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ABSTRACT

Cognitive deficits are a core symptom of schizophrenia, but research on their neural underpinnings has been challenged by the heterogeneity in deficits' severity among patients.

Here, we address this issue by combining logistic regression and random forest to classify two neuropsychological profiles of patients with high (HighCog) and low (LowCog) cognitive performance in two independent samples. We based our analysis on the cortical features grey matter volume (VOL), cortical thickness (CT), and mean curvature (MC) of $N = 57$ patients (discovery sample) and validated the classification in an independent sample ($N = 52$). We investigated which cortical feature would yield the best classification results and expected that the 10 most important features would include frontal and temporal brain regions. The model based on MC had the best performance with area under the curve (AUC) values of 76% and 73%, and identified fronto-temporal and occipital brain regions as the most important features for the classification. Moreover, subsequent comparison analyses could reveal significant differences in MC of single brain regions between the two cognitive profiles. The present study suggests MC as a promising neuroanatomical parameter for characterizing schizophrenia cognitive subtypes.

1. Introduction

Cognitive impairment is a core symptom of schizophrenia causing poor clinical and functional outcome (Green et al., 2000). It is highly prevalent, stable during the course of the disease (Heilbronner et al., 2016), and linked to genetic factors (Sabb et al., 2008), and thus, an important feature in neurodevelopmental etiology models (Howes and Murray, 2014). However, deficits' severity is heterogeneous, prompting the need to characterize cognitive subtypes to understand the underlying biological mechanisms (Carruthers et al., 2019). Previous studies linked different cognitive subgroups to neuroanatomical parameters such as grey matter volume (VOL, Wenzel et al., 2021) or cortical thickness (CT, Cobia et al., 2011). However, data on cortical curvature patterns within the distinctive cognitive profiles in schizophrenia are still scarce.

Schizophrenia is a multifaceted disorder that might arise as a result of interaction between genetic, environmental, and neurodevelopmental factors (neurodevelopment hypothesis) (Howes and Murray, 2014; Weinberger, 1987). Cortical folding could be an indication of neurodevelopment since it takes place during the second and

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third trimesters of pregnancy (Armstrong et al., 1995; Zilles et al., 2013). Indeed, abnormal gyrification as a result of early developmental insults is often observed in schizophrenia (Sasabayashi et al., 2021). An indicator of gyrification could be mean curvature (MC), which describes the folding of the cortical surface of a specific brain region in the three-dimensional space, where a high value indicates a sharper, more pointed curve (Ronan et al., 2011) (Fig. 1). An increase in MC is considered a marker for a higher level of gyrification (Luders et al., 2006), but could also reflect white matter atrophy (Deppe et al., 2014), and decreased cortical connectivity (Lubeiro et al., 2017). Several studies demonstrated larger MC values in both medicated (Lubeiro et al., 2017) and non-medicated patients with schizophrenia compared to controls (Jessen et al., 2019a). Moreover, the pattern of increased MC and not of cortical thinning could be a core feature of a distinct biological subtype in schizophrenia, also characterized by altered brain metabolism and more prominent negative symptoms (Lubeiro et al., 2016). Similarly, a recent study revealed unchanged CT but significantly higher MC in non-medicated patients with schizophrenia compared to healthy controls (Jessen et al., 2019b). Yet, previous work showed increased MC and simultaneously decreased CT in the parahippocampal, lingual, and V5/MT visual cortices (Schultz et al., 2010, 2013). Moreover, MC, surface area, and grey/white matter contrast contribute to regional discrepancies in grey matter VOL and CT findings in schizophrenia, supporting the notion of a complex interplay between cerebral parameters (Kong et al., 2015). In addition, cortical curvature patterns are associated with altered connectivity in schizophrenia (White and Hilgetag, 2011), specifically short-range connectivity (Ronan et al., 2012). Reduced fractional anisotropy values of the prefrontal cortex and its structural connections correlated with increased MC, suggesting it is affected by the integrity of short-range cortico-cortical connections (Lubeiro et al., 2017). Regarding cognition, higher MC values, especially in prefrontal structures, are associated with greater deficits (Jessen et al., 2019a; Lubeiro et al., 2017) and lower premorbid and current IQ values in patients with schizophrenia (Jessen et al., 2019b). Notably, data on cortical folding in schizophrenia are rather inconsistent with findings of increased, normal, and decreased gyrification indexes (Sasabayashi et al., 2021). This inconsistency might reflect differences in measurement techniques (Ronan et al., 2012), but also the neurobiological variability within the disorder (Sasabayashi et al., 2021). There are several measures for gyrification, based on curvature and cortical surface morphology such as MC, local gyrification index (LGI), and the sulcal index (SI) (Sasabayashi et al., 2021). In the present work, we focused on MC, because it relates not only to gyrification, but also to other important for schizophrenia cortical features such as abnormal connectivity (Camchong et al., 2011; Lubeiro et al., 2017) and white matter atrophy (Deppe et al., 2014).). Moreover, it is sensitive to neurobiological heterogeneity and, thus, emerges as a promising parameter for further characterizing cognitive profiles.

