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Links between adherence behavior and cognition in patients with bipolar disorder and schizophrenia

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Fragebogen zur medikamentösen Behandlung
Fragebogen Medikamenteneinnahme/ Adhärenz
Clinician Inventory of Depressive Symptomatology (IDS-C)
Positiv- und Negativ-Syndromskala (PANSS)
Young Mania Rating Scale (YMRS)
Clinical Global Impression (CGI)
Skala zur Globalen Erfassung des Funktionsniveaus (GAF)
Test Neuropsychologie

LIST OF ABBREVIATIONS

BDI-II	Becks Depression Inventory, Revision of the BDI
BMI	Body Mass Index
D1/ D2/ D3	Cognitive domains D1 - D3
DALYs	Disability-adjusted Life Years
df 1/2	Degrees of Freedom
DNA	Deoxyribonucleic Acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DST	Digit Symbol Test
GAF	Global Assessment of Functioning
HC	Heteroskedasticity-consistent
ICD-10	International Statistical Classification of Diseases
IDS-C30	Clinician Inventory of Depressive Symptomatology
Medication sum	Sum of prescribed psychiatric medication
PANSS	Positive and Negative Symptom Scale
RNA	Ribonucleic Acid
SC B	Standardized Coefficient
SD	Standard deviation
SE	Standard error
SCID	Structured Clinical Interview for DSM-5
TMT	Trail-Making Test
USC B	Unstandardized Coefficient ß
VDS	Verbal Digit Span
WHO	World Health Organization
YMRS	Young Mania Rating Scale

ZUSAMMENFASSUNG

Hintergrund: Die medikamentöse Adhärenz ist ein wesentliches Element bei der adäquaten Behandlung von chronischen Krankheiten. Leider sinkt insbesondere in der Psychiatrie die Adhärenz nach maximal sechs Monaten auf unter 50 %. Da kognitive Beeinträchtigungen ein Kernsymptom bei bipolaren und psychotischen Erkrankungen sind, wollten wir mit dieser Studie die Auswirkungen der Medikamentenadhärenz auf die Kognition und die globale Funktion (GAF) untersuchen.

Methode: PsyCourse, eine multizentrische Längsschnittstudie in Deutschland und Österreich, wurde für eine lineare Regression zweier Diagnosegruppen mit bipolaren und psychotischen Störungen verwendet (*N* = 862). Die Medikamentenadhärenz wurde anhand eines Fragebogens zur Selbstbeurteilung bewertet, und zur Beurteilung der kognitiven Leistung wurde eine umfassende neurokognitive Testbatterie eingesetzt (trail-making test, verbal digit span, digit symbol test). Informationen zur aktuellen Psychopathologie wurden mit Hilfe von PANSS, YMRS, IDS-C30 und GAF erhoben.

Ergebnisse: Adhärenz, Alter, Medikamentensumme und Diagnosegruppen erklärten einen signifikanten Anteil der Varianz im GAF (R^2_a = 0,153; F(5, 808) = 25,51, p <.001). Die Prädiktoren unter Beachtung der jeweiligen Symptome waren statistisch signifikant für den kognitiven Bereich "D3 - psychomotorische Geschwindigkeit" in der Gruppe der bipolaren Störungen: (R^2_a = 0,237; F(6, 328) = 15,88, p <.001) und der Gruppe der psychotischen Störungen: (R^2_a = 0,186; F(7, 404) = 12,79, p <.001).

Schlussfolgerung: Die medikamentöse Adhärenz hat keinen Einfluss auf die Kognition, aber auf die globale Funktionsfähigkeit bei psychiatrischen Patientinnen und Patienten. Sowohl bei Menschen mit bipolarer Erkrankung als auch bei Individuen mit psychotischer Erkrankung war die kognitive Funktion unabhängig von der Adhärenz, wurde aber durch das Alter und die Summe der eingenommenen Medikamente beeinflusst.

ABSTRACT

Background: Medication-adherence is an essential element for adequate treatment of chronic disorders. Unfortunately, especially in the psychiatric setting, adherence drops to less than 50 % after a maximum of six months. Since cognitive impairment is a core symptom in bipolar and psychotic disorders, with this study we sought to investigate the effects of medication adherence on cognition and global function.

Method: PsyCourse, a multicenter longitudinal study in Germany and Austria, was used for linear regression of two broad diagnostic groups with bipolar and psychotic disorders (*N* = 862). Treatment adherence was evaluated using a self-assessment questionnaire, and a comprehensive neurocognitive test battery was used to assess cognitive performance (trail-making test, verbal digit span, and digit symbol test). Information on the current clinical state was collected using PANSS, YMRS, IDS-C30, and GAF.

Results: Adherence, age, medication sum, and diagnostic groups explained a significant proportion of the variance in GAF (R^2_a= 0.153; $F(5, 808) = 25.51$, $p < .001$). Our predictors adjusted for symptoms were statistically significant on cognitive domain "D3 - psychomotor speed" in the bipolar disorder group: (R^2_a = 0.237; $F(6, 328) = 15.88$, $p < .001$) and psychotic disorder group: (R^2_a = 0.186; $F(7, 404) = 12.79$, $p < .001$).

Conclusion: Medication adherence does not influence cognition, but global functioning in psychiatric patients. In both, bipolar disorder and psychotic disorder, cognitive function was independent of medication adherence but was influenced by age and sum of taken medication.

1. Introduction

1.1 Background

In 2016, more than 1 billion people worldwide were affected by mental illness and addiction. Measured in DALYs (disability-adjusted life years), mental illness accounts for 7% of the total global burden of disease and 19% of all years lived with disability. Furthermore, mental illness accounts for around 40% of absence from work in many countries. The relative proportion of mental illness has increased in recent decades, partly due to stigma and lack of treatment (Rehm and Shield, 2019). The widespread stigma associated with mental health problems leads to discrimination and exclusion, affects people's self-esteem and leads to disruption of employment and family relationships with all its far-reaching consequences (ministerial WHO conference, 2006). In addition to the individual negative consequences, the costs relevant to society should not be underestimated. Whereas rising costs of psychiatric disorders are estimated to increase in the United States from 2.5 trillion US dollars in 2010 to 6.0 trillion US dollars in 2030 (Semahegn et al., 2018).

Many effective substances have been discovered to treat mental illness, but a considerable number of patients does not take their medication regularly. 56% of patients with schizophrenia, 50% of patients with severe depression and 44% of patients with bipolar disorder are considered non-adherent (Semahegn et al., 2018). Adherence is an essential basis for adequate treatment of diseases in general and chronic diseases in particular. Whereby adherence rate is generally lower for chronic diseases and drops further after 6 months for most patients (Osterberg and Blaschke, 2005). Adherence, i.e. the adherence to the therapeutic goals set jointly by the patient and the doctor with the patient's informed consent as a prerequisite, represents the basis of therapeutic success and plays a significant role in the treatment of mental illnesses. The concept of adherence can be seen as a "systemic approach". In contrast to adherence, compliance, as an outdated term, represents "adherence to therapy" and makes the patient solely responsible for the success of his or her therapy by following a therapy concept which is characterized by the authority and sole decision-making power of the doctor (Gray et al., 2002).

The WHO defines non-adherence with medication as "a case in which a person's behavior in taking medication does not correspond with agreed recommendations from health personnel" (Osterberg and Blaschke, 2005). Non-adherence can have various reasons and can be intentional or unintentional. However, in all cases, it must be seen as the responsibility of

psychiatrists and health care professionals to address the various factors of lack of adherence and to provide patients with an easier route to adequate treatment. The consequences of lack of adherence can have a severe impact on the individual patient, as it can lead to relapses, recurrences, suicidal tendencies and, as a consequence, frequent hospitalization and an unfavorable course of disease with a reduced quality of life and negative social consequences. Moreover, it increasingly wastes health resources and money, with 33 to 69 percent of all medication-related hospitalizations resulting from poor medication adherence, costing 1.25 billion euros a year in Europe. To improve the treatment of mental illness, adherence should be strengthened, especially regarding medication. For this purpose, both the treatment team's vigilance and the understanding of the risk factors of lack of adherence are essential. The adherence behavior can be discussed during the interview, measured by self-assessment or external assessment or by monitoring the medication levels (Lindström and Bingefors, 2000; Lacro et al., 2002; Osterberg and Blaschke, 2005; Cutler et al., 2018). A serious problem in psychiatric chronic illness is the even lower rate of adherent patients taking long-term medication. For two psychiatric disorders in particular, schizophrenia and bipolar disorder, the number of adherent patients in studies is estimated to be about 40 - 50 %, with some variance due to survey methods (García et al., 2016).

1.2 Etiology and diagnoses

A multifactorial etiology of affective disorders and schizophrenia is assumed, i.e. the presence of genetic, neurobiological and psychosocial factors. The addition of these factors is summarized in the so-called vulnerability-stress model (Möller et al., 2015). Besides the unchangeable and disease-specific genetic and neurobiological factors there are so-called life events, which are frequently found before the onset of the disease. Typical life events include the loss of important attachment figures, ongoing conflicts, divorce, puerperium, changes in habitual lifestyles and traumatization. The impact of life events can vary by the individual stress response (Härter and Schneider, 2012). Family, twin and adoption studies have shown a genetic disposition, especially for bipolar affective disorders and schizophrenia. The morbidity risk for a bipolar disorder if both parents do have an affective disorder is genetical 50 - 60% for their children. The recent genome-wide association study (GWAS) by Mullins et al. identified 64 genomic loci, 33 of which are new discoveries, resulting in a polygenic risk with epigenetic mechanisms such as Polymorphism in e.g. Transporters or Receptors.

Interestingly, 15 of the genes were clearly related to bipolar disorder through gene expression, including significant signal enrichment found in genes that are targets of psychotropic drugs (HTR6, MCHR1, DCLK3 and FURIN) (Mullins et al., 2021). But still, genetic disposition doesn't lead to 100 % penetrance. Other factors must be added to the genetic disposition within the framework of a vulnerability model.

In psychotic disorders, the basis of these factors is currently a complex mode of inheritance involving a large number of genetic variants that can be regarded as a kind of risk genes. Through genome-wide association studies with patients all over the world, first approaches of a transdiagnostic clinical reclassification with disease subgroups and adjusted prognostic values could be formed in the meantime (Adorjan et al., 2021). Through technical progress, over 100 gene loci associated with psychotic illness have been found worldwide to date (Yao et al., 2021; Blokland et al., 2022).

1.2.1 Psychotic disorder

The term schizophrenia (ICD-10 F20.X), i.e. the "splitting off of the mind", was introduced by the Swiss psychiatrist Paul Eugen Bleuler and is composed of the ancient Greek words σχίζειν (schizein) = to split off and φρήν (phrén) = soul (Bandelow et al., 2013).

Lifetime prevalence worldwide is about 1 %, and the lifetime risk is the same for both sexes, although men fall ill on average five years earlier than women. About 20 - 30% of patients in psychiatric hospitals have schizophrenia. People with schizophrenia have about two times higher mortality due to suicide and a higher risk of accidents or crime. Life expectancy is shortened by about 15 years (Nickl-Jockschat and Schneider, 2012). Patients with schizophrenia suffer from alterations in perception, thoughts, mood behavior, and psychomotor skills. Symptoms are characterized in positive and negative symptoms. The main positive symptoms are hallucinations (predominantly acoustic), delusions and distortions of self-experience. Negative symptoms comprise blunted affect, anhedonia, poverty of speech, lack of motivation with social withdrawal, and psychomotor alterations (amboss.de, 2020).

Based on the criteria of the ICD-10 catalogue, a distinction is made between "classic" paranoid schizophrenia, other forms of schizophrenia such as hebephrenic and catatonic schizophrenia, undifferentiated schizophrenia and post-schizophrenic depression (Bandelow et al., 2013).

To diagnose paranoid schizophrenia, at least one of the ICD-10 diagnostic criteria must be continuously met for at least one-month. Schizophrenia should not be diagnosed in cases of apparent brain disease, during intoxication or substance withdrawal (DGPPN e.V., 2019).

