

- 1. Familial risk for mood disorders**
- 2. Precursors of mood disorders**
- 3. Adverse familial environmental factors**
- 4. Risk factors assessed prospectively**

Environmental predictors for the onset of MDD and BPD in offspring (N=388)



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RESEARCH

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Environmental factors in offspring of parents with mood disorders and their role in parent–child transmission: findings from a 14-year prospective high-risk study



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Role of problematic familial environments in the transmission of mood disorders

- detrimental marital relationships,
- poor parental rearing,
- dysfunctional family system dynamics,
- early adversity

*Beardslee et al., 2011;
Thorup et al. (2022). BMC
Psychiatry, 22: 100.*

evidence mainly based on retrospective studies of adults or cross-sectional studies in high-risk offspring

Adverse environmental factors: prospective high-risk studies of bipolar disorder

Canadian study

neglect from mother and emotional sensitivity are predictors of early mood disorders

Doucette et al., 2014

Dutch study
Stressful life events play a role in etiology, independently of the familial load for mood disorders

Kemner et al., 2015

Quebec

Poor child-rearing reported by parents with BPD predict the development of MDD and substance misuse in offspring

Iacono et al., 2017

Sample characteristics

Offspring (N = 388)	Offspring of probands with BPD onset < 21 yrs (n = 52)	Offspring of probands with BPD onset > 21 yrs (n = 95)	Offspring of probands with MDD onset < 21 yrs (n = 40)	Offspring of probands with MDD onset > 21 yrs (n = 82)	Offspring of comparison probands (n = 119)		
Socio-demographic factors							
Age at first follow-up (yrs), mean (s.d.)	8.6 (5.1)	10.9 (4.1)	8.8 (3.4)	10.7 (3.9)	9.3 (4.8)	$F_4 = 2.2$	n.s.
Age at last follow-up (yrs), mean (s.d.)	21.6 (7.3)	26.7 (5.6)	21.7 (4.4)	23.5 (6.4)	23.6 (6.8)	$F_4 = 4.0$	0.004
Girls, %	61.5	47.4	67.5	45.1	46.2	$\chi^2_4 = 9.4$	n.s.
Number of assessments (%)	4.9 (1.7)	5.6 (1.6)	4.7 (1.1)	4.7 (1.6)	5.4 (1.6)	$F_4 = 6.0$	<0.001
Number of direct interviews (%)	3.8 (1.8)	4.8 (1.9)	3.9 (1.4)	3.8 (1.8)	4.2 (1.9)	$F_4 = 4.3$	<0.01
Duration of follow-up [yrs], mean (s.d.)	13.0 (5.2)	15.8 (4.5)	12.9 (3.3)	12.8 (4.1)	14.3 (4.7)	$F_4 = 6.7$	<0.001
BPD bipolar disorder, MDD major depressive disorder, yrs years, sd standard deviation, n.s. not statistically significant							
^a A value of 3 represents an SES of III (middle class) on the Hollingshead Scale							
^b Includes generalized anxiety disorder, social phobia, panic disorder, or agoraphobia							
^c This information was derived for 21 spouses with otherwise missing data							

Childhood adversity and parental separation

	Proband diagnostic status								
	BPD onset < 21 yrs		BPD onset > 21 yrs		MDD onset < 21 yrs		MDD onset > 21 yrs		Comparison
	%/m (SD)	OR ^a or β^a (95% CI)	%/m (SD)	OR ^a or β^a (95% CI)	%/m (SD)	OR ^a or β^a (95% CI)	%/m (SD)	OR ^a or β^a (95% CI)	%/m (SD)
Childhood adversity									
Traumatic events (N=388)	21.2	OR=2.0 (0.7, 5.4)	28.4	OR=2.5* (1.1, 5.5)	30.0	OR=3.2* (1.1, 9.4)	24.4	OR=2.6* (1.0, 6.8)	10.9
Family environment									
Parental separation (N=388)	69.2	OR=3.1** (1.4, 6.9)	76.8	OR=5.2*** (2.6, 10.3)	75.0	OR=3.5* (1.3, 9.1)	67.1	OR=3.5** (1.7, 7.4)	40.3

^a Models adjusted for sex, age and number of assessments in offspring, sex and age in proband, socio-economic status of the family, proband non-mood disorders and spouse mood and non-mood disorders (one single model for each outcome variable, imputed for missing spouse disorders)

