



Common and differential brain abnormalities in gambling disorder subtypes based on risk attitude



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HIGHLIGHTS

- GD has been suggested to be a heterogeneous disorder in risk attitude.
- We examined the heterogeneity of GD by combining loss aversion and brain structure.
- Low and high loss-aversion GD showed substantial differences in brain structure.
- This finding is useful for understanding neural mechanisms and treatment for GD.

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ABSTRACT

Studying brain abnormalities in behavioral addiction including GD enables us to exclude possible confounding effects of exposure to neurotoxic substances, which should provide important insight that can lead to a better understanding of addiction per se. There have been a few brain structural magnetic resonance imaging studies for GD, although the results have been inconsistent. On the other hand, GD was suggested to be a heterogeneous disorder in terms of risk attitude. We aimed to examine the heterogeneity of GD by combining a behavioral economics task and voxel-based morphometry. Thirty-six male GD patients and 36 healthy male control subjects underwent a task for estimation of loss aversion, which can assess risk attitude in real-life decision-making. The GD patients were divided into two groups based on their level of loss aversion, low and high. While both groups showed common gray matter volume reduction in the left supramarginal gyrus and bilateral posterior cerebellum, high loss-aversion GD showed pronounced reduction in the left posterior cerebellum and additional reduction in the bilateral medial orbitofrontal cortex. Our study suggests that the heterogeneity of GD is underpinned at the brain structural level. This result might be useful for understanding neurobiological mechanisms and for the establishment of precise treatment strategies for GD.

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1. Introduction

Gambling disorder (GD) is now classified into “Substance-Related and Addictive Disorders” in the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) (American Psychiatric Association, 2013). Thus, GD has been conceptualized as a form of behavioral addiction. Studying brain abnormalities in behavioral addiction including GD enables us to exclude possible confounding effects of

exposure to neurotoxic substances, which should provide important insight that can lead to a better understanding of addiction per se (Tsurumi et al., 2014). However, there have been a few studies using brain structural magnetic resonance imaging (MRI) on GD, but the results have been inconsistent. Initial studies using voxel-based morphometry (VBM) reported that there was no significant difference between healthy control (HC) subjects and GD patients in regional gray matter volumes (Joutsa, Saunavaara, Parkkola, Niemela, & Kaasinen, 2011; van Holst, De Ruiter, Van Den Brink, Veltman, & Goudriaan, 2012). Subsequent studies concerning regional gray matter volumes in GD patients reported reduction in the left hippocampus and right amygdala (Rahman, Xu, & Potenza, 2014), greater gray matter volume in the striatum and prefrontal cortex (Koehler, Hasselmann,

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Wustenberg, Heinz, & Romanczuk-Seiferth, 2015), and a reduction in the prefrontal cortex (Zois et al., 2016). Thus, alterations of brain structure in GD have not been sufficiently clarified.

Continual gambling in spite of continual loss may be attributed to altered decision-making under risk (Takeuchi et al., 2015). Behavioral economics tools can assess risk attitude in real-life decision-making (Camerer, 2004; Kahneman & Tversky, 1984). In the behavioral economics field, one of the most predominant and successful theories of decision-making under risk is the prospect theory (Kahneman & Tversky, 1979). A core part of this theory is loss aversion, meaning that a loss is subjectively felt to be larger than the same amount of gain, even if they are objectively equivalent. Tasks of behavioral economics have been employed in GD studies (Ligneul, Sescousse, Barbalat, Domenech, & Dreher, 2013; Giorgetta et al., 2014; Takeuchi et al., 2015).

We previously reported that GD patients could be categorized into two extremes in terms of loss aversion, that is, low loss-aversion GD and high loss-aversion GD (Takeuchi et al., 2015). The two groups in GD showed the specific personality traits that were proposed in the pathways model (Blaszczynski & Nower, 2002). Within this model, one group is characterized by high impulsivity and/or sensation-seeking and the other is characterized by emotional vulnerability with premonitory anxiety and/or depression. In line with this, low loss-aversion GD seems to correspond to the former group and high loss-aversion GD to the latter group.

