

# Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <http://orca.cf.ac.uk/105726/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Knöchel, Christian, Reuter, Johanna, Reinke, Britta, Stäblein, Michael, Marbach, Katharina, Feddern, Richard, Kuhlmann, Kristina, Alves, Gilberto, Prvulovic, David, Wenzler, Sofia, Linden, David E. J. and Oertel-Knöchel, Viola 2016. Cortical thinning in bipolar disorder and schizophrenia. *Schizophrenia Research* 172 (1-3) , pp. 78-85. 10.1016/j.schres.2016.02.007 file

Publishers page: <http://dx.doi.org/10.1016/j.schres.2016.02.007>  
<<http://dx.doi.org/10.1016/j.schres.2016.02.007>>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



**TITLE: Cortical thinning in bipolar disorder and schizophrenia**

Christian Knöchel<sup>a\*</sup>, Johanna Reuter<sup>a</sup>, Britta Reinke<sup>a,b</sup>, Michael Stäblein<sup>a,b</sup>, Katharina Marbach<sup>a</sup>, Richard Feddern<sup>a,b</sup>, Kristina Kuhlmann<sup>a</sup>, Gilberto Alves<sup>c</sup>, David Prvulovic<sup>a</sup>, Sofia Wenzler<sup>a</sup>, David E.J. Linden<sup>d</sup>, Viola Oertel-Knöchel<sup>a,b</sup>

**Institute Affiliations:**

a. Laboratory for Neuroimaging, Dept. of Psychiatry, Psychosomatic Medicine and Psychotherapy, Goethe-University, Frankfurt/Main, Germany.

b. Brain Imaging Center (BIC), Goethe-University, Frankfurt/Main, Germany.

c. Center for Alzheimer's Disease and Related Disorders, Universidade Federal do Rio de Janeiro, Brazil.

d. MRC Centre for Neuropsychiatric Genetics & Genomics, Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, United Kingdom.

**\*Address for correspondence and reprint requests:**

Christian Knöchel, Laboratory for Neuroimaging, Dept. of Psychiatry, Psychosomatic Medicine and Psychotherapy, Goethe-University, Heinrich-Hoffmann-Str. 10, 60528 Frankfurt; E-Mail: Christian.Knoechel@kgu.de; Phone: ++49 69 6301 5308.

**Number of words in the abstract:** 233      **Number of words in the text body:** 2992

**Number of tables / figures:** 3 / 2      **Supplemental material:** 1 table

**Key-words:** cortical thickness, schizophrenia, bipolar, psychosis, cognitive functioning, MRI

## **Abstract**

Although schizophrenia (SZ) and bipolar disorder (BD) share some clinical features such as psychotic symptoms and cognitive dysfunctions, little is known about possible pathophysiological similarities between both diseases. Therefore, we investigated the potential topographical overlap and segregation of cortical thickness abnormalities in SZ and BD patients.

We analyzed 3D-anatomical magnetic resonance imaging datasets with the FreeSurfer 5.1.0 software to examine cortical thickness and volumes in three groups of participants: n = 34 BD patients, n = 32 SZ patients and n = 38 healthy controls.

We observed similar bilateral cortical thickness reductions in BD and SZ patients predominantly in the pars opercularis of the inferior frontal gyrus and in the anterior and posterior cingulate. We also found disease-specific cortical reductions in the orbitofrontal cortex for BD patients and in dorsal frontal and temporal areas for SZ. Furthermore, inferior frontal gyrus cortical thinning was associated with deficits in psychomotor speed and executive functioning in SZ patients and with age at onset in both groups.

Our findings support the hypothesis that thinning of the frontal cortex may represent a biological feature shared by both disease groups. The associations between cognitive deficits and the reported findings in SZ and to a lesser degree in BD patients add to the functional relevance of our results. However, further studies are needed to corroborate a model of shared pathophysiological disease features across BD and SZ.

## **1. Introduction**

A major goal of recent structural imaging studies in schizophrenia (SZ) and bipolar disorder (BD) patients has been to detect potential overlap in structural and functional imaging markers. According to some studies, both diseases share frontal and subcortical abnormalities, which supports the spectrum-hypothesis of psychotic disorders (Ellison-Wright and Bullmore, 2010). However, other studies suggest that grey matter (GM) density reductions are unique to SZ (see i.e. Hirayasu et al., 2001) and support Kraepelin's dichotomy concept (Kraepelin, 1919). Only few researchers compared cortical thickness between SZ and BD patients directly (Hulshoff et al., 2012; Rimol et al., 2012). Those who did proposed a similarity in cortical thinning mainly in frontal regions (Rimol et al., 2012). Rimol and colleagues suggested that SZ patients are affected more severely than BD patients, showing more widespread temporal, occipital and parietal volume reductions and a decrease in cortical thickness (Rimol et al., 2012). Hulshoff and colleagues compared shared and segregated brain abnormalities in patients with SZ and BD and suggested that a smaller volume of overlapping white matter (WM) and common areas of thinner cortex indicated that both disorders share genetic and neurodevelopmental pathways (Hulshoff et al., 2012). Furthermore, Janssen and colleagues observed frontal thinning in adolescents with BD and SZ (Janssen et al., 2014).

Current knowledge indicates that deficits in several cognitive domains may be associated with cortical thinning in SZ (Ehrlich et al., 2012; Hartberg et al., 2010; Oertel-Knöchel et al., 2012) and BD (Gutierrez-Galve et al., 2011). In BD, significant associations have been reported between course of illness and sociodemographic variables, such as gender (Najt et al., 2007) or age (Brambilla et al., 2001; Lyoo et al., 2006) and cortical thickness in temporal lobes (for episodes of illness, see (Moorhead et al., 2007)) and in frontal lobes (for years of illness, see (Lyoo et al., 2006)). Padmanabhan et al. assessed a large sample of schizophrenia, schizoaffective and bipolar I patients (n = 455) and observed that positive

symptoms of psychosis were significantly associated with reductions in cortical thickness in frontal and temporal areas across groups, and that negative symptoms correlated with right frontal cortex thinning (Padmanabhan et al., 2014). However, the functional relevance of structural abnormalities may depend on which symptoms or cognitive domains are being assessed (Gutierrez-Galve et al., 2011; Lyoo et al., 2006; Rimol et al., 2010).

In the current study we directly compared cortical thickness and volumes in BD and SZ patients to healthy controls. As a main hypothesis, we suggest that SZ and BD share frontal cortical thinning and volume reductions. Additionally, we suggest that decreases in cortical thickness are directly associated with cognitive and clinical features of psychosis.

## **2. Material and Methods**

### ***2.1 Participants***

We examined 32 SZ patients ( $M_{age} = 39.56$  years ( $SD = 10.90$ )), 34 euthymic BD I patients ( $M_{age} = 43.93$  years ( $SD = 10.87$ )) and 38 healthy controls ( $M_{age} = 40.86$  years ( $SD = 11.91$ )). All patients were treated as outpatients at the time of the study and had been in remission for a minimum of one month. None of the patients had any comorbid axis I or II disorder (including substance abuse or addiction). To confirm the diagnoses in the patient groups and to ensure that none of the control participants was affected by a psychiatric disorders according to DSM-IV (APA, 1994) we conducted the Structured Clinical Interview for DSM IV Disorders (SCID-I and SCID-II; German version; (Wittchen et al., 1996)). The controls had no family history of affective disorder or psychosis. The three groups were matched for handedness (all were right handed as assessed using the Edinburgh Handedness Inventory, (Oldfield, 1971)), age, gender and years of education. The two patient groups were matched for duration of disease and age at disease onset.