*** $p < 0.001$

** $p < 0.01$

* $p < 0.05$

^o $p < 0.1$

Family cohesion and parental attitudes

	Proband diagnostic status								
	BPD onset < 21 yrs		BPD onset > 21 yrs		MDD onset < 21 yrs		MDD onset > 21 yrs		Comparison
	%/m (SD)	OR ^a or β^a (95% CI)	%/m (SD)	OR ^a or β^a (95% CI)	%/m (SD)	OR ^a or β^a (95% CI)	%/m (SD)	OR ^a or β^a (95% CI)	%/m (SD)
Family cohesion (N = 224)	31.4 (8.7)	$\beta = -5.3^{**}$ (-8.9, -1.7)	35.2 (7.4)	$\beta = -0.8$ (-3.3, 1.8)	34.3 (7.1)	$\beta = -0.0$ (-4.1, 4.1)	32.8 (7.8)	$\beta = -3.1^*$ (-6.3, 0.2)	36.3 (7.6)
Parental attitudes									
Proband (N = 221)									
Care	25.7 (7.5)	$\beta = -5.0^{***}$ (-7.7, -2.4)	28.8 (6.2)	$\beta = -1.3$ (-3.3, 0.7)	29.4 (4.3)	$\beta = -0.9$ (-4.1, 2.2)	28.4 (6.4)	$\beta = -1.6$ (-4.1, 0.9)	29.8 (5.2)
Denial of autonomy	6.1 (4.5)	$\beta = 1.0$ (-0.9, 2.8)	3.9 (3.2)	$\beta = -1.4^*$ (-2.7, -0.1)	5.8 (3.2)	$\beta = 0.0$ (-2.1, 2.1)	5.7 (4.4)	$\beta = -0.3$ (-2.0, 1.4)	5.4 (3.9)
Encouragement of freedom	12.2 (4.0)	$\beta = -0.4$ (-2.0, 1.3)	12.9 (3.2)	$\beta = 0.6$ (-0.6, 1.8)	13.3 (3.2)	$\beta = 0.7$ (-1.2, 2.6)	12.6 (3.9)	$\beta = 0.3$ (-1.2, 1.8)	12.1 (3.6)
Spouse (N = 223)									
Care	26.3 (8.4)	$\beta = -4.1^{**}$ (-7.2, -1.0)	26.9 (6.6)	$\beta = -2.7^*$ (-5.0, -0.4)	29.5 (5.7)	$\beta = -0.6$ (-4.2, 3.0)	28.6 (6.3)	$\beta = -0.8$ (-3.7, 2.1)	29.3 (6.6)
Denial of autonomy	5.1 (3.5)	$\beta = -0.4$ (-2.2, 1.4)	3.9 (3.4)	$\beta = -1.6^*$ (-3.0, -0.3)	6.4 (4.5)	$\beta = 1.3$ (-0.8, 3.4)	5.0 (4.1)	$\beta = -0.3$ (-2.0, 1.4)	6.0 (4.1)
Encouragement of freedom	12.5 (4.2)	$\beta = -0.2$ (-1.7, 1.4)	12.3 (3.4)	$\beta = -0.4$ (-1.5, 0.8)	12.0 (4.0)	$\beta = -1.0$ (-2.8, 0.8)	13.7 (3.0)	$\beta = 1.2$ (-0.2, 2.7)	12.2 (3.1)

