Schizophrenia Bulletin vol. 47 no. 1 pp. 249–258, 2021
doi:10.1093/schbul/sbaa094
Advance Access publication 7 July 2020

The Psychopathology and Neuroanatomical Markers of Depression in Early Psychosis

Rachel Upthegrove*[,1], Paris Lalousis[1], Pavan Mallikarjun[1], Katharine Chisholm[1,2], Sian Lowri Griffiths[1], Mariam Iqbal[1], Mirabel Pelton[1], Renate Reniers[1,3], Alexandra Stainton[4,5], Marlene Rosen[6], Anne Ruef[6], Dominic B. Dwyer[6], Marian Surman[7], Theresa Haidl[8], Nora Penzel[8], Lana Kambeitz-llankovic[6,8], Alessandro Bertolino[9], Paolo Brambilla[10,11], Stefan Borgwardt[12], Joseph Kambeitz[8], Rebekka Lencer[7,13], Christos Pantelis[14], Stephan Ruhrmann[8], Frauke Schultze-Lutter[15], Raimo K. R. Salokangas[16], Eva Meisenzahl[15], Stephen J. Wood[†,1,4,5], Nikolaos Koutsouleris[†,6], and the PRONIA Consortium[‡]

[1]Institute for Mental Health and Centre for Human Brain Health, University of Birmingham, Birmingham, UK; [2]Department of Psychology, Aston University, Birmingham, UK; [3]Institute of Clinical Sciences, University of Birmingham, Birmingham, UK; [4]Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne, Australia; [5]Centre for Youth Mental Health, University of Melbourne, Parkville, Australia; [6]Department of Psychiatry and Psychotherapy, Ludwig Maximilian University, Munich, Germany; [7]Department of Mental Health, University of Münster, Münster, Germany; [8]Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital, University of Cologne, Cologne, Germany; [9]Department of Basic Medical Science, Neuroscience and Sense Organs, University of Bari "Aldo Moro," Bari, Italy; [10]Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [11]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [12]Department of Psychiatry (Psychiatric University Hospital, UPK), University of Basel, Basel, Switzerland; [13]Department of Psychiatry and Psychotherapy, University Lübeck, Germany; [14]Melbourne Neuropsychiatry Centre, University of Melbourne and Melbourne Health, Melbourne, Australia; [15]Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany; [16]Department of Psychiatry, University of Turku, Turku, Finland

*To whom correspondence should be addressed; Institute for Mental Health, University of Birmingham, 52 Prichatts Road, Edgbaston, Birmingham B152TT, UK; tel: +44-(0)121-414-4932, fax:+44-(0)121-414-4897, e-mail: r.upthegrove@bham.ac.uk
[†]These authors are joint senior authors.
[‡]See full author list of the PRONIA Consortium above References section.

Depression frequently occurs in first-episode psychosis (FEP) and predicts longer-term negative outcomes. It is possible that this depression is seen primarily in a distinct subgroup, which if identified could allow targeted treatments. We hypothesize that patients with recent-onset psychosis (ROP) and comorbid depression would be identifiable by symptoms and neuroanatomical features similar to those seen in recent-onset depression (ROD). Data were extracted from the multisite PRONIA study: 154 ROP patients (FEP within 3 months of treatment onset), of whom 83 were depressed (ROP+D) and 71 who were not depressed (ROP−D), 146 ROD patients, and 265 healthy controls (HC). Analyses included a (1) principal component analysis that established the similar symptom structure of depression in ROD and ROP+D, (2) supervised machine learning (ML) classification with repeated nested cross-validation based on depressive symptoms separating ROD vs ROP+D, which achieved a balanced accuracy (BAC) of 51%, and (3) neuroanatomical ML-based classification, using regions of interest generated from ROD subjects, which identified BAC of 50% (no better than chance) for separation of ROP+D vs ROP−D. We conclude that depression at a symptom level is broadly similar with or without psychosis status in recent-onset disorders; however, this is not driven by a separable depressed subgroup in FEP. Depression may be intrinsic to early stages of psychotic disorder, and thus treating depression could produce widespread benefit.

Key words: schizophrenia/psychosis/depression/gray matter volume/psychopathology/machine learning

Introduction

Depression is a common comorbidity in schizophrenia, is seen most frequently in the early stages of psychosis, and has long-term negative consequences on functional recovery, quality of life, and suicidal behaviour.[1–5] Greater understanding of the symptom profile and neuroanatomical associations of depression in early psychosis may inform novel treatment targets that could prevent depression-related poor longer-term outcomes. Evidence to date demonstrates a relationship between depression and the duration of untreated psychosis and

the cognitive appraisal of positive symptoms with core depressive symptoms of loss and hopelessness.[6,7] Rather than being seen as a co-morbidity, depression may be viewed as intrinsic to psychosis, given its frequency in early stages, close relationship to psychotic symptoms and importance in predicting poor outcomes. In early stages of psychosis affective dysfunction may provide the fire of later 'burnt out' disorder.[11]

Recent evidence suggests that striatal and thalamic structural differences and related functional dysconnectivity may be key brain changes able to discriminate schizophrenia from affective disorders.[8–10] We have previously shown that structural magnetic resonance imaging (sMRI) is able to separate schizophrenia from depression with a moderate degree of accuracy; however, evidence also shows that, in early stages of psychotic disorders, the discrimination between schizophrenia and affective disorders is much more challenging.[11,12] Distinction of a depressed subgroup at earlier stages of developing psychotic disorders, if possible, may offer opportunities for developing and informing specific targeted treatment.

