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Lalousis, Paris Alexandros; Wood, Stephen; Schmaal, Lianne; Chisholm, Katie; Griffiths, Lowri; Reniers, Renate; Bertolino, Alessandro; Borgwardt, Stefan; Brambilla, Paolo; Kambeitz, Joseph ; Lencer, Rebekka; Pantelis, Christos; Ruhrmann, Stephan; Salokangas, Raimo K.R.; Schultze-Lutter, Frauke; Bonivento, C.; Dwyer, Dominic; Ferro, Adele; Haidl, Theresa; Rosen, Marlene

DOI:
10.1093/schbul/sbaa185

Document Version
Peer reviewed version

Citation for published version (Harvard):
Lalousis, PA, Wood, S, Schmaal, L, Chisholm, K, Griffiths, L, Reniers, R, Bertolino, A, Borgwardt, S, Brambilla, P, Kambeitz, J, Lencer, R, Pantelis, C, Ruhrmann, S, Salokangas, RKR, Schultze-Lutter, F, Bonivento, C, Dwyer, D, Ferro, A, Haidl, T, Rosen, M, Schmidt, A, Meisenzahl, E, Koutsouleris, N, Upthegrove, R & PRONIA Consortium 2021, 'Heterogeneity and classification of recent onset psychosis and depression: a multimodal machine learning approach', *Schizophrenia bulletin*, vol. 47, no. 4, sbaa185, pp. 1130-1140. https://doi.org/10.1093/schbul/sbaa185

OXFORD UNIVERSITY PRESS | Schizophrenia Bulletin

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Journal:	*Schizophrenia Bulletin*
Manuscript ID	SZBLTN-ART-20-0528.R1
Manuscript Type:	Regular Article
Date Submitted by the Author:	20-Nov-2020
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Keywords:	transdiagnostic, MRI, gray matter volume, comorbidity, support vector machine

Heterogeneity and Classification of Recent Onset Psychosis and Depression: a Multimodal Machine Learning Approach

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Keywords: psychosis, depression, transdiagnostic, machine learning, MRI, gray matter volume, comorbidity

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Word Count Manuscript

Abstract:	250
Introduction:	635
Methods:	877
Results:	750
Discussion:	1264
Figure Legends:	223
Total:	3999 (including abstract, text body, and figure and table legends)

Supplementary Methods and Results: 1 file

Abstract

Diagnostic heterogeneity within and across psychotic and affective disorders challenges accurate treatment selection, particularly in early stages. Delineation of shared and distinct illness features at the phenotypic and brain levels may inform the development of more precise differential diagnostic tools. We aimed to identify prototypes of depression and psychosis to investigate their heterogeneity, with common, comorbid transdiagnostic symptoms. Analysing clinical/neurocognitive and grey matter volume (GMV) data from the PRONIA database, we generated prototypic models of recent-onset depression (ROD) vs. recent-onset psychosis (ROP) by training support-vector machines to separate patients with ROD from patients with ROP, who were selected for absent comorbid features (pure groups). Then, models were applied to patients with comorbidity, i.e., ROP with depressive symptoms (ROP+D) and ROD participants with sub-threshold psychosis-like features (ROD+P), to measure their positions within the affective-psychotic continuum. All models were independently validated in a replication sample. Comorbid patients were positioned between pure groups, with ROP+D patients being more frequently classified as ROD compared to pure ROP patients (clinical/neurocognitive model: χ^2=14.874; p<0.001; GMV model: χ^2=4.933; p=0.026). ROD+P patient classification did not differ from ROD (clinical/neurocognitive model: χ^2=1.956; p=0.162; GMV model: χ^2=0.005; p=0.943). Clinical/neurocognitive and neuroanatomical models demonstrated separability of prototypic depression from psychosis. The shift of comorbid patients towards the depression prototype, observed at the clinical and biological levels, suggests that psychosis with affective comorbidity aligns more strongly to depressive rather than psychotic disease processes. Future studies should assess how these quantitative measures of comorbidity predict outcomes and individual responses to stratified therapeutic interventions.

Introduction:

Treatments for mental illness are currently based on categorical structures built on patterns of syndromes and their course, rather than aetiology[1]. The biological and clinical overlaps between these syndromes, and significant heterogeneity in outcomes, has become more apparent in recent years[2–4]. Advancement in both pharmacological and psychotherapeutic interventions has stalled, potentially as a result of continued focus on invalid disease categories[5,6]. The need for better treatments is particularly acute in psychosis and depression, which constitute major mental health challenges to the world's population[7–13]. The legacy of a Jaspers based hierarchical approach to symptom structures suggests that positive psychotic symptoms are of primary importance within psychotic spectrum disorders[14]. Yet the categorical and hierarchical division of psychotic disorders into affective and non-affective has been contested for decades[15], with clear demonstration of the presence of affective symptoms in psychosis and psychotic symptoms in affective disorders[8,11,16].

Heterogeneity is particularly noticeable in early and developing stages of illness, with high prevalence of affective symptoms across disorders[17]. The comorbidity of depression in early psychosis has been largely regarded as secondary to the primary disorder (psychosis), reinforcing a categorical, hierarchical approach[18,19]. There are increasing calls to use empirical evidence to develop alternative aetiologically informed structures[20]. The use of multidimensional item response modelling to predict psychosis biotypes has been shown to transcend traditional diagnostic boundaries; with suggestion of an underlying transdiagnostic dimension across psychotic diagnoses[21–23]. However, there are valid reasons why a categorical approach to mental illness has persisted; a significant number of individuals' presentation will 'fit' within distinct categories of mental illness and the course and outcome of their treatment can be predicted from such diagnostic structures[24]. When disorders are fully formed, course as well as symptom structure enable clearer distinction between categories. Imaging studies also show shared areas of interest, including the hippocampus and cerebellum[32], the prefrontal cortex and insula[33] and both depression and psychosis have been associated with heightened brain activation in regions central to emotional processing[33–35] with similarities particularly prominent in the early stages of illness[25,33–35].

The distinction between depression and schizophrenia is possible by structural brain data, but also, more challenging in early stages of illness when symptoms and course are more heterogeneous[25]. Transdiagnostic processes of mental health disorders are descriptively

transdiagnostic (i.e. being present in multiple disorders, without regard to how or why) or mechanistically transdiagnostic (i.e. reflecting neurobiological, physiological, or functional mechanisms)[26,27]. Both depression and psychosis are associated with transdiagnostic features of working memory, executive functioning, and verbal fluency deficits[28]. [30]. The importance of certain mechanistically transdiagnostic symptoms is potentially hidden in categorical structures, and they remain under-investigated[31].

Complex psychopathology and heterogeneity in developing mental health disorders presents the opportunity of fuller exploration of the significance of potential transdiagnostic symptoms, to provide further insight into aetiopathogenetic pathways of symptoms and through this to advance diagnostic structures[36,37]. However, novel approaches and powerful statistical tools such as machine learning techniques could help provide this deeper understanding by detecting complex patterns of data across diagnostic structures, and the delineation of shared and distinct features of these illnesses at the phenotypic and brain levels. This may inform the development of more precise differential diagnostic tools and improve the development of new treatments[36].

This study aimed to identify prototypes of pure depression and pure psychosis in order to investigate the heterogeneity of depression and psychosis with common, comorbid transdiagnostic symptoms. We hypothesized that developed models would correctly classify diagnostic groups without comorbid symptoms, in keeping with evidence of the utility in categorical diagnostic structure, and that grey matter volume (GMV) would add classification accuracy. We further hypothesised that a reduction of classification accuracy would be seen in groups with comorbid symptoms. Exploration and the delineation of shared and distinct features at both the phenotypic and biological levels may potentially inform future development of more precise treatments.

Materials and Methods

Study design

Data were taken from the discovery and replication samples of the PRONIA study, an EU-FP7 funded seven centre study aiming to optimize candidate biomarkers for the prediction and staging of mental health disorders. Details of the PRONIA study sites, recruitment protocol and quality control procedures are described in a previous publication[40] and in the supplementary methods (1.1, 1.2, 1.3, tables S2, S3).

Inclusion and Exclusion Criteria

The general inclusion criteria for the study 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: (1) an IQ below 70, (2) current or past head trauma with loss of consciousness (> 5 minutes), (3) current or past known neurological or somatic disorders potentially affecting structure or functioning of the brain, (4) current or past alcohol dependence, (5) polysubstance dependence within the past six months, and (6) any medical indication against MRI. ROP and ROD inclusion criteria can be found in the supplement (1.1).

Group identification

Pure ROP: any ROP patient who had a Beck Depression Inventory-II (BDI-II) score of 13 or lower, which is indicative of absent or minimal depressive symptoms[41,42]. Pure ROD: any ROD patient who had a Positive and Negative Symptom Scale (PANSS)[43] positive subscale score of no more than 7 and no Structured Interview of Psychosis-risk Syndromes positive (SIPS-P) severity score of 3 or more on any item.

ROP with depressive symptoms (ROP+D): any ROP participant with a BDI-II score of 14 or more. ROD with psychotic symptoms (ROD+P): any ROD participant with a SIPS positive item score of 2 or more and a Schizophrenia Proneness Instrument-Adult version (SPI-A) Cognitive Disturbances (COGDIS) item score of 3 or more.

Twenty-four ROP and 31 ROD patients from the discovery sample and 21 ROP and 53 ROD patients were not included in the analysis due to not meeting group identification criteria or not having neuroimaging data.

MRI imaging data acquisition, quality control, and preprocessing

Participants underwent a multi-modal MRI protocol. A minimal harmonization protocol, which the MR sequences across the different scanners had to comply with is described in the supplementary methods (1.3). In the current study, T1-weighted structural MRI (sMRI) images of the participants were analyzed. The sMRI images of six healthy travelling volunteers who were scanned at all sites with same parameters were also analysed as part of a calibration study. The images were processed using the open source CAT12 toolbox (version r1155; http://dbm.neuro.uni.jena.de/cat12/) (see supplementary methods 1.4). Employing

generalization theory[44,45], a between-site voxel reliability map (G coefficient map) was computed from the analysis of the GMV maps that were derived from the calibration study. During our neuroimaging based machine learning analyses the G coefficient maps were used for reliability-based voxel masking.

Classification Models

Using the pure ROP and ROD groups, a Support Vector Machine (SVM) classification model was built using individual item scores from broad clinical and neurocognitive tests that assess features commonly occurring in psychosis and depression including anhedonia, social functioning and cognition deficits (see supplementary methods 1.8). In total, 151 features were included in the model. The trained pure classification model was then applied to the comorbid ROP+D and ROD+P groups to determine the classification accuracy to their primary diagnosis.

A second model using GMV whole-brain voxel-wise data as features was developed in the pure ROD and ROP groups and then applied to the ROP+D and ROD+ P groups. The developed clinical/cognitive and GMV models were combined by using decision values from the pure clinical and pure GMV models (in order to build a model that learns from the meta-data) in a stacking-based data fusion framework[46,47]. Finally, all the models were applied to an independent replication sample.

Support Vector Machine Learning Analysis:

The machine learning analysis of pre-processed data (see supplementary methods 1.5) was performed using NeuroMiner (version 1.0; https://github.com/neurominer-git). A repeated nested pooled cross-validation (CV) was used with 10 outer CV2 permutations, 10 outer CV2 folds, 10 inner CV1 permutations, and 10 inner CV1 folds.

Imbalanced learning was corrected for, by increasing the C value in the minority class by multi-plying it by the inverse ratio of the training class sizes. A linear kernel was used with eleven C values (0.0156, 0.0312, 0.0625, 0.1250, 0.2500, 0.5000, 1, 2, 4, 8, and 16) in order to optimize the choice of C value and create an ensemble of predictive models to be applied to the CV_2 data to produce a single average robust prediction.

Balanced accuracy (BAC) regularized by SVM model complexity was used as a criterion for the hyperparameter optimization (see supplementary methods 1.6).

Finally, a stacking-based data fusion framework[46–49] was used to examine whether the combination of the clinical/neurocognitive and the neuroimaging-based models would provide a superior classification accuracy (see supplementary methods 1.7).

Independent Validation

All our models were validated in our independent replication sample (N=262) (see supplementary methods table S4) which was collected at a different timescale. The same group identification criteria were applied.

Supplementary analyses

A number of supplementary exploratory analyses, including correlation analyses between decision scores from our models, association and comparison analyses between correctly and mis-classified patients, GMV comparison between groups, decision score group comparisons, and regression analyses with 9 month functional outcomes were conducted and can be found in the supplement (Section 2).

Results:

Demographic Information

Data from 154 participants with ROP and 146 patients with ROD were included in the analysis as our Discovery sample. Thirty-eight ROP patients were included in the pure ROP group and 90 ROD patients in the pure ROD group. The mean age of the pure ROP group was 26.5 [SD 6.8]) and the mean age of the pure ROD group was 26.5 [SD 6.6]). There were 25 male and 13 female patients in the pure ROP group and 45 male and 45 female patients in the pure ROD group.

Ninety-two ROP subjects were included in the ROP+D group and 25 ROD subjects in the ROD+P group. The mean age of the ROP+D group was 26.5 [SD 6.8] and the mean age of the ROD+P group was 23.8 [SD 3.9]. There were 57 males and 35 females in the ROP+D group and 12 males and 13 females in the ROD+P group. A summary of demographic information is provided in table 1.

The independent validation sample consisted of 161 patients with ROP and 131 patients with ROD. Fifty ROP patients were included in the pure ROP group and 53 ROD patients in the

pure ROD group. The ROP+D and ROD+P groups consisted of 90 and 25 patients respectively. A full description is provided in the supplement (Table S4).

Machine Learning Analyses

Internal Validation of the Pure Group Differential Classifiers

Clinical and Neurocognitive Data

A repeated nested pooled cross validation model with classifiers of clinical and cognitive variables predicted pure diagnostic groups with a balanced accuracy (BAC) of 79.3%; 95% CI [77.2, 82.3] and an area under the curve (AUC) of 0.86 (Table 2 and Figure 1a). Assignment to the ROP category by the clinical classifier was driven by reduced scores in the RSA and elevated scores in the WSS, RSA, and SPIA. ROD group classification was informed by increased scores in the SPIA, WSS, together with reduced scores in the DSST. The contribution of the features was calculated by feature weights and by cross-validation ratio (Figure 2).

GMV Data

The repeated nested pooled cross-validation model using sMRI to predict diagnostic group in pure ROP and ROD produced a BAC of 62.5%; 95% CI [58.8, 64.0] and an AUC of 0.70 (Table 2 and Figure 1b). ROP patients showed pronounced reductions in the thalamus and the cerebellum, whereas depressed patients showed orbitofrontal, limbic and paralimbic volume reductions (Figure 3).

Stacking

Combining the outputs of the clinical predictors and sMRI using stacked generalization predicted diagnostic group with a BAC of 79.5%; 95% CI [77., 81.9] and an area under the curve (AUC) of 0.87 (Table 2 and Figure 1c).

Separability of Comorbid Groups

Clinical/Neurocognitive Data: The trained pure classification system comprising the collection of 11 clinical/neurocognitive models generated by the repeated nested cross-validation scheme on pure groups was then applied to the comorbid groups (ROP+D and ROD+P) to produce decision scores measuring ROP vs. ROD likeness. This model had a BAC of 62.5% and an AUC of 0.66. Misclassifications showed a directionality toward the

ROD group, with 63% of ROP+D patients being classified as ROD; Z=1.276, p=.0385) (see Table 2 and Figure 1a). ROP+D patients were more frequently classified as ROD compared to pure ROP patients (χ^2=14.874; p<0.001). In contrast, the assignment precision of ROD+P and ROD patients did not differ (χ^2=1.956; p=0.162).

