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MASTERS THESIS

Using resting state functional connectivity to predict functional outcome in individuals at clinical high risk for psychosis

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Abstract

Research in the psychosis prodrome using neuroimaging techniques has been applied in classification of patients along the psychosis spectrum (Koutsouleris et al., 2009), or distinguishing schizophrenia (SZ) from other psychiatric disorders (Calhoun et al., 2008) and healthy controls (Rathi et al., 2010) or predicting the rate of transition (Fusar-Poli et al., 2011; Koutsouleris et al., 2011). Functional outcome which includes social and role functioning is a vital component of psychosis recovery that has so far been largely underrepresented in comparison to transition to psychosis and has been limited to application of univariate methods. Clinical high risk (CHR) patients that do not transition to the full illness continue to have impairments in functioning, making it difficult for them to be independent and integrating into society.

In recent studies, the psychosis research community has shifted their focus from univariate methods to multivariate pattern analysis (MVPA) because of its capacity to make inferences at a single-subject level, their ability to inspect patterns of activity across voxels throughout the brain and work seamlessly with massive datasets. We employed Support Vector Machine (SVM), a linear machine learning classification algorithm embedded in a pooled nested double cross-validation scheme. Baseline (T0) resting state functional connectivities (rsFC) between 160 regions of interest (ROI) was used to classify functional outcome in CHR patients. Our cohort of 76 CHR subjects were recruited from seven different sites across Europe and were then divided into 'Good'(N = 37, GF Social > 7) and 'Poor'(N = 39, GF Social $\leq$ 7) groups.

The rsFC classifier was applied with a generalizability mask (Gmask) to control for site effects and was able to discriminate between the groups with a balanced accuracy of 68%, specificity at 71.8% and sensitivity of 64.9%. The most predictive

functional connectivities were present between the right inferior parietal lobule (IPL) and the right ventromedial prefrontal cortex (vmPFC). Other connectivities implicated regions such as the anterior insula, angular gyrus and dorsolateral prefrontal cortex (dlPFC). These regions are involved in social cognition, language and processing emotional information (Nierenberg et al., 2005; Wylie &Tregellas 2010), domains that are associated with social functioning .There were no significant correlations between the decision scores and clinical symptoms as measured by the positive and negative symptom scale (PANSS). The study shows that social outcome in CHR can be predicted with rsFC using MVPA.

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TABLE 1: List of important abbreviations found in the paper

Abbreviation	Full form
ACC	Anterior cingulate cortex (ACC)
APS	Attenuated Psychotic Symptoms
BAC	Balanced Accuracy
BDI	Beck's Depression Inventory
BLIPS	Brief Limited Intermittent Psychotic Symptoms
BOLD	Blood Oxygen Level Dependent
CHR	Clinical High Risk
COGDIS	Cognitive Disturbances
CSF	Cerebrospinal fluid
CV	Cross Validation
dlPFC	dorsolateral prefrontal cortex
DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
EPI	Echo Planar Imaging
EPOS	European Prediction of Psychosis Study
FC	Functional connectivity
FD	Framewise Displacement
FU	Follow-up
fMRI	functional Magnetic Resonance Imaging
FPN	Frontoparietal Network
GAF	Global Assessment of Functioning
GF	Global Functioning
GM	Gray Matter
HC	Healthy Controls
IPL	Inferior Parietal Lobule
ML	Machine Learning
mPFC	medial prefrontal cortex
MRI	Magnetic Resonance Imaging
MVPA	Multivariate Pattern Analysis
NAPLS	North American Prodrome Longitudinal Study
PANSS	Positive and Negative Syndrome Scale
PET	Positron Emission Tomography
PRONIA	Personalized Prognostic Tools for Early Psychosis Management
ROI	Region of Interest
rsfMRI	resting state Magnetic Resonance Imaging
rsFC	resting state functional connectivity
sMRI	structural Magnetic Resonance Imaging
SN	Salience Networ
SZ	Schizophrenia
SVC	Support Vector Clustering
SVM	Support Vector Machine
SVR	Support Vector Regression
UHR	Ultra High Risk
VBM	Voxel Based Morphometry
vmPFC	ventromedial prefrontal cortex
WM	White Matter

For Mama, for all you have done and continue to do.

Chapter 1

Introduction

1.1 Prologue

The onset of psychosis is now known to be preceeded by a pre-psychotic or prodromal phase and individuals within this pre-psychotic phase are referred to as CHR. The CHR cohort has been found to present with deficits that are already present in individuals with SZ, and include impairments in social and occupational functioning (combined referred to as functional outcome) in addition to deficits in cognitive abilities (Addington & Addington 2005; Simon et al., 2006; Fusar-Poli et al., 2011, de Paula et al., 2015). CHR individuals that do not transition to full psychosis continue to have lower levels of functioning as compared to healthy controls (HC) and only moderately better functioning as compared to individuals with psychosis (Addington et al., 2011; Fusar-Poli et al., 2015). The functioning impairments lead to a compromised quality of life and to a higher probability of suicide, social alienation and unemployment (Power et al., 2003). The societal costs and the affected quality of life of CHR patients has resulted in an increase in research investigating their functioning outcome. This has proven to be a challenge because later outcome in functioning depends on an individual's symptoms and can be influenced by various other factors differing between patients. These factors include functioning prior to illness

(Barajas et al., 2013), duration of illness and medication (Keshavan et al., 2003; Qin et al., 2014; Perkins et al., 2015; Zhang et al., 2018) making it difficult for researchers to find patterns that would help predict a patient's outcome in the future. Neuroimaging methods are largely being used to identify potential biomarkers which will aid in the assessment and diagnoses of patients. Clinical assessments alone are not reliable predictors of the illness trajectory of a patient and their future outcome. Biomarkers have the potential to be more efficient at identifying subgroups of a patient population at first presentation itself. Neuroimaging methods in combination with MVPA using machine learning (ML) are progressing further in order to identify potential biomarkers that would allow for a more subject specific prediction of functioning.

1.2 The Clinical High Risk in Psychosis

The idea of psychosis has moved from a narrow and strict concept and evolved into being understood as a continuum or a spectrum. This means that the psychosis expression is now considered not as an all-or-none phenomenon, but rather phenomenologically and temporally continuous across the general population (Guloksuz & Os., 2018). Based on this the notion of a pre-psychotic, at-risk or prodromal stage has emerged. The earliest definitions of a prodome in psychosis described it as, "a heterogeneous group of behaviours temporally related to the onset of psychosis" (Keith and Matthews 1991, p.53) or a period from first noticeable symptoms to first prominent psychotic symptoms (Beiser et al., 1993).

Due to the heterogeneity in inclusion criterion, the prodromal phase is now referred to by the terms CHR or as 'Ultra-High Risk '(UHR) (Fusar-Poli et al., 2013). Thought the terms are used interchangeably there are some differences between the

two. For UHR, inclusion requires one or more of the following criterions: i) Attenuated Psychotic Symptoms (APS), ii) Brief Limited Intermittent Psychotic Symptoms (BLIPS) and iii) Trait and state risk factor i.e., with a first degree relative with a psychosis disorder and a significant decrease in functioning (Genetic High Risk), or Schizotypal personality disorder (Yung & McGorry., 2007; Fusar-Poli et al., 2013) and represents a subgroup of at risk patients that are closest to manifesting psychosis (Simon et al., 2006). The CHR takes into account the basic symptoms (COGDIS), which are associated with the emergence of psychosis and known capture symptomatic expression underlying neurobiological processes of CHR (Schultze-Lutter & Theodoridou, 2017). COGDIS symptoms include impairments in domains such as attention, perception and thought content (Klosterkötter et al., 2001; Schultze-Lutter et al., 2008).

The earliest known examination of the CHR group was done by Häfner et al., (1998), which revealed that in over 70% of the patients, the disease is preceded by a pre-psychotic phase (Riecher-Roesser et al., 2007; Fusar-Poli et al., 2013). Recent findings state that approximately 18-36% of CHR individuals transition to a full psychosis (Tognin et al., 2013) and recent work estimates a prevalence of approximately 4% to 8% for psychotic symptoms or psychotic-like experiences in the general population (Fusar-Poli et al., 2013; Klosterkötter et al., 2001). The risk of developing psychosis in the CHR group is 20% over a period of twoyears (Fusar-Poli et al., 2016). Even within the group of CHR patients, the prevalence varies depending on the diagnosis. Monozygotic twins have a 40-50% concordance rate for the illness over lifetime (Tsuang et al., 2002) and first-degree relatives of SZ patients have approximately a 10-fold increased risk for later illness compared to non-relatives over lifetime (Chang et al., 2002).

As mentioned above, considerable impairments in academic performance and

occupational functioning along with the presence of other co-morbid illnesses (Fusar-Poli et al., 2012) together with difficulties in interpersonal relationships are often observed (Bechdolf et al., 2005; Ruhrmann et al., 2008). The CHR group offers the chance for early treatment of psychotic disorders and henceforth their timely management and may also prove to be relevant for detection of relapse and for prognosis (Fusar-Poli et al., 2013; McGorry et al., 2013). A delay in treatment has been associated with a lower rate of remission and/or a longer time to remission of symptoms (Gonszales-Valderrama et al 2015). Studying the CHR population offers an insight into the early stages of the disease without medication and other factors such as duration or chronicity as confounds. Simultaneously, allowing researchers to also build interventions that could be made available at this stage and delay or potentially avoid the onset of the disease. (Tognin et al., 2014). Using rsFC and related neuroimaging techniques to predict the functional outcome that leads to a high risk stage will help us understand the factors that play a role in increasing an individual's risk for psychosis.

These urgencies have led to the execution of large multisite investigations into the early phase of psychosis such as the North American Prodrome Longitudinal Study (NAPLS 1-3, 2003- Ongoing), the European Prediction of Psychosis Study (EPOS, 2001 - 2005) and the Personalised Prognostic Tools for Early Psychosis Management (PRONIA, 2013-Ongoing). These projects are trying to elucidate the predictors of psychosis, evaluate the CHR definition criterion and develop interventions and prognostic tools.Results from the NAPLS study showed increased risk for psychosis over time in the CHR population (Addington, 2012). Impairments in social cognition and in global neuropsychological functioning (Barbato et al., 2015) were also found. Recently, a risk calculator was developed (Fusar-Poli et al., 2017, 2018) to identify CHR patients and support transdiagnostic prediction of psychosis.This may

eventually lead to the implementation of an individualized prevention plan focused on improvement of outcomes. These studies used clinical data for their investigations and predictions. F involving neuroimaging methods are further developed in Section 1.4.

1.3 Neuroimaging in CHR

The use of neuropsychological and neurobiological methods are an important aspect of the ongoing research especially for detection and development of markers. Neuroimaging, (especially the various MRI) techniques such as structural MRI (sMRI) , functional MRI (fMRI), rsfMRI as well as electroencephalography (EEG) and positron emission tomography (PET) are widely used.

Using sMRI, GM reductions have been found in frontal, lateral temporal and medial temporal regions in CHR patients (Meisenzahl et al., 2008) which have specific patterns related to symptoms. Changes in temporal and prefrontal areas have been found to be associated with disorganized symptoms. Positive symptoms were found to be related to alterations in perisylvian regions and the thalamus whilst negative symptoms were linked to areas within the frontal, temporal as well as limbic and subcortical structures (Koutsouleris et al., 2009). CHR subjects show further abnormalities in the parietal lobe, superior temporal, and insula in comparison to those only with a genetic risk (Smieskova et al., 2013). Changes in GM volume are specific to and differ between different psychotic illnesses and hence can be a vital addition to predict and differentiate between diagnostic categories as well.

Using fMRI, disruptions have been generally found in frontal and striatal areas (Morey et al., 2005), the prefrontal areas (Fusar-Poli et al., 2011), fronto-temporal-parietal areas (Smieskova et al., 2012) and fronto-thalamic-cerebellar network (Whalley et al., 2004). These alteration in brain functions have also been found to be

directly related to structural abnormalities, specifically in the left middle frontal gyrus (Fusar-Poli et al., 2011). Hence, previous research has found various impairments and alterations across the brain in the CHR group. These findings are not always consistent, but importantly illustrate that CHR already show changes in the structure and functioning of their brain before the onset of the full illness and these changes could be precursors to those found in SZ.

1.4 Functional outcome in CHR

A critical feature of the prodromal phase is marked by deterioration in functioning outcome which is also known to be treatment resistent (Englisch & Zink, 2012).Greater social impairment, which is an aspect of social functioning was one of the five features that contributed to the predictive algorithm that was developed in the NAPLS 1 study (Cannon et al., 2008). Impairments in functional outcomr reduces independence, lowers productivity, and affects not only the individual but also the society at large. This provides a further need for understanding the factors leading to later outcome in psychosis as well as early intervention targeting social and occupational functioning. Additionally, as a large number of CHR individuals do not transit to a severe case of psychosis, being able to identify and predict patients at different risks for functional impairment will also help in preventing the decrease in quality of life and accompanying disabilities.

Different methods and factors have been utilized to predict functional outcome in CHR cohorts as well as first-episode or recent onset psychosis patients. Decreased performance in neurocognitive tests of processing speed and verbal memory along with basic symptoms such as deficiency in dividing attention, attenuated negative and general symptoms such as apathy, anhedonia, poor attention, disorientation

were found to be related to an increased risk for poor outcomes in the future (Carrión et al., 2013; Salokangas et al., 2014; Mucci et al., 2016). In first-episode psychosis, lower functioning scores have been found to be associated with a reduction in grey matter (GM) volume in prefrontal and cingulate areas and alterations in connectivity between these areas with subcortical structures (Dazzan et al., 2015). In CHR, using voxel based morphometry (VBM) a reduction in GM volume in the postcentral gyrus and the anterior cingulate have been shown to be related to self-reported social impairment (Lincoln & Hooker., 2014), in addition to impairments in frontal regions, changes in limbic areas and the cerebellum have also been found to be predictive of functional outcome (Reniers et al., 2017).

