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Predicting cognition in schizophrenia applying machine learning to structural MRI data

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Content

Zusammenfassung

Hintergrund

Charakteristisch für Patienten mit einer Schizophrenie sind Defizite in exekutiven Funktionen und Aufmerksamkeit sowie Störungen im episodischen und Arbeitsgedächtnis. Diese reduzieren das Funktionsniveau und die Lebensqualität der Patienten wesentlich. Die Defizite zeigen sich vor, während und nach der ersten Psychose und sind assoziiert mit strukturellen Veränderungen in präfrontalen und temporalen Hirnregionen. Trotz umfangreicher Forschung sind die neuronalen Mechanismen der Kognitionsdefizite bei Schizophrenie unklar. Diagnostisch erschwerend ist die unterschiedliche Ausprägung der Beeinträchtigungen – etwa 25% der Patienten erzielen in neuropsychologischen Tests ähnliche Leistungen wie gesunde Kontrollen. Wir adressierten diese Heterogenität, indem wir neuronalen Korrelate von zwei Kognitionsprofilen bei einer Stichprobe von Patienten mit Schizophrenie (SP), gesunden Kontrollprobanden (HC) und Verwandten (UR) mittels maschinellen Lernens untersuchten. Mittels eines Random-Forrest-Modell (RF) analysierten wir strukturelle Bildgebungsdaten, um zu identifizieren, ob und welche Gehirnregionen eine hohe (HighCog) und eine niedrige (LowCog) kognitive Leistung bei Schizophrenie mit einer Genauigkeit von über 50% vorhersagen können.

Methoden

Wir untersuchten das Gehirnvolumen mittels T1 Magnetresonanztomographie (MRI, MPRAGE Sequenz) in 54 SP, 54 HC und 19 UR. Im Anschluss untersuchten wir das episodische Gedächtnis, die Aufmerksamkeit, exekutive Funktionen und das Arbeitsgedächtnis mit dem Verbalen Lern- und Merkfähigkeitstest (VLMT), dem Digit Symbol Substitution Test (DSST), dem Trail Making Test A und B (TMT-A, TMT-B) und dem Digit Span Task (DST). Die Testergebnisse wurden standardisiert (z-Transformation), gewichtet und zu einem globalen Kognitionsindex gemittelt. Patienten mit einem Kognitionsindex bis zu oder über 1 SD des kumulierten Durchschnitts von SP und UR wurden den Untergruppen HighCog (n = 13) bzw. LowCog (n = 41) zugeordnet. Anschließend klassifizierten wir HighCog und LowCog mittels eines RF-Algorithmus mit volumetrischen Daten von SP, HC und UR und definierten die relevantesten Gehirnstrukturen für die Vorhersage. Darüber hinaus führten wir mehrere Regressionsanalysen durch, um die Beziehung zwischen der Kognition und den Volumina der sieben wichtigsten Regionen zu untersuchen. Schließlich verwendeten wir multivariate (MANOVA) und univariate Varianzanalysen (ANOVA), um Unterschiede zwischen den

Studienpopulationen (SP vs. HC vs. UR) und zwischen den kognitiven Profilen (HighCog vs. LowCog) in den Volumina der Hirnregionen zu ermitteln.

Ergebnisse

Die RF unterschied zwischen den beiden kognitiven Profilen mit einer Genauigkeit (Sensitivität/Spezifität) von 62,1% (62,1%/76,0%) und einer ausgeglichenen Genauigkeit (BAC) von 69,0%. Darüber hinaus wurden Volumina der grauen Substanz (GM) von Regionen im präfrontalen, temporalen, parietalen und okzipitalen Lappen als relevant für die Klassifizierung identifiziert. Die ermittelten Hirnregionen hatten relativ kleine Wichtigkeitswerte von 0,01 bis 0,03 und umfassten den rechten dorsolateralen Gyrus frontalis superior, den linken und rechten Gyrus frontalis medius, den linken operculare Gyrus frontalis inferior, den rechten Gyrus lingualis, den rechten Gyrus supramarginalis, und den linken Gyrus temporalis superior. Die anschließende Regressionsanalyse zeigte, dass große GM-Volumina aller Regionen, außer des linken Gyrus frontalis medius, eine gute kognitive Leistung in der gesamten Stichprobe signifikant vorhersagen (alle $p < 0{,}001$). Außerdem stellten die MANOVA und ANOVAs in allen Regionen signifikant geringere GM-Volumina in SP im Vergleich zu UR und HC fest (alle $p < 0{,}003$). Allerdings hatten SP und UR ein größeres GM-Volumen des linken Gyrus frontalis medius als HC. Entgegen unserer Hypothese zeigten die Regressionsanalysen keine signifikanten Beziehungen zwischen den wichtigsten Hirnregionen und dem Kognitionsindex in SP. Darüber hinaus gab es keine Gruppenunterschiede bei den GM-Volumina zwischen HighCog und LowCog.

Diskussion und Perspektive

Der aktuelle RF-Algorithmus mit volumetrischen Gehirndaten von Patienten, gesunden Verwandten und Kontrollen, konnte erfolgreich konservierte und beeinträchtigte Kognition bei Schizophrenie klassifizieren. Das Modell erreichte Vorhersagewerte im Einklang mit früherer Forschung und identifizierte Gehirnstrukturen, die mit Arbeitsgedächtnis, Aufmerksamkeit und verbaler Verarbeitung in Verbindung stehen. Die beiden kognitiven Profile unterschieden sich nicht in der Gehirnmorphologie, was eine Überlappung der zugrunde liegenden kortikalen Muster impliziert. Im Vergleich zu HC und UR hatten die Patienten signifikant geringere GM-Volumina in den relevantesten Regionen, was auf deren Potenzial als endophenotypische Marker bei Schizophrenie hinweist. Zukünftige Forschung sollte unsere Ergebnisse in einer größeren Stichprobe kreuzvalidieren und sie mit multimodaler Bildgebung, Genetik und soziokulturellen Daten kombinieren, um Erkenntnisse über die bei der Schizophrenie beeinträchtigten Kognition und deren zugrundeliegende Mechanismen zu gewinnen.

Abstract

Background

Deficits in executive functions, attention, episodic and working memory are characteristic of schizophrenia and lead to poor functional outcome and life quality. Previous research demonstrated their prevalence prior, during, and after the first onset of psychosis and linked them to altered prefrontal and temporal structures. Moreover, cognitive impairment in schizophrenia is associated with genetic factors and, thus, a fundamental component in modern etiology models. Despite extensive research in recent years, the neuronal mechanisms of cognition in schizophrenia are still poorly understood. One of the main difficulties is the observed heterogeneity, with approximately 25% of patients performing similarly to healthy controls in neuropsychological tests. In the current work, we addressed this issue by applying machine learning to investigate brain morphological correlates of two cognitive profiles in schizophrenia in a sample of patients (SP), healthy controls (HC), and unaffected relatives (UR). Specifically, we used a random forest (RF) model with neuropsychological and structural imaging data to identify if and which brain regions could predict high (HighCog) and low (LowCog) cognitive performance in schizophrenia with accuracy above 50%.

Methods

We measured brain volume via T1-weighted magnetic resonance imaging (MPRAGE MRI) in 54 SP, 54 HC, and 19 UR. We then assessed episodic memory, attention, executive functioning, and working memory using the Verbaler Lern- und Merkfähigkeitstest (VLMT: Verbal Learning and Memory Test), Digit Symbol Substitution Test (DSST), and the Trail Making Test A and B (TMT-A, TMT-B), and the Digit-Span-Task (DST). Test scores were standardized (z-transformation), weighted, and averaged into a global cognition index. Patients with a cognition index up to or above 1 SD of the cumulated average of SP and UR were assigned to HighCog (n = 13) and LowCog (n = 41) subgroups, respectively. We then conducted an RF analysis using volumetric data of SP, HC, and UR to classify HighCog and LowCog and to define the most relevant brain structures for the prediction. Furthermore, we performed several subsequent regression analyses to investigate the relationship between cognition and the volumes of the top seven regions. Finally, we used multivariate (MANOVA) and univariate analyses of variance (ANOVA) to detect differences between study populations

(SP vs. HC vs. UR) and between cognitive profiles (HighCog vs. LowCog) in the volumes of the seven most important brain regions.

Results

As expected, the RF distinguished between the two cognitive profiles with an accuracy (sensitivity/specificity) of 62.1% (62.1%/76.0%) and balanced accuracy (BAC) of 69.0%. Furthermore, it identified grey matter (GM) volumes of regions in the prefrontal, temporal, parietal, and occipital lobe as most relevant for the classification. The top seven brain regions with relatively small importance values of .01 – .03 were the right dorsolateral Superior Frontal Gyrus, left and right Middle Frontal Gyrus, left opercular Inferior Frontal Gyrus, right Lingual Gyrus, right Supramarginal Gyrus, left Superior Temporal Gyrus.

The subsequent regression analysis demonstrated that large GM volumes of all regions, but the left Middle Frontal Gyrus, significantly predict good cognitive performance in the whole study sample (all $p < .001$). Moreover, the MANOVA and ANOVAs revealed significantly smaller GM volumes in SP compared to UR and HC in all regions (all $p < .003$). Only GM volumes of the left Middle Gyrus SP and UR had a larger GM volume than HC.

Against our hypothesis, regression analyses between the most important brain regions and the cognition index in SP yielded no significant results. Moreover, there were no significant group differences in GM volumes between HighCog and LowCog.

Discussion and Perspective

The current RF algorithm with volumetric brain data from patients, healthy relatives, and controls successfully classified between preserved and compromised cognitive functioning in schizophrenia. The model achieved prediction values in line with previous research and identified brain structures associated with working memory, attention, and verbal processing. However, the two cognitive profiles did not differ in brain morphology, implying overlapping of the underlying cortical patterns. Nevertheless, compared to HC and UR, patients had significantly smaller GM volumes in the most relevant regions, suggesting their potential as endophenotypic markers in schizophrenia. Future research should cross-validate our findings in a larger sample and combine them with multimodal imaging, genetics, and social-cultural data to further unravel the mechanisms of cognition in schizophrenia.

Figures

Tables

Abbreviations

AAL	Automatic Anatomical Labeling
ACC	Anterior Cingulate Cortex
AFNI	Analysis of Functional Images
ANOVA	Analyses of Variance (univariat)
BAC	Balanced Accuracy
BACS	The Brief Assessment of Cognition in Schizophrenia
BDI-II	Beck Depression Inventory II
BET	Brain Extraction Tool
CGI-S	Clinical Global Impression Scale
COMT	Catechol-O-Methyltransferase
CPZ	Chloropromazine dose equivalence
CSF	Cerebrospinal fluid
DDD	Defined Daily Doses
DISC1	Disrupted in Schizophrenia 1
DLPFC	Dorsolateral Prefrontal Cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSST	Digit Symbol Substitution Test
DST	Digit Span Test
FA	Flip Angle
FGA	First-Generation Antipsychotics
FLIRT	FMRIB's Linear Image Registration Tool
fMRI	functional MRI
FN	False Negatives
FNIRT	FMRIB's Non-linear Registration Tool
FP	False Positives
FTND	Fagerström Test for Nicotine Dependence
GABA	Gamma-Amino-Butyric acid
GAF	Global Assessment of Functioning Scale
GM	Grey Matter
GWAS	Genome-wide-associations studies
HC	Healthy controls

HighCog	Patients with high cognitive performance
ICD	International Classification of Disorders and Related Problems
ICV	Intracranial Volume
IDS-C	Inventory of Depressive Symptomatology
K-S test	Kolmogorov-Smirnov test
LowCog	Patients with poor cognitive performance
MCCB	The MATRICS Consensus Cognitive Battery
M.I.N.I.	Mini-International Neuropsychiatry Interview
MANOVA	Multivariate Analyses of Variance
MIMICSS	Multimodal Imaging in Chronic Schizophrenia Study
MNU	Montreal Neurological Institute
MPRAGE	Magnetization Prepared Rapid Gradient Echo
MRI	Magnet Resonance Imaging
NMDA	N-Methyl-D-aspartate
NPV	Negative Predictive Value
NRG-1	neuregulin
PANSS	Positive and Negative Syndrome Scale
PET	Positron Emission Tomography
PPV	positive predictive value
RAVT	Rey Auditory Verbal Learning
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RF	Random Forest
SANS	Scale for the Assessment of Negative Symptoms
SGA	Second-Generation Antipsychotics
sMRI	structural MRI
SNP	Aingle Nucleotide Polymorphisms
SP	Patients with Schizophrenia
SPECT	Single Photon Emission Computed Tomography
SVM	Support Vector Machines
TDIDT	Top-Down Induction of Decision Trees
TE	Echo Time
TMT	Trail Making Test
TN	True Negatives

TP	True Positives
TR	Repetition Time
UR	Unaffected Relatives of patients with schizophrenia
VLMT	Verbaler Lern-und Merkfähigkeitstest
VLPFC	Ventrolateral Prefrontal Cortex
WM	White Matter
WST-R	Wortschatztest

1. Introduction

Schizophrenia is a severe neuropsychiatric disorder that affects approximately 1% of the world's population. Despite the low prevalence, it is one of the leading causes for health burden and disability (James et al., 2018; Whiteford et al., 2013) and thus an immense economic strain on health systems in Germany (Frey, 2014) and worldwide (Chong et al., 2016). Typically, patients experience distortions in thinking, perception, and behavior reflected in symptoms like delusions, hallucinations, apathy, and avolition (DGPPN, 2019). Most importantly, schizophrenia impairs cognition, decreasing patients' clinical outcome, social and occupational status, and quality of life (Green, Kern, Braff, & Mintz, 2000; Harvey et al., 2012; Hofer et al., 2005). Prior research demonstrated deficits in various domains such as executive functioning, attention (Orellana & Slachevsky, 2013), language processing (Crow, 1998), working, and episodic memory (Barch & Ceaser, 2012). These impairments are often present prior to the onset of the disease (Lencz et al., 2006), stable through its course (Heilbronner, Samara, Leucht, Falkai, & Schulze, 2016), and associated with abnormalities in prefrontal and temporal brain structures (Antonova, Sharma, Morris, & Kumari, 2004). Moreover, cognitive deficits are also observed in healthy first-degree relatives of patients, implying a strong genetic component and, thus, a fundamental factor in etiology models (e.g. Howes & Murray, 2014). Despite extensive research on cognitive impairment in schizophrenia, its underlying neural mechanisms are still unclear. One of the biggest challenges facing researchers is the heterogeneity of deficits, with previous work reporting ca. 25% of patients having almost healthy cognitive performance (Joyce & Roiser, 2007). In addition, the understanding of neuropsychiatric processes requires analysis of complex interactions between brain function, behavior, and environmental factors, where traditional statistical methods are often insufficient. Machine learning, however, has the capability to process and integrate big amounts of multi-dimensional data and thus has the potential to solve this methodological issue (N. Tandon & Tandon, 2019). In the present study, we applied machine learning to address heterogeneity in schizophrenia by investigating the neural correlates of different cognitive profiles in a sample of patients, unaffected relatives, and healthy controls. Upon neuropsychological and structural imaging data, we aimed to identify, if and which brain structures could predict high and low neuropsychiatric performance in schizophrenia.

1.1. Schizophrenia

Definition and diagnostic of schizophrenia have been continuously evolving since the beginning of the 20th century (R. Tandon, 2012). In 1899, Emil Kraepelin first described it as "*dementia praecox,"* a clinical syndrome with an early onset, characterized by neurocognitive deficits and poor prognosis in contrast to affective disorders (Kraepelin, 1899). Later, Bleuler (1916) recognized key symptoms such as disorganized thinking and speech and renamed it as *"schizophrenia"* ("splitting of the mind"). Schneider (1946) continued the work on the nosology of schizophrenia by classifying the symptoms in first-rank and second-rank, a concept that was adopted and further developed by modern classification systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) and the International Classification of Disorders and Related Problems (ICD-10) (WHO, 1993). Currently, the newest revisions of DSM and ICD try to integrate novel genetic and neurobiological research findings, to reduce heterogeneity by eliminating subtypes and introducing new pathological dimensions (R. Tandon, 2012; Zielasek & Gaebel, 2018).

1.1.1. Clinical presentation and diagnosis

Schizophrenia is a complex mental disorder characterized by a broad variety of symptoms affecting thinking, emotions, motor functions, and behavior (Mehl, Falkenberg, Leopold, Bechdolf, & Kircher, 2019). The symptoms are usually classified as "positive," "negative," and "cognitive" (Kahn et al., 2015). Positive or psychotic symptoms could be defined as exceeding the healthy experience and include odd behavior and distortion in thinking and perception. Specifically, patients often have hallucinations, delusions, disorganized speech, and appear to have lost sense of reality. In contrast, negative symptoms are characterized by the impairment or loss of healthy experiences and include social withdrawal, avolition, and diminished emotional expression. Cognitive symptoms refer to impairment in cognitive functions such as attention, memory, reasoning, and decision making (Kahn et al., 2015). For an overview and description of the most common schizophrenia symptoms, see Table 1. Various factors such as culture (Myers, 2011) and gender (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012) could influence the content of symptoms (e.g., the content of delusions), but not the overall symptom structure.

Table 1. *Overview of schizophrenia symptoms classified as 'positive,' 'negative,' and 'cognitive' (based on Lincoln, 2018; Mehl et al., 2019).*

Symptom	**Definition**
Positive symptoms	
Delusion	A personal belief/conviction that is not shared by others and persists despite lack of evidence or even despite evidence of the contrary. It is often described as bizarre or irrational. Common delusions: paranoia, grandiosity, delusions of reference
Hallucinations	Perceptions that occur without external stimuli. In schizophrenia, they could be: • acoustic (50% of patients, e.g., hearing voices) • visual (15% of patients, e.g., seeing points, stars, or even people) • olfactory • somatic
Formal thought disorder	Impairment of the thought process and speech. According to Kircher et al. (2018), they could be classified in: • *Positive:* increase in speech and thought production. Typical positive formal thought disorders are loosening of associations, circumstantial thinking, logorrhea (increase in speech production), and neologisms (using new non-existing words). • *Negative*: decrease in speech and thought production. Typical negative formal thought disorders are poverty of speech (alogia), slowed thinking, thought block.
Distortions of self-experience	Experiences where the line between the self and the environment is disrupted. Common symptoms in schizophrenia are (as first defined by Schneider (1946)): • *thought broadcasting*: patients have the feeling that their thoughts are being heard/understand by others • *thought insertion*: patients perceive personal thoughts as being inserted/generated by others

Symptom	Definition
	• *thought withdraw:* patients have the feeling that their thoughts are being taken away by others • *passivity experiences*: patients perceive that emotion, intentions, actions, sensations, or bodily functions are controlled/generated by others
Negative Symptoms	
Blunted Affect	Patients show no or diminished emotional expressions. They have reduced or "frozen" facial expressions and reduced emotional responsiveness to the outside world.
Anhedonia	Reduced or diminished ability to feel joy, even while participating in usually pleasurable activities
Avolition	Lack of motivation
Social withdraw	Reduction or lack of interest to maintain social contacts and friendships
Cognitive symptoms	
Memory	Deficits in verbal episodic memory, verbal and visual short-term and working memory (Aleman, Hijman, De Haan, & Kahn, 1999)
Attention and concentration	Impairment of information processing, orientation, selective attention (Heinrichs & Zakzanis, 1998)
Executive functions	Impaired planning and reasoning (Orellana & Slachevsky, 2013)
Social cognition	Deficits in the ability to understand and recognize that the thoughts, intentions, and emotions of others are different from one's own thought, intentions, and emotions (Theory of mind) (Bora, Yucel, & Pantelis, 2009)

Schizophrenia is diagnosed based on the criteria of the classification systems DSM-5 or ICD-10[1] upon psychopathological assessment, medical history, and clinical tests (DGPPN, 2019). In the present work, we applied ICD-10 (German version: Dilling & Freyberger, 2012), where criteria include positive and negative symptoms, consider their duration, and the course of the disease (specific criteria are presented in Table 2). ICD-10 distinguishes between several schizophrenia subtypes (e.g. paranoid schizophrenia, catatonic schizophrenia, schizophrenia simplex). However, this division in subtypes is poorly supported by research data and is therefore eliminated in DSM-5 and ICD-11 (R. Tandon, 2012; Zielasek & Gaebel, 2018). To confirm a diagnosis of schizophrenia, all other possible psychiatric conditions such as substance addiction, mania or depression, and possible somatic causes such as cerebral injury or autoimmune encephalitis should be ruled out (DGPPN, 2019).

