

Preliminary evidence for a compromised T cell compartment in maltreated children with depression and post-traumatic stress disorder

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Euro Global Summit and Medicare Expo on Psychiatry
Barcelona, Spain, 20/July/2015

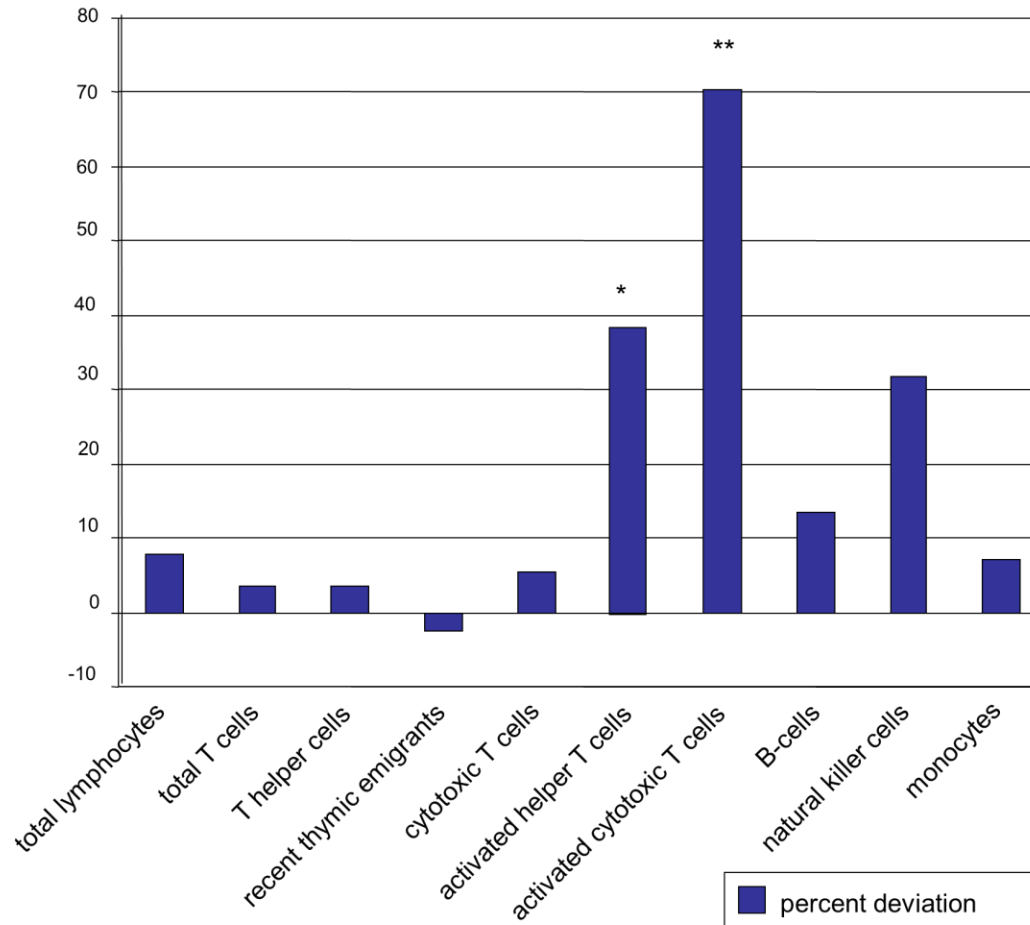
Maltreatment frequency

- Criminal records vs. Retrospective reports: below 1‰ vs lifetime prevalence of >10 % (Germany; Pillhofer 2011)
- Increasingly disregarded as appropriate for child education (survey among parents; Bussmann 2002)
- Poly-victimization: 22% with 1-year-prevalence (Finkelhor 2005)
- Traumatic exposure in youth (->subsequent PTSD; n=6.787, national survey in Switzerland; Landolt 2013)
 - Physical abuse at home 6.9% (->19.4%)
 - Sexual abuse 3.1% (->11.1%)
 - Witnessing severe violence 19.6% (->18.3%)

