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Predictive models in psychiatry: State of the art and future directions investigating cortical folding of the brain

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List of contents

Abbreviations

BAC: Balanced Accuracy

CHR: Clinical High Risk for psychosis

ICD: International Classification of Diseases

MRI: Magnetic Resonance Imaging

NNMF: Non-Negative Matrix Factorization

PSC: Patterns of Structural Covariance

SVM: Support Vector Machine

Publication list

Paper I

Sanfelici R.*, Dwyer D.*, Antonucci, L.A., Koutsouleris N. (2020). **Individualized diagnostic and prognostic models for patients with psychosis risk syndromes: a meta-analytic view of the state of the art.** Biological Psychiatry, 88(4): 349-360. *These authors contributed equally.

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Paper II

Sanfelici R., Ruef A., Antonucci LA., Penzel N., Sotiras A., Dong MS., Urquijo-Castro M., Wenzel J., Kambeitz-Ilankovic L., Hettwer MD., Ruhrmann S., Chisholm K., Riecher-Rössler A., Falkai P., Pantelis C., Salokangas RKR., Lencer R., Bertolino A., Kambeitz J., Meisenzahl E., Borgwardt S., Brambilla P., Wood SJ., Upthegrove R., Schultze-Lutter F., Koutsouleris N.*, Dwyer DB.*, and the PRONIA Consortium. (2021). **Novel gyrification networks reveal links with psychiatric risk factors in early illness.** Cerebral Cortex, published online on September 14th 2021. https://doi.org/10.1093/cercor/bhab288. *These authors contributed equally.

ISI Web of Knowledge: Cerebral Cortex

Impact factor 2020: 5.375
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Ranked 68th of 273 neuroscience journals

1. Contribution to the publications

1.1 Contribution to Paper I

In this work we present a systematic review and meta-analysis of diagnostic (i.e., distinguishing CHR from healthy individuals) and prognostic models (prediction of transition to psychosis or functioning) based on machine learning and Cox regression methods. I explored the complex areas of both machine learning and early recognition in psychiatry during my PhD, so that the knowledge I gained on these two topics allowed the production of an informed and informative meta-analysis. For this paper, I conducted an extensive online research of pertinent manuscripts following the PRISMA guidelines[1] using PubMed and Scopus search engines. I thoroughly screened in total 1103 articles following inclusion/exclusion criteria agreed with co-authors. I was responsible for conceptualization of the methodological approach in light of the main aims of our study, i.e.: I) definition of predictive models including not only transition, but also functional outcomes, II) focus on models developed using established machine learning methods, which have a realistic applicability in clinical practice, and III) investigation of models' performance and the potential influence of data modality, algorithm used and validation procedures. I drafted the whole manuscript, was primarily involved in the revision process and finalized the published article.

1.2 Contribution to Paper II

This work has been conducted within the international, large-scale European project PRONIA (www.pronia.eu) carried in 10 European early recognition centres. I worked as a psychologist for the project in the LMU psychiatric clinic— the main coordinating centre of the study. I was directly involved in the recruitment, neuropsychological testing, MRI scanning, interview, evaluation and differential diagnosis of patients with affective and psychosis spectrum disorders. I supervised and conducted follow-up examinations (in total 8 through 3 years for each participant) for around 50 patients and healthy controls. I conducted extensive neuroimaging pipeline testing (CAT12, FreeSurfer) and implementation of MRI quality control techniques in order to establish the most stable methods for brain surface reconstruction both for my project and for the whole consortium. Within a fruitful collaboration with Prof. Sotiras from the USA (Washington University) I learned and implemented a novel multivariate method (e.g., Non-Negative Matrix Factorization[2]) on my sample of study. I executed, under supervision, multiple multi- and univariate analyses on neuroimaging and clinical data from, in total, 1105 individuals from the PRONIA cohort. In parallel, I got

acquainted in the literature on the research field of interest (i.e., gyrifcation in psychiatry), while also collecting evidence on more basic biological mechanisms of cortical folding and disruptions thereof in other neurological pathologies. Furthermore, I was responsible for concepts and hypotheses generation, critical discussion and conclusions driven by the study's results. The manuscript, including tables, figures, supplementary material and full reference list, was entirely written by me and improved thanks to the support of supervisors.

