

The effect of trauma-focused therapy on the altered T cell distribution in individuals with PTSD: Evidence from a randomized controlled trial

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ABSTRACT

Posttraumatic stress disorder (PTSD) is associated with a reduced ratio of naïve cytotoxic T lymphocytes, an increased ratio of memory cytotoxic T lymphocytes, and a reduced proportion of FoxP3⁺ regulatory T lymphocytes. This study investigated whether these immunological alterations are reversible through an evidence based psychotherapeutic treatment. Therefore, 34 individuals with PTSD were randomly assigned to either a treatment condition of 12 sessions narrative exposure therapy (NET) or a waitlist control (WLC) group. PTSD symptoms were significantly reduced in the NET group, but not in the WLC group, four months post therapy (effect size: Hedges' $g = 1.61$). One year after therapy, PTSD symptoms were improved even further in the NET group compared to baseline (Hedges' $g = 1.96$). This symptom improvement was mirrored in an increase in the originally reduced proportion of regulatory T cells (T_{regs}) in the NET group at the one year follow up, when comparing subgroups matched for baseline T_{reg} numbers. However, no changes were found for the initially reduced proportion of CD45RA⁺CCR7⁺ naïve T lymphocytes. In conclusion, NET was effective in reducing trauma related PTSD symptoms and had a positive effect on the proportion of T_{regs} cells, thus demonstrating an effect of psychotherapy on an immunological level. Yet, the shift in the proportion of naïve and memory T lymphocytes in individuals with PTSD, discussed in the literature as a correlate of premature immunosenescence, was not reversible and thus might render these patients permanently more susceptible to infectious diseases.

1. Introduction

The probability of developing posttraumatic stress disorder (PTSD) after psychological trauma increases with the number of traumatic event types experienced (Neuner et al., 2004a; Kolassa et al., 2010). Likewise, a dose–response effect of trauma exposure during childhood has been demonstrated for the development of

physical health problems (Felitti et al., 1998) and impaired brain development (Teicher et al., 2012). Furthermore, an increased risk for somatic diseases like chronic pain, cancer, cardiovascular, respiratory, gastrointestinal, and autoimmune diseases has been reported for individuals with PTSD (Boscarino, 2004; Boscarino et al., 2010; Sareen et al., 2007), where the poor physical health found in individuals with PTSD might be moderated by altered immune functions and inflammatory processes (Von Känel et al., 2007; Pace and Heim, 2011; Spitzer et al., 2010).

However, linking PTSD to alterations of bulk T cell populations, representing a major branch of adaptive immunity, has been controversial: Whereas the number of circulating CD8⁺ cytotoxic T cells in individuals with PTSD has been found to be mostly lower (Ironson et al., 1997; Kawamura et al., 2001; Sommershof et al.,

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2009) or unchanged (Altemus et al., 2006; Laudenslager et al., 1998; Vidović et al., 2007; Wilson et al., 1999), the number of circulating CD3⁺ T lymphocytes or CD4⁺ T helper cells has been found to be lower, unchanged or even higher (Ironson et al., 1997; Laudenslager et al., 1998; Boscarino and Chang, 1999; Wilson et al., 1999; Kawamura et al., 2001; Boscarino, 2004; Vidović et al., 2007; Sommershof et al., 2009). As peripheral T lymphocytes consist of a range of functionally different subpopulations, one reason for these inconsistent findings might be that changes in PTSD might be specific to certain T lymphocyte activation and differentiation states. Sommershof et al. (2009) investigated this further differentiation of CD4⁺ T helper and CD8⁺ cytotoxic T cells in naïve, memory and effector cells, applying a differentiation model of T cells defined by changes in the expression of the lineage markers CD45RA and CCR7 (Hamann et al., 1999; Sallusto et al., 1999). They found a decreased ratio of (CD45RA⁺CCR7⁺) naïve CD8⁺ T cells and an increased proportion of (CD45RA⁻) memory CD8⁺ T cells in individuals with PTSD (Sommershof et al., 2009). As a shrinking repertoire of naïve T cells may correlate with an enhanced susceptibility to infectious diseases (Fagnoni et al., 2000; Shen et al., 1999), this reduction in naïve T cells represents a possible explanation for the enhanced risk of infectious diseases in individuals with PTSD (Sommershof et al., 2009). Furthermore, Sommershof et al. (2009) observed a 50% decrease in the proportion of CD4⁺CD25⁺FoxP3⁺ regulatory T cells (T_{reg}) in individuals with PTSD. T_{reg} cells are critical for maintaining balance in the immune system, regulating the immune response, and preventing autoimmune diseases (Vignali et al., 2008). Decreased counts of CD4⁺CD25⁺FOXP3⁺ T_{reg} cells have been associated with autoimmune diseases like diabetes, multiple sclerosis, rheumatoid arthritis, psoriasis, anemia and eczema (Bennett et al., 2001; Buckner, 2010; Wildin et al., 2002), conditions for which individuals with PTSD show an increased risk (Boscarino, 2004; Boscarino et al., 2010; Weisberg et al., 2002).

Given the considerable prevalence of traumatic stress, and in particular the high prevalence of PTSD in populations affected by conflict, terror and combat (Neuner et al., 2004a; Neuner and Elbert, 2007), a highly relevant question in the context of traumatic stress and physical disease is: Can effective treatment reverse the effects of traumatic stress not only on a psychological but also on an immunological level?

Trauma focused psychotherapeutic interventions may effectively reduce trauma related mental suffering in individuals with PTSD (Ehlers et al., 2010; Cloitre, 2009; Kleim et al., 2012; Seidler and Wagner, 2006), and, in individuals with PTSD with comorbid borderline personality disorder (Bohus et al., 2013) or comorbid substance abuse (van Dam et al., 2013). Moreover, it was demonstrated that successful psychotherapeutic treatment also significantly reduced cough, diarrhea, and fever (Neuner et al., 2008).

