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FULL-LENGTH REPORT

Negative correlation between habenular volume and duration of gambling disorder: Modulation by symptom severity and personality traits

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ABSTRACT

Background and aims: Gambling disorder (GD) patients continue to gamble despite negative consequences, and this behavior can be partly attributed to their insensitivity to failures and losses. GD may worsen over time and may stem from dysfunctions in the reward system and habenula, which encodes negative reward prediction errors. We aimed to elucidate habenular volume alterations that could intensify with illness duration and demonstrate heterogeneity in GD patients. *Methods:* Sixty-eight male GD patients and 75 male healthy controls were included. We computed the habenular volume by deep learning–based auto-segmentation from T1-weighted MRI data and examined the between-group differences. We retrospectively calculated illness duration and evaluated the effects of illness duration, personality traits, and symptom severity on habenular volume in GD patients. *Results:* GD patients showed comparable habenular volumes to those of healthy participants. After controlling for age, smoking status, IQ, and MRI scanner model, partial correlation analysis revealed a negative correlation between illness duration and habenular volume in GD patients ($r = -0.26$, $p = 0.029$). A significant correlation between habenular volume and illness duration appeared only in the severe subgroup ($r = -0.42$, $p = 0.011$). In the severe subgroup, higher neuroticism and lower conscientiousness were associated with larger habenular volume. *Discussion and Conclusions:* Habenular volume was negatively correlated with illness duration in GD patients, particularly in severe cases, and was influenced by symptom severity and personality traits. Habenular structural heterogeneity is based on severity and personality and possibly contributes to persistent gambling despite aversive consequences.

KEYWORDS

gambling disorder, habenula, illness duration, severity, personality, heterogeneity

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INTRODUCTION

Gambling disorder (GD) is a globally prevalent mental disorder associated with various negative consequences, including bankruptcy, legal and occupational problems, impaired

family relationships, suicidal behavior, and lower quality of life (Petry & Kiluk, 2002; Potenza et al., 2019; Tran et al., 2024). Patients with GD tend to experience a chronic course and frequently relapse despite these consequences, making it one of the most devastating mental disorders (Grant & Kim, 2001; Medeiros, Redden, Chamberlain, & Grant, 2017). Although the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) (American Psychiatric Association, 2022), includes items such as "to achieve the desired excitement" or "gambles when feeling distress," most gambling behaviors are accompanied by negative consequences, such as that associated with monetary loss, which can ultimately lead to disappointment and despair (Oakes, Pols, & Lawn, 2019). However, patients with GD do not wish to experience disappointment or despair; they expect to win and are convinced that they can (Potenza, 2014; Toneatto, 1999). These characteristics of patients with GD may stem from their desensitization to failure and loss (Lakey, Goodie, & Campbell, 2007; Romanczuk-Seiferth, Koehler, Dreesen, Wüstenberg, & Heinz, 2015). At the neural level, these patients have exhibited reduced responses to monetary losses in the brain's reward system, such as the prefrontal cortex (PFC) and ventral striatum (VS) (de Grcek et al., 2010; De Ruiter et al., 2009).

The habenula (Hb) is a brain region that has recently gained attention due to its influence on the reward system. It is a small neural nucleus located at the posterior end of the thalamus. It receives widespread inputs from the septum, basal ganglia, cingulate, and insular cortex and communicates with dopaminergic and serotonergic nuclei through both direct and indirect pathways (Hu, Cui, & Yang, 2020; Kim & Lee, 2012). Functionally, the Hb is involved in avoiding negative outcomes, processing negative prediction errors, and regulating impulsive behaviors in animals (Hikosaka, 2010; Matsumoto & Hikosaka, 2007). The habenula is also associated with adverse outcomes in humans (Lawson et al., 2014). Together, these findings suggest that impaired Hb function hinders aversive processing and is related to the pathophysiology of substance use disorder (SUD), in which patients are often exposed to negative consequences of substance use (Mathis & Kenny, 2019). Similar mechanisms are likely to underlie the pathophysiology of GD and manifest as insensitivity to negative consequences, such as monetary loss.

Although various characteristics of GD have been identified, it remains debatable whether these characteristics serve as vulnerability factors, develop during the course of the illness, or both (Brand, Müllerorcid, et al., 2025; Moreira, Azeredo, & Dias, 2023). Several characteristics have been shown to correlate with illness duration in patients with GD, including decreased quality of life (Medeiros et al., 2017), lower baseline cortisol levels(Maniaci, Goudriaan, Cannizzaro, & van Holst, 2018), and altered brain functions, such as decreased activation in the dorsomedial PFC during loss-chasing-like decision-making, and reduced insula activation during reward anticipation (Fujino et al., 2018; Tsurumi et al., 2014, 2020). As sensitivity to rewards appears to diminish over the course of illness in patients with GD (Tsurumi et al., 2014; Tsurumi, Aso, Kawada, Murai, & Takahashi, 2020), insensitivity to repeated failures and losses in patients with GD may also be aggravated throughout the illness. Therefore, investigating the correlation between Hb abnormalities and illness duration could provide insights into insensitivity to failures and losses in patients with GD.