2. Introduction

Psychosis is one of the most burdening psychiatric disorders, as measured by economic loss, morbidity, and mortality worldwide[3]. In the past two decades, the concepts of early recognition, early intervention and precision psychiatry have been introduced to try to detect potential risk pathways and prevent disease development[4]. Cutting-edge methods, such as machine learning, have been of central importance in the enduring attempt to construct personalized prognoses and have led to the development of several risk calculator models. Precision psychiatry needs, however, further basic investigation of potential endophenotypes (i.e., genetic/biological markers of a disease) in order to feed models with informative data for prediction.

To this extent, we present our complementary research based on I) a meta-analysis of the published machine learning-models for prediction in at-risk patients (Paper I), and II) investigation of cortical brain folding, or gyrification, as a potential marker for psychosis development or functional outcome (Appendix) and its broader role in psychopathology (Paper II).

2.1 Early recognition in psychiatry

The Clinical High Risk (CHR) concept describes a clinical condition characterized by sub-threshold psychotic symptoms and cognitive disturbances. This paradigm has facilitated research into the clinical underpinnings of help-seeking individuals potentially at risk for developing psychosis[5]. However, the actual transition rates based solely on the CHR readout have still been particularly low[6,7], suggesting that the symptomatology of risk alone is not able to detect the majority of transitions to the overt disease.

Therefore, research has been trying to discover and understand further biological, clinical and biographical risk factors able to both early detect a predisposition to the disease and also predict its development. For instance, findings have shown that CHR individuals experience more environmental adverse events[8], show hematological alterations[9] and differ from their healthy counterparts in the morphology[10], electrophysiology[11] and resting-state, as well as task-related function of their brain[12]. The complexity of the CHR state calls also for powerful methods, which are able to deal with the high dimensionality of the data at hand and, at the same time, enable a subject-specific risk estimation. To this extent, methodological proceedings have enabled an historical shift of paradigm by introducing machine learning to the field and suggesting a realistic future for personalized predictive psychiatry.

Machine learning is an area of artificial intelligence, which uses advanced algorithms that account for the multivariate structure of large, multimodal datasets (e.g., patients' cognitive, clinical, biological and sociodemographic information) to detect specific patterns, or structure, in the data[13]. Algorithms *learn* these patterns and are tuned to recognize the same structure in new, unseen data, so that models generalize to independent datasets. This multivariate pattern recognition framework can enable both more precise diagnoses (e.g., a classification between psychopathologies or between patients and healthy individuals) and prognoses (e.g., a prediction of disease development or functional outcome). Hence, models constructed with machine learning could be applied in psychiatric care to support clinicians' expertise and help them take critical therapeutic decisions. Research in the past two decades has leveraged the potential of machine learning and has produced a number of predictive models (or risk calculators) for at-risk individuals based on clinical, cognitive, and brain imaging data[14–17] reaching over 80% accuracy. However, still no published model has been applied in real-life clinical practice, mainly because of the still unknown degree of their overall accuracy and reliability.

To clarify the translational potential of the machine learning algorithms, we systematically reviewed and meta-analyzed all available diagnostic and prognostic models for CHR individuals based on machine learning methods (Paper I). Our results showed a relatively good accuracy of models overall and, importantly, a comparable performance between those based on clinical information (e.g., symptoms) and those based on biological information (e.g., brain morphology). Additionally, one important future direction emerging from our study was that further basic research on potential *biomarkers* (i.e., biological signs of risk of disease development) is of central importance to improve models' performance.

One family of biomarkers focuses on structural and functional brain properties, usually analyzed using Magnetic Resonance Imaging (MRI). Structural MRI has already offered the opportunity to detect disruptions in brain volume or density both in first-episode psychosis and at-risk persons[10], and differences between those who develop the disease and those who do not[18]. These findings could be important to promote the use of neurological information as a supplemental diagnostic and prognostic instrument in clinical practice. However, cortical brain volume is known to be influenced by several internal and external confounding factors like drug consumption, antipsychotic medication, plasticity mechanisms or lifestyle characteristics[18,19], potentially shadowing the unique underlying disease effects. As such, more stable measures may be required if predictions from brain MRI measures are to be used in machine learning pipelines.