For schizophrenia, risk factors besides genetic disposition are perinatal damage also known as “minimal brain dysfunction” and viral infections perinatal or as newborn. Neuropathologically, a brain development disorder is assumed as an additional vulnerability factor with progressive brain changes in the further course of the disease. These lead to macro and micro changes, i.e. also to a disturbed synaptic function. In addition, reduced blood flow and the associated hypometabolism can be observed in so-called “hypofrontality”. This can explain deficits of cognition (Möller et al., 2015). Psychosocial overstimulation, e.g. through emotional tension or occupational stress, seems to favor the occurrence of schizophrenic symptoms. Whereas psychosocial understimulation promotes the development of a residual state characterized by negative symptoms (Möller et al., 2015). Typically, first episodes of psychosis occur in late adolescence or early adulthood, often preceded by a prodromal phase. Thus, some studies show that cognitive impairment is already present in childhood, and children who will develop schizophrenia already start school with a full grade lower level of functioning than their comparison group. This difference even continues to increase until high school graduation (Kahn and Keefe, 2013; Keefe, 2014; Owen et al., 2016). It is interesting to note that schizophrenia occurs primarily in lower socio-economic status, and according to the 'drift hypothesis', it can be assumed that this is a case of slipping into lower social classes in the course of an illness (Möller et al., 2015).

In the diagnostic group of an acute transient psychotic disorder (ICD-10: F23.X), there is a heterogeneous group of disorders that do not meet the criteria of schizophrenia. These include acute schizophreniform psychotic disorder (F23.2) with symptoms of schizophrenia lasting less than a month, and acute polymorphic psychotic disorder (F23.0, F23.1) with disorders that begin and end abruptly, such as hallucinations, delusions and perceptual disorders, which can change within hours to days. They present similar to schizophrenia, but never exceed the diagnostic threshold of schizophrenia (Bandelow et al., 2013).

In schizoaffective disorder (ICD-10: F25.X), both symptoms of schizophrenia and symptoms of affective disorder exist simultaneously or separated by only a few days within a single episode of illness. The degree of severity of these symptoms alone would not justify a psychotic or affective disorder diagnosis. Lifetime prevalence is about 0.5 - 0.8% and about 10 - 30% of all

psychiatric hospital admissions due to psychotic disorders are schizoaffective disorders (Nickl-Jockschat and Schneider, 2012).

1.2.2 Affective disorder

Affective disorders are a group of diseases whose main characteristics include a pronounced change in mood and energy. In addition to the division into unipolar and bipolar courses, the ICD-10 distinguishes episodic affective disorders, i.e. with manic and depressive episodes, from chronically persistent affective disorders. Unipolar affective disorders include depressive disorder and mania. In affective disorders, the neurobiological risk factors include the monoamine-hypothesis, in which patients show a lower concentration of noradrenalin or serotonin, as well as the modification of the monoamine-hypothesis into a disbalance of different neurotransmitters and sensitivity changes of the receptors (Härter and Schneider, 2012).

Recurrent depressive disorder (ICD-10: F33.X) is one of the most common mental illnesses and is increasing worldwide with about one in four women and one in eight men becoming depressed during their lifetime. According to the Global Burden of Disease, depression is expected to cause the highest burden of disease in industrialized countries by 2030 (Rehm and Shield, 2019). The lifetime prevalence of a clinically relevant depressive disorder is about 16 - 20% worldwide, with about half of patients starting the disease before the age of 31.

According to the diagnostic guidelines (ICD-10), the main clinical features of a depressive episode is a depressed mood and lack of energy. For at least two weeks the patient must present with at least two of the three main symptoms such as a depressed mood, loss of interest as well as anhedonia and lack of energy. At least two additional symptoms must also be apparent during this period. These include, for example, reduced concentration and attention, reduced self-esteem and self-confidence, feelings of guilt and worthlessness, as well as pessimistic prospects, suicidal thoughts and actions, sleep disturbance and reduced appetite. Furthermore, the patient may suffer from psychotic symptoms such as nihilistic delusions. The severity of the depressive episode depends on the number of main and additional symptoms. The medical history must not include a hypomanic or manic episode and the depressive episode must not be due to substance abuse or an organic mental disorder. If the patient's medical history includes at least one other depressive episode in addition to

the index episode, this corresponds to the diagnosis of a recurrent depressive disorder (Härter and Schneider, 2012).

Mania (ICD-10: F30.X) in the sense of unipolar disorder is rare, its lifetime prevalence is about 0.2 - 0.3% in the general population. Both sexes are affected to the same extent, with the first occurrence occurring between the ages of 20 and 30. The main characteristic of a manic episode is a situationally inadequate euphoric mood with increased energy, activity and irritability. In this phase, it is not uncommon for the patient itself and others to be endangered by an increased risk behavior and to experience social difficulties such as separations, financial hardship and loss of employment, so that the positive mood is often overshadowed by far-reaching negative consequences. Furthermore, the patient may suffer from psychotic symptoms such as delusions of grandeur. According to the diagnostic guidelines (ICD-10), the mood must be predominantly elevated or irritable for at least one week, with at least three of the following symptoms present and with significant impairment of daily living: Increased energy or psychomotor restlessness, increased talkativeness to logorrhea, racing thoughts, loss of normal inhibitions, reduced need for sleep, exaggerated sense of well-being and self-confidence, distractibility, reckless or risky behavior and increased libido or sexual activity. Similar to depression, the episode must not be due to substance abuse or organic mental illness. If the criteria for a manic episode are not sufficiently fulfilled, the episode is called a hypomanic episode (Härter and Schneider, 2012).

Bipolar affective disorder (ICD-10: F31.X) must be distinguished from unipolar disorders, as both (hypo)manic and depressive or mixed episodes are present in the medical history. Their lifetime prevalence is stated as 3 - 5 % in the general population (amboss.de, 2019). The Diagnostic and Statistical Manual of Mental Disorders (Statistical Manual of Mental Disorders, Fourth Edition - DSM-IV-TR) also distinguishes between bipolar I disorder, which has a history of depressive and manic episodes, and bipolar II disorder with a history of depressive and hypomanic episodes. There are usually symptom-free intervals between the episodes, and if there are at least four mood changes per year, one also speaks of "rapid cycling" (Härter and Schneider, 2012).

1.3 Adherence behavior and cognition

Cognition is considered a core symptom in both psychotic and bipolar disorders and is enumerated, among numerous others, as a factor in medication non-adherence (Semahegn

et al., 2018). Regarding schizophrenia and adherence behavior, the results of a study by Kim et al. additionally suggest a strong association between impaired disease insight and nonadherence to antipsychotic medication in schizophrenia (Kim et al., 2020). Semahegn et al. indicated various risk factors for reduced adherence behavior in general. Sociodemographic characteristics such as unemployment, lower educational attainment and age (under 34 years and over 60) pose a risk for lack of adherence. Furthermore, comorbidities and substance abuse reduce adherence. Treatment-related factors such as adverse effects, drug therapy complexity, and the doctor-patient relationship's quality also play an essential role. Other important factors, especially among psychiatric patients, are attitudes towards drugs, perceived stigma and lack of understanding of their disease and cognitive deficits (Semahegn et al., 2018). The APA dictionary of Psychology defines *cognition* as "all forms of knowing and awareness, such as perceiving, conceiving, remembering, reasoning, judging, imagining, and problem solving. Along with affect and conation, it is one of the three traditionally identified components of mind" (Vandebos, 2021). In this diploma thesis, *cognition* and *cognitive impairment* reflects attention, memory, knowledge acquisition, reasoning, processing speed and executive function. The literature shows that patients with bipolar disorder and psychotic disorder perform worse than healthy controls on a variety of neurocognitive tests (Kahn and Keefe, 2013; Ceylan et al., 2020).

Cognitive deficits are regarded as a relevant symptom of many mental illnesses (Heinrichs and Zakzanis, 1998; Nakagome, 2017; Douglas et al., 2018). Nevertheless, there has been little research on the relationship between neurocognitive impairment and adherence in psychiatric disorders. In a review by Spiekermann et al., in eight of 18 studies comparing adherence behavior and cognition in patients with schizophrenia, a positive correlation between poorer cognitive performance and lower medication adherence was found. Cognitive impairment occurs in both psychiatric disorders, but differs in its severity. In psychotic disorders, it occurs as a persistent core symptom and thus leads to far-reaching effects on life. Approximately 60 – 70 % of patients with psychotic disorder are affected by cognitive impairment. The major disease influences were reported in the areas of verbal memory, action intelligence, sustained attention, and word fluency (Heinrichs and Zakzanis, 1998; Spiekermann et al., 2011). According to Ceylan et al., Schizophrenia patients showed significant difference in all neurocognitive domains, except working memory. In bipolar disorder, on the other hand, cognitive impairment appears to be primarily phase-dependent

and thus changing. Bourne et al. found in a meta-analysis of 31 studies (n = 2876) that bipolar patients, even in a euthymic phase, had moderate cognitive impairment on standard neuropsychological tests (Keefe, 2008; Bourne et al., 2013; Keefe, 2014; Ceylan et al., 2020). Martinez-Aran et al. found that nonadherent psychotic disorder patients have greater cognitive impairments in verbal learning tasks and some executive functions, as well as greater deterioration in spatial memory and their ability to inhibit interference than adherent patients. However, the causal interference between cognitive impairment and adherence remains unclear (Martinez-Aran et al., 2009). As reported by Saykin et al., cognitive impairments in psychotic disorder emerge before the onset of antipsychotic therapy; whereas according to Fuller et al., they begin in childhood or adolescence (Saykin et al., 1994; Fuller et al., 2002). Thus, there is evidence that negative and cognitive symptoms may result from abnormalities in glutamate transmission. In conclusion, however, our understanding of the neurobiology of schizophrenia, as well as neuroanatomical changes associated with the disorder, is largely incomplete (Owen et al., 2016). In the STEP-BD prospective cohort study also on patients with bipolar disorder (n=3640) by Perlis et al., remarkably only memory impairment was the sole significant predictor of non-adherence. Which may suggest that non-adherence is more a consequence of the cognitive deficits that are increasingly recognized in bipolar disorder (Perlis et al., 2010).

Therefore, this question's investigation is of particular interest, especially in a large and cross-diagnostic patient cohort. The PsyCourse study is an ideal resource for this purpose due to the high number of cases and the comprehensive phenotyping of a heterogeneous, cross-diagnostic patient cohort (Budde et al., 2019). The measurement of medication adherence in the form of a questionnaire provides a scientific insight into adherence, but it should be noted that adherence or non-adherence does not only refer to medication intake. Numerous important therapy-offers besides physical treatment can be taken up by affected persons and consist above all of psychotherapeutic and also psychosocial treatment which can affect quality of life positively.

1.4 Research question

With this project, we aimed to answer the following research questions:

1. Does medication adherence affect cognition?
2. Does medication adherence affect psychological, social and occupational functional areas measured by GAF?
3. Is there any difference in adherence affecting cognition within the diagnosis groups bipolar disorder and psychotic disorder?

2. Material and methods

2.1 The PsyCourse Study

The PsyCourse study, also called "Genome-wide analysis of genotype-phenotype relationships in the long-term course of psychosis", was launched in 2011 as a multicenter study in Germany and Austria (PsyCourse Team, 2019). This study aims to investigate genetic factors and environmental influences on the development and course of mental illness to contribute to the development of more efficient therapy and prevention. Study participants are patients from the affective and psychotic spectrum and healthy control persons. The study protocol includes extensive phenotypic surveys and the collection of biomaterial (DNA, RNA, plasma and serum) at four spaced points in time (every six months) over 18 months. Between 2011 and 2019, 1320 patients and 466 healthy controls were included at 20 different collaborating recruitment centers. Thus, the PsyCourse study represents an unique resource for exploring the complex relationship between psychopathology and biology in severe mental disorders in the longitudinal course and with a large numbers of participants and is not limited to traditional diagnostic boundaries. PsyCourse relies on collaboration in data collection and invites the worldwide exchange of data through the Open Data approach (Budde et al., 2019). Phenotypic data from the first study visit (data release v4.0, March 2020) was used to answer the scientific questions.

2.2 Study participants

Only cases with available information on adherence behavior and cognitive test performance were selected for this study. The final sample included 1103 subjects with the diagnoses of schizophrenia (F20.X), acute and transient psychotic disorder (F23.X), schizoaffective disorder (F25.X), bipolar disorder (F31.X), manic episode (F30.X) and recurrent depressive disorder (F33.X). The diagnostic classification was based on the structured clinical interview for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) diagnoses (SCID). Additionally, medical reports with ICD-10 diagnoses were used to form a consensus diagnosis.

2.3 Phenotypic data

The socio-demographic data included information on sex, age, year of birth, age of parents at birth, marital status (married, married but separated, single, divorced, widowed), status of the relationship, children and siblings, schooling and professional qualifications, employment and absenteeism.

