Work-related social support modulates effects of early life stress on limbic reactivity during stress

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Abstract

Early life stress (ELS) affects stress- reactivity via limbic brain regions implicated such as hippocampus and amygdala. Social support is a major protective factor against ELS effects, while subjects with ELS experience reportedly perceive less of it in their daily life. The workplace, where most adults spend a substantial amount of time in their daily lives, might serve as a major resource for social support. Since previous data demonstrated that social support attenuates stress reactivity, we here used a psychosocial stress task to test the hypothesis that work-related social support modulates the effects of ELS. Results show decreased amygdala reactivity during stress in ELS subjects who report high levels of work-related social support, thereby indicating a signature for reduced stress reactivity. However, this effect was only observable on the neural, but not on the behavioral level, since social support had no buffering effect regarding the subjective experience of stress in daily life as well as regarding feelings of uncontrollability induced by the stress task. Accordingly, our data suggest that subjects with ELS experiences might benefit from interventions targeted at lowering their subjective stress levels by helping them to better perceive the availability of social support in their daily lives.

Keywords: Work Related Social Support; Early Life Stress; Stress Reactivity; Limbic Reactivity

Introduction

A growing body of evidence shows that experiential factors like early life stress (ELS) can shape individual differences in stress reactivity (Davidson & McEwen, 2012; McEwen, 2012). Stressful social experiences in early life, e.g. emotional or physical neglect and abuse, are associated with a considerable increase in the risk to develop psychiatric disorders, such as major depressive disorder (MDD) and anxiety disorders in later life (Burke et al., 2005; Kendler et al., 2004). The experience of being harmed by persons who should provide support and protection has severe neurobiological, somatic and mental effects in the developing child,

compromising the ability to cope with somatic and psychic stressors throughout the lifespan (Teicher & Samson, 2016). Converging evidence from animal models and human studies indicates that ELS causes persisting changes to the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary system, resulting in altered stress-reactivity as indexed by both autonomic (e.g. heart rate) and endocrine (e.g. cortisol concentration) measures (Carpenter et al., 2007; Carpenter et al., 2009; Elzinga et al., 2008; Heim et al., 2008; Heim & Nemeroff, 2001; Klaassens et al., 2009; Morrison et al., 2017; Pryce et al., 2005; Sanchez et al., 2011; Strüber et al., 2014). Findings of both increased and decreased stress-reactivity after ELS have been related to structural and functional changes in brain regions implicated in autonomic- neuroendocrine control, such as hippocampus and amygdala (Dannlowski et al., 2012; Davidson & McEwen, 2012; Edmiston et al., 2011; Hanson et al., 2015; Heim & Binder, 2012; Nikolova et al., 2016; Tottenham, 2012). Furthermore, own recent data showed that ELS, specifically emotional abuse, is associated with blunted limbic deactivations and hormonal reactivity to psychosocial stress (Grimm et al., 2014) and an enhancement in stress-induced amygdala–hippocampal functional connectivity, which may in turn mediate the impact of ELS on neuroendocrine control (Fan et al., 2015).

While the exact pathogenic mechanisms of these alterations are still unclear, it has been suggested that early adverse experiences, that constantly exceed a child's coping resources, lead to persistent phases of stress, eventually resulting in a sensitization of the stress system (Elzinga et al., 2008; Pechtel & Pizzagalli, 2011; Sanchez et al., 2001). The inconsistent findings of either increased or decreased stress reactivity after ELS might be explained by a trajectory of initial hyperactivation of the stress system progressing to a state of chronic stress hyporeactivity (Fries et al., 2005; Pryce et al., 2005) as a type of counterregulatory adaptation after sustained exposure to stress during development (Miller & Chen, 2007). Previous studies in healthy subjects without ELS have reported widespread deactivation in limbic regions, including hippocampus and amygdala during psychosocial stress (Dedovic et al., 2009; Grimm et al., 2014; Khalili-Mahani, 2010; Lederbogen et al., 2011; Pruessner et al., 2008). These regions are HPA modulators (Herman et al., 2005), and

specifically the intensity of hippocampus deactivation seems to be relevant, as a persistent active state of the hippocampus exerts a tonic inhibition of HPA axis activity (Herman et al., 2003). In response to a stressor, the activity of the hippocampus might be curtailed, which then disinhibits the HPA axis and initiates stress hormone release (Herman et al., 2005; Jacobson, 2005; Pruessner et al., 2008).

On the other hand, physiologic stress reactivity is attenuated by social support, i.e. resources provided by others such as the expression of positive affect, social companionship, emotional support and instrumental support. There are three broad dimensions of social support (Barrera, 1986): (a) social networks (e.g. number of contacts or frequency of contact); (b) perceived social support; and (c) enacted support, i.e. practical and emotional support during stress. In particular, perceived support, the subjective belief that others are available to provide emotional and practical assistance, influences how individuals cope with stressful situations, possibly by way of shaping cognitive appraisals of stressful events (Cohen & Wills, 1985).