Gyrification could be such a stable candidate because it is the convolutional property of the human brain cortex, which is known to be mostly genetically driven[20], much less sensitive to external factors and to change during lifetime only slightly[21]. Hence, this morphological measure might be very informative of early neurodevelopmental processes and disruptions thereof, possibly underlying psychiatric diseases or impaired functional outcome. However, further investigation of gyrification is required before it can be used as a potential predictor of disease.

2.2 Gyrification

The cortical folding process is tightly linked to early neurodevelopment because it begins around the third semester of fetal life and peaks at about 2 years post conception[20]. Gyrification is genetically determined[22], and evidence shows that several complex processes play a role in the formation of the individual cortical morphology (e.g., biological and biomechanical forces, as well as anabolic and metabolic processes[23,24]). The importance of these structural cortical differences for human behavior is supported by severe cognitive impairments in gyrencephalic malformations[25] and folding abnormalities in several diseases accompanied by cognitive dysfunctions (e.g., schizophrenia[26], autism[27] or Williams syndrome[28]). The intuitive link between the complexity of the convoluted cortex and cognition has been also validated both in animals (e.g., species with increased gyrification show higher cognitive abilities,[29]) and in humans[30,31].

In mental diseases, gyrification abnormalities have been found in affective and non-affective psychotic syndromes[32,33], depression[34] and even before the first manifestation of psychosis[35]. Some evidence shows that at-risk individuals differ in their gyrification patterns from their healthy counterparts and even that folding aberrations might be predictive of a transition to the overt disease[35]. Nevertheless, results remain inconclusive and inconsistent[36], possibly because of methodological limitations in dealing with a high dimensional data space and the still understudied field of gyrification itself.

One the one hand, traditional statistical methods used to analyze gyrification (e.g., general linear models) are based on assumptions and attempt modelling the data following a-priori hypotheses, thereby potentially overseeing multidimensional and interconnected gyrification patterns. On the other hand, traditional statistics focuses on group-level differences allowing only descriptive conclusions and not testing the single-subject predictive potential of gyrification. Multivariate methods like machine learning enable individual predictions and might be more suited to complex neuroimaging data[13]. The little available

evidence on gyrification-based predictive models shows that cortical folding can predict negative symptoms trajectories[37] and that disorganized folding networks are predictive of psychosis transition in CHR individuals[38]. However, to the best of our knowledge, still no specific investigation of the role of cortical gyrification in prediction of transition to psychosis or of functional outcome based on machine learning exists.

In a first step towards a translational gyrification model, we therefore investigated the hypothesis that gyrification would predict transition or functional outcomes by using machine learning methods in 158 CHR patients (Appendix). Our results showed that gyrification could not predict either outcome category significantly above chance level. These negative findings suggest either I) a further methodological limitation, or II) that cortical folding is not specifically predictive of psychotic episodes, but rather plays a greater role in neurodevelopmental insults influencing psychiatric diseases regardless of diagnostic category.

To disentangle these speculations, we further explored the role of cortical gyrification in psychiatric risk (Paper II) by:

I)   using a novel and advanced statistical method that could address the challenges faced when dealing with high dimensional data that were incompletely addressed with standard gyrification pipelines, and

II)   focusing on transdiagnostic disease processes in order to determine whether gyrification abnormalities crossed diagnostic boundaries to broadly influence functional outcomes (i.e., as opposed to specifically influencing outcomes in a psychosis risk group).

2.3   Methodological proceedings in gyrification research

The high dimensionality of brain gyrification is usually handled with the use of traditional brain atlases based on coarse anatomical characteristics (e.g., borders between folds and gyri[39,40]), whereby the assumption that folding patterns follow observable surface boundaries must not necessarily be met.