Yet, to our knowledge no study investigated the effect of psychotherapy on T lymphocyte distribution in individuals with PTSD. So far, the impact of psychological interventions on T lymphocyte populations has mainly been examined in patients with cancer and human immunodeficiency virus (HIV), yielding mixed results. There are studies reporting a stabilization of CD4⁺ T lymphocytes after psychotherapeutic interventions (Creswell et al., 2009; Petrie et al., 2004; Sherman et al., 2000); however, CD4⁺ and CD8⁺ T lymphocytes were not affected in other studies (Antoni et al., 2006; Carrico et al., 2005; Hosaka et al., 2000).

Furthermore, we know that effective psychotherapy with Narrative Exposure Therapy (NET) can reverse the increased level of DNA strand breaks observed in individuals with PTSD compared to controls (Morath et al., in press). NET is a trauma focused treatment approach for PTSD, developed for survivors of war and torture (Schauer et al., 2011a). Its efficacy has been proven in a number of

randomized controlled trials in post conflict regions (Ertl et al., 2011; Neuner et al., 2004b) and in Europe (Hensel Dittmann et al., 2011; Robjant and Fazel, 2010).

The present study has two aims: 1) to extend the findings by Sommershof et al. (2009) in a larger sample of individuals with PTSD, trauma exposed non PTSD subjects and non exposed controls and 2) to investigate whether the altered T cell distribution in individuals with PTSD can be reversed by psychotherapeutic treatment with NET. Individuals with PTSD were investigated before treatment and four and 12 months after the end of therapy and T cell differentiation subsets were analyzed. We hypothesized that the NET treatment group would show an increase in the proportions of CD45RA⁺CCR7⁺ naïve CD8⁺ as well as in the proportion of CD4⁺CD25⁺FOXP3⁺ T_{reg} cells.

2. Methods

2.1. Participants

Thirty four individuals with PTSD and 43 non PTSD controls were recruited through the Center of Excellence for Psycho traumatology, University of Konstanz, and public advertisements. Sixteen subjects with PTSD and 27 controls were also participants in a previous study by Sommershof et al. (2009). After the initial screening, individuals with PTSD (age 16–47 years) – refugees (13 Africa, 21 Middle East) with a history of war and torture experiences – were randomly assigned to either a treatment (NET group: *n* = 17) or a waitlist control condition (WLC group: *n* = 17). The non PTSD control group (age 16–50 years) consisted of refugees and immigrants (9 Africa, 13 Balkan, 21 Middle East) without PTSD and varying traumatic load (0–9 traumatic event types). As the number of traumatic events experienced influences T cell distribution in a cumulative way (Sommershof et al., 2009), we further divided the control group into a group with substantial trauma exposure (*trauma exposed*, *n* = 24) and a control group with no or little trauma exposure (*non trauma exposed*, *n* = 19) by median split of a traumatic load index.²

Exclusion criteria were acute infections or chronic somatic illnesses (e.g., HIV, osteoarthritis, autoimmune diseases) and glucocorticoid medication. Non trauma exposed control group subjects were also excluded if they met the criteria for any mental disorder according to DSM IV or reported taking psychotropic medication. Individuals with PTSD and trauma exposed controls were excluded if they met the criteria for comorbid alcohol or substance abuse and dependence or a current or past history of a psychosis according to DSM IV. The inflammation load between the time points of assessment was documented, and no severe illnesses were reported in between.

Individuals with PTSD showed no significant group differences from trauma exposed and non trauma exposed controls with respect to age and smoking behavior, but groups differed significantly with respect to gender and intake of psychotropic medication (Table 1). Moreover, individuals with PTSD had experienced significantly more different traumatic event types (event list of the Clinician Administered PTSD Scale [CAPS], Blake et al., 1995), significantly more war and torture events (Vivo checklist, Schauer et al., 2011b), and showed higher symptom scores in the CAPS, the Hamilton Depression Rating Scale (HAM D; Hamilton, 1960) and the screening for somatoform symptoms (SOMS 7; Rief and

² Traumatic load index = [(number of traumatic event types on the CAPS event list/items on the CAPS event list) + (number of war experiences on the vivo checklist/items on the war checklist) + (number of torture experiences on the vivo checklist/items on the torture checklist)].

Table 1

Socio-demographic and clinical characteristics of PTSD patients assigned to the narrative exposure therapy (NET) and the Waitlist Control (WLC) group as well as of trauma-exposed individuals and control subjects.

Variables	PTSD		Trauma- exposed (n = 24)	Controls (n = 19)	p
	NET (n = 17)	WLC (n = 17)			
Age ^b (years)	28 (16–47)		32 (16–50)	25 (19–49)	.35
	28 (16–43)	31 (17–47)			.40
Sex (female/male) ^c	14/20 ^d		13/11 ^d	16/3	.01
	8/9	6/11			.36
Region of origin (%) ^c					.004
Africa	38.2		29.2	10.5	
Balkan	-		25.0	36.8	
Middle East	61.8		45.8	52.6	
Smokers (%) ^c	20.6		25.0	5.3	.22
	17.6	23.5			.68
Medication (%) ^c	41.2 ^{d,e}		16.7 ^d		.002
	41.2	41.2			1.0
Hypnotics	5.9	11.8	8.3		
Anxiolytics	5.9	11.8			
Antidepressives	35.3	23.5	8.3		
Neuroleptics	11.8				
Traumatic load index ^b	1.3 (.3–2.2) ^{d,e}		.8 (.3–2.2) ^d	.1 (0–.3)	<.0001
	1.3 (.3–2.1)	1.3 (.6–2.2)			.71
War/torture events ^b	9 (0–22) ^{d,e}		3 (0–20) ^d	0 (0–1)	<.0001
	9 (0–22)	8 (0–19)			.79
CAPS events ^a	7.0 ± 2.0 ^{d,e}		5.6 ± 1.9	2.2 ± 1.2	<.0001
	6.8 ± 2.3	7.2 ± 1.7			.62
CAPS score ^b	88 (56–114) ^{d,e}		.5 (0–57) ^d	0 (0–10)	<.0001
	91 (63–114)	75 (56–106)			.01
HAM-D score ^b	27.5 (0–44) ^{d,e}		7 (0–31) ^d	0 (1–5)	<.0001
	27 (0–44)	28 (15–39)			.63
SOMS-7 score ^b	21 (3–58) ^{d,e}		6 (0–41) ^d	1 (0–3)	<.0001
	21 (13–48)	21 (3–58)			.56

^a Group comparisons in continuous variables were performed with ANOVA. Data are presented as mean ± standard deviation.