Crystallized intelligence was assessed using the German equivalent of the “Spot-the-

Word test" (Mehrfachwahl-Wortschatz-Intelligenz-Test ((MWT-B; (Lehrl, 2005). Psychomotor speed and executive functioning were tested using the Trail-Making test (TMT A and TMT B (Reitan et al., 1988).

Current psychopathological symptoms in SZ patients were assessed using the Positive and Negative Syndrome Scale (PANSS; (Kay et al., 1987)) and the Revised Hallucination Scale (RHS; (Morrison et al., 2002)). We applied the remission criteria defined by (Andreasen et al., 2005). To define remission, we used the following PANSS (Kay et al., 1987) items: delusions, unusual thought content, hallucinations, conceptual disorganization, mannerisms and posturing, blunted affect, social withdrawal and lack of spontaneity. According to the criteria by Andreasen et al., the ratings of these items had to be mild or less over a 6-month period (Andreasen et al., 2005). For the euthymic BD patients we evaluated symptom severity using the German version of the Beck Depression Inventory (BDI II; (Hautzinger et al., 2006) for depressive symptoms (BDI II score of < 10) and the German version of the Bech-Rafaelsen Mania Scale (BRMAS; (Bech, 1981)) for mania symptoms (BRMAS score of < 7).

All patients had been on stable medication for at least four weeks prior to measurement (see Supplemental Material Table S1 for further details). None of the BD or SZ patients received any benzodiazepines and none of them were without medication. To compare different substances and doses, chlorpromazine (see the formula by (Woods, 2003)) and amitryptiline equivalents (Ali, 1998) were computed.

## ***2.2 Data Acquisition and Image Processing***

MRI measurements took place at the Goethe-University Brain Imaging Center, Frankfurt, Germany. We acquired a high-resolution, T1-weighted MDEFT sequence (Deichmann et al., 2004) for anatomical brain imaging (176 slices, 1x1x1 mm, matrix size 256\*256, slice thickness 1mm, flip angle: 16°) covering the entire brain of each participant on a Siemens

Magnetom Allegra 3 Tesla MRI system (Siemens Medical Systems, Erlangen, Germany). All anatomical T1-weighted MRI scans were reviewed by a neuroradiologist who did not find any neurological or other pathology (i.e. focal or local atrophy, lacunar infarctions or extensive microangiopathy).

Analysis of structural MRI data was performed using the software tools of MATLAB® (The Mathworks Inc., Natick, MA, USA), FreeSurfer® (Version 5.1.0) (FreeSurfer Troubleshooting Reconstruction Work Flow; <http://surfer.nmr.mgh.harvard.edu/>) and a FreeSurfer application (Qdec®).

### ***2.3 Data Preprocessing***

Cortical thickness was estimated at each vertex across the brain surface using the semi-automated approach of the FreeSurfer 5.1.0 software (Dale et al., 1999; Fischl et al., 1999). This procedure included reconstruction of the grey matter (GM) - white matter (WM) boundary and the cortical surface (Dale et al., 1999; Han and al., 2006; Rosas, 2002), a calculation of the distance between those surfaces at each point across the cortical mantle (Dale et al., 1999), a transformation of all data into the Talairach space and an automatic stripping of the skull and subcortical structures (see (Segonne et al., 2004)). The smoothing algorithm by (Dale et al., 1999) was used to alleviate the voxel-based nature of the initial curvature and potential topological defects were corrected using an automated topology fixer (see (Segonne et al., 2005)). The anatomies were further registered to a reference brain (an average template that included anatomical data sets) to visualize the results. The surfaces were spherically inflated and registered to a common space spherical deformation guided by automatically defined cortical features that were derived from a population atlas (Fischl et al., 1999). The resulting surfaces were transferred to Talairach space, allowing direct, anatomically accurate measurements of thickness. For quality control, all segmentations were

inspected, manually corrected and re-inspected as described by (Fischl et al., 2001) and (Goldman et al., 2009).

We used the resulting surfaces to compile all surface data into 33 cortical regions of interest (see (Desikan et al., 2006; Fischl et al., 2001)). Each subject's reconstruction was again visually inspected for gross topological inaccuracies. Cortical thickness was calculated for each vertex in the triangulated surfaces by finding the point on the white matter surface that was closest to a given point of the pial surface (and vice versa) (Fischl and Dale, 2000; Han and al., 2006). An average normal control surface was generated and thickness data from each subject were smoothed using a standard Gaussian filter and mapped to the average surface.

## ***2.4 Statistical Analysis***

Extracted values for cortical thickness and volumes as provided by the QDEC® application of all participants were fitted into three independent ANCOVA models as independent variables, with patient diagnosis (CON, BD, SZ) as a fixed factor and intracranial volumes (ICV) as a covariate. We also conducted independent ANOVAs to compute group comparisons of cognitive and clinical data. All group differences were deemed significant on a threshold level of  $p < 0.05$  after a correction for multiple comparisons using the false discovery rate ( $p^{\text{FDR}}$ ; (Genovese et al., 2002)).

We performed bivariate correlation analyses (Spearman rank correlation, 2-tailed; (Pearson product moment correlation, 2-tailed) between all structural imaging parameters that differed significantly between groups and cognitive, clinical and course of illness variables. We also conducted bivariate correlation analyses between the thickness values and the



medication scores as well as years of medication. All correlation analyses were corrected for multiple comparisons using the Bonferroni correction ( $p_{\text{Bonf}}$ ).

### **3. Results**

#### ***3.1 Statistical Comparisons of Cognitive and Clinical Data***

Statistical tests revealed no significant group differences in age, gender and years of education ( $p > 0.05$ ). The scores of the BDI II differed significantly between BD patients and controls ( $z = 15.65$ ,  $p = 0.001$ ), indicating some residual subclinical depressive symptoms in patients. There were no group differences regarding the BRMAS scores ( $z = 1.41$ ,  $p > 0.05$ ), showing that manic symptoms had remitted completely. SZ patients had higher scores in the RHS values (predisposition towards hallucinations) in comparison with controls ( $z = 11.82$ ,  $p < 0.01$ ). The cognitive and clinical data are documented in Table 1.

In the cognitive tests, the MWT-B values (crystallized intelligence) did not differ significantly across groups ( $F = 1.62$ ,  $p > 0.05$ ). The scores of the TMT A (psychomotor speed) showed significant group differences between controls and SZ patients ( $F = 3.82$ ,  $p < 0.05$ ) indicating poorer performance in SZ patients, but no significant differences between controls and BD patients or between BD patients and SZ patients (all  $p > 0.05$ ). In the TMT B (executive functioning), SZ patients showed significantly poorer performance than BD patients and controls ( $F = 32.72$ ,  $p < 0.001$ ). However, BD patients and controls did not differ significantly ( $p > 0.05$ ).

#### ***3.2 Statistical Comparisons of Structural Imaging***

There were significant group differences in *cortical thickness* parameters in the following brain regions: bilateral medial orbitofrontal gyrus, bilateral pars opercularis of the

inferior frontal gyrus, left rostral middle frontal gyrus, right cuneus, right inferior temporal gyrus and right rostral anterior cingulate ( $p^{\text{FDR}} < 0.05$ ).