GMV Data

The trained pure classification system (comprising of 11 GMV models generated by the repeated nested cross-validation scheme on pure groups) was then applied to the comorbid groups (ROP+D and ROD+P) to produce decision scores measuring ROP vs. ROD likeness. This produced a BAC of 47.8% and AUC of 0.43. Misclassifications showed a directionality toward the ROD group, with 80.4% of ROP+D patients being classified as ROD; Z=.713, p=.344) (see Table 2 and Figure 1b). Similarly to the clinical/neurocognitive model ROP+D patients were more frequently classified as ROD compared to pure ROP patients (χ^2=4.933; p=0.026). In contrast, the assignment precision of ROD+P and ROD patients did not differ (χ^2=0.005; p=0.943).

Stacking

When applied to the comorbid groups, the combined model predicted diagnostic group with a BAC of 58.5% and an area under the curve (AUC) of 0.66 (see Table 1 and Figure 1c).

Independent Validation

Application of our models to the independent validation sample replicated findings very well (pure clinical and neurocognitive model BAC 76.2; pure imaging model BAC 49.9; pure stacking model BAC 78.2). Full results from the independent validation analysis can be found in the supplement (Table S5).

Supplementary Analyses

See supplement S2 for additional exploratory analyses results.

Discussion:

Using repeated nested cross-validation techniques we built classification models based on transdiagnostic clinical and neurocognitive features and GMV data, together with a combined model integrating all data modalities, to classify prototype diagnostic groups of ROD and ROP participants without comorbidity. Eighty-seven per cent of patients with pure ROP and

ROD were accurately ascribed to their diagnostic group. Applying this model to groups with comorbidity, 88% of patients with ROD and psychotic features were ascribed to their primary diagnostic group (depression) whereas only 37% of patients with ROP and depressive features were ascribed to their primary diagnostic group (psychosis). The shift of comorbid psychosis patients towards the depression prototype was observed both at the clinical and biological levels. This suggests that when comorbid with affective symptoms, psychoses align more strongly to the disease processes of depressive than psychotic disorders. Using GMV measures only for classification, comorbid groups ROP patients with depressive symptoms largely resembled pure ROD. Results were generalisable to our independent validation sample.

Our findings suggest that clinical and neurocognitive transdiagnostic symptoms may have differential weight within psychosis and depression presentation with and without comorbidity. In pure groups, these symptoms could be seen as under the hierarchical umbrella of psychosis or depression, and may accurately reflect underlying pathology in these groups. However, in the face of comorbidity, transdiagnostic symptoms lean more to the depression domain. Given the prevalence and importance of depressive comorbidity in early psychosis this may support a model where depression could be more intrinsically important than is currently considered in early phases of illness[4,29]. When participants with ROP exhibited even mild depressive symptoms, their GMV classification was more likely to lie within the depression group than psychosis suggesting a potential depressive biological phenotype that exists in the psychosis spectrum. The implications of these findings suggest that understanding heterogeneity of brain structures may need to include specific focus on symptoms that may often be masked by more acute (e.g. positive) symptoms and simple solutions that some symptoms may be transdiagnostic, potentially belie the complexity of individual aetiology and psychopathology. Furthermore, these findings indicate a need to rethink current diagnostic classification to better reflect the biological reality and eventually develop better treatment options.

A classical diagnostic hierarchy in the structure of personal illness, reflected in current nosological classification systems, posits that mental disorders of the primary diagnosis have more weight and primacy over symptoms from lower classes, which are seen as secondary or comorbid[18,19]. We found that comorbid symptoms affect diagnostic structures in different ways. Sub-clinical psychotic-like symptoms appeared to not alter the signature of ROD

patients whilst depressive symptoms had a profound effect on ROP patients' classification accuracy.

Our findings add evidence to the debate around the validity of the system on which the DSM is built upon[50], suggesting that a descriptivist position in the diagnosis of mental disorder is not sufficient and that a novel multivariate approach of mental disorder is more appropriate. Comorbidity in psychiatric disorders presents a clinical as well as nosological challenge. There may be significant interplay between sets or clusters of symptoms over the development of disorder from prodrome via onset to potential chronicity. The frequency of depression within ROP may be a primary driver, rather than being a secondary symptom. If identified correctly, novel symptoms may be new targets that if treated effectively, ameliorate the other, e.g. positive symptoms.

Recent onset disorders may constitute groups of phenotypically highly individual symptoms with underlying aetiopathology, and it may be that personalized treatments could be tailored accordingly. Our SVM classification model found that different types of anhedonia (social and physical) were important in the classification of both psychosis and depression. Anhedonia has been suggested as a possible biomarker for depression[51] and has been found to be associated with decreased activation in ventral basal ganglia areas, the dorsal anterior cingulate, middle frontal gyrus, and medial frontal gyrus both in schizophrenia and depression[52]. Our GMV model revealed that orbitofrontal areas were higher weighted in the classification to the ROD group.

The relationship between psychotic and affective symptoms has been central to the dilemma of psychiatric classification. Substantial clinical and genomic evidence shows that schizophrenia and affective disorders may be distributed across a dimensional spectrum[53]. However, the dimensional spectra model does not allow for either the clinical reality of a complex and changing symptom profile, nor the investigation of clinical features commonly seen across all disorders; some of which may be of primary importance. Concerning the neurobiology of schizophrenia and depression, the majority of previous studies are based in subjects with depression or psychosis, but only rarely in both[25,54] and not previously in highly mixed recent onset comorbid disorders. Our results suggest that while GMV showed some distinction in prototype (pure) groups, when presented with complex comorbid groups, which may be the majority in clinical practice, there was a significant lack of any point of rarity between disorders. This builds on previous work suggesting distinction is more challenging,

but also that neuroimaging based data do not support categorical classification in recent onset disorders [25]. In recent onset disorders, early cognitive processes related to depression can both drive other more severe symptoms and/or be seen in isolation: for example, anhedonia could be an early indication of negative symptom clusters or a core feature of co-morbid depression[55].

Strengths and Limitations

The strengths of the present analysis include sufficiently large data, robust collection of clinical and imaging data from both depression and psychosis groups, independent validation analysis together with a novel approach to a challenging and essential clinically relevant research question, which speaks to the validity of diagnoses as the cornerstone of psychiatric practice. Our results however should be interpreted with certain caution due to limitations with the study. Regarding our definition of the ROD+P group we used a SIPS-P item score of 2 or more which is not a marker of formal psychotic symptoms, and thus would only measure low levels of psychotic-like symptoms. However to supplement this we used a SPI-A COGDIS item score of 3 or more. We did not include core symptomatology measures such as the PANSS and the BDI in our features due to the fact that primary groups are defined with these measures, and therefore including them would risk a circular analysis. Finally, there were more subjects identified in the pure ROD and comorbid ROP groups; ideally groups of equal size would have been used. Nevertheless, we addressed this imbalance in our analysis, by increasing the C value in the minority class by multiplying it by the inverse ratio of the training class sizes.

Conclusions

Findings from this large, multi-modal, replicated machine learning classification study in recent onset disorders suggest that whilst there may be a small subset of prototypically pure individuals with clear categorical disorder, the majority of patients share a number of transdiagnostic features, primarily from the depression domain. Brain structure of psychosis patients with co-morbid depressive symptoms largely resembles that of depression. The increasing interest in heterogeneity of early disorders and transdiagnostic symptoms as novel treatment targets needs to be fully informed of potential depression related co-morbidity**.** Our analysis in recent onset groups also highlight that both categorical and transdiagnostic approaches may ultimately fail at an individual patient level, as neither recognise the

possibility of pluripotent pathways that are both stage and context dependent. The implications, particularly for early intervention and prevention in mental health disorders is that ultimately a personalised medicine approach, encompassing the full potential of comorbidity, may be necessary to improve outcomes**.** Future studies should investigate the utility of targeting such transdiagnostic depression features to elucidate their prognostic value, and develop new treatments.

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Legends

Legend Figure 1: Classification Performance of the Pure and Applied Clinical and Neurocognitive, GMV, and Combined Models.

A. Pure Clinical and Neurocognitive Classification Balanced Accuracy 79.3%, Sensitivity 76.3%, Specificity 82.2%, AUC 0.86. Applied Clinical Classification Balanced Accuracy 57.6%, Sensitivity 39.1%, Specificity 76%, AUC 0.71.

B. Classification Performance of the Pure GMV Model and the Applied GMV Model. Pure GMV Classification Balanced Accuracy 62.5%, Sensitivity 39.5%, Specificity 85.6%, AUC 0.70. Applied GMV Classification Balanced Accuracy 50.3%, Sensitivity 20.7%, Specificity 80%, AUC 0.47.

C. Classification Performance of the Combined Model and the Applied Combined Model. Stacked Classification Balanced Accuracy 79.5%, Sensitivity 78.9%, Specificity 80%, AUC 0.87. Applied Stacked Classification Balanced Accuracy 64.6%, Sensitivity 53.3%, Specificity 76%, AUC 0.71.

Legend Figure 2: Feature Weights and Cross-Validations Ratios of the most Significant Features.

A. Feature Weights. Derived from 1000 random permutations of the outcome labels and features.

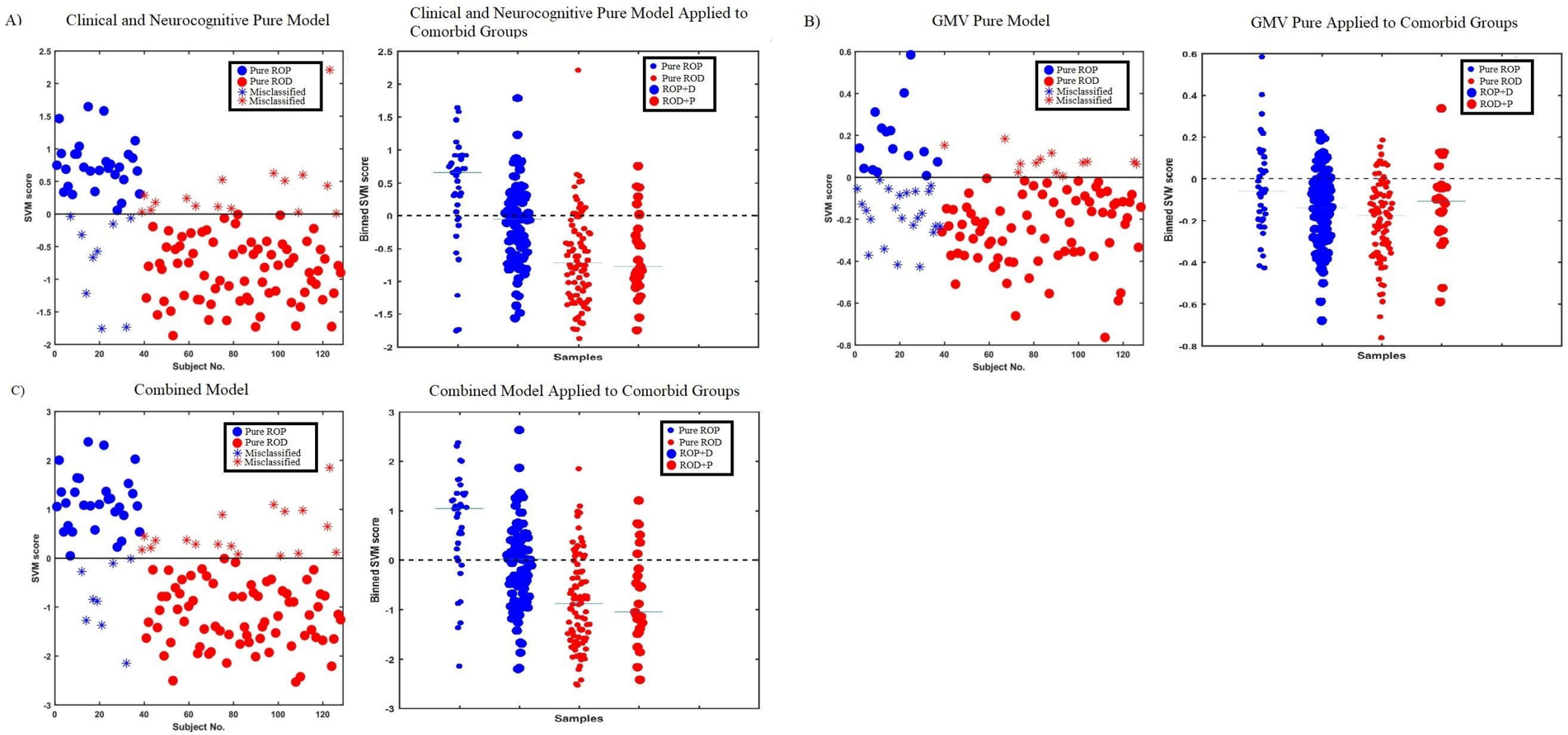
B. Cross-Validation Ratio. Sum of the median weights across all CV1 folds divided by the standard error.

Legend Figure 3: Significant Regions in the Imaging Classification Model. ROP GMV Reductions in the Thalamus and the Cerebellum, ROD GMV Reductions in Orbitofrontal, Limbic, and Paralimbic Regions.

Legend Table 1: Sample Sociodemographics. Sample Sizes, Participants per Study Site, Age, Sex, Education, Partnership Status, Population Density.

Legend Table 2: Classification Performance of the Clinical and Neurocognitive, GMV, and Combined Models and Validation Performance.

Figure 1. Classification Performance of the Pure and Applied Clinical, GMV, and Combined Models.



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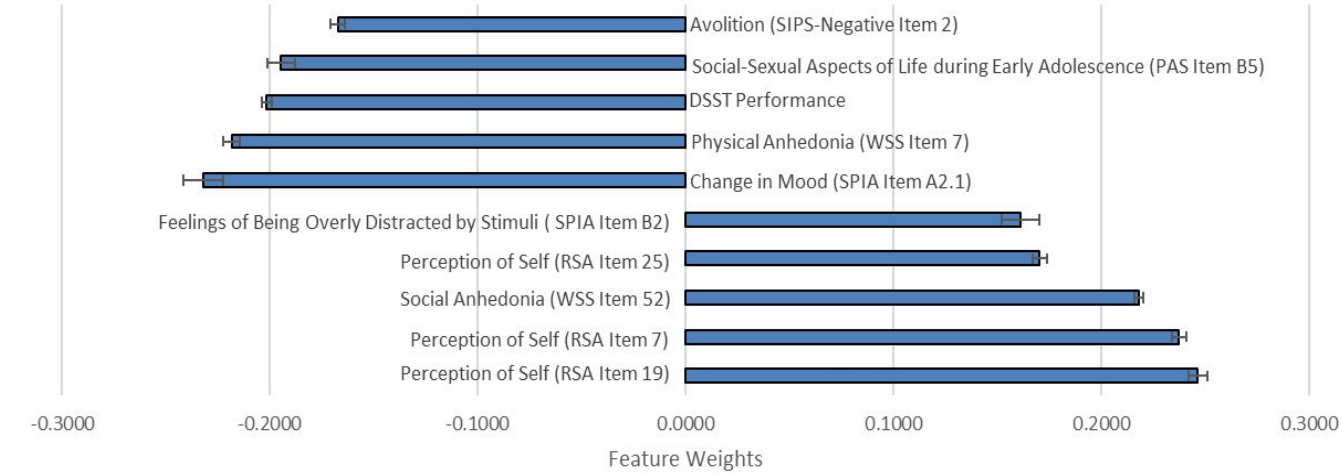
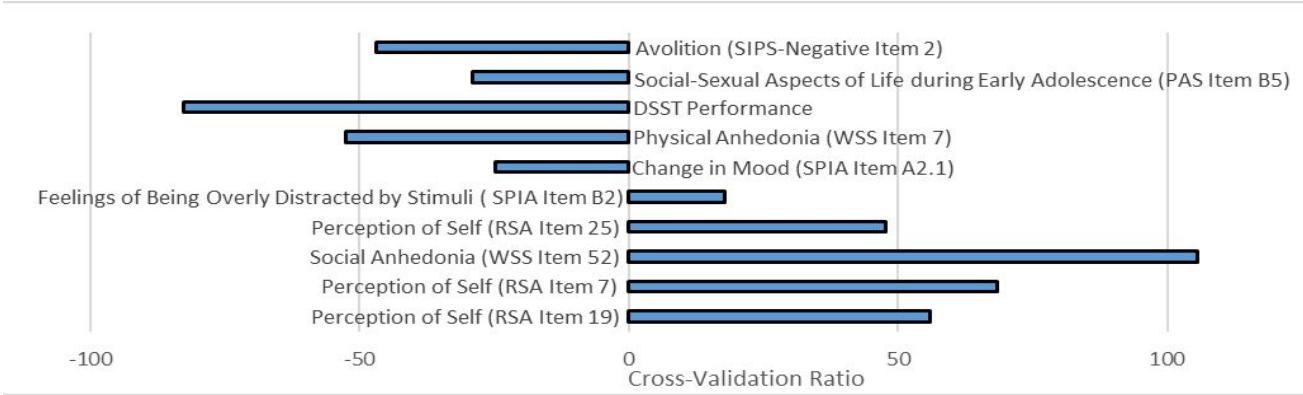


