# Differences in Neural Responses to Reward and Punishment Processing between Anorexia Nervosa Subtypes: An fMRI Study

Running title: Altered reward system in AN subtypes

Ema Murao, MD[1], Genichi Sugihara, MD, PhD[1], Masanori Isobe, MD, PhD[1], Tomomi Noda, MA[1], Michiko Kawabata, MS[1], Noriko Matsukawa, MD[2], Hidehiko Takahashi, MD, PhD[1], Toshiya Murai, MD, PhD[1], Shun'ichi Noma, MD, PhD[1*]

[1]Department of Psychiatry, Kyoto University Graduate School of Medicine, Kyoto, Japan

[2]Medical Center for Student Health, Kobe University, Kobe, Japan

***Corresponding author:**

Shun'ichi Noma, MD, PhD

Department of Psychiatry, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto, 6068507, Japan

Tel: +81-75-751-4947, Fax: +81-75-751-3246

E-mail: noma@kuhp.kyoto-u.ac.jp

The manuscript is being submitted to the following fields:

Primary: Neuroimaging; Secondary: Neurophysiology and psychophysiology

**Abstract**

**Aim:** Anorexia nervosa (AN) includes the restricting (AN-r) and binge-eating/purging (AN-bp) subtypes, which have been reported to differ regarding their underlying pathophysiologies as well as their behavioral patterns. However, the differences in neural mechanisms of reward systems between AN subtypes remain unclear. The aim of the present study was to explore differences in the neural processing of reward and punishment between AN subtypes.

**Methods:** Twenty-three female patients with AN (11 AN-r and 12 AN-bp) and 20 healthy women underwent functional magnetic resonance imaging while performing a monetary incentive delay task. Whole-brain one-way analysis of variance was conducted to test between-group differences.

**Results:** There were significant group differences in brain activation in the rostral anterior cingulate cortex and right posterior insula during loss anticipation, with increased brain activation in the AN-bp group relative to the AN-r and healthy women groups. No significant differences were found during gain anticipation.

**Conclusion:** AN-bp patients showed altered neural responses to punishment in brain regions implicated in emotional arousal. Our findings suggest that individuals with AN-bp are more sensitive to potential punishment than individuals with AN-r and healthy individuals at the neural level. The present study provides preliminary evidence that there are neurobiological differences between AN subtypes with regard to the reward system, especially punishment processing.

**Keywords:** anorexia nervosa; fMRI; insula; monetary incentive delay task; reward system

**Introduction**

Anorexia nervosa (AN) is an eating disorder characterized by significantly low body weight, intense fear of gaining weight, and body image distortion.[1] AN includes two subtypes: a restricting type (AN-r) and a binge-eating/purging type (AN-bp). Individuals with AN-r purely restrict their food intake and increase activity, while those with AN-bp usually restrict their food intake and regularly engage in binge eating and/or purging behaviors. In addition, the two subtypes are characterized by different behaviors and personality characteristics. Individuals with AN-r show high persistence and low novelty-seeking behaviors, whereas those with binge-eating disorders, including AN-bp, have high impulsivity, sensation-seeking, and novelty-seeking traits.[2] Psychiatric comorbidities also differ between the subtypes: individuals with AN-bp have more affective disorders, particularly major depression, than those with AN-r.[3] The prevalence of substance-use disorders[4] and impulsive behaviors[5] are higher in AN-bp than AN-r. Borderline personality disorder is more common in AN-bp, whereas avoidant personality disorder is more often observed in AN-r.[6]

AN subtypes also have divergent underlying causes,[7] while the etiology of AN as a whole has been linked to neural systems associated with hunger regulation, cognitive control, self-regulation, and reward processing.[8-10] Previous studies on behavioral measures have reported differences between AN subtypes in impulsive behavior[11, 12] and cognition.[7] In addition, different brain responses measured by functional magnetic resonance imaging (fMRI) have been observed between AN subtypes during a set-shifting task.[13] A better understanding of the neural underpinnings of AN subtypes may improve our knowledge of eating disorder pathophysiology and help to develop evidence-based treatment approaches and tailored treatment approaches for both AN subtypes. However, since few studies have used fMRI to examine differences in neural mechanisms between AN subtypes, the neurobiological basis for the two subtypes remains unclear.

Sensitivity to reward and punishment is related to sensation/novelty-seeking and risk-taking behaviors,[14] which differ among AN subtypes as mentioned above, although alteration of the reward system has also been reported in AN as a whole.[8-10] In addition, differences in sensitivity to reward and/or punishment between AN subtypes have been found using self-administered

questionnaires[15-17] and behavioral measures (i.e., temporal discounting and delay discounting).[18, 19] Moreover, neural responses in the caudate were reported to vary between women recovered from AN-r[20] and women recovered from bulimia nervosa[21] (similar to AN-bp in terms of binge-eating and purging) in fMRI studies of reward systems using a monetary guessing task.[22] These results suggested that reward system functionality differs between AN subtypes. However, no existing fMRI studies have investigated neural differences in reward systems between AN subtypes.

In the current study, to investigate differences in the neural responses of reward and punishment processing among AN-r, AN-bp, and CTL (healthy control participants), participants underwent fMRI while performing a Monetary Incentive Delay Task (MID) task[23]. Although food is the primary reward and may be very influential in the reward system of AN, it is extremely difficult to define reward and punishment using food, especially for patients with AN. Therefore, we used a secondary reward: money. The MID task has previously been used to examine the neural responses in incentive processing. An advantage of using the MID task is that it can examine the anticipation phase of gains and losses. The anticipation phase is important because the anticipation stage influences subsequent thought and behavior[24] and may account for the differences between AN subtypes (e.g., binge-eating and purging). Here, we elucidate differences in fMRI responses in the two AN subtypes during anticipation of reward and punishment processing (i.e., monetary gain and loss).

