

# Individualized differential diagnosis of schizophrenia and mood disorders using neuroanatomical biomarkers

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Magnetic resonance imaging-based markers of schizophrenia have been repeatedly shown to separate patients from healthy controls at the single-subject level, but it remains unclear whether these markers reliably distinguish schizophrenia from mood disorders across the life span and generalize to new patients as well as to early stages of these illnesses. The current study used structural MRI-based multivariate pattern classification to (i) identify and cross-validate a differential diagnostic signature separating patients with first-episode and recurrent stages of schizophrenia ( $n = 158$ ) from patients with major depression ( $n = 104$ ); and (ii) quantify the impact of major clinical variables, including disease stage, age of disease onset and accelerated brain ageing on the signature's classification performance. This diagnostic magnetic resonance imaging signature was then evaluated in an independent patient cohort from two different centres to test its generalizability to individuals with bipolar disorder ( $n = 35$ ), first-episode psychosis ( $n = 23$ ) and clinically defined at-risk mental states for psychosis ( $n = 89$ ). Neuroanatomical diagnosis was correct in 80% and 72% of patients with major depression and schizophrenia, respectively, and involved a pattern of prefronto-temporo-limbic volume reductions and premotor, somatosensory and subcortical increments in schizophrenia versus major depression. Diagnostic performance was not influenced by the presence of depressive symptoms in schizophrenia or psychotic symptoms in major depression, but earlier disease onset and accelerated brain ageing promoted misclassification in major depression due to an increased neuroanatomical schizophrenia likeness of these patients. Furthermore, disease stage significantly moderated neuroanatomical diagnosis as recurrently-ill patients had higher misclassification rates (major depression: 23%; schizophrenia: 29%) than first-episode patients (major depression: 15%; schizophrenia: 12%). Finally, the trained biomarker assigned 74% of the bipolar patients to the major depression group, while 83% of the first-episode psychosis patients and 77% and 61% of the individuals with an ultra-high risk and low-risk state, respectively, were labelled with schizophrenia. Our findings suggest that neuroanatomical information may provide generalizable diagnostic tools distinguishing schizophrenia from mood disorders early in the course of psychosis. Disease course-related variables such as age of disease onset and disease stage as well alterations of structural brain maturation may strongly impact on the neuroanatomical separability of major depression and schizophrenia.

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**Abbreviations:** ARMS = at-risk mental state; BrainAGE = Brain Age Gap Estimation; CV = cross-validation; FEP = first episode psychosis; PANSS = Positive and Negative Symptom Scale; RAVENS = regional analysis of brain volumes in normalized space

## Introduction

Psychiatric diagnoses arise from complex clinical processes and hence are prone to errors (Freedman *et al.*, 2013), depending on the patient's symptoms, the interviewer's experience and the classification systems' normative validity. Biological data so far only served the exclusion of somatic pathologies, leaving the question whether individualized differential diagnosis could benefit from the analysis of complex neurodiagnostic 'patterns' unanswered (Fu and Costafreda, 2013; Perkins *et al.*, 2014). Furthermore, pattern analysis could unveil overlaps between and heterogeneity within diagnoses, thus promoting the revision of psychiatric nosology, and ultimately the convergence of neuroscientific and clinical observation (Krystal and State, 2014).

Phenomenological heterogeneity particularly characterizes schizophrenic psychoses and mood disorders (Murray *et al.*, 2005; Linscott and Os, 2010): affective symptoms are a core feature of prodromal (Schultze-Lutter *et al.*, 2007; Addington *et al.*, 2014) and established schizophrenia (Baynes *et al.*, 2000; Marengo *et al.*, 2000; Chemerinski *et al.*, 2008; Romm *et al.*, 2010; Cotton *et al.*, 2012; Sönmez *et al.*, 2013) while psychotic symptoms frequently coalesce with mania and depression (Ohayon and Schatzberg, 2002; Goodwin and Jamison, 2007). At the brain level, heterogeneity appears as subgrouping and cross-nosological effects, including neuroanatomical correlates of different symptom dimensions (Koutsouleris *et al.*, 2008; Nenadic *et al.*, 2012; Zhang *et al.*, 2014), overlapping and segregating structural abnormalities (Bora *et al.*, 2008, 2010; Yu *et al.*, 2010; Du *et al.*, 2012; Hulshoff Pol *et al.*, 2012) and gradual transitions of brain activation patterns between diagnostic entities (Brandt *et al.*, 2014). Clinically, this heterogeneity may contribute to diagnostic uncertainty along the diversity of possible disease trajectories (Baca-Garcia *et al.*, 2007; Pope *et al.*, 2013; Salvatore *et al.*, 2013). Scientifically, it challenged the detection of diagnostically specific neurobiological markers and hence questioned the validity of the current disease taxonomy (Linscott and Os, 2010; Keshavan and Brady, 2011), suggesting that unipolar depression, bipolar disorder and schizophrenia may represent 'stages' or 'domains' along a

phenotypic and neurobiological disease continuum (Häfner *et al.*, 2005; Green *et al.*, 2009; Lin *et al.*, 2013).

To simultaneously address this debate and close the 'translational gap' between neurobiological findings and their clinical application, researchers increasingly used multivariate pattern analysis to quantify the sensitivity, specificity and generalizability of diagnostic brain signatures (Bray *et al.*, 2009; Fu and Costafreda, 2013) rather than describing them in terms of their constituents' group-level significance (Davatzikos, 2004). Using multivariate pattern analysis, the field recently demonstrated a high separability of different neuropsychiatric conditions versus healthy controls, thus foreshadowing a potential translation of neuroimaging findings into diagnostic tools (Orrù *et al.*, 2012; Kambeitz *et al.*, 2015). However, doubts remain whether multivariate pattern analysis-based biomarkers are really useful in discriminating neuropsychiatric illness from mental well-being, or whether they are rather needed as objective tools for a more reliable 'differential diagnosis' (Savitz *et al.*, 2013). Initial findings suggest that neuroimaging may aid in individually separating schizophrenia from bipolar disorder (Schnack *et al.*, 2014) and major depression (Ota *et al.*, 2013) or bipolar from unipolar depression (Mourão-Miranda *et al.*, 2012; Grotegerd *et al.*, 2013; Serpa *et al.*, 2014). However, as these studies focused on pairwise comparisons it remains unclear how the reported neurodiagnostic signatures would perform in patients with 'intermediate' phenotypes and early disease states as well as in populations broadly covering the different age windows of these phenotypes.

