CLINICAL PSYCHOLOGY

Specific reduction in cortisol stress reactivity after social but not attention-based mental training

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Psychosocial stress is a public health burden in modern societies. Chronic stress–induced disease processes are, in large part, mediated via the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary system. We asked whether the contemplative mental training of different practice types targeting attentional, socio-affective (for example, compassion), or socio-cognitive abilities (for example, perspective-taking) in the context of a 9-month longitudinal training study offers an effective means for psychosocial stress reduction. Using a multimethod approach including subjective, endocrine, autonomic, and immune markers and testing 313 participants in a standardized psychosocial laboratory stressor, we show that all three practice types markedly reduced self-reported stress reactivity in healthy participants. However, only the training of intersubjective skills via socio-affective and socio-cognitive routes attenuated the physiological stress response, specifically the secretion of the HPA axis end-product cortisol, by up to 51%. The assessed autonomic and innate immune markers were not influenced by any practice type. Mental training focused on present-moment attention and interoceptive awareness as implemented in many mindfulness-based intervention programs was thus limited to stress reduction on the level of self-report. However, its effectiveness was equal to that of intersubjective practice types in boosting the association between subjective and endocrine stress markers. Our results reveal a broadly accessible low-cost approach to acquiring psychosocial stress resilience. Short daily intersubjective practice may be a promising method for minimizing the incidence of chronic social stress–related disease, thereby reducing individual suffering and relieving a substantial financial burden on society.

INTRODUCTION

Throughout history and up to this day, mankind has been battling "ancient," potentially fatal stressors, such as threat to physical integrity, starvation, and physical hardship. However, it is the human tendency to mount a stress response also for purely psychosocial reasons (for example, a lack of predictability, sense of control, and social support) that has led to chronic stress exposure in modern Western societies (*1*, *2*). Through the stimulation of continual hypothalamic-pituitary-adrenal (HPA) axis and sympathetic-adrenal-medullary activation, which exert complex effects on the immune system (*3*), this chronic stress has detrimental health implications, including the promotion of cardiovascular, metabolic, and autoimmune diseases (*1*, *3*, *4*). Emerging stress-related expenses to society are substantial, with workplace stress alone costing the U.S. economy more than $300 billion annually (*5*). Given the profound individual and societal impact of psychosocial stress, finding ways to stress relief has become an imperative goal.

Since the late 1990s, scientific interest in secular meditation–based mental training programs has markedly increased (*6*). Aiming to foster stress resilience and improve mental and physical health, interventions, such as the 8-week mindfulness-based stress reduction program (MBSR) (*7*) and mindfulness-based cognitive therapy (MBCT) (*8*), have gained acceptance in mainstream clinical and educational settings (*6*). Whereas mindfulness-based interventions cultivate nonjudgmental moment-to-moment awareness of internal (for example, thoughts and bodily feelings) and external events (for example, sound and vision), compassion-based interventions [such as compassion-focused therapy (*9*) and mindful self-compassion program (*10*)] emphasize the social dimension of humans by targeting emotions, such as empathy and compassion. Training to compassionately relate to others instead of overidentifying with one's own self and emotions may be especially powerful in reducing psychosocial stress susceptibility.

Although the popularity of meditation-based mental training programs is undisputed, empirical evidence for their effectiveness in psychosocial stress reduction remains inconclusive. Significant findings of acute stress reduction after mental training are mainly based on changes in self-reported (*11*–*13*), autonomic (*12*, *14*), and immune reactivity (*13*, *15*). However, the investigation of cortisol release, an integral component of the human stress response (*3*), has yielded mixed results. Although one research group found evidence for lower cortisol responses to laboratory-induced psychosocial stress immediately after a mindfulness-based meditation session (*16*, *17*), this effect awaits independent replication (*12*–*15*, *18*). A recent study instead reported increased psychosocial stress–induced cortisol levels after a 3-day mindfulness training (*11*), indicating short-term stress sensitization rather than stress reduction. The interpretation of findings is further hampered by the multifaceted nature of mindfulness-based intervention programs, which typically combine diverse mental practice types targeting various functions, such as attention, socio-affective, and cognitive skills (*19*). This makes it difficult to isolate the specific effects of one particular practice type on the human stress response.

Given the state of the field, we asked whether different types of mental practice would differ in their effectiveness in reducing the psychosocial stress response to the Trier Social Stress Test (TSST) (*20*). This motivated performance task induces feelings of unpredictability, uncontrollability, and social threat, thus mimicking the type of everyday experiences that eventually accumulate to chronic stress in our society (*1*, *2*). We hypothesized that intersubjective practices focused on socio-affective and socio-cognitive skills would be superior to mindfulness practices focused on present-moment attention and interoception. We based this hypothesis on the notion that psychosocial

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stressors may lose their threatening potential if processed from a perspective of mutual acceptance and common humanity rather than ego-involvement. Note that this hypothesis implies the possibility that training to stabilize the mind through present-moment attention and interoceptive awareness may be superior for the reduction of nonsocial stressors, such as physical strain or pain. Finally, because mental training is argued to increase the accuracy of first-person accounts by enabling a more attentive stance toward inner experience (*6*), we asked whether the frequently lacking covariance between subjectively experienced and endocrine stress responses (*21*) would increase with mental training.

To answer these questions, 332 participants enrolled in a longitudinal training study, the ReSource Project (*22*), involving three distinct 3-month modules cultivating (i) Presence (present-moment focused attention and interoceptive awareness), (ii) Affect (gratitude, compassion, prosocial motivation, and dealing with difficult emotions), and (iii) Perspective (metacognition and perspective-taking on self and others) (Fig. 1A). Including classic meditation techniques, such as Breathing Meditation and Body Scan, as core curricular techniques, the Presence Module resembles typical mindfulness-based interventions [for example, MBSR (*7*) and MBCT (*8*)]. In contrast, the Affect and Perspective Modules target intersubjectivity by training either socio-emotional and socio-motivational or socio-cognitive skills. The division in Affect and Perspective Modules reflects recent research identifying distinct neural routes to social understanding: one socio-affective route including social emotions, such as empathy and compassion, and one socio-cognitive route including the capacity to take perspective on self and others (the latter termed Theory of Mind or mentalizing) (*23*, *24*). To train these intersubjective skills, we developed contemplative dyadic exercises and used these alongside classic meditation techniques (Loving-kindness Meditation in the Affect Module and Observing-thoughts Meditation in the Perspective Module) {see Materials and Methods and Singer *et al.* [(*22*), chap. 3] for a thorough description of all core exercises}. Creating these distinct process-oriented training modules allowed for systematically investigating the specific effects of different mental practice types—an essential step to establishing a theoretical framework for the scientific study of contemplative mental training (*19*).

The longitudinal ReSource study design included two major training cohorts that experienced the three 3-month training modules in different orders, one 3-month Affect only cohort and one retest control cohort, which took part in all testing but not in training activities (Fig. 1B). Of the initial 332 participants, 313 underwent the TSST (*20*), a psychosocial laboratory stressor involving free speech and mental arithmetic in front of a critical audience [also see Materials and Methods and Kirschbaum *et al.* (*20*)]. Because the TSST builds on deception to create a stress-inducing social-evaluative context, a cross-sectional design was applied: Participants were tested once, either without training, after 3-month Presence training, after 3-month Affect training, after 6-month Presence and Affect training, or after 6-month Presence and Perspective training (Fig. 1B). To allow maximal comparability with previous stress and mental training studies, we used a multimethod approach and assessed a broad range of stress markers, including cortisol representing HPA axis activity, α-amylase (AA) and heart rate (HR) representing sympathetic activity, and high-frequency HR variability (HF-HRV) representing parasympathetic activity. In addition, the inflammatory markers circulating interleukin-6 (IL-6) and high-sensitive C-reactive protein (hsCRP) as indicators of stress-influenced innate immune activity were examined. To assess subjective stress experience, we collected self-perceived cognitive, affective, and bodily states with the state scale of the State-Trait Anxiety Inventory (STAI) (*25*), the most frequently used validated questionnaire of stress-induced subjective emotional states (*26*).

