INVESTIGATION OF DIMENSIONAL PHENOMENOLOGY AND NEUROBIOLOGY ACROSS AFFECTIVE AND PSYCHOTIC DISORDERS

INAUGURAL-DISSERTATION

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ABBREVIATIONS

MDD	Major depressive disorder
BD	Bipolar disorder
SZ	Schizophrenia
SSD	Schizophrenia spectrum disorders
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Classification of Diseases
GMV	Gray matter volume
FA	Fractional anisotropy
FTD	Formal thought disorder
VBM	Voxel-based morphometry
HiTOP	Hierarchical taxonomy of psychopathology
ROI	Region-of-Interest

1. INTRODUCTION

1.1. The heterogeneity problem of categorical psychiatric nosology

Within more than a century, psychologists and psychiatrists have developed and revised the psychiatric nosology of the major psychiatric disorders [i.e. major depressive disorder (MDD), schizophrenia (SZ), bipolar disorder (BD), schizoaffective disorder (SZA)] previously established by Emil Kraepelin (Kraepelin, 1919). The Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 1994) as well as the International Classification of Diseases (ICD) (World Health Organization, 1993) constitute the major classification systems of mental disorders. While the US American DSM is organized in a five-part axial system diagnosing only mental health disorders, the ICD is a broader classification system covering general as well as mental health. Both are used as categorical classifications systems classifying psychiatric disorders based on a set of specific and standardized criteria assuming more or less strict boundaries between individuals with and without disorder, but also among different diagnostic categories (Tabb, 2015). Hence, the DSM and ICD classification systems are based on the following principle: in order to be given a diagnosis *X*, a patient must present a symptom *A* as well as other symptoms *B*,*C*, and *D* over a certain period of time *E*, and the symptoms *F* and *G* should not be present. Both the DSM and ICD are highly convergent and it is possible to adapt diagnoses (Tyrer, 2014). The DSM and ICD have been used to classify psychiatric disorders in clinical practice as well as research over the past decades, providing standardized precise criteria that also permit comorbidities. The use of the DSM and ICD allows diagnostic agreement and communication across multiple nations (Helzer et al., 2006). However, in light of the failure to validate these categories on a neurobiological level, there is increasing criticism of their use (Caspi & Moffitt, 2018; Conway et al., 2019; Hengartner & Lehmann, 2017; Krueger & Bezdjian, 2009) which can be summarized into two major aspects: (1) the overlap across mental disorders and (2) the categorical comparison of disorders and healthy control groups (Feczko et al., 2019).

The overlap across mental disorders (1) has been scientifically demonstrated on several levels. These include shared phenomenology across diagnostic categories, as there is evidence for elevated psychotic symptoms in MDD patients (Johns et al., 2004; Varghese et al., 2011). Vice versa, depressive symptoms in SZ (Upthegrove et al., 2016) have been reported to be an important factor for completed suicide (Dutta et al., 2011) and long term consequence for functional recovery (Conley et al., 2007). Moreover, formal thought disorder (FTD) has been reported across disorders, as well (Kircher et al., 2014, 2018). Evidence for a shared neurobiology is given by familial and molecular

genetic risk studies (Anttila et al., 2018) showing common variant risk across mental disorders. In addition, there is evidence for shared environmental factors [i.e. pregnancy risk factors, perinatal risk factors, childhood environment, drug use in adolescence] being associated with the major psychiatric disorders (Uher & Zwicker, 2017). Additionally, a meta-analysis of blood cytokine network alterations in the major psychiatric disorders showed that the levels of cytokines were commonly increased across acutely ill patients when compared to a healthy control group (Goldsmith et al., 2016). On a brain structural level, the comparison of SZ, BD, and MDD patients to a healthy control group revealed 87.9% of shared gray matter volume (GMV) decreases across disorders. These common anatomical structures were located in paralimbic and heteromodal regions including the temporal pole, orbitofrontal cortex, insula, hippocampal, cingulate and angular gyri (Chang et al., 2018). Common altered white matter brain structures across SZ and BD patients were reported in callosal, limbic-paralimbic-heteromodal, cortico-cortical, thalamocortical and cerebellar tracts, though this overlap was not reported for MDD patients (Chang et al., 2018). Further evidence for shared brain structural alterations across disorders is given by a meta-analysis pooling results from single case-control studies showing GMV loss across disorders converged in the dorsal anterior cingulate and bilateral insulae (Goodkind et al., 2015). Together, previous studies investigating the neurobiological overlapping of the major psychiatric disorders either focused on the comparison of one disorder to a healthy control group and were then pooled in meta-analyses, or on the comparison of multiple disorders to a healthy control group leading over to the second limitation. Using categorical approaches (2) comparing populations leads to two problematic aspects. First, categorical approaches are based on the assumption that a given disorder constitutes a homogeneous construct with distinct boundaries between categories (Feczko et al., 2019; Tabb, 2015). However, these boundaries often appear to be vague and research on single psychiatric categories failed to determine discrete taxa (Hengartner & Lehmann, 2017). Second, categorical approaches merely acknowledge characteristics above and below the categorical thresholds (Helzer et al., 2006), using not otherwise specified diagnoses that do not fit into official diagnoses. Using cut-off criteria to distinguish healthy controls from patients limits detecting sub-clinical symptoms and distorts findings from case-control studies. On a neurobiological level, there is already evidence for brain structural variations across the sub-clinical depression/anxiety spectra (Besteher et al., 2017, 2020) and sub-clinical psychotic like experiences (Meller et al., 2020) in the healthy population. Further importance for dimensional approaches is given by a meta-analysis reporting 15% greater reliability and a 68% chance of better test-retest reliabilities of dimensional assessments when compared to categorical measures (Markon et al., 2011).

1.2. Dimensional psychopathology

Dimensional methods investigating descriptive psychopathology rather than categorical approaches can overcome the limitations, particularly for research purposes, as described above (Feczko et al., 2019; Helzer et al., 2006; Hengartner & Lehmann, 2017; Reininghaus et al., 2016). Both supervised and unsupervised approaches are useful methods acknowledging this endeavor. While unsupervised approaches are based on the character of the data without prior assumptions, supervised approaches built on prior knowledge (Feczko et al., 2019). Moreover, the importance of complex dimensional modelling is highlighted by studies investigating predictors for disorder onset showing a combination of predictors including clinical, personality, and brain structural measures (Klein et al., 2013; Toenders et al., 2021).

Besides the need for complex models predicting disorders, there is also a demand for dimensional models to better understand the psychopathology after disorder onset. Hereof, several attempts have been made to delineate psychopathological dimensions focusing on continuously distributed phenomena (Conway et al., 2019). Previously, factor analyses have been reported to be a useful method to investigate dimensional psychopathology (Allsopp et al., 2019; Reininghaus et al., 2016).

Explorative and confirmatory factor analyses of psychopathological symptoms within single clinically defined categories revealed three to eleven factors in psychotic disorders (Emsley et al., 2003; Liddle, 1987; Peralta et al., 1997; Peralta & Cuesta, 1999; Rapado-Castro et al., 2010), one to four factors in MDD (Li et al., 2014), and five to seven factors in BD (Baek et al., 2018; Hanwella & de Silva, 2011; Harvey et al., 2008; Sato et al., 2002). Transdiagnostic investigations on the factorial structure across diagnosis [i.e. MDD, BD, SZ] indicated three (Romney & Candido, 2001) to five (van Dorn et al., 2016) factors. More recently, hierarchically structured models have been reported to better represent factorial dimensions (Anderson et al., 2018; Reininghaus et al., 2013, 2016, 2019). Using three psychopathological scales, Reininghaus et al. showed that symptom dimensions across psychotic BD and SZ are best described by a model comprising one general psychosis domain, two dimensions of affective and non-affective psychosis, and five additional factors (Reininghaus et al., 2019). Usually, these factor models comprised paranoid-hallucinatory, depressive, negative, and manic dimensions.

In light of hierarchical structured dimensional models, the hierarchical taxonomy of psychopathology (HiTOP) (Kotov et al., 2017) has been developed. This unsupervised model assumes psychopathology to be hierarchically structured with symptoms on the first level which are summarized into syndromes/disorders on the second level. The latter are nested within factors on the third level and are then pooled with broad spectra on the

fourth level. Lastly, on the fifth level, broader spectra are pooled in one superspectrum (Kotov et al., 2017, 2018).

Models such as HiTOP might be a first starting point for a new taxonomy or ultimately nosology in psychiatric research. In contrast to categorical approaches, transdiagnostic dimensional investigations account for neurobiological overlapping across disorders and can in a next step be used to investigate the neurobiology of the major psychiatric disorders on a dimensional, data driven level.

1.3. Neural correlates of dimensional psychopathology

Brain structural as well as functional magnetic resonance imaging measures are crucial methods which aid the prediction as well as the pathophysiological understanding of mental disorders. Recently, brain structural measures were used to predict the onset of depression reporting the surface area of the supramarginal gyrus to be a contributor to a complex predictive model (Toenders et al., 2021). Predicting a conversion to a diagnosis of SZ from a high-risk state showed a 94% accuracy when a complex model including psychopathology, neuro-cognition and brain structure was combined to a single learning algorithm (Zarogianni et al., 2017).

Besides the prediction of disorder onset, brain structural measures were also used to determine sub-groups or prototypes across disorders. In this regard, multimodal machine learning was used to identify prototypes of depression and psychosis showing that 87% of recent onset depression and psychosis patients could be accurately assigned to the primary diagnostic group based on GMV. However, when including psychotic patients with affective comorbidities, only 37% could be assigned accurately pointing to a lack of points of rarity across disorders, specifically in patients with complex comorbidities (Lalousis et al., 2021). Moreover, while the separation of SZ and MDD based on neuroanatomical data and machine learning algorithms is possible, specifically in patients with disorder onset at younger ages, neuroanatomical signatures fail to separate affective and psychotic disorders (Koutsouleris et al., 2015).

Beyond the prediction and separation of mental disorders based on neuro-anatomical features, it is also important to investigate transdiagnostic neural substrates of psychopathology gaining a more precise understanding of the pathophysiology underlying mental disorders. Results of such studies can in a next step be used to inform complex models predicting onset and disorder course. Studies investigating such substrates were mostly performed in diagnostic categories that specifically exhibit symptoms of such dimensional factors. For each symptom complex results are heterogeneous as some studies found evidence for correlations between psychopathology and GMV while others did not.

Summarizing studies on positive symptoms in SZ patients, a GMV network of temporal and frontal regions was negatively correlated with positive symptoms [i.e. delusions and hallucinations] (Mennigen et al., 2019; Padmanabhan et al., 2015; Palaniyappan et al., 2012). Moreover, one study suggested associations of both positives and depressive symptoms to be inversely correlated with the prefrontal cortex volume indicating that depressive symptoms might be involved in hearing voices (Siddi et al., 2019). Even though, previous research on the associations of GMV and positive symptoms revealed a set of core regions being implicated in positives symptoms, results remain heterogeneous as some other studies reported no associations (Gupta et al., 2015).

GMV correlates of FTD include volume reductions in the language network comprising the left frontal operculum, bilateral inferior frontal gyri, bilateral superior temporal gyri, and the left angular gyrus (Cavelti, et al., 2018; Kircher et al., 2018). Again, while there seems to be consensus about core regions being implicated in FTD, results continue to be mixed and there is a complete lack of transdiagnostic dimensional studies untangling brain structural correlates of FTD.

Negative symptoms in SZ patients have been associated with a number of GMV reductions. These included the orbitofrontal cortex, the anterior cingulate cortex, fusiform gyrus, thalamus, caudate, and the amygdala (İnce & Üçok, 2018; Walton et al., 2018). However, results on associations of negative symptoms and GMV are even more heterogonous than for positive or FTD symptoms as several studies reported no GMV associations (Banaj et al., 2018; Collin et al., 2012). In contrast to GMV, Padmanabhan et al. reported an inverse correlation of negative symptoms with a right frontal surface area including the right pars orbitalis, superior frontal and precentral surface (Padmanabhan et al., 2015), indicating other brain structural measures than GMV that might be implicated in negative symptoms.

Depressive symptoms in MDD patients have been associated with GMV reductions in the right orbitofrontal cortex, left hippocampal gyrus, and right dorsolateral prefrontal cortex (Vasic et al., 2008). However, there is evidence for structural alterations being associated with chronicity and cumulative severity rather than depressive symptomatology (Abe et al., 2010; Grieve et al., 2013; Zaremba et al., 2018a, 2018b).

To sum up, brain structural measures are a useful framework for both prediction and understanding mental disorders. A number of studies on the associations of psychopathology factors and GMV has been performed resulting in ambiguous findings. Specifically, the associations of transdiagnostic psychopathological factors and GMV across disorders remain largely elusive.

1.4. Neuro-cognitive correlates of dimensional psychopathology

Neuro-cognitive deficits across the major psychiatric disorders have become of great interest in both research and therapy. Neuro-cognition has been reported to be a predictor of conversion to SZ from at-risk states (Seidman et al., 2010) and functional impairment in SZ patients (Harvey et al., 2012). While some studies indicated poorer cognitive performance in psychotic disorders [i.e. SZ] than in affective disorders [i.e. MDD and BD] (Barch, 2009; Huang et al., 2020; Lee et al., 2018), there is increasing evidence for a great overlap of neuro-cognitive functioning across disorders (Ancín et al., 2013; Huang et al., 2020), as well. However, it remains unclear whether the impairment of cognitive functioning can be explained by the diagnosis itself or rather by multidetermined psychopathological factors (Millan et al., 2012; van Os & Reininghaus, 2016).

Studies investigating the association of dimensional psychopathology and neuro-cognition revealed moderate correlations of negative symptoms (Bozikas, Kosmidis, Kioperlidou, & Karavatos, 2004; de Gracia Dominguez et al., 2009; Huang et al., 2016) and FTD (de Gracia Dominguez et al., 2009) with neuro-cognition while correlations with positive (de Gracia Dominguez et al., 2009) and affective, depressive symptoms (Zhu et al., 2019) were significantly weaker. Though, few studies are available investigating the association of transdiagnostic psychopathology factors and neuro-cognition across disorders. In line with the results reported above, a recent transdiagnostic study reported correlations of negative and disorganized [i.e. FTD] symptoms with a broad range of cognitive functioning including verbal fluency, visuo-spatial working memory, and processing speed but no correlations of positive and depressive symptoms and neuro-cognition (Zhu et al., 2019). Importantly, correlations of neuro-cognition and psychopathology appear to be modulated by the severity and the course of illness. Neuro-cognitive impairment has been stated during acute episodes, while these findings were not present in remitted patients (Bowie et al., 2018; Zaremba et al., 2019). Besides the current state of patients, other clinical variables [i.e. age of onset, illness severity] have been reported to influence the neuro-cognitive impairment. For instance, one study suggested SZ patients with youth-onset had more severe cognitive deficits, while patients with late-onset retained cognitive functioning (Barder et al., 2013). Based on these findings, a more complex evaluation integrating the current state and illness course as well as other clinical variables is needed to link descriptive psychopathology and neuro-cognition appropriately.

1.5. Objectives and hypotheses

The studies of this dissertation aimed to examine the neurobiology of the major psychiatric disorders using a dimensional investigation of both phenotype as well as neuroanatomy and neuro-cognition.

In particular, the first objective was to establish a cross-validated factor model across disorders comprising a comprehensive set of symptoms including depressive, positive, negative, and anxiety symptomatology. Hereof, this dissertation hypothesized (**H_1**) psychopathology being clustered into three to five factors and these factors being present in all diagnoses tested. Beyond, (**H_2**) the extracted factors of first order would load on more global factors of second order confirming the better fit of hierarchically structured models.

The second objective was to link this model to neurobiological determinants [i.e. brain structure and neuro-cognition]. Referring to brain structural correlates of dimensional psychopathology factors, it was hypothesized (**H_3**) that local GMV associations previously reported in single DSM-IV disorders cut across affective and psychotic disorders. Further, these associations were hypothesized to be independent of diagnostic categories (**H_4**).

Based on previous studies on the associations of psychopathological factors and neuro-cognition, correlations were expected to be state-dependent (**H_5**).

Subsequently, FTD as core psychiatric symptom was mapped for phenotype dimensions as well as neuroanatomical signatures across disorders. Hereby, a factor model including one negative domain and further positive factors was assumed. Additionally, previous gray and white matter alterations reported in SZ only, were expected to be present across diagnoses, too (**H_6**).

2. AGGREGATION OF STUDY RESULTS

2.1. STUDY I: Factor analyses of multidimensional symptoms in a large group of patients with major depressive disorder, bipolar disorder, schizoaffective disorder and schizophrenia

Reference: **Stein F**, Lemmer G, Schmitt S, Brosch K, Meller T, Fischer E, Kraus C, Lenhard L, Köhnlein B, Murata H, Bäcker A, Müller M, Franz M, Förster K, Meinert S, Enneking V, Koch K, Grotegerd D, Nagels A, Nenadić I, Dannlowski U, Kircher T, Krug A. Factor analyses of multidimensional symptoms in a large group of patients with major depressive disorder, bipolar disorder, schizoaffective disorder and schizophrenia. Schizophr Res. 2020 Apr; 218:38-47. doi: 10.1016/j.schres.2020.03.011. (IF 4.6)

Although the dichotomization of „dementia praecox“ and „manic-depressive illness“ by Kraepelin (Kraepelin, 1919) has been confirmed to be useful from a clinical perspective, more than a century of research failed to define "points of rarity" between affective as well as psychotic disorders. In contrast, studies have shown evidence for a cross-disorder overlap in phenomenology (Johns et al., 2004; Rosen et al., 2012; Varghese et al., 2011), molecular genetic risk (Goldsmith et al., 2016;Lee et al., 2019), but also in environmental risk (Uher & Zwicker, 2017). Dimensional approaches rather than categorical comparisons of one disorder and a healthy control group, can serve as an important addition to traditional approaches overcoming a scientific deadlock which has one origin in a misguided reification of DSM diagnostic categories. Dimensional factor analyses can be a useful statistical method to provide significant progress for our understanding of a shared phenomenology. However, previous studies on factorial dimensions were limited to the investigation of only two diagnostic categories, not performing transdiagnostic analyses or only assessing a limited number of symptoms. Only few studies investigated the dimensional factorial structure across disorders showing three to five factors (Romney & Candido, 2001; Serretti et al., 2001; Serretti & Olgiati, 2004). A meta-analysis of five different factor models in SZ, MDD, BD, and patients with anxiety disorders revealed five factors (affective, positive, negative, disorganized, and cognitive processing) (van Dorn et al., 2016). A more recent approach accounting multidimensionality are hierarchical or bi-factorial models assuming broader general domains and additional sub-domains (Reise et al., 2007; Shevlin et al., 2017). Investigation of three psychopathological scales in psychotic disorders indicated one general psychosis dimension, two dimensions of affective and non-affective psychosis and five additional sub-dimensions (Reininghaus et al., 2019).

STUDY I aimed to (1) establish a transdiagnostic psychopathological factor model across MDD, BD, and schizophrenia spectrum disorders (SSD) patients covering mood, anxiety,

and psychotic symptomatology and (2) to explore whether the data would support a hierarchical model. Using five psychopathological scales with a total of 104 symptoms and *N*=1,182 patients, an exploratory and confirmatory cross-validation approach in two samples revealed a statistically valid five factor model comprising the factors *depression*, *negative syndrome*, *positive FTD*, *paranoid-hallucinatory syndrome*, and *increased appetite*. The extracted factors were intercorrelated with the *negative syndrome* and *depression* factors showing largest coefficients. Additionally, two second-order factors showing a comparable fit to unitarian models were extracted: (I) *negative/affective* comprising *depression*, *negative syndrome*, and *increased appetite*, and (II) *positive symptoms* including *positive FTD* and the *paranoid-hallucinatory syndrome*.

STUDY I was able to confirm results from previous studies in general population (Shevlin et al., 2017) and in psychotic patients (Reininghaus et al., 2013) in a transdiagnostic sample.

The factor *increased appetite* emerged as a novel dimension that has been previously only reported in MDD patients showing weight/appetite disturbance factors (Li et al., 2014) but not in psychotic patients. In STUDY I, *increased appetite* was predominantly present in BD patients and was correlated with antidepressant medication but with negligible effects.

Unsurprisingly, factors clustered with DSM-IV categories since diagnoses rest upon symptoms. Still, our identified factors were more or less present in all diagnoses confirming clinical experience (Kircher et al., 2018) as well as neurobiological findings (Chang et al., 2018; Goodkind et al., 2015).

2.2. STUDY II: Psychopathological syndromes across affective and psychotic disorders correlate with gray matter volumes

Reference: **Stein F**, Meller T, Brosch K, Schmitt S, Ringwald K, Pfarr JK, Meinert S, Thiel K, Lemke H, Waltemate L, Grotegerd D, Opel N, Jansen A, Nenadić I, Dannlowki U, Krug A, Kircher T. Psychopathological syndromes across affective and psychotic disorders correlate with gray matter volumes. Schizophr Bull. 2021. DOI: 10.1093/schbul/sbab037. (IF 7.96)

The hypothesis stating that particular psychopathological dimensions have a common brain structural correlate across affective and psychotic disorders has not been confirmed, yet (Wernicke, 1900). Evidence for shared GMV alterations across disorders is given by meta-analyses pooling results of single diagnostic categories (Goodkind et al., 2015), showing common alterations in the dorsal anterior cingulate and bilateral insulae across disorders. Most previous studies focused on the investigation of associations between psychopathological factors and GMV in single diagnosis

categories that especially exhibit symptoms of such factors [i.e. paranoid-hallucinatory syndrome predominately in SZ] albeit these symptoms have been reported in other single diagnosis categories, too [i.e. psychotic symptoms in MDD patients (Johns et al., 2004; Varghese et al., 2011)]. Studies investigating the association of transdiagnostic symptom dimensions and GMV are lacking. Based on findings of categorical comparisons and results from dimensional studies correlating one symptom complex in one disorder, it is reasonable to hypothesize that associations of psychopathological factors and local GMV previously detected in one disorder cut across affective and psychotic disorders.

Given the limitations of previous studies, STUDY II investigated the relationship of regional GMV and data driven transdiagnostic psychopathological factors derived from STUDY I in a sample of *N*=1,069 patients. Using voxel-based morphometry (VBM) whole brain and region of interest (ROI) multiple regression analyses, results of STUDY II confirmed the hypothesis of shared GMV alterations associated with psychopathology across disorders. The *paranoid-hallucinatory syndrome* was negatively associated with GMV of the right fusiform and left middle frontal gyri. *Positive FTD* was negatively correlated with the right middle frontal gyrus. Further ROI analyses confirmed a number of previous results in single diagnostic categories including negative associations of the *negative syndrome* with the bilateral frontal opercula, the *positive FTD* with the amygdala-hippocampus complex as well as the *paranoid-hallucinatory syndrome* with the bilateral thalami, left angular gyrus, left postcentral gyrus, and the left posterior cingulate gyrus. Interaction analyses of psychopathological factors and DSM-IV categorical diagnoses were performed to rule out potential effects driven by unequally distributed diagnostic categories. Results showed no interaction. Additionally, results from the total sample (*N*=1,069) were replicated in an age and sex matched sub-sample (same n per diagnosis), too, which again strengthens the hypothesis of shared transdiagnostic brain structural correlates.

In short, STUDY II offers three new insights: (1) associations of psychopathology and GMV were independent of formal diagnosis, (2) regression analyses were performed independently of the current state of patients, preventing subgroup effects that may arise when applying categorical approaches, (3) illness severity (e.g. life time cumulative duration of hospitalizations) moderated the associations of psychopathology and GMV emphasizing the significance of illness aspects other than clinical diagnosis. Finally, the reported diagnostically independent brain structural correlates of symptom dimensions of STUDY II open up completely new approaches for pathogenic and etiological research.

2.3. STUDY III: State of illness-dependent associations of neuro-cognition and psychopathological syndromes in a large transdiagnostic cohort

Reference: **Stein F**, Schmitt S, Brosch K, Meller T, Pfarr JK, Ringwald K, Lemmer G, Meinert S, Lemke H, Waltemate L, Thiel K, Franz M, Preuss UW, Metzger FG, Nagels A, Nenadić I, Dannlowski U, Kircher T, Krug A. State of illness-dependent associations of neuro-cognition and psychopathological syndromes in a large transdiagnostic cohort. (submitted)

Since there is well documented evidence for shared risk factors (Lee et al., 2019; Uher & Zwicker, 2017) and brain changes (Goodkind et al., 2015; Patel et al., 2020) across affective and psychotic disorders, it is reasonable to assume transdiagnostic neuro-cognitive correlates of psychopathology, as well. Comparable to brain structural correlates, most previous studies focused on formal comparisons of neuro-cognition between patient groups and a healthy control group. While meta-analyses in MDD patients showed small to medium effect sizes of neuro-cognitive impairment (Bora et al., 2013), in BD patients specifically executive functioning and working memory appear to be the most impaired (Mann-Wrobel et al., 2011). In addition, meta-analyses of SZ patients indicated an impairment of a broad spectrum of neuro-cognitive domains being most pronounced in verbal memory, motor skills and executive functioning (Dickinson et al., 2007). Transdiagnostic investigations of neuro-cognition across MDD, BD, and SZ showed differences between patient groups and healthy controls in all cognitive domains. However, motor speed was the only domain that separated affective and psychotic disorders with SZ patients performing worst and MDD and BD were located between SZ and HC performance on motor speed (Huang et al., 2020). These findings give evidence for characteristics different from formal diagnosis better differentiating patient groups (Lee et al., 2017). The dimensional, transdiagnostic investigation of neuro-cognition revealed a number of associations between neuro-cognition and psychopathological factors. For the psychopathological factors drawn from STUDY I these include previous correlations of positive FTD with executive functioning (Nagels et al., 2016) and negative symptoms with working and episodic memory (Delawalla et al., 2006). However, investigation of positive (Delawalla et al., 2006) and affective (Zhu et al., 2019) symptoms indicated no correlations with neuro-cognition. Further, studies suggested current severity and specifically the course of illness to be critically involved in neuro-cognition, indicating neuro-cognitive impairments during acute episodes but not in remission (Bowie et al., 2018; Zaremba et al., 2019). Based on the results of previous studies STUDY III aimed to (1) investigate the association of transdiagnostic psychopathology factors and neuro-cognition using partial correlation analyses corrected for age, sex, verbal IQ, years of education, and DSM-IV diagnostic categories, (2) explore the relation

to current state of illness, and (3) to test moderating effects of illness severity on the neuro-cognition – psychopathology associations. Results of STUDY III (*N*=1,064) showed differential correlations of neuro-cognition and psychopathological factors. Irrespective of the current state of disorder, the factors *negative syndrome*, *positive FTD* and the *paranoid-hallucinatory syndrome* showed largest correlation coefficients. These correlations included verbal fluency (categorical task), verbal working/episodic memory, and executive functioning. Corroborating previous results, state-dependent correlations emerged. In acute patients with a chronic course, *positive FTD* and the *paranoid-hallucinatory syndrome* were correlated with verbal episodic memory, while these correlations were not present in acute patients with remission between episodes. Acute patients with remission between episodes exhibited correlations of the *negative syndrome* with attention, verbal fluency, executive functioning, and verbal working memory and *positive FTD* with executive functioning. In line with previous studies, no correlations between psychopathological factors and neuro-cognition were present in remitted patients. Clinical variables [i.e. age of onset, illness severity] moderated the associations of the *negative syndrome* and *positive FTD* with neuro-cognition. This is in line with previous meta-analytic studies showing SZ patients with youth disorder onset having severe deficits whereas patients with late-onset retained cognitive functioning (Barder et al., 2013). The absence of moderating effects of clinical variables on the neuro-cognition associations with the *paranoid-hallucinatory syndrome* might be explained by being more responsive to antipsychotic medication than for example negative syndromes (Huhn et al., 2019; Veerman et al., 2017).

2.4. STUDY IV: Psychopathological dimensions of formal thought disorder and their relation to gray and white matter brain structure in affective and psychotic disorders

Reference: **Stein F**, Buckenmayer E, Brosch K, Meller T, Schmitt S, Ringwald KG, Pfarr JK, Steinsträter O, Enneking V, Grotegerd D, Heindel W, Meinert S, Leehr E, Lemke H, Thiel K, Waltemate L, Winter A, Hahn T, Dannlowki U, Jansen A, Nenadić I, Krug A, Kircher T. Psychopathological dimensions of formal thought disorder and their relation to gray and white matter brain structure in affective and psychotic disorders. (submitted).

Although FTD is a core symptom of SZ (Kircher et al., 2018), studies have shown elevated thought disorder in MDD and BD as well (Kircher et al., 2014). Further scientific significance for FTD as a core psychiatric syndrome is given by its prognostic features as it is a predictive factor for conversion from at-risk mental states to disorder onset or new episodes as well as for illness severity [i.e. patients with FTD have higher risk for

inpatient treatment (Roche, et al., 2015a)]. Studies on the dimensional factorial structure of this phenotype revealed one to six factors (Andreasen & Grove, 1986; Kircher et al., 2014; Toomey et al., 1997). However, results remain heterogeneous, especially the factorial structure of FTD across affective and psychotic disorder remains largely elusive. Previously, studies have shown one negative/poverty dimension (Nagels et al., 2013), whereas positive FTD has been divided into two to five dimensions in SZ patients (Cuesta & Peralta, 1999; Roche et al., 2015b).