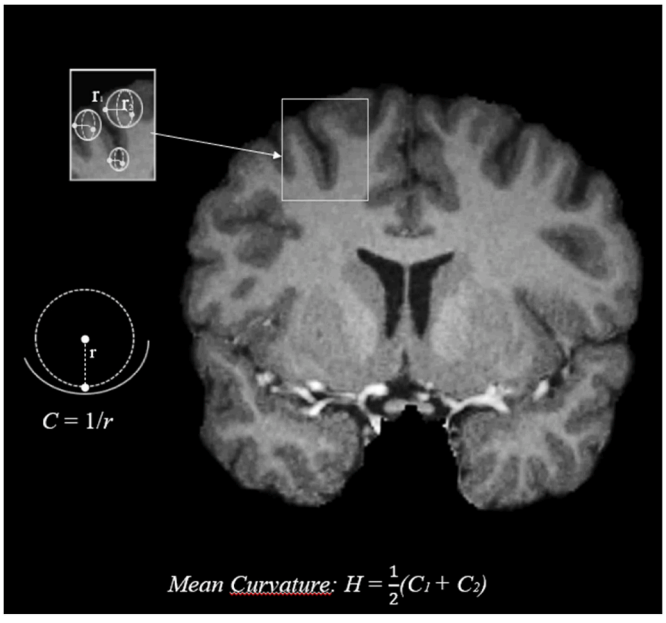

Fig. 1. Mean curvature (*H*) of a given vertexas the average of the two principal curvatures (C_1 and C_2), which are always orthogonal to each other. Curvature (*C*) at a single point of a curve is descripted by the inverse radius (*r*) of the osculating circle of that point. Mean curvature is calculated for each vertex. For details see (Ronan et al., 2011). Figure based on (Medic et al., 2019).

Cognitive impairment is a main feature of schizophrenia, with 80% of patients showing a significantly worse neuropsychological performance than the general population (Keefe and Fenton, 2007). Yet, 20–25% of patients show no cognitive deficits compared to healthy controls (Joyce and Roiser, 2007). Cognitive deficits are considered universally experienced, suggesting that all patients have a lower neuropsychological performance than expected, considering premorbid intelligence and maternal education (Kremen et al., 2000). To address this heterogeneity, recent research has focused on defining homogenous subtypes and linking them to brain and genetic characteristics, aiming the development of individualized and more efficient treatment options (e.g. Green et al., 2020). The presence of at least two subgroups with relatively intact and globally impaired cognitive function and of further profiles with moderate or specific cognitive deficits has been identified (Carruthers et al., 2019). Patients with schizophrenia could be clustered in four profiles with impairments in verbal fluency (1), verbal memory and motor control (2), face memory and processing (3), and (4) general cognitive functioning (Geisler et al., 2015). The subgroups were linked to specific structural and functional brain alterations, including reduced CT in Wernicke's area and lingual gyrus, reduced hippocampal grey matter VOL, and abnormal fronto-parietal activity (Geisler et al., 2015). Furthermore, a recent study applied cluster analysis to neuropsychological data of patients with schizophrenia, their siblings, and healthy controls and identified intact, intermediate, and cognitively impaired subgroups (Alkan and Evans, 2022). Moreover, significant differences in grey matter VOL of prefrontal, temporal, and insula structures between patients and controls disappeared after controlling for cognitive clusters, highlighting the association between neuropsychological performance and brain volume alterations (Alkan and Evans, 2022). Distinctive cognitive profiles are also characterized by altered connectivity in the salience network, fronto-parietal network, and the default mode network (Rodriguez et al., 2019). The application of machine learning (ML) could improve the characterization of schizophrenia subtypes. For instance, ML to whole-brain morphometry data could classify two cognitive subtypes from healthy participants with an accuracy of approx. 70% and indicate involvement of cortical (e.g. inferior temporal gyrus), subcortical (e.g. hippocampus) and cerebellar regions (vermis) (Gould et al., 2014). Similarly, recent onset psychosis patients with impaired cognitive functioning could be distinguished from healthy controls with approx. 60% accuracy, suggesting altered grey matter VOL of the fronto-temporo-parietal regions (Wenzel et al., 2021). However, in both studies, the classification accuracy patients with spared and compromised cognition based on neuroanatomical parameters was relatively small and did not reach significance (Gould et al., 2014; Wenzel et al., 2021).