Heterogeneity has been observed in various aspects of GD. Some studies have shown differences in the involvement of impulsivity and the degree of cognitive flexibility depending on the severity of GD (Leppink, Redden, Chamberlain, & Grant, 2016; Mestre-Bach et al., 2019). Our previous research demonstrated that patients with GD show heterogeneity in personality traits linked to varying loss sensitivities (Takeuchi et al., 2016). Another report suggested a relationship between GD severity and personality traits. This study showed that higher levels of neuroticism and lower levels of conscientiousness, both of which have been consistently reported in patients with GD (Cerasa et al., 2018; Dudfield, Malouff, & Meynadier, 2023), become more pronounced with greater disease severity (Brunborg, Hanss, Mentzoni, Molde, & Pallesen, 2016). Therefore, when conducting studies on patients with GD, it is crucial to consider the heterogeneity arising from symptom severity and personality traits as well as their interactions.

Despite the putative importance of Hb in addiction, studies on Hb in patients with addiction are scarce. Although only one study has shown impaired white matter integrity between the PFC and Hb in cocaine-addicted individuals (King et al., 2022), no study has examined its involvement in the pathophysiology of GD. This study aimed to elucidate the relationship between Hb volume and the persistence of gambling behaviors despite negative consequences, as well as its association with the course and heterogeneity of GD. Based on changes related to the persistence of gambling behavior despite negative consequences in GD, the role of Hb in processing aversive stimuli, and brain functions correlated with illness duration, we hypothesized that reduction in Hb volume in patients with GD compared to healthy controls would be more pronounced with longer illness durations. Furthermore, we assumed that these correlations might exhibit heterogeneity depending on the severity of GD and the personality traits of the patients.

METHODS

Participants

Sixty-eight male patients with GD (age range: 22–60 years) and 75 healthy male participants (age range: 19–57 years) were recruited (Table 1). Patients with GD were recruited from a treatment facility in Serenity Park, Japan, where gambling was strictly prohibited. None of the patients with GD met the diagnostic criteria for comorbid psychiatric disorders at the time of assessment. Healthy participants were recruited from the local communities. The inclusion

Table 1. Demographic, clinical, and personality profiles of study participants

Characteristic	Total GD (n = 68)	Mild + Moderate GD (n = 27)	Severe GD (n = 41)	Healthy (n = 75)	$F/t/\chi^2$	p
Age (years)	35.3 (9.8)	34.4 (9.2)	35.8 (10.1)	33.7 (9.7)	0.7	0.49
FTND	3.4 (2.2)	3.6 (2.1)	3.2 (2.3)	0.4 (1.2)	53.0	<0.001
FSIQ	101 (10)	99 (10)	102 (10)	108 (8)	12.4	<0.001
SOGS	13.4 (2.5)	12.2 (2.8)	14.1 (1.9)	0.6 (1.1)	912	<0.001
Illness duration (months)	135.1 (102.7)	115.2 (81.8)	148.2 (112.7)	–	−1.4	0.17
NEO PI-R						
Neuroticism	115 (22)	114 (23)	115 (22)	95 (22)	14.3	<0.001
Extraversion	101 (21)	104 (18)	99 (22)	100 (21)	0.6	0.56
Openness	106 (15)	107 (15)	105 (15)	114 (16)	5.9	<0.01
Agreeableness	100 (17)	99 (17)	102 (17)	110 (16)	6.3	<0.01
Conscientiousness	89 (23)	86 (26)	91 (21)	107 (20)	12.5	<0.001
MRI scanner model (Trio/Tim Trio)	34/34	11/16	23/18	41/34	1.9	0.40

The values in the cells are the mean (SD), except for Sex and MRI scanner model. SD, standard deviation; GD, gambling disorder; SOGS, South Oaks Gambling Screen; SCI-PG, Structured Clinical Interview for Gambling Disorder; FTND, Fagerström Test for Nicotine Dependence; FSIQ, Full Scale IQ; NEO PI-R, NEO Personality Inventory-Revised. The group mean differences in age, FTND, FSIQ, and SOGS between mild-to-moderate GD, severe GD, and healthy participants were examined using analysis of variance (ANOVA). Multiple comparisons among sample means were performed using Tukey's honest significant difference test. t-test and χ^2 -test were used to assess the differences in the illness duration and MRI scanner model, respectively.

criteria for patients with GD were as follows: (a) 16–60 years of age and (b) current diagnosis of GD. The inclusion criterion for healthy participants was: (a) 16–60 years of age. The exclusion criteria were participants with a history of traumatic brain injury, neurological disease, or substance abuse other than nicotine and those with contraindications to MRI. Healthy participants with a history of mental disorders were excluded from the study.

Measures

Diagnosis, severity, and illness duration. All patients with GD were investigated using the Structured Clinical Interview for Pathological Gambling (SCI-PG) (Grant, Steinberg, Kim, Rounsaville, & Potenza, 2004) and met the criteria for pathological gambling (PG) in the DSM-IV-TR and GD in the DSM-5-TR (American Psychiatric Association, 2022). The participants were classified as having mild (score 4–5), moderate (score 6–7), or severe GD symptoms (score 8–9) according to the number of DSM-5-TR criteria met, which were determined based on their gambling behavior before admission to the treatment facility. Since only two patients had mild GD, mild and moderate GD cases were pooled in the subsequent analysis. Illness duration was defined as the period between the age at which the participant first met the DSM-5 diagnostic criteria for GD (age of GD onset) and the most recent gambling episode before study participation, as assessed using the SCI-PG. The age of GD onset was determined retrospectively and used to calculate illness duration. Considering that the participants were under strict management in a treatment facility for GD, the duration of abstinence was nearly identical to the duration of treatment, and no relapse occurred.

