NeuroImage 281 (2023) 120349

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Data-driven multivariate identification of gyrification patterns in a transdiagnostic patient cohort: A cluster analysis approach

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ARTICLE INFO

Keywords:
Cluster analysis
Gyrification
Data-driven approach
Multivariate statistics
Transdiagnostic

ABSTRACT

Background: Multivariate data-driven statistical approaches offer the opportunity to study multi-dimensional interdependences between a large set of biological parameters, such as high-dimensional brain imaging data. For gyrification, a putative marker of early neurodevelopment, direct comparisons of patterns among multiple psychiatric disorders and investigations of potential heterogeneity of gyrification within one disorder and a transdiagnostic characterization of neuroanatomical features are lacking.

Methods: In this study we used a data-driven, multivariate statistical approach to analyze cortical gyrification in a large cohort of $N = 1028$ patients with major psychiatric disorders (Major depressive disorder: $n = 783$, bipolar disorder: $n = 129$, schizoaffective disorder: $n = 44$, schizophrenia: $n = 72$) to identify cluster patterns of gyrification beyond diagnostic categories.

Results: Cluster analysis applied on gyrification data of 68 brain regions (DK-40 atlas) identified three clusters showing difference in overall (global) gyrification and minor regional variation (regions). Newly, data-driven subgroups are further discriminative in cognition and transdiagnostic disease risk factors.

Conclusions: Results indicate that gyrification is associated with transdiagnostic risk factors rather than diagnostic categories and further imply a more global role of gyrification related to mental health than a disorder specific one. Our findings support previous studies highlighting the importance of association cortices involved in psychopathology. Explorative, data-driven approaches like ours can help to elucidate if the brain imaging data on hand and its a priori applied grouping actually has the potential to find meaningful effects or if previous hypotheses about the phenotype as well as its grouping have to be revisited.

1. Introduction

Multivariate statistical approaches offer the opportunity to investigate multi-dimensional interdependences between a large set of objects. This is particularly relevant to brain imaging data, where spatially distributed patterns are more powerful approaches to

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https://doi.org/10.1016/j.neuroimage.2023.120349
Received 17 April 2023; Received in revised form 14 July 2023; Accepted 23 August 2023
Available online 6 September 2023

characterizing the healthy and diseased brain (Etkin, 2019). Yet, many statistical approaches focus on univariate group-level comparisons in which brain regions are tested independently from another. In addition, data-driven approaches aimed at identifying patterns based on multivariate statistics have gained significant importance, as they allow (sub) grouping based on biological (rather than clinical) parameters (e.g., (Lynch et al., 2020; Meng et al., 2021; Sanfelici et al., 2022). These are particularly important in identifying associations of neural signatures spanning beyond prototypical disease categories, including transdiagnostic phenotypes or risks factors (Yeung et al., 2021), as well as subgroups within diagnostic categories (Lalousis et al., 2021; Wang et al., 2021).

Several structural brain imaging meta-analyses, for example, show large overlaps of gray matter loss across affective and psychotic disorders, including the anterior cingulate cortex or insula (Goodkind et al., 2015). At the same time, the case-control design of many original studies does not allow identification of subgroups (either within each diagnostic category or across these) that might be linked to more specific brain structural signatures due to their a priori defined subgrouping. This illustrates the need for novel approaches to analyzing MRI data (Feczko and Fair, 2020; Stein et al., 2021; Voineskos et al., 2020). Identifying stable patterns beyond clinical categories, however, requires not only deep phenotyping of clinical cohorts at multiple levels (e.g., (Bycroft et al., 2018; Kircher et al., 2019)) but also a stable brain structural parameter. As the awareness of the replication crisis in brain imaging research has risen (Marek et al., 2022), it becomes more and more important to go back to "pure data" and revisit commonly used cortical phenotypes (Bandettini et al., 2022; Ivleva et al., 2020).

1.1. Gyrification and its relationship to psychopathology

Cortical gyrification/folding might be particularly suitable as it is expressed early in life, are considered an indicator of early brain development, and yet remains rather stable (compared to other brain morphologic parameters like gray matter volume; (Hogstrom et al., 2013)) throughout most of the life-span (White et al., 2010). This cortical phenotype appears only in mammals, is considered to relate to the development of higher cognitive functions (Lui et al., 2011) and is predominantly formed prenatal: Patterns which emerge up to gestational week 32 seem to be relatively even between individuals (Abe et al., 2003). Folding after gestational week 36 and up to 2 years of age happens predominantly in association cortices (Matsuda and Ohi, 2018) and these patterns are more individualistic and also prone to effects of e.g., gender and early childhood circumstances (Kelly et al., 2013; Luders et al., 2008; Raznahan et al., 2011; White et al., 2010).

Compared to healthy controls, regional gyrification is shown to be altered across psychiatric disorders (Nenadic et al., 2015; Palaniyappan et al., 2011; Sasabayashi et al., 2021; Spalthoff et al., 2018) as well as in relation to disorder specific psychopathology (Kubera et al., 2018; McIntosh et al., 2009; Sasabayashi et al., 2017; Schmitgen et al., 2019). However, considering the high impact of genetic and biological factors on early cortical development and relative stability of global gyrification patterns over lifetime, transdiagnostic evaluation of gyrification and its relationship to early risk-factors could be more meaningful (Sanfelici et al., 2022). This is also supported by studies that show that aberrant gyrification in (sub-)clinical populations is associated with lifetime-manifestations (such as vulnerability factors for psychopathology per se) rather than current/transient disorder specific symptomatology (Al-Haddad et al., 2019; Birnbaum and Weinberger, 2017; Evermann et al., 2020; Mareckova et al., 2020; Papini et al., 2020; Pham et al., 2021; Sanfelici et al., 2022).

So far, results of univariate associations of psychiatric disorders and regional gyrification are still inconclusive as there is evidence for both increased and decreased gyrification in relation to different mental illnesses (Depping et al., 2018; Matsuda and Ohi, 2018; Nanda et al., 2014; Palaniyappan et al., 2011). Although there are studies comparing gyrification between different psychiatric disorders (e.g., (Cao et al., 2017; Madeira et al., 2020)), investigations of potential heterogeneity of gyrification within one disorder and a transdiagnostic characterization of neuroanatomical features are lacking (Sasabayashi et al., 2021).