On the basis of this evidence, we considered that the inconsistent results in terms of brain structure in GD might partly stem from the existence of subtypes, although other factors such as the severity of disorders and differences in brain imaging analyses might also account for such inconsistencies. The personality traits of impulsivity and sensation-seeking might be related to the fronto-parietal network, and emotional vulnerability might be related to the network of emotion-related regions. We hypothesized that there were significant differences in regional gray matter volume between low loss-aversion GD and high loss-aversion GD in these regions.

2. Method

2.1. Subjects

Thirty-six male GD patients, who had been referred to a treatment facility, participated in the current study. The treatment facility is a residential type where GD patients receive 12-step-based psychological therapy. Twenty-six of the GD patients were the same as in the previous study (Takeuchi et al., 2015). The GD patients were medication-free and participated after they had completed at least one cycle of 12-step-based intervention (about one month). The GD patients met the criteria for GD according to DSM-5. GD symptoms were investigated using the Structured Clinical Interview for Pathological Gambling (Grant, Steinberg, Kim, Rounsaville, & Potenza, 2004). Comorbid disorders were screened with the Structured Clinical Interview for DSM-IV-TR (American Psychiatric Association, 2000) (SCID). Thirty-six age-matched HC subjects were recruited from a local community. Twenty-one of the HC subjects were the same as in the previous study (Takeuchi et al., 2015). The HC subjects were examined using SCID, and were found to be free of any history of psychiatric disorders. All subjects were physically healthy at the time of the assessment. None of the subjects had any history of neurological injury or disease, severe medical disease, or illegal substance use that might have affected brain structure. Demographic data of all subjects were collected with respect to age and smoking status. Smoking status was assessed by the Fagerström Test for Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). The data were collected in the order of MRI imaging, clinical assessments and risky choice task, respectively. This study was approved by the Committee on Medical Ethics of Kyoto University. After offering a complete explanation of the study, written informed consent was received from all subjects.

2.2. Clinical assessment

Predicted IQ was estimated based on the Japanese Adult Reading Test (JART) short form (Matsuoka & Kim, 2006). We evaluated gambling severity using the South Oaks Gambling Screen (SOGS) (Lesieur & Blume, 1987). SOGS is a 16-item self-administered questionnaire, with a scoring range from 0 to 20. A score of 5 or higher indicates a risk of pathological gambling. The symptoms of craving were assessed using the Gambling Craving Scale (GACS) (Young & Wohl, 2009). GACS is a nine-item self-administered questionnaire with a 7-point scale. We used total scores for the analysis, with higher scores indicating more intense craving.

2.3. Risky choice task

We used a decision-making task to estimate the behavioral loss-aversion parameter. This task was the same as used in previous studies (Takahashi et al., 2013; Takeuchi et al., 2015). The subjects were presented with options between a mixed gamble (gain-loss) and a “stay” option on a computer monitor. Each mixed gamble had a 50% chance of losing a fixed amount of X and a 50% chance of gaining Y . A “stay” option was described as a mixed gamble that had a 50% chance of losing 0 yen and a 50% chance of gaining 0 yen (i.e., getting 0 yen for sure). We used 4 different possible losses ($-X$): -2500 yen, -5000 yen, $-10,000$ yen, and $-15,000$ yen. In each trial, the subjects chose between the mixed gamble and the “stay” option. The relative position (left or right) of the two options was randomized to counterbalance for order effects. The subjects were instructed as follows: “Two options of a mixed gamble will be presented to you. Make a choice between the two options according to your preference by pressing the right or left button. There is no correct answer and no time limit. Once you make a choice, the next pair of options will be presented.”

