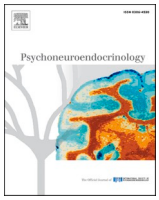
Psychoneuroendocrinology 170 (2024) 107192

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



Dynamic interplay of cortisol and BDNF in males under acute and chronic psychosocial stress – A randomized controlled study

Benedict Herhaus [a,*], Martin Heni [b,c], Wilhelm Bloch [d], Katja Petrowski [a]

[a] Medical Psychology and Medical Sociology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
[b] Division of Endocrinology and Diabetology, Department of Internal Medicine I, Ulm University Hospital, Ulm, Germany
[c] Department for Diagnostic Laboratory Medicine, Institute for Clinical Chemistry and Pathobiochemistry, University Hospital Tübingen, Tübingen, Germany
[d] Department Molecular and Cellular Sports Medicine, German Sport University Cologne, Institute of Cardiology and Sports Medicine, Cologne, Germany

ARTICLE INFO

Keywords:
Brain derived neurotrophic factor (BDNF)
Cortisol
Hypothalamic-pituitary-adrenocortical (HPA) axis
Trier Social Stress Test (TSST)

ABSTRACT

The neurotrophic protein brain-derived neurotrophic factor (BDNF) plays a pivotal role in brain function and is affected by acute and chronic stress. We here investigate the patterns of BDNF and cortisol stress reactivity and recovery under the standardized stress protocol of the TSST and the effect of perceived chronic stress on the basal BDNF levels in healthy young men. Twenty-nine lean young men underwent the Trier Social Stress Test (TSST) and a resting condition. Serum BDNF and cortisol were measured before and repeatedly after both conditions. The perception of chronic stress was assessed by the Trier Inventory for Chronic Stress (TICS). After the TSST, there was a significant increase over time for BDNF and cortisol. Stronger increase in cortisol in response to stress was linked to an accelerated BDNF decline after stress. Basal resting levels of BDNF was significantly predicted by chronic stress perception. The increased BDNF level following psychosocial stress suggest a stress-induced neuroprotective mechanism. The presumed interplay between BDNF and the HPA-axis indicates an antagonistic relationship of cortisol on BDNF recovery post-stress. Chronically elevated high cortisol levels, as present in chronic stress, could thereby contribute to reduced neurogenesis, and an increased risk of neurodegenerative conditions in persons suffering from chronic stress.

1. Introduction

Stress-related disorders have emerged as a major health concern in the early twenty-first century and have been linked to altered brain function (McEwen, 2017; WHO, 2001). Acute and chronic stress affects adult neurogenesis and activates a complex interplay of neural and endocrine mechanisms (Chu et al., 2021; Egeland et al., 2015). Glucocorticoids (GCs), as a key part of the body's stress response system, and brain-derived neurotrophic factor (BDNF), with its multiple roles in the nervous system, influence adult neurogenesis through their dynamic interactions in the context of acute and chronic stress (Miranda et al., 2019; Tsigos and Chrousos, 2002).

The neurotrophic protein BDNF plays a pivotal role in brain function throughout life (Miranda et al., 2019). BDNF protects existing neurons and synapses of the central nervous system (Acheson et al., 1995). In the neurogenesis BDNF acts through the family of high-affinity tyrosine kinase receptors i.e. the tropomyosin receptor kinase B (TrkB) receptor (Tapia-Arancibia et al., 2004; Zigova et al., 1998). In addition to these direct functions on neuronal structure, BDNF is known to contribute to the regulation of eating behaviour and physical activity (Tapia-Arancibia et al., 2004). In the hippocampus, BDNF is a key molecule related to learning and memory (Miranda et al., 2019). BDNF physiologically decreases with normal ageing (Erickson et al., 2010) and the development of cognitive impairment is affected by chronic stress (Wilson et al., 2007). Of note, altered BDNF were detected in different diseases, including depression (Lee and Kim, 2010) and Alzheimer's disease (Mori et al., 2021).

Different studies suggested that both acute and chronic stress could affect BDNF (Miranda et al., 2019). With regard to the acute stress, BDNF increases have been observed in healthy adults in response to acute psychosocial stress in the laboratory using the internationally established Trier Social Stress Test (Hermann et al., 2021; Linz et al., 2019; Meng et al., 2011). In animals, chronic stress caused a reduction in neuronal *Bdnf* mRNA expression (Murakami et al., 2005) and BDNF

* Correspondence to: Medical Psychology and Medical Sociology, University Medical Center of the Johannes Gutenberg University Mainz, Duesbergweg 6, Mainz 55128, Germany.
E-mail address: bherhaus@uni-mainz.de (B. Herhaus).

https://doi.org/10.1016/j.psyneuen.2024.107192
Received 16 November 2023; Received in revised form 19 September 2024; Accepted 19 September 2024
Available online 21 September 2024

protein levels (Gray et al., 2013). In line, decreases of BDNF levels were reported in hospital employees who were psychologically stressed through their work (Mitoma et al., 2008). There is also evidence of decreased BDNF levels in stress-related disorders (Brunoni et al., 2008; Schmitt et al., 2016). Thus, BDNF is a stress-dependent factor (Jeanneteau et al., 2012).

Of note, BDNF appears to interact with the hypothalamic-pituitary-adrenocortical (HPA)-axis, one of the major physiological stress systems. *BDNF* is expressed in the hypothalamus's paraventricular nucleus (PVN) (Castren et al., 1995), the upstream regulator of HPA-axis activity. In this brain area, corticotropin-releasing hormone (CRH) is a central regulator of the stress response to mediate allostasis (McEwen, 1998). CRH stimulated the release of adrenocorticotropic hormone (ACTH), which leads to secretion of cortisol and other GCs (Chrousos and Gold, 1992). GC action on glucocorticoid receptors in the PVN are crucial components of the negative feedback loop that controls HPA-axis activity (Herman et al., 2016). Of notice, dysregulation of glucocorticoid receptor function not only leads to a disturbed HPA-axis feedback loop with an increase in CRH-expression but also causes an increase of hypothalamic BDNF (Jeanneteau et al., 2012). This suggests a causal suppressive impact of glucocorticoid signaling on BDNF expression or release. Though, the relation between glucocorticoids and BDNF appears to be bi-directional, as intracerebroventricular BDNF injections also increased the CRH mRNA signal and increased ACTH and corticosterone levels (Givalois et al., 2004). How these mechanistic findings translate into humans is still not fully clear. However, it is hypothesized that the bidirectional interaction between BDNF and the HPA-axis may play a role in modulating stress responsiveness and resilience in humans. Dysregulation of this feedback loop could potentially contribute to the pathophysiology of stress-related psychiatric disorders, such as depression and anxiety. Further research is needed to clarify the exact role of these mechanisms in human physiology and their implications for mental health (Binder and Nemeroff, 2010; Holsboer, 2000).