The present study aims to further characterize different cognitive profiles in schizophrenia by applying ML methods to the parameters MC, VOL, and CT. Specifically, we defined two subgroups with high (HighCog) and low (LowCog) neurocognitive performance based on a global cognition index in two independent patient samples. We then performed in the discovery sample several models combining random forest and logistic regression with MC, grey and white matter VOL, CT, demographic and clinical data as predictors to classify between the cognitive profiles. All ML models were validated in an independent validation patient sample. We hypothesized that the ML model with the

best classification performance would include MC data.

2. Materials and methods

2.1. Study sample

The discovery sample consisted of 57 patients with schizophrenia from the observational case-control study MIMICSS ("Multimodal Imaging in Chronic Schizophrenia Study"). Data from MIMICSS were included in previous publications (Beller et al., 2019; Trossbach et al., 2019). As a reference for cognitive performance we used performance data from 55 healthy controls (16 female, $M_{age} = 32.69$, $SD_{age} = 11.48$) and 19 unaffected relatives (14 female, $M_{age} = 36.63$, $SD_{age} = 14.35$). The main analysis was performed with patient data. The independent validation sample included baseline data from a multicenter, longitudinal intervention study on the effects of aerobic endurance exercise in schizophrenia (Maurus et al., 2020; ClinicalTrials.gov identifier: NCT03466112). We included 52 patients with schizophrenia recruited at the Department of Psychiatry and Psychotherapy of the Ludwig-Maximilians-University in Munich, Germany. Participants from both samples were fully informed about the study procedures and gave their written informed consent. Both study protocols and their amendments were written according to the rules of the Declaration of Helsinki of 1975, revised in 2008, and approved by the local ethics committee (Medical Faculty of the Ludwig-Maximillian-University Munich; Discovery Sample Code 17-13; Validation Sample Code: 706-15). Descriptive characteristics of the study samples can be seen in Supplementary Table S1.

2.2. Clinical and cognitive measures

We applied the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987), the Clinical Global Impression Scale (CGI, Guy, 1976), and the Global Assessment of Functioning Scale (GAF, Goldman et al., 1992) to assess the severity of schizophrenia symptoms. We further collected clinical and demographic data on medication (CPZ), age of onset, Duration of Illness (DOI), and years of education.

Participants underwent neuropsychological testing on the domains (a) episodic verbal memory with the Verbaler Lern-und Merkfähigkeitstest (VLMT: Verbal Learning and Memory Test, Helmstaedter and Durwen, 1990), the German version of the Rey Auditory Verbal Learning (Muller et al., 1997); (b) motor speed with Trail Making Test A (TMT-A, Tombaugh, 2004) and Digit Symbol Substitution Test (DSST, Tewes, 1994); (c) cognitive flexibility with the Trial Making Test B (TMT-B, Tombaugh, 2004) and (d) working memory with the Digit Span Test (DST, Tewes, 1994). Test scores were preprocessed, z-transformed, and calculated to a weighted mean to build a composite score, our main measure of cognition (based on Hasan et al. (2016), for details see supplementary material S3). To discriminate between patients with good and bad cognitive performance, we set the cut-off value of 1.5 SD of the mean cognition index of the healthy controls and relatives in line with previous research (e.g., Keefe, 2014).

2.3. Imaging data acquisition and analysis

In both studies, MRI data were obtained using a Siemens 3.0 T MAGNETOM Skyra Scanner (Siemens Healthineers, Erlangen, Germany) with a 20-channel phased-array head and neck coil. To acquire high-resolution T1-weighted images, we used a 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence with 0.8 mm isotropic voxel (for scanning paramaters see Supplementary Table S2. All images were visually controlled for low image quality and MR artifacts. For preprocessing procedures, see (Karali et al., 2021). We used Freesurfer (Fischl, 2012; version 6.0, http://surfer.nmr.mgh.harvard.edu/) for cortical parcellation according to the Desikan-Killiany-Tourville-Atlas (Desikan et al., 2006; Fischl et al., 2004; Klein and Tourville, 2012) and for the calculation of MC, CT and grey and white VOL of all regions (Dale et al., 1999; Fischl et al., 1999; Fischl and Dale, 2000). For the complete list of regions, see (Klein and Tourville, 2012).