One alternative approach is to shift to an investigation of the cortical structural co-variance. The concept of co-variation of structural brain morphology has been widely recognized in the last two decades and expresses the phenomenon of inter-individual cortical differences co-varying with other, topologically distinct, brain regions[41,42]. Structural covariance is highly heritable, relates to behavioral variation in the population, and is thought to reflect coordinated developmental processes[42]. Seed- and network-based analyses or Principal Component Analyses have been the most popular techniques to investigate structural

covariance, yielding important insights into psychopathologies[43–46]. Only few studies have investigated gyrification structural networks in schizophrenia[47,48] and high-risk populations[38], highlighting the potential of this measure of inter-individual variation to better identify the underpinnings of psychiatric endophenotypes. One equally promising approach to investigate covariance has been newly proposed by Sotiras and colleagues[49], who applied Non-Negative Matrix Factorization (NNMF) in order to detect patterns of structural covariance of cortical thickness in a healthy population. NNMF is an unsupervised multivariate technique, which captures a sparse, parts-based representation of the data[2,50]. This method is particularly useful in the neuroimaging context for two main reasons: first, it is able to aggregate variance in a parcellation-like way, while also accounting for the multivariate nature of cortical features; second, NNMF allows subdividing covariance at different resolutions, which reflects the hierarchical and modular organization of the human brain cortex. Sotiras and colleagues[49] demonstrated the importance of cortical thickness-based covariance for the understanding of healthy coordinated cortical development. Investigating gyrification co-variation might shed light on even earlier developmental mechanisms, potentially reflecting the abnormal maturational processes leading to psychopathology. The solutions generated from the analyses could also be further used in machine learning pipelines in the future.

2.4 Transdiagnostic disease processes

In the last decades, psychiatric care has been evolving towards a more process-based, transdiagnostic approach, as opposed to the traditional diagnose-oriented one[51]. On the one hand, the trans-nosological nature of symptoms and comorbidities has been widely recognized; on the other hand, research has been pointing to common genetic, neurobiological, as well as pathophysiological underpinnings of major psychiatric diseases[52–54]. A transdiagnostic framework might be based on dysfunctions shared across diseases (for instance cognitive or functioning disabilities), which, in turn, might be caused by similar insults during early neurodevelopment. A more in-depth understanding of these risk factors might be of great value for the development of both more precise machine learning models, as well as tailored early transdiagnostic interventions[55].

Gyrification might be especially valuable for this challenge because of its neurodevelopmental nature and because folding abnormalities have been found across several disorders[56]. Nevertheless, transdiagnostic gyrification and its link to putative common disease manifestations—especially in the early phases of disease when diagnostic borders are more subtle—are still highly understudied.

Therefore, we aimed first at investigating data-driven structural covariance patterns of cortical gyrification in a healthy population (N=318) using NNMF, in order to overcome potential methodological limitations in the field. Further, we used a large clinical sample including individuals with a first episode of psychosis, a first episode of depression, and CHR (N=713) to investigate how patterns of gyrification are expressed in psychopathology, and whether they relate to similarities or differences between patients (Paper II). We found that patients' gyrification differed from that of healthy individuals, and that patterns were highly comparable across diagnostic categories. Furthermore, folding abnormalities were linked to commonly disrupted psychological mechanisms such as cognition and global functioning, and not to disease-specific symptoms.

Our results support the hypothesis of neurodevelopmental insults affecting the folding of the cerebral cortex and leading to psychopathological manifestations shared by typically distinct diagnostic categories. This transdiagnostic nature and the lack of associations between gyrification and specific symptoms suggests that gyrification abnormalities might be too unspecific to signal the manifestation of a psychotic episode or functional outcomes after one year, and thus might not be predictive when integrated in machine learning models, as we found in our analyses (Appendix). In fact, psychosis might be caused by more complex interactions of events, including a range of environmental factors[48], that are not captured by cortical folding. Nevertheless, gyrification might add important information within multivariate predictive models (Paper I) by expressing early insults on a neurobiological level, which signal common features of mental illness such as cognitive or functioning impairments—as we demonstrated in our study (Paper II).

In order to successfully build diagnostic and prognostic models, which can be integrated in psychiatric clinical practice, research must thus necessarily further pursue the challenge of understanding the neurobiological mechanisms leading to pathology. A deeper investigation of biomarkers linked to very early neurodevelopmental processes such as gyrification might be very useful to shed light on transdiagnostic features underlying psychiatric diseases and hence contribute to a broader conceptualization of risk in psychiatry.