Functional imaging studies using verbal fluency tasks have found an increase in activation in the frontal and limbic areas for CHR individuals with poor functional outcome, which may reflect a compensatory response or inefficient cortical function (Reniers et al., 2014, 2017). Within a group of CHR patients, a fMRI study using a working memory task found that individuals with a poor outcome showed alterations in frontal, temporal and striatal regions along with reduced deactivation within default-mode network (DMN) regions comprising of the posterior cingulate cortex, medial prefrontal cortex (mPFC), medial temporal lobe, and the inferior parietal cortex as compared to those with a good outcome. Other neuroimaging methods have also been used to explore functioning in both SZ and CHR. Using Diffusion Tensor Imaging (DTI), SZ patients showed impairments in the fractional anisotropy (FA) of the inferior longitudinal fasciculus and arcuate fasciculus to be associated with functional outcome (Behdinan et al., 2015). Similarly, changes in white matter (WM) integrity in the hippocampus and inferior longitudinal fasciculus was found to be related to functional outcome in CHR individuals (Karlsgodt et al., 2009).

The first MVPA study to predict outcomes in CHR populations used a cortical based pattern classification. Kambeitz-Ilankovic et al., (2015) used SVM to classify a cohort of CHR patients into either a 'Good' or a 'Poor' outcome group also using the Global Assessment of Functioning (GAF) scale and achieved an accuracy of 82%. Using sociodemographic, clinical and neruocognitive data Koutsouleris et al. (2016) predicted the functional outcomes at 4 weeks and 52 weeks follow-up (FU) in first episode psychosis patients with 75% accuracy and with 70% accuracy when validated across 44 European sites. De Wit et al., (2016) applied Support Vector Regression (SVR) to structural MRI data in CHR adolescents to predict long term clinical and functioning outcome and found a high correlation (r =0.42) between baseline subcortical volumes and long term functioning. Recently, combining clinical and neuroanatomical data outcomes were predicted with accuracies of 85.4%/62.7% (Koutsouleris., 2018). Research using MVPA to predict functional outcome is very limited, and hence requires further work.

1.5 rs connectivity in CHR

Resting state MRI works on the same haemodynamic principle as fMRI. The principle works on the different magnetization properties of oxy- and de-oxygenated blood (referred to as the blood oxygen level dependent (BOLD) signal) which are detected in the MR readout signal. These changes in the BOLD signal arise due to changes in neuronal activity following a change in brain state which may be produced for example, using a stimulus or task. The main difference is that rs does not involve a task and it focuses on spontaneous, low frequency fluctuations (<0.1 Hz) in the BOLD signal (Biswal et al., 1995). Functional connectivity (FC) is defined as the temporal dependency of neuronal activation patterns of anatomically separated brain regions.

Over the last decade, a large body of psychosis studies has combined rsfMRI and FC for rsFC and examined the statistical dependency between the time series of rs brain areas (Van Den Heuvel, 2010). rsFC allows for looking at the intrinsic activity of the brain, unaffected by cognitive or sensory stimulus (Smitha et al., 2017) and the lack of a task allows patients with difficulty understanding instructions to participate. As reported above, psychosis is associated with a range of symptoms and it is unlikely that these impairments can be explained by abnormalities in specific areas. The disconnection hypothesis put forth by Friston and Frith in 1995 theorized that the symptoms of psychosis are better understood in terms of abnormal interactions or integrations between different areas. On a neuronal level, these impairments manifest as abnormal functional connectivities. Investigating the interactions between brain regions can contribute to understanding large scale communication in the brain and it can provide information on the role of connectivity in disease phenotype and endotype.

In chronic SZ an increased connectivity between the left dlPFC and right inferior frontal gyrus as compared to healthy controls is seen (Liu et al., 2012). Interestingly, the researchers also found a commonality between chronic SZ patients and their unaffected siblings, providing evidence that their might already be impairments in brains of individuals at (genetic) risk for psychosis even without showing symptoms. Frontal areas specifically the dlPFC has long been implicated in psychosis (Dolan et al., 1993). rsFC has helped understand the role of this area in large-scale systems and has shown that systems that include dLPFC may alter relationships between systems responsible for other domains of information processing and might help to explain disparate network-level findings in schizophrenia (Satterthwaite et al., 2016). In classification studies using MVPA, a reduced FC between fronto-occipital, fronto-parietal, fronto-temporal and cortico-thalamic and an increased FC

between the left inferior temporal gyrus and parahippocampal gyrus was highly predictive in separating SZ from healthy control (Cabral et al., 2016). These alterations have also been linked to clinical symptoms in CHR cohorts (Dandash et al., 2013; Fornito et al., 2013).

A large scale FC network implicated in SZ is the salience network (SN), which is important for ascertaining the saliency of stimuli and includes the insula and regions in the anterior prefrontal cortex and anterior cingulate cortex (Pelletier-Baldelli et al., 2015). The insula has been found to be activated during emotional expression and hence as part of the SN may be of relevance for understanding salient emotional stimuli in an interaction. Pelletier-Baldelli et al., (2015) found poor social functioning ability associated with the a lower FC between the SN and the visual cortex for CHR. A deficit in a visual processing would lead to an impairment in interpreting facial emotions and subsequently social cues, which would then lead to a decrease in social functioning. This provides evidence that FC between seemingly varied regions of the brain show that lower-level (bottom-up) processes affect higher level cognitive processes. In prodromal patients disruptions in fronto-temporal connectivity, hyperconnectivity and hypoconnectivity within the DMN regions have also been discovered (Crossley et al., 2009; Shim et al., 2010). These connectivities and regions of the DMN, specifically the posterior part of the temporal cortex and the mPFC are involved in social cognition and emotion (Wible et al., 2009) which fall under the umbrella of social functioning.

1.6 MVPA and ML methods in CHR

In previous imaging studies of psychosis, classical univariate analysis methods have been the method of choice. Univariate methods (such as ANOVA, t-tests) detect group differences in activation and connectivity only within a region or voxel (Sun

et al., 2009). The limitation of univariate approaches is that they require averaging across brain areas and hence are unable to capture individual differences. Additionally, this approach is often limited to certain predefined areas (ROI) which do not allow for patterns of impairments or change to be captured (Zarogiani 2013). Univariate methods are also limited in combining information from high dimensional MRI data sets and also have difficulties with complex non-linear data. Due to these drawbacks, univariate methods have limited application in predictive studies. In order to overcome these disadvantages related to univariate methods, there has been a shift towards applying MVPA using ML techniques.

ML techniques are, "a varied group of statistical methods that automatically determine parameters to reach an optimal solution to a problem rather than being programmed by a human a priori to deliver a fixed solution" (Dwyer et al., 2018, pg. 94). There are two main types of ML methods, namely, supervised and unsupervised learning (Bishop., 2006). These methods have and are largely being used to solve either classification or regression problems. Classification problems identify the category to which a set of observations belong to based on a model built from labeled training data and regression problems involve predicting a continuous output. The applications of ML in psychiatry and clinical psychology are wide ranging and they can be used for treatment prediction, diagnosis, prognosis and detection and monitoring of potential biomarkers (Dwyer et al., 2018). The most widely used form of ML is supervised learning, where a data set with correct labels is presented to the computer and the computer then 'trains' and learns the relationship between the data and it's associated labels using a classification algorithm. The ultimate goal is to be able to correctly predict the labels for each individual data point given a new dataset.

In neuroimaging, MVPA aims to capture distributed patterns of activity within a

region in order to assess for example, how a distribution of voxels can differentiate between specific brain states (Yoon et al., 2008). These methods have been successfully used to classify SZ and HC using sMRI (Davatzikos et al. 2005; Sun et al., 2009; Nieuwenhuis et al., 2012) with accuracies in the range 70 - 86%. sMRI in combination with MVPA has also been applied to prediction of disease onset (Koutsouleris et al., 2009, 2011), identification of subgroups (Koutsouleris et al. 2014) and disease progression (Tognin et al., 2014) among others. Using fMRI data classifying of SZ and HC has resulted in accuracies in the range 80-90% (Demirci et al., 2008), fMRI has also been used in prediction of diverse disorders (Honorio et al., 2012) and determining subgroups within SZ (Yoon et al., 2012). Using resting state MRI in diverse applications with MVPA, accuracies in the range of 75% to 92% have been found (Jafri and Calhoun 2006, Shen et al., 2010). rsfMRI has been shown to have higher accuracy and sensitivity as compared to sMRI (Kambeitz et al., 2015; Cabral et al., 2016). This along with the aforementioned advantages of rsfMRI, makes it optimal to use for further research with MVPA and ML methods.

1.7 Hypotheses and Aims

In the current study of a cohort of CHR patients, we use rsFC to predict social outcome based on Global Functioning (GF) Social scores. The aim was to correctly classify which of the two social outcome groups i.e, 'Good 'or 'Poor'as defined by a threshold (further details in section 2.1) on the GF Social scale did the patients belong to.

In addition, we wanted to highlight the functional connectivities that are most predictive of discerning the two groups. Based on previous research we expected widespread connectivities between frontal regions and the rest of the brain specifically with areas responsible for social cognition and processes, for example, the

insula (Pelletier-Baldelli et al., 2015), the inferior parietal lobule (IPL), the anterior cingulate cortex (ACC) and also within the prefrontal areas involved in the DMN such as the mPFC (Brunet-Gouet Decety 2006; Wible et al., 2009).

Lastly, we wanted to determine whether there was a relationship between a patient's likelihood of belonging to either of the two social outcome groups and their symptom severity. This was done by correlating the decision scores from the classifier with the Positive and Negative Syndrome Scale (PANSS) scores. We expected to find a relationship between the two as negative and general symptoms have formerly been shown to be linked to functioning (Cotter et al., 2014; Meyer et al., 2014; Schlosser et al., 2015).

Chapter 2

Methods

2.1 Participants

The population analyzed in the current study are a subset of the PRONIA consortium baseline (T0) cohort as of May 2018 (Table 1.1). PRONIA is a collaboration project between various European and Australian researchers aiming to develop a prognostic tool for early psychosis management using machine learning methods.

TABLE 2.1: List of PRONIA Consortium Members

PRONIA Consortium Members
Ludwig-Maximilians-Universität München, University of Munich
Universitäre Psychiatrische Kliniken Basel, University of Basel
Universitätsklinikum Köln, University of Cologne
University of Birmingham
Turun Yliopisto, University of Turku
Universitàdegli Studi di Udine, University of Udine
University of Melbourne
Dynamic Evolution
General Electric Global Research
General Electric Healthcare
Universitàdegli Studi di Milano, University of Milan

The full cohort consisted of 759 patients and included 137 CHR patients collected from the PRONIA member sites. For the purposes of this analysis, T0 rsFC and FU outcome data of a total of 76 CHR patients from all 7 sites was used (Table 2.2

and 2.3). For the analyses, the subjects were separated into groups based on the GF Social and GF Role values thresholded at 7. Subjects with scores greater than 7 were in the 'Good 'outcome category and scores equal to or lesser than 7 were in the 'Poor 'outcome category. The GAF Disability scores were thresholded at 75 and values greater than 75 were placed under the 'Good' outcome category and values equal to or lesser than 75 were in the 'Poor' outcome category. These thresholds were set after calculating the median and average over all subjects, The median and average for GF Social were 7 and 7.25 respectively, for GF Role they were 6.93 and 7 and lastly for GAF Disability they were 75 and 70.45 respectively.

TABLE 2.2: List of exclusions from original CHR cohort

Exclusion reasons	
Preprocessing failure	15
Outliers in normalization homogeneity check	19
Outliers in wavelet despike homogeneity check	1
Outliers in covariate removal homogeneity check	23
Functional outcome scores not available	3
Total	61

Clinical and neurocognitive data are collected across the centres at T0 and subsequently at FUs of 9 months (T1) and 18 months (T2). Between these main follow-up time points, short clinical interval interviews are taken at 3 months (IV3), 6 months (IV6), 27 months (IV27) and 36 months (IV36) post baseline.

TABLE 2.3: List of subjects and the outcome points for their data

Time point	Number of subjects
IV3	1
IV6	14
IV12	0
IV15	0
T1	61
Total	76

Distribution of subjects across sites is listed in Table A.2 and demographic information is detailed below in Table 2.4.

