Biomarkers of brain injury in patients with stress-related exhaustion: A longitudinal study

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ABSTRACT

Introduction: Exhaustion Disorder (ED) is a stress-induced disorder, characterized by extreme fatigue, cognitive impairments, and intolerance to stress. These symptoms can be long-lasting, suggesting that the long-term stress may have initiated pathophysiological processes in the brains of patients with ED. The aims of the study were I) to investigate if plasma levels of neurofilament light (NfL), glial fibrillary acidic protein (GFAP), and phosphorylated tau (p-tau181) differ between patients with ED and healthy controls, and II) to investigate if these differences persist over time.

Method: Plasma NfL, GFAP and p-tau181 were quantified in 150 patients with ED at the time of diagnosis (baseline), 149 patients at long-term follow-up (7–12 years later, median follow-up time 9 years and 5 months), and 100 healthy controls.

Results: Plasma levels of NfL and GFAP were significantly higher in the ED group at baseline compared with controls (mean difference of NfL 0.167, 95% CI 0.055–0.279; mean difference of GFAP 0.132, 95% CI 0.008–0.257), while p-tau181 did not differ between the groups. Plasma levels of NfL were significantly lower in the ED group at follow-up than in the same group at baseline (mean difference 0.115, 95% CI 0.186–0.045), while plasma levels of GFAP did not differ between the groups, and plasma levels of p-tau181 were significantly higher in the ED group at follow-up than in the same group at baseline (mean difference 0.083, 95% CI 0.016–0.151). At follow-up, there were no significant differences between the ED group and the control group for any of the proteins.

Conclusion: Plasma levels of NfL and GFAP were increased in patients with ED during the first months of the disease, indicative of axonal and glial pathophysiological processes, but had normalized at long-term follow-up.

1. Introduction

Long-term sick leave due to psychiatric diagnoses has increased in many countries, including Sweden, and psychiatric diagnoses are now the most common cause of long-term sick leave (Försäkringskassan [The Swedish Social Insurance Agency], 2020). In Sweden, stress-related mental disorders have increased the most, and among these, exhaustion disorder (ED) is the most common diagnosis (Försäkringskassan [The Swedish Social Insurance Agency], 2020). ED is a stress-induced disorder characterized by physical and mental symptoms of exhaustion, markedly reduced mental energy, memory impairment, sleep disturbance, emotional instability, and intolerance to stress (National Board of Health and Welfare, 2003). The symptoms of ED and burnout are overlapping and most patients with ED also report high burnout scores (Jonsdottir et al., 2009). In addition,
The concentration of phosphorylated tau reflects the formation of neurofibrillary tangles, which is a core pathological feature of Alzheimer’s disease. Hence, NfL was quantified to investigate if long-term stress may induce neurodegeneration, and p-tau181 was quantified to investigate if long-term stress may induce Alzheimer-like pathological alterations. The aims of this study were (I) to investigate if plasma levels of NfL, GFAP and p-tau181 differ between patients with ED and healthy controls, and (II) to investigate if these differences persist over time.

Table 1
Diagnostic criteria for exhaustion disorder according to the National Board of Health and Welfare (2003). 