An established approach to measure how clinical intersections, disease stages and age windows impact on neurodiagnostic performance is to investigate these variables along a single disease dimension, which is first spanned by 'extreme' or clearly distinct clinical phenotypes and then applied to the 'intermediate' or moderating conditions. This approach has been used in the dementia field where morphometric patterns distinguishing patients with Alzheimer's disease from healthy controls were used to quantify disease progression and severity in patients with mild cognitive impairment (Davatzikos *et al.*, 2009). In the psychosis field, Fan *et al.* (2008b) used this framework to trace the neuroanatomical schizophrenia signature in

unaffected first-degree relatives of patients with schizophrenia, indicating that the latter display intermediate neuro-anatomical phenotypes between patients and controls. Herein, we took a similar approach to explore the hypothesis that the neuroanatomical signatures of major depression, bipolar disorder, the at-risk mental states for psychosis (ARMS) and schizophrenia lie along a single direction spanned by major depression and schizophrenia as the two end points of this continuum. Therefore, we first measured the single-subject separability of stable schizophrenia versus major depression in a representative database of 262 patients using MRI-based multivariate pattern analysis and then quantified differential diagnostic scores of independent persons with high-risk or first-episode states of psychosis ( $n = 112$ ) as well as patients with bipolar disorder ( $n = 35$ ). Second, we evaluated whether neurodiagnostic classification was moderated by important variables such as age of disease onset, disease stage and ‘accelerated ageing’ effects (Koutsouleris *et al.*, 2013) as well as cross-sectional psychopathological profiles overlapping between major depression and schizophrenia. We expected classification performance to be moderated by gradients of neuro-anatomical schizophrenia likeness increasing (i) from at-risk states to established schizophrenia; (ii) from major depression, over bipolar disorder to schizophrenia; and (iii) from later to earlier disease onsets across the life span.

## Materials and methods

### Participants

Patients with schizophrenia and major depression were examined at the Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University Munich (LMU) using the Structured Clinical Interview for DSM-IV – Axis I & II Disorders (SCID-I/II), the review of records and psychotropic medications and a semi-standardized assessment of the psychiatric and somatic history. Patients’ symptoms were evaluated using standard psychometric scales (Table 1). Patients received a consensus diagnosis by two experienced psychiatrists at study inclusion and were excluded in case of an unstable SCID diagnosis over a 4-year follow-up period. Further exclusion criteria were: (i) a history of (a) schizoaffective and/or bipolar disorder, (b) traumatic brain injury with loss of consciousness, mental retardation, anorexia nervosa, delirium, dementia, amnesic disorders, personality disorders, substance dependence, as defined by DSM-IV, (c) previous electroconvulsive treatments, and (d) somatic conditions affecting the CNS; as well as (ii) insufficient knowledge of German, IQ <70, and age <18 or >65. Eleven patients with major depression fulfilled criteria for psychotic depression (DSM-IV: 296.24/34). Psychotic psychopathology in the major depression group was further quantified by computing a composite Z-score from the Hamilton Depression Rating Scale items ‘feelings of guilt’, ‘hypochondriasis’, ‘depersonalization and derealization’ and ‘paranoid symptoms’. This score was significantly elevated in patients with psychotic major depression [psychotic major depression: mean (SD) = 1.2 (1.0); non-psychotic major

depression:  $-0.2$  (0.9);  $T = 4.5$ ,  $P < 0.001$ ]. In the schizophrenia group the severity of depressive symptoms was measured by summing the Positive and Negative Symptom Scale (PANSS items) ‘somatic concern’, ‘anxiety’, ‘guilt feelings’ and ‘depression’ and Z transforming this PANSS depression subscale score (Kontaxakis *et al.*, 2000; El Yazaji *et al.*, 2002).

Patients with an illness duration of <1 year, no previous inpatient treatment and <12 months (life-time) psychopharmacological treatment (antipsychotics in schizophrenia, antidepressants in major depression) were assigned to first episode subgroups, or to recurrently-ill (recurrent episode) samples, if they did not fulfil these criteria. These first episode criteria were chosen to mitigate potential secondary disease effects (e.g. continuous medication and frequent hospitalization) on brain structure in the respective major depression and schizophrenia subgroups. Illness duration was the time between MRI scanning and disease onset defined retrospectively by the onset of symptoms paralleled by a general decline in social and role functioning (Lieberman *et al.*, 2001). Following these definitions, the mean (SD) illness duration in the major depression/schizophrenia (MD<sub>FE</sub>/SZ<sub>FE</sub>) samples was 0.34 (0.24)/0.37 (0.68) years, while the respective values for the MD<sub>RE</sub>/SZ<sub>RE</sub> were 9.19 (8.22)/7.25 (7.14) years. Diagnosis had no significant main ( $F = 1.53$ ,  $P = 0.217$ ) or interaction effects ( $F = 1.63$ ,  $P = 0.203$ ) on illness duration in the first episode and recurrent episode samples.

The schizophrenia versus major depression classifier was independently validated in 23 patients with first episode psychosis (FEP) (Yung *et al.*, 1998) recruited at the Department of Psychiatry, University of Basel and 89 ARMS individuals pooled across the Ludwig-Maximilian-University (LMU;  $n = 52$ ) and Basel ( $n = 37$ ) early recognition services, which were detailed in previous work (Koutsouleris *et al.*, 2009) (Supplementary material and Table 1). ARMS individuals were stratified into (i) an early ARMS ( $n = 21$ ) defined either by predictive basic symptoms or a Global Functioning-Trait criterion; and (ii) late ARMS (ARMS,  $n = 68$ ) defined by attenuated or brief limited intermittent psychotic symptoms, which closely corresponded to internationally established high-risk criteria (Yung *et al.*, 1998; Klosterkötter *et al.*, 2001). Psychosis developed in 4.8% and 47.1% of early ARMS and late ARMS individuals, respectively, over a follow-up period of 4.5 years ( $n = 33$ , 87.9% diagnosed as schizophrenia). At MRI, 61% and 95% of FEP and ARMS individuals, respectively, were antipsychotic-naïve (FEP: six with antipsychotic treatment for <1 month, and three for 1–3 months; ARMS: four treated with low-dose atypical antipsychotics for <3 weeks). The diagnosis of patients with FEP was evaluated 5 years after baseline and all examined subjects met DSM-IV criteria for schizophrenic psychosis.

Furthermore, classifier validation involved 35 patients from LMU with an established SCID diagnosis of bipolar disorder (Table 1), who did not meet exclusion criteria i(b)–(d) and ii. Thirty and five of these patients fulfilled criteria for bipolar I and II disorder, respectively, with bipolar I patients showing depressive ( $n = 11$ ), manic ( $n = 12$ ), mixed episodes ( $n = 3$ ) and euthymic states ( $n = 4$ ). Psychotic episodes were present in six patients with bipolar I (four and two patients with manic and depressive states, respectively).

