Journal of Affective Disorders 365 (2024) 178–184

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

# Psychological resilience is positively correlated with Habenula volume

Qi Dai [a], Yusuke Kyuragi [a], Halwa Zakia [a], Naoya Oishi [a], Lichang Yao [a], Zhilin Zhang [a,b], Luyao Wang [c], Jiajia Yang [d], Toshiya Murai [a], Hironobu Fujiwara [a,e,f,*]

[a] Department of Neuropsychiatry, Graduate School of Medicine, University of Kyoto, Kyoto, Japan
[b] Research Center for Medical Artificial Intelligence, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, Guangdong, China
[c] School of Life Science, Shanghai University, Shanghai, China
[d] Graduate School of Interdisciplinary Science and Engineering in Health Systems, Okayama University, Japan.
[e] Artificial Intelligence Ethics and Society Team, RIKEN Center for Advanced Intelligence Project, Saitama, Japan
[f] The General Research Division, Osaka University Research Center on Ethical, Legal and Social Issues, Kyoto, Japan

ARTICLE INFO

*Keywords:*
Psychological resilience
Connor-Davidson Resilience Scale
T1-weighted image
Habenula volume
Depressive tendency
Subclinical depressive

ABSTRACT

*Background:* Psychological resilience is defined as the process and outcome of individuals' successful adaptation to challenging life experiences. The Habenula (Hb) is known to be involved in the stress response; however, the relationship between Hb volume and resilience in humans remains unclear. This study investigated the correlation among resilience, Hb volume, and depressive tendencies in adults.

*Methods:* Hb volumes were assessed using deep learning techniques applied to 110 healthy participants. Resilience and depression were evaluated using the Connor-Davidson Resilience Scale and Beck Depression Inventory-II, respectively. We examined the relationship between Hb volume and resilience and assessed the mediating effects of resilience on the relationship between Hb volume and depressive tendencies.

*Results:* Correlation analysis revealed a positive correlation between resilience and Hb volume (partial $r = 0.176$, $p = 0.001$), which was more pronounced in women (partial $r = 0.353$, $p = 0.003$). Hb volumes on the left and right sides exhibited significant lateralization (LI = 0.031, 95 % CI = [0.016, 0.046]). Despite Hb asymmetry, lateralization was not significantly associated with resilience. The mediation analysis shows significant indirect effect of resilience on the relationship between Hb volume and depressive tendencies ($\beta = -0.093$, 95%CI = [−0.189, −0.019]).

*Conclusion:* This study found that populations with lower resilience have smaller Hb volume. Previous research has shown that Hb volume decreased with the increasing severity of depression symptoms in patients. Our findings support this view and extend it to a population that has not been clinically diagnosed with depression. Additionally, we found that psychological resilience can be predicted by Hb volume and may serve as a mediating factor indirectly affecting depressive tendencies, even in healthy individuals.

*Limitations:* Due to its cross-sectional design, this study was unable to analyze dynamic changes in Hb volume during the process of resilience adaptation.

## 1. Introduction

Depression is a common, severely disabling, and recurrent mental disorder that significantly limits individuals' psychosocial functioning and diminishes the quality of their life. Early identification and intervention could serve as an effective initial step for harm reduction and prevention. Evidence suggests that psychological resilience (hereafter referred to as resilience) is a potential tool for screening individuals for depression (Miroševič et al., 2019). Resilience is defined as individuals' ability to successfully overcome negative conditions and adapt to them even when these individuals are faced with difficult conditions. Resilience has also been recognized as a measure of stress coping and a process through which individuals 'bounce back' from a difficult experience (Sisto et al., 2019). Accordingly, resilience is a significant target for the treatment of anxiety and depression (Connor and Davidson, 2003). Previous studies found a negative correlation between resilience and the risk of post-traumatic stress disorder, anxiety, and depressive symptoms (Jones-Bitton et al., 2020). Kermott et al. (2019) pointed out

* Corresponding author at: Department of Neuropsychiatry, Graduate School of Medicine, University of Kyoto, Kyoto, Japan.
*E-mail address:* hirofuji@kuhp.kyoto-u.ac.jp (H. Fujiwara).

https://doi.org/10.1016/j.jad.2024.08.012
Received 6 May 2024; Received in revised form 2 July 2024; Accepted 9 August 2024
Available online 14 August 2024

that the depression-prevalence rate of individuals with lower resilience were four times higher than those with higher resilience. Moreover, resilience was positively correlated with individuals' subjective well-being and negatively correlated with their perceived stress (Kermott et al., 2019). Thus, examining the neurobiological foundation of resilience helps explain how individuals cultivate resilience through adverse experiences. This finding holds particular clinical significance for understanding pathological mechanisms triggered by stress that leads to depressive symptoms. It is also beneficial for screening tendencies towards depression in the general population.

Recently, research has shown that the habenula (Hb) can play a significant role in regulating resilience (Li et al., 2021). Hb has been considered a key brain area involved in handling stress and depressive symptoms (Ely et al., 2016; Proulx et al., 2014). Hb is a bilateral nuclear cluster located in the dorsal diencephalon. Neurons in the lateral Hb neurons encode various stimuli, including those for rewards, omission, and punishment (Baker et al., 2016). A previous study found that stress induces a negative shift in the signaling of rewards in the lateral Hb, and the repeated occurrence of such effects contributes to the pathogenesis of depression (Shabel et al., 2019). Animal-model studies have suggested that Hb structure dynamically responds to constantly-changing environmental and contextual conditions (Mizumori and Baker, 2017). For instance, increased Hb metabolism has been observed in the depression of rodent models, indicating its involvement in altered monoaminergic transmission and stress-related behaviors (Shumake et al., 2003). Studies involving humans have discovered an elevation in regional cerebral blood flow in the Hb that correlates directly with depressed mood ratings and inversely with plasma-tryptophan levels in individuals with major depressive disorder (MDD) (Morris et al., 1999). A case report of patients with treatment-resistant MDD also described symptom improvement following deep brain stimulation (DBS) targeting the Hb (Kiening and Sartorius, 2013). Furthermore, as part of extensive research on the relationship between Hb and depression, an increasing number of studies have focused on Hb volume. A study on patients with MDD found an association between smaller Hb volume and more pronounced anhedonic symptoms (R. Lawson et al., 2017). In a structural neuroimaging study of Savitz et al. (2011), a decrease in total Hb volume was observed exclusively in female patients with MDD. A postmortem study on Hb volume in patients with depression revealed significant reductions in both medial and lateral Hb volume, with the left Hb volume being slightly smaller than the right one (Ranft et al., 2010). These findings indicate that Hb volume in patients with depression is smaller than that in healthy individuals. However, in individuals who have not yet developed depression or are considered subclinical, the existence of an association between resilience and Hb volume remains unclear and in this population the early identification and prevention of depression are crucial. Understanding the relationship between resilience and Hb volume can help identify individuals at higher risk of depression, thereby providing a basis for treatment and intervention strategies.