Group comparisons of *volume parameters* indicated significant group differences in the left medial orbitofrontal gyrus, in the right pars opercularis of the inferior frontal gyrus, in the right superior frontal gyrus, in the right rostral middle frontal gyrus and in the left insula.

Post-hoc group comparisons revealed lower thickness parameters in the pars opercularis bilaterally (thickness: left and right; volume: right), in the left rostral anterior cingulate thickness, in the right cuneus cortical thickness in SZ and BD patients in comparison with controls ( $p$  (FDR)  $< 0.05$ ; see Table 2, Figure 2 for further details).

In the left rostral middle frontal gyrus, we observed significantly decreased volume and thickness in SZ patients compared with BD patients and controls. Moreover, right inferior temporal gyrus thickness and volume were significantly lower in SZ patients compared with BD patients and controls ( $p^{\text{FDR}} < 0.05$ ; see Table 2). SZ patients had significantly lower left superior frontal gyrus volumes in comparison with controls ( $p^{\text{FDR}} < 0.05$ ), with BD patients showing no significant group differences to either SZ patients or controls ( $p^{\text{FDR}} > 0.05$ ).

BD patients showed a significant reduction of left medial orbitofrontal gyrus thickness and right medial orbitofrontal gyrus thickness and volume as compared to controls ( $p^{\text{FDR}} < 0.05$ ). However, SZ patients did not differ significantly from the other groups in any of these values ( $p^{\text{FDR}} > 0.05$ ).

### **3.3 Correlation Analysis**

Lower thickness of the left pars opercularis (inferior frontal gyrus) was significantly associated with earlier age at onset, lower psychomotor speed (TMT A) and executive functioning (TMT B) in SZ patients ( $p_{Bonf} < 0.05$ ). In both disorders, there was a significant inverse association between left medial orbitofrontal gyrus thickness and age at onset. None of the structural imaging parameters were significantly correlated with PANSS scores, duration of disease, medication dose equivalents or years of medication ( $p_{Bonf} > 0.05$ ).

There was no significant association of cognitive, clinical and cortical thickness parameters in the control group ( $p_{Bonf} > 0.05$ ; see Table 3 for further details).

## **4. Discussion**

Our study showed predominantly frontal (pars opercularis of the inferior frontal gyrus bilaterally) and limbic (rostral anterior cingulate, posterior cingulate) thinning of the cortical sheet in BD and SZ patients in comparison with controls. The results are in line with previous structural imaging findings suggesting comparable changes in SZ and BD patients, predominantly in the frontal and temporal lobes and cingulate gyrus (for BD, see (Bouras et al., 2001; Foland-Ross et al., 2011; Fornito et al., 2008; Fornito et al., 2009; Lyoo et al., 2006; Oertel-Knochel et al., 2015; Qiu et al., 2008); for SZ, see (Goldman et al., 2009; Haukvik et al., 2009; Kuperberg et al., 2003; Lawyer et al., 2008; Venkatasubramanian et al., 2008)). This may indicate shared pathophysiological mechanisms in BD and SZ (Craddock and Owen, 2005) (Craddock and Owen, 2010) and would contradict Kraepelin's suggestion that both disorders are entirely independent disease entities (Kraepelin, 1919).

However, the left rostral middle frontal gyrus and the right inferior temporal gyrus (in SZ) and the bilateral orbitofrontal cortices (in BD) were affected selectively. In fact, there

were graded changes from SZ to BD to CON in the left superior frontal gyrus volumes and in the right cuneus thickness. These findings support the hypothesis that segregated cortical abnormalities may represent correlates of different symptom clusters in BD and SZ. For instance, the orbitofrontal cortex is known to be involved in emotion and reward in decision making (Kringelbach, 2005). Cortical thinning in this area specific to BD patients might thus be related to the affective component of this disorder. In contrast, the middle frontal cortex is a core structure of executive functioning, a cognitive domain which is strongly affected in SZ. In future studies it may be of interest to examine the functional specifications of the regions under scrutiny to show differences across patient groups and to investigate whether specific brain alterations are associated with distinct symptom patterns in BD and SZ.

### ***Functional significance of structural imaging findings***

Our observation of significant associations between age of onset and frontal cortex thinning (left medial orbitofrontal gyrus, pars opercularis) suggests that loss of cortical volume may be progressive in BD and in SZ. Significant associations between course of illness, sociodemographic variables and cortical thickness in the temporal and frontal lobes have been reported before (Brambilla et al., 2001; Lyoo et al., 2006; Najt et al., 2007). With our cross-sectional design we cannot answer the question whether cortical thinning in psychosis is caused by neurodevelopmental or neurodegenerative factors. The fact that cortical thinning in our ROIs was not significantly connected with duration of illness would make neurodegenerative factors less likely but longitudinal designs would be needed in order to distinguish neurodevelopmental from neurodegenerative processes.

In SZ, higher psychomotor speed (TMT A) and executive functioning (TMT B) were directly related with frontal cortex thinning but not with clinical variables. This confirms previous findings by our work group and others (Ehrlich et al., 2012; Ehrlich et al., 2010;

Hartberg et al., 2010; Hartberg et al., 2011; Oertel-Knöchel et al., 2012) that show correlations between frontal cortical thinning and performance deficits in SZ.

### *Limitations*

Potential influence of psychopharmacological treatment on structural imaging markers may not be completely ruled out, although we observed no significant association between medication load and cortical thickness measures. Several groups suggested either no influence or that an increased volume correlated with the dosage of psychopharmacological treatment (Dazzan et al., 2005; Hafeman et al., 2012b; Hafeman et al., 2012a; Phillips et al., 2008). Particularly, lithium therapy in BD patients has been associated with increases in cortical volume on MRI scans (Moore et al., 2000). Antipsychotics in SZ and BD may cause changes in cortical thickness dependent on the type of antipsychotics: typicals were associated with an increased volume of the putamen and a decreased volume of cortical areas; atypical antipsychotics have been observed to be associated with an enlargement of the thalami (Dazzan et al., 2005; Moncrieff and Leo, 2010).

We have to emphasize that only non-acute SZ or euthymic BD patients were enrolled in our study, resulting in relatively low symptom severity scores (Bremner et al., 2002; Lacerda et al., 2004; Lai et al., 2000). In future studies, non-acute and acute patients need to be directly compared to test for possible relations of clinical severity with cortical thickness. Moreover, we did not directly test clinical similarities, for example, psychotic or affective symptoms, across patients groups. As we conducted different neuropsychological scales to assess individual psychopathology (BDI II, BRMAS in BD; PANSS in SZ), we had no possibility to directly compare affective symptoms in BD and SZ. However, the PANSS interview done with SZ patients includes several items referring to the affective state or to depressive symptoms of the patients, that are hyperactivity (P4), grandiosity (P5), Blunted

affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), Depression (G6) and active social avoidance (G16). Psychotic symptoms were examined in BD patients using the BRMAS. However, we did not observed associations between individual psychopathology and structural markers in either BD or SZ.

### ***Conclusions***

We report that BD and SZ share cortical thinning in the pars opercularis of the inferior frontal gyrus bilaterally and the anterior and posterior cingulate bilaterally (left: anterior; right: posterior). Frontal cortical thinning has been associated with deficits in psychomotor speed and executive functioning in SZ and age of onset in SZ and BD. However, we also reported segregated alterations between both patient groups, which indicate distinct pathophysiological patterns across BD and SZ.