Finally, 437 healthy volunteers previously described in Koutsouleris *et al.* (2013) and scanned at the same Munich scanner as the patient cohorts were used to correct the

**Table 1** Sociodemographic and clinical characteristics of study groups

Sociodemographic and clinical variables	Training and cross-validation database				Independent validation database			
	MD	SZ	T	P	BIP	FEP	ARMS-E	ARMS-L
<i>n</i>	104	158			35	23	21	68
<i>n</i> Basel [%] / Munich [%]	0 / 100	0 / 100			0 / 100	100 / 0	0 / 100	54 / 46
Mean age at baseline [yrs] (SD)	42.3 (12.0)	30.8 (10.0)	8.1‡	<.001	39 (9.6)	26.8 (6.5)	25.6 (5.6)	24.6 (5.9)
Sex (male) [%]	50	74	15.8†	<.001	51	74	48	68
Handedness (right) [%]	95	91	1.5†	ns	85	78	81	90
BMI [kg/m <sup>2</sup> ] (SD)	24.7 (4.6)	24.3 (4.4)	0.7‡	ns	25.6 (3.6)	–	21.1 (2.4)	23.0 (3.3) <sup>m</sup>
Schooling [yrs] (SD)	10.6 (2.0)	10.6 (2.1)	0.2‡	ns	11.6 (1.6)	10.0 (1.6)	11.5 (2.9)	11.1 (1.5)
Nicotine [cig./day]	9.7 (13.4)	13.2 (13.7)	–1.96‡	ns	11.4 (13.1)	–	7.0 (9.9)	7.0 (9.8) <sup>m</sup>
Alcohol [g/day]	11.2 (21.1)	11.2 (25.5)	–0.01‡	ns	5.6 (20.6)	–	2.9 (5.6)	7.7 (15.3) <sup>m</sup>
Mean age of disease onset [yrs] (SD; median)	36.5 (12.0)	25.5 (8.0)	8.1‡	<.001	26.1 (9.1)	–	–	–
Mean illness duration [yrs] (SD)	6.0 (7.8)	4.5 (7.0)	1.4‡	ns	13.9 (9.2)	–	–	–
Current treatment with typical antipsychotics [%]	10.0	30.7	17.7†	<.001	0.0	0.0	–	–
Current treatment with atypical antipsychotics [%]	9.0	67.3	86.7†	<.001	40.0	39.1	–	–
Current chlorpromazine equivalents [mg/d]	43.1 (162.0)	346.3 (373.4)	–8.6‡	<.001	189.2 (322.9)	244.0 (163)	–	–
Current treatment with antidepressants [%]	73.1	7.9	156.7†	<.001	16.7	21.7	23.8	12.9
Current treatment with mood stabilizers [%]	13.0	3.3	8.1†	<.01	66.7	0.0	0.0	0.0
Current treatment with lithium [%]	7.0	0.0	10.†	<.01	16.7	0.0	0.0	0.0
Mean BPRS (SD)	–	–	–	–	–	52.7 (13.6)	–	41.9 (10.6) <sup>b</sup>
Mean PANSS total (SD)	–	52.6 (29.2)	–	–	–	–	56.8 (14.0)	62.0 (22.2)
Mean PANSS positive (SD)	–	11.9 (8.0)	–	–	–	–	9.86 (2.6)	13.7 (4.5)
Mean PANSS negative (SD)	–	15.2 (9.7)	–	–	–	–	14.9 (6.7)	15.7 (8.5)
Mean PANSS general psychopathology (SD)	–	25.6 (16.1)	–	–	–	–	32.0 (7.9)	32.6 (11.1)
Mean SANS (SD)	–	45.0 (26.8)	–	–	–	10.0 (5.3)	–	9.5 (5.4) <sup>b</sup>
Mean HDRS (SD)	21.3 (9.5)	–	–	–	9.7 (9.8)	–	–	–
Mean YMRS (SD)	–	–	–	–	11.0 (12.0)	–	–	–
BrainAGE [yrs] (SD)	4.0 (6.2)	6.0 (6.0)	–2.55‡	<.05	3.8 (6.5)	5.1 (8.5)	–1.5 (7.7)	2.7 (6.8)

Descriptive analyses between major depression and schizophrenia patient groups were performed by means of  $\chi^2$ -tests for categorical data (†) and *t*-tests for continuous data (‡) *t*-tests. BMI = body mass index; BPRS = Brief Psychiatric Rating Scale; cig. = cigarettes; HDRS = Hamilton Depression Rating Scale; SD = standard deviation; YMRS = Young Mania Rating Scale. *m* data only available for the Munich subjects. *b* data only available for the Basel subjects.

patients' MRI data for age and sex effects as detailed below. The study was approved by each centre's local ethics committee. Written informed consent was obtained from each participant before inclusion.

## MRI data acquisition and preprocessing

Study participants were scanned using two SIEMENS MAGNETOM VISION 1.5 T scanners located at the University Hospital Basel and the Department of Radiology, Ludwig-Maximilian-University. In Basel, a T<sub>1</sub>-weighted 3D volumetric spoiled gradient recalled echo sequence generated 176 contiguous slices using the following protocol: echo time 4 ms; repetition time, 9.7 ms; flip angle, 12; field of view, 25.6 × 25.6 cm, matrix, 200 × 256; voxel dimensions, 1.28 × 1.0 × 1.0 mm. In Munich, a T<sub>1</sub>-weighted 3D-MPRAGE sequence was used: echo time, 4.9 ms; repetition time, 11.6 ms; field of view, 230 mm; matrix, 512 × 512; 126 contiguous axial slices; voxel dimensions, 0.45 × 0.45 × 1.5 mm. No calibration of MRI scanners was performed before or during the recruitment period.

MRI preprocessing first involved the segmentation of T<sub>1</sub>-weighted images into grey and white matter as well as CSF using the VBM8 toolbox (Koutsouleris *et al.*, 2013; Supplementary material) (Gaser, 2009). Then, the high-dimensional DRAMMS (Ou *et al.*, 2011, 2014) algorithm

registered each grey matter map to the single-subject MNI template. Resulting deformations and warped tissue maps were used to compute grey matter maps for a Regional Analysis of brain Volumes in Normalized Space (GM-RAVENS) (Davatzikos *et al.*, 2001).

## Correction for age and sex effects

To remove age- and sex-related differences between patient groups while retaining disease-associated neuroanatomical variation, the following strategy (Dukart *et al.*, 2011) was used. First, we calculated voxel-level  $\beta$ -coefficients for age and sex in our healthy control subjects' GM-RAVENS maps using partial correlation analysis. These coefficients described maps of (i) grey matter volume change from 18- to 65-year-old healthy control subjects; and (ii) grey matter volume differences between male and female healthy control subjects. Then we residualized the patient data using these coefficients to correct for age- and sex effects not attributable to disease-related factors. This strategy was validated as shown in the Supplementary material.

## Differential diagnostic pattern classification

We implemented a fully automated machine learning pipeline that extracted neuroanatomical features from the GM-



RAVENS maps and generated decision rules from these features to individually distinguish patients with major depression from those with schizophrenia. To strictly separate the training process from the evaluation of the classifier's generalizability, the pipeline was embedded into a repeated, double cross-validation (CV) framework (Filzmoser *et al.*, 2009) (Supplementary material), as detailed previously (Koutsouleris *et al.*, 2012; Borgwardt *et al.*, 2013). More specifically, the following analysis steps were wrapped into a  $10 \times 10$ -fold cross-validation cycle at the outer ( $CV_2$ ) and the inner ( $CV_1$ ) levels of repeated double CV: the training subjects' GM-RAVENS maps were initially corrected for age and sex effects (see above) and then scaled voxel-wise to  $[0, 1]$ . To reduce the maps' dimensionality and discard noisy information, principal component analysis (PCA) (Hansen *et al.*, 1999) projected correlated voxel sets to 170 uncorrelated eigenvariates, thus retaining 80% of the variance in each  $CV_1$  training partition. Correction, scaling, and PCA parameters were applied to the  $CV_1$  test data. Then, in each training partition, PCA features entered a recursive feature elimination algorithm (Guyon *et al.*, 2002) that used a linear support vector machine (Fan *et al.*, 2008a) to remove those eigenvariates that impaired separability on the respective  $CV_1$  test data (support vector machine penalty parameter:  $C = 1$ ).