Because of the small size of the Hb, measuring its volume in healthy individuals using magnetic resonance imaging (MRI) is extremely challenging. In postmortem studies, the Hb has been reported to be approximately 32 $mm^3$ (Ahumada-Galleguillos et al., 2017; Ranft et al., 2010). Most anatomical MRI studies manually define Hb by exploiting the high signal intensity relative to the surrounding tissues in T1-weighted (T1w) images (Lawson et al., 2013; Savitz et al., 2011) or through semi-automated segmentation (Kim et al., 2016). These methods result in a challenging and highly subjective delineation of the Hb structure that lacks repeatability. Recently, Kyuragi et al. (2024) successfully utilized deep learning to create a fully automatic model for Hb in T1w 3 Tesla MR images. Compared with earlier studies on the Hb structure, this model demonstrated the highest reliability and effectiveness. Using this method, we can measure Hb volume in a healthy population, which contributes to the understanding of the correlation between Hb volume and resilience in individuals before the onset of depressive symptoms. Additionally, focusing on a population with non-depression disorder enables researchers to more comprehensively explore the influence of factors, such as sex differences and brain lateralization, on the relationship between Hb volume and resilience. This could be a more precise approach for investigating the relationship between resilience in healthy individuals and Hb volume.

Previous studies have identified the association between Hb volume and depression (Schmidt et al., 2017; Kyuragi et al., 2024). This study aimed to utilize the latest segmentation models to calculate Hb volume in healthy individuals. Additionally, we will investigate the correlation between Hb volume and resilience in healthy individuals and explore whether resilience can mediate the impact of Hb volume on the tendency of depression. We hypothesized a positive correlation between Hb volume and resilience, suggesting that individuals with larger Hb volumes may exhibit higher resilience, and enhanced resilience may indirectly reduce depressive tendencies.

## 2. Methods

### 2.1. Participants

A total of 121 healthy adults volunteered to participate in this cross-sectional study. Participants were recruited through advertisements and individual contact. The participants were enrolled from January 2016 to January 2019. Data were collected at the Kyoto University Hospital, Japan. The criteria for inclusion were that the participants were 18–60 years of age; had no prior psychiatric disorders or severe medical conditions, as confirmed by two licensed psychiatrists who evaluated them using the Structured Clinical Interview Non-Patient Edition (SCID-I/NP); had a normal intelligence quotient indicated by the normal Japanese Version of the Adult Reading Test (JART) (Matsuoka et al., 2006); and were right-handed, as indicated by the Japanese Version of the Edinburg Handedness Inventory (EHI) (Hatta and Hotta, 2008). Participants were excluded if they did not fill in the questionnaire completely or were deemed outliers in the analysis. All participants agreed to participate and provided their informed written consent before the study. This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine and conducted in accordance with the guidelines of the Declaration of Helsinki.

### 2.2. Psychological questionnaire

The Connor–Davidson Resilience Scale (CD-RISC) is a self-rating questionnaire used to assess individuals' degree of resilience (Connor and Davidson, 2003). It contains 25 items, and responses are rated on a 5-point Likert scale (0–4 points). Higher CD-RISC scores indicate greater resilience. The CD-RISC contains five factors (Connor and Davidson, 2003): Factor 1 reflects the notion of personal competence, high standards, and tenacity; Factor 2 corresponds to trust in one's instincts, tolerance of negative affect, and strengthening the effects of stress; Factor 3 relates to the positive acceptance of change and secure relationships; Factor 4 is related to control; and Factor 5 is related to spiritual influences. The CD-RISC has been validated across various cultures and languages (Alfuqaha, 2023; Awano et al., 2020; Yu and Zhang, 2007).

We used the Japanese version of the CD-RISC (Ito et al., 2009). The reliability and validity of the Japanese version of the CD-RISC has been examined and confirmed: Cronbach's alpha coefficient ($\alpha = 0.90$) and the test-retest correlation were sufficiently high to confirm reliability (Ito et al., 2009).

Furthermore, regarding the relationship between resilience, Hb volume, and depression, the Japanese version of the Beck Depression Inventory-II (BDI-II) was used to evaluate depressive tendencies (Kojima et al., 2002). The self-rated BDI-II is a scale widely utilized to assess depressive moods. Its 21 items are scored on a scale ranging from 0 to 3, and the total BDI score ranges from 0 to 64, with higher scores indicating

a more severe depressive mood.

### 2.3. MRI acquisition

Three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequences were used to obtain structural MRI data and T1-weighted images. The parameters for the 3D-MPRAGE images were as follows: echo time (TE), 3.4 ms; repetition time (TR), 2000 ms; inversion time, 990 ms; field of view (FOV), 225 × 240 mm; matrix size, 240 × 256; resolution, 0.9375 × 0.9375 × 1.0 $mm^3$; and 208 total axial sections without intersection gaps.

### 2.4. Habenula segmentation

Structural brain images were preprocessed with the CAT12 toolbox version 12.7 (https://neuro-jena.github.io/cat/), an open-source software program operating on the SPM12 platform (Statistical Parametric Mapping software package; The Wellcome Department of Imaging Neuroscience, London, UK), and MATLAB 2018a (MathWorks, Natick, MA, USA). In the Hb segmentation process, several key steps were taken to ensure precision and reliability. The segmentation flow included CAT12 preprocessing, in which steps, such as SANLM denoising, bias field correction, and calculation of the inverse deformation field, were followed. Segmentation was performed through an automatic process utilizing a pre-created deep-learning model (Kyuragi et al., 2024). To refine the segmentation output, 0.9 threshold was applied to the model's results. This threshold filters out potential noise and reduces the number of predictions.