There is some evidence to suggest that it may be possible to identify the neuroanatomical structure of a subgroup of patients with depression in first-episode psychosis (FEP); eg, Salokangas et al[13] previously showed that patients with FEP and depression have larger ventricular and posterior sulcal cerebrospinal fluid volumes compared to FEP patients without depression. Calvo et al[14] reviewed 14 sMRI studies in FEP and reported volume loss in the frontotemporal and anterior cingulate in both affective and nonaffective psychosis, but insula and hippocampal reductions were seen only in nonaffective groups. During the early stages of psychosis, when depression is more prominent, active illness processes are ongoing, and disease trajectories are emerging, it may be more challenging but also more important to identify depression-specific related brain changes.[11,15] Machine learning (ML) and large samples may be useful in the investigation of co-morbid groups in early stages of illness when heterogeneity is significant, as they have potential to identify structure in complex data.

In this study, we aimed to use relatively large samples with first-episode, recent onset disorder to address whether the delineation of a specific subgroup of psychosis patients with comorbid depression is possible. We hypothesize that depression in recent-onset psychosis (ROP) is a distinct comorbidity and that (1) there would be a similar symptom structure of depression in ROP as seen in recent-onset depression (ROD) and (2) brain regions identified as significantly different in ROD subjects compared to healthy controls (HC) would be able to distinguish ROP participants with and without depression.

Method

We used a principal components analysis (PCA) and then supervised ML to examine the structure of depression symptoms and whether it was possible to accurately classify patients in ROD and ROP with depression (ROP+D) groups by symptom profile. We then tested the ability of sMRI data with regions of interest derived from ROD patients to classify ROP+D vs. ROP without depression (ROP−D) patients.

Sample

The total sample of 565 participants included 146 with ROD, 154 with ROP (minimally treated FEP), and 265 HC. Data were collected following the standardized recruitment and assessment protocol from the Personalised pROgNostic tools for early psychosIs mAnagement (PRONIA; https://www.pronia.eu) study across 7 European sites: Munich, Basel, Milan, Cologne, Birmingham, Turku, and Udine.

All adult participants provided their written informed consent prior to study inclusion. Minor participants (defined at all sites as those younger than 18 years) provided written informed assent and, their guardians, written informed consent. The study was registered at the German Clinical Trials Register (DRKS00005042) and approved by the local research ethics committees in each location.

See Koutsouleris et al for full methodology[16] and supplementary figure 1; however, in brief, participants were recruited from community and inpatient services. General inclusion criteria were: (1) age between 15 and 40 years, (2) sufficient language skills for participation, (3) capacity to provide informed consent/assent. General exclusion criteria were: an IQ below 70, current or past head trauma with loss of consciousness (>5 min), current or past known neurological or somatic disorders potentially affecting the structure or functioning of the brain, current or past alcohol dependence, polysubstance dependence within the past 6 months, and any medical indication against MRI.

ROP participants had to meet criteria for a first episode of affective or nonaffective psychotic episode as established by the Structured Clinical Interview for DSM-IV-TR (SCID)[17] or transition criteria defined by Yung et al[18] and be within 3 months of onset of first treatment with antipsychotic medication. Specific ROP exclusion criteria were: onset of psychosis exceeding the past 24 months and antipsychotic medication exceeding 90 days (cumulative in the past 24 months) with a daily dose rate at or above minimum dosage of the "First-Episode Psychosis" range of German Society for Psychiatry, Psychotherapy, and Nervous Diseases (DGPPN) S2 guidelines, with equivalency to 5 mg olanzapine.[19]

ROD patients had to meet criteria for major depression fulfilled within the past 3 months as established by the SCID. Specific ROD exclusion criteria were previous episode of DSM-IV-TR major depression prior to the

current or recent episode, duration of the current episode exceeding 24 months, or antipsychotic medication exceeding 30 days as defined above.

Participants were also excluded from ROD or ROP group if they met specific Clinical High Risk (CHR) criteria, including the presence of attenuated psychotic symptoms, brief intermittent psychotic symptoms, or a genetic risk with functional deterioration, and basic symptom criteria as previously published[16] (see supplementary table 1 for full details).

HC exclusion criteria were: any current or past DSM-IV axis I or II disorder; CHR status as defined above; a positive familial history (first-degree relatives) for affective or nonaffective psychoses; and intake of psychotropic medications more than 5 times/year and in the month before study inclusion.

Assessments

Data for the present analysis includes cross-sectional baseline data; demographic and clinical data information (age, gender, medication exposure, and cannabis use), SCID diagnosis,[17] Beck Depression Inventory-II (BDI-II),[20] Positive and Negative Symptom Scale (PANSS),[21] and sMRI.

All participants completed a neuroimaging procedure that included sMRI. In keeping with real-world scanner heterogeneity, and as part of the wider PRONIA objectives, a minimal harmonization protocol was used that required the PRONIA sites to (1) acquire isotropic or nearly isotropic voxel sizes of preferably 1 mm resolution, (2) set the Field of View (FOV) parameters accordingly to guarantee the full 3D coverage of the brain, including all parts of the cerebellum, and (3) define the relaxation time (TR) and echo time (TE), as well as other imaging parameters in a way that would maximize the contrast between cortical ribbon and the white matter (WM) and enhance the signal-to-noise ratio in the images. Supplementary table 2 lists the scanner and parameter details of the structural MR sequences used to examine the PRONIA sample participants. See previous PRONIA report Koutsouleris et al[17] for full MRI harmonization and data acquisition parameters.

Analysis

Demographic, study group-related, and symptom (mean BDI-II, PANSS positive and negative, medication, and cannabis use) data were explored and presented across ROP, ROD, and HC study groups. ROP participants were grouped into those with (ROP+D) and without (ROP−D) depression by current SCID secondary diagnosis of moderate or severe depressive disorder and a current BDI-II of >20 in keeping with previous literature and cutoff scores.[20] PCA with orthogonal (varimax) rotation was completed on the 21 BDI-II items separately in the ROD and ROP+D groups to explore the factor structure of symptoms.