RESULTS

Verification of successful stress induction

We verified the effectiveness of the TSST to activate the HPA axis. A subsistent stress response has been defined by an average cortisol peak of 1.5 nM above baseline levels (*27*). The TSST increased cortisol levels above this threshold of physiological significance in 75% of untrained participants (Fig. 1C), indicating successful stress induction.

Exploratory associations between stress reactivity scores

Although all of the assessed markers are generally stress-reactive, associations between them are only inconsistently found (*26*, *28*, *29*). In an initial analysis, we therefore explored bivariate correlations of the cortisol, AA, HR, HF-HRV, hsCRP, IL-6, and STAI state stress reactivity scores (operationalized as baseline-to-peak change; Δ) in the no training group. As expected from previous work, these correlations were low or nonsignificant, indicating the relative independence of stress markers and underlying (endocrine, autonomic, immune, and subjective) response systems following psychosocial stress induction (Table 1).

Effects of mental training on the stress response

For the stress markers with >2 measurement points (cortisol, AA, HR, HF-HRV, hsCRP, and STAI state), linear mixed model analyses focused on two facets of the stress response: reactivity (baseline-to-peak increase) and recovery (post-peak decline). All markers showed change over time indicated by significant reactivity and recovery effects (all P values ≤0.001) (Fig. 2 and Table 2). Because IL-6 levels increased until the last measurement time point, only two samples (baseline and peak) were analyzed. Consequently, a univariate general linear model with peak IL-6 levels as the dependent variable and baseline levels as the covariate was calculated; change over time was not determined in the context of this model.

The calculated linear mixed models indicated significant effects of mental training specifically on self-reported and cortisol stress responses. In detail, group differences were seen in reactivity [$F_{477} = 8.43$, $P \leq 0.001$] and recovery [$F_{480} = 8.68$, $P \leq 0.001$] for subjective experience and in reactivity for cortisol release [$F_{304} = 5.26$, $P \leq 0.001$] (Fig. 2, A and B, and Table 2). The assessed autonomic (AA, HR, and HF-HRV) and immune (IL-6 and hsCRP) markers were not influenced by mental training (Fig. 2, C to G and Table 3).

Between-group contrasts (Table 4) revealed that self-reported stress reactivity was reduced in all training groups relative to the no training group (all t values between −2.92 and −4.42, P values between ≤0.01 and ≤0.001). Training groups did not differ from one another. Percentage reductions in baseline-to-peak increase (ΔSTAI) amounted to 26% for Presence, 36% for Affect, 39% for Presence/Affect, and 31% for Presence/Perspective. Because of a floor effect at the final measurement point (that is, all groups had returned to baseline levels independent of the height of the previous stress peak), training groups also showed relatively flatter self-reported stress recovery than the no training group (all t values between 2.93 and 4.50, P values ≤0.001).

Between-group contrasts (Table 4) further showed that the cortisol stress response was unaffected by the 3-month mindfulness-based

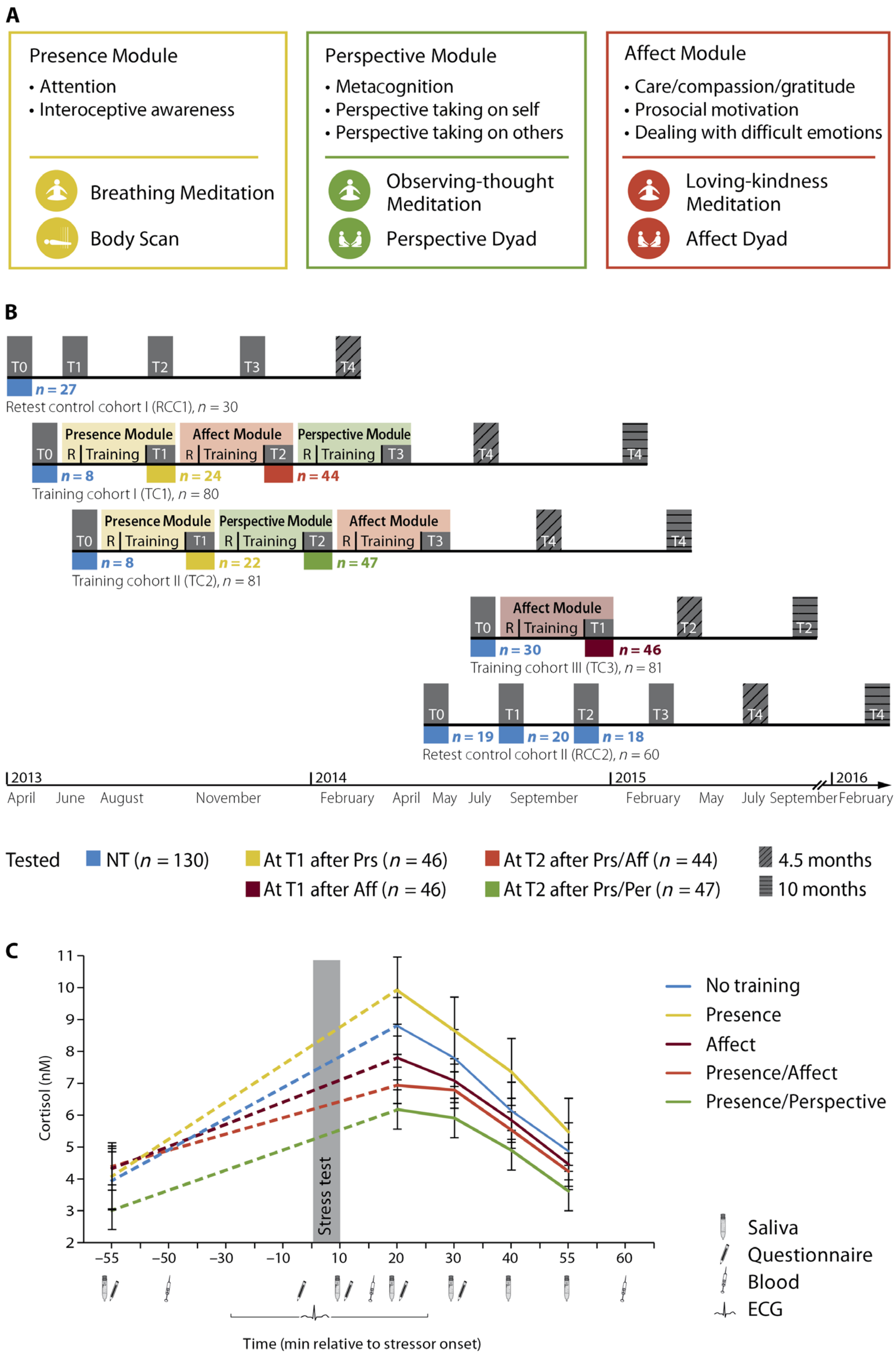

Fig. 1. Methodological details of the ReSource Project and the stress testing session. (**A**) Training modules and core exercises of the ReSource Project. (**B**) Time points of cross-sectional stress testing within the greater context of the ReSource training timeline and cohort membership of each participant. NT, no training; Prs, Presence; Aff, Affect; Prs/Aff, Presence/Affect; Prs/Per, Presence/Perspective. (**C**) Stress testing timeline and raw cortisol data (in nanomolar) (error bars represent SEM) over time (relative to stressor onset at 0 min), separated by group. Because covariates are not considered, results deviate from the model-derived depiction. ECG, electrocardiogram.

