted CCT). While we focused on the potential benefits of SCT as a standalone treatment, many studies have combined SCT with other targeted CCT programs (Fisher et al., 2015, 2017; Sacks et al., 2013; Subramaniam et al., 2012, 2014). These studies have shown improvements in both global and specific cognitive domains.

In one such study by Subramaniam et al. (2014), the authors utilized an 80-hour combined auditory, visual and social cognitive training. They reported an association

between improvement in a WM task at FU and both improvement in an external verbal WM task and occupational functioning in the patients who underwent the intervention. This association was only seen when relating improvement in WM after completion of training and the performance in verbal WM and occupational functioning 6 months later. The authors postulate that these effects show support for improved verbal WM serving as an important indicator of future functioning (Subramaniam et al., 2014).

Unfortunately, within our current study, no additional FU assessment took place after completion of the intervention. Nevertheless, we were able to show a significant relationship between improved VL and both social and role functioning improvements immediately following the intervention. Future studies should consider including an additional FU assessment after a specified period as this would also provide additional information with respect to the durability of such interventions.

Although we have covered a number of reasons why we may not have found significant improvements in GC nor the cognitive domains within this study, these reasons do not explain our lack of improvement seen in the domain of SC. Indeed both, meta-analyses investigating the effects of SCT described above have shown improvement in a number of social cognitive domains (Kurtz & Richardson, 2011; Kurtz et al., 2016). In the pilot study in 2014, that tested the feasibility and initial effects of the SCT used in our study, Nahum et al. (2014) showed significant improvements in social cognitive tests not specifically targeted by the intervention (i.e., prosody identification and facial memory). However, the improvements the authors reported in these domains were only significant within the speeded tests examining reaction times (Nahum et al., 2014). They did not show any significant improvements in social cognitive tests that measured performance based on the number of correct responses. Bartholomeusz et al. (2013) similarly investigated the effects of a 10-hour SCT (social cognition and interaction training) in patients with FEP. Here, the authors did not include a control condition and investigated the effects specifically on SC and functioning. When looking specifically at emotion recognition based on the total number of errors in the DANVA-2, they did not find a significant improvement post-treatment.

Similarly, within our study, we found neither a condition by time interaction nor pre-to-post test improvements in the SCT group in SC. The DANVA-2 was the cognitive test used to gauge SC in this study and has previously been used to test the accuracy of facial

emotion recognition. Here, participants are presented with faces expressing varying levels of four emotions: happy, sad, angry, and fearful (Nowicki & Duke, 1994). Our metric of performance used in this study was based on the number of correct responses. The lack of effects seen in Bartholomeusz et al. and our study when using the DANVA-2 could potentially result from ceiling effects in this particular test. Measuring reaction times might show greater sensitivity to changes in performance, especially since SCT also works by targeting processing speed.

There is a need for studies that investigate the psychometric properties of tests measuring multiple domains of social cognition. This is especially true when the intervention uses a paradigm specifically meant to target social cognition. The test chosen to measure SC for the MATRICS battery was the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), managing emotions branch (K. Nuechterlein & Green, 2006). This test uses fine-grained measures of SC and has been shown to correlate with independent living and self-care (Kee et al., 2009). Still, it only taps into one particular domain of SC: managing emotional reactions to others. Yet, SC can be divided into a number of additional subdomains (social cue perception, experience sharing, and inferring the thoughts and emotions of others), and finding appropriate measures to test each of these domains will be increasingly important as researchers continue to investigate the potential utility of SCT (Davidson, Lesser, Parente, & Fiszdon, 2017).

There are many tests that measure various aspects of SC. At the start of the study, there was not yet a consensus on which tests best measure the various domains on SC in patients with PSD. In 2014, researchers began such efforts with the Social Cognition Psychometric Evaluation study (SCOPE) (Pinkham et al., 2014). In 2018, the authors involved in this initial endeavor published their validated results and recommendations for specific social cognition tests. These tests were selected based on factors including reliability, utility as a repeated measure, associations with functioning, sensitivity to group differences, and internal consistency (Pinkham, Harvey, & Penn, 2018). Future studies should consider such recommendations when developing the study design of interventions that utilize any form of SCT.

Secondary Outcome Variables: Effects on Functioning

Across all subjects, patients showed improvements in each of our functioning measures. Moreover, we found a significant improvement in role functioning that was specific to the intervention. Namely, patients who underwent SCT showed greater improvement in role functioning at FU as compared to TAU. This was not the case in the pilot study by Nahum et al.. Patients included in their study, however, consisted of both chronic and ROP patients. The onset of symptoms ranged from within 2 years to greater than 5 years, with an average duration of 3.21 years. A number of studies have emphasized the positive effects of intervention strategies being implemented earlier in the course of illness in PSD (Bartholomeusz et al., 2013; Cullberg et al., 2006; Stafford et al., 2013). The positive effects of SCT may be especially important at an early stage, as social and role skills are established during late adolescence to early adulthood (Yung & McGorry, 1996). Studies targeting SC seem to be especially promising, although little research has been conducted in patients at an earlier stage of PSD. Chronicity of symptoms, with frequent hospitalizations, has also been shown to contribute to negative effects on functioning that may lead to the impairments in occupational functioning often seen in this population (Birchwood et al., 1998). Hence, the heterogeneity of the stages at which the patients were recruited in the study by Nahum et al. (2014) may have contributed to the lack of improvement in role functioning seen in their study in comparison with our results. Patients within our sample, with an onset of symptoms of less than two years, may represent a sample with a greater potential for improvement in functioning at this earlier stage.

Contrary to our expectations, we did not find improvement in social functioning specific to SCT. Within the two meta-analyses that have previously synthesized the effects of SCT, only one investigated the effects on psychosocial outcome (Kurtz & Richardson, 2011; Kurtz et al., 2016). Although Kurtz and Richardson (2011) showed moderate-to-large improvement in psychosocial functioning, this outcome measure covers a number of different domains spanning both social and role outcome measures. Moreover, Nahum et al. showed improvement in social functioning using the same measure that we used without our study (Global Functioning Scale: Social) in their pilot study that utilized the same SCT (SocialVille). However, the authors did not include a comparison control group within their study. The authors reported pre-to-post changes across individuals whom all received the intervention (Nahum et al., 2014).

Indeed, when looking at the changes in social functioning solely in those receiving SCT within our study, we similarly saw significant pre-to-post improvements in social functioning.

Despite the lack of treatment specific improvement in social functioning following SCT, we want to emphasize the clinical implications of the improvement in role functioning seen in this study. The GF-S and GF-R were developed specifically to better separate different aspects of functioning (Cornblatt et al., 2007). Moreover, these scales measure functioning without the additional confounds from symptoms, as in the GAF (Cornblatt et al., 2007). With respect to role functioning, the GF-R takes into account the current status of a patient—whether their role functioning is predominantly based on occupational, educational, and/or homemaker roles. The number of hours spent in their role, the length of time patients have been in a particular role, the degree of support or assistance needed within their role, and their performance are all taken into account (Cornblatt et al., 2007). Role functioning may, however, also be mediated by other environmental factors such as socio-economical status or physical characteristics of the environment (Javed & Charles, 2018).

While researchers have attempted to better separate social and role functioning, they can only be separated to a certain degree. The items measured within social functioning using the GF-S include aspects such as: the amount of time spent with friends, family or in a relationship, the number of friends, the strength of these relationships, the degree of initiative the patient takes in contacting and making plans with others, how they handle conflict, and whether or not they are in a romantic relationship. It may, therefore, be, that SCT acts by indirectly improving skills that are critical for role functioning—such as the social skills the training was meant to target. As we mentioned above, Bartholomeusz et al. (2013) used a different 10-hour SCT (called social cognition and interaction training), and similarly found a pre-to-post effect on role functioning, but not social functioning—further providing support for such effects. Such skills are necessary for everyday occupational, educational, and even homemaker roles.

Moreover, although both social and role functioning have been shown to already deteriorate prior to the onset of a FEP (Cornblatt et al., 2012), the deterioration in social functioning may have persisted for a longer period than role functioning. As a result, social functioning may be less malleable to SCT. In a multivariate analysis, the five

features that most contributed to the prediction of psychosis conversion in at-risk individuals included: genetic risk for schizophrenia with recent functional deterioration, unusual thought content, suspicion/ paranoia, social impairment, and history of any drug abuse (Cannon et al., 2008). Here, social impairment was both present prior to psychosis onset, and individuals with social impairment during the at-risk stage were also more likely to develop psychosis. Therefore, the 10-hour SCT may work on improving specific skills that are more critical for improving role functioning. In order to therefore also improve social functioning, patients with ROP may require a longer duration of training or the addition of psychosocial treatment strategies (Wykes et al., 2011).

The SCT used within this study was embedded within standard clinical care received (in a real-world clinical setting) while providing the option of training from home for patients with outpatient status. We chose a 10-hour total duration of SCT for half an hour per day, 4-5 times per week, as this seemed implementable within a clinical setting of standard medical care. This is especially important in a medical setting for real-world utility as the majority of studies to date that have implemented similar interventions have durations ranging anywhere from 40 to over 100 hours in total (Adcock et al., 2009; Dark, Harris, Gore-Jones, Newman, & Whiteford, 2018). Due to the low number of remission and recovery rates in early psychosis (Ventura et al., 2011), there is a need for treatment strategies that have a potential for improving functioning, especially in role functioning. The improvement we see in role functioning in patients who underwent SCT after only 10 hours of training speaks positively for such an intervention. In fact, factors including WM, verbal memory, and processing speed, attention, and early perceptual processing abilities have been shown to account for 52 % of the variance in work outcomes following a FEP (K. H. Nuechterlein et al., 2011). Although we do not see gains in these specific domains in our current study, the SCT used in this study nevertheless functions by precisely targeting these domains: processing speed, WM and attention to social cues (Nahum et al., 2013). Moreover, these exercises use neuroplasticity-based principles meant to target SC deficits known to be impaired in patients with PSD through the underlying brain regions involved in these processes (Nahum et al., 2013; Merzenich et al., 2014; Vinogradov et al., 2012). Several studies have provided support for improvement in cognition not being a prerequisite

for improvement in SC (Horan, Kern, et al., 2011; Horan & Green, 2017; Wölwer et al., 2005).