2.4. Classification analysis

To classify high and low cognitive performance in schizophrenia, we ran several ML models with (1) MC, CT, VOL; (2) only CT; (3) only VOL; (4) only MC; (5) CT and MC; (6) CT and VOL; (7) MC and VOL data. All models included the additional features: age, sex, total intracranial VOL, brain VOL without ventricles, school years, age of onset of disease, DOI, CPZ, smoking behavior, and German as a native language. We did not include other clinical data such as PANSS scores due to their short validity period (7 days). Each classification model was performed in both the discovery and validation study. All models used the same algorithm, a combination of random forest (Breiman, 2001) and logistic regression (Dreiseitl and Ohno-Machado, 2002), and were implemented in Python v3.7 with Scikit-learn (Pedregosa et al., 2011). The logistic regression model was used as a penalty criteria for an elastic net approach that combines both Ridge and LASSO regressions (Zou and Hastie, 2005). The hyperparameter α governs the amount of blending between Ridge and LASSO regression (Ridge: $\alpha = 0$, LASSO: $\alpha = 1$). Hyperparameter tuning in random forest included the number of trees and a maximum number of features considered for splitting a node. Each model was derived and evaluated using 1000 data splits. A data split was defined as a random division of the entire discovery data set into 80% training and 20% test data. All data were standardized before analysis. As a measure of feature importance, feature coefficients were used for logistic regression and impurity for random forest. The discovery dataset is standardized, and the most important features are depicted on the training set with random forest, based on impurity measurement, and with logistic regression based on the coefficient value of the logistic regression model. The algorithm was executed 1000 times, and the mean of each importance value of each feature of all runs was taken to estimate the overall importance of every feature in the training dataset. Hyperparameter optimization for the logistic regression and the random forest was conducted over a grid of different hyperparameter specifications and validated with 5-fold cross-validation. Each algorithm's top 5 most important features were merged to finally have 10 features. Using more than these top 10 features yielded worse classification results. The model for random forest and logistic regression was retrained on the training dataset and on the same grid of hyperparameter specifications, but training and consecutive testing on the discovery dataset was done with only the 10 most important features estimated earlier. A voting classifier for the two algorithms was used, which predicts the class label based on the maximum of the sums of each predicted probability. Lastly, the model, including the 10 most important features derived from the discovery set, was run on the validation set with adjusted hyperparameters. By evaluating the model on 1000 data splits with mutually exclusive training and test data, a complete internal validation of the model was ensured. We estimated the models' performance by calculating the area under the curve (AUC) as a primary outcome. We also calculated accuracy (ACC), sensitivity and specificity values.

2.5. Statistical analysis

All data preparation for calculating the cognition index and further statistical analysis was conducted using SPSS 28 (IBM Inc.) for Windows. For all statistical tests, the alpha level was set at $\alpha = 0.05$. Demographic and clinical differences between groups were assessed using χ^2-tests and t-tests with between factors 'study sample (discovery vs. validation set)' or 'cognitive profile (HighCog vs. LowCog). In case of violation of the assumption of normal distribution [Kolmogorov-Smirnov (K–S) test, $p < 0.005$], we applied the non-parametric Mann-Whitney-U test (M-W-U) for independent samples. To investigate how cognitive profiles

(HighCog vs. LowCog) differ in the most important features for the classification, we applied 10 *t*-tests or M-W-U in case of violated normal distribution for each feature as the dependent variable for both validation and discovery samples. To control for multiple testing, the significance level was Bonferroni-adjusted to $\alpha = 0.05/10 = 0.005$. Results of $p > 0.005$, but $p < 0.05$ were indicated as trends.