The HPA-axis regulates the acute and chronic stress response through the secretion of glucocorticoids, the most important of which is cortisol (Tsigos and Chrousos, 2002). While it is well established that BDNF and cortisol levels increase in response to acute stress (Miranda et al., 2019), how they interact under acute stress is less clear. As a possible mechanism, Suri and Vaidya (2013) described that stress-induced cortisol secretion has a downregulatory effect on BDNF secretion.

Human studies have shown stress-induced increases in both cortisol and BDNF in response to a psychosocial stressor (Hermann et al., 2021; Linz et al., 2019; Meng et al., 2011). However, possible interactions between BDNF and cortisol dynamics are not well-established. The three previous studies on the topic employed diverse methodologies. Factors like a single post-stress blood sample (Linz et al., 2019; Meng et al., 2011), salivary cortisol measurements (Linz et al., 2019), and no distinct analysis of BDNF/cortisol responses to stress and recovery (Hermann et al., 2021; Linz et al., 2019; Meng et al., 2011) make it hard to definitively determine their relationship.

Therefore, we aimed to clarify the patterns of BDNF and cortisol stress reactivity and -recovery under the standardized stress protocol of the TSST with repeated blood samples to determine cortisol and BDNF in parallel. Based on the previous studies investigating BDNF and cortisol stress reactivity (Hermann et al., 2021; Linz et al., 2019; Meng et al., 2011), we hypothesized stress-induced increase of BDNF and cortisol following the acute psychosocial laboratory stressor (Hypothesis 1). Given the postulated downregulatory effect of stress-induced cortisol on BDNF secretion (Linz et al., 2019; Suri and Vaidya, 2013), we hypothesized that elevated post-stress cortisol levels downregulate BDNF levels (Hypothesis 2). In view of the evidence of decreased BDNF levels in persons experiencing chronic stress (Mitoma et al., 2008) and in individuals with stress-related disorders (Brunoni et al., 2008; Schmitt et al., 2016), we hypothesized that chronic stress perception would be a predictor of basal resting levels of BDNF (Hypothesis 3).

2. Methods

2.1. Study participants

Twenty-nine healthy male individuals were recruited via electronic tendering and notice boards at the Johannes Gutenberg University Mainz. Study criteria were assessed by telephone interview using the full Structured Clinical Interview (SCID; (Wittchen et al., 1997)) for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, (APA, 2000)). Exclusion criteria were acute or chronic medical illness, mental disorders, medication or substance use, stressful life events in the past six months (Caspi et al., 1996), being younger than 18 or older than 35, and smoking more than ten cigarettes per day (Canals et al., 1997). Due to known age and gender specific differences in BDNF levels (Chan and Ye, 2017; Oh et al., 2016), only male participants aged between 18 and 35 years were included. The mean age of the participants was 24.34 ± 4.08 years of age with a body mass index (BMI) of 22.94 ± 1.61 kg/m^2. A detailed description of all participants, including demographic data and psychological status is given in Table 1. The study protocol was approved by the local Ethics Committee of the Landesärztekammer Rheinland-Pfalz, Germany (No#2019–14188).

2.2. Study design

Participants underwent two different conditions, stress and resting, on separate days within a seven-day period. Both conditions started between 2:00 p.m. and 5:00 p.m., and the order of testing was randomized. Participants were asked to refrain from eating, drinking, and smoking before and during the two-hour test session. To avoid a pain-induced release of BDNF and cortisol, the intravenous cannula was inserted 45 minutes before the first blood sample was taken. The experimental protocol began with a 15-minute pre-session, which included the collection of two blood samples. Participants then underwent two 15-minute conditions: stress and rest. The stress condition was the Trier Social Stress Test (TSST), following the Kirschbaum et al. (1993) protocol. It consisted of three sections: preparation, interview, and a calculation task, with each section lasting 5 minutes. In contrast, during the resting condition, participants were given the opportunity to read magazines. Cognitive appraisal was assessed three minutes after the start of each condition using the Primary Appraisal Secondary Appraisal (PASA) scale (Gaab, 2009). In addition, participants' self-reported perception of stress was measured immediately after both conditions using the visual analogue scale (VAS). After completing the stress and resting conditions, participants remained in a supine position on a bed for 105 min, during which nine blood samples were taken at different time points: +1, +5, +10, +20, +30, +45, +60, +75, and +105 minutes.

Table 1
Characteristics of the male participants.

	Individuals (N=29)
Demographic data	
Age (years)	24 (4)
Body mass index (kg/m^2)	22.9 (1.6)
Smoking, n (%)	3 (10)
Psychological Assessment	
BDI	5.62 (4.67)
SCL Global Severity Index	.36 (.29)
PSS	22.24 (6.78)
TICS-SCSS	12.10 (6.26)
FFKA - Total activity (min/day), M (SD)	219.07 (149.58)

Data are presented as mean (standard deviation)
BDI Beck Depression Inventory, *FFKA* Freiburg Questionnaire on Physical Activity, *PSS* Perceived Stress Scale, *SCL* Symptom-Check-List-90-R, *SCSS* Subscale of Chronic Stress, *TICS* Trier Inventory of Chronic Stress.

Table 2
BDNF, cortisol, and subjective appraisal during rest and in response to the Trier Social Stress Test.