Psychological instruments. The South Oaks Gambling Screen (SOGS) is a 16-item self-administered questionnaire, with scores ranging from 0 to 20, that assesses gambling symptoms and possible negative consequences (Lesieur & Blume, 1987). Smoking status was evaluated using the Fagerström Test for Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerström, 1991), because tobacco smoking and GD often co-occur (Jiménez-Murcia et al., 2021). We estimated full-scale intelligence quotient (FSIQ) using the Japanese Adult Reading Test (JART) (Matsuoka, Uno, Kasai, Koyama, & Kim, 2006). The personality traits of the participants were evaluated using the NEO Personality Inventory-Revised (NEO PI-R), which has been recommended as the preferred tool for assessing the Big Five personality traits (McCrae & Costa, 1997). The Big Five model evaluates five personality dimensions: neuroticism, extraversion, agreeableness, openness to experience, and conscientiousness. Each dimension consists of 48 items, with total scores ranging from 48 to 240 points. The construct validity of the psychological questionnaires, including the Japanese versions, was confirmed previously (Shimonaka, Nakazato, Gondo, & Takayama, 1998).

MRI acquisition. MRI was performed using a 3-Tesla whole-body scanner equipped with an 8-channel phased-array head coil (Trio, Siemens, Erlangen, Germany) or a 32-channel phased-array head coil (Tim Trio, Siemens, Erlangen, Germany). In Trio, the scanning parameters of the T1-weighted three-dimensional magnetization prepared rapid gradient-echo (3D-MPRAGE) sequence were as follows: repetition time (TR) = 2000 ms, echo time (TE) = 4.38 ms, inversion time = 990 ms, field of view = 225 × 240 mm, matrix size = 240 × 256, slice thickness = 1.0 mm, spatial resolution = 0.9375 × 0.9375 × 1.0 mm^3, and 208 total axial slices without intersection gaps. In the Tim Trio, the scanning parameters of the T1-weighted 3D-MPRAGE sequence were the same as those in the Trio, except for TE = 3.40 ms.

Habenula segmentation and quality control. Structural brain images were preprocessed using the CAT12 toolbox version 12.7 (https://neuro-jena.github.io/cat/), an open-source software program implemented on the SPM12 platform (Statistical Parametric Mapping software package; The Wellcome Department of Imaging Neuroscience, London, UK) and MATLAB 2018a (MathWorks, Natick, MA, USA). The preprocessing steps of the segmentation comprised Shifted and Adaptive Non-Local Means denoising, bias field correction, and the calculation of the inverse deformation field implemented in the CAT12 toolbox. Hb segmentation was performed automatically using a pre-trained deep learning model (Kyuragi et al., 2024). To improve the segmentation accuracy, a threshold of 0.9 was applied to the model output. In all cases, we visually confirmed that the Hb was appropriately segmented. Figure 1 shows representative examples of Hb segmentation across the slices, and Supplementary Figure S1 shows the Hb segmentation across all coronal slices. The segmentation process was validated by two image analysis experts (Y.K. and T.I.).

Statistical analysis

We first investigated the group mean differences in demographic, clinical, and personality data as well as Hb volume. We then examined the correlation between Hb volume and the duration of illness. To account for the effect of potential variations in brain size on Hb volume, the relative Hb volume (Hb volume divided by total intracranial volume) was used in all correlation and regression analyses (Cho et al., 2021; Lim et al., 2021). We performed principal component analysis (PCA) to investigate the effects of personality traits relevant to GD on Hb volume. Because neuroticism and conscientiousness are strongly associated with GD (Brunborg et al., 2016; Dudfield et al., 2023), the scores of these traits on the NEO PI-R were used in the PCA to extract Principal Component 1 (PC1) and Principal Component 2 (PC2). We named it PC1 Gambling Personality (GP) and used it for further analysis. Subsequently, we conducted hierarchical multiple regression analyses to clarify the independent and interactive effects of illness duration, GP, and GD severity on Hb volume. In the regression analyses, GD severity was operationalized as a categorical factor on the basis of DSM-5-TR severity specifiers, with participants classified as having mild-to-moderate or severe GD according to the number of endorsed DSM-5-TR diagnostic criteria. Finally, we used simple slope analysis to assess the interaction effects between illness duration, GP, and GD severity. Details of the statistical analysis are described in the Methods section of the Supplementary Material.

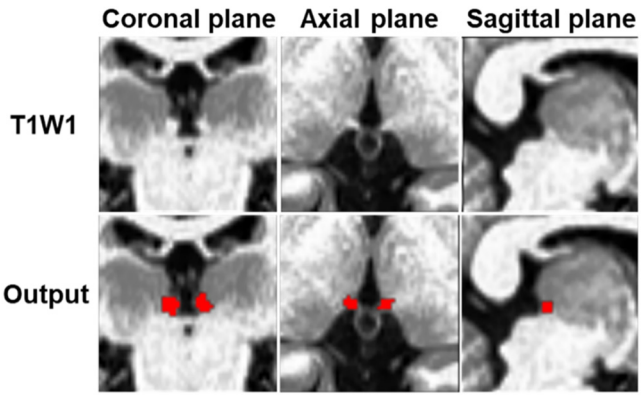

Fig. 1. Habenula segmentation. The upper panels show a T1-weighted image, while the lower panels show the output from the prediction model for habenula segmentation

Ethics

This study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee and conducted in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all the participants after providing a complete description of the study.