This process was repeated for all  $CV_1$  partitions, thus creating 100 diagnostic models for each  $CV_2$  partition. To obtain  $CV_2$  test predictions, the respective GM-RAVENS data were first processed using the correction, scaling and PCA parameters of each  $CV_1$  training partition, and then classified using the learned decision rules. Classification produced decision scores measuring the neuroanatomical schizophrenia versus major depression likeness of a given subject. Finally, a  $CV_2$  test case's group membership was predicted by an ensemble classifier that averaged the decision scores of those 1000  $CV_1$  base learners in the repeated double CV, in which the subject had not been involved in the training process (Supplementary material). The bipolar disorder, FEP, early ARMS and late ARMS samples were processed identically to the  $CV_2$  test subjects. Finally, the classifier's decision function was visualized in Fig. 3 and the underlying patterns of volumetric differences were quantified in Supplementary Fig. 7.

## Testing differential diagnostic gradients in the ARMS and patient cohorts

The decision scores generated by the differential diagnostic classifier entered ANOVAs that tested the hypotheses of neuroanatomical schizophrenia likeness increasing (i) from the major depression, through the bipolar disorder, to the schizophrenia group; and (ii) from the early ARMS, through the late ARMS to the FEP sample. In case of significant omnibus test statistics ( $P < 0.05$ ), *post hoc* tests were carried out to evaluate pairwise differences at  $P < 0.05$ , corrected for multiple comparisons using Tukey's HSD test (Fig. 1). Furthermore, a supplementary analysis was carried out in the ARMS sample to explore whether neurodiagnostic scores predicted a subsequent transition to psychosis (Supplementary material) or functional outcome as measured by the Global Assessment of Functioning Score at follow-up (Supplementary Fig. 5).

## Testing clinical and brain structural moderators of neurodiagnostic classification

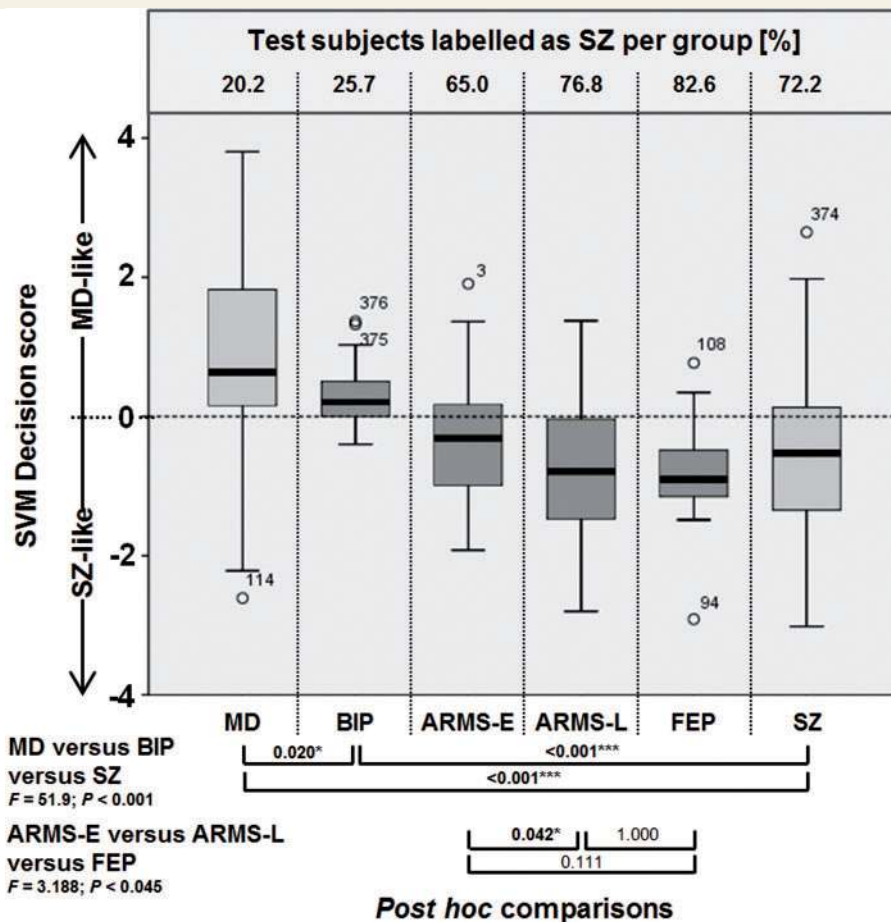
Potential moderating effects of disease stage on classification performance were evaluated at  $P < 0.05$  by stratifying major depression and schizophrenia patients into first episode versus recurrent episode subgroups and performing a  $\chi^2$  test on the misclassification error in these samples. Then, the impact of age of onset and BrainAGE (Brain Age Gap Estimation) (Koutsouleris *et al.*, 2013) on decision scores was investigated by median-splitting the schizophrenia and major depression groups according to the latter two variables. Main and interaction effects between decision scores and the factors 'Diagnosis', 'Early versus Late onset', 'Low versus High BrainAGE' were assessed at  $P < 0.05$  using the General Linear Model (Table 3 and Fig. 2A). Further analyses evaluated if classification of early-onset/high-BrainAGE patients versus late-onset/low-BrainAGE patients equalled diagnostic categorization (Fig. 2B and C). Based on these analyses, we assessed the separability within and between onset-defined diagnostic subgroups by performing pairwise support vector machine analyses as described above (Table 2 and Supplementary Fig. 6).

We explored potential moderating effects of psychometric psychosis on neurodiagnostic classification in major depression by comparing the decision scores of patients with high ( $n = 17$ ) versus low ( $n = 16$ ) scores on the standardized composite scale of Hamilton-Depression-Rating Scale items 2, 15, 19 and 20. These major depression subgroups were identified by thresholding the composite scale at  $Z > 1$  and  $Z < -1$ . The same procedure was used to measure the effect of psychometric depression on neurodiagnostic classification in schizophrenia: identical  $Z$  thresholds were applied to the standardized PANSS depression subscale and neuroanatomical decision scores were compared between the resulting schizophrenia subgroups with high ( $n = 30$ ) and low ( $n = 20$ ) depression scores. Finally, correlations between the decision scores and additional clinical variables of the major depression and schizophrenia samples were analysed in Supplementary Table 1. This supplementary analysis also explored whether neurodiagnostic scores were associated with verbal IQ in a subgroup of patients with schizophrenia stratified for early versus late disease onset.