In addition, clinical information was collected on diagnosis, duration of illness, psychopathology, functioning, current treatment setting, suicide ideas and suicide attempts, comorbidities such as physical illnesses or addictions, use of illegal drugs, alcohol consumption and current medication (number of antipsychotics, antidepressants, mood stabilizers and tranquillizers).

2.4 Neurocognitive testing

A comprehensive neurocognitive test battery was used to assess cognitive performance. The testing was performed by psychologists and medical doctors trained in standardized neurocognitive assessment. The cognitive domains “learning and memory”, “executive function” and “psychomotor speed” were obtained using Trail-Making Test (TMT), Verbal Digit Span (VDS) and Digit symbol test (DST). Z-scores were calculated to obtain a comparable scale of the different variables.

2.4.1 Trail-Making Test (TMT)

The Trail-Making-Test (TMT) measures several cognitive areas such as visual attention, psychomotor speed and task switching and is a good predictive value for assessing executive function. Using a pencil, the participant must connect numbers in ascending order (Part A) or alternately connect numbers and symbols (Part B). The time taken to complete each part of the test is measured. The time of part A is subtracted from part B to obtain an estimate of the switching process. While part A measures visuomotor function and visual processing speed, Part B assesses working memory, cognitive flexibility, executive functions and visuospatial abilities (Tischler and Petermann, 2010).

2.4.2 Verbal Digit Span (VDS)

The verbal digit span test (VDS) assesses short-term memory (forward digit span) and working memory (backward digit span). In the short-term memory task, the participant is asked to repeat sequences of numbers presented verbally by the interviewer. A point is awarded for each correctly recalled sequence of numbers, and the interviewer continues until the participant makes mistakes when recalling strings of the same length. At the end all points are added up to obtain the final mark.

The working memory task works in the same way, except that the participant should repeat the sequence of numbers presented by the interviewer in reverse order (Wahlstrom et al., 2016; PsyCourse Team, 2019).

2.4.3 Digit Symbol Test (DST)

The digit symbol test (DST) measures processing speed by showing the participants a series of numbers and a space under each number. The participant then is asked to fill in these spaces with symbols that match the numbers above. The respective number-symbol assignment is shown at the top of the test sheet. It is measured how many correct symbols the participant can fill in in 120 seconds (Molz et al., 2010).

2.5 Ethical requirements

Written consent was obtained from the study participants prior to study participation. The acquired data was collected and stored anonymously. In addition, study participants had the right to discontinue the study at any time without negative consequences. Information collected up to that point remains stored anonymously. The study was approved by the local ethics committee and is in line with the Helsinki Declaration.

2.6 Interviewers

„Interviewers were provided with instructions in written form for all instruments and each new interviewer was extensively trained in administering the phenotyping battery by an experienced interviewer. Depending on interviewer experience, training includes discussing the instructions in detail, watching an experienced investigator conducting a visit and

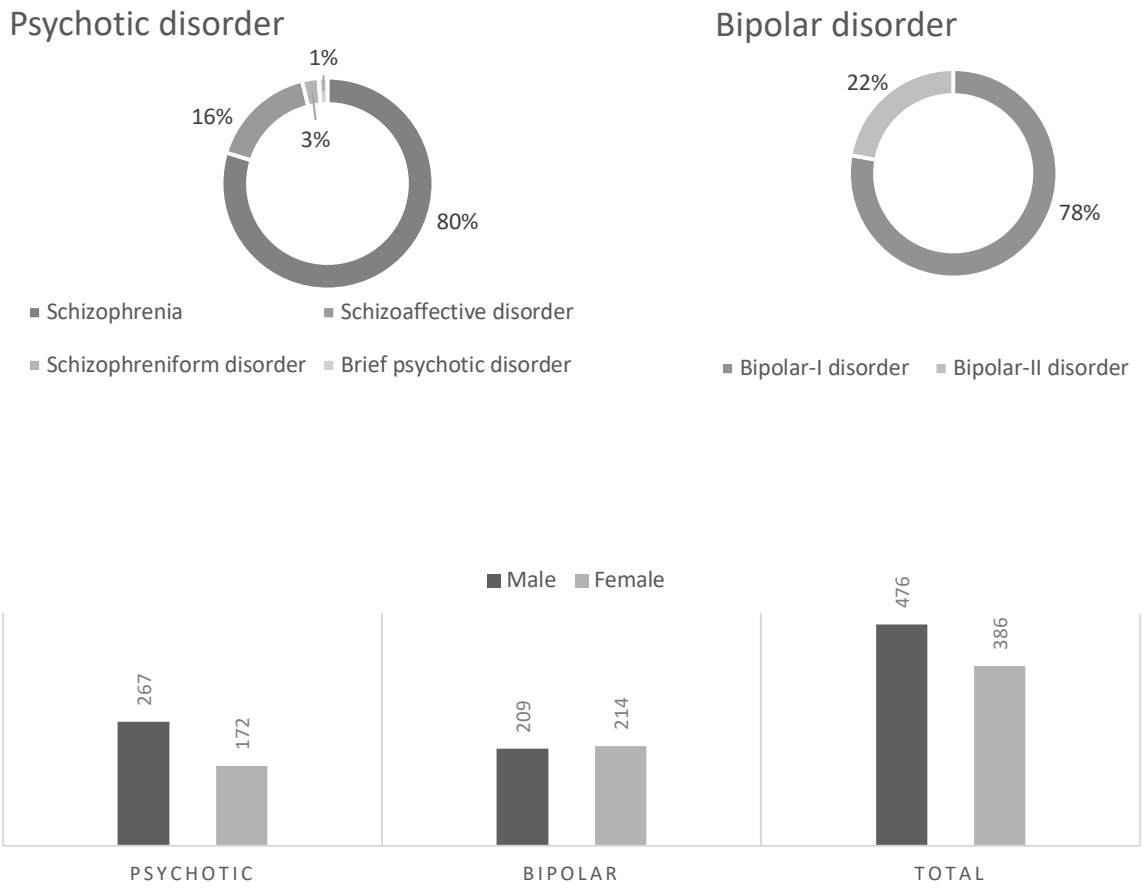
performing a visit under supervision of the latter. In addition, trainings for all investigators were held on a regular basis“ (Budde et al., 2019).

2.7 ICD-10 Diagnoses and diagnostic groups

For the analyses, the patients were grouped into three categories according to psychiatric diagnosis: psychotic disorder (schizophrenia, schizoaffective disorder, schizophreniform disorder and brief psychotic disorder), bipolar disorder (bipolar-I disorder, bipolar-II disorder) and unipolar depression.

As the unipolar disorder patients represented disproportionally the smallest group, they were excluded from all analyses.

Figure 1. *Diagnosis and sex distribution of the sample.*



2.8 Adherence measurement

To assess adherence, it was asked whether the psychopharmacological medication was taken as prescribed during the last seven days and the last six months. Answer options were classified as followed: 1 - "every day, exactly as prescribed", 2 - "every day, but not always as prescribed", 3 - "regularly, but not every day", 4 - "sometimes, but not regularly", 5 - "rarely", 6 - "not at all". For the analyses we only used information of the adherence behavior covering the last six months. For the descriptive analyses we built two categories: "daily medication intake" (graduation 1 - 2) and "irregular medication intake" (graduation 3 - 6). For simplicity we refer to patients with daily medication intake as *adherent patients* and to those with unregular medication intake as *nonadherent patients*. For the logistic regression analyses we used the adherence questionnaire as ordinal scale ("Codebook PsyCourse").

2.9 Medication sum

The variable *medication sum* contains the addition of all current psychotropic drugs taken at the time of the study visit (antidepressants, antipsychotics, mood stabilizers, tranquilizers and other psychiatric medication).

2.10 Psychopathology

Information on current psychopathology was obtained through the positive, negative and general score of the Positive and Negative Symptom Scale (PANSS) for psychotic disorder and the Young Mania Rating Scale (YMRS) and Clinician Inventory of Depressive Symptomatology (IDS-C30) for bipolar diagnosis group.

Functionality and severity of the disease were measured using the Global Assessment of Functioning (GAF).

2.10.1 Global Assessment of Functioning (GAF)

This clinician-rated assessment scale is used to assess the general psychosocial functional level of the study participants. Only the psychological, social or occupational functional areas are assessed; physical illnesses and environmental conditions impairing function should not be considered. This scale is continuous and ranges from 1 to 100, with points 91 - 100 standing

for "No symptoms. Superior functioning in a wide range of activities, the problems of life never seem to get out of control, is sought out by others for its or their many positive qualities". While points 1-10 describes a "Persistent risk of serious injury to self or others (e.g. recurrent violence) or persistent inability to maintain minimal personal hygiene, or severe suicide with clear expectation of death". According to Endicott et al. most psychiatric outpatients are classified as 31 to 70, most inpatients between 1 and 40 (Endicott, 1976).

2.10.2 Positive and Negative Symptom Scale (PANSS)

The Positive and Negative Symptoms Scale (PANSS) is an external assessment scale that measures positive and negative symptoms in schizophrenia with three subscales: positive, negative and general psychopathological symptoms. Each item is rated on an ordinal scale of one to seven. On the positive symptom scale, the items include delusions, conceptual disorganization, hallucinatory behavior, excitement, magnificence, suspicion/ persecution and hostility. Items on the negative symptoms scale are blunted affect, emotional withdrawal, poor rapport, passive/ apathic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. General psychopathological symptoms include somatic concerns, anxiety, guilt, tension, mannerisms and posture, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, will disorder, poor impulse control, anxiety and active social avoidance.

For all items, higher scores mean more severe symptoms. The scores refer to the last seven days (Kay et al., 1989; PsyCourse Team, 2019).

2.10.3 Clinician Inventory of Depressive Symptomatology (IDS-C30)

The Clinical Inventory of Depressive Symptoms (IDS-C30) is an external rating scale for measuring the severity of depressive symptoms (Trivedi et al., 2004). Each item is rated on an ordinal scale of zero to three, with zero indicating the absence of the symptom in question. The assessments are based on the last seven days. For all items, higher scores indicate more severe symptoms. Items include onset of insomnia, midnight insomnia, early morning insomnia, hypersomnia, mood (sad/ irritated/ anxious) and reactivity and quality of mood and mood swings. Information is also collected on appetite and weight, concentration/ decision

making, current and future outlook, suicidal thoughts, involvement, energy/ fatigue, pleasure/ pleasure (excluding sexual activities), sexual interest, psychomotor slowdown and arousal, somatic complaints, sympathetic arousal, panic/ phobia symptoms (gastrointestinal) and interpersonal sensitivity (PsyCourse Team, 2019).

2.10.4 Young Mania Rating Scale (YMRS)

The Young Mania Rating Scale (YMRS) is a clinician-rated 11 - item scale assessing the severity of mania symptoms. The ratings refer to the past forty - eight hours. On all items, higher scores mean more severe symptoms (Young et al., 1978).

2.11 Statistics

Statistical analyses were performed using IBM SPSS statistics, version 25.0. The final sample comprised 862 patients with all relevant data available.

The dependent variables cognition domain one to three as “D1 - learning and memory”, “D2 - executive function” and “D3 - psychomotor speed” as well as GAF were metrical. Independent variables adherence and diagnosis groups were nominal. Numerical and ordinal data was expressed as means ± standard deviation, median, minimum and maximum values. Nominal data was expressed as frequencies. Numerical and ordinal variables were compared by using the Mann-Whitney-U test for non-normally distributed measurements. Chi-squared tests (Phi and Cramer’s Test) and *t*-test were performed for comparison of categorical, nominal and ordinal data. The threshold for statistical significance was set at an alpha value of 0.05 ($p < 0.05$). The Bonferroni method was used to correct for alpha error accumulation in multiple testing.

2.11.1 Cognitive domains as z-scores

Observation of differences between learning and memory, executive function and psychomotor speed was done by dividing them into three domains. The cognitive domains included following test scores: Correct numbers of the Verbal Digit Span (forwards and backwards), correct numbers from the Digit-Symbol-Test (DST) and times in seconds in the Trail-Making-Test A/ B (TMT versions A and B; logarithmic transformed).

The cognitive domains were created by generating z-scores of the related variables, positively orienting the partially negative scores, and then summing the respective z-scores to obtain the three domains. For better comparability, the resulting domains were again subjected to a z-transformation, followed by a Rankit-based transformation, which was then z-transformed again.