TABLE 2.4: Demographic information for CHR patients based on the Global Functioning Social outcomes

	Baseline		Follow-up	
	Good	Poor	Good	Poor
N	37	39	37	39
Age (mean ± sd)	26.57±5.22	27.38 ± 5.39	26.57±5.22	27.38 ± 5.39
Sex (in %)	51% Females	49% Females	51% Females	49% Females
PANSS Negative (mean ± sd)	10.19± 3.77	15.36 ± 6.59	7.86 ± 1.64	11.81± 4.46
PANSS General (mean ± sd)	27.11 ±8.50	29.61 ± 7.97	18.64±3.54	25.58±7.82
PANSS Positive (mean ± sd)	10.54 ±3.24	10.39 ±2.89	6.46±3.56	8.69±3.78
Beck's Depression Inventory (BDI) II (mean ± sd)	22.60±12.00	27±12.93	9.06±9.46	19.64±12.00
GAF Symptoms (mean ± sd)	57.76 ±10.70	52.81 ± 9.91	75.08±9.21	60.84±10.35
GAF Disability (mean ± sd)	61.57 ±15.04	52.62 ± 11.52	78.97±7.69	62.35±13.19
GF Social (mean ± sd)	7.03±1.21	5.89±1.17	8.24±0.43	6.31±0.76
GF Role (mean ± sd)	6.68±1.29	5.70±1.22	8.05±0.70	5.87±1.60

2.2 Inclusion and Exclusion criterion

The general inclusion and exclusion criterion for participation in the study are detailed in Table 2.4. Reasons for exclusions in the preprocessing pipeline are present in Table 2.5

TABLE 2.5: General Inclusion and Exclusion Criterion

Inclusion Criterion
Age between 15-40 years
Language skills sufficient for participation
Sufficient capacity for consent
Exclusion Criterion
IQ below 70
Hearing is not sufficient for neurocognitive testing
Current or present head trauma with loss of consciousness >5 minutes
Current or past known neurological disorder
Current or past known somatic disorder potentially affecting the brain
Current or past alcohol dependency
Current polytoxicomania (poly-dependency) or within the past 6 months
MRI not possible

For inclusion as a CHR the follow criterion had to be met: i) COGDIS in the Schizophrenia Proness Instrument-Adult Version Cognitive Disturbance (SPI-A) which include impairments in attention, speech, thinking (Table A.3) ii) Brief Intermittent Psychotic Symptom Psychosis Risk Syndrome (BLIPS) iii) Attenuated Positive Symptom Psychosis Risk Syndrome (APS), and/or iv) Genetic Risk and Deterioration Psychosis Risk Syndrome, defined by a > 30% drop in functioning and a DSM-IV diagnosis of Schizotypal personality disorder and/or a 1st degree family member with psychosis in addition to > 30% drop in functioning as measured by GAF.

Exclusion criterion for CHR included i) Antipsychotic medication for > 30 days (cumulative number of days) at or above minimum dosage in the '1st episode psychosis'range of DGPPN S3 Guidelines or ii) Any intake of psychotic medication (i.e., independent of duration of intake) within the past 3 months before psychopathological baseline assessments (including self-ratings and screening assessments) at or above minimum dosage of the '1st episode psychosis'range of DGPPN S3 Guidelines

2.3 Scales

2.3.1 Functional outcome scales

Global Assessment of Functioning

GAF is a widely used clinical scale with two specific sub domains namely: symptoms and disability. The GAF disability is used to rate the social and occupational functioning of an individual on a hypothetical continuum ranging from the highest of a 100 (extremely high functioning) to the lowest rating 1 (severely impaired). It was constructed as an overall measure of how patients were functioning (Aas,

2011). The GAF Symptoms measure psychological functioning that includes symptom type and severity. Refer to section A.2 for further information.

Global Functioning scales

The GF Role and GF Social scales were developed during the NAPLS Phase 1 along the lines of the GAF and in order to fill the gaps that were left by other scales aiming to measure the same features. It separates social and role functioning in order to measure uneven functioning in different domains and was appropriate to use for prodromal patients among other advantages (Cornblatt et al., 2007). The GF Social scale assesses aspects of social functioning such as, peer relationships and conflicts, involvement with family and age appropriate intimate relationships. The GF Role scale assesses aspects of role functioning including type of age appropriate role (school/work/homemaking), quality of role (demands of the role) , performance in the specified role. It places emphasis on the appropriate level of accomplishments and independence in the role.

2.3.2 Symptom scale

Positive and Negative Symptom Scale

PANSS is clinical interview scale used for measuring the severity of positive and negative symptoms commonly associated with SZ (Kay et al., 1987). It consists of seven measures of positive symptom which include delusions, conceptual disorganization and grandiosity among others and seven measures of negative symptoms that include blunted affect, social withdrawal and poor rapport. Sixteen additional items measuring general psychopathology are also measured which take into account somatic concern, anxiety, disorientation and poor attention.

A list of other important clinical assessments used are detailed under section A.2 and a full list of the observer ratings and self ratings used in PRONIA are listed in Table A.2

2.4 MRI acquisition

All MRI images were obtained from a 3T Philips Ingenia scanner with a 32 channel radio-frequency coil in the Department of Radiology within the Ludwig-Maximilians-Universität clinic.

2.4.1 Structural Image acquisition

Anatomical images were obtained using a T1-weighted MPRAGE sequence (flip angle 8°, TE= 5.4, TR = 9.4). Each volume of consisted of 190 sagittal slices (FOV = 240 x 248,Matrix size = 256 x 256, Voxel size = 1x1x1mm).

2.4.2 Functional Image acquisition

Functional images were acquired using an echo planar imaging (EPI) sequence in 53 transverse slices of 3mm thickness (TE = 30,TR = 3000, flip angle = 30°, FOV = 230 x230, Matrix size = 78 x78, Voxel size = 3x3x3mm).

2.5 Image preprocessing pipeline

2.5.1 Structural Image Preprocessing

The anatomical images were preprocessed using the CAT12 toolbox [1] and consisted of the following steps: i) A denoising step based on Spatially Adaptive Non-Local

[1]://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf

Means (SANLM) filtering. ii) An Adaptive Maximum A Posteriori (AMAP) segmentation technique, which models local variations of intensity distributions as slowly varying spatial functions and thus achieves a homogeneous segmentation across cortical and subcortical structures. iii) A 2^{nd} denoising step using Markov Random Field approach which incorporates spatial prior information of adjacent voxels into the segmentation estimation generated by AMAP. iv) A Local Adaptive Segmentation (LAS) step, which adjusts the images for WM inhomogeneities and varying GM intensities caused by differing iron content in e.g. cortical and subcortical structures. The LAS step is carried out before the final AMAP segmentation. v) A Partial Volume Segmentation algorithm that is capable of modelling tissues with intensities between GM and WM, as well as GM and cerebrospinal fluid (CSF) and is applied to the AMAP-generated tissue segments. Lastly, a high-dimensional DARTEL registration of the images to the CAT12 Template 6 was done and individual flow fields were also generated. As a consequence,a normalized anatomical image was created which was to be later used for the fMRI preprocessing pipeline.

2.5.2 Functional Image Preprocessing

The rsfMRI images preprocessing pipeline was based on Patel et al., (2014) and included the following steps: i) The first 8 volumes for each participant were discarded in order to allow the scanner gradients to stabilize and the tissue to reach the necessary level of excitation ii) Slice time correction, in order to adjust for temporal variations in slice acquisition. iii) Realignment i.e, rigid-body head movement corrections to the first volume was applied in order to obtain the 6 motion parameters. These parameters were then used to calculate the Framewise Displacement (FD) value, defined as the sum of the absolute derivates of the 6 motion parameters representing 3 planes of translation and 3 planes of rotation (Patel et al., 2012).

FD thresholds (set at >=38.5%) were used as exclusion criterion for subjects. iv) Co-registration of the normalized T1-weighted anatomical image to the realigned images, resulting in the generation of new re-sliced images. Following this, deformations using the individualized flow fields generated in the sMRI preprocessing were applied to these re-sliced images. v) Normalization of the images into the standard Montreal Neurological Institute (MNI) template vi) GM mask from each individual was applied to the functional image in order to ensure that only GM functional connectivities were extracted later. vii) Spatial smoothing with a 6mm kernel. viii) Wavelet despiking to identify non-stationary events caused by motion, using a wavelet based approach which can detect spikes by providing multi-frequency information present in a signal. Through this, it is hence able to accommodate spatial and temporal heterogeneity of motion artifacts and remove a range of frequency artifacts related to movements from the fMRI time series. ix) Regressing out covariates, which included the values obtained by calculating the Friston 24-parameter model of our time series. The Friston 24-paramater includes 6 current motion parameters, 6 motion parameters from the previous time-point and a square of each of these, accounting for a total of 24. Using this approach removes effects of movement related artifacts that may be present even after realignment (Friston et al., 1996). In addition, the CSF signal and WM residual signal was also regressed out. x) Detrending and applying a temporal Fourier filter ($0.01 < f < 0.08$) (Figure 2.1).

Then, the brain was parcellated into 160 Dosenbach ROIs (Dosenbach et al., 2010) and following this a FC matrix for each subject was obtained by correlating average time series between each ROI. Steps i) to vii) were performed in Statistical Parametric Mapping (SPM) 12 software package (Wellcome Trust Centre for Neuroimaging, 2014) and Steps ix) and x) were performed in the RESTplus (V1.2) toolbox (Song et al., 2011). Wavelet despiking was performed in the BrainWavelet toolbox (Patel et

al., 2014). All of the packages and toolboxes were run in MATLAB and Statistics Toolbox (2015b).

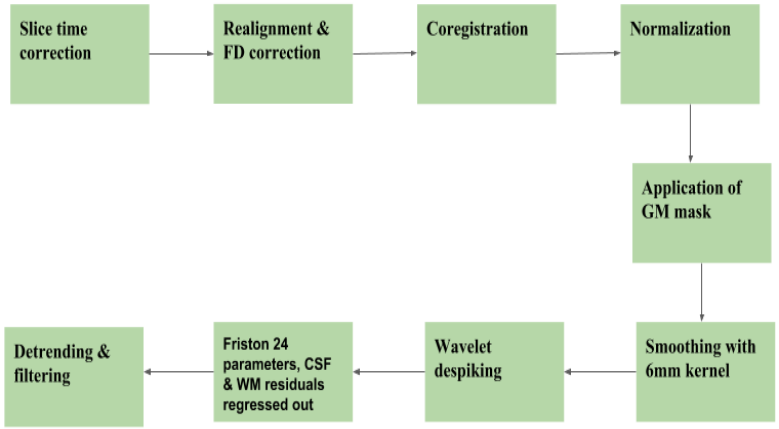

FIGURE 2.1: Illustration of the rfMRI preprocessing pipeline

2.6 MVPA analysis using Support Vector Machine

SVM is a type of supervised classification algorithm. More specifically, SVM is a parametric model allowing users to deal with a large set of features whilst bounding the complexity of the model (Maini, 2017). It is used for determining the class of a data point within a margin-based statistical framework (James et al., 2015). SVM aims to separate the data set into the two categories by finding a separating line (in 2D) or a hyperplane (in multi-dimensional space). It maximizes the margin defined by it's position with respect to certain data points which are nearest to either side of the line, referred to as 'support vectors '(Figure 2.2). The main steps of the method include training the classifier, testing it and lastly evaluating the it's performance

(Orrú et al., 2012). Data is input as features, which have to be transformed from their raw state in order to be able to accepted as features by SVM. Following this, the next step is feature selection wherein only a subset of all features are selected, in order to facilitate learning or to remove features that may be redundant. Feature selection aids in the development of a model by reducing computational load, makes interpretation of the model easier and increases the classifier's ability to discriminate between classes. After this initial step, the data is split into training and testing sets, in the which the algorithm computes the hyperplane i.e., learns to discriminate between classes in the training set and then predicts labels for the groups in the testing set. An important aim of predictive models is generalizability, which is the extent to which a statistical model generated in one group performs accurately in new groups or individuals (Dwyer et al., 2018). One way to achieve generalizability is by building a more robust model by means of cross-validation (CV) techniques. The simplest CV scheme is leave-one-out which works by breaking the data into *K* partitions or folds, and one fold acts as the test data and *K*-1 folds of the remaining data is used as training. This reiterates over each fold allowing each case to act as test and as training data. This helps to avoid overfitting of the model and hence in computing an unbiased estimation of generalizability (Orrû et al., 2012). CV also computes *C*, a regularization parameter that adds a penalty term into the loss function which measures the inaccuracy of our model. This penalty is added for building a model that assigns too much explanatory power to any one feature or allows too many features to be taken into account. (Maini, 2017). As a final step, the model's performance is evaluated using the specificity, sensitivity and accuracy measures.

- Specificity is the proportion of actual amount of negative cases (control subjects correctly identified as controls) that were correctly classified, and is calculated using $\frac{TN}{(TN+FP)}$,

where TN is the True Negative rate and FP is the False Positive rate

- Sensitivity is the proportion of truly positive cases (individuals with the disease correctly identified as having the disease) that were correctly classified and is calculated using $\frac{TP}{(TP+FN)}$,

  where TP is the True Positive rate and FN is the false negative rate.

- Accuracy, which is an overall measure of correct classifications and is computed using $\frac{TP+TN}{(TP+FN+TN+FP)}$

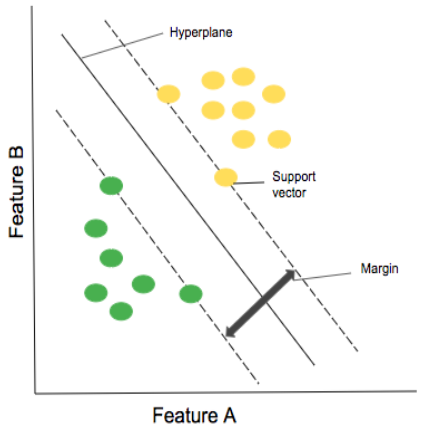

FIGURE 2.2: Illustration of a Support Vector Machine

2.7 Steps of the analysis

For the current analysis we used the in-house pattern recognition software NeuroMiner (NM) [2]. Our predictor variable, or set of features was a 76 x12720 matrix, consisting of 12720 resting state functional correlations between the 160 Dosenbach ROIs for each of our 76 subjects. The labels assigned to each of the data classes were GF Social, GF Role and GAF Disability values. The basic

[2]https://www.pronia.eu/fileadmin/websites/pronia/Neurominer/neurominer$_manual_v$1.pdf

preprocessing pipeline applied to the features was as follows, i) Pruning the data and removing non-informative features. ii) Dimensionality reduction using Principal Component Analysis (PCA) explaining 80% of the variance , iii) Scaling the data across the matrix between (0,1). Our preprocessing pipeline was embedded into a nested double CV scheme (Figure 2.3) which works as follows: there are two loops, an inner CV loop where an unbiased model is constructed based on the training data and an outer CV loop where the performance of the winning mode from the inner loop is measured on the testing data. We applied 10 permutations of 5 folds (10x5) in each of the two loops, to get a total of 50 models each.