	Healthy Men (N=29)			
	Resting Condition	TSST	Dependent Student *t*-test	
Derived BDNF parameters (pg/mL)	M (SD)	M (SD)	*t*	*p*
Peak	33565 (10566)	37677 (10881)	4.536	≤.001 (*d* =.84)
Delta $_{Peak\text{-}Baseline}$	4264 (5459)	7673 (5488)	2.514	≤.01 (*d* =.47)
AUC_I	21881 (126123)	99503 (104316)	2.555	≤.01 (*d* =.47)
Derived cortisol parameters (ng/mL)				
Peak	57.31 (15.88)	92.20 (24.76)	7.831	≤.001 (*d* = 1.47)
Delta $_{Peak\text{-}Baseline}$	4.96 (8.37)	40.08 (27.31)	6.736	≤.001 (*d* = 1.27)
AUC_I	−90.23 (273.66)	757.66 (689.28)	5.870	≤.001 (*d* = 1.11)
Subjective Appraisal				
PASA - Stress index	−2.68 (1.28)	−0.54 (1.39)	7.663	≤.001 (*d* = −1.41)
VAS	41.35 (11.23)	58.51 (9.42)	8.903	≤.001 (*d* = −1.65)

AUC_I incremental area under the curve with respect to increase, *d* Cohens d, *M* Mean, *PASA* Primary Appraisal Secondary Appraisal, *SD* Standard Deviation, *VAS* Visual Analogue Scale.

2.3. Blood analytics

Blood samples were collected in serum monovettes (S-Monovette® 7.5 mL Z, Sarstedt, Nümbrecht, Germany). After blood collection, the monovettes were left at room temperature for 30 min to allow the blood to coagulate. The monovettes were then centrifuged at 2500 g for 10 min at 20°C, divided into aliquots and stored at −80°C. BDNF concentration were determined by duplicate analysis using an enzyme-linked immunosorbent assay (ELISA) (Human Free BDNF Quantikine ELISA Kit–R&D Systems Europe, Ltd. Abingdon, United Kingdom). The detection limit of BDNF was 20–42,580 pg/mL. The intra- und inter-assay coefficients of variation of BDNF analyses were 5.0 % and 9.0 %, respectively. Serum cortisol concentrations were determined by single analysis and quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (IBL International GmbH, Germany). The detection limit of cortisol was 4.03–800 ng/mL with an analytical sensitivity of 3.79 ng/mL. The intra- und inter-assay coefficients of variation of cortisol analyses were 5.4 % and 6.6 %, respectively.

2.4. Questionnaires

The Beck Depression Inventory (BDI; (Beck et al., 1996)) was used to assess the severity of depression. The inventory is based on 21 items with a four-point rating scale from 0 to 3. The total score ranges from 0 and 63, with a higher total score indicating more depressive symptoms. The Perceived Stress Scale (PSS; (Cohen et al., 1983)) measures the level of stressful situations in one's life during the previous month. The questionnaire consists of 14 items on a 5-point scale ranging from 1 'never' to 5 'very often'. The Global Severity Index (GSI) of the Symptom Checklist-90-Revised (SCL-90-R; (Derogatis, 1977)) was used to measure the perceived impairment through physical and psychological symptoms. The screening subscale (SCSS) of the Trier Inventory for Chronic Stress (TICS), developed by Schulz et al. (2004), was used to assess the level of chronic stress experienced in the previous three months. Eleven items have to be answered on a five-point rating scale ranging from 'never' (0) to 'very often' (4). The Freiburg Questionnaire on Physical Activity (FFKA; (Frey et al., 1999)) was used to evaluate daily total physical activity.

2.5. Statistical analysis

A power analysis calculated with the G*power program (version: 3.1.9.2.) (Faul et al., 2007) showed that to expect a medium effect size of Cohen's f =.25 for the outcome measure of BDNF, using a two-way MIXED ANOVA for repeated measures as the statistical test to prove interaction of within-factor time (measurement points −1, +1, +5, +10, +20) and within-factor condition (stress vs. resting) with a significance level of p =.05 and power of 80 % (1-β =.80), a total sample size of n = 22 participants would be required. The BDNF and cortisol data were analyzed according to the normality of the distributions and, in case of non-normally distributed data, were subjected to logarithm naturalis transformations. Statistical analysis and visualization the data were performed with SPSS Statistics version 27 (IBM, Chicago, IL, USA) and Prism v.8.3.0 (GraphPad Software).

For the BDNF and cortisol response, the area under the curve with respect to increase (AUC_I) and the delta between peak and baseline (Δ Peak-Base) were calculated (Fekedulegn et al., 2007; Pruessner et al., 2003). All parameters (PASA, VAS, Cortisol-AUC_I, & Cortisol Δ Peak-Base) were analyzed by two-factorial MIXED ANOVA for repeated measurements with the within-factor condition (stress vs. resting) and within-factor time. Further post-hoc analyses with dependent student t-tests (Bonferroni correction) were performed to evaluate the differences along conditions and measurement points.

For the specification of the BDNF and cortisol stress reactivity and recovery during the stress condition, the area under the curve with respect to increase and decrease (AUC_I /AUC_D) were calculated using the formulas of Pruessner et al. (2003). Stress reactivity was defined as the incremental area under the curve from baseline to peak value. Stress recovery was defined as the decremental area under the curve from the peak value to the last measurement point. Both areas under the curve were calculated individually for each subject based on the individual peak values. The association between BNDF and cortisol stress reactivity and recovery was tested using Pearson's correlation test.

Regression was calculated to predict the influence of the subjective chronic stress on the basal serum BNDF concentration (-1 min time point) of the resting and stress condition.

3. Results

3.1. BDNF responses to acute stress compared to rest

Any influence of subjective physical activity on BDNF levels could be excluded (ANCOVA interaction effect time x condition x physical activity: $F_{(4,\ 108)} = 4.614$, p =.22). BDNF levels were comparable before both the stress and the resting condition (-1 min: t (28) =.433, p =.67, Fig. 1). ANOVA results indicated a significant effect of time over the five measurement points ($F_{(2.922,\ 81.820)} = 8.110$, $p \leq .001$, $\eta 2$ =.225). There was a significant main effect of condition on BDNF concentration, with higher values in the stress induction condition compared to the resting condition ($F_{(1,\ 28)} = 6.506$, $p \leq .05$, $\eta 2$ =.189) and a significant interaction effect time x condition ($F_{(4,\ 112)} = 5.532$, $p \leq .001$, $\eta 2$ =.165). In line, peak concentrations in BDNF (t (28) = 4.536, $p \leq .001$, d =.84), the absolute change in BDNF (t (28) = 2.514, $p \leq .01$, d =.47), and the incremental AUC_I (t (28) = 2.555, $p \leq .01$, d = −.47) were higher in the stress condition compared to the resting condition.