Each time a choice was made between a mixed gamble and a “stay” option in a trial, the amount of possible gain Y in the next trial was regulated and ten trials of mixed gambles with possible loss ($-X$) were iterated to successively narrow the range including the amount of possible gain to make up for a 50% chance of losing X . That is, we used a titration method to ensure consistent choices of the subjects. Adjustments in the amount of Y were made in the following manner. The initial range of Y was set between $0.5 \times X$ and $10 \times X$ (e.g. $X = 10,000$, the initial range was set between 5000 and 100,000). The range was separated into thirds (e.g. the ranges between 5000 and 36,666, 36,667 and 68,333, and 68,334 and 100,000). The one-third and two-thirds intersecting points of the initial range were used as possible gain Y in trials 1 and 2 (e.g. $X = 10,000$, Y in trial 1 = 36,666, Y in trial 2 = 68,333). If the subject accepted the mixed gamble of the two-thirds and refused the one-third in trials 1 and 2, the middle third portion of the initial range was used as a range for trials 3 and 4 (e.g. $X = 10,000$, the range of trials 3 and 4 was set between 36,667 and 68,333). If the subject accepted both mixed gambles of the thirds, the lower third part was then used as range (e.g. $X = 10,000$, the range of trials 3 and 4 was set between 5000 and 36,666). If the subject refused both mixed gambles of the thirds, the upper third part was then used (e.g. $X = 10,000$, the range of trials 3 and 4 was set between 68,334 and 100,000). The new range was again separated into thirds and the same procedure was iterated until the subject completed trial 10. The mean of the final range was used for the amount of gain Y_{final} to make up for a 50% chance of losing X . Once Y_{final} was estimated for a given loss ($-X$), the gambles with the next loss ($-X$) were chosen for the estimation, and so on. The order of X was randomized across the subjects.

2.4. Loss-aversion parameter λ assessment

The amount of gain Y_{final} to compensate the 50% chance of losing X is expressed as $Y_{\text{final}} = \lambda \times X$, where λ is a loss-aversion parameter. This λ parameter is similar to the parameter in the prospect theory but makes

the common simplifying presuppositions of a linear rather than a curvilinear value function, which is the same manner as used in previous studies (De Martino, Camerer, & Adolphs, 2010; Takahashi et al., 2013; Tom, Fox, Trepel, & Poldrack, 2007), and identical decision weights for a 0.5 probability of a gain or loss (note that the decision weight need not be equal to 0.5, as long as it is presumed to be the same for both gain and loss probability). Based on previous literature, we confined the range of λ from 0.5 to 10 during the estimation process. A smaller value of λ (closer to 0.5) means less loss aversion, and a higher value (closer to 10) means more loss aversion. The parameter was calculated by least-squares method.

First, we compared loss-aversion parameters between the GD patients and HC subjects. Next, based on the previous study (Takeuchi et al., 2015), we categorized both GD patients and HC subjects into three loss-aversion levels, a low loss-aversion group ($0 < \lambda \leq 3.33$), a middle loss-aversion group ($3.33 < \lambda \leq 6.66$) and a high loss-aversion group ($6.66 < \lambda \leq 10.00$), and we compared distribution of the three groups between the GD patients and HC subjects.

Statistical analyses of the demographic data, clinical data, and loss-aversion parameters λ were performed using SPSS 23 for Windows (SPSS Inc., Chicago, IL, USA).

2.5. MRI acquisition

Twenty-seven GD patients and 26 HC subjects underwent MRI scans by 3-T whole-body scanner equipped with an 8-channel phased-array head coil (Trio, Siemens, Erlangen, Germany). With an MRI machine version upgrade, 9 GD patients and 10 HC subjects underwent MRI scans by 3-T whole-body scanner equipped with 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: TR = 2000 ms, TE = 4.38 ms, TI = 990 ms, FOV = 225×240 mm, matrix = 240×256 , resolution = $0.9375 \times 0.9375 \times 1.0$ mm³, and 208 total axial sections without intersection gaps. In Tim Trio, the scanning parameters of the T1-weighted 3D-MPRAGE sequence were the same as Trio except TE = 3.40 ms.