Besides the transdiagnostic investigation of individual FTD dimensions, there is also a need for examining neuroanatomical correlates of this phenotype. Previous research on neuroanatomical substrates of FTD focused on the investigation of SZ patients. Positive FTD has been reported to be negatively correlated with GMV clusters of the bilateral superior temporal gyri, inferior frontal gyri, middle, medial and frontal gyri, and the amygdala-hippocampus complex (Cavelti et al., 2018; Sumner et al., 2018). Negative FTD was shown to be negatively associated with GMV of the bilateral insula, amygdala, and precuneus (Cavelti et al., 2018; Palaniyappan et al., 2015). In addition to GMV alterations, white matter fractional anisotropy (FA) has been used to investigate structural connectivity. In SZ, a general disconnectivity (Rolls et al., 2020) as well as a structural language disconnectivity (Horn et al., 2012) has been reported. Based on previous research on aphasia patients and FTD as a phenotype in SZ, the left uncinate fascicle and inferior fronto-occipital fascicle form part of the ventral language pathway, whereas the dorsal language pathway is constituted by the superior longitudinal fascicle and the arcuate fascicle (Cavelti et al., 2018). In addition, the cingulum bundle (Bopp et al., 2017; Hilal et al., 2020) and the anterior thalamic radiation (Hilal et al., 2020; Viher et al., 2018) have been reported to be implicated in FTD, previously too.

STUDY IV aimed to untangle both FTD phenotype and brain correlates across disorders. Exploratory and confirmatory cross-validation in two samples were used to examine the factorial structure of FTD in *N*=1,071 patients with affective and psychotic disorders. Latent factor scores of this analysis were used to investigate the association between FTD phenotype factors and GMV as well as FA. Interaction analyses were performed to test whether results were driven by DSM-IV single diagnostic categories.

Results indicated a three factor model including the factors *verbosity*, *emptiness*, and *disorganization*. This study extended previous factor models of FTD to a transdiagnostic model which also could be replicated in a matched sample.

FTD factors were differentially associated with gray and white matter brain structure. *Verbosity* was negatively associated with a GMV cluster comprising parts of the temporo-occipital language junction and positively with two fiber tracts [i.e. right posterior cingulum bundle and right inferior longitudinal fascicle]. This GMV cluster is part of the Wernicke

speech area which has been associated with FTD in a number of studies (Horn et al., 2009; Kircher et al., 2018). Further evidence is given from studies investigating aphasia patients linking this anatomical structure to semantic paraphasia and neologisms (Stark et al., 2019) coinciding with the *verbosity* factor of the present study as it includes derailed speech. The association of *verbosity* and the right inferior longitudinal fascicle as part of the semantic ventral stream (Herbet et al., 2018) is supported by previous studies, showing the inferior longitudinal fascicle to be implicated in lexical access (Catani & Dawson, 2017).

The *emptiness* factor was negatively correlated with GMV in the left hippocampus, thalamus and posterior cingulate gyrus, coinciding with results of previous studies (Cavelti et al., 2018; Palaniyappan et al., 2012; Sumner et al., 2018). No associations were present for emptiness and white matter FA.

Finally, the factor *disorganization* was not associated with GMV but with white matter FA. Results included a negative association the bilateral anterior thalamic radiation and a positive association with the hippocampal part of the right cingulum bundle. These findings corroborate previous results as altered FA in the anterior thalamic radiation has been reported in BD (Niida et al., 2018) and SZ (Mamah et al., 2010) patients and has been associated with global FTD language scores (Viher et al., 2018).

Importantly, the results drawn in STUDY IV did not interact with DSM formal diagnosis (factor x DSM-IV diagnostic category), pointing to diagnosis independent associations of FTD and gray and white matte brain structure.

In summary, STUDY IV provides first large-scale evidence for FTD factors being differentially correlated with gray and white matter anatomical brain structures across affective and psychotic disorders. As there was no correlation between gray and white matter brain structures implicated in FTD in this study, STUDY IV speculates the same psychopathological symptoms can result from changes in different neuroanatomical structures.

3. GENERAL DISCUSSION

This dissertation provides an insight into recent approaches investigating the neurobiology of the major psychiatric disorders [i.e. MDD, BD, SSD] on a dimensional, data driven level.

STUDY I established a cross-validated, data driven factor model of psychopathological symptoms across affective and psychotic disorders comprising five factors [i.e. *depression*, *negative syndrome*, *positive FTD*, *paranoid-hallucinatory syndrome*, *increased appetite*] confirming **H_1**. In addition, the extracted factors were not specific for single diagnostic categories pointing to a diagnosis shared phenomenology. **H_2** could also be confirmed as first order factors loaded on second order factors with comparable model fit.

The factor model of STUDY I was used for brain morphometric correlational analyses in STUDY II. Results indicated diagnosis-independent associations of current psychopathology and GMV which is in line with **H_4**. Further ROI based analyses confirmed results from previous studies investigating single disorders, verifying **H_3**.

Furthermore, psychopathological factors from STUDY I were used to examine neuro-cognitive correlates in STUDY III. STUDY III indicated associations of neuro-cognition and psychopathological factors in a state of illness-dependent manner confirming **H_5**. Results showed that almost all cognitive domains were implicated albeit to different degrees. *Positive FTD* and the *negative syndrome* showed most pronounced associations that were additionally moderated by aspects other than clinical diagnosis [i.e. illness severity, age of disorder onset].

Finally, STUDY IV aimed to investigate FTD as core psychiatric syndrome in more detail across diagnoses. Results on the dimensional factorial structure of FTD revealed a three factor model. In a further step, these FTD factors were associated with gray and white matter brain structure. As hypothesized, gray and white matter alterations previously reported in SZ only, were present across diagnosis, approving **H_6** and providing first evidence of common neurobiology substrates involved in FTD across affective and psychotic disorders.

3.1. Dimensional Psychopathology

Given the limitations of traditional psychiatric classification systems and the failure to validate these taxonomic distinctions regarding etiological aspects, there is emerging evidence for the validity of promising new approaches (Feczko et al., 2019; Hengartner & Lehmann, 2017). Hereof, dimensional investigations can be used as a basis for novel

group stratification. STUDY I and STUDY IV of this dissertation introduced a new factorial model across patients suffering from MDD, BD, and SSD.

STUDY IV provided evidence for FTD being present across diagnoses. STUDY IV extended previous factor analytic research revealing three FTD dimensions (i.e. *verbosity*, *emptiness*, *disorganization*) across disorders corroborating results from previous studies in SZ patients (Roche et al., 2015b).

In STUDY I, five factors were extracted. All of the five factors were present in all disorders investigated, mirroring previous studies (Conley et al., 2007; Dutta et al., 2011; Johns et al., 2004; Upthegrove et al., 2016; Varghese et al., 2011) on the overlapping phenomenology across disorders. When comparing the factor dimensions extracted in STUDY I to previous factor analytic studies, high levels of correspondence can be observed. Most previous studies partly focusing on psychotic disorders revealed factor models including depressive, psychosis related, negative and disorganization dimensions (Serretti et al., 2001; Serretti & Olgiati, 2004; van Dorn et al., 2016). This dissertation extended previous studies on psychotic patients by additionally investigating affective disorders, again pointing to a shared phenomenology across disorders that is also reflected by neurobiological studies (Anttila et al., 2018; Chang et al., 2018; Goodkind et al., 2015; Uher & Zwicker, 2017).

In addition, the extracted factors of STUDY I were intercorrelated. Specifically the *depression* and *negative syndrome* factor were correlated, corroborating results from a previous study investigating the general population (Shevlin et al., 2017). This relationship points to a considerable heterogeneity across negative and depressive symptomatology (Krynicki et al., 2018), leading to the question whether these two factors are combined into one factor in larger samples (Shevlin et al., 2017). Still, it is questionable that this observation is caused by the scales used to assess depressive and negative symptomatology that may contain depressive aspects when assessing negative symptoms (Shevlin et al., 2017).

The factor *increased appetite* of STUDY I emerged as a new dimension. In dimensional factor analyses, this dimension has only been reported in an atypical MDD subtype (Li et al., 2014). Interestingly, this factor was predominantly present in BD reflecting results from previous studies reporting atypical depression to be more frequent in BD than MDD (Benazzi, 2005; Łojko et al., 2015).

Moreover, STUDY I aimed to test whether a hierarchically structured model would better fit the data than unitary models. Therefore second-order modeling was performed, focusing on latent traits sharing variance of several sub-domains (Shevlin et al., 2017). Recently, several studies proposed hierarchically or bifactorial models to be better fitted than unitary models (Ahmed et al., 2018; Anderson et al., 2018; Reininghaus et al., 2016;

Shevlin et al., 2017). Specifically bifactorial models testing non-redundant, explained variance have been increasingly supported. Several studies reported such models comprising a general psychopathology factor (e.g. Caspi et al., 2014; Lahey et al., 2012). Results of STUDY I indicated comparable fits between the unitary and hierarchically structured model. Yet, it is questionable whether models building on more global factors [i.e. the p factor] are sufficient to explain the etiology and phenomenology across disorders.

3.2. Neurobiological underpinnings of dimensional psychopathology

Based on the assumption proposed long ago (Wernicke, 1900) of a shared pathophysiology across disorders that has been supported by several studies showing large neurobiological overlapping (Anttila et al., 2018; Chang et al., 2018; Goodkind et al., 2015; Koutsouleris et al., 2015; Lalousis et al., 2021; Uher & Zwicker, 2017), STUDIES II, III, and IV aimed to shed light on the neuro-anatomical and neuro-cognitive correlates across the major psychiatric disorders. The factors derived from STUDIES I and IV were associated with MRI brain structural measures including gray and white matter (only STUDY IV).

The *depression* factor derived from STUDY I did not correlate with GMV and only weakly with verbal fluency and executive functioning. These findings support previous studies reporting chronicity and cumulative severity of depression to be a better predictor than current psychopathology (Grieve et al., 2013; Zaremba et al., 2018a, 2018b).

Brain structural analysis of the *negative syndrome* (STUDY II) indicated a negative correlation with the bilateral frontal opercula volumes, a well-known finding from studies investigating SZ patients (Bergé et al., 2011; Bora et al., 2011; Kim et al., 2017). Additionally, several correlations to neuro-cognitive functioning in acute patients were present including attention, verbal fluency, executive functioning, and verbal memory. Further, this relationship was moderated by illness aspects other than clinical diagnosis highlighting the importance of more complex models integrating dimensional psychopathology and neurobiological measures.

The FTD factors in both STUDIES II and IV were differentially associated with gray and white matter brain structure. Both studies validated findings from studies investigating SZ patients only. Brain structures implicated in FTD included the GMVs of the right middle frontal gyrus, left temporo-occipital language junction, left hippocampus, and the left thalamus. Integrity of white matter microstructural circuits implicated in FTD were the right inferior longitudinal fascicle, the bilateral anterior thalamic radiation as well the posterior and hippocampal part of the cingulum bundle. These brain structures have been reported in numerous studies on speech in aphasia (Binder et al., 2009; Fridriksson

et al., 2009, 2018; Hilal et al., 2020) as well as in FTD (Cavelti et al., 2018; Horn et al., 2009; Palaniyappan et al., 2015; Sumner et al., 2018; Viher et al., 2018). Results of STUDIES II and IV provided first evidence for common neurobiological structures involved in FTD across the major psychiatric disorders indicating further core regions besides the traditional anatomical language structures [i.e. Broca area, Wernicke area, dorsal and ventral stream (Hickok & Poeppel, 2007)] being relevant to impaired speech. On a neuro-cognitive level, positive associations of *positive FTD* (factor derived from STUDY I) to verbal episodic memory in patients with a chronic course and to executive functioning in acute patients emerged. The GMV cluster negatively associated with FTD in STUDY II is part of the prefrontal cortex which has in turn previously reported to be related to executive functioning (Orellana & Slachevsky, 2013), indicating a complex interrelationship between brain structure, psychopathology and executive functioning.

GMV correlates of the *paranoid-hallucinatory syndrome* reported in STUDY II included a negative association with the right fusiform and left middle frontal gyri. Both anatomical structures have been reported previously in SZ (Mucci et al., 2019; Nenadic et al., 2010; Padmanabhan et al., 2015; Palaniyappan et al., 2012; Stan et al., 2020). Furthermore, a meta-analysis indicated that reductions in the right fusiform gyrus have largest effect sizes (van Erp et al., 2018). Results provided by this dissertation indicate a network of temporal and frontal regions implicated in hallucinations and delusions across disorders that needs further validation. Only weak associations between neuro-cognitive measures and the *paranoid-hallucinatory syndrome* were found in this dissertation which might reflect better treatment response (Huhn et al., 2019; Veerman et al., 2017).

Finally, interaction analyses in STUDIES II and IV revealed no results, pointing to diagnosis independent associations between psychopathology and brain structure, also mirroring results from other MRI (Chang et al., 2018; Goodkind et al., 2015; Kaczkurkin et al., 2018; Patel et al., 2020), molecular genetics (Anttila et al., 2018; Pettersson et al., 2016), and environmental risk (Uher & Zwicker, 2017) studies proposing large biological overlap across disorders. Genetic and environmental factors impact the developing brain at distinct time points with differential intensity. Affected networks or locations might depend on the factors impacting the brain. Networks being involved during development may regulate psychopathological symptoms after disorder onset.

In the end, this dissertation hints at the need for more complex models integrating psychopathology, neuro-anatomy, and neuro-cognition.

3.3. Limitations

Some limitations should be noted for the studies reported in this dissertation. First, in all four studies, diagnostic categories were unequally distributed since the MDD group was

the largest. The dimensional factor models in STUDY I and STUDY IV might be biased by different sample sizes. However, following the idea of no points of rarity equally distributed diagnostic categories might have resulted in different loadings on the factors but not in a different factorial model. Yet, this hypothesis needs to be confirmed by further studies applying the factor models proposed in this dissertation.

Second, in brain structural STUDIES II and IV associations of psychopathology factors and GMV were based on current symptoms ignoring past psychopathology. Current symptoms might be an indication for state-independent anatomical alterations outlasting current symptoms. Still, the investigation of both lifetime psychopathology and longitudinal factor models as well as brain structural correlates would help to better understand the underlying pathophysiology.

Third, in STUDIES II and IV, acute pharmacological treatment was accounted for, using three dummy coded variables considering the intake of antidepressants, mood stabilizers, and antipsychotics. It is unclear whether the lifetime intake of psychotropic medication might have biased our results. Albeit factors from STUDY I were merely associated with medication, a potential influencing effect cannot be excluded which might be applicable for STUDY III, too.

Fourth, the results presented in this dissertation were restricted to MDD, BD and SSD patients. In order to implement a comprehensive dimensional model, mental disorders besides the major psychiatric disorders need to be integrated as well.

Finally, numerous tests were performed, particularly in STUDY III. Although rigorous correction for multiple testing was applied in all studies, there is still a risk of type I errors. Therefore, the factorial models presented in this dissertation need to be replicated in independent, comparable cohorts. Gaining a better understanding of the neurobiological underpinnings across disorders, results from brain structural and neuro-cognitive STUDIES II, III, and IV need to be validated, as well.

3.4. Integration and implications

This dissertation provided evidence for the feasibility of dimensional approaches by establishing transdiagnostic factor models and by linking specific factors to brain structural and neuro-cognitive measures across disorders. Results endorsed the hypothesis of particular symptom complexes (i.e. syndromes/factors) sharing common (neuro-) biological mechanisms independent of ICD or DSM diagnostic categories (Chang et al., 2018; Goodkind et al., 2015; Kaczkurkin et al., 2018; Patel et al., 2020). While the results reported in this dissertation support hierarchically structured psychopathology models as proposed by other studies (Reininghaus et al., 2019; Shevlin et al., 2017), further research on the exact number of factors and levels across mental

disorder is needed. Even though initiatives as the studies reported here or Hi-TOP (Kotov et al., 2017) might be a starting point for a new topology or ultimately nosology in psychiatry, it is unclear whether such approaches can replace diagnostic categories. While there is support for completely abandoning traditional classification systems (Hengartner & Lehmann, 2017), a double tracked attempt, integrating categorical and dimensional definitions (Helzer et al., 2006) might achieve a better understanding of the etiology of mental disorders, as well. Retaining traditional classifications systems in clinical practice might be useful in terms of providing specificity and consistency (Helzer et al., 2006) across multiple nations. However, adding dimensional aspects to these systems would open up a completely new window to etiological research across disorders. An example for such an approach might be the study by Shankman et al. that adapted the structural clinical interview for DSM by adding dimensional severity scales. Results of this study indicated superior psychometric properties of the combined assessment of categorical and dimensional measures when compared to categorical diagnoses only (Shankman et al., 2018). Nevertheless, before adding or exclusively implementing such dimensional measures, the utility and validity of the dimensional models proposed within and across disorders needs further investigation in terms of replicating studies and longitudinal designs testing the stability of these models. Besides the implementation of transdiagnostic dimensional models, there is also a need to validate these models in terms of etiological measures including molecular genetics, neuro-anatomy and function, and environmental risk (Conway et al., 2019).

Finally, not only the etiological validity but rather the predictive validity of dimensional psychiatry needs to be further investigated, e.g. by machine learning models. Hereof, further research is needed to test whether dimensional compared to categorical approaches can adequately predict onset, conversion, and course of disorder. Even though, several attempts have been made to determine a set of prediction factors, there is still a need to examine the interplay of multiple metrics across disorders (Ermers et al., 2020).

In the end, this dissertation hints at the benefits of dimensional approaches. Even though, further investigation is needed to implement dimensional approaches in clinical practice as well as research, a dimensional nosology raises the possibility to significantly improve treatment and therapy across diagnosis as current treatments are based on research building on traditional diagnostic categories, resulting in weak to moderate and further heterogeneous treatment effects (de Vries et al., 2018; Imel et al., 2008).

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SUMMARY

For a long time, traditional classification systems have been used to categorize mental disorders into strict classes based on a set of specific and standardized criteria. Such classifications assume a clear cut off between disorders. However, research using these classification systems fail to identify transdiagnostic markers and “points of rarity” separating mental disorders. Categorical approaches are limited by the large neurobiological overlapping of phenomenology as well as molecular genetics, neuro-anatomy and function, and environmental risk across disorders. Moreover, categorical approaches merely consider characteristics above and below the given categorical thresholds using not otherwise specified diagnoses, not fitting to other officially specified categories. Given the limitations of categorical approaches, dimensional factor models can be used as a valuable framework providing significant progress for the understanding of the neurobiology of the major psychiatric disorders (major depressive disorder, bipolar disorder, schizophrenia spectrum disorder).

Previous studies show a range of different factor models, indicating that descriptive psychopathology might be organized in a bifactorial or hierarchical framework. However, there is still a lack of comprehensive factorial models comprising a broad range of symptoms across the major psychiatric disorders.

Moreover, the neuro-anatomical and neuro-cognitive correlates of transdiagnostic psychopathological factors remain largely elusive. Categorical studies on overlapping gray matter volume alterations across disorders compared to a healthy control group show paralimbic and heteromodal regions to be commonly altered across disorders. In addition, the transdiagnostic investigation of neuro-cognitive measures shows large overlaps and comparable results across disorders and domains with motor speed being the only domain separating disorders.

To overcome the reported obstacles, the studies underlying this dissertation investigate the factorial structure of a broad range of psychopathological symptoms across affective and psychotic disorders. Further, dimensional factors are used to determine the underlying neuro-anatomical and neuro-cognitive correlates of descriptive psychopathology.

STUDY I demonstrates a cross-validated factor model comprising five first order and two second order factors, supporting the use of hierarchical models. The extracted first order factors (*depression*, *negative syndrome*, *positive formal thought disorder*, *paranoid-hallucinatory syndrome*, *increased appetite*) are present in all diagnostic categories, suggesting a diagnosis-shared phenomenology.

STUDY II examines the brain structural correlates of the factors derived from STUDY I. Results include a negative association of the *negative syndrome* with the bilateral frontal opercula. *Positive formal thought disorder* is negatively associated with the right middle frontal gyrus and with the left amygdala-hippocampus-complex. The *paranoid-hallucinatory syndrome* is negatively associated with two whole brain clusters (right fusiform gyrus and left middle frontal gyrus) as well as regions-of-interest including the left angular gyrus, bilateral thalami, left postcentral gyrus and left posterior cingulate gyrus.

Investigating the neuro-cognitive correlates of psychopathological factors, STUDY III indicates state of illness-dependent associations in almost all cognitive domains. While *positive formal thought disorder* and the *negative syndrome* show most pronounced correlations, no or only weak correlations emerge for the other factors.

Finally, STUDY IV investigates formal thought disorder in more detail. Results indicate a three factor model (*verbosity*, *emptiness*, *disorganization*) that is differentially associated with gray and white matter brain structure. The *verbosity* factor is negatively associated with gray matter volume of the temporo-occipital language junction and positively with the white matter microstructure of the inferior longitudinal fascicle and the posterior part of the cingulum bundle. *Emptiness* is negatively associated with the gray matter volume of the left hippocampus and thalamus but not with white matter. The *disorganization* factor associates with the white matter structure of the bilateral anterior thalamic radiation and with the hippocampal part of the right cingulum bundle.

In conclusion, this dissertation can be interpreted as a first effort overcoming the limitations given by previous categorical approaches. The psychopathological factor models reported are linked to brain structural and neuro-cognitive measures, supporting the view of diagnosis shared and independent biological mechanisms. The studies of this dissertation open up completely new approaches for pathogenic and etiological research. Dimensional methods as applied in this dissertation constitute the basis for a new taxonomy that can in a next step be used to improve prediction, treatment and therapy of the major psychiatric disorders.

ZUSAMMENFASSUNG

Seit geraumer Zeit werden traditionelle Klassifizierungssysteme dazu verwendet, psychische Störungen anhand einer Reihe spezifischer und standardisierter Kriterien in diverse Klassen einzuteilen. Diese Vorgehensweise nimmt eine klare Abgrenzung zwischen einzelnen psychischen Störungen an. Kategorialen Studien ist es bisher jedoch nicht gelungen diagnosespezifische Marker sowie Seltenheitspunkte, welche die einzelnen Diagnosekategorien trennen, zu identifizieren. Kategoriale Ansätze sind durch die neurobiologischen Überschneidungen von Phänomenologie sowie molekularer Genetik, Neuroanatomie und -funktion und Umweltrisiken bei verschiedenen Störungen begrenzt. Darüber hinaus werden Charakteristika ober- und unterhalb spezifischer Diagnosekriterien nur hinreichend mittels nicht näher spezifizierten Diagnosen, welche nicht die Kriterien anderer offizieller Diagnosen erfüllen, berücksichtigt.

Angesichts der Einschränkungen kategorialer Ansätze, können dimensionale Faktormodelle als wertvolle Ergänzung verwendet werden, um das neurobiologische Verständnis psychiatrischer Störungen (Majore Depression, bipolare Störung, Schizophrenie-Spektrum-Störungen) zu verbessern.

Obwohl frühere Studien eine Reihe von verschiedenen Faktorenmodellen innerhalb bestimmter Diagnosekategorien zeigen, die darauf hinweisen, dass die deskriptive Psychopathologie bifaktoriell oder hierarchisch organisiert sein könnte, steht die umfassende Untersuchung eines breiten Spektrums von Symptomen noch aus.

Darüber hinaus sind die neuroanatomischen und neurokognitiven Korrelate transdiagnostischer, psychopathologischer Faktoren nach wie vor weitgehend unbekannt. Kategoriale Studien zu überlappenden Veränderungen des Volumens der grauen Substanz zeigen, dass paralimbische und heteromodale Regionen bei psychiatrischen Störungen verglichen zu einer gesunden Kontrollgruppe gleichermaßen verändert sind. Im Hinblick auf neurokognitive Domänen bestehen deutliche Überlappungen. Lediglich die motorische Geschwindigkeit scheint eine Trennung zwischen den Störungen zu ermöglichen. Ziel der Studien dieser Dissertation ist es, die dimensionale Struktur eines breiten Spektrums von psychopathologischen Symptomen über affektive und psychotische Störungen hinweg zu untersuchen. Auf Basis der extrahierten Faktoren werden die zugrundeliegenden neuroanatomischen und neurokognitiven Korrelate genauer untersucht.

STUDIE I zeigt ein kreuzvalidiertes Faktorenmodell mit fünf Faktoren erster Ordnung und weiteren zwei Faktoren zweiter Ordnung, was die Verwendung von hierarchischen Modellen unterstützt. Die extrahierten Faktoren erster Ordnung („*depression*, *negative syndrome*, *positive formal thought disorder*, *paranoid-hallucinatory syndrome, increased*

appetite“) sind in allen diagnostischen Kategorien vorhanden, was auf eine diagnoseübergreifende Phänomenologie hindeutet.

STUDIE II untersucht die hirnstrukturellen Korrelate der aus STUDIE I abgeleiteten psychopathologischen Faktoren. Das „*negative syndrome*“ ist mit einer Volumen Reduktion in den bilateralen frontalen Opercula assoziiert, wohingegen der Faktor „*positive formal thought disorder*“ mit dem rechten mittleren frontal Gyrus und mit dem linken Amygdala-Hippocampus-Komplex negativ assoziiert ist. Der Faktor „*paranoid-hallucinatory syndrome*“ ist mit dem rechten fusiformen Gyrus als auch dem linken mittleren frontal Gyrus sowie weiteren „regions-of-interest“, darunter der linke Gyrus angularis, bilaterale Thalami, der linke postzentrale Gyrus und der linke posteriorer cinguläre Gyrus negativ assoziiert.

Die Untersuchung neurokognitiver Korrelate der psychopathologischen Faktoren zeigt in STUDIE III Assoziationen zu einer Vielzahl kognitiver Domänen, welche vom aktuellen Patientenzustand abhängig sind. Während die Faktoren „*positive formal thought disorder*“ und „*negative syndrome*“ ausgeprägte Korrelationen zur Neurokognition aufweisen, können diese nicht für die anderen Faktoren nachgewiesen werden.

Schließlich ist es Ziel von STUDIE IV formale Denkstörungen genauer zu untersuchen. Es kann ein drei Faktoren Modell mit dem Faktoren „*verbosity*“, „*emptiness*“ und „*disorganization*“ ermittelt werden, was differentiell mit der grauen als auch weißen Substanz korreliert. Der Faktor „*verbosity*“ ist negativ mit dem Volumen der grauen Substanz des temporo-occipitalen Sprachnetzwerks und positiv mit der weißen Substanz des inferioren longitudinalen Faserbündels und des posterioren Teils des cingulären Faserbündels assoziiert. Der Faktor „*emptiness*“ korreliert negativ mit der grauen Substanz des linken Hippocampus und des Thalamus, nicht jedoch mit den Faserbündeln der weißen Substanz. Der Faktor „*disorganization*“ ist mit der bilateralen anterioren Thalamusstrahlung und mit dem hippocampalen Teil des rechten cingulären Faserbündels assoziiert.

Zusammenfassend kann diese Dissertation als eine erste Arbeit interpretiert werden, welche die Einschränkungen kategorialer Ansätze überwindet. Die berichteten psychopathologischen Faktormodelle sind mit hirnstrukturellen und neurokognitiven Maßen verknüpft, was die Auffassung von diagnoseübergreifenden und unabhängigen biologischen Mechanismen unterstützt. Die Studien dieser Dissertation eröffnen völlig neue Ansätze für die pathogenetische und ätiologische Forschung. Dimensionale Methoden, wie sie in dieser Dissertation angewandt werden, bilden die Grundlage für eine neue Taxonomie, welche in einem nächsten Schritt zur Verbesserung der Prädiktion, Behandlung und Therapie der wichtigsten psychiatrischen Störungen dienen kann.

A. APPENDIX

i. STUDY I: Publication Stein et al. (2020)

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Factor analyses of multidimensional symptoms in a large group of patients with major depressive disorder, bipolar disorder, schizoaffective disorder and schizophrenia

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ABSTRACT

Background: There is an ongoing discussion about which neurobiological correlates or symptoms separate the major psychoses (i.e. Major Depressive Disorder MDD, Bipolar Disorder BD, and Schizophrenia SZ). Psychopathological factor analyses within one of these disorders have resulted in models including one to five factors. Factor analyses across the major psychoses using a comprehensive set of psychopathological scales in the same patients are lacking. It is further unclear, whether hierarchical or unitarian models better summarize phenomena.
Method: Patients ($n = 1182$) who met DSM-IV criteria for MDD, BD, SZ or schizoaffective disorder were assessed with the SANS, SAPS, HAMA, HAM-D, and YMRS. The sample was split into two and analyzed using explorative and confirmatory factor analyses to extract psychopathological factors independent of diagnosis.
Results: In the exploratory analysis of sample 1 ($n = 593$) we found 5 factors. The confirmatory analysis using sample 2 ($n = 589$) confirmed the 5-factor model ($\chi^2 = 1287.842$, $df = 571$, $p < .0001$: $CFI = 0.932$; $RMSEA = 0.033$). The 5-factors were depression, negative syndrome, positive formal thought disorder, paranoid-hallucinatory syndrome, and increased appetite. Increased appetite was not related to medication. None of the factors was specific for one diagnosis. Second order factor analysis revealed two higher order factors: negative/affective (I) and positive symptoms (II).
Conclusion: This is the first study delineating psychopathological factors in a large group of patients across the spectrum of affective and psychotic disorders. In future neurobiological studies, we should consider transdiagnostic syndromes besides the traditional diagnoses.

1. Background

The division into dementia praecox and manic-depressive illness by Emil Kraepelin (Kraepelin, 1919) is still implicitly held in contemporary diagnostic systems. Kraepelin described these two disorders as separate nosological entities with putatively different etiology, symptomatology and outcome. Although this dichotomy is clinically useful, more than a century of intensive research has not been able to define a "point of rarity" between schizophrenia and affective disorders. There is now strong evidence that psychotic (schizophrenia, SZ; schizoaffective disorder, SZA) and affective disorders (Major Depressive Disorder, MDD; Bipolar Disorder, BD), henceforth referred to as Major Psychoses, are overlapping regarding outcome, course and phenomenology. Importantly, recent neurobiological research found the Major Psychoses across diagnoses share familial and molecular genetic risks (Brainstorm

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Consortium et al., 2018), environmental risks (Uher and Zwicker, 2017), brain changes (Chang et al., 2018; Goodkind et al., 2015) and other neurobiological "markers" (Goldsmith et al., 2016). Therefore it is time to rethink the taxonomy of the Major Psychoses, and several approaches have been made to overcome the scientific deadlock (Allardyce et al., 2007; Dikeos et al., 2006; Reininghaus et al., 2019, 2016). In the past, neurobiological research usually has focused on comparing one phenomenologically diagnosed patient group to a healthy control group (e.g. regarding brain structure, risk alleles, cytokines, etc.). This approach does not take into account the overlapping phenomenology and neurobiology across the psychotic and affective disorders (Allsopp et al., 2019). We therefore suggest a new avenue for group stratification that can in a second step, be validated using external criteria (course of illness, neurobiological findings, functional outcome, etc.). This novel typology may result in a new taxonomy or ultimately nosology.