There was no multicollinearity of D1 - D3. There was homogeneity of the error variances for the three cognitive domains (p >.05) as measured with the Levene's test. To test for normal distribution the Kolmogorov-Smirnov and Shapiro-Wilk test were performed. Not all three cognitive domains were normally distributed. However, the larger the sample size, the less important the normal distribution assumption becomes, since according to the Central Limit Theorem by Lindeberg-Lévy the mean value of independent and identically distributed variables tends towards a normal distribution (Fischer, 2011). Therefore, with the present sample size, the untransformed data and the three domains were evaluated further using parametric tests, despite the absence of the normal distribution assumption.

Figure 2. *Cognitive domains as composit z-scores.*

COGNITIVE DOMAIN 1	Learning and memory	Short-term memory	Digit span forwards	correct numbers
COGNITIVE DOMAIN 2	Executive function	Working memory	Digit span backwards	correct numbers
		Task switching	TMT B	time in seconds
			TMT B - TMT A	time in seconds
COGNITIVE DOMAIN 3	Psychomotor speed		TMT A	time in seconds
			Digit symbol test	number of correct symbols

2.11.2 Multiple linear regression

We performed four linear regression models to predict each cognitive domain (z-scores) as well as the GAF score. Each regression analysis was controlled for age, sex, illness duration, medication sum and diagnostic classification. The prerequisites of multiple linear regression were checked: A test of normal distribution was performed using Kolmogorov-Smirnov and Shapiro-Wilk test. There was a linear relationship between the variables and a check for

outliers was performed. But since any exclusion of a case from the total sample always involves a loss of power, the outliers found were left in the data set due to sample size and power. Further the predictors did not correlate with each other and the homoscedasticity of the residuals was given for “D1 - learning and memory” and “D2 - executive function”. For “D3 - psychomotor speed” heteroscedasticity is shown to be depressed (Durbin-Watson < 1), from which unequal variances of the variables' residuals can be inferred. Because of this, HC4-methode was conducted and heteroskedasticity-consistent standard errors were used further (Hayes and Cai, 2007). In addition, the residuals were normally distributed.

The goodness of fit as measured by adjusted R^2 (R^2_a) is assessed as small if ≤ 0.09, moderate between 0.1 and 0.3 and large effect if ≥ 0.3. An alpha value of 0.05 was considered significant. Bonferroni-correction for multiple testing was applied for the predictors, corresponding alpha values are indicated in each case.

In case of significant association between a cognitive domain and the variable diagnostic group, we performed the multiple linear regression for the group psychotic disorder and bipolar disorder separately. Analyzing this, we added factors relevant to symptomatic distress: Adjusting for schizophrenia-associated symptoms we used PANSS total sum score, PANSS sum score of positive symptoms, PANSS sum score of negative symptoms, and PANSS sum score of general symptoms in the psychotic group, for depressive using IDSC-30 sum score and manic symptoms adding YMRS sum score in the bipolar group.

The following values were collected as part of a multiple linear regression: The unstandardized regression coefficient beta (*USC B*) is a predictive value that describes the magnitude and direction of a relationship between a predictor and a disease. The adjusted R^2 (R^2_a) represents the proportion of the variance for a dependent variable that is explained by an independent variable.

3. Results

3.1 Descriptive analyses

The cohort for our analysis consisted of 862 individuals, of which 386 (44.8 %) were women and 476 (55.2 %) were men. The unipolar depression group was excluded prior because comparability was not possible due to group size (n = 86). Demographic data on age at first interview yielded a mean of 41.9 ± 12.48 years, with a range of 18 - 77 years. Nonadherent by medication intake of the last six months were reported 20.6 % of them, 60.5 % of them were male (p = 0.003) and younger (p < 0.001). The separate analyses of differences of the three cognitive domains within each of the diagnostic groups found no significant differences.

Based on the diagnosis distribution, different diagnosis groups could be formed as follows: Schizoaffective disorder, schizophrenia, brief psychotic disorder, and schizophreniform disorder are united to the psychotic disorder group (n = 439; 50.9 %), bipolar-I and -II were united to the bipolar disorder group (n = 423; 49.1 %).
Distribution of diagnoses were significantly different ($\chi^2(1) = 7.571$, p = 0.006*, ϕ = -0.094) with 48.5 % with psychotic disorder and 51.5 % bipolar patients in the adherent group, compared to 60.1 % patients with psychotic disorder and 39.9 % bipolar disorder patients in the nonadherent group.
All demographic and descriptive data are summarized in Table 1 and 2.

Table 1. *Descriptive characteristics of the sample.*

	N	MINIMUM	MAXIMUM	MEAN	SD
Age at first interview	862	18	77	41.99	12.48
Duration of illness in years	815	0	50	12.25	10.08
Educational status scale	838	0	6	3.66	1.57
Medication adherence scale	862	1	6	1.76	1.32
Clinical global impression (CGI)	859	1	7	4.05	1.01
Global assessment of functioning (GAF)	862	4	97	57.45	13.45
Number of antidepressants prescribed	862	0	3	0.44	0.61
Number of antipsychotics prescribed	862	0	5	1.38	0.96
Number of mood stabilizers prescribed	862	0	3	0.47	0.60
Number of tranquilizers prescribed	862	0	2	0.21	0.47

Medication sum	862	0	8	2.52	1.28
BMI kg/m²	849	16.46	58.64	28.19	6.09
D1 learning and memory (z-score)	862	-3.1436	2.8512	0.0518	0.9844
D2 executive function (z-score)	862	-3.2578	3.2578	0.0039	1.0044
D3 psychomotor speed (z-score)	862	-2.5931	3.2751	0.0672	0.9683
PANSS total score	819	30	114	49.45	16.44
IDS-C30 total score	774	0	55	12.99	10.52
YMRS total score	841	0	36	3.12	4.97

SD = Standard deviation
D1/ D2/ D3 = cognitive domains D1-D3 as z-standardized score.
PANSS = Positive and Negative Syndrome Scale: PANSS Total score
IDS-C30 = Inventory of depressive symptomatology: IDS-C30 total score
YMRS = Young Mania Rating Scale: YMRS total score

Table 2. *Descriptive data of the study population, comparing adherent (Adherence scale 1 - 2) with non-adherent (Adherence scale 3 - 6) patients.*

	N	**ADHERENT PATIENTS**	**NON-ADHERENT PATIENTS**			
	mean (SD) or *n* (%)	**mean (SD) or *n* (%)**	**mean (SD) or *n* (%)**	**Statistic**	***p*-value**	**Effect size**
Sex	862 (100.0)	684 (79.4)	178 (20.6)	χ^2 (1) = 8.98	***p* = 0.003***	Φ = 0.102
Female	386 (44.8)	324 (47.4)	62 (16.1)			
Male	476 (55.2)	360 (52.6)	116 (65.2)			
Age	862 (100.0)	684 (79.4)	178 (20.6)			
		43.02 (12.36)	38.02 (12.15)	*t*(860) = 4.83	***p* < .001***	95%-CI [2.97; 7.04]
SCID diagnoses	862 (100.0)	684 (79.4)	178 (20.6)	χ^2 (1) = 7.57	***p* = 0.006***	Φ = -0.094
Psychotic Disorder	439 (50.9)	332 (48.5)	107 (60.1)			
Bipolar Disorder	423 (49.1)	352 (51.5)	71 (39.9)			
Educational Status Scale**	838 (100.0)	663 (79.0)	176 (21.0)	χ^2 (6) = 8.44	*p* = 0.208	Φ = 0.100
0	6 (0.7)	4 (0.6)	2 (1.1)			
1	49 (5.8)	38 (5.7)	11 (6.3)			
2	163 (19.5)	122 (18.4)	41 (23.3)			
3	216 (25.8)	166 (25.1)	50 (28.4)			
4	142 (16.9)	110 (16.6)	32 (18.2)			
5	97 (11.6)	81 (12.2)	16 (9.1)			
6	165 (19.7)	141 (21.3)	24 (13.6)			
Medication Sum	862 (100.0)	684 (79.4)	178 (20.6)	χ^2 (8) = 15.13	*p* = 0.057	Φ = 0.132
0	8 (0.9)	4 (0.6)	4 (2.2)			
1	181 (21.0)	147 (21.5)	34 (19.1)			
2	283 (32.8)	210 (30.7)	73 (41.0)			
3	231 (26.8)	191 (27.9)	40 (22.5)			
4	93 (10.8)	75 (11.0)	18 (10.1)			
5	45 (5.2)	39 (5.7)	6 (3.4)			
6	13 (1.5)	11 (1.6)	2 (11)			
7	6 (0.7)	0 (0.0)	6 (0.9)			
8	2 (0.2)	1 (0.1)	1 (0.6)			

Duration of illness in years	815 (100.0)	647 (79.4) 12.78 (10.38)	168 (20.6) 10.20 (8.56)	*t*(860) = 7.22	***p* = 0.001***	95%-CI [1.060; 4.114]
D1 learning and memory	862 (100.0)	684 (79.4) 0.05199 (0.9694)	178 (20.6) 0.0513 (1.0429)	*t*(860) = 4.83	*p* = 0.993	95%-CI [-0.1619; 0.1634]
D2 executive function	862 (100.0)	684 (79.4) -0.0251 (1.0105)	178 (20.6) 0.1156 (0.9752)	*t*(860) = -1.67	*p* = 0.096	95%-CI [-0.3064; 0.0251]
D3 psychomotor speed	862 (100.0)	684 (79.4) 0.0557 (0.9730)	178 (20.6) 0.1113 (0.0713)	*t*(860) = -0.682	*p* = 0.496	95%-CI [-0.2155; 0.1044]
GAF Total Score	862 (100.0)	684 (79.4) 58.19 (13.18)	178 (20.6) 54.62 (14.14)	*t*(860) = 3.172	***p* = 0.002***	95%-CI [1.362; 1.362]
BMI kg/m²	849 (100.0)	671 (79.0) 28.32 (6.2)	178 (21.0) 27.74 (5.65)	*t*(847) = 1.141	*p* = 0.254	95%-CI [-0.422; 1.593]
PANSS Total score	819 (100.0)	651 (79.49) 47.79 (15.43)	168 (20.51) 55.9 (18.55)	*t*(817)= -5.82	***p* = <.001***	95%-CI [-10.85; -5.37]
IDS-C30 Total Score	774 (100.0)	610 (78.81) 12.48 (10.38)	164 (21.19) 14.87 (10.85)	*t*(249)= -2.59	***p* = 0.012***	95%-CI [-4,27; -0,53]
YMRS Total Score	841 (100.00)	666 (79.19) 3.08 (4.93)	175 (20.81) 3.26 (5.14)	*t*(264.5) = -0.41	*p* = 0.68	95%-CI [-1.03; 0.67]

**Significance level set at p < 0.05*

SCID = Structured Clinical Interview for DSM Disorders (SCID); Medication sum = sum of prescribed psychiatric medication; D1/ D2/ D3 = cognitive domains D1-D3 as z-standardized score; GAF = Global assessment of functioning; BMI = Body mass index; PANSS = Positive and Negative Syndrome Scale total score; IDS-C30 = Inventory of depressive symptomatology total score; YMRS = Young Mania Rating Scale total score

***Educational Status Scale: For the "educational status scale", an attempt was made to achieve comparability with English-speaking education systems. A survey of "high school level education" (0-3) and "professional education" (0-3) was added and transferred to the "educational status scale" from 0-6. Thus, the higher the score, the better the education.*

3.2 Multiple linear regression - cross-diagnostic analyses

3.2.1 Prediction of GAF functioning from adherence behavior

A goodness of fit of 15.3 % (R^2_a = 0.153) was obtained in the linear regression model with the factors adherence, sex, age, duration of illness, sum of medications and diagnostic groups, with 15.3 % of the variance in GAF explained by the variables. After Bonferroni correction (p < 0.008), the factors adherence, med sum and diagnosis remained significant.

The estimated increase in GAF is 1.424 per decreasing adherence scale (improvement in adherence behavior) (*USC* ß = -1.424; t(807) = -4.253; p < .001). Thus, the GAF increases as adherence increases. The estimated increase of one unit of GAF is per decreasing medication sum by 2.226 (*USC* ß = -2.226; t(807) = -6.493; p < .001). Fewer medications positively affect GAF or patients show a better level of function with them. The estimated increase in GAF is 7.693 per diagnostic group (*USC* ß = 7.693; t(807) = 8.618; p < .001). The bipolar group had a better functioning than the psychotic group by 7.693 units on the GAF scale. Adherence, age, medication sum, and diagnostic groups explained a significant proportion of the variance in GAF (R^2_a= 0.153; F(5, 808) = 25.51, p < .001).

The results of the multiple linear regression for GAF are shown in Table 3 and Diagram 1.