In addition SC has repeatedly been directly linked to outcome measures, including occupational status, community functioning, independent living skills (Addington, Saeedi, & Addington, 2006a; M. Bell et al., 2009; Couture et al., 2006; Fett et al., 2011; Horan, Green, et al., 2011; Irani, Seligman, Kamath, Kohler, & Gur, 2012; Sergi, Rassovsky, Nuechterlein, & Green, 2006; Vauth et al., 2004)—which are encompassed in role functioning. Indeed, SC has additionally been shown to better predict functioning than both cognition and symptoms (Horan, Green, et al., 2011). The SCT used within this study is built upon neuroplasticity principles with the goal of improving the brain in order to induce behavioral changes (Merzenich, 2013; Nahum et al., 2013; Vinogradov et al., 2012). It might, therefore, be the re-normalization of the brain regions underlying SC in patients receiving SCT that results in the improved role functioning we saw in this study. These implications will further be discussed within the scope of the second aim of the dissertation below.

Secondary Outcome Variables: Effects on Symptoms

We did not find significant improvements in the SCT group as compared to the TAU group in symptom changes. There was a main effect of time across both groups showing significant improvements in all three subdomains of symptoms. This is in line with a recent meta-analysis investigating the effects of facial affect recognition training in schizophrenia patients on symptoms and social functioning (Bordon, O'Rourke, & Hutton, 2017). While they found general improvement in social functioning, there were no significant benefits in symptom improvement following training (Bordon et al., 2017). As all patients were receiving clinical care (both as in-patient or outpatient) at the time of inclusion into the study, the improvement seen across symptoms may be the result of treatment received within the clinic. Indeed, in the meta-analysis investigating the effects of cognitive interventions in patients with early psychosis, the authors only showed a significant effect on symptoms when the intervention was delivered in a one-to-one setting with a therapist, and not when delivered in a group setting (Revell et al., 2015). Although we can not rule out such effects in our study, we maintained minimal contact with patients throughout the intervention in an attempt to reduce the

confounding effects of additional therapist contact often seen in psychosocial interventions. Moreover, only three subjects did not receive antipsychotic medication during their clinical treatment, and subjects improved in symptoms across both conditions. This suggests for the majority, both clinical treatment and antipsychotic medication may have contributed to the improvement in symptoms across patients with ROP.

Associations between Cognition and Functioning

Within this study, we saw a positive association between changes in VL and changes in both GF-R and GF-S. Namely, patients who showed greater improvement in VL after the intervention, also showed greater improvement in both social and role functioning. This was despite the fact that overall, patients worsened in VL from T0 to FU. These results were intervention specific, as no such associations were apparent in the TAU control condition. VL seems to be one of the most significant neuropsychological markers of risk for psychosis (Lin et al., 2011). This may explain why we see an association within this particular domain and social and role functioning, and not with other cognitive domains. As VL is embedded in psychosis pathophysiology, the degree of response in this domain at an early stage of psychosis as a result of SCT seems to indicate the level of improvement in both social and role functioning.

These results are in line with one of the largest meta-analyses that investigated the relationship between various neurocognitive, social cognitive and outcome measures (Fett et al., 2011). Across nine different neurocognitive domains that were assessed in this meta-analysis, aside from the domain of reasoning and problem solving, verbal learning and memory was the only other domain significantly associated with the four different measures of outcome. These outcome measures included: community functioning, social behavior in the milieu, social problem solving, and social skills. Interestingly, community functioning within their context was meant to capture everyday functioning and consists of both work and social functioning. Additionally, the mechanisms underlying the intervention used within our study involved social stimuli to target the domains of SC, while simultaneously exercising processing speed, WM, and attention control (Merzenich et al., 2014; Nahum et al., 2014). These mechanisms are the same ones underlying auditory CCT that have previously been shown to improve verbal memory (Fisher et al., 2009, 2010, 2015). Therefore our results support the claim that

patients who have a greater potential for improvement in verbal learning also show greater improvement in both social and role functioning when given a 10-hour SCT.

4.2 Effects of SCT on rsFC

CCT have emerged as a potential treatment strategy for improving various domains of cognitive functioning in patients with PSD. These gains may extend beyond the direct effects on cognition or SC, to improvement in functioning (Fett et al., 2011). Within the second aim of this dissertation, we moved from the behavioral to the neurobiological. Specifically, we investigated the rsFC changes induced by a 10-hour SCT in patients with ROP. We specifically focused on two a priori defined seeds-of-interest: the mPFC and amygdala. In addition, we further investigated the relationship between changes found in rsFC and changes in behavioral and clinical measures. Finally, we also assessed whether particular T0 measures of cognition, symptoms, or functioning were associated with the changes in rsFC specific to the SCT group.

We observed:

1. condition by time interactions in the rsFC between the mPFC and left temporal pole.

2. condition by time interactions in the rsFC between the mPFC and bilateral middle temporal gyrus.

3. condition by time interactions in the rsFC between the amygdala and right middle frontal gyrus.

4. no significant associations between rsFC changes and changes in cognition, symptoms, or functioning.

5. a significant negative association specific to the intervention between T0 SC and changes in the strength of connectivity between amygdala and the middle frontal gyrus.

Functional connectivity changes

To the best of our knowledge, this is the first study to investigate the effects of a computerized SCT focused solely on one modality (social) on rsFC in patients at an early stage of psychosis. To date, there have been only two other studies that have investigated the effects of a particular CCT on rsFC in early-course schizophrenia (Eack et al., 2016; Ramsay, Nienow, & MacDonald, 2017). The first utilized cognitive enhancement therapy, that spanned over two years with a total of 60 hours of CCT and an additional 45 1.5-hour social cognitive group sessions (Eack et al., 2016). This study showed promising results supporting neuroprotective effects of the intervention with preserved rsFC between the PCC and dlPFC over the course of the intervention, along with intervention-specific increases in rsFC between the PCC and right insula. The authors related the impairments in the regions that showed improvement back to impairments in executive function, emotion processing, and emotion regulation. Nevertheless, the relatively high attrition rates (50 % in patients in the control condition and 32 % in patients undergoing the active intervention) calls into question the feasibility of such an intervention in a clinical setting (Eack et al., 2016; Matsuda et al., 2018). Moreover, social cognitive group sessions took place once per week in the clinic, which may not be feasible for some patients.

The second study utilized a 48 hour "drill-and-practice" WM cognitive remediation program that spanned verbal, visual and spatial modalities (Ramsay, Nienow, & MacDonald, 2017). They found significant group by time interactions favoring the intervention group in connectivity increases between the thalamus and 1) right middle frontal gyrus and 2) anterior cingulate cortex. Moreover, the increases in the strength of connectivity specific to the intervention group between the thalamus and middle frontal gyrus were positively correlated with improvements in GC. This was not the case in their control condition. Their results support the idea that plasticity-based improvements relate to training-specific improvements in cognition (Ramsay, Nienow, & MacDonald, 2017). Despite the positive results, as the authors did not mention attrition rates within their study and have a relatively long duration of treatment, we do not know the feasibility of this intervention for clinical implementation.

In the second study of this dissertation, we were able to show fronto-temporal and fronto-amygdala rsFC increases in patients that received the SCT. This was not the case

in patients that were in the TAU control condition. The prefrontal cortex has often been implicated in the pathophysiology of schizophrenia (Fallon, Opole, & Potkin, 2003). The prefrontal cortex is one of the last brain regions to complete development (Gogtay et al., 2004) and has been associated with higher-order cognitive processes (E. K. Miller & Cohen, 2001) and WM (Goldman-Rakic, 1995). By inducing increases in rsFC between the frontal lobe and several regions of the temporal lobe and amygdala through the SCT, we may be able to restore neural integrity within these critical regions often implicated in psychosis. These alterations may lead to improvements in associated cognitive processes within these regions.

In another study that did not assess whole-brain rsFC, but instead the effects of a CCT combined with SCT on neural networks, Haut et al. (2017) showed similar increases in connectivity between the mPFC and temporal regions. This study was, however, done in patients that were at-risk for psychosis and not ROP patients. Nevertheless, these findings support the idea that neural alterations may be induced through CCT in patients at early stages of the disorder, including prior to the onset of psychotic symptoms.

Within our study, patients showed increases in rsFC after taking part in SCT without an additional CCT targeting other modalities. Research has shown targeted auditory CCT to have an effect on cognition (Fisher et al., 2015, 2017; Sacks et al., 2013; Subramaniam et al., 2012, 2014). Still, it becomes difficult to tease apart the direct effects of each training program (CCT versus SCT) when modules are combined. To date, no study has directly compared the neural effects of SCT with the effects of auditory targeted CCT. The results in this dissertation suggest that targeting SC alone may result in neuroplastic changes that improve functional connectivity within SC networks.

We were able to see these alterations by implementing only 10 hours of SCT. In fact, the majority of studies that have supplemented targeted CCT in other domains (auditory or visual) generally did so with fewer hours spent on the SCT module as compared to the other targeted modalities. For example, a number of studies combining both auditory CCT and SCT have had patients in the active intervention group complete approximately 50-80 hours of targeted auditory CCT and only 4-12.5 hours of SCT exercises (Hooker et al., 2012, 2013; Sacks et al., 2013; Subramaniam et al., 2012, 2014). These studies showed improvement in both cognition and social cognitive measures

following the combined training. The 10 hours used within our study are therefore within the bounds of the general duration of SCT that previously have been used—albeit without any additional training modules. Indeed, we have shown neural effects similar to other studies, along with an improvement in role functioning as described above. Moreover, altered medial temporal and prefrontal regions, including the networks connecting with subcortical structures seem to be promising neuroanatomical markers of poor symptom and functioning according to a recent review by Dazzan et al. (2015). While speculative, this seems to suggest, strengthening fronto-medial connectivity following the training might more directly relate to the increases in role functioning we see saw in the first study of this dissertation.