Onset of mood episodes or disorders in offspring by preceding risk factors

	Mania/hypomania onset in offspring			MDD onset in offspring ^b		
	Yes	No	HR ^a (95% CI)	Yes	No	HR ^a (95% CI)
	%/m (SD)	%/m (SD)		%/m (SD)	%/m (SD)	
	N = 42	N = 346		N = 181	N = 165	
Childhood adversity						
Traumatic events	33.3	19.9	1.3 (0.7, 2.7)	35.4	3.0	2.8*** (2.0, 3.8)
Family environment						
Parental separation	78.6	60.4	2.2° (1.0, 4.7)	65.2	55.2	1.1 (0.8, 1.6)
Family cohesion	34.8 (5.0)	34.7 (7.9)	1.0 (0.9, 1.1)	35.1 (8.1)	34.5 (7.9)	1.0 (1.0, 1.0)
Parental attitudes						
Proband						
Care	28.5 (5.2)	28.9 (6.0)	1.0 (0.6, 1.5)	28.9 (6.1)	28.8 (6.0)	1.0 (0.8, 1.2)
Denial of autonomy	4.3 (3.2)	5.2 (3.9)	1.0 (0.6, 1.5)	5.1 (3.7)	5.4 (4.1)	1.0 (0.8, 1.3)
Encouragement of freedom	13.6 (2.3)	12.4 (3.6)	1.0 (0.6, 1.5)	12.9 (3.8)	12.2 (3.5)	1.0 (0.8, 1.3)
Spouse						
Care	27.6 (4.3)	28.3 (6.9)	1.1 (0.7, 1.7)	28.2 (6.9)	28.4 (6.9)	1.0 (0.8, 1.3)
Denial of autonomy	5.2 (3.4)	5.2 (4.0)	1.1 (0.7, 1.6)	5.2 (4.1)	5.3 (4.0)	1.1 (0.8, 1.3)
Encouragement of freedom	13.4 (2.9)	12.4 (3.4)	1.1 (0.7, 1.6)	12.8 (3.2)	12.2 (3.6)	1.0 (0.8, 1.3)

Statistically significant values are in bold

MDD major depressive disorder, m mean value, SD standard deviation, HR hazard ratios, 95% CI 95% confidence intervals

*** $p < 0.001$

** $p < 0.01$

° $p < 0.1$

^a One overall model for the two offspring outcomes with imputations for mediating variables, adjusted for sex and number of assessments in offspring, and SES of the family

^b Excluding offspring with mania/hypomania

Onset of episodes/disorders in offspring by proband status with or without adjustment for risk factors as potential mediators

	Mania/hypomania onset in offspring				MDD onset in offspring ^c			
	Model 1 ^a		Model 2 ^b		Model 1 ^a		Model 2 ^b	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Parental mood disorder								
BPD onset < 21 yrs	8.0 (3.1–20.7)	<0.001	6.8 (2.6–18.1)	0.001	1.1 (0.6–2.0)	0.790	1.0 (0.6–1.9)	0.941
BPD onset > 21 yrs	1.1 (0.4–3.0)	0.930	0.9 (0.3–2.6)	0.824	0.9 (0.6–1.4)	0.710	0.8 (0.5–1.3)	0.366
MDD onset < 21 yrs	1.4 (0.3–5.6)	0.668	1.2 (0.3–4.8)	0.843	1.9 (1.1–3.2)	0.026	1.5 (0.8–2.6)	0.191
MDD onset > 21 yrs	0.6 (0.2–2.5)	0.514	0.5 (0.1–2.2)	0.384	1.3 (0.8–2.1)	0.402	1.1 (0.6–1.8)	0.783
Potential mediators								
Traumatic events	–	–	–	–	–	–	2.5 (1.7–3.6)	<0.001
Parental separation	–	–	1.8 (0.8–4.2)	0.160	–	–	–	–

Statistically significant values are in bold

BPD bipolar disorder, MDD major depressive disorder, HR hazard ratios, 95% CI 95% confidence intervals

^a Model 1 (imputed) with no mediators, adjusted for sex, age and number of assessments in offspring, sex and age in proband, socio-economic status of the family, proband alternate and non-mood disorders, spouse mood and non-mood disorders and intra-familial correlations

^b Models (imputed) successively including potential mediators, adjusted for the same variables as Model 1