Then, we used our open-source software NeuroMiner (https://github.com/neurominer-git) to train and cross-validate a model to discriminate the ROD from ROP+D using individual symptom items from BDI-II. Repeated nested cross-validation (rNCV) was used with 10 outer CV2 permutations, 10 outer CV2 folds, 10 inner CV1 permutations, and 10 inner CV1 folds. See supplementary material for further details. All features were scaled from 0 to 1 and missing values were imputed using the Euclidean distance-based nearest-neighbor search method (median of 7 nearest neighbors). Age, gender, cannabis use (heavy recent as defined on SCID diagnostic interview), and medication (olanzapine equivalent total exposure and selective serotonin reuptake inhibitor (SSRI) equivalent total exposure) were entered as covariates; see supplementary material for further details. We imputed missing values for medication status with linear interpolation and series median replacement in 26 (19.2%) subjects. We used Support Vector Machines (SVMs)[22] with a linear kernel, which optimizes across a regularization hyperparameter range of and 11 learning parameters in order to optimize the C value. The criterion used for hyperparameter optimization was mean Prognostic Summary Index (PSI) regularized by SVM model complexity. We reported the performance of classification of ROD and ROP+D groups with sensitivity, specificity, balanced accuracy (BAC), and area-under-the-receiver-operator curve (AUC) and visualized which features were used in the classification model. For the visualization of the feature weights, a permutation analysis was performed to create a null distribution of weights for each feature. The observed weights were compared to this distribution.[23] For sMRI data, see our previously published study[16] for full preprocessing details.

However, in brief, all images were visually inspected, automatically defaced, and anonymized using a Freesurfer-based script prior to data centralization. Then, the open-source CAT12 toolbox (version r1155; http://dbm.neuro.uni-jena.de/cat12/), an extension of SPM12 (http://www.fil.ion.ucl.ac.uk/spm), was used to segment images into gray matter (GM), WM, and cerebrospinal fluid maps and then to high-dimensionally register to the stereotactic space of the Montreal Neurological Institute (MNI-152 space). CAT12 toolbox was used with processing steps consisting of spatial filtering, segmentation, segmentation estimation, a local adaptive segmentation step, which adjusts the images for WM homogeneities and varying GM intensities, and a high-dimensional DARTEL registration of the image to an MNI template in the IXI database (http://www.braindevelopment.org).

Whole-brain voxel-based morphometry (VBM) analysis was conducted using a 2-sample *t*-test in SPM12 between ROD participants and HC to generate regions

of interest (ROI) using a cluster-level height threshold of $P < .05$, corrected with false discovery rate, with age, gender, antidepressant treatment (SSRI equivalent total exposure), cannabis use, and total intracranial volume entered as covariates. Data on cannabis use were missing from 3 subjects (1 HC and 2 ROD), which were excluded from this analysis. We used the unique PRONIA ROD group to generate ROIs for ML classification rather than existing literature as previous studies may be limited by being largely conducted in older subjects with recurrent depressive disorder, and our imaging procedures and parameters were the same across groups.

We extracted the mean raw intensity values of the ROIs that were significant using MarsBar 0.41 (http://marsbar.sourceforge.net/) and then inputted those values as features in an SVM model developed with Neurominer, using the same permutations and cross-validation procedures with age, gender, antidepressant treatment (SSRI equivalent total exposure), antipsychotic treatment (olanzapine equivalent total exposure), cannabis use, and total intracranial volume entered as covariates, in order to test their ability in the classification of ROP groups with and without depression (ROP+D and ROP−D). We additionally conducted a number of exploratory VBM analysis (see supplementary material) exploring ROP+D vs ROP−D.

Results

The mean age of the full sample was 24 years, and 46% were male. The ROP group ($n = 154$) had a majority diagnosis of schizophrenia spectrum psychosis ($n = 123/154$; 80%). Eighty-three (54%) fulfilled the ROP+D criteria. Positive symptoms were comparable in ROP patients with and without depression ($P = .72$; see table 1 for details). The mean BDI score in the ROP+D group was 27.72 (SD = 12.2), which was higher, but not significantly, than the ROD group mean 26.40 (SD = 13.9). See table 1 for further details and supplementary table 3 for the detailed diagnostic breakdown.

PCA of Depression Symptoms

The underlying structure of BDI-II items was determined by evaluating its principal components in terms of factors and the percentage of variance accounted for in each factor. In the ROD group, 4 factors were extracted accounting for 62% of the total variance in depression. Past failure, guilt, self-dislike, self-criticism, and worthlessness were significantly weighted in the first factor. In the ROP+D group, 56% of the cumulative variance was identified in 4 factors with a similar cluster of past failure, guilt, self-dislike, self-criticism, and worthlessness, with the addition of punishment and loss of interest significant in the first factor (see table 2).

ML Classifications

Classification by ML of ROP+D vs ROD groups using only the BDI-II items showed a sensitivity of 76.7%, specificity of 26.3%, BAC of 51.5%, and AUC of 0.54. Punishment and concentration difficulties weighted toward ROP, whereas sadness and worthlessness weighted toward ROD (see figure 1).