B. Cross-Validation Ratio. Sum of the median weights across all CV1 folds divided by the standard error.



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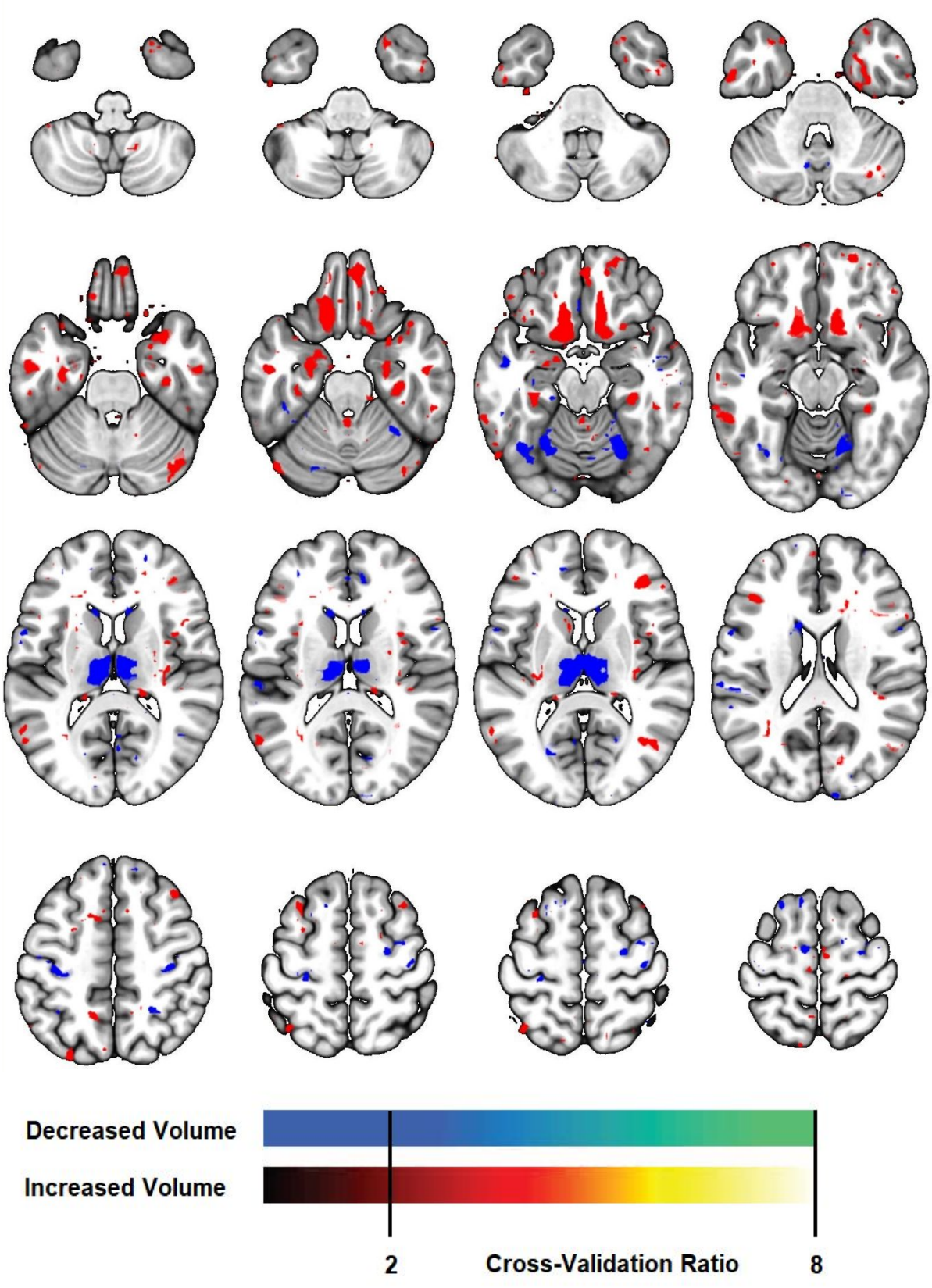

Table 1.Sample Sociodemographics. Sample Sizes, Participants per Study Site, Age, Sex, Education, Partnership Status, Population Density.

	ROP Group	ROD Group	t/χ2	P Value	Pure ROP Group	Pure ROD Group	t/z/χ2	P Value	ROP+D Group	ROD+P Group	t/z/χ2	P Value
Sample Sizes, No.	154	146			38	90			92	25		
Participants per site, No. (%)												
Basel	23 (7.7)	17 (5.7)			3 (2.3)	8 (6.9)			14 (12)	6 (5.1)		
Birmingham	10 (4.7)	10 (3.3)			4 (3.1)	0 (0)			10 (8.5)	2 (1.7)		
Cologne	27 (9)	27 (9)			4 (3.1)	19 (14.8)			22 (18.8)	3 (2.6)		
Milan	13 (4.3)	7 (2.3)	$\chi^2 = 8.9$	.257	8 (6.3)	5 (3.9)	$\chi^2 = 21.0$	.002	1 (0.9)	0 (0)	$\chi^2 = 6.1$	.517
Munich	46 (15.3)	47 (15.7)			10 (7.8)	35 (27.3)			31 (26.5)	7 (6)		
Turku	22 (7.3)	13 (4.3)			11 (8.6)	7 (5.5)			7 (6)	3 (2.6)		
Udine	12 (4)	21 (7)			2 (1.6)	12 (9.4)			3 (2.6)	3 (2.6)		
Age, Mean (SD)	24.7 (5.4)	25.5 (6.1)		.229	26.5 (6.8)	26.5 (6.6)		.959	24.6 (4.8)	23.8 (3.9)		.449
Sex (Male/Female)	94/60	67/79	$\chi^2 = 6.9$	.009	25/13	45/45	$\chi^2 = 2.6$	.101	57/35	12/13	$\chi^2 = .81$	.368
Education, mean (SD)	13.9 (2.4)	15.1 (7.5)	$t = 1.85$	.064	13.9 (2.2)	15.8 (9.3)	$t = 1.22$	.224	14.0 (2.6)	13.5 (2.3)	$t = -.838$	.404
Educational years repeated, mean (SD)	1.8 (2.5)	2.3 (2.7)	$t = 1.47$	.141	.83 (.87)	1.1 (1.8)	$t = 1.00$	.319	3.1 (4.8)	5.0 (5.4)	$t = 1.70$	.091

Having partnership most of the time in the year before study inclusion, No. (%)	72 (24.7)	85 (29.2)	$\chi^2 = 4.1$	.036	17 (13.4)	51 (40.2)	$\chi^2 = 1.6$	.194	48 (41.4)	18 (15.5)	$\chi^2 = 2.9$	.085
Population density in living area, mean (SD), habitants/km2	3717.8 (2532.3)	3529.8 (2377.1)	$t = -.544$	.587	4498.3 (2724.6)	3022.1 (2274.3)	$t = -2.640$	.010	3447.9 (2338.5)	5152.1 (2361.8)	$t = 2.547$	.013

Table 2. Classification Performance of the Clinical/Neurocognitive, GMV, and Combined Models and Validation Performance.

	True Positive, No.	True Negative, No.	False Positive, No.	False Negative, No.	Balanced Accuracy, %	AUC	Model P Value
Clinical/Neurocognitive Pure Model ROP-ROD	29	74	16	9	79.3	0.86	<0.001
Applied Clinical/Neurocognitive Model ROP+D-ROD+P	36	19	6	56	57.6	0.71	NA
Applied Clinical and Neurocognitive Model Validation Pure ROP-ROD	34	39	14	16	70.8	0.78	NA
Applied Clinical and Neurocognitive Mode Validation ROP+D-ROD+P	27	20	5	63	55	0.56	NA
GMV Pure Model ROP-ROD	15	77	13	23	62.5	0.7	<0.001
Applied GMV Model ROP+D-ROD+P	19	20	5	73	50.3	0.47	NA
Applied GMV Model Validation Pure ROP-ROD	17	38	15	33	52.8	0.59	NA
Applied GMV Model Validation ROP+D-ROD+P	31	17	8	59	51.2	0.6	NA
Combined Model ROP-ROD	30	72	18	8	79.5	0.87	NA
Applied Combined Model ROP+D-ROD+P	49	19	6	43	64.6	0.71	NA
Applied Combined Model Validation Pure ROP-ROD	36	38	15	14	71.8	0.78	NA

Applied Combined Model Validation ROP+D-ROD+P	31	18	7	59	53.2	0.56	NA

Transdiagnostic Features, Comorbidity and Classification of Recent Onset Psychosis and Depression: a Multimodal Machine Learning Approach

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Keywords: psychosis, depression, transdiagnostic, machine learning, MRI, comorbidity

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Supplementary Methods and Results

1. Supplementary Methods

1.1. PRONIA recruitment infrastructure

The 300 study participants (154 individuals with ROP and 146 individuals with ROD) analyzed in the present study were recruited following a standardized recruitment and ascertainment protocol (see **Figure S1** and **Table S3**). The observational study protocol involved follow-up examinations every three months after the index ascertainment and was implemented by the following 7 PRONIA sites:

Table S1: Characteristics of the recruiting institutions in the PRONIA consortium.

PRONIA Site	Institution Name	Country	Type of Service	Catchment Population	Screening population / year
Munich	Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University Munich	DE	Academic outpatient services including specialized service for early recognition of psychosis; tertiary care academic hospital	1,200,000	700
Basel	Department of Psychiatry and Psychotherapy, University of Basel	CH	Academic inpatient and outpatient services including specialized service for early recognition and intervention of psychosis; tertiary care academic hospital	500,000	200
Milan Niguarda	Department of Pathophysiology and Transplantation, University of Milan. Four recruitment hospitals: Niguarda, Policlinico, San Paolo, Villa San Benedetto Menni in Albese con Cassano	IT	Psychiatric outpatient services including specialized services for early recognition of psychosis and persons at high risk; Academic hospital, providing psychiatric inpatient services, psychiatric outpatient services and local services;	600,000	1,000
Cologne	Department of Psychiatry and Psychotherapy, University of Cologne	DE	Academic outpatient services including specialized service for early recognition of psychosis; tertiary care academic hospital	1,000,000	600
Birmingham	The University of Birmingham	UK	Academic specialised Early Intervention Service for Psychosis covering Birmingham and Solihull. Community and Inpatient	1,200,000	800
Turku	Department of Psychiatry, University of Turku	FI	Psychiatric outpatient and hospital services responsible for treatment of psychiatric patients in their catchment areas in the South-Western Finland.	284,000	2,300

Udine	Department of Psychiatry, University of Udine	IT	Psychiatic outpatient services, academic hospital and local services. Tertiary care neuropsychiatric service	600,000	500

Upon study enrolment, the participants were pseudonymized twice, locally at each site and centrally at the level of the PRONIA portal. The PRONIA portal consists of a multi-user database hosting the clinical and neurocognitive information, and defaced MR images obtained from the study participants. The data are organized into digital questionnaires, visits, and cases. The portal provides the case managers with a controlled web-based interface to enter and upload the different data into the respective questionnaires. Furthermore, the PRONIA consortium has implemented a PRONIA@home mobile device interface that allows the study participants to securely log into the portal and fill out the self-rating questionnaires of given visit. Upon completion of the data entry across all questionnaires of given visit, the data are checked by an automatic quality control procedure which executes approximately 1600 data integrity and dependency rules. These rules include (1) basic checking of missing data and data ranges, (2) checking of dependency within one questionnaire, (3) dependencies between two questionnaires within one visit, and (4) dependencies between two consecutive visits (such as consistency of dates). Detected errors are fed back to the respective case managers allowing for a manual correction of the respective issues. This process is re-iterated until the quality of the clinical questionnaires in the given visit is sufficient for the entire visit to be locked.

1.2. PRONIA study design and examination instruments

A comprehensive battery of ascertainment tools was used within a longitudinal observational study design to generate a multi-modal phenotypic profile of each study participant (see **Figure S1** and **Table S2**). The clinical part of the battery compiled questionnaires that capture sociodemographic, somatic, environmental, diagnostic, psychopathological, functional and quality-of-life related variables in the PRONIA study population. This battery was complemented by multi-domain neurocognitive and neuroimaging examinations as well as blood sampling for later genetic characterization, which were carried out at the baseline and 9-month follow-up timepoints.