In line with this assertion, prior research has found that social support is associated with reduced levels of saliva cortisol and cardiovascular reactivity (Ditzen et al., 2008; Heinrichs et al., 2003; Kirschbaum et al., 1995; Lepore et al., 1993; Uchino & Garvey, 1997) in response to acute laboratory stress. While so far mainly the influence of enacted, i.e. currently available social support on stress-reactivity, has been investigated, daily-life social support may also have a positive impact on the HPA axis (Rosal et al., 2004). Data by Eisenberger et al. (2007), for example, has shown that perceived social support across a 10-day period results in a diminished cortisol reactivity to a social stressor. In the same vein, research has found that social support is inversely related to total mortality, total morbidity, cardiovascular mortality, cardiovascular morbidity, and depression (Thorsteinsson et al., 2011). In sum, Sapolsky (2004) argued that the effect size of social support on all-cause mortality is comparable to the effects of hypertension, nicotine dependence, and obesity. The exact mechanism, however, by which social support affects stress-reactivity is presently unknown. This mechanism may function either by buffering an individual from negative

consequences of stressors (Brewin et al., 2000; Cobb, 1976; Cohen & Wills, 1985) or by directly enhancing an individual's well-being (Schumm et al., 2004).

As most adults spend at least 50% of their awake hours at work (U.S. Bureau of Labor Statistics, 2017; OECD, 2017), it might be particularly worthwhile to investigate the effects of work-related social support. Work-related social support might offer an especially prominent lever mitigating the effects of stress. This proposition is supported by prior research showing that social support in the work environment affects important stress-related outcomes. For example, empirical studies have demonstrated that social support at the workplace not only increases self-esteem and job satisfaction, but also lowers depressive symptoms (Dormann & Zapf, 1999; Schonfeld, 2001). Furthermore, past research has found that co-worker social support is negatively related to increased blood pressure or heart rate (Steptoe et al., 2000), cardiovascular disease prevalence (Johnson & Hall, 1988) and recency and extent of previous sickness absence (Knapstad et al., 2014). However, to the best of our knowledge, the effect of work-related social support on stress reactivity has not been investigated yet.

Also, so far, no studies have investigated the effects of work-related social support in adults with ELS experience. It is known, though, that social support is one of the main factors related to resilience after ELS (Banyard et al., 2017; Collishaw et al., 2007; van Harmelen et al., 2016; Werner et al., 1992). On the other hand, growing up with abusive or neglectful parents seems to negatively impact a person's ability to seek and maintain social ties, resulting in less supportive and satisfying social relationships later in life (Beutel et al., 2017; Germine et al., 2015; Repetti et al., 2003; Savla et al., 2013). It has been hypothesized that this reduction in social affiliation might be due to the fact that a person with ELS experience receives less of the practical, psychological, and physiological benefits that come from interpersonal relationships (Miller et al., 2009).

In this study, we used a psychosocial stress task to test the hypothesis that work-related social support modulates the previously demonstrated effects of ELS experience on both stress-reactivity and associated functional changes in limbic brain regions implicated in autonomic-neuroendocrine control, such as hippocampus and amygdala. Since previous data

demonstrated that work-related social support beneficially modulates the effects of stress, we hypothesize that it also attenuates reactivity in response to acute laboratory stress. Social support is a major protective factor against neurobiological, somatic and mental effects of ELS, while subjects with ELS experience reportedly perceive less of it in their daily life. This leads us to hypothesize that subjects with ELS experience are particularly sensitive toward social support, i.e. they tend to receive less, but if available it might be a particular useful resource for them. Hence, when adults with ELS experience obtain social support, we expect its effect on stress reactivity to be more pronounced than in their counterparts without ELS.

Materials and Methods

Subjects

Thirty-two healthy participants were recruited from a pre-existing community-dwelling-sample. Inclusion criteria were age 18- 65 years, absence of present and past diagnosis of psychiatric or neurologic disease, absence of major or unstable general medical conditions, and ability to participate in study procedures. Absence of present and past diagnosis of psychiatric disorders was measured using the short version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, SCID; Wittchen et al., 1997). Absence of present or past neurologic disorder and major or unstable medical conditions were measured via self-report (e.g. "Have you ever been diagnosed with a neurologic disorder?" or "Do you currently take any prescribed medication, e.g. aspirin, insulin, antibiotics, thyroid hormones, and so on?"). An additional item asking about difficulties regarding sleep (both falling asleep and sleeping through) was included due to the high prevalence of disturbed sleep in individuals with any psychiatric or somatic disorder. Subjects answering "yes" to any of the screening questions of the SCID or the additional questions regarding neurologic disorders or major/ unstable medical conditions were excluded from the study. Furthermore, the ability to participate in study procedures was measured using the WST with an IQ < 90 leading to exclusion. The study was carried out in accordance with the latest

version of the Declaration of Helsinki and approved by the Institutional Review Board of the Charité. All subjects gave written informed consent before screening and were reimbursed for participation.

