Individuals at increased risk for development of bipolar disorder display structural alterations similar to people with manifest disease

Supplementary materials

Supplementary Note 1: Power analysis

We performed the power estimation in performed in G*Power v.3.1.9.4. The target N = 310 would achieve a power of 70% and an alpha-error probability of 0.075. The calculation was based on the estimated effect sizes in prior studies: left pars opercularis Cohen's *d* = -.293 [9], hippocampus Cohen's *d* = -.232 [10].

Supplementary Note 2. Inclusion and exclusion criteria for the Early-BipoLife study.

Inclusion criteria

In order to include all proposed risk factors for bipolar disorder, we recruited the participants in three recruitment pathways[1].

1. Help-seeking persons:

• 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 Table 1. Overview of instruments for the bipolar risk assessment tools (adapted according to Bröckel et al.).

Instrument	Risk states	N (% Sample)	Validation	Note
BPSS-P	Attenuated mania symptom syndrome (AMSS)	54 (20.5)	Good internal consistency, convergent validity and inter-rater reliability[2]	Semi-structured interview based on the DSM-5 criteria for bipolar disorder and major depressive disorder[2]
	Genetic mania risk and deterioration syndrome (GMRDS)	2 (0.8)		
BAR criteria	Sub-threshold mania, assessed by BPSS-P	26 (9.9)	Increased risk of developing bipolar disorders (HR = 5.30), poor prognostic accuracy (Harrell's C = 0.659)[3]	Ultra-high-risk criteria for BD[4]
	Sub-threshold depression, assessed by BPSS-FP or SCID *and* cyclothymic features	148 (56.3)		
	Sub-threshold depression plus genetic risk	13 (4.9)		
Extended BAR criteria (BARS)	Mixed symptoms, assessed by BPSS-P	3 (1.1)	BARS criteria had an adequate prognostic accuracy (Harrell's C = 0.742) and clinical utility[3]	Extension of the BAR criteria (2 additional symptom domains)[3]
	Mood swings, assessed by EPI*bipolar*	117 (44.5)		
EPI*bipolar*	No-risk	32 (12.2)	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[5]
	Low-risk	130 (49.4)		
	High-risk	101 (38.4)		

Supplementary Table 2. Breakdown of demographic characteristics per study site.

Site	N- total	N - female (%)	Mean age (SD)	N – No-risk (%)	N – Low-risk (%)	N – High-risk (%)
Dresden	36 (13.7)	23 (63.9)	25.19 (3.640)	6 (16.7)	19 (52.8)	11 (30.6)
Marburg	70 (26.6)	28 (40)	24.11 (3.740)	9 (12.9)	34 (48.6)	27 (38.6)
Frankfurt	39 (14.8)	21 (53.8)	26.13 (4.697)	7 (17.9)	16 (41)	16 (41)
Berlin	59 (22.4)	27 (45.8)	24.71 (4.190)	5 (8.5)	30 (50.8)	24 (40.7)
Tuebingen	19 (7.5)	9 (47.4)	25.63 (3.639)	3 (15.8)	8 (42.1)	8 (42.1)
Bochum	8 (3.0)	4 (50)	28.0 (4.504)	2 (25.0)	5 (62.5)	1 (12.5)
Hamburg	32 (12.2)	15 (46.9)	23.41 (5.724)	0 (0)	18 (56.3)	14 (43.8)

Supplementary Table 3. Breakdown of lithium intake per recruitment pathway.

Recruitment pathway	**Mood stabilizers N (%)**	**Lithium N (%)**
Help-seeking persons	4 (3.5)	3 (2.5)
Young individuals with diagnosed depression	6 (5.3)	4 (3.5)
Patients with ADHD	1 (2.8)	0 (0)

Supplementary Table 4. EPI*bipolar* risk criteria[5]. Adopted according to Bröckel et al. (in submission). The former ultra high-risk and high-risk groups were fused. The former intermediate-risk group was renamed as low-risk.

<table>
<tr><th>Main risk factors</th><th>Secondary risk factors</th><th>Risk groups</th></tr>
<tr><td rowspan="3">Family history of bipolar disorder
Increasing cyclothymic mood swings with change of activity
Subtreshold manic symptoms</td><td>Group A
specific disturbances in sleep and/or circadian rhythm
increasing cyclothymic mood swings without change of activity
specific depressive features</td><td>No-risk:
none risk constellations mentioned below are met</td></tr>
<tr><td rowspan="2">Group B
positive family history for MDD, schizoaffective disorder or schizophrenia (not applicable if genetic vulnerability for bipolar disorder is a main risk factor)
any affective disorder lifetime
lifetime and present ADHD or conduct disorder
impairment in psychosocial functioning
specific substance misuse
episodic course of symptoms</td><td>Low-risk:
one or more risk factors of group A and one or more risk factors of group B, without any main risk-factor
family history of bipolar disorder as main factor, without any other risk factors</td></tr>
<tr><td>High-risk:
one main risk factors and one or more secondary risk-factors of group A and/or group B are met
or more than one main risk factor</td></tr>
</table>

Supplementary Figure 1. Partial plot for the linear effect of EPI*bipolar* risk on thickness of the left pars opercularis. To create the diagram showing the linear effect of EPI*bipolar* risk on thickness of the left parsopercularis while holding the other independent variables constant, we plotted cortical thickness minus all other regression components as a function of the risk score.