## Results

### Sociodemographic and clinical variables

Schizophrenia and major depression patient groups did not differ regarding handedness, BMI, schooling years, nicotine or alcohol consumption (Table 1). Patient groups differed in the prescribed antipsychotic, antidepressant and mood-stabilizing medications. However, all of these variables had no effect on neurodiagnostic decision scores (Supplementary Table 1). Group-level differences were observed for age at scan, sex and age of disease onset, but not illness duration. Finally, schizophrenia patients had a higher mean (SD)



**Figure 1** Box plot comparison and ANOVAs of support vector machine (SVM) decision values. Box plot includes the major depression (MD) and schizophrenia (SZ) training database (light grey) and independent validation data consisting of bipolar disorder (BIP), ARMS (early, E and late, L) and FEP samples (dark grey). Box plots describe decision value distributions in terms of 5%, 25%, 50%, 75% and 95% confidence intervals. Frequency of schizophrenia-positive diagnosis is measured as percentage of subjects per group labelled as schizophrenia by the classifier (top of the box plot chart). P-values of post hoc comparisons in both ANOVAs are provided below and were corrected for multiple comparisons using Tukey's HSD method (SPSS version 20, IBM Inc.).

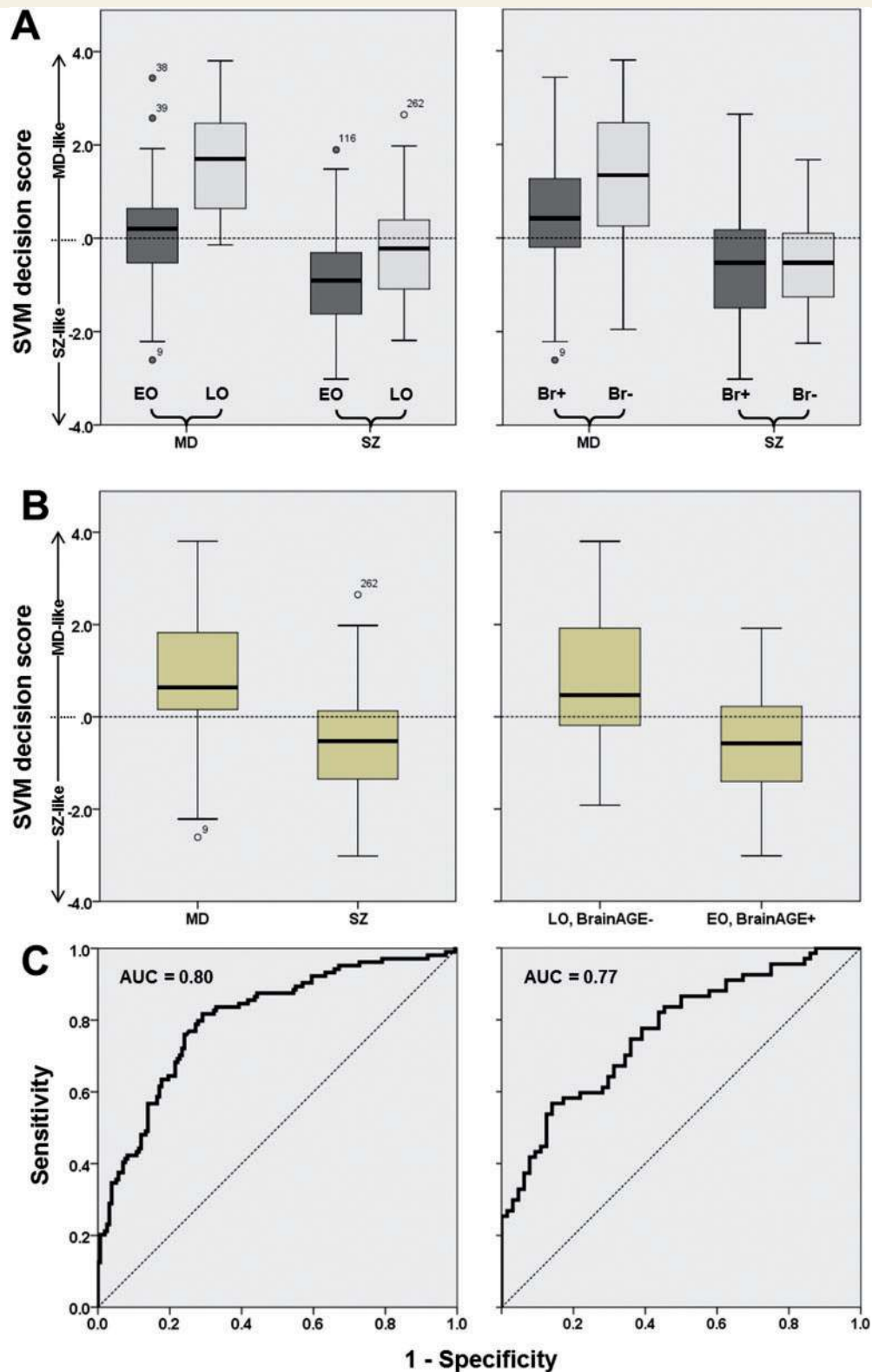
BrainAGE score of +5.99 (6.00) compared to patients with major depression [+4.04 (6.19)].

## Neuroanatomical classification and influence of moderating variables

The MRI classifier diagnosed unseen major depression and schizophrenia patients with a balanced accuracy of 76% (sensitivity/specificity = 79.8%/72.2%, diagnostic odds ratio = 10.2; Table 2). Recurrently-ill patients were more likely misclassified compared to first-episode patients (error rates MD<sub>FE</sub>/SZ<sub>FE</sub>: 15.0%/11.5%; MD<sub>RE</sub>/SZ<sub>RE</sub>: 23.4%/28.8%;  $\chi^2 = 6.6$ ; P = 0.010). The neuroanatomical decision function (Fig. 3) involved grey matter reductions in schizophrenia versus major depression covering the perisylvian structures (inferior frontal, insular, supramarginal, angular, superior temporal and temporopolar cortices) with extensions to the orbitofrontal, inferior temporal and medial temporal cortices. Further reductions covered the

ventromedial prefrontal, anterior cingulate, medial parietal, occipital and dorsolateral prefrontal cortices. Grey matter reductions in major depression versus schizophrenia were localized in a spatially distinct pattern including the brainstem regions, cerebellum, periventricular areas and the somatosensory cortices, extending to the premotor, parietal and supplementary motor areas.

The medians of age of onset/BrainAGE used to stratify patients were 36.3/+3.57 in the major depression group and 23.8/+5.62 in the schizophrenia sample. The General Linear Model evaluating effects of diagnosis, age of onset and BrainAGE factors on diagnostic scores detected significant main effects as well as a significant interaction between the 'diagnosis' and 'early versus late' factors (Table 3). Box plot analyses showed that early disease onset and high BrainAGE increased schizophrenia likeness in both disease groups, with this effect being more pronounced in major depression compared to schizophrenia (Fig. 2A). Using the diagnostic decision scores, late-onset, low-BrainAGE patients were separable from early-onset,



**Figure 2** Box plot and receiver operator characteristics analyses comparing the separability of diagnosis-based versus age of onset and BrainAGE-based patient groups. (A) Effects of age of onset (left; early, EO and late, LO) and BrainAGE (right) on diagnostic separability in major depression (MD) versus schizophrenia (SZ) patients. (B) Diagnostic separability of diagnostic groups (major depression versus schizophrenia, left) versus separability in cross-nosological patient groups (right) defined by early versus late disease onset and high versus low BrainAGE (Br+ versus Br-). (C) Receiver operator characteristics analyses of MRI-based decision scores in the classification of diagnosis (left) and EO/Br+ versus LO/Br- groups. SVM = support vector machine; AUC = area under the curve.