1.2. Cluster analyses of biological and phenotypic data

Cluster analysis is a multivariate approach to find similarities between given objects (or data points) and to cluster those objects based on their amount of similarity into smaller, homogeneous chunks of data. The goal is to identify groups which are homogenous within but as a whole separate to the other groups (Hennig et al., 2015). Compared to other statistical methods, cluster analysis operates without a priori defined characteristics, hence unsupervised and solely exploratively (Landau and Chis Ster, 2010). This also means that an adjustment of the data by covariates for the initial cluster analysis is not in the nature of the method. In contrast to case-control studies, which are typically tied to (current) clinical conceptualisations of disease categories with little or no basis in biological data, clustering therefore has the potential to identify and establish subgroups across large cohorts sharing particular brain structural or functional features (Hawco et al., 2021; Wang et al., 2021; Yeung et al., 2021).

This approach has been applied to genetic (Pelin et al., 2021), inflammation (Lempriere, 2020), cognitive (Van Rheenen et al., 2017), imaging combined with phenotypic/inflammation data (Lizano et al., 2021; Talpalaru et al., 2019; Van Dam et al., 2017), and also to neuroimaging data on its own (Hawco et al., 2021, 2019). Thus, clustering indeed provides a useful data-driven approach to identify patterns of neurobiological parameters independent of clinical data.

1.3. Goal of the present study

We argue that by sorting mental disorders based on clinical diagnosis categorization the multidimensional nature of phenotypes is partly overlooked as the diagnostic categorization does not necessarily uniformly map on a biological level (Bandettini et al., 2022). The often a priori diagnosis-related grouping of brain morphometric measurements therefore might miss the possibility that there are biological correlates which do not correlate with the disease manifestation itself but appear more impactful for the disease trajectory for multiple mental disorders, i.e., shared risk factors. As the morphometric measurements of cortical thickness and gray matter volume are heavier impacted by factors such as age (Fjell et al., 2009; Lee et al., 2018; Madan and Kensinger, 2018) compared to gyrification and multiple previous studies confirmed a relationship of gyrification with vulnerability for psychopathology (see Section 1.1), gyrification as one morphometric phenotype has the potential to be investigated with an exploratory method.

Consequently, the goal of this study is to elucidate the question whether gyrification offers the potential to delineate subgroups beyond diagnoses from the Diagnostic and Statistical Manual of Mental Disorders (DSM). This addresses the currently open question whether gyrification patterns might be associated with transdiagnostic markers of psychopathology or risk, rather than distinct clinical diagnostic categories (Sasabayashi et al., 2021). Besides a primary methodological goal of this study, results might also have implications in the process of early detection of psychopathology.

For this purpose, our study used data-driven multivariate cluster analysis of a large and clinically heterogeneous transdiagnostic patient cohort ($N = 1028$ including patients with Major depressive disorder (MDD), bipolar disorder (BD), schizoaffective disorder (SZA), and schizophrenia (SZ)) to identify biological patterns of cortical gyrification and further to relate these to transdiagnostic and sub-group related factors of risk for psychopathology. With this approach we are able to identify a structure based on gyrification that is already present in the data, thus biologically defined subgroups that are similar in their gyrification pattern, independent of a priori imposed structuring. To

further validate the behavioral relevance of the newly formed subgroups, we considered variables for associations which are not confounded by state effects or clinical parameters associated with patient age (e.g., disease duration, number of hospitalizations etc.) rather than early neurodevelopmental impacts. Hence, cognitive performance as well as early environmental risk factors are used for post-clustering association analyses with clusters. To acknowledge the possibility of important clinical parameters affecting the clustering results of our heterogeneous patient cohort, we calculated the differences in hospitalization, age of onset, and Medication-Index (Benkert and Hippius, 2021; Reynolds, 2008) for both, the DSM groups as well as the cluster groups. Furthermore, we used DSM-IV-diagnoses labelled groups to examine if diagnostic labeling is able to discriminate gyrification patterns unique to diagnostic groups.

We did not include healthy controls in our cluster analysis as our objectives of this study are specifically drawn toward the distribution of gyrification within the psychiatric disease spectra and therefore healthy controls would only bring an increase in variance but not contributing qualitatively to the aim of our analyses.

2. Methods

2.1. Participants

We analysed data from 1028 patients drawn from the ongoing, multicentric FOR2107 study (http://for2107.de; (Kircher et al., 2019)). Participants were recruited via university wide emails, local advertisements as well as local in- and out-patient departments in Marburg and Münster, Germany. We included individuals with at least one major psychiatric disorder (MDD: $n = 783$, BD: $n = 129$, SZA: $n = 44$, SZ: $n = 72$) as diagnosed by the Structured Clinical Interview (SCID-I; (Wittchen et al., 1997)) based on the DSM-IV-TR administered by trained raters. Our transdiagnostic approach included patients from the affective and psychotic disorder spectrum, incl. MDD, BD, SZA, and SZ; hence, we focus on patients with severe mental disorders. We included individuals with available brain imaging data and excluded participants with an IQ<80, history of head trauma, current benzodiazepine intake, and neurological illness.

The study protocol was approved by the Ethic Committees of the Philipps-University of Marburg, School of Medicine, and the University of Münster according to the latest Declaration of Helsinki. All subjects gave written informed consent to our study protocol and received financial compensation after participation. Descriptive characteristics of our sample are shown in Table 1.

2.2. Neuroimaging

2.2.1. MRI acquisition

MR-scanning took place at two sites, Marburg and Münster, using a 3-Tesla MRI (Münster: Prisma, Siemens, Erlangen, Germany, 20-channel head matrix Rx-coil; Marburg: Tim Trio, Siemens, Erlangen, Germany, 12-channel head matrix Rx-coil). Acquisition and pooling of MRI data was performed according to an extensive and already published quality assurance protocol (Vogelbacher et al., 2019, 2018).