Table 2. *Diagnostic criteria for schizophrenia, according to ICD-10 (WHO, 1993, Chapter F20 - F29 Schizophrenia, Schizotypal and Delusional Disorders).*

G1. Either at least <u>one</u> of the symptoms of a) – d) or at least <u>two</u> of the symptoms of e) – h) should be present for most of the time during an episode of psychotic illness lasting for <u>at least one month</u>:

a) Thought echo, thought insertion or withdrawal, or thought broadcasting.
b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations, delusional perception.
c) Hallucinatory voices giving a running commentary on the patient's behavior, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body.
d) Persistent delusions of other kinds that are culturally inappropriate and completely impossible (e.g., being able to control the weather, or being in communication with aliens from another world.
e) Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent over-valued ideas
f) Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech.

[1] ICD-11 is set to be released in Germany on 1. January 2022 (https://www.dimdi.de/dynamic/de/klassifikationen/icd/icd-11). Therefore, in the present work, we focus on criteria of ICD-10

g) Catatonic behavior, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor.

h) “Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses (it must be clear that these are not due to depression or to neuroleptic medication).

G2. Most commonly used exclusion criteria: If the patient also meets criteria for manic episode (F30) or depressive episode (F32), the criteria listed under G1 above must have been met before the disturbance of mood developed.

G3. The disorder is not attributable to organic brain disease (in the sense of F0), or to alcohol- or drug-related intoxication, dependence or withdrawal.

1.1.2. Epidemiology and prognosis

Patients are usually diagnosed with schizophrenia as young adults with the onset of positive symptoms, shaping a first psychotic episode. The first psychotic phase is preceded by a prodromal stage, defined by social withdraw, decline in cognitive functioning, and a negative affect (Zielasek, Hasan, & Gaebel, 2019). The prodromal stage is often overlooked and could begin over ten years prior to the first psychosis (Haijma et al., 2013). The acute psychotic episode is followed by the manifestation of mostly negative symptoms and eventually by a remission phase (McGlashan & Johannessen, 1996). About 20% of the patients experience a single schizophrenia episode, about 30% have multiple episodes with full remission in-between. In the rest 50% of the patients the disease has a chronic course, with the majority (40%) progresses with increasing residual symptoms and thus lowers social-economic status and quality of life (Watts, 1985). Schizophrenia affects men and women equally. However, men tend to develop it approximately five years earlier than women do. Specifically, schizophrenia begins in the early 20s in male patients and in the late 20s or early 30s in female patients. Furthermore, schizophrenia could have late-onset in women with begin of menopause (Häfner, 2003). Due to the earlier onset and the more common comorbidities, men tend to have a more severe progression of the disease and a poorer outcome (Häfner, 2003; Seeman, 2004, 2012).

Overall, patients with schizophrenia have lower life expectancy than the general population, with some estimates revealing a discrepancy of approximately 20 years (Laursen, Nordentoft, & Mortensen, 2014; Schmitt et al., 2018). A systematic review revealed a 2.6 higher risk of mortality for patients with schizophrenia, a trend which has been worsening in

the past decades (McGrath, Saha, Chant, & Welham, 2008). The main factors for the increased mortality in schizophrenia are suicide, somatic comorbidities such as metabolic syndrome, cardiovascular diseases and diabetes, smoking, and unhealthy lifestyle (Hoang, Stewart, & Goldacre, 2011; McGrath et al., 2008; Schmitt et al., 2018). Moreover, the stable fatality rate and the growing gap in mortality indicate that patients with schizophrenia have not profited from medical care advances and prevention as the general population (Saha, Chant, & McGrath, 2007).

1.1.3. Etiology, Pathophysiology, and Risk factors

The underlying mechanism for the development and chronification of schizophrenia, although still unclear, is hypothesized as a complex gene-environment interaction involving abnormalities in neurotransmission, changes in brain function and structure, and compromised neurodevelopment (Kahn et al., 2015; Schmitt, Falkai, & Schulze, 2019).

1.1.3.1. Neurotransmission

Circumstantial evidence from psychopharmacological and post-mortem studies led to the two leading theories regarding neurotransmitters - the *dopamine* and the *glutamate hypothesis* (Howes, McCutcheon, & Stone, 2015). The *dopamine* hypothesis states that dopamine hyperactivity in limbic and subcortical areas causes positive symptoms in schizophrenia (Schmitt et al., 2019). It is based on first observations of psychotic symptoms after intake of amphetamine, which increases dopamine levels (Lieberman, Kane, & Alvir, 1987). The dopamine hypothesis is further supported by the positive effect of drugs, which act as D2 receptor antagonist and thus decrease dopamine concentration (Wålinder, Skott, Carlsson, & Roos, 1976). Post-mortem studies provided some evidence of neuroanatomical changes such as an increase in D2 receptor density (F. Owen et al., 1978) and changes in pre- and postsynaptic expression of D2 autoreceptors (Kaalund et al., 2014). Application of Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) imaging revealed specific dysfunction patterns in vivo, i.e., abnormalities in presynaptic dopamine availability (Howes et al., 2009), altered dopamine content in the prefrontal cortex, anterior cingulate gyrus, and hippocampus (Patel, Vyas, Puri, Nijran, & Al-Nahhas, 2010). Especially in the latter region, the dopaminergic system showed hyperactivity in schizophrenia patients (Grace, 2012). Dopaminergic dysfunction could also be responsible for cognitive symptoms, as research reveals abnormalities in the D1 receptor to influence working memory (Goldman-Rakic, Castner, Svensson, Siever, & Williams, 2004), where both hyper- and

hypoactivity lead to deficits (Williams & Goldman-Rakic, 1995). Despite inconsistencies in research findings on molecular markers and pathways, the dopamine hypothesis forms the basis for all current antipsychotic medications (Kahn et al., 2015).

The *glutamate* hypothesis stated initially that schizophrenia is associated with an overall glutamate deficiency. For instance, there were early findings of reduced glutamate levels in liquor (Kim, Kornhuber, Schmid-Burgk, & Holzmüller, 1980). However, after excessive research of various glutamatergic receptors in recent years, the hypothesis was modified mainly as a hypofunction of the N-Methyl-D-aspartate (NMDA) receptor (Stone, Morrison, & Pilowsky, 2007). It was developed upon findings of phencyclidine and ketamine, both NMDA/glutamate antagonists, could induce schizophrenia-like symptoms, positive as well as negative (Javitt, 2007; Krystal et al., 1994; Morgan & Curran, 2006). Post-mortem brain studies provide some evidence of abnormalities in the glutamatergic system, i.e., decreased number of glutamatergic neurons and morphological alterations in their dendrites (Hu, MacDonald, Elswick, & Sweet, 2015). However, findings in a reduction in NMDA receptor density and glutamate subunits are still inconclusive (Hu et al., 2015; McCullumsmith, Hammond, Funk, & Meador-Woodruff, 2012). The specific pathways of the glutamatergic dysfunction in schizophrenia are still unknown, but recent research indicates the involvement of gamma-amino-butyric acid (GABA) interneurons (Schmitt et al., 2019). NMDA-antagonists lead to NMDA inhibition that, in turn, reduces the activity of GABA interneurons and, consequently, the release of GABA in the synaptic cleft. The decreased GABA levels cause disinhibition of the pyramidal cell and thus increase their firing rate (Homayoun & Moghaddam, 2007). Findings from post-mortem (M. J. Schmidt & Mirnics, 2015) and genetic studies (Guillozet-Bongaarts et al., 2014) provide conclusive evidence for the alterations of GABA neuronal activity. Yet, the underlying mechanism of the GABA system dysfunction and its specificity for schizophrenia are still unclear (Kahn et al., 2015).

Dopamine, glutamate, and GABA all modulate the cortical function and are in constant interplay, implying that neurotransmission models for schizophrenia involve complex pathways and interactions within neuronal networks (Kahn et al., 2015).

1.1.3.2. Gene-Environment Interaction

Genetic factors are of great importance for the etiology of schizophrenia, as twin studies reveal heritability of approximately 80% that decreases with the degree of relation. (Cardno & Gottesman, 2000; Sullivan, Kendler, & Neale, 2003). However, a substantial part of the

heritability, approximately 11%, could be explained with shared environmental factors (Sullivan et al., 2003), underlying the notion of schizophrenia due to gene-environment interaction (Schmitt, Malchow, Hasan, & Fallkai, 2014).

Genome-wide-associations studies (GWAS) indicated that schizophrenia is polygenetic, i.e., multiple gene risk variations (single nucleotide polymorphisms, SNPs) are involved (Schwab & Wildenauer, 2013). Ripke et al. (2014) investigated a sample of 36,989 patients and 113,075 controls and identified 108 loci of genomic significance. In a more recent work, Pardinas et al. (2018) were able to define additional loci (>250) associated with schizophrenia. Among those loci are variations related to the dopamine D2 receptor (DRD2), glutamate receptors (i.e., GMR3), and NMDA receptor (i.e., SRR). Other genetic risk variants include neuregulin (NRG-1), associated with NMDA receptor expression (Stefansson et al., 2002); catechol-O-methyltransferase (COMT), involved in the dopaminergic system (Mattay et al., 2003; Shifman et al., 2002), and disrupted in schizophrenia 1 (DISC1), associated mostly with negative and cognitive symptoms (Hennah, Thomson, Peltonen, & Porteous, 2006). NRG-1 (Grimm et al., 2014), COMT (Erk et al., 2011), and DISC1 (Callicott et al., 2005) have also been linked with structural and functional brain imaging to elicit neuroimaging phenotypes. Yet, the polygenic risk variants have a rather small overall effect. For instance, according to Ripke et al. (2013), 8,300 relevant SNPs could collectively make up approximately 32% of the common risk for schizophrenia, suggesting the importance of environmental factors.

Many studies have investigated relevant environmental factors across the life span (Kahn et al., 2015; Schmitt et al., 2014). A large body of research established prenatal and perinatal risks like birth and obstetric complications, abnormal fetal growth (Cannon, Jones, & Murray, 2002), and perinatal hypoxia (Fineberg, Ellman, Buka, Yolken, & Cannon, 2013). Adverse childhood events (e.g., childhood trauma, parental neglect) increase the risk of psychosis as well (Varese et al., 2012). Furthermore, social stress during childhood and adolescence could also contribute to the development of schizophrenia (Veling, Pot-Kolder, Counotte, van Os, & van der Gaag, 2016). One of the most investigated risk factors is substance abuse (Murray, Paparelli, Morrison, Marconi, & Di Forti, 2013). Specifically, the use of cannabis in adolescence has been repeatedly linked to an increased risk of psychosis (Semple, McIntosh, & Lawrie, 2005). Other environmental factors include migration status (Cantor-Graae & Selten, 2005) and urbanicity (Vassos, Pedersen, Murray, Collier, & Lewis, 2012).

These findings can be integrated into the neurodevelopment hypothesis, which states that gene and environmental factors (both risk and protective) are in constant interaction and affect neurodevelopment and cause schizophrenia (Schmitt et al., 2019). The theory was first proposed in the late 80s (Murray & Lewis, 1987; Weinberger, 1987) and since then has progressed to one of the leading etiology theories for schizophrenia (Fatemi & Folsom, 2009). In the 2-hit model within this framework, Keshavan proposes impaired neurodevelopment during two critical stages - early brain development and adolescence (Keshavan, 1999; Keshavan & Hogarty, 1999). Specifically, genetic predispositions combined with prenatal adverse events could negatively impact the formation of individual networks and lead to a neurobiological vulnerability and first premorbid symptoms. This vulnerability could impair brain maturation during adolescence, causing excessive synaptic pruning and provoking first schizophrenia symptoms (Keshavan, 1999). The neurodevelopmental theory has been supported by a large body of work showing gene variations involved in neuronal development to be perturbed in schizophrenia. Moreover, imaging studies demonstrating altered brain structure and function as well as reports of premorbid symptoms at an early age, years before the first onset of the disease, further support the notion of schizophrenia as a neurodevelopmental disorder (Fatemi & Folsom, 2009). However, a recent review suggested that the 2-hit model could oversimplify the pathogenesis process of risk factors interacting with each other and with genetic predispositions during multiple critical stages for neurodevelopment and cumulating to the onset of schizophrenia (Davis et al., 2016).

1.1.3.3. Alterations in brain function and structure

Imaging methods extend the understanding of the pathophysiology of schizophrenia by linking neurobiological findings to brain anatomy, behavioral symptoms, and progression of the disease (Kahn et al., 2015). A meta-analysis investigating structural magnetic resonance imaging (sMRI) data from 317 studies demonstrated volumetric brain abnormalities in schizophrenia (Haijma et al., 2013). Specifically, both first episode and chronic schizophrenia patients had reduced total grey and white matter as well as total brain and intracranial volumes compared to healthy controls. In contrast, cerebrospinal fluid (CSF) and ventricular volumes were increased. Prefrontal, temporal, parietal structures (e.g., Olabi et al., 2011) and the insula (Wylie & Tregellas, 2010) are particularly affected (McDonald et al., 2005). Furthermore, brain volumetric changes are observed in unaffected relatives (Boos, Aleman, Cahn, Pol, & Kahn, 2007; W. Zhang et al., 2020) and high-risk individuals (Chan, Di, McAlonan, & Gong, 2009) as well. In addition, reduction in global grey matter volume was associated with duration of

illness and medication dose, suggesting morphological changes as a result of impaired neuronal development and disease progression (Haijma et al., 2013; Olabi et al., 2011). In unmedicated patients, a decrease in volumes of the thalamus and nucleus cuadales were more pronounced than in medicated patients, implying that morphological changes in subcortical regions occure prior beginn of treatment and are eased by antipsychotics (Haijma et al., 2013). Moreover, studies revealed cortical thinning which is associated with poor oucome and advances with the course of the disease (van Haren et al., 2011). Neuroimaging studies using functional MRI (fMRI) and PET have linked positive and negative symptoms with brain activation. For instance, auditory verbal hallucinations are associated with increased activation of fronto- and media-temporal areas involved with language processing and memory (Jardri, Pouchet, Pins, & Thomas, 2011). Negative symptoms like emotional processing and social cognition impairments are related to altered activatons of the amygdala, medial prefrontal cortex and the inferior paretial lobe (Brunet-Gouet & Decety, 2006; Pankow et al., 2013). Neuroimaging research, investigating cognitive symptoms, is summarized in Chapter 1.2.1.

1.1.4. Treatment

According to the German clinical practice guideline, schizophrenia is best treated by combining medication, psychotherapy, and psychosocial therapy (DGPPN, 2019). Antipsychotics act as dopamine antagonists and improve mostly positive symptoms (Huhn et al., 2019). They can be divided into two groups: typical or first-generation (FGAs, e.g., chlorpromazine, haloperidol) and atypical or second-generation antipsychotics (SGAs, e.g., clozapine, olanzapine, risperidone). Although effective, antipsychotics could cause severe side effects (e.g., Parkinsonism with FGAs and metabolic syndrome with SGAs) and contribute to the emergence of comorbid somatic conditions (e.g., diabetes) (for details, see Kahn et al., 2015), which have been linked to the increased mortality in schizophrenia (McGrath et al., 2008). Moreover, neuroimaging studies reveal that antipsychotics could be involved in brain anatomy changes, such as grey matter reduction (Guo et al., 2015). There is no effective pharmacological treatment for negative and cognitive symptoms (Leucht et al., 2017; Nielsen et al., 2015), but in a subgroup of patients, they could be managed with psychotherapy, cognitive remediation therapy, and, as novel research shows, noninvasive brain stimulation (DGPPN, 2019).

1.2. Cognitive deficits in schizophrenia

Cognitive impairment is a main characteristic of schizophrenia. First described by Kraepelin (1919) and Bleuler (1916), deficits in various neuropsychological domains could be observed across patients' lifespan (Keefe & Fenton, 2007). In the last decades, research on this topic has rapidly increased, investigating the neurobiological pathways of cognitive dysfunction (Barch & Ceaser, 2012) and recognizing its potential as an intermediate phenotype for schizophrenia (e.g., Park & Gooding, 2014). Thus, cognition has been included as a fundamental component in etiology models such as the integrated sociodevelopmental-cognitive model (Howes & Murray, 2014) and the neurodevelopmental hypothesis (M. J. Owen, O'Donovan, Thapar, & Craddock, 2011).

1.2.1. Domains and neuronal pathways of cognitive dysfunction in schizophrenia

Schizophrenia is associated with a global cognitive impairment (Schaefer, Giangrande, Weinberger, & Dickinson, 2013). Various domains like episodic memory, working memory, executive functioning, attention, processing speed, problem-solving, and social cognition are significantly affected (Nuechterlein et al., 2004).

Attention is a core cognitive function, often considered to be hierarchical and fractioned in several dimensions by neuropsychological theories (Lezak, Howieson, Bigler, & Tranel, 2012). Sohlberg and Mateer (1989) differentiated in their clinical model of attention between (1) *focused attention*, the ability to direct attention as a response to stimuli; (2) *sustained attention or vigilance,* the capacity to keep high attentional activity over time; (3) *selective attention,* the ability to focus our attention to relevant stimuli, while suppressing distractions; (4) *alternating attention*, the capacity to switch attention between tasks and (5) *divided attention,* the ability to operate on different tasks simultaneously. Recent research using machine learning revealed that performance across the attention domains could discriminate between schizophrenia patients and healthy controls with 90.70% accuracy, indicating psychomotor speed, sustained and divided attention to be crucial for the classification (Shen et al., 2014). These findings are supported by a large body of research showing lower performance on vigilance tasks in schizophrenia (e.g., Nuechterlein et al., 2015) during active psychosis and remission (Nuechterlein et al., 1992). Moreover, a recent fMRI meta-analysis linked impairment in sustained attention to reduced activation in the insular cortex and the inferior frontal gyrus, to hyperactivation in the thalamus, and altered activation in the anterior cingulate cortex (ACC), indicating dysfunction in the latter two regions to be specific for schizophrenia

and not for bipolar disorder (Sepede et al., 2014). Deficits in selective attention have also been repeatedly observed (e.g., Carter, Robertson, & Nordahl, 1992) and are associated with altered activations of the ACC (Carter, Mintun, Nichols, & Cohen, 1997) and the prefrontal cortex (Weiss et al., 2003).

Working memory refers to the ability to process, temporally maintain and manipulate information (Baddeley, 2010), and it is crucial for academics (Alloway & Alloway, 2010) and professional success (Higgins, Peterson, Pihl, & Lee, 2007). In Baddeley's model of working memory (2007), it is conceptualized as a multi-modal system with limited capacity, consisting of (1) a *central executive*, a supervisory system that directs attention, inhibits irrelevant stimuli and updates, encodes and coordinates information flow, and (2) modality-specific subsystems (*phonological loop, episodic buffer* and *visuospatial sketchpad*). Deficits in working memory in schizophrenia are observed across domains and modalities (Forbes, Carrick, McIntosh, & Lawrie, 2009; J. Lee & Park, 2005), with the most noticeable results for the central executive (Barch & Ceaser, 2012). Encoding and maintenance of information are significantly affected (Park & Gooding, 2014). Moreover, neuroimaging studies have repeatedly demonstrated abnormal activation of the dorsolateral prefrontal cortex (DLPFC) (e.g., Potkin et al., 2009), a region anatomically and functionally associated with working memory (Esposito, Detre, Alsop, & Shin, 1995). Several neuroimaging studies revealed hypoactivation of DLPFC during working memory tasks compared to healthy controls (Barch, Csernansky, Conturo, & Snyder, 2002; Carter et al., 1997) and patients with major depression (Barch, Sheline, Csernansky, & Snyder, 2003), indicating the specificity of the deficit for schizophrenia. However, there is also evidence of both hypo- and hyperactivation of the DLPFC regarding factors such as task demand, suggesting an overall DLPFC insufficiency (Manoach, 2003; Potkin et al., 2009). Working memory impairment is further associated with the prefrontal cortex's abnormal connectivity to the intraparietal cortex and the hippocampus (Henseler, Falkai, & Gruber, 2010). Moreover, DLPFC-hippocampus dysconnectivity in relation to working memory deficits, has been repeatedly reported to be more common in schizophrenia than other psychiatric disorders (M. Schneider et al., 2017).