We propose, that descriptive psychopathology across the psychotic and affective disorders constitutes a basis for novel group stratification (Conway et al., 2019). In the past, the standard approach has been factor analyses of symptoms using operationalized scales. Factor analyses across the major psychoses using a comprehensive set of psychopathological scales in the same patient groups are lacking.

1.1. Factor models within diagnoses

There are many studies on psychopathological factor analyses within one of the clinically defined DSM or ICD diagnoses. Factor models in psychotic disorders (SZ or schizophrenia spectrum) have revealed three to eleven factors using one or two psychopathological scales in the same patients (Emsley et al., 2003; Liddle, 1987; Peralta et al., 1997; Peralta and Cuesta, 1999; Rapado-Castro et al., 2010). In DSM-IV defined MDD, studies reported one (Li et al., 2014) to four factors. Within patients suffering from BD, studies showed five to seven factors (Baek et al., 2018; Hanwella and de Silva, 2011; Harvey et al., 2008; Sato et al., 2002).

1.2. Hierarchical models within diagnoses

A more recent approach accounting for multidimensionality of psychopathological symptoms is hierarchical or bifactorial models. Both models assume one or more general domains that are considered to be conceptually broader than sub-domains (Reise et al., 2007; Shevlin et al., 2017). While bifactorial models test the nonredundant, explained variance by competing general and specific factors, second-order modeling focusses on latent traits that share variance of several subdomains (Shevlin et al., 2017).

In psychotic disorders (DSM-IV, using The Comprehensive Assessment of Symptoms and History, CASH (Andreasen et al., 1992) there was evidence for a low- and higher-order factor structure showing four primary factors (depression, catatonia, bizarre delusions, paranoid delusions) and five second-order factors (bipolar negative-mania, disorganization, psychomotor retardation, hallucinations, grandiosity) (Peralta et al., 2013). A cross-cultural study using the Brief Negative Symptom Scale (BNSS) in SZ/SZA (DSM-IV/ICD-10) showed a hierarchically structured model displaying five first order (anhedonia, asociality, avolition, blunted affect, alogia) and two second order factors (Ahmed et al., 2018). Comparing unitary, bifactorial and multidimensional models in psychotic disorders, a general psychosis factor including negative and positive symptoms and five specific factors (negative symptoms, positive symptoms, mania, disorganization and depression) (Reininghaus et al., 2013) have been extracted.

1.3. Factor models across diagnoses

There are only very few studies investigating the dimensional factor structure across disorders. A meta-analysis of five studies (using the PANSS or BPRS) focusing on SZ patients and a small MDD, BD and other diagnosis (e.g. anxiety) sample showed in a split-half exploratory and confirmatory analysis five factors: affective, positive, negative, disorganized, and cognitive processing (Van Dorn et al., 2016). Confirmatory analyses of six competing factor models investigating lifetime symptoms (OPCRIT), including SZ patients, delusional disorder and BD (DSM-IV) indicated that dimensions are better described by a 4- or 5-factor model than by models with fewer factors (Serretti and Olgiati, 2004). Symptom dimensions in a sample of SZ and MDD patients (DSM-III-R) could be explained by a 3-factor model encompassing depression, positive and negative symptoms (Romney and Candido, 2001). In a study investigating lifetime symptoms (OPCRIT), four symptom dimensions (excitement, psychotic, depression, and disorganization) could be identified in a group of SZ, delusional disorder, BD and MDD patients (DSM-IV) (Serretti et al., 2001).

Some studies found also hierarchical solutions across diagnoses. Using the OPCRIT a study (Reininghaus et al., 2016) showed that symptom dimensions in BD and SZ (DSM-IV) can be best described by a bifactor model with one general transdiagnostic psychosis factor and five additional dimensions (positive, negative, disorganized, manic and depressive). Investigation of PANSS items in BD, SZ and SZA (DSM-IV) showed evidence for a bifactorial model with better fit than in a unitary 5-factor model (Anderson et al., 2018). Another study applying the PANSS, YMRS, MADRS in SZ, SZA or BD with psychotic features (DSM-IV) revealed one general psychosis dimension, two dimensions of affective and non-affective psychosis, and additional five specific dimensions (Reininghaus et al., 2019).

1.4. Present study

In summary, previous studies that have included patients across diagnoses often (1) are limited to two diagnoses or even to subgroups within a diagnosis (e.g. BD with psychotic features), (2) have assessed patient reported lifetime psychopathology, which is of somewhat limited validity, (3) have focused on acute inpatients not giving tribute to (partly or fully) remitted patients, and/or (4) only have assessed a limited number of symptoms mostly focusing on psychotic or affective symptoms, assessed by no more than three operationalized rating scales, thus not covering a broad psychopathological spectrum. (5) Further, it is unclear whether hierarchical or non-hierarchical models best describe the factor structure across diagnoses. To overcome these limitations, our first aim was to establish a psychopathological factor model in a large, transdiagnostic group of MDD, BD, and schizophrenia disorders (henceforth referred as SZ) patients using a comprehensive set of psychopathological scales measuring mood, anxiety and psychotic symptomatology (i.e. SANS, SAPS, HAM-D, HAMA, and YMRS). Our second aim was to explore whether our data support a hierarchical model.

2. Method

2.1. Participants

All patients were recruited as part of the FOR2107 cohort, a bicentral (cities of Marburg und Münster, Germany) study focusing on the neurobiology of the major psychoses (for detailed information see (Kircher et al., 2018b) and www.for2107.de). Patients were recruited from in- and out patients of the university hospitals in Marburg and Münster, from the departments of participating local hospitals in about 50 km radius around these cities, and via postings in local newspapers and flyers. Exclusion criteria for this study were IQ < 80, history of head trauma or unconsciousness, medical illnesses (cancer, autoimmune diseases, and infections), neurological illness, and substance dependence. After excluding patients with incomplete data, we analyzed 1182 (remitted, acute and chronic) in- and out-patients (aged 18–65) who met DSM-IV criteria for MDD (296.2× or 296.3×, $n = 887$, f = 571/m = 316), BD (292.5×, 292.6×, 292.7×, 296.0×, 296.4×, 296.5×, 296.6×, 296.7× or 296.8×, $n = 151$, f = 81/m = 70), and SZ (295.X,

295.7 $n = 144$, f = 65/m = 79)) (see Tables 1a and 1b). All patients were interviewed at the Departments of Psychiatry and Psychotherapy in Marburg or Münster, Germany. Procedures were approved by the local Ethics Committee according to the Declaration of Helsinki and patients gave written informed consent to the study protocol. Patients received a finical compensation after finishing the participation.

2.2. Psychopathological assessment

Psychopathological phenomena were assessed during a clinical interview including SCID-I and different psychopathological scales. Ratings were done during or immediately after the interview. We restricted our analyses to rater based scales to increase reliability and to reduce heterogeneity. The following scales were used: the SANS and the SAPS are two six-point scales that assess current positive or negative symptoms (Andreasen, 1984, 1983). Within our study the temporal assessment was the last two weeks. The HAMA includes 14 symptoms, rated on a five-point scale, that are related to psychic and somatic anxiety during the last seven days (Hamilton, 1959). The HAM-D contains 17 items measuring depressive symptoms during the last seven days. The scaling in some variables is defined by increasing severity, while others are rated by equal-valued terms (Hamilton, 1960). The Young Mania Rating Scale (YMRS) is a 5-point scale consisting of 11 items measuring current manic symptoms (Young et al., 1978). All interviewers were psychologists, familiar with and trained in the evaluation of the respective psychopathological scales. Interrater reliability (ICC) achieved excellent values of >0.86 in all scales.

2.3. Statistical analyses

Descriptive statistics for age, sex, age of onset, functioning, educational level and sum scores of the psychopathological scales were calculated and summarized in Table 1a and 1b. First we separated the sample ($n = 1182$) into two samples (sample 1: $n = 593$ and sample 2: $n = 589$) using the "mindiff" package (Papenberg, 2019) in R (R Development Core Team, 2008) taking into account sex and age as covariates. This package separates groups by minimizing differences with regard to certain criteria. In a next step we carried out an explorative factor analysis (EFA) of sample 1 to investigate the factorial symptom structure of several psychopathological scales. Therefore we used the *Statistical Package for Social Science* (IMB, SPSS), version 22, Armonk, NY. Varimax rotation was chosen to be consistent with previous studies. As criterion for factor extraction we chose the Kaiser's (Kaiser, 1960) eigenvalue greater-than-one, since this standard procedure is probably one of the most reliable methods (Peralta and Cuesta, 1999). Due to different scaling z-transformed values were used for analyses.

The global syndrome-rating scores of SANS and SAPS were not included in the analyses, because they merely summarize single symptom ratings. Due to no variance, items 5a and b of HAM-D (measuring loss of weight) and item 9 of YMRS (disruptive-aggressive behavior) were not included in the analysis. According to the scree plot, we examined the factor structure of a 4, 5, and 6-factor model. Suitability of data was checked using Kaiser-Meyer-Olkin test (KMO) (Kaiser, 1974) and Bartlett's test of sphericity (Bartlett, 1937). The internal consistency of the extracted explorative factors was tested with Cronbach's alpha coefficients (Cronbach, 1951).

In a next step a confirmatory factor analysis (CFA) was performed on the second sample using M*plus* (version 8). Goodness of fit was measured with: chi-square significance test, comparative fit index (CFI) (Bentler, 1990), and Root Mean Square Error of Approximation (RMSEA) (Steiger, 1990). The chi-square test tests the strict null hypothesis of a perfect model fit. Because of this strictness and because the chi-square value increases not only with deviance of the replicated variance-covariance matrix from the empirical matrix but also with sample size. CFI values equal or >0.90 can be classified as acceptable (Bentler, 1990). RMSEA values equal or <0.05 indicate good fit (Browne and Cudeck, 1993). The model was estimated using the MLR method (Muthén and Muthén, 1998). Additionally, we tested the model for the whole sample ($n = 1182$). Finally, we also performed a second order analysis investigating factors of higher order (within the whole sample).

Table 1a
Characteristics of sample 1 $n = 593$ patients.

	Major depressive disorder ($n = 444$)	Bipolar disorder ($n = 76$)	Schizophrenia disorders ($n = 73$)	Group comparison (*F*-values in brackets)
Age	37.16 (13.27)	41.78 (12.28)	38.22 (12.1)	$p = .02$[a] (4.11)
Sex	f = 286, m = 158	f = 41, m = 35	f = 33, m = 40	$p = .003$
Educational level (in years)	13.19 (2.81)	13.72 (2.81)	12.15(2.88)	$p = .003$[b] (5.85)
Age of onset	26.23 (12.86)	24.44 (10.78)	22.17 (8.59)	$p = .024$[c] (3.78)
SANS	7.26 (8.09)	6.14 (7.92)	12.95 (11.19)	$p < .0001$[d] (15.67)
SAPS	0.7 (2.07)	2.08 (3.54)	9.48 (13.19)	$p < .0001$[e] (92.78)
HAMA	12.28 (8.63)	9.37 (7.56)	8.85 (6.34)	$p < .0001$[f] (8.28)
HAM-D	8.61 (6.75)	6.21 (5.72)	5.84 (4.66)	$p < .0001$[g] (9.11)
YMRS	1.38 (1.94)	3.21 (4.68)	2.33 (4.56)	$p < .0001$[h] (15.27)
GAF	63.8 (16.24)	58.58 (17.07)	52.05 (17.6)	$p < .0001$[i] (13.53)

Values indicate means of total values and standard deviations (SD) (in brackets). Post hoc differences between groups:
[a] =MDD < BD.
[b] =SZ < MDD.
[c] =SZ < MDD.
[d] =MDD < SZ; BD < SZ.
[e] =MDD < SZ; BD < SZ.
[f] =MDD > SZ, BD.
[g] =SZ < MDD; SZ < BD.
[h] =MDD < BD,SZ.
[i] =MDD > SZ.

Table 1b
Characteristics of sample 2 n = 589 patients.

	Major depressive disorder (n = 443)	Bipolar disorder (n = 75)	Schizophrenia disorders (n = 71)	Group comparison (F-values in brackets)
Age	37.15 (13.23)	41.79 (12.66)	38.2 (11.01)	p = .016[a] (4.16)
Sex	f = 285, m = 158	f = 40, m = 35	f = 32, m = 39	p = .003
Educational level (in years)	13.07 (2.63)	13.96 (2.87)	12.42 (2.42)	p = .003[b] (5.84)
Age of onset	26.25 (12.73)	25.37 (12.01)	22.18 (9.47)	p = .039[c] (3.26)
SANS	8.16 (9.38)	5.13 (6.76)	15.07 (13.43)	p < .0001[d] (21.14)
SAPS	0.7 (2.21)	2.87 (4.83)	10.97 (11.44)	p < .0001[e] (145.8)
HAMA	13.07 (8.81)	9.44 (7.08)	10.72 (8.1)	p < .0001[f] (7.24)
HAM-D	8.59 (6.3)	6.67 (5.91)	7.73 (6.1)	p = .037[g] (3.31)
YMRS	1.52 (2.38)	4.8 (6.87)	3.07 (4.74)	p < .0001[h] (29.43)
GAF	62.08 (15.84)	61.74 (11.39)	48.49 (16.79)	p < .0001[i] (20.15)

Values indicate means of total values and standard deviations (in brackets). Post hoc differences between groups:
[a] =MDD < BD.
[b] =MDD < BD; SZ < BD.
[c] =SZ < MDD.
[d] =MDD < SZ; BD < SZ; MDD > BD.
[e] =MDD < SZ; MDD < BD; BD < SZ.
[f] =BD < MDD.
[g] =BD < MDD.
[h] =MDD < BD, SZ.
[i] =MDD > SZ; BD > SZ.

To satisfy traditional clinical convention we performed one-way ANOVAs studying latent mean differences in factor scores across the categorical diagnosis groups using Tuckey's post hoc test.

Moreover, we were interested in differences in factor scores regarding the clinical status of the patients. Based on remission cut-offs for each scale (Andreasen et al., 2005; Berk et al., 2008; Heinig et al., 2017; Riedel et al., 2010) and on the information about the clinical course (operationalized by item 90 of the OPCRIT 4 (McGuffin et al., 1991), we divided patients into three groups. The specific criteria were as follows: "acute" status: SANS global ratings (items 7, 12, 16, and 21) >2 (Andreasen et al., 2005), SAPS global ratings (items 7, 20, 25, 34) >2 (Andreasen et al., 2005), HAMA sum score >19 (Heinig et al., 2017), HAM-D sum score (17 item version) >6 (Riedel et al., 2010), and YMRS sum score >4 (Berk et al., 2008). When exceeding one of the above remission criteria cut-off, the patient was classified as "acute". A "chronic course" was defined as item 90 of the OPCRIT 4 scoring >2, a clinical course with times in full "remission" was defined as item 90 of the OPCRIT 4 scoring ≤2. The groups were defined as "acute patients with a chronic course", as "acute patients with full remission between episodes", and "remitted patients" at the time of psychopathological assessment.

3. Results

The sociodemographic and clinical characteristics of the participants are described in Tables 1a and 1b.

3.1. Explorative factor analysis

The KMO score of sample adequacy was 0.771 indicating that the data fit the factor model well. Barlett's test of sphericity showed highly significant values (χ^2 = 2283.291, df = 5151). Small factor loadings <0.5 were not considered (Pituch and Stevens, 2015). After varimax rotation, the determined eigenvalue >1 criterion and the suggestion of the ScreePlot, factor analyses revealed a 5-factor structure (Table 2). The symptoms summarized in factor models with less than five factors did not make sense clinically, such that patients with combinations of these symptoms would be extremely unusual and rare. A factor model with more than five factors could be declined due to less internal consistency, implausible factors and less plausibility in the dimensional content.

The 5-factor model included the following factors (Table 2) (explaining 24.35% of variance): depression (α = 0.9), negative syndrome (α = 0.901), formal thought disorder (α = 0.732), paranoid-hallucinatory syndrome (α = 0.749) and increased appetite (α = 0.834).

3.2. Confirmatory factor analysis

In order to confirm the explorative results we performed confirmatory factor analyses in our second sample. We could confirm the previously explorative assumed model. Model fit indices for sample 2 (n = 589) showed good fit (χ^2 = 1011.951, df = 571, p < .0001, CFI = 0.925, $RMSEA$ = 0.036). Additionally we tested the fit indices for sample 1 which has been explorative tested before. Again indices showed good fit (χ^2 = 1172.759, df = 571, p < .0001, CFI = 0.90, $RMSEA$ = 0.042). To test whether our model fit the whole sample, we performed confirmatory factor analysis in the whole sample (n = 1182) showing a good fit. (χ^2 = 1287.842, df = 571, p < .0001, CFI = 0.932, $RMSEA$ = 0.033), too. Confirmatory factors were intercorrelated (Table 3). We also tested models that included higher order factors (see Fig. 1). Factor 1, 2 and 5 loaded on a different higher order factor (I *negative/affective*) as opposed to factors 3 and 4 (II *positive symptoms*) (χ^2 = 1332.922, df = 575, p < .0001, CFI = 0.928, $RMSEA$ = 0.033).

3.3. Association between symptom dimensions and categorical disorders

To satisfy traditional clinical convention, latent standardized factor scores of each patient were tested for differences between DSM-IV diagnostic categories. There was no difference across diagnostic groups for the factor increased appetite (F (2, 1179) = 0.8; p = .45), but for the other factors (Table 4 and Fig. 2).

Table 2
Explorative factors: 5-factor model of Sample 1 $n = 593$.

Factor	Item	Symptom	Loading	Cronbach's alpha
1 (Depression)	HAMA6	depressed mood	0.706	0.9
	HAMD1	depressed mood	0.671	
	HAMA2	tension	0.635	
	HAMA1	anxious mood	0.615	
	HAMDa7	fatigability	0.615	
	HAMD9	somatic symptoms - general	0.608	
	HAMD2	work and activities	0.602	
	HAMA4	insomnia	0.602	
	HAMA5	intellectual	0.594	
	SANS17	recreational interests and activities	0.582	
	HAMDa1	social withdrawal	0.554	
	HAMD12	anxiety - psychic	0.531	
	SANS15	physical anergia	0.517	
	HAMD13	anxiety - somatic	0.515	
2 (Negative syndrome)	SANS6	lack of vocal inflections	0.795	0.901
	SANS3	paucity of expressive gestures	0.776	
	SANS2	decreased spontaneous movements	0.763	
	SANS1	unchanging facial expression	0.752	
	SANS5	affective nonresponsivity	0.751	
	SANS8	poverty of speech	0.662	
	HAMD16	retardation	0.566	
3 (Positive formal thought disorder)	SAPS29	illogicality	0.764	
	SAPS28	incoherence	0.701	
	SAPS24	repetitive or stereotyped behavior	0.682	
	SAPS30	circumstantiality	0.576	
	SAPS31	pressure of speech	0.558	
	SAPS27	tangentiality	0.527	
	YMRS6	speech (rate and amount)	0.503	
4 (Paranoid-hallucinatory syndrome)	SAPS8	persecutory delusions	0.667	0.749
	SAPS1	auditory hallucinations	0.588	
	SAPS13	somatic delusions	0.573	
	SAPS14	delusions of reference	0.559	
	SAPS5	olfactory hallucinations	0.539	
5 (Increased appetite)	HAMDa4	increased eating	0.860	0.834
	HAMDa3	appetite increase (want to eat)	0.833	
	HAMDa5	carbohydrate craving or eating	0.515	

3.4. Relationship between factors and clinical status

Investigation of the relationship between factor scores and the clinical status of patients revealed differences in almost all factors (F (2, 1179) = 78.24; $p \leq .0001$) (see Table 5). "Acute patients with chronic course" had the highest loadings on our factors while "remitted patients" had the lowest loadings.

"Acute patients with chronic course" did not differ from "acute patients with remission between episodes" in factor 5 (increased appetite) (F (2, 586) = 9.23; $p = .1$).

3.5. Factor 5: increased appetite

The increased appetite dimension differed between patients with ($n = 814$) and without ($n = 329$) psychopharmacological medication F (1, 1141) = 9.43; $p = .002$, $\eta^2 = 0.008$). Regarding antidepressive medication patients with and without antidepressive medication differed significantly in the factor increased appetite (F (1, 1141) = 13.49; $p \leq .0001$, $\eta^2 = 0.01$). We further tested the relationship to specific subclasses of antidepressive medication. We found significant but

Table 3
Correlations between confirmatory factors within the whole sample.

Factor	Factor	Estimate	S.E.	Est./S.E.	Two-tailed p-value
Factor 2 (negative syndrome)					
	Factor 1	0.32	0.03	10.04	**0.0001**
Factor 3 (positive formal thought disorder)					
	Factor 1	0.02	0.03	0.67	0.51
	Factor 2	0.08	0.04	2.14	**0.003**
Factor 4 (paranoid-hallucinatory syndrome)					
	Factor 1	0.06	0.05	1.25	0.21
	Factor 2	0.27	0.06	4.26	**0.0001**
	Factor 3	0.49	0.1	4.67	**0.0001**
Factor 5 (increased appetite)					
	Factor 1	0.18	0.03	5.82	**0.0001**
	Factor 2	0.02	0.03	0.48	0.63
	Factor 3	0.03	0.04	0.89	0.37
	Factor 4	0.05	0.05	1.16	0.25

Bold printed numbers indicate significant correlations between factors.

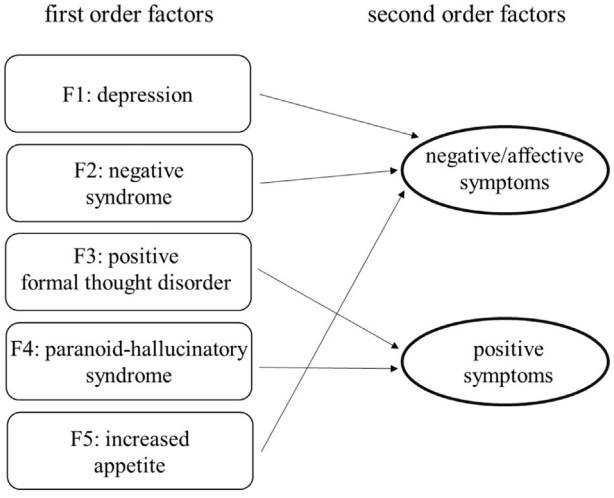

Fig. 1. Confirmatory factor model.

Table 4
Distribution of factors across DSM-IV diagnoses ($n = 1182$).

	Major depressive disorder	Bipolar disorder	Schizophrenia disorders	Group comparison (*F*-values in brackets)
Depression	0.09 (1.04)	−0.35 (0.96)	−0.23 (0.99)	$p < .0001$[a] (17.16)
Negative syndrome	−0.03 (0.49)	−0.14 (0.37)	0.36 (0.74)	$p < .0001$[b] (42.63)
Positive formal thought disorder	−0.04 (0.1)	0.04 (0.21)	0.19 (0.35)	$p < .0001$[c] (116.06)
Paranoid-hallucinatory syndrome	−0.07 (0.13)	−0.04 (0.13)	0.45 (0.67)	$p < .0001$[d] (239.15)
Increased appetite	−0.01 (0.53)	0.07 (0.68)	0.04 (0.48)	$p = .2$ (1.61)

Values indicate means of latent factor scores and standard deviations (in brackets).
Post hoc differences between groups:
[a] =MDD > BD, SZ.
[b] =SZ > MDD, BD.
[c] =SZ > MDD, BD; BD > MDD.
[d] =SZ > BD, MDD.

negligible effects for: Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs) (F (1, 1091) = 17.31; $p \leq .0001$; $\eta^2 = 0.016$) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) (F (1, 1091) = 4.45 $p = .03$; $\eta^2 = 0.004$). Patients medicated with NaSSAs (factor 5: *mean* 0.25, *SD* 0.84) had more appetite than those patients without NaSSAs (factor 5: *mean* − 0.01, *SD* 0.52). Patients receiving SNRIs also had more appetite (factor 5: *mean* 0.07, *SD*.64) than those without (factor 5: *mean* − 0.01, *SD*.53).

There were no significant associations for: Selective serotonin reuptake inhibitors (SSRI) (F (1, 1091) = 1.15; $p = .283$; $\eta^2 = 0.001$), norepinephrine–dopamine reuptake inhibitors (NDRI) (F (1, 1091) = 0.512; $p = .474$; $\eta^2 = 0.001$), agomelatine (F (1, 1091) = 3.39; $p = .06$; $\eta^2 = 0.003$), anticonvulsants (F (1, 1091) = 0.56; $p = .45$; $\eta^2 = 0.001$), and lithium (F (1,1091) = 0.69; $p = .4$; $\eta^2 = 0.001$). The use of neuroleptics was also not associated with "increased appetite" (F (1, 1091) = 1.33; $p = .25$; $\eta^2 = 0.001$).

4. Discussion

4.1. Main findings

This is the first study cross-validating the underlying latent variables (i.e. factor dimensions) in two, transdiagnostic samples of MDD, BD, and SZ patients using a comprehensive set of psychopathological scales measuring affective, anxiety, and psychotic symptomatology (SANS, SAPS, HAM-D, HAMA, YMRS). The symptoms can be best explained by a statistically valid five-factor model. First-order dimensions in the confirmatory five-factor model were depression, negative syndrome, positive formal thought disorder, paranoid-hallucinatory syndrome, and increased appetite. Cronbach's Alpha showed good internal consistency within the extracted factors. We could further reveal second-order factors: *(I) negative/affective* comprising depression, negative syndrome and increased appetite, and *(II) positive symptoms* including positive formal thought disorder and the paranoid-hallucinatory syndrome.

4.2. Comparison with previous factor models

While most previous studies were restricted to inpatients focusing on acute symptomatology, we considerably expanded this previous approach in terms of acute, chronic and remitted patients across three diagnostic categories, who we examined with five psychopathological scales covering a broad range of symptoms. The present study revealed five factors across the major psychoses.

Additionally, first order factors were intercorrelated showing that symptoms are related and occur simultaneously. Specifically, the correlation of the factors depression and negative symptoms is worth mentioning ($r = 0.32$) since this finding was reported in a previous study investigating psychotic symptoms in the general population (Shevlin et al., 2017).

We did not observe a separate anxiety factor in our analyses. Anxiety symptoms segregated in the first factor depression (see Table 2) showing that these symptoms are closely related to depressive

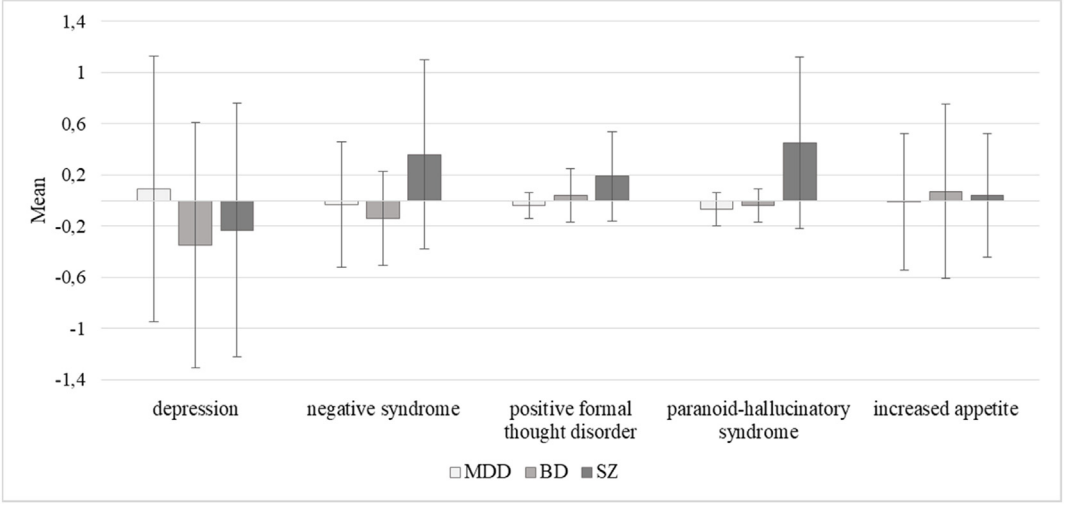

Fig. 2. Factor dimensions and diagnostic categories ($n = 1182$).

Table 5
Relationship between factors and clinical status ($n = 1182$).

	Acute patients with chronic course ($n = 170$) (1)	Acute patients with remission between episodes ($n = 599$) (2)	Remitted patients ($n = 413$) (3)	Group comparison (*F*-values in brackets)
Depression	0.6 (0.97)	0.41 (0.94)	−0.84 (0.47)	$p < .0001$[a] (346.67)
Negative syndrome	0.34 (0.77)	0.02 (0.52)	−0.17 (0.29)	$p < .0001$[b] (64.16)
Positive formal thought disorder	0.09 (0.29)	0.01 (0.19)	−0.04 (0.08)	$p < .0001$[c] (30.57)
Paranoid-hallucinatory syndrome	0.25 (0.61)	−0.02 (0.24)	−0.08 (0.1)	$p < .0001$[d] (77.57)
Increased appetite	0.11 (0.71)	0.05 (0.57)	−0.12 (0.39)	$p < .0001$[e] (16.38)

Values indicate means of latent factor scores and standard deviations (in brackets).
Post hoc differences between groups:
[a] =1 > 2, 3; 2 > 3.
[b] =1 > 2, 3; 2 > 3.
[c] =1 > 2, 3; 2 > 3.
[d] =1 > 2, 3; 2 > 3.
[e] =1 > 3; 2 > 3.

symptomatology. The result has been reported previously in studies of the general population (Shevlin et al., 2017) and psychotic patients (Reininghaus et al., 2013).

