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The psychopathology and neuroanatomical markers of depression in early psychosis

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Abstract

Depression frequently occurs in first episode psychosis and predicts longer term negative outcomes. It is possible depression seen is from a distinct subgroup, which if identified could allow targeted treatments. We hypothesize that patients with recent onset psychosis and co-morbid depression would be identifiable by symptom and neuroanatomical features similar to that seen in recent onset depression. Data were extracted from the multi-site PRONIA study: 154 recent onset psychosis (ROP) patients (first episode psychosis within 3 months of treatment onset), of whom 83 were depressed (ROP+D) and 71 who were not depressed (ROP-D), 146 recent onset depression (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 first episode psychosis. Depression may be intrinsic to early stages of psychotic disorder and thus treatment focused on depression could produce widespread benefit.

Key words: schizophrenia, psychosis, depression, grey matter volume, psychopathology, machine learning

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Introduction

Depression is a common co-morbidity 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]. We have also previously argued that depression may be intrinsic to the disorder itself, and be particularly relevant in early stages of psychosis; affective dysfunction the fire of later stage 'burnt out' disorder[3]. Recent evidence suggests striatal and thalamic structural differences and related functional dysconnectivity may be key brain changes able to discriminate schizophrenia from affective disorders [8 9, 10]. We have previously shown that structural magnetic resonance imaging (sMRI) is able to separable schizophrenia from depression with 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, 12,13]. 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 sub-group of patients with depression in first episode psychosis (FEP); for example Salokangas et al [14] previously showed that patients with FEP and depression have larger ventricular and posterior sulcal cerebrospinal fluid volumes compared to first episode psychosis patients without depression. Calvo et al. [15] reviewed 14 sMRI studies in FEP, and reported volume loss in the frontotemporal and anterior cingulate in both affective and non-affective psychosis, but insula and hippocampal reductions were seen only in non-affective 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 [13,16]. Machine learning and large samples may be useful in this investigation of co-morbid groups in early stages of illness when heterogeneity is significant, as they are able 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 co-morbid depression is possible. We hypothesize that depression in recent onset psychosis is a distinct comorbidity and that a) there would be a similar symptom structure of depression in recent onset psychosis (ROP) as seen in recent onset depression (ROD) and b) 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 and then supervised machine learning (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 structural magnetic resonance imaging (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 recent onset ROP (minimally treated first episode psychosis) and 265 healthy controls.

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 [17] 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 minutes), 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 six months, and any medical indication against MRI.

ROP participants had to meet criteria for a first episode of affective or non-affective Psychotic Episode as established by the Structured Clinical Interview for DSM-IV-TR (SCID)[18] or transition criteria defined by Yung et al [19], 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 5mg Olanzapine [20].

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 CHR criteria, including of the presence of attenuated psychotic symptoms, brief intermittent psychotic symptoms or a genetic risk with functional deterioration), and basic symptom criteria as previously published[17] (see supplementary table 1 for full details).

Healthy control (HC) exclusion criteria were; any current or past DSM-IV axis I or II disorder; CHR status as defined above; a positive familial history (1st degree relatives) for affective or non-affective 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, cannabis use), SCID diagnosis (Structured Clinical Interview for DSM-IV)[21], BDI-II (Beck Depression Inventory-II)[22], Positive and Negative Symptom Scale (PANSS)[23] and structural MRI (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 and enhance the signal-to-noise ratio in the images. Supplementary table 2 lists the scanner and parameters 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 cut off scores [22].

Principal component analysis 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 materials 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), medication (olanzapine equivalent total exposure and SSRI equivalent total exposure;) were entered as covariates, see **supplementary materials** 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)[24] with a linear kernel which optimizes across a regularization hyperparameter range of $2^{[-3 \underset{\in \mathbb{Z}}{\rightarrow} +4]}$ and eleven 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 report the performance of classification of ROD and ROP+D groups with sensitivity, specificity, balanced accuracy (BAC), 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[25].

For sMRI data, see our previously published study[17] 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), white matter, 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 white matter (WM) homogeneities and varying gray matter (GM) intensities, and a high-dimensional DARTEL registration of the image to a MNI-template in the IXI database (http://www.braindevelopment.org).

Whole brain voxel based morphometry (VBM) analysis was conducted using a two-sample t-test in SPM12 between ROD participants and HC to generate regions of interest (ROI) using a cluster-level height threshold of $p<0.05$, corrected with false discovery rate (FDR), 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 three subjects (one HC and two 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 a 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 classification of ROP groups with and without depression (ROP+D and ROP-D).

We additionally conducted a number of exploratory VBM analysis (see supplementary materials) exploring ROP+D vs ROP-D.