| A. Physical and mental symptoms of exhaustion with minimum two weeks duration. The symptoms have developed in response to one or more identifiable stressors which have been present for at least 6 months. |
| B. Markedly reduced mental energy, which is manifested by reduced initiative, lack of endurance, or increase of time needed for recovery after mental efforts. |
| C. At least four of the following symptoms have been present most of the day, nearly every day, during the same 2-week period: |
| 1. Persistent complaints of impaired memory. |
| 2. Markedly reduced capacity to tolerate demands or to work under time pressure. |
| 3. Emotional instability or irritability. |
| 4. Insomnia or hypersomnia. |
| 5. Physical weakness or fatigue. |
| 6. Physical symptoms such as muscular pain, chest pain, palpitations, gastrointestinal problems, vertigo or increased sensitivity to sound. |
| D. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. |
| E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism, diabetes, infectious disease). |
| F. IF. If criteria for major depressive disorder, dysthymic disorder or generalized anxiety disorder are met, exhaustion disorder is set as a comorbid condition. |
regarding self-reported symptoms of burnout, anxiety, or depression. At the follow-up clinical assessment, 13 of the 163 patients were excluded due to other conditions that could explain the fatigue, 51 patients still fulfilled the diagnostic criteria for ED, and 99 patients no longer fulfilled the criteria for ED. The follow-up clinical assessment included in the study cohort. The healthy controls were recruited from advertisements in newspapers, in social media, and at the region's intranet. The inclusion criteria for the healthy control group were 1) healthy, and 2) 20–50 years of age. The exclusion criteria were (1) self-rated exhaustion disorder; (2) somatic or psychiatric disease; (3) pregnancy or lactation; (4) overconsumption of alcohol. Hence, the study population consisted of 100 healthy controls, 150 patients with ED at baseline and the same 150 patients at follow-up, 7–12 years later. Blood sampling was not possible in one patient at follow-up, hence the follow up group consisted of 149 former patients at the clinic.

Those who consented to participate in the study after having been given a full oral and written description of the study procedure donated blood at baseline and at follow-up, i.e., 7–12 years later. Baseline samples were collected in 2004–2010, and follow-up samples were collected in 2016–2017. Median time between baseline and follow-up was 9 years and 5 months, and mean time between baseline and follow-up were 9 years and 4 months. The healthy controls only donated blood at one timepoint (baseline). Blood samples from the control group were collected in 2017–2018. Blood was drawn in 4 ml K2EDTA tubes (VACUETTE®) and centrifuged at 3500 rpm at + 4 °C for 15 min. The blood plasma was separated in 1 ml aliquots and stored at – 80 °C.

2.2. Protein analysis

Plasma NfL and GFAP concentrations were measured using commercially available kits on a Single molecule array (Simoa) HD-X Analyzer according to instructions from the kit manufacturer (Quanterix, Billerica, MA). Plasma p-tau181 concentrations were measured using an in-house method described previously (Karikari et al., 2020). The measurements were performed in one round of experiments using one batch of reagents by a researcher who was blinded to clinical data. Intra-assay coefficients of variation were below 10 %. One sample with an abnormally high p-tau concentration (300 pg/ml) was considered an outlier and thus excluded from further analysis.

2.3. Ethics

All participants gave their written informed consent before entering the study. This study was performed in accordance with the Declaration of Helsinki and was approved by the Regional Ethical Review Board in Gothenburg, Sweden, which is a part of the Swedish national committee for ethical approval (Dnr 668–15 and 242–15).

2.4. Statistical analyses

Differences in demographic variables between the patients and controls were analyzed using independent samples t-test for continuous variables and Pearson chi-square for dichotomous variables. Differences in demographic variables between two timepoints within the same group were analyzed using paired samples t-test.

Differences in protein concentrations between the ED group at baseline and the control group, between the ED group at follow-up and the control group, and between the group that was recovered and not recovered at follow-up were analyzed using general linear model, adjusting for sex and age. Differences in protein concentrations between the ED group at baseline and the same group at follow-up were analyzed using mixed models adjusting for age, sex, and time. Estimated marginal means for the proteins differ somewhat between the tables due to different adjustments in the models. Data not showing normal distribution were log-transformed before parametric tests. The statistical analyses were performed using the IBM SPSS Statistics version 25.

3. Results

3.1. Baseline characteristics

There were significantly more women in the ED group than in the control group and the ED group was significantly older. Body mass index (BMI) did not differ between the control group and the ED group at baseline, but the ED group had significantly higher BMI at follow-up than at baseline. Marital status did not differ between the groups. The control group had a larger proportion of participants with at least 1 year of university education than the ED group. A significantly larger proportion of the patient group had depression, anxiety, and antidepressant medication compared with the control group. The proportion of patients with depression and anxiety was significantly larger in the ED group at baseline than in the same group at follow-up, while the proportion of patients reporting antidepressant medication did not differ between the two timepoints (Table 2).