Table 3. *Multiple linear regression analysis in the cross-diagnostic sample based on the predictors adherence behavior, sex, age, duration of illness, medication sum and diagnostic classification on cognitive performance.*

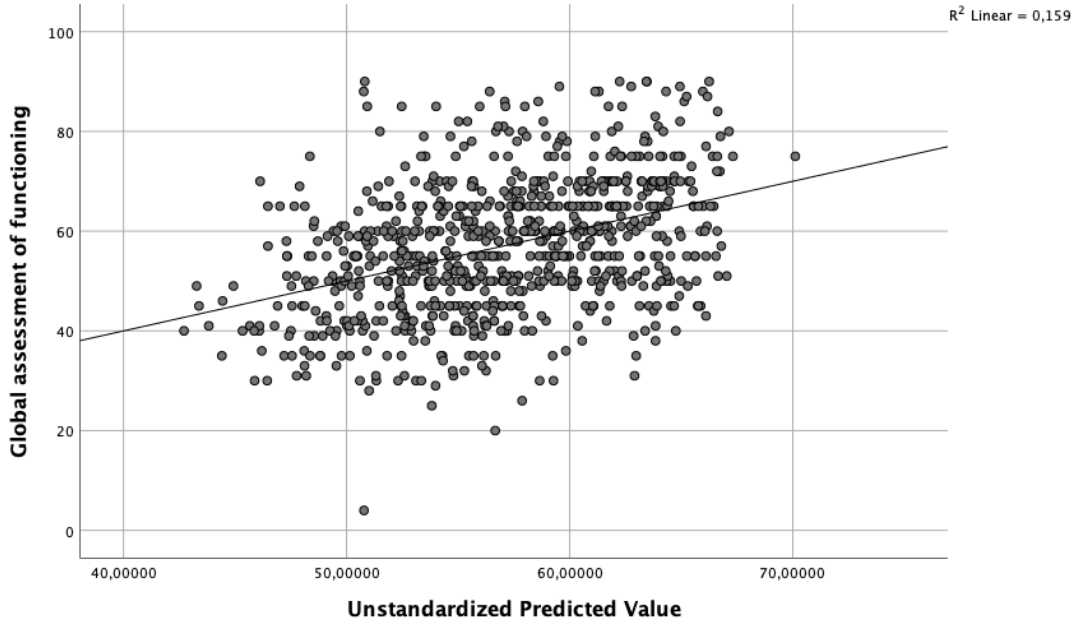
Cross-diagnostic group

		Unstandardized		Standardized						
		USC B	*SE*	*SC B*	*t*-value	*p*-value	R^2	R^2_a	*df*1	*df*2
GAF						**<.001****	0.159	0.153	5	808
	Adherence scale	-1.424	0.335	-0.141	-4.253	**<.001****				
	Sex	0.885	0.873	0.033	1.014	0.311				
	Age	0.046	0.043	0.043	1.072	0.284				
	Illness duration	-0.028	0.052	-0.021	-0.546	0.585				
	Medication sum	-2.226	0.343	-0.213	-6.493	**<.001****				
	Diagnostic classification	7.693	0.893	0.29	8.618	**<.001****				

***p < 0.008 significant (corrected for multiple testing)*

USC B = unstandardized coefficient ß; SE = standard error; SC B = standardized coefficient; df = degrees of freedom

Diagram 1. *Scatterplot regression model with GAF for cross-diagnostic sample*



3.2.2 Prediction of cognitive domain 1 – Learning and memory from adherence behavior

The estimated increase in "D1 – learning and memory" value is 0.01 per decreasing year of age (*USC* ß = -0.01; *t*(807) = -3.089; *p* = 0.002). The estimated increase in D1 score is 0.27 per diagnostic group (*USC* ß = 0.27; *t*(807) = 3.775; *p* < .001). The bipolar group performed better than the psychotic group by 0.27 units on composite score for learning and memory.

Age and the diagnostic groups explained a significant portion of the variance in "D1 learning and memory" of (R^2_a = 0.024; *F*(5, 808) = 4.28, *p* < .001).

The results of the multiple linear regression are shown in Table 4.

Table 4. *Multiple linear regression analysis in the cross-diagnostic sample based on the predictors adherence behavior, sex, age, duration of illness, medication sum and diagnostic classification on cognitive performance.*

Cross-diagnostic group

		Unstandardized		Standardized						
		USC B	*SE*	*SC B*	*t*-value	*p*-value	R^2	R^2_a	*df*1	*df*2
D1 Learning and memory						**<0.001****	0.031	0.024	5	808
	Adherence scale	-0.03	0.03	-0.04	-1.10	0.270				
	Sex	-0.02	0.07	-0.01	-0.30	0.765				
	Age	-0.01	0.00	-0.13	-3.09	**0.002****				
	Illness duration	0.00	0.00	0.01	0.13	0.899				
	Medication sum	-0.04	0.03	-0.05	-1.52	0.130				
	Diagnostic classification	0.27	0.07	0.14	3.78	**<0.001****				

**p < 0.008 significant (corrected for multiple testing)

USC B = unstandardized coefficient β; SE = standard error; SC B = standardized coefficient; df = degrees of freedom

3.2.3 Prediction of cognitive domain 2 – Executive function from adherence behavior

A goodness of fit of 10.4 % (R^2_a = 0.104) was obtained in the linear regression model with the factors adherence, sex, age, duration of disease, total medications, and diagnostic groups. Age, number of prescribed medications and the diagnostic groups explained a significant portion of the variance in "D2 - executive function" of (R^2_a = 0.104; $F(5, 808) = 16.70$, $p < .001$). The estimated increase in domain 2 - executive function value is 0.02 per decreasing year of life (*USC* ß = -0.02; $t(807) = -7.350$; $p < .001$). Younger age positively influences the executive function. The estimated increase "domain 2 - executive function" value is 0.080 per decreasing medication sum (*USC* ß = -0.080; $t(807) = -3.042$; $p = 0.002$). Fewer medications positively affect cognition D2. The estimated increase in D2 score is 0.34 per diagnostic group (*USC* ß = 0.34; $t(807) = 4.946$; $p < .001$). The bipolar group is better than the psychotic group by 0.34 units on composite score for executive function.

The results of the multiple linear regression are shown in Table 5 and Diagram 2.

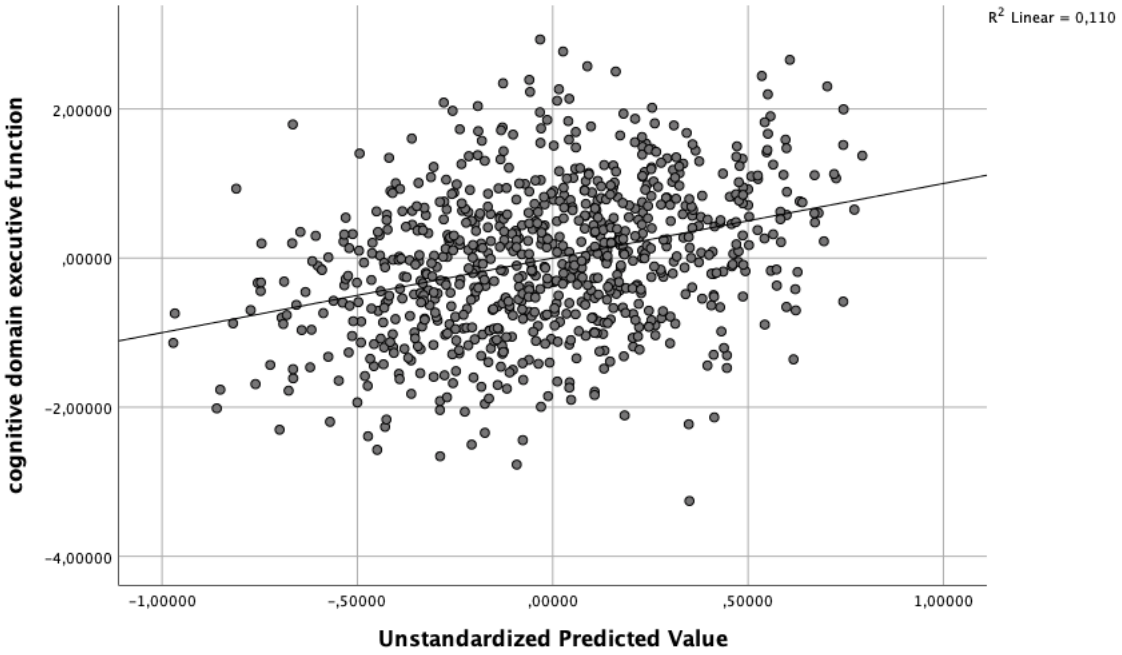
Table 5. *Multiple linear regression analysis in the cross-diagnostic sample based on the predictors adherence behavior, sex, age, duration of illness, medication sum and diagnostic classification on cognitive performance.*

Cross-diagnostic group		Unstandardized		Standardized						
		USC B	*SE*	*SC B*	*t*-value	*p*-value	R^2	R^2_a	*df*1	*df*2
D2 Executive function						**<.001****	0.110	0.104	5	808
	Adherence scale	0.00	0.026	-0.001	-0.028	0.978				
	Sex	-0.01	0.067	-0.004	-0.121	0.904				
	Age	-0.02	0.003	-0.302	-7.35	**<.001****				
	Illness duration	0.00	0.004	-0.001	-0.037	0.971				
	Medication sum	-0.08	0.026	-0.103	-3.042	**0.002****				
	Diagnostic classification	0.34	0.068	0.171	4.946	**<.001****				

**p < 0.008 significant (corrected for multiple testing)

USC B = unstandardized coefficient β; SE = standard error; SC B = standardized coefficient; df = degrees of freedom

Diagram 2. *Scatterplot regression model cognitive domain "D2 - executive function" for cross-diagnostic sample.*



3.2.4 Prediction of cognitive domain 3 – Psychomotor speed from adherence behavior

Cognitive domain "D3 - psychomotor speed" is predicted and a goodness of fit of 19.6% (R^2_a = 0.196) was obtained in the linear regression model with the factors adherence, sex, age, duration of illness, sum of medications, and diagnostic group. These variables explained 19.6 % of the variance of D3. After Bonferroni correction (p < 0.008) the factors age, sex, sum of medication and diagnostic group remained significant. The estimated increase in D3 score is 0.028 per decreasing year of life (*USC* ß = -0.028; t(807) = -9.88; p < .001). Younger age positively influences cognition D3. Females are better than males by 0.173 units of the cognitive domain psychomotor speed. The estimated increase in D3 score is 0.092 per decreasing medication sum (*USC* ß = -0.092; t(807) = -3.88; p < .001). Fewer medications positively affect D3. The estimated increase in D3 score is 0.493 per diagnostic group (*USC* ß = 0.493; t(807) = 7.75; p < .001). The bipolar group performed better than the psychotic group by 0.493 units on composite score for psychomotor speed. Age, gender, medication sum, and diagnostic group explained a significant proportion of the variance in D3 psychomotor speed of (R^2_a= 0.196; F(5, 808) = 34.05, p < .001). Heteroskedasticity-consistent numbers of the HC4 method were used.

The results of the multiple linear regression are shown in Table 6 and Diagram 3.