3.2. Cortisol responses to acute stress compared to rest

Resting serum cortisol was comparable between the two study days

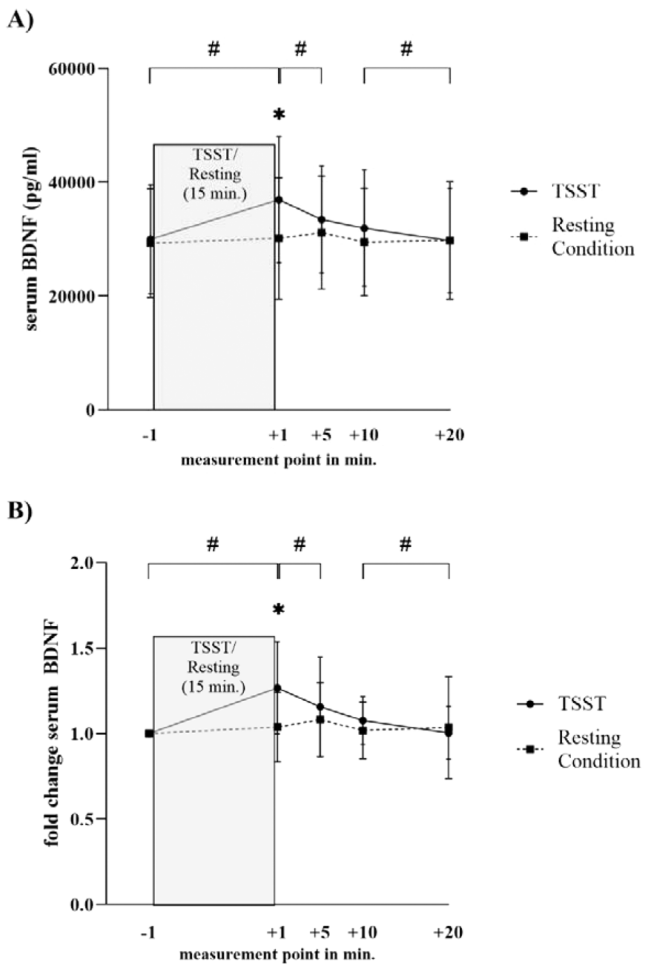


Fig. 1. BDNF concentration during Trier Social Stress Test and resting condition in healthy men (N=29). Presented are means +/- SD. *: significant difference (p ≤ 0.05) between TSST and resting condition analyzed by post-hoc analyses with dependent student t-tests (Bonferroni correction). #: significant differences (p ≤ 0.05) between consecutive measurement points analyzed by post-hoc analyses with dependent student t-tests (Bonferroni correction).

(-1 min: t (27) = −.089, p =.93, Fig. 2). There were significant time ($F_{(3.691,\ 99.653)}$ = 63.186, p ≤.001, $\eta 2$ =.701), condition ($F_{(1,\ 27)}$ = 40.111, p ≤.001, $\eta 2$ =.598), and time x condition effect ($F_{(4.125,\ 111.386)}$ = 16.947, p ≤.001, $\eta 2$ =.386) on serum cortisol. Peak cortisol (t (27) = 7.831, p ≤.001, d = 1.47), the absolute change in cortisol (t (27) = 6.736, p ≤.001, d = 1.27), as well as the incremental AUC_I (t (27) = 5.870, p ≤.001, d = 1.11) were higher in the stress condition compared to the resting condition.

3.3. Psychological responses to stress induction versus rest

Analyses of the two questionnaires showed that the TSST was successful in inducing stress: male participants showed significantly higher scores in the VAS (t (28) = 7.633, p ≤.001, d = 1.41) and on the tertiary scale 'stress index' of the PASA (t (28) = 8.903, p ≤.001, d = 1.65).

3.4. Association between BDNF and cortisol stress reactivity and their recoveries

Regarding to the relationship between BDNF and cortisol reactivity/recovery patterns, a negative significant correlation was found between cortisol stress reactivity and BDNF stress recovery (r (26) = −.39, p ≤.05). No significant correlation was found between BDNF and cortisol stress recovery nor between BDNF stress reactivity and cortisol stress reactivity/recovery (see Table 3). With regard to the psychological measures, there was only a significant correlation between cortisol stress reactivity and the perceived stress scale (r (26) = −.42, p ≤.05; see Supplemental Table 1).

3.5. Influence of chronic stress on basal BDNF

Chronic stress is a significant predictor of basal serum BNDF concentrations in both conditions (stress: $F_{(1,27)}$ = 4.320, Adj. R^2 =.14, p ≤.05; resting: $F_{(1,27)}$ = 4.483, Adj. R^2 =.14, p ≤.05). A higher chronic stress is associated with an increase in basal serum BDNF concentration and vice versa.

4. Discussion

We assessed the responses in BDNF and cortisol stress to a standardized stress task as well as their recovery. The applied stressor was sufficient to induce robust increases in BDNF and cortisol, which was not the case in the control condition. Interestingly, a strong cortisol response to stress was linked to an accelerated BDNF decline post-stress. Furthermore, higher chronic stress levels were linked to lower basal BDNF.

The stress-induced increases in BDNF and cortisol in our current study are well in line with earlier studies that also applied the TSST (Hermann et al., 2021; Linz et al., 2019; Meng et al., 2011). The activation of the acute stress system activation triggers a cascade of physiological changes, including the release of the stress hormone cortisol and the upregulation of BDNF. The latter likely serves as a neuroprotective mechanism to maintain brain health and cognitive function during stress (Miranda et al., 2019).

The most important finding of our current study is the link between the cortisol response to stress and the subsequent BDNF recovery. This supports the hypothesis of Linz et al. (2019) of an antagonistic relation between cortisol and BDNF in response to stress.