Whole-brain VBM analysis of ROD patients compared to HC identified significant differences in 4 GMV clusters

Table 1. Clinical and demographic sample details

Group	HC	ROD	ROP	ROP+D	ROP−D	ANOVA
Number	265	146	154	83	71	
Age mean (SD)	25.05 (6.5)	25.60 (6.2)	24.78(5.4)	24.57 (4.6)	25.42 (6.5)	2297 = 2.17 ($P = .12$)
Sex *n* (%) male	105 (40%)	67 (46%)	94 (61%)	53 (63%)	41 (57%)	22.11 (df 4; $P = .01$)[a]
Cannabis misuse *n* (%)	3 (1%)	17 (9%)	49 (31%)	23 (27%)	26 (38%)	1.4 (df 1.0; $P = .23$)[b]
SSRI *n* (%)/mean exposure[e]	—	118 (72%) 3357 mg	64 (41%) 2301 mg	40 (48%) 3433 mg	24 (35%) 899 mg	$F(5,617) = 9.58$, $P = .98$[c]
Antipsychotic *n* (%)/mean exposure[e]	—	29 (20%) 20 mg	137 (89%) 534 mg	74(89%) 661 mg	63 (89%) 341 mg	$F(1,144) = 01.13$, $P = .28$[d]
PANSS positive mean (SD)	—	—	17.95 (1.2)	17.80 (5.8)	17.56 (6.9)	$F(1,144) = 0.13$, $P = .72$[d]
PANSS negative mean (SD)	—	—	16.57 (7.9)	17.65 (8.5)	15.22 (6.9)	$F(91,144) = 3.45$, $P = .06$[d]
BDI-II mean (SD)	—	26.40 (13.9)	21.47 (12.6)	27.72 (12.2)	12.84 (9.4)	$F(1,201) = 0.20$, $P = .65$[c]

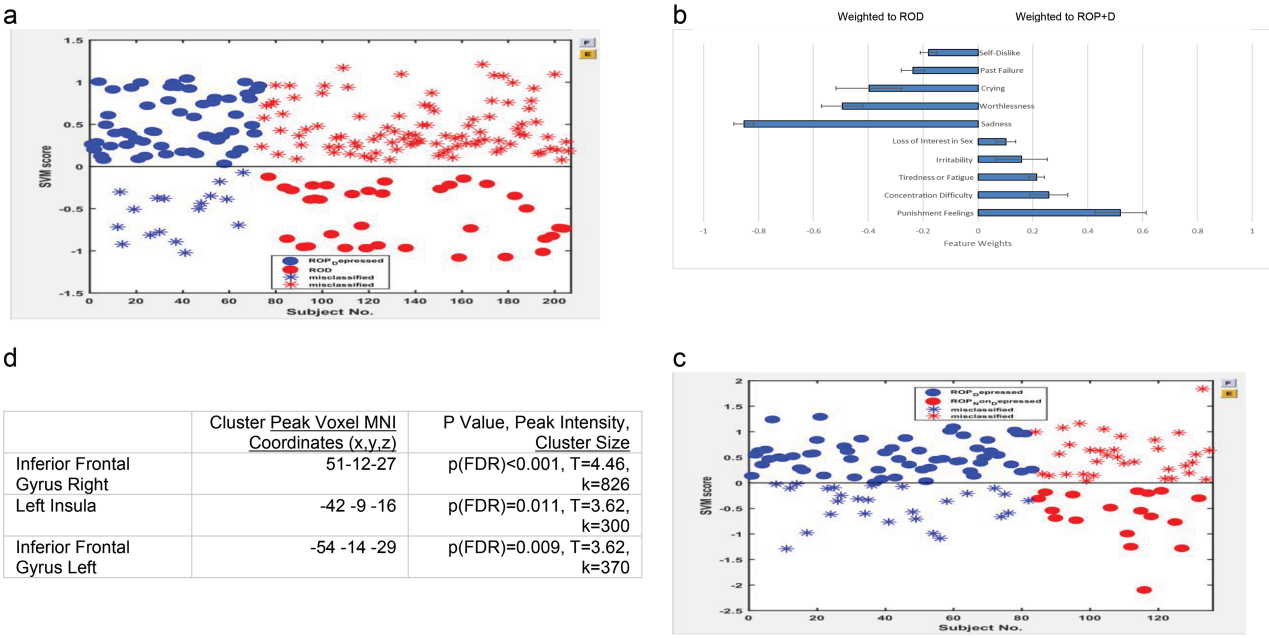
Note: HC, healthy controls; ROD, recent onset depression; ROP+D, recent onset psychosis with depression; ROP−D, recent onset psychosis without depression; PANSS, Positive and Negative Symptom Scale; BDI-II, Beck Depression Inventory-II.
[a]Chi-sq ROD; ROP.
[b]Chi-sq ROP+D/ROP−D.
[c]ANOVA comparing, ROD and ROP+D groups.
[d]ANOVA comparing ROP+D and ROP−D group mean.
[e]Lifetime exposure SSRI/Olanzapine equivalent to baseline assessment.

Table 2. Principle components analysis of BDI-II items in ROD and ROP+D groups: summary of factor loadings