A 3D MP-RAGE sequence was used to obtain T1-weighted images (slice thickness=1.0 mm, voxel size=1.0 × 1.0 × 1.0 mm, FOV=256 mm) with the following parameters in Marburg: TR=1.9 s, TE=2.26 ms, TI=900 ms, flip angle=7°; and in Münster: TR=2.13 s, TE=2.28 ms, TI=900 ms, flip angle=8°

2.2.2. Preprocessing and ROI extraction

T1-weighted scans were preprocessed using the pipeline of the CAT12 toolbox (r1184, Structural Brain Mapping Group, Jena University Hospital, Jena, Germany, http://www.neuro.uni-jena.de/cat/) implemented in SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK) running under MATLAB (version R2017a, The MathWorks, USA) with default parameter settings. Cortical surfaces were extracted using a projection-based approach (Dahnke et al., 2013), applying topological correction (Yotter et al., 2011) and surfaces were spherically registered with an adopted diffeomorphic DARTEL algorithm (Ashburner, 2007). We then estimated cortical gyrification by local absolute mean curvature (Luders et al., 2006) and extracted ROI-based measures from the Desikan-Killiany-40 (DK-40; (Desikan et al., 2006)) atlas. DK-40 atlas by Luders et al. (Luders et al., 2006) combines the two existing gyrification index definitions, i.e., perimeter-based method and curvature-based method by defining a local gyrification index and smoothing the magnitude of the mean curvature, which brings useful information about the surface bending.

2.3. Neuropsychological and risk-factor assessment

Neuropsychological data was chosen from the extensive neuropsychological test battery in the FOR2107. As we only used neuropsychological data for secondary analyses and some of the assessed tests measure the same cognitive domain, we chose one test that best represented each of the four subdomains of cognition: 1. Digit Symbol Substitution Test (DSST; (Wechsler, 1958)) for executive functioning/associative ability, 2. the d2 Test of Attention (d2; (Brickenkamp, 1962)) for sustained attention, 3. the Corsi block-tapping test (CBTT total score; (Berch et al., 1998)) for visuospatial working memory performance, and 4. the verbal fluency test (VF; (Aschenbrenner et al., 2000)) for semantic processing (for an overview of the complete neuropsychological test battery in FOR2107 see (Kircher et al., 2019)).

Based on self-reported data of the participants we calculated a prenatal risk-score as well as a birth-complication risk score, as prenatal and early postnatal development potentially most impact gyrification (Abe et al., 2003). For the prenatal risk-score participants were asked if at least one of the following prenatal influences were given: maternal infection, maternal alcohol- or drug-abuse, maternal malnutrition, maternal or paternal smoking. For birth-complication risk score participants were asked if at least one of the following birth complications were given: ventouse birth, forceps delivery, casarean delivery or others. For both risk scores, scoring was in a yes-/no-manner (no risk=0, at least one risk=1).

The Medication-Index was calculated based on conversion and cut-off recommendations by Reynolds (2008) and Benkert and Hippius (2021). Patients are assigned a score of 0, 1, or 2 according to their daily psychiatric medication doses. Psychiatric medications include

Table 1
Descriptives of our $N = 1028$ sample, total and divided for DSM-labelled groups.

Sample Group	n	Mean Age	Sex	Mean Age of Onset	Mean Hospitalization Duration in Weeks	Mean Medication-Index
Total	1028	37.41	390 m, 638 f	25.34	17.68	1.66
MDD	783	36.74	270 m, 513 f	26.01	12.05	1.38
BD	129	41.24	58 m, 71 f	24.12	32.41	2.52
SZA	44	38.39	20 m, 24 f	20.95	49.25	3.18
SZ	72	37.25	42 m, 30 f	22.74	37.73	2.32
p Welch-ANOVA/χ^2		.003*	<0.001**	<0.001**	<0.001**	<0.001**

* $p<.05$.
** $p<.001$.

antipsychotics, antidepressants, lithium, mood-stabilizer, benzodiazepines, as well as Z-drugs.

2.4. Statistical analyses

2.4.1. Pre-clustering analyses

Descriptive analyses and Welch-ANOVA for the above-mentioned clinical parameters were run. Additionally, ahead of the cluster analysis, several statistical analyses were run on the original gyrification data matrix to assure plausibility for the choice of applying a clustering procedure and further regarding clustering method, dissimilarity-matrix computation as well as clustering algorithm (for an overview for recommended steps applying cluster analysis see (Landau and Chis Ster, 2010)):

We ran correlation analyses between all 68 brain areas included as well as between subjects. Furthermore, to better understand how gyrification across regions is distributed in our sample, we applied the PHATE visualization method (Moon et al., 2019) to our data using the R package *phateR*. PHATE brings high dimensional biological data into lower-dimensional embeddings (2 dimensions) while capturing both local and global nonlinear structure. Fig. 1 shows gyrification data of the 68 DK-40 regions embedded in 2 dimensions as well as color labelled for diagnostic groups as classified by DSM-IV-TR. Based on the results of the computed pre-clustering analyses (see Section 3.1), data appeared to be suited for applying hierarchical agglomerative cluster analysis using ward-algorithm on a computed dissimilarity-matrix using Euclidean distance. Briefly, hierarchical clustering was chosen as no previous information on number of clusters was apparent from other studies. On the same incentive, agglomerative clustering was chosen to cluster the data in a bottom-up manner. The ward-algorithm was chosen due to showing the highest computed agglomerative coefficient (AC=0.9) compared to other algorithms. See Supplement S1. for description of argumentation for procedure selection.

2.4.2. Cluster analysis

Cluster analysis was run on the dissimilarity matrix (computed with the function *daisy* implemented in R) with the package *cluster* in R using the *agnes*-function for hierarchical clustering. Dissimilarity matrix was computed using Euclidean distance and non-standardized gyrification data. Clusters were fused by ward-algorithm. We did not apply a standardization on gyrification data, as we only included data with the same metric for the cluster analysis. To validate the choice of number of clusters, Jaccard-bootstrapping with 100 permutations was run (function *clusterboot* implemented in R) for all possible cluster solutions of $k = 2$ to $k = 10$. *Clusterboot* resamples the data and computes Jaccard similarities of the original clusters to the resampled data. It then uses the mean over these similarities for stability of clusters (Hennig, 2007). For further validation of choice of cluster solution, cluster analysis and some of the post-clustering analyses were run again on 80% of the initial data.