The majority of studies that have investigated the effects of CCT on neurobiology have used task-based functional designs with patients undergoing WM and executive tasks while in the scanner. Patients with PSD in the active CCT consistently showed T0 to FU increases in activation mainly in prefrontal regions (see Isaac and Januel (2016) and Penadés et al. (2017) for a review). These results support the hypothesis of hypofrontality in patients with PSD (Penadés et al., 2017). This hypothesis posits that cognitive interventions elicit their response by increasing brain activation in prefrontal regions during cognitively demanding tasks. Moreover, the degree of brain activation increases has also been shown to correlate with improvement in various measures of cognition (Isaac & Januel, 2016; Ramsay, Nienow, Marggraf, & MacDonald, 2017; Wei et al., 2016) and even quality of life 6 months later (Subramaniam et al., 2014). Such studies show support for the neuroplastic effects of CCT on the brain. Yet, this becomes less clear when looking at rsFC, where connectivity between certain regions during rsfMRI acquisition, is said to be impaired with greater functional connectivity in some regions, and in other regions impaired when patients show reduced functional connectivity (Dodell-Feder, Delisi, & Hooker, 2014). Nevertheless, the majority of studies seem to show hypo-connectivity between and within the majority of networks in the brain (Dong et al., 2018; Sharma et al., 2018).

The amygdala and mPFC have emerged as critical regions for both emotion and cognitive processing, as well as various aspects of SC (Green et al., 2015). Patients with schizophrenia generally showed reduced rsFC between amygdala-frontal regions (Yue et al., 2018), as well as reduced functional connectivity between fronto-temporal regions in patients with both chronic schizophrenia (Khadka et al., 2013) and FEP (Mwansisya et

al., 2017; Solé-Padullés et al., 2017). Such impairments lead to deficits across a number of social cognitive domains, especially in emotion recognition, and have been shown to relate to outcome (Green et al., 2000). Previous studies have shown impairments in both fronto-temporal and amygdala-frontal neural systems in patients with schizophrenia—critical for emotional and cognitive processing (Mwansisya et al., 2017; Phillips, Drevets, Rauch, & Lane, 2003). Indeed, impairment in mentalization, along with an inability to distinguish the source of willed intentions (self and non-self intentions) has been thought to relate to the psychotic symptoms patients experience (Corcoran, Cahill, & Frith, 1997; Phillips et al., 2003). Moreover, fronto-temporal connectivity has been shown to correlate with the severity of positive symptoms (Rotarska-Jagiela et al., 2010). By improving neural systems related to these processes through cognitive interventions such as SocialVille, we may be able to help ameliorate further declines in these domains. The additional improvement in role functioning seen here further supports the positive potential of such an intervention.

Several cognitive functions such as executive control, memory, and learning, rely on frontal-temporal integrity (Cabeza & Dennis, 2012), and disconnection between these regions has also been related to cognitive decline in normal aging (W. Cao et al., 2016; W. Li, Mai, & Liu, 2014). Interestingly, cognitive decline seems to also be malleable through the implementation of cognitive interventions—with increases in connectivity between fronto-temporal regions post-intervention (W. Li et al., 2014). Moreover, cognitive training has been shown to be able to reduce aging-related dysfunctions of higher cognitive networks (W. Cao et al., 2016). This is especially important as patients at risk for developing psychosis have been shown to deviate in their cognitive age in comparison to their biological age (Kambeitz-Ilankovic et al., 2019). Increases in rsFC have also been shown in participants who received intranasal oxytocin, known to be involved in socio-affective behaviors including attachment, stress and anxiety (Sripada et al., 2013). We were able to show similar increases on amygdala-frontal rsFC through a non-invasive computerized SCT. These results are in line with our current findings. In sum, our results provide further support for the potential neurobiological effects of a 10-hour SCT in increasing rsFC.

Although the finding of increased rsFC specific to the intervention speaks for the potential of inducing effects in the brain using neuroplasticity-based interventions, it would be equally important to know whether there are in fact neural abnormalities

that need repair. Patients with greater impairment at T0 might benefit more from such an intervention. Alternatively, it could be that patients who present with impairments deviating too much from HC cannot actually benefit from the intervention without moderately functioning systems. Thus, as changes to outcome measures may rely on particular T0 factors, disentangling these relationships is critical for understanding characteristics that may help inform intervention-specific changes.

Associations between changes in rsFC and clinical or behavioral changes

An additional aim of this study was to explore the associations of rsFC changes with alterations in cognition, symptoms, and outcome. We did not find any significant associations between changes in rsFC and changes in any other clinical or behavioral domains in patients receiving the intervention. Similar to the above, it might be that we do not see the relationship between functional connectivity changes and cognition changes immediately after the intervention. Unfortunately, we did not have an additional FU assessment period within the scope of this study.

Alternatively, the cognitive tests that we used within this study may not have been sensitive to capture the associated alterations. Indeed, within the first aim of this study, we did not find any cognitive performance changes specific to the intervention. This is especially the case due to our single measure in the domain of SC that is measured based on the number of correct responses. We have shown above, that this metric may not be sufficient in gauging improvement in SC. Future studies should include social cognitive tests that tap into particular subdomains of SC: emotion perception, Theory of Mind, social cue perception, empathy, and attributional style. Pinkham et al. (2018) made a recommendation for a number of tests that show strong psychometric properties and should be considered for future studies utilizing social cognitive interventions.

Moreover, within the first aim, improvement in VL was associated with improvement in both social and role functioning. However, we did not find any direct associations between rsFC alterations and changes in functioning or VL. Nevertheless, patients with PSD have shown marked impairments in language related to disorganized thoughts and verbal hallucinations (DeLisi, 2001). Moreover, these language-related impairments in PSD have been shown to relate to impaired fronto-temporal connections (Friston &

Frith, 1995; Leroux, Delcroix, & Dollfus, 2014). The increases in fronto-temporal rsFC that we see in patients who underwent SCT might thus relate to improved connectivity in the language network. As we mentioned above, it might be the case that we don't see the associations at the group-level between rsFC changes and improvement in VL, due to the lack of counterbalancing between the list of words used at T0 and FU. This was the only domain in which patients performed worse across both groups. As studies have previously shown, studies utilizing CCT have shown heterogeneity of effects (Prikken et al., 2019; Wykes et al., 2011). Heterogeneity of response to SCT may also have contributed to the lack of effects at the group-level. Some individuals seem to show greater benefits from computerized interventions than others. Patients resistant to the effects of SCT might mask the actual effects of the intervention. Therefore, there is still a need for individualized predictors of response, which was the goal of the third and final aim of this dissertation.

Baseline measures associated with rsFC changes

Before describing the results of the multivariate prediction analyses we performed within the third aim of this dissertation, we additionally investigated associations between T0 measures of cognition, symptoms, and functioning that might be related to the changes in rsFC we observed. We observed a negative association between baseline SC and changes in amygdala-frontal rsFC specific to the intervention. Namely, patients who had a worse performance at T0 in identifying emotions from faces showed greater increases in connectivity between the amygdala and middle frontal gyrus. This association was not significant in patients in the TAU control condition.

Both the amygdala and mPFC have often been implicated in SC (Green et al., 2015), and amygdala-frontal connectivity has specifically been shown to be associated with self-related processing (Blair, 2008) and the regulation of emotion (Kim et al., 2011). Moreover, amygdala-frontal connectivity disruptions appear in schizophrenia (Hoptman et al., 2010; H. Liu et al., 2014). It might thus be, that the patients that present with impairments at T0 in the ability to identify emotions are the same individuals who most benefit from such a SCT as the one used in this study. Patients with a lower SC performance at T0 showed the greatest gains in strengthening the rsFC between two regions specifically known to be involved in social cognition and emotion processing.

4.3 Utility of multivariate methods for investigating response to SCT

Until now, we have focused on the group-level analyses in order to gauge the general response to SCT. We have shown intervention-specific effects on role functioning. We have critically assessed potential reasons for the lack of improvement shown in this study on GC and cognitive domains. Post-hoc analyses additionally revealed greater improvement in visual WM following the intervention. Moreover, patients who showed greater gains in VL also showed greater improvement in both social and role functioning. This was not the case in the TAU control condition.

At the neural level, we were able to show significant increases in a priori seed-based rsFC between fronto-temporal and amygdala-frontal regions in patients who underwent SCT. Although the changes in connectivity in these regions were not associated with any changes in cognition, symptoms, or functioning, we were able to show a significant negative association between T0 SC and changes in the strength of connectivity between the amygdala and right middle frontal gyrus. Patients with worse performance in our test of SC at T0 showed greater increases in amygdala-frontal connectivity. These regions are involved in emotion perception and SC. Now, we move from the group-level statistics to the individual. We have utilized two methods in order to investigate treatment response to a 10-hour SCT at the individual level.

4.3.1 Neuromonitoring of individual rsFC restoration using an independent HC-ROP classification model

HC-ROP rsFC Classifier

This is, to the best of our knowledge, the first study utilizing an externally generated healthy-to-patient rsFC model that was applied to an intervention study. This model was meant to gauge neural response (based on whole-brain rsFC) across two time-points on a case-by-case basis. The validation of such a model on another sample would not be possible without the model itself being reliable. Our findings revealed that rsFC

can separate patients with ROP from HC with a BAC of 70.8 %. This model was highly significant with a $P < 0.001$ after 1000 permutations.

Our results are in line with the previous investigations utilizing neuroimaging to discriminate patients with schizophrenia from HC (Kambeitz et al., 2015; Wolfers et al., 2015). Across studies, using rsfMRI showed significantly greater sensitivity (84 %) than sMRI (76 %). Numerous studies have shown the potential of rsfMRI in classifying patients with schizophrenia from HC (Anderson & Cohen, 2013; Bae et al., 2018; Bassett, Nelson, Mueller, Camchong, & Lim, 2012; Cabral et al., 2016; Du et al., 2012; Tang, Wang, Cao, & Tan, 2012; Venkataraman, Whitford, Westin, Golland, & Kubicki, 2012; Y. Yu et al., 2013). Accuracies ranged from 62 % (Y. Yu et al., 2013) to above 90 % (Arbabshirani, Kiehl, Pearlson, & Calhoun, 2013; Du et al., 2012; Tang et al., 2012).