^b When residuals of the model were not normally distributed, non-parametric testing in continuous variables was done with the Kruskal–Wallis test (χ^2). Data are presented as median and range.

^c Group comparisons in categorical variables were performed with chi-squared tests (χ^2). CAPS, Clinician-Administered PTSD Scale; HAM-D, Hamilton Depression Rating Scale; SOMS-7, Screening for Somatoform Symptoms-7.

^d Significantly different from non-exposed controls.

^e Significantly different from trauma-exposed controls.

Hiller, 2003) than trauma exposed and non exposed controls. Trauma exposed individuals differed significantly from non exposed controls with respect to CAPS, HAM D and SOMS 7 scores (Table 1). In accord with the building block effect of traumatic stress (Kolassa et al., 2010; Neuner et al., 2004a), the traumatic load index correlated positively with PTSD symptom severity ($r = .65$; $p < .0001$).

2.1.1. Concerning the treatment study

The NET group and the WLC did not differ significantly with respect to age, sex, ethnicity, smoking behavior or intake of psychotropic medication, number of traumatic event types experienced, HAM D score, or SOMS 7 score. However, the NET group showed a significantly higher PTSD symptom score (Table 1).

2.2. Procedure

2.2.1. Baseline screening

All participants were screened with a clinical diagnostic interview by trained clinical psychologists from the Center of Excellence for Psychotraumatology in Konstanz, always starting at 10 a.m. If participants were not fluent in English or German, diagnostic interviews were completed with the help of trained interpreters. The interview started with socio-demographic and health related information (e.g. smoking behavior, use of psychotropic medication, physical disorders). Then, the number of different traumatic event types experienced and PTSD symptom severity were assessed using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995). In addition, the Vivo Checklist of War, Detention, and Torture Events

(Schauer et al., 2011b) was administered to assess war and torture experiences in more detail. Depressive symptoms were quantified by the Hamilton Depression Scale (HAM D; Hamilton, 1960) and somatic complaints by a shortened version of the Screening for Somatoform Symptoms (SOMS 7; Rief and Hiller, 2003). Comorbid psychiatric disorders were assessed using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). The same clinical diagnostic interview was repeated four and 12 months post test.

2.2.2. Treatment study

The trial was conducted in an ambulant setting and therapists were clinical psychologists specialized in the field of trauma and experts for narrative exposure therapy (NET). The 34 individuals with PTSD were randomly assigned to either the NET group or a WLC group. The NET group received 12 weekly treatment sessions of 90 min (Schauer et al., 2011a). Treatment adherence was monitored by regular supervision. The WLC group waited for about eight months without any standardized intervention. Post tests were conducted four months (t_1), and one year (t_2) after the end of NET. For the participants in the WLC group, the time spans between pre and post tests were individually matched with the NET group. For ethical reasons, the WLC group received treatment with NET after the first post test, therefore only the NET group was invited to the one year follow up. Participant flow is shown in Fig. 1. The clinicians who performed the outcome evaluations were never the same as the clinician who performed the baseline evaluation or the psychotherapeutic intervention; moreover, the two follow up evaluations were performed by different clinicians. Diagnosticians