While animal models demonstrated an increase in both cortisol and hippocampal *Bdnf* mRNA expression in response to short-term stressors (Neeley et al., 2011). However, studies in animals furthermore demonstrated that elevated stress cortisol levels decrease hippocampal *Bdnf* mRNA expression (Hansson et al., 2006; Lee et al., 2008). This mechanistic data together with our findings and those from Linz et al. (2019), highlight a dynamic relationship between cortisol and BDNF during stress. Initially, both factors increase in response to stress. Yet, as the stress response concludes, GC signaling could suppress BDNF. One possible explanation might be that this pattern suggests an adaptive mechanism: an initial boost in BDNF could enhance cognitive function and neural plasticity during stress, while its subsequent suppression by GC signaling may help conserve energy and return the system to a baseline state once the stressor has passed (Egeland et al., 2015; Suri and Vaidya, 2013; Tsigos and Chrousos, 2002). By conserving energy and reducing metabolic demands, this mechanism might protect the organism from the harmful effects of prolonged stress, thus balancing the need for immediate cognitive enhancement with long-term homeostasis. A further explanation might be that the GC-induced suppression of BDNF during recovery could be disadvantageous, potentially impairing neural protection and plasticity at a time when these processes are crucial for recovery. Moreover, the GC-induced suppression of BDNF during recovery may hinder critical processes like neural protection and plasticity, which are essential for effective recovery and long-term resilience. Further research is necessary to fully understand the implications of GC-BDNF interactions during the stress response and recovery phase.

Our data provide further support that high chronic stress perception might be linked to low basal serum BDNF levels. A comparable cross-sectional result of lower basal BDNF levels and higher psychological job stress was also observed in hospital employees (Mitoma et al., 2008). There is also evidence of decreased BDNF levels in individuals with

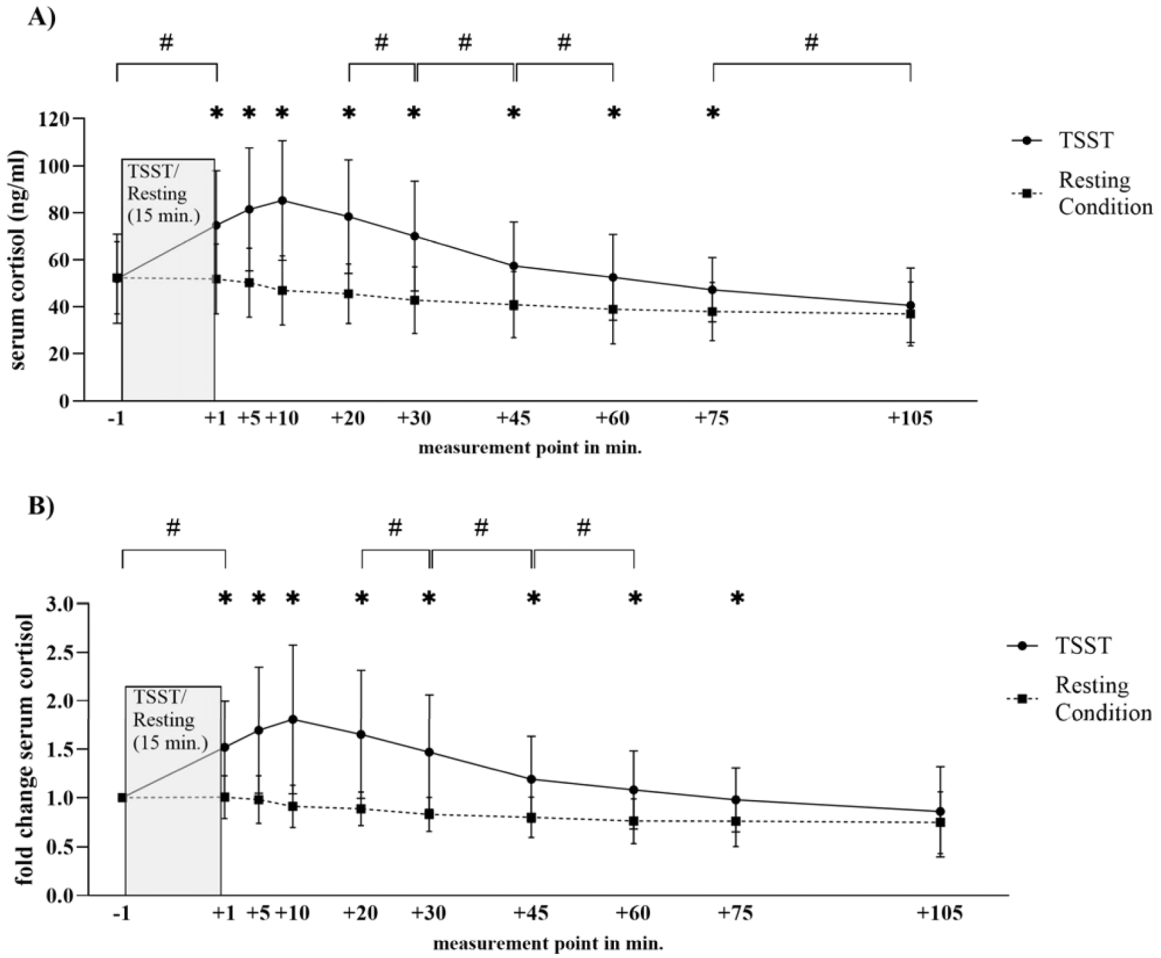


Fig. 2. Cortisol concentration during Trier Social Stress Test and resting condition in healthy men (N=29). Presented are means +/- SD. *: significant difference ($p \leq 0.05$) between TSST and resting condition analyzed by post-hoc analyses with dependent student t-tests (Bonferroni correction). #: significant differences ($p \leq 0.05$) between consecutive measurement points analyzed by post-hoc analyses with dependent student t-tests (Bonferroni correction).

Table 3
Pearson's correlations (r) between BNDF and cortisol stress reactivity and stress recovery.