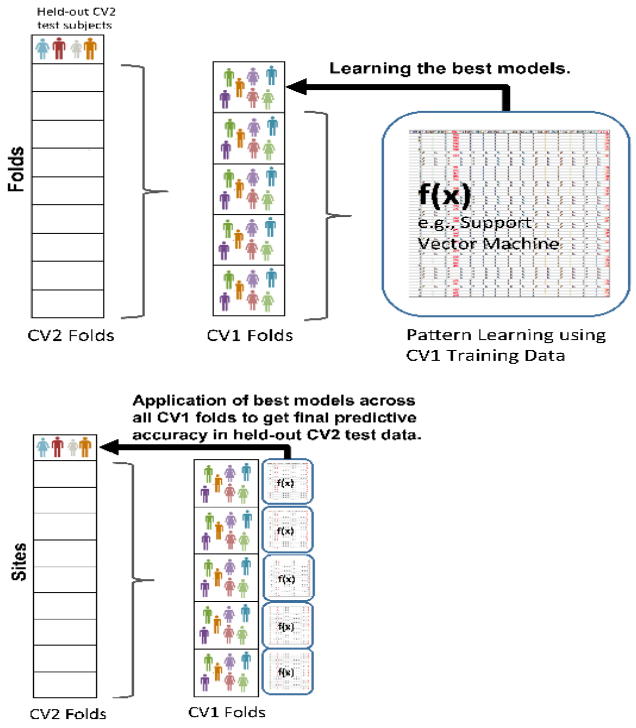

FIGURE 2.3: Illustration of the nested double cross validation scheme applied in NeuroMiner. (Dwyer et al., 2017, p. 27)

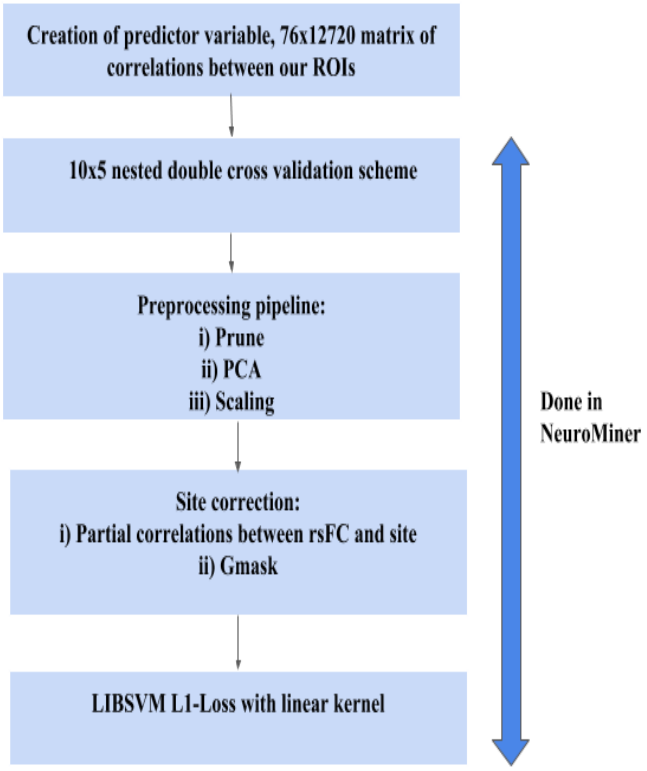

FIGURE 2.4: Illustration of the steps of the current analysis

The data were trained using LIBSVM 3.1.2 (Change and Lin, 2011) with L1-Loss support vector clustering (SVC) and using a linear kernel. Finally, the classifier was visualized in NM.

2.7.1 Correlation with PANSS

Decision scores, based on our rsFC classifier were extracted from NeuroMiner. These scores represent the distance of a data point (in our case a subject) from the decision boundary based on their functional outcome i.e., the likelihood of a subject being classified as good or poor. These decision scores were correlated with each of PANSS subscores using Pearson's *r*.

2.8 Site Effect Correction

The 76 participants that made up the final dataset came from 7 different sites and hence were vulnerable to various site influences such as rater bias and scanner effects. In order to control for these effects, we applied two different site corrections namely, i) Partial correlations between the rs features and scanner sites and ii) Making a generalization mask of the 12720 features using traveller's data from all sites based on Cronbach et al., (1963) and Mushquash and O'Connor (2006). They were then incorporated into the basic preprocessing pipeline mentioned above.

2.8.1 Partial correlation between the rs features and scanner sites: Site as a covariate

A vector of size 76 containing the list of sites matched to each of our participants was input as a covariate in NM and was regressed out as an additional step in our preprocessing pipeline. The fundamental reason for including site as a covariate is to accurately separately our classes without the confounding factor of sites. The step was added after the pruning and before PCA.

2.8.2 Generalizability Theory Mask

Generalizability theory (Gtheory) was first introduced by Cronbach et al., (1963) and is used for determining the reliability of a measure. Gtheory compares the sources of error in a metric along with estimating the variance contributed by each source. iT provides estimates of the variance associated with interactions between the various sources (Mushquash O'Connor, 2006). Based on the scripts for implementing Gtheory in MATLAB provided by Mushquash

and O'Connor, 2006 and using rsFC data from 5 travelling subjects (who were scanned at each of the seven sites) a mask of 1x12720 features (Gmask) was made.

This was then input as an external mask in NeuroMiner with a soft threshold set at 15%, 25% , 50% and 75%. The aim of the Gmask is to remove any spurious correlations that may arise due to the site effect. The step was added before pruning the data.

Chapter 3

Results

3.1 Demographic and participant information

There was no significant difference between the two groups at T0 or FU in age and sex. At T0, PANSS Negative was significantly higher for the Poor group (t(74) = -3.603, $p < 0.001$) and GF Social was significantly lower (t(74)= 4.181, $p < 0.001$). GAF Symptoms (t(74) = 2.134), GAF Disability (t(74) = 2.977) and GF Role (t(74) =3.114) were all significantly lower for the Poor group at $p < 0.05$. At FU, PANSS Negative (t(74)= -4.517) and General (t(74) = -4.194) along with BDI (t(74) =-4.015) scores were significantly higher for the Poor group ($p < 0.001$) along with PANSS Positive at (t(74) = -2.647, $p < 0.05$). GAF Symptoms (6.318), GAF Disability (t(74) = 6.662), GF Social (t(74) = 13.445) and GF Role (t(74) = 7.652) scores were significantly lower for the Poor group ($p < 0.001$).

The percentage of subjects having a co-morbid DSM-IV diagnosis at baseline was 72.36% (N = 55). Table 3.1 lists the different co-morbid diagnoses for the current study cohort. At baseline, 26.31% (N=20) subjects fulfilled the COGDIS criterion, 67.10% (N=51) subjects fulfilled the APS criterion, 3.7% (N=3) fulfilled the BLIPS criterion and 2.63% (N=2) fulfilled the APS and genetic risk criterion. There were no transition cases present at FU.

TABLE 3.1: List of co-morbid diagnoses of CHR patients as measured by the Structured Interview for DSM IV (SCID)

SCID Diagnoses	
Bipolar I Disorder	1
Bipolar II Disorder	1
Other Bipolar Disorder	1
Major Depressive Disorder (MDD)	30
Dysthymic disorder	2
Depressive disorder not otherwise specified	3
Substance Use Disorder	1
Schizophrenia (SZ)	3
Social phobia	1
Obsessive Compulsive Disorder (OCD)	3
Generalized anxiety	1
Panic disorder	1
Anxiety Disorder not otherwise specified	1
Somatization disorder	1
Body Dysmorphic Disorder	1
Adjustment disorder	2
Dissociative disorder	2
None	11

3.2 SVM results

3.2.1 GF Social Results

The classifier achieved a balanced accuracy (BAC) of 63% ($p < 0.05$) which is defined as: $\frac{Sensitivity}{Specificity}$, with sensitivity at 56.8%, specificity at 69.2% and accuracy at 63.2% with no site corrections as well as with partial correlations between the rsFC and site. The highest BAC was achieved with with the application of the Gmask at 68% ($p < 0.001$) with sensitivity at 64.9%, specificity at 71.8% and an accuracy of 68.4% (Figure 3.1). Out of 76 subjects, 13 subjects in the good group were misclassified as being poor and 11 subjects in the poor group were misclassified as being good social outcomers.

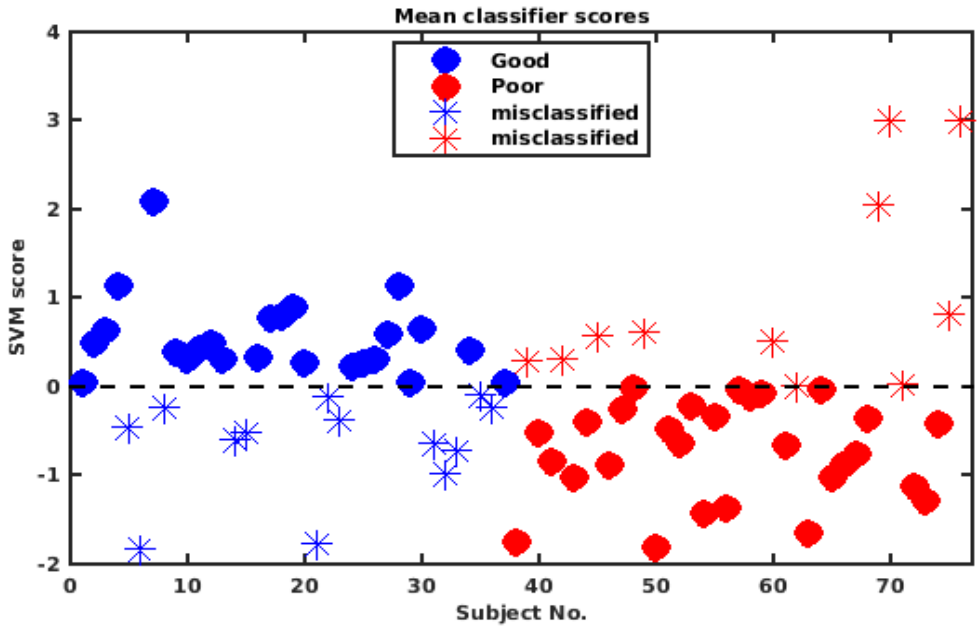

FIGURE 3.1: Illustration of the rsFC classifier in application with the Gmask in separating Good from Poor subjects based on their GF Social scores

3.2.2 GF Role Results

The classifier achieved a BAC of 50% with sensitivity at 0%, specificity at 100% and accuracy at 53.9% with no site corrections. With partial correlations between the rsFC and site BAC was 48.8% with sensitivity at 0%, specificity at 97.6% and accuracy at 52.6%. With the Gmask, the classifier achieved a BAC of 49.6% with sensitivity at 11.4%, specificity at 87.8% and accuracy at 52.6%. None of the classifiers were significant at $p < 0.05$.

3.2.3 GAF Disability Results

The classifier achieved a BAC of 49.1% with sensitivity at 22.6%, specificity at 75.6% and accuracy at 53.9% with no site corrections. With partial correlations between the rsFC and site the BAC was 46.7%, sensitivity 0%, specificity 93.3% and accuracy 55.3%. Application of Gmask resulted in a BAC of 50%, with sensitivity at 0.0%, specificity at 100% and accuracy at 59.2%. None of the classifiers were significant at $p < 0.05$.

