



Neurobiological and temperamental assessment in the offspring of bipolar patients with different degrees of lithium response.



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Excellent lithium responders (ELR)

Patients in whom lithium monotherapy caused complete remission of manic and depressive episodes for 10 or more years (Grof, 1999)	ELR make up about 1/3 of lithium treated patients (Rybakowski et al., 2001)
Response to lithium is associated with clinical features of an episodic course, bipolar family history and low psychiatric comorbidity (Grof, 2010)	ELR constitute a phenotype for pharmacogenetic studies due to significant genetic background (Rybakowski, 2013)

BDNF

- BDNF levels are decreased during depressive and manic episodes with tendency to increase after treatment (Cunha et al., 2006).
- Decrease in serum BDNF as a marker of later stage of bipolar disorder (Kauer-Sant'Anna et al., 2009).
- ELR have normal BDNF levels and cognitive functions (Rybakowski and Suwalska, 2010).

Assays performed using enzyme-linked immunosorbent assays (ELISA), R&D Quantikine System.

Subjects studied

- 50 persons
27 females, 23 males;
aged 17-54 (34±9) years

the offspring of 36 long-term lithium treated patients (5-38 years, mean 16±9).

In which response to lithium was evaluated by the Alda scale and three categories scale (excellent lithium responders – ELR, partial responders, non-responders) (Grof et al., 2002)

- 13 offspring of ELR and 37 of remaining groups
No differences in age and proportion of females

TEMPS-A and ELR offspring

Group → Temperament ↓	The offspring of excellent lithium responders (ELR)			The offspring of lithium partial or non-responders n=37
	With mood disorders N=6	Healthy N=7	Total n=13	
Depressive	0.54±0.18	0.32±0.25*	0.42±0.24	0.27±0.15*
Cyclothymic	0.56±0.24	0.31±0.27	0.42±0.28	0.20±0.20*
Hyperthymic	0.34±0.24	0.51±0.20*	0.43±0.22	0.46±0.22
Irritable	0.38±0.20	0.24±0.22	0.31±0.22	0.15±0.13**
Anxious	0.53±0.25	0.32±0.24*	0.41±0.26	0.19±0.19*

Difference between ELR and remaining patients significant *p<0.01; **p<0.001 (t-test)
Difference between ELR patients with mood disorders and ELR healthy significant *p<0.05 (Mann-Whitney test)

Temperament and ELR offspring

TEMPS-A

- ELR offspring obtained significantly higher scores on all affective temperaments, except for hyperthymic one
- Healthy ELR offspring had significantly higher scores on hyperthymic temperament and lower on depressive and anxious temperament than ELR offspring with mood disorders.

O-LIFE

- ELR offspring had significantly higher scores for cognitive disorganisation
- Healthy ELR offspring had significantly lower scores on cognitive disorganisation than ELR offspring with mood disorders.

The aim of the study

To find possible differences in neurobiological:

- BDNF – brain derived neurotrophic factor
- MMP-9 – matrix metalloproteinase-9
- IL-6 – interleukin-6
- TNF-α – tumor necrosis factor alpha

and temperamental:

- TEMPS-A – Temperament Scale of Memphis, Pisa, Paris, and San Diego Auto-questionnaire
- O-LIFE – Oxford-Liverpool Inventory of Feelings and Experiences

features in the offspring of ELR responders and the remaining groups (partial and non-responders).

MMP-9

- Biomarker for depression (Domenici et al., 2010).
- Higher MMP-9 levels in younger patients with bipolar depression during episode and remission (Rybakowski et al., 2013a).
- The functional -1562 C/T polymorphism of the MMP-9 gene is associated with predisposition to bipolar illness (Rybakowski et al., 2009).
- Assays performed using enzyme-linked immunosorbent assays (ELISA), R&D Quantikine System.

IL-6 and TNF-α

- Higher levels of proinflammatory cytokines during acute episode of bipolar disorder (Remlinger-Molenda et al., 2012; Brietzke, Kapczinski 2008).
- Assays performed using bead-based immunoassays (CBA), BD Human Enhanced Sensitivity Flex Sets.

Clinical assessment

Significantly higher percentage of persons treated for mood disorders in ELR offspring. (p=0.03, chi-square test).

- 46% of ELR offspring (6/13) treated (one for bipolar I disorder, four for bipolar II disorder and one for major depressive episode) vs
- 16% in the remaining groups (6/37) (four for bipolar II disorder and two for depressive episode)

O-LIFE and ELR offspring

Group → Schizotypal dimension ↓	The offspring of excellent lithium responders			The offspring of lithium partial or non-responders n=37
	With mood disorders N=6	Healthy N=7	Total n=13	
Unusual experiences	0.29±0.24	0.12±0.14	0.19±0.20	0.11±0.16
Cognitive disorganisation	0.56±0.28*	0.29±0.24	0.41±0.28	0.21±0.18*
Introverted anhedonia	0.37±0.10	0.31±0.21	0.34±0.17	0.27±0.12
Impulsive nonconformity	0.32±0.15	0.16±0.11	0.23±0.15	0.25±0.14

Difference between ELR and remaining patients significant *p=0.002 (t-test)
Difference between ELR patients with mood disorders and ELR healthy significant *p<0.05 (Mann-Whitney test)

Conclusions

ELR offspring show higher frequency of clinical mood disorders.

A tendency to higher BDNF and lower IL-6 may be familial.

Hyperthymic temperament and low cognitive disorganisation may be protective against emergence of mood disorders in ELR

Higher MMP-9 levels in ELR offspring possibly due to more depressive episodes

Bipolar offspring

Ten-fold increased risk of developing BD (Goodwin and Jamison, 2007) and up to half may show any psychiatric diagnoses (Lapalme et al., 1997).

Offspring with mood disorders demonstrate clinical and neurobiological characteristics similar to their parents, including a familial factor of response to lithium (Duffy, 2013).

The markers of hypothalamic-pituitary-adrenal axis and immune system suggested as biological indicators of illness risk (Duffy et al., 2012).

Neurobiology and temperament related to parental lithium response have not been studied so far.

Temperamental evaluation

- TEMPS-A measures five temperaments: Depressive, Cyclothymic, Hyperthymic, Irritable, Anxious (Akiskal et al., 2005)
- The response to lithium correlates positively with hyperthymic temperament (Rybakowski et al., 2013b).
- O-LIFE measures four dimensions of schizotypy: Unusual experience, Cognitive disorganisation, Introverted anhedonia, Impulsive nonconformity (Mason, 2011)
- The response to lithium correlates negatively with cognitive disorganisation (Dembinska-Krajewska et al., 2012).

Neurobiological correlates and ELR offspring

	The offspring of excellent lithium responders n=13	The offspring of lithium partial or non-responders n=37
BDNF (ng/ml)	35.8±13.7 (37.4)	29.3±10.6 (27.4)
MMP-9 (ng/ml)	382±155 (353)	322±207 (258)
IL-6 (pg/ml)	1.48±2.08 (0.83)	3.77±7.94 (1.41)
TNF-α (pg/ml)	0.16±0.15 (0.12)	0.31±0.67 (0.09)

Values are given as mean ± SD (median).

Neurobiological correlates and ELR offspring

- Significantly higher serum: BDNF P=0.036 (Mann-Whitney test) and MMP-9 levels P=0.050 (Mann-Whitney test)

- Numerically lower: IL-6 levels (not significant)
- No differences in TNF-α levels

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No potential conflict of interest