Table 6. *Multiple linear regression analysis in the cross-diagnostic sample based on the predictors adherence behavior, sex, age, duration of illness, medication sum and diagnostic classification on cognitive performance.*

Cross-diagnostic group

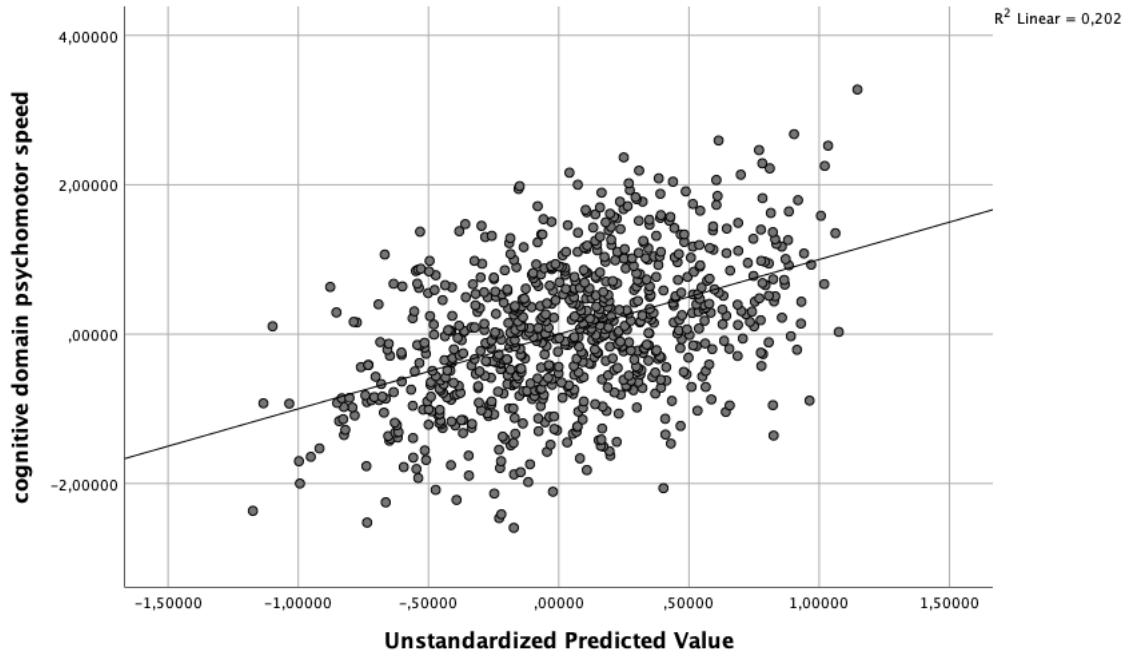
		Unstandardized		Standardized						
		USC B	*SE*	*SC B*	*t*-value	*p*-value	R^2	R^2_a	*df*1	*df*2
D3 Psychomotor speed**						**<.001***	0.202	0.196	5	808
	Adherence scale	-0.038	0.023	-0.053	-1.59	0.111				
	Sex	0.173	0.061	0.091	2.80	**0.005***				
	Age	-0.028	0.003	-0.363	-9.88	**<.001***				
	Illness duration	-0.004	0.004	-0.044	-1.20	0.23				
	Medication sum	-0.092	0.024	-0.122	-3.88	**<.001***				
	Diagnostic classification	0.493	0.062	0.259	7.75	**<.001***				

*p < 0.008 significant (corrected for multiple testing)

**robust standard errors after HC4-correction

USC B = unstandardized coefficient β; SE = standard error; SC B = standardized coefficient; df = degrees of freedom; HC = heteroskedasticity-consistent

Diagram 3. *Scatterplot regression model cognitive domain "D3 - psychomotor speed" for cross-diagnostic sample.*



3.3 Analyses in the diagnostic groups

Finally, the multiple linear regression analyses were conducted separately in schizophrenia spectrum diagnoses and patients with bipolar disorder.

3.3.1 Study participants with psychotic disorder

In the sample of patients with psychotic disorder, the results showed statistically significant effects for the regression model based on the predictors adherence behavior, sex, age, duration of illness, medication sum and PANSS (sum score of positive symptoms, sum score of negative symptoms and sum score of general symptoms on "cognitive domain 1 - learning and memory" ($F(7, 404) = 4.71$, $p < .001$, $R^2_a = 0.067$), on "cognitive domain 2 - executive function" ($F(7, 404) = 10.93$, $p < .001$, $R^2_a = 0.162$) and on "cognitive domain 3 - psychomotor speed" ($F(7, 404) = 12.79$, $p < .001$, $R^2_a = 0.186$).

The results of the multiple linear regression are shown in Table 7 and Diagram 4 - 8.

Table 7. *Multiple linear regression analyses in the group of patients with psychotic disorder based on the predictors adherence behavior, sex, age, duration of illness, medication sum and PANSS scores on cognitive performance.*

Psychotic group

		Unstandardized		Standar-dized						
		USC B	*SE*	*SC B*	*t*-value	*p*-value	R^2	R^2_a	*df*1	*df*2
D1 Learning and memory						**<.001***	0.085	0.067	7	404
	Adherence scale	-0.02	0.04	-0.03	-0.48	0.630				
	Sex	-0.02	0.10	-0.01	-0.16	0.875				
	Age	-0.02	0.01	-0.17	-2.73	0.007*				
	Illness duration	0.00	0.01	-0.04	-0.67	0.501				
	Medication sum	0.00	0.04	-0.01	-0.11	0.910				
	PANSS positive sum score	-0.02	0.01	-0.13	-1.89	0.059				
	PANSS negative sum score	-0.04	0.01	-0.23	-3.57	**<.001****				
	PANSS general sum score	0.01	0.01	0.11	1.28	0.202				
D2 Executive function						**<.001***	0.178	0.162	7	404
	Adherence scale	0.01	0.03	0.02	0.35	0.724				
	Sex	-0.03	0.09	-0.01	-0.29	0.772				
	Age	-0.02	0.01	-0.25	-4.12	**<.001****				
	Illness duration	-0.01	0.01	-0.13	-2.13	0.034*				
	Medication sum	0.00	0.04	0.00	0.05	0.961				
	PANSS positive sum score	-0.02	0.01	-0.12	-1.84	0.066				
	PANSS negative sum score	-0.04	0.01	-0.26	-4.17	**<.001****				
	PANSS general sum score	0.01	0.01	0.05	0.62	0.534				
D3 Psychomotor speed***						**<.001***	0.202	0.186	7	404
	Adherence scale	0.01	0.03	0.02	0.47	0.636				
	Sex	0.16	0.08	0.09	1.92	0.055				

Age	-0.02	0.00	-0.26	-4.64	**<.001****
Illness duration	-0.01	0.01	-0.13	-2.54	0.012*
Medication sum	0.00	0.03	0.00	0.10	0.921
PANSS positive sum score	-0.01	0.01	-0.07	-1.06	0.289
PANSS negative sum score	-0.04	0.01	-0.27	-4.60	**<.001****
PANSS general sum score	0.00	0.01	-0.01	-0.11	0.914

*$p < 0.05$ significant

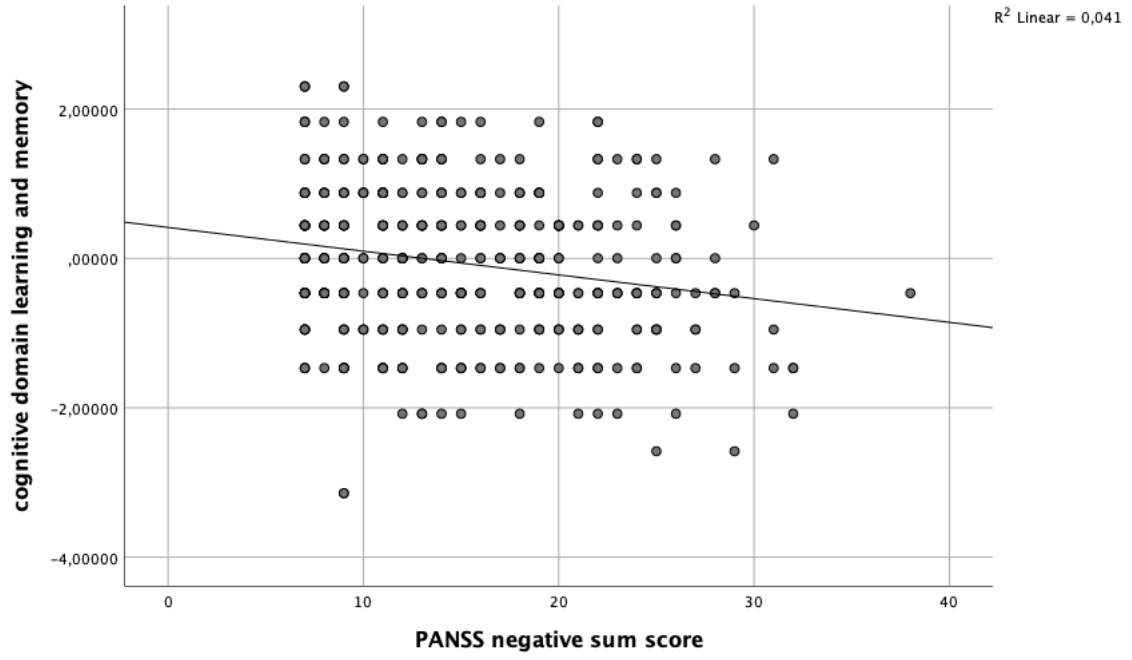
**$p < 0.006$ significant (corrected for multiple testing)

***robust standard errors after HC4-correction

USC B = unstandardized coefficient β; *SE* = standard error; *SC B* = standardized coefficient; *df* = degrees of freedom; PANSS = Positive and Negative Symptom Scale; HC = heteroskedasticity-consistent

After correcting for multiple testing (Bonferroni adjustment 0.05/ 8 = $p < 0.006$) the results indicate that the association between the predictors and learning and memory is significantly driven by PANSS negative symptoms sum score. Less negative symptoms ($p < .001$) predicted better performance in the cognitive domain "D1 - Learning and memory".

Diagram 4. *Scatterplot cognitive domain "D1 - learning and memory" and PANSS neg sum score for psychotic disorder.*



After correcting for multiple testing (Bonferroni adjustment 0.05/ 8 = $p < 0.006$) the results indicate that the association between the predictors and executive function is significantly driven by age and PANSS negative symptoms sum score. Decrease in age ($p < .001$), and less negative symptoms ($p < .001$) predicted better performance in the domain executive function.

Diagram 5. *Scatterplot regression model cognitive domain "D2 - executive function" for diagnostic group psychotic disorder.*

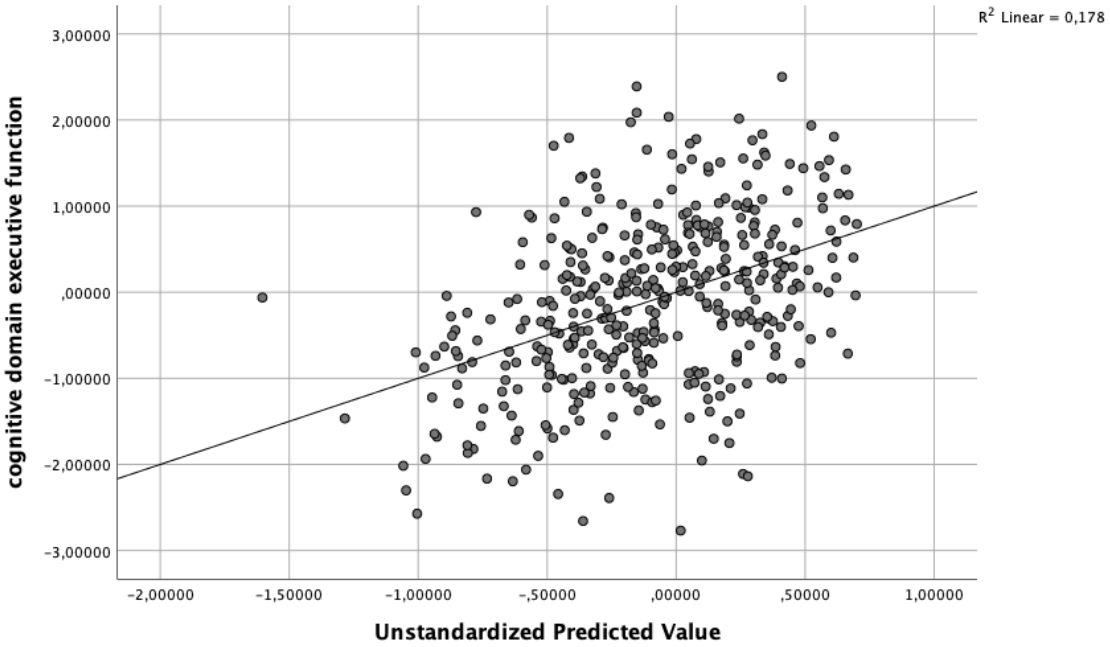
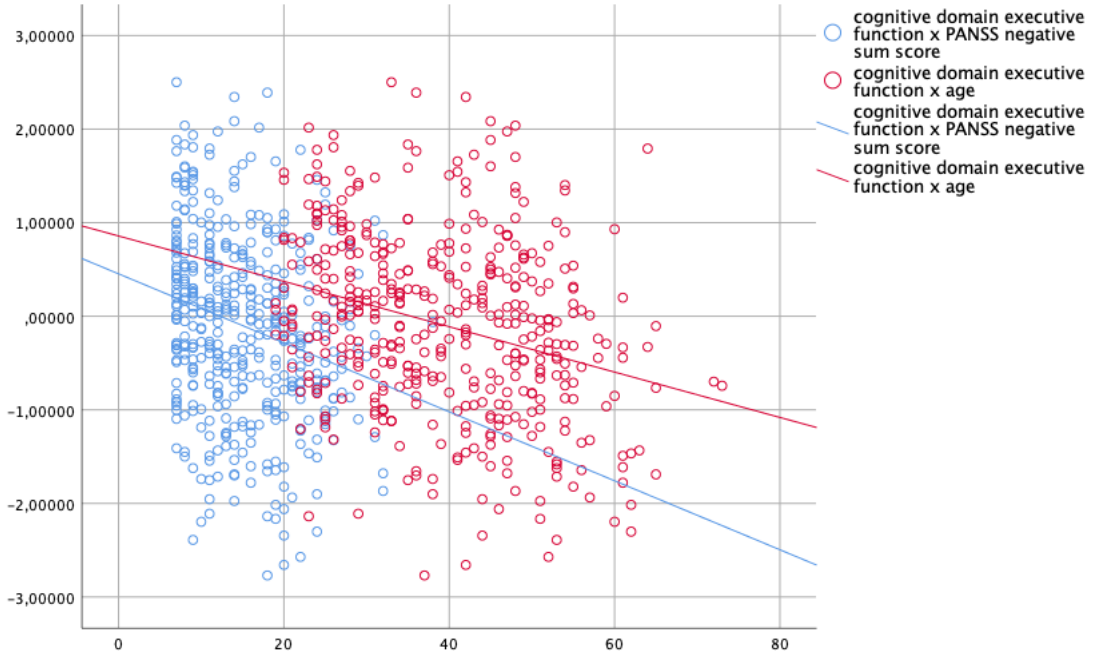