	BDNF stress reactivity AUC_I	**BDNF stress recovery AUC_D**
Cortisol stress reactivity AUC_I	.35, $p = .07$	−.39, $p \leq .05$
Cortisol stress recovery AUC_D	−.24, $p = .11$	.13, $p = .25$

Data are presented as coefficient, *p* values; N=28
AUC_I incremental area under the curve with respect to increase, AUC_D decremental area under the curve with respect to decrease

stress-related disorders (Brunoni et al., 2008; Schmitt et al., 2016). McEwen's allostatic load model suggests that ongoing stress harms brain structures and overburdens the stress system, leading to prolonged high cortisol levels (McEwen, 2017, 1998). These repeated elevations in cortisol could decrease BDNF, affect neurogenesis, and contribute to neurodegenerative diseases (Numakawa et al., 2017). Understanding the effects of chronic stress on BDNF may help to develop interventions and therapeutic strategies to mitigate the negative effects of chronic stress on the brain and overall well-being (de Lima et al., 2022; Puhlmann et al., 2021).

A major strength of this study is the within-subjects design using the standardized and reliable psychosocial stress test (TSST) and a resting control condition regarding to the circadian rhythm of BDNF (Begliuomini et al., 2008). In addition, there was a frequent assessment of serum BDNF and cortisol to accurately measure stress-induced dynamics, including peaks and recovery processes.

However, the present study has some limitations. Given the known age- and gender- specific differences in BDNF levels (Chan and Ye, 2017; Oh et al., 2016), we limited our study to young male participants. Thus, further research need to test our findings in women and older persons. In the present study serum BDNF levels were measured, which is a common highly reproducible method for BDNF quantification. It must be considered that serum BDNF do not directly reflect BDNF regulation in the hippocampus, because BDNF in the serum primarily originates from peripheral sources like platelets (Klein et al., 2011). Furthermore, factors such as stress and physical activity can influence serum BDNF levels, challenging their interpretation in relation to hippocampal BDNF regulation (Filimonova et al., 2023; Puhlmann et al., 2021). Serum cortisol analyses were performed with the precise and reliable ELISA procedure. However, it must be taken into account that cortisol concentrations were determined using single analyses and not, as recommended, using duplicate analyses, which may affect the measurement accuracy and reliability.

In conclusion, the present study showed that acute psychosocial stress increases serum BDNF and cortisol. The rise in cortisol appears to regulate the decline in BDNF post-stress. Chronic stress could lead to significant changes in BDNF in the circulation and presumably also in the brain. These finding suggest a potential link between reduced neurogenesis and an increased risk of neurodegenerative conditions in

persons experiencing chronic stress. Future research could explore this connection further, with a focus on developing interventions that may counteract the negative effect of chronic stress on BDNF, potentially offering long-term benefits for brain health and overall well-being.

Ethics Statement

The studies involving human participants were reviewed and approved by Local Ethics Committee of the Landesärztekammer Rheinland-Pfalz. The participants provided their written informed consent to participate in this study.

Author Contributions

BH: substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; Drafting the work. MH: interpretation of data for the work; revising the work critically for important intellectual content WB: interpretation of data for the work; final approval of the version to be published. KP: substantial contributions to the conception and design of the work; revising the work critically for important intellectual content; final approval of the version to be published. All authors revised the manuscript and approved its final version.

Funding

This research received no external funding.

CRediT authorship contribution statement

Wilhelm Bloch: Writing – review & editing, Supervision. **Katja Petrowski:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Martin Heni:** Writing – review & editing, Supervision. **Benedict Herhaus:** Writing – original draft, Project administration, Methodology, Formal analysis, Data curation.

Declaration of Competing Interest

The authors certify that they have NO conflict of interest to disclose.

Acknowledgments

We thank the medical PhD students J.K., A.B., S.T., L.B., S.B. & E.K. for assisting with data collection.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2024.107192.

References

Acheson, A., Conover, J.C., Fandl, J.P., DeChiara, T.M., Russell, M., Thadani, A., Squinto, S.P., Yancopoulos, G.D., Lindsay, R.M., 1995. A BDNF autocrine loop in adult sensory neurons prevents cell death. Nature 374, 450–453. https://doi.org/10.1038/374450a0.

APA, 2000. Diagnostic and Statistical Manual of Mental disorders. DSM-IV-TR, 4th ed. American Psychiatric Association, Washington DC.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Beck Depression Inventory: second edition manual, 2nd ed. The Psychological Corporation, San Antonio, TX.

Begliuomini, S., Lenzi, E., Ninni, F., Casarosa, E., Merlini, S., Pluchino, N., Valentino, V., Luisi, S., Luisi, M., Genazzani, A.R., 2008. Plasma brain-derived neurotrophic factor daily variations in men: correlation with cortisol circadian rhythm. J. Endocrinol. 197, 429–435. https://doi.org/10.1677/JOE-07-0376.

Binder, E.B., Nemeroff, C.B., 2010. The CRF system, stress, depression and anxiety—insights from human genetic studies. Mol. Psychiatry 15, 574–588. https://doi.org/10.1038/mp.2009.141.

Brunoni, A.R., Lopes, M., Fregni, F., 2008. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. Int. J. Neuropsychopharmacol. 11, 1169–1180. https://doi.org/10.1017/S1461145708009309.

Canals, J., Colomina, M.T., Domingo, JoséL., Domènech, E., 1997. Influence of smoking and drinking habits on salivary cortisol levels. Pers. Individ Dif. 23, 593–599. https://doi.org/10.1016/S0191-8869(97)00093-7.

Caspi, A., Moffitt, T.E., Thornton, A., Freedman, D., Amell, J.W., Harrington, H., Smeijers, J., Silva, P.A., 1996. The Life History Calendar: A Research and clinical assessment method for collecting retrospective event-history data. Int. J. Methods Psychiatr. Res 6, 101–114. https://doi.org/10.1002/(SICI)1234-988X(199607)6:2<101::AID-MPR156>3.3.CO;2-E.

Castren, E., Thoenen, H., Lindholm, D., 1995. Brain-derived neurotrophic factor messenger RNA is expressed in the septum, hypothalamus and in adrenergic brain stem nuclei of adult rat brain and is increased by osmotic stimulation in the paraventricular nucleus. Neuroscience 64, 71–80. https://doi.org/10.1016/0306-4522(94)00386-J.