Study Design

Stress task

Psychosocial stress was induced using the Montreal Imaging Stress Task (MIST; Dedovic et al., 2005). The MIST uses a block design, and consists of mental arithmetic challenges that must be answered under time pressure (see Dedovic et al., 2005 for full description). It induces psychosocial stress using elements of uncontrollability and social evaluative threat. The MIST algorithm continuously varies task difficulty based on user performance by adjusting the time constraints per question and the complexity of the arithmetic problems, to yield a 45–50% correct performance for all subjects. Subjects receive correct or incorrect feedback from the computer after each math question and a performance bar shows their cumulative performance as well as the expected performance of the ‘average subject’, which is artificially set to 80% success. This task has been shown to induce behavioral and physiological stress and anxiety responses (Pruessner et al., 1999) and limbic deactivation (Pruessner et al., 2008). The scanning session consisted of three 7-minute runs containing three stimulus conditions presented in block format: the static arithmetic interface screen (0.5 min), control arithmetic questions presented without feedback, progress bar or time constraint (1 min; control condition), and stressful arithmetic questions with a time limit and a visible progress bar (2 min; stress condition), always in this order. Each condition was presented twice in each run. After each 7-minute scanning run, a confederate delivered the scripted negative verbal feedback and emphasized the need to improve performance via headphones for about one minute. Stimuli were presented via video goggles (Visual Stim Digital for fMRI, Resonance Technology Inc., Northridge, CA, USA). Participants responded by pushing a fiber-optic light sensitive key press. After the session, subjects were debriefed, told that the task was designed to be impossible to accomplish and that it did not assess their

ability to perform mental arithmetic.

Psychological measures

Intelligence was assessed using the *WST* (Schmidt & Metzler, 1992), which is functionally equivalent to the widely used National Adult Reading Test (NART; Nelson & O'Connell, 1978). History of ELS experience was assessed using the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998; Klinitzke et al., 2012), which consists of 28 items that are assigned to the following five subscales: emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse. Scores range from 5 to 25 for each subscale with high scores indicating a strong exposure to early life stressors. We focused on the effects of emotional abuse (EA) and classified participants according to whether they had been exposed to EA or not (Scher et al., 2001). The *PANAS-X* (Positive Affect and Negative Affect Schedule-Expanded form, Watson & Clark, 1999) was used to measure participants' general experience of positive affect and negative affect. The scale consists of a series of adjectives that pertain to different feelings and emotions. Participants are asked to rank each of the 60 items in a 5-point Likert scale according to their experience in the past four weeks. The *Perceived Stress Questionnaire* (PSQ; Levenstein et al., 1993) was used to assess the subjective experience of perceived stressful situations and stress reactions in the last two years. Subjects also completed the German version of the *Spielberger State Anxiety Inventory* (STAI; Spielberger & Sydeman, 1994) to assess transient anxiety and feelings of negativity and uncontrollability induced by the stress task. *Coworker Social Support* was measured with the German version of a six-item subscale of Karasek et al.'s (1998) Job Content Questionnaire (JCQ; Formazin et al., 2015). These six items had the stem "My coworkers ..." and continued as follows: (1) "are competent in their work," (2) "are interested in me," (3) "act hostile toward me" (reverse-scored item), (4) "act friendly toward me," (5) "encourage each other to work together," and (6) "are helpful in getting the work done." We used Cronbach's alpha to assess the internal consistency of the Coworker Social Support subscale. Alpha indicates the degree to which a

set of items measures a single unidimensional latent construct. Values above .80 are generally considered good (Nunally, 1978). Alpha coefficient was .85. *Coworkers' Emotional Carrying Capacity* was assessed with a three-item measure adapted from Stephens et al. (2013). Two independent bilingual researchers translated the items of the adapted Coworkers' Emotional Carrying Capacity scale from English into German and then translated them back into English (Brislin, 1986), as there did not exist a German version of this scale. The three items were (1) "My coworkers have no problem expressing their feelings toward each other," (2) "when a coworker expresses uncomfortable feelings she or he always does it in a constructive way," and (3) "my coworkers are not afraid to express both good and bad feelings at work." Alpha coefficient was .83.

Physiological measures

Pre-arrival instructions asked the participants to abstain from alcohol consumption and excessive exercise 24 hours prior to the experiment, to abstain from any food or drink except for water and physical activity one hour prior to the experiment as well as from smoking 30 minutes prior to the experiment, in order to avoid confounding of measurement (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). To ensure relatively stable endogenous cortisol levels, all subjects arrived between 1 and 3 p.m. in our laboratory.

Five saliva samples were collected with the Salivette sampling device (Sarstedt Inc.) throughout the experiment at the following time-points: baseline (T0), immediately before (T2), immediately after (T3) as well as 20 min (T4), and 80 min after completion of the MIST (T5). Saliva-derived cortisol was analyzed using a time-resolved fluorescence immunoassay (Dressendorfer et al., 1992).