2.6. MRI data preprocessing and assessment

MRI data were processed using SPM12 (Wellcome Trust Center for Neuroimaging, London, UK) running on Matlab R2014a (MathWorks, Natick, MA, USA). In brief, all images were tissue classified and spatially normalized to the same stereotaxic space by using the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) algorithm (Ashburner, 2007). The voxel values of segmented and normalized gray matter images were modulated by Jacobian determinants obtained from nonlinear normalization steps. We used the default parameters of SPM12. Finally, the resultant gray matter images were smoothed with a Gaussian kernel of 8 mm full-width at half-maximum, on which all analyses were performed.

First, we examined regions of gray matter volume differences among low loss-aversion GD, high loss-aversion GD and HC using one-way analysis of covariance (ANCOVA) applying a height threshold: $p < 0.005$ (uncorrected), with an extent threshold of 200 voxels. An inclusion mask was created from the ANCOVA result for the following post hoc analyses, which were conducted to identify regional gray matter volume differences between respective pairs of groups, with a height threshold of $p < 0.001$ (uncorrected), and an extent threshold of 200 voxels. The effects of IQ (predicted IQ using JART), smoking status (FTND score), total brain volume (TBV) and MRI machine model (Trio or Tim Trio) were treated as nuisance covariates.

3. Results

3.1. Loss-aversion parameter assessment

The GD patients and HC subjects did not differ in terms of loss-aversion parameter λ (GD patients: median = 2.55; HC subjects: median = 3.18; Mann-Whitney's U test, $p = 0.86$). The HC group consisted of 19 subjects in the low loss-aversion group, 10 in the middle loss-aversion group, and 7 in the high loss-aversion group. The GD group consisted of 23 patients in the low loss-aversion group, none in the middle loss-aversion group, and 13 in the high loss-aversion group. In order to investigate the distribution of the three groups between the GD patients and HC subjects, we conducted Fisher's exact test. There was a significant difference in distribution between the GD patients and HC subjects ($p = 0.002$). The HC subjects were uniformly classified into the three groups (low, middle, high) of loss aversion, whereas the GD patients were classified into the two extremes, with no GD patients into the middle loss-aversion group. In addition, we conducted a hierarchical cluster analysis with Ward's method using Euclidean square distance to the loss-aversion parameters of each GD group and HC group. The result showed that the GD group was divided into two groups at most in accordance with the low loss-aversion group and the high loss-aversion group mentioned above. On the other hand, the HC group was divided into four groups at most. This result strongly supported the notion that there were two groups in GD in terms of loss aversion.

3.2. Demographic and clinical data

The demographic and clinical data are presented in Table 1. In order to investigate the differences among the three groups (i.e., low loss-aversion GD, high loss-aversion GD and HC), we conducted one-way analysis of variance (ANOVA) in terms of age, predicted IQ, FTND score, gray matter volume (GMV), white matter volume (WMV), TBV and SOGS. There were significant differences among the three groups in terms of predicted IQ based on JART, FTND score, and SOGS. Then, we conducted post hoc comparisons using Bonferroni multiple correction with the significance level set at $p = 0.016$ ($1/3$ of 0.05) among the three groups in terms of the data showing the differences among the three groups. Both GD groups showed lower levels than the HC group in predicted IQ and higher levels in FTND score and SOGS, whereas the two GD groups did not differ significantly in terms of these three variables. We also compared the data in terms of onset age, duration of illness, abstinence and GACS score between the two GD groups. There was a significant difference between the two GD groups in terms of GACS score, with low loss-aversion GD showing higher GACS score than high loss-aversion GD. There was no significant difference in terms of the ratio of the MRI machine model (i.e., Trio and Tim Trio) among the three groups.

3.3. Regional gray matter volume

We examined regional gray matter volume differences among low loss-aversion GD, high loss-aversion GD and HC using one-way ANCOVA. The result showed that there were significant differences among the three groups in the bilateral posterior cerebellum, the left supramarginal gyrus (SMG), dorsal part of the left medial orbitofrontal cortex (mOFC), and ventral part of the bilateral mOFC (Table 2).