ROD	Negative self-evaluation	Depressive cognition	Physical symptoms	Other symptoms
Eigenvalue (% explained)	8.89 (42.33)	1.88 (8.89)	1.22 (5.79)	1.03 (4.92)
Rotation sums of loading % variance	20%	17%	12%	11%
BDI-II Item				
3. Past failure	0.82*	0.20	0.181	0.14
5. Guilt	0.79*	0.13	0.17	0.04
8. Self-criticism	0.77*	0.13	0.25	0.16
7. Self-dislike	0.74*	0.19	0.20	0.12
14. Worthlessness	0.74*	0.35	0.20	0.08
2. Pessimism	0.41	0.51*	0.20	0.15
1. Sadness	0.21	0.71*	0.35	0.15
6. Punishment	0.28	0.54*	0.85	0.22
9. Suicidal thoughts	0.47	0.64*	0.13	0.16
11. Agitation	0.25	−0.30	0.70*	0.22
15. Loss of energy	0.09	0.37	0.71*	0.19
16. Change in sleep	0.09	0.37	0.71*	0.19
19. Concentration	0.40	0.18	0.62*	0.11
20. Fatigue	0.10	0.38	0.73*	0.01
4. Loss of pleasure	0.24	0.22	0.38	0.61*
10. Crying	0.40	0.12	0.29	0.67*
12. Loss of interest	0.10	0.41	0.45	0.62*
21. Change in libido	−0.01	0.10	−0.27	0.86*
18. Change in appetite	0.10	0.31	0.47	0.34
13. Indecisiveness	0.35	0.32	0.46	0.10
17. Irritability	0.24	0.28	0.49	0.09
ROP+D	**Negative self-evaluation**	**Depressive cognition**	**Physical symptoms**	**Other symptoms**
Eigenvalue (% explained)	7.99 (38.07)	1.58 (7.55)	1.10 (5.25)	1.07 (5.12)
Rotation sums of loading % variance	18%	13%	12%	9.0%
BDI-II Item				
3. Past failure	0.64*	0.36	0.19	0.09
5. Guilt	0.77*	0.14	0.10	−0.05
8. Self-criticism	0.65*	0.08	0.14	0.34
7. Self-dislike	0.73*	0.13	0.19	0.03
12. Loss of interest	0.51*	0.47	0.33	−0.15
14. Worthlessness	0.67*	0.22	−0.14	0.24
6. Punishment	0.54*	0.24	0.39	−0.62
1. Sadness	0.34	0.50*	0.13	0.20
2. Pessimism	0.50	0.53*	0.13	0.20
4. Loss of pleasure	0.33	0.60*	0.35	0.14
9. Suicidal thoughts	0.19	0.72*	−0.32	0.005
21. Change in libido	0.01	0.19	0.61*	0.22
11. Agitation	0.10	0.24	0.70*	−0.12
15. Loss of energy	0.25	0.38	0.50*	0.45
16. Change in sleep	0.05	−0.15	0.57*	0.30
20. Fatigue	0.21	0.09	0.60*	0.48
17. Irritability	0.32	0.30	0.57*	0.05
19. Concentration	0.23	0.43	0.48	0.51*
18. Change in appetite	0.05	0.13	0.00	0.83*
10. Crying	0.13	0.28	0.22	0.07
13. Indecisiveness	0.35	0.28	0.16	0.28

Note: % Variance indicates the percentage of variance in the data accounted by the rotated factor solution.
ROD, recent onset depression; BDI-II, Beck Depression Inventory-II.
*Significant loadings.

in regions corresponding to left inferior frontal gyrus, right inferior frontal gyrus, and insula (see figure 1). Using these identified ROIs in ML classification to predict ROP+D and ROP−D, little separation was seen between groups, with sensitivity 67.4%, specificity 34.6%, a BAC of 50.1%, and AUC 0.58. The model highly misclassified ROP−D



d

	Cluster Peak Voxel MNI Coordinates (x,y,z)	P Value, Peak Intensity, Cluster Size
Inferior Frontal Gyrus Right	51-12-27	p(FDR)<0.001, T=4.46, k=826
Left Insula	-42 -9 -16	p(FDR)=0.011, T=3.62, k=300
Inferior Frontal Gyrus Left	-54 -14 -29	p(FDR)=0.009, T=3.62, k=370

Fig. 1. Classification performance of Neurominer support vector machine (SVM) learning with (a) SVM classification model of recent onset psychosis with depression (ROP+D) vs recent onset depression (ROD) using Beck Depression Inventory-II (BDI-II) individual scores: balanced accuracy 51.5%, sensitivity 76.7%, specificity 26.3%, area under the curve (AUC) 0.54, (b) visualization of feature weights of BDI-II classification, (c) SVM classification model of ROP+D vs ROP without depression (ROP−D) using neuroanatomical variables: balanced accuracy 50.1%, sensitivity 67.4%, specificity 34.6%, AUC 0.58, (d) neuroanatomical variables entered in to (c) as derived from ROD vs healthy controls (HC).

subjects as ROP+D. Supplementary materials (supplementary table 4) include report exploratory VBM analysis of ROP+D and ROP−D groups.

Discussion

In a large sample of patients with ROP and ROD, and using 2 different analytical methods, we found little difference in the psychopathology of depression across groups. In PCA, the depressive syndrome was similarly constructed in both groups; a 4-factor model explained the majority of structure with similar weighting of symptoms. The primary distinction was that the ROP+D group had punishment and loss of interest within the principal component first factor. In ML classification of ROP+D and ROD diagnostic group using depression symptom measures, separability was minimal (BAC of 51%), with punishment weighted toward the psychosis group. Our hypothesis that brain regions identified as significantly different in ROD subjects from HC would be able to distinguish ROP participants with and without depression was not upheld. Structural brain changes were identified in our relatively young ROD subjects in the left inferior frontal gyrus, right inferior frontal gyrus, and insula, compared to HC, and this is in keeping with previous literature.[24] However, these areas were not useful in discriminating those patients with psychosis who did and did not have comorbid depression; and a large proportion of ROP−D participants were misclassified as ROP+D.

Depression and anxiety have been explored as driving forces for positive symptoms in early psychosis,[3] with cognitive appraisals central to the distress and persistence of psychosis. In the present data, punishment was a potential distinguishing feature of depression in psychosis. This reflects cognitive models of depression as related to negative self-evaluation and the context of past experience.[25] In keeping with Birchwoods' model of depression in early psychosis being a "smoking gun" for common childhood adversity,[13] Salokangas et al[14] propose that individual influences of childhood adversity experience occurs across disorders, and it is possible that adverse early experiences precede such negative self-evaluations driving positive symptoms via depression. Indeed recent evidence suggests that differential effects of childhood trauma, mediated by affect, may play out in differing patterns of structural brain change.[26,27]

Results from our PCA showed greater weighting of loss of interest in psychosis, which may also reflect capturing some transdiagnostic features of negative symptoms (eg, anhedonia). Previous studies have well established the need to make distinction between primary negative symptoms and depression. However, whilst our sample of psychosis patients with depression had significant level of depression symptoms, they had only moderate mean negative symptom scores. Results suggest that, once developed, depressive disorder itself is similarly experienced whether in isolation or as a comorbidity and largely unrelated to negative symptoms in early psychosis.