A pulse oximeter (SIEMENS) attached on the index finger of the left hand was used to assess mean heart rate (HR) during the MIST (50 Hz sampling). Participants were requested to abstain from moving this hand during the measurement. After acquisition, R-peaks were

detected using Brain Vision Analyzer 2.1.1 (Brain Products GmbH, 2015) and inter-beat-intervals (IBIs) were computed as the time distance between two consecutive R-peaks. IBIs were later processed with Kubios HRV 2.1 (Tarvainen et al., 2014) and visually inspected for artifacts. Abnormal or biologically implausible data was excluded. HR is reported in beats per minute (bpm).

Functional Imaging

Functional data were acquired on a Siemens Trio 3T scanner using a standard echo planar imaging sequence with 37 oblique axial slices of 3 mm (field of view 192 mm, 3 x 3 mm in-plane, repetition time 2 s, echo time 30 ms, flip angle 70°). Three runs of 220 volumes were acquired, as well as a T1-weighted high-resolution MP-RAGE scan.

Statistical analysis

Psychological and physiological data

We used a general linear model to assess the effect of emotional abuse on physiological measures of stress reactivity (cortisol concentrations, HR) and psychological data. Exposure to emotional abuse (EA) was coded into a 2-level variable (no exposure to EA/ exposure to EA). Further statistical analysis was conducted using t-test comparisons. All tests were two-tailed and the significance threshold was set at a probability of $p < 0.05$. Statistical analyses were carried out using SPSS (version 22; SPSS Inc., Chicago, IL, USA).

FMRI data

FMRI data were analyzed using MATLAB 2010 (The Mathworks Inc., Natick, MA, USA) and SPM12 (Statistical parametric mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk>). Functional data were realigned to the first volume, corrected for motion artifacts, mean-adjusted by proportional scaling, normalized into standard stereotactic space (template provided by the Montreal Neurological Institute), and spatially smoothed using a 6 mm FWHM Gaussian kernel. The time series were high-

pass filtered to eliminate low-frequency components (filter width 128 s). Statistical analysis was performed by modeling the different conditions convolved with a hemodynamic response function as explanatory variables within the context of the general linear model on a voxel-by-voxel basis. Realignment parameters were included as additional regressors in the statistical model. A fixed-effect model at a single-subject level was performed to create images of parameter estimates. Region of interest (ROI) analyses were performed for investigation of signal changes during psychosocial stress and for elucidating the relationship with physiological and behavioral data. Regions of interest in bilateral amygdala (-24 0 -20; 24 -2 -20) and hippocampus (-26 -14 -20; 28 -14 -18) were defined by centering spheres with a radius of 5 mm on the peak voxels reported in a meta-analysis of 790 fMRI studies on emotional processing and stress- reactivity (Fig 1; Yarkoni et al., 2011).

Fig 1. Regions of interest in bilateral hippocampus (a) and amygdala (b).

For the ROI analyses, beta values for the different conditions were extracted for each subject separately using Marsbar (<http://marsbar.sourceforge.net/>). Data were analyzed using a MANOVA to assess the effect of EA. Greenhouse–Geisser corrections were applied where appropriate. Further statistical analysis was conducted using t-test comparisons. All tests were two-tailed and the significance threshold set at a probability of $p < 0.05$. To detect the

association of signal changes in response to psychosocial stress with cortisol concentrations, HR, and psychological measures, we performed Pearson correlation analyses. We used hierarchical regression analyses to test the interaction effects between EA and coworkers social support (respective, coworkers' emotional carrying capacity) on BOLD- signal changes during the stress task and cortisol concentration and HR after the stress task. Statistical analyses were carried out using SPSS (version 22; SPSS Inc., Chicago, IL, USA).

Results

Sample

Gender distribution did not differ significantly between groups with and without exposure to EA ($\chi^2(1) = 0.055$, $p = .815$). There were no significant differences between groups with respect to age and IQ (Table 1). Four participants had to be excluded from the analysis FMRI data due to excessive head movements. Two participants did not fill in the questionnaires for the Coworker Social Support and the Emotional Carrying Capacity scales.

Table 1. Sociodemographic and questionnaire data of study participants.