**Table 2** Diagnostic performance

Dataset	TP	TN	FP	FN	Sens [%]	Spec [%]	BAC [%]	FPR [%]	PPV [%]	NPV [%]	DOR
<b>Cross-validation</b>	83	114	44	21	79.8	72.2	76.0	27.8	65.4	84.4	10.2
MD [+ I] versus SZ [– I]											
<b>Age-of-onset stratified multi-group classifier</b>											
MD-E versus SZ-E	38	51	24	14	73.1	68.0	70.5	30.2	61.3	78.5	5.8
MD-E versus MD-L	42	45	7	10	80.8	86.5	83.7	13.5	85.7	81.8	27.0
MD-E versus SZ-L	31	42	34	21	59.6	55.3	57.4	44.7	47.7	66.7	1.82
SZ-E versus MD-L	67	52	0	8	89.3	100.0	94.7	0.0	100.0	86.7	–
SZ-E versus SZ-L	47	47	29	28	62.7	61.8	62.3	38.2	61.8	62.7	2.72
MD-L versus SZ-L	46	64	12	6	88.5	84.2	86.3	15.8	79.3	91.4	40.9
MD versus SZ (collapsed)	79	104	47	25	76.0	68.9	72.4	31.1	62.7	80.6	6.99

The performance of the MRI diagnostic system was evaluated by means of sensitivity (Sens), specificity (Spec), balanced accuracy (BAC), false positive rate (FPR), positive/negative predictive value (PPV / NPV) and Diagnostic Odds Ratio (DOR). These measures were calculated from the confusion matrix containing the number of true positives (TP), false negatives (FN), true negatives (TN) and false positives (FP). MD-E = early-onset major depression; MD-L = late-onset major depression; SZ-E = early-onset schizophrenia; SZ-L = late-onset schizophrenia.

high-BrainAGE patients to a similar degree [area under the curve (AUC) = 0.77] as major depression from schizophrenia patients (AUC = 0.80, Fig. 2B and C). Finally, the onset-stratified subgroup classification showed (i) a better separability of early versus late-onset major depression patients (balanced accuracy = 83.7%) than early versus late-onset schizophrenia patients (62.3%, Table 2); and (ii) a particularly low separability of early-onset major depression versus late-onset schizophrenia patients (57.4%). When diagnostic subgroup probabilities were collapsed into major depression versus schizophrenia diagnoses, the balanced accuracy was lower (72.2%) than in the original whole-group analysis.

The comparison of the neurodiagnostic scores in schizophrenia patients with high versus low psychometric depression scores [mean (SD): –0.59 (1.30) versus –0.57 (0.98)] did not yield significant differences ( $T = -0.04$ ;  $P = 0.966$ ). Similarly, major depression patients with high psychometric psychosis scores did not significantly differ from patients with low scores [mean (SD): 1.64 (1.41) versus 0.77 (1.17);  $T = 1.88$ ;  $P = 0.071$ ]. Additionally, major depression patients with versus without a DSM-IV diagnosis of psychotic depression did not differ in their neurodiagnostic scores [1.25 (1.63) versus 0.84 (1.24);  $T = 0.98$ ;  $P = 0.331$ ] or in their misclassification rates (20.0% versus 20.2%;  $\chi^2 = 0.00$ ;  $P = 1.000$ ). Finally, increasing neurodiagnostic schizophrenia likeness in patients with early-onset schizophrenia was significantly associated with lower verbal IQ ( $r = 0.46$ ,  $P = 0.013$ ), whereas this correlation was not observed in late-onset schizophrenia ( $r = 0.03$ ,  $P = 0.906$ ; see Supplementary material).

## Presence of a schizophrenia-like neuroanatomical signature in ARMS, FEP and bipolar disorder subjects

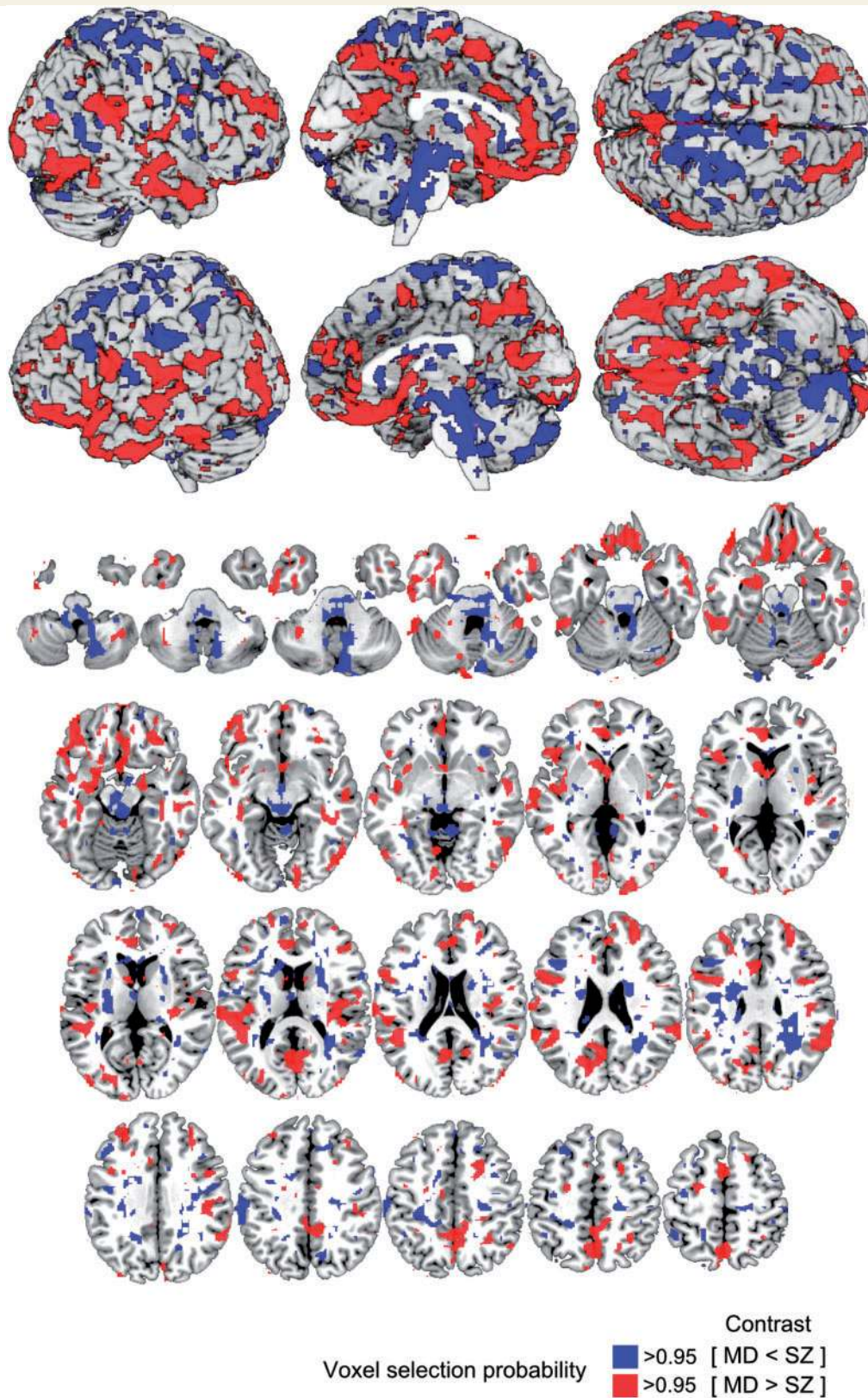
Decision scores obtained from the independent validation data showed that schizophrenia likeness was most