RESULTS

Demographic, clinical, and personality profiles of the study participants

Demographic, clinical, and personality data are summarized in Table 1. No significant differences were found among the three groups, mild to moderate GD (n = 27), severe GD (n = 41), and healthy participants, in terms of age (F (2, 140) = 0.7, p = 0.49). The mild to moderate GD (Tukey's honest significant difference [HSD] = 3.2, $p < 0.001$) and severe GD groups (HSD = 2.8, $p < 0.001$) exhibited significantly higher FTND scores than the healthy participants. Both groups showed significantly lower predicted IQ scores than healthy participants (mild to moderate GD, HSD = −9.2, $p < 0.001$; severe GD, HSD = −5.8, $p < 0.01$). There were no significant differences between the two GD groups in terms of FTND (HSD = −0.4, p = 0.66) and FSIQ (HSD = 3.5, p = 0.27). The SOGS scores differed significantly between the mild to moderate GD and severe GD groups (HSD = 1.9, $p < 0.01$), whereas illness duration showed no significant difference (t = −1.4, p = 0.17).

On the NEO PI-R, the mild to moderate GD (HSD = 19.2, $p < 0.001$) and severe GD groups (HSD = 20.4, $p < 0.001$) had significantly higher neuroticism scores than healthy participants. No significant differences in extraversion were found among the three groups (F (2, 140) = 0.6, p = 0.56). Only the severe GD group showed a significantly lower openness score than healthy participants (HSD = −9.5, $p < 0.01$). The mild-to-moderate GD (agreeableness, HSD = −11.5, $p < 0.01$; conscientiousness, HSD = −20.7, $p < 0.001$) and severe GD groups (agreeableness; HSD = −8.2, p = 0.03, conscientiousness: HSD = −16.0, $p < 0.001$) had significantly lower agreeableness and conscientiousness scores than healthy participants, while both groups of GD did not differ from each other in this measure.

Regarding the DSM-5-TR criteria, when comparing the mild to moderate and the severe GD group, significant differences were found only for tolerance (odds ratio = 9.7, false discovery rate [FDR]–corrected p [p_{FDR}] < 0.01), cessation attempts (odds ratio = infinite, p_{FDR} < 0.001), withdrawal (odds ratio = 29.8, p_{FDR} < 0.001) and jeopardized or lost significant matters (odds ratio = infinite, p_{FDR} = 0.04) (Table S1).

Hb volume comparison between patients with GD and healthy participants

Table 2 shows the detailed findings of the Hb volume. No significant differences were found between patients with GD and healthy participants in the total (F (2, 140) = 2.0, p = 0.14), left (F (2, 140) = 1.5, p = 0.22), right (F (2, 140) = 1.8, p = 0.17), or relative Hb volume (F (2, 140) = 2.1, p = 0.13). There was also no significant difference in the total intracranial volume between the patients with GD and healthy participants (F (2, 140) = 0.4, p = 0.68).

Associations among relative Hb volume, illness duration, and patients' personality traits

After controlling for age, FTND, FSIQ, and the MRI scanner model (partial r = −0.26, 95% confidence interval (CI) [−0.47, −0.02], p = 0.029), the results of Pearson's partial correlation analysis showed that illness duration was negatively correlated with relative Hb volume in patients with GD (Fig. 2). A PCA was conducted to extract information related to neuroticism and conscientiousness into a single dimension. PC1, one of the extracted principal components, explained 82.5% of the total variance in neuroticism and conscientiousness (Fig. 3). PC1 was influenced by both neuroticism and conscientiousness to a similar extent, whereas the contributions of neuroticism and conscientiousness to PC1 were the opposite (Table 3).

Table 4 presents the results of the hierarchical multiple regression analysis. In Step 1, the results indicated that age, FTND, FSIQ, and MRI scanner models were not associated with relative Hb volume. In Step 2, age (β [standardized] = 0.43, p = 0.04) and severity of GD (β = 0.53, p = 0.04) were positively correlated with relative Hb volume, whereas illness duration (β = −0.46, p = 0.02) was negatively

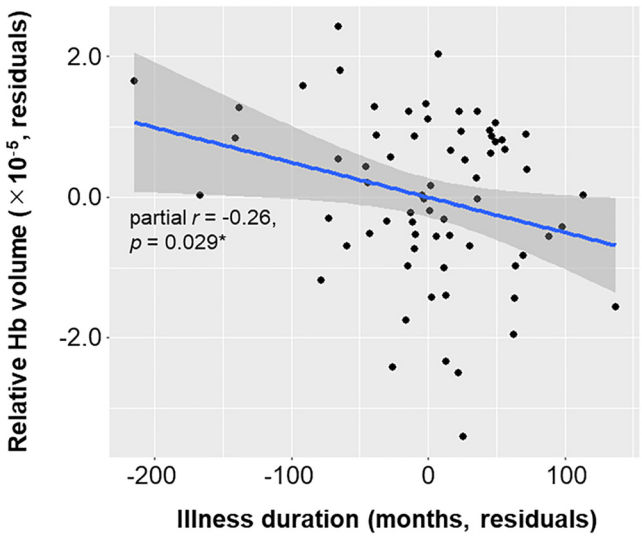

Fig. 2. The correlation between illness duration and relative Hb volume in patients with gambling disorder. Age, FTND, FSIQ, and MRI scanner model were used as covariates. Hb, habenula; FTND, Fagerström test for nicotine dependence; FSIQ, full-scale intelligence quotient. $^{*}p < 0.05$