Study Variables		EA	No EA
N		17	14
Gender			
	Female	8	6
	Male	9	8
		M ± SD	M ± SD
Age		38.6 (10.3)	35.4 (11.9)
IQ		116.1 (15.6)	109.1 (14.5)
CTQ		40.7 (13.3)	29.1 (3.8)**
	Emotional Neglect	11.0 (6.0)	7.6 (2.4)*
	Emotional Abuse	9.7 (3.3)	5.4 (0.5)**
	Physical Neglect	7.2 (2.9)	6.0 (1.8)
	Physical Abuse	7.0 (3.0)	5.0 (0.2)

	Sexual Abuse	5.1 (0.3)	5.0 (0.0)
PANAS-X			
	Positive Affect	18.3 (2.8)	19.2 (4.4)
	Negative Affect	9.1 (2.7)	7.3 (3.0)
STAI		34.8 (8.7)	29.0 (7.2)*
PSQ		38.2 (7.8)	32.8 (5.4)*
Co-Worker Social Support		19.7 (1.9)	20.0 (2.6)
Co-Workers Emotional Carrying Capacity		10.2 (1.4)	9.1 (2.4)

Note. EA Emotional Abuse, M mean, SD standard deviation, IQ Intelligence Quotient, CTQ Childhood Trauma Questionnaire, PANAS-X Positive Affect and Negative Affect Schedule, , STAI State Anxiety Inventory, PSQ Perceived Stress Questionnaire.

* $p < .05$, ** $p < .01$.

Psychological and physiological data

Subjects with EA exposure had significantly higher CTQ scores as well as higher subscores regarding emotional neglect. Furthermore, scores for perceived stress in the last 2 years and anxiety and feelings of negativity and uncontrollability induced by the stress task were higher in the EA group. There were no group differences with regard to the general experience of positive and negative affect (PANAS-X) and work-related social support as indicated by coworker social support and coworkers' emotional carrying capacity (Table 1). Cortisol concentrations at T1 and T2 were significantly lower in the group with EA exposure ($p < 0.05$). While concentrations were numerically lower in the EA group at the other time-points as well, differences did not reach a level of statistical significance.

To confirm the effect of the distinct MIST conditions, main effects of condition (rest, control, and stress) and run (3) as within-subjects factors on HR were examined. ANOVA for repeated measures revealed a highly significant main effect of MIST conditions on heart rate, $F(2, 21) = 27.00$, $p = .000$. Post hoc analyses revealed significant differences between HR in all conditions (all tests $p < .01$). HR was highest in the stress condition and lowest in the rest condition. There was also a highly significant main effect of MIST runs on HR, $F(2, 21) = 10.60$, $p = .001$. There was no significant main effect of EA on heart rate. To test the moderating effects of both coworker social support and coworkers' emotional carrying capacity we used

hierarchical regression analysis. The interaction between EA and coworker social support (respective coworkers' emotional carrying capacity) on cortisol concentrations after the stress task (T3 and T4) were non-significant. Similarly, the interaction between EA and coworker social support (respective emotional carrying capacity) on HR after the stress task did not gain significance.

fMRI results

Effect of emotional abuse

A MANOVA was performed to assess the effect of EA on BOLD- signal changes in bilateral amygdala and hippocampus. There was a significant EA effect on signal changes during the stress as well as during the control condition in left (stress: $F(1,29)= 13.01$, $p= .002$; control: $F(1,29)= 8.75$, $p= .007$) and right hippocampus (stress: $F(1,29)= 8.40$, $p= .009$; control: $F(1,29)= 7.12$, $p= .014$). Post-hoc analyses revealed that subjects with no exposure to EA showed significantly higher deactivation both during the stress condition ($p< .01$) and the control condition ($p< .05$) (Fig 2). EA had no significant effect on BOLD- signal changes in amygdala, even though results indicate stronger deactivation in subjects with EA exposure in both stress and control condition (Fig 2).

Fig 2. BOLD signal changes during stress and control conditions in subjects with and

without emotional abuse.

Association of psychological, physiological data_and BOLD- signal changes

The subjective experience of perceived stressful situations and stress reactions in the last two years was associated with both increased anxiety induced by the stress task ($r = 0.76$, $p < 0.01$) as well as with increased experience of negative affect ($r = 0.65$, $p < 0.01$). Explorative analyses revealed that these correlations were driven by subjects with EA experience, while in the non-EA group there were no such associations. Instead, we here found that both emotional carrying capacity and social support were associated with decreased subjective experience of perceived stressful situations and stress reactions ($r = -0.67$, $p < 0.05$) and decreased experience of negative affect ($r = -0.75$, $p < 0.01$). Also, in these subjects the increase in cortisol concentrations induced by the stress task was positively associated with subjective experience of perceived stressful situations ($r = 0.90$, $p < 0.01$) and negatively with coworker social support ($r = -0.78$, $p < 0.05$) and coworkers' emotional carrying capacity ($r = -0.90$, $p < 0.01$).

Next, we tested the interaction between EA experience and coworker social support on bilateral amygdala activity during the stress task using hierarchical regression analyses. Results are shown in Table 2. To test the interaction effect on the left amygdala, we first entered the control variables (Model 1a), followed by EA experience and left amygdala activity (Model 2a), as well as the interaction of EA experience and left amygdala activity (Model 3a). The coefficient for the interaction between EA experience and coworker social support on left amygdala activity during the stress task was significant ($B = .46$, $SE = .12$, $p < .01$). Fig 3 shows the interaction effect between EA experience and coworker social support.