Far fewer studies to-date have successfully shown similar separability in patients at an earlier stage of this disorder. P. Huang et al. (2018) used whole-brain rsFC to separate patients with a FEP from HC with an accuracy of 81.3 %. In another study, Mikolas et al. (2016) utilized voxel-wise seed-based rsFC of the PCC for the DMN, dlPFC for the central executive network and the anterior insula for the salience network. Here, patients with FEP were distinguishable from HC only based on connectivity within the salience network (73.0 %). Despite our classification results being somewhat lower than that of (P. Huang et al., 2018), the model was nevertheless significant after permutation testing. The heterogeneity of diagnoses within our sample which includes FEP, but also other diagnoses (see 2.5) might explain our lower classification results. This study already shows a potential to distinguish patients at the early stages of psychosis from HC on the basis of rsFC alterations.

Features most discriminative for classification

Furthermore, our results reveal that the HC-ROP most discriminative connections involved widespread regions of the brain including PCC/precuneus and parietal, temporal regions with the thalamus and cerebellum, occipito-parietal, and fronto-parietal regions. A number of regions of the DMN including the PCC, precuneus, parietal and temporal regions reported in this study are in line with previous studies of altered functional connectivity within this network in patients with PSD (Karbasforoushan & Woodward, 2012; Whitfield-Gabrieli et al., 2009; Woodward, Rogers, & Heckers, 2011).

Moreover, a number of studies have shown a greater expansion of connectivity with the DMN, similar to our findings which may represent compensatory mechanisms as a result of impaired neural systems (Mannell et al., 2010; Salvador et al., 2010; Skudlarski et al., 2010; Woodward et al., 2011). While studies have shown both increases and decreases in rsFC across studies (Schmidt et al., 2014; Q. Yu et al., 2012), we find in this study, a majority of rsFC patterns showed greater strengths in the ROP group.

Interestingly, regions of increased strength of functional connectivity in the ROP group also overlap with those implicated in patients at even earlier stages of the disorder prior to the onset of psychotic symptoms (Shim et al., 2010). Moreover, increased connectivities with the occipital gyrus (Chen et al., 2013) as well as the cerebellum (H. Huang et al., 2019) have also similarly been reported. Within the top 20 features extracted from the HC-ROP classifier in this study, the two connections that showed greater strength in the HC group were with the frontal regions. Similarly, Karbasforoushan and Woodward showed reduced rsFC with the prefrontal cortex in patients with schizophrenia. In sum, our multivariate HC-ROP classifier was able to replicate previous results and distinguish patients from HC with good accuracy. The features that most contributed to this separation 1) have been implicated in previous studies and 2) support the dysconnectivity hypothesis of schizophrenia which posits a disruption in normal integration and segregation processes in the brain (Friston & Frith, 1995; Karbasforoushan & Woodward, 2012).

Neuromodulation of rsFC

Although the separability of HC from patients with ROP using rsFC is crucial for the investigation of the research question we endeavored to answer within this study, it was not the main goal. Instead, we applied the HC-ROP rsFC model to patients within the intervention study in order to monitor neural response to SCT at the individual level. By applying the HC-ROP model (i.e., validating the model) to our study sample, we were able to extract the decision scores, which are representative of the degree of rsFC "HC-likeness" (misclassification) or "ROP-likeness" (correctly classified) at the two time points: T0 and FU.

We expected patients in the SCT group to show significantly greater shifts in the "HC-like" direction than patients in the TAU control condition. There were, however, no

condition by time differences between groups in their changes in decision scores. There might be a number of reasons why we did not see any significant differences between the two groups over time with respect to the direction of decision score changes. First and foremost, despite our power analysis, this study included a relatively small sample size. We have included 26 subjects in each condition, which, although modest and meets the needed sample size based on our power analysis, is still relatively few participants. Alternatively, some patients within each condition shifted in one direction whereas others shifted in the opposite direction. The degree and number of subjects shifting in each direction may have masked the differences we might have seen between the two conditions. Thus, we split patients into two sub-groups: patients that shifted across the SVM hyperplane in the "HC-like" direction versus patients who shifted across the SVM hyperplane in the "ROP-like" direction). Although here, patients in the SCT condition showed a greater amount of shift in the "HC-like" direction as compared to the TAU group, these differences were not significant.

Intervention specific differences in cognition based on the direction of neural response

As we were interested in the effects of the intervention itself, we also took a closer look at differences within the group that received SCT and compared patients with decreased decision scores over time ("HC-like") to those with increased decision scores over time ("ROP-like"). Here, we found significant differences in changes over time between the two sub-divisions in GC and attention. Patients who's decision scores shifted in the "HC-like" direction based on rsFC also showed improvement in GC. Patients with shifts in decision scores in the "ROP-like" direction showed no changes in GC over time. Moreover, there was no significant difference between patients who shifted in the "ROP-like" direction versus those who shifted in the "HC-like" direction in the TAU group, indicating these findings are intervention specific. Similarly, with respect to the cognitive domain of attention, patients showing "HC-like" rsFC patterns at FU, also showed greater improvement in attention, whereas patients who's decision scores increased at FU showed worsening in performance in the attention task. There were no such differences seen in the TAU control condition.

These findings are compelling in light of the nonsignificant effects we saw on cognition in the first study. The model used was independent of the study sample, and validated using OOCV. Although there were no significant associations between the degree of shift in the healthy- or "ROP-like" direction and any other clinical or behavioral measures, we do see differences based on the direction of shift. By separating patients who exhibited neural response to SCT, using our externally-generated HC-ROP rsFC model, we were able to show differential changes in attention and GC between patients who neurally showed rsFC patterns that shifted in the "HC-like" direction versus the "ROP-like" direction. Namely, "HC-like" rsFC corresponded with improved performance in attention and GC. Interestingly, within the domain of attention, we actually saw an overall decrease in performance across patients who received SCT in comparison to the TAU control condition at the group-level.

Moreover, the features that were most informative for the separation of HC and ROP patients included regions often implicated in attentional tasks (Antonucci et al., 2016; Kellermann et al., 2012; Roiser et al., 2013; Sepede et al., 2014). The improvements in overall cognition and attention may have been driven by the increased "HC-like" rsFC patterns that patients presented with after the intervention, supporting the neuroplasticity-based nature of such a training paradigm. Indeed, within the second aim of this dissertation, we showed intervention specific increases in rsFC between fronto-temporal and amygdala-frontal regions. We managed to show parallel improvement in the neurobiological and cognitive functioning in a particular subset of patients that underwent SCT. These results indicate rsFC may be a viable neuromarker to monitor treatment response to SCT at the individual level through neuromodulation.

A number of studies have emphasized treatment response heterogeneity to various interventions including various forms of CCT or antipsychotic medication (Demjaha et al., 2017; Gabrieli, Ghosh, & Whitfield-Gabrieli, 2015; Wykes et al., 2011). With respect to antipsychotic medication, out of 74 patients who were followed over a 10-year period after the initial onset of FEP, 23 % were treatment-resistant (Demjaha et al., 2017). Moreover, of the 23 % that were resistant to antipsychotic medication, 84 % were already resistant at the initial onset of treatment. Unfortunately, we currently do not have treatment response rates in the field of NCIs, mainly as a result of the heterogeneity of such interventions. The heterogeneity might stem from factors such as variable duration, type, or combination of treatment strategies. Developing models,

similar to the model we have generated within this study, may help inform clinicians of treatment response to specialized interventions in a systematic way. Clinicians could, for example, perform regular neuroimaging assessments at specified intervals. Such assessments require little time, are non-invasive, and with respect to rsfMRI—may be done in the absence of a particular task. Across multivariate studies, rsfMRI has been shown to provide greater sensitivity that sMRI, and therefore might serve a more viable neuromarker especially for short-term interventions such as the one used in this study (Kambeitz et al., 2015).

There are two potential outcomes for the patients who failed to shift in the "HC-like" direction: 1) they would not respond to this particular type of SCT, or 2) they may need a greater number of hours of intervention in order to show similar effects as the subgroup who shifted in the "HC-like" direction. Keshavan et al. (2011) showed patients with schizophrenia with neural reserve showed accelerated social cognitive response to a cognitive enhancement therapy. Importantly, patients who had lower initial neural reserve still showed benefits from the intervention—through increased treatment duration. Monitoring neural changes in specified intervals would enable researchers to better understand these effects over time and allow fine-tuning of cognitive interventions at the single subject level. Within this study, we have moved from the group to the individual in order to monitor changes in individual rsFC. Despite the importance of such a model, we were equally interested in investigating whether we could predict response to SCT. True prediction is achievable only through the use of T0 features to predict a particular outcome—which we assessed in this last part of the third aim.

4.3.2 Individual prediction of response to SCT using baseline rsFC

Good-Poor Role Functioning rsFC Classifier

Within the final aim of this dissertation, we tested the predictive ability of a multivariate model using rsFC at T0 to predict treatment response to a 10-hour SCT at FU. Specifically, we used T0 whole-brain rsFC in patients who underwent the SCT to predict good versus poor role functioning at FU. This is, to the best of our knowledge,

the first study reporting the successful application of rsFC-based machine learning to the prediction of individual responses to a SCT program in patients with ROP. We found that role functioning impairments could be correctly predicted in up to 74.2 % of patients that received SCT. These results suggest that SCT might differentially affect the neural integrity in patients who take part in such an intervention.

While there is a consensus that neuromarkers contribute to the identification of patients with PSD (Kambeitz et al., 2015; Rodrigues-Amorim et al., 2017; Wolfers et al., 2015), relatively few studies to date, have investigated neuromarkers predictive of treatment response to NCIs in PSD. Across diagnoses and interventions, studies have successfully used sMRI to predict treatment response to antidepressive medication in patients with depression (F. Liu et al., 2012), and even response to repetitive transcranial magnetic stimulation in patients with schizophrenia (Koutsouleris, Wobrock, et al., 2018). rsfMRI has been also been shown to predict response to antipsychotic medication in patients with a FEP (B. Cao et al., 2018), but also treatment response to cognitive behavioral therapy in patients with social anxiety disorder (Whitfield-Gabrieli et al., 2016). These studies provide evidence of differential intervention-specific effects in subsets of patients who undergo various interventions.

