Prediction of estimated risk for bipolar disorder using machine learning and structural MRI features

Supplemental materials

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Supplementary note 1: Inclusion and exclusion criteria for the three recruitment pathways.

Inclusion criteria

1. Youth and young adults consulting early recognition centres/facilities:

- Age: 15 to 35 years
- Consultation of an early recognition centre/facility
- Presence of at least one of the proposed risk factors for bipolar disorder: Family history of bipolar disorder, (sub)threshold affective symptomatology/depressive syndrome, hypomanic/mood swings, disturbances of circadian rhythm/sleep other clinical hints

2. Young individuals with diagnosed depression:

- Age: 15 to 35 years
- In- or outpatients with a depressive syndrome in the context of: Major depressive disorder, dysthymic disorder, cyclothymic disorder, minor depressive disorder, recurrent brief depressive disorder, adjustment disorder with depressed mood, depressive disorder Not Otherwise Specified (NOS)

3. Patients with ADHD:

- Age: 15 to 35 years
- In- or outpatients with a clinically confirmed ADHD diagnosis

Exclusion criteria:

- Diagnosis of: bipolar disorder, schizoaffective disorder, schizophrenia
- Diagnosis of anxiety, obsessive–compulsive or substance dependence disorder that fully explains the whole symptomatology
- Limited ability to comprehend the study
- Implied expressed negative declaration of intent to participate in the study by a minor and
- Acute suicidality

Supplementary note 2: The list of 20 selected features for secondary analysis according to Hibar et al.[41]

lh_parsopercularis_thickness
lh_fusiform_thickness
lh_rostralmiddlefrontal_thickness
lh_parstriangularis_thickness
rh_fusiform_thicknes
lh_caudalmiddlefrontal_thickness
lh_inferiorparietal_thickness
rh_rostralmiddlefrontal_thickness
rh_inferiorparietal_thickness
rh_superiorfrontal_thickness
lh_supramarginal_thickness
lh_middletemporal_thickness
lh_inferiortemporal_thickness
rh_parsopercularis_thickness
lh_parsorbitalis_thickness
rh_parsorbitalis_thickness
lh_superiorfrontal_thickness
rh_parstriangularis_thickness
rh_medialorbitofrontal_thickness
rh_middletemporal_thickness

Supplementary note 3: Analysis of the diagnoses ADHD and depression on the classification.

In the Results – primary analysis section, we report post-hoc tests of the correctly and incorrectly classified subjects, in order to evaluate the potential confounders on the classification. Here, we compared the proportion of participants from the three recruitment pathways (early recognition / depression / ADHD) between the correctly and incorrectly classified subjects. However, for ADHD, there were 19 participants both in the early recognition and depression recruitment pathways. Taking only the ADHD diagnosis irrespective of recruitment pathway into account, there was no difference between the correctly and incorrectly classified subjects ($df = 1$, $Chi^2 = 0.016$, $p = 0.898$). For the lifetime or present major depression, we did not perform post-hoc tests, as depression and specific depressive symptoms belong to criteria of the risk syndromes according to BPSS-P (similarly to BARS as well as EPI*bipolar*).

Supplementary note 4: Secondary analysis of EPI*bipolar* risk

We analyzed EPIbipolar in more detail in two exploratory analyses. First, we performed a classification using all three groups – no-risk, low-risk and high-risk (N = 32 / 104 / 137 respectively) achieving a balanced accuracy of 34.7 % (95% CI 31.1- 38.3) (i.e. chance level for a three category outcome) in the 10-fold crossvalidation. Second, we removed the low-risk group from the sample, retaining the no-risk and high-risk groups exclusively (N = 136), and used the left pars opercularis thickness as a single feature, achieving a balanced accuracy of 60.9 % (95% CI 48.4- 73.4) in the 10-fold crossvalidation and 55.5 % (95% CI 42.4- 68.6) in the leave-one-site-out crossvalidation (i.e. chance level for a binary outcome considering the CI).

Supplementary table 1: Overview of the risk assessment tools and corresponding sample sizes (adapted according to Bröckel et al. and Mikolas et al.[43]).