2.4.3. Post-clustering analyses

To evaluate which brain regions had the highest impact (importance) on forming the cluster solution, effect sizes were calculated for each brain region. To evaluate the association with basic cognition, we ran an ANOVA for the neuropsychological tests reported above as well as for the clinical parameters hospitalization, age of onset, and Medication-Index. Furthermore, we applied a χ^2-test for association between our prenatal risk-score as well as the birth-complication risk-score and clusters. Likewise, we ran binomial tests for comorbidity vs. no comorbidity to evaluate if our cluster solution also maps on an overall index of comorbidity. We also ran subsequent binomial tests to see if diagnostic groups are equally distributed over clusters and no diagnostic group is over- or underrepresented in a cluster.

Secondary goal of this study was to see if diagnostic groups show significant different gyrification patterns to exclude the possibility of diagnostic groups being the best solution to explain gyrification variability.

Even though scanning protocols between the two sites were harmonized (Vogelbacher et al., 2018) and a quality assurance protocol was followed (Vogelbacher et al., 2019) we ran a *t*-test for the gyrification data to consider possible effects of the different scanning sites. Results did not yield any significant differences in gyrification between the two sites ($p<.0007$ after correction for multiple comparisons; see complete output table here: https://github.com/julia-pfarr/cluster_supplements/tree/main/supp_analyses).

Furthermore, although we did not include a healthy control group in the primary analysis of this paper (=cluster analysis), as the goal was a transdiagnostic one, we plotted the distribution of gyrification in a

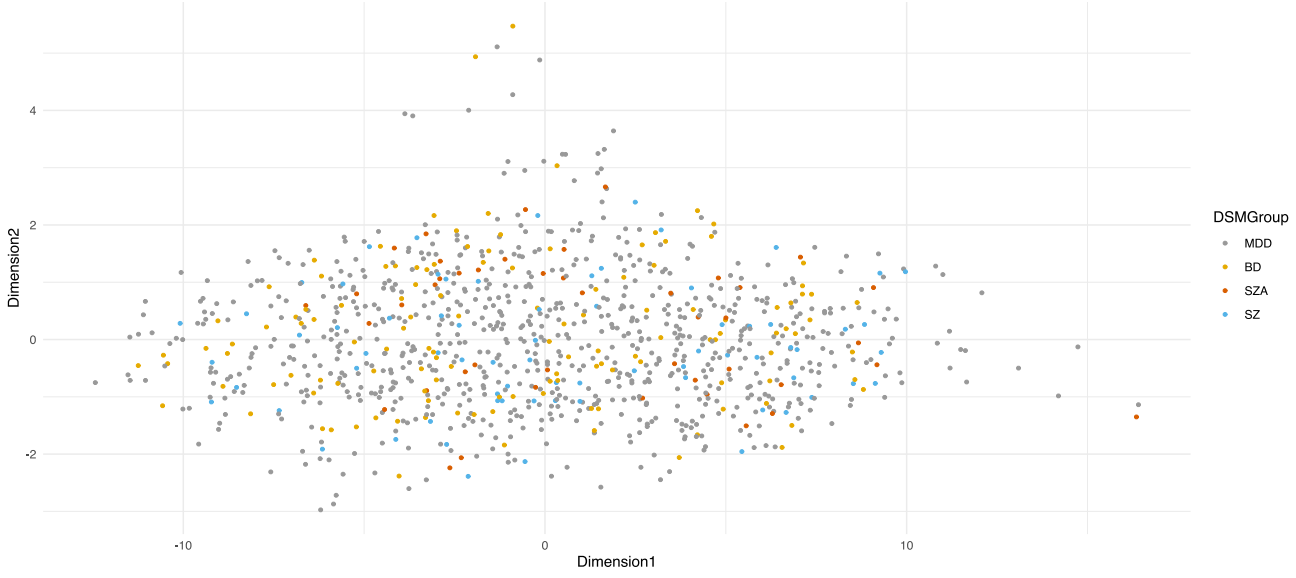


Fig. 1. Scatterplot of gyrification data as distributed in our $N = 1028$ sample, coloured by DSM-groups. Figure shows a diffuse distribution of DSM-IV-TR diagnostic groups embedded in the two gyrification dimensions.
Note: Axes of the figure are the two PHATE dimensions after applying the PHATE (=Potential of Heat diffusion for Affinity-based Transition Embedding) algorithm for dimensionality reduction to our data matrix. Values of the axes represent the normalized affinities after embedding distances and affinities of the data matrix using Multidimensional Scaling method (Carroll and Arabie, 1998).

healthy control group (n = 901; mean age 34,91; m = 332, w = 569) together with the gyrification distribution of our newly formed cluster groups as an additional reference for comparison or interpretation of the clusters.

3. Results

3.1. Pre-clustering results

Table 1 shows descriptive statistics and results of the Welch-ANOVA for clinical parameters of DSM-labelled groups. Descriptive analyses of the gyrification data showed to be normally distributed over subjects and identified expected variability in range and mean of individual areas (see Supplement S2.-Table 1 for descriptive table). Correlation of gyrification data between brain areas yielded overall low to moderate correlation with highest correlation coefficient being r = 0.66 (p<.001) between the right and left superiorfrontal cortex (see Supplement S3.-figure 1 for complete correlation matrix). Furthermore, correlation of gyrification data between subjects showed overall high correlation coefficients (see Supplement S4.-figure 2 for correlation matrix), indicating a rather globally underlying relationship between subjects based on their gyrification than a local one.

Fig. 1 shows a diffuse distribution of DSM-labelled groups in the reduced 2-dimensional scatterplot of gyrification data, hence indicating that clinical diagnoses do not cluster patients in homogeneous gyrification groups.

3.2. Clustering results

Decision on number of clusters was made using the elbow method on a screeplot, which was based on the total-within-distances of 10 clusters (for screeplot and dendrogram see Supplement S5.-figure 3a and b). Screeplot indicated the optimal number of clusters to be 3. Bootstrapping showed cluster 1 to be highly stable and cluster 2 and cluster 3 to be quite stable (cluster stabilities: cluster 1 = 0.79, cluster 2 = 0.75, cluster 3 = 0.72; (Mount and Zumel, 2019); cluster stabilities for further cluster solutions are listed in Supplement S6). Results of the cluster analysis on 80% of the initial data yielded similar results (with some expected variation) and can be found in Supplement S7.