In one particular study, Koutsouleris, Kambeitz-Ilankovic, et al. (2018) investigated the prediction of functioning (albeit without an active intervention) in patients with recent onset depression and individuals at clinical high risk for psychosis using GF-R and GF-S. Here, T0 functioning and sMRI were used as features for their multivariate predictor. Greater prediction accuracies were seen for social functioning (70 % for patients with recent onset depression and 83 % for patients at risk for psychosis) as compared with role functioning (63 % for patients with recent onset depression and 65 % for patients at risk for psychosis) when using combined T0 clinical and neuroanatomical features. While the sMRI model was able to predict social functioning in patients with clinical high risk for psychosis with good accuracy (76.2 %), classification accuracy was relatively lower when predicting role functioning in the same group (56.7 %) (Koutsouleris, Kambeitz-Ilankovic, et al., 2018). Moreover, the authors found volume reductions spanning a number of critical networks often implicated in PSD contributed to the prediction of social functioning. These regions included: the salience network, perisylvian language-associated system, DMN, and central executive network. These

findings point to disturbed cortical reorganization at the structural level already in patients prior to psychosis onset.

Whereas the findings above stem from a naturalistic study, our current study integrated a 10-hour SCT. Only one other study has investigated response prediction to a different cognitive intervention using cognitive behavioral therapy (Tolmeijer, Kumari, Peters, Williams, & Mason, 2018). Here, the authors showed a task-based functional Magnetic Resonance Imaging (fMRI) study measuring the neural response to facial affect stimuli (threat-related or prosocial) at T0 could predict the improvement in symptoms following the intervention. Additionally, Tolmeijer et al. showed that it was not possible to predict symptom changes using the fMRI features in patients who were in a TAU control condition. While task-based studies may provide insight into neural activation in regions associated with a particular task, task-absent measures (rsfMRI) have several advantages. Patients at an acute stage of illness, during which cognitive abilities might be impaired, could result in a subset of patients unable to perform some tasks. Moreover, rsfMRI is relatively easy to obtain, and a number of measures can be derived from such scans (for a review of various measures please refer to (Smitha et al., 2017)).

We were able to distinguish poor from good role functioning using T0 rsFC patterns. Our findings extend previous studies by providing evidence for the capability of distinguishing individuals who likely benefit from SCT based on rsFC patterns in particular brain regions at intake. Such rsFC neuromarkers bring us one step closer to better understanding the treatment response heterogeneity often reported across NCIs meta-analyses (Kurtz & Richardson, 2011; Kurtz et al., 2016; McGurk et al., 2007; Wykes et al., 2011). Yet, as not all individual patients respond in the same way to antipsychotic medication or other treatments, the implementation of cognitive interventions may not be for everyone. Although we have shown intervention-specific improved role functioning, in study 1, in this last study we see that not every patient showed improvement in role functioning. This divergence may be attributable to specific T0 differences in clinical presentation, neuromarkers, or a combination of both (Keshavan et al., 2011; Ramsay et al., 2018).

To date, one study has used T0 clinical and environmental measures including demographic variables, cognition, symptoms, functioning, and illness duration in order to predict treatment response to a targeted CCT (Ramsay et al., 2018). T0 GC and educa-

tion were shown to be predictive of GC improvement following their intervention. A number of studies have also shown improvements in prediction accuracies by combining modalities (Cabral et al., 2016; Koutsouleris, Kambeitz-Ilankovic, et al., 2018; Moser et al., 2018). Further research is needed to understand for which individuals NCIs are likely to be beneficial. Alternatively, patients who presented with poor role functioning at FU may simply require a greater dosage in order to experience similar gains to those with good role functioning (Keshavan et al., 2011). Large multi-site studies may help us better understand the reliability and validity of the effects of NCIs. With the help of machine learning, tackling such research questions seems to be feasible.

The computerized SCT used here was meant to improve low-level perceptual processes through the use of social stimuli while engaging reward systems. Ultimately, SCT was meant to improve neural integrity that in turn may affect higher-level cognitive abilities such as WM, attention and executive functioning (Merzenich et al., 2014; Nahum et al., 2013). As the current study focused on predicting role functioning following a CCT targeting SC, this might suggest an interplay between social and role functioning. Evert, Harvey, Trauer, and Herrman (2003) has shown a strong association between social and role functioning. Specifically, the authors revealed patients with PSD who had contact with family and/or friends were more likely to also have employment ($r = 0.71$) (Evert et al., 2003). Training social cognitive processes may thus indirectly lead to improvements in skills necessary for successful role functioning. Additionally, the effects of the SCT might interact with additional environmental factors not measured in this study to improve role functioning (Evert et al., 2003; Koutsouleris, Kambeitz-Ilankovic, et al., 2018).

While the results shown here are preliminary in nature, to the best of our knowledge, this study is the first to demonstrate the feasibility of a rsFC-based prediction of SCT improvement in role functioning following a relatively short treatment duration. Such studies have the potential of further disentangling treatment response heterogeneity reported across studies through the use of relatively easy-to-obtain rsfMRI neuromarkers. Since only 38 % of patients with FEP showed work recovery within the first year of symptoms (Ventura et al., 2011), improving role functioning seems to be a critical target. Moreover, interventions targeting patients at early stages of the disorder may help to deter the poor prognosis often associated with PSD (Birchwood et al., 1998). Though the validation of our predictor in larger samples is warranted, such a model

may help clinicians make quick, informed treatment choices for patients presenting with psychotic symptoms in the clinic for the first time.

Features most discriminative for classification

Within this study, we used rsFC to predict role functioning at FU. A recent meta-analysis suggests promising neuroanatomical markers of poor symptom and functioning to include medial temporal and prefrontal cortical alterations, as well as connections from these regions to subcortical structures (Dazzan et al., 2015). While this study reported structural alterations related to functioning, as we have previously mentioned, rsfMRI has been shown to provide greater sensitivity across studies when separating patients from HC (Kambeitz et al., 2015). rsFC may thus have the capability of detecting fine-grained differences between patients with early psychosis, where structural abnormalities may not yet be as pronounced (Hager & Keshavan, 2015). Within this study, greater strength of connectivity patterns at T0 between fronto-parietal, fronto-inferior temporal, precentral and superior temporal gyrus, and ventral frontal cortex with the inferior parietal lobule were seen in poor outcomers. In contrast, interhemispheric connectivity within parietal, frontal and temporal regions, as well as intrahemispheric connectivity between superior frontal with both temporal and parietal regions, and superior parietal and inferior temporal regions were seen at T0 in patients with good outcomes. A number of these regions have been shown to exhibit increases as a result of various CCT, including the inferior, middle, and superior frontal gyrus, the precentral gyrus, and the parietal lobe (Ramsay & MacDonald III, 2015). As a result, differences in connectivity patterns between particular brain regions may help to inform which patients will show a response to SCT.

Although we did not observe any clinical variables that relate to the decision scores that were extracted from this model, it is important to note that this study has shown results which support a viable way to measure treatment response using T0 imaging information in individual subjects. Moreover, our validation analysis showed that the SCT treatment response predictor was both accurate and intervention-specific since the model was not able to distinguish between good and poor role functioning in patients who were in the TAU control condition. However, as a number of individuals with poor role functioning at FU had decision scores that were close to zero, the classifier

may not have had enough information from the current sample to learn to separate the patients close to the boundary of good versus poor functioning. These results, however, are preliminary and warrant further investigation with larger sample sizes. Nevertheless, these results point to the potential utility of multivariate methods in contributing to better-individualized tailoring of treatments to move towards truly personalized medicine.

4.4 Limitations

There are several limitations that need to be taken into account within the studies conducted in this dissertation.

1. Despite having a sufficient number of participants within each condition based on the power analysis we conducted at the start of this study, a greater sample size could result in bigger effect sizes. Additionally, the amygdala-frontal connectivity changes were only significant at the uncorrected level. More robust results might be seen with a larger sample size.

   When using multivariate methods, however, the number of subjects necessary for reliable results is still unclear (Thirion et al., 2007). Thus, when investigating treatment response specific to individuals who underwent SCT using multivariate methods, our sample size might be insufficient and will need to be replicated in larger samples. This reduced sample may have contributed to the subset of the subjects with decision scores close to zero in the good versus poor outcome predictor. The classifier might not have been able to optimally learn to discriminate these particular individuals. Despite the small sample size, the findings within this study were still significant and point to specific differences in the integrity of rsFC at the individual level. Still, our model was able to distinguish patients who will likely benefit from the intervention with good role functioning based on rsFC acquired shortly after admission to the clinic. Moreover, we used an independent sample to generate the HC-ROP rsFC classification model. This model was then validated on the current study sample using OOCV at T0 and FU. By extracting the decision scores from the OOCV at each time-point, we

were able to monitor individual shift across the SVM HC-ROP hyperplane over time in patients across both conditions (SCT and TAU).

2. We did not include a HC comparison group in our study. As a result, we were not able to show whether patients with ROP who took part in the study showed significant impairments in clinical, behavioral, or neural rsFC as compared to the HC population. Although we found increases in fronto-temporal, as well as amygdala-frontal connectivity in patients receiving SCT, we do not know the extent to which rsFC was intact versus impaired in these patients at T0 as compared to HC. Without including HC as an additional control condition, we, therefore, do not have a measure of comparison to determine whether neural connections or cognitive abilities were in fact altered, and if they were, to what degree in patients with ROP.

3. Neither the researchers who conducted the assessments nor the patients in the study themselves were blind to the condition assignment of patients. Rater blinding was not feasible within this study due to the number of researchers working on this particular study. Future larger studies across multiple sites would allow for rigorous study designs with blinding (at least at the rater-level). Patients who participated in the study and other similar intervention studies were clearly aware of whether they were in the intervention condition or not. Even in studies that utilize a computer games control condition, patients may have been aware that exercises such as battleship, tic-tac-toe, or crossword puzzles, as examples, were not meant to target specific cognitive abilities.