Chan, C.B., Ye, K., 2017. Sex differences in brain-derived neurotrophic factor signaling and functions. J. Neurosci. Res. 95, 328–335. https://doi.org/10.1002/jnr.23863.

Chrousos, G.P., Gold, P.W., 1992. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA 267, 1244–1252.

Chu, B., Marwaha, K., Sanvictores, T., Ayers, D., 2021. StatPearls. Physiology, Stress Reaction. StatPearls Publishing.

Cohen, S., Kamarck, T., Mermelstein, R., 1983. A global measure of perceived stress. J. Health Soc. Behav. 24, 385. https://doi.org/10.2307/2136404.

de Lima, N.S., De Sousa, R.A.L., Amorim, F.T., Gripp, F., Diniz e Magalhães, C.O., Henrique Pinto, S., Peixoto, M.F.D., Monteiro-Junior, R.S., Bourbeau, K., Cassilhas, R.C., 2022. Moderate-intensity continuous training and high-intensity interval training improve cognition, and BDNF levels of middle-aged overweight men. Metab. Brain Dis. 37, 463–471. https://doi.org/10.1007/s11011-021-00859-5.

Derogatis, L., 1977. Administration, scoring, and procedures manual for the SCL-90-R. Clinical Psychometric Research, Baltimore.

Egeland, M., Zunszain, P.A., Pariante, C.M., 2015. Molecular mechanisms in the regulation of adult neurogenesis during stress. Nat. Rev. Neurosci. 16, 189–200. https://doi.org/10.1038/nrn3855.

Erickson, K.I., Prakash, R.S., Voss, M.W., Chaddock, L., Heo, S., McLaren, M., Pence, B. D., Martin, S.A., Vieira, V.J., Woods, J.A., McAuley, E., Kramer, A.F., 2010. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. J. Neurosci. 30, 5368–5375. https://doi.org/10.1523/JNEUROSCI.6251-09.2010.

Faul, F., Erdfelder, E., Lang, A.-G., Buchner, A., 2007. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav. Res. Methods 39, 175–191. https://doi.org/10.3758/BF03193146.

Fekedulegn, D.B., Andrew, M.E., Burchfiel, C.M., Violanti, J.M., Hartley, T.A., Charles, L. E., Miller, D.B., 2007. Area under the curve and other summary indicators of repeated waking cortisol measurements. Psychosom. Med. 69, 651–659. https://doi.org/10.1097/PSY.0b013e31814c405c.

Filimonova, E.A., Pashkov, A.A., Moysak, G.I., Tropynina, A.Y., Zhanaeva, S.Y., Shvaikovskaya, A.A., Akopyan, A.A., Danilenko, K.V., Aftanas, L.I., Tikhonova, M.A., Rzaev, J.A., 2023. Brain but not serum BDNF levels are associated with structural alterations in the hippocampal regions in patients with drug-resistant mesial temporal lobe epilepsy. Front. Neurosci. 17. https://doi.org/10.3389/fnins.2023.1217702.

Frey, I., Berg, A., Grathwohl, D., Keul, J., 1999. Freiburger Fragebogen zur körperlichen Aktivität-Entwicklung, Prüfung und Anwendung. Soz. - und Pr. äventivmedizin SPM 44, 55–64. https://doi.org/10.1007/BF01667127.

Gaab, J., 2009. PASA - Primary appraisal secondary appraisal. Ein Fragebogen zur Erfassung von situationsbezogenen kognitiven Bewertungen. Verhaltenstherapie 19, 114–115. https://doi.org/10.1159/000223610.

Givalois, L., Naert, G., Rage, F., Ixart, G., Arancibia, S., Tapia-Arancibia, L., 2004. A single brain-derived neurotrophic factor injection modifies hypothalamo–pituitary–adrenocortical axis activity in adult male rats. Mol. Cell. Neurosci. 27, 280–295. https://doi.org/10.1016/j.mcn.2004.07.002.

Gray, J.D., Milner, T.A., McEwen, B.S., 2013. Dynamic plasticity: the role of glucocorticoids, brain-derived neurotrophic factor and other trophic factors. Neuroscience 239, 214–227. https://doi.org/10.1016/j.neuroscience.2012.08.034.

Hansson, A.C., Sommer, W.H., Metsis, M., Stromberg, I., Agnati, L.F., Fuxe, K., 2006. Corticosterone actions on the hippocampal brain-derived neurotrophic factor expression are mediated by exon IV promoter. J. Neuroendocr. 18, 104–114. https://doi.org/10.1111/j.1365-2826.2005.01390.x.

Herman, J.P., McKlveen, J.M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., Scheimann, J., Myers, B., 2016. Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. in: Comprehensive Physiology. Wiley, pp. 603–621. https://doi.org/10.1002/cphy.c150015.

Hermann, R., Schaller, A., Lay, D., Bloch, W., Albus, C., Petrowski, K., 2021. Effect of acute psychosocial stress on the brain-derived neurotrophic factor in humans – a randomized cross within trial. Stress 24, 442–449. https://doi.org/10.1080/10253890.2020.1854218.

Holsboer, F., 2000. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 23, 477–501. https://doi.org/10.1016/S0893-133X(00)00159-7.

Jeanneteau, F.D., Lambert, W.M., Ismaili, N., Bath, K.G., Lee, F.S., Garabedian, M.J., Chao, M. v, 2012. BDNF and glucocorticoids regulate corticotrophin-releasing hormone (CRH) homeostasis in the hypothalamus. Proc. Natl. Acad. Sci. 109, 1305–1310. https://doi.org/10.1073/pnas.1114122109.

Kirschbaum, C., Pirke, K.M., Hellhammer, D.H., 1993. The 'Trier Social Stress Test'–a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28, 76–81. https://doi.org/10.1159/000119004.

Klein, A.B., Williamson, R., Santini, M.A., Clemmensen, C., Ettrup, A., Rios, M., Knudsen, G.M., Aznar, S., 2011. Blood BDNF concentrations reflect brain-tissue BDNF levels across species. Int J. Neuropsychopharmacol. 14, 347–353. https://doi.org/10.1017/S1461145710000738.

Lee, B.-H., Kim, Y.-K., 2010. The roles of BDNF in the pathophysiology of major depression and in antidepressant treatment. Psychiatry Invest. 7, 231. https://doi.org/10.4306/pi.2010.7.4.231.