Table S2: Clinical and neurocognitive examinations performed in the CHR, ROD, ROP, and HC groups during the 18-month follow-up period of the study. **Clinical assessment types:** *OR* Observer-based rating instrument, *SR* Self-rating-based instrument. **Examination timepoints:** *T0* Baseline examination, *IV3/IV6/IV12/IV15* 3, 6, 12, 15-month examinations conducted only in the clinical study participants, *T1* 9-month examination, *T2* 18-month follow-up examination. **Observer-based instruments:** CAARMS Comprehensive Assessment of the At-Risk Mental States[1], *CHR Criteria* Clinical High-Risk criteria summary questionnaire, *FROGS* Functional Remission in General Schizophrenia[2], *GAF* Global Assessment of Functioning, *GF:S/R* Global Functioning: Social / Role[3], *PANSS* Positive and Negative Symptom Scale[4], *PAS* Premorbid Adjustment Scale[5], *SANS* Scale for the Assessment of Negative Symptoms[6], *SCID-IV Screening/Summary* Structured Clinical Interview for DSM-IV[7], *SIPS* Standardized Interview for the Assessment of Prodromal Symptoms (modified version 5.0)[8], *SPI-A [COGDIS/COPER]* Schizophrenia Proneness Instrument [Cognitive disturbances (COGDIS) / Cognitive-Perceptual (COPER) disturbances][9], Transition Criteria Interval questionnaire for the assessment of transition criteria, *UHR - Schizotypy, Genetic Risk* Interview for the Assessment of Schizotypal personality traits, and familial risk for psychosis. **Self-rating instruments:** *BDI-II* Beck Depression Inventory II[10], *CISS-24* Coping Inventory for Stressful Situations – 24 items[11], *CTQ* Childhood Trauma Questionnaire[12], *EHI-SR* Edinburgh Handedness Inventory – Short Version[13], *EDS* Everyday Discrimination Scale – Modified Version[14], *LEE* Level of Expressed Emotions[15], *MSPSS* the Multidimensional Scale for Perceived Social Support[16], *NEO-FFI* NEO Five Factor Inventory of Personality Traits[17], *RSA* Resilience Scale for Adults[18], *SPIN* Social Phobia Inventory[19], *WHO-QOL-BREF* WHO Quality of Life Questionnaire-Brief Version[20]. Neurocognitive tests: *CPT-IP* Continuous-Performance Test-Identical Pairs (adapted tablet version)[21], *DANVA* Diagnostic Analysis of Non-Verbal Accuracy 2 (adapted tablet version)[22], *DS* Auditory Digit Span (Forward/Backward) adapted from the PEBL battery, *DSST* Digit-Symbol-Substitution Test from the BACS battery, *ROCF* Rey-Osterrieth complex figure[23], *SAT*

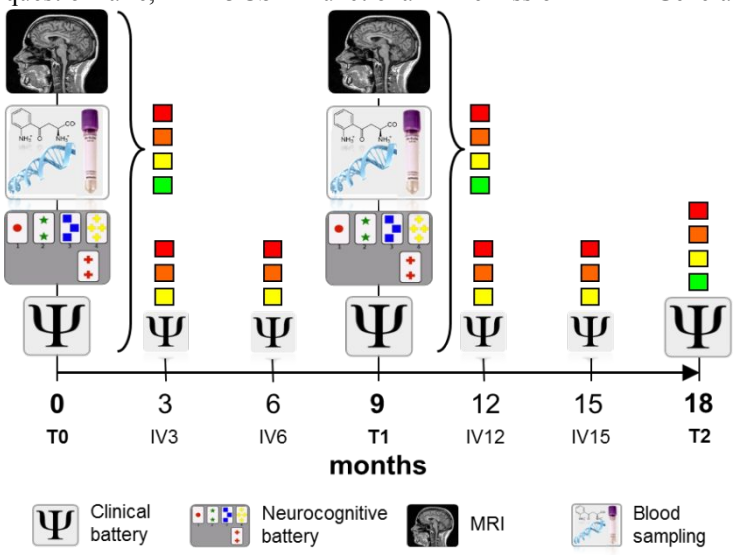

Figure S1: Observational study design of PRONIA. Colored boxed indicate type of assessment / visits conducted in each of the study groups: Healthy controls (green), patients with recent-onset depression (yellow), persons with a clinical high-risk for psychosis (orange), patients with recent-onset psychosis (red).

Salience Attribution Task (adapted version)[24], *SOPT* self-ordered pointing task (adapted version)[25], *TMT-A/-B* Trail-Making Test A and B[26], *VF* phonemic/semantic verbal fluency test.

Instrument	Form	Screening		T0		IV3	IV6	T1		IV12	IV15	T2	
		PAT	HC	PAT	HC	PAT	PAT	PAT	HC	PAT	PAT	PAT	HC
General Data	OR	X	X					X	X			X	X
Reasons for Referral	OR	X											
Treatment Documentation	OR	X	X			X	X	X	X	X	X	X	X
Somatic state and Health History	OR	X	X					X	X			X	X
SPI-A COGDIS/COPER	OR	X	X			X	X	X	X	X	X	X	X
SIPS positive symptoms	OR	X	X			X		X	X			X	X
CAARMS	OR	X	X			X		X	X			X	X
GAF	OR	X	X			X		X	X			X	X
UHR – Schizotypy, Genetic Risk	OR	X	X			X		X	X			X	X
CHR Criteria	OR	X	X					X	X			X	X
Transition Criteria	OR					X	X			X	X		
SCID-IV Screening	OR	X	X					X	X			X	X
SCID-IV Summary	OR	X	X					X	X			X	X
Demographic and Biographic Data	OR			X	X			X	X			X	X
PAS	OR			X	X			X				X	
SPI-A	OR			X	X			X				X	
SIPS negative, disorganized and general symptoms	OR			X	X			X				X	
PANSS	OR			X		X	X	X		X	X	X	
SANS	OR			X				X				X	
Chart of Life Events	OR			X	X	X	X	X	X	X	X	X	X
FROGS	OR			X				X				X	
GF: Social & Role	OR			X	X	X	X	X	X	X	X	X	X
Prognostic evaluation	OR			X				X				X	
MSPSS	SR			X	X			X	X			X	X
RSA	SR			X	X			X	X			X	X
CISS 24	SR			X	X			X	X			X	X
SPIN	SR			X	X			X	X			X	X
BDI-II	SR			X	X	X	X	X	X	X	X	X	X
WHO-QOL-BREF	SR			X	X			X	X			X	X
EHI-SR	SR			X	X								
LEE	SR			X	X			X	X			X	X
Wisconsin Scales	SR			X	X								
EDS	SR			X	X								
Bullying Scale T0	SR			X	X								
CTQ	SR			X	X								
NEO-FFI	SR			X	X								
DS backward (BACS)	NPT			X	X			X	X				
DS forward (BACS)	NPT			X	X			X	X				
CPT-IP (BACS)	NPT			X	X			X	X				
DANVA	NPT			X	X			X	X				
DSST	NPT			X	X			X	X				
RAVLT	NPT			X	X			X	X				
ROCF	NPT			X	X			X	X				
SAT	NPT			X	X			X	X				
SOPT	NPT			X	X			X	X				
TMT-A	NPT			X	X			X	X				
TMT-B	NPT			X	X			X	X				
VF phonetic	NPT			X	X			X	X				
VF semantic	NPT			X	X			X	X				
WAIS-III	NPT			X	X			X	X				

1.3. MRI harmonization and data acquisition

When setting up the PRONIA study, we decided to generate a MRI database that would represent the MR scanner sequence heterogeneity encountered in clinical real-world. The aim of this strategy was to strengthen the generalizability and clinical applicability of the predictive models developed by our machine learning analyses. Thus, we agreed on a minimal harmonization protocol that required the PRONIA sites to only (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. At every site all the images were visually inspected, automatically defaced and anonymized using an in-house Freesurfer-based script before the data was centralized. **Table S3** lists the parameters defining the structural MR sequences used to examine in the PRONIA discovery sample participants.

Table S3: MR scanner systems and structural MRI sequence parameters used at the respective PRONIA sites.

PRONIA Site	Model	Field Strength	Coil Channels	Flip Angle	TR [ms]	TE [ms]	Voxel Size [mm]	FOV	Slice Number
Munich	Philips Ingenia	3T	32	8	9.5	5.5	0.97 x 0.97 x 1.0	250 x 250	190
Milan Niguarda	Philips Achieva Intera	1.5T	8	12	Shortest (8.1)	Shortest (3.7)	0.93 x 0.93 x 1.0	240 x 240	170
Basel	SIEMENS Verio	3T	12	8	2000	3.4	1.0 x 1.0 x 1.0	256 x 256	176
Cologne	Philips Achieva	3T	8	8	9.5	5.5	0.97 x 0.97 x 1.0	250 x 250	190
Birmingham	Philips Achieva	3T	32	8	8.4	3.8	1.0 x 1.0 x 1.0	288 x 288	175
Turku	Philips Ingenuity	3T	32	7	8.1	3.7	1.0 x 1.0 x 1.0	256 x 256	176
Udine	Philips Achieva	3T	8	12	Shortest (8.1)	Shortest (3.7)	0.93 x 0.93 x 1.0	240 x 240	170

1.4. MRI processing pipeline

The manual of the CAT12 toolbox (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf) details the processing steps applied to the structural images. These steps consist of:

(1) A 1st denoising step based on Spatially Adaptive Non-Local Means (SANLM) filtering[27].

(2) An Adaptive Maximum A Posteriori (AMAP) segmentation technique, which models local variations of intensity distributions as slowly varying spatial functions and thus achieves a homogeneous segmentation across cortical and subcortical structures[28].

(3) A 2nd denoising step using Markov Random Field approach which incorporates spatial prior information of adjacent voxels into the segmentation estimation generated by AMAP[28].

(4) A Local Adaptive Segmentation (LAS) step, which adjusts the images for white matter (WM) inhomogeneities and varying gray matter (GM) intensities caused by differing iron content in e.g. cortical and subcortical structures. The LAS step is carried out before the final AMAP segmentation.

(5) A Partial Volume Segmentation algorithm that is capable of modeling tissues with intensities between GM and WM, as well as GM and cerebrospinal fluid (CSF) and is applied to the AMAP-generated tissue segments.

(6) A high-dimensional DARTEL registration of the image to a MNI-template generated from the MRI data of 555 healthy controls in the IXI database (http://www.braindevelopment.org).

(7) The GM maps were then multiplied with the Jacobian determinants that were obtained during registration in order to produce GM volume maps.

(8) The Quality Assurance framework of CAT12 was used to check the quality of the GMV maps.

1.5. Support Vector Machine Learning Preprocessing

Prior to the machine learning analysis the following preprocessing steps were completed: a) every feature was scaled from 0 to 1 and completely non-finite features were zeroed-out; b) any feature that had infinite values was pruned; c) missing values were imputed using KNN Euclidean distance median replacement using 7 nearest neighbours. For each missing value of a given CV1 or CV2 subject, a subset of cases that had values for the given variable and had values in all other variables which were non-empty were identified. Subjects in the source subset were sorted according to their similarity with the target subject using the Euclidean distance. Then, the median of the given variable was computed using the 7 nearest neighbours. The original, non-imputed training matrix was used at all times d) site effects were corrected for. This step consisted of i) performing a principal components analysis, ii) identifying the components that are most correlated with site variance, and iii) reconstructing the data without these components in order to effectively remove such effects from the data. Any component with a Spearman correlation coefficient greater than 0.5 was excluded from the analysis and 90% of the variance was retained. e) the data was scaled again. The model performance criterion that was used was balanced accuracy and the learning algorithm that was chosen was LIBSVM. Imbalanced learning was corrected for by increasing the C value in the minority class by multiplying it by the inverse ratio of the training class sizes (weighting the hyperplane). The kernel type that was linear with eleven learning parameters in order to optimize the choice of C value. Wrapper methods were activated at all parameter combinations with greedy sequential backward feature selection (Stop at k=90% of features; Feature stepping at 10% of worst performing features at each cycle). Starting with the full feature set the SVM was ran iteratively with the 10% worst performing features being eliminated at each cycle until 10% of the feature pool was left. In order to assess the models' statistical significance we performed permutation analysis to create an

empirical null distribution of weights for each feature and then compare the observed weight to this distribution. The models were retrained in the cross-validation framework using the respective feature and label subsets obtained from the observed-label analyses 1000 times. For each permutation the predictions were accumulated into a permuted ensemble prediction for each CV2 subject. In that way a null distribution of out-of-training classification performance for the prediction models was produced. The significance of the observed out-of-training classification performance was calculated as the number of events where the permuted out-of-training classification performance was higher or equal to the observed classification performance divided by the number of permutations performed. Then the significance of the model was determined according to a p threshold of $p<0.05$. Furthermore we applied a sign-based consistency algorithm to calculate the number of times that the sign of each feature (positive or negative) was consistent within an ensemble multiplied by the number of times that the feature was non-zero. The measure is between 0 to 1, with 1 representing perfect consistency within the ensemble and 0 if the weights are equally positive and negative or when the feature is omitted with a zero weight. A p-value was then calculated by defining a hypothesis test for the importance score with a null hypothesis of 0. A z-score was calculated as the importance divided by the square root of the variance of the importance scores. A standard p-value was then calculated using a normal cumulative distribution function to choose the right-tailed significance. P-values were then corrected using the false-discovery rate.

For the neuroimaging model the same steps used apart from: 1) when inputting the grey matter volume (GMV) images into the modality a G-theory mask[29] was used for quantifying the degree of reliability for the imaging modalities based on a travelling participants study and 2) during preprocessing of the neuroimaging model the following additional steps were completed a)any

feature that had infinite values was pruned; b) features were ranked up using external ranking by means of hard selection thresholds (15%, 25%, and 50%). Only the top 15%, 25%, and 50% features as defined by the G-theory mask were kept; c) Principal Component Analysis (PCA) Dimensionality Reduction (dimensions: 0.8); d) every feature was scaled from 0 to 1 and completely non-finite features were zeroed out; 3) when visualizing the classification a 8 FWHM kernel was used to smooth the images.

Finally, a stacking-based data fusion framework[30,31] was used to examine whether the combination of the clinical-based and the neuroimaging-based models would provide a superior classification accuracy. To achieve this, the decision scores of the neuroimaging and the clinical models were combined, standardized, and forwarded to a greedy sequential forward search algorithm[32] which found a parsimonious combination of classifiers maximizing $\overline{\text{PSI}_{\text{reg}}}$ across the C parameter range by employing L2-regularized logistic regression (L2LR)[33]. Each L2LR ensemble was then applied to the standardized neuroimaging and clinical based decision scores available for the CV_2 validation data. Class prediction was achieved by using majority voting on Majority voting on P_{ens}.

1.6. Hyperparameter Optimization

For hyperparameter optimization, we computed

$\overline{\text{BAC}_{\text{reg}}} = \sum_{i=1}\left(\frac{n_{TP_i}}{n_{TP_i}+n_{FN_i}}+\frac{n_{TN_i}}{n_{TN_i}+n_{FP_i}}\right)\Big/2$ at given parameter combination across all k CV_1 partitions with $n_{TP_i}/n_{TP_i}+n_{FN_i}$ being Sensitivity and $n_{TN_i}/n_{TN_i}+n_{FP_i}$ being Specificity, and the fraction of the training population serving as support vectors in the i^{th} CV_1 partition. Our optimization technique's aim was to find a combination of T_G, PCs and the SVM's regularization

parameter C [range: $2^{[-3 \overrightarrow{\in \mathbb{Z}} +4]}$ that maximized $\overline{\text{BAC}_{\text{reg}}}$ within a 3 (T_G) × 5 (PC) × 8 (C) hyperparameter cube. The optimized ensemble was then applied to the CV_2 validation data to produce a mean decision score ($\overline{D_{ens}}$) and majority voting-based class membership probabilities (P_{ens}) for each CV_2 validation subject. This produced a mean decision score ($\overline{\text{(D\_ens)}}$) and majority voting-based class membership probabilities (P_ens) for each CV2 validation subject.

1.7. Stacking Fusion Framework

The decision scores of the neuroimaging and the clinical models were combined, standardized, and forwarded to a greedy sequential forward search algorithm[32] which found a parsimonious combination of classifiers maximizing $\overline{\text{PSI}_{\text{reg}}}$ across the C parameter range by employing L2-regularized logistic regression (L2LR)[33]. Each L2LR ensemble was then applied to the standardized neuroimaging and clinical based decision scores available for the CV_2 validation data. Class prediction was achieved by using majority voting on Majority voting on P_{ens}.

1.8. Clinical/Neurocognitive Model List of Tests

The clinical and neurocognitive tests used to train the clinical support vector machine learning model were the following: (1) Wisconsin Schizotypy Scale (WSS) physical and social anhedonia subscales[34–36]; (2) Premorbid Adjustment Scale (PAS)[37,38], (3) Functional Recovery Scale in Schizophrenia (FROGS)[2]; (4) SIPS-negative[39]; (5) Schizophrenia Proneness Instrument, Adult version (SPI-A)[40]; (6) Resilience Scale for Adults (RSA)[18,41,42]; and a range of neurocognitive tests: (1) Digit Span Test (DST)[43,44]; (2) Phonemic Verbal Fluency (PVF)[43,45]; (3) Semantic Verbal Fluency (SVF)[43,45]; (4) Auditory-Verbal Learning Test (AVLT)[43], and (5) Digit Symbol Substitution Test (DSST)[43,44].