   Researchers that have evaluated the design of intervention studies viewed a TAU control condition as less rigorous of a control as compared to active controls (R. S. E. Keefe et al., 2011). Nevertheless, Wykes et al. (2011) pointed out that the effects on cognition did not seem to depend on the type of control condition used in their meta-analysis. However, significant effects in functioning were only seen when the intervention group was contrasted with an active control condition (Wykes et al., 2011). Trained researchers were instructed to follow standard protocols throughout this study when setting up the SCT for patients who trained in the clinic. In doing so, we had attempted to minimize (although

we may not have eliminated) additional therapeutic effects patients may have experienced from contact with our research personnel.

4. Giving the option to complete the training from home instead of the clinic makes it possible to provide SCT to a greater number of patients who otherwise would not take part in such an intervention. Nevertheless, this can also be seen as a limitation due to potential site differences. After the first three sessions, patients within this study had the option of completing the training from home or in the clinic. We saw significant differences in the number of days between assessments with patients training from home completing the training sooner. Additionally, patients training from home showed greater improvement in social functioning after SCT. The greater improvement in social functioning seen in patients training from home might have related to patients having a higher degree of contact with their social networks from home as opposed to from the clinic. Additionally, site differences may be attributed to potential differences in motivation. Although this may serve as a viable explanation, it should be taken with caution as we did not have a metric to directly assess motivation within our study.

5. DANVA-2 was the only metric assessed for the domain of SC. Although this measure has previously been used in other studies, it measures only one domain of SC: facial affect recognition. Yet, other tests have the capability of measuring the other three domains of SC: social cue perception, theory of mind or mentalizing, and attributional style (Pinkham et al., 2014). Although there is still a debate as to which tests should be used to measure SC (Horan & Green, 2017), Pinkham et al. (2018) recently recommended a number of tests that show strong psychometric properties as a result of a joint effort among clinicians. The tests they mentioned have shown reliability as well as tolerability and can be used to measure social cognitive domains at multiple time points.

5 Future Directions and Conclusion

5.1 Future Directions

As discussed in depth in the previous chapters, CCT targeting specific modalities have contributed to improving a number of outcome measures including cognition, symptoms, and functioning in patients with ROP. Yet, CCT such as the SCT we have employed are currently not integrated into standard clinical care as a supplementary treatment option for patients. Progress in developing robust interventions that may help to alleviate cognitive deficits and improve outcomes in patients with PSD is slowed due to the high degree of variability and often long durations of various training programs. These interventions use different programs, total number of sessions, differing intensities (frequency and duration per session in a week), and some studies include a therapist (Cella, Reeder, & Wykes, 2015).

This calls into question the comparability and effectiveness of various CCT. The even broader NCIs that exist to date also vary in terms of their underlying conceptual foundations and intervention modalities (R. S. E. Keefe et al., 2011). Even when the same type of intervention is used, studies vary with respect to the combination of modalities targeted. For example, studies that have utilized interventions developed by Posit Science, Inc., have combined 1) auditory plus social modalities; 2) auditory and visual modalities; 3) auditory, visual and social modalities, or even 4) auditory or social training alone. Future work should aim to assess direct differences between various NCIs as well as between modalities within the same type of intervention. Such studies may provide additional information as to which interventions are more effective for

particular outcome measures. Moreover, studies utilizing multivariate methods would additionally make it possible to identify specific individuals who may better profit from a particular type of intervention.

We chose a CCT targeting SC for two main reasons. First, studies have shown SCT as an added modality seems to show additional effects on SC performance (specific to those who received the supplemented intervention). Second, SC is highly related to functioning. While studies have shown added effects when combining modalities, it is difficult to understand which modality in the combined CCT programs effects which outcome measures. We chose to focus on one modality within this study in order to better understand the direct effects of the social cognition aspect of the training. Future studies that choose to combine several target modalities (auditory, visual, or social training) may want to consider including multiple assessment time-points after the completion of each modality.

Moreover, interventions such as SCT work by improving neural integrity within the brain. The acquisition of neurobiological information is relatively fast and easy and provides us with reliable measures of brain structure and function. Currently, neuroimaging techniques such as sMRI or rsfMRI are generally requested by clinicians in order to exclude organic diseases, and not for measuring potential treatment response. In order for the field of clinical psychiatry to progress, the identification of robust neuromarkers capable of informing treatment response to particular NCIs will be crucial. Therefore, depending on the type of intervention used, duration, and targeted patient group, future studies may want to consider also investigating alternative neuromarkers.

Within this dissertation, we placed an emphasis on the potential utility of rsFC for monitoring neural response to SCT, and also as a T0 predictor of future good versus poor role functioning. In comparison to clinical or cognitive measures, rsfMRI is relatively easy to acquire, has greater sensitivity, and does not depend on the clinical expertise of researchers conducting such assessments. Nevertheless, future studies may want to combine multiple characteristics, such as multiple imaging modalities, or include clinical and/or cognitive characteristics. Such studies would help us better understand which clinical, behavioral, or neurobiological characteristics best contribute to measuring a response to various NCIs (Penadés et al., 2013).

With respect to the multivariate framework used within the last study of this dissertation, we focused on one particular measure of outcome: role functioning. Aside from the known association between SC and functioning, we were particularly interested in understanding the effects of SCT on every-day real-world functioning. Improvement in every-day functioning is critical for recovery in patients with PSD especially for those presenting at the clinic for the first time. Although a number of measures could have been utilized as a response metric within this study, we were interested in the transferability of this standalone targeted SCT to real-world functioning. Other studies have used various neuroimaging measures to gauge outcomes such as improvement in symptoms, cognition, and other functioning measures not included in this study. Other researchers may want to consider alternative measures based on the targeted goals of the particular intervention they implement.

Finally, in order for NCIs, such as SCT, to be incorporated into routine clinical practice, future studies will need to replicate current results within the field. Future intervention studies should recruit larger samples, ideally across multiple sites, in order to ensure our results are robust and replicable. This is especially important when utilizing multivariate measures that generally include a high number of features (such as in neuroimaging), but a low number of cases (such as patients or HC).

5.2 Conclusion

The studies conducted within this dissertation have provided the following novel contributions to the field of translational psychiatry:

1. Within the first aim of this dissertation, we investigated the effects of using a 10-hour SCT on cognition, functioning, and symptoms in patients with ROP. SCT has shown real-world applicability by improving role functioning in patients with ROP after only 10 hours of the intervention. This duration is much shorter than the majority of CCT to-date. These results speak for the feasibility and benefit of implementing a short, yet intense, CCT that focuses particularly on SC, in patients at an early stage of ROP. Additionally, with the use of a computerized SCT done on a tablet, we were able to broaden our reach by providing patients

with the option of completing the training in the clinic or from home. However, we did not find any effects on global or SC in this study.

2. Within the second aim of this dissertation, we attempted to further understand the neural effects of SCT. To this end, we investigated whether SCT had the capability of restoring rsFC within two brain regions involved in social cognition, and that have previously shown impairments in patients with PSD using a seed-based approach. Using the mPFC as a seed of the DMN, we showed intervention specific increases in fronto-temporal connectivity. Similarly, within the social brain network, using the amygdala as a seed, we found increases in amygdala-frontal rsFC in patients who underwent SCT. This suggests, that SCT may work by strengthening connectivities within networks critical for social cognition. Moreover, patients with worse performance in our SC task at T0 were the patients who showed a greater degree of change in rsFC between the amygdala and middle frontal gyrus. This not only suggests that SCT has the capability of improving functional integrity brain networks critical for SC, but also that patients with the greater impairment in SC seem to most benefit from the effects of SCT on rsFC in the brain.

3. Within the third aim of this dissertation, we created an independent HC-ROP rsFC model that could be applied to patients in our study sample. Such a model could be used in order to monitor neural response to the intervention at the individual level. Here, we derived a novel measure of neural response by assessing the changes in decision scores extracted at each time-point. Patients who underwent SCT that showed decision score changes in the "HC-like" direction, also showed significantly greater improvement over time in both global cognition and attention. Patients who's decision scores shifted in the "ROP-like" direction, showed no change in GC and worsening in attention. Moreover, no such differences were seen within the TAU control condition. We did not find any significant differences in the degree of shift in the "HC-like" or "ROP-like" direction between SCT and TAU.

   We additionally wanted to determine whether T0 rsFC could help to distinguish patients with good versus poor role functioning following the intervention. This investigation was the first to utilize rsFC in order to predict treatment response

based on role functioning in patients with ROP. We were able to successfully predict good versus poor role functioning at FU in patients that underwent the intervention. This suggests that a particular pattern of neural integrity at T0 may contribute to an improved response to SCT in a subset of individuals.

In summary, we have shown the effects of a novel short, albeit intensive, 10-hour SCT on both role functioning and increases in rsFC within regions often implicated as impaired in ROP. Moreover, within the final aim of this dissertation, we were able to utilize multivariate methods—which are advantageous over univariate measures as inferences can be made at a single-subject level. This is crucial from a clinical perspective. We showed the potential utility of developing an external model in order to monitor neural response. Additionally, we were able to predict role functioning in patients that underwent the SCT using T0 neuromarkers. These findings elucidate a potential way for machine learning to subserve clinical practice by giving novel insight about key observable correlates, as well as neurobiological markers, of SCT treatment response. These neuromarkers may be specifically integrated into individual early identification and intervention programs, thus resulting in a likely cheaper and more effective personalized psychiatry application.