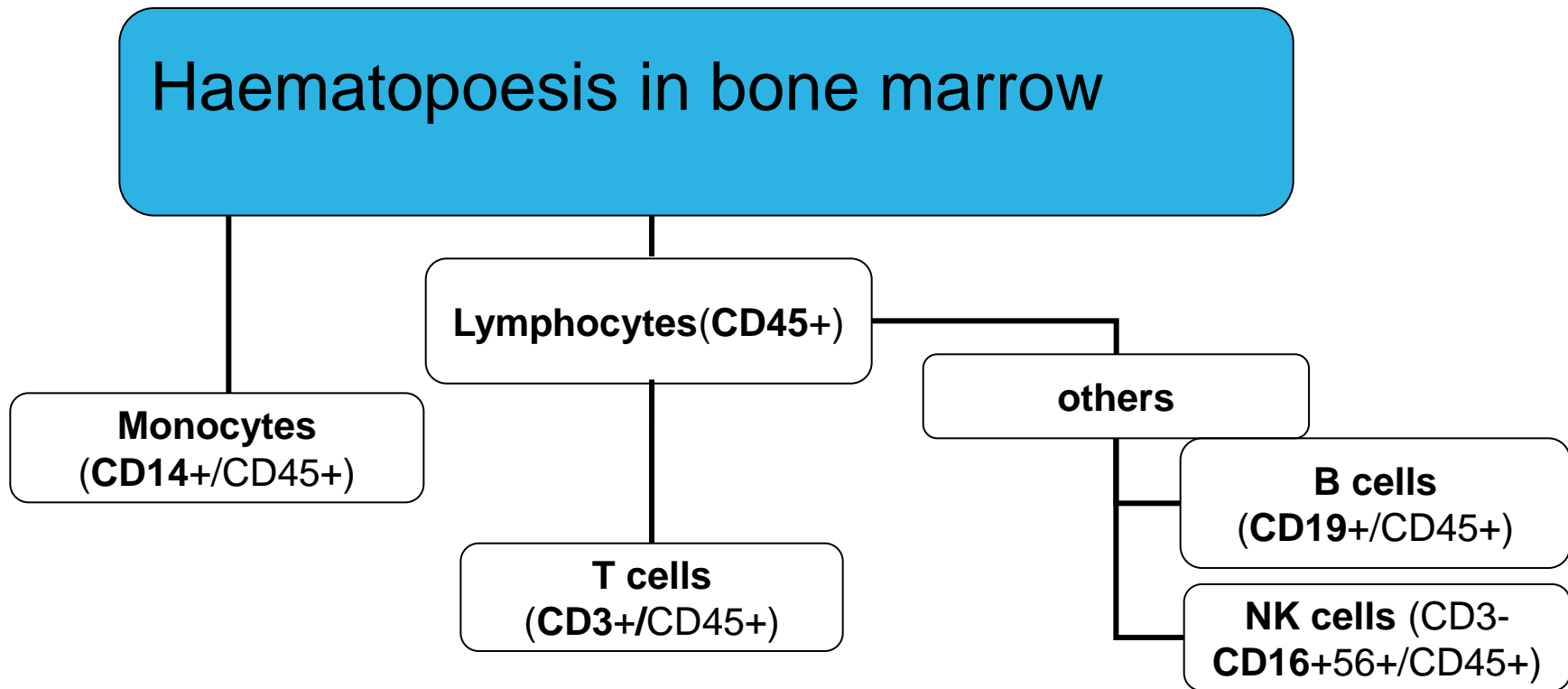
Childhood maltreatment affects adult physical health

- Dysregulated hypothalamus-pituitary-adrenal-axis (HPA; Van 2013)
- ↑ IL6 (Carpenter 2010)
- ↑ hsCRP (> 3mg/l) in case of depression (Danese 2008)
- ↑ Risk of adult cardiovascular diseases, arthritis, adipositas (Felitti 1998; Afifi 2013)
- ↑ Hospitalisation due to autoimmune disease (Dube 2009; Review: Fagundes 2013)