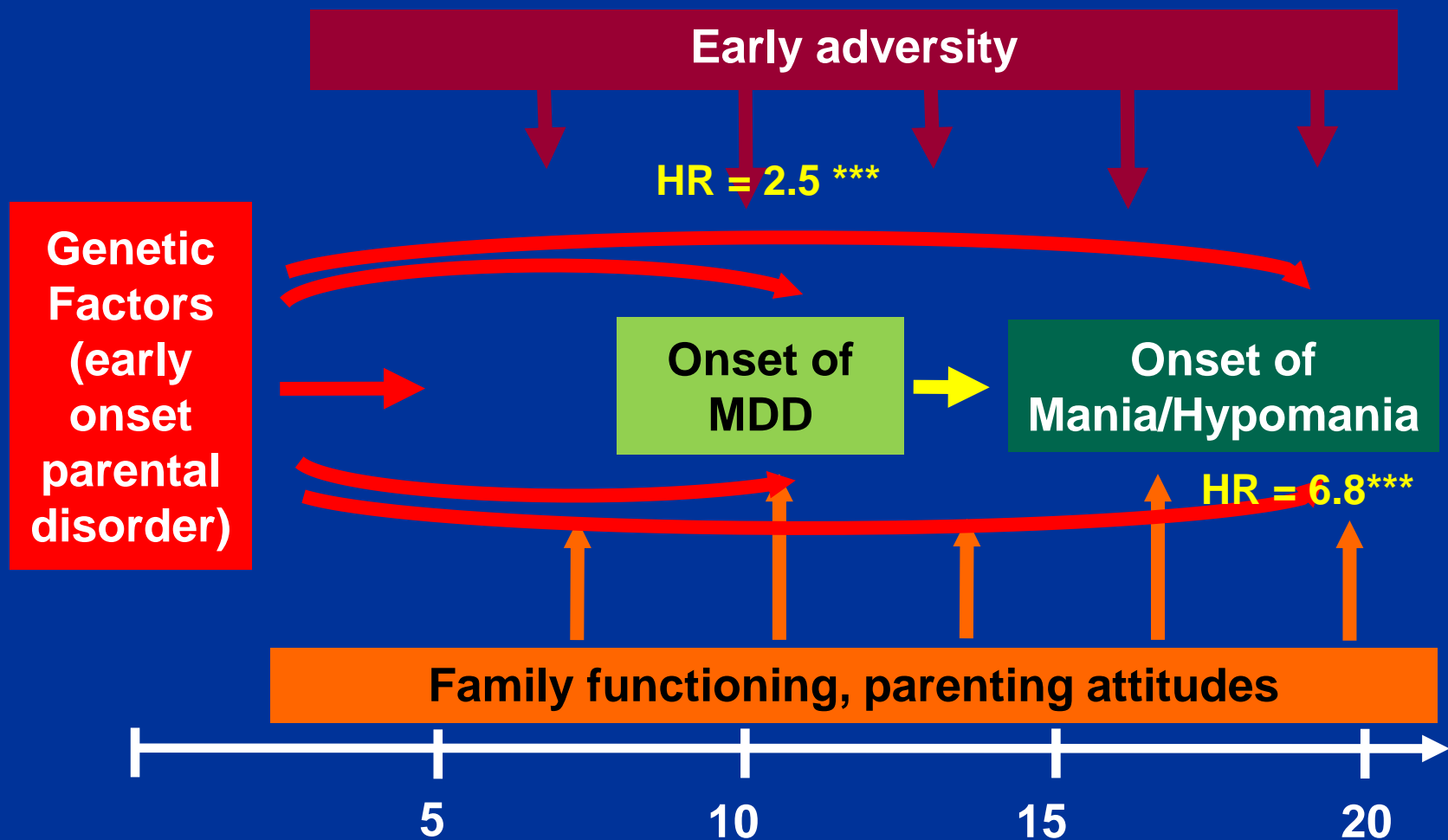
^c Offspring with mania/hypomania excluded

Summary

Family environment, family cohesion and parental attitudes

- Offspring of probands with later-onset BPD and MDD reported traumatic events more frequently than offspring of controls;
- Exposure to parental separation was more frequent in all groups of high-risk offspring.
- Familial cohesion and parenting attitude scores differed between offspring of probands with BPD and comparison offspring.
- None of these factors was associated with the risk of BPD, whereas traumatic events were associated with the risk of MDD in offspring.
- None of the assessed factors were mediators of the parent–child transmission of BPD, whereas traumatic events mediated the transmission of early onset of MDD and represent a target for preventive measures.

