



## 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 pre-morbid 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 Structure 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  $Y_{\text{final}}$  to make up for a 50% chance of losing X. Once  $Y_{\text{final}}$  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 $\lambda$ assessment

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

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