Executive function is a group of cognitive abilities that are crucial for planning, executing, and coordinating complex behavior and managing everyday life (Lezak et al., 2012). It includes planning, cognitive flexibility, attention, problem-solving and working memory (Orellana & Slachevsky, 2013). According to Miyake et al. (2000), the main three underlying functions are (1) *shifting or cognitive flexibility,* the ability to switch between tasks, (2)

updating, monitoring, and adjusting of working memory contents and (3) *inhibition,* suppressing an automatic response (later revised as a common executive function) (Miyake & Friedman, 2012). In their unity/diversity framework, Miyake and Friedmann (2012) postulate that the executive functions are both unique and highly correlated; they have a genetic basis and stability across the lifespan; are related to psychopathology in several disorders. Indeed, a recent review revealed that deficits in executive functions (including working memory) are observed in affective and mood disorders, but are most prominent in schizophrenia (Snyder, Miyake, & Hankin, 2015). These results correspond with previous findings of executive dysfunction in schizophrenia (Heinrichs & Zakzanis, 1998; Orellana & Slachevsky, 2013). Anatomically, executive functioning impairment is associated with the prefrontal cortex's abnormal structure, specifically with volumetric alterations of the parahippocampal gyrus, superior temporal gyrus, and integrity of the striatum, hippocampus, and ACC (Antonova et al., 2004). A meta-analysis of 41 fMRI studies demonstrated that healthy controls and schizophrenia patients activate the same networks during executive functioning (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). However, the pattern is altered in schizophrenia, where the activation of DLPFC, right ventrolateral prefrontal cortex (VLPFC), thalamus, cerebellum, temporal and parietal areas is reduced. In contrast, other prefrontal areas compensate for hyperactivation (Minzenberg et al., 2009), supporting the hypothesis of disturbed functioning not of single brain regions but also neural circuits (Schmitt, Hasan, Gruber, & Falkai, 2011). There is growing evidence of executive impairment resulting from dysfunction of prefronto-striato-thalamic, prefronto-parietal, and prefronto-temporal networks (Orellana & Slachevsky, 2013).

Memory is a complex multidimensional and hierarchical system (Milner, Squire, & Kandel, 1998) that has been repeatedly reported to be impaired in schizophrenia (Aleman et al., 1999). *Episodic memory,* a subsystem of long-term memory retaining phenomenological memories (e.g., events) (Tulving & Markowitsch, 1998), is particularly affected (Barch & Ceaser, 2012). Indeed, several meta-analyses indicated that patients with schizophrenia perform poorly on visual and verbal episodic memory tasks (Aleman et al., 1999; Heinrichs & Zakzanis, 1998). A recent review demonstrated greater deficits during recall than recognition, especially during encoding (Danion, Huron, Vidailhet, & Berna, 2007). Anatomically, episodic memory performance is associated with structures of the medial temporal lobe (Leavitt & Goldberg, 2009), specifically the hippocampus, where numerous studies reported reduced volume (Nelson, Saykin, Flashman, & Riordan, 1998) and cellular abnormalities (Heckers &

Konradi, 2002) in schizophrenia. A meta-analysis of 18 fMRI studies showed hypoactivation of the left inferior prefrontal cortex and the hippocampus in patients during episodic memory tasks than healthy controls (Achim & Lepage, 2005). However, a more recent review suggested that the direction of the altered prefrontal and hippocampal activation could be multilateral (Leavitt & Goldberg, 2009). Furthermore, episodic memory impairment is associated with disturbed fronto-temporal connectivity, including the DLPFC, parahippocampus and superior temporal gyrus (Wolf et al., 2007). For instance, in a computational model study, Talamini et al. (2005) demonstrated that reduced parahippocampal connectivity could result in schizophrenia-like memory deficits.

The extensive evidence of deficits in various neuropsychological domains has led to the hypothesis of the generalized or broad cognitive deficit in schizophrenia (Braff et al., 1991; Gold & Dickinson, 2013). Indeed, Wilk et al. (2004) demonstrated that 575 patients with schizophrenia perform on average 2 SDs poorer than healthy controls as measured by the total scale of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), including domains like processing speed, attention, and memory. Besides, a recent meta-analysis of 100 studies with a total of 9048 patients and 8841 controls showed moderate to severe deficits in all investigated cognitive domains in schizophrenia, where processing speed and episodic memory were most affected. Moreover, the evidence of impairment has persisted over time despite changing diagnostic criteria, materials, and research methods (Schaefer et al., 2013). Global cognitive deficits have been linked to an overall whole brain volume and grey matter reduction, increased ventricles and grey matter reduction in frontal and temporal structures (Antonova et al., 2004), and white matter abnormalities (Dickinson & Harvey, 2008). Furthermore, a recent review of resting-state fMRI studies indicated that cognitive impairment is associated with lower connectivity between cortical (e.g., prefrontal cortex) and subcortical regions (e.g., thalamus, cerebellum, basal ganglia), which is not specific to particular neuropsychological functions (Sheffield & Barch, 2016). However, the generalized deficit hypothesis has been challenged by findings of preserved cognitive functions in schizophrenia and suggesting a more *selective* impairment of specific abilities (Chapman & Chapman, 1989; Green, Horan, & Sugar, 2012). Nevertheless, deficits in attention, working memory, executive functioning, and episodic memory are considered to be characteristic of schizophrenia (Reichenberg & Harvey, 2007) and hypothesized to have a common underlying mechanism and neurobiological pathways involving mostly prefrontal and temporal cortical and

subcortical structures (Barch & Ceaser, 2012; Lesh, Niendam, Minzenberg, & Carter, 2011; Silver & Feldman, 2005).

1.2.2. Prevalence and heterogeneity

With estimates of about 80% of schizophrenia patients performing at least 1 SD worse than the general population's mean, cognitive impairment is considered widespread in schizophrenia (Keefe & Fenton, 2007). Yet, this would mean that a significant subgroup of patients shows no clinically relevant neuropsychological deficits. Indeed, previous studies indicated that approximately 20-30% of patients with schizophrenia have comparable neurocognitive functioning as healthy controls (Holthausen et al., 2002; Palmer et al., 1997). However, there is evidence that despite no relevant neuropsychological deficit, all patients with schizophrenia are performing worse than expected (Keefe, Eesley, & Poe, 2005; Wilk et al., 2005), especially regarding premorbid intelligence and maternal education (Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000). For instance, patients with high intelligence have similar cognitive decrements as patients with low or average intelligence, despite achieving results within the normal range on neuropsychological testing (Vaskinn et al., 2014). Moreover, studies with monozygotic twins discordant for schizophrenia provide further cognitive decline findings due to psychosis (Goldberg et al., 1990). Nevertheless, there is persistent evidence of heterogeneity in cognitive impairment in schizophrenia (Joyce & Roiser, 2007). Studies using cluster analysis classified neuropsychological functioning in schizophrenia in three to four subgroups; each solution consisted of a high or average cognition and a severely impaired cluster. In addition, subgroups with moderate or specific deficits in processing speed, executive function, and/or memory were also defined (Bechi et al., 2019; G. Goldstein, Allen, & Seaton, 1998; G. Goldstein & Shemansky, 1995; Hill, Ragland, Gur, & Gur, 2002). Geisler et al. (2015) differentiated between four cognitive profiles of patients with compromised (1) verbal fluency, (2) verbal memory and motor control, (3) low face memory and processing, and (4) general cognitive impairment. Each cluster was associated with a distinct pattern of altered brain morphology and function, including cortical thinning overall and specifically in Wernicke's area and lingual gyrus, reduced hippocampal volume and abnormal fronto-parietal activity (Geisler et al., 2015). Most recently, different cognitive profiles in first episode schizophrenia patients could be elicited and linked to altered brain connectivity in e.g. the salience network, fronto-parietal network, the default mode network (Rodriguez et al., 2019). In sum, the large body of research suggests a widespread cognitive decline in schizophrenia, which is

heterogeneous in nature regarding severity and distinctive patterns of deficits and could be linked to neuronal pathways (Geisler et al., 2015; G. Goldstein et al., 1998; Hill et al., 2002).

1.2.3. Heritability and course of cognitive deficits

Previous research showed that neuropsychological impairment accompanies patients with schizophrenia across their lifetimes (Woodberry, Giuliano, & Seidman, 2008). For instance, cognitive deficits during early childhood (Cannon, Caspi, et al., 2002; Seidman et al., 2013), and later in fluid intelligence in the preteen years (Reichenberg et al., 2010) and in verbal processing in adolescence (MacCabe et al., 2013) are present in children, who later develop schizophrenia. In addition, individuals with a high risk for schizophrenia perform worse than healthy controls in various neuropsychological domains (Keefe, 2014), such as attention, working memory, and episodic memory (Fusar-Poli et al., 2012; Seidman et al., 2010). Accordingly, a recent meta-analysis comparing 197 high-risk with 199 healthy participants demonstrated the most considerable discrepancies in overall cognition, processing speed, and attention, whereas effects regarding working memory, problem-solving, and learning were moderate (Zheng et al., 2018). Moreover, unaffected first-degree relatives of people with schizophrenia also show cognitive abnormalities, yet milder than patients (Bora et al., 2014; Snitz, Macdonald, & Carter, 2006). The neuropsychological decrements are most prominent in participants that later develop schizophrenia (Seidman et al., 2010). Moreover, as in schizophrenia patients, changes in brain morphology and function associated with cognition have been demonstrated in first-degree relatives, including grey matter reduction overall, in the hippocampus, thalamus, and ventricular enlargement (Boos et al., 2007; de Zwarte et al., 2019; W. Zhang et al., 2020). Due to the consistent evidence of cognitive deficits in schizophrenia patients and their first-degree relatives, they are proposed to be heritable and linked to genetic polymorphisms (Sabb et al., 2008). Indeed, a recent review of 82 molecular studies determined several candidate genes, thereunder COMT and DISC1, and revealed empirical evidence, though inconsistent, of their role in cognitive impairment in schizophrenia (Zai, Robbins, Sahakian, & Kennedy, 2017).

Prodromal neuropsychological abnormalities intensify during the first episode of schizophrenia, where deficits in verbal memory and processing speed are most prominent according to meta-analytical findings (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). However, a more recent meta-analysis of 25 studies with 905 first-episode patients, 560 high-risk patients, and 405 healthy controls indicated no progression of the preexisting

cognitive deficits due to psychosis. Moreover, neuropsychological impairment decreased with the improvement of negative symptoms (Bora & Murray, 2013). Despite heterogeneous findings on the initial cognitive decline with the first onset of schizophrenia, longitudinal and meta-analytical studies indicate stability of neuropsychological functioning in chronic patients (Albus et al., 2019; Heilbronner et al., 2016). Regarding psychopathology, cognitive deficits are mostly associated with negative symptoms, especially with disorganization syndrome (de Gracia Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2009). Furthermore, cognitive impairment has been demonstrated to be more critical for everyday functioning, employability, socializing, and overall quality of life than other symptom clusters (Bryson & Bell, 2003; Green et al., 2000). Despite its significance, there are only few treatment options with cognitive remediation and antipsychotic therapy having no significant overall effects (Nielsen et al., 2015) with exception of few clinical subgroups, where small improvement is achieved (Krug, Stein, & Kircher, 2020).

1.3. Machine Learning

Despite extensive research, the underlying cognitive impairment mechanisms in schizophrenia are still unclear, mostly due to the heterogeneity of deficits and overall psychopathology. Moreover, research on this topic involves a large amount of multidimensional data of complex neuronal pathways, behavioral performance, social and environmental factors, which are in constant interaction and could be only poorly analyzed by classical statistical methods (Bzdok & Meyer-Lindenberg, 2018). However, with the rapid advancement in computer power, machine learning methods emerged as a powerful tool to address these methodological issues (Dwyer, Falkai, & Koutsouleris, 2018). Indeed, schizophrenia research using machine learning, particularly in neuroimaging, is steeply increasing in the last years (N. Tandon & Tandon, 2019).

1.3.1. Machine learning: definition, types, and application in schizophrenia research

Machine learning is a field within artificial intelligence, involving the development of computer systems capable of improving and adjusting using previous experiences (Jordan & Mitchell, 2015). Specifically, algorithms apply pattern recognition techniques to large amounts of data, test various assumptions about its structure, and then *learn* from these assumptions by comparing them and modifying single aspects of the models. Thus, it involves repeated parameter estimation, performance evaluation, error identification, and correction until the model maximizes accuracy (Dwyer et al., 2018; N. Tandon & Tandon, 2019). Machine learning algorithms are classified into three main categories: (a) *supervised* where the cases of the output variable are labeled (e.g., binary/multiclass classification); (b) *unsupervised* where the aim is to identify the structure (e.g., dimension reduction); (c) *reinforcement* where the learning is reinforced through immediate reward or penalties (mostly used in robotics) (Jordan & Mitchell, 2015; N. Tandon & Tandon, 2019). Machine learning analysis follows three main steps: (1) data preparation (data preprocessing and division in training and test subset), (2) learning (choice of parameters, model tuning, estimator parameter regularization), and (3) evaluation (application of the parameters to the test subset) (N. Tandon & Tandon, 2019). In the field of schizophrenia, machine learning has been successfully applied for diagnosis, the prognosis of clinical outcome, and treatment (Dwyer et al., 2018). For instance, a meta-analysis including 38 studies showed that implementing multivariate pattern recognition techniques to neuroimaging data could differentiate patients with schizophrenia from controls with sensitivity and specificity of ~80% (Kambeitz et al., 2015). Similarly, a more recent systematic

review demonstrated that machine learning analysis of functional and structural MRI data could diagnose schizophrenia with an accuracy of 60%-80%, which could be improved by integrating various machine learning algorithms (de Filippis et al., 2019). Moreover, fMRI studies attain greater specificity (Kambeitz et al., 2015) and overall accuracy (de Filippis et al., 2019) than sMRI studies. Regarding specific algorithms, support vector machines (SVM) are the most frequently used (de Filippis et al., 2019; Dwyer et al., 2018). Pattern recognition techniques could also be applied to elicit different cognitive profiles in schizophrenia. For instance, Gould et al. (2014) used SVM to whole-brain morphometry to differentiate patients with compromised and spared cognitive subtypes from each other and from healthy controls. With approximately 70% accuracy both cognitive subtypes could be recognized from healthy controls, suggesting similar neuroanatomical abnormalities in cortical (e.g. inferior temporal gyrus), subcortical (e.g. hippocampus) and cerebellar regions (e.g. vermis). However, the classification of patients with compromised and spared cognition was only ≤ 60% but increased to 83% in female sample when stratified for gender (Gould et al., 2014). Regarding prediction of clinical and treatment outcome in schizophrenia, machine learning algorithms have previously obtained balanced accuracy values of >70% (e.g. prognosis of first-episode psychosis, Koutsouleris et al., 2016) and 85% (e.g. response to repetitive transcranial brain stimulation, Koutsouleris et al., 2017).

Despite promising results, machine learning methods in schizophrenia research should be applied and interpreted with caution due to limitations such as future selection bias, overfitting, biased reporting of classification results, small sample sizes, heterogeneity of diagnostic labels, clinicians' insufficient computational knowledge, and lack of transparency in model and data presentation (Arbabshirani, Plis, Sui, & Calhoun, 2017; Dwyer et al., 2018; N. Tandon & Tandon, 2019). Regarding sample size, Schnack and Kahn (2016) demonstrated its influence with a small sample size leading to high accuracy and low generalizability and vice versa.

1.3.2. Random Forrest Classification: general principles and application

The random forest (RF) classifier is a supervised ensemble learning method, proposed by Breiman (1999, 2001). It is based on bootstrap aggregation (bagging) of classification trees. A classification tree is a type of decision tree, where the outcome is a class label. A class describes a group of items with common properties, whereas the class label is the name of the

class (Drummond, 2010b). Each class is defined by its characteristics or features. (Drummond, 2010a).

A decision tree is an old classification model with a tree-like structure (e.g., Breiman, Friedman, Olshen, & Stone, 1984; Quinlan, 1986), commonly used in machine learning and statistics. Figure 1A shows a simple example of a decision tree that aims to classify a fictional letter sequence by the attributes color and letter type. The classification process starts at the root node, representing the entire data set and then splits it using the attribute color (Blue?). It then moves down the branch that refers to a specific characteristic of the attribute (here, "yes" or "no"). This step is repeated until it arrives at an unsplittable leaf node (Fürnkranz, 2010). In the current example, the branch "no" arrives at a leaf node "not blue," whereas the branch "yes" arrives at an internal node "blue" that is further split using the attribute letter type (B?). The process moves then down the branches "yes" and "no" to the according leaf nodes "blue B" and "blue, not B" (see Figure 1A). In machine learning, the induction of decision trees is mostly based on recursive top-down algorithms (e.g., Top-Down Induction of Decision Trees, TDIDT), where the selection of a suitable attribute is essential (Fürnkranz, 2010). Attribute selection is typically based on the node impurity, describing whether the data points included in the node belong to a single class. If the node consists only of examples of a single class, it is a pure node. Impurity is typically measured by the information-theoretic entropy (Quinlan, 1986) or the Gini index (Breiman et al., 1984). Despite the many advantages of decision trees learners, such as feasibility and simple interpretation, they are vulnerable to overfitting by constructing over-complex trees. A typical technique to avoid overfitting is to simplify the tree by removing sub-nodes (pruning) (Fürnkranz, 2010).

RF classifiers combine many uncorrelated classification trees, where each tree carries out a class prediction, and the class with the most votes is taken as a prediction model (see Figure 1B). Every classification tree is built applying bagging, where the training data set is generated by selecting a bootstrap sample, a random subset from the data set with replacement (Breiman, 1996). Moreover, unlike a classical decision tree, each tree in an RF considers not all but only a random subset of features (Breiman, 2001). In this way, the individual trees are trained on different data sets using different features, which reduces the correlation between trees. In an RF, trees are inducted upon the Gini Index or the information gain/entropy as attribution selection methods. Trees are not pruned but grown to a maximum depth. Overfitting is avoided by application of the Strong Law of Large Numbers (Breiman, 2001).

RF algorithms have been successfully applied in neuroimaging research. For instance, a recent systematic review demonstrated that the RF classifier is robust to overfitting and outliers and could recognize between patients with Alzheimer's disease and healthy controls with accuracy up to 90%, especially when applied to multi-modal neuroimaging data (Sarica, Cerasa, & Quattrone, 2017). In schizophrenia, the analysis of EEG data with RF could exclude patients from healthy participants with an accuracy of 100% (Buettner et al., 2019). In addition, RF models have obtained high predictive accuracy for mapping cognitive subtypes with schizophrenia-associated genes (Zheutlin et al., 2018). Applied to sMRI data, an RF algorithm using cortical thickness could classify patients with childhood-onset schizophrenia from healthy controls with 73.7% accuracy, identifying prefrontal, left precuneus, and temporal regions as most important for the model (Greenstein, Weisinger, Malley, Clasen, & Gogtay, 2012). Moreover, RF outperformed SVM and logistic regression in classifications of symptom profiles in schizophrenia based on cortical thickness achieving >70% accuracy (Talpalaru, Bhagwat, Devenyi, Lepage, & Chakravarty, 2019). Thus, RF can be a feasible and effective classification model using complex imaging data.