Then, in order to examine gray matter volume differences among the three groups in detail, we compared regional gray matter volumes between respective pairs of groups (i.e., low loss-aversion GD vs HC, high loss-aversion GD vs HC, and low loss-aversion GD vs high loss-aversion GD). Low loss-aversion GD showed gray matter volume reduction relative to HC in the left SMG and bilateral posterior cerebellum (Table 3; Fig. 1), but did not show any regional gray matter volume increment relative to HC. High loss-aversion GD showed regional gray matter volume reduction relative to HC in the bilateral posterior

Table 1
Demographic and clinical data.

	Low loss-aversion GD (n = 23)	High loss-aversion GD (n = 13)	HC (n = 36)	Stats
Age (year)	36.3 ± 10.6	35.6 ± 5.5	35.9 ± 6.9	p = 0.97
Predicted IQ (JART)	102.7 ± 8.2	101.1 ± 7.2	108.8 ± 7.1	p < 0.005
Handedness (R/L)	20/3	13/0	35/1	
FTND score	3.6 ± 2.2	3.0 ± 2.1	0.5 ± 1.4	p < 0.001
GMV (cm ³)	758.6 ± 66.6	755.9 ± 33.6	773.9 ± 61.2	p = 0.51
WMV (cm ³)	469.7 ± 41.3	463.1 ± 35.9	469.3 ± 48.3	p = 0.90
TBV (cm ³)	1228.3 ± 91.5	1219.0 ± 54.9	1243.1 ± 103.0	p = 0.68
SOGS	13.8 ± 2.9	14.2 ± 1.8	0.6 ± 1.1	p < 0.001
Onset age (year)	23.1 ± 6.5	22.7 ± 6.0		p = 0.84 ^a
Duration of illness (year)	13.2 ± 10.1	12.9 ± 6.7		p = 0.94 ^a
Abstinence (month)	13.7 ± 31.5	8.8 ± 9.3		p = 0.60 ^a
GACS score	23.0 ± 7.0	19.3 ± 9.9		p < 0.05 ^b
Machine model (Trio/Tim Trio)	16/7	11/2	26/10	p = 0.59 ^c

Abbreviations: JART = Japanese Adult Reading Test, FTND = Fagerström Test for Nicotine Dependence, GMV = gray matter volume, WMV = white matter volume, TBV = total brain volume, SOGS = South Oaks Gambling Screen, GACS = Gambling Craving Scale.

^a Independent *t*-test.

^b Mann-Whitney's *U* test.

^c Fisher's exact test.

cerebellum, the left SMG, dorsal part of the left mOFC, and ventral part of the bilateral mOFC (Table 3; Fig. 2), but did not show any regional gray matter volume increment relative to HC. High loss-aversion GD showed regional gray matter volume reduction in the left posterior cerebellum relative to low loss-aversion GD, but did not show any regional gray matter volume increment relative to low loss-aversion GD (Table 3).

In order to examine whether regional gray matter volume differences associated with the degree of loss aversion were specific to GD, we separated the HC group into two groups using median-split on loss-aversion parameters. Comparison between low loss-aversion HC and high loss-aversion HC revealed no significant regional gray matter volume difference.

4. Discussion

To our knowledge, this is the first study to investigate regional gray matter volume differences in two GD groups categorized by the levels of loss aversion, low and high. The two groups in GD had specific characteristics in terms of clinical symptoms and regional gray matter volumes.