Diagram 6. *Scatterplot cognitive domain "D2 - executive function" and age and PANSS negative sum score for psychotic disorder.*



After correcting for multiple testing (Bonferroni adjustment 0.05/ 8 = $p < 0.006$) the results indicate that the association between the predictors and psychomotor speed is significantly driven by age and PANSS general psychopathology sum score. Decrease in age ($p < .001$), and

less general psychopathology (*p* <.001) predicted better performance in the domain "D3 - psychomotor speed".

Diagram 7. *Scatterplot regression model cognitive domain "D3 - psychomotor speed" for diagnostic group psychotic disorder.*

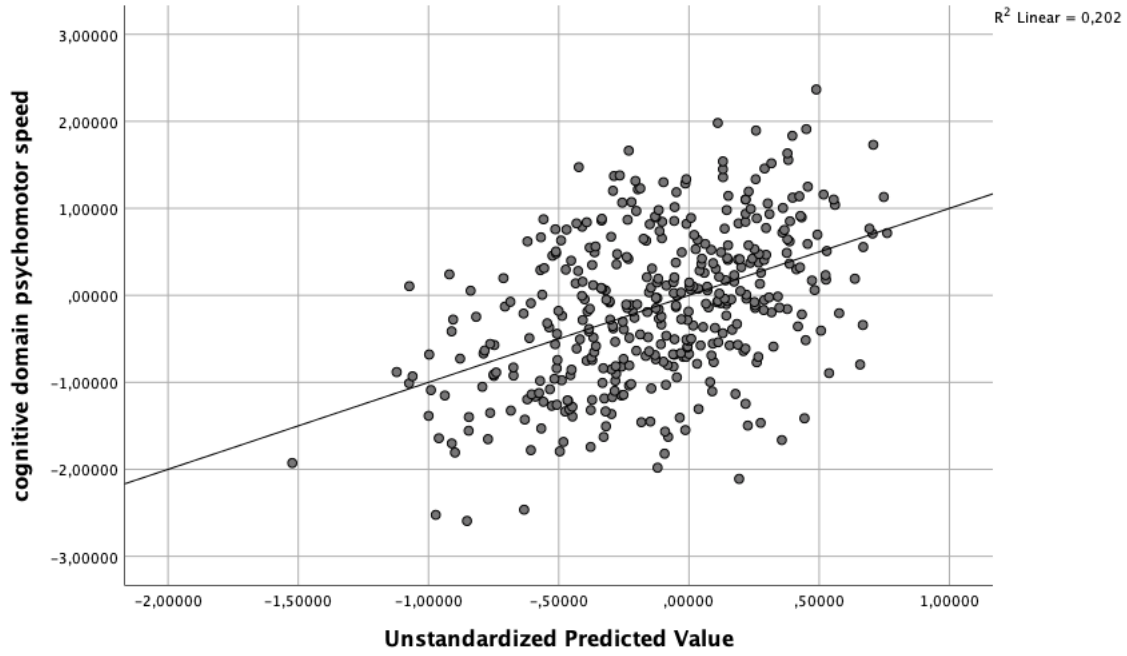
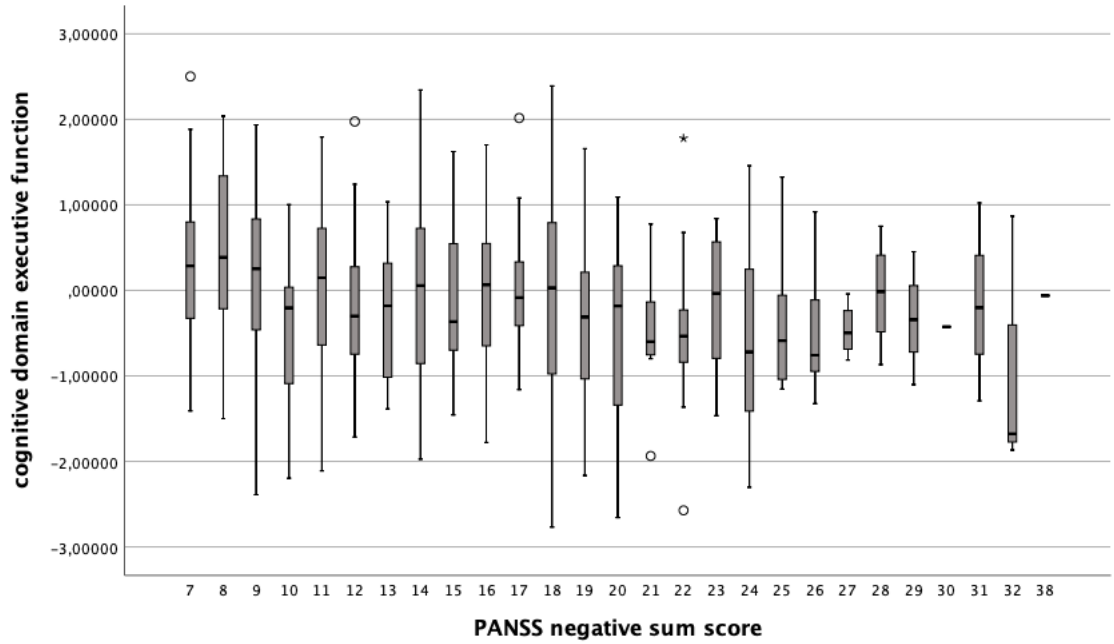


Diagram 8. *Boxplot cognitive domain "D2 - executive function" and PANSS negative sum score for psychotic disorder.*



3.3.2 Study participants with bipolar disorder

In the bipolar group, the results showed statistically significant effects for the regression model based on the predictors adherence behavior, sex, age, duration of illness, medication sum and depressive (IDS-C sum score) and manic symptoms (YMRS sum score) on cognitive domain "D2 - executive function" ($F(6, 328) = 8.09$, $p < .001$, $R^2_a = 0.129$), and on cognitive domain "D3 - psychomotor speed" ($F(6, 328) = 15.88$, $p < .001$, $R^2_a = 0.237$).

The results of the multiple linear regression are shown in Table 8 and Diagram 9 and 10.

Table 8. *Multiple linear regression analyses in the bipolar group sample based on the predictors adherence behavior, sex, age, duration of illness, medication sum, YMRS score and IDS-C30 score on cognitive performance.*

Bipolar group

		Unstandardized		Standardized						
		USC B	*SE*	*SC B*	*t*-value	*p*-value	R^2	R^2_a	*df*1	*df*2
D1 Learning and memory						0.265	0.023	0.002	6	328
	Adherence scale	-0.02	0.05	-0.03	-0.47	0.639				
	Sex	-0.10	0.11	-0.05	-0.94	0.350				
	Age	-0.01	0.01	-0.11	-1.68	0.093				
	Illness duration	0.00	0.01	0.02	0.27	0.786				
	Medication sum	-0.05	0.04	-0.07	-1.25	0.211				
	YMRS sum score	-0.01	0.01	-0.06	-1.10	0.274				
	IDS-C30 sum score	0.00	0.01	-0.04	-0.66	0.509				
D2 Executive function						**<.001***	0.147	0.129	6	328
	Adherence scale	0.04	0.05	0.05	0.86	0.393				
	Sex	-0.03	0.11	-0.02	-0.29	0.770				
	Age	-0.03	0.01	-0.33	-5.58	**<.001****				
	Illness duration	0.01	0.01	0.08	1.32	0.188				
	Medication sum	-0.12	0.04	-0.15	-2.85	**0.005****				
	YMRS sum score	-0.03	0.01	-0.19	-3.62	**<.001****				
	IDS-C30 sum score	0.00	0.01	-0.05	-0.88	0.377				
D3 Psychomotor speed***						**<.001***	0.253	0.237	6	328
	Adherence scale	-0.03	0.05	-0.03	-0.53	0.600				
	Sex	0.09	0.10	0.05	0.98	0.329				
	Age	-0.03	0.00	-0.44	-8.22	**<.001****				
	Illness duration	0.00	0.01	-0.03	-0.58	0.564				
	Medication sum	-0.12	0.04	-0.16	-3.08	**0.002****				
	YMRS sum score	-0.01	0.01	-0.07	-1.51	0.131				
	IDS-C30 sum score	-0.01	0.01	-0.13	-2.25	0.025*				

*$p < 0.05$ significant

**$p < 0.008$ significant (corrected for multiple testing)

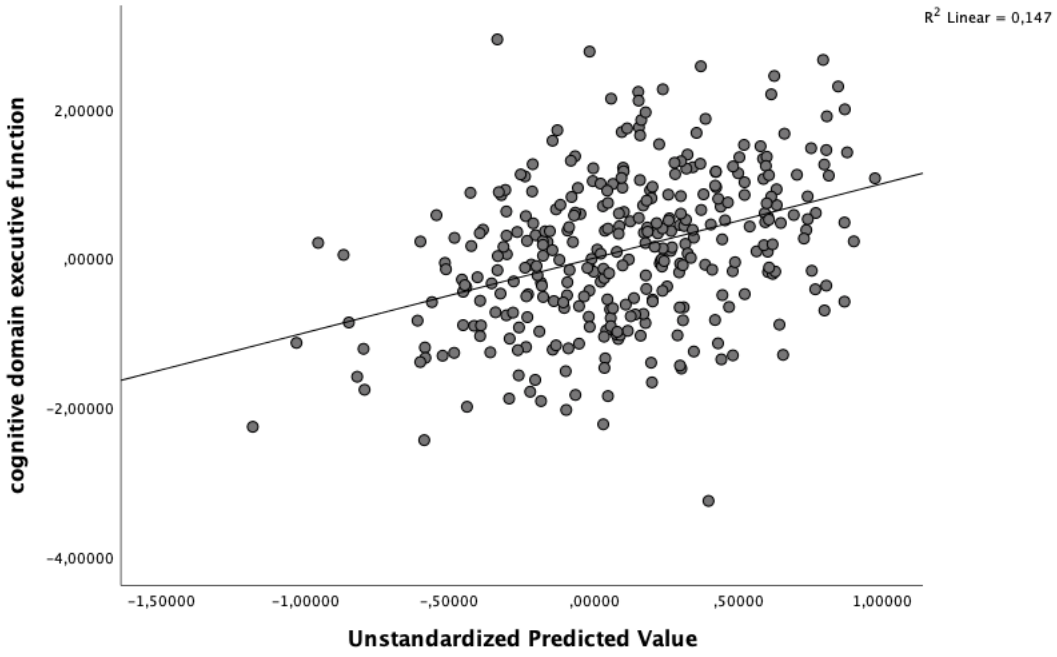
***robust standard errors after HC4-correction

USC B = unstandardized coefficient β; *SE* = standard error; *SC B* = standardized coefficient; *df* = degrees of freedom; YMRS = Young Mania Rating Scale, IDS-C30 = Inventory of Depressive Symptoms, clinician-rated; HC = heteroskedasticity-consistent

There were no significant results for the regression model based on the predictors adherence behavior, sex, age, duration of illness, medication sum and depressive (IDS-C sum score) and manic symptoms (YMRS sum score) on cognitive domain "D1 - learning and memory" ($F(6, 328) = 1.12$, $p = 0.35$, $R^2_a = 0.02$).