3.   Zusammenfassung:

Das Psychoserisikosyndrom ermöglicht die Untersuchung phänotypischer und mechanistischer Faktoren, die das Risiko junger Menschen beeinflussen eine Psychose zu entwickeln - eine der belastendsten psychiatrischen Erkrankungen weltweit[3]. Die Erforschung von Biomarkern spielt in der Früherkennung von Psychosen eine große Rolle[58]. Biomarker sind biologische/physiologische oder klinische Variablen, die das Risiko eines möglichen Übergangs von einem Psychose-Risiko-Syndrom in eine manifeste Psychose reflektieren oder z.B. mit Änderungen des Funktionsniveaus assoziiert sind. Mit Hilfe von Biomarkern und fortschrittlichen statistischen Methoden, wie Maschinellem Lernen (machine learning)[13], konnten zahlreiche multivariate diagnostische und prädiktive Modelle entwickelt werden, die in Zukunft den klinischen Alltag mittels personalisierter Vorhersagen effizienter gestalten könnten. Um machine learning-Modelle auf die psychiatrische Versorgung zu übertragen, müssen jedoch zwei entscheidende Forschungszweige parallel verfolgt werden: I) Nachweis der Wirksamkeit, Zuverlässigkeit und Replizierbarkeit bestehender prädiktiver Modelle und II) die Suche nach weiteren aussagekräftigen Biomarkern, die in der personalisierten Psychiatrie eingesetzt werden können.

In der vorliegenden Arbeit stellen wir uns dieser Herausforderung, indem wir I) eine systematische Review und Meta-Analyse veröffentlichter diagnostischer und prognostischer Modelle für Psychoserisikosyndrome durchführen (Paper I), II) die Rolle der Hirngyrifizierung als potentiellen Biomarker für Risikopersonen untersuchen (Appendix) und III) die Bedeutung der Gyrifizierung im weiteren Rahmen psychiatrischer Erkrankungen und deren Risiko erforschen (Paper II).

Unsere systematische Review zeigte, dass machine learning-basierte diagnostische und prognostische Modelle für Risikopersonen grundsätzlich eine gute Genauigkeit (67-78% Sensitivität und 77-78% Spezifität) zeigen, unabhängig von den verwendeten Datenmodalitäten oder dem gewählten Algorithmus. Hohe Heterogenität in den Studien und ein Publikationsbias könnten jedoch unsere Ergebnisse beeinflusst haben, so dass eine eindeutige Schlussfolgerung schwer zu ziehen ist.

Um die Rolle der Hirngyrifizierung als möglichen Biomarker in Hochrisikopatienten zu untersuchen, entwickelten wir machine learning Modelle zur Prädiktion des Funktionsniveaus einerseits und der Transition in eine klinisch manifeste Psychose andererseits, welche Ergebnisse knapp über dem Zufallsniveau erreichten (max. ausgeglichene Genauigkeit 53,4%). Dies deutet darauf hin, dass die Rolle der Gyrifizierung nicht spezifisch für das Psychoserisiko ist, sondern mit neurologischen Entwicklungsprozessen

zusammenhängen könnte, die ein breiteres Spektrum psychiatrischer Erkrankungen betreffen.

Um diese Hypothese zu untersuchen, analysierten wir die strukturelle Kovarianz der Gyrifizierung in einer großen transdiagnostischen Patientenpopulation, bestehend aus Patienten mit einer ersten psychotischen Episode, depressiven Patienten und Hochrisikopatienten, im Vergleich mit einer gesunden Kontrollpopulation. Hierbei zeigte sich eine reduzierte Gyrifizierung in der Patientenpopulation, welche mit entwicklungsbedingten Risikofaktoren (Neurokognition und Funktionsfähigkeit) assoziiert war, jedoch nicht mit dem Schweregrad der Symptome korrelierte. Diese Faltungsanomalien könnten somit das Korrelat früher fehlerhafter neuronaler Entwicklungsprozesse sein, die die Vulnerabilität für psychiatrische Erkrankungen erhöhen.

Wie unsere Ergebnisse zeigen, ist der Weg zu belastbaren prognostischen Modellen in der psychiatrischen Diagnostik noch lang und erfordert weitere Grundlagenforschung. Hirnmorphologische Maße wie die Gyrifizierung können ein besseres Verständnis entscheidender Mechanismen neuronaler Entwicklungsprozesse ermöglichen, die einem breiten Spektrum psychiatrischer Erkrankungen zu Grunde liegen.