Results

The mean age of the full sample was 24 years, and 46% were male. The ROP group (n154) had a majority diagnosis of schizophrenia spectrum psychosis (n123/154; 80%). 83 (54%) fulfilled the ROP+D criteria. Positive symptoms were comparable in ROP patients with and without depression (p=0.73, see table 1 for details). The mean BDI score in the ROP+D group was 27,72 (s.d. 12.2), which was higher, but not significantly, than the ROD group mean 26.40 (s.d.13.9). See **table 1** for further details and supplementary table 3 for detailed diagnostic breakdown.

Principal component analysis 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, four 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 cumulative variance was identified in four factors with a similar cluster of past failure, guilt, self-dislike, self-criticism, worthlessness, with the addition of punishment and loss of interest significant in the first factor. See **table 2**.

Machine Learning classifications:

Classification by machine learning (ML) of ROP+D vs ROD groups using only the BDI-II items showed a sensitivity of 76.7%, specificity of 26.3% and balanced accuracy of 51.5%, area under the curve (AUC) of 0.54. Punishment and concentration difficulties weighted toward ROP whereas sadness and worthlessness weighted towards ROD. See figure 1.

Whole brain VBM analysis of ROD patients compared to HC identified significant differences in four GMV clusters in regions corresponding to left inferior frontal gyrus, right inferior frontal gyrus and insula. See **figure 1**. Using these identified ROI's in ML classification to predict ROP+D and ROP-D, little separation was seen between groups, with sensitivity 67.4%, specificity 34.6%, a balanced accuracy of 50.1% and AUC 0.58. The model highly misclassified ROP-D subjects as ROP+D.

Supplementary material (table 4 and figure 3) include report exploratory VBM analysis of ROP+D and ROP-D groups.

Discussion:

In a large sample of patients with recent onset psychosis and recent onset depression, and using two different analytical methods, we found little difference in the psychopathology of depression across groups. In principal components analysis the depressive syndrome was similarly constructed in both groups, a four-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 machine learning classification of ROP+D and ROD diagnostic group using depression symptom measures, separability was minimal (balanced accuracy of 51%), with punishment weighted towards 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[26]. However, these areas were not useful in discriminating those patients with psychosis who did and did not have co-morbid depression; and a large proportion of ROP-D participants were mis-classified 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 [27]. In keeping with Birchwoods' model of depression in early psychosis being a 'smoking gun' for common childhood adversity[14], Salokangas et al[14] propose 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 differential effects of childhood trauma, mediated by affect, may play out in differing patterns of structural brain change[28, 29].

Results from our principal component analysis also showed greater weighting of loss of interest in psychosis; which may also reflect capturing some transdiagnostic features of negative symptoms (e.g. 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 co-morbidity 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 two-factor latent structure of depression/hopelessness and guilt/self-depreciation, which they reported had no association with negative symptoms[30]. Principal components analysis (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 the all 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 two populations. A further novelty in the present analysis is that our support vector machine learning 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 two groups on symptoms alone.

ROD patients had structural brain changes compared to healthy controls similar to those seen in previous imaging studies in MDD, specifically relating to the frontal regions and insula [15, 31]. These areas are significant in emotional processing, salience and motivation [32]. 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 [33], which may be a result of our relatively young sample who did not a long history of chronic disorder or repeated episodes. However, the areas we did identify as significantly different to heathy controls in the ROD group showed no discriminant value in separating depressed from non-depressed 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 recent onset psychosis with co-morbid depression cannot be identified; rather 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[34, 35], suggesting these may represent a transdiagnostic neuroanatomical signature of general psychiatric morbidity rather than diagnostic specific changes. In addition, in co-morbid groups such as ROP+D,

single modal analysis such as we have conducted may not have sufficient discriminative power to untangle complex neurobiological aetiopathology.

We have previously suggested that in schizophrenia, structural heterogeneity may relate to specific patterns of grey matter volume differences that share some common prefrontal patterns [36] 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 exists at the individual subject level, whereas between groups larger differences are only seen between healthy subjects and broadly defined 'patients'.

Our findings may have implications for 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 [37,38] and outcomes are better over the course of illness for those co-prescribed antidepressant medication[39].

Our present analysis has a number of strengths, including recent onset subjects, both healthy control and depression comparison groups, a recent onset psychosis sample with limited medication exposure (less than 3 months) and large sample size and the same data acquisition and pre-processing methodology used for all groups. However, results do need to be interpreted with clear acknowledgement 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 recent onset psychosis 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 with in the early ROP stage 3) our ROP+D group had 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 symptom 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 analysis were controlled for age, gender, medication exposure, 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 recent onset depression as when co-morbid with recent onset first episode psychosis. A clear neuroanatomical signature identified in recent onset depression participants was not able to separate a psychosis sub-group with depression from those psychosis patients without depression. Depression in first episode psychosis is a marker for poorer prognosis[1, 40], 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.