The detection of overlap, as suggested by (Craddock and Owen, 2005), and distinction, as suggested by (Kraepelin, 1919) contribute to and modify the neurophysiological models of psychotic disorders and may help to clarify the pathways that contribute to individual symptom patterns (Linden, 2012). Further studies are needed to elucidate and corroborate a model of shared pathophysiological disease features across BD and SZ and should incorporate additional analysis techniques, such as network-level approaches (Wheeler et al., 2015).

**Acknowledgments & Funding Sources:**

MRI scans were performed at the Frankfurt Brain Imaging Center, supported by the German Research Council (DFG) and the German Ministry for Education and Research (BMBF; Brain Imaging Center Frankfurt/Main, DLR 01GO0203). Viola Oertel-Knöchel was supported by the Prize “Adolf-Messer-Preis” for Young Researchers from the “Freunde der Universität, Goethe-University, Germany”. There is no conflict of interest.

## **List of abbreviations**

BDI II – Beck Depression Inventory

BRMAS – Beck-Rafaelsen Mania Scale

SCID – Structured Clinical Interview for DSM-IV Disorders

RHS – Revised Hallucination Scale

PANSS – Positive and Negative Syndrome Scale

SZ –Schizophrenia

BD–Bipolar disorder

CON–Healthy controls

WM – White Matter

GM – Gray Matter

TMT – Trail Making Test

MWT-B – Mehrfachwahl-Wortschatz-Intelligenztest (Spot-the-Word test)



## References

- Ali, I.M., 1998. Long-term treatment with antidepressants in primary care. Are sub-therapeutic doses still being used? *Psychiatric Bulletin* 22(15-19).
- Andreasen, N.C., Carpenter, W.T., Jr., Kane, J.M., Lasser, R.A., Marder, S.R., Weinberger, D.R., 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry* 162(3), 441-449.
- APA, 1994. *Diagnostic and statistical manual of mental disorders (4th edition)*. American Psychiatric Association Washington, D.C.
- Bech, P., 1981. Rating scales for affective disorders: Their validity and consistency. *Acta Psychiatr. Scand.* 64.
- Bouras, C., Kövari, E., Hof, P.R., Riederer, B.M., Giannakopoulos, M., 2001. Anterior cingulate cortex pathology in schizophrenia and bipolar disorder. *Acta Neuropathologica* 102, 373-379.
- Brambilla, P., Harenski, K., Nicoletti, M., Mallinger, A.G., Frank, E., Kupfer, D.J., Keshavan, M.S., Soares, J.C., 2001. Differential Effects of Age on Brain Gray Matter in Bipolar Patients and Healthy Individuals. *Neuropsychobiology* 43, 242-247.
- Bremner, J.D., Vythilingam, M., Vermetten, E., Nazeer, A., Adil, J., Khan, S., Staib, L.H., Charney, D.S., 2002. Reduced volume of orbitofrontal cortex in major depression. *Biological psychiatry*, 273-279.
- Craddock, N., Owen, M.J., 2005. The beginning of the end for the Kraepelinian dichotomy. In: *The British Journal of Psychiatry*. 186, 364-366.
- Craddock, N., Owen, M.J., 2010. The Kraepelinian dichotomy - going, going... but still not gone. *Br J Psychiatry* 196(2), 92-95.
- Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 9(2), 179-194.

Dazzan, P., Morgan, K.D., Orr, K., Hutchinson, G., Chitnis, X., Suckling, J., Fearon, P., McGuire, P.K., Mallett, R.M., Jones, P.B., Leff, J., Murray, R.M., 2005. Different effects of typical and atypical antipsychotics on grey matter in first episode psychosis: the AESOP study. *Neuropsychopharmacology* 30(4), 765-774.

Deichmann, R., Schwarzbauer, C., Turner, R., 2004. Optimisation of the 3D MDEFT sequence for anatomical brain imaging: technical implications at 1.5 und 3T. *Neuroimage* 21:757-767.

Desikan, R.S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 31(3), 968-980.

Ehrlich, S., Brauns, S., Yendiki, A., Ho, B.C., Calhoun, V., Schulz, S.C., Gollub, R.L., Sponheim, S.R., 2012. Associations of Cortical Thickness and Cognition in Patients With Schizophrenia and Healthy Controls. *Schizophr Bull Sep*;38(5), 1050-1062.

Ehrlich, S., Morrow, E.M., Roffman, J.L., Wallace, S.R., Naylor, M., Bockholt, H.J., Lundquist, A., Yendiki, A., Ho, B.C., White, T., Manoach, D.S., Clark, V.P., Calhoun, V.D., Gollub, R.L., Holt, D.J., 2010. The COMT Val108/158Met polymorphism and medial temporal lobe volumetry in patients with schizophrenia and healthy adults. *NeuroImage* 53(3), 992-1000.

Ellison-Wright, I., Bullmore, E., 2010. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. *Schizophrenia research* 117(1), 1-12.

Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America* 97(20), 11050-11055.

Fischl, B., Liu, A., Dale, A.M., 2001. Automated manifold surgery: constructing

geometrically accurate and topologically correct models of the human cerebral cortex. . IEEE Trans Med Imaging. 20(1):70–80.

Fischl, B., Sereno, M.I., Dale, A.M., 1999. Cortical surface-based analysis, II: inflation, flattening, and a surface-based coordinate system Neuroimage 9(2):195-207. .

Foland-Ross, L.C., Thompson, P.M., Sugar, C.A., Madsen, S.K., Shen, J.K., Penfold, C., Ahlf, K., Rasser, P.E., Fischer, J., Yang, Y., Townsend, J., 2011. Investigation of Cortical Thickness Abnormalities in Lithium-Free Adults With Bipolar I Disorder Using Cortical Pattern Matching. American Journal of Psychiatry 168, 530-539.

Fornito, A., Malhi, G.S., Lagopoulos, J., Ivanovski, B., Wood, S.J., Saling, M.M., Pantelis, C., Yücel, M., 2008. Anatomical abnormalities of the anterior cingulate and paracingulate cortex in patients with bipolar I disorder. Psychiatry Research: Neuroimaging 162, 123-132.

Fornito, A., Yücel, M., Wood, S.J., Bechdolf, A., Carter, S., Adamson, C., Velakoulis, D., Saling, M.M., McGorry, P.D., Pantelis, C., 2009. Anterior cingulate cortex abnormalities associated with a first psychotic episode in bipolar disorder. British Journal of Psychiatry 194, 426-433.

Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 15(4), 870-878.

Goldman, A.L., Pezawas, L., Mattay, V.S., Fischl, B., Verchinski, B.A., Chen, Q., Weinberger, D.R., Meyer-Lindenberg, A., 2009. Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. Archives of general psychiatry 66(5), 467-477.

Gutierrez-Galve, L., Bruno, S., Wheeler-Kingshott, C.A., Summers, M., Cipolotti, L., Ron, M.A., 2011. IQ and the fronto-temporal cortex in bipolar disorder. J Int Neuropsychol Soc 18(2), 370-374.

Hafeman, D.M., Chang, K.D., Garrett, A.S., Sanders, E.M., Phillips, M.L., 2012a. Effects of

---

medication on neuroimaging findings in bipolar disorder: an updated review. *Bipolar Disord* Jun(14(4)), 375-410.