4. Abstract (English):

The Clinical High Risk (CHR) has enabled research into phenotypic and mechanistic factors highlighting the potential risk for young individuals to develop psychosis—one of the most burdening psychiatric conditions worldwide[3]. Detection of risk for psychosis has been supported by so-called biomarkers, i.e., biological readouts of risk, which could potentially signal a transition to the overt disease or negative functional outcomes[58]. Several multivariate diagnostic or predictive models based on biomarkers have been developed using advanced methods like machine learning[13], producing personalized predictions, which could support everyday clinical decisions. However, in order to translate machine learning models to psychiatric care, two crucial research directions need to be followed in parallel to: I) prove the efficacy, reliability and replicability of existing predictive models, and II) further investigate particularly meaningful biomarkers which can be employed in personalized psychiatry. In the presented work, we pursued this challenge by: I) Conducting a systematic review and meta-analysis of published diagnostic and prognostic models for CHR (Paper I); II) Investigating the potential role of brain gyrification as a biomarker for at-risk individuals (Appendix); and III) Further exploring the significance of gyrification in extended psychiatric etiology and risk (Paper II).

In the meta-analysis, we discovered that machine learning- models for CHR individuals showed relatively good accuracy (67-78% sensitivity and 77-78% specificity) and all models worked equally well, irrespective of data analyzed or algorithm chosen. High heterogeneity throughout studies and a publication bias could have affected our results, so that we could not draw definite conclusions.

Machine learning models constructed on gyrification in at-risk individuals could predict functional outcome or transition to psychosis only slightly above chance level (max. balanced accuracy 53.4%). These results suggested that the role of gyrification in risk might not necessarily be specific, but rather linked to neurodevelopmental processes affecting a wider range of psychiatric diseases (i.e., transdiagnostically).

To investigate the transdiagnostic neurodevelopmental hypothesis, we analyzed gyrification structural covariance in a large transdiagnostic population of first episode psychosis and depression and CHR individuals. Our results revealed reduced gyrification in patients compared to healthy controls, which was associated with developmentally mediated risk factors (i.e., neurocognition and functioning), but not current symptoms. Hence, these cortical folding abnormalities might reflect early neurodevelopmental insults that increase individuals' vulnerability to psychiatric disorders.

Taken together, the road to usable prognostic models for psychiatry is still long and requires further basic research. Brain morphological measures such as gyrification might facilitate a better understanding of crucial neurodevelopmental mechanisms potentially influencing a broader spectrum of psychiatric diseases.

5. Paper I

Individualized diagnostic and prognostic models for patients with psychosis risk syndromes: A meta-analytic view on the state of the art.

Psychosis risk syndromes have been extensively investigated in the past two decades with the aim of predicting and possibly preventing transition to the overt disorder in help-seeking individuals. Novel statistical methods like machine learning and Cox proportional hazard regression have been crucial to develop personalized models able to diagnose risk for psychosis and predict a future outcome in these individuals based on different data modalities (e.g., neurocognitive or neuromorphological characteristics). However, despite their great potential, these models have still not been translated into clinical practice.

To shed light on the current state of published machine learning- and Cox regression-based diagnostic and prognostic models, we thoroughly reviewed the literature and conducted a meta-analysis on accuracy performances. We investigated different methodological approaches and data modalities, specifically focusing on performance differences between clinical (i.e., based on symptoms, cognition and environmental factors) and biological models (i.e., constructed on brain morphology and function).

We selected 44 articles, including in total 3707 individuals for prognostic and 1052 for diagnostic studies. Psychosis risk syndromes could be relatively accurate diagnosed (78% sensitivity and 77% specificity), while prognostic models reached overall a sensitivity and specificity of 67% and 78%, respectively. Machine learning models gained a 10% higher sensitivity compared to those using Cox regression, however validation techniques also vastly differed between the two approaches. These results were not moderated by the type of data modality, the algorithm used, or the at-risk population studied. Importantly, we detected a publication bias for prognostic studies, which points to inflated results reported by studies with smaller sample sizes.

Our results showed comparable performance between clinical and biological models, which calls for improvement in basic research on brain markers of disease. Further, findings may be affected by I) heterogeneity in the field, including definitions of clinical populations, data domains and machine learning algorithms used, and II) degree of methodological validity, reliability and generalizability. These factors might hinder the translation of diagnostic and prognostic models to clinical practice and need to be thoroughly taken into consideration in future research.