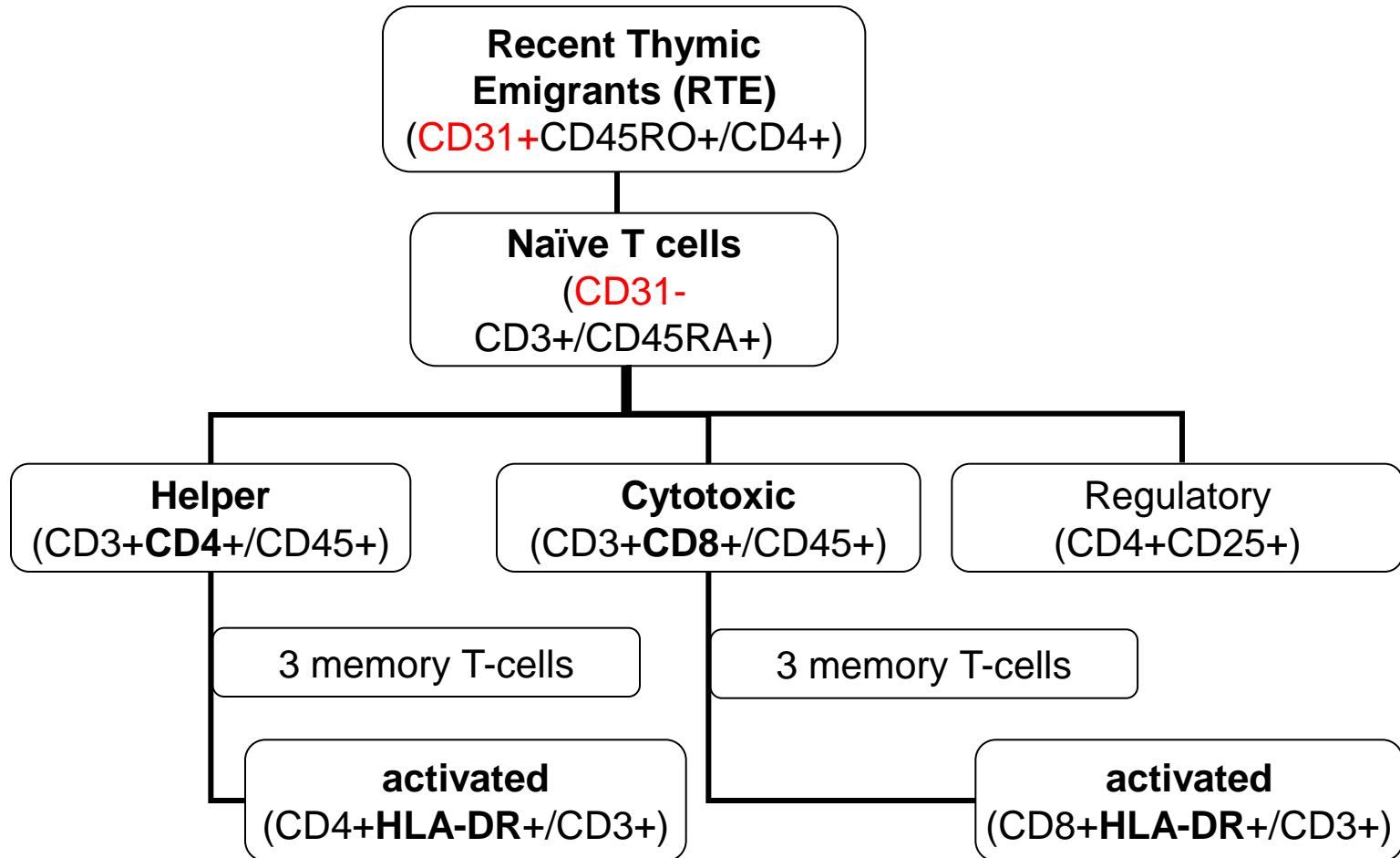
Activated T cells among maltreated minors (Bielas 2012)