We categorized the total subjects into three groups according to loss-aversion levels based on our previous study (Takeuchi et al., 2015). All GD patients were then categorized into groups of extreme loss-aversion level, low and high. The two groups showed different clinical characteristics regarding craving intensity. Low loss-aversion GD showed higher craving intensity than high loss-aversion GD. As

hypothesized, the two GD groups showed differences in brain structure levels. While both groups showed common gray matter volume reduction in the left SMG and bilateral posterior cerebellum relative to HC, high loss-aversion GD showed pronounced reduction in the left posterior cerebellum and additional reduction in the bilateral mOFC. On the other hand, the comparison between the two groups of HC using median-split on loss-aversion parameters showed no significant difference in regional gray matter volume. It was suggested that these gray matter alterations were specific to GD.

The left SMG was a common region where gray matter volume reduction was seen in the two groups in GD. SMG has been considered to be a part of the TPJ (Gaser, Nenadic, Volz, Buchel, & Sauer, 2004; Vercammen, Knegeting, Den Boer, Liemburg, & Aleman, 2010). Although the TPJ is reported to be involved in various functions, this region is included in the ventral fronto-parietal network and its core function is considered to be attention-reorienting (Corbetta & Shulman, 2002; Carter & Huettel, 2013). Accumulating evidence has suggested that attentional bias caused by a deficit of attention-reorienting is an important feature for substance dependence (Field & Cox, 2008). Common volume reduction in the left SMG might be related to attentional deficit in GD (Rugle & Melamed, 1993).

Both GD groups showed gray matter volume reduction in the bilateral posterior cerebellum relative to HC. Although the cerebellum has been considered to be a crucial region for sensorimotor control

Table 2
Regional gray matter volume differences among low loss-aversion GD, high loss-aversion GD and HC.

Region	Peak-level MNI coordinate			F value	Cluster size
	X	Y	Z		
Left posterior cerebellum	−12	−51	−51	14.95	1983
Right posterior cerebellum	11	−51	−51	10.71	
Left posterior cerebellum	−3	−62	−44	6.97	
Left supramarginal gyrus	−63	−38	27	11.94	1201
	−57	−27	20	9.44	
Left posterior cerebellum	−44	−74	−32	8.64	810
	−50	−60	−26	6.51	
Left middle orbital gyrus	−11	62	−3	8.55	532
Left superior frontal gyrus	−24	65	6	7.16	
Bilateral rectal gyrus	0	38	−18	8.09	273
	0	48	−17	6.62	
Right posterior cerebellum	42	−75	−41	7.93	627
	51	−69	−36	6.57	

Table 3
Regional gray matter volume reduction.

Region	Peak-level MNI coordinate			T value	Cluster size
	X	Y	Z		
HC > Low loss-aversion GD					
Left supramarginal gyrus	−63	−38	30	4.18	933
	−56	−27	20	4.02	
Left posterior cerebellum	−42	−75	−32	4.02	648
Right posterior cerebellum	44	−77	−41	3.81	559
	50	−71	−36	3.62	
HC > High loss-aversion GD					
Left posterior cerebellum	−11	−51	−53	5.00	966
Left supramarginal gyrus	−65	−38	26	4.54	621
	−59	−35	35	3.69	
Right posterior cerebellum	11	−51	−50	4.51	512
	18	−54	−51	3.72	
Left middle orbital gyrus	−11	62	−2	3.93	512
Left superior frontal gyrus	−24	65	6	3.77	
Bilateral rectal gyrus	0	38	−18	3.90	242
Low loss-aversion GD > High loss-aversion GD					
Left posterior cerebellum	−14	−51	−51	4.64	550
	−3	−62	−44	3.43	