## Methods

Participants and Clinical Assessments

All participants were women aged 20 to 49. The study sample comprised 11 patients with AN-r, 12 with AN-bp, and 20 healthy control women. All participants were right-handed except one with AN-bp. All AN participants were recruited from Kyoto University Hospital. Three trained psychiatrists administered the Japanese version of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders[25] and Axis II Disorders[26] to all participants. All 11 AN-r participants and eight AN-bp participants fulfilled the criteria of the DSM-IV. To avoid the effects of diagnostic crossover as much as possible, we chose only patients whose duration of illness was over five years. In addition, all AN-r participants reported no previous history of other eating disorders. Four AN-bp participants did not fulfill the AN criteria because they continued menstruating. Furthermore, two of these participants had body mass indices (BMIs) slightly above 18.5 $kg/m^2$. However, all four of these participants fulfilled the criteria of AN-bp or AN-bp in partial remission according to the DSM-5 criteria. Therefore, we included these four participants in the AN-bp group. None of the participants with AN were using contraceptives or receiving hormonal therapy. In addition, no AN participants had previous or current diagnoses of psychotic disorders, or met current diagnosis criteria for major depressive disorder or bipolar disorder. However, some AN participants had comorbid symptoms such as anxiety, depressive mood, aggression, and/or impulsiveness. For the treatment of these comorbid symptoms, two AN-r participants and four AN-bp were undergoing stable medical treatment that included combinations of psychoactive medications (i.e., antipsychotics, antidepressants, antianxiolytics, and antiepileptics) (Table S1). The exclusion criteria for the CTL group were a history of any Axis I or Axis II disorder of DSM-IV-TR, a history of psychopharmacological treatment, a history of neurological problems, or concomitant medical diseases. The present study was approved by the Committee on Medical Ethics of Kyoto University and was carried out in accordance with the Code of Ethics of the World Medical Association and the standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent from each of the participants was obtained after offering a complete description of the present study.

In all participants, degrees of severity for eating disorder, depressive state, and trait anxiety were assessed with the Japanese version of the Eating Disorder Examination Questionnaire 6.0 (EDE-Q),[27, 28] the Beck Depression Inventory-Second Edition (BDI-II),[29, 30] and the State-Trait Anxiety Inventory in Japanese (STAI-JYZ),[31] respectively. While anxiety was assessed by the STAI-JYZ, the examination was performed not before the fMRI but during a prior psychological examination or interview. Therefore, we focused on trait-anxiety, not state-anxiety, in the present study.

MID Task

All participants completed a Japanese version of the MID task[32] based on the original version.[23] The MID task consisted of 90 trials. In each trial, shapes appeared in the following order: 1) one of nine cue shapes (2001 ms); 2) a crosshair for a variable interval (2000–2500 ms); and 3) finally, a white square target for a variable duration (160–500 ms). Participants tried to press a button during the presentation of the white target. If participants succeeded in doing so, they gained, or avoided losing, money. After the target disappeared, feedback appeared (1919 ms), which notified participants not only how much money they had gained or lost in that trial but also their total acquisition amount up to that point. For all participants, the target duration started at 200 ms. During the task, target durations were changed according to each participant's reaction time and set such that participants would succeed in approximately 66% of the trials.

There were nine shapes used as cues: four types of circles, four types of squares, and one type of triangle. Circles were potential gain cues. A circle with zero, one, two, or three horizontal lines signaled the possibility of winning ¥0, ¥20, ¥100, or ¥500, respectively. In contrast, squares were potential loss cues. Squares with zero, one, two, or three horizontal lines signaled the possibility of losing ¥0, ¥20, ¥100, or ¥500, respectively. Each type of circle and square appeared nine times during a run. The triangle signaled that no response was required and that participants should not press the button during the trial. The triangle appeared 18 times during a run. Cues appeared pseudo-randomly within a run. The participants were trained for about 5 min and tested for their understanding of the cues. The participants were told that they would receive real money of the same amount that they

gained during this task after the experiment. Stimulus presentation and response collection were performed using E-Prime 2.0 Professional software (Psychology Software Tools, Sharpsburg, PA, USA).

fMRI Acquisition

Acquisition of functional imaging was conducted on a 3-T whole-body scanner equipped with a 32-channel phased array head coil (Trio, Siemens, Erlangen, Germany). The image-acquisition parameters were as follows: TR = 2000 ms; TE = 30 ms; flip angle = 90°; field of view = 192 × 192 mm; matrix size = 64 × 64; and 34 interleaved axial slices with 4 mm thickness without gaps (4-mm cubic voxels). The first two volumes were discarded to allow for signal stabilization. Real-time reconstruction, z-shimming correction, and a tilted acquisition sequence at –30° to the anterior commissure-posterior commissure line were used to minimize signal loss in the orbitofrontal and temporal cortex.[33] Each run included 368 volumes. Each participant lay supine on a scanner bed and held a button-response device in the dominant hand. The visual stimuli were back-projected onto a display through a built-in mirror.

fMRI and Statistical Analyses

Imaging data were analyzed with SPM8 (Wellcome Department of Imaging Neuroscience, University of London, London, UK) on MATLAB 2014b (MathWorks, Natick, MA, USA). The functional images were corrected for the different timing of acquisition of different slices. The timing-corrected images were spatially realigned to the first image to remove head movement artifact. The realigned images were spatially normalized to fit to the EPI template provided in SPM8. Then, the normalized images were spatially smoothed with a Gaussian kernel with a full width at half maximum (FWHM) of 8 mm.