Table 1. Bivariate correlations of stress reactivity scores (Δ) in the no training group.

	Response system						
	HPA axis	Autonomic			Immune		Self-report
Marker	ΔCortisol	ΔAA	ΔHR	ΔHF-HRV	ΔhsCRP	ΔIL-6	ΔSTAI
ΔCortisol	1	−0.004	0.165	0.138	0.184*	−0.049	0.044
ΔAA		1	0.141	−0.027	−0.101	0.028	0.079
ΔHR			1	−0.434***	0.019	0.099	0.041
ΔHF-HRV				1	−0.117	−0.265**	−0.087
ΔhsCRP					1	−0.049	−0.080
ΔIL-6						1	0.087
ΔSTAI							1

*$P \leq 0.05$. **$P \leq 0.01$. ***$P \leq 0.001$.

attention training (Presence) relative to no training. However, 3-month compassion-based Affect training alone and both intersubjective modules tested after 6 months of training (Affect or Perspective following Presence) reduced cortisol stress reactivity relative to no training (Affect: $t_{304} = -2.06$, $P \leq 0.05$; Presence/Affect: $t_{304} = -2.99$, $P \leq 0.01$; Presence/Perspective: $t_{304} = -3.22$, $P \leq 0.001$). Percentage reductions in baseline-to-peak increase (Δcortisol) were 32% for Affect, 48% for Presence/Affect, and 51% for Presence/Perspective groups. The degree of cortisol stress reduction did not differ between the socio-affective (Affect) and socio-cognitive (Perspective) groups. Comparing 3-month Presence with 3-month Affect training revealed lower reactivity following the Affect Module ($t_{304} = -2.21$, $P \leq 0.05$). Thus, compassion-based training was more effective in psychosocial stress reduction than attention-based training, even after only 3 months of training time. Untrained participants tested at baseline or 3 or 6 months into the study showed similar self-reported and cortisol stress responses. Thus, stress habituation due to longer study duration in training relative to no training groups was ruled out as a confound in the above results (see the Supplementary Materials).

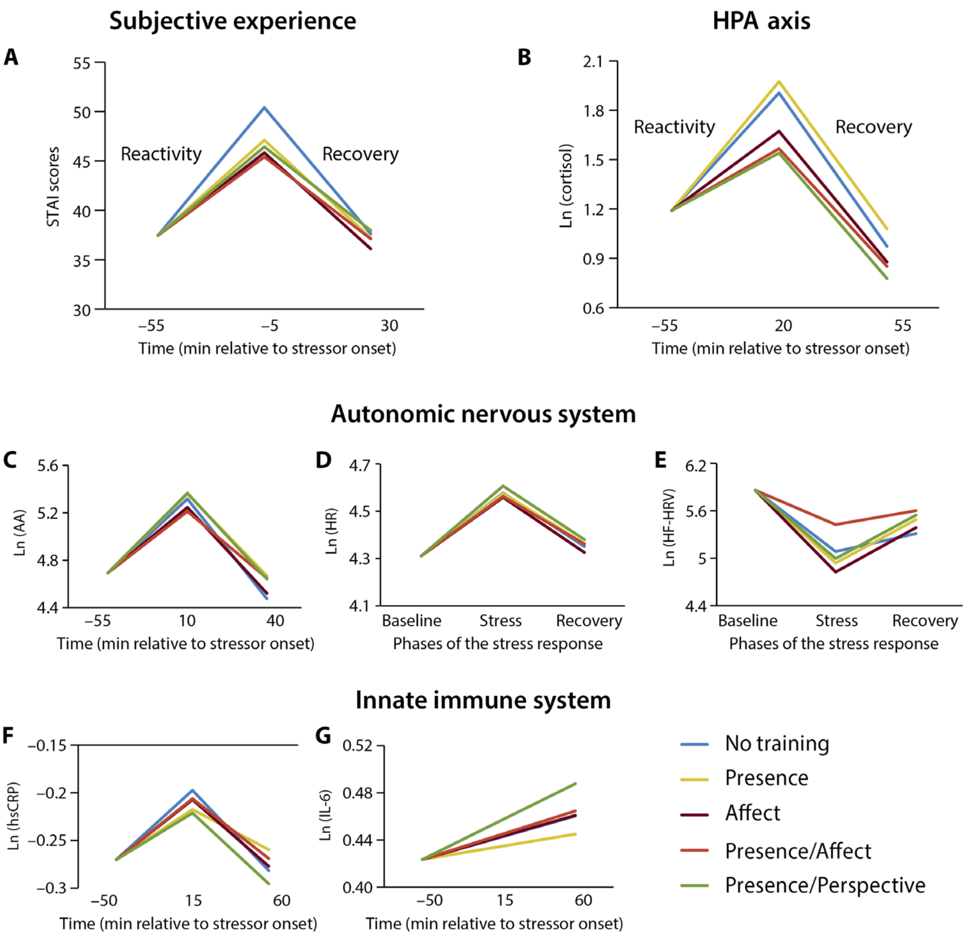

Fig. 2. Parameter estimates from hierarchical linear models showing training effects on stress markers. Values at the first measurement point are equalized, representing statistical control for baseline scores. (**A**) Training groups, which did not differ from one another (all P values >0.10), showed reduced self-reported stress reactivity [assessed with the STAI (*25*)] compared to the no training group (all P values between ≤0.01 and ≤0.001). (**B**) Three-month Presence relative to no training had no impact on the HPA axis stress response ($P > 0.10$). Three-month Affect ($P \leq 0.05$), 6-month Presence/Affect ($P \leq 0.01$), and 6-month Presence/Perspective training ($P \leq 0.001$) reduced cortisol stress reactivity relative to no training. Affect and Perspective groups did not differ from one another ($P > 0.10$). Compared to 3-month Presence training, 3-month Affect training reduced cortisol stress reactivity ($P \leq 0.05$). Mental training did not influence (**C**) AA, (**D**) HR, (**E**) HF-HRV, (**F**) hsCRP, and (**G**) IL-6 stress responses (all P values >0.10).

Table 2. Omnibus *F* tests in linear mixed models for training effects on self-reported and HPA axis stress responses. Removing the covariates from a respective model did not change the pattern of significance.

	STAI		Cortisol	
Fixed effects				
	F (df)	*P*	*F* (df)	*P*
Intercept (peak)				
Intercept	13180.99 (473)	≤0.001	1450.30 (303)	≤0.001
Group	8.43 (477)	≤0.001	5.26 (304)	≤0.001
Baseline	113.00 (476)	≤0.001	15.74 (304)	≤0.001
Sex/hormones	2.76 (283)	0.098	9.79 (300)	≤0.001
Age	0.72 (283)	>0.300	0.85 (300)	>0.300
Time of day			11.37 (300)	≤0.001
Recovery slope				
Intercept	770.32 (480)	≤0.001	653.77 (307)	≤0.001
Group	8.68 (480)	≤0.001	2.10 (307)	0.080
Baseline	2.51 (480)	>0.100	5.09 (308)	0.025
Random effects				
	Estimate (SE)		Estimate (SE)	
Subject	25.53 (2.66)		0.40 (0.03)	
Recovery slope	0.005 (.003)		≤0.001 (≤0.001)	

Effects of mental training on psychoendocrine covariance

Next, we tested whether mental training improved psychoendocrine covariance using linear regression. Relative to the untrained group, mental training influenced the association between self-report and cortisol stress markers [$F_{9,296} = 4.01$, $P \leq 0.001$, $R^2 = 0.11$]. The initial 3-month attention-based Presence ($b = 0.25$, $t = 2.45$, $P = 0.015$), the sequential Presence/Perspective ($b = 0.21$, $t = 1.98$, $P = 0.049$), and the sequential Presence/Affect training (albeit only marginally; $b = 0.15$, $t = 1.72$, $P = 0.086$) increased the association of ΔSTAI and Δcortisol. The 3-month Affect training alone had no effect on psychoendocrine covariance ($b = 0.09$, $t = 1.08$, $P > 0.20$) (Fig. 3). Changes in psychoendocrine covariance did not differ between the training groups (all P values >0.10). Consistent with the idea of weakened mind-body connections with age (*30*), we show an influence of age on these training-induced changes in psychoendocrine covariance in an additional post hoc analysis (see the Supplementary Materials).