3. Results

3.1. Demographics, clinical data

There were significant differences between the discovery and validation sample regarding gender ($p = 0.001$) and smoking behavior ($p = 0.028$), both factors are included as co-founders in the ML analysis. Moreover, the validation sample showed less severe psychopathology as measured by CGI, GAF, and PANSS (all $p < 0.005$) and better cognitive performance ($p = 0.029$). Differences in psychopathology do not affect ML analyses since they are conducted separately for both samples. Patients were assigned to HighCog and LowCog based on their cognitive performance and the cut-off value was set at −0.29 (1.5 SD below mean cognition index of the reference samples). In the discovery sample, HighCog ($n = 25$) had significantly less PANSS negative symptoms ($p = 0.004$) than LowCog ($n = 32$). In the validation sample, HighCog ($n = 30$) had higher GAF values ($p = 0.042$) and more school years ($p = 0.003$) than LowCog ($n = 22$). In both samples, cognitive profiles did not differ in age, gender, CPZ, DOI, and severity of positive symptoms (all $p > 0.05$). For details, see Table 1.

3.2. ML classification

The model based on MC data showed the best classification performance with an AUC of 76% in the discovery and 73% in the validation samples compared to the other models. Notably, the second-best model was based on CT with an AUC of 71% (discovery sample) and 69% (validation sample). Table 2 shows the performance values for the different models. As expected, the model based on MC indicated brain regions of the prefrontal, temporal, and occipital regions as most important for classifying both cognitive subtypes. Moreover, six were among the top 10 most important features in the model based on CT, MC, and VOL, which further underlines the advantage of MC as a parameter for the classification of HighCog and LowCog. The top 10 most important features are presented in Table 3 and Fig. 2. No demographic or clinical data were among the most important features. Moreover, enforcement of using the features "age", "gender", "CPZ", "DOI", "school years", "smoking", and "native German language" as input for the classification led to a worse AUC of 62% in the discovery and 60% in the validation sample. Furthermore, using more than 10

Table 2
AUC, ACC, sensitivity and specificity values of the different classification models in both the discovery (N = 57) and the validation sample (N = 52).

Model	*N* Features	Discovery Sample (*N = 57*)		Validation Sample (*N = 52*)	
		AUC	ACC (sensitivity/specificity)	AUC	ACC (sensitivity/specificity)
MC, CT and VOL	446	65%	73% (67%/80%)	61%	70% (75%/67%)
MC ***	148	76%	82% (80%/83%)	73%	80% (80%/80%)
VOL	148	69%	69% (60%/67%)	66%	70% (80%/60%)
CT	150	71%	74% (64%/67%)	69%	72% (63%/65%)
VOL and CT	298	69%	76% (73%/74 %)	67%	77% (69%/71%)
VOL and MC	296	70%	76% (71%/75%)	68%	74% (69%/72%)
MC and CT	298	67%	72% (72%/69%)	64%	70% (71%/66%)

Abbreviations: AUC: area under the curve; ACC: accuracy; MC: mean curvature; CT: cortical thickness, VOL: volume. *** *the model with the highest AUC values.*

Table 1
Descriptive statistics of the two cognitive profiles (LowCog, HighCog) across the discovery (N = 57) and validation (N = 52) samples.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; #Mann-Whitney-U-test.

	Discovery Sample (N = 57)							*Validation Sample (N = 52)*						
	LowCog		HighCog		LowCog vs. HighCog			LowCog		HighCog		LowCog vs. HighCog		
	(*n* = 32)		(*n* = 25)		χ^2	(*df*)	*p*	(*n* = 22)		(*n* = 30)		χ^2	(*df*)	*p*
Gender (m: f)	27 : 5		20 : 5		0.19	(1)	0.667	10 : 12		18 : 12		1.08	(1)	0.299
Hand preference (r: l: b)	29 : 2: 1		23 : 2: 0		0.85	(2)	0.655	19 : 2: 1		24 : 5: 1		0.65	(2)	0.722
Native Language (German: other)	27 : 5		21 : 4		<0.01	(1)	0.969	13 : 9		24 : 6		2.70	(1)	0.100
Smoker (y: n)	20 : 12		15 : 10		0.37	(1)	0.847	11 : 11		20 : 10		1.46	(1)	0.226
	M	***(SD)***	***M***	***(SD)***	***t/M-W-U***	***(df)***	***p***	***M***	***(SD)***	***M***	***(SD)***	***t/M-W-U***	***(df)***	***p***
Age	36.56	(12.10)	34.08	(10.00)	0.83	55	0.411	39.73	(13.39)	35.70	(11.26)	1.18	50	0.245
Onset	26.91	(8.11)	25.50	(9.32)	335.50#		0.299	27.86	(12.02)	25.43	(9.43)	310.50		0.717
DOI	9.56	(9.81)	8.58	(8.281)	378.00#		0.723	11.86	(7.64)	10.27	(9.73)	0.64	50	0.526
CPZ	501.43	(361.78)	473.76	(287.81)	390.50#		0.878	433.38	(180.49)	339.34	(251.66)	1.49	50	0.142
School Years	11.06	(2.29)	11.76	(1.90)	303.00#		0.113	10.45	(1.70)	12.17	(3.11)	144.50#		0.003**
Cognition Index	−0.95	(0.48)	0.11	(0.32)	<0.01#		<0.001***	−0.77	(0.29)	0.18	(0.33)	−10.80	50	<0.001***
CGI	4.06	(0.95)	4.00	(0.88)	381.00#		0.958	3.73	(0.70)	3.47	(0.73)	272.00#		0.240
GAF	54.22	(8.83)	56.60	(10.71)	−0.91#	54	0.366	58.45	(10.60)	64.30	(9.46)	−2.09	50	0.042*
PANSS Total	64.06	(17.83)	59.00	(14.57)	333.00#		0.398	51.50	(13.86)	46.20	(9.18)	1.66	50	0.103
PANSS Positive	14.03	(6.47)	14.42	(4.47)	332.50#		0.392	12.05	(3.75)	10.83	(3.28)	268.00#		0.248
PANSS Negative	18.66	(4.79)	14.79	(4.65)	3.02	54	0.004**	13.05	(5.89)	11.53	(3.71)	93.00#		0.490
PANSS General	31.38	(9.12)	29.79	(7.26)	355.00#		0.631	26.41	(6.65)	23.83	4.51	1.66	50	0.102