### 2.5. Quality check of segmentation

Fig. 1. shows the examples of Hb segmentation in each slice. In a thorough evaluation of the segmentation quality, all slices on the axial image were examined. All segmented areas, excluding Hb, were accurately delineated. The mis-segmentation occurred in two participants, extending to brain regions outside the Hb. Manual correction was performed to eliminate the mis-segmented areas, and the Hb volume was recalculated. The identification process was validated by three image-analysis experts (Y.K., D.Q., and H.Z.).

### 2.6. Statistical analysis

Demographic characteristics were analyzed using descriptive measurements, including means and standard deviations (SDs) for continuous variables and proportions for categorical variables. To test above-mentioned correlations, Pearson's correlation coefficients were used if an initial exploration of the dataset indicated the normal distribution of the data, and Spearman's rank-order correlation coefficients were used if the data were not normally distributed. Normality was assessed using the Kolmogorov-Smirnov test. To evaluate potential variations in brain size affecting Hb volume, we utilized relative Hb volume (Hb volume/total intracranial volume) for subsequent analysis. Owing to the skewness of the data, partial Spearman's correlation analyses were used to find correlations between the CD-RISC scores and relative Hb volume, while treating age, sex, and duration of education as covariates. Similarly, partial Spearman's correlations were separately computed between the CD-RISC scores and relative volume of the left and right Hb, with Bonferroni correction applied to the results. Subsequently, partial Spearman's correlation analyses were also performed to investigate the impact of sex differences on the relationship between relative Hb volume and resilience and to assess the correlation between relative Hb volume and CD-RISC scores in men and women, with age as a covariate. To investigate the impact of Hb volume lateralization on resilience, we calculated the laterality index (LI = (left Hb volume - right Hb volume)/total Hb volume) using the method described by Seghier (2008). Partial Spearman correlation analyses were used to find correlations between the LI and CD-RISC scores while treating age, sex, and duration of education as covariates. Finally, to confirm the relationship between the CD-RISC score, BDI-II score, and Hb volume of the participants, a mediation analysis was conducted using the mediation package (SPSS PROCESS v4.2) with a bootstrap of 5000. The significance level was set at $p < 0.05$. The Bonferroni correction was used to consider multiple testing across all analyses. Standard statistical analyses were performed using the IBM SPSS Statistics for Windows (version 26; IBM Corp., Armonk, NY, USA) and R software (version 4.3.2).

## 3. Results

### 3.1. Participants' characteristics and psychological data results

Ten participants did not fill out the questionnaire completely, and one participant had a total intracranial volume (TIV) exceeding the mean value by three times the standard deviation (SD), leading to the participant's inability to accurately segment Hb volume owing to an image preprocessing error. Consequently, these outliers were excluded from analysis. Thus, 110 participants remained in the study after these

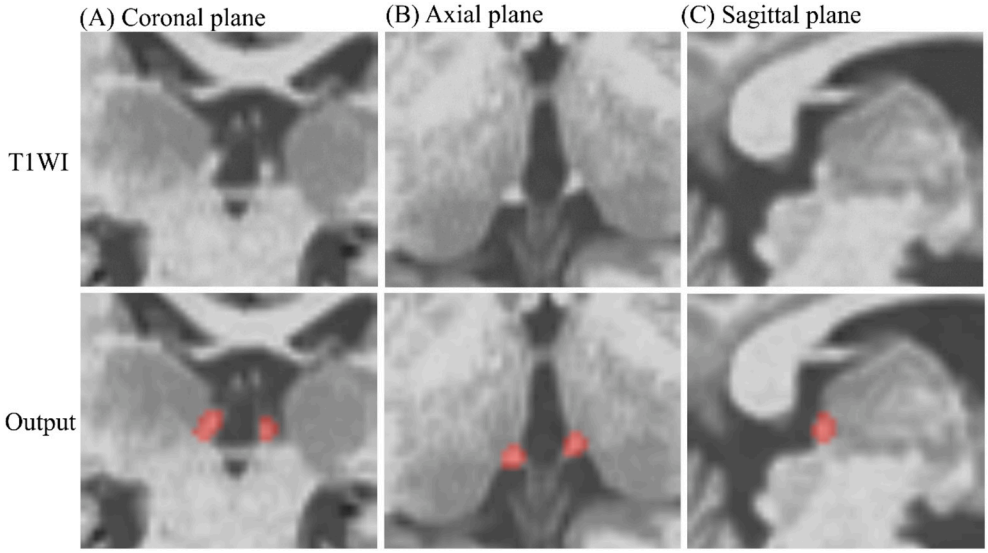


**Fig. 1.** Habenula segmentation. The upper part shows TIW image, and below is the output of the prediction model.

exclusions. The mean age of the participants was 28.4 years (SD = 11.0). Male participants' mean and SD of age was 29.8 and 11.8 ($n$ = 70), respectively. Female participants' mean and SD of age was 25.9 and 9.1 ($n$ = 40), respectively. The CD-RISC and BDI-II scores are shown in Table 1. The mean and SD of total scores on CD-RISC were 58.1 and 14.9 for all participants, 58.1 and 14.2 for male participants, and 58.0 and 16.1 for female participants. The mean and SD of total scores on BDI-II were 6.5 and 5.7 for all participants, 6.4 and 5.5 for male participants, and 6.6 and 6.0 for female participants. The Cronbach's alpha value was 0.923 for CD-RISC and 0.861 for BDI-II, indicating excellent reliability for both measures in the current study. The Kolmogorov-Smirnov test did not reject the hypothesis of normality of the data distribution for the total CD-RISC scores for all participants ($p$ = 0.19). There was no significant correlation between the CD-RISC total score and participants' sex and age.

### 3.2. Correlation of the CD-RISC scores with relative Hb volume

Table 1 shows the detailed findings of relative Hb volume. The mean of Hb volume for all participants was 110.26 ± 16.63 $mm^3$ for left and right Hb volume, 56.82 ± 9.56 $mm^3$ for the left-Hb volume, and 53.44 ± 9.05 $mm^3$ for the right-Hb. The total intracranial volume was measured at 25.58 ± 2.49 × $10^5$ $mm^3$. We found a significant negative correlation between age and relative Hb volume (partial $r$ = −0.239, $p$ = 0.011). Additionally, women' relative Hb volume was significantly higher than men's (women's relative Hb volume = 7.43 × $10^{-6}$, $p$ = 0.002).