Three conditions were modeled during the anticipation phase: neutral, all magnitudes of gains (i.e., +¥0, +¥20, +¥100, and +¥500), and all magnitudes of losses (i.e., –¥0, –¥20, –¥100, and –¥500). In the present study, we analyzed brain activation during the anticipation phase, defined as the 4 s spanning from the onset of presentation of the cue shape to the onset of presentation of the white square target. Each of the three conditions (i.e., neutral, all magnitudes of gains, and all magnitudes of

losses) was separately modeled as a regressor for first-level multi-regression analysis. Six motion parameters were included as additional nuisance regressors. Low frequency noise was removed by high-pass filtering the time series using a cut-off period of 128 s. By applying the linear contrast to the parameter estimates, images reflecting the magnitude of correlation between the signals and the model of interest were computed for each of the three conditions. Then, the following two contrasts were computed: (a) all magnitudes of gains > neutral; and (b) all magnitudes of losses > neutral. The resultant images were used for the subsequent second-level analysis.

Second-level statistical parametric maps were produced using a one-sample t-test for each group and had significance thresholds of $p < 0.001$ uncorrected at the voxel level and $p < 0.05$ family-wise error rate-corrected at the cluster level. Between-group analysis was conducted using whole-brain one-way analysis of variance (ANOVA). To avoid setting the minimum cluster size threshold arbitrarily, between-group analysis was conducted with a corrected threshold of $p < 0.05$, which was determined using the AlphaSim program in the REST software (http://www.restfmri.net) (parameters: single voxel $p < 0.001$, 1000 iterations, FWHM = 8 mm). This AlphaSim-corrected threshold of $p < 0.05$ was equal to a combined threshold of $p < 0.001$ for each voxel and a cluster size of at least 70 voxels. We also performed analysis of covariance (ANCOVA) including BMI as a covariate. Additional analyses on the parameter estimates extracted at each of the peak voxels of significant clusters in which group differences were found in the whole-brain one-way ANOVA (i.e., the rostral anterior cingulate cortex [ACC] and right posterior insula; see Results) were conducted with one-way ANOVA using SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA). In addition, following the previous studies,[23, 34] we also examined the effects of gain or loss magnitude (¥0, ¥20, ¥100, and ¥500) on the extracted parameter estimates at each peak voxel of significant clusters in the rostral ACC and right posterior insula. Each of the nine conditions (i.e., neutral, four magnitudes of gains, and four magnitudes of losses) was separately modeled as a regressor for first-level multi-regression analysis. Then, the following eight contrasts were computed: (a) –¥500 > neutral; (b) –¥100 > neutral; (c) –¥20 > neutral; (d) –¥0 > neutral; (e) +¥500 > neutral; (f) +¥100 > neutral; (g) +¥20 > neutral; and (h) +¥0 > neutral. To investigate group differences, the parameter estimates of

each peak voxel of each contrast were compared using a mixed-model ANOVA (magnitude × group) for each incentive valence (loss, gain) with magnitudes (¥0, ¥20, ¥100, ¥500) as within-participant factors and group (CTL, AN-r, and AN-bp) as the between-participant factor, using SPSS.

Statistical analyses of clinical data, as well as correlation analyses between brain activation and clinical data, were also performed. For between-group comparisons of the mean, distribution normality was tested using the Shapiro-Wilk Normality Test. Then, normally and non-normally distributed data were analyzed using one-way ANOVA and the Kruskal-Wallis test, respectively. Correlations between brain activation of each large incentive condition (+¥500, –¥500) > neutral in the peak voxels and demographic/clinical data (age, BMI, global score of EDE-Q, BDI-II, and trait anxiety) were determined by Pearson correlation coefficients in each group. A corrected alpha of 0.01 (0.05/5 [five clinical measures]) was chosen as a significance threshold.

**Results**

Participant Characteristics

Clinical characteristics are summarized in Table 1. The CTL, AN-r, and AN-bp participants did not differ in terms of age, years of education, or duration of AN ($p > 0.05$), but there were significant differences in BMI, the global score of EDE-Q, BDI-II, and trait anxiety score of STAI-JYZ ($p < 0.001$). Post-hoc analyses showed that AN-bp participants had significantly higher scores in the global score of EDE-Q and trait anxiety than CTL and AN-r participants. In addition, AN-bp and AN-r participants had significantly higher scores in BDI-II than CTL participants. CTL, AN-r, and AN-bp participants did not differ in terms of the performance of the MID task (Table 1).

fMRI Data

**Whole-brain one-way ANOVA. Gain anticipation.** In each of the three groups, overall anticipation of gains > neutral induced activation in the striatum (i.e., putamen and caudate), thalamus, pallidum, supplementary motor area, frontal pole, and cerebellum (Figure 1A). However, whole-brain analyses with neither one-way ANOVA nor one-way ANCOVA (including BMI as a covariate) showed a significant main effect of group.