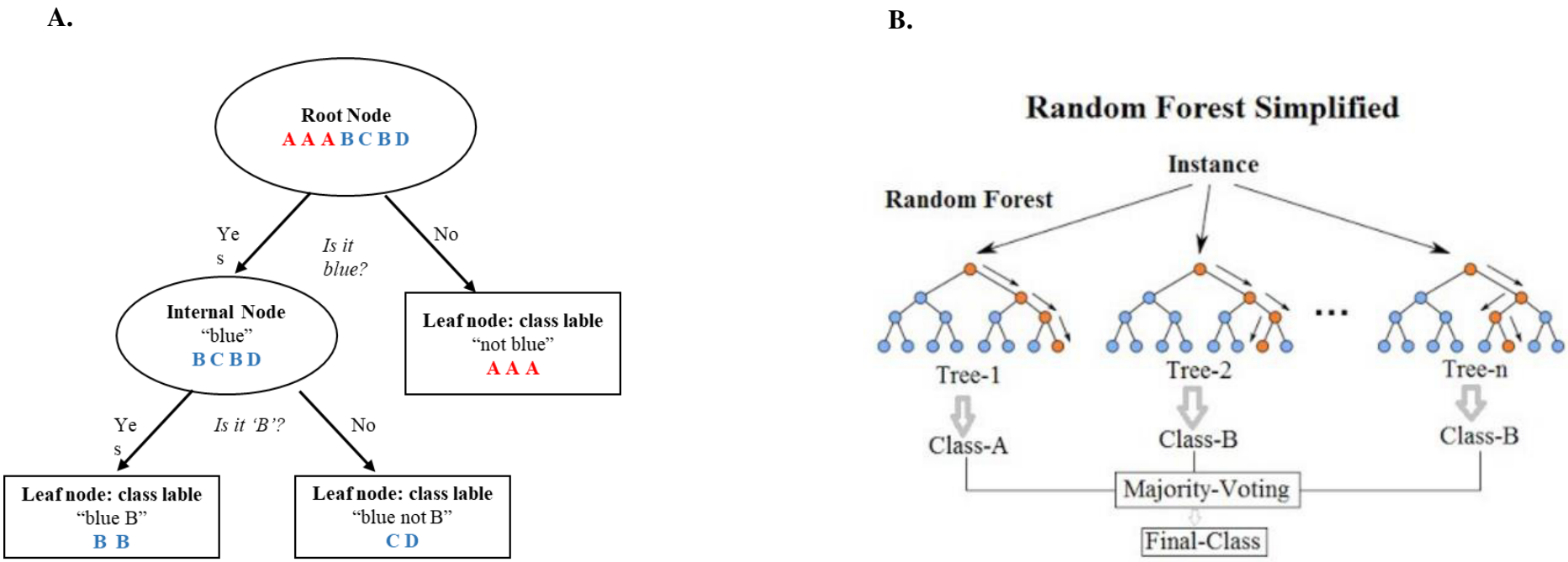


Figure 1. Graphic illustrations of classification models. (**A**) Decision tree describing a fictive data (based on, Fürnkranz, 2010); **(B)** Random Forest Classifier (Source: Venkata Jagannath, https://community.tibco.com/wiki/random-forest-template-tibco-spotfirer-wiki-page).

1.4. The present study

The main aim of the present study is to link cognitive heterogeneity in schizophrenia to brain structure. To do so, we used a data-driven approach to define high and low cognitive profiles in a study sample of patients with schizophrenia, unaffected relatives, and healthy controls. We then applied an RF algorithm with neuroanatomical variables as predictors of the two cognitive profiles and identified the most important anatomical structures for the classification. Then, we explored the relationship between the most important regions and cognition via regression analyses. We further used group comparisons to investigate if and how study groups and cognitive profiles differ in the anatomical regions of importance. Therefore, we obtained demographic, clinical, neuroimaging (sMRI), and cognitive data in this observational case-control study. The neuropsychological testing included assessments of episodic verbal memory, working memory, processing speed, attention, and executive functions (cognitive flexibility), and results were cumulated in a global cognition index.

We hypothesized that the RF model with volumetric measures as predictors and trained with data from all study groups would classify high and low cognitive performance in schizophrenia with accuracy above 50%. Moreover, we expected that the prefrontal and temporal regions would be most important for the prediction. We further assumed that volumes of the best seven predictors would significantly predict cognition, differ between high and low cognitive profiles, and between patients, healthy controls, and unaffected relatives.

2. Methods

2.1. Study Design

The current work presents data from the MIMICSS study ("Multimodal Imaging in chronic Schizophrenia Study"), part of the KFO 241 working group (http://www.kfo241.de/) and later of the PsyCourse consortium (http://www.psycourse.de/). MIMICSS is an observational case-control study that investigates genetics, neurocognition, brain morphology, and function as factors for the development of schizophrenia with a 2-year follow-up. The study protocol and its amendments were written according to the rules of the Declaration of Helsinki of 1975, revised in 2008, and approved by the local ethic committee (Medical Faculty of the Ludwig-Maximillian-University Munich: Code 17-13; Date of Approval: 25th of February 2013 and 25th of March 2014). Here, we present clinical, neurocognitive, and structural MRI data from the first time of measurement.

2.2. Participants

Originally, 74 patients with schizophrenia (SP, n = 74, 17 female, M_{age} = 35.04, SD_{age} = 11.77), 56 controls (HC, n = 56, 16 female, M_{age} = 33.13, SD_{age} = 11.83) and 22 unaffected relatives (UR, n = 22, 17 female, M_{age} = 40.91, SD_{age} = 17.33) participated in the study. SPs were recruited at the Department for Psychiatry and Psychotherapy, Clinic of the University of Munich, where they were currently in- or outpatients. Diagnosis of schizophrenia disorder without psychiatric comorbidity was made according to ICD-10 (F20.x) by a consulted physician and confirmed by a senior psychiatrist. URs were recruited through their affected relatives or the clinics' psychoeducation group for relatives of psychosis patients. Upon study participation, URs showed an official document (e.g., medical history, physician's letter) to confirm the schizophrenia diagnosis of their first-degree relative. HCs were recruited via flyers in the Munich area. Both UR and HC were screened using the Mini-International Neuropsychiatry Interview (M.I.N.I.) (Sheehan et al., 1998) to exclude mental illness. Detailed in- and exclusion criteria are presented in Table 3. All participants were fully informed about the study background and its procedures and gave their written informed consent. In the case of legal representation, patients' representatives were contacted, informed, and gave their written consent. All participants received a 50 € (7.50 €/h) compensation for their participation. UR and HC received another 50 € for their travel expenses. Furthermore, a travel-accident insurance for the patients was obtained (ECCLESIA mildenberger HOSPITAL GmbH).

Table 3. *Overall and specific inclusion and exclusion criteria for patients with schizophrenia (SP), healthy controls (HC), and unaffected relatives (UR).*

	Inclusion Criteria	Exclusion Criteria
Overall	• Age: >18 • Language: sufficient German knowledge • Capability to consent	• Neurological disorder (e.g., epilepsy) • Current alcohol abuse or dependence • Current substance abuse or dependence • MRI contraindications (e.g., claustrophobia, metal implants)
SP	• Diagnosis of schizophrenia (F20.x)	• Psychiatric comorbidity
HC	• No additional inclusion criteria	• Psychiatric disorder • First-degree relatives with a psychiatric or a neurological disorder
UR	• A first-degree relative with schizophrenia	• Psychiatric disorder

Eighteen participants (15 SP, 1 HC, and 2 UR) were excluded from further analysis due to false diagnosis or missing data. Thus, we analyzed cognitive data with 59 SP (10 female, M_{age} = 34.93, SD_{age} = 11.39), 55 HC (16 female, M_{age} = 32.69, SD_{age} = 11.48) and twenty UR (M_{age} = 37.95, SD_{age} = 15.16). We excluded seven more participants due to imaging artifacts and conducted the analysis of imaging data with 54 SP, 54 HC, 19 UR (see Figure 2 for CONSORT-Flow diagram).

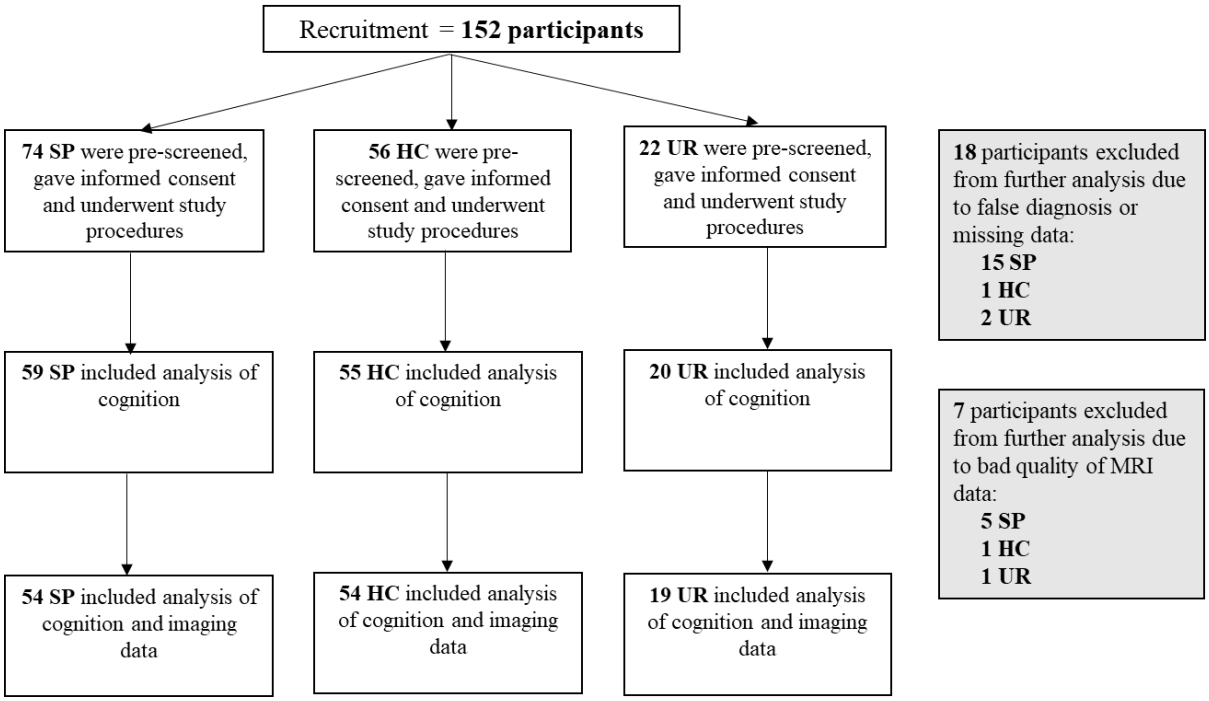


Figure 2. Consort-Flow diagram

2.3. Measures

2.3.1. Demographics

Participants completed a questionnaire on demographics, including data about education, current occupation, German language proficiency, and relationship status. Furthermore, detailed information about their smoking behavior was collected using the Fagerström Test for Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). The FTND is a 6-item scale based on biochemical measures for nicotine dependence and yields an overall score between 0 (very low dependency) and 10 points (very high dependency). We furthermore assessed hand preference using the Edinburgh handedness inventory (Oldfield, 1971). Here, participants assigned 2 points (very strong preference), 1 point (preference with occasional use of the other hand), or 1 point for each side (indifferent) for the completion of 10 everyday activities (e.g., writing, drawing). Laterality is then calculated by the difference between points for the right (R) and left hand (L), divided by the total score and multiplied by a hundred: [(R-L)/(R+L)]*100. Thus, the handedness score varies from -100 (pure left-hander) to +100 (pure right-hander).

2.3.2. Clinical measures

Medication and clinical history

Participants reported clinical history data, including age during the first onset, duration of illness, and number of hospitalizations. Furthermore, daily dose and time of administration of current stable and PRN medication were collected. Using the Defined Daily Doses (DDD) method, we converted antipsychotic medication to chlorpromazine dose equivalence (CPZ) (for details see, Leucht, Samara, Heres, & Davis, 2016).

Schizophrenia symptoms

The severity of schizophrenia symptoms was evaluated with the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989). PANSS is widely used in clinical research and is considered a standard instrument for assessing psychopathology in schizophrenia (T. Suzuki, 2011). Upon a semi-structured interview with the patient and relevant clinical information from primary care workers, the examiner rates the severity of positive (Positive Scale, 7 items, e.g., hallucinations), negative (Negative Scale, 7 items, e.g., emotional withdraw), and global symptoms (Global Psychopathology Scale, 16 items, e.g., anxiety) during the last seven days on a scale from 1 (absent) to 7 (extreme). Noticeably, PANSS includes not only content-related information on productive symptoms (e.g., delusions) but also observations on social behavior (e.g., hostility), body movement (e.g., mannerisms and posturing), and thought disorder (e.g., stereotyped thinking). To calculate PANSS scores, item ratings are summed for each scale and overall for all 30 items, yielding possible ranges of 7 – 49 points for both Positive and Negative Scales, 16 – 112 points for the Global Psychopathology Scale, and 30 – 210 for PANSS total. To increase standardization, here, PANSS was administered upon the Structured Clinical Interview for PANSS (SCI-PANSS) (for details see, Kay et al., 1987).

Negative symptoms were further explored using the German version of SANS (Andreasen, 1989; Dieterle, Albus, Eben, Ackenheil, & Rockstroh, 1986). SANS measures negative symptoms across the domains affective blunting (German version: 7 Items, original version: 8 items); alogia (5 items), avolition/apathy (4 items), anhedonia/asociality (5 items), and attention (3 items) on a six-point scale from 0 (not at all) to 5 (severe). Each domain includes a global rating item. Ratings are based on data collected from the clinical interview and primary caregivers. The sums of the five global items (summary global score) and all 24

items (composite score) are calculated and serve as negative syndrome measures with a range of 0 – 25 and 0 – 120, respectively.

Depression symptoms

Symptoms of depression, which are very common in schizophrenia (e.g., Hafner et al., 2005), were assessed with the Inventory of Depressive Symptomatology (IDS-C) (Rush, Carmody, & Reimitz, 2000; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996) and Beck Depression Inventory II (BDI-II) (Beck, Steer, & Brown, 1996). IDS-C is a semi-structured 30-item interview, where a clinician rates severity of patients' depressive symptoms on a four-point scale from 0 (absent) to 3 (max. symptom severity). IDS-C includes i.e. items on sleep problems (e.g., early morning insomnia), mood (e.g., sadness, anxiety, quality and variation of mood), outlook (e.g., on future), cognition, and physical symptoms (e.g., appetite). Since only one of the items about appetite (increase/decrease) and weight (increase/decrease) should be answered, 28 items are included in the overall score that therefore varies between 0 and 84 (for further details, see Rush et al., 2000; Rush et al., 1996). In contrast to IDS-C, BDI-II is a self-report measure with 21 items (Beck et al., 1996). Here, patients had to rate the severity of their depressive symptoms in the last two weeks between 0 and 3. The sum of all items serves as a measure of depression (range: 0 – 63).

Global ratings

We rated the overall severity of patients' symptoms using the Clinical Global Impression Scale (CGI-S) (Guy, 1976) that varies between 1 (normal, not at all ill) and 7 (among the most ill patients). Additionally, we applied the Global Assessment of Functioning Scale (GAF) (Endicott, Spitzer, Fleiss, & Cohen, 1976; Goldman, Skodol, & Lave, 1992) to rate the psychological, social, and occupational functioning of the patient on a scale of 1 (persistent danger of severely hurting self or others) to 100 (superior functioning).

2.3.3. Neuropsychological measures

Crystalline intelligence

Crystalline intelligence (IQ) was measured using a German vocabulary test, Wortschatztest (WST-R) (K.-H. Schmidt & Metzler, 1992). The WST-R included 42 items, where participants had to recognize the existing word in the German language among five non-existing pseudo-words. There was no time limit for completion. The number of correct items (max. 42) was converted using a norming table to a verbal IQ value.

Episodic Verbal Memory

Episodic Verbal Memory was measured with the Verbaler Lern-und Merkfähigkeitstest (VLMT: Verbal Learning and Memory Test). VLMT (Helmstaedter & Durwen, 1990) is developed for the German language area and is based on the Rey Auditory Verbal Learning Test (RAVT) (Muller, Hasse-Sander, Horn, Helmstaedter, & Elger, 1997). First, the investigator read out a list of 15 nouns in a fixed order at a two-second-pace five times (*Learning List A)*. After each learning trial, the participant was required to recall as many words as possible in a free order *(Free Recall)*. After completing this first learning phase, the investigator read out another list of 15 independent nouns *(Interference List B).* Here, the participant had to again recall as many nouns from List B as possible. Next, the participant was asked to freely recall the words from List A without a further list presentation *(Trial* 6). After a 30 min. delay, the procedure was repeated – a free retrieval of List A without a renewed reading-out of the list *(Trial 7)*. The test finished with a recognition trial, where the investigator read out a list containing the words of List A, of List B and 10 words with a semantic and 10 words with a phonetic similarity to the words of List A and B *(Recognition List W)*. Here, the participant had to answer with "yes" or "no" if the word was part of List A. VLMT assesses multiple episodic verbal memory features, including short-term memory and long-term memory parameters. Here, we focused on the following factors: (a) *learning* as the sum of correct words during the learning phase (Trial 1 to 5); (b) *long-term memory consolidation* as the decrease of learning performance after the 30 min. delay (Trial 5 minus Trial 7); and (c) *correct recognition* as the subtraction of false answers from the correct recognized List A words (Trial W- F).

Processing speed, visual attention, cognitive flexibility

Trail Making Test (TMT) (Tombaugh, 2004) is a popular neurocognitive paper-pencil test to assess visual attention, motor speed, and cognitive flexibility and consists of two parts: A and B. In TMT-A, participants were presented with a paper sheet with circles with the

numbers 1 to 25, which they must connect in a consecutive order as quickly as possible. In TMT-B, the task sheet included again 25 circles with the numbers 1 - 13 and with the letters A – L . Here, participants had to shift strategies and quickly connect the circles in the right numerical or alphabetical order, alternating between numbers and letters (e.g., 1-A-2-B). Before both TMT-A and -B, participants completed a task training sample with eight circles each. Participants were corrected during task performance when needed. Time of task completion in s served as a measure of processing speed (TMT-A) and cognitive flexibility (TMT-B). The Digit Symbol Substitution Test (DSST, a subtest of the Hamburg-Wechsler Intelligence Test) (Tewes, 1994) is also a paper-pencil test applied to measure motor speed and visual memory. Here, participants were presented with nine simple symbols. Each symbol was assigned to a number (1 – 9). The task sheet consisted of seven rows with 20 numbers each. Participants were required to fill the blank spaces below each number with the according symbol in 120 s. The first 7 digits were training trials. The assignment of symbols to digits was visible at all times. Outcome measure was the number of correctly completed symbols (range: 0 – 133).

Working memory

In the Digit Span Test (DST, a subtest of the Hamburg-Wechsler Intelligence Test) (Tewes, 1994), the investigator read out numeric sequences at a one-second rhythm that participants had to memorize and recall forwards (DST forwards) or backward (DST backward), immediately after the presentation. DST forwards included eight levels of difficulty representing the length of the numeric sequences (2 – 9 digits). Levels of difficulty were administrated in a consecutive order. When participants could not complete both trials of a level, the task was stopped. DST backward had an identical procedure but consisted only of seven levels of difficulty. The number of correct recalled numeric sequences forwards (range: 0 – 16) served as a measure of attention and concentration, and backward (range: 0 – 14) – as a measure of working memory.

2.3.4. Cognition index

We calculated a cognition index as the primary measure of cognitive functioning. The cognition index was constructed upon scores from VLMT (Sum of Trial 1 to 5, Trial 5 minus Trial 7, W - F), TMT (A and B, in s), DST (forwards and backward), and DSST (number of correct symbols) and calculations were based on the neurocognitive composite score described by Hasan et al. (2016). It included data from 59 SP, 55 HC, 20 UR (see Figure 2) and was constructed using SPSS in the following steps:

(1) Imputation of missing data: There were three missing data points from the data set. Using Little's Missing Completely at Random (MCAR) test, we confirmed that they were MCARs ($\chi^2 = 12.57$ (13), $p = .479$) and therefore replaced them via the Expectation Maximation Method (EM).