Fig 3. Moderating effect of coworker social support on the relationship between early childhood emotional abuse and left amygdala activity during stress task.

Using a procedure recommended by Aiken and West (1991), we classified coworker social support into a high group (+1 SD) and a low group (-1 SD), and then tested the significance level of the simple slopes. These simple slope analyses revealed that, at high levels of coworker social support, EA experience and left amygdala activity were positively associated ($B = .67$, $SE = .18$, $p < .01$), whereas at low levels of coworker social support, this association was non-significant ($B = -.25$, $SE = .15$, ns). Furthermore, to test the interaction effect on right amygdala activity during the stress task, we first entered the control variables (Model 1b), followed by EA experience and right amygdala activity (Model 2b), as well as the interaction of EA experience and right amygdala activity (Model 3b). The coefficient for the interaction between EA experience and coworker social support on right amygdala activity was non-significant ($B = .07$, $SE = .08$, ns).

Table 2. Regression results of the interaction between early childhood emotional abuse and coworker social support on bilateral amygdala activity.

Variable	Left amygdala activity during stress task				Right amygdala activity during stress task			
	Model 1a		Model 2a		Model 1b		Model 2b	
Constant	<i>B</i>	<i>SE</i>	<i>B</i>	<i>SE</i>	<i>B</i>	<i>SE</i>	<i>B</i>	<i>SE</i>
<i>Controls</i>	-.81	.67	-.62	.64	-.74 [†]	.37	-.68 [†]	.36
Age	.01	.01	.00	.01	.01	.01	.01	.01
Gender ($\delta = 1, \phi = 2$)	-.29	.31	-.19	.30	-.14	.17	-.11	.16
<i>Predictors</i>								
Early childhood emotional abuse			.31 [†]	.15			.13	.08
Coworker social support			.14	.15			.06	.08
Early childhood emotional abuse x coworker social support								
							.46 ^{**}	.12
Effect size (Cohen's f^2)	.05		.29		.10		.27	
ΔR^2	.05		.18		.09		.12	
								.33
								.03

Note. $N = 25$ subjects. Cohen (1988) identifies $f^2 = .02$ as small effect, .15 as moderate effect, and .26 as large effect. Unstandardized regression coefficients are reported.

[†] $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$ (two-tailed).

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Then, we examined the interaction between EA experience and coworkers' emotional carrying capacity on bilateral amygdala activity during the stress task applying hierarchical regression analyses. Results are depicted in Table 3.

Table 3. Regression results of the interaction between early childhood emotional abuse and coworkers' emotional carrying capacity on bilateral amygdala activity.

Variable	Left amygdala activity during stress task				Right amygdala activity during stress task			
	Model 4a		Model 5a		Model 4b		Model 5b	
Constant	B	SE	B	SE	B	SE	B	SE
	-.87	.67	-.51	.65	-.50	.58		
<i>Controls</i>								
Age	.01	.02	-.01	.02	-.01	.02	.01	.01
Gender ($\delta=1, \eta=2$)	-.29	.31	-.16	.31	-.10	.28	-.14	.17
<i>Predictors</i>								
Early childhood emotional abuse			.27 ⁺	.16	.25 ⁺	.14	.11	.08
Coworkers' emotional carrying capacity			.15	.17	.30 ⁺	.16	.05	.10
Early childhood emotional abuse x Coworkers' emotional carrying capacity					.37 [*]	.15		.04
								.11

Effect size (Cohen's f^2)	.05	.29	.71	.10	.25	.27
ΔR^2	.05	.18	.19 [*]	.09	.11	.01

Note: $N = 25$ subjects; Cohen (1988) identifies $f^2 = .02$ as small effect, .15 as moderate effect, and .25 as large effect. Unstandardized regression coefficients are reported.

⁺ $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$ (two-tailed).

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To test the interaction effect on the left amygdala, we first entered the control variables (Model 4a), followed by EA experience and left amygdala activity (Model 5a), as well as the interaction of EA experience and left amygdala activity (Model 6a). The coefficient for the interaction between EA experience and left amygdala activity was significant ($B = .37$, $SE = .15$, $p < .05$). Fig 4 shows the interaction between EA experience and coworkers' emotional carrying capacity.

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Simple slope analyses showed that, at high levels of coworkers' emotional carrying capacity, EA experience and left amygdala activity were positively associated ($B = .67$, $SE = .26$, $p < .05$), whereas at low levels of coworkers' emotional carrying capacity, this relationship was

non-significant ($B = -.07$, $SE = .17$, ns). To test the interaction effect between EA experience and coworkers' emotional carrying capacity on the right amygdala, we first entered the control variables (Model 4b), followed by EA experience and right amygdala activity (Model 5b), as well as the interaction of EA experience and right amygdala activity (Model 6b). The coefficient for the interaction between EA experience and coworkers' emotional carrying capacity on right amygdala activity was non-significant ($B = .04$, $SE = .11$, ns).