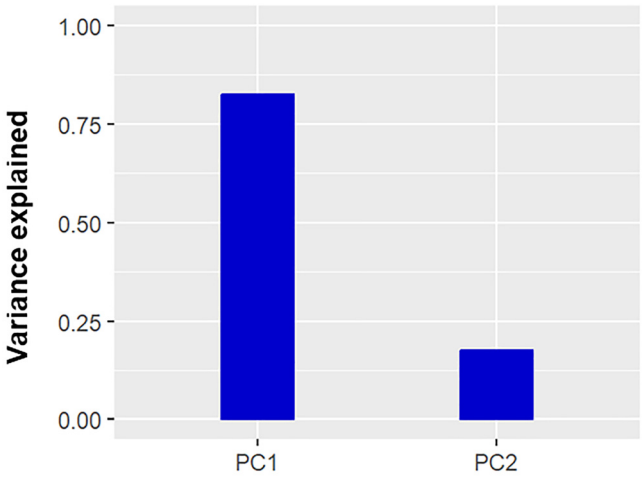

Fig. 3. Proportion of variance explained by the two principal components derived from neuroticism and conscientiousness. Principal component analysis was conducted to reduce the dimensionality of these two personality traits. The bar chart shows the proportion of total variance accounted for by PC1 and PC2. PC1, principal component 1; PC2, principal component 2

Table 2. Comparison of Hb volume between patients with severe and moderate-to-mild GD

	Total GD	Mild + Moderate GD	Severe GD	Healthy	F	p
Hb (mm^3)	107.6 (20.1)	102.2 (23.2)	111.1 (16.9)	106.7 (16.5)	2.0	0.14
Left-Hb (mm^3)	55.9 (11.0)	53.5 (12.3)	57.5 (9.7)	55.1 (8.8)	1.5	0.22
Right-Hb (mm^3)	51.7 (10.9)	48.8 (12.2)	53.6 (9.5)	51.6 (9.6)	1.8	0.17
TIV ($\times 10^5$ mm^3)	15.3 (1.3)	15.2 (1.4)	15.4 (1.2)	15.5 (1.3)	0.4	0.68
Relative Left-Hb volume (Left-Hb/TIV, $\times 10^{-6}$)	36.5 (6.6)	35.0 (7.6)	37.5 (5.7)	35.8 (6.2)	1.4	0.25
Relative Right-Hb volume (Right-Hb/TIV, $\times 10^{-6}$)	33.7 (6.7)	31.8 (7.0)	35.0 (6.2)	33.5 (6.2)	2.1	0.13
Relative Hb volume (Hb/TIV, $\times 10^{-6}$)	70.2 (12.0)	66.8 (13.3)	72.4 (10.4)	69.3 (11.2)	2.1	0.13

Values in the cell represent the mean (SD). SD, standard deviation; GD, gambling disorder; Hb, habenula; TIV, total intracranial volume.

Table 3. Component analysis of the two components extracted from the analysis of neuroticism and conscientiousness

Personality trait	PC1	PC2
Neuroticism	0.707	−0.707
Conscientiousness	−0.707	−0.707

PC1; principal component 1, PC2; principal component 2.

associated with relative Hb volume. Adding illness duration, GP, and severity of GD improved the model fit of relative Hb volume ($\Delta R^2 = 0.14$, ΔF (3, 60) = 3.32, $p = 0.03$, Cohen's $f^2 = 0.17$). In Step 3, the illness duration × severity of GD was negatively associated with relative Hb volume ($\beta = -0.60$, $p = 0.03$), whereas GP × severity of GD was positively associated with relative Hb volume ($\beta = 0.49$, $p = 0.04$). After controlling for age, FTND, FSIQ, and MRI scanner model, subsequent Pearson's partial correlation analyses revealed that the association between illness duration and relative Hb volume was stronger in severe GD group (partial $r = -0.42$, 95% CI [−0.65, −0.13], $p_{FDR} = 0.011$), while there was no significant association in mild to moderate GD group (Fig. 4A). Like wise, the association between GP and relative Hb volume was significant only in the severe GD group (partial $r = 0.35$, 95% CI [0.051, 0.60], $p_{FDR} = 0.047$) (Fig. 4B), although when combining the mild-to-moderate and severe GD groups, this correlation became non-significant (partial $r = 0.12$, 95% CI [−0.12, 0.35], $p = 0.34$) (Fig. S2). The simple slope analyses and simple slope tests of the interactions are shown in Fig. S3 were consistent with the results of Pearson's partial correlation analyses; the gradient of the slopes between the illness duration and relative Hb volume in mild to moderate GD was not significant ($\beta = 0.14$, $t = 0.50$, $p_{FDR} = 0.62$), while it was significant in severe GD ($\beta = -0.64$, $t = -3.31$, $p_{FDR} < 0.01$); the gradient of the slopes between GP and relative Hb volume in mild to moderate GD was not significant ($\beta = -0.22$, $t = -1.35$, $p_{FDR} = 0.18$), while it was significant in severe GD ($\beta = 0.46$, $t = 2.64$, $p_{FDR} = 0.02$) (Fig. S3). Adding the two-way interactions improved the model fit of relative Hb volume ($\Delta R^2 = 0.19$, ΔF (3, 57) = 5.56, $p = 0.002$, Cohen's $f^2 = 0.30$). In Step 4, the interaction effects of illness duration × GP × severity of GD was negatively associated with relative Hb volume at a significant level ($\beta = -0.78$, $p = 0.002$). Simple slope analysis and simple slope test revealed that the association between illness duration and relative Hb volume was varied by the level of severity of GD and GP; the gradient of the slopes in mild to moderate GD ($\beta = 0.90$, $t = 2.61$, $p_{FDR} = 0.04$) and severe GD ($\beta = -0.72$, $t = -2.47$, $p_{FDR} = 0.04$) were significant at higher GP (+1SD), but not at lower GP (−1SD) (mild to moderate GD, $\beta = -0.28$, $t = -1.07$, $p_{FDR} = 0.29$; severe GD, $\beta = -0.35$, $t = -1.68$, $p_{FDR} = 0.13$) (Fig. S4). The three-way interaction explained a significant amount of variance beyond the previous steps ($\Delta R^2 = 0.10$, ΔF (1, 56) = 10.24, $p = 0.002$, Cohen's $f^2 = 0.19$).