A meta-analysis of studies using the PANSS and BPRS (Van Dorn et al., 2016) focusing on SZ patients and small numbers of MDD, BD and other patients (e.g. anxiety) revealed five factors, i.e. affective, positive, negative, disorganized, and cognitive processing. While Van Dorn et al. (2016) used two complementary schizophrenia scales, we have applied five scales, assessed by the same raters. Our three factors depression, negative and paranoid-hallucinatory syndrome overlapped with those of Van Dorn et al. (2016). The differences in methodological aspects between the two studies may explain the different results.

In a study investigating lifetime symptoms with the OPCRIT within SZ, delusional disorder, BD and MDD patients, four factors were defined: excitement symptoms, psychotic features, depression and disorganization (Serretti et al., 2001). We could also find a depression and psychotic features factor. Nevertheless, we could expand the results of Serretti et al., 2001 considerably in terms of the evaluation of current psychopathology with a comprehensive set of scales, resulting in a more detailed factorial structure and showing a novel factor "increased appetite". The use of lifetime patient reported psychopathology might be less valid than assessment of current symptoms.

4.3. Hierarchical models

Some previous studies have shown hierarchically structured models only in psychotic disorders. Usually there are one or two general factors and several specific factors (Anderson et al., 2018; Reininghaus et al., 2013). Our hierarchical model divides psychopathological symptoms into two main dimensions, namely affective/negative (I) and positive symptoms (II). Fit indices (RMSEA, CFI) of the confirmatory first order factor model and the model with second order factors were comparable showing that both solutions are equally valid and explain a comparable amount of variance. Factors 1, 2, and 5 loaded on higher-order factor I (affective/negative) while factors 3 and 4 loaded on the second higher-order factor II (positive symptoms).

Furthermore, our model shows a great overlap with the bifactorial models in the general population reported by Shevlin et al., 2017 as well as in psychotic patients (SZ, SZA, delusional disorder, schizophreniform disorder) using the OPCRIT by Reininghaus et al., 2013. These authors also reported a depression, negative, disorganization and positive symptom dimension similar to our study. However, within our study formal thought disorders were examined in more detail with the SANS/SAPS which include disorganized thinking and speech, into contrast to the scales in other studies.

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4.4. Categorical diagnoses, course of illness

Although this was not the primary aim of our study, we wanted to acknowledge traditional clinical convention and showed that our factors clustered with the existing DSM-IV categories - unsurprisingly, since the diagnoses mainly rest on the prevailing syndrome a patient presents with. However, no syndrome was specific for a diagnosis, i.e. all syndromes were present more (i.e. "increased appetite") or less in all diagnoses. This confirms clinical experience (Kircher et al., 2018a) and recent neurobiological findings, which have not found a "point of rarity" between diagnoses (Chang et al., 2018; Goldsmith et al., 2016; Goodkind et al., 2015). An alternative approach for future neurobiological studies could be the separation of groups according to their psychopathology transgressing clinical diagnoses (Kaczkurkin et al., 2018). We and others have shown the feasibility of a syndrome based approach (Cavelti et al., 2018; Kircher et al., 2001) in structural and functional brain imaging.

In a further descriptive analysis, we related our factors to course of illness. The severity of psychopathology in all factors roughly increased from "remitted patients" across "acute patients with remission between episodes" to "acute patients with chronic course", a result with further confirms the clinical validity of our findings.

4.5. Factor 5 "increased appetite"

The factor "increased appetite" emerged as an independent domain in our factor solutions. This factor has not been reported in psychotic disorders but in MDD, previously. Some studies reported a typical decreased appetite factor in depression (Romera et al., 2008) while others showed an increased appetite dimension (Li et al., 2014; Van Loo et al., 2012). In our study the factor "increased appetite" remained stable across different models. It has been shown that this factor segregates if psychopathological scales are applied with items capturing vegetative symptoms (Li et al., 2014; Stewart et al., 1993) as in our study: the HAM-D has a subscale specifically measuring appetite, so it is conceivable that it came up as a separate factor.

We found associations of SNRIs and NaSSAs with the factor "increased appetite", but no relation to other antidepressant or antipsychotic medication. However, the effects were negligible (effect sizes between 0.004 and 0.016) and we do not think they explain this factor.

Our finding is supported by studies investigating the impact of psychopharmacological medication on symptom dimensions showing that there is no difference within the dimensions before and after treatment of SZ patients with antipsychotics (Harvey et al., 1996). Taking these issues together, the factor "increased appetite" is a relevant and somewhat overlooked symptom in the major psychoses that deserves further investigation.

4.6. Limitations

Our sample purposefully represents roughly the disorder prevalences in the population, therefore the MDD group is our largest. Our primary goal was not to investigate symptom prevalence within categorical diagnoses, but dimensionally across the disorders. The idea was that there are no "points of rarity" between the DSM diagnoses, therefore equal sample sizes for the diagnoses would have contradicted our approach, for a comparable objective see (Conway et al., 2019). Additionally, we think that our factors would have remained stable, if diagnostic subgroups had been enriched, only individual factor loadings would have changed. We have deliberately analyzed only rater based scales and not self-rating scales because this reduces heterogeneity and has limited the number of symptoms/items entering the analyses.

The temporal assessment of the rating scales used was slightly different (HAM-D, HAMA, and YMRS: last week; SANS, SAPS: last 2 weeks). Nevertheless, ratings had a close temporal overlap and were performed according to the published and validated manuals.

Explained variance of the explorative factors in sample 1 was smaller than in previous studies. This might have several reasons. First, previous studies mostly focused on psychotic disorders which leads to less heterogeneity than in our sample. Second, the use of several psychopathological scales combing a wide range of symptoms might also have reduced possible variance explained since not every symptom included in the analyses was present in all patients.

5. Conclusion

The main strength of the present study is the use of a large cohort, a comprehensive set of psychopathological scales, and the inclusion of patients with psychotic and affective disorders in acute, chronic, and remitted states, something which has not been examined before. Our findings give new evidence for a factorial structure across the major psychoses. These factors may serve as an important and novel addition to categorical diagnostic approaches (Ahmed et al., 2018) in future research.

Contributions

FS and GL performed the statistical analyses, FS, AK and TK wrote the first draft of the manuscript. GL helped choosing the statistical designs and wrote the confirmatory statistics method part. SS, KB, TM, EF, CK, LL BK, HM, AB, MM, MF, KF, SM, VE, KK, DG and AN participated in data acquisition, quality checking and preparation, and assisted in literature search. AK, TK, IN and UD designed the study protocol. All authors contributed to and have approved the final manuscript.

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Ethics approval

Patients gave written informed consent to the study protocol. This study was approved by the local Ethics Committee Marburg (AZ:07/14) and Münster (AZ:2014–422-b-S) according to the Declaration of Helsinki.

Declaration of competing interest

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All PIs take responsibility for the integrity of the respective study data and their components. All authors and coauthors had full access to all study data.

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Psychopathological Syndromes Across Affective and Psychotic Disorders Correlate With Gray Matter Volumes

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Introduction: **More than a century of research on the neurobiological underpinnings of major psychiatric disorders (major depressive disorder [MDD], bipolar disorder [BD], schizophrenia [SZ], and schizoaffective disorder [SZA]) has been unable to identify diagnostic markers. An alternative approach is to study dimensional psychopathological syndromes that cut across categorical diagnoses. The aim of the current study was to identify gray matter volume (GMV) correlates of transdiagnostic symptom dimensions.** ***Methods:*** **We tested the association of 5 psychopathological factors with GMV using multiple regression models in a sample of *N* = 1069 patients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria for MDD (*n* = 818), BD (*n* = 132), and SZ/SZA (*n* = 119). T1-weighted brain images were acquired with 3-Tesla magnetic resonance imaging and preprocessed with CAT12. Interactions analyses (diagnosis × psychopathological factor) were performed to test whether local GMV associations were driven by DSM-IV diagnosis. We further tested syndrome specific regions of interest (ROIs).** ***Results:*** **Whole brain analysis showed a significant negative association of the positive formal thought disorder factor with GMV in the right middle frontal gyrus, the paranoid-hallucinatory syndrome in the right fusiform, and the left middle frontal gyri. ROI analyses further showed additional negative associations, including the negative syndrome with bilateral frontal opercula, positive formal thought disorder with the left amygdala-hippocampus complex, and the paranoid-hallucinatory syndrome with the left angular gyrus. None of the GMV associations interacted with DSM-IV diagnosis.** ***Conclusions:*** **We found associations between psychopathological syndromes and regional GMV independent of diagnosis. Our findings open a new avenue for neurobiological research across disorders, using syndrome-based approaches rather than categorical diagnoses.**

Key words: voxel-based morphometry/transdiagnostic/dimensional/major psychiatric disorders

Introduction

There is strong evidence that psychotic (schizophrenia [SZ] and schizoaffective disorder [SZA]—both henceforth referred as schizophrenia spectrum disorder [SSD]) and affective disorders (major depressive disorder [MDD] and bipolar disorder [BD]) (henceforth, together referred to as major psychiatric disorders) are overlapping regarding symptoms, course, and outcome.[1,2] Neurobiological research showed that these major psychiatric disorders share familial and molecular genetic risk,[3] environmental risks,[4] structural brain changes,[5–8] and other neurobiological markers.[9] On a phenomenological level, the major psychiatric disorders share many syndromes such as depression, mania, and psychosis.[10–12]

Since research using diagnostic categories might overlook psychopathological mechanisms across disorders, transdiagnostic, dimensional approaches[13–15] can serve as an important addition to traditional approaches comparing diagnostic groups. In studies on a shared psychopathological factor structure across SSD, MDD, and BD, 3–5 factors have been delineated.[16–19] Most commonly paranoid-hallucinatory, depressive, negative, disorganized, and manic dimensions can be identified as separate dimensions.[16,18,20] Confirmatory analyses of 6 competing factor models revealed that symptom dimensions are better represented by factor models including 4 or 5 factors rather than by models with fewer factors.[17]

In our own previous study, we cross-validated a 5-factor model comprising depression, negative syndrome, positive formal thought disorder (pFTD), paranoid-hallucinatory syndrome, and increased appetite across the major psychiatric disorders.[2]

For a long time,[21] it has been hypothesized that particular syndromes might share a common brain structural network alteration, independent of the diagnostic category.[1,5–7,22] But up to now, most studies investigating gray matter volume (GMV) alterations across disorders focused on categorical approaches.[6,7] Using a multimodal machine learning approach aiming to classify recent onset psychosis and depression revealed no points of rarity on a brain structural level indicating comparable GMV across psychosis patients with comorbid depressive symptoms and patients with recent onset depression.[8] This result is further supported by a study[23] showing that specifically in patients with younger age disorder onset, neuroanatomical disease signatures fail to separate affective and psychotic disorders. Based on these findings, we aim to shed light on brain structural correlates of psychopathological factor dimensions across disorders. Below, we summarize results of previous voxel-based morphometry (VBM) studies on structural correlates of psychopathological factors. We focus on the neural substrates of the 5 psychopathological factors derived from our previous study.[2]

The paranoid-hallucinatory syndrome has mostly been investigated in studies including SZ patients. There is meta-analytical evidence that auditory verbal hallucinations are negatively correlated with GMV in the left insula and right superior temporal gyrus (STG).[24] Further core regions[25] negatively associated with the paranoid-hallucinatory syndrome are the thalamus,[26–28] the left planum temporale,[29] left anterior cingulate, and the bilateral insulae.[30,31]

pFTD have been frequently associated with neuroanatomical alterations in the left STG, frontal opercula, and left middle temporal gyrus, (ie, Wernicke and Broca area).[32,33] Dimensional analyses of pFTD in SZ patients showed negative associations in the bilateral inferior frontal gyri, the orbito-frontal cortex (OFC), the middle, medial, and superior frontal gyri, the left amygdala-hippocampus complex, the precuneus, and the insula.[34,35]

Meta-analyses of negative symptoms in SZ patients reported GMV reductions in the OFC, the anterior cingulate cortex, fusiform gyrus, thalamus, caudate, and amygdala associated with the severity of negative symptoms.[36,37] However, results are heterogeneous. Some studies reported no association between GMV and negative symptoms on a whole brain level.[38–40]

Testing dimensional depressive symptomatology and GMV in MDD, there were correlations in the right OFC, the left hippocampal gyrus, and the right dorsolateral prefrontal cortex.[41] Investigation of subclinical depressive symptoms in healthy populations revealed inconsistent associations in the anterior cingulate, OCF, and thalamus.[42–44] Nevertheless, several studies found no associations between GMV and psychopathological measures in MDD patients.[45–47]

The psychopathological factor "increased appetite" from our phenomenological study has not been reported in previous factor analytical approaches.[2] This dimension has only been reported within atypical MDD patients.[48,49] One study investigating subtypes of MDD patients indicated that a severely increased appetite MDD subtype showed lower surface area in the anterior insula when compared to a healthy control group.[50] Neurobiological research investigating obesity in otherwise healthy controls indicated the amygdala, hippocampus, insula, OFC, and the striatum to be central regions of appetite behavior.[51,52] A study investigating MDD patients revealed lower temporo-frontal cortical thickness to be associated with obesity (body mass index > 30).[53]

In summary, most transdiagnostic GMV studies are limited by (1) results from studies comparing diagnostic categories (as opposed to dimensional investigations), or (2) dimensional psychopathological investigations restricted to 2 diagnostic groups, and/or by (3) investigating one psychopathological dimension not covering the whole psychopathological spectrum. To overcome these limitations, our aim was to investigate associations of psychopathological dimensions with GMV on a dimensional, transdiagnostic, data-driven level across MDD, BD, and SSD. Based on previous findings,[5,6,8,23] we hypothesize that associations between psychopathological syndromes and local GMV that have previously been detected within one diagnosis, cut across MDD, BD, and SSD, and do not interact with diagnostic categories.

Materials and Methods

Participants

We included structural magnetic resonance imaging (MRI) data of acute and remitted patients (aged 18–65) meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (SCID-I) for MDD (296.2X, 296.3X: n = 818, F = 530/M = 288), BD (292.5X, 292.6X, 292.7X, 296.0X, 296.4X, 296.5X, 296.6X, 296.7X, or 296.8X: n = 132, F = 71/M = 61), SZ (295.X: n = 74, F = 32/M = 42), and SZA (295.7: n = 45, F = 24/M = 21). This MRI sample is a subgroup of our previous study on psychopathological factors,[2] from which, after quality checks of the brain scans n = 113 patients had to be excluded, leaving N = 1069 participants for the current analyses (see table 1). Patients were part of the DFG FOR2107 consortium[54] and were interviewed and scanned at the Departments of Psychiatry and Psychotherapy Marburg or Münster Universities, Germany. In- and outpatients were recruited from these Universities and local psychiatric hospitals (Vitos Marburg, Gießen, Herborn,

Table 1. Sample Characteristics

	Major Depressive Disorder (n = 818)	Bipolar Disorder (n = 132)	Schizophrenia Spectrum Disorder (n = 119; SZ n = 74, SZA n = 45)	P (F/χ^2)
Age	36.95 (13.19)	41.03 (11.94)	38.13 (11.81)	.003[a] (5.82)
Sex	M = 288, F = 530	M = 61, F = 71	M = 63, F = 56	< .001 (17.53)
Years of education	13.19 (2.74)	14.02 (2.8)	12.61 (2.68)	< .001[b] (8.07)
Age of onset	26.12 (12.62)	24.26 (11.29)	22.46 (9.4)	.005[c] (5.39)
Life time cumulative duration of hospitalizations (months)	11.68 (17.84)	33.23 (33.59)	38.46 (38.91)	< .001[d] (96.71)
Duration of current episode (months)	22.84 (46.46)	12.92 (35.61)	30.2 (56.93)	.093 (2.39)
Verbal IQ	112.67 (13.78)	114.98 (15.62)	111.82 (14.79)	.161 (1.83)
Psychopathological factors				
Depression (F1)	0.69 (1.02)	−0.33 (0.95)	−0.29 (0.88)	< .001[e] (13.83)
Negative syndrome (F2)	−0.06 (0.47)	−0.14 (0.36)	0.33 (0.74)	< .001[f] (35.42)
Positive formal thought disorder (F3)	−0.04 (0.1)	0.04 (0.21)	0.19 (0.37)	< .001[g] (107.14)
Paranoid−hallucinatory syndrome (F4)	−0.07 (0.13)	−0.03 (0.13)	0.47 (0.71)	< .001[h] (219.5)
Increased appetite (F5)	−0.01 (0.53)	0.09 (0.71)	−0.04 (0.51)	.12 (2.13)

Note: SZ, schizophrenia; SZA, schizoaffective disorder. Values indicate means and SD (in brackets). Post hoc differences between groups.
[a]Bipolar disorder (BD) > major depressive disorder (MDD).
[b]BD > MDD, schizophrenia spectrum disorder (SSD).
[c]MDD > SSD.
[d]SSD > MDD, BD > MDD.
[e]MDD > SSD, BD.
[f]SSD > MDD, BD.
[g]SSD > BD, MDD; BD > MDD.
[h]SSD > BD, MDD.

and Haina, LWL Münster, Germany) and via posting in local newspapers and flyers. Exclusion criteria were any history of neurological (head trauma or unconsciousness) and medical condition, substance dependence, current use of benzodiazepines, and IQ ≤80. The assessment of psychopathological symptoms and MRI data acquisition was performed within the same week. n = 341 patients (31.9%) did not receive any psychotropic medication, 53.5% received antidepressants, 12.1% mood stabilizers, and 29.6% antipsychotics at time of data collection. Based on DSM-IV criteria, n = 12 MDD (296.24, 296.34) patients and n = 6 BD (295.04, 296.44, 296.54) patients presented with psychotic features. A small number of participants were diagnosed with a past alcohol (n = 52) or substance (n = 26) abuse. Patients gave written informed consent to study protocols approved by the local Ethics Committees according to the Declaration of Helsinki.

MRI Data Acquisition and Preprocessing

MRI data acquisition was done according to an extensive quality assurance protocol.[55] In Münster, a 3T MRI scanner (Prisma, Siemens, Germany) and a 20-channel head matrix Rx-coil were used. MRI data in Marburg were obtained using a 3T MRI scanner (Tim Trio, Siemens, Germany) and a 12-channel head matrix Rx-coil. At both sites, we used a fast gradient echo MP-RAGE sequence with a slice thickness of 1.0 mm consisting of 176 in Marburg and 192 in Münster sagittal orientated slices and a field of view of 256 mm. Parameters were differing across sites: Marburg: time of repetition [TR] = 1.9 seconds, echo time [TE] = 2.26 milliseconds, inversion time [TI] = 900 milliseconds, flip angle = 9°; Münster: TR = 2.13 seconds, TE = 2.28 milliseconds, TI = 900 milliseconds, flip angle = 8°. Before preprocessing, all scans were visually inspected regarding artifacts and anatomical abnormalities by a senior clinician (U.D.). Structural MRI data were preprocessed[56] using default parameters as implemented in the CAT12-Toolbox (Computation Anatomy Toolbox for SPM, build 1184, Structural Brain Mapping group, Jena University Hospital, Germany; http://dbm.neuro.uni-jena.de/cat/) building on SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK) providing bias-corrected, tissue classified, and normalized data ratings. During preprocessing, images were segmented[57] into gray matter, white matter, and cerebrospinal fluid. Images were spatially registered, segmented, and normalized[58] using a DARTEL algorithm. All scans underwent the automated quality assurance, using the CAT12 "check data quality using covariance" procedure. After preprocessing and the described quality assurance protocols, we excluded n = 113 patients, due to major artifacts or abnormalities not accomplishing

the CAT12 quality criteria, leaving $N = 1069$ for the current study. MRI data sets were spatially smoothed with a Gaussian kernel of 8 mm full width at half maximum.

Statistical Analyses

Multidimensional Factors. Using a cross-validation approach within 2 samples, we had performed an exploratory and confirmatory psychopathological factor analysis in our previous study.[2]The scale for the assessment of negative symptoms,[59] scale for the assessment of positive symptoms,[60] Young mania rating scale,[61] Hamilton anxiety rating scale,[62] and the Hamilton depression scale[63] with a total of 104 symptoms were used to identify multidimensional, psychopathological factors across diagnosis. Psychopathological data were obtained during a clinical interview and were rated immediately afterwards by clinically trained psychologists (for detailed information see, Stein et al.[2]). Interrater reliability achieved excellent values of >.86 in all scales. Summarizing the procedures, we divided the total sample and conducted a varimax-rotated principal axis factor analysis in the first sample. To validate the explorative factor solution, we performed a confirmatory factor analysis in the second sample using Mplus[64] (MLR model estimation) showing a good fit: $\chi^2 = 1287.842$, df = 571, $P < .0001$, comparative fit index = 0.932, root mean square error of approximation = 0.036. The following factors were found in our previous study: depression, negative syndrome, pFTD, paranoid-hallucinatory syndrome, and increased appetite. Latent, standardized factor scores for each patient of the current study were used from this previous study,[2] to test whether the previously established dimensional factors were associated with GMV.

Voxel-Based Morphometry Analyses: Whole Brain Level. We used smoothed GMVs and standardized latent factor scores for each patient to perform separate linear regression models for each transdiagnostic factor (not for each diagnostic group). Analyses were carried out using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/). To avoid potential confounders, we applied several covariates of no interest: age, sex, site and total intracranial volume, and the change of one gradient coil.[54,55] As previously reported in our factor analytic study,[2] increased appetite was not correlated to antipsychotics, only to intake of serotonin-norepinephrine reuptake inhibitors and noradrenergic and specific serotonergic antidepressants with negligible effects. Therefore, we used 3 dummy-coded covariates accounting for the intake of at least one antidepressant, mood stabilizer, and antipsychotic. As recommended for VBM analyses, absolute threshold masking with a threshold value of 0.1 was used. Cluster labeling was applied using the dartel space Neuromorphometrics atlas (http://www.neuromorphometrics.com/).

For each psychopathological factor, associations with GMV (whole brain) at peak-level threshold $P < .05$, family-wise error (FWE) corrected, and cluster extend threshold $k = 10$ were investigated. To investigate if our transdiagnostic brain correlates were driven by DSM-IV diagnostic categories, we performed ANCOVA interaction analyses (diagnostic category × factor) in SPM on whole brain level.

Due to the unbalanced distribution of DSM-IV categories, in further confirmatory analyses, we used whole brain clusters of the total sample and tested them as regions of interest (ROIs) in an equally distributed sample matched for age and sex ($n = 357$) (matching was performed using the "MatchIt" package[65] in R[66]). We also performed ANCOVA interaction analyses in the matched sample. For the matched sample, significance level was set at $\alpha < .05$, false discovery rate (FDR) corrected.

Clinical variables, ie, life time cumulative duration of hospitalizations,[67,68] duration of current episode,[69] years of education,[70,71] and verbal IQ[72] were tested for potentially moderating effects on the associations between brain structure and psychopathological factor. Therefore, eigenvariates (weighted mean) as an approximation of mean value inside the clusters were extracted. Moderator models (PROCESS macro v3.3 for SPSS,[73] model number 1) were corrected for the same covariates as VBM analyses.

Voxel-Based Morphometry: ROI Analyses. We tested whether our 5 psychopathological factors[2] were associated with GMV across diagnoses, using a ROI approach. To objectively select ROIs, we performed a comprehensive literature search using MEDLINE (PubMed.gov interface) and additionally went through references in the articles identified. For inclusion of a ROI for our analyses, the following literature selection criteria were applied: (1) meta-analyses published after 2010, or if a meta-analysis for a factor was not available review article in a high ranking journal; (2) investigating at least one of the 5 syndromes in patients with MDD, SSD, or BD dimensionally (ie, correlating psychopathological scores with GMV; studies performing a mere patient-healthy control design were not included); and (3) the ROIs had to be replicated in 2 individual original studies, published after 2005. Based on these criteria, the literature search revealed the meta-analyses and ROIs listed in table 2.

Masks for the ROIs were created using the "dartel space neuromorphometrics" atlas (http://www.neuromorphometrics.com/) in CAT12. Using the batch mode, the search space for each factor and the selected ROIs was restricted beforehand. We accounted the same covariates as for whole brain analyses using a $P < .05$, peak-level FWE corrected, and $k = 10$ threshold. Since all ROIs were reported to be negatively associated with the symptom dimensions, we performed one sided t tests. Furthermore, interactions analyses were performed to test if ROIs were driven by DSM-IV diagnostic categories.

Table 2. Psychopathological Factors Derived From Our Patients,[2] Meta-Analysis or Review Article on Structural Brain Correlates of These Syndromes and Selected Regions for Our Region-of-Interest Analysis

Psychopathological Factor	Literature	Region
Depression (F1)	Schmaal et al. (2017)[46]	Right middle frontal gyrus Left hippocampus Bilateral superior frontal gyri
Negative syndrome (F2)	İnce and Üçok (2018)[37]	Left middle frontal gyrus Bilateral thalami Bilateral insulae Bilateral frontal opercula
Positive formal thought disorder (F3)	Sumner et al. (2018)[34]; Cavelti et al. (2018)[35]	Bilateral orbitofrontal cortices Left superior temporal gyrus Left planum temporale Left amygdala-hippocampus complex Left anterior cingulate gyrus Bilateral superior temporal gyri Bilateral amygdalae
Paranoid-hallucinatory syndrome (F4)	Mucci et al. (2019)[25]	Bilateral thalami proper Bilateral insulae Bilateral planum temporale Left anterior cingulate gyrus Left insula Bilateral superior temporal gyri Left angular gyrus Left postcentral gyrus
Increased appetite (F5)	Gibson et al. (2010)[52]	Bilateral nuclei accumbens Bilateral amygdalae

Results

Whole Brain Analyses

In the total sample, the pFTD factor (F3) was negatively associated with GMV in the right middle frontal gyrus (MFG) (k = 30 voxels, $x/y/z$ = 34/46/16, T = 4.85, Z = 4.82, P = .01, FWE). The paranoid-hallucinatory syndrome factor was negatively correlated with GMV in the right fusiform gyrus (k = 24 voxels, $x/y/z$ = 38/−21/−20, T = 5.08, Z = 5.05 P = .005, FWE) and in the left MFG (k = 27 voxels, $x/y/z$ = −32/62/−3, T = 4.79, Z = 4.76 P = .02, FWE) (see figure 1). No FWE-corrected association was present for the other factors. Interaction analyses of diagnostic group × factor in the total sample (N = 1069) showed no significant results.

To rule out potential effects of differences in the number of patients per diagnoses, we performed multiple regression and ANCOVA interaction analyses again in the age- and sex- matched subsample (n = 357). We replicated the negative association of the right MFG Cluster and pFTD in the matched sample, too (k = 30 voxels, $x/y/z$ = 33/46/16, T = 4.25, Z = 4.2 P = 1.198*10^{-7}, FDR). The negative association of the paranoid-hallucinatory syndrome and the right fusiform gyrus (k = 24 voxels, $x/y/z$ = 38/−21/−20, T = 4.14, Z = 4.09 P = 1.384*10^{-4}, FDR), as well as the left MFG cluster (k = 27 voxels, $x/y/z$ = −33/57/0, T = 4.73, Z = 4.65 P = 9.022*10^{-6}, FDR) were also present in the matched sample. Interaction analyses of diagnostic group × factor showed no significant results.

Post hoc moderator analyses of illness variables showed a significant moderation of life time cumulative duration of hospitalizations on the association of F4 "paranoid-hallucinatory syndrome" and the right fusiform cluster (R^2 = .018, F = 20.76; P < .001) and the left MFG cluster (R^2 = .009, F = 10.01; P = .002). The duration of current episode moderated associations of GMV clusters and F4 (right fusiform gyrus: R^2 = .01, F = 6.54; P = .012; left MFG: R^2 = .011, F = 7.23; P = .007). Both life time cumulative duration of hospitalizations (R^2 = .002, F = 1.86; P = .173) and the duration of the current episode (R^2 = .002, F = 0.12; P = .727) did not moderate the right MFG cluster (F3). Years of education moderated the association of pFTD and the right MFG (R^2 = .007, F = 8.16; P = .004). There was no moderating effect of verbal IQ.

ROI Analyses

Based on our literature search, we applied separate ROI analyses for each factor, in the total sample. We found FWE peak-level corrected GMV negative associations in the selected ROIs for the negative syndrome, pFTD, and the paranoid-hallucinatory syndrome (see table 3). The selected ROIs for the depression and increased appetite factor revealed no significant association. Interaction analyses (diagnoses × psychopathological factor) revealed no interaction in all ROIs in both the total sample and in the age- and sex- matched sample (same n per diagnosis).