3.3 rsFC of the classifier

All 12720 features used for classification were sorted in order of their discriminative power, and the top fifteen features were extracted. These are represented in the Figure 3.2. The most predictive FC were found in between the parietal and frontal areas in both hemispheres of the brain. The connectivities were both intrahemispheric (N = 9) as well as interhemispheric (N = 6) and were distributed across brain region (Table 3.2). The highest discriminative connectivity was found between the IPL and vmPFC, followed by the angular gyrus and dorsal frontal cortex (dFC). The FC of the precuneus and dorsolateral prefrontal cortex (dlPFC) was the only long range connectivity amongst the top fifteen FC. Other than the fronto-parietal and occipto-frontal connections, the IPL with the inferior temporal cortex and the temporal cortex with the anterior insula have shown also as most predictive features. The mean weights of the 15 functional connectivities for the two groups are also displayed in Table 3.2

TABLE 3.2: List of the top 15 features, their mean feature weights and corresponding mean correlations between ROIs for Good and Poor outcomers

Region 1	Region 2	Mean feature weight	Mean correlation (Good)	Mean correlation (Poor)
R Inferior parietal lobule	R Ventral medial prefrontal cortex	-0.504	-0.084	-0.037
L Inferior parietal lobule	L Ventral medial prefrontal cortex	0.456	-0.217	-0.142
R Angular gyrus	L Dorsal frontal cortex	0.403	-0.183	-0.071
R Angular gyrus	L Dorsal frontal cortex	0.402	-0.01	0.139
L Inferior parietal lobule	L Inferior temporal	0.388	-0.145	-0.014
L Angular gyrus	L Inferior parietal lobule	0.388	0.192	0.332
L Angular gyrus	R Dorsal frontal cortex	0.382	0.054	0.201
R Angular gyrus	R Ventral medial prefrontal cortex	0.364	0.081	0.201
R Inferior parietal lobule	L Frontal	0.355	0.205	0.208
L Precuneus	L Dorsolateral prefrontal cortex	0.349	-0.086	0.025
R Inferior parietal sulcus	R Frontal	0.338	0.114	0.205
R Temporal	R Anterior insula	0.335	-0.009	0.1
R Inferior parietal lobule	L Medial prefrontal cortex	0.328	-0.131	-0.026
R Inferior parietal lobule	R Ventral medial prefrontal cortex	0.323	-0.103	-0.044
R Angular gyrus	L Dorsal frontal cortex	0.317	0.130	0.287

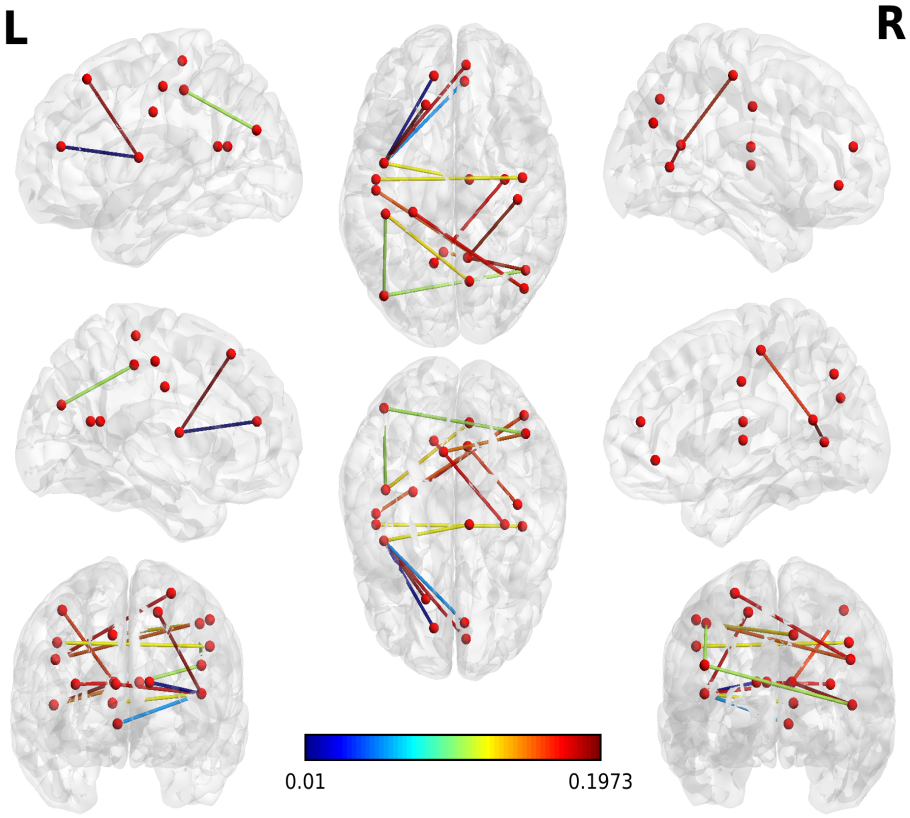

FIGURE 3.2: Illustration of the top 15 functional connectivities with the highest discriminative power to classify Good and Poor social outcome in CHR subjects. Visualized using BrainNetViewer by Xia et al., (2013)

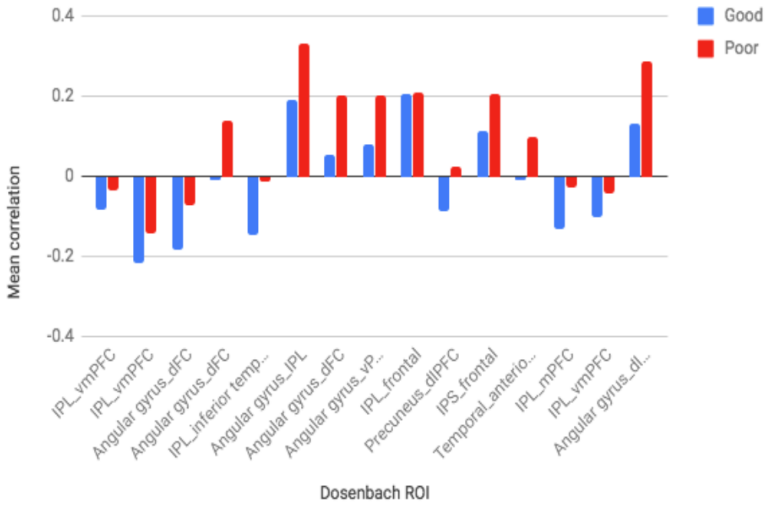

FIGURE 3.3: A graphic representation of the 15 most discriminative functional connectivities in descending order for both Good and Poor social outcome CHR subjects.

3.4 Correlation of decision scores and PANSS

The PANSS negative, positive and general scores were correlated with the decision scores obtained from the GF Social classifier (Table 3.3). PANSS Total with the poor group was trending towards significance (r (74) = 0.645, p = 0.076). No other significant correlations were found.

TABLE 3.3: Results of correlating the rsFC classifier decision scores with the Good and Poor social outcome groups PANSS scores.

	Good	Poor
PANSS Negative	p = 0.975 r = 0.005	p = 0.457 r = 0.123
PANSS Positive	p = 0.646 r = -0.078	p = 0.619 r = -0.082
PANSS General	p = 0.994 r = 0.001	p = 0.565 r = 0.095
PANSS Total	p = 0.854 r = -0.031	p = 0.076 r = 0.645

Chapter 4

Discussion

4.1 Using a rsFC to separate CHR subjects based on functional outcome

The main aim of the study was to use rsFC to predict functional outcome in a cohort of CHR patients at FU. By using MVPA, our rsFC classifier was able to separate CHR patients with good from poor social outcome with a BAC of 68% based on GF Social scores. his is an exciting finding because the GF Social scale represents social functioning in general, but could be a proxy for all the other aspects of social functioning such as management of interpersonal relationships, social cognitive abilities including evaluating emotions, empathy and theory of mind. Abilities and aspects of functioning that have time and again been implicated in behaviour and well as brain changes in the psychosis spectrum. Based on GF Role scores, the classifier was able to separate CHR patients with good from poor role outcome with a highest BAC of 50%. Finally, general functional outcome represented by GAF Disability scores had a BAC of 50%.

Previous research using these methods has focused on classification of patients

from HC (Shen et al., 2010; Nieuwenhuis et al., 2012), or transition in CHR patients (Koutsouleris et al., 2009) and differentiating between SZ patients from those with other psychiatric disorders (Schnack et al., 2014). The few studies on predicting outcome have achieved high correlations (De Wit et al., 2016) and accuracies (Kambeitz-Ilankovic et al., 2015; Koutsouleris et al., 2016).

4.2 Predictive rsFC based on our classifier

Research employing univariate as well as MVPA methods has so far used various data modalities to predict functional outcome in psychosis spectrum patients. Previous studies have found negative symptoms (Cacciotti-Saija et al., 2015), family history (Käkelä et al., 2014), duration and severity of illness (Diaz-Caneja et al., 2015; Suttajit et al., 2015) and lower grey matter density in mPFC, orbitofrontal cortex, anterior cingulate cortex (Reniers et al., 2017) as well as functional connectivities in the DMN and SN (Crossley et al., 2009; Pelletier-Baldelli et al., 2015) to predict functional outcome in SZ and CHR cohorts.

As detailed in Table 3.2, we identified a list of the highest predictive FC that were able to discriminate between the two social outcome groups. The most predictive out of the top fifteen features was the FC between the right IPL and right vmPFC which are part of the frontoparietal network (FPN). The IPL was involved in five out of the top fifteen FC and and previously, due to it's role in various aspects of cognition, was used during therapeutic application of transcranial magnetic stimulation in SZ (Palaniyappan 2012). The interhemispheric connectivity between the right angular gyrus and the left dFC along with the intrahemispheric connectivity between the left precuneus left dlPFC are also

part of the FPN. Previous studies on alterations in the rsFC of FPN has reported reduced FC in SZ as compared to HC (Tu et al., 2013) though discordant results have been found as well (Unschuld et al., 2014). In family members of SZ patients the same pattern of varying alterations in FC of regions in the FPN have been found (Chang et al., 2014). In CHR patients, impairments in the FC of this network has been found to be related to social cognition (Lieberman., 2007), cognitive dysfunction and cognitive control (Peeters et al., 2015), working memory (Schmidt et al., 2014), , executive functions and language (Broome et al., 2009; Palaniyappan 2012). The FPN is theorized to be the link between different kinds of information processing such as between self oriented memory processing and externally oriented information processing and hence a disruption within the connectivities of the network might cause changes in the information processing in the brain and subsequently cause problems in other brain networks. This may be in line with the heterogeneous set of symptoms that SZ often presents with and may contribute to the identification of schizophrenia endophenotypes and ultimately to the determination of SZ risk genes (Liu et al., 2013). Finding a trace of this disruption in CHR patients provides evidence for a possible biomarker that may be able to detect CHR individuals who have poor social outcome.This can then be used to develop and offer early individualized intervention to CHR patients in order to avoid having a deterioration in functioning and prevent them from transitioning.

Another top feature implicated the intrahemispheric FC between the temporal cortex and the anterior insula and these areas have been shown to be related to the clinical symptoms present in SZ (Woodruff et al., 1997; Pang et al., 2017). The anterior insula is also known to be involved in anticipating and evaluating emotional stimuli (Lovero et al., 2009), and is likely also involved in empathy

(Iacoboni and Dapretto 2006) both essential aspects of social functioning. It also acts as a multimodal sensory integration unit (Pang et al., 2017) and alterations in this functioning along with the temporal cortex which houses the primary auditory cortex may lead to some aspects of the general psychopathology of SZ (Pang et al., 2017). The FC between precuneus and dlPFC was also highly discriminative of the groups. The dlPFC plays a role in context processing, executive processes (Delawalla et al., 2008; Zhou et al., 2015) and is also involved in regulation of affective states (Phillips & Seidman, 2008). An unimpaired processing of context coupled with higher order cognition allows an individual to make appropriate responses and communicate in an effective manner. All of which are central aspects of social relationships. On the other hand, the precuneus is involved in self representation (Lou et al., 2004) and retrieval of episodic memory (Cavanna & Trimble, 2006), both integral parts of social interaction and social identity.

Most interhemispheric connectivities we found were located between the parietal and frontal/prefrontal areas, which has also been shown in previous research with SZ (Schlösser et al., 2003). Most aberrant functional connectivities in psychosis involve interhemispheric connections (Guo et al., 2013) and have also been found in unaffected siblings of patients with SZ (Guo et al., 2014).This also goes hand in hand with research showing structural deficiencies of the corpus callosum (Arnone et al., 2008; Collinson et al., 2014) and has been related to severity of negative symptoms (Ribolsi et al., 2011). This along with our the current results provides evidence that the 'disconnectivity'found in SZ might already be present in CHR patients.

4.3 Decision scores and PANSS

Deterioration in social and occupational functioning are key characteristics of schizophrenia (Bellack et al., 1990) and are amongst the most disabling and treatment resistent aspects of the illness (Bellack et al., 2007). Over the past years, a growing body of research is focusing on interventions in early spectrum psychosis in the hope of decreasing the adverse impact of schizophrenia on functional outcome. A substantial amount of impairment in functioning takes places in the early stages of psychosis and affects later social and occupational dysfunction (Niendam et al., 2009). Though most patients in the CHR stage recover, one-thirds have poor functional outcome and many still suffer from functioning deficits (Salokangas et al., 2013) and there is not enough follow-up data to clarify whether patients improve long term despite not converting (Brandizzi et al., 2015). A recently completed 15-year follow-up study found that CHR individuals continued to develop symptoms years after initial presentation (Fusar-Poli et al., 2013). The worsening of symptoms can lead to an impairment various domains of functioning, the daily aspects of living such as interactions with friends and family and employment.

Whilst elucidating a link between symptoms and social outcome, we found no significant relationship between the decision scores of our classifier and PANSS scores. Previous research on the other hand has found a relationship between PANSS positive and negative symptoms and resting state activity (Sorg et al., 2012; Dandash et al., 2013; Liu et al., 2018). In our study, the relationship between poor social outcomers and their PANSS summary score was trending significance, and this could be because our group of poor outcomers are generally more symptomically impaired as compared to the good social outcomers. Additionally, it could be that the modality is not yet able to pick specific rsFC

social outcome signature between the groups and their symptom types. Although, it is still able to give evidence that altered functional connectivities in poor social outcome are associated with their general symptom severity. Lastly, it is important to take into account that the previous studies mentioned did not employ MVPA methods and also had different functional networks and FC. A further look into the medication of the subjects, the severity and kind of symptoms and the duration of their illness (Larsen et al, 2000) might give us a better outlook into understanding the lack of a relationship between PANSS and our decision scores.

4.4 Limitations and evaluations

Our classifier was unable to discriminate groups based on GF Role which measures functioning during education, or at work and in the home. Role functioning is found to be a variable vulnerability trait and is reflective of treatment and environmental change which are heavily influenced by site (Cornblatt et al., 2007). Low performance of the classifier could also reflect the modality's specificity for social functioning.