3.2. Protein analysis

The plasma levels of NfL were significantly higher in the ED group at baseline than in controls (mean difference 0.167, 95 % CI 0.055–0.279) (Table 3), and significantly lower in the ED group at follow-up than in the same group at baseline (mean difference –0.115, 95 % CI –0.186–(-0.045) (Table 4). There was no significant difference in plasma levels of NfL between the ED group at follow-up and controls (Table 5).

The plasma levels of GFAP were significantly higher in the ED group at baseline than in controls (mean difference 0.132, 95 % CI 0.008–0.257) (Table 3). There were no significant differences in plasma levels of GFAP between the ED group at follow-up and the same group at baseline (Table 4), nor between the ED group at follow-up and controls (Table 5).

The plasma levels of p-tau181 were significantly higher in the ED group at follow-up than in the same group at baseline (mean difference 0.083, 95 % CI 0.016–0.151) (Table 4). There were no significant differences in plasma levels of p-tau181 between the ED group at baseline and controls (Table 3), nor between the ED group at follow-up and controls (Table 5).

There were no significant differences in biomarker levels at follow-up between the group that had recovered from ED and the group that had not recovered (Supplementary table 1). Likewise, there were no significant differences in biomarker levels at baseline between the group that would go on to recover at follow-up and the group that would not recover (Supplementary table 2).

Fig. 1. Flow chart of included patients.
Higher education is defined as at least 1 year of university/college education.

Estimated marginal means adjusted for age, sex and time.

Log transformed before statistical analyses.

Analyzed using independent samples t-test ctrl vs ED baseline

Analyzed using paired samples t-test ED baseline vs ED follow-up

- at follow-up, % (n) n.a. 28 % (41) 0.764
- at baseline, % (n) 1 % (1) 29 % (44)

Antidepressant medication

- at follow-up, % (n) n.a. 27 % (31)
- at follow-up, % (n) 7 % (7) 0.083 0.016

Depression

- at follow-up, % (n) n.a. 21 % (31)
- at follow-up, % (n) 71 % (71) 0.1 \times 10^{-3}

Education

- at follow-up, % (n) n.a. 20 % (20) 0.009 0.009
- at follow-up, % (n) 71 % (71) 0.115

Marital status

- at follow-up, % (n) n.a. 1 % (1) 0.119
- at follow-up, % (n) 9 % (9) 0.279

Log transformed before statistical analyses.

Estimated marginal means adjusted for age and sex.

Table 3

| Protein Concentration | Control (n = 100) | ED (n = 150) | p-value |
|-----------------------|------------------|-------------|---------|
| NfL (pg/ml)           | 1.734 (0.040)    | 1.901 (0.039) | 0.167 0.055 - 0.279 |
| GFAP (pg/ml)          | 4.633 (0.045)    | 4.766 (0.043) | 0.132 0.008 - 0.257 |
| p-tau181 (pg/ml)      | 2.207 (0.036)    | 2.226 (0.034) | 0.019 -0.081 - 0.119 |

* Estimated marginal means adjusted for age and sex.

Table 4

| Protein Concentration | ED baseline (n = 150) | ED follow-up (n = 149 *) | Difference |
|-----------------------|-----------------------|--------------------------|------------|
| NfL (pg/ml)           | 2.099 (0.037)         | 1.983 (0.035)            | -0.115 -0.186 - 0.115 |
| GFAP (pg/ml)          | 4.858 (0.047)         | 4.867 (0.044)            | 0.009 -0.076 - 0.094 |
| p-tau181 (pg/ml)      | 2.239 (0.031)         | 2.323 (0.029)            | 0.063 0.016 - 0.151 |

* Estimated marginal means adjusted for age, sex and time.

Table 5

| Protein Concentration | Controls (n = 100) | ED follow-up (n = 149 *) | Difference |
|-----------------------|-------------------|--------------------------|------------|
| NfL (pg/ml)           | 1.916 (0.047)     | 1.920 (0.041)            | 0.004 -0.131 - 0.139 |
| GFAP (pg/ml)          | 4.776 (0.052)     | 4.800 (0.046)            | 0.024 -0.125 - 0.174 |
| p-tau181 (pg/ml)      | 2.243 (0.040)     | 2.303 (0.035)            | 0.060 -0.055 - 0.176 |

* Estimated marginal means adjusted for age and sex.