DISCUSSION

Identifying effective ways to reduce stress and thus attain a healthier lifestyle has gained critical importance in our stress-ridden society. We conducted a large-scale 9-month longitudinal study, the ReSource Project (*22*), to test whether we could find convincing evidence for psychosocial stress reduction after long-term mental training. Using a multimethod approach, a broad range of subjective and physiological stress markers was assessed. It is unique to the ReSource Project that training was extended beyond the usual 8 weeks of established secular mindfulness-based programs (*7*, *8*) and that different types of contemplative practice—namely, present-moment attention-based, socio-affective, and socio-cognitive practice—were parceled into three independent 3-month training modules (Presence, Affect, and Perspective). This approach allowed for systematically investigating the specific effects of each practice type.

Our results reveal that, indeed, different types of mental practice varied in their influence on the psychosocial stress response. Although we observed training effects on subjective and cortisol stress reactivity, the assessed autonomic and immune markers were unaffected by mental training. In detail, 3 months of Presence training cultivating attention and nonjudgmental moment-to-moment awareness through the core techniques Breathing Meditation and Body Scan lowered self-reported stress intensity by 26% but failed to influence cortisol secretion. Although challenging the notion that present-moment and attention-based meditation techniques are a remedy for social stress, this result reflects existing research. Mindfulness-based interventions have been shown to reduce self-reported (*11*–*13*), sympathetic (*14*), and immune (*15*) reactivity yet lack reliable effects on the acute cortisol stress response. To our knowledge, only one laboratory reported diminished cortisol reactivity to acute stress exposure immediately after a session of integrative body-mind training (*16*, *17*). Several other studies yielded null results (*14*, *18*) or even found stress sensitization (*11*). Because reduced subjective stress experience after committing to effortful mental practice may result from social desirability response bias (the tendency to present oneself in a favorable light) (*31*), we argue that claims of stress reduction based solely on self-reports (without a physiological basis) should be considered with more caution. Together, the previous and current results suggest that the training of attention and interoceptive awareness alone may not be the optimal strategy for cortisol stress reduction following psychosocial challenge. Although a sharpened sense for the physiological state of the body may successfully prevent rumination during acute psychosocial stress, it may be ineffective to buffer the bodily stress symptoms. However, it is conceivable that with longer practice time, reduced subjective stress reactivity will progressively manifest in reduced cortisol release. In this context, it is important to consider that mindfulness-based intervention programs, such as MBSR (*7*) and MBCT (*8*), typically go beyond the scope of the Presence Module. That is, besides the practice of present-moment attention and interoceptive awareness (through, for example, Breathing Meditation and Body Scan), mindfulness-based interventions include practices targeting emotional and cognitive capacities (for example, Loving-kindness Meditation and Observing-thoughts Mediation) (*19*).

Contrary to the 3-month attention-based Presence training, the 3-month compassion-based Affect training reduced self-reported and cortisol stress reactivity by 36 and 32%, respectively. We can conclude that 3 months of mental training is sufficient for physiologically meaningful (*27*) psychosocial stress reduction—provided the right practice is performed. The observed ineffectiveness in decreasing cortisol stress levels after 3 months of Presence training was thus specific to the particular training type and not to a lack of practice time. However, note that although statistically nonsignificant, when preceded by Presence, cortisol stress reduction after the Affect Module did increase from 32 to 48%. This suggests that the previous cultivation of attention and interoceptive awareness may promote stress reduction by optimizing compassion-based Affect training, consistent with the order in which these practice types are taught traditionally (*19*). Our results match cross-sectional studies showing that individuals high in questionnaire-assessed trait compassion (*32*) or instructed to adopt a compassionate stance through a brief cognitive intervention (*33*) exhibited lower cortisol

Table 3. Omnibus *F* tests in linear mixed models for training effects on autonomic and immune stress responses. Removing the covariates from a respective model did not change the pattern of significance. BMI, body mass index.

Autonomic markers

	AA		**HR**		**HF-HRV**	
Fixed effects						
	F (df)	*P*	*F* (df)	*P*	*F* (df)	*P*
Intercept (peak)						
Intercept	29132.77 (367)	≤0.001	317646.14 (371)	≤0.001	5253.12 (433)	≤0.001
Group	0.91 (368)	>0.400	0.98 (374)	>0.400	1.79 (436)	>0.100
Baseline	321.53 (368)	≤0.001	230.68 (374)	≤0.001	101.47 (417)	≤0.001
Sex	5.79 (299)	0.017	1.72 (257)	>0.100	5.98 (251)	0.015
Age	0.46 (298)	>0.400	2.12 (258)	>0.100	8.47 (252)	0.004
BMI	2.15 (298)	>0.100	0.38 (258)	>0.500	0.22 (252)	>0.600
Recovery slope						
Intercept	360.90 (369)	≤0.001	938.89 (254)	≤0.001	26.96 (250)	≤0.001
Group	1.92 (369)	>0.100	0.67 (254)	>0.600	1.33 (250)	>0.200
Baseline	1.41 (373)	>0.200	0.05 (258)	>0.800	2.87 (249)	0.091
Random effects						
	Estimate (SE)		Estimate (SE)		Estimate (SE)	
Subject	0.18 (0.02)		0.009 (0.001)		0.43 (0.08)	
Recovery slope	≤0.001 (≤0.001)		No variance; excluded		No variance; excluded	

Immune markers

	hsCRP		**IL-6**	
Fixed effects				
	F (df)	*P*	*F* (df)	*P*
Intercept (peak)				
Intercept	1160.07 (469)	≤0.001	<0.01 (1)	>0.900
Group	0.64 (473)	>0.600	0.43 (4)	>0.700
Baseline	27503.27 (452)	≤0.001	260.49 (1)	≤0.001
Sex	0.36 (283)	>0.500	7.07 (1)	0.008
Age	3.69 (284)	0.056	0.02 (1)	>0.900
BMI	1.09 (284)	>0.200	2.04 (1)	>0.100
Recovery slope				
Intercept	55.34 (281)	≤0.001		
Group	0.74 (281)	>0.500		
Baseline	0.11 (282)	>0.700		
Random effects				
	Estimate (SE)			
Subject	0.004 (≤0.001)			
Recovery slope	No variance; excluded			

Table 4. Between-group contrasts and effect sizes for training effects in self-reported and HPA axis stress reactivity. Between-group Cohen's *d* effect sizes were calculated using *t* values and degrees of freedom. Aff, Affect; NT, no training; Per, Perspective; Prs, Presence.