Our classifier also only had accuracies at chance or below chance level when separating the groups using GAF disability, though previous research has found good accuracies with the GAF scale in general (Koutsouleris et al., 2016). GAF disability is a summary score consisting of both role and social aspects whereas GF Social assesses the quality and quantity of peer relationships and interactions, age appropriate intimate relationships, peer conflict and relationship with family members and hence the focus is on social withdrawal and isolation (Cascio et al., 2017). As mentioned earlier, it could be that our rsFC were

perhaps able to only distinguish between the groups based on stark difference in social aspects. Our threshold of 75 for GAF, though based on the sample is not the threshold present for the general population (Scott et al., 2013) and hence not representative or applicable.

It is also important to note that many functional outcome scores were taken from varying time points and could have affected the classifier's accuracy. Forty-three subjects were excluded as outliers in the homogeneity check, this also limits the generalizability of our classifier because the current sample represents a very small part of the general high risk patient population. Patients that are unwell are more likely to have movements in their MR images either because of medication or severity of symptoms. This is relevant to note because movements might be a brain signature and exclusions due to this lead to severe biases in the chosen sample.

Follow-up analyses could combine our current classifier with other modalities as done by Cabral et al., (2016) and a deeper look into the role of co-morbid illnesses in predicting outcome can be another possible path of research. Correlating the decision scores with neurocognitive data will also be vital as previously neurocognitive domains such as attention, executive functioning, working memory and processing speed have been implicated in numerous studies of functional outcome (Green et al., 2004; Niendam et al., 2007; Bowie et al., 2008; Meyer et al., 2014). Lastly, incorporating more subjects will increase the generalizablility and robustness of our classifier.

4.5 Conclusion

In conclusion, using rsFC we were able to classify CHR subjects into good and poor social outcome groups with an accuracy of 68%. The classifier used a site correction method in form of a Gmask in order to control for scanner and similar site effects. The most predictive connectivities included the FC between fronto-parietal regions which included the IPL, angular gyrus and parts of the prefrontal cortex. Most of the FC were short range and were distributed between and within the hemispheres. The FPN provides evidence for impairments in cognitive control, social cognition and information processing which are known to be impaired in SZ and CHR patients. The classifier was unable to distinguish the groups based on GF Role and GAF Disability scores. There were no significant correlations between the clinical symptoms as measured by PANSS and the tendency as measured by decision scores of a subject to be classified as having a good or poor social outcome. Lastly, a larger sample size with a balanced distribution between different sites, information regarding medication and illness duration and analyses combining additional modalities will be able to provide a better outlook, robust biomarkers and a deeper understanding of functional outcome in CHR cohorts. This would in turn help develop early intervention programs focused on an individual's need.

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Appendix A

Appendix

A.1 Participant Information

TABLE A.1: Distribution of subjects per site

Site name	Combined subjects	Good GF Social	Poor GF Social
University of Munich	21	8	13
University of Basel	13	9	4
University of Milan	3	1	2
University of Cologne	12	7	5
University of Birmingham	10	7	3
University of Turku	10	2	8
University of Udine	7	3	4
Total	76	37	39

A.2 Clinical Assessments

A.2.1 Structured Interview for Prodromal Symptoms (SIPS)

SIPS is a structured diagnostic interview used for diagnosing prodromal symptoms and also includes operational definitions of the Criteria of Prodromal Syndromes (COPS) and for Presence of Psychotic Syndrome or psychosis onset (POPS) (Miller et al., 2003). It measures 5 symptoms namely i) unusual

TABLE A.2: List of observer rating and self rating questionnaires in PRONIA

Observer Rating
Demographic and Biographic Data
Global Assessment of Functioning
Global Functioning Social / Role
Schizophrenia Proneness Instrument - Adult Version
Schizophrenia Proness Instrument-Adult Version Cognitive Disturbance
Structured Interview for Prodromal Syndromes Positive Items
Structured Interview for Prodromal Syndromes Negative and General Items
CAARMS Items
Positive and Negative Symptom Scale
Structured Clinical Interview for DSM IV 1 - Screening
Structured Clinical Interview for DSM IV 1 - Summary
Clinical High Risk Criteria
Functional Remission in General Schizophrenia
Ultra High Risk Criteria (Schizotypy/Genetic Risk)
Somatic state and health history
Substance Use
Treatment Documentation
Self Rating Questionnaires
Beck Depression Inventory - II
Bullying Scale
Coping Inventory for Stressful Situations
Level of Expressed Emotion Scale
Multidimensional Scale of Perceived Social Support
Resilience Scale for Adults
Social Phobia Inventory
The Everyday Discrimination Scale
WHO Quality Of Life - Short Version

thought content/delusions ii) suspisciousness/persecutory ideas iii) grandiose ideas iv) perceptual abnormalities/hallucinations and v) disorganized communication.

A.2.2 Beck's Depression Inventory (BDI)

The BDI is a self-rating questionnaire consisting of 21 items that measures the signs and symptoms of depression (Beck et al., 1961) such as i) sadness ii) suicidality iii) changes in appetite iv) loss of energy v) guilt feelings, among others. The responses to these items are on a 4 point scale, where 0 is not present and 4 is severe.

A.2.3 Schizophrenia Proneness Instrument - Adult version

The Schizophrenia Proneness Instrument - Adult version (SPI-A) (Schultze-Lutter et al., 2007) is based on the basic symptoms concept of psychosis by Gerd Huber (1985). Basic symptoms include but are not limited to impairments in dividing attention, disturbances in speech and perception (For a full list please refer to Appendix table tbd). These symptoms are distinct from attenuated or frank psychotic symptoms such as delusions, paranoid ideas, odd thinking and speech, negative symptoms and formal thought disorders. These symptoms are phenomenologically different from the patient's original 'normal' mental states and are also distinct from subtle disturbances described as traits in those at genetic high-risk. Basic symptoms were thought to be the most immediate psychopathological expression of the somatic changes underlying the development of psychosis thus the term 'basic'. (https://basicsymptoms.org/materials/schizophrenia-proneness-instruments/)

TABLE A.3: List of SPI-A Symptoms

SPI-A Symptoms
Inability to divide attention
Thought interference
Thought pressure
Thought blockages
Disturbance of receptive speech
Disturbance of expressive speech
Unstable ideas of reference
Disturbances of abstract thinking
Captivation of attention by details of the visual field

PRONIA Assessments

UHR – SIPS P-Items (+CAARMS)

GLOBAL ASSESSMENT OF FUNCTIONING

GAF: When scoring considers psychological, social and occupational functioning on a hypothetical continuum of mental health/illness. Do not include impairment in functioning due to physical health (or environmental) limitations.

Global Assessment of Functioning (GAF)

GAF scale SYMPTOMS: burdening symptoms during **the last month**. Choose the level of burden that most resembles the situation during the last month. Use intermediate codes when appropriate, e.g. 45, 68, 72.

91-100	No symptoms.
81-90	Absent or minimal symptoms (e.g., mild anxiety before an exam).
71-80	If symptoms are present, they are transient and expectable reactions to psychosocial stressors (e.g., difficulty concentrating after family argument).
61-70	Some mild symptoms (e.g., depressed mood and mild insomnia).
51-60	Moderate symptoms (e.g., flat affect and circumstantial speech, occasional panic attacks).
41-50	Severe symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting).
31-40	Some impairment in reality testing or communication (e.g., speech is at times illogical, obscure, or irrelevant).
21-30	Behaviour is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation).
11-20	Some danger of hurting self or others (e.g., suicidal attempts without clear expectation of death; frequently violent; manic excitement) OR gross impairment in communication (e.g., largely incoherent or mute).
1-10	Persistent danger of severely hurting self or others (e.g., recurrent violence) OR serious suicidal act with clear expectation of death.

PRONIA Assessments

UHR – SIPS P-Items (+CAARMS)

GAF scale DISABILITY/IMPAIRMENT: burdening disabilities during the last month. Choose the level of burden that most resembles the situation during the last month. Use intermediate codes when appropriate, e.g., 45, 68. 72. Do not include impairment in functioning due to physical limitations.

91 - 100	Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities.
81 – 90	Good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns (e.g., an occasional argument with family members).
71 – 80	No more than slight impairment in social occupational, or school functioning (e.g., temporarily failing behind in schoolwork).
61 – 70	Some difficulty in social occupational, or school functioning (e.g., occasional truancy or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships.
51 – 60	Moderate difficulty in social, occupational, or school functioning (e.g., few friends, conflicts with peer or co-workers).
41 – 50	Any serious impairment in social, occupational or school functioning (e.g., no friends, unable to keep a job).
31 – 40	Major impairment in several areas, such as work or school, family relations, judgment or thinking (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).
21 – 30	Inability to function in almost all areas (e.g., stays in bed all day, no job, no home, no friends).
11 – 20	Occasionally fails to maintain minimal personal hygiene (e.g., smear faeces).
1 - 10	Persistent inability to maintain minimal personal hygiene.

Highest level GAF scale "SYMPTOMS": life time[1]:__ past year:__ past month:__

Highest level GAF scale "DISABILITY/IMP.".: life time[1]:__ past year:__ past month:__

Consider only GAF disability/impairment for inclusion.

[1] Rate only at baseline

PRONIA Assessments

GF: Social Scale

I. Globales Funktionsniveau: Sozial-Skala

Aktuell:	
Niedrigstes im letzten Jahr[1]:	
Höchstes im letzten Jahr[1]:	
Höchstes im Leben[2]:	

1a. Die Beurteilung basiert auf Informationen von folgenden Personen *(Mehrfachnennungen möglich)*:
☐ Befragter
☐ Familienmitglieder/ Freunde
☐ Pflegepersonal/ Sozialarbeiter/ andere feste Betreuungspersonen

Instruktion:

Bitte schätzen Sie das höchste Ausmaß an Beeinträchtigung des sozialen Funktionsniveaus des Patienten für den angegeben Zeitraum, indem Sie das „niedrigste" Level auswählen, das sein/ihr Funktionieren in dieser Periode beschreibt. Für „aktuell" beurteilen Sie bitte das höchste Ausmaß an Beeinträchtigung des sozialen Funktionsniveaus in der „letzten Woche". Beurteilen Sie das aktuelle Funktionieren unabhängig von der Ätiologie sozialer Probleme. Wenn der Patient/die Patientin gerade offiziell Schulferien hat (z.B. Sommerferien) oder weniger als 2 Wochen im Krankenhaus lag und momentan wieder entlassen ist, aber noch nicht die Möglichkeit hatte, seine oder ihre gewohnten sozialen Aktivitäten zwischen Entlassung und Erhebung wieder aufzunehmen (z.B. bei Messung am Tag der Entlassung), schätzen Sie das Funktionsniveau, das direkt vor dieser Situation bestand (z.B. vor dem Krankenhausaufenthalt). Ist die Person zur Zeit der Messung im Krankenhaus und zwar für weniger als 2 Wochen, beurteilen Sie das Funktionsniveau gemäß des Ausmaßes an sozialem Funktionieren direkt vor dem Krankenhausaufenthalt. Lag die Person länger als 2 Wochen aufgrund nicht-psychischer Beschwerden im Krankenhaus (z.B. komplizierte Grippe), beurteilen Sie ebenso gemäß des Ausmaßes an sozialem Funktionieren direkt vor dem Krankenhausaufenthalt (entsprechend wie bei Schulferien). Wenn eine Person sich in einer Übergangsphase befindet (z.B. zwischen Schule und Universität oder zwischen zwei Arbeitsstellen) beurteilen Sie ebenso gemäß des Ausmaßes an sozialem Funktionieren direkt vor dieser Situation (entsprechend wie bei Schulferien).

Anmerkung: Der Schwerpunkt liegt auf sozialem Kontakt/Interaktionen mit Personen außerhalb der Familie, es sei denn, es besteht nur interpersoneller Kontakt zu Familienmitgliedern (z.B. am unteren Ende der Skala). Beachten Sie zudem, dass die Beurteilung von intimen Beziehungen im Hinblick auf die Beurteilung primärer Freundschaften nebensächlich ist und das Alter der Person berücksichtigen sollte. Zum Beispiel könnte man bei älteren Personen erwarten, dass sie intime Beziehungen haben, die konstante Verabredungen, Zusammenwohnen oder Ehe beinhalten, während man bei jüngeren Personen erwarten könnte, dass sie nur romantisches Interesse (d.h. flirten oder für eine Person schwärmen) oder enge Freundschaften haben.

[1] Abweichende Referenzperiode bei follow-ups: Zeitspanne seit dem letzten Besuch
[2] Nur bei TD zu beurteilen
Anmerkung: Beim follow-up kann der höchste Wert in der letzten Beobachtungsperiode nur über dem aktuellen Wert beim letzten Besuch liegen und nicht darunter, (d.h. wenn niedriger, definiert der aktuelle Wert beim letzten Besuch den höchsten Wert der letzten Beobachtungsperiode (in der Regel 3 Monate)). Der niedrigste Wert in der letzten Beobachtungsperiode kann nur unter dem aktuellen Wert beim letzten Besuch liegen und nicht darüber.