Varagas et al have recently reported a confirmatory factor analysis of depression in CHR and schizophrenia groups, with a 2-factor latent structure of depression/hopelessness and guilt/self-depreciation, which they reported had no association with negative symptoms.[28] PCA and confirmatory factor analysis are similar in some respects, yet their different approaches may explain our differing findings compared to Varagas et al. Unlike confirmatory factor analysis, PCA does not assume an underlying common construct; in our present analysis, PCA did not assume that depression (as an underlying construct) was responsible for all the symptoms entered into the analysis, rather; it demonstrated the weight of individual components in a linear combination of variables and was, therefore, more able to demonstrate differences in structure in data from 2 populations. A further novelty in the present analysis is that our support vector ML analysis also suggests that the symptoms of depression in recent-onset disorders are largely the same experience with or without psychosis status, as no clear separability could be seen between the 2 groups on symptoms alone.

ROD patients had structural brain changes compared to HC similar to those seen in previous imaging studies in Major Depressive Disorder (MDD), specifically relating to the frontal regions and insula.[14,29] These areas are significant in emotional processing, salience, and motivation.[30] Our analysis of ROD compared to HC did not find differences in hippocampal or other medial temporal regions seen in recent meta-analyses of structural imaging studies in depression,[31] which may be a result of our relatively young sample who did not have a long history of chronic disorder or repeated episodes. However, the areas we did identify as significantly different from HC in the ROD group showed no discriminant value in separating depressed from nondepressed ROP groups. This may be a result of structural brain changes seen in psychosis overshadowing any depression specific changes. Alternatively, it may be that, contrary to our hypothesis, a distinct subgroup of ROP with comorbid depression cannot be identified; rather both, depression and psychosis-related structural brain changes are seen in early phases across psychosis. It is also noteworthy that the structural brain changes in our relatively young ROD subjects compared to HC are also often seen in early psychosis,[32,33] suggesting that these may represent a transdiagnostic neuroanatomical signature of general psychiatric morbidity rather than diagnostic specific changes. In addition, in comorbid groups, such as ROP+D, single modal analysis, such as we have conducted, may not have sufficient discriminative power to untangle complex neurobiological etiopathology.

We have previously suggested that, in schizophrenia, structural heterogeneity may relate to specific patterns of GM volume differences that share some common prefrontal patterns,[34] and our current findings, and the heterogeneity demonstrated, are in keeping with this. When exploring the underlying neurobiology of clinical phenotypes in early stage disorder, individual patterns of symptoms mean that group-level changes may not be readily apparent.[12] There may be subtle differences that exist at the individual subject level, whereas between groups, larger differences may only be seen between healthy subjects and broadly defined "patients."

Our findings may have implications for the development of treatment options; with similar phenomenology and lack of accurate subgroup identification, treatments for MDD could potentially be imported into broadly defined early psychosis with potentially good effect. Indeed, there is some existing evidence to this effect; antidepressant medication may be as effective in treating depression in schizophrenia as in major depressive disorder as evidenced in meta-analysis,[35,36] and outcomes are better over the course of illness for those coprescribed antidepressant medication.[37]

Our present analysis has a number of strengths, including recent onset subjects, both HC and depression comparison groups, an ROP sample with limited medication exposure (less than 3 months), a large sample size and the same data acquisition and preprocessing methodology used for all groups. However, results do need to be interpreted with clear acknowledgment of limitations, including (1) the cross-sectional nature of our data: this is significant in interpretation when there may be dynamic and changing symptom profiles that are not captured; (2) the heterogeneity within groups; whilst this was our intention from the outset, our ROP sample is not exclusively recent-onset schizophrenia. It is possible that true categorical classifications of bipolar disorder, affective psychosis, and schizophrenia would give clearer results; however, our decision to include all ROP is based on the diagnostic uncertainty and fluidity present within the early ROP stage. (3) Our ROP+D group had a slightly higher mean negative symptom score, although this was not a statistically significant difference, to the ROP−D group. It is possible that primary negative symptoms were influencing depression scores group to some extent. Using an additional measure, such as the Calgary Depression Scale for Schizophrenia, would be needed for further clarity of the influence of negative symptoms on BDI-II structure; however, it should be noted that, whilst PANSS negative scores were only marginally different in ROP+D and ROP−D groups, BDI scores were very distinct, suggesting that the influence of negative symptoms is likely to be slight. (4) Although the analysis was controlled for age, gender, medication exposure, and significant cannabis use, we were not able to control for milder or infrequent cannabis use.

In summary, however, the present analysis confirms that, at a symptom level, the experience of depression is largely the same in ROD as when comorbid with recent-onset FEP. A clear neuroanatomical signature identified in ROD participants was not able to separate

a psychosis subgroup with depression from those psychosis patients without depression. Depression in FEP is a marker for poorer prognosis,[1,38] and this may be an indication of more significant transdiagnostic structural brain changes. Multivariate analyses with data from more than one modality (combining clinical symptoms, blood-based markers, MRI, and other data, such as adverse childhood experiences) together with longitudinal samples will be needed for further elucidation. The present findings support a hypothesis of depression as intrinsic to psychosis with potentially poorer outcome and this could inform the development of novel and repurposed therapies.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

Acknowledgments

C.P. acknowledges support by an Australian National Health & Medical Research Council (NHMRC) Senior Principal Research Fellowship (ID: 1105825), a NHMRC Program Grant (ID: 1150083).