Fig. 2 shows the data of the correlational analysis of CD-RISC scores and Hb volume. Spearman's partial correlation analysis, with age, sex, and duration of education as controls, yielded a significant positive correlation between the CD-RISC score and relative Hb volume (partial $r$ = 0.176 $p$ = 0.001). The results indicated a positive correlation between Factors 3 and 5 and relative Hb volume after Bonferroni correction (Factor 3: partial $r$ = 0.283, $p$ < 0.001; Factor 5: partial $r$ = 0.207, p < 0.001; see Supplementary Fig. S1 for details).

**Table 1**
Relationship between age, sex, the CD-RISC scores, and Hb volume.

| | Total (mean ± SD) | Age | | Sex | |
|---|---|---|---|---|---|
| | | r | p | r | p |
| **Sociodemographic** | | | | | |
| Age (years) | 28.36 ± 11.04 | | | | |
| Sex (M/F) | 70/40 | | | | |
| **CD-RISC ($N$ = 110)** | | | | | |
| **Total** | 58.07 ± 14.86 | 0.111 | 0.248 | 0.017 | 0.860 |
| Factor 1 | 18.99 ± 5.66 | 0.089 | 0.356 | 0.002 | 0.980 |
| Factor 2 | 15.61 ± 4.12 | **0.189** | **0.049*** | −0.161 | 0.092 |
| Factor 3 | 12.73 ± 3.10 | 0.141 | 0.143 | 0.103 | 0.282 |
| Factor 4 | 6.71 ± 2.53 | 0.027 | 0.777 | 0.088 | 0.360 |
| Factor 5 | 3.76 ± 1.99 | 0.099 | 0.305 | **0.191** | **0.045*** |
| **BDI-II** | 6.48 ± 5.69 | −0.111 | 0.252 | −0.010 | 0.921 |
| **Habenula volume** | | | | | |
| Hb ($mm^3$) | 110.26 ± 16.63 | **−0.239** | **0.012*** | −0.099 | 0.303 |
| Left-Hb ($mm^3$) | 56.82 ± 9.56 | **−0.257** | **0.014*** | −0.096 | 0.693 |
| Right-Hb ($mm^3$) | 53.44 ± 9.05 | −0.187 | 0.050 | −0.126 | 0.191 |
| **TIV ($10^5 mm^3$)** | 25.58 ± 2.49 | 0.036 | 0.709 | **−0.655** | **< 0.001***** |
| **Relative Hb volume ($X10^{-6}$)** | | | | | |
| Relative Hb | 74.48 ± 12.42 | **−0.241** | **0.011*** | **0.290** | **0.002**** |
| Relative Left-Hb | 38.39 ± 7.13 | **−0.236** | **0.026*** | **0.275** | **0.008**** |
| Relative Right-Hb | 36.09 ± 6.56 | −0.188 | 0.098 | **0.225** | **0.036*** |

Note: r = Spearman's correlation; * p < 0.05; ** p < 0.01; ***p < 0.001 (corrected by Bonferroni); Hb = habenula; CD-RISC = Connor–Davidson Resilience Scale; Left Hb = left habenula; Right Hb = right habenula; TIV = total intracranial volume.

### 3.3. Relationship of habenula volume with sex and lateralization

Fig. 3. shows that Hb has laterality in both male and female participants, with the relative left-Hb volume always larger than the right-Hb volume (female: $p$ = 0.008, male: $p$ = 0.012, corrected by Bonferroni). The correlation analysis results between the CD-RISC scores and the left and right relative Hb volumes indicated a nearly significant positive correlation with the Left Hb volume, a significant positive correlation with the Right Hb volume (left Hb: partial $r$ = 0.15, $p$ = 0.058; right Hb: partial r = 0.17, $p$ = 0.025), and almost no difference in the correlation between the relative volume of both hemispheres of the Hb and CD-RISC scores (see Supplementary Fig. S3 for details). The LI of Hb revealed significant laterality (mean = 0.031, $p$ < 0.001, 95 % CI = [0.016, 0.046]). However, there was no significant correlation between LI and CD-RISC scores (partial $r$ = −0.02, $p$ = 0.765).

As shown in Fig. 4, male and female participants separately underwent correlation analyses between the CD-RISC scores and relative Hb volume with age and duration of education as controls. In the group of male participants, no significant positive correlation was observed ($n$ = 70, partial $r$ = 0.055, $p$ > 0.05). In contrast, in female participants, a significant positive correlation was identified after Bonferroni correction ($n$ = 40, partial $r$ = 0.353, $p$ = 0.003). Table 2 shows the detailed comparison between male and female participants.

### 3.4. Mediation analysis

In this analysis, Hb volume was set as the independent variable, BDI-II score as the dependent variable, and CD-RISC score as the mediator variable (see Fig. 5). Spearman partial correlation analysis with age, sex, and duration of education as controls yielded a significant positive correlation between relative Hb volume and CD-RISC score (partial $r$ = 0.176, $p$ = 0.001), a significant negative correlation between CD-RISC score and BDI-II score (partial $r$ = −0.245, p < 0.001; see Supplementary Fig. S2 for details), and an insignificant negative correlation between relative Hb volume and BDI-II score ($r$ = − 0.083, $p$ = 0.131). Shrout and Bolger (2002) suggested that the independent-to-dependent