Instrument (N)	**Risk states**	**N (% Sample)**	**Validation**	**Note**
BPSS-P (276)	Attenuated mania symptom syndrome (AMSS)	54 (19.6)	Good internal consistency, convergent validity and inter-rater reliability[27]	Semi-structured interview based on the DSM-5 criteria for bipolar disorder and major depressive disorder[27]
	Genetic mania risk and deterioration syndrome (GMRDS)	2 (0.7)		
BARS (264)	Sub-threshold mania, assessed by BPSS-P	26 (9.8)	BARS criteria had an adequate prognostic accuracy (Harrell's C = 0.742) and clinical utility[25]	Extension of the BAR criteria (2 additional symptom domains)[25]
	Sub-threshold depression, assessed by BPSS-FP or SCID *and* cyclothymic features	149 (56.4)		
	Sub-threshold depression plus genetic risk	13 (4.9)		
	Mixed symptoms, assessed by BPSS-P	3 (1.1)		
	Mood swings, assessed by EPI*bipolar*	118 (44.7)		
EPI*bipolar* (273)	No-risk	32 (11.6)	No longitudinal (ongoing study) Includes and integrates items from validated tools (BPSS-P, BAR) as well as genetic risk	Semi-structured interview Integrates risk factors based on a systematic review of literature[24]
	Low-risk	137 (49.6)		
	High-risk	104 (37.7)		

Supplementary table 2. Breakdown of sample sizes and participants fulfilling and not fulfilling the risk criterion per study site.

		Site							Total
		Berlin	Bochum	Dresden	Frankfurt	Hamburg	Marburg	Tübingen	
BPSS-P criterion	not fullfilled	57	7	31	21	21	67	16	220
	fullfilled	6	1	5	20	13	7	4	56
Total		63	8	36	41	34	74	20	276

Supplementary table 3. Ranking of features according to their SVM coefficients.

Feature	Mean SVM coefficient
lh_precuneus_thickness	1.783976879
rh_parstriangularis_thickness	1.608533374
rh_fusiform_thickness	0.928239047
lh_transversetemporal_thickness	0.800646946
rh_superiorfrontal_thickness	0.789743825
rh_cuneus_thickness	0.713079441
lh_inferiorparietal_thickness	0.658000082
lh_parstriangularis_thickness	0.642315548
lh_caudalanteriorcingulate_thickness	0.631354016
rh_caudalanteriorcingulate_thickness	0.492421592
rh_parahippocampal_thickness	0.471491982
rh_insula_thickness	0.431770073
rh_frontalpole_thickness	0.420177869
rh_lateraloccipital_thickness	0.405688992
lh_frontalpole_thickness	0.395092914
rh_medialorbitofrontal_thickness	0.391455904
rh_rostralanteriorcingulate_thickness	0.382318411
lh_supramarginal_thickness	0.359961695
rh_supramarginal_thickness	3.40E-01
lh_inferiortemporal_thickness	0.292938256
lh_posteriorcingulate_thickness	0.267600265
lh_superiorparietal_thickness	0.240793864
lh_parahippocampal_thickness	0.232690747
rh_postcentral_thickness	0.218904162
rh_pericalcarine_thickness	0.167581752
rh_parsopercularis_thickness	0.156305279
rh_precentral_thickness	0.124376678
lh_temporalpole_thickness	0.118953415
rh_lateralorbitofrontal_thickness	0.03930299
lh_entorhinal_thickness	0.027801043
rh_superiortemporal_thickness	0.012469632
lh_bankssts_thickness	0.009063421
rh_bankssts_thickness	0.005956208
rh_transversetemporal_thickness	-0.00309838

Feature	Mean SVM coefficient
lh_superiorfrontal_thickness	-0.03653334
lh_insula_thickness	-0.04220697
rh_inferiortemporal_thickness	-0.05566412
lh_superiortemporal_thickness	-0.05851827
rh_caudalmiddlefrontal_thickness	-0.07425086
rh_inferiorparietal_thickness	-0.08364897
lh_pericalcarine_thickness	-0.08678666
lh_precentral_thickness	-0.09148176
lh_parsorbitalis_thickness	-0.14161886
lh_middletemporal_thickness	-0.226009
lh_isthmuscingulate_thickness	-0.22893125
lh_cuneus_thickness	-0.26492932
rh_temporalpole_thickness	-0.27046636
lh_lateralorbitofrontal_thickness	-0.28265985
lh_lateraloccipital_thickness	-0.28658943
lh_medialorbitofrontal_thickness	-0.29211138
lh_rostralanteriorcingulate_thickness	-0.3898791
rh_entorhinal_thickness	-0.39351071
lh_paracentral_thickness	-0.47477732
lh_caudalmiddlefrontal_thickness	-0.48499482
lh_fusiform_thickness	-0.51077598
rh_isthmuscingulate_thickness	-0.51830264
rh_parsorbitalis_thickness	-0.55182755
lh_rostralmiddlefrontal_thickness	-0.57001052
rh_precuneus_thickness	-0.59037961
rh_lingual_thickness	-0.59452749
rh_middletemporal_thickness	-0.59767057
lh_lingual_thickness	-0.60498745
rh_superiorparietal_thickness	-0.66991654
rh_rostralmiddlefrontal_thickness	-0.7187164
lh_parsopercularis_thickness	-0.84061014
rh_posteriorcingulate_thickness	-1.08693179
lh_postcentral_thickness	-1.1165027
rh_paracentral_thickness	-1.14023448