DISCUSSION

We found that although the Hb volume did not differ between patients with GD and healthy participants, it was negatively correlated with illness duration. This negative correlation was attributed to the presence of severe GD. By contrast, in the severe GD group, patients with more pronounced GP, a characteristic personality trait of patients with GD, had larger Hb volumes. Furthermore, in patients with a higher GP, a longer illness duration was associated with a larger Hb volume in the mild-to-moderate GD group and a smaller Hb volume in the severe GD group.

Table 4. Hierarchical multiple regression analyses accounting for relative Hb volume from duration of GD, GP, severity of GD, and their interaction

	Step1			Step2			Step3			Step4		
Independent variables	*β*	*t*	*p*	*β*	*t*	*p*	*β*	*t*	*p*	*β*	*t*	*p*
Age	0.04	0.32	0.75	0.43	2.14	**0.04***	0.33	1.79	0.08	0.31	1.83	0.07
FTND	0.09	0.77	0.45	0.07	0.60	0.55	−0.06	−0.51	0.61	−0.02	−0.23	0.82
FSIQ	0.17	1.39	0.17	0.12	1.03	0.31	0.17	1.50	0.14	0.09	0.84	0.40
MRI scanner model	−0.07	−0.30	0.77	0.03	0.13	0.90	0.00	−0.01	0.99	−0.04	−0.17	0.86
Illness duration				−0.46	−2.35	**0.02***	0.17	0.63	0.53	0.31	1.23	0.22
GP				0.10	0.75	0.46	−0.10	−0.60	0.55	−0.04	−0.24	0.81
Severity of GD				0.53	2.13	**0.04***	0.41	1.84	0.07	0.17	0.77	0.45
Illness duration × GP							0.19	1.48	0.14	0.59	3.42	< **0.01****
Illness duration × Severity of GD							−0.60	−2.26	**0.03***	−0.84	−3.28	< **0.01****
GP × Severity of GD							0.49	2.09	**0.04***	0.41	1.87	0.07
Illness duration × GP × Severity of GD										−0.78	−3.20	< **0.01****
ΔR^2		0.04			**0.14***			**0.19****			**0.10****	
adj R^2		−0.02			0.08			0.25			0.36	

FTND, Fagerström Test for Nicotine Dependence; FSIQ, Full-Scale IQ; GD, gambling disorder; GP, gambling personality. Bold values indicate significant differences ($p < 0.05$) *$p < 0.05$, **$p < 0.01$.