Table 3
Comparisons of the top 10 features of importance between the machine learning model based on volume, cortical thickness and mean curvature and the model based on mean curvature.

Rank of importance	Model based on volume, cortical thickness, and mean curvature	Model based on mean curvature
1	Subcallosal gyrus (right) [MC]	Subcallosal gyrus (right) [MC]
2	Inferior frontal sulcus (right) [MC]	Transverse temporal sulcus (right) [MC]
3	Transverse temporal sulcus (right) [MC]	Inferior frontal sulcus (right) [MC]
4	Inferior frontal triangular gyrus (left) [CT]	Inferior frontal sulcus (left) [MC]
5	Inferior supramarginal gyrus (right)[VOL]	Superior frontal sulcus (left) [MC]
6	Superior and transversal occipital sulcus (left) [MC]	Inferior occipital gyrus und sulcus (left) [MC]
7	Inferior frontal sulcus (left) **[MC]**	Intraparietal sulcus and Precuneus transversal (left) **[MC]**
8	Inferior occipital gyrus and sulcus (left) [VOL]	Superior and transversal occipital sulcus (left) **[MC]**
9	Medial orbital sulcus/olfactory sulcus (right) [CT]	Long gyrus and Central sulcus of insula (right) [MC]
10	Intraparietal sulcus and Precuneus transversal (left) **[MC]**	Subcallosal gyrus (left) [MC]

Abbreviations: MC: mean curvature; CT: cortical thickness, VOL: volume.

features in the validation sample led to worse classification results.

Consequent group comparison analyses for the top 10 features revealed significant results for individual brain regions. In the discovery sample, HighCog had lower MC values of the right transverse temporal sulcus ($p = 0.002$) and of the left superior frontal sulcus ($p = 0.039$, trend), and the left inferior occipital gyrus and sulcus ($p = 0.038$, trend) than LowCog. In addition, MC values of the left inferior frontal sulcus were slightly higher in the HighCog ($p = 0.047$, trend). In the validation sample, the MC of the left intraparietal sulcus and precuneus transversal region was significantly higher in the LowCog than in the HighCog ($p = 0.001$). There was a statistical trend for the left inferior occipital gyrus, but in the opposite direction, where MC values were higher in the HighCog group ($p = 0.025$, trend). For detailed descriptive and *t*-test statistics, see Supplementary Table S4.

4. Discussion

In the present study, we demonstrated that two cognitive profiles in schizophrenia can be successfully categorized using MRI-derived anatomical features. Specifically, we performed several combinations of ML algorithms including MC, CT, and VOL to differentiate between patients with high and low cognitive performance in two independent cohorts. The model based on MC achieved the best classification accuracy with an AUC of 76% and 73%. We identified 10 critical brain regions including fronto-temporal, parietal, and occipital areas as the primary distinguishing features for classification. Subsequent comparison analysis indicated significant differences in MC of the right transverse temporal sulcus, the left intraparietal sulcus, and the transversal precuneus between the two cognitive profiles.