6. Paper II

Novel gyrification networks reveal links with psychiatric risk factors in early illness

Evidence of altered gyrification has been found in clinical populations diagnosed with schizophrenia, depression, and psychosis risk states. Such findings may reflect a developmental-related, transdiagnostic, signature, but this hypothesis has not been investigated yet and existing studies may be methodologically limited.

Thus, we aimed to derive gyrification-specific covariance maps in order to investigate associations with symptoms, cognition, and functioning in a sample of individuals in early illness stages. A recently introduced, data-driven method, Orthogonal Projective Non-Negative Matrix Factorization, delineated gyrification-based Patterns of Structural Covariance (PSC) in 308 healthy controls. The PSC-map was applied to a sample of patients with recent onset psychosis or depression, and clinical high-risk for psychosis (N=713). Gyrification differences compared to controls were determined, and associations with diagnosis, symptoms, cognition, and functioning were investigated using linear models.

We detected 18 PSCs in controls, the majority of which were externally validated in an independent healthy sample (N=84). PSCs differed between patients and controls in temporal-insular, lateral occipital, and lateral fronto-parietal areas ($p^{FDR}<0.01$). Gyrification abnormalities were observable in high-risk, psychotic, and early depression patients. Altered cortical folding demonstrated associations with cognitive domains and role functioning, but not with symptomatology.

Our findings highlight a sparse representation of cortical gyrification in controls, which is altered in early psychiatric illnesses and high-risk individuals and is not associated with symptom severity. A neurodevelopmentally-linked signature was suggested by relationships with cognition and lifetime role functioning. Further studies are required to delineate how and to what extent gyrification might add important information within predictive models by expressing early insults at a neurobiological level, which signal common features of mental illness.

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Appendix: Gyrification-based predictive models

Methods

A total of 158 CHR individuals (mean age: 23.87, SD: 5.43; 49.4% females) were recruited as part of the PRONIA consortium (see Supplementary Material of Paper II for further information). Twenty-three patients transitioned to psychosis after one year (Table 1).

Table 1. Basic demographic information of the study sample.

N	158
Age [years, mean] (SD)	23.87 (5.43)
Sex [females, N] (%)	78 (49.4)
Psychosis Transition [N] (%)	23 (14.6)
GF-R Baseline [mean] (SD)	6.0 (1.59)
1year Follow-up	6.55 (1.74)
GF-S Baseline [mean] (SD)	6.34 (1.44)
1year Follow-up	6.89 (1.44)

Abbreviations: GF: Global Functioning Role (R) or Social (S), [0:10],higher scores indicate better functioning.

Cortical surfaces were reconstructed from structural MRI images using the FreeSurfer software package (v. 6.0.0, https://surfer.nmr.mgh.harvard.edu/). Local gyrification Index (LGI)[59] was calculated across the whole cortical mesh (Supplementary Material of Paper II).

We built supervised machine learning models based on a Support Vector Machine algorithm using the in-house software NeuroMiner (http://proniapredictors.eu/neurominer/), which ensures a strict validation procedure through a nested cross-validation design[15]. Models were trained and tested to I) predict transition at follow-up (i.e., one year after study inclusion), and II) predict role and social functioning outcome at follow-up using the Global Functioning scale at a cut-off of 7 (GF:R and GF:S[60])[14]. As part of the machine learning pipeline, patients' gyrification meshes underwent preprocessing steps as follows: 1) age and sex correction using partial correlation analysis, 2) site correction thresholding for between-scanner voxel reliability[14] at the 25%, 50%