pronounced in the Basel FEP patients (86.9% labelled as schizophrenia, Fig. 1) followed by the cross-centre late ARMS group (77.9%) and the Munich early ARMS sample (61.0%). Schizophrenia likeness was lower in the Munich bipolar disorder group (25.7%) resulting in 74% of these patients being classified as having major depression. Significant group differences were detected in all pairwise *post hoc* contrasts of the major depression versus bipolar disorder versus schizophrenia comparison (Fig. 1). In the early ARMS versus late ARMS versus FEP analysis, we observed a significant increase of schizophrenia likeness in the late ARMS compared to the early ARMS group ( $P = 0.042$ ) with the former being on par with the FEP sample ( $P = 1.000$ ). Finally, we did not find significant differences between subsequent converters versus non-converters to psychosis. However, increasing schizophrenia likeness at baseline predicted the ARMS individuals' GAF scores at follow-up with  $R^2 = 0.204$  ( $P = 0.018$ , Supplementary Fig. 5).

## Discussion

This is to our knowledge the first structural MRI study to report a cross-validated, single-subject separability of 76% in a representative cohort of patients with a stable diagnosis of either schizophrenia or major depression. This finding is in keeping with the balanced accuracy of 78% reported by Ota *et al.* (2013) who examined 25 age-matched female patients with schizophrenia or major depression using fractional anisotropy and grey matter volumes in predefined regions of interest. We observed that neuroanatomical markers successfully generalized to patients with first-episode psychosis who were examined at an independent centre using a different MRI protocol and were prospectively diagnosed with schizophrenia. Validation also showed that diagnostic sensitivity extended to the ARMS and grew with symptomatic proximity to overt psychosis. Strikingly, the neurodiagnostic classifier assigned 74% of





**Figure 3** Voxel probability map (VPM) of reliable contributions to the major depression versus schizophrenia decision boundary. Voxels with a probability of > 50% were overlaid on the single subject MNI template using the MRIcron software package (<http://www.mccauslandcenter.sc.edu/mricro/mricron/>). Methodological descriptions on how the voxel probability maps were computed can be found in the Supplementary material. MD = major depression; SZ = schizophrenia.

**Table 3** Moderators of MRI-based differential diagnosis

Data set	E	SE	95%-CI Low / Up	F	P
<b>Main effects</b>					
MD versus SZ [mean difference]	1.49	0.13	1.24 / 1.75	134.0	<.001
MD [marginal mean]	0.89	0.10	0.70 / 1.09		
SZ [marginal mean]	−0.60	0.08	−0.76 / −0.44		
Early versus late-onset	−1.03	0.13	−1.29 / −0.78	62.6	<.001
Early-onset	−0.37	0.09	−0.55 / −0.19		
Late-onset	0.66	0.09	0.48 / 0.85		
Low versus High BrainAGE	0.41	0.13	0.15 / 0.67	9.8	.002
Low BrainAGE	0.35	0.09	0.17 / 0.53		
High BrainAGE	−0.06	0.09	−0.24 / 0.13		
<b>Two-way interaction effects</b>					
MD versus SZ × Early versus Late-Onset				8.3	0.004
MD × Early-Onset	0.19	0.14	−0.09 / 0.47		
MD × Late-Onset	1.59	0.14	1.32 / 1.88		
SZ × Early-Onset	−0.93	0.12	−1.16 / −0.70		
SZ × Late-Onset	−0.27	0.12	−0.50 / −0.04		
MD versus SZ × Low versus High BrainAGE				3.7	0.056
MD × Low BrainAGE	1.22	0.14	0.95 / 1.50		
MD × High BrainAGE	0.56	0.12	0.29 / 0.84		
SZ × Low BrainAGE	−0.52	0.12	−0.74 / −0.29		
SZ × High BrainAGE	−0.68	0.12	−0.91 / −0.44		

Main and two-way interaction effects of diagnosis, early versus late disease onset and low versus high BrainAGE on diagnostic scores were analysed using univariate linear modelling in SPSS (version 20, IBM Inc.). E = estimate (mean difference or marginal mean); SE = standard error; 95%-CI Low/Up = 95% confidence interval with lower and upper bounds; F = F-statistic; MD = major depression; SZ = schizophrenia.

patients with bipolar disorder to the major depression group, suggesting that schizophrenia may be differentiated from mood disorders at the single-subject level. In addition, we did not find evidence that neurodiagnostic classification was significantly influenced by the presence of psychotic symptoms in major depression or depressive symptoms in schizophrenia patients, nor by life-style factors or different medications at the time of MRI scanning (Supplementary Table 1). However, we identified a neuroanatomical signature shared by schizophrenia and major depression patients with an average disease onset at 26.5 years (Supplementary Table 2) and accelerated brain ageing effects (Koutsouleris *et al.*, 2013), which led to a ‘non-separability’ of these subgroups.

Our findings partly agree with recent studies that used structural imaging data (Ota *et al.*, 2013) or near-infrared spectroscopy (Takizawa *et al.*, 2014) to differentiate between functional psychoses at the single-subject level. However, comparability to these studies is limited because we did not mitigate naturally occurring demographic differences between schizophrenia and major depression by studying matched patient samples. Instead, we adjusted our data using a representative database of healthy controls that fully covered the age range of our patient population (Dukart *et al.*, 2011). Therefore, potential confounds like divergent illness durations and equalized sex distributions were avoided *a priori*. This approach facilitated the evaluation of the neurodiagnostic pattern, its presence in partly overlapping clinical phenotypes and its clinical moderators across the adult life span. First, we identified a pattern of

perisylvian, prefrontal and temporo-limbic grey matter volume reductions used by the classifier to separate schizophrenia from major depression at the single-subject level. Similar patterns were repeatedly described to distinguish patients with schizophrenia from healthy controls (Honea *et al.*, 2005; Bora *et al.*, 2011) and were interpreted in line with a disconnection syndrome (Friston, 1999) underlying the cognitive, perceptual and thought disturbances of psychosis (Modinos *et al.*, 2012; Sans-Sansa *et al.*, 2013). Our finding of a grey matter volume ‘reduction’ signature (Supplementary Fig. 7) in schizophrenia compared to major depression patients, who were on average 11.5 years older, adds to the concept of schizophrenia being a neurodevelopmentally-mediated, cognitive illness (Kahn and Keefe, 2013) marked by more unfavourable disease outcomes compared to unipolar depression (Harrow *et al.*, 2000). In contrast, somatosensory, periventricular and subcortical abnormalities distinguished major depression from schizophrenia in line with previously reported structural abnormalities in major white matter tracts of depressed patients (Disabato *et al.*, 2014; Guo *et al.*, 2014). Alterations of these regions may subserve core features of depression, such as psychomotor and mood disturbances (Serafini *et al.*, 2011).