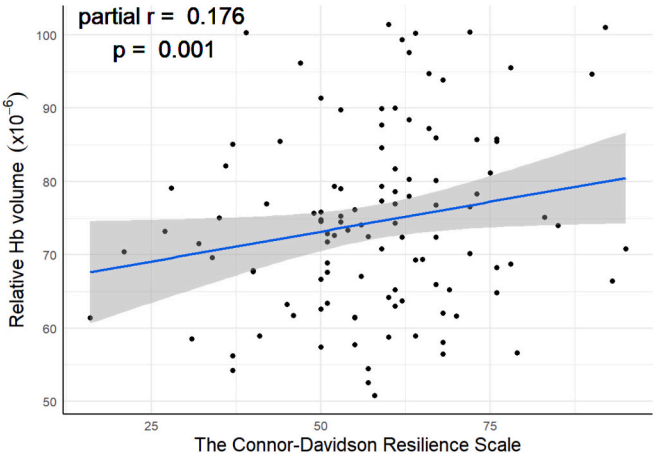


**Fig. 2.** The correlation between CD-RISC and relative habenula volume.

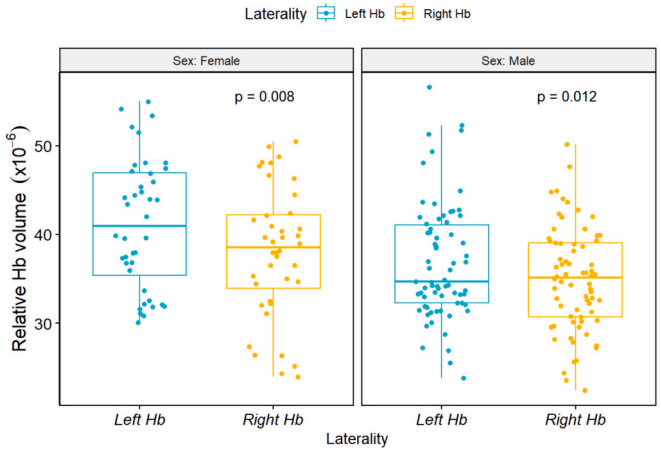


**Fig. 3.** Sex differences in left and right relative habenula volume.

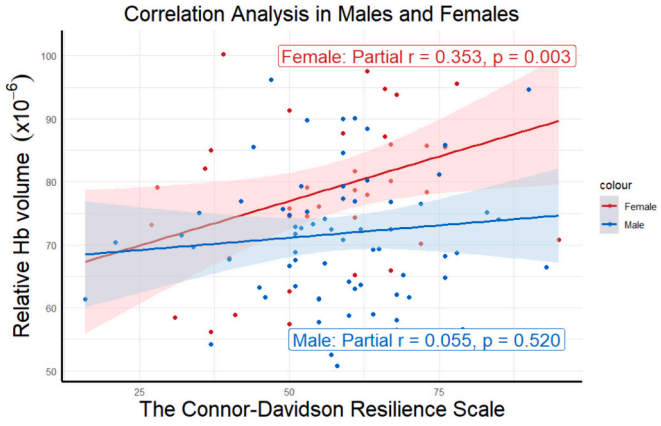


**Fig. 4.** The correlation between the CD-RISC and relative habenula volume in male and female participants.

**Table 2**
Comparison between male and female participants.

| | Male participants (mean ± SD) | Female participants (mean ± SD) | t-value | p |
|---|---|---|---|---|
| Number | 70 | 40 | | |
| Age (years) | 29.8 ± 11.8 | 25.9 ± 9.1 | 1.917 | 0.058 |
| Education (years) | 15.5 ± 2.7 | 15.1 ± 1.7 | 1.094 | 0.276 |
| BDI-II | 6.6 ± 5.5 | 6.6 ± 6.0 | −0.06 | 0.952 |
| CD-RISC | 58.1 ± 14.2 | 58.0 ± 16.1 | 0.039 | 0.969 |
| Relative HbV | 71.8 ± 11.2 | 79.2 ± 13.2 | −3.14** | 0.002 |

Note: t-value = t-value in independent *t*-test; BDI-II = Beck Depression Inventory; CD-RISC = Connor–Davidson Resilience Scale; Relative HbV = Habenula volume/total intracranial volume; ** $p < 0.01$.

variable association for statistical significance should not be a requirement when there is an a priori belief that the effect size is small, or suppression is a possibility. Therefore, we proceeded with mediation analysis. The results showed a nearly significant total effect between Hb volume and BDI-II score (path c, β = −0.154, 95%CI = [−0.161, 0.021]), but an insignificant direct effect (path c', β = −0.061, 95%CI = [−0.116, 0.061]). We also found a significant effect of Hb volume on the CD-RISC score (path a, β = 0.261, 95%CI = [0.080, 0.546]) and the CD-RISC score on the BDI-II score (path b, β = −0.356, 95%CI = [−0.207, −0.064]), and a significant indirect effect (path ab, β = −0.093, 95%CI = [−0.189, −0.019]). Mediation analyses for female and male participants were also employed separately. In female participants, the mediation analysis

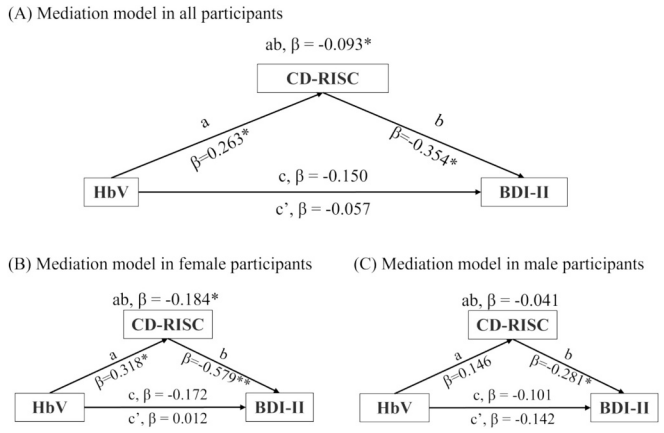


**Fig. 5.** Mediation Models of Habenula Volume, Resilience, and Depression. (A) Results of mediation analyses of all participants. (B) Results of mediation analyses of female participants. (C) Results of mediation analyses of male participants. β indicates the standardized beta value. * Indicates that the bootstrapped 95 % confidence interval does not include 0.

showed a significant indirect effect (path ab, β = −0.1840, 95 % CI = [−0.350, −0.036]). However, in male participants, it showed an insignificant indirect effect (path ab, β = −0.041, 95 % CI = [−0.149, 0.018]).

## 4. Discussion

This study explored the relationship between resilience in healthy participants and Hb volume in the brain, along with depressive tendencies. This study offered two main findings. First, a positive correlation was observed between resilience and Hb volume. Furthermore, relative Hb volume was significantly higher in women than in men. Additionally, the positive correlation between resilience and Hb levels was stronger in women. Irrespective of sex, the left Hb was significantly larger than the right Hb. However, no association was observed between lateralization and resilience. Second, resilience had a significant indirect effect on the association between Hb volume and depressive tendency.