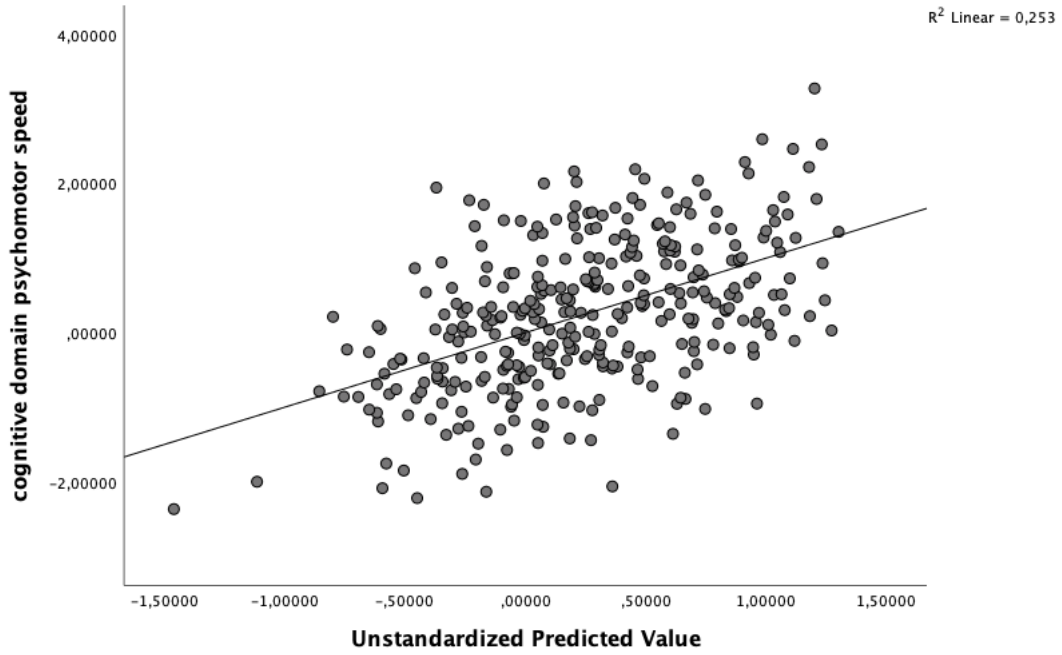
After correcting for multiple testing (Bonferroni adjustment $0.05/8 = p < 0.007$) the results indicate that the association between the predictors and cognitive domain "D2 - executive function" is significantly driven by age, number of prescribed medication and manic symptoms. Decrease in age (p <.001), less prescribed medication ($p = 0.005$) and less manic symptoms ($p < .001$) predicted better performance in executive function.

Diagram 9. *Scatterplot regression model cognitive domain executive function for diagnostic group bipolar disorder.*



After correcting for multiple testing (Bonferroni adjustment 0.05/ 8 = $p < 0.007$) the results indicate that the association between the predictors and cognitive domain "D3 - psychomotor speed" is significantly driven by age and number of prescribed medications. Decrease in age ($p < .001$), less prescribed medication ($p = 0.001$) predicted better performance in psychomotor speed.

Diagram 10. *Scatterplot regression model cognitive domain psychomotor speed for diagnostic group bipolar disorder.*



4. Discussion

This project investigated whether medication adherence influences cognitive performance in patients suffering from chronic bipolar or psychotic disorders. Furthermore, we wanted to investigate if adherence influences psychological, social, and occupational functional areas measured by GAF and if there is any difference in adherence affecting cognition within the diagnostic groups bipolar disorder and psychotic disorder.

The most important finding of this project is that medication adherence does not influence cognitive performance, but influences global functioning. Moreover, cognition was significantly affected by age and sum of medications taken in both bipolar and psychotic disorder. In the psychotic disorder group, younger age and lower PANSS negative sum score influenced all three cognitive domains positively. In the group of patients with bipolar disorder younger age, less prescribed medication and YMRS sum score influenced the domains "executive function" and "psychomotor speed" positively.

Our results partly contradict previous studies that have examined the relationship between cognitive impairment as important correlate of psychosocial functioning and adherence behavior with conflicting findings. In eight of 18 studies comparing adherence behavior and cognition in patients with schizophrenia, a positive correlation between poorer cognitive performance and lower medication adherence was found (Spiekermann et al., 2011b). Puschner et al. proposed the concept of differentiating intentional and non-intentional non-adherence (Puschner et al., 2009). Reasons for non-intentional nonadherence comprise cognitive impairments, which lead to difficulties in grasping information about treatment and transferring its importance and effectiveness to their own life situation, leading to non-intentional non-adherence (Martinez-Aran et al., 2009; Puschner et al., 2009; Spiekermann et al., 2011a).

4.1 Main Results

As briefly outlined in the previous section, the main results are discussed in more detail here. Linear regression models were used to examine the data set, with GAF and the three cognitive domains as dependent variables related to adherence, controlled for age, sex, disease duration, sum of medications and diagnose groups.

We found evidence that taking medications according to the treatment plan improved disease symptoms and reduced their negative impact on psychological, social, and occupational functional areas, measured by GAF. Treatment of serious psychiatric disorders is greatly affected by medication non-adherence and non-adherence has been shown in numerous studies to lead to poorer outcomes in terms of symptoms, hospitalization duration and rate, suicide risk and use of emergency assistance. This is also associated with higher health and social care costs (Higashi et al., 2013). Nevertheless, the regression models also showed that a lower number of medications lead to a better level of function.

Analyzing the three cognitive domains "D1 - learning and memory", "D2 - executive function" and “D3 - psychomotor speed" in more detail, we found a significant influence of age and psychiatric diagnose, but no influence of medication adherence. Age has already been observed in numerous studies to be an important driver of cognitive impairment, as brain damage increasingly occurs and cognitive performance thus becomes physiologically impaired (Grady, 1998).

As the factor diagnostic group was significant in the cross-diagnostic regression models, we performed the regression models again in the psychotic and bipolar disorders group separately. The regression models were now adjusted taking symptomatology into consideration.

In the psychotic disorder group, the multiple linear regression analyses were based on the predictors adherence behavior, sex, age, duration of illness, medication sum and PANSS sum scores (positive, negative and general sum score) on cognitive performance. The cognitive domain “D1 - learning and memory” was found to be mainly influenced by PANSS negative sum score, with cognitive performance being worse the higher the PANSS negative sum score was. In general, a major part of long-term morbidity and functional impairment in patients with schizophrenia derives from negative symptoms (Buchanan, 2007) and additional previous studies have also shown that negative symptoms have a strong association with cognitive impairment (Keefe, 2014). Unfortunately, mainly positive symptoms are treatable with antipsychotic medications. However, there are no medications that specifically address glutamatergic dysfunction in psychotic patients. A more detailed understanding of the biological, psychopathological, and clinical aspects will hopefully lead to the development of

more effective and better tolerated treatments with improved specificity for certain symptoms such as cognitive deficits.

The duration of illness should as well be addressed here. In psychotic disorder, duration of untreated psychosis over six months is assumed to lead to deterioration in cognitive performance (Gaynor et al., 2009). However, the literature provides conflicting results on the relationship between cognition and duration of illness. It is also controversial whether cognitive deficits occur only in the first phase of schizophrenia or during the whole duration of illness (Altamura et al., 2015). Interestingly, duration of illness and the adherence behavior did not influence cognitive performance in our sample. Thus here as well, it may be an attempt to explain that to date there are no drugs that treat glutamatergic dysfunction, in which there is a strong link with impaired cognition and negative symptoms (Barch and Ceaser, 2012). This could then explain why medication adherence does not affect cognitive performance in psychotic patients and why cognitive impairment is more of a trait alongside social impairment (Spiekermann et al., 2011a).

In the bipolar disorder group, the multiple linear regression model was based on the predictors adherence behavior, sex, age, duration of illness, medication sum, YMRS and IDS-C30 on cognitive performance. The variables we chose did not represent an explanatory model in the cognitive domain “D1 - learning and memory”, which may be because other variables we did not examine, such as genetic or structural abnormalities, act as predictors (Kieseppä et al., 2005). Age, the sum of prescribed medication taken and a higher load of manic symptoms turned out to predict the cognitive domain “D2 - executive function”. A distinction can be made between deficits that decline during euthymia, such as impulsivity and risk taking, and those that persist during euthymia, such as attention and executive functions involved in reasoning, planning, problem solving, and managing one's life (Bowden, 2010; Blair, 2017). In order to master executive functional tasks, inhibitory control is necessary for overriding stimulus-driven behavioral responses (Diamond, 2013). Executive function may be impaired because during manic episodes, stimulus inhibition is often abolished. The significant results of this cognitive domain can also be explained by the assumption that cognitive impairment is a state rather than a trait in bipolar disease (Keefe, 2008).

The domain “D3 - psychomotor speed” could be explained by the factors age and medication sum. Since especially mood stabilizers, antipsychotics and antidepressants have

anticholinergic side effects, they may impair cognitive performance (Lupu et al., 2017). And since, polypharmacy has a significantly worse effect on cognitive performance than monotherapy, this may explain our significant medication sum result (Quon et al., 2020). However, again, only medication sum and not medication adherence was significant, so this is in line with the current state that cognitive performance cannot be improved by any current medication. According to Lally and MacCabe, not taking them makes no relevant difference either (Lally and MacCabe, 2015).

4.2 Limitations

Despite the interesting findings and strengths (large sample size and well phenotyped cross-diagnostic sample) of our study, some limitations have to be addressed. There was a difference between the distribution of diagnoses in the adherent and nonadherent groups. Medication adherence was assessed by a non-standardized self-rating questionnaire that only asks about the regularity of medication intake, but does not consider other information such as additional non-medicational therapy, disease insight or i.e. the serum concentration of medications taken. The medications taken for the variable medication sum were also only assessed as a number and not in more detail. Detailed information on the medication such as chlorpromazine equivalents was not available. That could have provided additional interesting aspects in the evaluation of cognitive performance. In addition, the PsyCourse dataset consists primarily of data from chronic patients and non-euthymic patients, as seen by ICS30-score, so data from acute and first-time sufferers would also be of interest. Furthermore, adherence behavior and all other variables were collected on the same day, so that an interaction cannot be excluded.

Randomized controlled trials are needed to obtain a complete picture and more far-reaching conclusions regarding psychiatric therapy and adherence.

4.3 Conclusion and outlook

In conclusion, our hypotheses can be answered as follows:

1. Medication adherence does not influence cognition in psychiatric patients.
2. Medication adherence influences global functioning in psychiatric patients.
3. In both, bipolar disorder and psychotic disorder, cognitive function was independent of medication adherence but was influenced by age and sum of taken medication.

In psychiatric therapy it is of massive importance to discover the numerous reasons of non-adherence, as intentional and un-intentional non-adherence is a clinically important and widespread issue. It influences both, the taking place of a therapy as well as therapy goals and further therapy success.

The results of this study could be used, for example, to establish and offer special cognitive training for specific patient groups as a clinical implication in order to improve adherence behavior and most important increase the quality of life. Motivational interviewing can be used to build intrinsic motivation and enhance their self-esteem. Interventions to strengthen adherence behavior should be adapted to whether non-adherence is intentional or unintentional and whether the cognitive deficits can be compensated for, for example, with the help of behavioral techniques. The point at which clinical implications regarding adherence arise are individual and broad for every affected person. An assessment of the patient's condition is all the more important, because depending on the stage of the disease, self-responsible measures can also overwhelm the patient.

Of course, further research on risk genes and improved pharmacological therapies for newly defined and fitted groups of psychiatric patients will be a major advance in the treatment of bipolar and psychotic disorders and the closely related issue of adherence and polypharmacy.

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6. Appendix

Für die Arbeit wurden folgende zusätzliche Dokumente verwendet:

1. Fragebogen zur medikamentösen Behandlung
2. Fragebogen Medikamenteneinnahme/ Adhärenz
3. Clinician Inventory of Depressive Symptomatology (IDS-C)
4. Positiv- und Negativ-Syndromskala (PANSS)
5. Young Mania Rating Scale (YMRS)
6. Clinical Global Impression (CGI)
7. Skala zur Globalen Erfassung des Funktionsniveaus (GAF)
8. Test Neuropsychologie