Second, the high rate of major depression classifications in our bipolar disorder sample suggests that bipolar disorder and unipolar depression share a common structural denominator different from schizophrenia, in line with Kraepelin’s original dichotomic concept of functional psychoses (Kraepelin, 1899). This finding agrees with initial

reports of a good single-subject separability of schizophrenia and bipolar disorder based on structural (Schnack *et al.*, 2014) or functional MRI (Costafreda *et al.*, 2011). It may also point to an increased sensitivity of multivariate pattern analysis techniques in detecting points of rarity in high-dimensional neuroimaging data compared to univariate methods, which frequently reported considerable overlaps between bipolar disorder and schizophrenia (Arnone *et al.*, 2009). On the other hand, we found a significant difference in the neurodiagnostic scores of the major depression and bipolar disorder groups (Fig. 1), which adds to the growing evidence for structural and functional brain signatures separating these two largely overlapping conditions (Almeida and Phillips, 2013; Redlich *et al.*, 2014). However, it remains unclear whether the configuration of schizophrenia, bipolar disorder and major depression found in our neuroanatomical analysis is conserved in functional neuroimaging domains. Hence, future studies are needed that simultaneously acquire structural and functional imaging data from larger samples of bipolar and schizoaffective patients and directly quantify the neurodiagnostic separability of these ‘intermediate’ phenotypes in the multi-modal imaging space (Lawrie *et al.*, 2011). This will provide us with a comprehensive picture of continuities and discontinuities in the functional psychoses spectrum (Laursen *et al.*, 2009).

Third, we found that an ‘earlier disease occurrence’ correlated with lower differential diagnostic accuracy, rendering major depression patients with earlier disease onsets inseparable from schizophrenia patients—despite distinct cross-sectional phenotypes. This observation was corroborated by the high separability of age of onset-defined major depression samples (83.7%, Table 2) compared to the respective schizophrenia subgroups (62.3%), which suggests that neuroanatomical surrogates of depressive syndromes strongly covary with the disease onset axis. This hypothesis has recently received support from studies showing a pronounced thinning in prefrontal, cingulate, precuneal and inferior temporal cortices of early versus late-onset major depression patients and healthy controls (Truong *et al.*, 2013) (Supplementary Fig. 6). Hence, our results may point to more disrupted neurodevelopmental processes in early depression, potentially manifesting as an accelerated brain ageing effect (Koutsouleris *et al.*, 2013). These processes may also be linked to a more severe clinical phenotype of depression, entailing greater illness severity, higher relapse rates, more cognitive disturbances, as well as overall poorer disease outcomes and higher familial co-aggregation with schizophrenia (Maier *et al.*, 1993; Zisook *et al.*, 2004; Dekker *et al.*, 2007; Korten *et al.*, 2012). Hence, the overlaps between schizophrenia and early-onset depression may lead to a diagnostic dilemma, particularly in the early phases of these illnesses when overt psychotic symptoms have not yet evolved or patients are not explored during psychotic phases. Our results indicate that this challenge cannot be resolved by our neuroanatomical classifier, which would frequently diagnose these early-onset

depressed patients with schizophrenia. Thus, it remains to be elucidated whether different imaging modalities and combinations thereof may help increase the diagnostic specificity in the neurobiological classification of early-onset depression.

Fourth, we observed an increasing schizophrenia likeness from the early ARMS to the FEP individuals, suggesting that the neurodiagnostic fingerprint of schizophrenia is already detectable in persons with basic symptoms, and further intensifies as attenuated, brief limited intermittent and frank psychotic symptoms emerge. This finding agrees with previous studies reporting longitudinal grey matter volume changes in the ARMS, indicating a progressive course of neuroanatomical alterations as the at-risk state evolves into overt psychosis (Koutsouleris *et al.*, 2010; Cannon *et al.*, 2015). However, due to the cross-sectional design of our study, it remains unclear (i) whether the increase of schizophrenia likeness along these early states of psychosis also occurs at the level of neuroanatomical disease trajectories; and (ii) which protective factors contribute to a non-conversion to psychosis despite the presence of the schizophrenia-specific pattern in a given patient. Beyond the arbitrary clinical endpoint of disease transition [see Supplementary material and Yung *et al.* (2010)], our supplementary results indicate that an increased schizophrenia likeness in the ARMS may be associated with poorer functional outcomes at follow-up, suggesting that the identified MRI pattern may not only have differential diagnostic validity but also potential prognostic relevance.

Finally, one caveat has to be considered when interpreting our findings: different medication and treatment histories in our schizophrenia versus major depression groups may have influenced the separability of our patients as long-standing antipsychotic treatment has been previously shown to interact with disease-related brain changes (Ho *et al.*, 2011). Although life-time medication data were not available for the current data set, the high diagnostic sensitivity in our minimally-treated ARMS and FEP groups argues against major treatment effects on our results. Furthermore, our finding of a significantly higher classification performance in first-episode compared to recurrently-ill patients is at odds with the expectation that relapsing illness stages and—in consequence—accumulating disease-specific treatment effects would increase the neuroanatomical gaps between schizophrenia and unipolar depression. The higher diagnostic error in the recurrently-ill patient sample could be interpreted as a ‘dilution effect’, which may arise from increasing neuroanatomical heterogeneity as patients evolve along divergent disease trajectories. Hence, this heterogeneity may result from (i) structural brain variation linked to differential disease courses (Mourao-Miranda *et al.*, 2012) and treatment outcomes (Palaniyappan *et al.*, 2013); (ii) distinct neuroanatomical correlates of positive, negative, disorganized and depressive subsyndromes of schizophrenia, as revealed by factor analytic studies (Koutsouleris *et al.*, 2008; Nenadic *et al.*, 2010, 2012; Zhang *et al.*, 2014); and (iii) temporal shifts



of these profiles over time, with negative and depressive symptoms becoming increasingly prominent in the course of the disease (Salvatore *et al.*, 2013). Nevertheless, our results did not support a moderating or ‘diluting’ effect of depressive/psychotic syndromes in schizophrenia/major depression on neurodiagnostic classification performance. Thus, the strong impact of longitudinal disease variables such as age of disease onset and disease stage may suggest that the identified neuroanatomical biomarker is linked to the temporal and neurodevelopmental characteristics of these clinical phenotypes rather than to their cross-sectional psychopathological features (Gogtay *et al.*, 2011).

In summary, our findings partly confirm and partly question the Kraepelinian dichotomy of functional psychoses into schizophrenia and affective disorders. This is not surprising if one considers the plethora of studies in support of either a phenomenological and neurobiological continuum or a division between these two nosological groups (Kotov *et al.*, 2013). Our results suggest that the diagnostic boundaries drawn by a neuroanatomical disease signature become increasingly porous as patients develop depressive disorders at younger ages, potentially mediated by a cross-nosological disruption of neurodevelopmental processes. This gradient of diagnostic uncertainty does not only challenge clinical and biomarker-based diagnosis, it highlights also the utility of pattern recognition methods to probe the neurological basis of psychiatric illnesses and potentially refine nosological disease constructs.

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## Supplementary material

Supplementary material is available at *Brain* online.

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