(2) Recoding of variables: The variables VLMT Trial 5 minus VLMT Trial 7, TMT-A, and TMT-B were multiplied by -1 so that larger values would refer to a better performance.

(3) Z-transformation: All variables were transformed into z-standard scores (with $M = 0$, $SD = 1$), to avoid influence of different scaling.

(4) Calculation of cognition index: The cognition index was constructed as the weighted means of the z-scores using the formula:

$$Cognition\ index = \frac{1}{4}\text{Mean}\left(\text{zVLMT}_{\text{Sum(Trial 1 to Trial5)}}, \text{zVLMT}_{\text{Trial5-Trial7}}, \text{zVLMT}_{\text{W-F}}\right) +$$

$$\frac{1}{4}\text{Mean}(\text{zTMT}_{\text{A}}, \text{zTMT}_{\text{B}}) + \frac{1}{4}\text{zDSST} + \frac{1}{4}\text{Mean}\ (\text{zDST}_{\text{forwards}}, \text{zDST}_{\text{backward}})$$

2.3.5. Imaging Data

Data acquisition

MRI data were obtained using a Siemens 3.0 Tesla MAGNETOM Skyra Scanner (Siemens Healthineers, Erlangen, Germany) with a 20-channel phased-array head and neck coil. To acquire high-resolution T1-weighted images, a 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence with 176 slices of 0.80 mm thickness, echo time (TE) = 2.22 ms, repetition time (TR) = 1900 ms, flip angle (FA) = 9° and 0.8 mm isotropic voxels. Before scanning, small cushions were placed on both sides of participants' head and a roller cushion underneath participants' legs to minimize head movement during scanning and possible back strain. All data images were visually controlled for low image quality and MR artifacts.

Data preprocessing and segmentation

Data preprocessing and segmentation was carried out by application of an in-house high-performance-computing applicable pipeline that includes software libraries of FSL 5.0.9 (https://fsl.fmrib.ox.ac.uk) (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) and AFNI (Analysis of Functional Images; https://afni.nimh.nih.gov/) (Cox, 1996). Preprocessing and segmentation procedures are described in detail by Beller et al. (2019) and Malchow et al. (2016). First, we applied the brain extraction tool (BET) (Smith, 2002) and the 3dskullstrip (AFNI) to remove the skull and other non-brain tissue (e.g., fat, skin), to reorientate the image to FSL-friendly space, and to create a binary mask. Next, images were segmented into grey matter (GM), white matter (WM), and CSF using FMRIB's Automated Segmentation Tool (FAST) (Y. Zhang, Brady, & Smith, 2001). Then, we run the FMRIB's Linear Image Registration Tool (FLIRT) (Jenkinson, Bannister, Brady, & Smith, 2002) and Non-linear Registration Tool (FNIRT) (Andersson, Jenkinson, & Smith, 2007) to carry out an affine and a non-linear registration and warped individuals' images onto the Automatic Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) in MNI standard space (Montreal Neurological Institute, Montreal, Canada). Herewith, we calculated parameters for total GM, total WM, total CSF, 45 cortical, and subcortical regions for the left and right hemisphere (AAL90) and 26 (AAL-2) cerebellum regions (list of regions, see Appendix A). All measures were carried out in mm^3 and voxels. Total intracranial volume (ICV) for each participant was also calculated as the sum of WM, GM, and CSF volumes (Dell'Oglio et al., 2015) and used as a standardizing parameter for all brain regions, applying the residual-method (Pintzka, Hansen, Evensmoen, & Håberg, 2015): $VOLcor = VOLraw - b(ICV - \overline{ICV})$, where VOLcor is the

corrected volume, VOLraw is the original volume, b is the slope of the linear regression of VOLraw on ICV, ICV is the ICV for the subject and $\overline{ICV}$ is the mean ICV of the study sample.

2.4. Data Analysis

2.4.1. Random Forest Classification

To examine if and which brain regions could predict cognitive performance, we applied an RF classification algorithm with a total of 238 features: age, sex, and the volume calculations of ICV, total GM, total WM, total CSF, and WM and GM of 116 cortical and subcortical areas (for details, see Appendix A). Since ICV was included in the model, we carried out calculations with uncorrected volumes for all brain regions. The cut-off value to divide cognitive performance was 1 SD below the average the cognition index means of HC und UR and set at -0.1, resulting in two classes of patients with high cognitive (HighCog, n = 13) and low cognitive performance (LowCog, n = 41, for details see Chapter 3.1.2.1.). The RF classifier was conducted using the scikit-learn version 0.21.3 tool (3.2.4.3.1. sklearn.ensemble.RandomForestClassifier) (Pedregosa et al., 2011) for Python 3.7.3. The model builds 380 trees with a maximal depth of 20 leaves each and Gini Index (see Chapter 1.3.2.) as a splitting criterion, which is calculated as $Gini(D) = 1 - \sum_{J=1}^{n} {p_j}^2$ (Breiman et al., 1984), where n is the number of classes and p^j the frequency of class j in the subset D. D goes up to the number of attributes for the feature. To control the bootstrapping's randomness and the sampling of the features, we set the seed for the random number generator at 12. For all parameters, see Appendix B. First, participants were randomly assigned to a training test consisting of SP, UR, and HC (n = 110) and to a test set consisting only of SP (n = 17). Second, the model is trained and then cross-validated with the left-out test set. This procedure was repeated 1000 times. Every time, the confusion matrix for each class was reported, consisting of correctly identified participants as class members (true positives, TP), correctly identified participants as class nonmembers (true negatives, TN), falsely categorized participants as class members (false positives, FP) and falsely categorized participants as class nonmembers (false negatives, FN) (Ting, 2017). Upon these values, the overall and balanced accuracy (BAC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and F1-score were calculated as presented in Table 4. The average parameters over the 1000 runs

served as measures for classification performance. Due to the imbalanced dataset, we weighted parameters by class size.

Table 4. *Definitions and calculations for the classification parameters.*

Parameter	Formula	Definition
Accuracy	(TP+TN)/(TP+TN+FP+FN)	The proportion of the study sample that is classified correctly [a)]
BAC	(sensitivity + specificity)/2	Average of the accuracy for each class (correcting for imbalanced data) [a)]
Sensitivity	TP/(TP+FN)	The proportion of positive examples that a correctly classified by the model [b)]
Specificity	TN/(TN+FP)	The proportion of negative examples that a correctly classified by the model [b)]
PPV	TP/(TP+FP)	The ratio of positive examples correctly classified by the model and the total number of examples [b)]
NPV	TN(TN+FN)	The ratio of negative examples correctly classified by the model and the total number of negative examples [b)]
F1-score	2*[Sensitivity*PPV/(Sensitivity+PPV)	The harmonic mean of sensitivity and PPV [c)]

a) (Mower, 2005); b) (Ting, 2017); c) ("F1-Measure," 2017)

Finally, we estimated Gini importance, a parameter for feature importance, to detect the most relevant brain regions for high and low cognitive performance classification. Each split of a node on a variable results in a decrease of the impurity criterion Gini index for the descendent nodes. Gini importance for each variable is calculated as the averaged sum of the decrease of node impurity (Gini index), weighted by the probability of reaching that node, over all trees in the forest (Breiman, 2001; Breiman et al., 1984). Thus, the larger the value, the more important the feature for the classification model. The Gini importance values of all features sum up to 1 (Pedregosa et al., 2011). The top seven most important features and their averaged Gini importance values over the 1000 runs were determined.

2.4.2. Statistical Analysis

All data preparation for calculating the cognition index and further statistical analysis was conducted at $\alpha = .05$ using SPSS 24 (IBM Inc.) for Windows. Demographic and clinical differences between groups were assessed using χ^2-tests and one-way analyses of variance (ANOVAs) with between factor 'experimental group' or 'cognitive profile' and post-hoc Tukey HSD tests. Via Pearson's correlation analysis, we investigated the relationship between cognition index and age of onset, duration of illness, CPZ equivalents, and number of hospitalizations. We used Kolmogorov-Smirnov (K-S) tests to test the normal distribution of cognition index in each study group.

To explore the relationship between cognition and the most important features for the classification, we conducted seven separate linear regression analyses with the dependent variable 'cognition index' and the ICV corrected volumes of each region as predictors. A multiple regression analysis was not performed because the assumption of independence of residuals was violated (Durbin-Watson test = 0.84 in the whole study sample and 0.27 in SP). Therefore, we applied the Bonferroni-correction for multiple testing and conducted the regressions analyses at $\alpha = .007$. We performed seven regression analyses for the whole study sample ($N = 127$) and only for the patient sample ($n = 54$).

We then conducted two identical multivariate analyses of variance (MANOVA) with the most important features as dependent variables and SP cognitive profile (HighCog vs. LowCog) (MANOVA 1) and study group (SP vs. HC vs. UR) (MANOVA 2) as the independent variable to explore group differences. MANOVA 1 was carried out using only the SP sample ($n = 54$) and with seven post-hoc ANOVAs to test how HighCog and LowCog differ in the ICV corrected GM volumes of the most important structures. MANOVA 2 analyzed data from the whole sample ($N = 127$), and we performed seven one-way ANOVAs with between-subject factor 'experimental group,' and post-hoc Tukey HSD tests for the ICV corrected grey matter volumes of each region. All post-hoc ANOVAs were conducted at $\alpha = .007$ (Bonferroni-corrected). In case of violation of the assumption of homogeneity of variance, the Welch correction estimates were reported.

3. Results

3.1. Demographic and clinical characteristics

3.1.1. Study sample for calculation of cognition index (*N* = 134)

Experimental groups did not differ in age (p = .232), handedness (p = .521) and language use (p = .492), but in sex distribution (p < .001) (see Table 5). Subsequent paired χ^2-tests indicated that the effect is due to the UR group, since SP and HC had similar sex distribution ($\chi^2(1) = 2.38$, p = .123). As expected, there was a significant group difference in cognition index (p < .001), where SP had the smallest values. Moreover, cognition index did not correlate with CPZ equivalents ($r(57) = -.02$, p = .913), duration of illness ($r(57) = -.14$, p = .28), age of onset ($r(57) = -.166$, p = .209) and number of hospitalizations ($r(55) = .02$, p = .911).

Table 5. *Demographic and neuropsychological characteristics of the study sample for analysis of cognitive data (N = 134).*

	SP (*n* = 59)	**HC (*n* = 55)**	**UR (*n* =20)**	**χ2 (*df*)**	***p***
Sex (m : f)	49 : 10	39 : 16	6 : 14	20.10 (2)	< .001***
Handedness (right : left : both)	53 : 5 : 1	49 : 6	16 : 4	3.23 (4)	.521
Language (native : foreign)	50 : 9	48 : 7	19 : 1	1.42 (2)	.492
	M (SD)	***M (SD)***	***M (SD)***	***F* (df_1, df_2)**	***p***
Age	34.93 (11.39)	32.69 (11.48)	37.95 (15.16)	1.47 (2, 131)	.232
Cognition Index	-0.54 (0.66)	0.47 (0.50)	0.28 (0.65)	44.30 (2, 131)	<.001***

*p < .05, **p < .01, ***p < .001

3.1.2. Study sample for the machine learning analysis (*N* = 127)

There were no differences between experimental groups regarding age (p = .461), handedness (p = .460) and language use (p = .555). We observed again a significant effect of experimental group in sex distribution (p < .001). Direct comparison of HC and SP, however, showed no differences ($\chi^2(1) = 2.55$, p = .110). As expected, the groups further differed in smoking behavior (p < .001), educational years (p = .007) and crystalline intelligence (p<.001) (see Table 4). Tukey HSD post-hoc tests revealed that SP had significantly fewer educational years (p = .009) and smaller value for crystalline intelligence (WST-R: p < .001; IQ: p < .001) than HC. UR also had greater values for crystalline intelligence than SP (WST-R: p = .003; IQ:

p = .001). There were no significant differences between SP and UR (all p > .005, for descriptive data, see Table 6).

Table 6. *Demographic and neuropsychological characteristics of the sample for the machine learning analysis (N = 127).*

	SP (*n* = 54)	**HC (*n* = 54)**	**UR (*n* =19)**	***χ2 (df)***	***p***
Sex (m : f)	45 : 9	38 : 16	5 : 14	21.52 (2)	<.001***
Handedness (right : left : both)	48 : 5 : 1	49 : 5	15 : 4	3.62 (4)	.460
Language (native : foreign)	46 : 8	47 : 7	18 : 1	1.17 (2)	.555
Smoking (no : yes)	18 : 36	41 : 12	16 : 3	27.18 (2)	<.001***
	M (SD)	***M (SD)***	***M (SD)***	***F*** (df_1, df_2)	***p***
Age	34.31 (10.91)	32.80(11.57)	36.63(14.35)	0.78 (2, 124)	.461
Crystalline IQ	103.09(14.70)	114.43(11.56)	116.16(13.20)	12.45 (2, 124)	<.001***
WST-R	29.74 (7.74)	34.69 (3.97)	35.05 (4.40)	11.25 (2, 59.96)	<.001***
Edinburgh Scale	0.72 (0.41)	0.75 (0.51)	0.67 (0.67)	0.15 (2, 116)	.860
Education Years	14.57 (4.18)	16.56 (2.71)	16.63 (3.01)	5.23 (2, 124)	.007**
Cognition Index	-0.53 (0.66)	0.47 (0.50)	0.32 (0.65)	40.34 (2, 124)	<.001***

*p < .05, **p < .01, ***p < .001

3.1.2.1. Results on cognition index

As expected, the one-way ANOVA on cognition index revealed a significant difference between experimental groups (p < .001, Table 6). A Tukey HSD post hoc test showed that the cognition index was statistically lower in the SP group than in the HC (p < .001) and UR (p < .001) groups. Although HC had numerically higher cognition index than UR, the difference did not reach significance (p = .614). Pearson's correlation analysis showed no significant correlations between cognition index and clinical parameters such as age of onset (r(52) = -.01, p = .350), duration of illness (r(52) = -.13, p = .480), CPZ equivalents (r(52) = -.10, p = .941) and number of hospitalizations (r(51) = .07, p = .604).

Cognition index was normally distributed in SP (K-S test: p = .796), in HC (K-S test: p=.437) and in UR (K-S test: p = .758). The cut-off value for SP's high and low cognitive performance was set at -0.1, approximately 1 SD below the collective cognition index score of SP and UR (M = 0.43, SD = 0.55). As previously demonstrated (Keefe & Fenton, 2007), while

SP's distribution was shifted about 2 SDs below the distribution of HC, both distributions still overlapped substantially. Specifically, 24.1% of SP (n = 13) performed as the majority of HC with cognition index values above -0.1 (see Figure 3). Accordingly, small part of HC (9.3%, n = 5) and UR (15.8%, n = 3) achieved a cognition index score below -0.1 as the majority of SP (75.9 %, n = 41). The resulted patient groups with high (HighCog) and low cognitive (LowCog) did not differ in their age (p = .201), sex distribution (p = .319), medication use and overall clinical data. LowCog had significant lower values in negative symptoms, which include cognitive deficits, as measured by PANSS (p = .008) and SANS (p < .001) than HighCog. Detailed descriptive and statistical data are presented in Table 7.

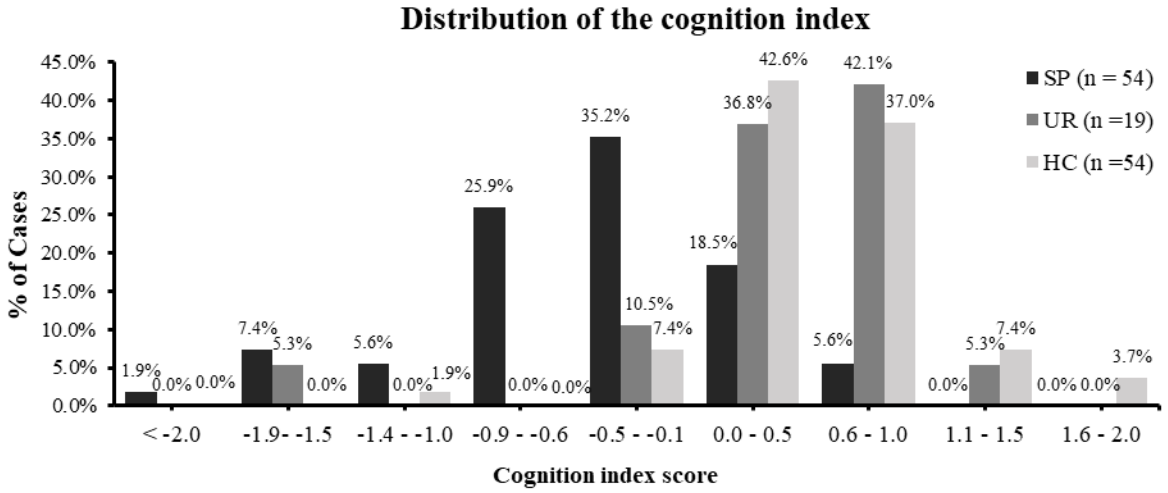


Figure 3. Distribution of cognition index score across all experimental groups (N = 127): schizophrenia patients (SP, n = 54), healthy controls (HC, n = 54) and unaffected relatives (UR, n = 19).

3.1.2.2. Description of the patient group (SP, n = 54).

On average, patients had mild to moderate schizophrenia symptoms as indicated by PANSS Total (M = 60.23, SD = 15.93) (Leucht et al., 2005) and SANS composite (M = 35.83, SD = 16.96) scores. Furthermore, values of BDI-II (M = 14.32, SD = 9.11) and IDS-C (M = 19.38, SD = 9.93) revealed mild symptoms of depression. In accordance, ratings of CGI (M = 3.92, SD = 0.87) and GAF (M = 56.40, SD = 9.24) suggested a mild to moderate symptom severity and difficulties in social, occupational, school functioning. In line with previous research (e.g., Rüther et al., 2014), the majority of the patients were tobacco users (66.7 %, n = 36) and had a moderate level of nicotine dependence as measured by FTND (M = 4.44, SD = 2.16). All but two patients were medicated, and 51.9% (n = 24) received antipsychotic

monotherapy. SP consisted of patients at different stages of illness, since one third of them (33.3 %, *n* = 18) had schizophrenia for less than 2 years, and another third of them (29.6%, *n* = 16) - for more than 10 years (see Table 7).