Table S4: DGPPN S3 Guidelines for the treatment of first-episode psychosis and schizophrenia *(translated English version of Table 4.1 stated in the short version of the guideline manual available in https://www.dgppn.de/_Resources/Persistent/a6e04aa47e146de9e159fd2ca1e6987853a055d7/S3_Schizo_Kurzversion.pdf).* ***Candidate CHR and ROD patients were excluded if they had received antipsychotic medication (1) for more than 30 cumulative days at or above the minimum target dosage threshold for the treatment of first-episode psychosis, or (2) within the past 3 months before psychopathological baseline assessments at or above the minimum target dosage threshold for the treatment of first-episode psychosis. Abbreviations:*** DI *dosage interval,* [2]*maximum recommended dosage according to prescribing information.*

Substance	Recommended starting dosage (mg/d)	DI'	Target dosage first-episode psychosis (mg/d)	Target dosage relapsing schizophrenia (mg/d)	Maximum dosage recommended (mg/d)[2]
Atypical Antipsychotics					
Amisulpride	200	(1)-2	100-300	400-800	1200
Aripiprazole	(10)-15	1	15-(30)	15-30	30
Olanzapine	5-10	1	5-15	5-20	20
Quetiapine	50	2	300-600	400-750	750
Risperidone	2	1-2	1-4	3-6-(10)	16
Ziprasidone	40	2	40-80	80-160	160
Typical Antipsychotics					
Fluphenazine	0.4-10	2-3	2.4-10	10-20	20-(40)
Flupentixole	2-10	1-3	2-10	10-60	60
Haloperidole	1-10	(1)-2	1-4	3-15	100
Perazine	50-150	1-2	100-300	200-600	1000
Perphenazine	4-24	1-3	6-36	12-42	56
Pimozide	1-4	2	1-4	2-12	16
Zotepine	25-50	2-(4)	50-150	75-150	450
Zuclopenthixole	2-50	1-3	2-10	25-50	75

Table S3: SCID DSM-IV diagnoses detailed breakdown in ROP groups (Discovery Sample)

	ROP total N=154
DSM Diagnosis	N (%)
Schizophrenia	72 (46.7)
Schizophreniform	13 (8.0)
Psychosis NOS	18 (11.7)
Delusional Disorder	11 (7.1)
Brief psychotic disorder	6 (3.8)
Substance Induced	3 (1.9)
Schizoaffective Disorder	10 (6.5)
Bipolar Disorder	12 (7.8)
Severe depression with psychosis	9 (5.7)

Table S4: Demographics of Replication Sample

	ROP Group	ROD Group	t/χ2	P Value	Pure ROP Group	Pure ROD Group	t/χ2	P Value	ROP+D Group	ROD+P Group	t/χ2	P Value
Sample Sizes, No.	161	131			50	53			90	25		
Age, Mean (SD)	25.6 (6.1)	25.0 (5.9)	*t* =.787	.432	25.8 (6.3)	25.7 (6.1)	*t* = .039	.969	25.3 (6.1)	25.5 (6.5)	*t* = -.156	.876
Sex (Male/Female)	89/71	68/62	χ^2 =.339	.844	30/20	24/29	χ^2 =2.234	.135	48/42	15/10	χ^2 =.351	.554

2. Supplementary Results

A number of exploratory supplementary analyses are presented in the supplementary results. These include a) correlational analyses between the clinical and imaging decision scores of the four different groups (Pure ROP/Pure ROD/ROP+D/ROD+P), in order to explore whether there was an association between clinical, and neuroanatomical features driving misclassification; b) association and comparison analyses between patients who were correctly classified and patients who were misclassified, to explore any potential 'sub-group' identification of misclassified participants; c) whole brain GMV comparison between the whole ROP and the whole ROD group, between subjects who were classified as ROP and subjects who were classified as ROD; and d) group level comparisons of the decisions scores of the three machine learning models.

2.1. Correlation of Clinical and Imaging Decision scores.

We wanted to examine the relationship between the clinical and imaging decision scores of our different groups (Pure ROP/Pure ROD/ROP+D/ROD+P) employing a Pearson correlation test. In figure S2 the non-significant positive correlation between the clinical and imaging decision scores in the Pure ROP group can be seen ($r = 0.005$, $p<.05$) In figure S3 we can see the positive correlation between the clinical and imaging decision scores in the Pure ROD group ($r = .112$, $p=.073$). Figure S4 shows the positive correlation between the clinical and imaging decision scores in the ROP+D group ($r = .062$, $p <.05$). Finally, figure S5 shows the positive correlation between the clinical and imaging scores in the ROD+P group ($r = .387$, $p =0.14$).