Lymphocytes



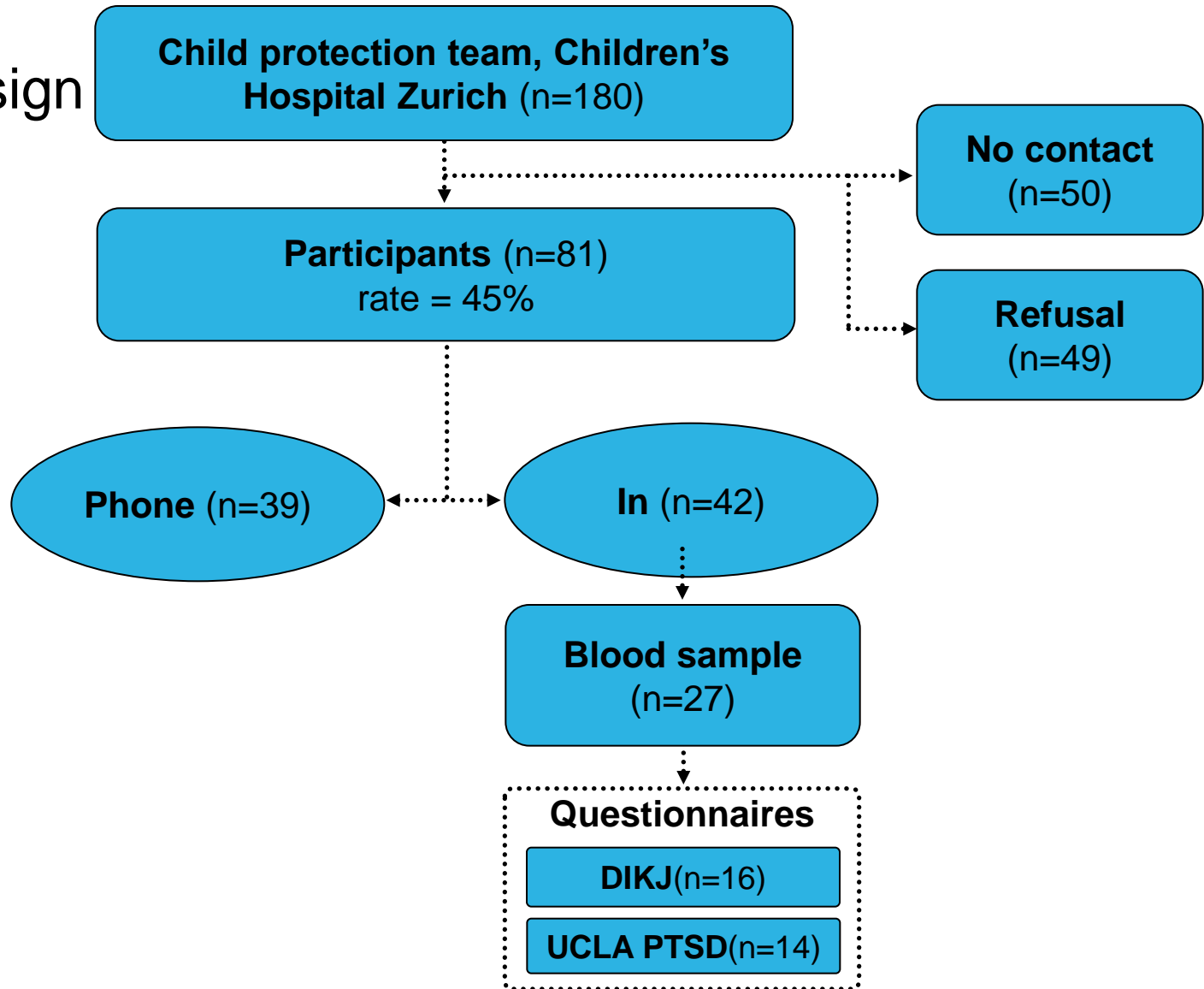
Maturation of T cell compartment



Stress and T cell maturation (Engler & Stefanski 2003)

- **subordinate** male rats after 24h dominant **opponent**
- Increased apoptosis in thymus
- Decreased proliferative response of thymocytes (to Concanavalin A)
- Decrease in thymic export as indicated by a reduction in the number of **recent thymic emigrants (RTE)**
- Adrenalectomy abolished stress induced alteration of thymus functioning **but:**
- Counts and response to stimulation of thymus cells remained decreased (similar as to GR-antagonists)

Study design



Sample

		Depression score		PTSD	
		<12 (n=8)	>12 (n=8)	No (n=9)	Yes (n=5)
Age mean (SD)		10.30 (2.93)	11.29 (3.23)	10.63 (2.86)	12.00 (3.66)
Gender	m/f	2/6	3/5	3/6	2/3
Socio-economic status	Low	3	4	5	1
	Middle	3	2	2	2
	High	1	0	1	0
Immigration	Swiss/other	4/4	4/4	5/4	3/2
CD4+ cell number	In norm	7	8	8	5
	Altered	1	0	1	0
Type of maltreatment	sex/phys/ psyc/neglect	4/2/1/1	2/4/1/1	3/3/2/1	1/2/1/1

Depression impact

Counts (cells/nl)

Total lymphocytes

Total T cells (CD3+/CD45+)

Helper T cells (CD3+/CD4+/CD45+)

Naïve T cells (CD4+/CD45RA+/CD3+)¹

RTE (CD3+/ CD45RA+/CD4+/ CD31+)¹

Cytotoxic T cells (CD3+CD8+/CD45+)