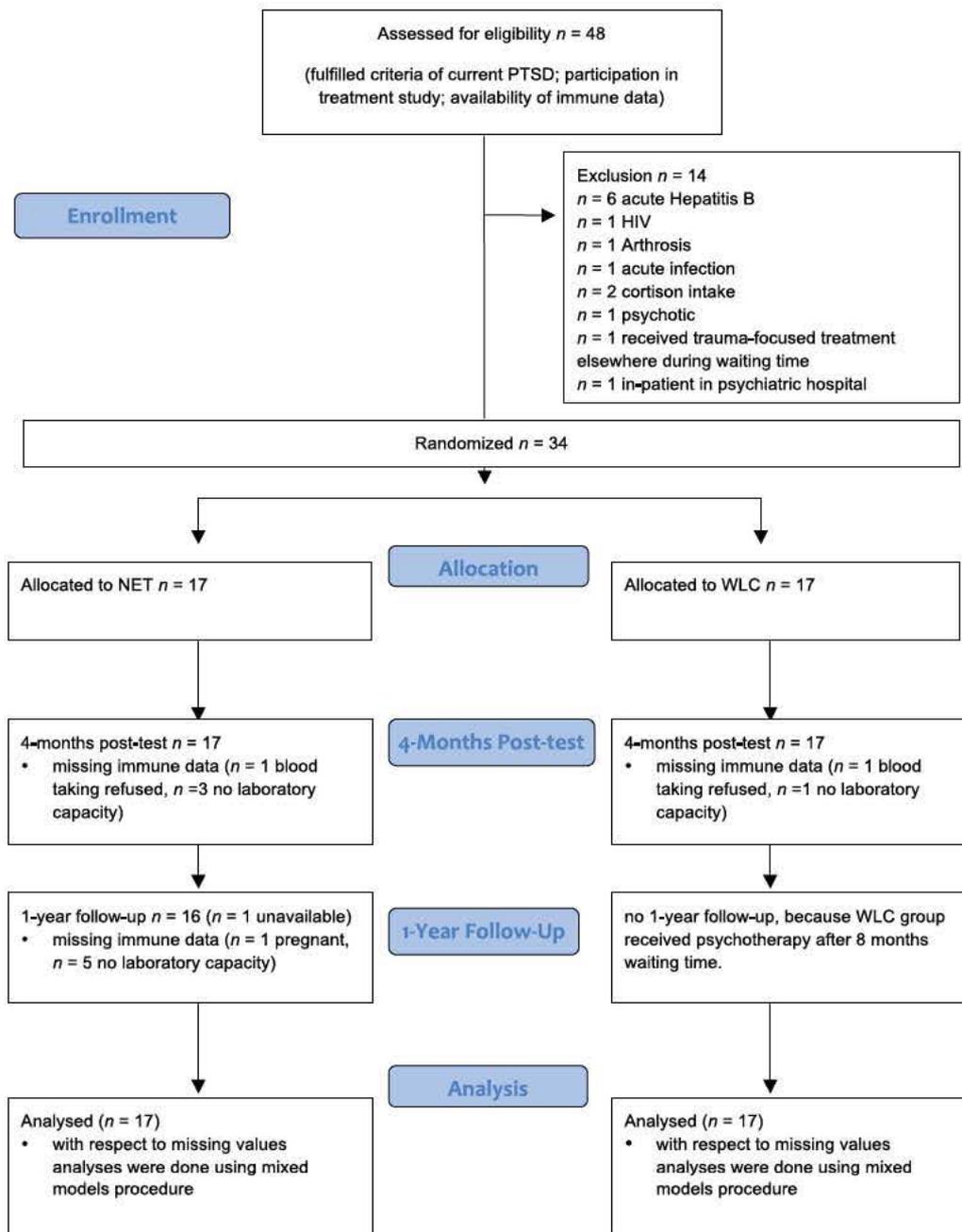


Fig. 1. Flow of participants through the study. PTSD indicates Posttraumatic Stress Disorder; NET indicates Narrative Exposure Therapy and WLC indicates Waitlist Control Group.

were blind with regard to group membership at baseline and at both post tests.

The study was conducted in line with the principles of the Declaration of Helsinki. The University of Konstanz Ethics Committee approved the study. All participants provided advance written informed consent and received 30 € remuneration for each blood drawing. Treatment with NET was provided for free. The study was registered at <http://clinicaltrials.gov/ct2/show/NCT01206790>.

2.3. Blood collection and lymphocyte phenotyping

Blood drawings and lymphocyte phenotyping were performed before NET started (t_0), four months post treatment (t_1), and one year post treatment (t_2). Blood was collected always at 10:00 a.m. in EDTA buffered tubes. Peripheral blood was sent within 1 h to the

Laboratory of Immunology, University of Konstanz, Germany, for further processing. Blood samples were coded to guarantee blinding of the laboratory staff involved. The method used for lymphocyte phenotyping was stringently equal to the method used by Sommershof et al. (2009).

In a first step, the total number of monocytes, granulocytes and lymphocytes were counted in whole peripheral blood samples. Lymphocytes were subdivided into B cells ($CD19^+$), NK cells ($CD16^+CD56^+$), $CD3^+$ T cells, $CD3^+CD4^+$ T helper cells, $CD3^+CD8^+$ cytotoxic T cells, and $CD4^+CD25^+FoxP3^+$ T_{reg} cells. The surface molecules CD45RA and CCR7 were used to characterize distinct T cell maturation subsets: naïve ($CD45RA^+CCR7^+$), central memory (T_{CM} : $CD45RA^-CCR7^+$), effector memory (T_{EM} : $CD45RA^-CCR7^-$) and CD45RA positive effector memory cells (T_{EMRA} : $CD45RA^+CCR7^-$). For a detailed description of the different classes of T cells, their

Table 2
Different classes of T cells, their main function and tissue localization.

T Cells	Phenotype	Main function	Tissue localization
Naïve	CD45RA(+) CCR7(+)	Immune responses to <i>de novo</i> pathogenic organisms	Circulate between secondary lymphoid organs via the lymph and blood
Memory		Immune response to recurrent encounters with the same pathogenic organism	
Central Memory (CM)	CD45RA(−) CCR7(+)	Secondary effector function; high proliferative potential	Secondary lymphoid organs (lymph nodes and spleen)
Effector Memory (EM)	CD45RA(−) CCR7(−)	Immediate effector function; low expansion potential	Peripheral tissues (lung, liver, intestine, spleen, and blood)
T _{EMRA}	CD45RA(+) CCR7(−)	Immediate and high effector function; low expansion potential	Peripheral tissues (lung, liver, intestine, spleen, and blood)
Regulatory T cells (T _{reg})	CD4(+) CD25(+) FoxP3(+)	Controlling immune responses and maintaining self-tolerance by inhibiting autoreactive T cells	Secondary lymphoid organs (lymph nodes and peripheral tissue)

main function and their relevance to the current study, please see [Table 2](#).

Absolute numbers of lymphocytes were obtained using an automated hematology analyzer (XT 2000i, Sysmex, Horgen, Switzerland). For a detailed description of lymphocyte phenotyping, please see [Sommershof et al. \(2009\)](#).

2.4. Outcomes

Outcome measures were changes in PTSD symptom severity (CAPS score), in depressive symptoms (HAM D score), in somatic complaints (SOMS 7 score) and in (CD45RA⁺CCD7⁺) naïve and (CD45RA[−]) memory subsets of CD3⁺, CD4⁺, and CD8⁺ T cells as well as in CD4⁺CD25⁺FoxP3⁺ T_{reg} cells four months and one year after NET.

2.5. Statistics

2.5.1. Group differences at baseline (*t*₀)

Differences between groups (PTSD, trauma exposed controls, non exposed controls) in clinical characteristics and T cell distributions were analyzed by ANOVA. As age influences T cell distribution ([Fagnoni et al., 2000](#); [Hong et al., 2004](#)), age was included as a covariate in the models as also suggested by AIC ([Burnham et al., 2002](#)). Including smoking and gender or excluding participants taking psychotropic medication did not alter results.

The Kruskal–Wallis test was used to analyze group differences when ANOVA residuals were not normally distributed. As we had specific hypotheses for the direction of T cell changes (reduction in

the proportion of CD8⁺ naïve and T_{reg} cells), one sided independent *t* tests or the Wilcoxon–Mann–Whitney test were used for post hoc analyses for these variables. Correlations were analyzed with the Kendall tau rank correlation.