Hafeman, D.M., Chang, K.D., Garrett, A.S., Sanders, E.M., Phillips, M.L., 2012b. Effects of medication on neuroimaging findings in bipolar disorder: an updated review. *Bipolar disorders* 14(4), 375-410.

Han, X., al., e., 2006. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer *NeuroImage* 32(1), 180-194.

Hartberg, C.B., Lawyer, G., Nyman, H., Jonsson, E.G., Haukvik, U.K., Saetre, P., Bjerkan, P.S., Andreassen, O.A., Hall, H., Agartz, I., 2010. Investigating relationships between cortical thickness and cognitive performance in patients with schizophrenia and healthy adults. *Psychiatry research* 182(2), 123-133.

Hartberg, C.B., Student, K., Rimol, L.M., Haukvik, U.K., Lange, E.H., Nesvåg, R., Dale, A.M., Melle, I., Andreassen, O.A., Agartz, I., 2011. Brain cortical thickness and surface area correlates of neurocognitive performance in patients with schizophrenia, bipolar disorder, and healthy adults. *Journal of International Neuropsychological Society* 17(6), 1080-1093.

Haukvik, U.K., Lawyer, G., Bjerkan, P.S., Hartberg, C.B., Jonsson, E.G., McNeil, T., Agartz, I., 2009. Cerebral cortical thickness and a history of obstetric complications in schizophrenia. *Journal of psychiatric research* 43(16), 1287-1293.

Hautzinger, M., Keller, F., Kühner, C., 2006. Das Beck Depressionsinventar II. Deutsche Bearbeitung und Handbuch zum BDI II. Harcourt Test Services, Frankfurt a. M.

Hulshoff, P.H.E., van Baal, G.C., Schnack, H.G., Brans, R.G., van der Schot, A.C., Brouwer, R.M., van Haren, N.E., Lepage, C., Collins, D.L., Evans, A.C., Boomsma, D.I., Nolen, W., Kahn, R.S., 2012. Overlapping and segregating structural brain abnormalities in twins with schizophrenia or bipolar disorder. *Arch Gen Psychiatry* Apr;69(4), 349-359.

Janssen, J., Aleman-Gomez, Y., Schnack, H., Balaban, E., Pina-Camacho, L., Alfaro-Almagro, F., Castro-Fornieles, J., Otero, S., Baeza, I., Moreno, D., Bargallo, N., Parellada, M., Arango, C., Desco, M., 2014. Cortical morphology of adolescents with bipolar disorder and with schizophrenia. *Schizophrenia research* 158(1-3), 91-99.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Symptom Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin* 13, 261-276.

Kraepelin, E., 1919. *Dementia Praecox and Paraphrenia*. Livingstone, Edinburgh.

Kringelbach, M.L., 2005. The orbitofrontal cortex: linking reward to hedonic experience. *Nature Reviews Neuroscience* 6, 691-702.

Kuperberg, G.R., Broome, M.R., McGuire, P.K., David, A.S., Eddy, M., Ozawa, F., Goff, D., West, W.C., Williams, S.C., van der Kouwe, A.J., Salat, D.H., Dale, A.M., Fischl, B., 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. *Archives of general psychiatry* 60(9), 878-888.

Lacerda, A.L.T., Keshavan, M.S., Hardan, A.Y., Yorbik, O., Brambilla, P., Sassi, R.B., Nicoletti, M., Mallinger, A.G., Frank, E., Kupfer, D.J., Soares, J.C., 2004. Anatomic evaluation of the orbitofrontal cortex in major depressive disorder. *Biological Psychiatry*, 353-358.

Lai, T.-J., Payne, M.E., Byrum, C.E., Steffens, D.C., Krishnan, K.R.R., 2000. *Biological psychiatry*, 971-975.

Lawyer, G., Nesvag, R., Varnas, K., Frigessi, A., Agartz, I., 2008. Investigating possible subtypes of schizophrenia patients and controls based on brain cortical thickness. *Psychiatry research* 164(3), 254-264.

Lehrl, S., 2005. *Mehrfachwahl-Wortschatz-Intelligenztest M-W-T B*. Spitta Verlag GmbH, Göttingen.

Linden, D.E., 2012. The challenges and promise of neuroimaging in psychiatry. *Neuron* 73(1),

8-22.

Lyoo, I.K., Sung, Y.H., Dager, S.R., Friedmann, S.D., Lee, J.-Y., Kim, S.J., Kim, N., Dunner, D.L., Renshaw, P.F., 2006. Regional cerebral cortical thinning in bipolar disorder. *Bipolar Disorder* 8, 65-74.

Moncrieff, J., Leo, J., 2010. A systematic review of the effects of antipsychotic drugs on brain volume. *Psychol Med* 40(9), 1409-1422.

Moore, G.J., Bebchuk, J.M., Wilds, I.B., Chen, G., Manji, H.K., 2000. Lithium-induced increase in human brain grey matter. *Lancet* 356(9237), 1241-1242.

Moorhead, T.W.J., McKirdy, J., Sussmann, J.E.D., Hall, J., Lawrie, S.M., Johnstone, E.C., McIntosh, A.M., 2007. Progressive Gray Matter Loss in Patients with Bipolar Disorder. *Biological Psychiatry* 62, 894-900.

Morrison, A.P., Wells, A., Nothard, S., 2002. Cognitive and emotional predictors of predisposition to hallucinations in non-patients. *British Journal of Clinical Psychology* 41(3), 259-270.

Najt, P., Nicoletti, M., Chen, H.H., Hatc, J.P., Caetano, S.C., Sassi, R.B., Axelson, D., Brambilla, P., Keshavan, M.S., Ryan, N.D., Birmaher, B., Soares, J.C., 2007. Anatomical measurements of the orbitofrontal cortex in child and adolescent patients with bipolar disorder. *Neuroscience Letters* 413, 183-186.

Oertel-Knöchel, V., Knochel, C., Rotarska-Jagiela, A., Reinke, B., Prvulovic, D., Haenschel, C., Hampel, H., Linden, D.E., 2012. Association between Psychotic Symptoms and Cortical Thickness Reduction across the Schizophrenia Spectrum. *Cereb Cortex*.

Oertel-Knochel, V., Reuter, J., Reinke, B., Marbach, K., Feddern, R., Alves, G., Prvulovic, D., Linden, D.E., Knochel, C., 2015. Association between age of disease-onset, cognitive performance and cortical thickness in bipolar disorders. *Journal of affective disorders* 174, 627-635.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9(1), 97-113.

Padmanabhan, J.L., Tandon, N., Haller, C.S., Mathew, I.T., Eack, S.M., C, lementz, B.A., Pearlson, G.D., Sweeney, J.A., Tamminga, C.A., Keshavan, M.S., 2014. Correlations Between Brain Structure and Symptom Dimensions of Psychosis in Schizophrenia, Schizoaffective, and Psychotic Bipolar I Disorders. *Schizophr Bull Jun* 6.

Phillips, M.L., Travis, M.J., Fagiolini, A., Kupfer, D.J., 2008. Medication effects in neuroimaging studies of bipolar disorder. *Am J Psychiatry Mar*; 165(3), 313-320.

Qiu, A., Vaillant, M., Barta, P., Ratnanather, J.T., Miller, M.I., 2008. Region-of-Interest-Based Analysis With Application of Cortical Thickness Variation of Left Planum Temporale in Schizophrenia and Psychotic Bipolar Disorder. *Human Brain Mapping* 29(8), 973-985.