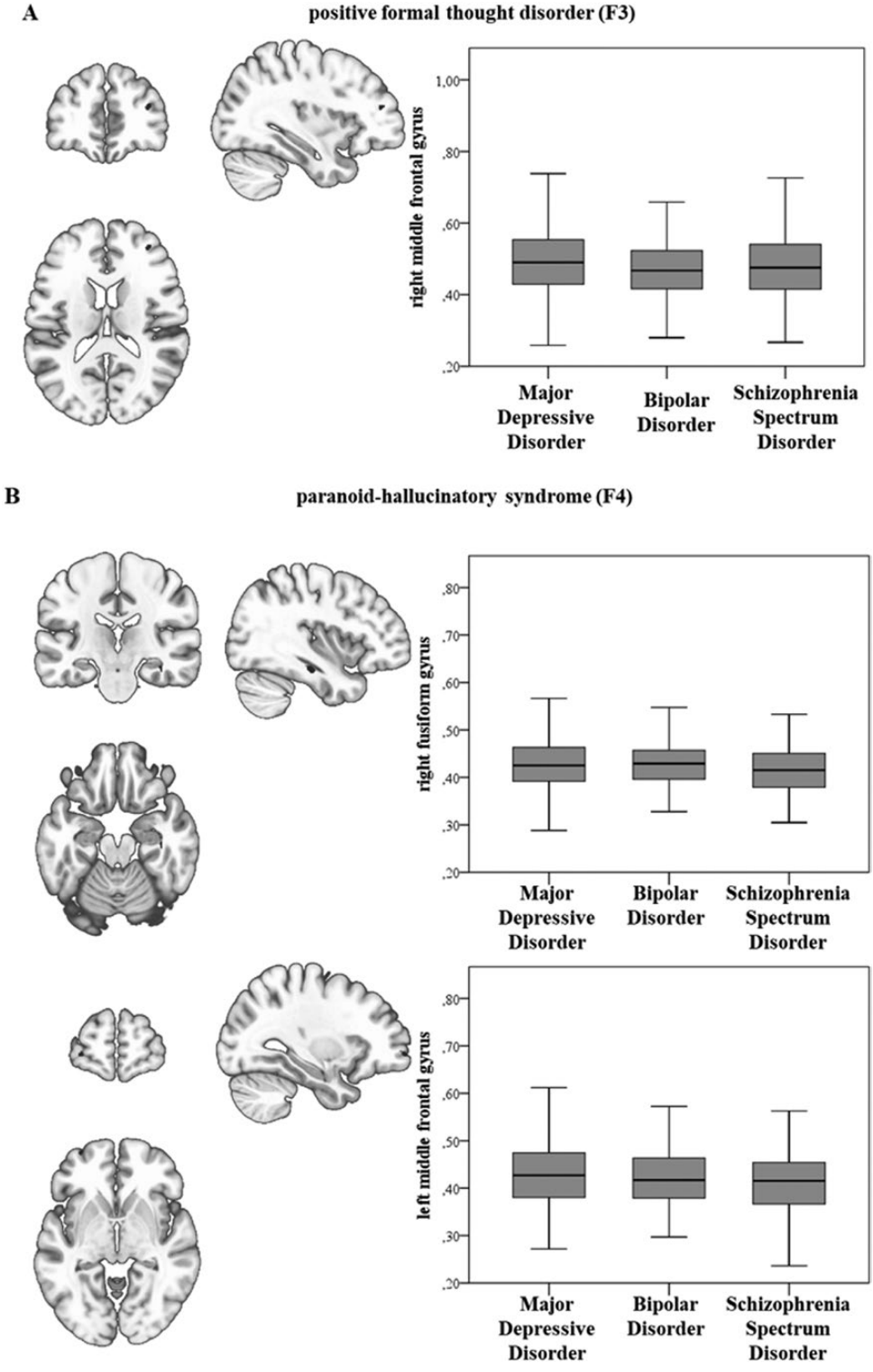

Fig. 1. (A, B) Negative correlations between gray matter volume for (A) positive formal thought disorder and the right middle frontal gyrus and (B) between the paranoid-hallucinatory syndrome and the right fusiform and left middle frontal gyrus, family-wise error peak-level corrected. Bar graphs on the right represent extracted eigenvariates of the clusters for each diagnostic group.

Discussion

Given the limitations of meta-analytic studies pooling single DSM diagnoses, our study investigated the relationship between regional brain volumes and dimensional, transdiagnostic psychopathological syndromes in one large sample comprising patients with MDD, BD, and SSD. Building on our previous work, we had derived 5 psychopathological factors (ie, depression, negative syndrome, pFTD, paranoid-hallucinatory syndrome, and increased appetite).[2] On whole brain level, we found negative associations for pFTD with the right MFG and the paranoid-hallucinatory syndrome with the right fusiform gyrus and the left MFG. Using ROI analyses, we were able to confirm a number of previous results across diagnoses: The negative syndrome was negatively associated with the bilateral frontal opercula, pFTD with the left amygdala-hippocampus complex and the paranoid-hallucinatory syndrome with the bilateral thalami proper, the left postcentral gyrus, the left posterior cingulate gyrus, and the left angular gyrus. Based on these findings, we can draw 3 new insights. First, there was no interaction effect of DSM-IV diagnostic categories × psychopathological factors in all GMV associations on whole brain level and within the ROI analyses in both the total sample and in the matched sample containing the same *n* per diagnosis, strengthening our assumption of shared transdiagnostic, psychopathological factor-local GMV associations[74–77] within MDD, BD, and SSD. Additionally, whole brain clusters found in the total sample could be replicated in the matched sample, too. This mirrors meta- or mega-analytic results from brain structural,[5,6,8,23] molecular genetic genome-wide association studies,[3,78] immunology,[9] and environmental factors,[4,79] showing large biological overlapping across these disorders. In contrast to these previous pooling studies, we included only patients from one large study. Interestingly, important clinical variables which have previously been related to brain structural alterations, such as life time cumulative duration of hospitalizations[67,68] and duration of the current illness episode,[69] did indeed moderate the extracted GMV clusters in our study. This validates our findings and confirms the significance of illness aspects other than the clinical diagnosis. Based on these converging findings across modalities, we hypothesize that genetic and environmental factors impact the developing brain at different times and intensities across individuals affected regional brain structure, with the particular location/network depending on the individual factors. The involved network during development determines the psychopathological syndrome predominant later in life after disorder onset. Second, the approach applied here allowed us to investigate symptom complexes such as the paranoid-hallucinatory syndrome across disorders, which has previously been mostly investigated in SZ patients. But it is well known that MDD patients also show elevated psychotic symptoms.[10,11] Regression analyses were performed independent of the state of patients (ie, acute, chronic, and remitted). Thus, our approach is less prone to subgroup effects that may arise when applying categorical approaches. Third, by using whole brain and ROI-based approaches, we exploratively tested transdiagnostic brain structures on whole brain level and identified anatomical signatures across disorders previously reported to be associated with psychopathological syndromes within 1 or 2 disorders.

We did not find associations between GMV and the depression factor, a finding in line with the vast majority of previous studies.[45,46,80] Structural alterations in patients with MDD are not correlated with current depressive symptomatology but rather chronicity and cumulative severity.[45,47,81,82]

Within the ROI analysis, the negative syndrome was associated with the bilateral frontal opercula volumes. This is a well-known finding from structural imaging studies investigating SZ patients.[83–87] GMV reductions in the frontal opercula correlated with persistent negative symptoms.[37,83,88]

Table 3. Significant Gray Matter Volume Reductions in the ROIs, FWE Peak-Level Corrected

Factor	ROI	*Coordinates*	*P* FWE	*k*	*T*	*Z*
Negative syndrome (F2)	Bilateral frontal opercula	[−48; 18; 21]	.031	21	3.512	3.501
Positive formal thought disorder (F3)	Left amygdala-hippocampus complex	[−34.5; −22.5; −15]	.018	99	3.386	3.376
Paranoid-hallucinatory syndrome (F4)	Bilateral thalami proper	[−6; −12; 12]	.006[a]		3.995	3.979
		[−13.5; −25.5; 10.5]	.007	1201	3.943	3.928
		[9; −3; 1.5]	.013		3.760	3.747
	Left angular gyrus	[−55.5; −64.5; 27]	.026	15	3.627	3.615
	Left postcentral gyrus	[−61.5; −19.5; 31.5]	.003[a]		4.267	4.248
		[−58.5; −21; 39]	.005[a]	405	4.172	4.154
		[−57; −22.5; 25.5]	.007		4.076	4.059
	Left posterior cingulate gyrus	[−13.5; −40.5; 3]	.011	11	3.633	3.621

Note: FWE, family-wise error; ROI, region of interest. ROIs tested are listed in table 2.
[a]Significant difference after Bonferroni correction for multiple ROI testing.

The pFTD factor was negatively associated with the right MFG on whole brain level, and the left amygdala-hippocampus complex in the ROI analysis. Previously, pFTD in SZ has been associated with neuroanatomical alterations in Wernicke's and Broca's language areas, as well as the middle frontal gyri and the left amygdala-hippocampus complex.[32–35] We could replicate these findings in our transdiagnostic sample. As opposed to the left, we found the right MFG homologue associated with pFTD, an area which is involved in language processing in SZ patients.[32,34,35] Furthermore, there is evidence that the hippocampus plays a major role in word generation tasks which coincides with our findings.[89,90]

On a whole brain level, the paranoid-hallucinatory syndrome was negatively associated with the right fusiform gyrus and the left MFG. Previous studies[24,25,27,31,40,91] showed that medial temporal regions are correlated with "positive" symptomatology, which mainly comprises the paranoid-hallucinatory syndrome. Besides the inferior temporal gyri, the bilateral fusiform gyri have been reported as a significant correlate of positive symptoms (measured with Positive and Negative Syndrome Scale [PANSS]).[40,91] A meta-analysis including 4474 paranoid-hallucinatory SZ patients showed that reductions in both the right fusiform gyrus and the bilateral inferior temporal gyri have the largest effect sizes.[92] Several studies have shown negative associations of GMV and the paranoid-hallucinatory syndrome factor in the overall frontal volume[93] as well as GMV reductions in the left pars orbitalis and the left superior frontal gyrus.[40] The left MFG has been shown to be deactivated in preceding auditory hallucinations.[94] The ROI analyses revealed significant associations between the paranoid-hallucinatory syndrome and the bilateral thalami proper,[27,28,95] the left angular gyrus, the postcentral gyrus, and the left posterior cingulate gyrus,[25,27] confirming many previous studies.

The factor "increased appetite" was, independent of medication, a dimension in our psychopathological factor analytic study[2] that has been shown to emerge if psychopathological scales are used that capture vegetative symptoms.[48,96] We did not find associations with GMV neither on whole brain level nor within the ROI analyses. This may indicate that biological influences other than GMV have an impact on the manifestation of increased appetite. Nevertheless, increased appetite is a relevant syndrome across disorders that deserves further investigation.

Limitations

Some limitations must be noted. First, patient groups were unequally distributed which potentially biased our results since the MDD group was the largest. However, we were able to confirm the results of our interaction analyses (total sample) in an age- and sex-matched subsample (same *n* in each diagnosis). Second, the MDD group only marginally presented with psychotic symptoms compared to BD and SSD patients resulting in restricted variance found for psychotic symptoms (ie, factor 4 "paranoid-hallucinatory syndrome"). Third, the extracted factors were based on current psychopathology. Correlating current state measures with brain structure misses past psychopathology. However, specific current symptoms are an indication for a particular neuroanatomical, state-independent alteration that outlasts current symptoms. Still, it would be of great interest to investigate the stability of both factor dimensions and their relationship to brain structure validating the present cross-sectional results. Fourth, pharmacological treatment was considered in our models using 3 dummy-coded variables accounting for the intake of antidepressants, mood stabilizers, and antipsychotics. However, the influence of both dosage and duration of intake on GMV is not considered.

Conclusion

In sum, our findings provide a novel anatomical mapping of psychopathological symptom dimensions across disorders. The main strength of the present study is the use of a large transdiagnostic cohort, innovative data-driven psychopathological factors, and the inclusion of patients across psychotic and affective disorders. Our findings give evidence for shared and diagnosis-independent GMV reductions associated with symptom dimensions. We try to overcome a current deadlock in scientific approaches which has one origin in a misguided reification of DSM diagnoses.

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iii. STUDY III: Manuscript

State of illness-dependent associations of neuro-cognition and psychopathological syndromes in a large transdiagnostic cohort

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Abstract

Background:
There is a lack of knowledge regarding the relationship between dimensional psychopathological syndromes and neurocognitive functions, particularly across the major psychiatric disorders (i.e., Major Depressive Disorder (MDD), Bipolar Disorder (BD), and Schizophrenia (SZ)).

Method:
SANS, SAPS, HAMA, HAM-D, and YMRS were assessed in 1,064 patients meeting DSM-IV criteria for MDD, BD, SZ or schizoaffective disorder (SZA). In addition, a comprehensive neuropsychological test battery was administered. Psychopathological syndromes derived from factor analysis and present state of illness were used to explore psychopathology-cognition relationships. Correlational analyses were corrected for age, sex, verbal IQ, years of education, and DSM-IV diagnosis. Age of onset and total duration of hospitalizations as proxies for illness severity were tested as moderators on the cognition – psychopathology relationship.

Results:
The *negative syndrome*, *positive formal thought disorder* as well as the *paranoid-hallucinatory syndrome* exhibited associations with neuro-cognition in an illness state-dependent manner, while the psychopathological factors *depression* and *increased appetite* only showed weak associations. Illness severity showed moderating effects on the neurocognitive-psychopathology relationship only for the *negative syndrome* and *positive formal thought disorder.*

Conclusions:
This study suggests the relationship of neuro-cognition and psychopathology to be highly state of illness-dependent across affective and psychotic disorders. Results hint at the moderating effects of illness severity on psychopathological factors that might be more treatment resistant.

Keywords
neuro-cognition, major psychiatric disorders, neuropsychology, factor analysis, transdiagnostic, psychopathology

1. Introduction

More than a century of research on the neurobiological underpinnings of psychotic (schizophrenia, SZ; schizoaffective disorder, SZA) and affective disorders (Major Depressive Disorder, MDD; Bipolar Disorder, BD) - collectively referred to as major psychiatric disorders - has been unable to identify transdiagnostic markers within the major psychiatric disorders. There is evidence that the major psychiatric disorders share familial and molecular genetic risk [1, 2], environmental factors [3], and changes in brain structure [4, 5]. Even though these overlaps have been well documented, there is a lack of studies investigating the relationship between psychopathology and neuropsychological functioning in transdiagnostic samples, especially taking current state and course of the illness into account.

1.1 Factor models of psychopathological symptoms across diagnoses

In light of the challenges given by categorical approaches comparing disorders to a healthy control group not considering the overlaps between disorders, dimensional approaches have been increasingly performed [6, 7]. However, most studies focused on psychopathological factors being prominent in the diagnostic category investigated (i.e. psychotic symptoms in SZ) or were restricted to one or two diagnostic groups only using one psychopathological scale, not covering a wide range of symptomatology. Investigating a transdiagnostic samples Reininghaus et al. showed 3 to 5 factor solutions [8]. Previously, a meta-analysis of five studies including SZ, MDD, BD, and anxiety patients measuring psychopathology with the PANSS or BPRS revealed five factors: affective, positive, negative, disorganized, and cognitive processing [9]. Investigation of six lifetime psychopathological factor models in SZ patients, patients with delusional disorder and BD (all diagnosed with DSM-IV) revealed that 4- or 5 factor models better describe symptomatology than models with less factors [10]. Recently, we identified and confirmed a five-factor model in a sample comprising of more than 1,100 patients with MDD, BD, SZ or SZA [11]. The extracted factors were depression, negative syndrome, positive formal thought disorder (pFTD), paranoid-hallucinatory syndrome and increased appetite. All five factors were present in all patients supporting the view of overlapping phenomenology [11] as well as shared neuro-anatomy [12] across disorders.

1.2 Neuropsychological impairments in major psychiatric disorders

Meta-analyses in MDD showed that depending on the domain tested, patients' impairments have small to medium effect sizes. However, there was no clear-cut difference between current depression or remission [13] regarding their neuropsychological performance. In another meta-analysis, small effect sizes could still

be observed even when comparing healthy controls (HC) to euthymic MDD. However, it could be shown that the course or onset of the disorder affects cognition as late-onset depression was associated with more pronounced cognitive impairment [14]. The reason for the discrepancy in these findings may be explained by a recent study that showed gray matter volume in areas critical for cognitive performance such as the hippocampus is affected by illness severity rather than by current psychopathology [15]. Thus, cognitive performance depending on these structures such as episodic memory [16] might be better explained by illness severity rather than by acute psychopathology.

In BD, even in euthymic phases, meta-analytical findings point to impairments in almost all domains tested [17]. Largest effect sizes are found in executive functioning and working memory and impairments in executive functioning might be indicative of a poor clinical course of the disorder. Possible moderators of these impairments include level of education, age, and duration of illness [17].

In SZ, early meta-analyses already pointed to impairments in all domains reported [18]. Largest effect sizes were reported for verbal memory, motor skills and executive functioning. However, other meta-analyses suggested that processing speed impairments could be an underlying deficit partly explaining impairments in other domains [19]. More recently, it could be demonstrated that neuropsychological test performance remains relatively stable [20] while psychopathology may vary to some degree during the course of the disorder.

Recently, in a study investigating cognition in MDD, BD and SZ it could be found that all three patient groups differed from HC [21]. Within this study, differences between patient groups and HC emerged for all domains. However, “executive functioning” was the only domain showing differences between SZ and HC, while MDD and BD did not differ significantly. The only domain however, that exhibited differences between all groups investigated was “motor Speed”, with the SZ had the poorest performance and MDD and BD were located between SZ and HC. For several cognitive domains, differences in performance do not differ between BD and SZ in the majority of studies. This is in particular true when the groups compared also include patients with SZA and/or BD with psychotic features [22]. Because of these results, characteristics different from diagnosis per se might better differentiate between patient groups like global (cognitive) functioning [23].

1.3 Neuropsychological performance, psychopathology, course and state of illness

To date, only few studies are available describing the relationship of current psychopathology and neurocognitive functioning in transdiagnostic samples consisting

of more than two patient groups. However, several studies comparing SZ and BD have been conducted showing that cognitive performance is potentially related to a number of factors [22] which are not restricted to current psychopathology: Own or parental level of education and number of hospitalizations could potentially influence cognition, depending on diagnosis and cognitive domain studied.

In a transdiagnostic sample (MDD, BD and SZ), objectively observable rather than subjectively reported positive and negative symptoms of FTD were correlated with several cognitive domains [24]: pFTD had a significant negative association with executive functioning while negative FTD was negatively associated with different markers of verbal fluency and verbal working memory. The relationship of impaired executive functioning and pFTD was most pronounced in BD while negative formal thought and verbal fluency impairments were most pronounced in SZ and HC.

In a study investigating SZ, siblings of patients, and HC, it was found that negative symptoms as well as disorganization symptoms showed correlations, especially with working memory and episodic memory [25] while there were no significant correlations between positive symptoms and neuropsychological test results. Recently, in a transdiagnostic sample, it was reported that only a negative/disorganized symptoms factor showed correlations with cognitive performance, while other factors such as affective symptoms did not [26].

Current severity and course of disorders have been found to play an important role in cognition and cognitive performance: In acutely depressed patients, impairments in a variety of domains such as working memory have been described while this relationship was not found in remitted patients [27]. Similar results were found in BD and SZ [28]: Acuity of psychotic symptoms was associated with greater cognitive impairments. SZ with acute symptoms was additionally associated with greater impairments in processing speed. But there is not only a relationship of symptoms and cognitive impairments in major psychiatric disorders, these impairments have been demonstrated to have predictive value: Impairments in verbal memory have been shown to predict conversion to first-episode schizophrenia in clinical high-risk individuals [29].

Based on the studies outlined above, several open questions were to be addressed in the present study: 1. Based on own recent factor-analytical findings, current psychopathology was to be correlated with neuropsychological performance across affective and psychotic disorders. Hereof, we hypothesized correlations between negative and FTD symptoms and cognitive performance, while weaker or no correlations with affective (depression) and positive symptoms (paranoid-hallucinatory symptoms) were expected. 2. Since previous studies reported cognitive performance to be highly influenced by the current state of disorder, we further assessed the relationship between

neuro-cognition and psychopathology factors in a current state of illness dependent manner. Therefore, remission and disease course cut-offs based on psychopathological measures were used rather than DSM criteria as there is no coding for the course of psychotic disorders implemented in the DSM. 3. Lifetime total duration of hospitalizations and age of disorder onset were used as illness severity proxies and were tested for moderating effects on the neuro-cognition – psychopathology associations. Total duration of hospitalizations were expected to positively predict neuro-cognition – psychopathology associations (i.e. magnify neuro-cognition – psychopathology associations) while for age of disorder onset negative moderation effects were hypothesized.

2. Material and methods

2.1 Participants

Participants were part of the FOR2107 cohort [30]. Psychopathological scales and neurocognitive tests were administered at the Departments of Psychiatry and Psychotherapy in Marburg or Münster, Germany. Participants were recruited via inpatient facilities of the University Hospitals and from the departments of participating local hospitals. Outpatients were recruited via flyers and postings in newspaper. To be included in the present study verbal IQ had to be > 80, patients had to be free of serious medical illnesses (cancer, autoimmune diseases), neurological illness, and current substance dependence. Furthermore, we had to exclude *n*=118 patients from the original study [11] due to incomplete neuropsychological data resulting in *N*= 1,064 patients (aged 18-65) meeting DSM-IV criteria for MDD (*n*=821, f=535/m=286), BD (*n*=130, f=65/m=65), and SZ/SZA (*n*=113, f=52/m=61)) (see Table 1) for the present study. At time of assessment *n*=330 patients were in inpatient care (*n*=247 MDD, *n*=36 BD, *n*=47 SSD). The local ethics committees approved the study protocol. Patients gave written informed consent to the study protocol.

2.2 Psychopathological assessment and factor score calculation

The complete procedure has been reported in [11]. In short, the following scales with a total of 104 symptoms were administered during a clinical interview (including SCID-I): the SANS and the SAPS [31, 32], HAMA [33], HAM-D [34], and the YMRS [35]. Psychopathological scales were rated by trained interviewers achieving good inter-rater reliability (>.86 in all scales). Following the procedure described in [11], we performed a cross-validation approach using varimax rotated explorative and confirmatory factor analyses in two samples. Results revealed a 5-factor model comprising: F1: Depression, F2: Negative Syndrome, F3: Positive Formal Thought Disorder, F4: Paranoid-Hallucinatory Syndrome and F5: Increased Appetite. For the present study, we used the

latent factor scores for each patient and factor of our previous analyses for further calculations.

2.3 Neuropsychological assessment

The following tests were administered in all subjects: The d2 test of attention [36], verbal fluency [37], symbol-coding [38], spatial span [39], letter-number span [40], Trail-Making Test A and B (TMT) [41], and the German Verbal Learning and Memory Test (VLMT) [42]. Verbal IQ was assessed with the multiple choice vocabulary test (MWT) estimating premorbid intelligence [43]. Taken together, these tests assess performance in the domains of attention (d2), executive functioning (symbol-coding, verbal fluency, TMT), verbal and visuo-spatial working memory (letter-number span and spatial span), verbal learning (VLMT) as well as verbal episodic memory, retrieval and recognition (VLMT). In the case of verbal fluency, semantic verbal fluency ("sem. VF"; category "animals"), lexical verbal fluency ("lex. VF"; starting letter "p") and category switching ("cat. VF"; alternating between sports/fruit) were assessed for one minute each. For further calculations, the sum of backward and forward processing of the spatial span were summarized and results of the TMT part A were subtracted from part B.

2.4 Statistical Analyses

Descriptive statistics are summarized in Table 1. To investigate our first hypothesis, we performed, partial correlation analyses for neuropsychological results and latent factor scores of the five factors in the total sample (N=1,064). Within this procedure, age, sex, years of education, and verbal IQ were controlled for (see Table 2). Verbal IQ and years of education were correlated (p<0.0001, r=0.352) but multicollinearity for these two variables was absent (*tolerance*=1.0, *VIF*=1.0). To rule out potential effects of DSM-IV diagnostic categories, we added a three steps DSM-IV diagnosis variable to our correlational model.

Following our second assumption of state of illness dependent associations between neuro-cognition and psychopathology, the same partial correlation analyses were performed for subgroups based on clinical status. Since remission criteria for affective but not for psychotic disorders are implemented in the DSM-IV, the clinical status was defined based on published remission cut-offs for the used scales [44–47]. The clinical course was defined using item 90 of the OPCRIT 4 ("course of disorder" [48]). Based on information drawn by the semi-structural interview and hospital records, item 90 of the OPCRIT assesses the following courses: single episode with remission, multiple episodes with remission between episodes, multiple episodes with partly remission between episodes, chronic course, and persistent chronic course.

Subsequently, both the information on the clinical status (acute psychopathology rating scales) and the information on the course of disorder (OPCRIT item 90) were combined dividing the patients of the present study into three groups. An “acute patient with a chronic course” was defined when exceeding one of the following cutoffs: SANS global ratings (items 7 “affective flattening”, 12 “Alogia”, 16 “Avolition-apathy”, and 21 “Anhedonia-asociality”) >2 [44], or SAPS global ratings (items 7 “Hallucinations”, 20 “Delusions”, 25 “Bizarre behavior”, 34 “Positive formal thought disorder) >2 [44], or HAMA sum score >19 [45], or HAM-D sum score (17 item version) >6 [47], or YMRS sum score >4 [46], and when item 90 of the OPCRIT 4 was >2 (i.e. chronic or persistent chronic course). The second group “acute patients with full remission between episodes” was defined like the first group except for item 90 of the OPCRIT 4 (scoring ≤2, i.e. single episode with remission or multiple episodes with remission or partly remission). The third group “remitted patients” did not exceed any of the above cutoffs at the time of psychopathological assessment. All partial correlations were corrected per table for multiple testing using the false discovery rate (FDR) [49] and two-tailed *p*-values were used in all analyses.

Since sample sizes across the three clinical course groups differed, we performed power analyses (G Power, version 3.1.9.7) [50] to estimate the sample size needed to detect significant correlations. Therefore non-significant correlation coefficients of the three clinical subgroups that were previously significant in the total sample were used. Power was set at 0.8 and significance at $p<.05$.

Finally, we were interested in moderating effects of clinical variables (i.e. lifetime total duration of hospitalizations, age of disorder onset). Therefore, we used moderator models (PROCESS macro v3.3 for SPSS, model number 1) that were corrected for the same covariates as correlational analyses. Moderator models were only performed for significant correlations between neuro-cognition and psychopathology as presented in Table 2. To account for multiple testing moderation results were corrected per moderator using FDR correction.

3. Results

Table 1 describes the sociodemographic and clinical characteristics of the participants, results of the partial correlation analyses are described in Table 2. Analyses based on clinical state subgroups are depicted in Tables 3a-c.

Table 1

Characteristics of the sample; *N*=1,064 patients

	Major Depressive Disorder (*n*=821)	Bipolar Disorder (*n*=130)	Schizophrenia Disorders (*n*=113)	Group comparison (*F*-values in brackets)
Age	36.89 (13.21)	42.23 (12.15)	38.59 (11.39)	p= 0.001[a] (7.29)
Sex	f=535 m=286	f=65 m=65	f=52 m=61	p< .0001 (23.29)
educational level (in years)	13.12 (2.7)	13.73 (2.78)	12.28 (2.65)	p= 0.017[b] (4.07)
Age of Onset	26.04 (12.72)	24.82 (11.47)	22.28 (9.18)	p= 0.006[c] (5.13)
GAF	62.96 (16.14)	60.86 (14.88)	51.32 (18.31)	p< 0.0001[b] (19.47)
F1: Depression	0.09 (1.03)	-0.35 (0.94)	-0.29 (0.83)	p< 0.0001[d] (9.13)
F2: Negative Syndrome	-0.04 (0.47)	-0.14 (0.37)	0.3 (0.69)	p< 0.0001[e] (24.27)
F3: Positive Formal Thought Disorder	-0.04 (0.1)	0.04 (0.21)	0.15 (0.3)	p< 0.0001[f] (85.77)
F4:Paranoid-Hallucinatory Syndrome	-0.07 (0.14)	-0.04 (0.13)	0.4 (0.64)	p< 0.0001[e] (142.25)
F5: Increased Appetite	-0.01 (0.52)	0.02 (0.59)	-0.09 (0.34)	p= .23 (1.47)
D2 (KL)	168.04 (42.18)	158.92 (46.18)	139 (42.85)	p< 0.0001[b] (17.47)
sem. VF	23.15 (5.79)	21.8 (6.03)	20.52 (5.05)	p= 0.001[c] (7.54)
lex. VF	11.14 (4.11)	11.15 (4.82)	9.6 (4.36)	p= 0.023[b] (3.8)
cat. VF	15.19 (3.35)	14.69 (3.55)	13.03 (3.89)	p< 0.0001[b] (13.8)
symbol coding	56.35 (12.35)	51.58 (11.34)	46.81 (11.74)	p< 0.0001[g] (24.18)
spatial span (total)	16.74 (3.3)	16.27 (2.99)	15.08 (3.08)	p< 0.0001[b] (9.89)
letter number span	15.75 (3.34)	15.4 (3.19)	13.11 (3.53)	p< 0.0001[b] (22.14)
TMT (difference)	30.11 (18.94)	33.12 (20.99)	42.49 (24.57)	p< 0.0001[e] (12.4)
VLMT (total correct words)	55.45 (9.9)	52.94 (10.01)	47.12 (10.25)	p< 0.0001[h] (25.2)
VLMT (loss delayed recall)	1.21 (1.75)	1.67 (1.94)	2.16 (2.07)	p< 0.0001[i] (11.87)

VLMT (recognition)	13.13 (2.91)	12.29 (3.91)	11.51 (3.67)	$p< 0.0001^{e}$ (12.29)
verbal IQ	112.65 (13.69)	114.86 (14.6)	111.8 (14.62)	$p= 0.171$ (1.77)

Values indicate means of total values and standard deviations (SD) (in brackets). Post hoc differences between groups: [a]= MDD < BD. [b]= SZ < MDD, BD. [c]= SZ < MDD. [d]= MDD > SZ, BD. [e]= SZ > MDD, BD. [f]= SZ > MDD, BD; BD> MDD. [g]= SZ < MDD, BD; BD < MDD. [h]= MDD > SZ, BD; BD > SZ. [i]= MDD < BD, SZ.