PRONIA Assessments

GF: Social Scale

Fragen, die bei der Beurteilung des Globalen sozialen Funktionierens behilflich sind:

1. Erzählen Sie mir etwas über Ihr Sozialleben. Haben Sie Freunde?
2. Sind das entfernte oder enge Freunde? Wenn es entfernte Freunde sind – sind es nur Schulfreunde oder Freunde von der Arbeitsstelle? Wenn es enge Freunde sind – wie lange sind Sie schon eng befreundet?
3. Wie oft treffen Sie sich mit Freunden? Sehen Sie ihre Freunde außerhalb des Arbeitsplatzes/der Schule? Wann war das letzte Mal, dass Sie einen ihrer Freunde außerhalb des Arbeitsplatzes/der Schule getroffen haben? (Versuchen Sie das aktuelle Ausmaß an sozialem Kontakt vs. dem wahrgenommenen Ausmaß an sozialem Kontakt zu bestimmen)
4. Sind Sie in der Regel derjenige/diejenige, der/die den Kontakt aufnimmt oder gemeinsame Aktivitäten mit Freunden initiiert oder rufen ihre Freunde normalerweise Sie an oder laden Sie ein? Haben Sie schon einmal den Kontakt mit Freunden vermieden?
5. Haben Sie manchmal Probleme/Zerwürfnisse mit Freunden gehabt? Auseinandersetzungen oder Streits? Wie werden diese üblicherweise geklärt?
6. Haben Sie Verabredungen mit potenziellen Partnern oder sind interessiert an Verabredungen mit potenziellen Partnern? (Bei Bedarf zur Erfassung altersadäquater intimer Beziehungen ändern)
7. Verbringen Sie Zeit mit Familienmitgliedern (zu Hause)? Wie oft sprechen Sie mit ihnen? Haben Sie schon einmal den Kontakt mit Familienmitgliedern vermieden?

PRONIA Assessments

GF: Social Scale

Globales soziales Funktionsniveau

10	Überragendes soziales/interpersonelles Funktionsniveau	**Überragendes Funktionieren in einem breiten Bereich sozialer und interpersoneller Aktivitäten.** Trifft häufig Freunde und hat viele befriedigende interpersonelle Beziehungen, darunter viele sowohl enge als auch lockere Freundschaften. Wird von anderen wegen seiner/ihrer vielseitigen positiven Eigenschaften aufgesucht. Altersadäquate Einbindung in intime Beziehungen.
9	Überdurchschnittliches soziales/interpersonelles Funktionsniveau	**Gutes Funktionieren in allen sozialen Bereichen und interpersonell effektiv.** Interessiert an und involviert in einem breiten Bereich sozialer und interpersoneller Aktivitäten mit sowohl engen als auch lockeren Freundschaften. Altersadäquate Einbindung in intime Beziehungen. Nur alltägliche interpersonelle Probleme oder Belange (z.B. gelegentliche Auseinandersetzung mit Partner, Freunden, Kollegen oder Klassenkameraden). In der Lage, solche Konflikte adäquat zu lösen.
8	Gutes soziales/interpersonelles Funktionsniveau	**Einige vorübergehende leichte Beeinträchtigungen des sozialen Funktionierens.** Leichte soziale Beeinträchtigung liegt vor, ist aber vorübergehend und eine zu erwartende Reaktion auf psychosoziale Stressoren (z.B. nach geringfügigen Auseinandersetzung mit Partner, Freunden, Kollegen oder Klassenkameraden). Hat einige bedeutsame Beziehungen zu Gleichaltrigen (lockere und enge Freunde), und/oder altersadäquate intime Beziehungen. Vereinzelte interpersonelle Konflikte mit Gleichaltrigen.
7	Leichte Probleme im sozialen/interpersonellen Funktionsniveau	**Einige überdauernde leichte Beeinträchtigungen des sozialen Funktionierens.** Leichte Beeinträchtigung liegt vor, die NICHT allein eine zu erwartende Reaktion auf psychosoziale Stressoren ist (z.B. leichte Konflikte mit Gleichaltrigen, Kollegen oder Klassenkameraden; Schwierigkeiten bei der adäquaten Konfliktlösung). Hat einige bedeutsame Beziehungen zu Gleichaltrigen (lockere und/oder enge Freunde). Einige Schwierigkeiten bei der Entwicklung oder Aufrechterhaltung altersadäquater intimer Beziehungen (z.B. viele kurzlebige Beziehungen).
6	Moderate Beeinträchtigung im sozialen/interpersonellen Funktionsniveau	**Moderate Beeinträchtigung des sozialen Funktionierens.** Moderate Beeinträchtigung vorhanden (z.B. wenige enge Freunde; bedeutsame, aber diskontinuierliche Konflikte mit Gleichaltrigen, Kollegen oder Klassenkameraden). Moderate Schwierigkeiten in der Entwicklung altersadäquater intimer Beziehungen (z.B. seltene Verabredungen). Sucht andere nur gelegentlich auf, geht aber auf Einladungen anderer ein, an einer Aktivität teilzunehmen.
5	Schwerwiegende Beeinträchtigung im sozialen/interpersonellen Funktionsniveau	**Schwerwiegende Beeinträchtigung des sozialen Funktionierens.** Keine engen Freunde oder intimen Partner, aber einige lockere Kontakte (z.B. Bekanntschaften, Freunde nur aus Schule/Arbeitsstelle). Trifft sich nur selten mit anderen. Gelegentliches kämpferisches oder (verbal) streitlustiges Verhalten gegenüber Gleichaltrigen. Beginnender Rückzug von Familienmitgliedern (z.B. initiiert keine Gespräche mit der Familie, geht aber darauf ein, wenn er/sie angesprochen wird).
4	Wesentliche Beeinträchtigung im sozialen/interpersonellen Funktionsniveau	**Wesentliche Beeinträchtigung des sozialen Funktionierens.** Schwerwiegende Beeinträchtigung in Beziehungen zu Freunden oder Gleichaltrigen (z.B. sehr wenige oder gar keine Freunde, häufige Konflikte mit Freunden oder häufiges Meiden von Freunden). Häufiges kämpferisches oder (verbal) streitlustiges Verhalten gegenüber Gleichaltrigen. Seltener Kontakt zu Familienmitgliedern (z.B. reagiert manchmal nicht auf Familie oder meidet Familienmitglieder).
3	Grenzwertige Fähigkeit, sozial zu funktionieren	**Grenzwertige Fähigkeit, sozial zu funktionieren oder interpersonelle Beziehungen aufrecht zu erhalten.** Häufig alleine und sozial isoliert. Schwerwiegende Beeinträchtigung in Beziehungen zu allen Gleichaltrigen, auch in Bekanntschaften. Wenige Interaktionen mit Familienmitgliedern (z.B. oft alleine im Raum). Schwerwiegende Einschränkung in der Kommunikation mit anderen (z.B. Vermeidung der Teilnahme an den meisten sozialen Aktivitäten).
2	Unfähigkeit sozial zu funktionieren	**Unfähig, sozial zu funktionieren oder interpersonelle Beziehungen aufrecht zu erhalten.** In der Regel alleine und sozial isoliert. Verlässt nur selten das Haus. Geht selten ans Telefon oder zur Tür. Nimmt selten an Interaktionen mit anderen teil, sowohl zuhause als auch in anderen Settings (z.B. Schule, Arbeit).
1	Extreme soziale Isolation	**Extreme soziale Isolation.** Überhaupt keine sozialen oder familiären Kontakte. Verlässt das Haus nicht. Weigert sich, ans Telefon oder zur Tür zu gehen.

Note: This scale has been partially derived from the Social and Occupational Functioning Assessment Scale (SOFAS) from *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) and the GAF as it appears in the Scale of Prodromal Symptoms (SOPS). Item content has been changed to focus specifically on social and interpersonal functioning.

PRONIA Assessments

GF: Role Scale

II. Globales Funktionsniveau: Rollen-Skala

Aktuell:	
Niedrigstes im letzten Jahr[2]:	
Höchstes im letzten Jahr[2]:	
Höchstes im Leben[2]:	

1b. Die Beurteilung basiert auf Informationen von folgenden Personen *(Mehrfachnennungen möglich)*:

☐ Befragter
☐ Familienmitglieder/ Freunde
☐ Pflegepersonal/ Sozialarbeiter/ andere feste Betreuungspersonen

Instruktion:

Bitte schätzen Sie das „niedrigste" Funktionsniveau in berufsbezogenen, schulischen und/oder haushaltsbezogenen Rollen ein, in einem entsprechend festgelegten Zeitrahmen. Beurteilen Sie für „aktuell" das höchste Ausmaß an Beeinträchtigung im Funktionsniveau in der „letzten Woche". Beurteilen Sie das aktuelle Funktionieren unabhängig von der Ätiologie sozialer Probleme. Wenn der Patient/die Patientin gerade offiziell Schulferien hat (z.B. Sommerferien) oder weniger als 2 Wochen im Krankenhaus lag und momentan wieder entlassen ist, aber noch nicht die Möglichkeit hatte, seine oder ihre gewohnte Rolle zwischen Entlassung und Erhebung wieder einzunehmen (z.B. bei Messung am Tag der Entlassung), schätzen Sie das Funktionsniveau, das direkt vor dieser Situation bestand (z.B. vor dem Krankenhausaufenthalt). Ist die Person zur Zeit der Messung im Krankenhaus und zwar für weniger als 2 Wochen, beurteilen Sie das Funktionsniveau gemäß des Ausmaßes an Funktionieren direkt vor dem Krankenhausaufenthalt. Lag die Person länger als 2 Wochen aufgrund nichtpsychischer Beschwerden im Krankenhaus (z.B. komplizierte Grippe), beurteilen Sie ebenso gemäß des Ausmaßes an Funktionieren direkt vor dem Krankenhausaufenthalt (entsprechend auch bei Schulferien). Wenn eine Person sich in einer Übergangsphase befindet (z.B. zwischen Schule und Universität oder zwischen zwei Arbeitsstellen) beurteilen Sie ebenso gemäß des Ausmaßes an Funktionieren direkt vor dieser Situation (entsprechend auch bei Schulferien).

Bestimmen und beurteilen Sie das Funktionieren in primären Rollen (Arbeit, Schule, Zuhause)basierend auf den unten aufgeführten Fragen. Wenn die Person mehrere Rollen besetzt, berücksichtigen Sie die GESAMTE Zeit, die mit rollenbezogenen Aktivitäten verbracht wird (d.h. Teilzeit Schule plus Teilzeit Arbeit gleicht einem Vollzeit Rollenstatus).

Vorgegebene Rollen:

Wenn der Patient unter 18 Jahren ist und die Sekundarstufe I nicht abgebrochen oder abgeschlossen hat, ist die vorgegebene Rolle Schule. Wenn der Patient über 18 ist und nicht mehr die Schule besucht, ist die vorgegeben Rolle Arbeit. Wenn die Person mehrere Rollen besetzt, berücksichtigen Sie die GESAMTE Zeit, die mit rollenbezogenen Aktivitäten verbracht wird (d.h. Teilzeit Schule plus Teilzeit Arbeit gleicht einem Vollzeit Rollenstatus).

Anmerkung:

Die vorliegende Skala betont den Grad an Unterstützung, die aus dem Umfeld der Person bereitgestellt wird und die mit dieser Unterstützung erbrachte Leistung. Der im vorliegenden Instrument verwendete Ausdruck „selbstständig" impliziert, dass die Person auf einem „altersangemessenem Level" funktioniert, ohne externe Unterstützung oder Entgegenkommen.

Beispiele für selbstständiges Funktionieren beinhalten (1) altersangemessenes Funktionieren in einer Regelschule ohne extra Hilfe, spezielle Kurse oder spezielle Erleichterungen für Klassenarbeiten zu benötigen; (2) kompetitive Vollzeitbeschäftigung ohne zusätzliche Anleitung, Betreuung, Arbeitstrainings oder andere Formen von spezieller Unterstützung; und (3) Vollzeit HausFrau/Hausmann mit Verantwortung für das Generieren, Organisieren und Steuern von Haushaltstätigkeiten und Aktivitäten für die Familie ohne zusätzliche Anleitung, Betreuung oder Unterstützung.

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[1] Abweichende Referenzperiode bei follow-ups: Zeitspanne seit dem letzten Besuch
[2] Beurteilen Sie nur auf der baseline
Anmerkung: Beim follow-up kann der höchste Wert in der letzten Beobachtungsperiode nur über dem aktuellen Wert beim letzten Besuch liegen und nicht darunter, (d.h. wenn niedriger, definiert der aktuelle Wert beim letzten Besuch den höchsten Wert der letzten Beobachtungsperiode (in der Regel 3 Monate)). Der niedrigste Wert in der letzten Beobachtungsperiode kann nur unter dem aktuellen Wert beim letzten Besuch liegen und nicht darüber.

PRONIA Assessments

GF: Role Scale

Fragen, die bei der Beurteilung des Globalen Rollenfunktionierens behilflich sind:

1. Wie verbringen Sie ihre Zeit? Wie sieht ihr Tagesablauf aus?

2. Wenn zurzeit in Arbeit:
   a. Wo arbeiten Sie? Was sind Ihre Aufgaben bei der Arbeit?
   b. Wie viele Stunden pro Woche arbeiten Sie?
   c. Wie lange sind Sie schon bei ihrer derzeitigen Arbeitsstelle beschäftigt? Hat sich ihr Beschäftigungsstatus kürzlich verändert (z.B. Verlust der Arbeitsstelle, aufgehört zu arbeiten, Position oder Arbeitspensum geändert)?
   d. Brauchen Sie üblicherweise Unterstützung oder regelmäßige Beaufsichtigung bei der Arbeit? Wie oft brauchen Sie zusätzliche Hilfe? Gibt es Aufgaben, die Sie nicht alleine bewältigen können?
   e. Haben Sie Schwierigkeiten ihr Arbeitspensum zu erledigen? Wenn Sie im Rückstand liegen, sind Sie fähig diesen wieder aufzuholen?
   f. Haben Sie bezüglich ihrer Leistung irgendwelche Anmerkungen (positive oder negative) oder formale Mitarbeiterbeurteilungen erhalten? Wurden bestimmte Dinge von anderen besonders hervorgehoben, weil Sie diese gut oder schlecht gemacht haben?