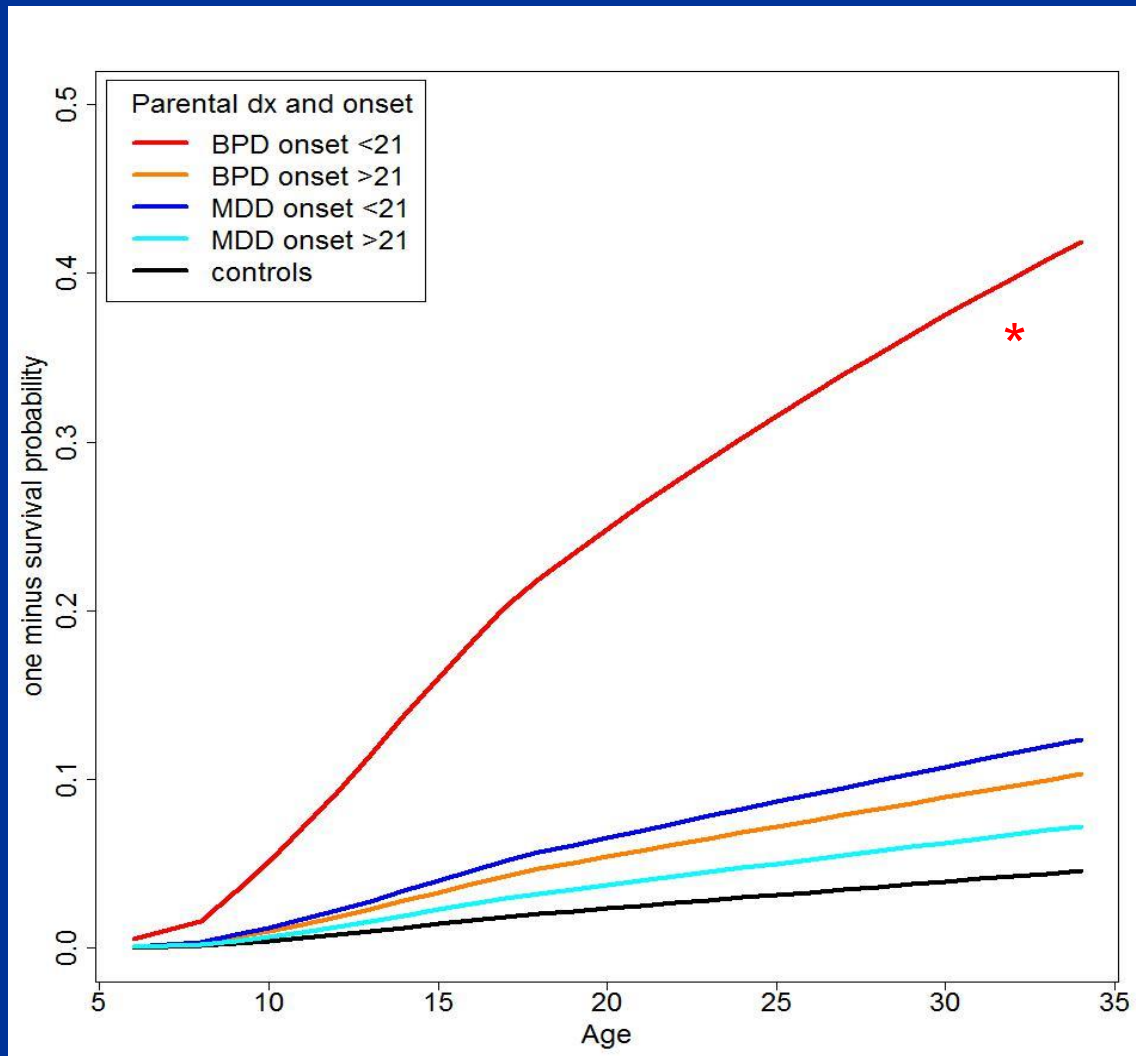
Early adversity predicts MDD and early onset parental BPD predicts Mania/Hypomania in offspring



*** $p < 0.001$

Moulin et al. (2022) International Journal of Bipolar Disorders, 10:11.