2.5.2. Treatment study

Linear mixed models were used to analyze changes in clinical characteristics and lymphocyte differentiations from *t*₀ to *t*₁. Age was included as covariate for T cell analysis. Since residuals in the model of CD3⁺ total T cells and CD8⁺ memory T cells were not normally distributed, data were retested with a logarithmized data set and results remained stable. Changes from *t*₀ to *t*₁ and *t*₂ within the NET group were analyzed by linear mixed models and paired *t* tests for post hoc comparisons. Treatment effect sizes were calculated by Hedges' *g* ([Hedges, 1981](#)).

3. Results

3.1. The effect of traumatic stress and PTSD on T cell distribution at *t*₀

There was no difference in the absolute cell number of lymphocytes (χ^2 .72; *p* .70) between individuals with PTSD (median 1939, range 1249–2800), trauma exposed individuals (median 1960, range 1301–2938), and non traumatized controls (median 1815, range 1308–2965), but the percentage of total CD3⁺ T cells was significantly reduced in individuals with PTSD compared to non traumatized controls ([Table 3](#)). Extending the results of [Sommershof et al. \(2009\)](#), we found a significant main effect for

Table 3
T Lymphocyte distribution in whole peripheral blood of individuals with PTSD, of trauma-exposed individuals and of control subjects, at baseline (*t*₀).

Variables (%)	PTSD (<i>n</i> 34)		Trauma-exposed (<i>n</i> 24)		Controls (<i>n</i> 19)		Statistics	<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
CD3⁺								
Total ^a	68.6 ^c	36.5	66.2 ^c	40.0	73.9	51.4	χ^2 7.03	.03
Naïve ^b	34.9	11.4	37.1	9.6	41.0	12.8	<i>F</i> (2,72) 1.89	.16
CD45RA memory ^b	41.5 ^c	9.9	39.0	8.1	34.5	9.4	<i>F</i> (2,72) 3.70	.03
T _{EMRA} ^a	21.9	8.5	23.4	3.9	20.2	8.4	χ^2 .17	.92
CD8⁺								
Total ^b	22.0	5.3	23.1	5.3	25.4	5.1	<i>F</i> (2,70) 2.64	.08
Naïve ^b	30.8 ^c	12.7	30.9 ^c	13.2	41.0	19.5	<i>F</i> (2,68) 3.72	.03
CD45RA memory ^a	31.7 ^{c,d}	12.2	24.1	10.4	23.5	10.1	χ^2 8.65	.01
T _{EMRA} ^b	36.6	13.2	43.4	15.5	34.9	15.5	<i>F</i> (2,68) 1.99	.14
CD4⁺								
Total ^b	35.9	7.9	39.2	7.0	39.1	8.1	<i>F</i> (2,72) 1.68	.19
Naïve ^b	43.6	13.7	43.6	12.3	48.6	11.9	<i>F</i> (2,70) 1.07	.35
CD45RA memory ^b	53.7	13.1	52.7	12.4	46.9	11.8	<i>F</i> (2,70) 1.84	.17
T _{EMRA} ^a	1.7	.5	2.8	.2	1.9	.6	χ^2 2.89	.24
T _{regulatory} ^a (CD4 ⁺ CD25 ⁺ FoxP3 ⁺)	1.4 ^{c,d}	.5	2.7	1.2	2.4	1.0	χ^2 9.79	.007

^a Residuals of the model were not normally distributed; median and range are displayed; non-parametric testing was done with the Kruskal–Wallis test (χ^2).

^b Analysis were done with age as covariate using ANCOVA; means and standard deviations (SD) are displayed.

^c Significantly different from non-exposed controls.

^d Significantly different from trauma-exposed controls.

Group with respect to the percentage of naïve CD8⁺ T cells ($F_{(2,68)} = 3.72$; $p = .03$), with post hoc tests revealing significant group differences between individuals with PTSD and non traumatized controls ($t_{(27,0)} = 2.04$; $p = .04$; one sided) and between trauma exposed subjects and controls ($t_{(31,5)} = 1.87$; $p = .03$; one sided), but not between individuals with PTSD and trauma exposed controls ($t_{(38,9)} = .04$; $p = .49$; one sided; see Table 3). Again, there was a significantly increased percentage of memory

CD8⁺ T cells in individuals with PTSD compared to non PTSD controls ($\chi^2 = 8.65$; $p = .01$). Post hoc tests revealed significant group differences between individuals with PTSD and non traumatized controls ($W = 181.5$; $p = .005$; one sided) and between individuals with PTSD and trauma exposed subjects ($W = 456.0$; $p = .01$; one sided), but not between trauma exposed subjects and controls ($W = 171$; $p = .31$; one sided). Furthermore, we confirmed the reduction in the percentage of T_{reg} cells in