**Loss anticipation.** Activation during overall anticipation of losses > neutral was topographically similar to those during anticipation of gain (Figure 1B). A one-way ANOVA showed a significant main effect of group in the rostral ACC ($x = 4$, $y = 26$, $z = –4$, 152 voxels, $Z = 3.67$) and the right posterior insula ($x = 44$, $y = –2$, $z = –10$, 75 voxels, $Z = 3.48$). Analyses on the parameter estimates extracted at the peak voxels revealed that there was a statistically significant difference between the groups in both the rostral ACC [$F (2, 40) = 12.06$, $p < 0.001$, $\eta^2 = 0.38$] and right posterior insula [$F (2, 40) = 10.30$, $p < 0.001$, $\eta^2 = 0.34$]. Games-Howell post-hoc analyses showed that the AN-bp group had significantly ($p < 0.05$) higher brain activity than the AN-r and CTL groups in both regions. In contrast, there was no significant difference between AN-r and CTL in both the rostral ACC ($p = 0.79$) and right posterior insula ($p = 0.47$) (Figure 2). A one-way ANCOVA including BMI as a covariate did not alter the result (Figure S1), suggesting that the findings were not attributable to BMI.

**Magnitude effects.** Because the whole-brain analysis showed significant group effects on brain activation in two regions (i.e., the rostral ACC and right posterior insula) during loss anticipation, a mixed-model ANOVA (magnitude × group) for loss was conducted for the two peak voxels, the rostral ACC (x = 4, y = 26, z = –4) and the right posterior insula (x = 44, y = –2, z = –10). A main effect of magnitude was found in the rostral ACC [$F (3, 120) = 4.34$, $p = 0.006$, partial $\eta^2 = 0.098$], but not in the right posterior insula [$F (3, 120) = 0.17$, $p = 0.92$, partial $\eta^2 = 0.004$]. In addition, a linear trend analysis indicated that each of the groups showed a linear increase in activation in the rostral ACC, but again not in the right posterior insula. A significant interaction between group and magnitude was not found in either region (Figure 3).

In each group, there was no significant correlation between brain activation in response to each large incentive condition (+¥500, –¥500) > neutral in the peak voxels and any of the demographic/clinical variables (i.e., age, BMI, global score of EDE-Q, BDI-II, and trait anxiety).

**Discussion**

To our knowledge, this is the first fMRI study to investigate differences in the neural processing of reward and punishment between AN subtypes (i.e., AN-r and AN-bp). We found a significant group difference in brain response during punishment processing, but not during reward processing (i.e., during the anticipation of losses but not gains). Specifically, the AN-bp group showed higher brain activation than either the AN-r or the CTL group during loss anticipation in the rostral ACC and the right posterior insula. These findings suggest that different neurobiological correlates during incentive processing may exist between AN subtypes.

The main finding of the present study was that AN-bp participants showed greater recruitment of the rostral ACC and the posterior insula during loss anticipation compared with AN-r and CTL participants. The ACC and the posterior insula have been suggested to be involved in modulating the emotional aspects of the sensory perception of painful stimuli.[35, 36] Brain activity in the rostral ACC has been linked to aversive stimuli such as monetary losses[37] and errors during the punishment condition[38] and has been associated with emotional information processing and emotional conflict resolution.[39, 40] In contrast, the insula plays a role in integrating the body's homeostatic and emotional information via connections with the limbic and cortical areas[41] and in cognitive, affective, and regulatory functions.[42] Specifically, the posterior part of the insula is functionally connected to the primary and secondary somatomotor cortices and is activated in relation to somatosensory stimuli with affective or motivational significance.[43] Therefore, the observed higher brain activation in the rostral ACC and the posterior insula in AN-bp participants during loss anticipation may reflect higher emotional and somatosensory arousal for potentially punishing stimuli in AN-bp participants.

Moreover, in the present study, each of the groups showed increased brain activation relative to the increased magnitude of loss in the rostral ACC, but not of that in the right posterior insula. A previous study using fMRI reported that the ACC, but not the posterior insula, showed increased signal changes in relation to the expectation of pain with increased unpleasantness.[35] In addition, rostral ACC activation has been shown to predict valence ratings of prosody from positive, neutral, and negative categories,[44] and to be correlated with the change in pain ratings.[45] In another

study, however, such effects were not observed in the posterior insula.[36] These studies suggest that activation in the rostral ACC, but not in the posterior insula, may correlate with unpleasantness such as pain intensity. In fact, a previous study showed that the rostral ACC and posterior insula are involved in different aspects of pain processing.[36] Our findings of different patterns of brain activation between the rostral ACC and posterior insula may be in line with the results of the previous study; the rostral ACC and posterior insula may be involved in different aspects of the processing of potential aversive stimuli.

The regions that showed altered brain responses in the present study (i.e., the rostral ACC and posterior insula) have been implicated in AN pathology.[46] Insular dysfunction has specifically been reported.[47-49] Furthermore, studies have reported insular function differences among AN subtypes. For example, one previous study showed altered brain activation in the insula between AN-r and AN-bp during a set-shifting task.[13] Another study found altered brain activation in the insula in response to the taste of sucrose between recovered AN-r and recovered bulimia nervosa.[50] The combination of these earlier results and our findings imply that insular dysfunction is more evident in AN-bp and may contribute to binge-eating behavior in AN-bp.

In the present study, participants with AN-bp showed greater recruitment of neural regions implicated in emotional and somatosensory arousal compared with AN-r and CTL participants. These altered brain responses suggest that individuals with AN-bp would be more sensitive to potential punishment stimuli. This is consistent with a study that used self-administered questionnaires and found that individuals with AN-bp displayed higher levels of punishment sensitivity than those with AN-r, whereas there were no differences in reward sensitivity between the two groups.[17] Additionally, binge eating has been thought to occur in response to strong negative emotions to release the individual from the momentary negative emotional experience.[51, 52] Our findings suggest that individuals with AN-bp have higher sensitivity to aversive stimuli, which may lead to strong negative emotions in daily life and, in turn, to a continuation of binge eating.