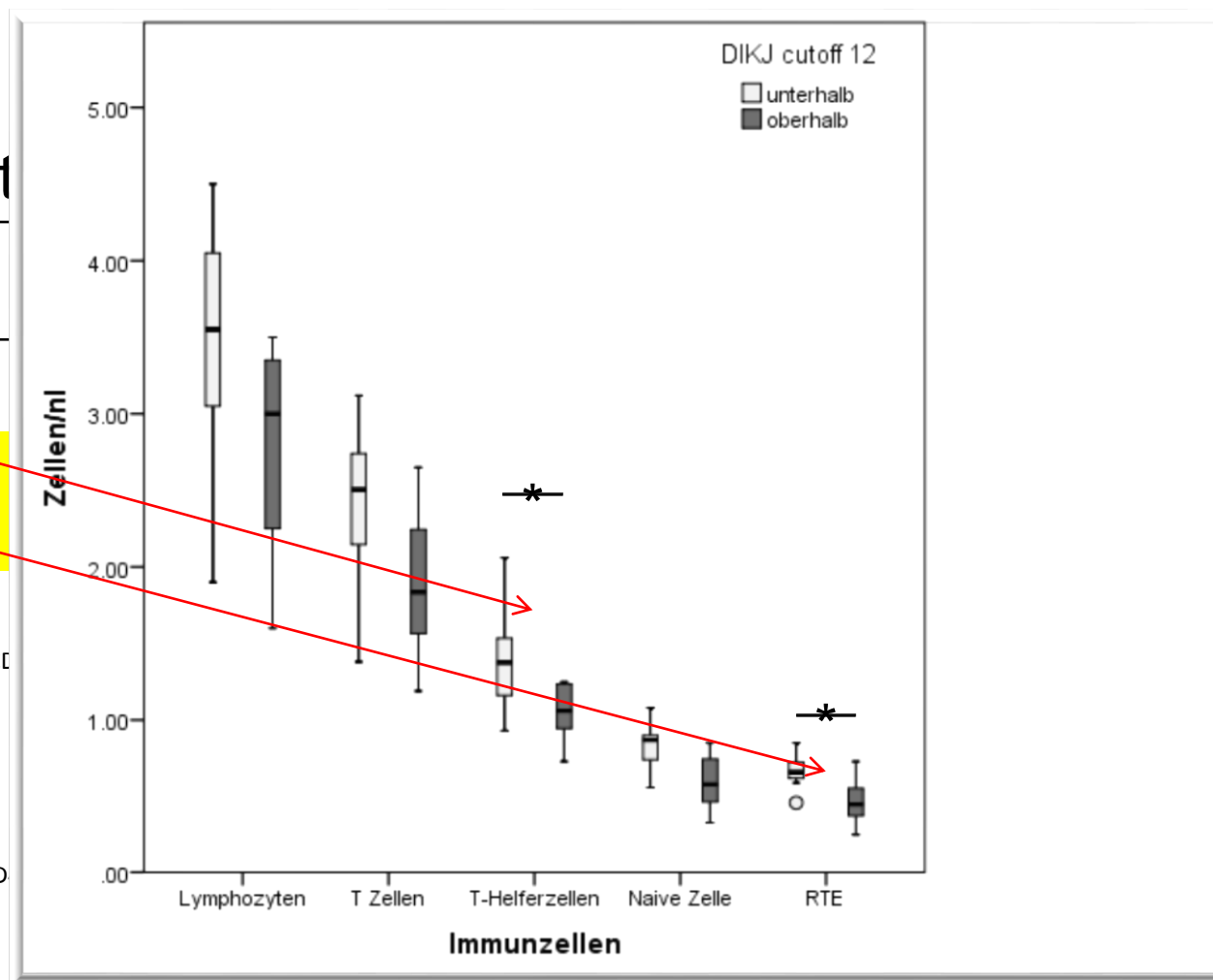
Activated helper T cells (CD3+CD4+/CD45+HLA-DR+)¹

Activated cytotoxic T cells (CD3+CD8+/CD45+/HLA-DR+)¹

B-cells (CD19+/CD45+)

Natural killer cells (CD3-CD16+56+/CD45+)