STAI	NT		Prs		Aff		Prs/Aff		Prs/Per	
	t (df)	*d*	*t*	*d*	*t*	*d*	*t*	*d*	*t*	*d*
NT			−2.92** (477)	0.27	−4.12*** (478)	0.38	−4.42*** (476)	0.41	−3.65*** (476)	0.33
Prs	2.92** (477)	0.27			−0.97 (477)	0.09	−1.24 (476)	0.11	−0.54 (476)	0.05
Aff	4.12*** (478)	0.38	0.97 (477)	0.09			−0.28 (477)	0.03	0.44 (477)	0.04
Prs/Aff	4.42*** (476)	0.41	1.24 (476)	0.11	0.28 (477)	0.03			0.72 (476)	0.07
Prs/Per	3.65*** (476)	0.33	0.54 (476)	0.05	−0.44 (477)	0.04	−0.72 (476)	0.07		
Cortisol										
	NT		Prs		Aff		Prs/Aff		Prs/Per	
	t (df)	*d*	*t*	*d*	*t*	*d*	*t*	*d*	*t*	*d*
NT			0.63 (304)	0.07	−2.06* (304)	0.24	−2.99** (304)	0.34	−3.22*** (304)	0.37
Prs	−0.63 (304)	0.08			−2.21* (304)	0.25	−2.97** (304)	0.34	−3.17** (304)	0.36
Aff	2.06* (304)	0.24	2.21* (304)	0.25			−0.79 (304)	0.09	−0.96 (304)	0.11
Prs/Aff	2.99** (304)	0.34	2.97** (304)	0.34	0.79 (304)	0.09			−0.17 (304)	0.02
Prs/Per	3.22*** (304)	0.37	3.17** (304)	0.36	0.69 (304)	0.11	0.17 (304)	0.02		

*$P \leq 0.05$. **$P \leq 0.01$. ***$P \leq 0.001$.

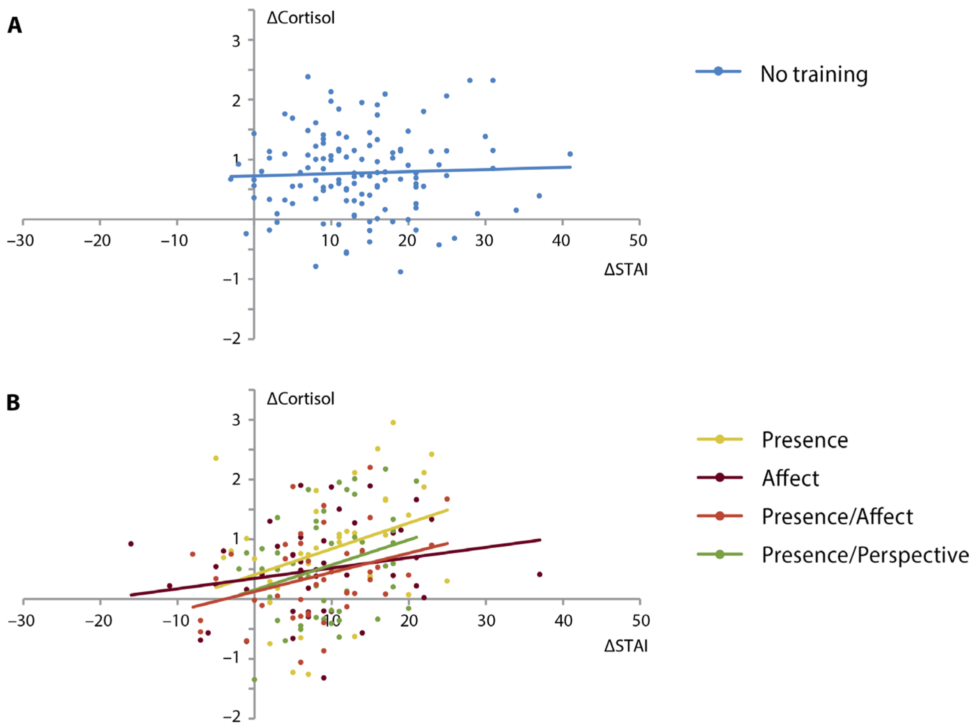

Fig. 3. Psychoendocrine covariance after training relative to no training. For illustrative purpose, we show bivariate correlations between STAI and cortisol baseline-to-peak change scores (Δ) in (**A**) the no training group and (**B**) all training groups. Linear regression showed that relative to the untrained group, mental training influenced the association between subjective and cortisol stress markers ($P \leq 0.001$). Both the initial 3-month attention-based Presence ($P = 0.015$) and the sequential Presence/Perspective training ($P = 0.049$) significantly increased the association of ΔSTAI and Δcortisol. The sequential Presence/Affect training only induced a marginal change ($P = 0.086$). Three-month Affect training alone had no effect on psychoendocrine covariance ($P > 0.20$). Changes in psychoendocrine covariance did not differ between the training groups (all *P* values >0.10).

responses to psychosocial challenge. In contrast, 6 weeks of (self-) compassion training without dyadic exercises (as implemented in the current protocol) solely reduced self-reported and immune reactivity (*12*, *13*).

Whereas both mindfulness- and compassion-based intervention programs have previously been investigated, the Perspective Module with its focus on metacognition and perspective-taking on self and others has no precedence in secular contemplative intervention research. We observed that Affect and Perspective trainings were equally successful in reducing psychosocial stress. Self-reported reactivity was lowered by 39 and 31% and cortisol reactivity by 48 and 51% after Affect training and Perspective training (both following Presence), respectively. The comparable effectiveness of these two modules likely originates from their common intersubjective content. Although targeting different processes, either socio-affective or socio-cognitive in nature (*23*, *24*), both aim to improve an individual's social relations, be it by taking an empathic and compassionate stance or by engaging in perspective-taking on others' minds. With the realization of contemplative dyads, the two modules share another important aspect distinguishing them from both Presence training and previously studied mindfulness-based interventions, which mostly failed to detect cortisol effects after acute psychosocial challenge. We suggest that regular self-disclosure and consequent exposure to the potential evaluations of their fellow trainees within the daily dyadic practice (*34*, *35*) may have "immunized" participants against the fear of social shame and judgment by others. A psychosocial stressor like the TSST, the stressful nature of which largely depends on the experience of an uncontrollable threat to the social self (*36*), would consequently lose its negative impact. Future research will need to isolate the specific effects of contemplative dyadic exercises and classic meditation techniques that were coupled as daily core exercises in the two social modules of the ReSource Project (for example, Loving-kindness Meditation in the Affect Module and Observing-thoughts Meditation in the Perspective Module). From a mechanistic perspective, it can be hypothesized on the basis of previous research that the Affect Module stimulates positive affect systems (*37*) linked to care and affiliation and modulated by oxytocin and opiates (*38*, *39*). Given their additional involvement in stress regulation (*40*, *41*), these neuropeptides are prime candidates for mediating stress reduction after compassion-based practice. Stress reduction after Perspective training is likely mediated by different mechanisms linked to an improved understanding of own and others' perspectives and the ability to detach from invasive, stress-inducing thoughts.

Because both subjectively experienced and HPA axis responses represent indicators of the construct "stress," they are expected to correlate substantially. One reason for the often reported lack of psychoendocrine covariance (*21*) may be the participants' inability to accurately intercept their internal states. It has been a long-standing hypothesis that meditation enhances first-person accounts by sharpening interoception and enabling a more granular description of internal experience. Subjective first-person and objective third-person measures should consequently be more closely aligned (*6*). Our results demonstrate that mental training unspecifically increased the correlation of subjectively experienced and cortisol stress reactivity. This is in line with other findings from the ReSource Project showing equal increases in self-reports of body awareness after all meditation types (*42*) and a steady improvement in heartbeat perception accuracy over the course of the training (*43*). We propose that increased psychoendocrine covariance may reflect the development toward a healthier stress response, that is, a balanced state in which subjective stress experience is coupled with the necessary endocrine adaptations (namely, the release of cortisol) to cope with a stressor and, vice versa, there is enhanced awareness of the source of stress-induced physiological activation.