Log transformed before statistical analyses.

Estimated marginal means adjusted for age and sex.

4. Discussion

The main finding of the study was that the patients suffering from ED had higher plasma levels of NfL than the healthy controls. At follow-up, 7–12 years later, the plasma NfL levels of the ED group no longer differed from those of the control group.

Even though the NfL levels were significantly higher in the patients compared with the controls during the first months of the disease, the mean plasma levels of NfL in the ED group were still within the normal range. In our study, 95 % of the healthy control group had plasma NfL levels < 10 pg/ml, which may be considered a reference value for that age group. The corresponding number for the patient group was 79 %, thus 21 % of the ED group at baseline had NfL levels above 10 pg/ml. The mean value for the ED group at baseline was around 8 pg/ml (Supplementary table 3), whereas plasma NfL levels above 100 pg/ml are found in neurodegenerative disorders such as amyotrophic lateral sclerosis (Ashton et al., 2021). Furthermore, in our study, the plasma NfL levels in the ED group at baseline were on average 1.4-fold higher than the plasma NfL levels in the control group. Comparatively, Alzheimer’s disease patients have on average 1.8-fold higher plasma NfL levels than controls (Ashton et al., 2021). The lower levels of plasma NfL in ED than in Alzheimer’s disease is likely due to the degree of axonal damage being less severe in ED than in Alzheimer’s disease. Hence, although there was a statistically significant difference between patients with ED and healthy controls in our study, our data do not support a massive neurodegeneration in ED. Increased levels of NfL have also been found in another stress-induced disorder, namely post-traumatic stress disorder, with higher NfL levels being associated with more severe PTSD symptoms (Guedes et al., 2021). One possible mechanism for stress-induced neuronal damage and astrocytic activation could be via activation of inflammatory pathways. Chronic psychosocial stress has been associated with increased levels of inflammatory markers (Johnson et al., 2013). Chronic inflammation may lead to neuroaxonal injury, putatively via mechanisms such as oxidative stress, mitochondrial dysfunction, and ion channel dysfunction (Friese et al., 2014).

NfL levels normally increase with age (Khalil et al., 2020). When adjusting for age, we found that the NfL levels had returned to normal levels at follow-up, indicating that the axonal injury seen at baseline do not persist over time. However, many patients still experience problems with memory, stress intolerance, extreme fatigue (Glise et al., 2020), and cognition (Elihov et al., 2021) at this timepoint. Interestingly, a recent study on astrocytic and neuronal injury after COVID-19 found with memory, stress intolerance, extreme fatigue (Glise et al., 2020), and cognition (Elihov et al., 2021). In multiple sclerosis, NfL levels normalize in response to effective treatment. NfL is thus considered a marker of ongoing axonal injury (Teunissen and Khalil, 2012) and our data suggest that patients with ED have some degree of ongoing axonal injury in the acute phase of the disease.
At follow-up, the NfL levels are no longer increased, indicating that axons are no longer degrading. However, the axons that were affected in the acute phase of the disease may not recover, and the potential loss of axons may possibly contribute to the sustained symptoms.

A recent study showed that patients with ED have significantly higher plasma concentration of GFAP-positive extracellular vesicles than healthy controls (Wallensten et al., 2021). This is in line with our study, where patients with ED had significantly higher plasma concentration of GFAP than healthy controls. Similar results have been found in animal studies, where chronic mild stress upregulates GFAP immuno-reactivity (Du Preez et al., 2021). However, the plasma concentration of GFAP in the ED group at follow-up was not significantly different from neither the patients at baseline nor from controls. Upregulation of GFAP is often used as a marker of reactive astrogliaisis, which is a characteristic change in the morphology and function of astrocytes seen in many CNS pathologies including neurodegenerative disorders. Reactive astroglialysis has been proposed to reduce the extent of neurodegeneration and limit the tissue damage in the acute phase of CNS injury. On the other hand, persisting reactive astroglialysis can reduce regeneration and functional recovery at a later stage (Hol and Pekny, 2015). Possibly, this could be a part of the reason why ED patients experience cognitive impairments many years after the onset of the disease.