3.3. Post-clustering results

Descriptive statistics and Welch-ANOVA results of the clusters are shown in Table 2. Subsequent binomial tests showed that diagnostic groups are equally distributed over clusters and no diagnostic group is over- or underrepresented in a cluster (see Supplement S8.-Table 2). Additionally, in Fig. 2 mean gyrification (sorted frontal-parietal-temporal-occipital) for clusters was plotted. Results show, that 1) cluster analysis identified a global, rather than local pattern of gyrification and 2) cluster 2 globally shows highest, cluster 1 moderate and cluster 3 lowest gyrification. Further, some local variations in gyrification can be found mainly in cluster 1: different to its global pattern (mid-high gyrification), cluster 1 shows highest gyrification in the left pars opercularis, pars orbitalis, pars triangularis, and the right transverse temporal cortex. In the left caudal anterior cingulate, the left and right parahippocampal gyrus as well as the left and right entorhinal cortex, cluster 1 shows lowest gyrification (see Supplement S9.-Table 3 for ANOVA post-hoc tests for gyrification between data-driven groups). Fig. 3 shows brain regions with η^2>0.14 (see Supplement S13.-Table 5 for all effect sizes).

Cluster 3 shows overall lowest performance (see Fig. 4) and ANOVA yielded significant differences (p<.05, Bonferroni-correction for multiple comparisons) for VF, DSST and CBBT. Prenatal-risk score showed significant association with our cluster solution (χ^2(4)=11.035, p=.026). Largest contribution to the χ^2 statistic comes from cluster 2 which shows more subjects without and less subjects with prenatal risk than statistically expected. Cluster 3 shows significantly less subjects without prenatal risk and trends toward more subjects with prenatal risk than statistically expected (see Table 3). Birth-complication score was not significantly associated with our cluster solution. Binomial tests for comorbidity (comorbidity vs. no comorbidity; test proportion 0.42/0.58) did not yield significant results (cluster 1: p=.208, cluster 2: p=.368, cluster 3: p=.362).

Results of the ANOVA between diagnostic groups yielded significant difference of gyrification in only seven of the 68 brain areas included (p<.05; see Supplement S10.-Table 4 and Supplement S11.-figure 4 for results).

The plot of gyrification data in a healthy control group together with the distribution of gyrification in our cluster groups shows that the gyrification distribution of the healthy control group is the most similar to the gyrification distribution in cluster group 1 (see Supplement S12.-figure 5).

4. Discussion

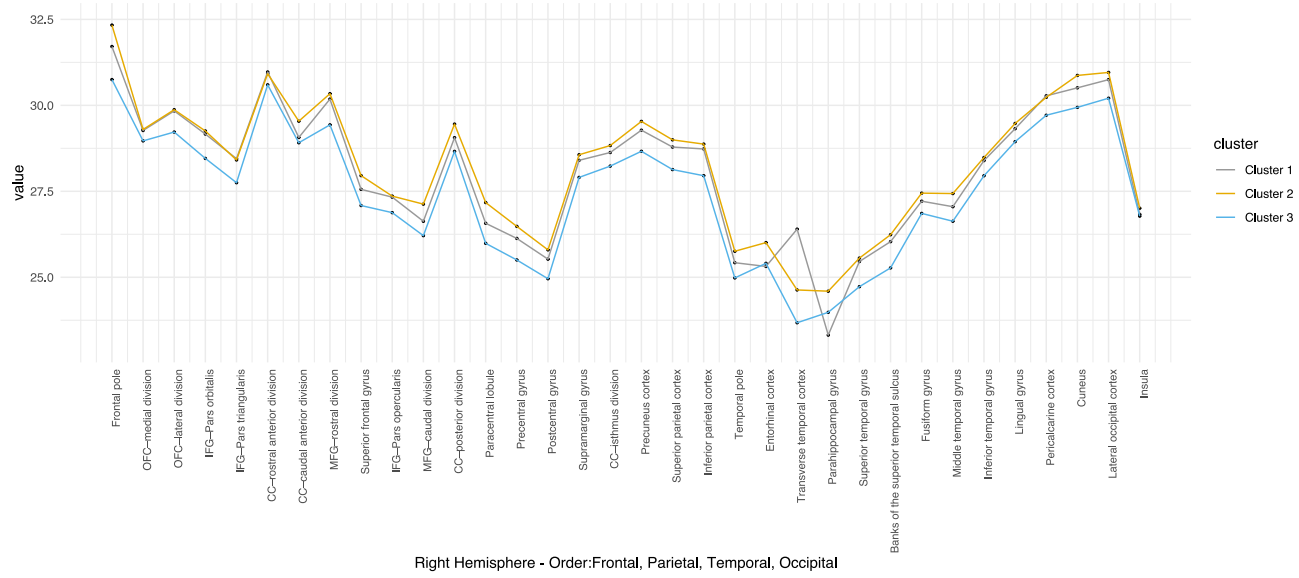
In this study we investigated gyrification as a cortical phenotype and its relationship to basic psychopathology rather than DSM-IV-TR diagnoses using a data-driven multivariate approach. Cluster analysis identified three clusters which did not delineate along diagnostic groups but rather point towards transdiagnostic, global gyrification patterns underlying a considerable portion of variation in the data. These clusters are characterized by both differences in gyrification as well as differences in cognitive performance and early environmental risk. Main differences in gyrification between clusters and regions important for

Table 2
Descriptives for our k = 3 cluster solution.