Monocytes (CD14+/CD45+)¹



Ratio Helper T cells/Total lymphocytes

0.41 ± 0.04 0.39 ± 0.04 0.26 **7.16*** .355 1.15 .081

Ratio CD4+/CD8+

1.74 ± 0.53 1.69 ± 0.41 0.11 **4.68*** .265 0.40 .030

Ratio Naïve T cells/Total lymphocytes¹

0.24 ± 0.04 0.21 ± 0.05 0.66 1.69 .133 2.66 .195

Ratio RTE/Total lymphocytes¹

0.20 ± 0.04 0.16 ± 0.04 **1.00** 1.18 .097 **3.44(*)** .238

Ratio RTE/ Naïve T cells¹

0.81 ± 0.05 0.79 ± 0.06 0.36 0.35 .031 0.23 .020

... but does not affect T cell activation

Counts (cells/nl)	CDI <cutoff	CDI >cutoff	Cohen's <i>d</i>	ANCOVA			
	(<i>M</i> ± <i>SD</i> , <i>n</i> =7)	(<i>M</i> ± <i>SD</i> , <i>n</i> =7)		F(3,16) _{age}	η_p^2 _{age}	F(3,16) _{dep}	η_p^2 _{dep}
Total lymphocytes	3.46 ± 0.83	2.79 ± 0.71	0.87	14.88**	.534	3.17(*)	.196
Total T cells (CD3+/CD45+)	2.41 ± 0.54	1.89 ± 0.49	1.01	13.44**	.512	4.47(*)	.256
Helper T cells (CD3+/CD4+/CD45+)	1.39 ± 0.34	1.06 ± 0.19	1.20	1.98	.132	4.91*	.274
Naïve T cells (CD4+/CD45RA+/CD3+) ¹	0.83 ± 0.17	0.60 ± 0.20	1.23	3.14	.222	4.60(*)	.295
RTE (CD3+/ CD45RA+/CD4+/ CD31+) ¹	0.67 ± 0.12	0.47 ± 0.16	1.41	3.78	.256	5.47*	.332
Cytotoxic T cells (CD3+CD8+/CD45+)	0.87 ± 0.32	0.67 ± 0.25	0.70	7.80*	.375	1.35	.094
Activated helper T cells (CD3+CD4+/CD45+/HLA-DR+) ¹	0.12 ± 0.05	0.09 ± 0.04	0.66	1.43	.115	0.83	.070
Activated cytotoxic T cells (CD3+CD8+/CD45+/HLA-DR+) ¹	0.14 ± 0.12 ²	0.11 ± 0.05	0.33	1.64	.130	0.08	.007
B-cells (CD19+/CD45+)	0.70 ± 0.26	0.59 ± 0.32	0.38	5.93	.313	0.19	.014
Natural killer cells (CD3-CD16+56+/CD45+)	0.34 ± 0.21	0.25 ± 0.10 ²	0.55	0.63	.046	0.91	.066
Monocytes (CD14+/CD45+) ¹	0.55 ± 0.26	0.45 ± 0.13	0.49	0.50	.043	0.49	.043
Ratio Helper T cells/Total lymphocytes	0.41 ± 0.04	0.39 ± 0.04	0.26	7.16*	.355	1.15	.081
Ratio CD4+/CD8+	1.74 ± 0.53	1.69 ± 0.41	0.11	4.68*	.265	0.40	.030
Ratio Naïve T cells/Total lymphocytes ¹	0.24 ± 0.04	0.21 ± 0.05	0.66	1.69	.133	2.66	.195
Ratio RTE/Total lymphocytes ¹	0.20 ± 0.04	0.16 ± 0.04	1.00	1.18	.097	3.44(*)	.238
Ratio RTE/ Naïve T cells ¹	0.81 ± 0.05	0.79 ± 0.06	0.36	0.35	.031	0.23	.020

PTSD impacts T cell

Counts (cells/nl)

Total lymphocytes

Total T cells (CD3+/CD45+)

Helper T cells (CD3+/CD4+/CD45+)

Naïve T cells (CD4+/CD45RA+/CD3+)¹

RTE (CD3+/ CD45RA+/CD4+/ CD31+)¹

Cytotoxic T cells (CD3+/CD8+/CD45+)

Activated helper T cells (CD3+/CD4+/CD45RA+/CD45RO+)¹

Activated cytotoxic T cells

(CD3+CD8+/CD45+/HLA-DR+)¹

B-cells (CD19+/CD45+)