Additionally, we tested the interaction between EA experience and coworker social support (respective coworkers' emotional carrying capacity) on bilateral hippocampus activity during the stress task. Neither the interaction between EA experience and coworker social support nor the interaction between EA experience and coworkers' emotional carrying capacity on left or right hippocampus activity during the stress task gained significance (Fig 4).

Fig 4. Moderating effect of coworkers' emotional carrying capacity on the relationship between early childhood emotional abuse and left amygdala activity during stress task.

Discussion

To our knowledge, this is the first study to investigate whether work-related social

support modulates the effect of ELS on stress reactivity during acute psychosocial stress. Consistent with previous studies we found blunted stress reactivity as indicated by diminished cortisol concentrations and limbic deactivation particularly in hippocampus, in subjects with ELS experience. Our findings furthermore demonstrate that in the case of low work- related social support, subjects with and without ELS experience do not differ in their amygdala reactivity to psychosocial stress. A high level of work- related social support, however, modulates amygdala reactivity in subjects with, but not in those without ELS experience. The decreased amygdala reactivity during psychosocial stress in ELS subjects who report high levels of work- related social support indicates a signature for reduced stress reactivity. Interestingly, though, this effect was only observable on the neural, but not on the behavioral level, since unlike in subjects without ELS experience, work- related social support had no buffering effect regarding the subjective experience of stress in daily life as well as regarding feelings of negativity and uncontrollability induced by the stress task. In subjects with ELS experience we found an association between subjective stress and negative affect in daily life with increased anxiety induced by the stress task, but no relationship of any of these measures with work-related social support. On the other hand, in subjects without ELS, work-related social support was associated with decreased subjective stress and negative affect in daily life as well as with reduced hormonal reactivity to the psychosocial stress task.

As in previous studies investigating the effects of psychosocial stress, we observed a deactivation during stress in the hippocampus, which was significantly reduced in subjects with ELS experience (Fan et al., 2014; Grimm et al., 2014; Pruessner et al., 2008). Since this region is considered a HPA modulator (Herman et al., 2005) our data thereby further supports the idea that its persistent active state exerts a tonic inhibition of HPA axis activity. In response to a stressor, hippocampal activity might be curtailed, which then disinhibits the HPA axis and initiates stress hormone release (Dedovic et al., 2009; Pruessner et al., 2008). Reduced hippocampal deactivation likely indicates blunted stress reactivity after ELS, accordingly, previous data showed associated diminished cortisol responses, particularly in subjects who experienced emotional abuse (Carpenter et al., 2009; Grimm et al., 2014). However, even

though our data shows a dampened neuroendocrine response to acute psychosocial stress in ELS subjects, effects are not significant, which might be due to the fact that we investigated healthy subjects without a previous history of psychiatric disorders, who had experienced only moderate emotional abuse (Bernstein & Fink, 1998). Furthermore, neuronal activation patterns in hippocampus might be a more sensitive indicator for stress reactivity than changes in saliva cortisol, which occur with a considerable time-lag after stress onset and are less pronounced in the MIST than in the more commonly used Trier Social Stress Test, that is however not applicable for neuroimaging (Kirschbaum et al., 1993; Pruessner et al., 2008). Along that line, work-related social support did not modulate ELS effects on hormonal, cardiovascular and hippocampal reactivity to psychosocial stress, but significantly attenuated amygdala reactivity in subjects with ELS experience. Amygdala structure and function are highly susceptible to the influence of ELS and children who experienced stressful caregiving in early life display heightened anxiety and amygdala activity (Davidson & McEwen, 2012; Lederbogen et al., 2011; Tottenham et al., 2010, 2012). The amygdala responds to dangerous or threatening stimuli, signals the emotional significance of the perceived stimuli and thereby prepares our brain and body for suitable responses (Davis & Whalen, 2001; LeDoux, 2000). As a key locus in the limbic–prefrontal circuit, the amygdala is reciprocally interconnected with regions involved in autonomic–neuroendocrine control, memory, and salience processing (Freese & Amaral, 2009) and amygdala–hippocampal connectivity predicts the capacity of the HPA axis to restore homeostasis after perturbation (Kiem et al, 2013). ELS has previously been associated with amygdala hyperreactivity to negative facial cues cues (Dannlowski et al, 2013), as well as with enhanced stress-induced amygdala–hippocampal connectivity (Fan et al., 2015), which may mediate the impact of ELS on neuroendocrine control and memory during stress. The stress regulation circuit and the neural circuit for learning and memory largely overlap in the amygdala and hippocampus and enhanced connectivity between these two regions has an important role in both encoding and consolidation of emotional memory (Henckens et al, 2009; Richter- Levin & Akirav, 2000).