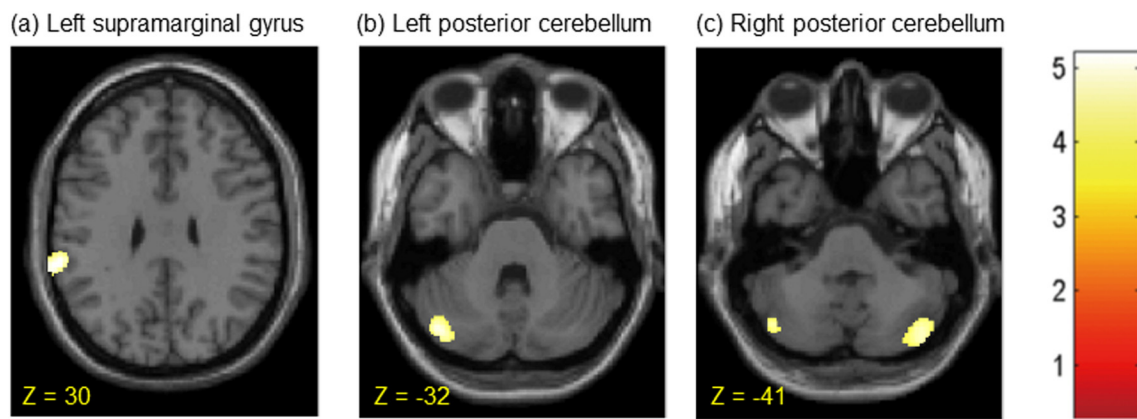


Fig. 1. Regional gray matter volume reduction in low loss-aversion GD relative to HC. The color bar represents the T scores. (a) left supramarginal gyrus (b) left posterior cerebellum and (c) right posterior cerebellum. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(Schmahmann, 2004), posterior cerebellum regions have been implicated in executive and affective processing (Schmahmann & Sherman, 1998). A line of substance addiction studies has reported gray matter volume reduction in posterior cerebellum regions (Barros-Loscertales et al., 2011; Gallinat et al., 2006; Mechtcheriakov et al., 2007; Walhovd et al., 2007). In line with these findings, these alterations in posterior cerebellum regions might also be common characteristics in addictive disorders. Because suffering from GD does not originate from neurotoxic substance, our finding suggests that alteration in the posterior cerebellum could not be solely explained by the effect of neurotoxic substance.

High loss-aversion GD showed significant gray matter volume reduction in the bilateral mOFC relative to HC, whereas low loss-aversion GD showed no such difference. We previously showed that high loss-aversion GD corresponded to GD with emotional vulnerability in the pathways model (Takeuchi et al., 2015). OFC is considered to be important for affective function including integration of cognition with emotion (Damasio, 1994; Damasio, 1999). Damage to OFC causes impairments in decision-making characterized by a lack of ability to adopt behavioral strategies according to the results of decisions (Bechara, Damasio, Damasio, & Anderson, 1994; Rolls, Hornak, Wade, & Mcgrath, 1994). It has been considered that OFC represents the motivational value of stimuli, permitting it to integrate and assess the incentive value of predicted results in order to lead to future behavior (Schoenbaum, Setlow, Nugent, Saddoris, & Gallagher, 2003). This group also showed pronounced reduction in the left posterior cerebellum. This finding might be associated with more explicit manifestation of emotional and affective dysfunction in this group (Schmahmann & Sherman, 1998).

Identification of subtypes of GD is also important from a clinical perspective. The effectiveness of pharmacotherapy for GD has been examined. For instance, studies investigating the effect of antidepressants have so far provided mixed results (Lupi et al., 2014). The effects of psychostimulants utilized for attention deficit hyperactivity disorder (ADHD) showing high impulsivity and/or sensation-seeking, such as amphetamine (Zack & Poulos, 2004) and modafinil (Smart, Desmond, Poulos, & Zack, 2013; Zack & Poulos, 2009), were also examined for GD, but so far pharmacological treatment for GD remains to be established. Interestingly, modafinil was reported to decrease and increase the desire to gamble in high and low impulsivity gamblers, respectively (Zack & Poulos, 2009). This strongly indicates that inconsistencies might partly stem from the existence of subtypes, emphasizing the necessity of precise pharmacotherapy according to the GD subtype.