and 75% percentile, 3) dimensionality reduction using Principal Component Analysis (PCA; 10, 20, 40, 80 and 160 eigenvariates) and 4) standardization using median and winsorization. We used a linear, non-kernelized L2-regularized, L1-loss SVM algorithm and employed wrapper-based feature selection strategies to extract the most predictive features among the large gyrification mesh. Model optimization included hyperparameter combination (i.e., map percentile thresholds, PCA dimensions and SVM's *C* regularization parameter range of $2^{[-4 \underset{\in \mathbb{Z}}{\rightarrow} +4]}$) across all *k*=50 (=5 repetitions × 10 folds) available models in the training partition. The wrapper-based feature selection strategy was based on a greedy sequential forward search (SFS) at each SVM *C* regularization parameter, stopping when 80% of the features had been selected. Models' effectiveness was calculated based on the Balanced Accuracy (BAC) resulting from the test partition. Machine learning pipeline is represented in Figure 1.
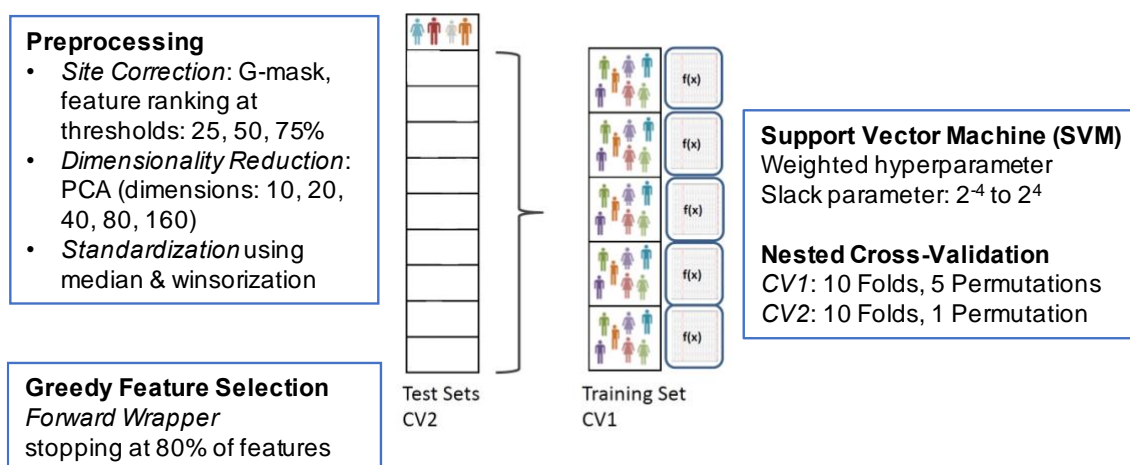
Figure 1. Machine learning pipeline in NeuroMiner.

Results

The SVM algorithm could not predict a transition to psychosis above chance based on gyrification patterns (BAC: 45.9%, sensitivity: 38.5% specificity: 53.3%) and the classification didn't reach statistical significance (Wilcoxon test Z=-1.60, p=.11). Similar results were found for prediction of functional outcome at 1 year follow-up, both for the social subscale (BAC: 50.0%, Z=-0.3, p=0.76) and the role subscale (BAC: 53.6, Z=0.3, p=0.73). Results are summarized in Table 2:

Table 2. Machine learning results

	Transition	GF:S follow-up	GF:R follow-up
Balanced accuracy [%]	45.9	50.0	53.6
Sensitivity [%]	38.5	50.0	55.6
Specificity [%]	53.3	50.0	51.7
Positive predictive value [%]	6.8	34.7	63.3
Negative predictive value [%]	90.6	65.3	43.7

Abbreviations: GF: Global Functioning Role (R) or Social (S), [0:10],higher scores indicate better functioning. Positive and negative predictive value were calculated in NeuroMiner from the initial true/false positive and true/false negative matrix.

Conclusion

Gyrification patterns in CHR individuals were not informative of a future transition to the overt disease, nor they could predict functional outcome after one year. These negative findings suggest that gyrification might be influenced both by early neurodevelopmental factors and by re-wiring processes during adolescence, which might be detectable throughout several psychiatric diseases, rather than in samples of at-risk subjects wherein the etiology and ultimate prognosis is unknown.

In order to better investigate differences in cortical folding and address the role of gyrification as neuroanatomical biomarker for psychosis, future research should focus further on transdiagnostic psychiatric populations in the early stages of disease. The high complexity of this cortical measure also calls for more advanced multivariate statistical approaches, which might be able to better capture subtler morphological patterns. We tackled this challenge by using cutting-edge methods to extract structural covariance at the neuroanatomical level, as well as by investigating larger and more heterogenous psychiatric samples at early disease stages (Paper II).

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