This study employed a deep learning-based segmentation method, which a previous study has validated and demonstrated its excellent performance in structural localization (Kyuragi et al., 2024). In contrast, traditional methods, such as manual marking (Savitz et al., 2011; Bocchetta et al., 2016), may be limited by subjectivity and require substantial human intervention. Additionally, semi-automated segmentation methods (Kim et al., 2016; Schmidt et al., 2017) based on image thresholding (gray-level intensity or myelin-sensitivity) are time-consuming and prone to potential missegmentation. The segmentation method used in this study facilitates more accurate identification and localization of the habenula structure, thus providing more reliable volume measurements. To our knowledge, this is the first neuroimaging study to investigate the correlation between Hb volume and resilience in healthy individuals by employing a deep learning-based segmentation method. As hypothesized, there was a positive correlation between Hb volume and resilience, which suggests that individuals with larger Hb volumes have higher resilience and lower depressive tendencies. A study on Hb structure in patients with MDD demonstrated a significant decrease (20 %) in their right Hb volume and a substantial reduction in the neuronal count and cell area of the bilateral medial Hb (approximately 30 %–40 %); however, no such changes were observed in patients with schizophrenia (Ranft et al., 2010). This aligns with the findings of the present study. A potential explanation for the weaker resilience and smaller Hb volumes in individuals is excitotoxicity. Repeated stress-induced elevation of adrenal steroid secretion can lead to dendritic atrophy in the neurons of the hippocampus, prefrontal cortex, and specific amygdala nuclei, which is known as excitotoxicity

(McEwen et al., 2002). The existence of a similar phenomenon is also speculated in the Hb, as studies suggest that neurons in the lateral Hb are excited in response to negative stimuli, which cause severe structural and functional damage (Hu et al., 2020; R. Lawson et al., 2017; Matsumoto and Hikosaka, 2007). A postmortem study proposes a potential explanation that the reduction in Hb volume observed in the group of individuals with BD who do not undergo medication may not solely reflect dendritic remodeling but may also involve a neurotoxic process leading to neuronal death (Ranft et al., 2010). A previous study indicated a negative correlation between Hb volume and the severity of depressive symptoms, which suggests association between smaller Hb volume and more depressive symptoms (Kyuragi et al., 2024). The present study found that Hb volume can influence depressive symptoms to some extent, although no statistically significant differences were observed in the participants because of their relatively small sample size and because they were individuals without depression. However, the indirect effect was significant. In other words, resilience plays an important suppressive role between Hb volume and depressive symptoms. This further underscores the significant role of resilience in mental health and even in processes involving complex neurobiological structures.

Additionally, this study found that factor 3 (positive acceptance of change and secure relationships) and factor 5 (spiritual influences) in CD-RISC were positively correlated with Hb volume. The positive acceptance of change and secure relationships positively correlates with Hb volume. A potential explanation is the Hb's role in emotional processing and stress regulation. Previous studies suggest that individuals who are more adept at accepting change and maintaining secure relationships may promote well-being and enhance their stress-coping mechanisms (Di Fabio and Gori, 2016). Individuals' ability to positively accept change and maintain secure relationships can mitigate their stress and negative emotions, which aligns with the Hb's function in regulating mood and emotional responses. Regarding spiritual influences, spiritual practices and beliefs can offer a sense of meaning, purpose, and connection. Therefore, spirituality has repeatedly been shown to be linked to resilience, enhancing individuals' ability to cope with stress and adversity (Southwick and Charney, 2012). The Hb is involved in regulating reward and aversion processes, which might reflect the structural impact of these coping mechanisms, suggesting that spiritual influences help modulate the brain's response to stress and emotional challenges. Correlations between these specific CD-RISC factors and Hb volume suggest that Hb plays a key role in neural mechanisms underlying resilience, particularly in areas related to emotional regulation, stress management, and the influence of spiritual beliefs.

This study found a greater positive correlation between Hb volume and resilience in women and a greater indirect effect of resilience on Hb volume and depressive tendencies, which is likely attributed to differences in sex hormones. An animal-model study showed that female rats exhibited greater stress-induced lateral Hb neuronal activity than male rats did (Sood et al., 2018). Another animal-model study discovered that expression of estrogen receptor-1 (Esr1+) in the lateral hypothalamic area of lateral Hb neurons plays a crucial role in inducing aversive responses (Calvigioni et al., 2023). Previous reports suggest that female sex hormones perhaps influence women to become more sensitive to sociocultural stress and prone to experiencing more severe symptoms of anxiety disorders (Altemus et al., 2014; Hodes and Epperson, 2019). Epidemiological studies have indicated that women may face a higher risk of developing anxiety disorders or worsening symptoms during various stages of reproductive life, such as adolescence, menstruation, pregnancy, postpartum, and menopause (Maeng and Milad, 2015). These periods of increased risk coincided with the periods of intense hormonal fluctuations, suggesting a profound impact of sex hormones on the stress-coping process in women.

Through calculation of the LI and comparisons between male and female participants, this study observed that, regardless of sex, the left Hb volume was larger than the right one. This is consistent with the findings of previous studies. Researchers have conducted postmortem volume analyses of individual brain samples, reporting an asymmetry in the human Hb volume (Ahumada-Galleguillos et al., 2017). Previous fMRI studies in humans have suggested the asymmetric activation of the Hb and observed that there was significantly increased activation in the left Hb when it was processing aversive information (Hennigan et al., 2015). Further, another study has indicated elevated activity in the left Hb of patients with MDD (Furman and Gotlib, 2016) and found that lateralization did not influence the CD-RISC scores. There was no significant correlation between left and right Hb volumes and resilience. Two potential reasons for the partial inconsistency with previous research are considered. First, our study involved healthy participants, and differences in Hb volumes between the left and right sides may not be as pronounced as in individuals with severe depression. Second, the participants were right-handed, suggesting the likely effect of handedness and unrelatedness to resilience on lateralization of the habenular structure. Thus, further research is required to determine the association between Hb lateralization and resilience.