Long-term stress in midlife has been associated with an increased risk of dementia, especially Alzheimer’s disease, later in life (Johansson et al., 2010). While NfL is a general marker of neuronal injury, p-tau181 is a specific marker of Alzheimer’s disease that can differentiate Alzheimer’s disease from other neurodegenerative disorders. Moreover, plasma p-tau181 increases along the Alzheimer’s disease continuum and can be detected at very early stages of the disease (Karikari et al., 2020).

We did not find any difference in plasma p-tau181 levels when comparing patients with ED at baseline and healthy controls. However, we found a small but significant increase in plasma p-tau181 in the ED patients at follow-up compared with the same group at baseline, even though we adjusted for age, suggesting that p-tau181 may increase over time in this group. It should be noted, however, that the p-tau181 levels in the ED group at follow-up was not significantly different from those of the control group and far from the plasma p-tau levels seen in Alzheimer’s disease (Karikari et al., 2020). The raw p-tau181 levels in our study were around 10 pg/ml (Supplementary table 3), which is in the same range as cognitively unimpaired adults in previous studies (Karikari et al., 2020).

About one third of the patients in our study still fulfilled the diagnostic criteria for ED at the long-term follow-up (Glise et al., 2020). However, we could not detect any differences in biomarker levels between the group that were still exhausted at follow-up compared with the group that were no longer exhausted. Also, there were no differences in biomarker levels at baseline between the group that would go on to recover from ED compared with the group that would still be exhausted 7–12 years later. These data indicate that the long-term ED is not due to increased neurodegeneration in these patients. Moreover, higher levels of these biomarkers at baseline do not predict disease status 7–12 years later. In contrast, both p-tau181 and NfL can be used to predict neurodegeneration and cognitive decline in Alzheimer’s disease (Moscoso et al., 2021).

Previous studies aiming to find biological alterations in ED/burnout have been inconclusive. Most studies have focused on the hypothalamus-pituitary-adrenal (HPA) axis, where the results are conflicting, showing increased, decreased, as well as no difference in cortisol levels and other HPA axis markers (Jonsdottrir and Sjors Dahlman, 2019). Studies on other hormones, including thyroid hormones, prolactin, and growth hormone, as well as studies regarding immune function, and the growth factors EGF and VEGF, show the same conflicting results (Jonsdottrir and Sjors Dahlman, 2019). However, lower levels of brain-derived neurotrophic factor (BDNF) have been found in patients with ED/burnout compared with healthy controls in several studies (He et al., 2017; Osen Sertoz et al., 2008; Sjors Dahlman et al., 2019). BDNF is a neurotrophic factor, which promotes hippocampal adult neurogenesis (Lee et al., 2002). BDNF has also been proposed to render neuronal cells resilient to neurodegeneration (Colucci-D’Amato et al., 2020). Stress reduces BDNF expression in the hippocampus (Smith et al., 1995) and inhibits hippocampal adult neurogenesis (Gould et al., 1997). Stress-induced reduction of hippocampal adult neurogenesis has been proposed to be the biological and cellular basis of altered brain plasticity resulting in stress-related syndromes like burnout (Eriksson and Wallim, 2004). These studies, together with the results from the present study, suggest that patients with ED may have increased neurodegeneration and decreased neurogenesis, which may contribute to the symptomatology of ED.