Cluster	n	Frequency DSM-groups within cluster	Mean age	Sex	Mean Age of Onset	Mean Hospitalization Duration in Weeks	Mean Medication-Index
1	256	MDD=193, *75.4%* BD=36, *14.1%* SZA=12, *4.7%* SZ=15, *5.9%*	40.04	91 m, 165 f	26.92	16.71	1.53
2	378	MDD=292, *77.2%* BD=48, *12.7%* SZA=11, *2.9%* SZ=27, *7.1%*	34.24	118 m, 260 f	23.05	16.48	1.62
3	394	MDD=298, *75.6%* BD=45, *11.4%* SZA=21, *5.3%* SZ=30, *7.6%*	38.74	181 m, 213 f	26.51	19.49	1.79
p Welch-ANOVA/ χ^2			<0.001**	<0.001**	<0.001**	.238	.149

** p<.001.

(a)



(b)

Fig. 2. a&b Plot of mean gyrification index per cluster for every region, ordered frontal-parietal-temporal-occipital. a) Left hemisphere, b) right hemisphere.

forming the cluster solution are mostly located in association cortices (superior frontal gyrus, middle frontal gyrus, cingulate cortex, superior temporal cortex, superior and inferior lateral parietal cortex, paracentral, postcentral, and precentral gyrus as well as precuneus; see Fig. 3) which further underlines transdiagnostic similarities in gyrification. The lack of significance of DSM-group analyses points toward super-ordinate factors that are only indirectly related to diagnostic categories. These findings have important implications for our understanding of data-driven classification based on biological parameters in general, as well as the usefulness of gyrification/cortical folding as a marker of risk for psychiatric disorders or life-time psychopathology:

First, our findings of the cluster analysis showed global vs. regional variations of gyrification and transdiagnostic effects in specific regions. The identified clusters are characterized by an overall global pattern, namely a separation by the degree of gyrification over all brain regions, as well as an even distribution of diagnostic groups over clusters. This was also confirmed by an additional cluster analysis including only 80% of the data. Cluster 1 however shows some variation apart from its global gyrification pattern, mainly in fronto-temporal regions. This can be embedded in results of previous studies of gyrification showing involvement of fronto-temporal regions in (early) risk for psychopathology (Evermann et al., 2020; Pham et al., 2021; Rosa et al., 2021), as cluster 1 also showed to be highly stable after bootstrapping. It furthermore speaks for the argument, that a transdiagnostic evaluation of global gyrification patterns is well suited to evaluate the relationship of gyrification and basic risk factors for psychopathology. This is supported by the fact that these local shifts in fronto-temporal regions only appear present in our newly formed, transdiagnostic cluster but not in the DSM-defined group comparison (see Supplement S11.-figure 4).

Yet, our cluster solution is associated with cognitive and prenatal markers of psychopathology, which cross diagnostic boundaries, and rather reflect transdiagnostic risk for life-time psychopathology: cluster

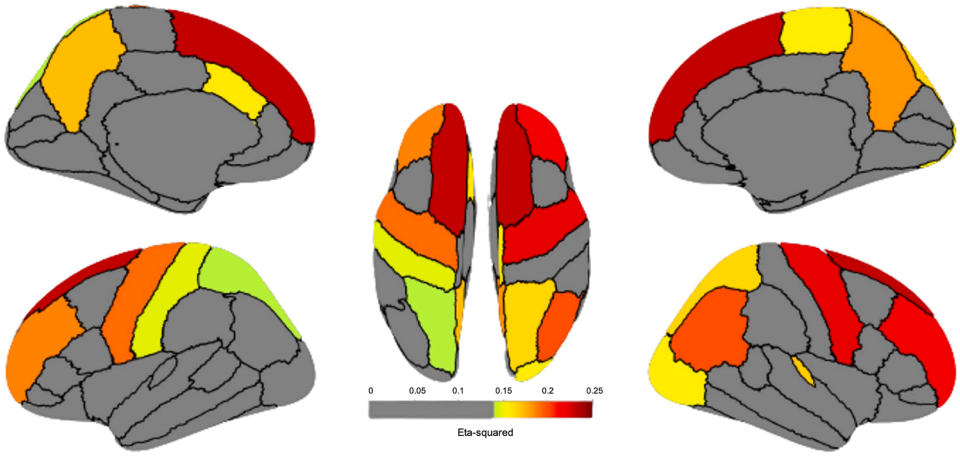


Fig. 3. Figure shows brain regions that contributed most to our cluster solution (η^2>0.14; brain regions with an effect-size η^2<0.14 are colored in gray).

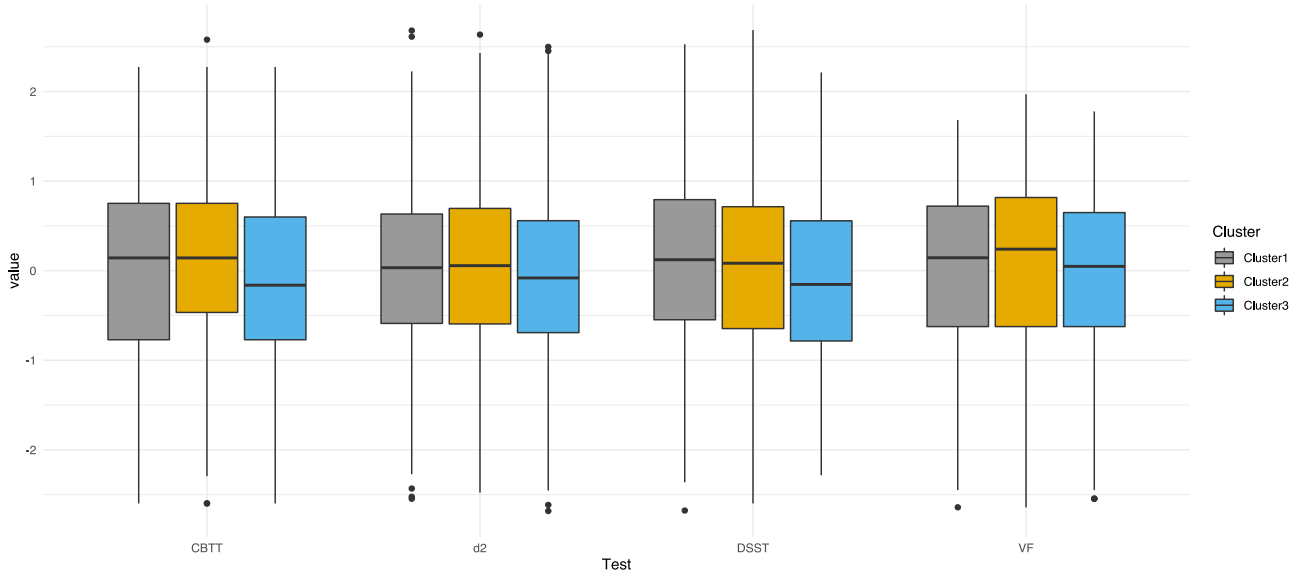


Fig. 4. Boxplots for neuropsychological test scores (z-standardized), grouped by clusters. Cluster 3 shows significantly poorest performance across all tests.
Note: CBTT=Corsi block-tapping test; d2=d2 Test of Attention; DSST=Digit Symbol Substitution Test; VF=Verbal fluency.