This study had some limitations that warrant cautious interpretation. First, owing to its cross-sectional design, this study could not analyze dynamic changes in Hb volume during the process of resilience adaptation. Future research could benefit from adopting a longitudinal design to track individuals over time, specifically by examining dynamic alterations in Hb volume as resilience evolves in response to adversity, thus providing a more comprehensive understanding of this relationship. Second, despite the relatively large sample size, there was an imbalance in sex distribution in this study, with a significant difference between men and women (Male: Female = 70:40). To more accurately explore the influence of sex on the relationship between Hb volume and resilience, future research should increase female participants' number to ensure better consistency and generalizability of the results. Third, this study used a convenience sample, with participants selected based on the research team's ease of access. A limitation of this approach is that the sample may not be fully representative, which could affect the generalizability of the results. Future research should include a broader sample, including individuals with varying levels of depression, to further validate these findings and explore mechanisms underlying the relationship between Hb volume, resilience, and depression.

## 5. Conclusions

This study found a positive correlation between resilience and Hb volume in a healthy population, with resilience potentially serving as a mediating factor indirectly influencing depressive tendencies. Additionally, women exhibited a significantly larger relative Hb volume than men did, and the positive correlation between psychological resilience and Hb volume was stronger in women. However, while the left Hb volume was generally larger than the right one, this lateralization difference showed no correlation with resilience. These findings support the notion that resilience and Hb volume can serve as potential markers to identify healthy individuals at higher risk of depression, thereby providing a basis for treatment and intervention strategies.

## Role of the funding source

This work was funded by Japan Society for the Promotion of Science Grant-in-Aid for Scientific Research (B) (21H02849), Grant-in-Aid for Scientific Research (C) 23K07013), Grant-in-Aid for Early-Career Scientists (JP24K18738, JP24K21084), Grant-in-Aid for Transformative Research Areas (A) JP21H05173). This work was also supported by Grant-in-Aid by the Smoking Research Foundation, and Grant-in-Aid by the Telecommunications Advancement Foundation. The funding sources had no role in the design of the study.

## CRediT authorship contribution statement

**Qi Dai:** Writing – original draft, Visualization, Methodology, Data curation, Conceptualization. **Yusuke Kyuragi:** Writing – review & editing. **Halwa Zakia:** Methodology. **Naoya Oishi:** Writing – review & editing. **Lichang Yao:** Writing – review & editing, Methodology, Data curation. **Zhilin Zhang:** Writing – review & editing. **Luyao Wang:** Writing – review & editing. **Jiajia Yang:** Writing – review & editing. **Toshiya Murai:** Writing – review & editing, Project administration, Funding acquisition. **Hironobu Fujiwara:** Writing – review & editing, Project administration, Funding acquisition, Formal analysis.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

We would like to appreciate all the participants of this study and all research collaborators for their invaluable work in data collection and analysis.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.08.012.