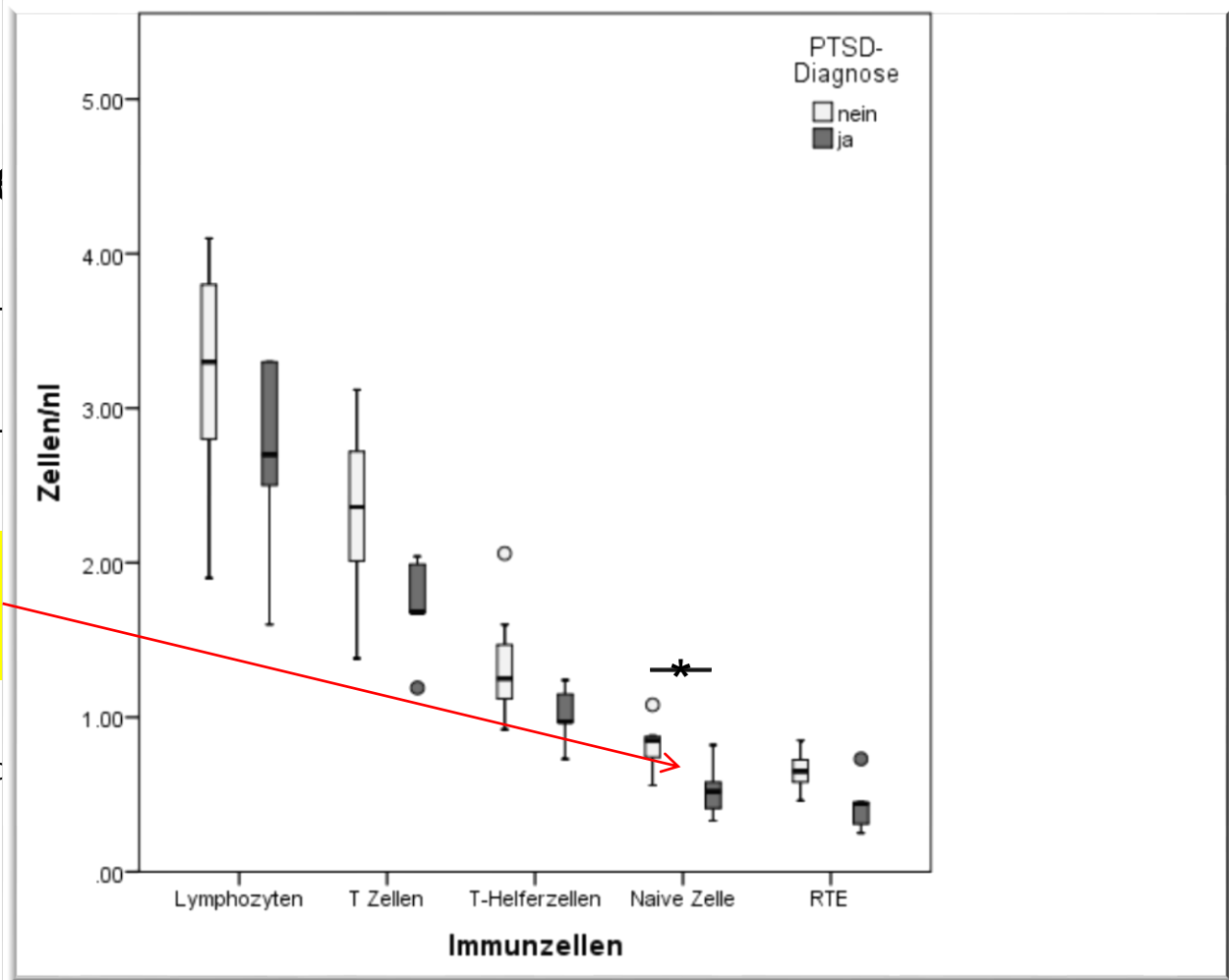
Natural killer cells (CD3-/CD16+/CD45+/CD56+)

Monocytes (CD14+/CD45+)

Ratio Naïve CD4/Total lymphocytes

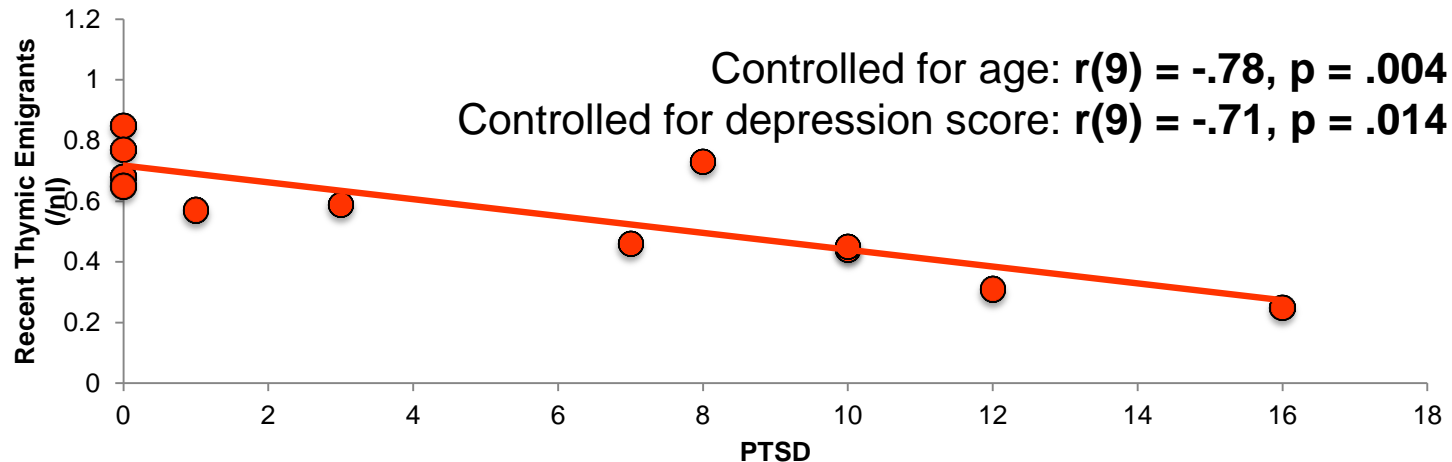
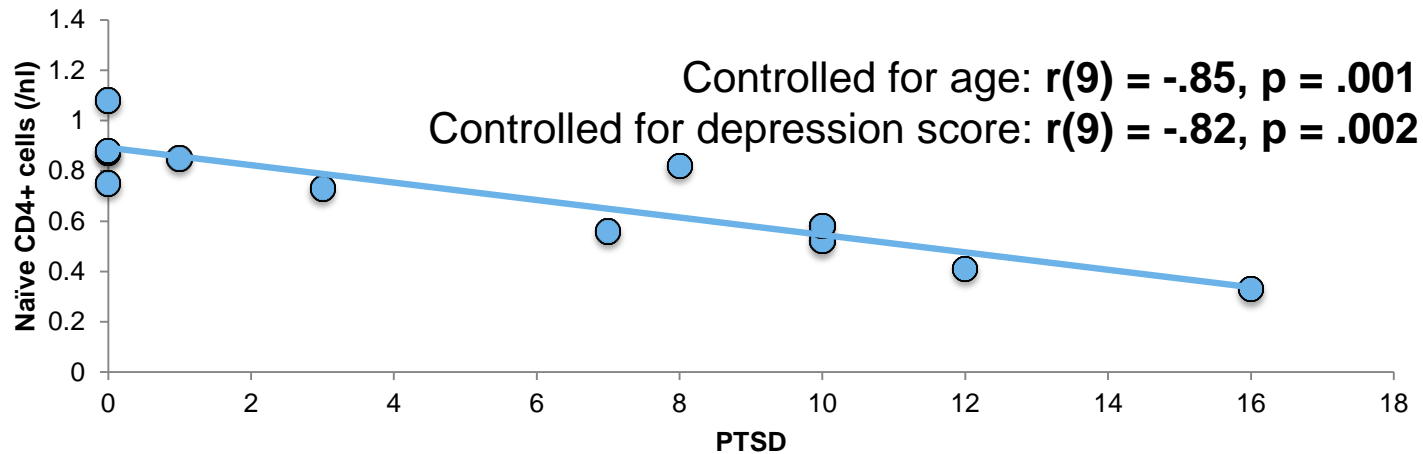
Ratio RTE/Total lymphocytes