Table 2

Partial Correlation Analyses of Neuropsychology and Psychopathology (whole sample, *N*= 1,064 patients)

	F1: Depression	F2: Negative Syndrome	F3: Positive Formal Thought Disorder	F4: Paranoid - Hallucinatory Syndrome	F5: Increased Appetite
D2 (KL)	-0.046	**-0.085****	**-0.1*****	-0.04	-0.014
Sem. VF	-0.049	-0.055	-0.004	0.000	*-0.068**
Lex. VF	-0.056	**-0.067***	-0.007	0.017	-0.046
Cat. VF	**-0.086****	**-0.124*****	**-0.084****	*-0.07**	*-0.075**
Symbol-Coding	**-0.08****	**-0.106*****	-0.059	-0.029	-0.02
Spatial Span (total)	-0.028	-0.033	-0.044	-0.053	-0.012
Letter-number-span	-0.057	**-0.108*****	**-0.083****	-0.019	0.019
TMT (difference)	0.046	**0.093****	**0.106*****	0.037	-0.032
VLMT (total correct words)	-0.024	**-0.089****	-0.004	*-0.067**	0.018
VLMT (loss delayed recall)	-0.032	*0.06**	**0.068***	*0.066**	0.013
VLMT (recognition)	-0.045	**-0.098*****	**-0.103*****	*-0.067**	-0.023

Age, sex, verbal IQ, years of education and DSM-IV coded diagnoses were controlled for. Bold letters indicate significant correlation coefficients (r) after FDR correction for multiple testing. **p*≤.05; ***p*≤ .01; ****p*≤ .001, *italics* indicate significant results without correction for multiple testing.

Table 3a

Partial Correlation Analyses of Neuropsychology and Psychopathology in acute patients with a chronic course (*n*=147; MDD *n*=94, BD *n*= 10, SZ *n*=43)

	F1: Depression	F2: Negative Syndrome	F3: Positive Formal Thought Disorder	F4: Paranoid-Hallucinatory Syndrome	F5: Increased Appetite
D2 (KL)	0.036	0.073	-0.150	-0.095	-0.052
Sem. VF	-0.017	-0.065	0.064	0.077	-0.108
Lex. VF	-0.052	-0.044	0.084	0.074	-0.062
Cat. VF	-0.002	-0.129	-0.103	-0.06	-0.007
Symbol-Coding	-0.068	-0.011	-0.054	-0.045	-0.048
Spatial Span (total)	0.02	0.019	-0.154	-0.095	0.033
Letter-number-span	-0.057	0.005	-0.128	0.074	0.03
TMT (difference)	0.151	0.140	0.043	0.033	0.081
VLMT (total correct words)	-0.09	-0.09	-0.041	-0.035	-0.042
VLMT (loss delayed recall)	0.038	0.059	**0.227****	**0.263****	0.057
Recognition (VLMT)	-0.05	-0.004	-0.14	-0.052	-0.048

Age, sex, verbal IQ, years of education and DSM-IV coded diagnoses were controlled for. Bold letters indicate significant correlation coefficients (r) after FDR correction for multiple testing. *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$, *italics* indicate significant results without correction for multiple testing.

Table 3b

Partial Correlation Analyses of Neuropsychology and Psychopathology in acute patients with full remission between episodes (*n*=538; MDD *n*=423, BD *n*= 81, SZ *n*=34)

	F1: Depression	F2: Negative Syndrome	F3: Positive Formal Thought Disorder	F4: Paranoid-Hallucinatory Syndrome	F5: Increased Appetite
D2 (KL)	-0.073	**-0.136****	*-0.107***	-0.033	0.045
Sem. VF	-0.04	-0.068	-0.023	-0.029	-0.036
Lex. VF	-0.067	**-0.1***	-0.011	0.015	0.011
Cat. VF	-0.086	**-0.097***	-0.086*	-0.076	-0.081
Symbol-Coding	-0.023	**-0.121****	-0.046	0.015	0.047
Spatial Span (total)	-0.057	-0.038	0.014	-0.006	0.022
Letter-number-span	-0.031	**-0.143*****	-0.075	-0.028	0.062
TMT (difference)	0.037	0.081	**0.123****	-0.026	-0.071
VLMT (total correct words)	0.0	-0.079	-0.035	-0.049	0.077
VLMT (loss delayed recall)	-0.065	0.087	0.024	0.024	0.008
Recognition (VLMT)	0.007	**-0.134****	*-0.108***	-0.071	0.007

Age, sex, verbal IQ, years of education and DSM-IV coded diagnoses were controlled for. Bold letters indicate significant correlation coefficients (r) after FDR correction for multiple testing. **p*≤.05; ***p*≤ .01; ****p*≤ .001, *italics* indicate significant results without correction for multiple testing.

Table 3c

Partial Correlation Analyses of Neuropsychology and Psychopathology in remitted patients (*n*=379; MDD *n*=304, BD *n*= 39, SZ *n*=36)

	F1: Depression	F2: Negative Syndrome	F3: Positive Formal Thought Disorder	F4: Paranoid-Hallucinatory Syndrome	F5: Increased Appetite
D2 (KL)	-0.021	*-0.118**	-0.084	-0.052	-0.096
Sem. VF	-0.04	-0.005	-0.001	0.011	-0.095
Lex. VF	0.005	-0.001	-0.043	-0.026	*-0.13**
Cat. VF	-0.04	*-0.123**	*-0.104**	*-0.133***	-0.085
Symbol-Coding	0.066	-0.029	-0.048	-0.007	-0.074
Spatial Span (total)	0.085	-0.008	-0.043	-0.052	*-0.115**
Letter-number-span	0.028	-0.091	-0.056	-0.096	-0.034
TMT (difference)	-0.025	0.03	0.083	0.028	-0.03
VLMT (total correct words)	0.022	*-0.108**	0.028	-0.072	-0.033
VLMT (delayed recall)	-0.024	0.054	0.055	0.08	-0.01
Recognition (VLMT)	0.005	-0.014	0.059	-0.044	-0.028

Age, sex, verbal IQ, years of education and DSM-IV coded diagnoses were controlled for. Bold letters indicate significant correlation coefficients (r) after FDR correction for multiple testing. *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$, *italics* indicate significant results without correction for multiple testing.

Associations in the three sub-samples were differential compared to those of the total sample, unsurprisingly as sample sizes across the three clinical course groups differed which might have resulted in restricted power. To address this, we performed power analyses estimating the sample size needed to detect significant correlations. Depending on the neuro-cognitive test at least *n*=367 (association of the negative syndrome and categorical VF, see Table 3a) acute patients with a chronic course would be needed to detect significant associations. For acute patients with remission during episodes at least *n*=832 patients (association of depression and categorical VF, see Table 3b) and for remitted patients at least *n*=1796 patients (association for depression and symbol coding, see Table 3c) would be needed to identify significant correlations of psychopathology and neuro-cognition.

Moderator analyses showed the following moderating effects of the clinical variables tested (see also Figure 1 and 2): the total duration of hospitalizations positively moderated the associations of the Negative Syndrome with executive functioning (symbol coding) (total model: R^2=32.81%, F(8,1019)=62.19, p<0.001, moderation effect: b=0.04, F(8,1019)=5.66, p=0.018), and attention (total model: R^2=32.93%, F(8,1019)=62.53, p<0.001, moderation effect: b=0.13, F(8,1019)=4.43, p=0.035), while the age of onset negatively moderated the associations of the Negative Syndrome with executive functioning (TMT difference) (total model: R^2=17.66%, F(8,1047)=28.07, p<0.001, moderation effect: b=-0.17, F(8,1047)=3.92, p=0.048) and verbal episodic memory (total model: R^2=18.91%, F(8,1047)=30.52, p<0.001, moderation effect: b=-0.03, F(8,1047)=4.77, p=0.029). Total duration of hospitalization positively moderated the association of pFTD and verbal episodic memory (total model: R^2=18.37%, F(8,1019)=28.67, p<0.001, moderation effect: b=0.03, F(8,1019)=5.35, p=0.037). The association of pFTD and verbal episodic memory was negatively moderated by the age of onset (total model: R^2=18.98%, F(8,1047)=30.67, p<0.001, moderation effect: b=-0.1 F(8,1047)=5, p=0.026). However, when correcting for multiple testing (FDR) no moderation effect was present for both the lifetime duration of hospitalizations and age of disorder onset.

Figure1

Moderation effects of total duration of hospitalization and age of onset on the associations of the Negative Syndrome (F2) and neuro-cognition (models were corrected for age, sex, verbal IQ, years of education, and DSM-IV diagnosis)

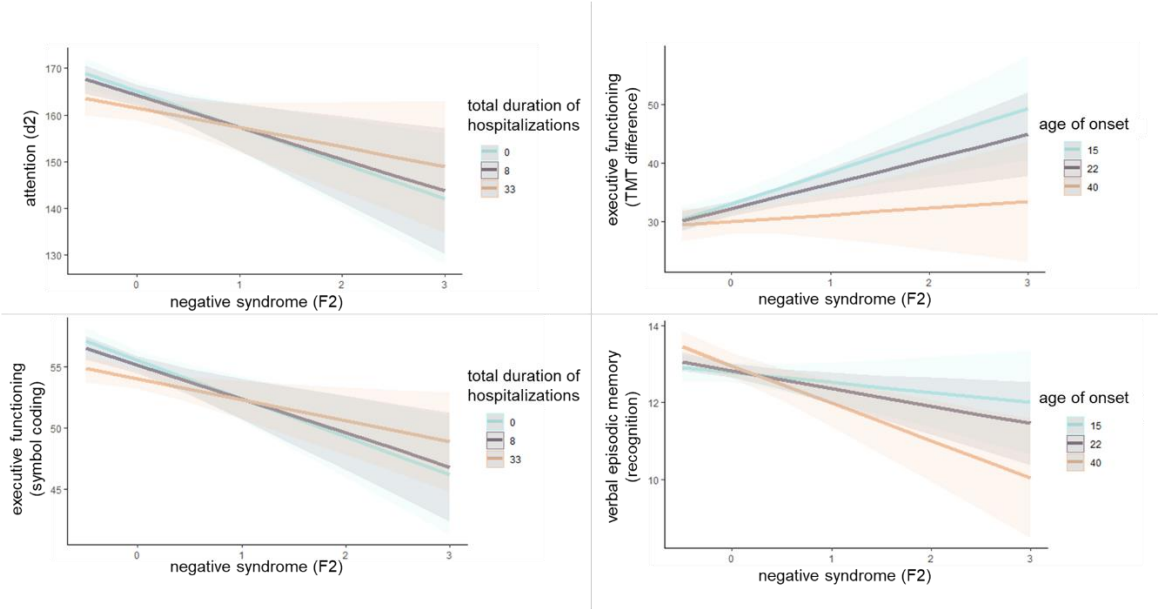
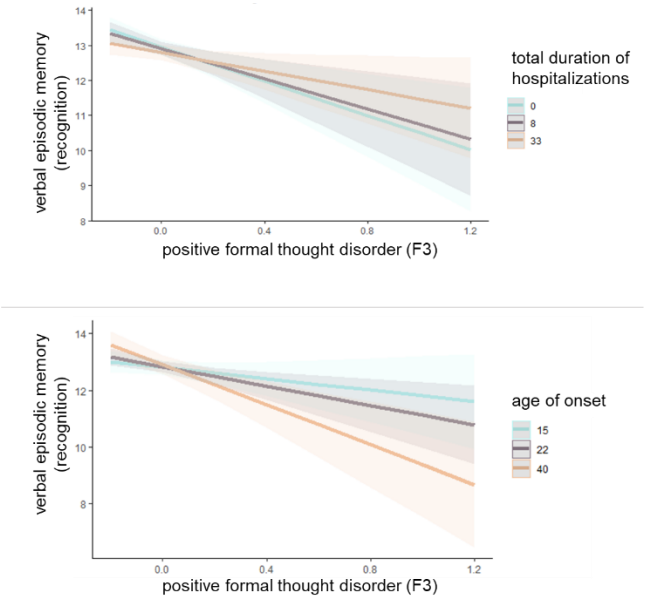


Figure2

Moderation effects of total duration of hospitalization and age of onset on the associations of the Positive Formal Thought Disorder (F3) and neuro-cognition (models were corrected for age, sex, verbal IQ, years of education, and DSM-IV diagnosis)



4. Discussion

In the present study, correlations of neuropsychological test scores and current psychopathological syndromes were examined. Of note, when studying the results, if no such significant correlation can be detected, this does not mean that symptoms or potential cognitive deficits are absent, rather, their respective values do not correlate during the time of investigation. Furthermore, clinical variables (i.e. lifetime total duration of hospitalizations, age of onset) were tested for moderating effects on the psychopathology – neuro-cognition associations.

The main findings can be summarized as follows:

1. According to the results of the neuropsychological testing, patients with SZ performed worse than both other groups and patients with BD scoring mostly in between patients with MDD and SZ.

2. Independent of diagnosis and current state of disorder, the three factors Negative Syndrome, pFTD and Paranoid-Hallucinatory Syndrome showed largest correlation coefficients. However, depending on the current state of the disorder, different correlation patterns emerged (see below). In contrast, Depression and Increased Appetite rarely showed significant correlations.

3. For the two factors Negative Syndrome and pFTD, state-dependent correlations with neuropsychological test results emerged: In remitted patients, neuropsychological test results were not correlated with any of the psychopathological factors after correction for multiple testing. In acute patients with full remission between episodes, correlations were found for the Negative Syndrome and pFTD while in acute patients with a chronic course, correlations were found for the pFTD and Paranoid-Hallucinatory syndrome. In previous meta-analyses, it has been found that a potential correlation between negative and/or disorganization symptoms and executive functioning is found in chronic courses of SZ while in first-episode SZ, these relationships are either weaker or absent [51]. However, this is not necessarily true for the other disorders studied here.

4. Lifetime total duration of hospitalizations and age of onset were used as proxies for illness severity and tested for moderating effects on the psychopathology – neuro-cognition associations. While the total duration of hospitalizations enhanced the associations between the neuro-cognitive performance and the factors Negative Syndrome and FTD, the moderator age of disorder had the opposite effect (i.e. negative moderation). However, after applying corrections for multiple testing no moderation effects were present.

Upon closer inspection of the individual factors, several additional results deserve discussion. When interpreting state of illness-dependent associations two limiting factors

should be considered. First, the range of symptoms might by truncated in each of the state of illness subgroups. Depending on the state of illness and diagnostic group variance of psychopathological symptoms might be restricted resulting in a lack of correlations detected. This would explain the absence of psychopathology – neuro-cognition associations in remitted patients. While neuro-cognitive impairment [20] is reported to be stable over time, psychopathological symptoms vary. There is meta-analytical evidence that cognitive remediation therapy might result in an improvement of cognition, while effects on psychopathology are limited [52, 53]. Based on current findings, it could be argued that during remission, these trainings might be most effective as current psychopathology is less pronounced and thus should not interfere as much with training sessions. Second, the absence of correlations reported in the total sample in the three subgroups might be explained by different sample sizes and therefore less statistical power across analyses. Depending on the cognitive domain and state of illness, samples sizes of at least 367 to 1796 patients would be needed to detect significant associations.

Large differences between states of disorder types occurred for the factor Paranoid-Hallucinatory Syndrome. Patients with a chronic course of their respective disorder displayed an association between the current psychopathology and verbal episodic memory. This relationship was completely absent in patients in full remission and in patients with an acute episode and full remission between episodes which might be explained by the treatment response to antipsychotic medication [54, 55].

The association of pFTD and neuro-cognition seems to follow a comparable trend: While patients with a chronic course show a correlation with verbal episodic memory, acute patients with full remission between episodes show a correlation with executive functioning. No associations were present in patients in current remission.

The Depression factor did not show any association with cognitive performance in different illness states. In the total sample, Depression was correlated with verbal fluency (categorical task) and executive functioning. This finding is in line with previous findings in large transdiagnostic samples [26]. Given that this factor is mainly driven by MDD patients, it has been shown that cognitive impairments also tend to remit after symptom remission [13] so that a correlation in acute patients is the most probable.

The Negative Syndrome was correlated with cognitive performance in a number of domains which is consistent with previous reports [25, 26]. This relationship is most pronounced in the total sample. However, when considering the different stages and courses of disorder, this relationship is only strong in acute patients with full remission between episodes. This could be explained by the heterogeneity of the course of negative symptoms while neuro-cognition remains stable or vice versa. A full remission

between episodes hints at the improvement of negative syndromes across all diagnoses, although they remain relatively stable in SZ while positive symptoms show a larger amount of improvement over time in all groups [56].

Finally, when considering cognitive domains rather than psychopathology, it becomes clear that all domains show associations with psychopathology, though to different degrees depending on the state of illness. In VF, category fluency (switching) is the most consistently associated test with psychopathology, most likely because it is the most demanding of the VF tests. Other domains, such as executive functioning (symbol-coding and TMT) and working memory (spatial span and letter-number-span) also show high levels of consistency in their association across syndromes and states. It is somewhat surprising that verbal episodic memory does only rarely show associations with current psychopathology. Given that verbal memory is often found to be impaired in MDD even in an euthymic state [14] and it is the most severely impaired domain in SZ, these relationships warrant additional clarification in future research.

Further analyses of moderators on the neuro-cognition – psychopathology relationship revealed that total duration of hospitalizations as well as age of onset did indeed moderate correlations with the Negative Syndrome and pFTD, but not the other factors in the total sample. While the total duration of illness positively moderated associations between neuro-cognition and psychopathology (i.e. more duration of hospitalization predicts the relationship between neuro-cognition and psychopathology to be stronger), age of onset weakens the associations between neuro-cognition and psychopathology. Previously, a meta-analyses [57] of age of onset and cognition in SZ patients reported individuals with youth-onset having severe cognitive deficits while patients with late-onset revealed somehow retained cognitive functioning. In a longitudinal study [58], illness severity has been negatively associated with neuro-cognition (i.e. verbal learning and working memory) in SZ patients pointing to a significantly better neuro-cognitive performance when patients spent less time hospitalized during follow-up. This is in line with the present study showing a moderating effect of total duration of hospitalizations (lifetime) since patients spending more time in hospital also showed worse cognitive performance being associated with higher load on psychopathological factors. Additionally, the absence of moderating effects regarding the neuro-cognition and Paranoid-Hallucinatory Syndrome associations might be explained by being more responsive to antipsychotic medication than negative syndromes [54, 55]. In the light of current results, pFTD thus might be also more persistent than paranoid-hallucinary symptoms [20, 59]. As such, one might argue that illness severity (onset and duration of hospitalizations) should impact more on uncontrollable factors. As Depression only showed few significant correlations with neuro-cognition, the absence

of moderating influence of illness severity was to be expected. Comparable to the Paranoid-Hallucinatory Syndrome, the absence of moderating effects might hint at the possibility that depressive symptoms could be less stable over time and might show a higher degree of remission and are thus less influenced by illness severity. Overall, it appears that for the Negative Syndrome as well as pFTD, illness severity impacts on the neuro-cognition – psychopathology relationship, albeit these results did not survive correction for multiple testing.

5. Limitations

The MDD group is the largest representing the prevalence of the investigated disorders in the population. Since we hypothesized that there are no “points of rarity”, equal sizes of diagnostic categories might discount our approach. Moreover, we wanted to investigate syndrome-cognition associations dimensionally and not within categorical diagnoses.

On a methodical level, it has to be noted that a high number of tests was performed due to the number of psychopathological factors, neurocognitive tests and state of illness. Even though after correction for multiple testing table-wise, some of these correlations could be considered false-positives. Some of these associations appear to have small effects only and reach significance due to sample size.

Another limitation is that no healthy control subjects (HC) were entered into the analyses because of lack of variance in psychopathological symptoms. The lack of HC in the present study prevents us from drawing conclusions regarding the relative level of potential cognitive impairments. However, this was not the scope of this investigation as correlations between psychopathology and neuro-cognition were of main interest. When interpreting the results, sample characteristics have to be considered: The sample had a mean history of their respective disorder ranging from about 10.5 years (MDD) to about 18 years (BD). Thus, factors such as years of medication intake could potentially influence the present associations.

Finally, a cross-sectional design was employed. It would be of great interest to assess course of illness, current psychopathology as well as neuro-cognition in a longitudinal design to validate the present results prospectively.

6. Conclusion

To the best of our knowledge this is the first study investigating the association of psychopathological dimensions and neuro-cognition using several validated scales and neurocognitive tests across psychotic and affective disorders in acute, chronic, and remitted states. Our findings give new evidence for a state-dependent association of

psychopathological symptoms and cognitive performance across the major psychiatric disorders. The results presented here may serve as an important starting point for future longitudinal transdiagnostic investigations regarding symptom-cognition associations as well as treatment targets in transdiagnostic samples.

Declarations:

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Ethics approval

Patients gave written informed consent to the study protocol. This study was approved by the local Ethics Committee Marburg (AZ:07/14) and Münster (AZ:2014-422-b-S) according to the Declaration of Helsinki.

Conflict of interest

Tilo Kircher received unrestricted educational grants from Servier, Janssen, Recordati, Aristo, Otsuka, neuraxpharm. All other authors declare no conflict of interest.

Data availability

The data that support the findings of this study are available in https://www.zenodo.org at 10.5281/zenodo.4555628.

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iv. STUDY IV: Manuscript

Psychopathological dimensions of formal thought disorder and their relation to gray- and white matter brain structure in affective and psychotic disorders

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Abstract:

Objective:

Factorial dimensions and neurobiological underpinnings of formal thought disorders (FTD) have been extensively investigated in schizophrenia spectrum disorders (SSD). However, FTD are also highly prevalent in other disorders. Still there is a lack of knowledge about transdiagnostic, structural brain correlates of FTD.

Method:

In *N*=1,071 patients suffering from DSM-IV major depressive disorder, bipolar disorder, or SSD, we calculated a psychopathological factor model of FTD based on the SAPS and SANS scales. We tested the association of FTD dimensions with 3 T MRI measured gray matter volume (GMV) and DTI white matter fractional anisotropy (FA) using regression and interaction models in SPM12. We performed post hoc confirmatory analyses in diagnostically equally distributed, age- and sex-matched sub-samples to test whether results were driven by diagnostic categories.

Results:

Cross-validation (explorative and confirmatory) factor analyses revealed three psychopathological FTD factors: verbosity, emptiness and disorganization. The verbosity dimension was negatively correlated with a GMV cluster comprising parts of the middle occipital and angular gyri and positively with FA in the right posterior cingulum bundle and inferior longitudinal fascicle. Emptiness was negatively associated with left hippocampus and thalamus GMV. Disorganization was negatively associated with FA in bilateral anterior thalamic radiation, and positively with the hippocampal part of the right cingulum bundle. None of the gray or white matter associations interacted with diagnosis.

Conclusion:

Our results provide a refined mapping of FTD phenotype dimensions and neuroanatomical signatures, pointing to language associated gray and white matter structures that are involved in FTD domains, independent of DSM-IV disorder.

Keywords: formal thought disorder, white matter, gray matter volume, transdiagnostic, dimensional, brain structure

Introduction

Formal thought disorder (FTD) refers to a construct measuring deviant thinking, speech and communication (1). FTD has been extensively investigated in schizophrenia (SZ), and schizoaffective disorder (SZA) (henceforth referred to as schizophrenia spectrum disorders, SSD), but much less in bipolar disorder (BD) and major depressive disorder (MDD) (all together henceforth referred to as major psychiatric disorders) (1,2). Prevalence rates of FTD range from 53% in MDD up to 80% in SZ (1). Patients with FTD have a higher risk for inpatient treatment, and they stay significantly longer in hospital (3).

Factor analyses of FTD symptomatology were previously performed in SZ patients. Only few studies investigated FTD dimensions across diagnosis showing common psychopathological dimensions (2,4–6). Depending on the scale and population, FTD can be broken down into one to six factors (2,7–9). Meta analyses (9,10) revealed two factors (i.e. positive and negative FTD). While there is consensus about one negative/poverty domain (11), positive FTD (pFTD) has been divided into two (e.g. disorganization, verbosity) to five (e.g. disorganization, idiosyncratic, semantic, attentional, referential) factors in SZ patients (8,9). pFTD symptoms are best represented by an increased amount of speech, tangentiality, derailment and circumstantiality (1). Negative FTD (nFTD) usually comprise a quantitative deficit resulting in poverty of speech, blocking and increased latency (2).

Language production and processing is constituted by distributed cortical and subcortical networks (12). Altered brain structure in these language circuits might result in FTD. Diagnostically independent brain structural correlates of FTD symptoms would completely open up new approaches for pathogenic and etiological research. Similarly to FTD symptomatology, the neuroanatomical correlates of FTD have mainly been examined in SZ patients, but not in other diagnoses. Studies in SZ patients have shown that positive/disorganized FTD measured with the Positive and Negative Syndrome Scale (PANSS) (13), the Scale for the Assessment of Positive Symptoms (SAPS) pFTD subscale or the Scale for Thought, Language and Communication (TLC) (14) correlated negatively with the gray matter volumes (GMV) of the bilateral superior temporal gyri, inferior frontal gyri (IFG), the middle, medial and superior frontal gyri, the left amygdala-hippocampus complex, the precuneus, the planum temporale, and the insula (15–17). nFTD have been negatively associated with GMV in the bilateral insula, the precuneus, the amygdala, the anterior and posterior cingulate gyri, and the medial frontal/orbitofrontal cortex (16,18). GMV associations with FTD across the major psychiatric disorders remain largely elusive.

The association of FTD dimensions and white matter diffusion tensor imaging (DTI) has been investigated to a much lesser extent than GMV in SZ and not at all in other diagnoses. Specifically in SZ patients a general dysconnectivity has been proposed (19). Moreover, one study indicated a structural language dysconnectivity in the semantic network which may be linked to FTD (20). Fiber tracts which have been associated with FTD are the inferior longitudinal fascicle (ILF), the left uncinate fascicle (21), the superior longitudinal fascicle (21), the inferior fronto-occipital fascicle (22), the cingulum bundle (CB) (23,24), and the anterior thalamic radiation (ATR) (22,24). There are no studies investigating white matter associations of FTD across the major psychiatric disorders, although FTD is common in all of these disorders.

In order to provide significant progress for our understanding of FTD as a core psychiatric syndrome, both, phenotypes and brain correlates, must be untangled across diagnoses. This transdiagnostic endeavor is further driven by results showing large overlaps across MDD, BD, and SSD not only in symptomatology, but also in molecular genetic (25,26) and early environmental risk (27). Besides, it has long been hypothesized, but not yet scientifically confirmed, that a particular psychopathological symptom/syndrome (e.g. disorganization) has a common brain structural correlate across psychiatric disorders (28). In our study, we therefore used an explorative-confirmatory cross-validation approach to disentangle the psychopathological factorial structure of FTD across MDD, BD and SSD. We associated the psychopathological factors with gray and white matter brain structure measured with MRI in a large patient sample (*N*=1,071). Based on previous findings (29), we hypothesized a factor model including one negative/emptiness factor, and additional positive domains (i.e. increased productivity and speech disorganization). Moreover, we hypothesized that the gray and white matter alterations previously associated with FTD in SZ patients (see above) are present in patients independent of MDD, BD or SSD diagnosis.

Method

Participants

As part of the FOR2107 cohort (for detailed information see (30)), a broad spectrum from acutely ill to remitted in- and outpatients from the departments of psychiatry, university hospitals in Marburg and Münster, Germany and other psychiatric hospitals in their vicinity, were included in the study. All procedures were approved by the local Ethics Committees according to the Declaration of Helsinki and patients gave written informed consent to the study protocol.

We excluded patients with IQ<80, history of head trauma or unconsciousness, current intake of benzodiazepines, and neurological illness from the present study. After

quality checks (as detailed below) of the T1 weighted scans and exclusion of patients with incomplete data, we analyzed 1,071 patients (aged 18-65) who met the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) for MDD (*n*=821, *f*=536/*m*=285), BD (*n*=133, *f*=73/*m*=60), and SSD (*n*=117, *f*=57/*m*=60; SZA *n*=42, SZ *n*=75)) (see Table 1). For the DTI analyses we excluded additional *n*=241 patients due to artifacts and caliber gaps, leaving a DTI sample of *n*=830 (MDD *n*=642, *f*=399/*m*=225; BD n=103, *f*=56/*m*=47; SSD *n*=103, *f*=50/*m*=53) (see supplement eTable 3).

Table 1: Descriptive statistics of the psychopathological factor analysis and voxel-based morphometry sample (*N*=1,071)

	Major depressive disorder (*n*=821)	Bipolar disorder (*n*=133)	Schizophrenia spectrum disorders (*n*=117)	*p*
age	36.67 *(13.19)*	41.34 *(11.93)*	38.23 *(11.72)*	< .001[a]
TIV	1561.53 *(152.8)*	1578.32 *(144.88)*	1578.83 *(183.53)*	.303
years of education	13.21 *(2.74)*	14.06 *(2.78)*	12.52 *(2.68)*	< .001[b]
SANS alogia subscale	0.49 *(1.31)*	0.62 *(1.37)*	1.83 *(2.64)*	< .001[c]
SAPS pFTD subscale	0.36 *(1.4)*	1.71 *(3.21)*	3.13 *(4.47)*	< .001[d]
SANS sum	7.47 *(8.65)*	5.74 *(7.33)*	13.57 *(12.4)*	< .001[c]
SAPS sum	0.66 *(2.08)*	2.37 *(4.3)*	10.03 *(12.52)*	< .001[d]
YMRS sum	1.43 *(2.1)*	3.89 *(5.92)*	2.69 *(4.94)*	< .001[d]
HAM-D sum	8.38 *(6.4)*	6.78 *(5.82)*	6.74 *(5.79)*	.002[e]

Note: Mean (*standard deviation*); TIV (= total intracranial volume); SANS (= scale for the assessment of negative symptoms (32)); SAPS (= scale for the assessment of positive symptoms (31)); YMRS (= Young mania rating scale (65)); HAM-D (=Hamilton rating scale for depression (66)). Tukey´s post hoc test was performed to investigate group differences.
[a] MDD<BD
[b] MDD<BD; SSD<BD
[c] MDD<SSD; BD<SSD
[d] MDD<BD,SSD; BD<SSD
[e] SSD<MDD; BD<MDD

Psychopathology assessment

FTD symptoms were assessed during a clinical interview including the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) and psychopathology scales.