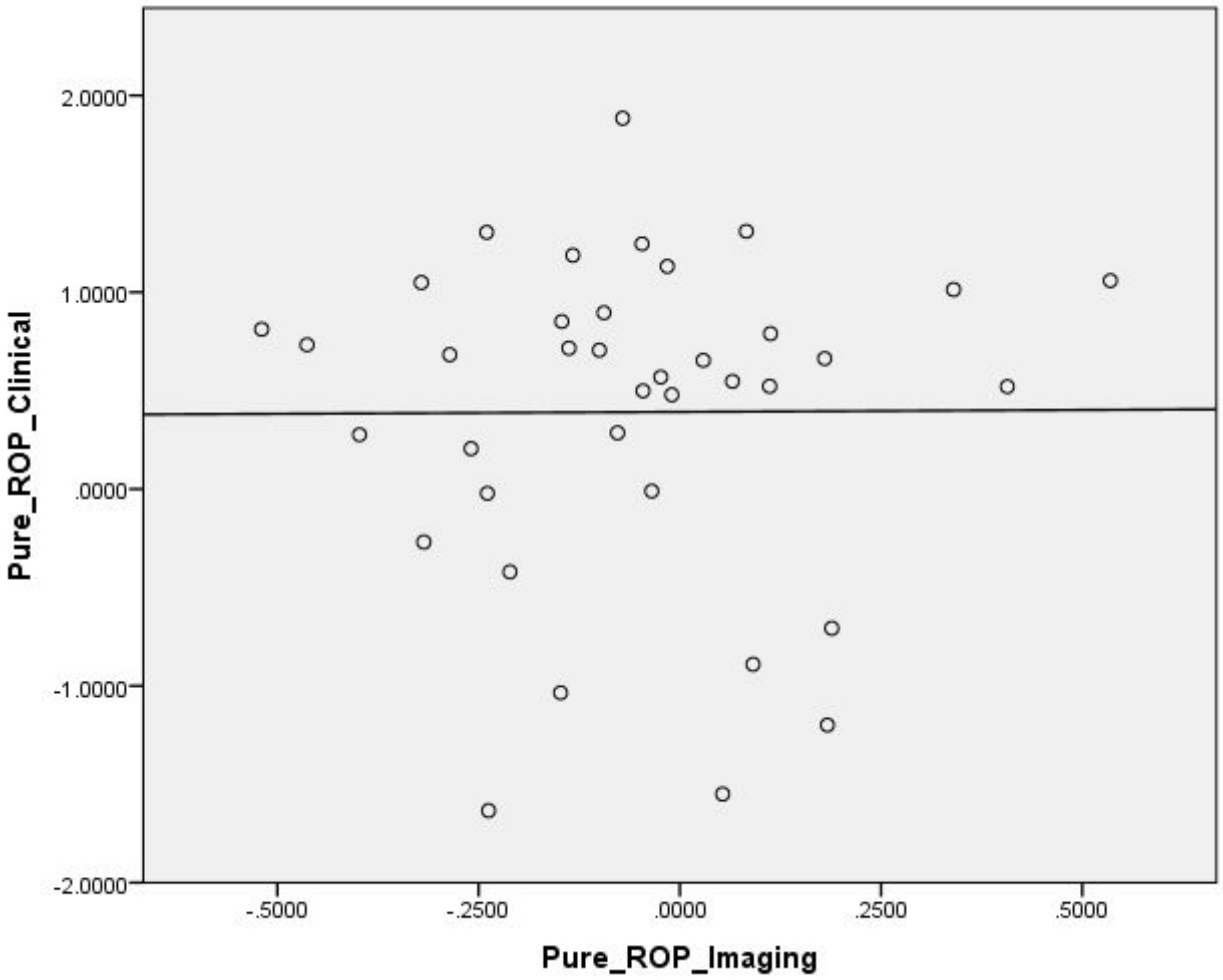

Figure S2. Pure ROP Clinical and Imaging Decision Scores Correlation

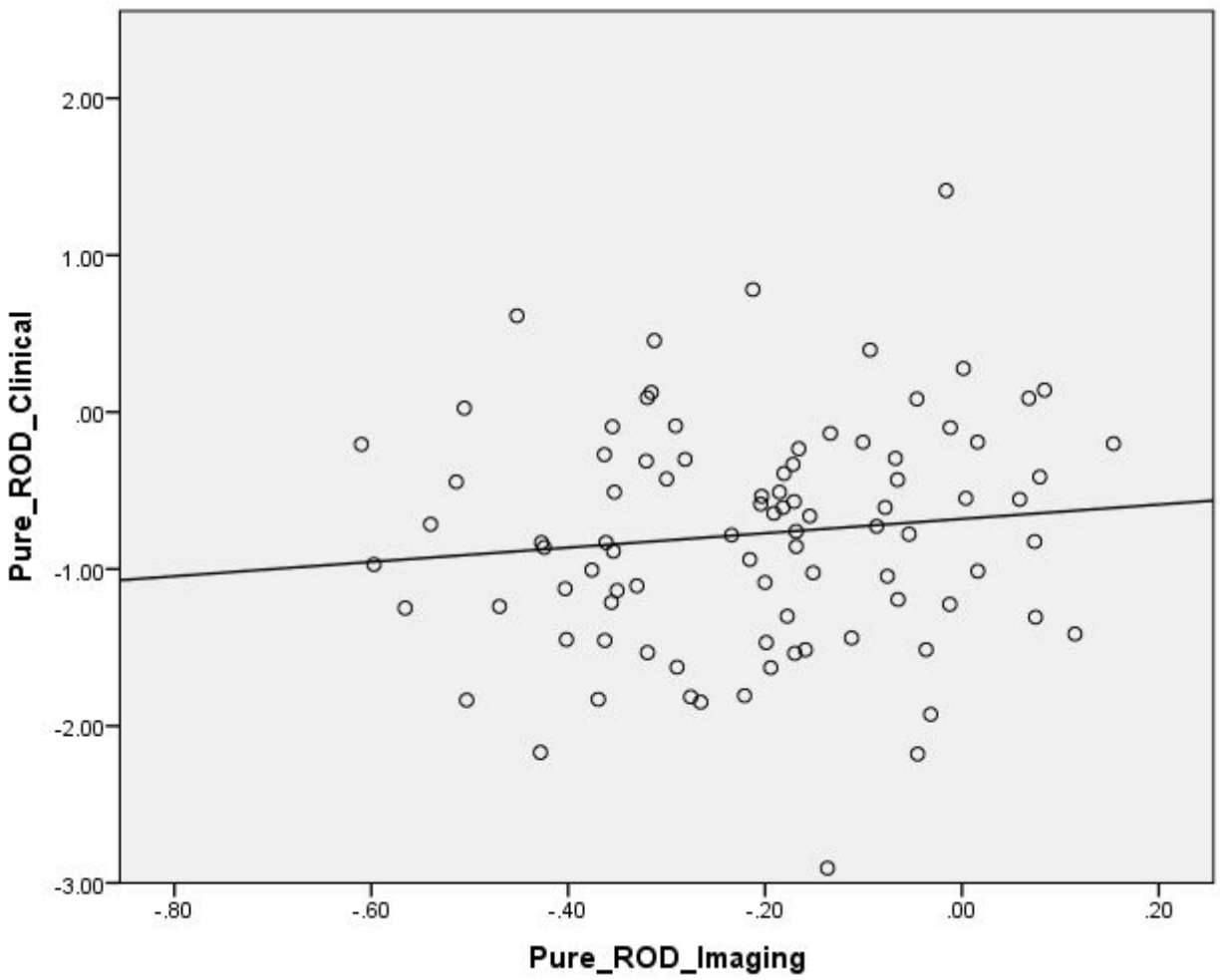

Figure S3. Pure ROD Clinical and Imaging Decision Scores Correlation

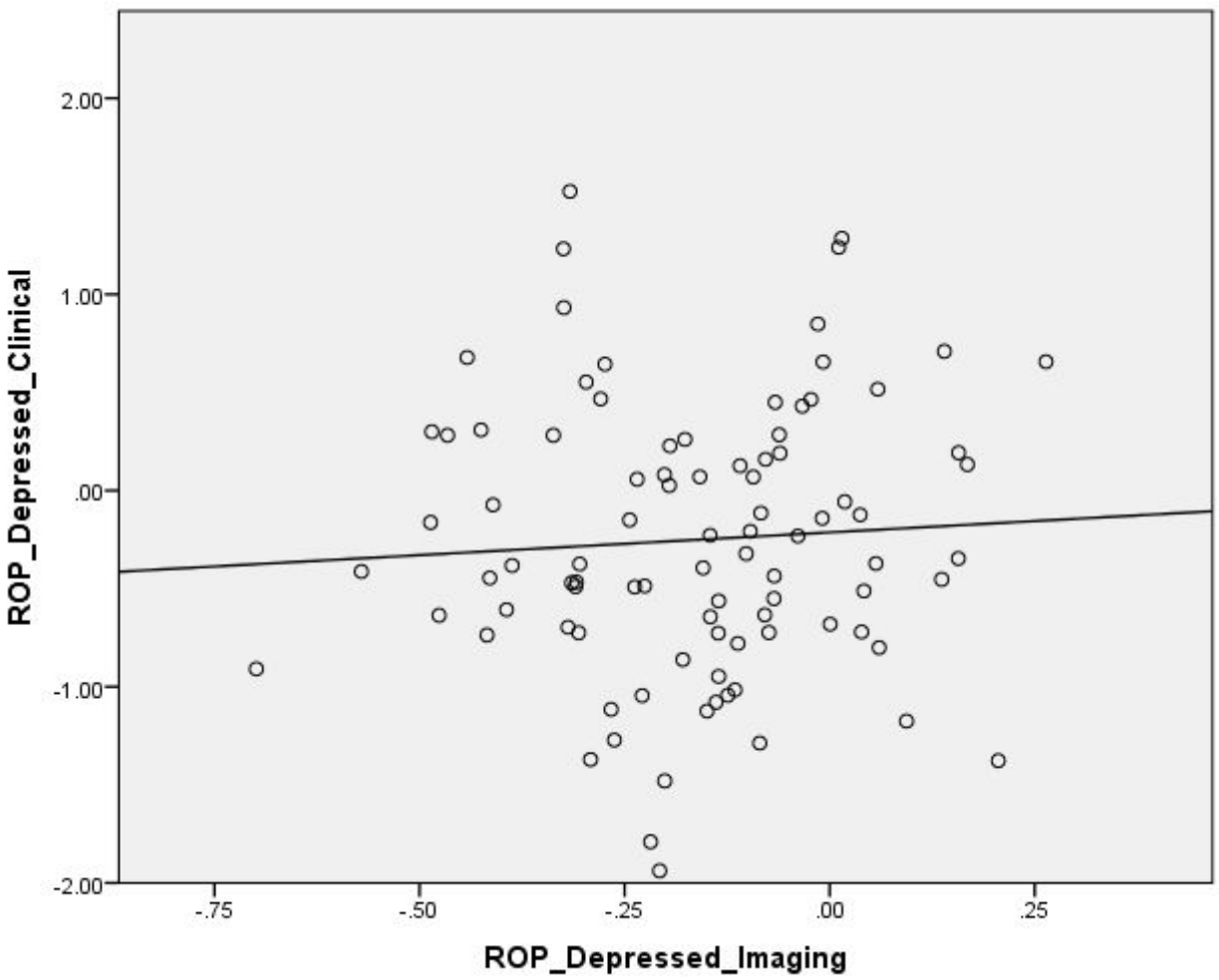

Figure S4. ROP Depressed Clinical and Imaging Decision Scores Correlation

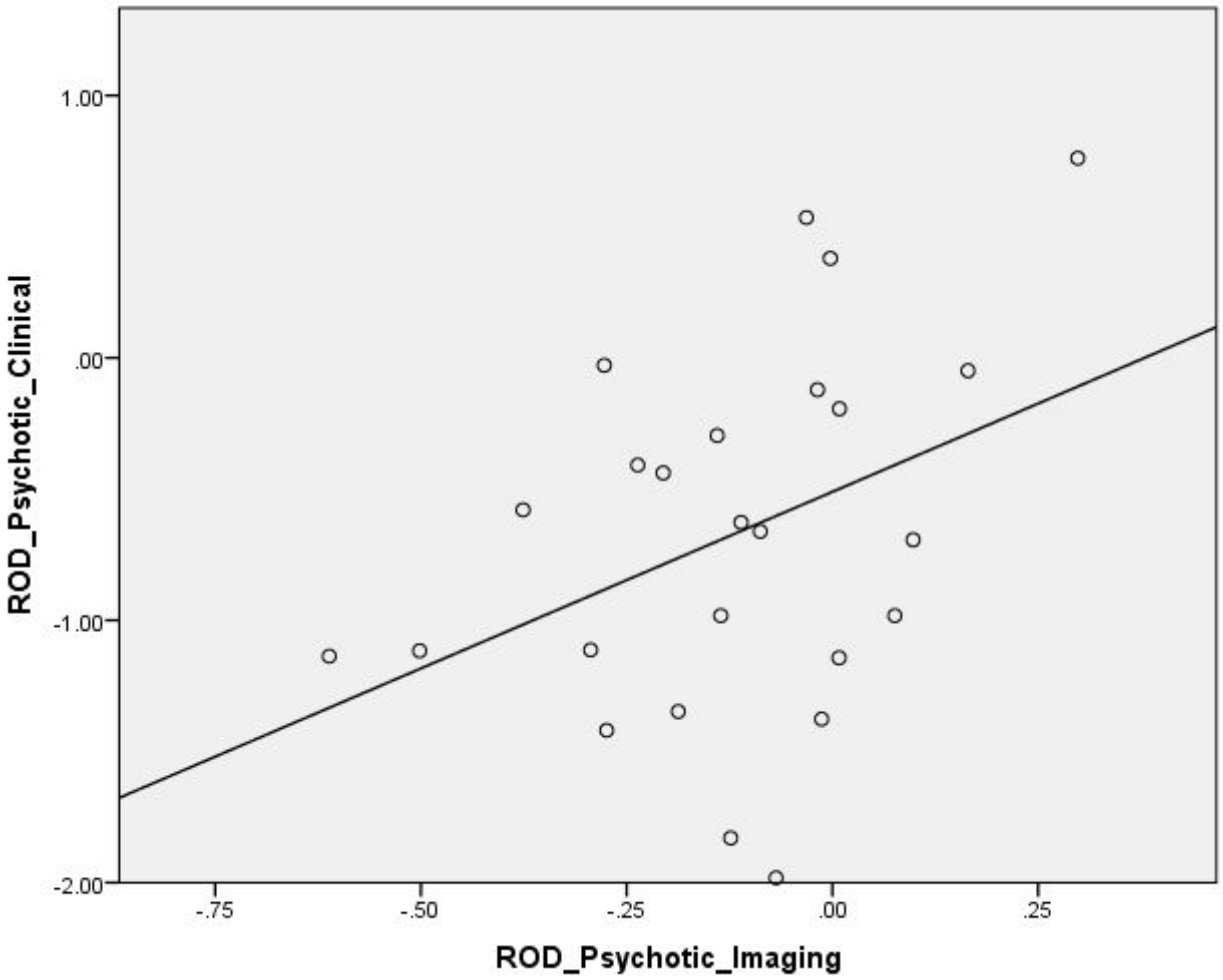

Figure S5. ROP Depressed Clinical and Imaging Decision Scores Correlation

2.2. Association and comparison analysis between patients who were correctly classified and patients who were misclassified

To understand the reasons why some of the patients in our sample were misclassified we performed a series of association and comparison analysis between those patients who were correctly classified and those who were misclassified using clinically relevant measures. In table S5 we can see the association between Pure ROP patients who were correctly classified as ROP and Pure ROP patients who were misclassified as ROD both in the clinical and imaging models. In Table S6 we have compared Pure ROP patients who have been correctly classified and Pure ROP patients who have been misclassified in seven clinically relevant measures (PANSS

Positive, WSS Perceptual Aberration, CAARMS Unusual Thought Content, CAARMS Non-Bizarre Ideas, and CAARMS Disorganized Speech), both in the clinical and the imaging models. Furthermore we performed an association analysis between ROP+D patients who had been correctly classified and ROD+D patients who had been misc**lassified (Table S7). C**orrectly classified ROP+D patients were compared to misclassified ROP+D patients in the same seven measures that were mentioned previously (Table S8).

Table S5. Association Analyses between Pure ROP Classification and Schizotypy Criteria

		SPD Criteria Not Met Count	SPD Criteria Not Met Expected Count	SPD Criteria Met Count	SPD Criteria Met Expected Count	$\chi 2$	P Value
Clinical Classification	Correct Classification	23	23.8	3	2.2		
	Misclassification	10	9.2	0	0.8	1.25	.131
Imaging Classification	Correct Classification	12	12.8	2	1.2		
	Misclassification	21	20.2	1	1.8	1.06	.151

329

330 **Table S6. Comparison Analyses between Pure ROP Correctly Classified and Pure ROP**
331 **Misclassified (P-Values with an asterisk survive FDR (Benjamini-Hochberg) correction**
332 **threshold)**

		Correctly Classified Mean and Standard Deviation	Misclassified Mean and Standard Deviation	*t*	P Value
Clinical Classification	PANSS Positive Total	16 (5.3)	13.7 (8.0)	1.013	.159
	WSS Magical Ideation Total	2.0 (2.0)	3.5 (2.7)	-1.780	.041*
	WSS Perceptual Aberration Total	.5 (.9)	1.1 (1.8)	-1.208	.117
	CAARMS Unusual Thinking Content	4.8 (2.1)	5.2 (1.9)	-.485	.315
	CAARMS Non Bizarre Ideas	4.6 (2.1)	2.7 (2.9)	2.203	.017*
	CAARMS Perceptual Abnormalities	3.6 (2.7)	5.2 (1.4)	-1.740	.045*
	CAARMS Disorganized Speech	2.4 (2.0)	2.0 (2.4)	.544	.295
Imaging Classification	PANSS Positive Total	13.1 (4.5)	16.8 (6.6)	-1.888	.034
	WSS Magical Ideation Total	2.8 (2.4)	2.1 (2.1)	.965	.170
	WSS Perceptual Aberration Total	.4 (1.3)	.8 (1.2)	-.846	.201
	CAARMS Unusual Thinking Content	4.6 (2.1)	5.0 (2.0)	-.599	.276

	CAARMS Non Bizarre Ideas	4.4 (2.3)	3.8 (2.5)	.724	.237
	CAARMS Perceptual Abnormalities	4.6 (2.2)	3.6 (2.6)	1.123	.134
	CAARMS Disorganized Speech	2.2 (1.9)	2.3 (2.2)	-.114	.455

Table S7. Association Analyses between ROP Depressed Classification and Schizotypy Criteria

		SPD Criteria Not Met Count	SPD Criteria Not Met Expected Count	SPD Criteria Met Count	SPD Criteria Met Expected Count	$\chi 2$	P Value
Clinical Classification	Correct Classification	28	30.3	6	3.7		
	Misclassification	54	51.7	4	6.3	2.55	.055
Imaging Classification	Correct Classification	16	16	2	2		
	Misclassification	66	66	8	9	.001	.485

Table S8. Comparison Analyses between ROP Depressed Correctly Classified and ROP Depressed Misclassified (P-Values with an asterisk survive FDR (Benjamini-Hochberg) correction threshold)

		Correctly Classified Mean and Standard Deviation	Misclassified Mean and Standard Deviation		

				t	P Value
Clinical Classification	PANSS Positive Total	20.0 (7.2)	17.9 (5.3)	1.609	.055*
	WSS Magical Ideation Total	5.1 (3.0)	4.1 (3.1)	1.540	.063
	WSS Perceptual Aberration Total	2.5 (2.7)	3.0 (3.5)	-.749	.228
	CAARMS Unusual Thinking Content	4.8 (1.9)	5.1 (1.6)	-.651	.258
	CAARMS Disorganized Speech	2.4 (2.2)	1.3 (1.6)	2.497	.007*
	CAARMS Non Bizarre Ideas	5.06 (1.9)	4.6 (2.1)	1.042	.150
	CAARMS Perceptual Abnormalities	3.1 (2.5)	3.4 (2.5)	-.505	.307
Imaging Classification	PANSS Positive Total	20.4 (6.3)	18.2 (6.0)	1.495	.069
	WSS Magical Ideation Total	4.2 (2.7)	4.5 (3.2)	-.385	.350
	WSS Perceptual Aberration Total	2.5 (2.9)	2.9 (3.3)	-.605	.258

CAARMS Unusual Thinking Content	5.3 (1.2)	4.9 (1.9)	1.073	.143
CAARMS Disorganized Speech	2.2 (1.7)	1.6 (1.9)	1.392	.083
CAARMS Non Bizarre Ideas	4.3 (2.4)	4.9 (1.9)	-1.187	.119
CAARMS Perceptual Abnormalities	3.6 (2.4)	3.2 (2.5)	.770	.215

2.3 GMV differences between groups

We also wanted to understand the neurobiology that was driving the classifications and misclassifications in our models. We therefore performed whole brain GMV comparisons a) between the whole ROP group and the whole ROD group b) between subjects from all groups who were classified as ROP (regardless of whether it was a correct classification or a misclassification) and c) between Pure subjects and co-morbid subjects. In figure S5 (a,b,c) we can see the GMV differences between the whole of the ROP group and the whole of the ROD group. The ROP group had increased GMV in the superior and inferior frontal gyrus whereas decreased GMV areas were detected in the left cerebellum, the Supramarginal gyrus, and the inferior temporal gyrus when compared to the ROP group (Table S9). Furthermore we compared subjects who were classified as ROP to subject who were classified as ROD according to our imaging model (figure S6 (a,b,c)). Subjects who were classified as ROP showed increased GMV in the insula, the caudate, and the precuneus

among others, whereas they showed decreased GMV in the lingual gyrus and the thalamus (Table S10). Finally we performed a whole brain GMV analysis between patients who were in Pure groups (both ROP and ROD) and patients who were in co-morbid groups (both ROP+D and ROD+P) (figure s7 (a,b,c)). Pure subjects showed pronounced GMV increases in the left cerebellum and the middle occipital gyrus and decreased GMV in the superior frontal gyrus and the lingual gyrus (Table S11).