Reitan, R.M., Hom, J., Wolfson, D., 1988. Verbal processing by the brain. *J Clin Exp Neuropsychol.* 10(4), 400-408.

Rimol, L.M., Hartberg, C.B., Nesvåg, R., Fennema-Notestine, C., Hagler Jr., D.J., Pung, C., Jennings, R., Haukvik, U.K., Lange, E., Nakstad, P.H., Melle, I., Andreassen, O.A., Dale, A.M., Agartz, I., 2010. Cortical Thickness and Subcortical Volumes in Schizophrenia and Bipolar Disorder. *Biological Psychiatry* 68, 41-50.

Rimol, L.M., Nesvåg, R., Hagler, D.J.J., Bergmann, O., Fennema-Notestine, C., Hartberg, C.B., Haukvik, U.K., Lange, E., Pung, C.J., Server, A., Melle, I., Andreassen, O.A., Agartz, I., Dale, A.M., 2012. Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder. *Biological psychiatry* 15(71(6)), 552-560.

Rosas, H.D., et al., 2002. Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology Neurology* 58(5):695–701. .

Segonne, F., Dale, A.M., Busa, E., Glessner, M., Salat, D., Hahn, H.K., Fischl, B., 2004. A hybrid approach to the skull stripping problem in MRI. *Neuroimage* 22(3), 1060-1075.

Segonne, F., Grimson, E., Fischl, B., 2005. A genetic algorithm for the topology correction of cortical surfaces. *Inf Process Med Imaging* 19, 393-405.

Venkatasubramanian, G., Jayakumar, P.N., Gangadhar, B.N., Keshavan, M.S., 2008.

Automated MRI parcellation study of regional volume and thickness of prefrontal cortex (PFC) in antipsychotic-naive schizophrenia. *Acta psychiatrica Scandinavica* 117(6), 420-431.

Wheeler, A.L., Wessa, M., Szeszko, P.R., Foussias, G., Chakravarty, M.M., Lerch, J.P.,

DeRosse, P., Remington, G., Mulsant, B.H., Linke, J., Malhotra, A.K., Voineskos, A.N., 2015.

Further neuroimaging evidence for the deficit subtype of schizophrenia: a cortical connectomics analysis. *JAMA psychiatry* 72(5), 446-455.

Wittchen, H.-U., Wunderlich, U., Gruschwitz, S., Zaudig, M., 1996. *Strukturiertes Klinisches Interview für DSM-IV (SKID)*. Beltz-Test, Göttingen

Woods, S., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry* 64(6), 663-667.



**Table 1:** Sociodemographic and clinical characteristics and cognitive performance across groups. SD values are in brackets. Abbreviations: CON = healthy controls, BD = bipolar patients, SZ = schizophrenia patients, BDI II = Beck Depressions Inventory, BRMAS = Bech-Rafaelsen Mania Scale, TMT = Trail Making Test, RHS = Revised Hallucination Scale, PANSS = Positive and Negative Syndrome Scale, MWT-B = Multiple-choice-word-comprehension-test \*: p = significant on a < 0.05-threshold, \*\*: p = significant on a < 0.01-threshold, \*\*\*: p = significant on a < 0.001-threshold, ns = not significant. <sup>a</sup>: defined as the timespan between first hospitalization and study participation.

Variable	CON	BD	SZ	Significance
<b>Number</b>	38	34	32	-
<b>Gender</b> <i>f/m</i>	15 / 23	15 / 19	16 / 16	$\chi^2 = 0.21$ , ns (Chi-square)
<b>Age (years)</b>	40.86 (11.91) 21-59	43.93 (10.87) 19-58	39.56 (10.90) 20-57	$F = 2.34$ , ns
<b>Education</b> (years)	15.70 (1.80)	15.47 (1.74)	14.69 (2.78)	$F = 2.19$ , ns
<b>Handedness</b>	All right handed			-
<b>Duration of disease</b> (years) <sup>a</sup>	-	9.76 (6.65)	9.33 (5.31)	$t = 0.04$ , ns
<b>Number of episodes of illness</b>	-	depressive: 6.13 (2.34) manic: 3.56 (1.23)	4.25 (1.23)	-
<b>Age of onset (years)</b>	-	31.00 (10.37)	27.17 (9.55)	$t = 1.21$ , ns
<b>BDI II</b>	2.11 (2.10)	9.58 (9.27)	-	$z = 5.65$ ***
<b>BRMAS</b>	1.45 (1.12)	2.10 (2.75)	-	$z = 1.41$ , ns
<b>RHS</b>	25.29 (4.19)	-	34.57 (9.47)	$z = 11.82$ **
<b>PANSS</b>	-	-	PANSS pos: 17.01 (5.34) PANSS neg: 17.88 (5.87) PANSS gen: 33.01 (8.49) PANSS sum: 66.85 (8.34)	
<b>TMT A</b>	27.32 (9.27) CON / BD: ns	35.28 (10.56) BD / SZ: ns	42.41 (29.09) CON / SZ: *	$F = 3.82$ *
<b>TMT B</b>	40.70 (7.25) CON / BD: ns	51.67 (7.25) BD / SZ: ***	140.71 (10.62) CON / SZ: ***	$F = 32.72$ ***
<b>MWT-B</b>	30.53 (3.07)	30.40 (3.15)	28.28 (5.19)	$F = 1.62$ , ns

**Table 2:** The table contains all regions which showed significant differences in cortical thickness and volumes across groups (group contrast; left column; FDR corrected). Abbreviations: CON = healthy controls, BD = bipolar patients, SZ = schizophrenia patients, T = cortical thickness, V = volume, IFG = inferior frontal gyrus. \*: p = significant on a < 0.05-threshold, \*\*: p = significant on a < 0.01-threshold, \*\*\*: p = significant on a < 0.001-threshold, ns = not significant.

Group comparisons					
Region (area)	Hemisphere	Mean [mm], SD	F (df=99)	p	Post-hoc test
<b>pars opercularis (IFG) T</b>	left	CON: 2.15 (0.05) BD: 1.69 (0.34) SZ: 1.63 (0.21)	4.99	0.009	CON / BD* CON / SZ**
	right	CON: 2.16 (0.05) BD: 2.09 (0.17) SZ: 1.89 (0.25)	4.99	0.009	CON / SZ** CON / BD*
<b>pars opercularis (IFG) V</b>	right	CON: 473.12 (1.08) BD: 443.45 (1.03) SZ: 401 (1.00)	1.31	0.04	CON / SZ*** CON / BD***
<b>rostral anterior cingulate T</b>	left	CON: 3.44 (0.71) BD: 2.79 (0.48) SZ: 2.35 (0.44)			CON / SZ** CON / BD*
<b>Cuneus T</b>	right	CON: 1.811 (0.66) BD: 1.486 (0.16) SZ: 1.343 (0.37)	3.08	0.05	CON / BD* CON / SZ*
<b>Superior frontal gyrus V</b>	left	CON: 2245.37 (392.56) BD: 2127.81 (341.35) SZ: 2001.35 (243.34)	3.05	0.05	CON / SZ**
<b>rostral middle frontal gyrus T</b>	left	CON: 2.32 (0.29) BD: 2.26 (0.56) SZ: 1.79 (0.17)	5.30	0.007	CON / SZ* SZ / BD*
<b>rostral middle frontal gyrus V</b>	left	CON: 4056.56 (668.16) BD: 3981.36 (745.14) SZ: 3765.15 (574.51)	4.05	0.004	CON / SZ** SZ / BD**
<b>inferior temporal gyrus T</b>	right	CON: 2.51 (1.94) BD: 2.23 (1.02) SZ: 2.03 (1.00)	6.65	0.002	CON / SZ** SZ / BD*
<b>Inferior temporal gyrus V</b>	right	CON: 10488.90 (2172.46) BD: 10132.33 (1823.23) SZ: 10050.28 (1564.57)	3.58	0.03	CON / SZ* SZ / BD*