3. Wenn zurzeit eine Schule besucht:
   a. Was für eine Art von Schule besuchen Sie? (Allgemeinbildende Schule, nicht-öffentliche Schule, Förderschule)
   b. Haben Sie schon einmal sonderpädagogischen Unterricht oder anderen Förderunterricht besucht?
   c. Wie lange sind Sie schon an dieser Schule? Gab es kürzlich irgendwelche Veränderungen bezüglich des Schulbesuchs?
   d. Erhalten Sie irgendwelche besonderen Hilfen oder Erleichterungen in ihrer Klasse? Bekommen Sie Nachhilfe oder zusätzliche Unterstützung in der Schule oder nach der Schule? Erhalten Sie zusätzliche Zeit für Klassenarbeiten oder dürfen Sie den Klassenraum verlassen, um die Klassenarbeit an einem ruhigen Ort zu schreiben?
   e. Haben Sie Schwierigkeiten, ihre Hausaufgaben zu erledigen? Wenn Sie mit den Hausaufgaben im Rückstand liegen, sind Sie fähig diesen wieder aufzuholen?
   f. Wie sind ihre Zensuren (beste und schlechteste Note)? Fallen Sie in irgendeinem Fach durch?

4. Wenn zurzeit Hausfrau/Hausmann:
   a. Was sind Ihre Aufgaben rund um das Haus oder für die Familie?
   b. Wie lange sind Sie schon verantwortlich für den Haushalt?
   c. Wieviele Stunden pro Woche verbringen Sie mit Haushaltstätigkeiten?
   d. Können Sie ihre Pflichten im Haushalt erfüllen? Geraten Sie je in Rückstand? Wenn ja, können sie diesen wieder aufholen oder brauchen Sie Hilfe von anderen? Vermeiden Sie irgendwelche Aufgaben? Brauchen Sie regelmäßig Unterstützung oder Anleitung bei irgendwelchen Tätigkeiten im Rahmen des Haushaltes?

PRONIA Assessments

GF: Role Scale

Globales Rollenfunktionsniveau

10	**Überragendes Rollenfunktionsniveau**	Hält eigenständig überragendes Funktionieren innerhalb anspruchsvoller Rollen aufrecht (Vollzeit oder äquivalenter Zeitrahmen). Erhält ausnahmslos überragende Leistungsbeurteilungen im kompetitiven beruflichen Kontext. In allgemeinen schulischen Kontexten werden ausschließlich sehr gute Noten erzielt. Mit Leichtigkeit werden alle Aufgaben der Haushaltsführung entwickelt, organisiert und ausgeführt.
9	**Überdurchschnittliches Rollenfunktionsniveau**	Hält eigenständig sehr gutes Funktionieren innerhalb anspruchsvoller Rollen aufrecht (Vollzeit oder äquivalenter Zeitrahmen). Selten abwesend oder nicht in der Lage zu arbeiten. Erhält gute bis überragende Leistungsbeurteilungen im kompetitiven beruflichen Kontext. In allgemeinen schulischen Kontexten werden gute bis sehr gute Noten erzielt. Alle Aufgaben der Haushaltsführung werden entwickelt, organisiert und ausgeführt.
8	**Gutes Rollenfunktionsniveau**	Hält eigenständig gutes Funktionieren innerhalb anspruchsvoller Rollen aufrecht (Vollzeit oder äquivalenter Zeitrahmen). Fällt ab und zu in der Erfüllung von Aufgaben zurück, holt jedoch immer wieder auf. Erhält zufriedenstellende Leistungsbeurteilungen im kompetitiven beruflichen Kontext. In allgemeinen schulischen Kontexten werden mindestens befriedigende Noten erzielt. Gelegentliche Schwierigkeiten bei der Entwicklung und Organisation von Aufgaben der Haushaltsführung. Oder: Aufrechterhaltung überdurchschnittlicher Leistungen mit minimaler Unterstützung (z.B. Nachhilfe/Tutor, Streckung von Lernihalten durch Ausbildungsverlängerung, zusätzliche Anleitungen bei der Arbeit 1-2 Mal pro Woche). Gute bis sehr gute Noten, gute Schul-/Arbeitsbeurteilungen, Aufrechterhaltung aller Haushaltsaufgaben mit diesem Ausmaß an Unterstützung
7	**Leichte Beeinträchtigung im Rollenfunktionsniveau**	Leichte Einschränkungen des eigenständigen Funktionierens innerhalb anspruchsvoller Rollen. Fällt oft in der Erfüllung von Aufgaben zurück oder ist unfähig Leistung zu erbringen. Erhält oft schlechte Leistungsbeurteilungen im kompetitiven beruflichen Kontext. In allgemeinen schulischen Kontexten werden mindestens ausreichende Noten erzielt. Häufige Schwierigkeiten bei der Entwicklung oder Organisation von Aufgaben der Haushaltsführung. Oder: Aufrechterhaltung guter Leistungen mit minimaler Unterstützung (z.B. minimale Angleichungen/Entgegenkommen in der Schule, zusätzliche Anleitungen und Unterstützung bei der Arbeit 1-2 Mal pro Woche). Mindestens befriedigende Noten, befriedigende Schul-/Arbeitsbeurteilungen, Aufrechterhaltung der meisten Haushaltsaufgaben mit diesem Ausmaß an Unterstützung.
6	**Moderate Beeinträchtigung im Rollenfunktionsniveau**	Moderate Beeinträchtigung des selbständigen Funktionierens. In allgemeinen schulischen Kontexten können gelegentlich mangelhafte Noten erzielt werden. Erhält andauernd schlechte Leistungsbeurteilungen im kompetitiven beruflichen Kontext; wechselt möglicherweise aufgrund schlechter Leistungen wiederholt den Job. Überdauernde Schwierigkeiten bei der Entwicklung oder Organisation von Aufgaben der Haushaltsführung. Oder: benötigt partielle Unterstützung (spezielle Förderkurse, erhält Anleitung und Unterstützung bei der Arbeit mehr als 2 Mal pro Woche). Kann weniger anspruchsvolle oder Teilzeittätigkeit und/oder Betreuung im häuslichen Umfeld benötigen, funktioniert mit Hilfe dieser Unterstützungen jedoch zufrieden stellend bzw. adäquat (kann bei der Erfüllung übertragener Aufgaben zurückfallen, erfüllt sie aber letztlich; erhält zufrieden stellende Beurteilungen im Job oder wird in der Schule von Klasse zu Klasse versetzt).
5	**Schwerwiegende Beeinträchtigung im Rollenfunktionsniveau**	Schwerwiegende Beeinträchtigung des selbständigen Funktionierens. In allgemeinen schulischen Kontexten werden mehrere für eine Versetzung notwendige Leistungen nicht erzielt. Kann den Job verlieren (z.B. in der Probezeit) oder unfähig sein, die meisten Aufgaben der Haushaltsführung selbständig auszuführen. Oder: Besucht ausschließlich Förderklasse/-kurse. Benötigt weniger anspruchsvolle Tätigkeit und tägliche Anleitung/Unterstützung. Kann berufliche Rehabilitation benötigen und/oder teilweise Betreuung im häuslichen Umfeld, ABER Aufrechterhaltung überdurchschnittlicher Leistungen (erhält gute bis sehr gute Noten, gute Leistungsbeurteilungen in Schule/Beruf, führt alle Aufgaben aus).

PRONIA Assessments

GF: Role Scale

4	**Wesentliche Beeinträchtigung im Rollenfunktionsniveau**	Sehr schwerwiegende Beeinträchtigung des selbständigen Funktionierens. In allgemeinen schulischen Kontexten werden ausschließlich mangelhafte Leistungen erzielt oder völliges schulisches Scheitern. Kann keine eigenständige Tätigkeit aufnehmen oder erhalten (z.B. kürzlich entlassen worden, mehrere Kurzzeitbeschäftigungen in der jüngsten Vergangenheit, sucht aber aktiv nach einer neuen Arbeitsstelle in der näheren Zukunft) oder ist unfähig, so gut wie alle Aufgaben der Haushaltsführung eigenständig auszuführen. Oder: adäquates bis gutes Funktionieren mit wesentlicher Unterstützung. Benötigt Assistenz bei der Arbeit, speziellen Förderunterricht, besucht nicht-öffentliche oder psychiatrische Schule oder Beschulung zuhause, um nötige Unterstützung zu gewährleisten. Und/oder unterstütztes häusliches Umfeld bei adäquatem Funktionsniveau bei gegebener Unterstützung (kann bei der Ausführung zugewiesener Aufgaben zurückfallen, erhält zufrieden stellende Beurteilung in Schule/Beruf bzw. wird von Klasse zu Klasse versetzt).
3	**Grenzwertige Fähigkeit, zu funktionieren**	Beeinträchtigtes Funktionieren mit wesentlicher Unterstützung. Benötigt betreutes Arbeitsumfeld, ausschließlich spezieller Förderunterricht möglich, nicht-öffentliche oder psychiatrische Schule oder Beschulung zuhause, um nötige Unterstützung zu gewährleisten. Und/oder: unterstütztes häusliches Umfeld bei trotz gegebener Unterstützung schlechtem Funktionsniveau (permanentes Zurückfallen bei der Ausführung zugewiesener Aufgaben, oft unfähig Leistung zu erbringen, erhält schlechte Beurteilungen in Schule/Beruf oder wird nicht von Klasse zu Klasse versetzt).
2	**Unfähigkeit zu funktionieren**	Arbeitsunfähig, aber in der Lage, an strukturierten Aktivitäten teilzunehmen. Behindertenstatus oder gesetzliche Betreuung. Keine Erwerbstätigkeit, keine schulische Notengebung, keine eigenständige Haushaltsführung. Verbringt 5 oder mehr Stunden pro Woche in strukturierter rollenbezogener Aktivität (z.B. Ehrenamt, geschützte Arbeitsprogramme).
1	**Extreme Rollendysfunktion**	Schwer behindert. Behindertenstatus oder gesetzliche Betreuung. Keine Erwerbstätigkeit (z.B. schon lange Zeit bestehende Arbeitslosigkeit oder nie auf dem ersten Arbeitsmarkt UND nicht auf der Suche nach einer Arbeitsstelle), keine schulische Notengebung, keine eigenständige Haushaltsführung. Verbringt weniger als 5 Stunden pro Woche in strukturierter rollenbezogener Aktivität.

Note: This scale has been partially derived from the Social and Occupational Functioning Assessment Scale (SOFAS) from Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) and the GAF, as it appears in the Scale of Prodromal Symptoms (SOPS). Item content has been changed to focus specifically on role functioning.

A.3 SVM Results

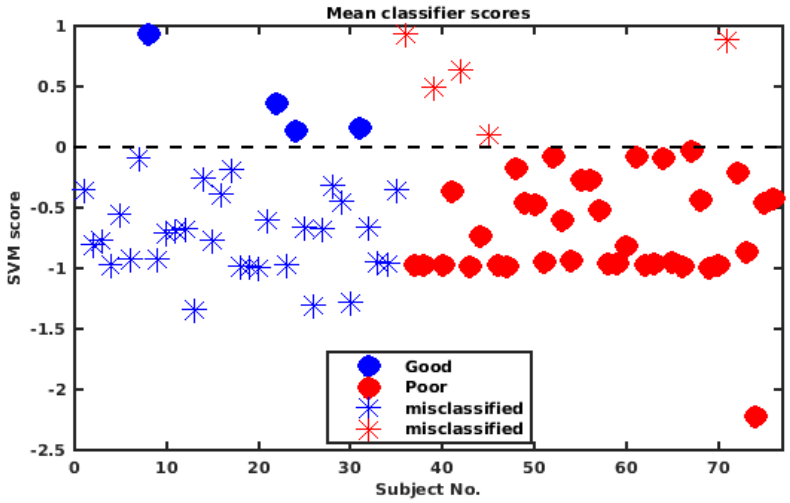

FIGURE A.1: Illustration of the rsFC classifier in application with the Gmask in separating Good vs Poor subjects based on their GF Role scores

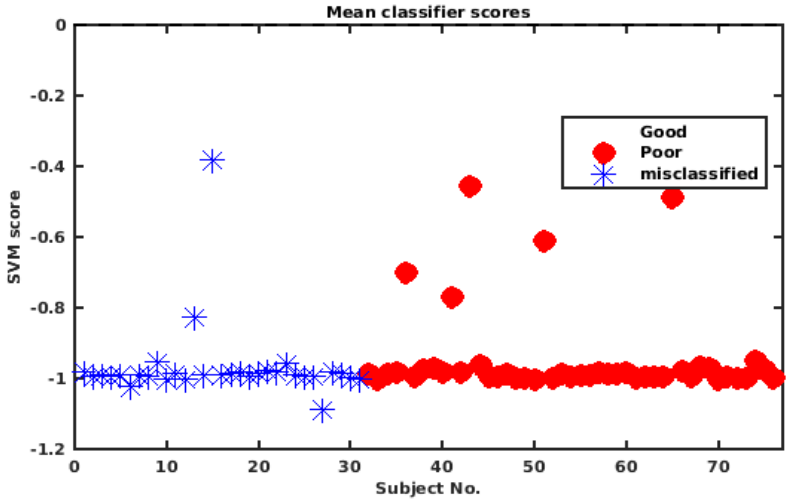

FIGURE A.2: Illustration of the rsFC classifier in application with the Gmask in separating Good vs Poor subjects based on their GAF Disability scores

List of Figures

List of Tables

Declaration of Authorship

I, Ifrah Khanyaree, declare that this thesis and the work presented in it are my own. I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University.
- Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
- I have acknowledged all main sources of help.
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself.

Signed:

_____

Date:

_____