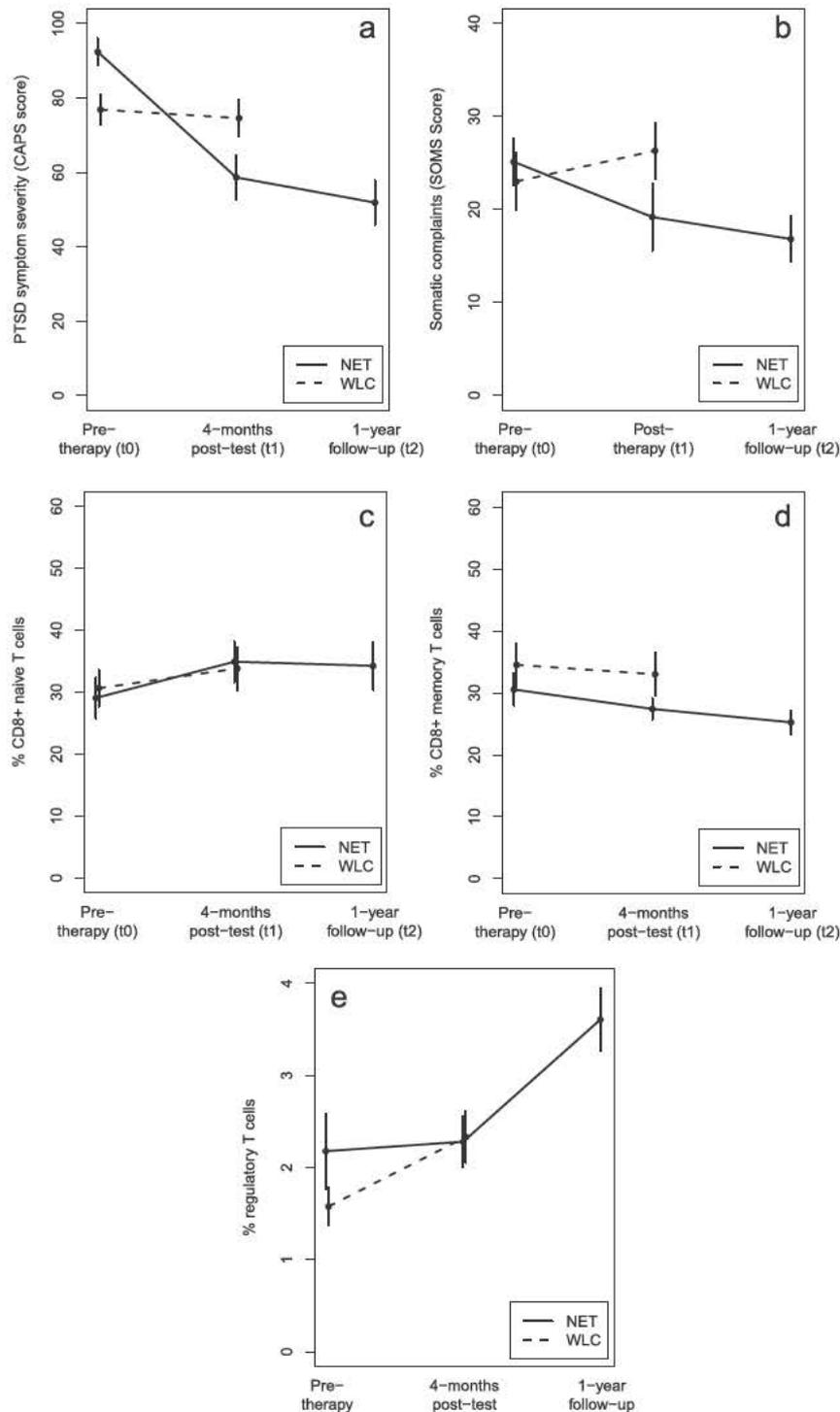


Fig. 2. a) PTSD symptom severity (CAPS score), b) somatic complaints (SOMS-7 score) c) percentages of (CD45RA⁺CCR7⁺) naïve CD8⁺ T cells and d) percentages of (CD45RA⁻) memory CD8⁺ T cells in the narrative exposure therapy (NET) group and the Waitlist Control (WLC) group pre-therapy (t₀), 4-months post (t₁) and 1-year post-treatment (t₂) e) percentages of (CD4⁺CD25⁺FOXP3⁺) regulatory T cells in the NET and WLC subgroups parallelized for baseline T_{reg} numbers.

individuals with PTSD ($\chi^2 = 9.79$; $p = .007$): T_{reg} cells were significantly reduced in the PTSD compared to the non traumatized control group ($W = 140.5$; $Z = 1.9$; $p = .03$; one sided); similarly, individuals with PTSD showed a larger reduction in T_{reg} cells than trauma exposed controls ($W = 157.5$; $Z = 2.9$; $p = .0015$; one sided); there was no significant difference between trauma exposed subjects and the control group ($W = 111$; $Z = 1.0$; $p = .15$; one sided). No significant group differences were found for the percentage of total $CD8^+$ or $CD8^+ T_{EMRA}$ cells as well as for the percentage of total $CD4^+$, $CD4^+$ naïve, memory and T_{EMRA} cells (see Table 3).

The number of different traumatic event types experienced correlated negatively with the percentage of naïve $CD8^+$ T cells ($r = -.24$; $p = .04$), i.e. higher values in traumatic load as measured by the traumatic load index were associated with a stronger reduction in naïve $CD8^+$ T cells.

3.2. Effects of NET on T cell distribution

Four months after treatment, PTSD symptom severity (CAPS sum score) had declined significantly in the NET compared to the WLC group (Time \times Treatment $F_{(1,32)} = 16.90$; $p = .0003$). The effect size of treatment in the NET group was large (Hedges' $g = 1.61$). Post hoc tests showed a significant decline in symptom severity in the NET group from t_0 to t_1 ($t_{(16)} = 5.99$; $p < .0001$), whereas symptom severity remained stable in the WLC group. At t_2 , the NET group showed an even greater decline in symptoms (Time $F_{(1,32)} = 32.04$; $p = .0001$) with an effect size of Hedges' $g = 1.96$ from t_0 to t_2 (Fig. 2a). NET also improved somatic symptoms, as measured with the SOMS 7, in the treatment but not in the WLC group (Time \times Treatment, $F_{(1,31)} = 6.19$; $p = .02$; Fig. 2b). However, depressive symptoms (HAM D) were not significantly improved in the NET compared to the WLC group (Time \times Treatment, $F_{(1,32)} = .89$; $p = .35$, see Table 4).

Against our hypothesis, there was no treatment specific increase in the percentage of naïve $CD8^+$ T cells from t_0 to t_1 (Time \times Treatment $F_{(1,25)} = .05$; $p = .82$, Table 4 and Fig. 2c), or from t_0 to t_2 within the PTSD group (Time $F_{(1,21)} = 2.17$; $p = .16$). Furthermore, there were no treatment specific alterations in the percentage of memory $CD8^+$ T cells in the NET, compared to the WLC group (Time \times Treatment $F_{(1,25)} = .60$; $p = .45$) and no significant changes in the percentage of memory $CD8^+$ T cells over time (Time $F_{(1,21)} = .28$; $p = .60$) within the NET group (see Fig. 2d).