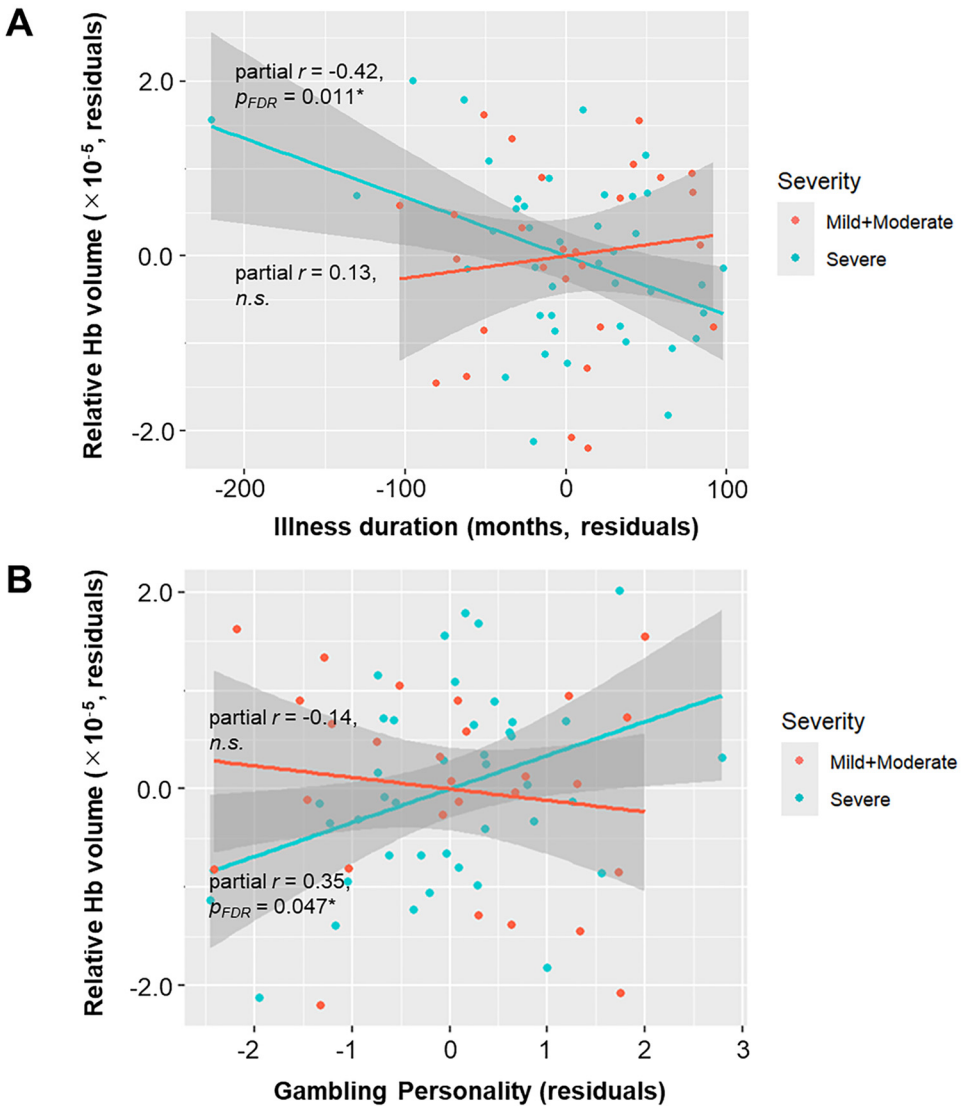

Fig. 4. The correlation among illness duration, GP, and relative Hb volume in Pearson's partial correlation analysis. The correlations between the illness duration and relative Hb volume, and between GP and relative Hb volume are shown in panel A and panel B, respectively. Age, FTND, FSIQ, and MRI scanner model were used as covariates. Hb, habenula; GP, gambling personality; FTND, Fagerström test for nicotine dependence; FSIQ, full-scale intelligence quotient; FDR, false discovery rate; n.s., not significant. $^{*}p < 0.05$ (corrected by FDR)

Age was not a significant predictor in the initial model but became significant after illness duration was included. Given the strong correlation between age and illness duration ($r = 0.72$, $p < 0.001$; Table S2), the inclusion of illness duration reallocated the shared variances between these variables, thus resulting in a suppression effect that revealed the unique contribution of age. This finding suggests that age itself is not independently associated with Hb volume, and that its apparent effect emerges only when illness duration is considered, thus highlighting the importance of jointly modeling these interrelated variables.

There was no difference in Hb volume between patients with GD and healthy participants. However, Hb volume was negatively correlated with illness duration only in patients with severe GD. The Hb is known to respond to negative reward predictions and consequences (Hikosaka, 2010; Matsumoto & Hikosaka, 2007). In patients with GD who are continuously exposed to punishment, such as repeated monetary losses and criticism, the Hb may become chronically and persistently activated. Given that the Hb receives abundant inputs from glutamatergic neurons originating in other brain regions (Hu et al., 2020), mechanisms such as glutamate-induced excitotoxicity might be induced in patients with GD (Nicosia, Giovenzana, Misztak, Mingardi, & Musazzi, 2024; Pittenger & Duman, 2008). If Hb hyperactivation persists, it may initially undergo transient hypertrophy through mechanisms such as gliogenesis, similar to those reported in the hippocampus and amygdala (Rajkowska & Miguel-Hidalgo, 2007; Schmidt et al., 2017). However, as the condition progresses, glutamate-induced excitotoxicity may trigger atrophy and cell death in the Hb, potentially becoming the predominant process. This mechanism may account for the observed negative association between the Hb volume and illness duration. Consequently,

the dysfunction of aversive processing associated with Hb function may make it more difficult to inhibit gambling behavior, potentially promoting the recurrence and chronicity of GD.

However, these mechanisms apply only to the severe GD group, and different pathophysiologies should be considered in the mild to moderate GD group. Even in the severe GD group, no decrease in Hb volume was observed compared to that in the healthy group. This differs from the reduced Hb volume associated with heroin dependence, which is thought to be caused by heroin-induced neurotoxicity (Müller et al., 2020). Unlike patients with SUD, patients with GD do not ingest addictive substances that cause neurotoxicity, which may explain why a relative decrease in the Hb volume was not observed. Therefore, the negative correlation between Hb volume and illness duration observed in the severe GD group may represent a course of addiction-related GD.

Regarding personality, our participants with GD exhibited higher neuroticism and lower conscientiousness scores than the healthy participants, which is consistent with the findings of several previous studies (Cerasa et al., 2018; Dudfield et al., 2023). Therefore, it is reasonable to unify these characteristics as GP using principal component analysis. Our results showed that higher levels of neuroticism and lower levels of conscientiousness were associated with larger Hb volume in the severe GD group. In addition, a longer illness duration was associated with a larger Hb volume in patients with mild-to-moderate GD and higher GP scores. Conversely, a longer illness duration was associated with a smaller Hb volume in the severe GD group, and this negative correlation was more pronounced in the higher GP group (Fig. S4). Patients with severe GD and high GP scores may be more frequently exposed to punishment, such as criticism from those around them and repeated losses, which could facilitate stronger Hb activation, resulting in chronic and persistent cellular damage. However, given the involvement of Hb in encoding aversive stimuli, it remains difficult to interpret the association between higher GP scores, longer illness durations, and larger Hb volumes observed in some patients with GD. Although processes such as volume increases due to gliogenesis, as observed in the hippocampus and amygdala (Rajkowska & Miguel-Hidalgo, 2007; Schmidt et al., 2017), might also occur in the Hb, this has yet to be studied and warrants further investigation. The complexity of the interactions among illness duration, GP, and GD severity suggests a need for further research. Moreover, these interactions highlight the importance of stratifying patients according to GD heterogeneity.