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A Appendix

Tabelle 4.1. Empfohlene Dosierung (oral) der Antipsychotika in der Akuttherapie

Substanz	Empfohlene Startdosis (mg/d)	DI [1]	Zieldosis Ersterkrankte (mg/d)	Zieldosis Mehrfach-erkrankte (mg/d)	Höchste empfohlene Dosis (mg/d) [2]
Atypika					
Amisulprid	200	(1)–2	100–300	400–800	1200
Aripiprazol	(10)–15	1	15–(30)	15–30	30
Clozapin [3]	25	2–(4)	100–250	200–450	900
Olanzapin	5–10	1	5–15	5–20	20
Quetiapin	50	2	300-600	400-750	750
Risperidon	2	1–2	1–4	3–6–(10)	16
Ziprasidon	40	2	40–80	80–160	160
Konventionelle Antipsychotika					
Fluphenazin	0,4–10	2–3	2,4–10	10–20	20–(40)
Flupentixol	2–10	1–3	2–10	10–60	60
Haloperidol	1–10	(1)–2	1–4	3–15	100
Perazin	50–150	1–2	100–300	200–600	1000
Perphenazin	4–24	1–3	6–36	12–42	56
Pimozid	1–4	2	1–4	2–12	16
Zotepin	25–50	2–(4)	50–150	75–150	450
Zuclopenthixol	2–50	1–3	2–10	25–50	75

[1] DI (Dosierungsintervall): Empfohlene Verteilung der genannten Gesamtdosis über den Tag – Ein Zeitpunkt = 1, Zwei Zeitpunkte = 2 usw., Höchstdosierungen müssen ggf. auf mehrere Zeitpunkte verteilt werden.

[2] Höchste zugelassene Dosis nach Angaben der Fachinformationen. Insbesondere bei den neueren Antipsychotika werden jedoch auch in der klinischen Praxis oft höhere Dosierungen verwendet („off-label-use") und positive Erfahrungen damit (kasuistisch) berichtet.

[3] Clozapin wird üblicherweise nicht zur Behandlung von Ersterkrankungen eingesetzt.

Figure A.1: Medication guidelines taken from the German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN) with recommended dosages for particular antipsychotic medication. These guidelines are used in determination of individuals who may be included in the study based on the amount and length of time patients have been taking particular medication.

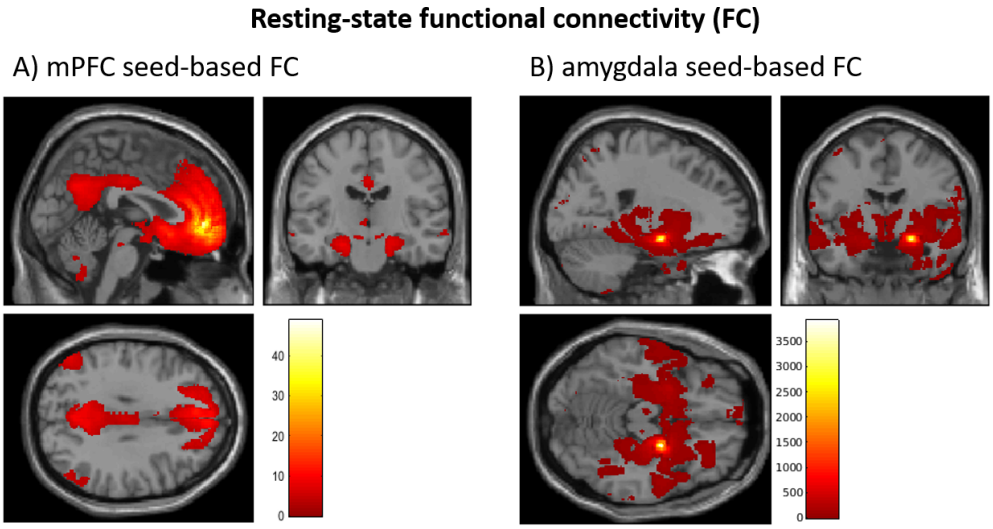

Figure A.2: Depiction of the regions of functional connectivity with A) mPFC and B) amygdala using a one-sample t-test across subjects.

Table A.1: Complete set of neuropsychological tests included under PRONIA guidelines. These tests are administered for each participant in one session lasting 1.5 hours.

Neuropsychological Assessments
Rey–Osterrieth complex figure test (ROCF)
Recognition
Immediate recall
Delayed recall
Diagnostic Analysis of Non-Verbal Accuracy
Auditory Digit Span
Forward
Backward
Verbal Fluency
Phonetic
Semantic
Rey Auditory Verbal Learning Test
Immediate repetition trial List A (1-5)
Interference list immediate repetition trial List B
After interference immediate repetition List A
Delayed repetition List A
Recognition List A
Trail Making Test
Part A
Part B
Continuous Performance Task - Identical pairs version
Self-ordered Pointing Task
Digit-Symbol Substitution Test
Salience Attribution Test
Wechsler Adult Intelligence Scale
Verbal IQ - Vocabulary Test
Performance IQ - Matrix Reasoning Test

Table A.2: Somatic diseases potentially affecting the structure and functioning of the brain used as exclusion criteria for all patients and HC in the study.

SOMATIC DISEASE
Known history of grade 2 hypertension if not well treated
Sarcoidosis
Inflammatory vascular disease
1. Systemic vasculitis 2. Periarteritis nodosa 3. Arteritis cranialis
Hepatic cirrhosis
Encephalopathy
1. Pancreatic encephalopathy 2. Wernicke's disease
Endocrinological disease
1. Known history of Diabetes mellitus if not well treated 2. Hyper-/Hypothyroidism 3. Addison's disease 4. Cushing's syndrome
Blood
1. Leukaemia 2. Polycythaemia vera
Immune system
1. Lupus erythematosus
Cancer

Table A.3: Neurological diseases potentially affecting the structure and functioning of the brain used as exclusion criteria for all patients and healthy individuals in the study.

NEUROLOGICAL DISEASE
Intrauterin and perinatal acquired brain damage
Little's disease, hemolytic disease of the newborn, rubella embryopathy, connatal toxoplasmosis, other connatal embryopathy (Lues, cytomegalovirus , HIV, Mumps), fetal alcohol syndrome
Malformations of the brain
Micro-/Macrocephaly, Meningo-/Encephalocele, hydrocephalus, neurofibromatosis (i.e. Recklinghausen disease), tuberous sclerosis, cephalotrigeminal angiomatosis
Intracranial tumors
Medulloblastoma, astrocytoma, oligodendroglioma, glioblastoma, acoustic neuroma, meningioma, adenoma, metastasis
Degenerative disease
Dementia (Alzheimer's disease, Frontotemporal dementia (FTD, Lewy body dementia)
Dystonia
Tourette syndrome
Metabolic diesase
Lipoidosis (leukodystrophy, poliodystrophy, Tay-Sachs disease, Refsum disease, Niemann–Pick disease, Gaucher's disease), phenylketonuria, Maple syrup urine disease, Hartnup disease, galactosaemia, Wilson's disease
Inflammatory disease
Multiple sclerosis, meningitis, encephalitis, neurosyphilis, HIV encephalopathy, Behçet's disease
Parkinson's disease
Huntington's disease
Epilepsy/seizures
Autism
Acquired brain damage (intracranial bleeding)
Stroke
Known history of migraines and reoccurring episodes within last 3 months

Table A.4: Positive and Negative Syndrome Scale symptoms (Kay et al., 1987).

Positive Symptoms	General Symptoms
P1. Delusions	G1. Somatic concerns
P2. Conceptual disorganization	G2. Anxiety
P3. Hallucinatory behavior	G3. Guilt feelings
P4. Excitement	G4. Tension
P5. Grandiosity	G5. Mannerisms and posturing
P6. Suspiciousness/persecution	G6. Depression
P7. Hostility	G7. Motor retardation
	G8. Uncooperativeness
Negative Symptoms	G9. Unusual thought content
N1. Blunted affect	G10. Disorientation
N2. Emotional withdrawal	G11. Poor attention
N3. Poor rapport	G12. Lack of judgement and insight
N4. Passive/apathetic social withdrawal	G13. Disturbance of volition
N5. Difficulty in abstract thinking	G14. Poor impulse control
N6. Lack of spontaneity and flow of conversation	G15. Preoccupation
N7. Stereotyped thinking	G16. Active social avoidance

Table A.5: Complete battery of tests used to assess patients and HC in PRONIA. The observer-rated assessments are split up into two sessions of screening and baseline, while individuals are given the self-rated assessments to complete themselves.

	ROP	HC
Screening Assessments		
1. General Data (Patient Main Data)	x	x
2. Reasons for Referral (Reasons Referral)	x	
3. Somatic state and health history (SOMAT)	x	x
4. CHR Assessment Tool I	x	x
4.1. Schizophrenia Proness Instrument – Adult Version Cognitive Disturbance (SPI-A COGDIS)	x	x
4.2. Structured Interview for Prodromal Syndromes P Items (SIPS P)	x	x
4.3. CAARMS Items (CAARMS)	x	x
4.4. Ultra High Risc Criteria – Schizotypy, Genetic Risk (UHRSCHIZO/GENETIC)	x	x
4.5. Global Assessment of Functioning To (GAF To)	x	x
5. Clinical High Risk Criteria	x	x
5.1. Clinical High Risk Criteria (CHR Criteria)	x	x
5.2. SIPS CHR Intake Criteria (SIPS Intake Criteria)	x	x
5.3. CAARMS CHR Criteria (CAARMS CHR Criteria)	x	x
6. Treatment Documentation (TREATMENT)	x	x
7. Structured Clinical Interview for DSM IV 1 – Screening (SCID-1 Screening)	x	x
8. Structured Clinical Interview for DSM IV 1 – Summary (SCID-1 Summary)	x	x
9. Inclusion/Exclusion Criteria (IC/EC)	x	x
Baseline Assessments		
10. Demographic and Biographic Data To (DEMOG To)	x	x
11. Premorbid Adjustment Scale (PAS)	x	x
12. CHR Assessment Tool II	x	x
12.1. Schizophrenia Proneness Instrument – Adult Version (SPI-A)	x	x
12.2. Structured Interview for Prodromal Syndromes N-G Items (SIPS N-G)	x	x
13. Positive and Negative Symptom Scale (PANSS)	x	
14. Scale for the Assessment of Negative Symptoms (SANS)	x	
15. Chart of Life Events (CoLE)	x	x
16. Functional Remission in General Schizophrenia (FROGS)	x	
17. Global Functioning Social / Role To (GF S/R To)	x	x
18. Prognostic Evaluation (PROGNOSTIC EVAL)	x	x
Self-Rated Assessments		
1. WHO Quality Of Life - Short Version (WHOQOL-BREF)	x	x
2. Multidimensional Scale of Perceived Social Support (MSPSS)	x	x
3. Resilience Scale for Adults (RSA)	x	x
4. Coping Inventory for Stressful Situations (CISS-24)	x	x
5. Social Phobia Inventory (SPIN)	x	x
6. Beck Depression Inventory – II (BDI-II)	x	x
7. Edinburgh Handedness Inventory – Short Version (EHI-SV)	x	x
8. Level of Expressed Emotion Scale (LEE)	x	x
9. Wisconsin Schizotypy Scales - Short Form (WSS)	x	x
10. The Everyday Discrimination Scale To (EDS To)	x	x
11. Bullying Scale To (BS To)	x	x
12. Childhood Trauma Questionnaire (CTQ)	x	x
13. NEO Five-Factor Inventory (NEO-FFI)	x	x

Table A.6: PRONIA complete set of self-rated assessment batteries included.