Our finding that the AN-r group was not significantly different from CTL regarding neural responses in reward and punishment processing is incompatible with the results of previous fMRI

studies[20, 53, 54] that showed that reward or punishment processing in AN-r differs from that in CTL. In previous studies using a monetary guessing task[22], AN-r showed altered response in the striatum.[20, 53] In addition, another study using the MID task showed that recovered AN (mainly AN-r) had elevated dorsolateral prefrontal cortex activity during the anticipation phase of gains.[54] Differences among studies may have arisen for several reasons. First, the studies using a monetary guessing task focused on the outcomes of loss and gain,[20, 53] while we examined the anticipation of loss and gain. The study using the MID task focused on anticipation, but only that of gain.[54] Second, the previous studies used different analysis methods (e.g., region of interests[20, 53, 54] and time course analysis[20]) and focused on the main effect of condition (loss/gain)[53] and the group-by-condition interaction.[20, 53] Third, our result of no significant differences between the two groups may be attributable to our limited sample size, especially when employing whole-brain analyses. Fourth, while participants in the previous studies were individuals with recovered AN-r[20, 54] or adolescents with AN-r[53], the participants of our study were adults with AN-r who had not recovered.

There are limitations to the present study. Firstly, the sample sizes of both of AN-r and AN-bp groups were small by current normative standards. Because of the small sample size, more variable and weak brain activations would not be detected,[55] and group differences may have been overlooked. Secondly, the participants were all women, and these findings may not generalize to men. In addition, the AN participants were chronically affected, and the average age was over 30 years. Therefore, our findings may not generalize to adolescents or young adult women. Thirdly, while we chose individuals whose duration of illness was over five years and whose diagnosis had never changed in the AN-r group, the possibility of potential diagnostic crossover cannot be excluded, as a previous study has pointed out.[56] Finally, some participants had mild mood/emotional symptoms and received psychoactive medications, which have the potential ability to modify the central reward system, and may diminish brain activity in the reward system.[57-60] Therefore, the effects of medicines cannot be excluded in the current study.

In conclusion, this is the first fMRI study to investigate differences in reward and punishment processing between AN subtypes. The present study provides preliminary evidence that

there are neurobiological differences between AN subtypes in the reward system, especially punishment processing. This advances our understanding of these disorders, which may inform the development of evidence-based treatment approaches and tailored treatment approaches for AN subtypes. However, the specific neurobiological differences between AN subtypes are still uncertain, and further studies are needed to clarify differences in the etiology of the AN subtypes.

**Acknowledgements**

This work was supported by JSPS KAKENHI Grant Numbers JP15K09864, JP24591707, JP16H06397, JP16H06402, JP16H06395, and JP15H01690 and MEXT KAKENHI Grant Numbers JP23120009 and JP16H06572.

**Disclosure Statement**

Dr. Sugihara reports grants from Japan Society for the Promotion of Science, during the conduct of the study. Dr. Takahashi reports grants from The Ministry of Education, Culture, Sports, Science and Technology, during the conduct of the study. Dr. Murai reports grants from Japan Society for the Promotion of Science, during the conduct of the study. Dr. Noma reports grants from Japan Society for the Promotion of Science, during the conduct of the study. Rest of the authors, declare no conflicts of interest.

**Author Contributions**

Conception and design of the study: S.N., H.T., E.M., M.I.

Acquisition and analysis of data: E.M., S.N., G.S., M.I., T.N., M.K., N.M.

Interpretation of data: E.M., G.S., S.N., H.T., T.M.

Drafting the manuscript or figures: E.M., G.S., H.T., S.N., T.M.

All authors read and approved the final version of the manuscript.

**References**


1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th ed.* American Psychiatric Association, Alexandria, VA, 2013.

2. Cassin SE, von Ranson KM. Personality and eating disorders: a decade in review. *Clin. Psychol. Rev*. 2005; **25**: 895-916.

3. Herzog DB, Keller MB, Sacks NR, Yeh CJ, Lavori PW. Psychiatric comorbidity in treatment-seeking anorexics and bulimics. *J. Am. Acad. Child Adolesc. Psychiatry*. 1992; **31**: 810-818.

4. Fouladi F, Mitchell JE, Crosby RD *et al.* Prevalence of Alcohol and Other Substance Use in Patients with Eating Disorders. *Eur. Eat. Disord. Rev*. 2015; **23**: 531-536.

5. Nagata T, Kawarada Y, Kiriike N, Iketani T. Multi-impulsivity of Japanese patients with eating disorders: primary and secondary impulsivity. *Psychiatry Res*. 2000; **94**: 239-250.

6. Diaz-Marsa M, Carrasco JL, Saiz J. A study of temperament and personality in anorexia and bulimia nervosa. *J. Pers. Disord*. 2000; **14**: 352-359.

7. Van Autreve S, De Baene W, Baeken C, van Heeringen C, Vervaet M. Do restrictive and bingeing/purging subtypes of anorexia nervosa differ on central coherence and set shifting? *Eur. Eat. Disord. Rev.* 2013; **21**: 308-314.

8. Wierenga CE, Ely A, Bischoff-Grethe A, Bailer UF, Simmons AN, Kaye WH. Are Extremes of Consumption in Eating Disorders Related to an Altered Balance between Reward and Inhibition? *Front. Behav. Neurosci*. 2014; **8**: 410.

9. O'Hara CB, Campbell IC, Schmidt U. A reward-centred model of anorexia nervosa: a focussed narrative review of the neurological and psychophysiological literature. *Neurosci. Biobehav. Rev*. 2015; **52**: 131-152.

10. Steinglass JE, Walsh BT. Neurobiological model of the persistence of anorexia nervosa. *J. Eat. Disord*. 2016; **4**: 19.