Furthermore, several imaging studies have shown cerebral changes in patients with ED compared with controls. Amygdala has been found to be enlarged, the caudate volumes decreased, and the medial frontal cortex thinner in patients with ED compared with healthy controls (Savic, 2015). Moreover, patients with ED have reductions in the gray matter volumes of the anterior cingulate cortex and the dorsolateral prefrontal cortex, and reduced volumes of caudate and putamen (Slix et al., 2013). A longitudinal study found that patients with ED have enlarged amygdala volumes, reduced caudate volumes, and reduced thickness in the prefrontal cortex and superior temporal gyrus. After 1–2 years the thinning of the prefrontal cortex and reduction of the caudate volume had normalized, while the amygdala enlargement and the superior temporal gyrus thinning remained (Savic et al., 2018). Also functional alterations have been found in ED. Patients with ED have an altered functional connectivity between the amygdala and the medial prefrontal cortex (Golkar et al., 2014; Jovanovic et al., 2011) and a reduced functional activity in the prefrontal cortex (Skau et al., 2021). Taken together, these cerebral changes have raised the question whether the brain has been injured in ED and, in that case, if the injury is reversible or permanent. A recent study on TBI showed similar results to our study; blood levels of NfL and GFAP were increased compared with controls, while there was no change in tau. Moreover, the NfL levels in mild TBI were in the same range as in our ED cohort (Shahim et al., 2020), suggesting that the extent of neuronal injury in ED may be comparative to the extent of neuronal injury in mild TBI. Supportively, patients with ED and mild TBI show many similarities. Both patient groups show altered functional activity in the frontal cortex during cognitive testing compared with controls, and the experimental procedure resulted in reduced mental energy in both patient groups, but not in controls. Moreover, both patient groups report the same degree of mental fatigue in daily life, and the mental fatigue levels in the patient groups are significantly higher than in the control group (Skau et al., 2019, 2021). However, while the NfL levels in our study had normalized after 7–12 years, the NfL levels in mild TBI were still significantly increased compared with controls after 5 years (Shahim et al., 2020). These results suggest that patients with ED initially have a neuronal injury comparative to that in mild TBI, but there is no permanent neurodegeneration in ED.

4.1. Methodological considerations

A major strength of this study is its longitudinal design and relatively large number of patients. A limitation is that we have not controlled for the potential influence of medication on plasma protein levels. The main reason is that the healthy control group were not on any medication. However, within the patient group, the plasma levels of the studied proteins did not differ between users and nonusers of SSRIs, SNRIs, or other antidepressants. Another possible confounder is previous history of TBI and/or concussion. Previous history of TBI and/or concussion was assessed using self-reported data from the follow-up clinical assessment. Out of the 150 patients with ED, 41 patients had a previous history of concussion, 108 patients had no previous history of concussion, and for 1 patient this information was missing. This information was not assessed for the controls; therefore, this possible confounder could not
be adjusted for in the models. However, to investigate whether the observed differences in NfL and GFAP were due to previous history of concussion, we compared the biomarker levels between the patients with previous concussion and the patients without previous concussion and found no differences between the groups. It should also be mentioned that although GFAP is predominantly expressed by astrocytes with previous concussion and the patients without previous concussion, samples were stored at temperatures lower than the blood samples from the other groups. However, the blood samples from the ED group at baseline were stored several years longer than the blood samples from the other groups. Hence, it is possible that they represent more severe cases of ED compared with patients with ED in primary care. Thus, the results of this study should be validated in a more heterogeneous cohort of patients preferably in a primary care setting.

5. Conclusion

In conclusion, here we show that plasma levels of NfL and GFAP were increased in patients with ED during the first months of the disease, indicative of axonal and glial pathophysiological processes, but had normalized at long-term follow-up.

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Author contributions

CH contributed to the conception and design of the study, analyzed and interpreted the data, and wrote the original draft of the manuscript. HZ contributed to the planning of the analysis, interpretation of data and reviewed and edited the manuscript. AS contributed to data collection, reviewed, and edited the manuscript. KB contributed to the interpretation of data and reviewed the manuscript. IJ contributed to the design of the study, interpretation of data and reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

Conflict of interests

HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, Annexon, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Noven, Novo Nordisk, Pinteon Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, BioArctic, Biogen, JOMD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Ono Pharma, Pharmanutrophix, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper. CH, AS and IJ declare no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105929.

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