Ratings were conducted during or immediately after the interview. All interviewers were familiar and trained with evaluation of the psychopathological scales. Acute positive and negative symptoms were assessed with the scale for the assessment of positive symptoms (SAPS) (31) and the scale for the assessment of negative symptoms (SANS) (32). Interrater reliability was assessed with the interclass coefficient achieving good reliability of $r>.86$ in both scales. For the present analysis, we used the items of the alogia subscale of the SANS and the pFTD subscale items of the SAPS. Global alogia and pFTD rating items were not included in our analysis since they merely summarize single symptom ratings.

FTD psychopathology factor analyses

In a first step, we investigated the factorial structure of FTD symptoms in the VBM sample. To cross-validate FTD factorial dimensions in two sub-samples, we divided the total sample of N=1,071 using the "mindiff" package (33) in R (version 4.0.4) (34). To provide a comparable distribution of diagnostic categories in both samples, we split each diagnostic group separately accounting for age and sex as covariates, resulting in the explorative psychopathology sub-sample 1 with n=537 (see supplement eTable1) and the confirmatory psychopathology sub-sample 2 with n=534 (see supplement eTable2).

To investigate the explorative factorial structure of FTD, we performed a principal axis factor analysis (PFA) with varimax rotation of sub-sample 1 using the *Statistical Package for Social Science* (IMB, SPSS), version 25, Armonk, NY. Due to interpretability, items with factor loadings < 0.5 were not considered in the analysis (6). Cronbach's alpha coefficients (35) were used to test the internal consistency.

To validate our explorative model, we performed a confirmatory factor analysis (CFA) using *Mplus* (version 8.4) (36) in the sub-sample 2. Additionally, we tested the confirmatory model for the whole sample (N=1,071). To rule out potential effects caused by the unequal distribution of DSM-IV diagnostic categories, we tested the model again in a smaller subsample with the same number of patients from each diagnosis, matched for age-and sex (see supplement eTable4, eTable5). Matching of the subsamples was performed using the "MatchIt" package (37) in R (34). We used the maximum-likelihood-method (MLM) to estimate our confirmatory model since this estimator is robust to standard errors and is one of the most common estimators (38). Goodness of fit was measured with chi-square significance test, comparative fit index (CFI) (39) and root mean square error of approximation (RMSEA) (40). To analyze the association of FTD dimensions and brain structure we extracted latent standardized factor scores for each patient using *Mplus*.

MRI data acquisition

T1 weighted images and diffusion weighted images were obtained using a 3 T MRI scanner (Münster: Prisma, Siemens, Erlangen, Germany; Marburg: Tim Trio, Siemens, Erlangen, Germany). In Münster, a 20 channel head matrix Rx-coil was used. MRI data in Marburg were obtained in cooperation with the Core-Unit Brainimaging, Faculty of Medicine, University of Marburg, Germany using a 12 channel head matrix Rx-coil. MRI data was acquired according to an extensive quality assurance protocol (41).

T1 weighted images were acquired using a fast gradient echo MP-RAGE sequence with a slice thickness of 1.0 mm consisting of 176 sagittal orientated slices in Marburg and 192 slices in Münster and a FOV of 256mm and the following parameters at the two sites: Marburg: TR=1.9s, TE=2.26ms, TI=900ms, flip angle=9°; Münster: TR=2.13s, TE=2.28ms, TI=900ms, flip angle=8°.

DTI scans were acquired using an epi2d sequence (TR 7300ms, TE 90ms, FOV 320mm, phase encoding anterior-posterior, 56 slices with 2.5 mm slice thickness in Münster, 3mm thickness in Marburg) with a final voxel resolution of 2.5 x 2.5 x 2.5 mm^3. For all patients, two sets of 30 diffusion-weighted images (b=1000s/mm^2) and four non-diffusion weighted images (b=0s/mm^2) were acquired. MRI data acquisition and the assessment of FTD symptoms were performed within the same week.

Pre-processing

For T1 weighted images, we used the default parameters as implemented in the CAT12 toolbox (Computation Anatomy Toolbox for SPM, build 1184, Christian Gaser, Structural Brain Mapping group, Jena University Hospital, Germany) (http://dbm.neuro.uni-jena.de/cat/) building on SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK). During pre-processing, images were spatially registered, segmented (42,43) and normalized (44). T1-MRI data sets were spatially smoothed with a Gaussian kernel of 8 mm FWHM. Total intracranial volume (TIV) was calculated during pre-processing.

Before pre-processing, all DTI scans were visually inspected for major artifacts or caliber gaps. For DTI analyses, we used a tract-based spatial statistics (TBSS) approach running under FSL (version 6.0; the Oxford Centre Functional Magnetic Imaging Software Library; Oxford, UK (45)). Data were pre-processed using default parameters. During pre-processing, data were corrected for motion and Eddy-Current artefacts (46). Images were non-linearly registered into standard Montreal Neurological Institute (MNI) space (47) using a FSL template. Fractional anisotropy (FA) maps were projected on mean skeletons with a 0.2 threshold to prevent alignment errors.

Voxel-based morphometry and diffusion-tensor-imaging statistical analyses

All brain structural analyses were performed using separate linear regression analyses for each factor. Several covariates of no interest were included in both analyses (age, sex, site and TIV, and the change of a gradient coil) (30,41). To consider potential medication effects, three dummy coded covariates accounting for the intake of antidepressants, mood stabilizers and antipsychotics were used.

VBM analyses were performed using SPM12 (v6906) (https://www.fil.ion.ucl.ac.uk/spm/). As recommended for VBM analyses, absolute threshold masking with a threshold value of 0.1 was used (http://dbm.neuro.uni-jena.de/cat/). Results were considered significant at $p<.05$ cluster-level family wise error-corrected (FWE) for multiple comparisons after an initial threshold of $p<.001$ uncorrected, and a $k>10$ threshold. Cluster labeling was applied using the Dartel space Neuromorphometrics atlas (http://www.neuromorphometrics.com/).

Tract-based, voxel-wise DTI analyses were performed using threshold-free cluster enhancement (TFCE). We performed 5000 permutations for GLM contrast generation (48). The JHU DTI 81 white-matter labels atlas and the JHU white-matter-tractography atlas (49) were used for cluster labelling. MNI coordinates were retrieved with the cluster tool of FSL. Results were considered significant at $p<.05$ FWE-corrected (peak-level), and threshold $k>10$.

ANCOVA interaction analyses for each factor with DSM-IV diagnostic categories were performed in SPM and FSL (factor x diagnosis, full-factorial model), to test whether transdiagnostic brain correlates of FTD dimensions were driven by DSM-IV diagnostic categories. Adding DSM-IV diagnostic categories as covariates to the multiple regression analyses would have contradicted our approach as diagnoses somehow rest on symptoms, therefore interaction analyses were performed for both the GMV and DTI analyses.

Since DSM-IV categories were unequally distributed, we again performed multiple regression analyses as described above in a sub-sample with equal patient numbers for each of the three diagnoses ($n=351$ for the VBM sample and $n=309$ for the DTI sample). Therefore, we used significant clusters from the total sample analyses as ROIs for the analyses in the matched sample. Again, ANCOVA interaction analyses in SPM and FSL were performed in the matched sample.

To better understand brain structural mechanisms across white and gray matter, we tested whether the VBM and DTI clusters correlating with one of the psychopathological factors were associated, using partial correlations including the covariates from brain structural analysis. Eigenvariate values approximating mean volume/FA of significant clusters were extracted.

Results

Exploratory psychopathology factor analysis of sub-sample 1

After varimax rotation and the suggestion of the ScreePlot (eFigure1), the principal axis factor analysis revealed a 3-factor structure (Table 2). Symptoms summarized in less than three factors did not make sense clinically and were superficial. In factor models with more than three factors (i.e. four factors) the last factor comprised only one symptom (SAPS32: distractibility). Factors only including one item cannot be considered as a symptom dimension. The 3-factor model included the following factors (explaining 50.58% of variance): verbosity (α=.857; 21.76 % of variance), emptiness (α=.757; 15.23% of variance), and disorganization (α=.728; (13.58% of variance).

Table 2: Explorative psychopathological FTD factors of sample 1 (*n*=537)

Factor	Item	Symptom	Loading	Cronbach´s Alpha
verbosity	SAPS 27	tangentiality	0.926	0.857
	SAPS 26	derailment	0.734	
	SAPS 30	circumstantiality	0.695	
	SAPS 31	pressure of speech	0.657	
emptiness	SANS 8	poverty of speech	0.755	0.757
	SANS 9	poverty of content	0.698	
	SANS 11	increased latency of response	0.652	
	SANS 10	blocking	0.545	
disorganization	SAPS 28	incoherence	0.874	0.728
	SAPS 29	illogicality	0.590	
	SAPS 32	distractibility	0.527	

Confirmatory psychopathology factor analysis of sub-sample 2

To cross-validate our explorative factor model, we performed a confirmatory factor analysis using the second sample (*n*=534). We confirmed the 3-factor model. Fit

indices of the second sample showed an acceptable fit: χ^2=44.88, *df*=21, *p*<.0001, *CFI*=0.909, *RMSEA*=0.046. To test whether our model fit the whole sample, we performed a confirmatory factor analysis in the whole sample (*N*=1,071) also showing a good fit χ^2=66.097, *df*=21, *p*<.0001, *CFI*=0.928, *RMSEA*=0.045. We were able to replicate the explorative model in the age- and sex-matched sample, too, presented in eResults 1 (supplement).

Association of FTD psychopathology factors with gray matter volume

In a next step, we investigated the association of each FTD factor and GMV in the whole sample (*N*=1,071), using latent standardized factor scores for each patient and factor in multiple regression models. Verbosity correlated negatively with a cluster including the left (L) middle occipital gyrus (MOG) (63%), L inferior occipital gyrus (29%), and the L angular gyrus (7%) (*k*=872, x/y/z=-40.5/-66/12, *t*=4.7, *p*=.035 FWE cluster-level corrected) (see Figure 1A). Emptiness showed a negative correlation with a cluster comprising the L hippocampus (41%), L cerebral white matter (36%), L thalamus proper (7%), L parahippocampal gyrus (7%), and the L posterior cingulate gyrus (5%) (*k*=842, x/y/z=-31.5/-25.5/-15, *t*= 4.19, *p*=.039 FWE cluster-level corrected) (see Figure 1B). There was no FWE cluster-level corrected association for the disorganization factor. Full-factorial interaction analyses in SPM (DSM-IV diagnostic category x FTD factor) were performed to test if local GMV associations with FTD dimensions were driven by DSM-IV diagnoses. There was no interaction effect at the suggested threshold (*p*<0.05 cluster-level FWE-corrected) in the total sample (*N*=1,071).

To further test if GMV associations were driven by DSM-IV diagnoses, we performed regression analyses again in an age- and sex matched sample which included the same number of patients from each of the three diagnostic categories (*n*=351). Significant clusters from the whole brain analysis in total sample could be replicated in the diagnostically matched sample (see eResults2). Comparable to the total sample, there was no interaction with DSM-IV diagnoses for both the verbosity and the emptiness factor on GMV in the diagnostically matched sample, either.

Association of FTD factors and FA

We tested the relationship of FTD factors and the microstructure of white matter (FA) DTI tracts using multiple regression analyses for each factor in the whole sample (n=830) (see Figure 2A and B). FWE peak-level corrected results are presented in Table 3. Verbosity and disorganization were differentially associated with white matter FA, including positive associations of verbosity with the R ILF and posterior cingulum bundle. Disorganization was correlated negatively with the bilateral ATR and positively with the

hippocampal part of the cingulum bundle. There was no FWE peak-level association for the emptiness factor. We were able to retrieve significant clusters of the total sample in the age- and sex-matched sample (same n per diagnosis), too (see supplement eTable6). Comparable to GMV analyses, we performed interactions analyses (DSM-IV diagnoses x FTD factor) in FSL to test if local white matter associations were driven by DSM-IV diagnoses. There was no interaction effect in the total and in the diagnostically matched sample.

Table 3: Association of formal thought disorder factors and fractional anisotropy diffusion tensor imaging tracts (*n*=830)

Factor	**Corre-lation**	**Coordinates of the maximum intensity voxel (x/y/z) MNI**	**Anatomical labelling**	**Hemisphere**	***k***	***p***
verbosity	positive	11/-48/26	posterior cingulum	R	14	.036
	positive	46/-7/-16	inferior longitudinal fasciculus	R	60	.038
disorgani-zation	negative	-12/2/4	anterior thalamic radiation	L	201	.02
	negative	14/1/6	anterior thalamic radiation	R	157	.012
	positive	23/-44/2	cingulum/ hippocampus	R	24	.028

Note: R=right, L=left

Figure 1 A and B: Association of formal thought disorder dimensions and gray matter volume in patients with major depressive disorder, bipolar disorder, and schizophrenia spectrum disorder (N=1,071). Clusters of significant negative (blue) correlations at $p < 0.05$, cluster-level family wise error-corrected (initial cluster-defining threshold of $p<0.001$).

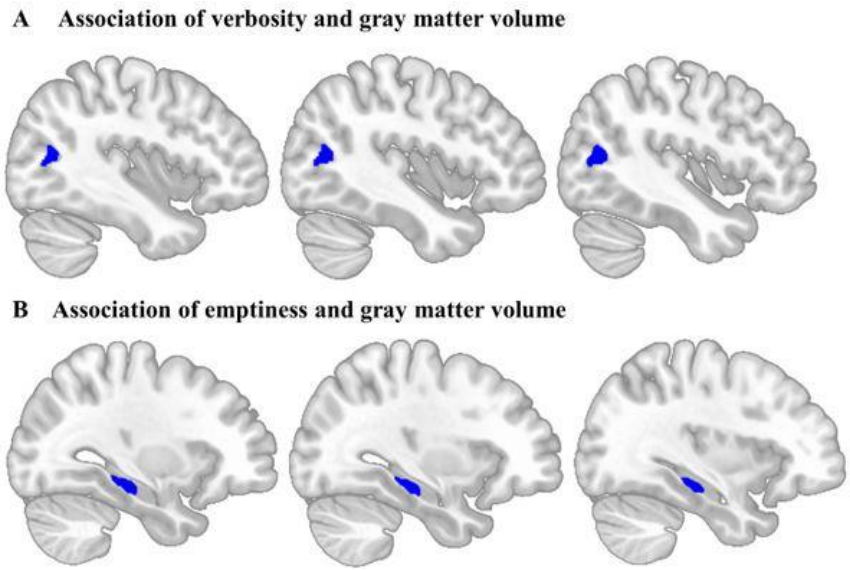
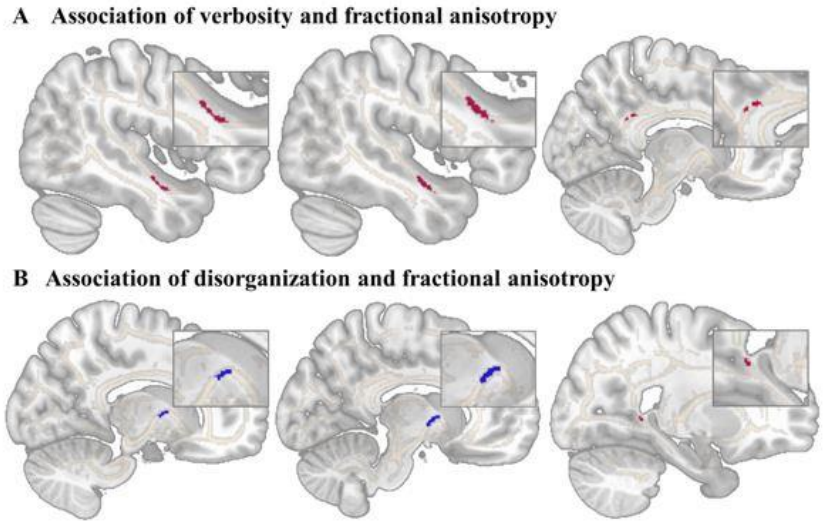


Figure 2 A and B: Association of formal thought disorder dimensions and fractional anisotropy in the whole DTI sample (*n*=830). Clusters of significant positive (red) and negative (blue) correlations at p<.05, peak-level family-wise-error-corrected. The clippings show an enlargement of the clusters.



Association of significant GMV and DTI clusters

As we detected alterations in both brain modalities (gray and white matter) for the verbosity factor, we investigated the correlation between these results to better understand brain structural mechanisms. Therefore, we used partial correlation analyses for the verbosity FTD dimension in the whole sample and correlated GMV clusters with FA white matter tracts. There was no correlation between any of the VBM and DTI clusters.

Discussion

We investigated the association of FTD psychopathological dimensions with white and gray matter in a large transdiagnostic cohort of patients with MDD, BD and SSD. Our study revealed an exploratory and confirmatory psychopathological three factor model across disorders comprising verbosity, disorganization and emptiness FTD dimensions. The verbosity dimension was negatively associated with a GMV cluster comprising parts of the temporo-occipital language junction including the L MOG and angular gyrus. Furthermore, we found a positive fiber tract association of the verbosity factor with the R posterior CB and the R IFL. The disorganization FTD factor was negatively associated with the bilateral ATR, and positively with the R cingulum/hippocampus bundle. The emptiness dimension was negatively associated with a GMV cluster comprising the L hippocampus and thalamus. Importantly, all VBM and DTI – FTD psychopathology factor associations were independent of DSM-IV diagnoses. This points to a shared relationship between FTD dimensions and brain structure across diagnoses. Furthermore, there was no correlation between VBM and DTI clusters of the verbosity factor indicating one given FTD syndrome/dimension can arise from different brain structural changes, a result well known e.g. from aphasia research.

Previous studies using the SAPS and SANS that only included patients with SZ, showed a three factor model encompassing emptiness (poverty/nFTD), verbosity, and disorganization (9). Unlike previous studies focusing only on SZ patients (1,8,9), we extend existing psychopathological factor models of FTD across psychotic and affective disorders using a cross-validated model. Our results demonstrate that FTD encompass three independent dimensions across categorical disorders.

Moreover, our study provides first large-scale evidence that FTD dimensions are differentially correlated with gray and white matter anatomical structures across diagnoses. The verbosity factor was negatively associated with a GMV cluster in the L temporo-occipital language junction comprising parts of the angular and middle occipital gyri. The L angular gyrus is part of the Wernicke speech area which has been associated

with the total severity of FTD symptoms in SZ patients (50), corroborating our results. Moreover, the L MOG has been linked to semantic paraphasia and neologisms during free speech production in aphasia patients (51) pointing to derailed speech which coincides with the verbosity dimension across psychiatric patients in the present study. In aphasia patients, the L MOG has been associated with semantic errors in naming tasks (52,53). In our study, verbosity was further positively correlated with FA of two white matter tracts: the R ILF and the R posterior CB. Previously, the ILF has been associated with verbosity in SZ patients (22). It indirectly connects posterior temporal and occipital areas and the frontal lobe (54). Together with other ventral white matter tracts, the ILF forms part of the semantic ventral stream (55), which is, e.g. implicated in linking objects to the appropriate lexical meaning (56) and more generally to lexical access. The right lateralization might indicate a reversed lateralization in patients which has also been observed during fMRI speech production tasks in SZ (57). These associations might indicate a global brain structural dysconnectivity which has already been reported in SZ patients (19), being generally implicated in FTD (20,58).

The factor disorganization was correlated with white matter tracts in the bilateral ATR and the R cingulum-hippocampus bundle. The ATR connects the dorsolateral prefrontal cortex with the thalamus (59). Altered FA in the ATR has been reported in BD (59) and SZ (60) patients. Our results further coincide with a previous SZ study (22) showing bilateral associations of the ATR with a global FTD language score. Further evidence is given by lesion studies in aphasia patients (24) indicating that the reduced FA of the ATR is associated with impairments in verbal fluency tasks. There was no association of the disorganization factor and GMV indicating differential brain structural mechanisms being involved in different FTD domains.

The emptiness factor in our study was negatively associated with a GMV cluster comprising parts of the L hippocampus, thalamus, and posterior cingulate gyrus. This result is in line with previous studies in SZ patients (15,16,18). Additionally, functional imaging studies in SZ indicated that impaired free word generation is mediated by the hippocampus (61,62). No correlations to white matter FA were present.

In summary, the brain structural correlates of our psychopathological FTD factors in MDD, BD and SSD have previously been implicated with speech pathology in aphasia and SZ patients. This corroborates our results and opens a new road to psychopathological syndrome -and not diagnosis - based etiological and pathogenic research in mental disorders.

Limitations

Some limitations should be considered. First, the MDD group was the largest in our transdiagnostic sample which might have biased our results. However, interaction analyses in both the whole and the diagnostically matched sample revealed no interaction of DSM-IV diagnostic categories and FTD factors on local brain structural correlates. Second, the SANS and SAPS are designed to measure a broad variety of symptoms, rather than specifically FTD (2,63). Using more detailed scales collecting even more FTD symptoms might result in a higher number of extracted factors and subsequently in differential brain structural correlates of FTD. Nevertheless, SANS and SAPS are two economical and well-validated scales that have been widely used in FTD research. Third, factor dimensions were based on current FTD symptoms and statistical models did not include remission of patients. Correlating current state measures with brain structure might lead to volatile results (64). Nevertheless, acute syndromes may be an indication for a particular neuroanatomical, state independent alteration that outlasts current symptoms. The investigation of the stability of FTD factors across time and their association to brain structure would be of great interest.

Conclusion

Together, our results provide first evidence of common neurobiological structures involved in FTD across affective and psychotic disorders. Since the anatomical correlates of white and gray matter did not correlate with each other, we speculate that firstly, the same psychopathological symptoms can result from changes in different neuroanatomical substrates, a fact known from aphasia research, which might explain in part the heterogeneous findings of FTD neural correlates in SZ. Secondly, these different neuroanatomical correlates might be due to a diverse range of environmental and genetic factors (and their interactions) impacting at different time points in the developing brain. Consequently, different etiologies may result in a range of diverse brain changes, nevertheless giving rise to a homogeneous syndrome, e.g. disorganization or verbosity. Dimensional approaches as applied in this present study are a key in overcoming a scientific deadlock in neurobiological research disentangling the dimensional variety of FTD symptoms across disorders.

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Supplement:

eResults1: Confirmatory factor analysis of the age- and sex-matched sample

To test whether results were driven by unequal sample sizes of each DSM-IV diagnostic category we performed factor and brain structural analyses again in an age- and sex-matched sample. The matched VBM sample included *n*=351 patients (MDD *n*=117, BD *n*=117, SSD *n*=117). Confirmatory factor analyses of the matched VBM sample showed a good fit: χ^2=51.43, *df*=20, *p*=.0001, *CFI*=0.924, *RMSEA*=0.045. The matched DTI sample included *n*=309 patients (MDD *n*=103, BD *n*=103, SSD *n*=103). Confirmatory factor analyses of the matched DTI sample also showed a good fit: χ^2=44.88, *df*=20, *p*=.0011, *CFI*=0.926, *RMSEA*=0.039.

eResults 2: Associations of FTD factors and brain structure in the age- and sex-matched sample

To rule out potential effects caused by the unequal distribution of DSM-IV diagnostic categories we performed regression analyses again in an age- and sex-matched VBM sample (*n*=351). Therefore, significant clusters of the total sample were used as ROIs. We were able to replicate results of the total sample in the matched sample, too (F1, L MOG cluster: *k*=95, x/y/z=-39/-68/12, *p*=.011, FWE cluster-level corrected; F2 L hippocampus cluster: *k*=23, x/y/z=-21/-42/-2, *p*=.024 FWE cluster-level corrected). DTI results are presented in *eTable6*. For both GMV and FA clusters no interaction (analyses performed in SPM/FSL) of factor x DSM IV diagnostic categories was present.

eTable 1: Descriptive statistics of the explorative psychopathology sample n=537

	Major depressive disorder (*n*=411)	Bipolar disorder (*n*=67)	Schizophrenia spectrum disorders (*n*=59)	*p*
age	36.67 *(12.91)*	41.34 *(11.87)*	38.24 *(11.31)*	.007[a]
TIV	1564.41 *(155.14)*	1579.78 *(136.79)*	1573.2 *(183.06)*	.67
years of education	13.25 *(2.7)*	14.06 *(2.79)*	12.54 *(2.54)*	.008[b]
SANS alogia subscale	0.53 *(1.47)*	0.52 *(1.16)*	2.24 *(2.98)*	<.001[c]
SAPS pFTD subscale	0.29 *(1.23)*	2.19 *(3.55)*	3.49 *(4.4)*	<0.001[d]
SANS sum	7.84 *(9.31)*	5.6 (7.38)	14.36 *(14.62)*	<.001[c]
SAPS sum	0.58 *(1.87)*	2.96 *(4.81)*	11.17 *(13.36)*	<.001[d]
YMRS sum	1.44 *(1.85)*	4.85 *(6.44)*	3.08 *(5.31)*	<.001[d]
HAM-D sum	8.37 *(6.47)*	6.36 *(5.97)*	6.97 *(6.14)*	.003[e]

Mean (*standard deviation*); TIV (= total intracranial volume); SANS (= scale for the assessment of negative symptoms (31)); SAPS (= scale for the assessment of positive symptoms (32)); YMRS (= Young mania rating scale (33)); HAM-D (=Hamilton rating scale for depression (34)). Tukey´s post hoc test was performed to investigate group differences.

[a] MDD<BD
[b] SSD<BD
[c] MDD<SSD; BD<SSD
[d] MDD<BD,SSD; BD<SSD
[e] BD<MDD

eTable 2: Descriptive statistics of the confirmatory psychopathology sample n=534

	Major depressive disorder (*n*=410)	Bipolar disorder (*n*=66)	Schizophrenia spectrum disorders (*n*=58)	*p*
age	36.67 *(13.47)*	41.33 *(12.07)*	38.22 *(12.22)*	.021[a]
TIV	1558.64 *(150.56)*	1576.83 *(153.7)*	1584.56 *(185.41)*	.216
years of education	13.18 *(2.77)*	14.06 *(2.78)*	12.5 *(2.84)*	.009[b]
SANS alogia subscale	0.46 *(1.13)*	0.73 *(1.56)*	1.41 *(2.19)*	<.001[c]
SAPS pFTD subscale	0.42 *(1.54)*	1.23 *(2.76)*	2.76 *(4.54)*	<.001[d]
SANS sum	7.11 *(7.92)*	5.88 *(7.32)*	12.78 *(9.75)*	<.001[c]
SAPS sum	0.75 *(2.28)*	1.77 *(3.65)*	8.9 *(11.64)*	<.001[c]
YMRS sum	1.42 *(2.33)*	2.91 *(5.22)*	2.29 *(5.54)*	.001[a]
HAM-D sum	8.39 *(6.33)*	7.21 *(5.69)*	6.52 *(5.545)*	.049[e]

Mean (*standard deviation*); TIV (= total intracranial volume); SANS (= scale for the assessment of negative symptoms (31)); SAPS (= scale for the assessment of positive symptoms (32)); YMRS (= Young mania rating scale (33)); HAM-D (=Hamilton rating scale for depression (34)). Tukey´s post hoc test was performed to investigate group differences.

[a] MDD<BD
[b] MDD<BD; SSD<BD
[c] MDD<SSD; BD<SSD
[d] MDD<BD,SSD; BD<SSD
[e] SSD<MDD

eTable 3: Descriptive statistics of the DTI subsample n=830

	Major depressive disorder (*n*=624)	Bipolar disorder (*n*=103)	Schizophrenia spectrum disorders (*n*=103)	*p*
age	37.37 *(13.4)*	40.27 *(11.83)*	38.79 *(11.59)*	.056
TIV	1556.41 *(149.46)*	1587.15 *(143.88)*	1577.05 *(166.96)*	.095
years of education	13.13 *(2.77)*	14.31 *(2.84)*	12.68 *(2.77)*	.001 [a]
SANS alogia subscale	0.54 *(1.38)*	0.58 *(1.34)*	1.68 *(2.46)*	<.001[b]
SAPS pFTD subscale	0.4 *(1.47)*	1.63 *(3.04)*	3.15 *(4.6)*	<.001[c]
SANS sum	7.71 *(8.84)*	5.55 *(7.28)*	12.71 *(10.74)*	<.001[d]
SAPS sum	0.73 *(2.15)*	2.18 *(3.77)*	9.63 *(12.28)*	<.001[c]
YMRS sum	1.37 *(2.09)*	3.21 *(5.1)*	2.68 *(5.04)*	<.001[e]
HAM-D sum	8.38 *(6.57)*	6.48 *(6.01)*	6.33 *(5.27)*	<.001[f]

Mean (*standard deviation*); TIV (= total intracranial volume); SANS (= scale for the assessment of negative symptoms (31)); SAPS (= scale for the assessment of positive symptoms (32)); YMRS (= Young mania rating scale (33)); HAM-D (=Hamilton rating scale for depression (34)). Tukey´s post hoc test was performed to investigate group differences.