Lee, T., Saruta, J., Sasaguri, K., Sato, S., Tsukinoki, K., 2008. Allowing animals to bite reverses the effects of immobilization stress on hippocampal neurotrophin expression. Brain Res. 1195, 43–49. https://doi.org/10.1016/j.brainres.2007.12.013.

Linz, R., Puhlmann, L.M.C., Apostolakou, F., Mantzou, E., Papassotiriou, I., Chrousos, G. P., Engert, V., Singer, T., 2019. Acute psychosocial stress increases serum BDNF levels: an antagonistic relation to cortisol but no group differences after mental training. Neuropsychopharmacology 44, 1797–1804. https://doi.org/10.1038/s41386-019-0391-y.

McEwen, B.S., 2017. Neurobiological and systemic effects of chronic stress, 247054701769232 Chronic Stress 1. https://doi.org/10.1177/2470547017692328.

McEwen, B.S., 1998. Protective and damaging effects of stress mediators. N. Engl. J. Med. 338, 171–179. https://doi.org/10.1056/NEJM199801153380307.

Meng, D., Wu, T., Rao, U., North, C.S., Xiao, H., Javors, M.A., Adinoff, B., 2011. Serum NPY and BNDF response to a behavioral stressor in alcohol-dependent and healthy control participants. Psychopharmacol. (Berl.) 218, 59–67. https://doi.org/10.1007/s00213-011-2414-1.

Miranda, M., Morici, J.F., Zanoni, M.B., Bekinschtein, P., 2019. Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain. Front. Cell Neurosci. 13. https://doi.org/10.3389/fncel.2019.00363.

Mitoma, M., Yoshimura, R., Sugita, A., Umene, W., Hori, H., Nakano, H., Ueda, N., Nakamura, J., 2008. Stress at work alters serum brain-derived neurotrophic factor (BDNF) levels and plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) levels in healthy volunteers: BDNF and MHPG as possible biological markers of mental stress? Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 679–685. https://doi.org/10.1016/j.pnpbp.2007.11.011.

Mori, Y., Tsuji, M., Oguchi, T., Kasuga, K., Kimura, A., Futamura, A., Sugimoto, A., Kasai, H., Kuroda, T., Yano, S., Hieda, S., Kiuchi, Y., Ikeuchi, T., Ono, K., 2021. Serum BDNF as a potential biomarker of Alzheimer's disease: verification through assessment of serum, cerebrospinal fluid, and medial temporal lobe atrophy. Front. Neurol. 12. https://doi.org/10.3389/fneur.2021.653267.

Murakami, S., Imbe, H., Morikawa, Y., Kubo, C., Senba, E., 2005. Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly. Neurosci. Res. 53, 129–139. https://doi.org/10.1016/j.neures.2005.06.008.

Neeley, E.W., Berger, R., Koenig, J.I., Leonard, S., 2011. Strain dependent effects of prenatal stress on gene expression in the rat hippocampus. Physiol. Behav. 104, 334–339. https://doi.org/10.1016/j.physbeh.2011.02.032.

Numakawa, T., Odaka, H., Adachi, N., 2017. Actions of brain-derived neurotrophic factor and glucocorticoid stress in neurogenesis. Int. J. Mol. Sci. 18, 2312. https://doi.org/10.3390/ijms18112312.

Oh, H., Lewis, D.A., Sibille, E., 2016. The role of BDNF in age-dependent changes of excitatory and inhibitory synaptic markers in the human prefrontal cortex. Neuropsychopharmacology 41, 3080–3091. https://doi.org/10.1038/npp.2016.126.

Pruessner, J.C., Kirschbaum, C., Meinlschmid, G., Hellhammer, D.H., 2003. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 28, 916–931. https://doi.org/10.1016/S0306-4530(02)00108-7.

Puhlmann, L., Vrtička, P., Linz, R., Papassotiriou, I., Chrousos, G.P., Engert, V., Singer, T., 2021. Serum BDNF increase and the role of cortisol reduction following contemplative mental training. Psychoneuroendocrinology 131, 105510. https://doi.org/10.1016/j.psyneuen.2021.105510.

Schmitt, K., Holsboer-Trachsler, E., Eckert, A., 2016. BDNF in sleep, insomnia, and sleep deprivation. Ann. Med. 48, 42–51. https://doi.org/10.3109/07853890.2015.1131327.

Schulz, P., Schlotz, W., Becker, P., 2004. Trierer Inventar zum chronischen Stress (TICS). Hogrefe, Göttingen.

Suri, D., Vaidya, V.A., 2013. Glucocorticoid regulation of brain-derived neurotrophic factor: Relevance to hippocampal structural and functional plasticity. Neuroscience 239, 196–213. https://doi.org/10.1016/j.neuroscience.2012.08.065.

Tapia-Arancibia, L., Rage, F., Givalois, L., Arancibia, S., 2004. Physiology of BDNF: focus on hypothalamic function. Front. Neuroendocr. 25, 77–107. https://doi.org/10.1016/j.yfrne.2004.04.001.

Tsigos, C., Chrousos, G.P., 2002. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. J. Psychosom. Res. 53, 865–871. https://doi.org/10.1016/S0022-3999(02)00429-4.

WHO, 2001. The World Health Report 2001. Mental Health: New Understanding. WHO, New Hope. https://doi.org/10.1007/s001270170010.

Wilson, R.S., Schneider, J.A., Boyle, P.A., Arnold, S.E., Tang, Y., Bennett, D.A., 2007. Chronic distress and incidence of mild cognitive impairment. Neurology 68, 2085–2092. https://doi.org/10.1212/01.wnl.0000264930.97061.82.

Wittchen, H.U., Zaudig, M., Fydrich, T., 1997. Strukturiertes Klinisches interview für DSM-IV. Hogrefe. Göttingen.

Zigova, T., Pencea, V., Wiegand, S.J., Luskin, M.B., 1998. Intraventricular administration of BDNF increases the number of newly generated neurons in the adult olfactory bulb. Mol. Cell. Neurosci. 11, 234–245. https://doi.org/10.1006/mcne.1998.0684.