	ROP	HC
Self-Rated Assessments		
1. WHO Quality Of Life - Short Version (WHOQOL-BREF)	x	x
2. Multidimensional Scale of Perceived Social Support (MSPSS)	x	
3. Resilience Scale for Adults (RSA)	x	x
4. Coping Inventory for Stressful Situations (CISS-24)	x	x
5. Social Phobia Inventory (SPIN)	x	x
6. Beck Depression Inventory – II (BDI-II)	x	x
7. Edinburgh Handedness Inventory – Short Version (EHI-SV)	x	x
8. Level of Expressed Emotion Scale (LEE)	x	x
9. Wisconsin Schizotypy Scales - Short Form (WSS)	x	x
10. The Everyday Discrimination Scale To (EDS To)	x	x
11. Bullying Scale To (BS To)	x	x
12. Childhood Trauma Questionnaire (CTQ)	x	x
13. NEO Five-Factor Inventory (NEO-FFI)	x	

Table A.7: Demographic information, and changes in scores on cognitive measures, symptom ratings, and functional outcomes (FU-T0) of participants who received SCT that either trained in the clinic or from home. CPZ = chlorpromazine equivalent; FDR = False Discovery Rate; FU = follow-up; GAF = Global Assessment of Functioning; PANSS = Positive and Negative Syndrome Scale; SCT = social cognitive training; SD = standard deviation; T0 = baseline.

	SCT only			
	Home (N = 11)	Clinic (N = 15)	T/ $\chi 2$	P value
Demographics				
Number of female (%)	5 (45.45 %)	6 (40.0 %)	0.077	0.781
Age (*SD*)	28.67 (5.70)	25.49 (6.58)	1.285	0.211
Years education (*SD*)	15.32 (2.80)	15.03 (4.26)	0.193	0.849
Premorbid IQ (*SD*)	100.45 (14.91)	97.00 (15.45)	0.572	0.573
Days between assessments (*SD*)	43.91 (8.57)	53.60 (11.62)	-2.333	0.028*[1]
Medication at baseline (*SD*) CPZ quivalent	49.70 (38.30)	82.19 (89.40)	-1.127	0.271
Cognition				
Δ Global cognition (*SD*)	0.05 (0.36)	0.39 (0.77)	-1.367	0.184
Δ Social cognition (*SD*)	0.00 (1.01)	-0.03 (1.02)	0.071	0.944
Δ Speed of processing (*SD*)	0.14 (0.91)	1.71 (2.39)	-2.067	0.050*[1]
Δ Working memory (*SD*)	0.58 (0.66)	0.13 (0.59)	1.860	0.075
Δ Verbal Learning (*SD*)	0.01 (0.44)	-0.18 (0.80)	0.683	0.501
Δ Attention (*SD*)	-0.01 (0.93)	-0.23 (1.45)	0.441	0.663
Δ Executive functioning (*SD*)	0.19 (0.81)	1.00 (1.72)	-1.442	0.163
Functional Outcome				
Δ GAF Disability/Impairment rating past month (*SD*)	14.73 (19.40)	6.13 (14.67)	1.288	0.210
Δ Global Functioning - Role (*SD*)	1.55 (1.75)	0.80 (1.15)	1.313	0.202
Δ Global Functioning - Social (*SD*)	1.09 (0.94)	0.20 (1.01)	2.277	0.032*[1]
Symptoms				
Δ PANSS total (*SD*)	29.00 (17.70)	19.87 (23.59)	1.079	0.292
Δ PANSS positive (*SD*)	11.18 (6.13)	7.60 (6.63)	1.404	0.173
Δ PANSS negative (*SD*)	4.73 (5.14)	3.07 (7.09)	0.659	0.516
Δ PANSS general psychopathology (*SD*)	13.09 (9.33)	9.20 (12.80)	0.854	0.402

* Significant at $P < 0.05$

[1] No longer significant after correcting for multiple comparisons using FDR correction.

B CV

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Department of Radiology of the LMU Munich Since 09.2015
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In Preparation
Haas, S. et al., (In prep.). Tracing Response to Computerized Cognitive Remediation Using Functional Connectivity in Recent Onset Psychosis: a Multivariate Neuromonitoring Approach.

Penzel, N.[1], Haas, S.[1], et al., (In prep.). Structural and functional brain alterations across the psychosis spectrum: a meta-analysis.

Conference Presentations & Workshops

Kambeitz-Ilankovic, L., Koutsouleris, N., Wenzel J., Haas, S., Fisher, M., Vinogradov, S., Subramaniam, K. (2019). 5.4 Individualized Prediction of Functional Outcomes in Schizophrenia Patients in Response to Neuro-Cognitive Intervention: a Machine Learning Analysis. *Schizophrenia Bulletin*, 45(Suppl 2), S94-S95.
Accepted to the *Schizophrenia International Research Society Conference*; April 2019.

Haas, S., Koutsouleris, N., Ruef, A., Biagianti, B., Kambeitz, J., Dwyer, D., ... Kambeitz-Ilankovic, L. (2018). F70. Computerized Social Cognitive Training (sct) Improves Cognition And Restores Functional Connectivity In Recent Onset Psychosis: An Interim Report. Schizophrenia Bulletin, 44(Suppl 1), S246.
Accepted to the *Schizophrenia International Research Society Conference*; April 2018.

Weiske, J., Ruef, A., Haas, S., Bonivento, C., Koutsouleris, N., Kambeitz-Ilankovic, L. (2018). T137. Classification Of Recent-onset Psychosis Based On Resting-state Functional Connectivity And The Relationship To Neurocognitive Impairment. Schizophrenia Bulletin, 44(Suppl 1), S168.
Accepted to the *Schizophrenia International Research Society Conference*; April 2018.

Kambeitz-Ilankovic, L., Haas, S., Meisenzahl, E., Möller, H.J., Falkai, P., Koutsouleris, N. (2016). 1305. Altered Neurocognitive Aging in Adults with Clinical High Risk for Psychosis.
Accepted to the *Organization for Human Brain Mapping Conference*; June 2016.
Workshop: Meta-Analytic Network Modelling Workshop.

Haas, S., Cabral, C., Urquijo, M., Von Saldern, S., Kambeitz, J., Koutsouleris, N., Kambeitz-Ilankovic, L. 206. Separation of recent-onset psychosis patients from healthy controls based on resting-state functional connectivity pattern classification.
Accepted to the *Fourth Biennial Conference on Resting State Brain Connectivity*; Fall 2014.
Workshop: Pre-conference Workshop: Basic and Advanced Brain Connectivity - theory and methods.

[1] Shared first authors

Haas, S., Cabral, C., Urquijo, M., Von Saldern, S., Kambeitz, J., Koutsouleris, N., Kambeitz-Ilankovic, L. M154. Separation of recent-onset psychosis patients from healthy controls based on resting-state functional connectivity pattern classification. npj Schizophrenia (2016) 2, Article number: 16008; doi:10.1038/npjschz.2016.8.
Accepted to the *Schizophrenia International Research Society Conference*; April 2016.

Honors & Awards

- Member of the Elitenetwork Bavaria — Since 2016
- Top Overall Poster Award - Schizophrenia Bulletin — 04.2016
  Schizophrenia International Research Society Conference

Skillset

- **Methods:** MVPA, sMRI, fMRI, resting-state fMRI, ICA, Meta-analysis.
- **Programming Languages:** Matlab, R.
- **Software:** SPSS, SPM, REST Toolbox, NeuroMiner, GIFT, MRICron, BrainNet Viewer, GingerALE, Seed-based d Mapping.
- **Clinical batteries:** Structured Clinical Interview for DSM-IV (SCID), Schizophrenia Proneness Instrument, for Child and Youth (SPI-CY) and Adults (SPI-A), Structured Interview of Psychosis-Risk Syndrome (SIPS), Positive and Negative Syndrome Scale (PANSS), Functional Remission of General Schizophrenia (FROGS), Global Assessment of Functioning (GAF), Global Functioning: Social (GF: Social) and the Global Functioning: Role (GF: Role).
- **Miscellaneous:** Microsoft Office, LaTeX, Adobe Creative Suite, Photography.

Professional Memberships

- Member - Organization for Human Brain Mapping (OHBM) — Since 2017
- Member - Early Intervention in Mental Health (IEPA) — Since 2016

Voluntary activities

Operations Manager & Curation Support in the core team of TEDxTUM organizing: — Since 2015
TEDxTUM 2018: Conscious Reflection
TEDxTUM Salon 2018: Tiny Superpowers
TEDxTUM 2017: Reformations of tomorrow
TEDxTUM Salon 2017: Reconnect
TEDxTUM 2016: Entelechy
TEDxTUM Salon 2016: The common extraordinary
TEDxTUM 2015: Facets (volunteer)

Peer to Peer Mentor Per semester for 1-2 Bachelor students of Psychology (LMU) — 2014 – 2016

Languages

- **English:** Native proficiency
- **German:** Professional proficiency (C2)
- **Tagalog:** Professional proficiency