<b>medial orbitofrontal gyrus T</b>	left	CON: 2.27 (0.08) BD: 1.86 (0.11) SZ: 1.99 (0.17)	3.14	0.04	CON / BD*
	right	CON: 2.21 (0.17) BD: 1.75 (0.07) SZ: 1.95 (0.12)	3.12	0.04	CON / BD*
<b>medial orbitofrontal gyrus V</b>	left	CON: 4199.85 (672.11) BD: 3972.34 (733.23) SZ: 4013.23 (574.23)	3.54	0.03	CON / BD*

**Table 3:** The table contains all significant correlations (Spearman rank correlation ( $\rho$ ; two-tailed). Abbreviations: BD = bipolar patients, SZ = schizophrenia patients, T = cortical thickness, l = left, TMT = Trail Making Test. \*:  $p$  = significant on a  $< 0.05$ -threshold, \*\*:  $p$  = significant on a  $< 0.01$ -threshold, \*\*\*:  $p$  = significant on a  $< 0.001$ -threshold.

<b>Significant correlations</b>			
	<b>CON</b>	<b>BD</b>	<b>SZ</b>
<b>l. medial orbitofrontal gyrus T</b>		Age at onset: $\rho = 0.54^{**}$	Age at onset: $\rho = 0.61^{**}$
<b>l. pars opercularis of the inferior frontal gyrus T</b>	TMT A: $\rho = -0.21$ , ns TMT B: $\rho = -0.12$ , ns	TMT A: $\rho = -0.39$ , ns TMT B: $\rho = -0.41$ , ns	Age of onset: $\rho = 0.73^{**}$ TMT A: $\rho = -0.52^{**}$ TMT B: $\rho = -0.84^{***}$

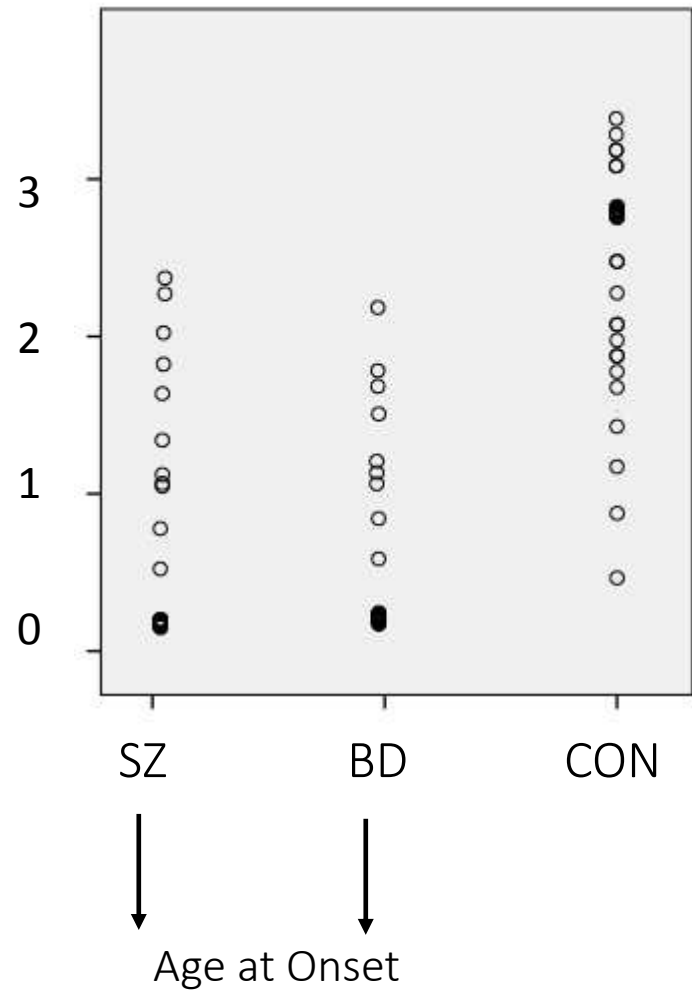
**Figure legend:**

**Figure 1:** Statistical group comparisons (F-test) between all groups in cortical thickness values of the left (l) medial orbitofrontal gyrus thickness (T) and the left (l) pars opercularis of the inferior frontal gyrus thickness (T). Moreover, the image presents significant correlations between the structural imaging data and cognitive and clinical variables. Abbreviations: TMT=Trail making Test, CON= controls, BD = bipolar patients, SZ = schizophrenia patients.

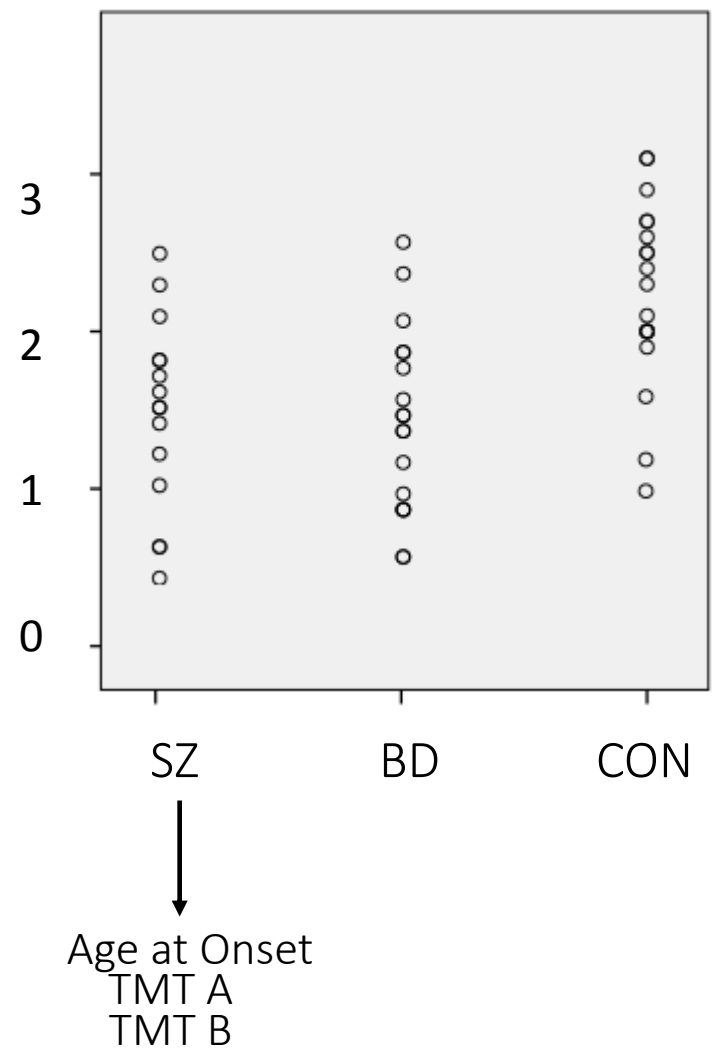
**Figure 2:** Overlapped or distinct patterns of structural abnormalities across patient groups.