Contrary to previous studies (*12*–*15*), no effect of mental training on autonomic and innate immune markers was found. However, our study had a larger sample size, longer training time, and used a more sensitive modeling technique than previous studies. Because the results of underpowered studies are less likely to represent true effects (*44*), this failure to replicate despite increased statistical power indicates that the relation between mental training and both autonomic and immune markers is less clear-cut than presumed. Furthermore, differences in the specific composition of training regimes and methodological study details may account for divergent findings. For example, Pace *et al.* (*13*) detected training effects on IL-6 within their meditation group (as opposed to the health discussion control group) only after considering individual differences in the amount of reported meditation practice. Similar to our study, the authors found no main effect of group assignment. In addition to using the TSST, Rosenkranz *et al.* (*15*) used topical application of capsaicin cream to stimulate neurogenic inflammation in the skin. This combinatorial approach of inducing psychosocial stress and targeted inflammation was likely more sensitive in detecting subtle immunological changes than the measurement of inflammatory markers in the blood.

We suggest that the discrepancy between HPA axis and autonomic/immune findings reflects differences in the reactivity of these response systems. Whereas HPA axis activity is stress-specific and strongly determined by internal evaluations (*36*), autonomic activity is a sign of general moment-to-moment arousal equally responding to emotional stimuli of positive and negative valence (*45*). Training of intersubjective capacities as implemented in the Affect and Perspective Modules seems to target the processing of socially and ego-relevant information, thus buffering the threat inherent to social-evaluative stress and not its arousing nature. The discrepancy between HPA axis and immune findings may be explained by the fact that although activated by stress (*28*), inflammatory markers are not principal effectors of the stress response (*3*). Accordingly, associations between cortisol and inflammatory markers are not consistently found, both in the present and in previous studies (*28*), and reductions in stress-induced innate immunity after mindfulness-based interventions were seen in the absence of cortisol effects (*13*, *15*). Future research will need to explore how baseline immune activity relates to different types of contemplative practice and whether the current results generalize to nonpsychosocial stressors, such as physical strain or pain.

It is a limitation of the present study that we focused solely on the magnitude of the stress response. A more fine-grained metric of stress is proposed in the biopsychosocial model of challenge and threat, which differentiates between the physiological signatures of adaptive and maladaptive responses to acute stressful situations (*46*, *47*). We would like to encourage future research to investigate whether mental training shifts stress appraisals and sympathetic output from threat-like to challenge-like response patterns. Rather than in HR and HF-HRV, training-induced change may manifest in these more subtle sympathetic measures.

In conclusion, despite the relative absence of physical threat in modern society, the wear and tear of psychosocial stress increasingly contributes toward negative mental and physical health outcomes (*1*). Consequent financial costs to society are significant (*5*). Alleviating psychosocial stress must hence be a primary societal goal. Our data reveal substantial reduction in self-reported and cortisol stress responses by up to 51%, specifically after intersubjective mental training focused on compassion and cognitive perspective-taking skills. Integrating short intersubjective mental practice into our daily routine would be a broadly accessible, low-cost approach to preventing stress-related disease and the associated financial burden to society. It would involve the additional benefit of improving social capacities, such as compassion, social intelligence, and prosocial behavior (48).

MATERIALS AND METHODS

Participants

For detailed information on the multistage recruitment procedure, inclusion/exclusion criteria, and the final sample description of the ReSource Project, see Singer *et al.* [(22), chap. 7]. In short, all volunteers underwent a comprehensive face-to-face mental health diagnostic interview with a trained clinical psychologist. The interview included a computer-assisted German version of the Structured Clinical Interview for DSM-IV Axis-I disorders, the SCID-I DIA-X (49), and a personal interview for Axis-II disorders, the SKID-II (50, 51). Volunteers were excluded if they fulfilled the criteria for an Axis-I disorder within the past 2 years or for schizophrenia, psychotic disorder, bipolar disorder, substance dependency, or any Axis-II disorder at any time in their life. Volunteers taking medication influencing the HPA axis were also excluded. Of the 332 initial ReSource participants, 313 (185 women; age mean ± SD, 40.68 ± 9.30 years; age range, 20 to 55 years) underwent the TSST (20). The missing 19 participants either dropped out of the study (n = 10; six women), were excluded from the study (n = 4; three women), or were repeatedly unavailable for testing (n = 5; three women). Reasons for study dropout were time constraints (n = 5; two women) and discomfort with the study or experiments (n = 5; four women). Reasons for exclusion were medical (n = 3; two women) and previous mental training experience (n = 1; one woman). Table S1 gives an overview of the available data per stress marker and measurement time point. Female hormonal status was assessed via self-report on the testing day. Forty-seven women had no menstrual cycle because of menopause or polycystic ovary syndrome, 35 took hormonal contraceptives, and 103 had a natural menstrual cycle. Thirty-seven participants were cigarette smokers (≤10 cigarettes/day). Participants with differing hormonal status and smokers were equally distributed among groups (no training, Presence, Affect, Presence/Affect, and Presence/Perspective) (table S2). The ReSource Project was registered with the Protocol Registration System (www.ClinicalTrials.gov) under the title "Plasticity of the Compassionate Brain" (identifier NCT01833104). It was approved by the Research Ethics Boards of Leipzig University (ethic number: 376/12-ff) and Humboldt University Berlin (ethic numbers: 2013-20, 2013-29, and 2014-10). Participants gave their written informed consent, could withdraw from the study at any time, and were financially compensated.

Experimental design

Stress testing was organized in a cross-sectional design, that is, groups of participants underwent the TSST at different phases of the ReSource Project. One hundred thirty participants were tested without training (no training group). Of these, 84 participants were part of the retest control cohorts and tested either at baseline (T0; n = 46), in the first test phase (T1; n = 20), or in the second test phase (T2; n = 18); 46 were part of the training cohorts and tested before training at T0. Of the remaining training participants, 46 were tested at T1 following Presence, 46 at T1 following Affect, 44 at T2 following Presence/Affect, and 47 at T2 following Presence/Perspective training (Fig. 1B).

Because cortisol secretion is characterized by a strong circadian rhythm (52), testing was performed between 12 and 6 p.m. in one 130-min session. To adjust blood sugar levels, participants had a standardized snack upon arrival. Throughout testing, they refrained from taking anything by mouth except water. Fifteen minutes after arrival, a baseline questionnaire and saliva sample for the measurement of self-reported stress and cortisol/AA were collected (at −55 min). Subsequently, the baseline blood sample for the measurement of immune activity was drawn (at −50 min), followed by a 30-min resting phase to overcome potential stress induced by the blood draw. Participants were then provided with the test instructions. After 10 min of anticipating the TSST, anticipatory self-reported stress was assessed (at −5 min) (amounting to a 15-min anticipation phase) and followed by the 10-min stress phase. Immediately after stress induction, saliva, questionnaire, and blood samples were collected (at 10 to 15 min). During the 60-min recovery phase, repeated questionnaire and saliva samples were collected. At the end of the testing session (60 min), a final blood sample was drawn. Cardiac measures were recorded from 30 min before until 25 min after stressor onset (Fig. 1C).

ReSource training program

In the ReSource Project, we investigated the specific effects of commonly used mental training techniques by parceling the training program into three separate modules (Presence, Affect, and Perspective), each cultivating distinct cognitive and socio-affective capacities (22). Participants were divided in two 9-month training cohorts experiencing the modules in different orders, one 3-month Affect training cohort and one retest control cohort. In detail, two training cohorts (TC1 and TC2) started their training with the mindfulness-based Presence Module. They then underwent Affect and Perspective Modules in different orders, thereby acting as Mutual active control groups. To isolate the specific effects of the Presence Module, a third training cohort (TC3) underwent a 3-month Affect Module only (Fig. 1B).