Conflict of interest: R.U. reports grants from Medical Research Council, grants from the National Institute for Health Research, and personal fees from Sunovion, outside the submitted work. N.K. and R.S. received honoraria for talks presented at education meetings organized by Otsuka/Lundbeck. C.P. participated in advisory boards for Janssen-Cilag, AstraZeneca, Lundbeck, and Servier and received honoraria for talks presented at educational meetings organized by AstraZeneca, Janssen-Cilag, Eli Lilly, Pfizer, Lundbeck, and Shire. P.M. has received honorariums from Sunovion and Sage. All other authors report no biomedical financial interests or potential conflicts of interest.

Funding

The PRONIA study is a Collaboration Project funded under the 7th Framework Programme under grant agreement no 602152.

The PRONIA consortium: The authors listed here performed the screening, recruitment, rating, examination, and follow-up of the study participants. They were involved in implementing the examination protocols of the study, setting up its IT infrastructure, and organizing the flow and quality control of the data analyzed in this manuscript between the local study sites and the central study database.

Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Munich, Germany: Linda Betz, Eva Gussmann, Shalaila Haas, Ifrah Khanyaree, Aylin Melo, Susanna Muckenhuber-Sternbauer, Janis Köhler, Ömer Öztürk, Nora Penzel, David Popovic, Adrian Rangnick, Rachele Sanfelici, Moritz Spangemacher, Maria Fernanda Urquijo, Johanna Weiske, Antonia Wosgien.

Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany: Karsten Blume, Dominika Julkowski, Nathalie Kaiser, Ruth Milz, Alexandra Nikolaides, Mauro Seves, Silke Vent, and Martina Wassen.

Department of Psychiatry (Psychiatric University Hospital, UPK), University of Basel, Basel, Switzerland: Christina Andreou, Laura Egloff, Fabienne Harrisberger, Claudia Lenz, Letizia Leanza, Amatya Mackintosh, Renata Smieskova, Erich Studerus, Anna Walter, and Sonja Widmayer.

Institute for Mental Health and School of Psychology, University of Birmingham, Birmingham, United Kingdom: Shauna Benton, Ayesha Chander, Chris Day, Keshiaa De Valliere, Dean Fitzpatrick, Kimberley Griffin, Solin Hamawandy, Michael Horwood, Mariam Iqbal, Aneela Khan, Katherine Kidd, Carl Krynicki, Zoe Morrice, Amy Murphy, Barry O'Mahony, Mirabel Pelton, Alice Philips, Bhavna Sidhpara, Alexandra Stainton, Andreea Tudor, Ashley White, and Sofia Zahid.

Department of Psychiatry, University of Turku, Turku, Finland: Alexander Denissoff, Anu Ellilä, Tiina From, Markus Heinimaa, Tuula Ilonen, Päivi Jalo, Heikki Laurikainen, Antti Luutonen, Akseli Mäkela, Janina Paju, Henri Pesonen, Reetta-Liina Säilä, Anna Toivonen, and Otto Turtonen.

General Electric Global Research Inc, USA: Ana Beatriz Solana, Manuela Abraham, Nicolas Hehn, and Timo Schirmer.

Department of Psychiatry, University of Milan, Milan, Italy: Marika Belleri, Francesca Bottinelli, Ludovica Dabate, Adele Ferro, Luisa Marra, and Elena Pillarella.

Department of Psychiatry, University of Udine, Udine, Italy: Matteo Balestrieri, Carolina Bonivento, Giuseppe Cabras, Olivia Danzi, Franco Fabbro, Adele Ferro, Livia Fornasari, Marco Garzitto, Monica Leskovec, Sara Piccin, and Marta Re.

Data Sharing: Requests for sharing the anonymized database should be addressed to the lead authors.

References

1. Conley RR, Ascher-Svanum H, Zhu B, Faries DE, Kinon BJ. The burden of depressive symptoms in the long-term treatment of patients with schizophrenia. *Schizophr Res.* 2007;90(1–3):186–197.
2. Upthegrove R, Birchwood M, Ross K, Brunett K, McCollum R, Jones L. The evolution of depression and suicidality in first episode psychosis. *Acta Psychiatr Scand.* 2010;122(3):211–218.