With respect to the percentage of T_{reg} cells, we found no Time \times Treatment interaction ($F_{(1,23)} = 3.06$; $p = .09$) from t_0 to t_1 (Table 4), and no significant increase in the percentage of T_{reg} over time (Time $F_{(1,20)} = 3.40$; $p = .08$) within the NET group. However there was a significant time effect from t_1 to t_2 within the NET group ($t_{(6)} = 2.37$; $p = .05$). Since the NET and the WLC group differed significantly at t_0 in T_{reg} cell counts ($t_{(22,7)} = 2.24$; $p = .04$), which could have induced spurious effects through regression to the mean, we performed an additional analysis excluding the two subjects with the highest percentage of T_{regs} in the NET and the two subjects with the lowest percentage of T_{regs} in the WLC group, parallelizing groups with respect to T_{reg} cell counts ($t_{(20,6)} = 1.32$; $p = .20$). Again, there was no Time \times Treatment interaction from t_0 to t_1 ($F_{(1,19)} = .85$; $p = .37$), but the NET group showed a significant increase in T_{regs} over time (Time $F_{(1,17)} = 8.06$; $p = .01$; Fig. 2e). Post hoc tests revealed a significant increase from t_0 to t_2 ($t_{(7)} = 1.45$; $p = .05$) and from t_1 to t_2 ($t_{(5)} = 2.56$; $p = .05$), but not from t_0 to t_1 . Furthermore, there was a marginally significant but large positive association between PTSD symptom reduction from t_0 to t_2 and the increase of T_{regs} from t_0 to t_2 ($r = .75$; $p = .09$).

No treatment specific alterations were found for the other T cell subtypes investigated (see Table 4) except for the total percentage of $CD4^+$ T cells, increasing significantly from t_0 to t_2 within the NET group ($F_{(1,22)} = 6.53$; $p = .02$).

Table 4

Changes in clinical characteristics and T cell distribution in the narrative exposure therapy (NET) and the Waitlist Control (WLC) group.

Variables	Group	Pre-therapy <i>M</i> (<i>SD</i>)	4-months Post <i>M</i> (<i>SD</i>)	1-year post <i>M</i> (<i>SD</i>)	Statistics (treatment \times time)	<i>p</i>
CAPS	NET	92.41 ^b (14.95)	58.65 (24.93)	51.88 (24.52)	$F_{(1,32)} = 16.90$.0003
	WLC	76.88 (15.95)	74.59 (20.42)			
HAM-D	NET	22.82 (11.73)	17.00 (9.81)	17.63 (9.84)	$F_{(1,32)} = .89$.35
	WLC	25.94 (6.55)	24.18 (9.21)			
SOMS	NET	25.12 (10.55)	19.18 (14.93)	16.81 (10.00)	$F_{(1,31)} = 6.19$.02
	WLC	23.00 (12.75)	26.31 (12.38)			
% CD3 total ^a	NET	65.10 (11.18)	67.65 (12.57)	69.05 (6.04)	$F_{(1,25)} = .17$.68
	WLC	65.53 (7.54)	65.25 (11.45)			
% CD3 naïve	NET	35.11 (11.69)	38.36 (11.38)	35.61 (12.31)	$F_{(1,26)} = .00$.98
	WLC	34.71 (12.05)	36.73 (12.59)			
% CD3 memory	NET	40.15 (9.01)	40.19 (9.23)	40.15 (11.03)	$F_{(1,26)} = .08$.78
	WLC	42.94 (10.15)	44.73 (12.11)			
% CD8 total	NET	23.96 ^b (5.55)	23.64 (4.70)	23.72 (6.89)	$F_{(1,26)} = .34$.56
	WLC	20.17 (4.52)	20.99 (5.40)			
% CD8 naïve	NET	29.06 (13.42)	34.91 (13.42)	34.24 (15.93)	$F_{(1,25)} = .07$.80
	WLC	30.63 (12.33)	33.82 (14.21)			
% CD8 memory ^a	NET	30.55 (10.58)	27.41 (7.16)	25.26 (7.80)	$F_{(1,25)} = .60$.45
	WLC	34.53 (14.42)	32.61 (13.67)			
% CD4 total	NET	34.54 (7.13)	38.23 (5.49)	39.03 (6.52)	$F_{(1,25)} = .05$.83
	WLC	38.02 (8.71)	42.04 (6.52)			
% CD4 naïve	NET	43.29 (16.39)	42.28 (15.99)	43.17 (15.72)	$F_{(1,25)} = .29$.61
	WLC	42.06 (13.54)	38.01 (14.57)			
% CD4 memory	NET	53.84 (15.26)	55.99 (15.03)	55.11 (15.29)	$F_{(1,25)} = .05$.82
	WLC	55.28 (13.37)	59.37 (14.42)			
% T reg	NET	2.50 ^b (1.73)	2.42 (1.02)	3.54 (1.25)	$F_{(1,23)} = 3.06$.09
	WLC	1.46 (.81)	2.35 (1.04)			

Abbreviations: CAPS, Clinical Administered PTSD Scale; HAM-D, Hamilton Depression Rating Scale; SOMS, Screening for Somatoform Symptoms; Statistics: *M* (mean), *SD* (standard deviation). Age was included as covariate into the models of T cell analysis.

^a Since residuals of the model were not normally distributed, data were retested with a logarithmized data set and results remained stable.

^b Significantly different from WLC at t_0 .

4. Discussion

Extending the findings of [Sommershof et al. \(2009\)](#) in a larger sample, we found a decreased proportion of (CD45RA⁺CCR7⁺) naïve CD8⁺ T cells, an increased proportion of (CD45RA⁻) memory CD8⁺ T cells, and a decreased proportion of CD4⁺CD25⁺FOXP3⁺ T_{reg} cells at baseline in individuals with PTSD compared to controls with no or little trauma exposure. Moreover, trauma exposed non PTSD subjects showed a significantly lower proportion of naïve CD8⁺ T cells than non exposed controls, and the number of traumatic event types experienced was significantly negatively correlated with the percentage of naïve CD8⁺ T cells, indicating a cumulative effect of exposure to traumatic stressors. As we found no differences between non PTSD subjects with or without trauma exposure with respect to T_{reg} cells, we propose that the reduction of naïve CD8⁺ T cells is a consequence of trauma burden rather than an explicit feature of PTSD, whereas alterations in regulatory T cells seem to be specifically associated with the chronic stress experienced by individuals with PTSD. The decrease in naïve and the increase in memory CD8⁺ T cells in individuals with PTSD are in accordance with a T lymphocyte distribution typical for older individuals ([Dorshkind et al., 2009](#); [Fagnoni et al., 2000](#); [Hong et al., 2004](#)). Therefore, the alterations in T lymphocyte distributions in individuals with PTSD might indicate a process of premature immunosenescence, which is in line with previous findings showing that psychological stress is associated with immunological aging ([Bosch et al., 2009](#); [Epel et al., 2004](#); [Kiecolt Glaser et al., 2003](#)). This immunosenescence might be related to a higher wear and tear of the immune system, as the consequences of chronic/traumatic stress may be reflected in a blunted immunity that increases the probability for diseases and associated inflammation responses.