As illustrated in Fig. 1A, the core psychological processes targeted in the Presence Module are attention and interoceptive awareness, which are trained through the two meditation-based core exercises Breathing Meditation and Body Scan. The Affect Module targets the cultivation of social emotions, such as compassion, loving kindness, and gratitude. It also aims to enhance prosocial motivation and dealing with difficult emotions. The two core exercises of the Affect Module are Loving-kindness Meditation and Affect Dyad. In the Perspective Module, participants train metacognition and perspective-taking on self and others through the two core exercises Observing-thoughts Meditation and Perspective Dyad. Participants were free to conduct each of the two core practices of a given module at their best convenience. Although our recommendation was to train for a minimum of 30 min (for example, 10-min contemplative dyad and 20-min classic meditation) 5 days per week, there was no guideline on when the two different core practices had to be realized. The dyadic interactions had to be coordinated in advance with a respective dyadic partner and could therefore not be carried out as flexibly as the classic meditation practice. The average numbers of weekly practice sessions for each mental training exercise performed in Presence, Affect, and Perspective Modules are shown in table S3.

The two contemplative dyads address different skills but are similar in structure. In each 10-min dyadic practice, two randomly paired participants share their experiences with alternating roles of speaker and listener. Dyads are conducted using a custom-designed website or smartphone application, which randomly chooses one participant as first speaker. The speaker contemplates on a chosen topic for 5 min. The listener is silent, mindfully listens, and does not respond. Then the roles reverse. This contemplative dialog is understood as a "loud meditation." The dyadic format is designed to foster interconnectedness by providing opportunities for self-disclosure and mindful listening (*35*). The unique elements of each dyad teach specific skills relevant to social interactions. In the Affect Dyad, the speaker spends 2.5 min describing a difficult situation (with accompanying feelings and bodily sensations) that occurred in the past 24 hours. For another 2.5 min, the speaker describes a situation that elicited gratitude with accompanying feelings and bodily sensations. This exercise should help with both the acceptance of difficult emotions and the cultivation of positive emotions. The dyadic partner is instructed to practice nonjudgmental empathic listening. In the Perspective Dyad, the speaker describes a situation that occurred in the past 24 hours from the perspective of a previously identified and randomly assigned inner part, that is, a personality aspect or inner schema. Examples of inner parts are "the judge," "the manager," or the "caring mother." This exercise aims at training perspective-taking on internal aspects of the self. It should help realize how we cocreate our realities and social interactions by identifying with our inner personality aspects (*34*, *35*). The listener attempts to infer which inner part of the other is currently speaking and thus practices cognitive perspective-taking.

Stress induction

Participants were exposed to the TSST (*20*), the most frequently used social-evaluative laboratory stressor that reliably provokes subjective and physiological stress responses (*36*). The stressful nature of the TSST was shown to depend on the elements of novelty, unpredictability, uncontrollability, and social-evaluative threat (*36*). In short, after a preparatory anticipation phase of variable length (15 min in the current study), participants are required to give an audio- and videotaped mock job talk (5 min) and engage in difficult mental arithmetic (5 min) while being verbally probed and evaluated by a committee of two alleged behavioral analysts.

Stress markers

Cortisol and AA

Relative to stressor onset (at 0 min), saliva samples were collected at −55, 10, 20, 30, 40, and 55 min to capture cortisol and AA peaks and recoveries (Fig. 1C). Saliva was sampled into Salivette collection devices (Sarstedt). As recommended by Rohleder and Nater (*53*), participants placed the collection swabs in their mouth and refrained from chewing for 2 min. Salivettes were stored at −30°C until assay. Cortisol levels (expressed in nanomolar) were determined using a time-resolved fluorescence immunoassay (*54*) with intra- and interassay variabilities of less than 10 and 12%, respectively. AA activity (expressed in U/ml) was determined using an enzyme kinetic method (*55*, *56*).

HR and HF-HRV

HF-HRV measures the variability of HR in the respiration frequency range of 0.15 to 0.4 Hz and is considered a reliable marker of parasympathetic, specifically vagus nerve, activity (*57*, *58*). To capture HR and HF-HRV from 30 min before until 25 min after TSST onset, we assessed a continuous ECG with the Zephyr BioHarness 3 (Zephyr Technology), an ambulatory measurement device that is strapped around the participant's chest and samples at a frequency of 250 Hz. The 65-min ECG recording covered a 10-min time frame within the baseline resting phase (from −30 to −20 min), a 20-min time frame during which the participants were brought to the testing room, received testing instructions, and anticipated the TSST (from −20 to 0 min), the 10-min stress phase (from 0 to 10 min), and a 15-min time frame within the recovery phase, during which the post-stress blood sample was drawn and participants returned to their resting rooms (from 10 to 25 min). Because of interindividual variation in the transition between phases, only the middle 8-min ECG sequences of baseline and stress phases were included in the analysis (that is, first and last minutes per phase were excluded). Likewise, because the post-stress blood draw varied in length between participants, only the final 8-min ECG sequence of the recovery phase was included. The anticipation phase was dropped from the analysis because no equivalent anticipation samples for cortisol and AA were used.

ECGs were extracted with the software Matrix Laboratory (Matlab; version R2014a). Raw recordings were automatically checked for artifacts using in-house software and subsequently manually corrected for further artifacts. Average HR (expressed in beats per minute) and HF-HRV (expressed in square millisecond) were then calculated for the 8-min time frames of each experimental phase (baseline, stress, and recovery) with the software ARTiiFACT (version 2) (*59*).

hsCRP and IL-6

Relative to stressor onset (at 0 min), blood samples were collected at −50, 15, and 60 min to capture hsCRP and IL-6 stress responses (Fig. 1C). Blood (5.5 ml) was collected into serum vacutainers (Sarstedt), allowed to clot for 30 to 45 min, and subsequently centrifuged at 3500 rpm for 15 min. Serum was frozen at −80°C until assay. hsCRP measurements were performed by a latex-enhanced immunoturbidimetric assay using the Siemens Advia 1800 Clinical Chemistry System (Siemens Healthineers). Intra- and interassay coefficients of variation were <4.4 and <3.8%, respectively. IL-6 levels were measured with a solid-phase enzyme-labeled chemiluminescence immunometric assay using a random access chemiluminescence immunoassay system (IMMULITE 2000, Siemens Healthineers). Intra- and interassay coefficients of variation were <7.4 and <5.8%, respectively.

Subjective stress experience

Because subjective stress experience results from the appraisal of a stimulus as harmful and threatening (*60*), we used the 20-item state scale of the STAI (*25*) to assess self-reports of stress. Relative to stressor onset (at 0 min), the STAI state scale was administered at baseline (−55 min), after anticipation (at −5 min), and after stressor termination at 10, 20, and 30 min. Among the validated questionnaires, the STAI state scale is the most frequently used measure of stress-induced subjective-emotional states (*26*), asking for acute feelings of apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system. To show that the STAI state scale goes beyond merely measuring anxiety (see the Supplementary Materials), participants additionally completed the conceptually broader 65-item Profile of Mood States (POMS) (*61*) at the peak of subjective stress experience (−5 min). The POMS is the second most frequently used measure of subjective-emotional stress experience (*26*), measuring fluctuations along the dimensions tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. Because of its length, the POMS is unsuitable for repeated administration.