11. Claes L, Nederkoorn C, Vandereycken W, Guerrieri R, Vertommen H. Impulsiveness and lack of inhibitory control in eating disorders. *Eat. Behav*. 2006; **7**: 196-203.

12. Galimberti E, Martoni RM, Cavallini MC, Erzegovesi S, Bellodi L. Motor inhibition and cognitive flexibility in eating disorder subtypes. *Prog. Neuropsychopharmacol. Biol. Psychiatry*. 2012; **36**: 307-312.

13. Van Autreve S, De Baene W, Baeken C, van Heeringen K, Vancayseele N, Vervaet M. Differential Neural Correlates of Set-Shifting in the Bingeing-Purging and Restrictive Subtypes of Anorexia Nervosa: An fMRI Study. *Eur. Eat. Disord. Rev*. 2016; **24**: 277-285.

14. Geier C, Luna B. The maturation of incentive processing and cognitive control. *Pharmacol. Biochem. Behav*. 2009; **93**: 212-221.

15. Harrison A, O'Brien N, Lopez C, Treasure J. Sensitivity to reward and punishment in eating disorders. *Psychiatry Res*. 2010; **177**: 1-11.

16. Jappe LM, Frank GK, Shott ME *et al.* Heightened sensitivity to reward and punishment in anorexia nervosa. *Int. J. Eat. Disord*. 2011; **44**: 317-324.

17. Glashouwer KA, Bloot L, Veenstra EM, Franken IH, de Jong PJ. Heightened sensitivity to punishment and reward in anorexia nervosa. *Appetite*. 2014; **75**: 97-102.

18. Steinglass JE, Figner B, Berkowitz S, Simpson HB, Weber EU, Walsh BT. Increased capacity to delay reward in anorexia nervosa. *J. Int. Neuropsychol. Soc*. 2012; **18**: 773-780.

19. Decker JH, Figner B, Steinglass JE. On Weight and Waiting: Delay Discounting in Anorexia Nervosa Pretreatment and Posttreatment. *Biol. Psychiatry*. 2015; **78**: 606-614.

20. Wagner A, Aizenstein H, Venkatraman VK *et al.* Altered reward processing in women recovered from anorexia nervosa. *Am. J. Psychiatry*. 2007; **164**: 1842-1849.

21. Wagner A, Aizenstein H, Venkatraman VK *et al.* Altered striatal response to reward in bulimia nervosa after recovery. *Int. J. Eat. Disord.* 2010; **43**: 289-294.

22. Delgado MR, Nystrom LE, Fissell C, Noll DC, Fiez JA. Tracking the hemodynamic responses to reward and punishment in the striatum. *J. Neurophysiol*. 2000; **84**: 3072-3077.

23. Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH. Neural responses to monetary incentives in major depression. *Biol. Psychiatry*. 2008; **63**: 686-692.

24. Knutson B, Taylor J, Kaufman M, Peterson R, Glover G. Distributed neural representation of expected value. *J. Neurosci*. 2005; **25**: 4806-4812.

25. Takahashi S, Kitamura N, Okano T, Tomita T, Kikuchi A. *Japanese version of Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-IV)*. Nihon Hyoronsha, Tokyo, 2010.

26. Takahashi S, Ohsone A. *Japanese version of SCID-II (Structured Clinical Interview for DSM-IV Axis II Personality Disorders).* Igaku-Shoin, Tokyo: 2002.

27. Fairburn CG, Beglin SJ. Eating disorder examination questionnaire (EDE-Q 6.0). In: Fairburn CG (ed.). *Cognitive behavior therapy and eating disorders.* Guilford Press, New York, 2008; 309-313.

28. Nakai Y, Noma S, Nin K, Teramukai S, Wonderlich SA. Eating disorder behaviors and attitudes in Japanese adolescent girls and boys in high schools. *Psychiatry Res*. 2015; **230**: 722-724.

29. Beck AT, Steer RA, Brown GK. *Manual for the beck depression inventory-II*. Psychological Corporation, San Antonio, TX, 1996.

30. Kojima M, Furukawa TA, Takahashi H, Kawai M, Nagaya T, Tokudome S. Cross-cultural validation of the Beck Depression Inventory-II in Japan. *Psychiatry Res*. 2002; **110**: 291-299.

31. Hidano T, Fukuhara M, Iwawaki M, Soga S, Spielberger CD. *New STAI Manual State-Trait Anxiety Inventory-form JYZ.* Jitsumu Kyouiku Press, Tokyo, 2000.

32. Funayama T, Ikeda Y, Tateno A *et al.* Modafinil augments brain activation associated with reward anticipation in the nucleus accumbens. *Psychopharmacology (Berl).* 2014; **231**: 3217-3228.

33. Weiskopf N, Hutton C, Josephs O, Deichmann R. Optimal EPI parameters for reduction of susceptibility-induced BOLD sensitivity losses: a whole-brain analysis at 3 T and 1.5 T. *Neuroimage.* 2006; **33**: 493-504.

34. Samanez-Larkin GR, Gibbs SE, Khanna K, Nielsen L, Carstensen LL, Knutson B. Anticipation of monetary gain but not loss in healthy older adults. *Nat. Neurosci*. 2007; **10**: 787-791.

35. Sawamoto N, Honda M, Okada T *et al.* Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal

operculum/posterior insula: an event-related functional magnetic resonance imaging study. *J. Neurosci*. 2000; **20**: 7438-7445.

36. Rance M, Ruttorf M, Nees F, Schad LR, Flor H. Real time fMRI feedback of the anterior cingulate and posterior insular cortex in the processing of pain. *Hum. Brain Mapp*. 2014; **35**: 5784-5798.