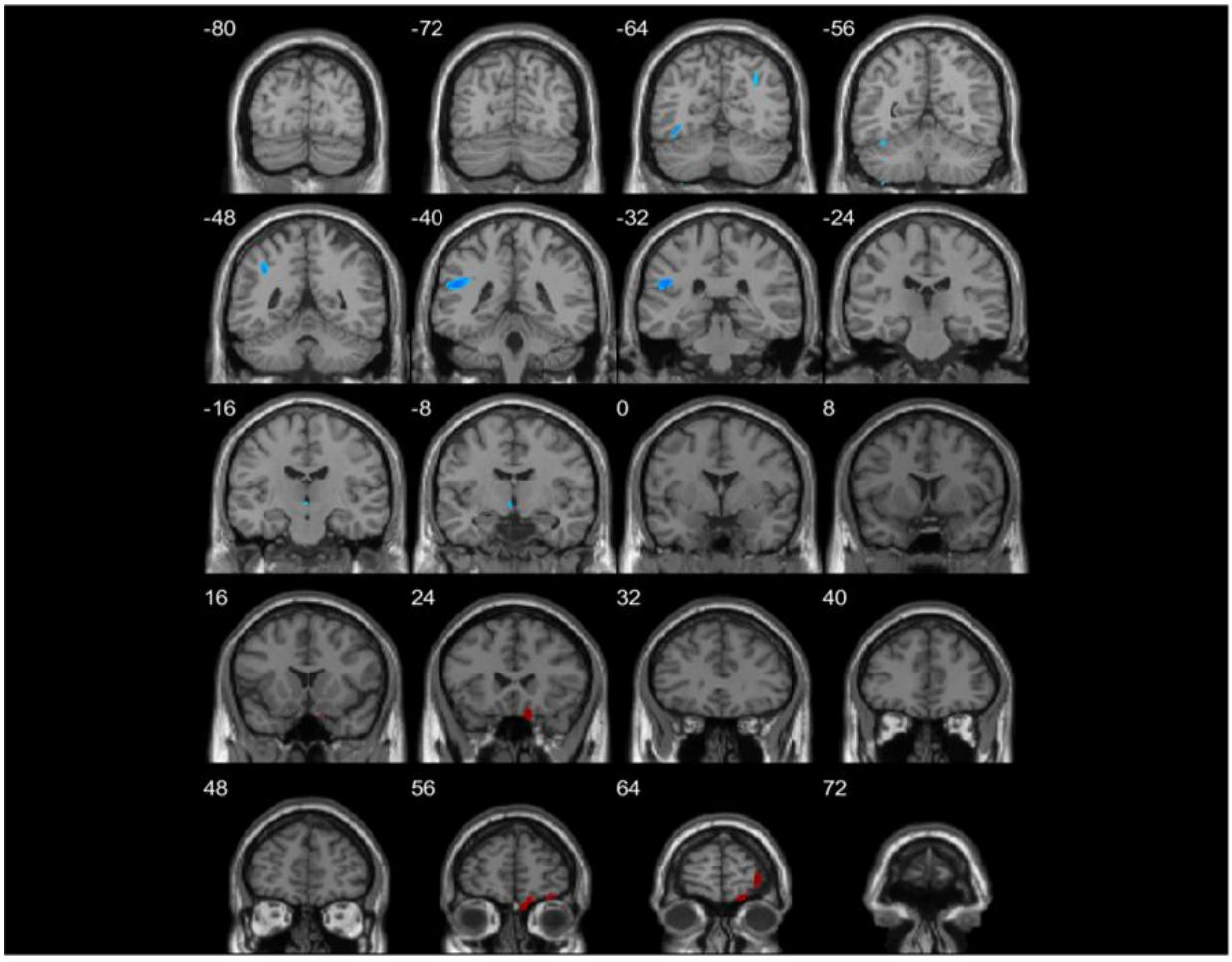

Figure S5a. Whole ROP Group vs Whole ROD Brain Differences

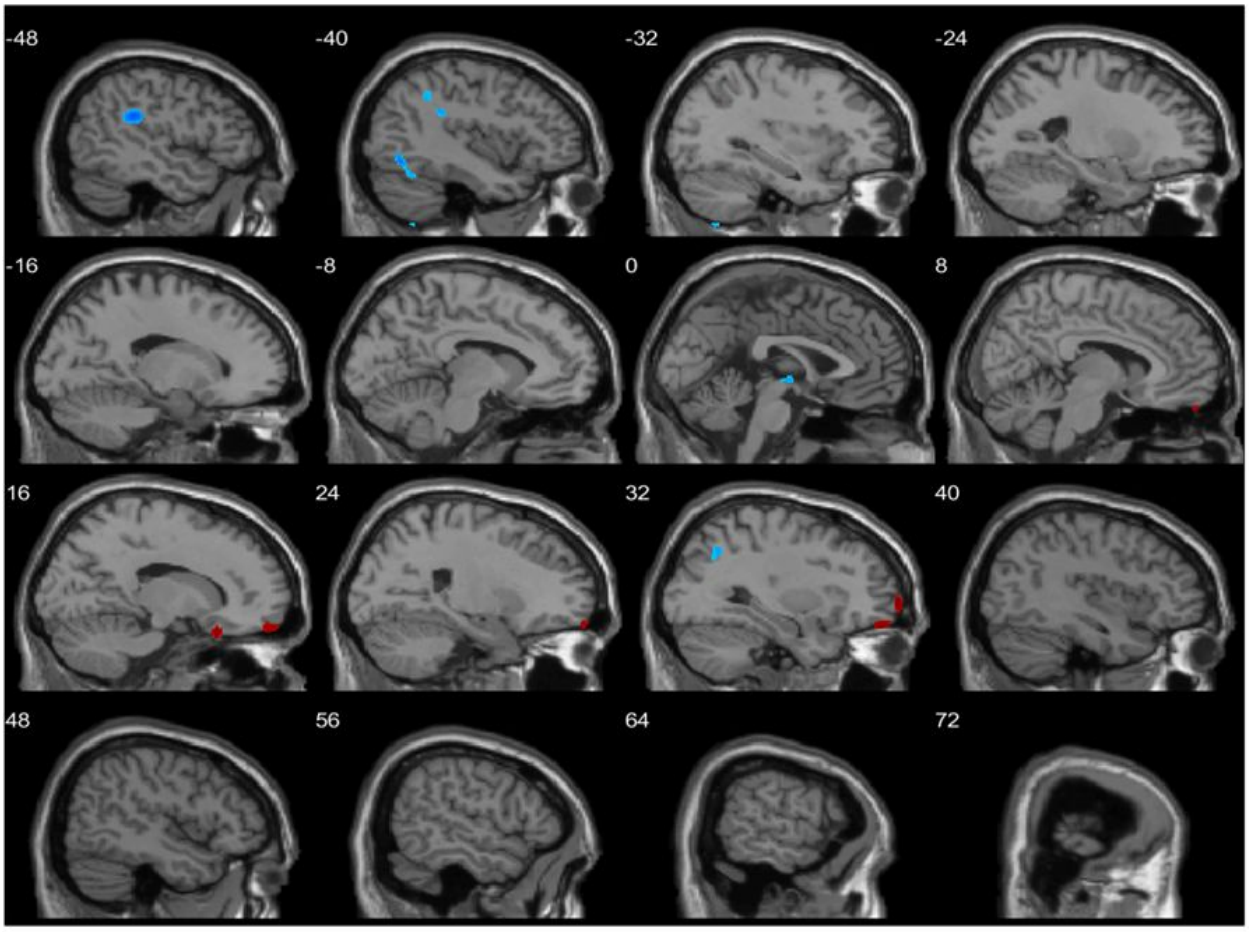

Figure S5b. Whole ROP Group vs Whole ROD Brain Differences

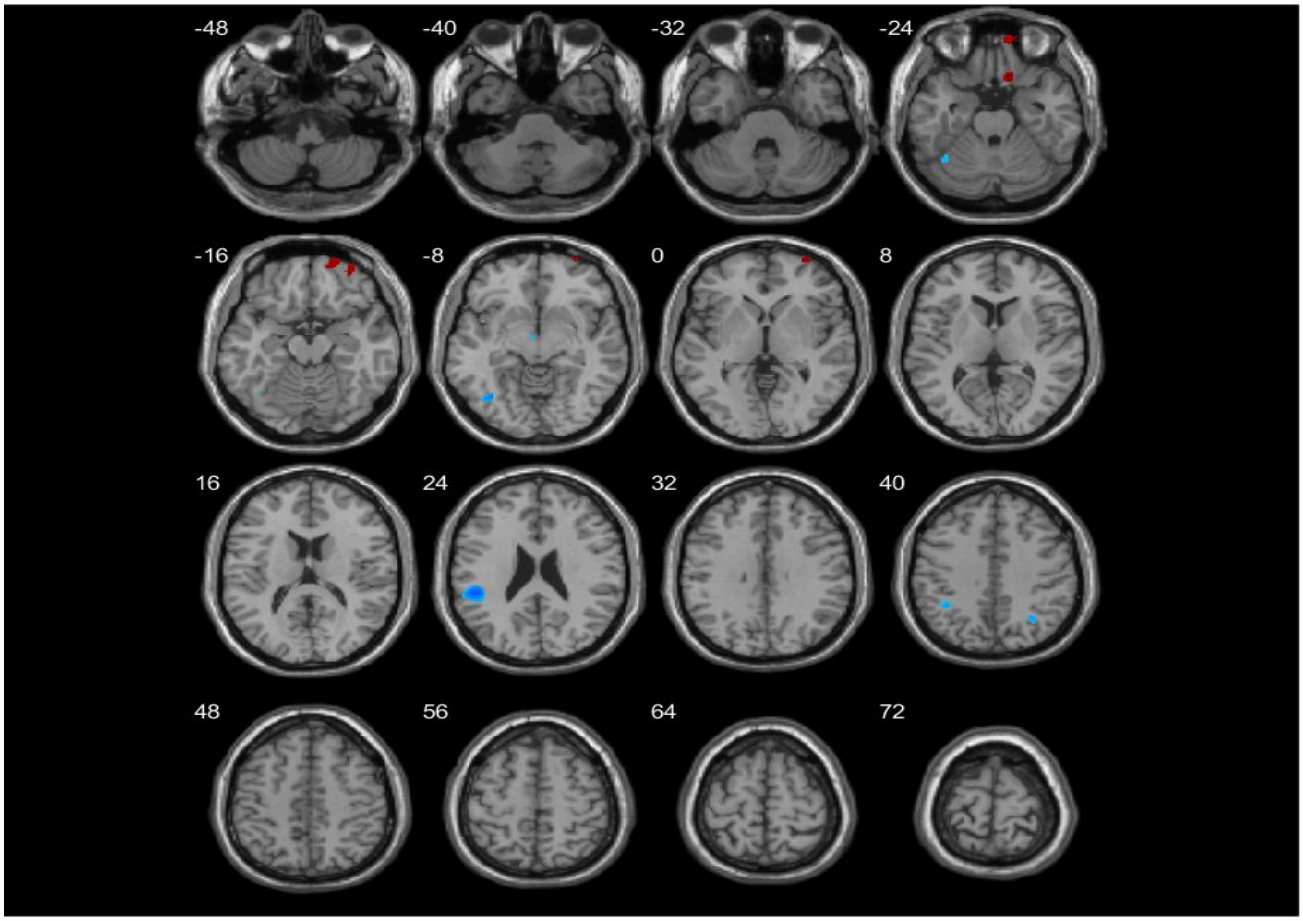

Figure S5c. Whole ROP Group vs Whole ROD Brain Differences

Table S9. Significant clusters from the Whole ROP Group vs Whole ROD Brain Differences analysis. Red=ROP greater GMV than ROD, Blue=ROP less GMV than ROD

Clusters ROP vs ROD

Brain Area	Cluster Peak Voxel MNI Coordinates	P Value, Peak Intensity, Cluster Size
Superior Frontal Gyrus	20 61 -19	p(FDR)=0.013, T=3.64, k=300
Inferior Frontal Gyrus	14 22 -25	p(FDR)=0.057, T=3.84, k=154
Left Cerebellum	-38 -66 -11	p(FDR)=0.044, T=-4.16, k=208
Supramarginal Gyrus	-50 -36 24	p(FDR)=0.001, T=-4.17, k=548
Inferior Temporal Gyrus	-22 3 -55	p(FDR)=0.001, T=-4.55, k=682

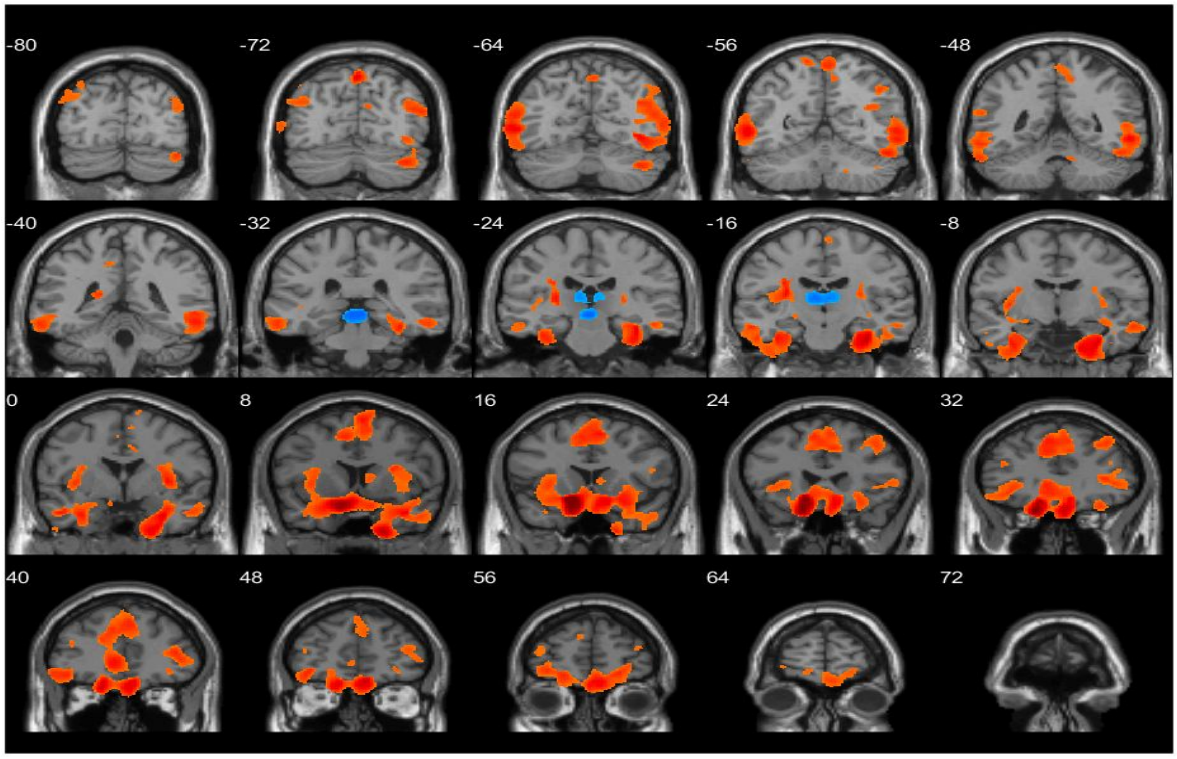

Figure S6a. Subjects Classified as ROP vs Subjects who were classified as ROD

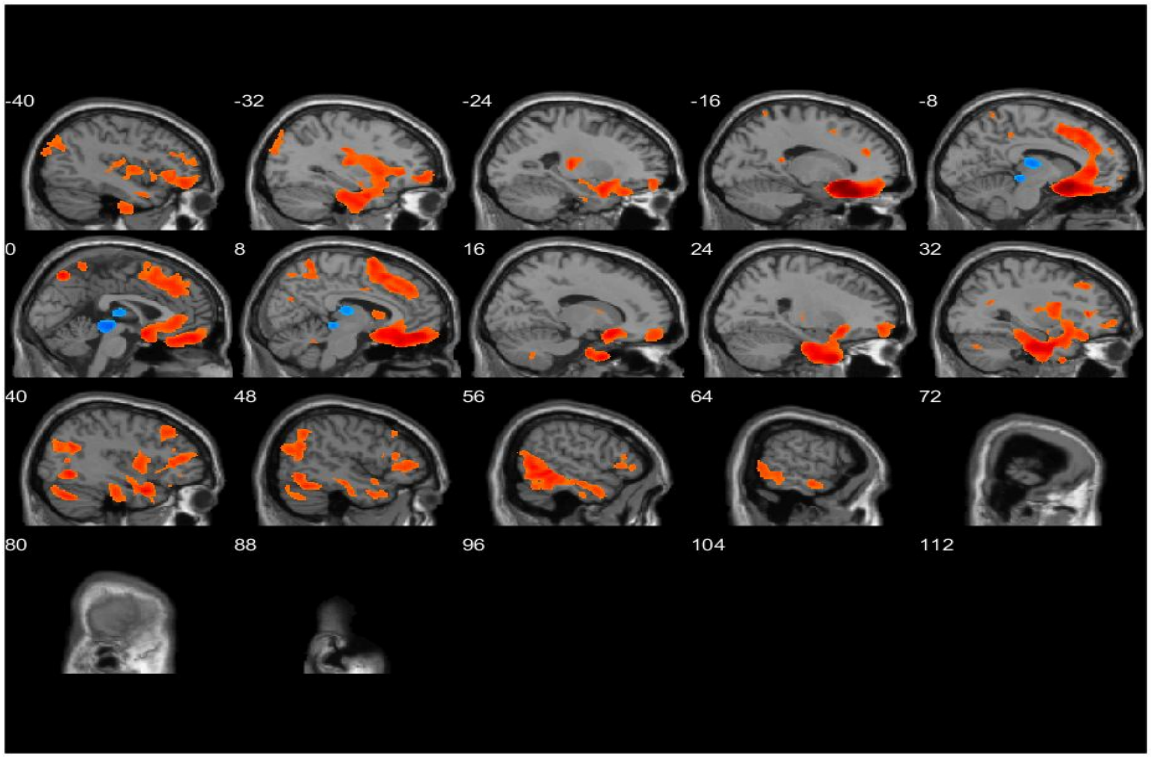

Figure S6b. Subjects Classified as ROP vs Subjects who were classified as ROD

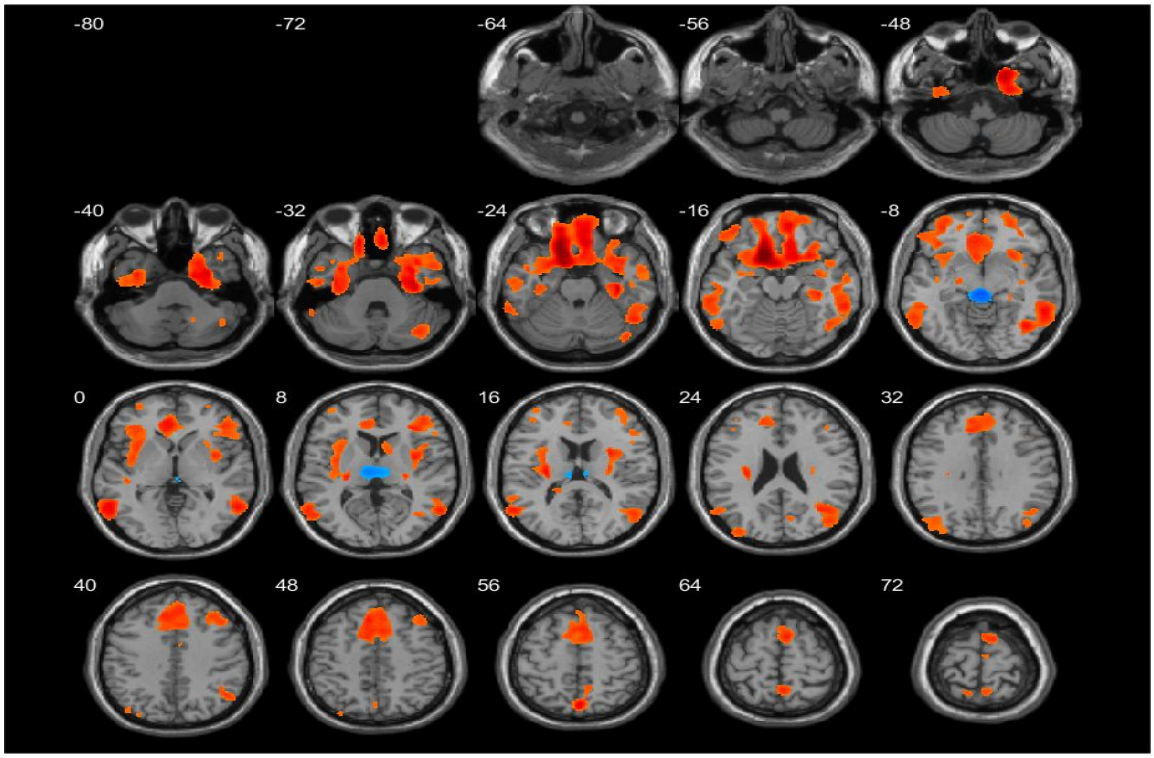

Figure S6c. Subjects Classified as ROP vs Subjects who were classified as ROD

Table 10. Subjects from all Groups Classified as ROP vs Subjects from all Groups Classified as ROD According to the Imaging Model. Red=ROP greater GMV than ROD, Blue=ROP less GMV than ROD