Risk of bipolar disorder as a function of the type and onset of the parental mood disorder, adjusted for low parental care and early adversity (n=372)



HR = 6.7

*** p < .05**

Constellation of environmental and familial risk factors predict psychopathology

Constellation of adverse environmental factors including familial and parenting dysfunction but also stressful life events and low socio-economic status together predict psychopathology in offspring

Barker et al., 2012

Familial loading for BPD and early adversity have combined effect to predict earlier onset of BPD among adults

Post et al., 2016

- 1. Familial risk for mood disorders**
- 2. Precursors of mood disorders**
- 3. Adverse familial environmental factors**
- 4. Risk factors assessed prospectively**

Risk factors for mood disorders among offspring of parents with bipolar disorder: Findings from a discordant-sibling study



Risk factors for mood disorders among offspring of parents with bipolar disorder: Findings from a discordant-sibling study

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ABSTRACT

The purpose of this naturalistic, prospective study was to identify risk factors for mood disorders in offspring of parents with bipolar disorder (BPD) using the discordant-sibling design by comparing parentified psychopathology or symptoms, temperament, personality traits and coping style as well as the perception of family-related characteristics among affected and unaffected siblings within the same family. This approach controls for confounding by unmeasured genetic and environmental factors shared within families. Our sample comprised 24 families of a parent with BPD with at least one child that developed BPD or major depressive disorder (n = 31), and at least one child who did not. Offspring were followed for a mean duration of 16.2 (s.d. 4.6) years. Information was collected from the offspring themselves. Generalized linear mixed models only revealed differences in three dimensions of the Dimension of Temperament Survey-Revised (DOTS-R) version: Offspring with mood disorders scored higher on "Approach-withdrawal", "Rhythmicity for daily habits", and "Task orientation" than their unaffected siblings. The higher scores, and not lower scores as expected, on these temperament dimensions observed in offspring that subsequently developed mood disorders may reflect increased vulnerability, but they could also mirror parentified mood swings or strategies to cope with them.

1. Introduction

There is substantial evidence for the importance of studying risk factors early in development, particularly in children and adolescents at risk for mental illness through exposure to the parental disorder (Duffy, 2018; Duffy et al., 2022; Luthar, 2006; Thorup et al., 2013) known as "high-risk offspring" within the realm of family studies.

A recent systematic review has given a broad overview of social, familial and psychological risk factors for mental health according to sibling studies in neurocognitive disorders (Wolff et al., 2022). Among them, low socioeconomic status (SES), symptom severity and anxiety of the affected individual were found to be risk factors for mental health issues in unaffected siblings (Wolff et al., 2022). However, high

methodological heterogeneity has been observed across sibling studies (Wolff et al., 2022).

One potent tool to study risk factors within families is the discordant-sibling design whereby full siblings, who are discordant either in exposure or outcome, are compared (Li et al., 2014; Schömer and Ellis, 2016). Compared to other sampling strategies, this design allows researchers to better control for confounding by unmeasured or even unknown family-level risk factors shared by the siblings including genetic and environmental factors such as culture, SES or religion (Li et al., 2014; Schömer and Ellis, 2016; Sjölander et al., 2022). Hence, individual differences can be assessed by reducing extraneous variability to a minimum (Li et al., 2014; Sjölander et al., 2022).

One area of particular interest is children of parents with bipolar

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¹ MP, KP and CLV provided supervision for this paper.