37. Taylor SF, Martis B, Fitzgerald KD *et al.* Medial frontal cortex activity and loss-related responses to errors. *J. Neurosci*. 2006; **26**: 4063-4070.

38. Simoes-Franklin C, Hester R, Shpaner M, Foxe JJ, Garavan H. Executive function and error detection: The effect of motivation on cingulate and ventral striatum activity. *Hum. Brain Mapp*. 2010; **31**: 458-469.

39. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn. Sci*. 2000; **4**: 215-222.

40. Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron*. 2006; **51**: 871-882.

41. Villafuerte S, Heitzeg MM, Foley S *et al.* Impulsiveness and insula activation during reward anticipation are associated with genetic variants in GABRA2 in a family sample enriched for alcoholism. *Mol. Psychiatry*. 2012; **17**: 511-519.

42. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. *Brain Struct. Funct*. 2010; **214**: 655-667.

43. Deen B, Pitskel NB, Pelphrey KA. Three systems of insular functional connectivity identified with cluster analysis. *Cereb. Cortex*. 2011; **21**: 1498-1506.

44. Gröne M, Dyck M, Koush Y *et al.* Upregulation of the rostral anterior cingulate cortex can alter the perception of emotions: fMRI-based neurofeedback at 3 and 7 T. *Brain Topogr*. 2015; **28**: 197-207.

45. deCharms RC, Maeda F, Glover GH *et al.* Control over brain activation and pain learned by using real-time functional MRI. *Proc. Natl. Acad. Sci. USA*. 2005; **102**: 18626-18631.

46. Kaye WH, Fudge JL, Paulus M. New insights into symptoms and neurocircuit function of anorexia nervosa. *Nat. Rev. Neurosci*. 2009; **10**: 573-584.

47. Nunn K, Frampton I, Fuglset TS, Torzsok-Sonnevend M, Lask B. Anorexia nervosa and the insula. *Med. Hypotheses*. 2011; **76**: 353-357.

48. Strigo IA, Matthews SC, Simmons AN *et al.* Altered insula activation during pain anticipation in individuals recovered from anorexia nervosa: evidence of interoceptive dysregulation. *Int. J. Eat. Disord*. 2013; **46**: 23-33.

49. Frank GK, Collier S, Shott ME, O'Reilly RC. Prediction error and somatosensory insula activation in women recovered from anorexia nervosa. *J. Psychiatry Neurosci*. 2016; **41**: 304-311.

50. Oberndorfer TA, Frank GK, Simmons AN *et al.* Altered insula response to sweet taste processing after recovery from anorexia and bulimia nervosa. *Am. J. Psychiatry*. 2013; **170**: 1143-1151.

51. Miltenberger RG. The role of automatic negative reinforcement in clinical problems. *Int. J. Behav. Consult. Ther*. 2005; **1**: 1-11.

52. Culbert KM, Lavender JM, Crosby RD *et al.* Associations between negative affect and binge/purge behaviors in women with anorexia nervosa: Considering the role of negative urgency. *Compr. Psychiatry*. 2016; **66**: 104-112.

53. Bischoff-Grethe A, McCurdy D, Grenesko-Stevens E *et al.* Altered brain response to reward and punishment in adolescents with Anorexia nervosa. *Psychiatry Res.* 2013; **214**: 331-340.

54. Ehrlich S, Geisler D, Ritschel F *et al.* Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa. *J. Psychiatry Neurosci*. 2015; **40**: 307-315.

55. Seghier ML, Lazeyras F, Pegna AJ, Annoni JM, Khateb A. Group analysis and the subject factor in functional magnetic resonance imaging: analysis of fifty right-handed healthy subjects in a semantic language task. *Hum. Brain Mapp*. 2008; **29**: 461-477.

56. Eddy KT, Dorer DJ, Franko DL, Tahilani K, Thompson-Brenner H, Herzog DB. Diagnostic crossover in anorexia nervosa and bulimia nervosa: implications for DSM-V. *Am. J. Psychiatry*. 2008; **165**: 245-250.

57. Marutani T, Yahata N, Ikeda Y *et al.* Functional magnetic resonance imaging study on the effects of acute single administration of paroxetine on motivation-related brain activity. *Psychiatry Clin. Neurosci.* 2011; **65**: 191-198.

58. McCabe C, Mishor Z, Cowen PJ, Harmer CJ. Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. *Biol. Psychiatry*. 2010; **67**: 439-445.

59. Kirsch P, Ronshausen S, Mier D, Gallhofer B. The influence of antipsychotic treatment on brain reward system reactivity in schizophrenia patients. *Pharmacopsychiatry*. 2007; **40**: 196-198.

60. Wise RG, Lujan BJ, Schweinhardt P, Peskett GD, Rogers R, Tracey I. The anxiolytic effects of midazolam during anticipation to pain revealed using fMRI. *Magn. Reson. Imaging.* 2007; **25**: 801-810.

**Figure Legends**

Figure 1. Functional magnetic resonance imaging showing brain activity for each of the groups

A. Overall anticipation of gains > neutral contrasts for the three groups. B. Overall anticipation of losses > neutral contrasts for the three groups. AN-bp = binge eating/purging-type anorexia nervosa; AN-r = restricting-type anorexia nervosa; CTL = healthy control participants. The threshold for significant differences was $p < 0.001$ uncorrected at the voxel level; $p < 0.05$ familywise error rate-corrected at the cluster level.