Figure 1

Left medial orbitofrontal gyrus T

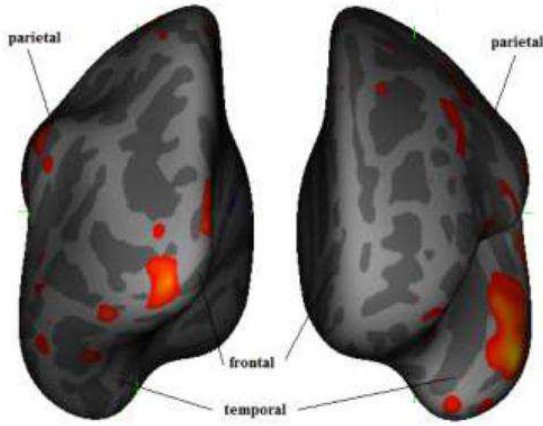
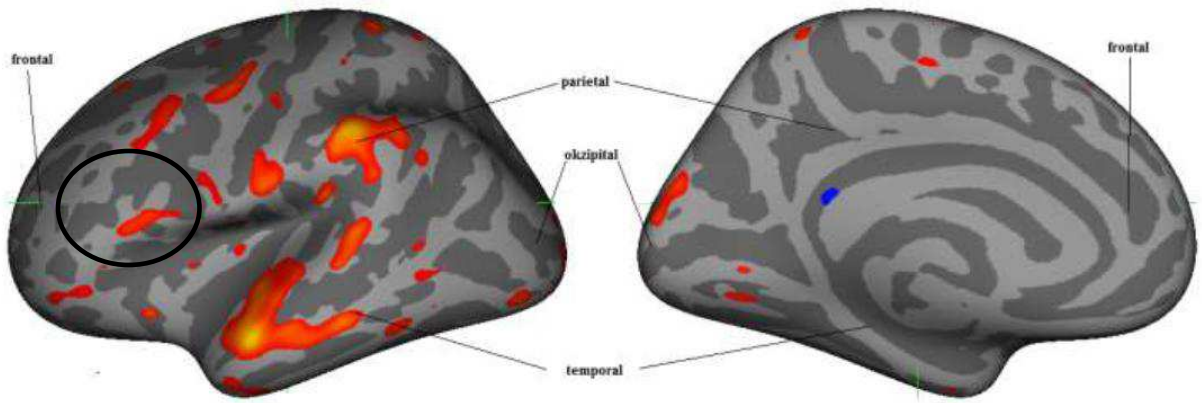


Left pars opercularis of the inferior frontal gyrus T



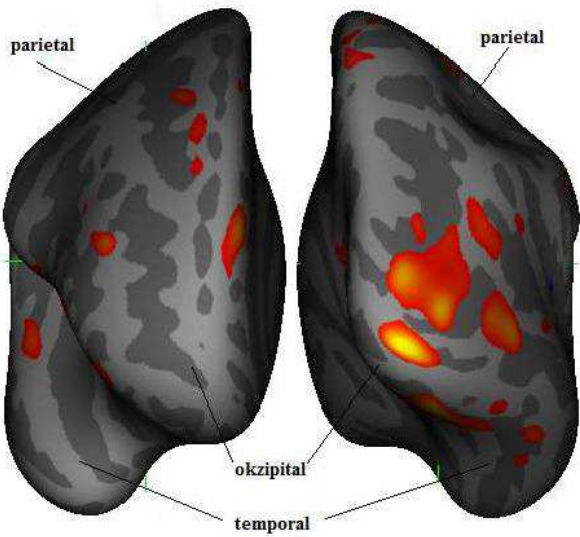
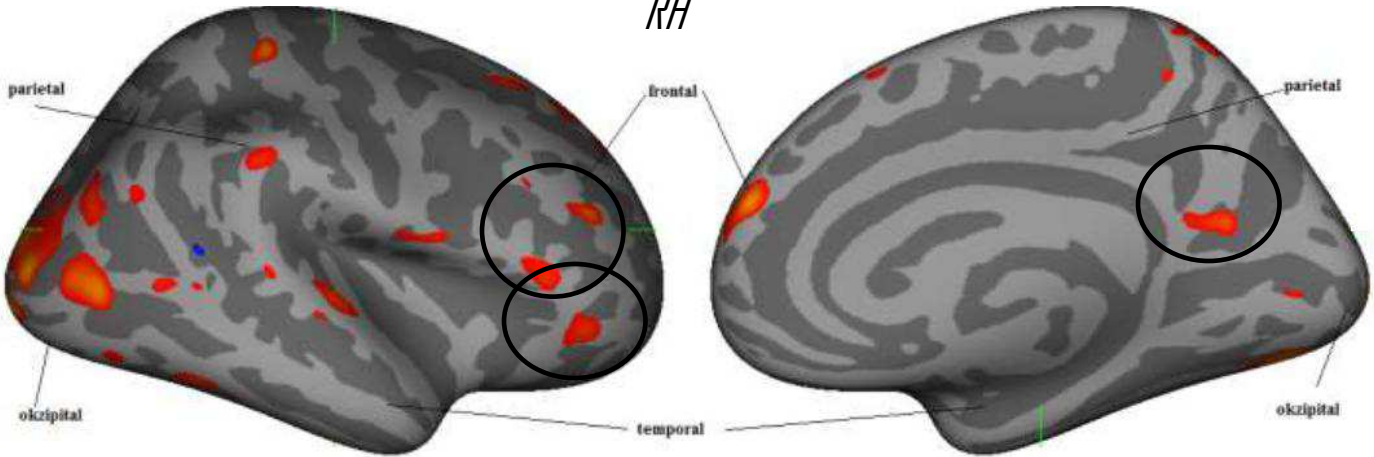
# Cortical thickness in SZ or BD patients in comparison with controls

*LH*



**Black circles:** overlapped disturbed regions in SZ and BD

*RH*



**Black circles:** overlapped disturbed regions in SZ and BD

**Acknowledgements:**

MRI scans were performed at the Frankfurt Brain Imaging Center, supported by the German Research Council (DFG) and the German Ministry for Education and Research (BMBF; Brain Imaging Center Frankfurt/Main, DLR 01GO0203). Viola Oertel-Knöchel was supported by the Prize “Adolf-Messer-Preis” for Young Researchers from the “Freunde der Universität, Goethe-University, Germany”. There is no conflict of interest.



## **Conflict of interest**

The authors report no conflict of interest

**Contributors:**

Christian Knöchel: data assessment, analyzing the data, writing the manuscript

Johanna Reuter: data assessment

Britta Reinke: data assessment

Michael Stäblein: data assessment

Katharina Marbach: data assessment

Richard Feddern: data assessment

Kristina Kuhlmann: data assessment

Gilberto Alves: analyzing the data

David Prvulovic: writing the manuscript

David E.J. Linden: writing the manuscript

Viola Oertel-Knöchel: analyzing the data, writing the manuscript

**Role of the funding sources:**

MRI scans were performed at the Frankfurt Brain Imaging Center, supported by the German Research Council (DFG) and the German Ministry for Education and Research (BMBF; Brain Imaging Center Frankfurt/Main, DLR 01GO0203). Viola Oertel-Knöchel was supported by the Prize “Adolf-Messer-Preis” for Young Researchers from the “Freunde der Universität, Goethe-University, Germany”.