Ratio RTE/ Naïve T cells



	0.29 ± 0.12	0.25 ± 0.10	0.54	0.16	.015	0.85	.071
	0.54 ± 0.26	0.46 ± 0.08	0.42	0.52	.055	0.13	.014
Ratio Naïve CD4/Total lymphocytes	0.25 ± 0.04	0.20 ± 0.06	0.98	---	---	2.72	.214
Ratio RTE/Total lymphocytes	0.20 ± 0.03	0.16 ± 0.05	0.97	---	---	2.26	.191
Ratio RTE/ Naïve T cells	0.80 ± 0.07	0.81 ± 0.06	-0.15	1.25	.122	0.27	.029

Inverse correlation of PTSD severity & immature T cells



Conclusion

- First study associating psychopathology and a compromised T cell compartment in maltreated children & adolescents
- Increased expression of HLA-DR+ on T cells related to childhood maltreatment is **not** further enhanced due to psychopathology
- **Suggestion: PTSD or depression promote an accelerated aging of the T cell compartment**
- more differentiated memory CD4 and CD8 T cells are known to display a persistent low-level of activation
- “ready-to-go” status in T cells exhausts the host’s reserve of naïve cells, reduces clonal diversity, and leads to impaired functionality
- Limitation: sample size & cross-sectional pilot study -> replication!
- Prospective or longitudinal data are needed

Outlook for future research

- Association with cytokine profile
- T cell stimulation in vitro
- HPA-axis
- **Gene/Epigene/Protein expression?**
 - Increased serotonin transporter gene (SERT) DNA methylation is associated with bullying victimization and blunted cortisol response to stress in childhood: a longitudinal study of discordant monozygotic twins. (Ouellet-Morin, 2013)
- **PTSD and depression in other populations**

Thanks to the staff at the Kinderspital and all participants!

Thank you for your interest!



Studie zu Immunbiologischen Veränderungen nach frühkindlicher Misshandlung oder Vernachlässigung

INAMA - Immunological and neurobiological alterations in maltreated children and adolescents

INFORMATION FÜR ELTERN UND KINDER
Wir suchen Kinder und Jugendliche in der Schweiz, welche bereit sind, sich im Rahmen der Studie untersuchen zu lassen.

KINDERSPITAL ZÜRICH
UNIVERSITÄTS-KINDERSPITAL - EIDGENÖSSISCHE KINDER-UND JUGENDPSYCHIATRIE - STIFTUNG



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