## References

Ahumada-Galleguillos, P., Lemus, C.G., Díaz, E., Osorio-Reich, M., Härtel, S., Concha, M. L., 2017. Directional asymmetry in the volume of the human habenula. Brain Struct. Funct. 222, 1087–1092.
Alfuqaha, O.A., 2023. Validating the Arabic version of the Connor-Davidson resilience scale among university students. PLoS One 18 (10), e0293384.
Altemus, M., Sarvaiya, N., Epperson, C.N., 2014. Sex differences in anxiety and depression clinical perspectives. Front. Neuroendocrinol. 35 (3), 320–330.
Awano, N., Oyama, N., Akiyama, K., Inomata, M., Kuse, N., Tone, M., Akagi, Y., 2020. Anxiety, depression, and resilience of healthcare workers in Japan during the coronavirus disease 2019 outbreak. Intern. Med. 59 (21), 2693–2699.
Baker, P.M., Jhou, T., Li, B., Matsumoto, M., Mizumori, S.J., Stephenson-Jones, M., Vicentic, A., 2016. The lateral habenula circuitry: reward processing and cognitive control. J. Neurosci. 36 (45), 11482–11488.
Bocchetta, M., Gordon, E., Marshall, C.R., Slattery, C.F., Cardoso, M.J., Cash, D.M., Espak, M., Modat, M., Ourselin, S., Frisoni, G.B., Schott, J.M., Warren, J.D., Rohrer, J.D., 2016. The habenula: an under-recognised area of importance in frontotemporal dementia? J. Neurol. Neurosurg. Psychiatry 87 (8), 910–912.
Calvigioni, D., Fuzik, J., Le Merre, P., Slashcheva, M., Jung, F., Ortiz, C., Nikolakopoulou, I., 2023. Esr1+ hypothalamic-habenula neurons shape aversive states. Nat. Neurosci. 1–11.
Connor, K.M., Davidson, J.R., 2003. Development of a new resilience scale: the Connor-Davidson resilience scale (CD-RISC). Depress. Anxiety 18 (2), 76–82.
Di Fabio, A., Gori, A., 2016. Developing a new instrument for assessing acceptance of change. Front. Psychol. 7, 197329.
Ely, B.A., Xu, J., Goodman, W.K., Lapidus, K.A., Gabbay, V., Stern, E.R., 2016. Resting-state functional connectivity of the human habenula in healthy individuals: associations with subclinical depression. Hum. Brain Mapp. 37 (7), 2369–2384.
Furman, D.J., Gotlib, I.H., 2016. Habenula responses to potential and actual loss in major depression: preliminary evidence for lateralized dysfunction. Soc. Cogn. Affect. Neurosci. 11 (5), 843–851.
Hatta, T., Hotta, C., 2008. Which inventory should be used to assess Japanese handedness? Comparison between Edinburgh and HN handedness inventories. J. Hum. Environ. Stud 6, 45–48.
Hennigan, K., D'Ardenne, K., McClure, S.M., 2015. Distinct midbrain and habenula pathways are involved in processing aversive events in humans. J. Neurosci. 35 (1), 198–208.
Hodes, G.E., Epperson, C.N., 2019. Sex differences in vulnerability and resilience to stress across the life span. Biol. Psychiatry 86 (6), 421–432.
Hu, H., Cui, Y., Yang, Y., 2020. Circuits and functions of the lateral habenula in health and in disease. Nat. Rev. Neurosci. 21 (5), 277–295.
Ito, M., Nakajima, S., Shirai, A., Kim, Y., 2009. Cross-cultural validity of the Connor-Davidson Scale: data from Japanese population. In: Paper Presented at the Poster Presented at the 25th Annual Meeting of the International Society of Traumatic Stress Studies, Atlanta, GA.
Jones-Bitton, A., Best, C., MacTavish, J., Fleming, S., Hoy, S., 2020. Stress, anxiety, depression, and resilience in Canadian farmers. Soc. Psychiatry Psychiatr. Epidemiol. 55, 229–236.
Kermott, C.A., Johnson, R.E., Sood, R., Jenkins, S.M., Sood, A., 2019. Is higher resilience predictive of lower stress and better mental health among corporate executives? PLoS One 14 (6), e0218092.
Kiening, K., Sartorius, A., 2013. A new translational target for deep brain stimulation to treat depression. EMBO Mol. Med. 5 (8), 1151–1153.
Kim, J.-W., Naidich, T.P., Ely, B.A., Yacoub, E., De Martino, F., Fowkes, M.E., Xu, J., 2016. Human habenula segmentation using myelin content. Neuroimage 130, 145–156.
Kojima, M., Furukawa, T.A., Takahashi, H., Kawai, M., Nagaya, T., Tokudome, S., 2002. Cross-cultural validation of the Beck Depression Inventory-II in Japan. Psychiatry Res. 110 (3), 291–299.
Kyuragi, Y., Oishi, N., Hatakoshi, M., Hirano, J., Noda, T., Yoshihara, Y., Ito, Y., Igarashi, H., Miyata, J., Takahashi, K., Kamiya, K., Matsumoto, J., Okada, T., Fushimi, Y., Nakagome, K., Mimura, M., Murai, T., Suwa, T., 2024. Segmentation and volume estimation of the Habenula using deep learning in patients with depression. Biological psychiatry global open science 4 (4), 100314.
Lawson, R.P., Drevets, W.C., Roiser, J.P., 2013. Defining the habenula in human neuroimaging studies. Neuroimage 64, 722–727.
Lawson, R., Nord, C., Seymour, B., Thomas, D., Dayan, P., Pilling, S., Roiser, J., 2017. Disrupted habenula function in major depression. Mol. Psychiatry 22 (2), 202–208.
Li, Z.-L., Wang, Y., Zou, H.-W., Jing, X.-Y., Liu, Y.-J., Li, L.-F., 2021. GABA (B) receptors within the lateral habenula modulate stress resilience and vulnerability in mice. Physiol. Behav. 230, 113311.
Maeng, L.Y., Milad, M.R., 2015. Sex differences in anxiety disorders: interactions between fear, stress, and gonadal hormones. Horm. Behav. 76, 106–117.
Matsumoto, M., Hikosaka, O., 2007. Lateral habenula as a source of negative reward signals in dopamine neurons. Nature 447 (7148), 1111–1115.
Matsuoka, K., Uno, M., Kasai, K., Koyama, K., Kim, Y., 2006. Estimation of premorbid IQ in individuals with Alzheimer's disease using Japanese ideographic script (Kanji) compound words: Japanese version of National Adult Reading Test. Psychiatry Clin. Neurosci. 60 (3), 332–339.
McEwen, B., Magarinos, A., Reagan, L., 2002. Structural plasticity and tianeptine: cellular and molecular targets. Eur. Psychiatry 17 (S3), 318s–330s.
Miroševič, Š., Klemenc-Ketiš, Z., Selič, P., 2019. The 14-item resilience scale as a potential screening tool for depression/anxiety and quality of life assessment: a systematic review of current research. Fam. Pract. 36 (3), 262–268.
Mizumori, S.J., Baker, P.M., 2017. The lateral habenula and adaptive behaviors. Trends Neurosci. 40 (8), 481–493.
Morris, J., Smith, K., Cowen, P., Friston, K., Dolan, R.J., 1999. Covariation of activity in habenula and dorsal raphe nuclei following tryptophan depletion. Neuroimage 10 (2), 163–172.
Proulx, C.D., Hikosaka, O., Malinow, R., 2014. Reward processing by the lateral habenula in normal and depressive behaviors. Nat. Neurosci. 17 (9), 1146–1152.
Ranft, K., Dobrowolny, H., Krell, D., Bielau, H., Bogerts, B., Bernstein, H.-G., 2010. Evidence for structural abnormalities of the human habenular complex in affective disorders but not in schizophrenia. Psychol. Med. 40 (4), 557–567.
Savitz, J.B., Nugent, A.C., Bogers, W., Roiser, J.P., Bain, E.E., Neumeister, A., Marrett, S., 2011. Habenula volume in bipolar disorder and major depressive disorder: a high-resolution magnetic resonance imaging study. Biol. Psychiatry 69 (4), 336–343.
Schmidt, F.M., Schindler, S., Adamidis, M., Strauß, M., Tränkner, A., Trampel, R., Walter, M., Hegerl, U., Turner, R., Geyer, S., Schönknecht, P., 2017. Habenula volume increases with disease severity in unmedicated major depressive disorder as revealed by 7T MRI. Eur. Arch. Psychiatry Clin. Neurosci. 267 (2), 107–115.
Seghier, M.L., 2008. Laterality index in functional MRI: methodological issues. Magn. Reson. Imaging 26 (5), 594–601.
Shabel, S.J., Wang, C., Monk, B., Aronson, S., Malinow, R., 2019. Stress transforms lateral habenula reward responses into punishment signals. Proc. Natl. Acad. Sci. 116 (25), 12488–12493.
Shrout, P.E., Bolger, N., 2002. Mediation in experimental and nonexperimental studies: new procedures and recommendations. Psychol. Methods 7 (4), 422.
Shumake, J., Edwards, E., Gonzalez-Lima, F., 2003. Opposite metabolic changes in the habenula and ventral tegmental area of a genetic model of helpless behavior. Brain Res. 963 (1–2), 274–281.
Sisto, A., Vicinanza, F., Campanozzi, L.L., Ricci, G., Tartaglini, D., Tambone, V., 2019. Towards a transversal definition of psychological resilience: a literature review. Medicina 55 (11), 745.
Sood, A., Chaudhari, K., Vaidya, V.A., 2018. Acute stress evokes sexually dimorphic, stressor-specific patterns of neural activation across multiple limbic brain regions in adult rats. Stress 21 (2), 136–150.
Southwick, S.M., Charney, D.S., 2012. The science of resilience: implications for the prevention and treatment of depression. Science 338 (6103), 79–82.
Yu, X., Zhang, J., 2007. Factor analysis and psychometric evaluation of the Connor-Davidson Resilience Scale (CD-RISC) with Chinese people. Soc. Behav. Personal. Int. J. 35 (1), 19–30.