Although rarely used by previous research, we demonstrated that MC as a gyrification marker could be more precise for characterizing different cognitive profiles in schizophrenia than CT and VOL. This finding align with previous observations of neuropsychological performance in schizophrenia negatively correlating with MC of the prefrontal cortex (Jessen et al., 2019a, 2019b; Lubeiro et al., 2017). Moreover, our results support the neurodevelopmental hypothesis (Howes and Murray, 2014; Weinberger, 1987), postulating schizophrenia as a consequence of impaired neurodevelopment during critical stages, especially during early brain maturation, when cortical folding occurs (Armstrong et al., 1995; Zilles et al., 2013). In accordance, prior research indicated gyrification as a more suitable measurement for these early insults (Sasabayashi et al., 2021), suggesting it is more stable during the lifespan and less susceptible to duration of illness and medication (Zilles et al., 2013) than CT (van Haren et al., 2011) and VOL (Fusar-Poli et al., 2013; Guo et al., 2015). Linking MC to cognition further supports the neurodevelopmental hypothesis, where neuropsychological deficits are seen as premorbid signs of schizophrenia (Howes and Murray, 2014), since they are observed before the onset of the disease (Lencz et al., 2006). However, alterations in neurodevelopment and gyrification patterns are not specific to schizophrenia but also observed in other psychiatric disorders such as major depression, autism, and bipolar disorder (Sasabayashi et al., 2021). Moreover, previous research demonstrated non-linear changes in gyrification with aging that differed between healthy and psychiatric populations (Cao et al., 2017; Pham et al., 2021), prompting the need for longitudinal studies. In addition, MC as a cortical surface parameter is just one of many possible gyrification measures and some studies suggested that is less specific than the local gyrification index (Shimony et al., 2016). Therefore, future research should include several curvature markers such as Ricci curvature (Yadav et al., 2023), and gyrification index to further investigate the neurodevelopmental hypothesis in schizophrenia.

The model based on MC identified only neuroanatomical features as most important for the classification. Remarkably, demographic and clinical data like age, education, and medication were not among the top features. However, they are associated with cognition (Han et al., 2012) and neuroanatomical abnormalities (Hashimoto et al., 2018) in schizophrenia. Moreover, when enforced as features, they led to poorer classification results. This surprising finding could be explained by the high similarity of the cognitive profiles since they did not differ in most demographic and clinical data. As expected, we identified structures of the fronto-temporal, parietal, occipital, and insular cortex, all of which have

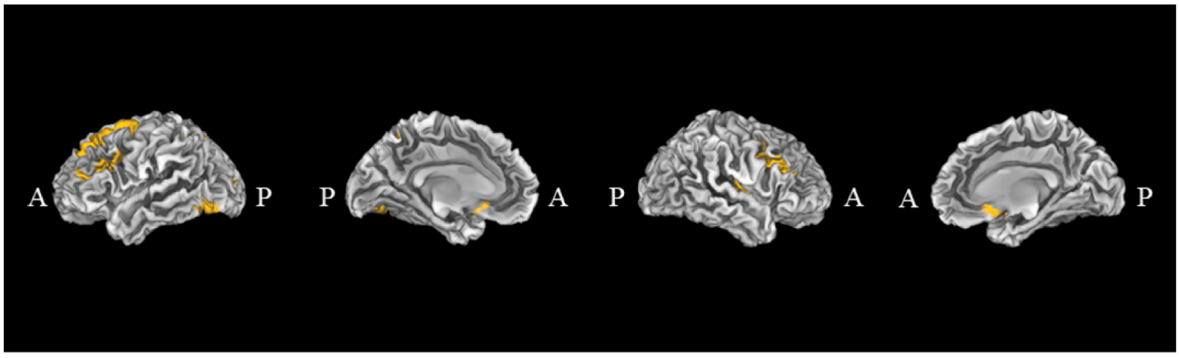

Fig. 2. Depicted in yellow, the 10 most important brain regions for the classification between schizophrenia patients with high and low cognitive performance based on mean curvature.

been associated generalized cognition (Colom et al., 2010) and with structural and functional abnormalities and cognitive deficits in schizophrenia (e.g. Antonova et al., 2004; Barch and Ceaser, 2012; Sasabayashi et al., 2017; Sheffield and Barch, 2016; Sheffield et al., 2021). Furthermore, the comparison analyses showed significant differences between the cognitive profiles for the right transverse temporal sulcus in the discovery sample and the left intraparietal sulcus and transversal precuneus in the validation sample. In line with previous heterogeneous results of increased and decreased gyrification in schizophrenia (Sasabayashi et al., 2021), we could not find a clear direction of abnormalities in MC. In addition, the subtle differences in diverse brain structures support the notion that cognitive functions rely not on single specific regions but instead on whole neuronal networks (Lynn and Bassett, 2019). Our findings could also be explained with the method of assignment to HighCog or LowCog using a theory-based cut-off value of 1.5 SD (Keefe, 2014) that like a median split could overestimate group differences (MacCallum et al., 2002). Future research could achieve clearer results by defining cognitive profiles based on other methods such as clustering or extreme groups from a larger patient sample.