Although there is considerable knowledge concerning the positive effects of perceived

social support on morbidity and mortality risks (Sapolsky, 2004; Thorsteinsson et al., 2011), the underlying mechanisms remain largely unexplored. Most previous studies investigated the effect of social support on stress reactivity by means of enacted, i.e. currently available social support and consistently reported reduced neuroendocrine and autonomic reactivity (Ditzen et al., 2008; Heinrichs et al., 2003; Kirschbaum et al., 1995; Lepore et al., 1993; Uchino and Garvey 1997). Data on effects of perceived daily-life social support on stress reactivity is sparse, but a previous study by Eisenberger et al. (2007) showed that perceived social support across a 10-day period results in a diminished cortisol reactivity to a social stressor. Together with our findings of reduced amygdala reactivity in subjects with high levels of work-related social support, this indicates that similar to enacted social support, also perceived social support leads subjects to appraise an acute stressor as less threatening and more controllable than unsupported subjects. This notion is in accordance with Cohen and Wills' (1985) proposal that social support alters the perception of potentially threatening conditions in a way that they are no longer perceived as stressful. Thus, feeling supported and cared for may lead an individual to be less likely to perceive certain conditions as threatening, thereby preventing the onset of physiological stress reactivity. To the extent that social support down-regulates threat-related reactivity, it may accordingly be associated with less activity in limbic structures that are typically involved in responding to negative or threatening experiences, such as the amygdala.

It is known that ELS impacts the ability to seek and maintain social ties, resulting in less stable and satisfying social relationships as well as in lower levels of perceived social support later in life (Beutel et al., 2017; Germine et al., 2015; Repetti et al., 2003; Savla et al., 2013). Inadequate social support networks are discussed as a main factor linking ELS to adverse later life health, such as symptoms of depression, anxiety and somatoform complaints (Beutel et al., 2017; Friedman et al., 2015). On the other hand, adults with ELS experience who obtain social support in their daily life report better health (Banyard et al., 2017). While it has been discussed that the reduction in social affiliation might be due to the fact that a person with ELS experience receives less of the practical, psychological, and physiological benefits

that come from interpersonal relationships (Miller et al., 2009), recent evidence indicates deficits in adult social cognitive functioning after ELS (Germine et al., 2015; Grimm et al., 2017). Accordingly, subjects with ELS experience might be limited in their ability to infer whether their counterpart in a social interaction is supportive or not. While in our sample, ELS experience did not impact the perception of work-related social support, it is striking that unlike in subjects without ELS, work-related emotional support was not associated with less subjective stress and less negative affect in daily life. On a neural level though, amygdala reactivity to psychosocial stress was reduced in subjects who reported high levels of work-related support, which indicates that they perceived the situation as less threatening. Accordingly, one might assume that the subjective experience or awareness of social support is disturbed after ELS experience. If that proved to be the case, psychotherapy or training of social cognition abilities might provide a correctional experience to improve social and emotional information processing and thereby the perception of social support, resulting in less subjective stress and negative affect in daily life and eventually in better overall health.

It might be considered a limitation of our study that ELS assessment was based on retrospective self-report and is hence susceptible to subjectivity bias in perception of early environment and in reconstructive memory. We did not include any 'objective' measure of ELS (e.g. medical records). However, our subjects mainly reported moderate to severe ELS on the emotional neglect and emotional abuse subscale (Bernstein and Fink, 1998; Scher et al., 2001). Such information on emotional maltreatment is unlikely to be reflected in medical records. As the perception and recall of ELS are influenced by various factors, including personality traits and coping skills, it is important to acknowledge the subjectivity in our measurement of ELS when interpreting the findings. However, there is also solid support for a good correspondence of retrospective and prospective assessment (Scott et al., 2012). Our sample consisted of healthy individuals with various degrees of ELS exposure. While subjects in the ELS group had experienced moderate emotional abuse, overall ELS severity was lower than in previously described psychiatric samples. Although this helps to dissociate ELS effects from psychiatric symptoms and medication effects, it is not known whether the subjects will

develop psychiatric diseases later in life. It is critical for future clinical studies to identify individuals who are vulnerable and resilient to the detrimental influence of ELS (Cisler et al., 2013; van der Werff et al., 2013).

In conclusion, our data shows that work-related social support modulates the effect of ELS on stress reactivity on the neural, but not on the behavioral level. In order for subjects with ELS to benefit from social support by means of less subjective stress and negative affect in daily life and eventually reduced vulnerability for stress-related disorders, one should consider devising interventions tailored at targeting social and emotional information processing thus enabling them to better perceive the availability of social support in their daily lives.

Compliance with Ethical Standards

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Social support and early life stress

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625 Conflict of Interest

626 All authors declare they have no conflict of interest.

627 Ethical Approval

628 All procedures performed in studies involving human participants were in accordance with the

629 ethical standards of the institutional and/or national research committee and with the 1964

630 Helsinki declaration and its later amendments or comparable ethical standards.

631 Informed consent

632 Informed consent was obtained from all individual participants included in the study.

633

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