Table 7. *Demographic and clinical data of the patient group (SP, n = 54), the patient subgroups with high cognitive (HighCog, n = 13) and low cognitive (LowCog, n = 41) performance*

	SP (***n* = 54**)	**HighCog SP** (***n* = 13**)	**LowCog SP** (***n* = 41**)	**χ2** ***(df)***	***p***
Sex (m : f)	45 : 9	12 : 1	33 : 8	0.99 (1)	.319
Handedness (right : left : both)	48 : 5 : 1	10 : 3	38 : 2 : 1	4.12 (2)	.127
Language (native : foreign)	46 : 8	11 : 2	35 : 6	<.01 (1)	.947
Smoking (no : yes)	18 : 36	5 : 8	13 : 28	.203 (1)	.910
Antipsychotic monotherapy (y : n)	24 : 30	4:9	20 : 21	1.30 (1)	.255
Antipsychotic combination therapy (y: n)	28 : 26	8: 5	20 : 21	0.64 (1)	.422
Clozapine (y : n)	9 : 45	0 : 13	9 : 32	3.42 (1)	.064
Antidepressants (y : n)	9 : 45	1: 12	8 : 33	0.99 (1)	.319
Benzodiazepine (y : n)	8 : 46	3 : 10	5 : 36	.93 (1)	.336
	M(SD)	***M (SD)***	***M (SD)***	***F*** (df_1, df_2)	***p***
Cognition Index	-0.53 (0.66)	0.23 (0.31)	-0.77 (0.55)	39.01 (1,52)	<.001***
Age	34.31 (10.91)	30.92 (10.19)	35.39 (11.02)	1.68 (1,52)	.201
Education Years	14.57 (4.18)	15.85 (5.58)	14.17 (3.62)	1.61 (1,52)	.210
FTND	4.44 (2.16)	3.25 (1.98)	4.79 (2.11)	3.37 (1,34)	.075
CPZ equivalents	488.45 (334.88)	517.98 (345.64)	479.08 (335.23)	0.13 (1,52)	.719
Age of onset	25.84 (8.74)	24.12 (7.04)	26.39 (9.23)	0.66 (1,52)	.419
Duration of illness	8.42 (8.70)	6.81 (7.92)	8.93 (8.97)	0.58 (1,52)	.450
Hospitalizations	3.43 (2.71)	3.15 (2.67)	3.58 (2.75)	0.23 (1,51)	.632
PANSS Positive Scale	13.51 (5.25)	13.38 (4.82)	13.55 (5.44)	0.01 (1,51)	.923
PANSS Negative Scale	16.75 (5.14)	13.54 (3.80)	17.80 (5.13)	7.59 (1,51)	.008**
PANSS General Scale	29.96 (8.06)	29.31 (6.98)	30.18 (8.45)	0.11 (1,51)	.739
PANSS Total	60.23 (15.93)	56.23 (14.77)	61.53 (16.25)	1.09 (1,51)	.302
CGI-S	3.92 (0.87)	3.69 (0.95)	4.00 (0.85)	1.22 (1,51)	.274
GAF	56.40 (9.24)	60.15 (11.84)	55.18 (8.03)	2.96 (1,51)	.092
SANS summary global score	8.87 (3.97)	4.85 (2.58)	10.18 (3.43)	26.34 (1,51)	<.001***
SANS composite score	35.83 (16.96)	19.54 (12.68)	41.13 (14.72)	22.46 (1,51)	<.001***
IDS-C	19.38 (9.93)	20.67 (9.31)	19.00 (10.19)	0.26 (1,51)	.614
BDI-II	14.32 (9.11)	14.58 (5.55)	14.24 (9.97)	0.23(1,33.39)	.880

*$p < .05$, **$p < .01$, ***$p < .001$

3.2. Machine Learning Analysis

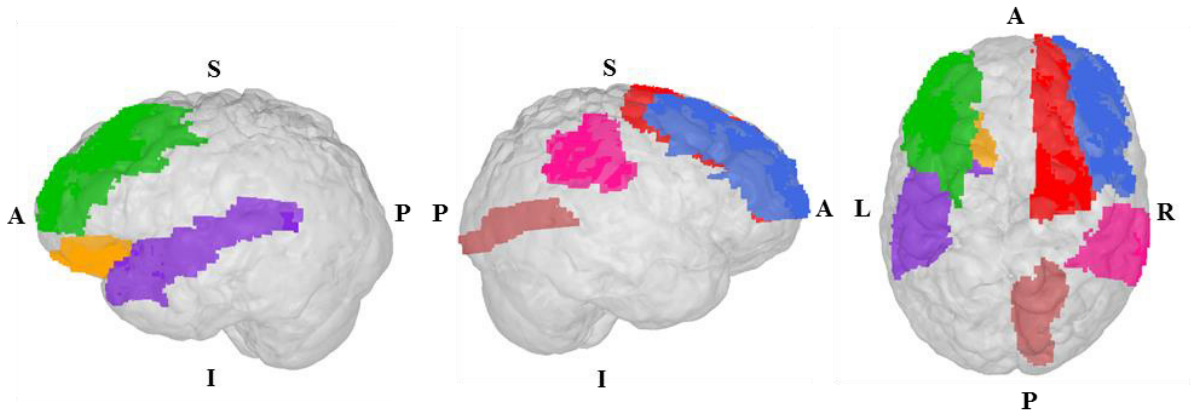
The RF classifier determined between SP with high and low performance based on sMRI features with average accuracy (sensitivity/specificity) of 62.1% (62.1%/76.0%) and BAC of 69.0%. Furthermore, the classifier achieved a mean PPV (F1-score) of 79.7 % (0.65) and an NPV of 48.6%. Each class's results individually indicated that HighCog is classified more sensitively, whereas the specificity for LowCog was higher (both values 82.3%)[2].

Table 8. *Classification performance parameters overall and for each class (HighCog vs. LowCog*

	RF-Classifier		HighCog[2]		LowCog[2]	
	M	**95%CI [LL, UL)**	***M***	**95%CI [LL, UL)**	***M***	**95%CI [LL, UL)**
Accuracy	62.1%[2]	[61.4%, 62.7%]				
BAC	69.0%	[68.3%, 69.7%]				
Sensitivity	62.1%	[61.4%, 62.7%]	82.3%[2]	[81.0%, 83.5%]	55.7%	[54.9%, 56.45%]
Specificity	76.0%	[75.0%, 77.0%]	55.7%[2]	[54.9%, 56.5%]	82.3%	[81.0%, 83.5%]
PPV	79.7%	[79.1%, 80.2%]	36.8%[2]	[36.0%, 37.7%]	91.4%	[91.0%, 92.0%]
NPV	48.6%	[47.6%, 49.5%]	91.4%[2]	[91.0%, 92.0%]	36.8%	[36.0%, 37.7%]
F1-score	0.65	[0.64, 0.65]	0.49	[0.48, 0.50]	0.68	[0.68, 0.69]

As expected, the model identified GM volumes of prefrontal regions as features of highest importance (right dorsolateral Superior Frontal Gyrus, left and right Middle Frontal Gyri, left opercular Inferior Frontal Gyrus) for the classification. Among the seven most important features were also GM volumes of regions of the occipital lobe (right Lingual Gyrus), the parietal lobe (right Supramarginal Gyrus), and the temporal lobe (left Superior Temporal gyrus). All importance values are rather small (range .01-.03) and summed up to 0.10 (see Figure 4).

[2] In the context of binary classifiers, calculations of performance parameters (as presented in Table 4) result in identical values of sensitivity and PPV of Class 1, and specificity and NPV of Class 2 and vice versa. Overall ACC equals balanced sensitivity



x = 0.8; y = 0.78; z = 0.78

	Brain Region	Importance
	Superior Frontal Gyrus, dorsolateral part (right)	.027924
	Middle Frontal Gyrus (left)	.014565
	Middle Frontal Gyrus (right)	.013542
	Inferior Frontal Gyrus, opercular part (left)	.012815
	Lingual Gyrus (right)	.012354
	Supramarginal Gyrus (right)	.011344
	Superior Temporal Gyrus (left)	.011267

Figure 4. Results of Random Forest Classification: Mean importance values of the top seven features for classification accuracy

3.2.1. Subsequent regression analysis

The subsequent separate linear bivariate regression analysis on cognition of the whole study sample (N = 127) as the dependent variable and the brain regions as predictors revealed significant results for all structures (all $p < .001$), but for the left Middle Frontal Gyrus (p = .062, see Table 9). The regression coefficients indicate a positive relationship, viz. a higher GM volume of right Superior Frontal Gyrus, right Middle Frontal Gyrus, Inferior Frontal Gyrus, right Lingual Gyrus, right Supramarginal Gyrus, and left Superior Temporal Gyrus predicts a higher cognition index. In contrast, the regression coefficient for the left Middle Frontal Gyrus is negative, so a low GM volume causes a high cognition index (not significant). For linear regression coefficients and equations, see Table 9 and Figure 5.

Table 9. *Results from the separate bivariate regression analysis with the dependent variable 'cognition index' and the ICV-corrected grey matter volumes of the most important brain regions as predictors in the whole study sample (N = 127).*

Predictors	**β**	***t***	***P***	R^2	***F***	(df_1, df_2)	***P***
Superior Frontal Gyrus, dorsolateral part (right)	.495	6.37	< .001***	.245	40.55	(1, 125)	< .001***
Middle Frontal Gyrus (left)	-.166	-1.89	.062	.020	3.56	(1, 125)	.062
Middle Frontal Gyrus (right)	.484	6.19	< .001***	.235	38.33	(1, 125)	< .001***
Inferior Frontal Gyrus, opercular part (left)	.322	3.80	< .001***	.103	14.41	(1, 125)	< .001***
Lingual Gyrus (right)	.314	3.69	< .001***	.098	13.65	(1, 125)	< .001***
Supramarginal Gyrus (right)	.369	4.45	< .001***	.137	19.76	(1, 125)	< .001***
Superior Temporal Gyrus (left)	.418	5.14	< .001***	.175	26.46	(1, 125)	< .001***

***$p < .001$

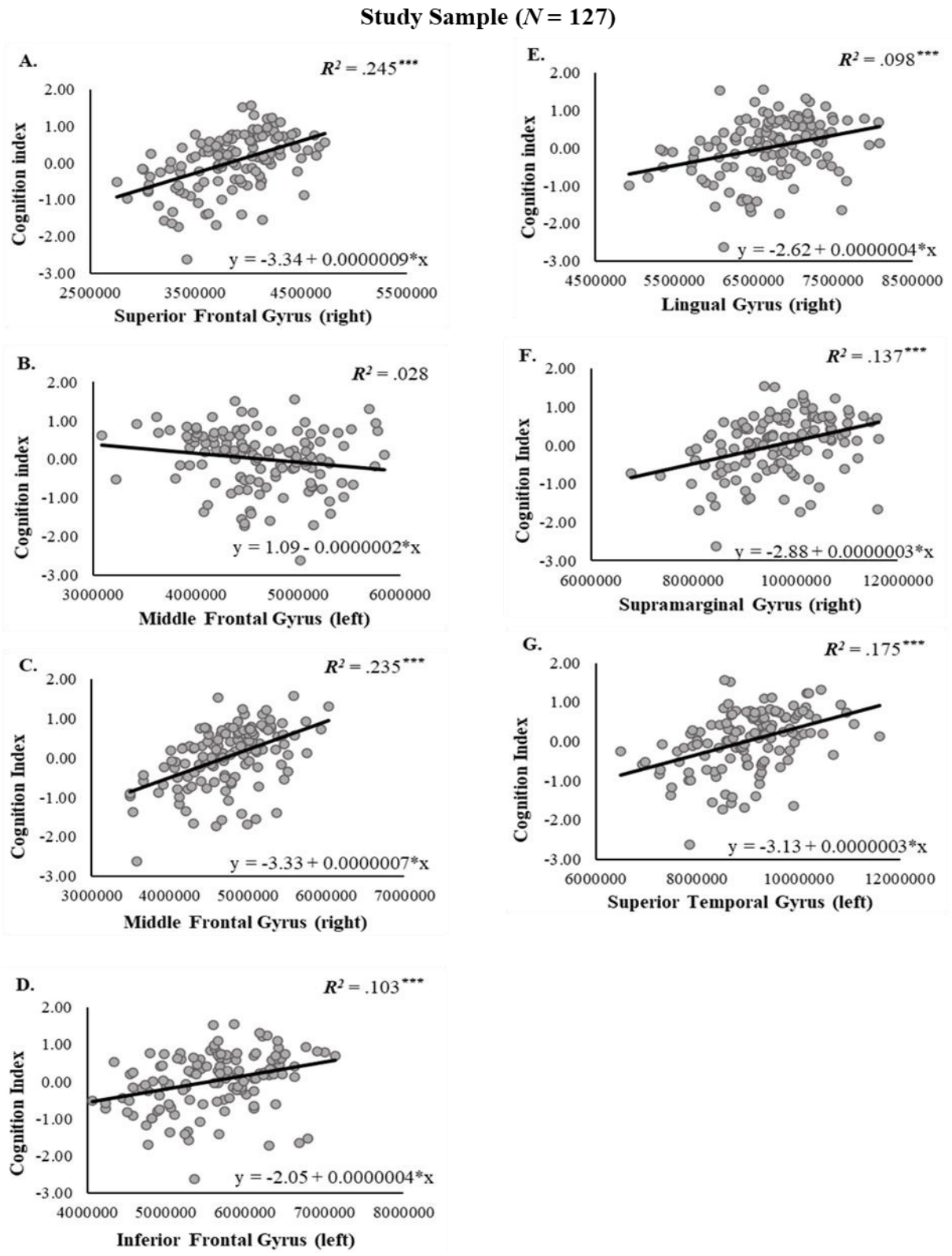


Figure 5. Linear regression analysis using the whole study sample (N = 127) with dependent variable 'cognition index' (y-axis) and predictors (x-axis): **A.** Superior Frontal Gyrus, dorsolateral part (right); **B.** Middle Frontal Gyrus (left); **C.** Middle Frontal Gyrus (right), **D.** Inferior Frontal Gyrus, opercular part (left); **E.** Lingual Gyrus (right); **F.** Supramarginal Gyrus (right) and **G.** Superior Temporal Gyrus (left).
$^{***}p < .001$

The subsequent separate linear bivariate regression analysis on cognition of SP (n = 54) as the dependent variable and the brain regions as predictors revealed no significant results (see Table 10). Despite not reaching statistical significance, the results' pattern, including the regression direction, resembled those in the whole study sample (Figure 6).

Table 10. *Results from the separate bivariate regression analysis with the dependent variable 'cognition index' and the ICV-corrected grey matter volumes of the most important brain regions as predictors in the patient group (N = 54).*

Predictor	**β**	***t***	***P***	R^2	***F***	(df_1, df_2)	***p***
Superior Frontal Gyrus, dorsolateral part (right)	.282	2.12	.039	.080	4.50	(1, 52)	.039
Middle Frontal Gyrus (left)	-.077	-0.56	.580	.006	0.31	(1, 52)	.580
Middle Frontal Gyrus (right)	.192	1.41	.164	.037	1.99	(1, 52)	.164
Inferior Frontal Gyrus, opercular part (left)	.108	0.78	.438	.012	0.61	(1, 52)	.438
Lingual Gyrus (right)	.071	0.51	.611	.005	0.26	(1, 52)	.611
Supramarginal Gyrus (right)	.222	1.64	.106	.049	2.70	(1, 52)	.106
Superior Temporal Gyrus (left)	.124	0.90	.374	.015	0.81	(1, 52)	.374

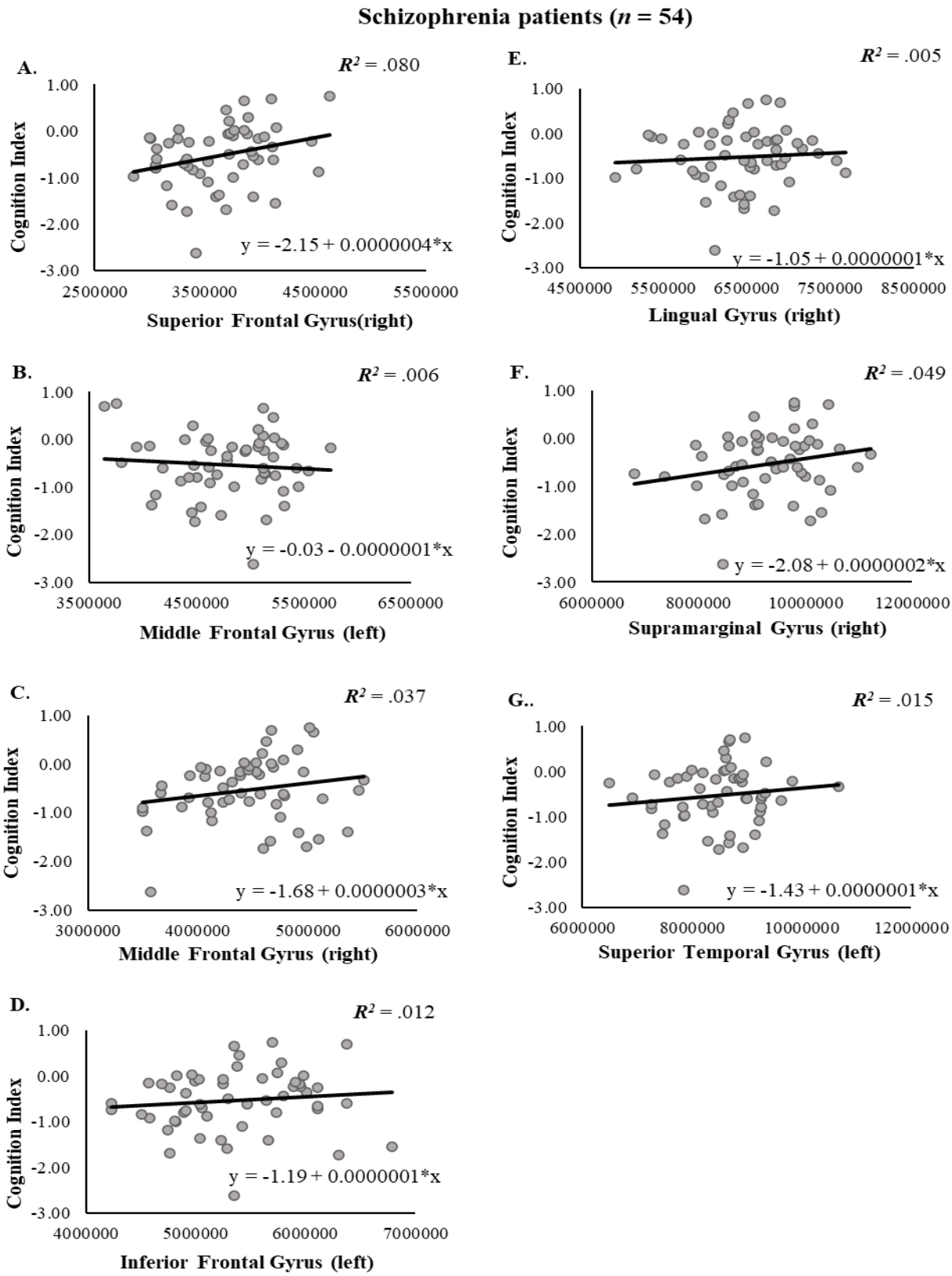


Figure 6. Linear regression analysis using the patient group (n = 54) with dependent variable 'cognition index' (y-axis) and predictors (x-axis): A. Superior Frontal Gyrus, dorsolateral part (right); **B.** Middle Frontal Gyrus (left); **C.** Middle Frontal Gyrus (right), **D.** Inferior Frontal Gyrus, opercular part (left); **E.** Lingual Gyrus (right); **F.** Supramarginal Gyrus (right) and **G.** Superior Temporal Gyrus (left).

3.2.2. Subsequent group comparison analysis

3.2.2.1. Schizophrenia Cognitive Profiles (LowCog vs. HighCog)

The one-way MANOVA showed no significant difference between the cognitive profiles in SP (LowCog vs. HighCog) on the combined dependent variables (ICV corrected GM volumes of the most important regions) with $F(7, 46) = 1.75$, $p = .210$, Wilks $\Lambda = .79$. The post-hoc ANOVAs indicated no significant differences between groups in volumes of all seven brain regions (all $p > .007$) (see Table 11). HighCog had numerically larger GM volumes of right Superior Frontal Gyrus, right Middle Frontal Gyrus, left Inferior Frontal Gyrus, right Supramarginal Gyrus, and left Superior Temporal Gyrus than LowCog. In contrast, the GM volumes of left Middle Frontal Gyrus and right Lingual Gyrus were numerically greater in LowCog (see Figure 7). However, none of these numerical differences reached statistical significance.