3 shows overall lowest gyrification and overall lowest performance in cognitive tasks. Furthermore, cluster 3 contains more individuals with a prenatal risk and less individuals without prenatal risk than statistically expected. Although not significantly, cluster 3 also has the highest mean in hospitalization duration as well as the Medication-Index. Being able to relate overall low gyrification, low performance in cognitive tasks, and higher prenatal risks further supports the hypothesis of a high impact of early developmental influences to manifest in gyrification (Al-Haddad et al., 2019; Birnbaum and Weinberger, 2017; Pham et al., 2021). Although there are no significant differences between cluster 1 and 2 in prenatal risk, birth complications, cognitive tasks or clinical variables, plotting the gyrification distribution of our newly formed clusters together with the gyrification distribution of a healthy control group (Supplement S12.-figure 5) points toward cluster 1 showing the distribution most similar to gyrification in individuals without psychiatric disorders. Cluster 1 also does not show significant results of prenatal risk (other than cluster 2; Table 3) which also speaks for this cluster being the most "normative". Future studies could therefore apply a cluster analysis on gyrification data of subclinical populations for identification of similar gyrification patterns of individuals without clinical psychopathology but high prenatal risk. This could break down the actual potential of gyrification as a neurobiological marker for mental illness proneness.

Our cluster groups do show different gyrification patterns, but differences are partly restricted to particular brain regions. Cluster 3, in comparison to Cluster 1 and 2, shows significant lower gyrification in almost every brain region. Significant differences in local gyrification between these two clusters can primarily be found in the association cortices. This is in line with the fact, that diverse or transdiagnostic symptom representations are consistently found to be rather associated with alterations in association cortices than regions of lower hierarchy (Sydnor et al., 2021). In addition, brain regions important for discriminating groups of individuals and hence forming our cluster solution (regions with effect-sizes of η^2>0.14; Fig. 3) can be characterized as brain regions of association cortices (Sydnor et al., 2021). Our cluster solution therefore might reflect that variability in association cortices is higher and that group differences based on gyrification should rather be investigated in those areas, as these tend to have the power to discriminate between groups. Together with evidence showing that late prenatal and postnatal cortical folding primarily happens in association cortices (Matsuda and Ohi, 2018), our cluster solution can serve as a basis for further narrowing brain regions included for association with particular prenatal and postnatal variables.

Given the significant difference in mean age between the cluster

Table 3
Results of the χ^2-test of prenatal risk * cluster groups. Adjusted residuals >1.96 or >−1.96 indicate a significantly different number of expected counts (positive value = more counts than expected; negative value = less counts than expected). Largest contribution to the χ^2 statistic ($\chi^2(4)=11.035$, $p=.026$) comes from cluster 2 which shows more subjects without and less subjects with prenatal risk than statistically expected. Cluster 3 shows significantly less subjects without prenatal risk than statistically expected.

		Missing values	0 = no prenatal risk	1 = at least one prenatal risk	Total
Cluster 1	Count	14	108	134	256
	Expected Count	12.2	117	126.8	
	Adjusted Residual	.6	−1.3	1	
Cluster 2	Count	14	198	166	378
	Expected Count	18	172.8	187.2	
	Adjusted Residual	−1.2	3.3	−2.7	
Cluster 3	Count	21	164	209	394
	Expected Count	18.8	180.1	195.1	
	Adjusted Residual	.7	−2.1	1.8	

Note:.
Count = Observed number of subjects within the respective cluster in our data.
Expected Count = Statistically expected number of subjects within the respective cluster in our data.
Adjusted Residual = raw residuals (or the difference between the observed counts and expected counts) divided by an estimate of the standard error.

groups, discussion of this result is needed. Even though gyrification shows relative stability over lifetime in comparison to other morphometric measurements, significant age effects on gyrification have been shown in previous studies (e.g., (Hogstrom et al., 2013)). With the data included without prior control for age, we cannot exclude an effect of age on our cluster solution but there are multiple arguments which let us conclude that age did not play a significant role: 1) Age only showed a small effect size of $\eta^2=0.036$ for our cluster solution. 2) Brain areas identified by Hogstrom et al. (2013) with linear age effects for gyrification are indeed brain areas that contributed strongly to our cluster solution (η^2 between 0.129 to 0.241) but so did frontal lobe areas (amongst others) as well which Hogstrom et al. (2013) found to be non-linear and not significantly correlated with age. Furthermore, additional regression analyses showed that age is a significant predictor for gyrification in some of the brain areas but not systematic for the brain areas that contributed most to our cluster solution (see Supplement S13.-Table 5). 3) The healthy control group with its mean age of 34,91 showed the most similar pattern with cluster 1. The healthy control group is significantly younger than cluster 1 but still the most similar in gyrification. 4) Cluster 1 and 3 are not significantly different in age ($p=.610$) but in gyrification. Future studies could build upon this result by e.g., comparing cluster solutions between samples with and without age regressed out prior to clustering.

Sex also showed a significant difference between the cluster groups ($\chi^2(2)=18.586$, $p<.001$, Cramer's $V = 0.27$). Sex composition in cluster 1 was not significant, cluster 2 contains significantly more female and less male individuals than expected. Cluster 3 contains significantly more male and less female individuals than expected (see output table here: https://github.com/julia-pfarr/cluster_supplements/tree/main/supp_analyses). Previous studies identified significant sex differences in gyrification which are restricted to certain brain areas (e.g., (Forde et al., 2017; Mutlu et al., 2013; Papini et al., 2020). We therefore need to acknowledge that our cluster solution might partly be due to the effect of sex which should be addressed in future studies.