A major advantage of the present study is the application of ML that both allows group classification and the ranking of the most important factors out of a large number of heterogeneous variables and overcomes the limitations of traditional regression models (Dwyer et al., 2018). We applied two established ML algorithms in psychiatry, logistic regression and random forest, since a combination of ML was proven to improve classification results (de Filippis et al., 2019). In addition, we validated our classification model in an independent sample, as suggested by previous work (Tandon and Tandon, 2019). We used an identical grid of hyperparameters for both datasets but retrained on this grid for the validation dataset. This was necessary to better represent the individual cohort's characteristics but could have limited our results' generalizability. Further advantages of our study are the use of several neuroanatomical parameters, the inclusion of demographic and clinical data in the classification analysis, and the well characterized schizophrenia study sample.

Although our study sample size is comparable with previous work in the field (see Arbabshirani et al., 2017), it is still rather small for an ML analysis. Indeed, previous research has demonstrated the crucial role of sample size in classification analysis, especially in a heterogeneous study cohort such as schizophrenia (Schnack and Kahn, 2016). Furthermore, despite our classification results being rather high compared to previous research on cognition subgroups in schizophrenia (e.g. Gould et al., 2014), they could still be improved by the inclusion of further modalities such as fMRI (de Filippis et al., 2019). Third, we used a literature-based cut-off value to define the cognitive profiles. As previously suggested, a data-driven approach such as exploratory clustering could be better for exploring the heterogeneous cognitive data in schizophrenia and yield more homogenous subgroups (e.g. Carruthers et al., 2019). Lastly, we assessed cognition with standard and widely used but less specific tests (Snyder et al., 2015). Thus, we might have condensed cognitive subtypes defined by impairment of specific domains (e.g. processing speed, face memory, Geisler et al., 2015) into one group, reducing the precision of our characterization. Applying more specific instruments for different cognitive domains could lead to defining more distinctive cognitive subgroups.

In conclusion, we demonstrated that MC as a neurodevelopmental marker emerges as a promising parameter for characterizing specific cognitive profiles in schizophrenia. However, future research using ML algorithms on multimodal data in large patient cohorts is needed to resolve the heterogeneity of cognitive deficits in schizophrenia to create novel and individualized approaches for their treatment.

CRediT authorship contribution statement

Irina Papazova: Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Stephan Wunderlich:** Writing – original draft, Visualization, Software, Formal analysis, Data curation. **Boris Papazov:** Writing – review & editing, Conceptualization. **Ulrike Vogelmann:** Writing – review & editing, Data curation. **Daniel Keeser:** Writing – review & editing, Software, Data curation. **Temmuz Karali:** Software, Formal analysis, Conceptualization. **Peter Falkai:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Susanne Rospleszcz:** Writing – review & editing, Software, Data curation. **Isabel Maurus:** Writing – review & editing, Data curation. **Andrea Schmitt:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Alkomiet Hasan:** Writing – review & editing, Funding acquisition. **Berend Malchow:** Writing – review & editing, Supervision, Methodology. **Sophia Stöcklein:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

IP, SW, BP, UK, IM, TK, SR, BM declare no conflict of interest. **PF** is a co-editor of the German (DGPPN) schizophrenia treatment guidelines and a co-author of the WFSBP schizophrenia treatment guidelines; he is on the advisory boards and receives speaker fees from Janssen, Lundbeck, Otsuka, Servier, Boehringer-Ingelheim and Richter. **AH** is editor of the German (DGPPN) schizophrenia treatment guidelines and first author of the WFSBP schizophrenia treatment guidelines; he has been on the advisory boards of and has received speaker fees from Janssen-Cilag, Lundbeck, Recordati, Rovi and Otsuka. **AS** was an honorary speaker for TAD Pharma and Roche and a member of Roche advisory boards.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.03.019.

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