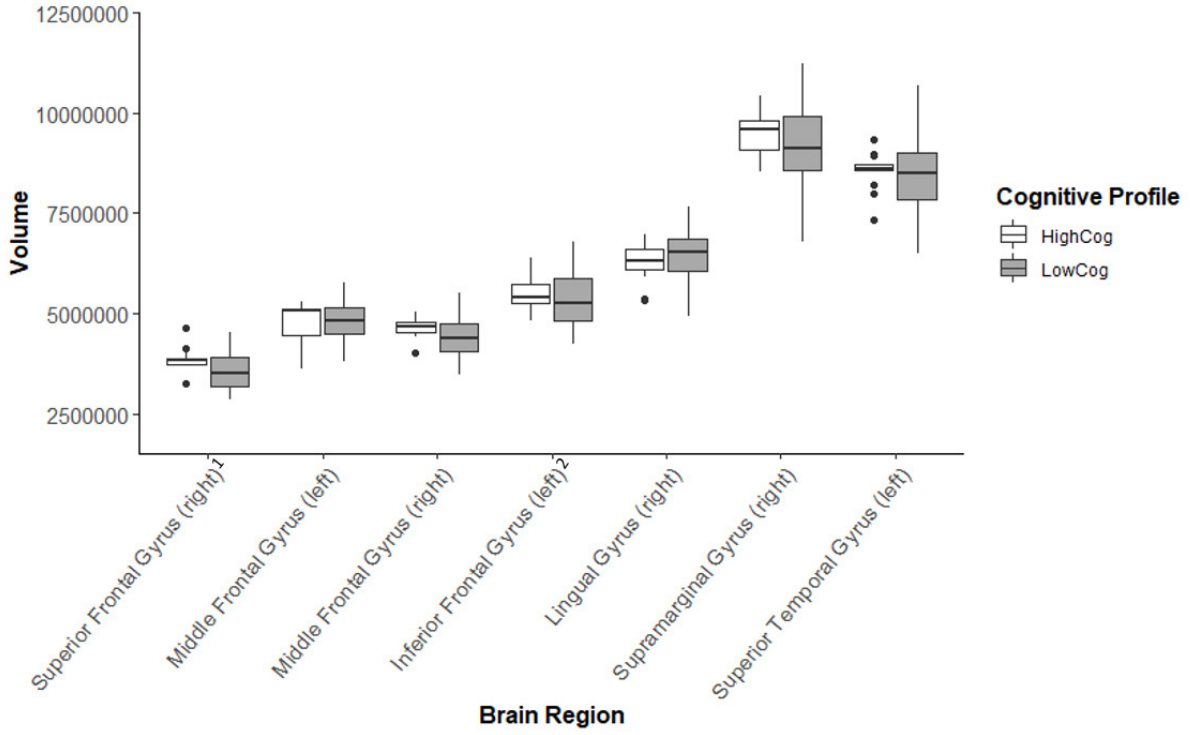


Figure 7. Box plots of the grey matter volumes of the most important brain regions across cognitive profiles in schizophrenia patients HighCog ($n = 13$) and LowCog ($n = 41$). Boxes represent the ICV corrected values within the 25th and 75th percentile. Central horizontal lines indicate medians. Whiskers indicate the 1.5 interquartile distance. Filled circles represent outlier data points outside the 1.5 interquartile range. [1]dorsolateral part, [2]opecular part

Table 11. *Effects of the post-hoc one-way ANOVAs with between-subject factor 'cognitive profile' (HighCog vs. LowCog) on the ICV-corrected grey matter volumes of the most important brain regions in the patient group (SP, n = 54).*

	HighCog SP (*n* = 13)		**LowCog SP (*n* =41)**		***F* (df_1. df_2)**	***p***
	M	***(SD)***	***M***	***(SD)***		
Superior Frontal Gyrus, dorsolateral part (right)	3863142.00	(315184.35)	3550009.63	(422642.00)	8.17 (1, 26.96)	.008
Middle Frontal Gyrus (left)	4733883.31	(555831.49)	4810721.49	(469435.52)	0.24 (1, 52)	.625
Middle Frontal Gyrus (right)	4646749.15	(269666.76)	4396657.24	(535684.72)	4.97 (1, 41.38)	.031
Inferior Frontal Gyrus, opercular part (left)	5489685.77	(434427.77)	5323721.10	(623642.32)	0.79 (1, 52)	.377
Lingual Gyrus (right)	6288919.00	(515276.55)	6473147.27	(604846.03)	0.98 (1, 52)	.327
Supramarginal Gyrus (right)	9502148.77	(562718.98)	9238014.73	(963253.30)	0.88 (1, 52)	.354
Superior Temporal Gyrus (left)	8551993.23	(497381.28)	8473412.98	(845095.95)	0.17 (1, 35.18)	.683

3.2.2.2. Experimental groups

The one-way MANOVA showed a significant difference between the experimental groups (SP vs. HC vs. UR) on the combined dependent variables (ICV corrected GM volumes of the most important regions) with $F(14, 238) = 6.80$, $p < .001$, $\eta_p^2 = 0.29$, Wilks $\Lambda = .51$. The post-hoc ANOVAs indicated significant differences between groups in volumes of all seven brain regions (all $p < .007$) (see Table 12). Post-Hoc Tukey HSD tests indicated that SP had significantly smaller GM volumes of right Superior Frontal Gyrus, right Middle Frontal Gyrus, Inferior Frontal Gyrus, right Lingual Gyrus, right Supramarginal Gyrus, and left Superior Temporal Gyrus than HC and UR (all $p < .05$). In contrast, there were no differences between HC and UR (all $p > .05$). Surprisingly, the volumes of left Middle Frontal Gyrus were in SP and UR significantly greater than in HC (both $p < .001$). For details, see Table 12 and Figure 8.

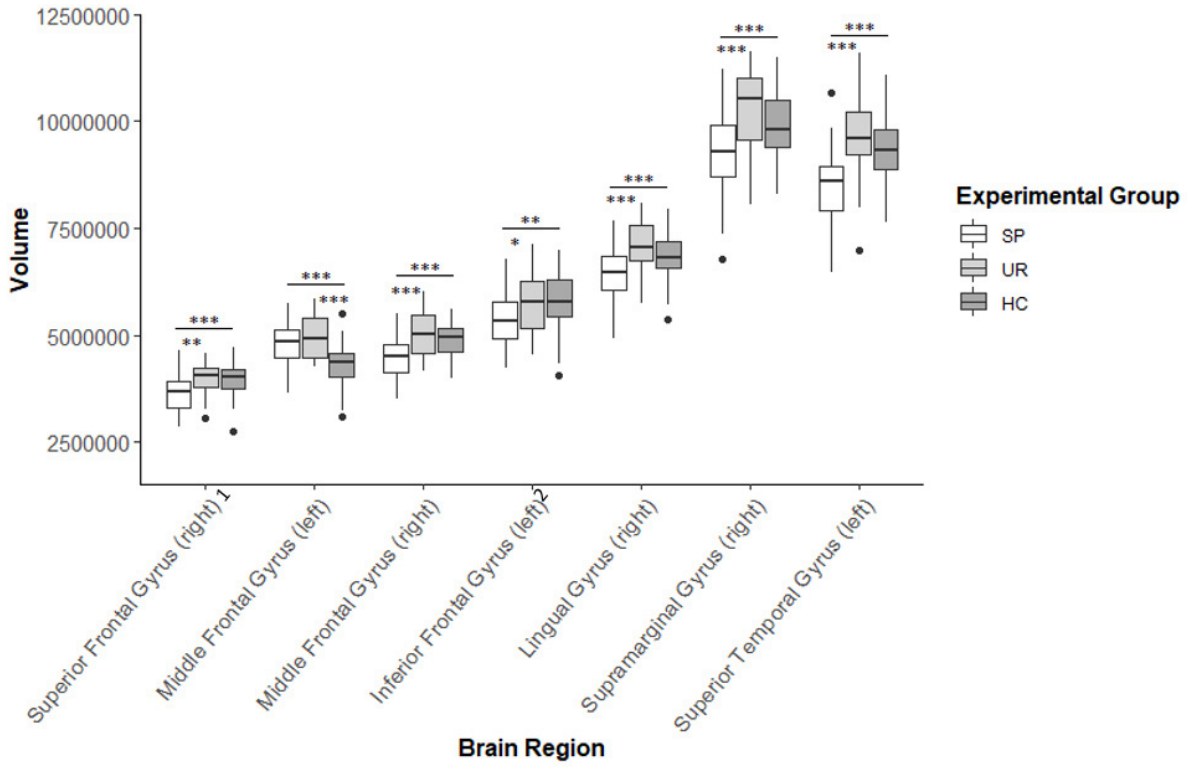


Figure 8. Box plots of the grey matter volumes of the most important brain in the patient (SP, $n = 54$), control (HC, $n = 54$), and unaffected relatives (UR, $n = 19$) groups. Boxes represent the ICV corrected values within the 25th and 75th percentile. Central horizontal lines indicate medians. Whiskers indicate the 1.5 interquartile distance. Filled circles represent outlier data points outside the 1.5 interquartile range.[1]dorsolateral part, [2]opecular part, $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$

Table 12. *Effects of the post-hoc one-way ANOVAs with between-subject factor 'experimental group' (SP vs. HC vs. UR) with post-hoc Tukey HSD tests on the ICV-corrected grey matter volumes of the most important brain regions.*

	SP *M (SD)*	**HC** *M (SD)*	**UR** *M (SD)*	$F\ (df_1.\ df_2)$	p	η_p^2	*Tukey HSD: p*	
Superior Frontal Gyrus, dorsolateral part (right)	3625393.35 (419004.95)	3962935.93 (368765.76)	3979844.63 (411535.75)	11.52 (2, 124)	< .001***	.157	SP vs. HC SP vs. UR HC vs UR	< .001*** .003** .986
Middle Frontal Gyrus (left)	4792223.41 (487203.18)	4342992.33 (473589.11)	4966560.42 (553714.27)	16.58 (2, 124)	< .001***	.211	SP vs. HC SP vs. UR HC vs UR	< .001*** .382 < .001***
Middle Frontal Gyrus (right)	4456864.56 (494656.70)	4892600.85 (390736.36)	5043278.42 (578205.34)	16.76 (2, 124)	< .001***	.213	SP vs. HC SP vs. UR HC vs UR	< .001*** < .001*** .450
Inferior Frontal Gyrus, opercular part (left)	5363675.56 (584287.85)	5776020.50 (632394.36)	5788460.16 (783874.38)	6.60 (2, 124)	.002**	.096	SP vs. HC SP vs. UR HC vs UR	.003** .036* .997
Lingual Gyrus (right)	6428796.02 (585269.96)	6829137.98 (499915.75)	7103278.21 (629769.71)	12.81 (2, 124)	< .001***	.171	SP vs. HC SP vs. UR HC vs UR	< .001*** < .001*** .160
Supramarginal Gyrus (right)	9301602.56 (885978.11)	9874891.56 (779171.97)	10200397.32 (1123531.57)	9.59 (2, 124)	< .001***	.134	SP vs. HC SP vs. UR HC vs UR	.003** < .001*** .353
Superior Temporal Gyrus (left)	8492330.44 (772121.47)	9302882.35 (704953.45)	9661914.42 (1052610.10)	21.64 (2, 124)	< .001***	.259	SP vs. HC SP vs. UR HC vs UR	< .001*** < .001*** .210

*p < .05, **p < .01, ***p < .001

4. Discussion

The present study aimed to distinguish between different cognitive subtypes in schizophrenia using machine learning. Specifically, we expected an RF algorithm applied to GM and WM volumetric data of SP, HC, and UR to classify with accuracy above 50% between patients with high and low cognition and identify the most relevant brain structures. As expected, the RF algorithm achieved an accuracy of 62.1% and BAC of 69.0%. Furthermore, it recognized prefrontal, temporal, parietal, and occipital structures among the seven most important for the classification. Greater volumes of all identified structures, except the left Middle Frontal Gyrus, significantly predicted good cognitive performance. However, these regression analyses reached significance only in the whole study sample and not in the patient group alone. Similarly, against our hypothesis, there were no differences in the most important features between HighCog and LowCog. Finally, group comparisons revealed significantly smaller GM volumes in all identified structures than UR and HC, except for the left Middle Frontal Gyrus, where SP and UR had significantly greater volumes than HC.

4.1. Performance parameters of the RF algorithm

The obtained overall and balanced accuracy is within the range of 60-80% reported by prior studies using machine learning to sMRI data to discriminate schizophrenia patients from controls (de Filippis et al., 2019). Moreover, our model achieved slightly higher accuracy values than the only previous work that applied multivariate pattern analysis (SVM) to neuroanatomical variables to classify two cognitive subtypes in schizophrenia with accuracy <60% (Gould et al., 2014). Both sensitivity and specificity were above 50%, with higher values for specificity (76%), indicating that the model could better recognize a non-member than a member of HighCog or LowCog. Similarly, the PPV value (~80%) was much higher than the NPV value, the latter being <50%. However, these findings could be due to the imbalanced class sizes, since binary classifiers are often biased towards the majority class (LowCog) (López, Fernández, García, Palade, & Herrera, 2013). Indeed, the sensitivity of HighCog and the specificity of LowCog were relatively high (>80%), where HighCog is more than three times smaller in size than LowCog. It is plausible that the algorithm recognized most members of the smaller class but had difficulties to discriminate them from the majority class and thus obtained high sensitivity and low specificity values (for calculations, see Table 4).

Consequently, the results of other performance parameters mirrored this effect with very high PPV for LowCog and very high NPV for HighCog (>90%).

4.2. Neuroanatomical structures of importance

The top seven most relevant features included GM volumes of prefrontal (the right dorsolateral Superior Frontal Gyrus, bilateral Middle Frontal Gyrus, left opercular Inferior Frontal Gyrus), temporal (the left Superior Temporal Gyrus), parietal (the right Supramarginal Gyrus), and occipital (the right Lingual Gyrus) regions. Notably, their importance indexes were small and summed up to 0.10 from max. 1.0, indicating that neuropsychological performance in schizophrenia and overall is associated not with single brain regions but with whole neuronal networks. This notion is supported by modern neuroscience, demonstrating cognitive processes as a result of dynamic and complex structural and functional connections, hierarchical and heterogeneous in nature (e.g., Lynn & Bassett, 2019; Mazoyer et al., 2001). Overall, intelligence, attention, and executive functions have been associated with general GM volume, ICV, volumes of the prefrontal lobe and the cerebellum (e.g., Andreasen et al., 1993; Hogan et al., 2011), a more effective brain organization (Y. Li et al., 2009) and the global connectivity of the prefrontal cortex (Cole, Yarkoni, Repovs, Anticevic, & Braver, 2012). In accordance, we found that large GM volumes of the right dorsolateral Superior Frontal Gyrus, right Middle Frontal Gyrus, left opercular Inferior Frontal Gyrus, right Lingual Gyrus, right Supramarginal Gyrus, and left Superior Temporal Gyrus predicted strong cognitive performance in the whole study sample. Furthermore, these regions had reduced GM volume in SP compared to HC and UR. The present findings are in line with previous evidence of an association between cognitive deficits and the decreased whole brain and GM volumes, specifically in frontal and temporal structures in schizophrenia (Antonova et al., 2004).

The dorsolateral Superior Frontal Gyrus is anatomically and structurally connected to the Middle Frontal Gyrus, which includes the DLPFC, and the Inferior Frontal Gyrus and are all associated with working memory and attention (W. Li et al., 2013). Furthermore, fMRI studies have demonstrated that the right Middle Frontal Gyrus is essential for switching between top-down and bottom-up attentional control networks (Japee, Holiday, Satyshur, Mukai, & Ungerleider, 2015), filtering distracting information (Marini, Demeter, Roberts, Chelazzi, & Woldorff, 2016), and numeracy (Koyama, O'Connor, Shehzad, & Milham, 2017). The left Inferior Frontal Gyrus is associated with language processing, working memory, empathy (Liakakis, Nickel, & Seitz, 2011), action observation, and imitation (Molnar-Szakacs,

Iacoboni, Koski, & Mazziotta, 2005). Its opercular part includes a portion of Broca's area and is involved in speech production (Brown, Ingham, Ingham, Laird, & Fox, 2005) and phonological processing (Nixon, Lazarova, Hodinott-Hill, Gough, & Passingham, 2004). Noticeably, language processing requires the activation of other most important features like the Supramarginal Gyrus and the Superior Temporal Gyrus, among others (Price, 2012). The Supramarginal gyri are involved in phonological processing and verbal memory (Deschamps, Baum, & Gracco, 2014), where the right one is associated with empathy and emotional processing as well (Preckel, Kanske, & Singer, 2018; Silani, Lamm, Ruff, & Singer, 2013). The left Superior Temporal Gyrus often includes the Wernicke area and is responsible for phonological and semantic language comprehension (Buchsbaum, Hickok, & Humphries, 2001; Leff et al., 2009). The right Lingual Gyrus is associated with visual processing (Fink et al., 1996) and divergent thinking (L. Zhang et al., 2016). In conclusion, the RF classifier identified cortical structures of the attentional, cognitive control, and language processing networks that have been previously found to be altered in schizophrenia (Barch & Ceaser, 2012; Sommer, Ramsey, & Kahn, 2001).

Indeed, numerous studies have reported reduced GM volumes of the prefrontal and temporal structures in relation to executive dysfunction in schizophrenia (e.g., Antonova et al., 2004). Several findings have demonstrated reduced GM volume of the Superior (Yamasue et al., 2004), Middle (J. M. Goldstein et al., 1999; M. Suzuki et al., 2005), and Inferior (Buchanan et al., 2004; Buchanan, Vladar, Barta, & Pearlson, 1998) Prefrontal Gyri, with some evidence indicating strongest effects for the latter two regions (Harms et al., 2010). A large amount of research focused on the DLPFC (part of the Middle Frontal Gyrus) as a neuronal basis for working memory and executive functions. GM volume reductions and functional abnormalities of the DLPFC (Kawada et al., 2009; Kikinis et al., 2010; Wright et al., 1999) regarding working memory impairment have been repeatedly observed in schizophrenia (Barch & Ceaser, 2012). Moreover, DLPFC plays a crucial role in encoding and is thus associated with episodic memory deficits in schizophrenia (Guo, Ragland, & Carter, 2019). The decrease in the GM volume of the left Superior Temporal Gyrus has also been consistently shown in schizophrenia and linked to both positive symptoms such as auditory hallucinations and thought disorder (Rajarethinam, DeQuardo, Nalepa, & Tandon, 2000) and cognitive impairment (Antonova et al., 2004). Furthermore, structural abnormalities in the Supramarginal and Lingual Gyri have been associated with deficits in verbal fluency, face memory, and motor speed (Geisler et al., 2015). Notably, the right Supramarginal gyrus is also crucial for social cognition (Silani et al., 2013)

and could be hyperactivated during perspective-taking in schizophrenia (Jáni & Kašpárek, 2018). In addition, altered activation in the Lingual Gyri has been previously associated with major depression (W.-N. Zhang, Chang, Guo, Zhang, & Wang, 2013). This finding is particularly interesting since both social cognition deficits (Nuechterlein et al., 2004) and depression symptoms (Hafner et al., 2005) are characteristic of schizophrenia but were not explicitly investigated by the present work. Thus, it supports the notion of neurocognition, social cognition, and negative symptoms being distinctive, yet strongly related to each other constructs that possibly share some common neuronal pathways (K.-H. Lee, Farrow, Spence, & Woodruff, 2004; Penn, Sanna, & Roberts, 2008; Sander et al., 2005). Surprisingly, hippocampal structures were not among the most important for the cognitive classification, despite their role in episodic memory in schizophrenia (Nelson et al., 1998). This result could be explained by the cognition index's construction, of which episodic memory makes up for only 25% (see Chapter 2.3.4.). The other 75% include executive functions, working memory, attention, and motor speed, all associated with prefrontal structures. Moreover, as described beforehand, episodic memory is strongly related to working memory and attention and consequently involves activation of the DLPFC (Guo et al., 2019), which we found to have reduced GM volume in schizophrenia.

Although the RF algorithm identified structures associated with cognition and schizophrenia, we could not find any distinctive neuronal patterns for the different cognitive subtypes. This finding is in line with previous work, suggesting that the structural differences between HighCog and LowCog might be too minor to detect (Gould et al., 2014). One possible explanation for this effect is the division of the SP sample into two groups, which, similarly to a median split, could have led to the overestimation of group differences (MacCallum, Zhang, Preacher, & Rucker, 2002). Future research of extreme groups (e.g., best and worst 10%) from a larger patient pool could reveal more clear results on neuronal correlates of cognitive heterogeneity in schizophrenia. Another unexpected result was the significantly lower GM volumes in the left Middle Frontal Gyrus in controls than SP and UR. This finding was so unusual that we reviewed the image quality again and could attribute it to artifacts in the left frontal lobe that were slightly more prominent in the healthy sample.