Using DSM-IV-TR diagnoses for definition of subgroups within the cohort had little, if any, power in discriminating global gyrification patterns (see Supplement S10.-Table 4 and Supplement S11.-figure 4). Mean comparison of gyrification between diagnostic groups yielded significant differences in only seven of the 68 brain regions included in our analysis. As shown in Fig. 1 this is not a surprising result, as distribution of groups within gyrification dimensions is diffuse and do not tend to form separate data-clouds. This does not mean that DSM-labelled grouping is not an appropriate approach for investigating local differences is gyrification specific to diagnoses, as small, locally based effects cannot be captured with a simple mean comparison. However, it could imply that meaningful impacts of altered gyrification on psychopathology in general are missed due to the categorical clinical grouping.

This study contributed to approaching the challenge of population sorting in psychiatric neuroimaging studies. A priori defined groups based on clinical diagnoses limits the power of brain structural and functional analyses by oversimplifiying the neural correlates associated with mental disorders (Bandettini et al., 2022). Classic Brian Wide Association Studies (BWAS) are helpful and necessary for identifying the most common effects over a large study cohort, but the most common effects do not necessarily equal the most meaningful effects for a particular disorder (Gratton et al., 2022). With data-driven approaches like ours, biological underpinnings of a disease can be detected which would have been left unknown with a classic BWAS approach.

There are some limitations to our study that need to be addressed. Individuals with a diagnosis of MDD were overrepresented in our sample (see output of a cluster analysis with MDD patients only of our sample here: https://github.com/julia-pfarr/cluster_supplements/tree/main/supp_analyses/MDDonly). For a more comprehensive transdiagnostic evaluation the sample would need a more even ratio of diagnostic groups. To be able to have more certainty on parameters regarding the cluster analysis (which was the main analysis) we did not go with a smaller, matched sample but went with the higher sample size. Cluster analysis is an explorative approach. It is expected that changes, e.g., in sample size yield a different cluster solution than ours. Results of cluster analyses are also highly dependent on the clustering algorithm used which is based on external characteristics unique to the data included, making comaprisons between studies with different clustering algorithms difficult. Furthermore, as we only included brain data but no other phenotypic data in our initial cluster analysis, the identified clusters can only be certainly characterized by their gyrification data and pattern but not as holistic defined subgroups. As well, we only included rather broad brain regions (DK40 atlas). Using another, more specific brain atlas might capture more complex patterns in the data.

5. Conclusion

Our study is the first to identify gyrification patterns based solely on themselves. Explorative, data-driven approaches like ours can help to elucidate if the brain imaging data on hand actually has the potential to find meaningful associations in relation to diagnostic categories (as commonly described by univariate approaches) or if the underlying biological structure implies another embeddedness of psychopathology.

Our findings implicate transdiagnostic risk factors for life-time psychopathology to be associated with global (and some regional) variation in gyrification rather than associations with narrowed diagnostic categories. Results of this study might thus have implications in the process of early detection of psychopathology as identified gyrification patterns are not bound to specific diagnostic categories but offer a broader perspective on psychopathology risk and therefore on risk evaluation. Group-analyses based on DSM categories thus might not be the best way to actually detect meaningful associations. Therefore, finding transdiagnostic similarities regarding gyrification and underlying factors responsible for its variation might be more promising for elucidating the global relationship of gyrification and psychopathology.

Funding

This work is part of the German multicentre consortium "Neurobiology of Affective Disorders. A translational perspective on brain structure and function", funded by the German Research Foundation (Research Unit FOR2107). Principal investigators are: MACS cohort: Tilo Kircher (coordinator; KI588/14–1, KI588/14–2), Udo Dannlowski (DA1151/5–1, DA1151/5–2), Axel Krug (KR3822/5–1, KR3822/7–2), Igor Nenadić (NE2254/1–2, NE2254/2–1, NE2254/3–1, NE2254/4–1), Carsten Konrad (KO4291/3–1), Andreas Jansen (JA1890/7–1 and JA1890/7–2). Igor Nenadić was supported by grants from UKGM and Forschungscampus Mittelhessen. Open access funding provided by the Open Access Publishing Fund of Philipps-Universität Marburg with support of the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation).

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The FOR2107 cohort project was approved by the Ethics Committees of the Medical Faculties, University of Marburg (AZ:07/14) and University of Münster (AZ:2014–422-b-S).

Data and code availability statement

Original data matrix cannot be shared due to privacy restrictions but can be requested from the corresponding author (upon reasonable request and data user agreement). Use of R codes is described in the methods section and R code as well as output tables of additional analyses can be found in this GitHub repository: https://github.com/julia-pfarr/cluster_supplements.

CRediT authorship contribution statement

Julia-Katharina Pfarr: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Tina Meller:** Data curation, Investigation. **Katharina Brosch:** Data curation, Investigation, Writing – review & editing. **Frederike Stein:** Data curation, Investigation, Writing – review & editing. **Florian Thomas-Odenthal:** Data curation, Investigation, Writing – review & editing. **Ulrika Evermann:** Data curation, Investigation, Writing – review & editing. **Adrian Wroblewski:** Data curation, Writing – review & editing. **Kai G. Ringwald:** Data curation, Investigation. **Tim Hahn:** Validation, Writing – review & editing. **Susanne Meinert:** Data curation, Investigation, Writing – review & editing. **Alexandra Winter:** Data curation, Investigation, Writing – review & editing. **Katharina Thiel:** Data curation, Investigation. **Kira Flinkenflügel:** Data curation, Investigation, Writing – review & editing. **Andreas Jansen:** Funding acquisition, Resources, Supervision, Writing – review & editing. **Axel Krug:** Funding acquisition, Project administration, Supervision. **Udo Dannlowski:** Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. **Tilo Kircher:** Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. **Christian Gaser:** Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Igor Nenadić:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Biomedical financial interests or potential conflicts of interest: Tilo Kircher received unrestricted educational grants from Servier, Janssen, Recordati, Aristo, Otsuka, neuraxpharm. All other authors declare no conflict of interest.

Data availability

Data will be made available on request.

Acknowledgments

This work is part of the German multicentre consortium "Neurobiology of Affective Disorders. A translational perspective on brain structure and function", funded by the German Research Foundation (Research Unit FOR2107). We are deeply indebted to all study participants and staff. A list of acknowledgments can be found here: www.for2107.de/acknowledgements

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2023.120349.

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