3. Upthegrove R, Marwaha S, Birchwood M. Depression and schizophrenia: cause, consequence, or trans-diagnostic issue? *Schizophr Bull.* 2017;43(2):240–244.
4. Sandhu A, Ives J, Birchwood M, Upthegrove R. The subjective experience and phenomenology of depression following first episode psychosis: a qualitative study using photo-elicitation. *J Affect Disord.* 2013;149(1–3):166–174.
5. Fried EI, Nesse RM. Depression is not a consistent syndrome: an investigation of unique symptom patterns in the STAR*D study. *J Affect Disord.* 2015;172:96–102.
6. Herniman SE, Allott K, Phillips LJ, et al. Depressive psychopathology in first-episode schizophrenia spectrum disorders: a systematic review, meta-analysis and meta-regression. *Psychol Med.* 2019;49(15):2463–2474.
7. Krynicki CR, Upthegrove R, Deakin JFW, Barnes TRE. The relationship between negative symptoms and depression in schizophrenia: a systematic review. *Acta Psychiatr Scand.* 2018;137(5):380–390.
8. Brandl F, Avram M, Weise B, et al. Specific substantial dysconnectivity in schizophrenia: a transdiagnostic multimodal meta-analysis of resting-state functional and structural magnetic resonance imaging studies. *Biol Psychiatry.* 2019;85(7):573–583.
9. Li A, Zalesky A, Yue W, et al. A neuroimaging biomarker for striatal dysfunction in schizophrenia. *Nat Med.* 2020;26(4):558–565.
10. Steullet P. Thalamus-related anomalies as candidate mechanism-based biomarkers for psychosis. *Schizophr Res.* 2019. doi:10.1016/j.schres.2019.05.027
11. Kambeitz J, Kambeitz-Ilankovic L, Leucht S, et al. Detecting neuroimaging biomarkers for schizophrenia: a meta-analysis of multivariate pattern recognition studies. *Neuropsychopharmacology.* 2015;40(7):1742–1751.
12. Koutsouleris N, Meisenzahl EM, Borgwardt S, et al. Individualized differential diagnosis of schizophrenia and mood disorders using neuroanatomical biomarkers. *Brain.* 2015;138(Pt 7):2059–2073.
13. Salokangas RK, Schultze-Lutter F, Schmidt SJ, et al. Childhood physical abuse and emotional neglect are specifically associated with adult mental disorders. *J Ment Health.* 2019:1–9. doi:10.1080/09638237.2018.1521940
14. Calvo A, Delvecchio G, Altamura AC, Soares JC, Brambilla P. Gray matter differences between affective and non-affective first episode psychosis: a review of Magnetic Resonance Imaging studies: special Section on "Translational and Neuroscience Studies in Affective Disorders" Section Editor, Maria Nobile MD, PhD. The main aim is to briefly summaries relevant research findings in clinical neuroscience with particular regards to specific innovative topics in mood and anxiety disorders. *J Affect Disord.* 2019;243:564–574.
15. Hartmann JA, Nelson B, Ratheesh A, Treen D, McGorry PD. At-risk studies and clinical antecedents of psychosis, bipolar disorder and depression: a scoping review in the context of clinical staging. *Psychol Med.* 2019;49(2):177–189.
16. Koutsouleris N, Kambeitz-Ilankovic L, Ruhrmann S, et al.; PRONIA Consortium. Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or with recent-onset depression: a multimodal, multisite machine learning analysis. *JAMA Psychiatry.* 2018;75(11):1156–1172.
17. First MB. Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition* (pp. 94-1). New York, NY: 2002.
18. Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Aust NZ J Psychiatry.* 2005;39(11–12):964–971.
19. Psychiatrie P und P und N (DGPPN). Deutsche Gesellschaft für. DGPPN S3. *Treatment Guideline Schizophrenia and Psychotic Disorders*. Germany: AWMF; 2006.
20. Beck AT, Steer RA, Brown GK. *Beck Depression Inventory-II*. San Antonio, TX: Psychological Association; 1996.
21. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13(2):261–276.
22. Chang C-C, Lin C-J. LIBSVM: a library for support vector machines. 2001. http://www. csie. ntu. edu. tw/~ cjlin/libsvm; Accessed December 12, 2019.
23. Saeys Y, Inza I, Larrañaga P. A review of feature selection techniques in bioinformatics. *Bioinformatics.* 2007;23(19):2507–2517.
24. Vasic N, Walter H, Höse A, Wolf RC. Gray matter reduction associated with psychopathology and cognitive dysfunction in unipolar depression: a voxel-based morphometry study. *J Affect Disord.* 2008;109(1–2):107–116.
25. Birchwood M, Iqbal Z, Upthegrove R. Psychological pathways to depression in schizophrenia: studies in acute psychosis, post psychotic depression and auditory hallucinations. *Eur Arch Psychiatry Clin Neurosci.* 2005;255(3):202–212.
26. Salokangas R, Hietala J, Armio R, et al. Effect of childhood physical abuse on social anxiety is mediated via reduced frontal lobe and amygdala-hippocampus complex volume in adult clinical high-risk subjects. *Schizophr Res.* 2020. doi:10.1016/j.schres.2020.05.041
27. Popovic D, Ruef A, Dwyer DB, et al. Traces of trauma—a multivariate pattern analysis of childhood trauma, brain structure and clinical phenotypes. *Biol Psychiatry.* 2020. doi:10.1016/j.biopsych.2020.05.020
28. Vargas T, Ahmed AO, Strauss GP, et al. The latent structure of depressive symptoms across clinical high risk and chronic phases of psychotic illness. *Transl Psychiatry.* 2019;9(1):1–12.
29. Lai CH, Wu YT. Frontal-insula gray matter deficits in first-episode medication-naïve patients with major depressive disorder. *J Affect Disord.* 2014;160:74–79.
30. Koenigs M, Grafman J. The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behav Brain Res.* 2009;201(2):239–243.
31. Arnone D, Job D, Selvaraj S, et al. Computational meta-analysis of statistical parametric maps in major depression. *Hum Brain Mapp.* 2016;37(4):1393–1404.
32. Dazzan P, Morgan KD, Orr KG, et al. The structural brain correlates of neurological soft signs in AESOP first-episode psychoses study. *Brain.* 2004;127(Pt 1):143–153.
33. Borgwardt SJ, McGuire PK, Aston J, et al. Structural brain abnormalities in individuals with an at-risk mental state who later develop psychosis. *Br J Psychiatry Suppl.* 2007;51:s69–s75.
34. Koutsouleris N, Gaser C, Jäger M, et al. Structural correlates of psychopathological symptom dimensions in schizophrenia: a voxel-based morphometric study. *Neuroimage.* 2008;39(4):1600–1612.

35. Helfer B, Samara MT, Huhn M, et al. Efficacy and safety of antidepressants added to antipsychotics for schizophrenia: a systematic review and meta-analysis. *Am J Psychiatry.* 2016;173(9):876–886.
36. McGinty J, Sayeed Haque M, Upthegrove R. Depression during first episode psychosis and subsequent suicide risk: a systematic review and meta-analysis of longitudinal studies. *Schizophr Res.* 2018;195:58–66.
37. Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P. Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. *Arch Gen Psychiatry.* 2012;69(5):476–483.
38. McGinty J, Upthegrove R. Depressive symptoms during first episode psychosis and functional outcome: a systematic review and meta-analysis. *Schizophr Res.* 2020; 218:14–27.