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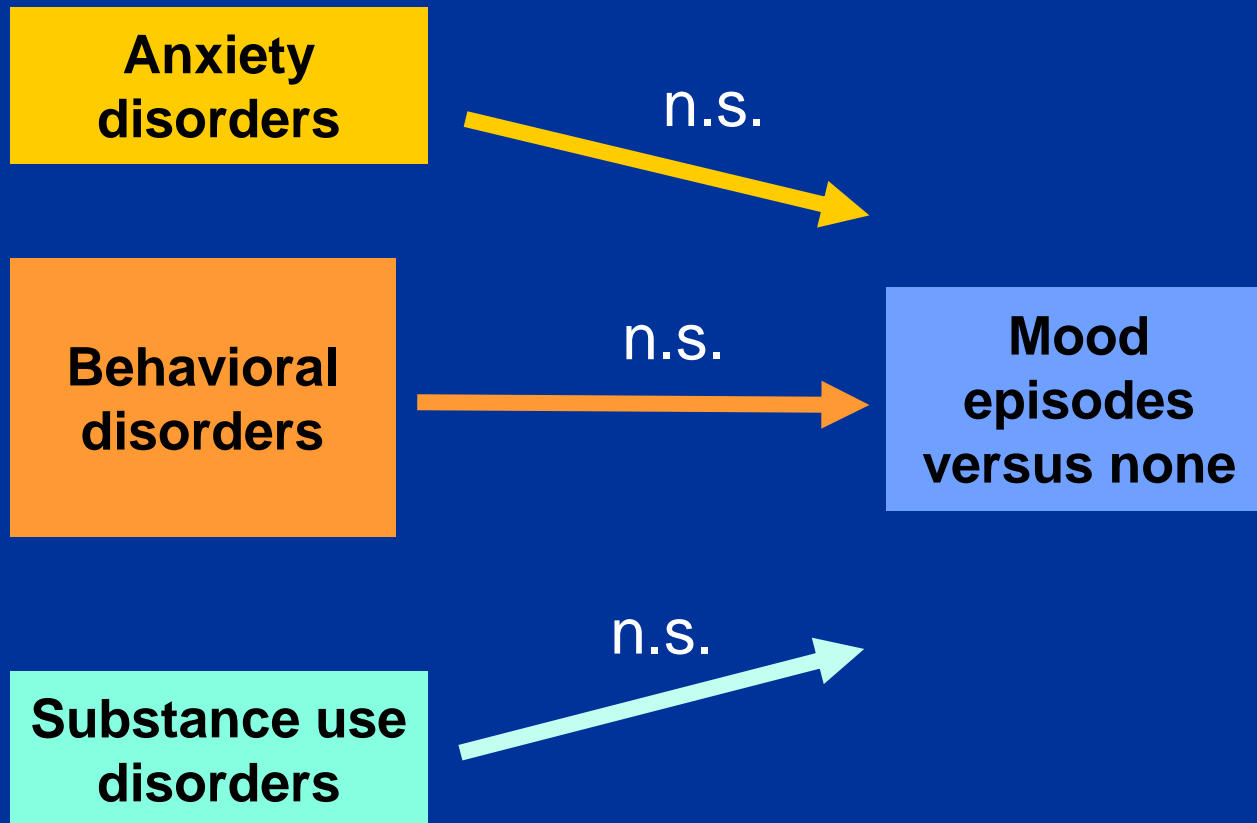
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Premorbid psychopathology among siblings with mood episodes compared to those with no mood episodes



Prior self-rating assessments among siblings with mood episodes compared to those with no mood episodes

Scale	Mood episode	No mood episode	Beta (95% CI)	P-value
Parental Bonding				n.s.
Family Cohesion and adaptability				n.s.
Family Attitude				n.s.
Behavioral inhibition				n.s.
Temperament				
Approach - withdrawal	20.7 (2.1)	19.0 (2.7)	1.43 (0.16 – 2.7)	0.028
Rhythmicity (habits)	10.7 (2.4)	9.0 (2.5)	2.29 (0.55 – 4.04)	0.010
Task orientation	22.6 (4.2)	19.3 (2.6)	3.4 (1.11-5.69)	0.004
CBCL psychopathology				n.s.
STAI anxiety				n.s.
Coping				n.s.
Personality traits				n.s.

Three dimensions of temperament distinguished offspring who subsequently developed mood disorders from those who did not within families of a parent with BPD, suggesting that **higher task-orientation, higher rhythmicity of habits** and **higher approach to novelty** may in fact be precursors of the development of mood disorders.

The **higher and not lower scores** on these temperament dimensions observed in offspring that subsequently developed mood disorders could reflect **increased vulnerability to mood disorders**, but they could also be the **indirect consequences of premorbid mood swings or else strategies to cope with them**.

Conclusions

- **High specificity of the transmission of BPD and MDD;**
- **Strong impact of the age of onset of parental disorders on the parent-child transmission of mood disorders;**
- **Evidence of different precursors of BPD and MDD; however they either lack sensitivity or specificity;**
- **Offspring of parents with BPD who developed a mood disorder themselves and those who did not only differ in some temperamental dimensions.**
- **Evidence for unequal distribution of environmental risk factors between offspring of parents with mood disorders and controls, which are also involved in the parent-child transmission of MDD, but not in that of BPD.**

Limitations

- **Small sample size regarding BPD: only 44 offspring developed (hypo)mania during the follow-up;**
- **Relative young age of the cohort at the end of the follow-up: we could not accurately determine the incidence of disorders after age 20;**
- **High risk sample: problem of representativeness;**
- **3-year intervals between assessments: risk of inaccurate recall of disorders and their onset.**



Thank-you for listening!