NET led to reduced PTSD symptoms four months after treatment and even further in the one year follow up and improved somatic complaints such as headache, diarrhea, nausea or unspecific chronic pain conditions – consistent with the reported benefits of NET on physical health conditions ([Neuner et al., 2008](#)). Depressive symptoms did not improve through NET. The reduced proportion of CD8⁺CD45RA⁺CCR7⁺ naïve T lymphocytes in PTSD did not increase through treatment, suggesting that the shift in the proportion of naïve and memory T lymphocytes in individuals with PTSD is not reversible and thus might render these patients permanently more susceptible to infectious diseases ([Fagnoni et al., 2000](#); [Shen et al., 1999](#)). In accordance with our outcomes, CD8⁺ T lymphocytes have been reported to be stable over time and not affected by psychotherapeutic interventions in cancer or HIV patients ([Carrico et al., 2005](#); [Hosaka et al., 2000](#)).

However, the reduced proportion of CD4⁺CD25⁺FOXP3⁺ T_{reg} cells increased with symptom improvement in the NET group at the one year follow up when comparing subgroups matched for baseline cell numbers. T_{reg} cells, originally termed suppressor T cells, are essential for controlling immune responses and maintaining self tolerance by inhibiting autoreactive T cells. A decrease in number or function of peripheral T_{reg} cells has been associated with the development of autoimmune diseases, such as multiple sclerosis, asthma, type 1 diabetes, psoriasis, and rheumatoid arthritis ([Costantino et al., 2008](#)). Interestingly, antidepressant medication in individuals suffering from a depressive episode improved not only depressive symptoms but increased also T_{reg} (CD4⁺CD25^{hi}) cell counts ([Himmerich et al., 2010](#)). Moreover, autoimmune diseases seem to react favorably to psychological interventions ([Carlson, 2012](#)). Finally, therapeutic intervention studies focusing on selective enhancement of antigen specific T_{reg} populations *in vitro* or *in vivo* have become a promising target for novel immunotherapeutic approaches in order to reduce or prevent

immune mediated pathologies in human autoimmune diseases ([Cools et al., 2007](#)). Considering the fundamental role of T_{reg} cells in controlling both immunity and tolerance, it will be important to establish whether restoration of T_{reg} numbers by psychotherapeutic treatment can prevent the induction of autoimmune pathology or even reverse established disease in PTSD patients.

Limiting factors for the interpretation of our data are: 1) the lack of a one year follow up in the WLC group; 2) missing information about T cell distributions in healthy controls four months and one year after the baseline assessment. Yet, in a study with healthy university students, T cell subpopulations remained stable over a period of 3 months free of examinations ([Hamuni et al., submitted for publication](#)); 3) The intake of psychotropic medication in about 40% of the individuals with PTSD, which was, however, equally distributed across groups before and after treatment and thus should not be able to be the factor accounting for the observed effects. 4) The relatively small sample size; and 5) the varied ethnicities of study participants. However, since treatment with NET has been shown to be effective in various populations all over the world ([Robjant and Fazel, 2010](#)), we can assume that there is no cultural difference in the biological processing of traumatic stress; 5) We investigated a severely traumatized PTSD sample with high symptom scores, allowing us to study consequences of extreme stress. However, treatment with NET in such an affected sample resulted only in a significant reduction of symptoms, but not in a full recovery from PTSD (58.8% of the NET group still fulfilled PTSD criteria four months post test). Moreover, individuals with PTSD continued to live under stressful life circumstances (e.g. 88.2% of the individuals with PTSD have an insecure asylum status and fear deportation). These factors might have precluded stronger therapy effects concerning T cell maturations subsets and might also explain the persistence of depressive symptoms.

In conclusion, some biological consequences of traumatic stress, such as the shift in the proportion of naïve and memory T lymphocytes, seem to not be reversible through trauma focused psychotherapy, while other consequences such as the reduction of T_{reg} cells similar to the increased level of DNA damage in peripheral blood mononuclear cells of PTSD patients seem to be alterable through therapy ([Morath et al., in press](#)). Further studies on the long term effects of psychotherapy on the immune system are necessary. If the results of this study can be replicated, this would underline the need for effective treatment of PTSD in trauma affected populations to prevent the manifestation of secondary physical diseases in the long run.

Contributors

J Morath, H Gola and A Sommershof contributed equally to this interdisciplinary work. J Morath and H Gola coordinated the psychological part of the study; A Sommershof coordinated the biological part of the study. J Morath recruited study participants, carried out a large number of the clinical interviews and psychotherapies, performed statistical analyses and drafted the manuscript. H Gola prepared the study, recruited study participants, carried out a large number of the clinical interviews and psychotherapies and revised the manuscript. A Sommershof carried out the biological analyses and revised the manuscript critically for important biological content. G Hamuni and H Adenauer carried out clinical interviews and psychotherapies. C Catani, M Ruf Leuschner, M Schauer carried out clinical interviews and psychotherapies and supervised clinical work. S Kolassa programmed R scripts, supervised statistical analyses, and drafted the manuscript with a focus on the statistics. M Groettrup, IT Kolassa and T Elbert designed the study, interpreted the study and revised the manuscript. In addition, IT Kolassa supervised every step of this study and

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Conflict of interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership; employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent licensing arrangements), or non financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or material discussed in this manuscript.

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