Statistical analysis

Analyses were performed with the software SPSS (Statistical Package for the Social Sciences; version 23). Physiological data were ln-transformed to account for skewness. To facilitate interpretation, continuous predictors were mean-centered. Outliers were winsorized to 3 SDs from the mean. All tests were two-sided, and a P value of ≤ 0.05 was considered statistically significant. Reflecting Bonferroni correction for multiple tests within a conceptual cluster, the α threshold was lowered to $\leq 0.05/3$ for autonomic markers and to $\leq 0.05/2$ for immune markers.

Matching

Participants were selected from a larger pool of volunteers and assigned to training and retest control cohorts matched in demographics and various self-reported traits using bootstrapping without replacement {for details on the matching criteria, see Singer *et al.* [(*22*), chap. 7]}. For the current cross-sectional stress testing design, groups were rematched on a subset of variables with potential influence on stress reactivity: sex, hormonal status in women, city of residence (Berlin/Leipzig), number of smokers, age, depressed mood [Major Depression Inventory (*62*)], trait anxiety [STAI (*25*)], and chronic stress [Perceived Stress Scale (*63*)] using Pearson's χ^2 tests and one-way analyses of variance (ANOVAs) (all χ^2 values ≤6.50, F values ≤0.77, P values >0.30; see table S2 for descriptive statistics).

Exploratory associations between stress reactivity scores

To explore training-independent associations between the assessed stress markers and their underlying response systems, bivariate correlations of cortisol, AA, HR, HF-HRV, hsCRP, IL-6, and STAI state stress reactivity scores (operationalized as baseline-to-peak change; Δ) were calculated in the no training group.

Effects of mental training on the stress response

Linear mixed models were used to analyze the data (with the exception of IL-6; see below). In each model, repeated measures of a respective stress marker were nested within individuals. The first measurement point represented the peak stress reaction (at 20 min for cortisol, 10 min for AA, 15 min for hsCRP, during the stress phase at average 5 min for HR and HF-HRV, and at −5 min for self-reported stress). The continuous variable "time" (hereafter referred to as "recovery slope") was operationalized as the number of minutes between the peak in stress reaction and the succeeding measurement points returning to baseline (at 55 min for cortisol, 40 min for AA, 60 min for hsCRP, during the recovery phase at average 20 min for HR and HF-HRV, and at 30 min for self-reported stress). By centering the time variable at the peak, the model intercept provided an estimate of the magnitude of the peak stress reaction. Because of an influence on the dynamics of the stress response (law of initial value) (*64*), baseline levels of a respective marker and their interactions with the recovery slope were included as level 2 predictors in the model. This additional information was necessary in accounting for the likelihood that both the peak in stress reaction and the steepness of the recovery slope would inversely relate to baseline levels. Additional level 2 predictors were the group (no training, Presence, Affect, Presence/Affect, and Presence/Perspective) and the two-way interaction of group and recovery slope. Given their influence on cortisol levels, hormonal status (*65*) and time of day (*66*) were added to the cortisol model. Common covariates added to the autonomic and immune models were sex and BMI (*67*–*69*). Because of the considerable age range of our participant sample (20 to 55 years) and to be consistent with other publications from the ReSource Project, we added age as a covariate to all models.

Provided that there was sufficient variance in the data, subject-level random effects for intercept (stress peak) and recovery slopes were added to the model to accurately reflect the nature of our data as a sample from a larger population that is the true target of our inferences. Covariances between random effects were set to zero. Including random effects for critical parameters increases generalizability, reduces the likelihood of type I error for within-person effects by increasing the accuracy of SE estimates, and may reduce the likelihood of type II error for between-person effects by reducing the amount of residual variance left by the model (*70*). In detail, the following model was specified using Raudenbush and Bryk (*71*) notation (covariates vary per dependent variable)

Level 1: $DV_{ti} = \beta_{0i} + \beta_{1i}\,(\text{recovery slope})_{ti} + e_{ti}$

Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}\,(\text{Presence}) + \gamma_{02}\,(\text{Affect}) + \gamma_{03}\,(\text{Presence/Affect}) + \gamma_{04}\,(\text{Presence/Perspective}) + \gamma_{05}\,(\text{baseline level}) + \gamma_{06}\,(\text{control variable } x) + \gamma_{07}\,(\text{control variable } y) + r_{0i}$

$\beta_{1i} = \gamma_{10} + \gamma_{11}\,(\text{Presence}) + \gamma_{12}\,(\text{Affect}) + \gamma_{13}\,(\text{Presence/Affect}) + \gamma_{14}\,(\text{Presence/Perspective}) + \gamma_{15}\,(\text{baseline level}) + r_{1i}$

Fixed effects: $DV = \gamma_{00} + \gamma_{01}\,(\text{Presence}) + \gamma_{02}\,(\text{Affect}) + \gamma_{03}\,(\text{Presence/Affect}) + \gamma_{04}\,(\text{Presence/Perspective}) + \gamma_{05}\,(\text{baseline levels}) + \gamma_{06}\,(\text{control variable } x) + \gamma_{07}\,(\text{control variable } y) + \gamma_{10}\,(\text{recovery slope}) + \gamma_{11}\,(\text{recovery slope})\,(\text{Presence}) + \gamma_{12}\,(\text{recovery slope})\,(\text{Affect}) + \gamma_{13}\,(\text{recovery slope})\,(\text{Presence/Affect}) + \gamma_{14}\,(\text{recovery slope})\,(\text{Presence/Perspective}) + \gamma_{15}\,(\text{recovery slope})\,(\text{baseline level})$

Random effects: $DV_i = r_{0i} + r_{1i}\,(\text{recovery slope}) + e_{ti}$

where γ_{00} represents the intercept (stress peak) and γ_{10} represents the recovery slope of estimated cortisol, AA, HR, HF-HRV, hsCRP, or self-reported stress levels. Unstandardized coefficients for predictors of the slope represent the change in slope per minute during stress recovery resulting from a one-unit change on the scale of the predictor.

In the case of an overall training effect, estimates for between-group tests were calculated using contrasts. Contrasts were not corrected for multiple comparisons because estimates are "shrunk" toward a common mean within the multilevel model framework. This "partial pooling" accounts for the dependence of estimates calculated within the same model without compromising power (*72*). Because IL-6 levels increased until 60 min after stressor onset, a univariate general linear model with peak IL-6 levels as dependent variables, group and sex as fixed factors, and baseline IL-6, age, and BMI as covariates was calculated.

Effects of mental training on psychoendocrine covariance

Baseline-to-peak change scores were calculated to quantify the average stress-induced rise in subjective stress experience (ΔSTAI) and cortisol levels (Δcortisol). A linear regression modeling Δcortisol from ΔSTAI, the dummy-coded training groups, and the interaction of ΔSTAI with the dummy-coded training groups was calculated. The ΔSTAI by training group interactions examined the improvement in psychoendocrine covariance in each training group relative to the no training group. To subsequently assess whether improvements in psychoendocrine covariance differed between training groups, we repeatedly executed the linear regression with the different training groups as changing reference categories. This allowed contrasting each training group with the respective other training groups.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/3/10/e1700495/DC1

Supplementary Materials and Methods

fig. S1. Parameter estimates from hierarchical linear models showing effects of study duration on self-reported and cortisol stress reactivity and recovery.

table S1. Number of participants with available data (and winsorized outliers) per stress marker and measurement time point.

table S2. Descriptive statistics per group.

table S3. Mean number (SD) of weekly practice sessions for each mental training exercise per training module.

table S4. Omnibus *F* tests in linear mixed models for habituation effects on self-reported and HPA axis stress responses.
table S5. Coefficients from a linear regression examining improvement in psychoendocrine covariance (association of ΔSTAI and Δcortisol) in each training group relative to the no training group.
Source data (Excel file)

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