[a] MDD<BD; SSD<BD
[b] MDD<SSD; BD<SSD
[c] MDD<BD,SSD; BD<SSD
[d] MDD<SSD; BD<SSD
[e] MDD<SSD, BD
[f] BD<MDD; SSD<MDD

eTable 4: Descriptive statistics of the VBM subsample with the same n for each of the three diagnoses, matched for age- and sex n=351

	Major depressive disorder (*n*=117)	Bipolar disorder (*n*=117)	Schizophrenia spectrum disorders (*n*=117)	*p*
age	38.21 *(11.71)*	39.74 *(11.62)*	38.23 *(11.71)*	.407
sex	*f*=57 *m*=60	*f*=62 *m*=55	*f*=57 *m*=60	.752
TIV	1594.3 *(162.73)*	1585.33 *(141.86)*	1578.83 *(183.53)*	.651
years of education	13.2 *(2.75)*	14.23 *(2.78)*	12.52 *(2.67)*	<.001[a]
SANS alogia subscale	0.5 *(1.1)*	0.56 *(1.32)*	1.83 *(2.64)*	<.001[b]
SAPS pFTD subscale	0.4 *(1.31)*	1.85 *(3.35)*	3.13 *(4.47)*	<.001[c]
SANS sum	7.7 *(7.83)*	5.48 *(7.15)*	13.57 *(12.4)*	<.001[b]
SAPS sum	0.6 *(1.51)*	2.6 *(4.49)*	10.03 *(12.52)*	<.001[b]
YMRS sum	1.35 *(2.21)*	3.85 *(5.92)*	2.69 *(4.94)*	<.001[d]
HAM-D sum	9.13 *(6.86)*	6.54 *(5.92)*	6.74 *(5.79)*	.005[e]

Mean (*standard deviation*); TIV (= total intracranial volume); SANS (= scale for the assessment of negative symptoms (31)); SAPS (= scale for the assessment of positive symptoms (32)); YMRS (= Young mania rating scale (33)); HAM-D (=Hamilton rating scale for depression (34)). Tukey´s post hoc test was performed to investigate group differences.

[a] MDD<BD; SSD<BD
[b] MDD<SSD; BD<SSD
[c] MDD<SSD, BD; BD<SSD
[d] MDD<BD
[e] BD<MDD; SSD<MDD

eTable 5: Descriptive statistics of the DTI subsample with the same n for each of the three diagnoses, matched for age- and sex n=309

	Major depressive disorder (*n*=103)	Bipolar disorder (*n*=103)	Schizophrenia spectrum disorders (*n*=103)	*p*
age	38.06 *(11.65)*	40.27 *(11.83)*	38.79 *(11.59)*	.295
sex	*f*=50 *m*=53	*f*=56 *m*=47	*f*=50 *m*=53	.627
TIV	1589.3 *(149.88)*	1587.15 *(143.88)*	1577.05 *(166.96)*	.732
years of education	13.37 *(2.75)*	14.31 *(2.84)*	12.68 *(2.77)*	<.001[a]
SANS alogia subscale	0.39 *(0.94)*	0.58 *(1.34)*	1.68 *(2.46)*	<.001[b]
SAPS pFTD subscale	0.3 *(0.88)*	1.63 *(3.04)*	3.15 *(4.6)*	<.001[c]
SANS sum	7.49 *(7.58)*	5.55 *(7.28)*	12.71 *(10.74)*	<.001[b]
SAPS sum	0.53 *(1.2)*	2.18 *(3.77)*	9.63 *(12.28)*	<.001[b]
YMRS sum	1.35 *(2.06)*	3.21 *(5.1)*	2.68 *(5.04)*	<.001[d]
HAM-D sum	9.11 *(7.08)*	6.48 *(6.01)*	6.33 *(5.27)*	<.001[e]

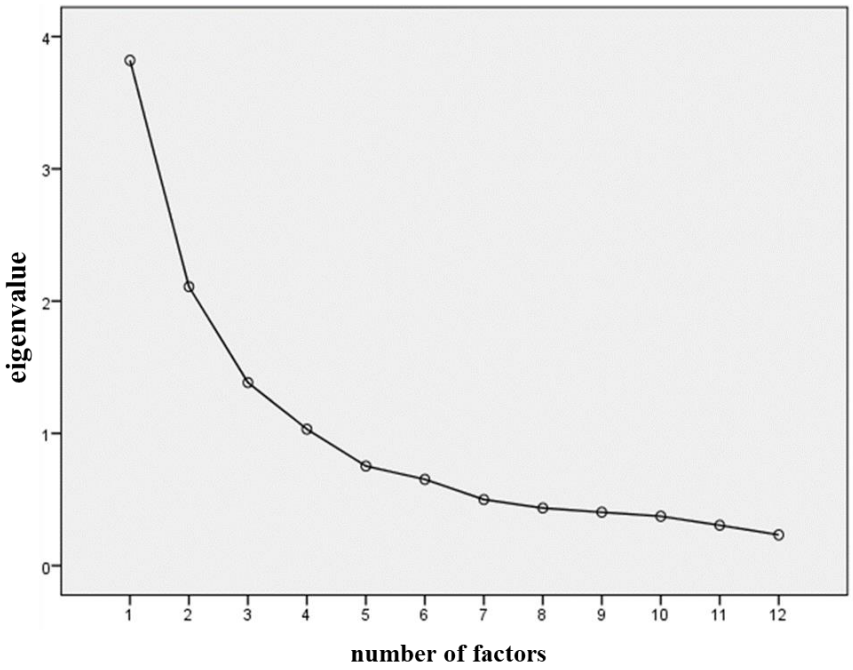
Mean (*standard deviation*); TIV (= total intracranial volume); SANS (= scale for the assessment of negative symptoms (31)); SAPS (= scale for the assessment of positive symptoms (32)); YMRS (= Young mania rating scale (33)); HAM-D (=Hamilton rating scale for depression (34)). Tukey´s post hoc test was performed to investigate group differences.

[a] SSD<BD
[b] MDD<SSD; BD<SSD
[c] MDD<SSD, BD; BD<SSD
[d] MDD<BD
[e] BD<MDD; SSD<MDD

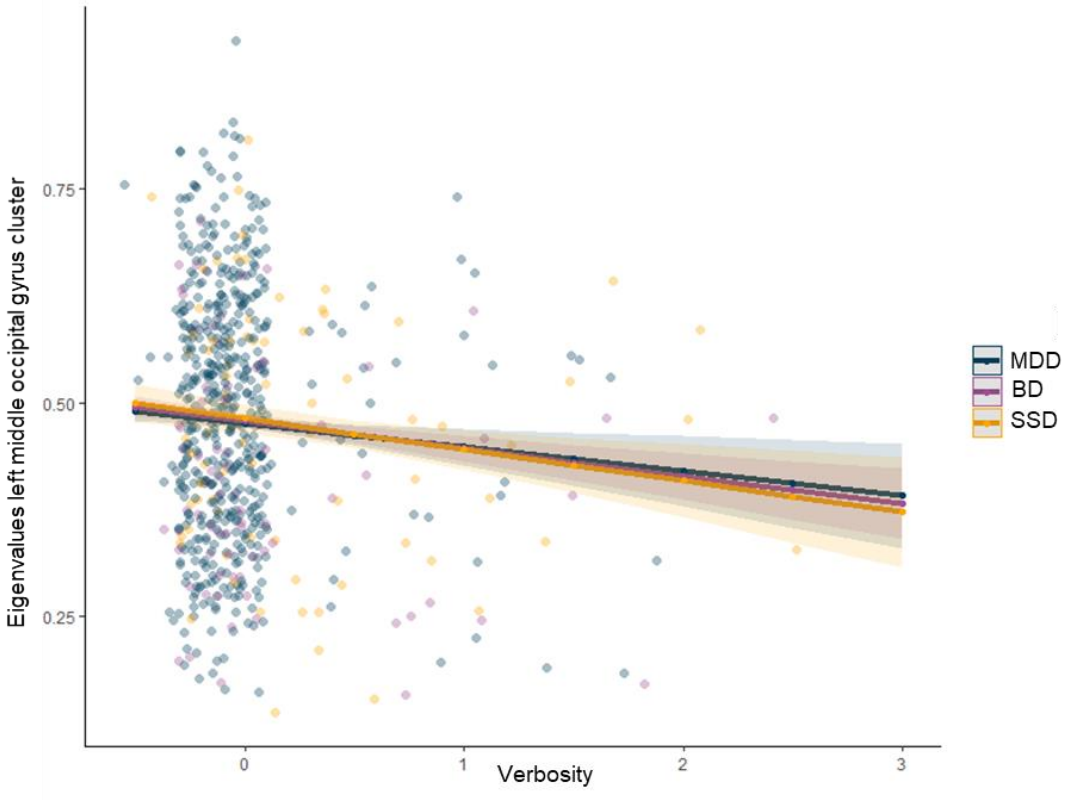
eTable 6: Association of FTD factors and DTI tracts in the subsample with the same n for each of the three diagnoses, matched for age- and sex n=309, at p < 0.05, TFCE, FDR corrected

Factor	Correlation	Coordinates of the maximum intensity voxel (x/y/z) MNI	Anatomical labelling	Hemisphere	*k*	*p*
verbosity	positive	26/-18/12	posterior cingulum	R	4	.032
	positive	47/3/-30	inferior longitudinal fasciculus	R	37	.032
disorganization	negative	-16/18/-4	anterior thalamic radiation	L	61	.03
	negative	30/-29/0	anterior thalamic radiation	R	76	.002
	positive	25/-47/0	cingulum/ hippocampus	R	179	.002

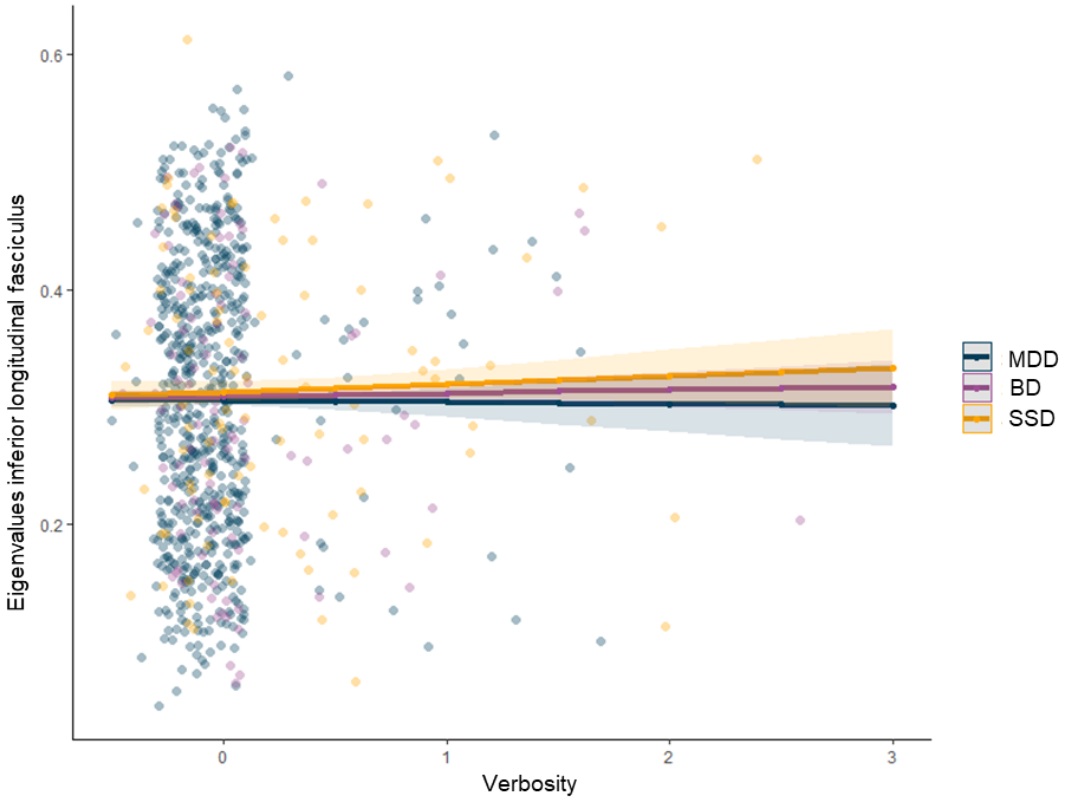
eFigure1: Screeplot of the exploratory factor analysis in psychopathological sub-sample 1 n=537



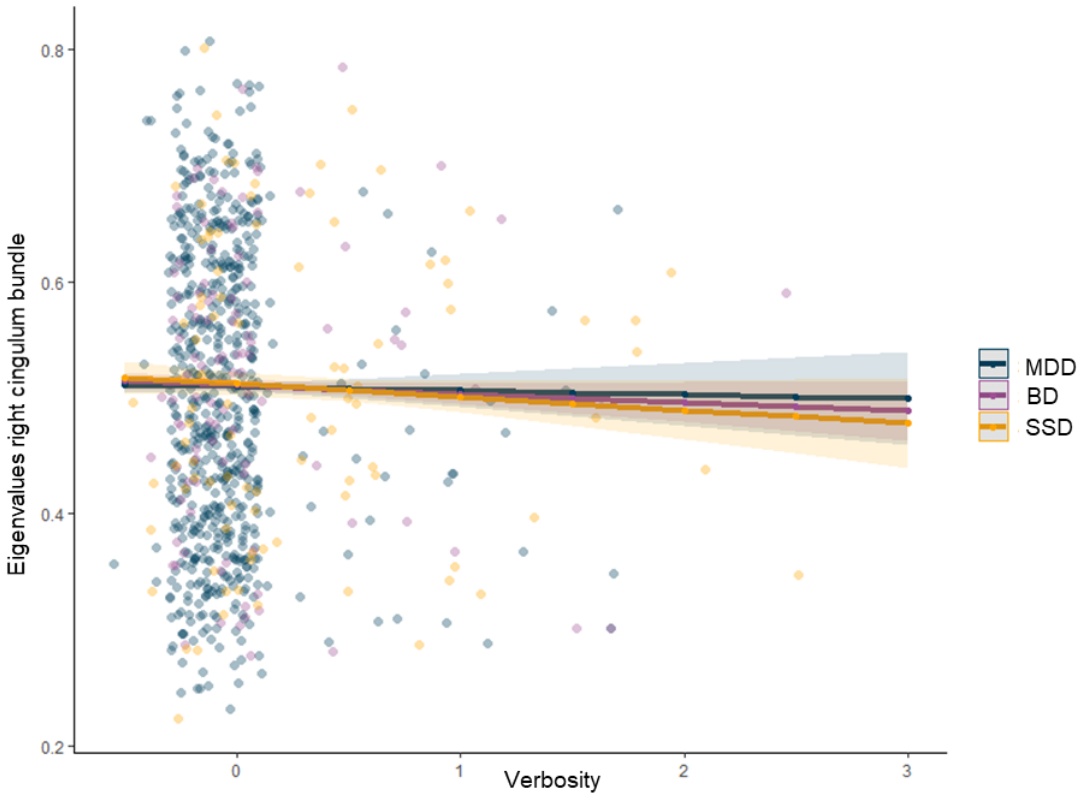
eFigure2: Post hoc visualization of the interaction analyses of the left middle occipital gyrus cluster and factor 1 “verbosity”. No interaction of categorical diagnosis and factor 1 was present (p=.625)



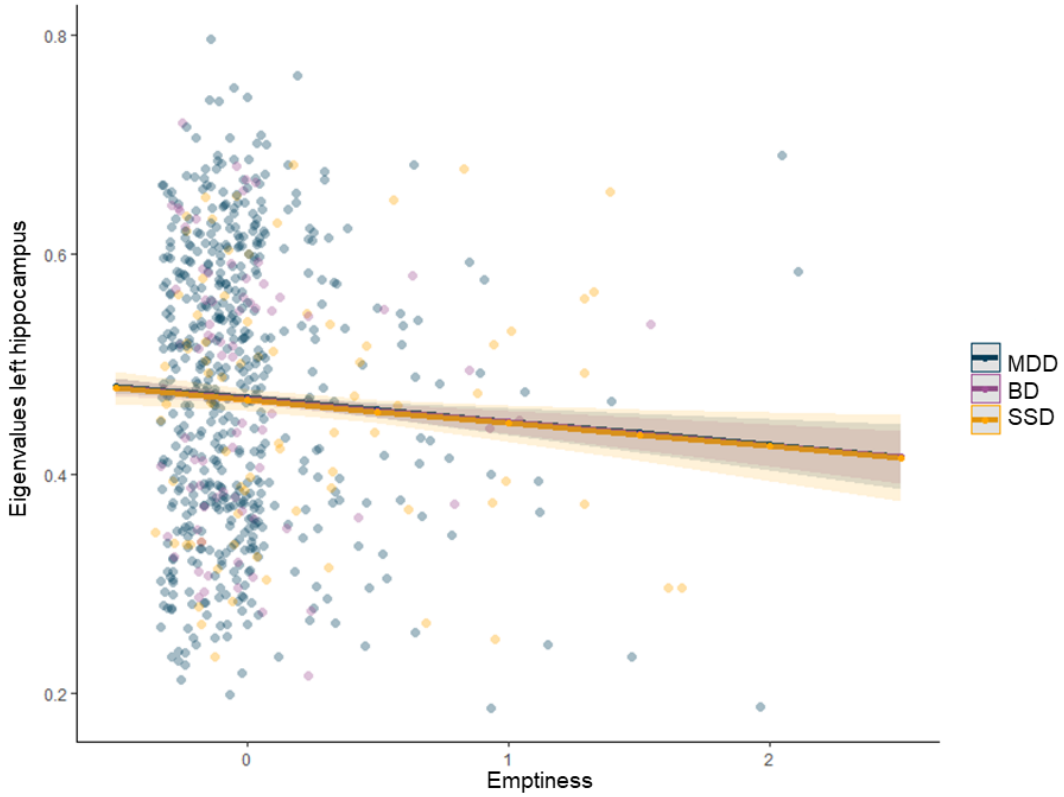
eFigure3: Post hoc visualization of the interaction analyses of the right inferior longitudinal fascicle FA and factor 1 "verbosity". No interaction of categorical diagnosis and factor 1 was present (p=.373)



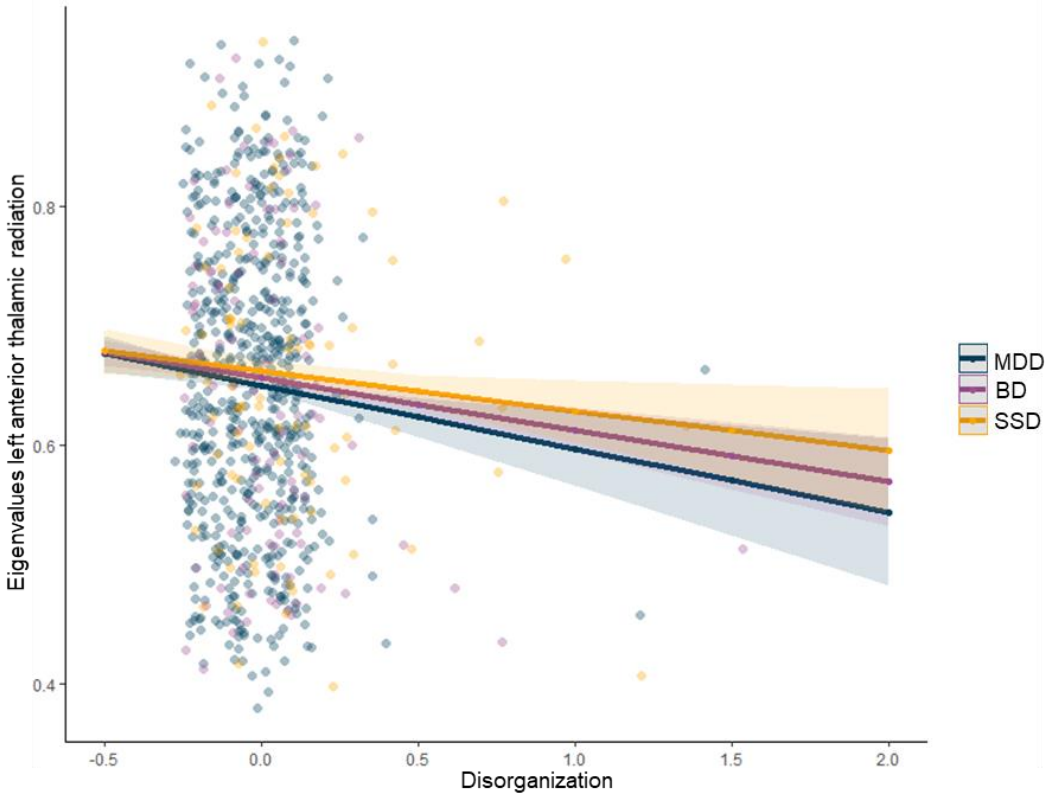
eFigure4: Post hoc visualization of the interaction analyses of the right cingulum bundle FA and factor 1 "verbosity". No interaction of categorical diagnosis and factor 1 was present (p=.446)



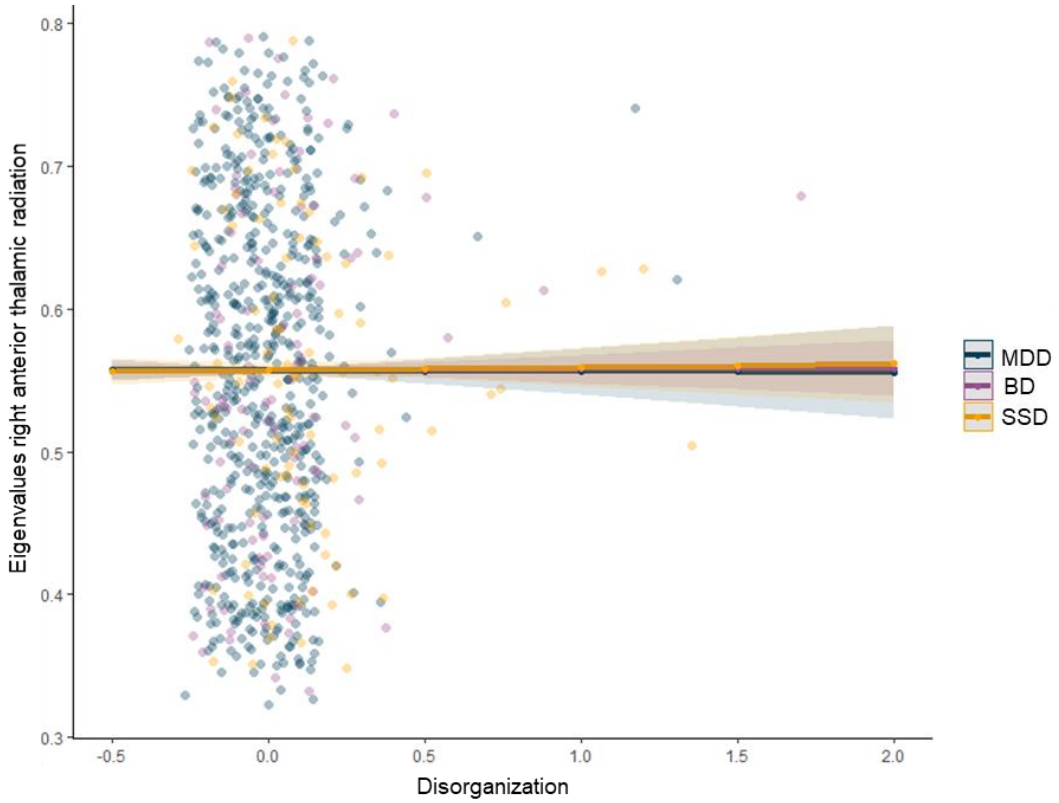
eFigure5: Post hoc visualization of the interaction analyses of the left hippocampal cluster and factor 2 “emptiness”. No interaction of categorical diagnosis and factor 2 was present (p=.996)



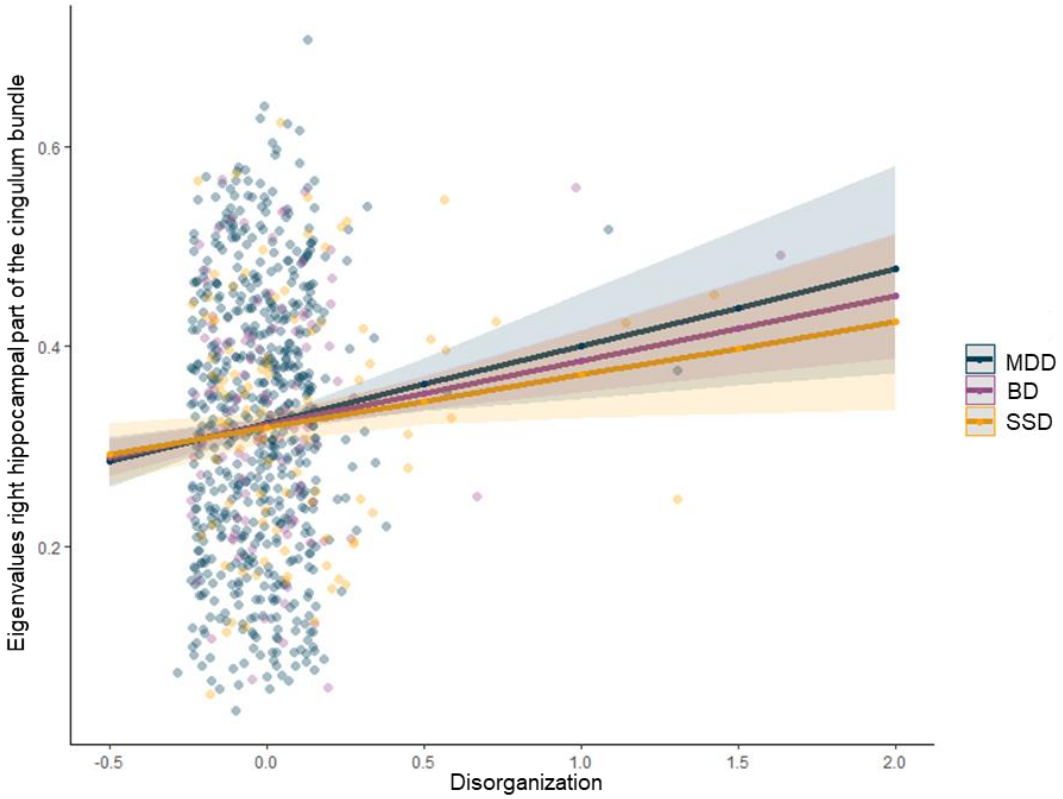
eFigure6: Post hoc visualization of the interaction analyses of the left anterior thalamic radiation FA and factor 3 “disorganization”. No interaction of categorical diagnosis and factor 3 was present (p=.376)



eFigure7: Post hoc visualization of the interaction analyses of the right anterior thalamic radiation FA and factor 3 “disorganization”. No interaction of categorical diagnosis and factor 3 was present (p=.818)



eFigure8: Post hoc visualization of the interaction analyses of hippocampal part of the right cingulum bundle FA and factor 3 "disorganization". No interaction of categorical diagnosis and factor 3 was present (p=.517)



V. MANUSCRIPT CONTRIBUTIONS

STUDY I:

Stein F, Lemmer G, Schmitt S, Brosch K, Meller T, Fischer E, Kraus C, Lenhard L, Köhnlein B, Murata H, Bäcker A, Müller M, Franz M, Förster K, Meinert S, Enneking V, Koch K, Grotegerd D, Nagels A, Nenadić I, Dannlowski U, Kircher T, Krug A. Factor analyses of multidimensional symptoms in a large group of patients with major depressive disorder, bipolar disorder, schizoaffective disorder and schizophrenia. Schizophr Res. 2020 Apr;218:38-47. doi: 10.1016/j.schres.2020.03.011. (IF 4.6)

CONTRIBUTION: 60%. Together with AK and TK, FS developed the statistical design. FS performed formal statistical analysis consulting GL. FS wrote the original draft of the manuscript.

STUDY II:

Stein F, Meller T, Brosch K, Schmitt S, Ringwald K, Pfarr JK, Meinert S, Thiel K, Lemke H, Waltemate L, Grotegerd D, Opel N, Jansen A, Nenadić I, Dannlowki U, Krug A, Kircher T. Psychopathological syndromes across affective and psychotic disorders correlate with gray matter volumes. DOI: 10.1093/schbul/sbab037. (IF 7.96)

CONTRIBUTION: 70%. FS, AK and TK conceptualized the study design. FS performed the formal analysis and wrote the original draft of the manuscript.

STUDY III:

Stein F, Schmitt S, Brosch K, Meller T, Pfarr JK, Ringwald K, Lemmer G, Meinert S, Lemke H, Waltemate L, Thiel K, Franz M, Preuss UW, Metzger FG, Nagels A, Nenadić I, Dannlowski U, Kircher T, Krug A. State of illness-dependent associations of neuro-cognition and psychopathological syndromes in a large transdiagnostic cohort. (submitted)

CONTRIBUTION: 55%. AK conceptualized the study design. FS performed the formal analysis. AK and FS wrote the original draft of the manuscript. FS was responsible for the visualization of results.

STUDY IV:

Stein F, Buckenmayer E, Brosch K, Meller T, Schmitt S, Ringwald KG, Pfarr J, Steinsträter O, Enneking V, Grotegerd D, Heindel W, Meinert S, Leehr E, Lemke H, Thiel K, Waltemate L, Winter A, Hahn T, Dannlowki U, Jansen A, Nenadić I, Krug A, Kircher T. Psychopathological dimensions of formal thought disorder and their relation to gray and white matter brain structure in affective and psychotic disorders. (submitted).

CONTRIBUTION: 75%. FS developed the study design. EB performed factorial analysis. FS performed all other formal analysis. FS wrote the original draft of the manuscript and created the graphic representation of results.

vi. CURRICULUM VITAE

Die folgenden Seiten 121-126 (Lebenslauf) enthalten persönliche Daten. Sie sind deshalb nicht Bestandteil der Veröffentlichung.

vii. Verzeichnis der Lehrenden

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Dr. Tanja Giessler

Prof. Dr. Heiko Girnth

Prof. Dr. Joachim Herrgen

Prof. Dr. Arne Nagels

Prof. Dr. Richard Wiese

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Prof. Dr. Matthias Schlesewsky

Dr. Mark Schmalz

Dr. Irene Weiss de Seng

viii. DANKSAGUNG

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IV. EHRENWÖRTLICHE ERKLÄRUNG

Die Seiten 129-130 (ehrenwörtliche Erklärung) wurden vor Drucklegung entfernt und sind daher nicht Bestandteil der Veröffentlichung.