Previous studies have shown that severity classification based on the number of diagnostic criteria for GD in the DSM-5-TR does not align with clinical manifestations, raising doubts about the severity categories in the DSM-5-TR (Mestre-Bach et al., 2019; Sleczka, Braun, Piontek, Bühringer, & Kraus, 2015). In contrast, other studies have revealed differences in impulsivity, cognitive distortions, and cognitive flexibility between groups of patients with GD stratified by the DSM-5-TR severity criteria (Ledgerwood et al., 2020; Leppink et al., 2016; Mestre-Bach et al., 2019). These findings suggest that the severity classification based on the DSM-5-TR clarifies some aspects of GD heterogeneity.

Our results support severity classification based on the DSM-5-TR. The interaction between illness duration and GD severity (Table 4) suggests the heterogeneity of GD because a correlation between illness duration and Hb volume was found only in the severe GD group (Fig. 4, Fig. S3). Taking particular note of each item of the DSM-5-TR, the severe GD group had significantly higher scores on items related to cessation attempts and withdrawal than the mild-to-moderate GD group (Table S1). Animal studies have reported that cocaine withdrawal activates the lateral Hb (Mathis & Kenny, 2019; Meye et al., 2016) and that nicotine withdrawal increases nicotine sensitivity in the medial Hb (Görlich et al., 2013). Although the biological mechanisms of withdrawal in GD and SUD may differ, the Hb response may also be high in patients with severe GD during withdrawal. Consequently, repeated withdrawal throughout the course of GD may have led to excitotoxicity, resulting in a decrease in Hb volume, which correlated with the illness duration. The fact that the correlation between illness duration and Hb volume was in the opposite direction for mild-to-moderate and severe patients in the high GP group supports the DSM-5-TR-based severity classification and suggests GP-based heterogeneity. This finding is consistent with previous studies (Blaszczynski & Nower, 2002; Takeuchi et al., 2016), which also highlighted the heterogeneous nature of GD in terms of personality.

This study had several limitations. First, the cross-sectional design precluded any causal interpretation of the results. Longitudinal studies are needed to investigate the causal relationships. Second, the limited sample size, due to the stratification of patients with GD, may have led us to overlook variables that could have had a statistically significant influence on Hb volume. Therefore, studies with larger sample sizes are needed to determine the relationship between illness duration, GP, and GD severity more accurately. Third, although none of the participants in the present study exhibited depressive symptoms above the diagnostic threshold, previous studies have suggested an association between depressive symptoms and Hb volume (Lawson et al., 2017). Therefore, it is possible that depressive symptoms were also related to Hb volume in our participants. Future studies should objectively assess depressive symptoms and consider their potential influence on Hb volume. However, as none of the patients with GD in this study exhibited depressive symptoms above the diagnostic threshold, the potential impact of depressive symptoms can be presumed to be minimal. Fourth, none of the patients with GD in the present study met the diagnostic criteria for comorbid psychiatric disorders and depressive symptoms. This is unusual compared with typical clinical GD populations. This characteristic of our sample reflects the recruitment from a treatment facility without on-site medical staff, which was reluctant to accept patients with comorbid conditions. Therefore, the generalizability of the present findings to the general GD populations may be

limited. However, the relatively homogeneous nature of our GD sample may also be advantageous for isolating neural correlates that are more specifically associated with GD, independent of the confounding effects of comorbid psychiatric disorders. Fifth, although the age of GD onset was retrospectively determined on the basis of the participants' self-reports, the potential influence of recall bias cannot be entirely excluded. Sixth, because the number of patients with mild GD was limited to two, we combined the mild and moderate groups and conducted analyses by using a mild-to-moderate category. However, this stratification does not represent an official classification based on DSM-5-TR. Accordingly, these findings should be interpreted with caution, and future studies with larger sample sizes are required to distinguish between mild and moderate GD. Seventh, interpretations based on individual DSM-5-TR items, such as those related to withdrawal, remain speculative. To date, no study has elucidated the biological mechanisms underlying withdrawal in GD or has compared these mechanisms with those observed in SUD. Therefore, studies focusing on withdrawal-related biological mechanisms and studies that compare GD and SUD are required. Finally, we conducted only local volumetric evaluations of Hb. Combining connectivity analyses between Hb and other regions would provide a more detailed understanding of its role in addiction. For instance, because the insula has been reported to interact with the Hb in reward-related decision-making (Khalighinejad, Garrett, Priestley, Lockwood, & Rushworth, 2021), the connectivity between the Hb and the insula might play an important role in addiction.

CONCLUSIONS

We identified heterogeneous Hb volume changes in patients with GD. This heterogeneity was observed among patients with GD of different severities and personalities. Considering the accumulated preclinical evidence, Hb plays a key role in the insensitivity to punishment and aversive processing, leading to persistent gambling behaviors despite negative consequences in patients with GD. Therefore, Hb may serve as a potential therapeutic target for neuromodulation in patients with GD.

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Data availability: Data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available because they contain information that could compromise the privacy of the research participants.

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SUPPLEMENTARY MATERIAL

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