Clusters Classified as ROP vs Classified as ROD

Brain Area	Cluster Peak Voxel MNI Coordinates	P Value, Peak Intensity, Cluster Size
Middle Temporal Gyrus/Inferior Frontal Gyrus/Insula	-16 18 -13	p(FDR)<0.001, T=6.53, k=61340
Caudate	11 9 6	p(FDR)=0.057, T=3.58, k=288
Middle Frontal Gyrus	-40 34 21	p(FDR)=0.057, T=3.63, k=273
Superior Occipital Gyrus/Precuneus	-35 -86 24	p(FDR)<0.001, T=3.78, k=1117
Middle Frontal Gyrus	40 28 43	p(FDR)<0.001, T=3.98, k=826

Precuneus	1 -72 55	p(FDR)<0.001, T=5.12, k=1133
Lingual Gyrus	-2 -27 -8	p(FDR)<0.001, T=-4.35, k=888
Thalamus	4 -18 10	p(FDR)<0.001, T=-4.06, k=992

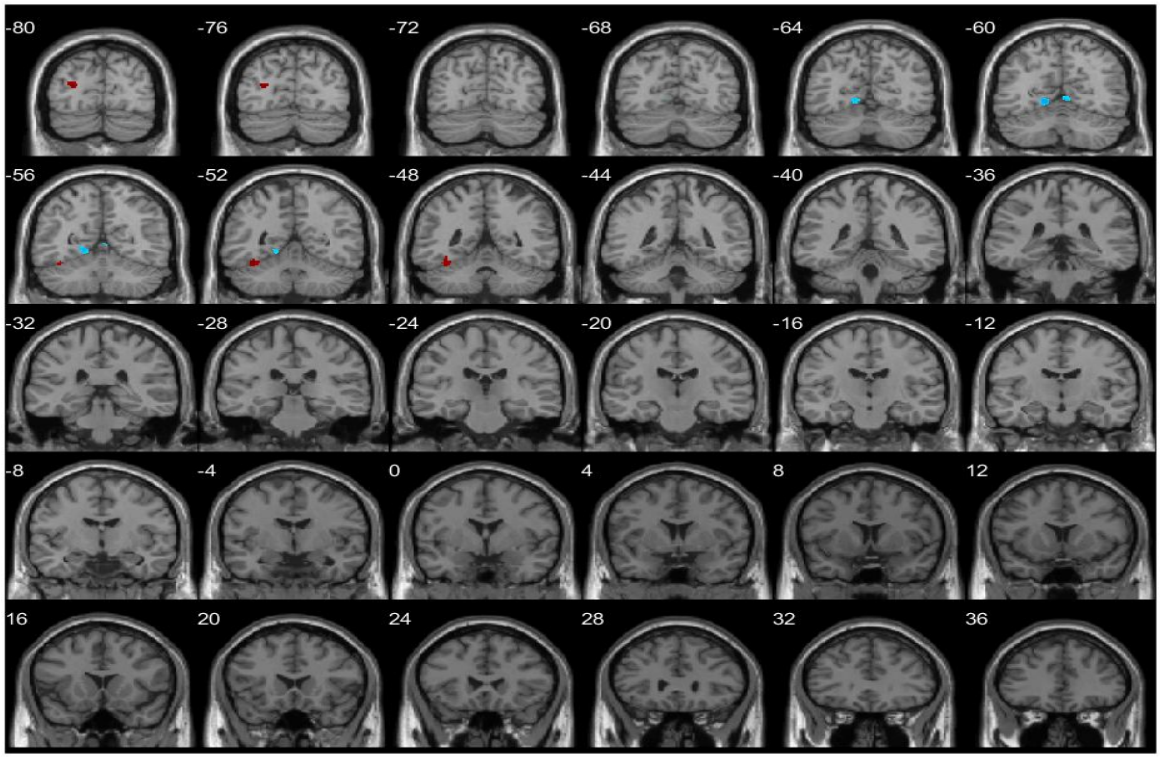

Figure S7a. Subjects in Pure Groups vs Subjects in Co-Morbid Groups

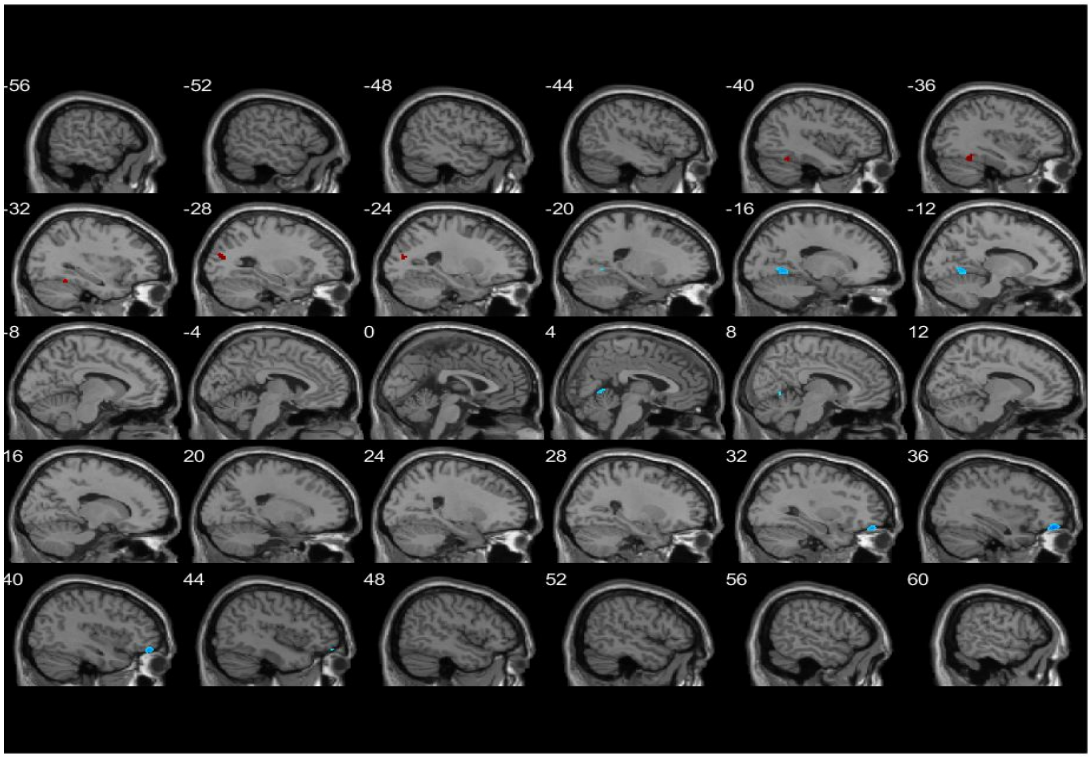

Figure S7b. Subjects in Pure Groups vs Subjects in Co-Morbid Groups

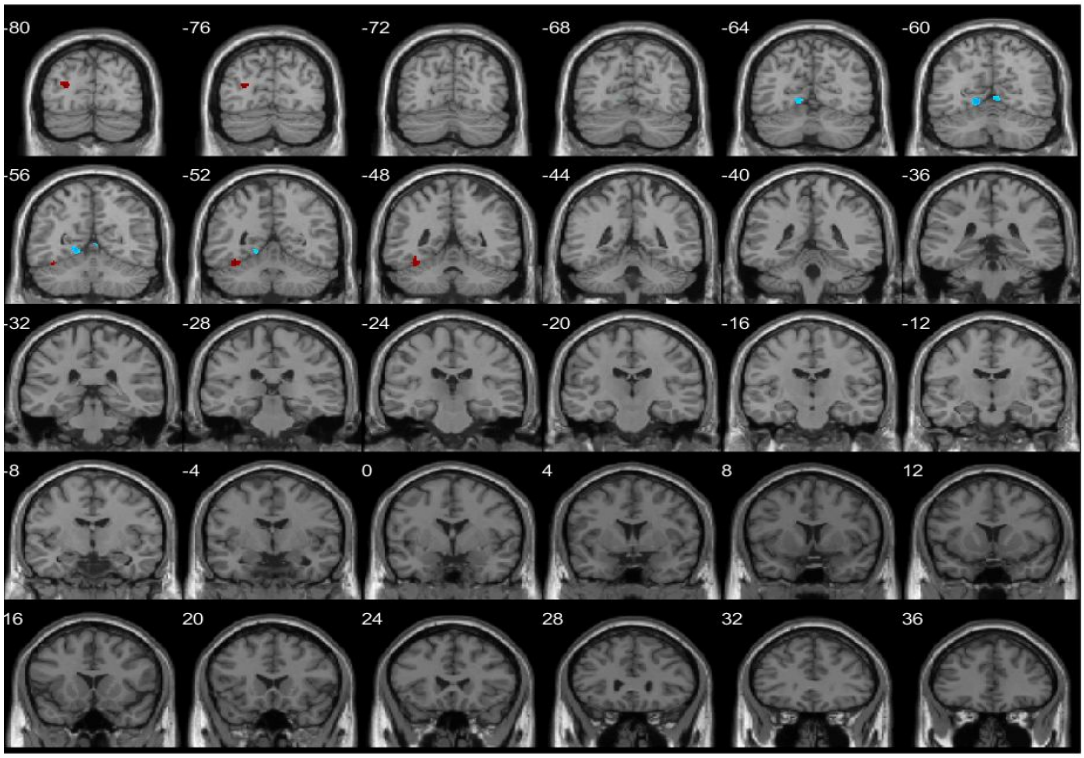

Figure S7c. Subjects in Pure Groups vs Subjects in Co-Morbid Groups

Table S11. Subjects in Pure Groups (Both ROP and ROD) vs Subjects in Co-Morbid Groups (Both ROP Depressed and ROD Psychotic) Brain Differences. Red=ROP greater GMV than ROD, Blue=ROP less GMV than ROD

Clusters Pure vs Co-Morbid

Brain Area	Cluster Peak Voxel MNI Coordinates	P Value, Peak Intensity, Cluster Size
Left Cerebellum	-38 -51 -21	p(FDR)=0.080, T=3.80, k=155
Middle Occipital Gyrus	-27 -80 17	p(FDR)=0.080, T=3.70, k=120
Superior Frontal Gyrus	37 51 -20	p(FDR)=0.013, T=-4.59, k=304
Lingual Gyrus	-16 -57 -4	p(FDR)=0.018, T=-3.85, k=230

2.5. Decision Scores Group Differences

We wanted to test the differences of the decision scores between the groups (ROP and ROD as well as ROP+D and ROD+P). In the pure clinical model the mean decision score for the ROP group was .4108 (*SD*=0.805) and for the ROD group -.7760 (*SD*=0.726). An independent samples t-test showed that the difference between the two groups was significant (*t*=8.177, *df*=126, *p*<.0001). In the pure neuroanatomical model the mean decision score for the ROP group was -.0579 (*SD*=0.227) and for the ROD group -.2096 (*SD*=0.178). An independent samples t-test showed that the difference between the two groups was significant (*t*=4.039, *df*=126, *p*=.0001). In the pure combined model the mean decision score for the ROP group was .6988 (*SD*=1.121) and for the ROD group -1.019 (*SD*=1.012). An independent samples t-test showed that the difference between the two groups was significant (*t*=8.490, *df*=126, *p*<.0001).

In the applied clinical model the mean decision score for the ROP group was -.2507 (*SD*=0.698) and for the ROD group -.6742 (*SD*=0.701). An independent samples t-test showed that the difference between the two groups was significant (*t*=2.686, *df*=115, *p*=.005). In the applied neuroanatomical model the mean decision score for the ROP group was -.1619 (*SD*=1.859) and for the ROD group -.1217 (*SD*=0.201). An independent samples t-test showed that the difference between the two groups was not significant (*t*=-.942, *df*=115, *p*=.187). Finally, in the applied combined model the mean decision score for the ROP group was -.2798 (*SD*=1.003) and for the ROD group -.8769 (*SD*=1.008). An independent samples t-test showed that the difference between the two groups was significant (*t*=2.635, *df*=115, *p*=.006).

2.6. Decision Scores Regression with 9 Month Functional Outcome

Finally we wanted to test whether decision scores were related to 9 month global functioning outcome using the Global Functioning: Social (GFS) and Global Functioning Role (GFR) scales. Good functioning was interpreted as a score on either scale of more than 7, and the impaired functioning was interpreted as score on either scale of 7 or less[46]. A logistic regression was performed to determine the likelihood that patients had an impaired functional outcome at 9 months using decision scores from our SVM models as predictors. None of the models was statistically significant. GFS model using pure SVM model decision scores: $\chi2(3) = 2.259$, $p = .520$; GFR model using pure SVM model decision scores: $\chi2(3) = 3.638$, $p = .303$; GFS model using comorbid SVM model decision scores: $\chi2(3) = 7.179$, $p = .066$; GFR model using comorbid SVM model decision scores: $\chi2(3) = 3.353$, $p = .340$. Table S12 contains information from the logistic regression models.

Table S12. Odds Ratios (OR) for Impaired Functional Outcomes for Decision Scores from the SVM models

			Beta/OR (95% Confidence Intervals)					
Global Functioning Scale	Outcome	No.	Pure Clinical & Neurocognitive Model	Pure GMV Model	Pure Stacking Model	Comorbid Clinical & Neurocognitive Model	Comorbid GMV Model	Comorbid Stacking Model
GFR	Impaired	Pure: 70 Comorbid: 84						
	Good	Pure: 58 Comorbid: 33	-1.372/.254 (.008-7.812)	-.956/.384 (.063-2.348)	.814/.2.256 (.200-25.406)	23.189/1178.0 (.003-4263.0)	.319/1.375 (.155-12.175)	-15.961/.000 (.000-61.799)
GFS	Impaired	Pure: 69 Comorbid: 77						
	Good	Pure: 59 Comorbid: 40	1.474/4.365 (.138-137.5)	-1.023/.359 (.060-2.144)	-.912/.402 (.035-4.582)	34.917/1460.0 (251.3-8478.0)	.564/1.758 (.215-14.389)	-24.104/.000 (.000-.025)

2.7. Chi-Square Analysis of Misclassifications in the Replication Sample

In the clinical/neurocognitive model, ROP+D patients were more frequently classified as ROD compared to pure ROP patients (χ^2=18.878; p<0.001). In contrast, the assignment precision of ROD+P and ROD patients did not differ (χ^2=.379; p=0.538). Similarly to the clinical/neurocognitive model ROP+D patients were more frequently classified as ROD compared to pure ROP patients (χ^2=.003; p=0.958), at a statistically not significant level potentially driven by the fact that the majority of pure ROP patients were classified as ROD. The assignment precision of ROD+P and ROD patients did not differ (χ^2=0.112; p=0.738).

Acknowledgements:

Author Contributions: Mr. Lalousis, Dr. Koutsouleris, and Prof. Upthegrove had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed, revised, and approved the final version of the manuscript.

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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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