There are limitations to our study. First, we decided not to use real money and gamble-related stimuli in abstinent and treatment-seeking GD patients for ethical reasons. Although decision-making on hypothetical rewards does not necessarily reflect decision-making in real life, validity of the outcomes of experiments with hypothetical rewards has been reported (Locey, Jones, & Rachlin, 2011). Second, it remains unclear whether the brain structural alterations were causes or results of the psychopathology in GD, and therefore longitudinal studies are recommended. Third, all GD patients in the current study were undergoing treatment. It is conjectured that just a minor portion of GD patients is actually under active treatment at any given time. Fourth, although we excluded alcohol use disorder from the current study using SCID, the effect of alcohol cannot be completely ruled out. Fifth, although our predictions concerning brain regions were modest, regions such as the SMG and cerebellum have multi-functions. At the same time, the

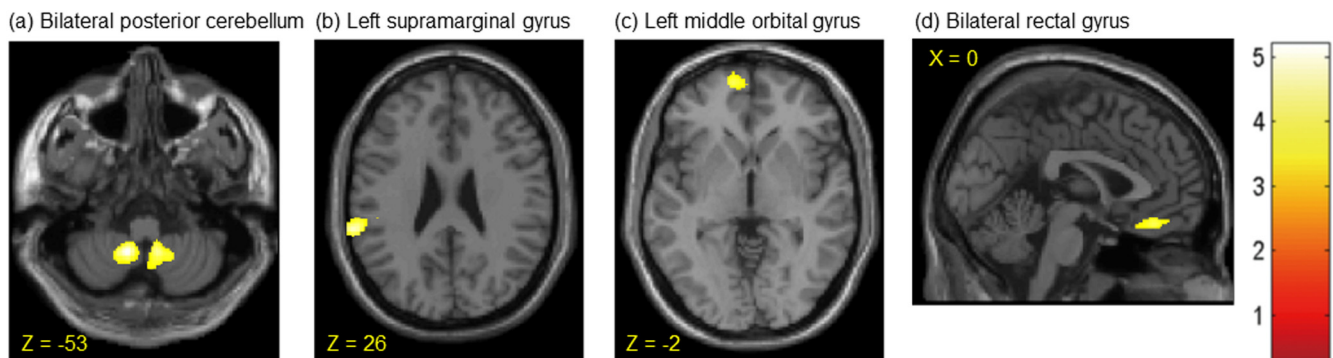


Fig. 2. Regional gray matter volume reduction in high loss-aversion GD relative to HC. The color bar represents the T scores. (a) bilateral posterior cerebellum (b) left supramarginal gyrus (c) dorsal part of left medial orbitofrontal cortex and (d) ventral part of bilateral medial orbitofrontal cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

current study did not assess any direct link between a cognitive process and related brain regions. Thus, interpretation of our results regarding brain functions should be approached with caution. Finally, although the results of Fisher's exact test and cluster analysis strongly support that GD consists of two subtypes, it still might be a slightly arbitrary classification. Thus, any generalization of our findings needs to be approached with caution.

In conclusion, the two subtypes of GD classified based on risk attitude showed differential clinical symptoms and brain structure. Common gray matter volume reduction in the left SMG and bilateral posterior cerebellum was found in both subtypes, whereas high loss-aversion GD showed pronounced reduction in the left posterior cerebellum and additional reduction in the bilateral mOFC. Our findings support that GD is not a uniform but rather a heterogeneous disorder. Future studies, especially concerning clinical treatment and neurobiological research, are needed to focus on the heterogeneity in GD in terms of risk attitude, clinical symptoms and brain structure.

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Contributors

H. Takeuchi, K. Tsurumi, A. Takemura, T. Murao, R. Kawada, T. Murai, and H. Takahashi designed the study. H. Takeuchi, K. Tsurumi, A. Takemura, T. Murao, R. Kawada, S. Urayama, and T. Aso contributed acquisition of data. H. Takeuchi, G. Sugihara, J. Miyata and H. Takahashi contributed analysis and interpretation of data. H. Takeuchi and H. Takahashi drafted the article, and the other authors revised it critically for important intellectual content. All authors approved for publication.

Conflict of interest

All authors declare that they have no conflicts of interest.

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