In contrast to previous results of abnormalities in brain morphology in healthy relatives of patients with schizophrenia (W. Zhang et al., 2020), our findings showed no group differences between UR and HC. UR even had numerically, but not significantly, larger GM volumes of the relevant regions than HC. We attribute this finding to the substantial difference

in group sizes - UR is more than two times smaller and more homogenous than HC. Furthermore, all included URs were highly educated, a factor positively correlating with GM volumes (Arenaza-Urquijo et al., 2013), which might further contribute to the effect.

4.3. Strengths

The present study is the first to predict cognition in schizophrenia using a machine learning paradigm on sMRI data of patients, unaffected relatives, and healthy controls. On the one hand, we incorporated previous evidence of cognitive heterogeneity in schizophrenia (Joyce & Roiser, 2007), partial heritability of neuropsychological deficits (Bora et al., 2014), and the common but compromised neurocognitive brain networks in patients compared to healthy controls (Minzenberg et al., 2009). On the other hand, we applied a less common machine learning method in psychiatry, an RF classifier (Dwyer et al., 2018). Hence, the current study both provides further evidence for the neurobiological pathways of cognitive deficits in schizophrenia and contributes to the methodological knowledge by demonstrating the feasibility of the RF classifier. Only one previous work applied similar methods to classify two cognitive subtypes in schizophrenia upon sMRI data (Gould et al., 2014). Here, the authors applied a VBM model only to patient data to discriminate between the predefined cognitive subgroups and achieved an accuracy initially slightly lower (<60%), which then increased to >80% for female patients after sex stratification. They also conducted several other VBM analyses to discriminate each cognitive profile from healthy controls (Gould et al., 2014). However, they did not perform the analysis including cognitive data from healthy participants. Thus, the present work complements their findings by showing the effective classification of patients' cognitive performance by including HC and UR data.

Another key strength of the current study is that the patient sample accurately represented the clinical picture of schizophrenia in Germany. For instance, we included in and outpatients with mild to moderate-severe symptoms, most of whom received antipsychotic medication. Furthermore, they were in different stages of the disease, with DOI ranging from less than one to over ten years. Moreover, the results on cognition of SP, HC, and UR mirrored previous findings patients' neuropsychological being ca. 2 SDs worse than in healthy participants with significant overlapping of both distributions (Keefe & Fenton, 2007). Therefore, we believe that our study has high external validity for schizophrenia.

Lastly, another advantage of the current work is the application of standard testing tools and, thus, the high comparability with previous research. For instance, we assessed cognitive performance with traditional tests used in general neuropsychological diagnostic (Lezak et al., 2012; Tewes, 1994) and are also part of specific test batteries for schizophrenia like RBANS (Wilk et al., 2004), BACS[3] (Keefe et al., 2004) and MCCB[4] (Nuechterlein & Green, 2006). Moreover, the tests are applied in numerous observational and treatment studies on cognitive deficits in schizophrenia (e.g., Hasan, Guse, et al., 2016; Malchow et al., 2016). The comparability is further increased by the assessment of psychopathology with PANSS (Kay et al., 1987) and SANS (Andreasen, 1989), which are standard tools in clinical research (T. Suzuki, 2011).

4.4. Limitations

The main critical point of the current work is the relatively small study sample of 127 participants, which could have limited the generalizability of our results. Although comparable with previous publications (for an overview, see Arbabshirani et al., 2017, page 146, Table 3), recent research demonstrated the disadvantages of studies with similar case numbers when applying multivariate pattern recognition tools (Dwyer et al., 2018; N. Tandon & Tandon, 2019). The sample size is especially crucial in works investigating heterogeneous groups, directly affecting prediction accuracy (Schnack & Kahn, 2016). A possibility to increase the findings' generalizability is cross-validation of the current model with an independent sample (Schnack & Kahn, 2016; N. Tandon & Tandon, 2019). Unfortunately, an independent dataset of schizophrenia patients with similar cognitive, imaging, and clinical variables was unavailable. In the future, however, we plan to validate our findings cooperating with the Exercise study (Maurus et al., 2020), which has an almost identical dataset but is still in the data acquisition phase.

Another critical point is the calculation Gini importance as future importance. Although widely used due to its low computation cost, it could lead to an inflation of the importance of continuous variables (Wright, Dankowski, & Ziegler, 2017). In future models, a correction could be applied to avoid this bias (Nembrini, König, & Wright, 2018)

[3] BACS: The Brief Assessment of Cognition in Schizophrenia
[4] MCCB: The MATRICS Consensus Cognitive Battery

Our findings could also be limited by the operationalization of neuropsychology and the definition of cognitive subgroups. As aforementioned, we used standard measures to assess cognitive deficits and increase comparability. Although feasible and effective in a clinical context, these traditional tests are often criticized for being unspecific (Snyder et al., 2015). We attempted to address this issue by constructing a global cognition index in line with the generalized cognitive deficit hypothesis (Braff et al., 1991; Gold & Dickinson, 2013). However, several authors have opposed this theory demonstrating more selective neuropsychological impairments in schizophrenia (Chapman & Chapman, 1989; Green et al., 2012). Most recently, Geisler et al. (2015) defined four cognitive subgroups with specific deficits and linked them to distinct structural and functional brain patterns. Therefore, applying more precise neuropsychological measures (Snyder et al., 2015) could help us elicit clearly defined subgroups and better understand the neural basis of cognitive heterogeneity in schizophrenia.

Moreover, the separation of the patient sample in HighCog and LowCog upon a data-driven cut-off value could also be problematic. First, as described in Chapter 4.2., a dichotomization of a continuous variable could cause several methodological issues such as information loss and overestimation of effect size (MacCallum et al., 2002). Second, despite using standard methods for setting the cut-off value (e.g., Keefe & Fenton, 2007), this method is still very oriented to the particular dataset and could lower results' generalizability.

Lastly, the RF algorithm did not include duration of illness, age of onset, and antipsychotic medication as features, all associated with structural brain alterations in schizophrenia (Guo et al., 2015; Hashimoto et al., 2018; van Erp et al., 2018) and thus, potential confounding variables. Despite demonstrating that these factors did not correlate with cognition or differ between cognitive profiles (see Chapter 3.1.2), we cannot make any assumptions about their impact on the classification. Moreover, we used only cross-sectional data, which could further limit the generalizability of the current findings.

4.5. Implications

The current findings have several implications for both treatment and research. First, they provide further empirical evidence of the neurobiological underprints of cognitive dysfunction and, consequently, new possible avenues to treat them. For instance, novel neurostimulation methods applied to the DLPFC could improve working memory in schizophrenia (Hasan, Guse, et al., 2016; Papazova et al., 2018). However, most studies focus

only on the prefrontal cortex (Hasan, Strube, Palm, & Wobrock, 2016). Our findings confirm the role of temporal, occipital, and parietal brain regions in cognitive processing and indicate them as possible stimulation targets. Future trials should investigate if brain stimulation of these areas would successfully treat cognitive deficits in schizophrenia.

Second, our findings underline the potential of cognitive profiling to tackle heterogeneity in schizophrenia (Chapman & Chapman, 1989). Here, we were able to determine critical brain regions by linking them to two neuropsychological subgroups. In addition, previous research linked cognitive dysfunction to several candidate genes (e.g., DISC1) in schizophrenia (Zai et al., 2017). Indeed, cognitive impairment and specific deficits (e.g., working memory) emerged in recent years as possible endophenotypes for genetic liability in schizophrenia (Gur, 2007; Park & Gooding, 2014; Snitz et al., 2006). For instance, a recent work applied an RF algorithm to predict six cognitive subtypes upon genetic data (Zheutlin et al., 2018). Therefore, combining cognitive, molecular, and imaging findings with machine learning algorithms is the next step in characterizing distinctive schizophrenia endophenotypes. It could even help us move away from the broad construct of schizophrenia towards a psychosis spectrum with several subgroups with specific symptom patterns (Guloksuz & van Os, 2018; N. Tandon & Tandon, 2019).

Finally, the current work provides a basis for future research. Here, we predicted cognition in schizophrenia, using only volumetric brain data. However, previous research linked neuropsychological deficits to further parameters such as cortical thickness (Ehrlich et al., 2011), WM density (measured with DTI) (Dwork, Mancevski, & Rosoklija, 2007), and resting-state connectivity (Sheffield & Barch, 2016). Moreover, various socio-demographic factors, such as educational background (Heinrichs, 2005), a history of childhood trauma (Aas et al., 2014), are also associated with neuropsychological functioning. Combining biological and demographic parameters into the prediction model would deepen our understanding of cognitive deficits in schizophrenia. Further research should also include “hot” neuropsychological functions such as emotional processing and social cognition, which are also compromised in patients with schizophrenia (Kohler & Martin, 2006; Penn et al., 2008). Increasing the modalities of both features and dependent variables would not only benefit our theoretical understanding but will also improve our prediction model. Indeed, previous studies have demonstrated that the inclusion of multi-modal data and the combination of several machine learning techniques increase classification accuracy (de Filippis et al., 2019; Sarica et al., 2017). Therefore, future research with prediction models combining several machine

learning tools and incorporating multi-modal parameters on cognition in schizophrenia are much needed.

4.6. Conclusions and Outlook

Overall, we demonstrated that an RF algorithm with combined sMRI data from patients, healthy relatives, and controls could successfully classify two cognitive profiles in schizophrenia with BAC of 69%. Moreover, the prediction model replicated previous findings of prefrontal, temporal, parietal, and occipital structures playing a pivotal role in neuropsychological functions like working memory, attention, and verbal processing (Antonova et al., 2004; Barch & Ceaser, 2012; Sommer et al., 2001). Although the GM volumes did not differ between the two cognitive profiles, they were significantly smaller in the patient group than in the other two study samples. Thus, the cortical structures emerged as potential biomarkers for schizophrenia, and their association with neuropsychological deficits underlines the importance of cognition in etiology models in schizophrenia (e.g., Howes & Murray, 2014; M. J. Owen et al., 2011). However, the current findings should be considered with caution since 69% BAC is rather low in a clinical context, and the relatively small study sample limits the generalizability.

Nevertheless, the present work provides further evidence of machine learning's potential to resolve heterogeneity in schizophrenia and define subgroups with distinctive symptom patterns (N. Tandon & Tandon, 2019). Future research should combine multimodal imaging, genetics, and socio-cultural background with machine learning methods to large samples with longitudinal data to fully understand the mechanisms of cognitive deficits in schizophrenia and help create novel approaches for their treatment.

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Appendix A:

Nr	AAL label	Brain Region
1.	Precentral_L	Precental gyrus (left)
2.	Precentral_R	Precental gyrus (right)
3.	Frontal_Sup_L	Superior frontal gyrus, dorsolateral (left)
4.	Frontal_Sup_R	Superior frontal gyrus, dorsolateral (right)
5.	Frontal_Sup_Orb_L	Superior frontal gyrus, orbital part (left)
6.	Frontal_Sup_Orb_R	Superior frontal gyrus, orbital part (right)
7.	Frontal_Mid_L	Middle frontal gyrus (left)
8.	Frontal_Mid_R	Middle frontal gyrus (right)
9.	Frontal_Mid_Orb_L	Middle frontal gyrus, orbital part (left)
10.	Frontal_Mid_Orb_R	Middle frontal gyrus, orbital part (right)
11.	Frontal_Inf_Oper_L	Inferior frontal gyrus, opercular part (left)
12.	Frontal_Inf_Oper_R	Inferior frontal gyrus, opercular part (right)
13.	Frontal_Inf_Tri_L	Inferior frontal gyrus, triangular part (left)
14.	Frontal_Inf_Tri_R	Inferior frontal gyrus, triangular part (right)
15.	Frontal_Inf_Orb_L	Inferior frontal gyrus, orbital part (left)
16.	Frontal_Inf_Orb_R	Inferior frontal gyrus, orbital part (right)
17.	Rolandic_Oper_L	Rolandic operculum (left)
18.	Rolandic_Oper_R	Rolandic operculum (right)
19.	Supp_Motor_Area_L	Supplementary motor area (left)
20.	Supp_Motor_Area_R	Supplementary motor area (right)
21.	Olfactory_L	Olfactory cortex (left)
22.	Olfactory_R	Olfactory cortex (right)
23.	Frontal_Sup_Medial_L	Superior frontal gyrus, medial (left)
24.	Frontal_Sup_Medial_R	Superior frontal gyrus, medial (right)
25.	Frontal_Mid_Orb_L	Superior frontal gyrus, medial orbital (left)
26.	Frontal_Mid_Orb_R	Superior frontal gyrus, medial orbital (right)
27.	Rectus_L	Gyrus rectus (left)
28.	Rectus_R	Gyrus rectus (right)
29.	Insula_L	Insula (left)
30.	Insula_R	Insula (right)

31.	Cingulum_Ant_L	Anterior cingulate and paracingulate gyri (left)
32.	Cingulum_Ant_R	Anterior cingulate and paracingulate gyri (right)
33.	Cingulum_Mid_L	Median cingulate and paracingulate gyri (left)
34.	Cingulum_Mid_R	Median cingulate and paracingulate gyri (right)
35.	Cingulum_Post_L	Posterior cingulate gyrus (left)
36.	Cingulum_Post_R	Posterior cingulate gyrus (right)
37.	Hippocampus_L	Hippocampus (left)
38.	Hippocampus_R	Hippocampus (right)
39.	ParaHippocampal_L	Parahippocampal gyrus (left)
40.	ParaHippocampal_R	Parahippocampal gyrus (right)
41.	Amygdala_L	Amygdala (left)
42.	Amygdala_R	Amygdala (right)
43.	Calcarine_L	Calcarine fissure and surrounding cortex (left)
44.	Calcarine_R	Calcarine fissure and surrounding cortex (right)
45.	Cuneus_L	Cuneus (left)
46.	Cuneus_R	Cuneus (right)
47.	Lingual_L	Lingual gyrus (left)
48.	Lingual_R	Lingual gyrus (right)
49.	Occipital_Sup_L	Superior occipital gyrus (left)
50.	Occipital_Sup_R	Superior occipital gyrus (right)
51.	Occipital_Mid_L	Middle occipital gyrus (left)
52.	Occipital_Mid_R	Middle occipital gyrus (right)
53.	Occipital_Inf_L	Inferior occipital gyrus (left)
54.	Occipital_Inf_R	Inferior occipital gyrus (right)
55.	Fusiform_L	Fusiform gyrus (left)
56.	Fusiform_R	Fusiform gyrus (right)
57.	Postcentral_L	Postcentral gyrus (left)
58.	Postcentral_R	Postcentral gyrus (right)
59.	Parietal_Sup_L	Superior parietal gyrus (left)
60.	Parietal_Sup_R	Superior parietal gyrus (right)
61.	Parietal_Inf_L	Inferior parietal, but supramarginal and angular gyri (left)

62.	Parietal_Inf_R	Inferior parietal, but supramarginal and angular gyri (right)
63.	SupraMarginal_L	Supramarginal gyrus (left)
64.	SupraMarginal_R	Supramarginal gyrus (right)
65.	Angular_L	Angular gyrus (left)
66.	Angular_R	Angular gyrus (right)
67.	Precuneus_L	Precuneus (left)
68.	Precuneus_R	Precuneus (right)
69.	Paracentral_Lobule_L	Paracentral lobule (left)
70.	Paracentral_Lobule_R	Paracentral lobule (right)
71.	Caudate_L	Caudate nucleus (left)
72.	Caudate_R	Caudate nucleus (right)
73.	Putamen_L	Lenticular nucleus, putamen (left)
74.	Putamen_R	Lenticular nucleus, putamen (right)
75.	Pallidum_L	Lenticular nucleus, pallidum (left)
76.	Pallidum_R	Lenticular nucleus, pallidum (right)
77.	Thalamus_L	Thalamus (left)
78.	Thalamus_R	Thalamus (right)
79.	Heschl_L	Heschl gyrus (left)
80.	Heschl_R	Heschl gyrus (right)
81.	Temporal_Sup_L	Superior temporal gyrus (left)
82.	Temporal_Sup_R	Superior temporal gyrus (right)
83.	Temporal_Pole_Sup_L	Temporal pole: superior temporal gyrus (left)
84.	Temporal_Pole_Sup_R	Temporal pole: superior temporal gyrus (right)
85.	Temporal_Mid_L	Middle temporal gyrus (left)
86.	Temporal_Mid_R	Middle temporal gyrus (right)
87.	Temporal_Pole_Mid_L	Temporal pole: middle temporal gyrus (left)
88.	Temporal_Pole_Mid_R	Temporal pole: middle temporal gyrus (right)
89.	Temporal_Inf_L	Inferior temporal gyrus (left)
90.	Temporal_Inf_R	Inferior temporal gyrus (right)
91.	Cerebelum_Crus1_L	Crus I of cerebellar hemisphere (left)
92.	Cerebelum_Crus1_R	Crus I of cerebellar hemisphere (right)
93.	Cerebelum_Crus2_L	Crus II of cerebellar hemisphere (left)

94.	Cerebelum_Crus2_Rs	Crus II of cerebellar hemisphere (right)
95.	Cerebelum_3_L	Lobule III of cerebellar hemisphere (left)
96.	Cerebelum_3_R	Lobule III of cerebellar hemisphere (right)
97.	Cerebelum_4_5_L	Lobule IV, V of cerebellar hemisphere (left)
98.	Cerebelum_4_5_R	Lobule IV, V of cerebellar hemisphere (right)
99.	Cerebelum_6_L	Lobule VI of cerebellar hemisphere (left)
100.	Cerebelum_6_R	Lobule VI of cerebellar hemisphere (right)
101.	Cerebelum_7b_L	Lobule VIIB of cerebellar hemisphere (left)
102.	Cerebelum_7b_R	Lobule VIIB of cerebellar hemisphere (right)
103.	Cerebelum_8_L	Lobule VIII of cerebellar hemisphere (left)
104.	Cerebelum_8_R	Lobule VIII of cerebellar hemisphere (right)
105.	Cerebelum_9_L	Lobule IX of cerebellar hemisphere (left)
106.	Cerebelum_9_R	Lobule IX of cerebellar hemisphere (right)
107.	Cerebelum_10_L	Lobule X of cerebellar hemisphere (left)
108.	Cerebelum_10_R	Lobule X of cerebellar hemisphere (right)
109.	Vermis_1_2	Lobule I, II of vermis
110.	Vermis_3	Lobule III of vermis
111.	Vermis_4_5	Lobule IV, V of vermis
112.	Vermis_6	Lobule VI of vermis
113.	Vermis_7	Lobule VII of vermis
114.	Vermis_8	Lobule VIII of vermis
115.	Vermis_9	Lobule IX of vermis
116.	Vermis_10	Lobule X of vermis

Appendix B:

Random Forest Classification Parameters:

- bootstrap=True
- class_weight=None
- criterion='gini'
- max_depth=20
- max_features='auto'
- max_leaf_nodes=None
- min_impurity_decrease=0.0
- min_impurity_split=None
- min_samples_leaf=1
- min_samples_split=2
- min_weight_fraction_leaf=0.0
- n_estimators=380
- n_jobs=None
- oob_score=False
- random_state=12
- verbose=0
- warm_start=False

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Affidavit

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN | Promotionsbüro Medizinische Fakultät | MMRS

Eidesstattliche Versicherung

Papazova, Irina

Name, Vorname

Ich erkläre hiermit an Eides statt,

dass ich die vorliegende Dissertation mit dem Titel

Predicting cognition in schizophrenia applying machine learning to structural MRI data

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, 10.03.2021

Ort, Datum

Irina Papazova

Unterschrift Doktorandin bzw. Doktorand

Publications

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