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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.

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The phenomenology and neuroanatomical markers of depression in early psychosis

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Figure 1: Classification Performance of Neurominer support vector machine (SVM) learning with a) SVM classification model of ROP+D vs ROD using BDI-II individual scores: Balanced Accuracy 51.5%, Sensitivity 76.7%, Specificity 26.3%, AUC 0.54 b) visualisation of feature weights of BDI-II classification c) SVM classification model of ROP+D vs ROP-D using neuroanatomical variables: Balanced Accuracy 50.1%, Sensitivity 67.4%, Specificity 34.6%, AUC 0.58 d) Neuroanatomical variables entered in to b) as derived from ROD vs HC.

Table 1. Clinical and demographic sample details

Group	**HC**	**ROD**	**ROP**	**ROP+D**	**ROP-D**	**ANOVA**
Number	265	146	154	83	71	
Age mean (s.d.)	25.05 (6.5)	25.60 (6.2)	24.78(5.4)	24.57 (4.6)	25.42 (6.5)	2,297=2.17 (p=0.12)
Sex N (%) Male	105 (40%)	67 (46%)	94 (61%)	53 (63%)	41 (57%)	22.11(df 4) (p=0.01)[a]
Cannabis Misuse N(%)	3 (1%)	17 (9%)	49 (31%)	23 (27%)	26 (38%)	1.4 (df1.0) (p=0.23)[b]
SSRI N(%)/mean exposure[e]	-	118 (72%) 3357mg	64 (41%) 2301mg	40 (48%) 3433mg	24(35%) 899mg	F (5,617) =9.58, p=0.98[c]
Antipsychotic N(%)/mean	-	29 (20%) 20mg	137(89%) 534mg	74(89%) 661mg	63(89%) 341mg	F(1,144)=01.13, p=0.28[d]

exposure[e]						
PANSS Positive mean (s.d.)	-	-	17.95(s.d.1.2)	17.80 (5.8)	17.56(6.9)	F(1,144)=0.13, p=0.72[d]
PANSS Negative mean (s.d.)	-	-	16.57(7.9)	17.65(8.5)	15.22(6.9)	F(91,144)=3.45, p=0.06[d]
BDI-II mean (s.d.)	-	26.40 (13.9)	21.47(12.6)	27.72(12.18)	12.84 (9.4)	F(1,201)=0.20,p =0.65[c]

[a] chi-sq ROD; ROP
[b] chi-sq ROP+D/ROP-D
[c] Analysis of variance (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 items in ROP and ROD+D groups: Summary of factor loading. % Variance indicates the percentage of variance in the data accounted by the rotated factor solution. * = significant loadings.

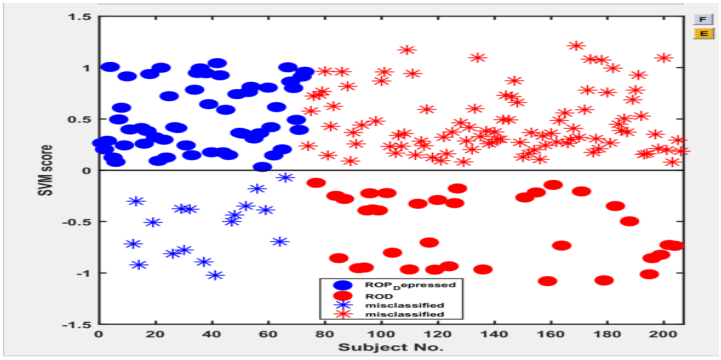
ROD	Negative self-evaluation	Depressive Cognition	Physical symptoms	Other symptoms
Eigenvalue (% explained)	8.89 (42.33)	1.88(8.89)	1.22(5.79)	1.03 (4.92)
Rotation sums of loading % Variance	20%	17%	12%	11%
BDI-II Item				
3. Past Failure	0.82*	0.20	0.181	0.14
5. Guilt	0.79*	0.13	0.17	0.04
8. Self Criticism	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

Figure 1. Classification Performance of Neurominer support vector machine (SVM) with learning

a) SVM classification model of ROP+D vs ROD using BDI-II individual scores: Balanced Accuracy 51.5%, Sensitivity 76.7%, Specificity 26.3%, AUC 0.54 b) visualisation of feature weights of BDI-II classification c) SVM classification model of ROP+D vs 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 RODvsHC.

a



b

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

c