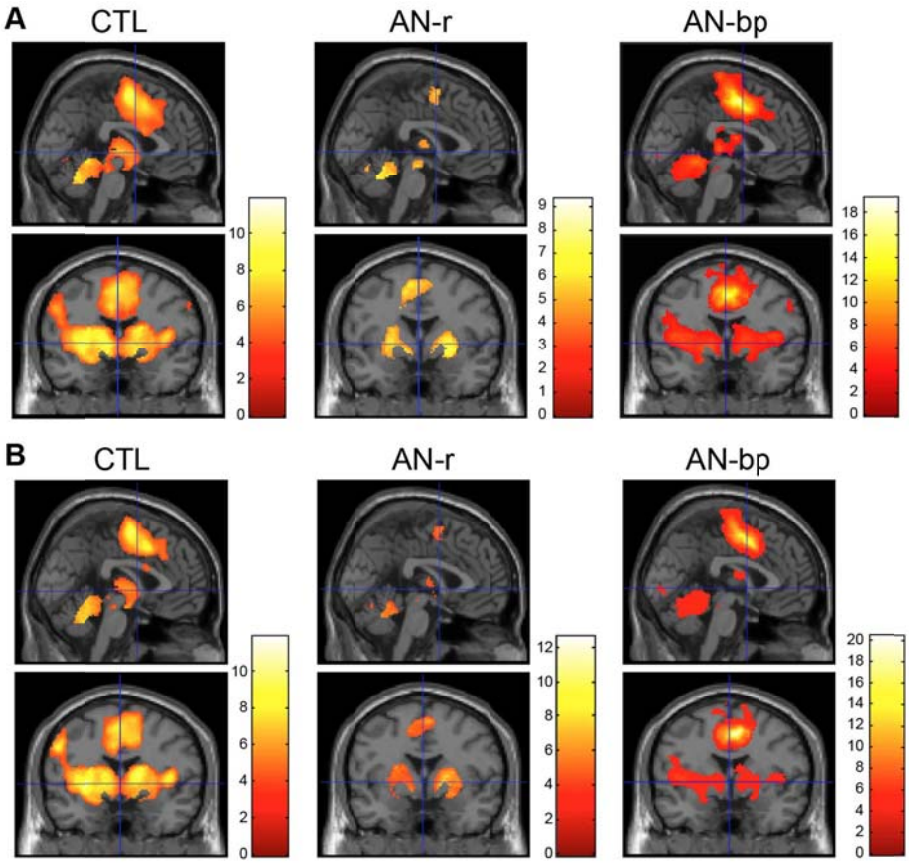



Figure 2. Group differences (Loss > Neutral) in functional magnetic resonance imaging

Significant clusters determined by ANOVA (main effect of group). A1–A2. Scans (A1) and contrast estimates of peak voxel (A2) in the rostral ACC [4, 26, –4]. B1–B2. Scans (B1) and contrast estimates of peak voxel (B2) in the right posterior insula [44, –2, –10]. Mean ± SD is shown for each trial type.

ACC = anterior cingulate cortex; AN-bp = binge eating/purging-type anorexia nervosa; AN-r = restricting-type anorexia nervosa; CTL = healthy control participants.

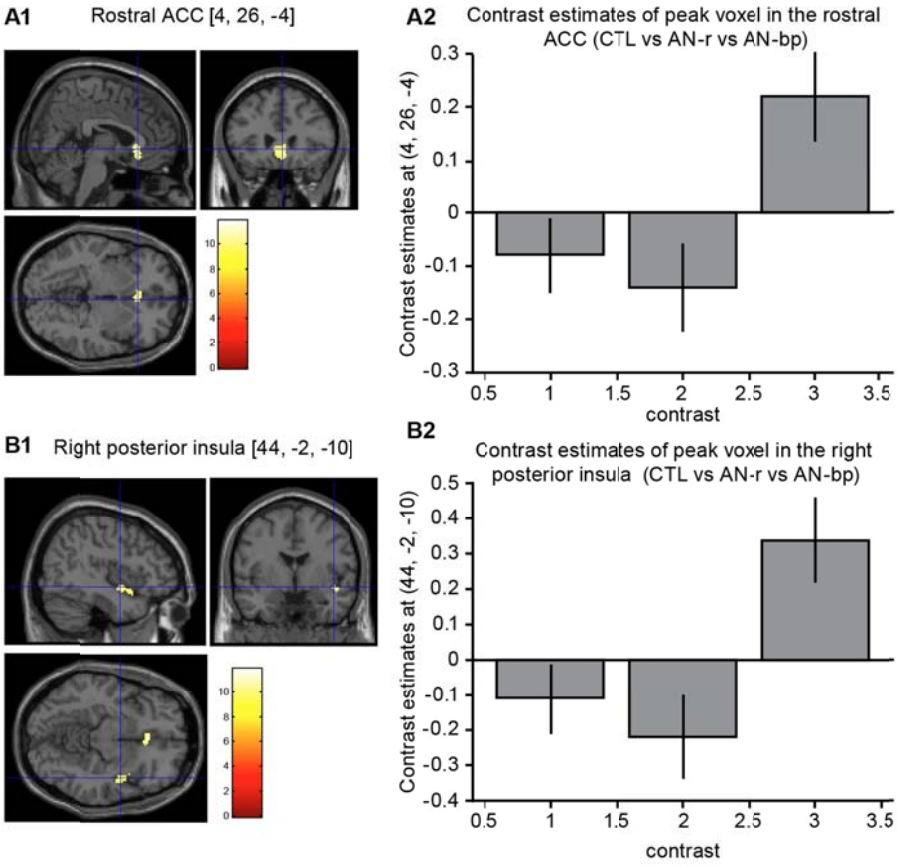
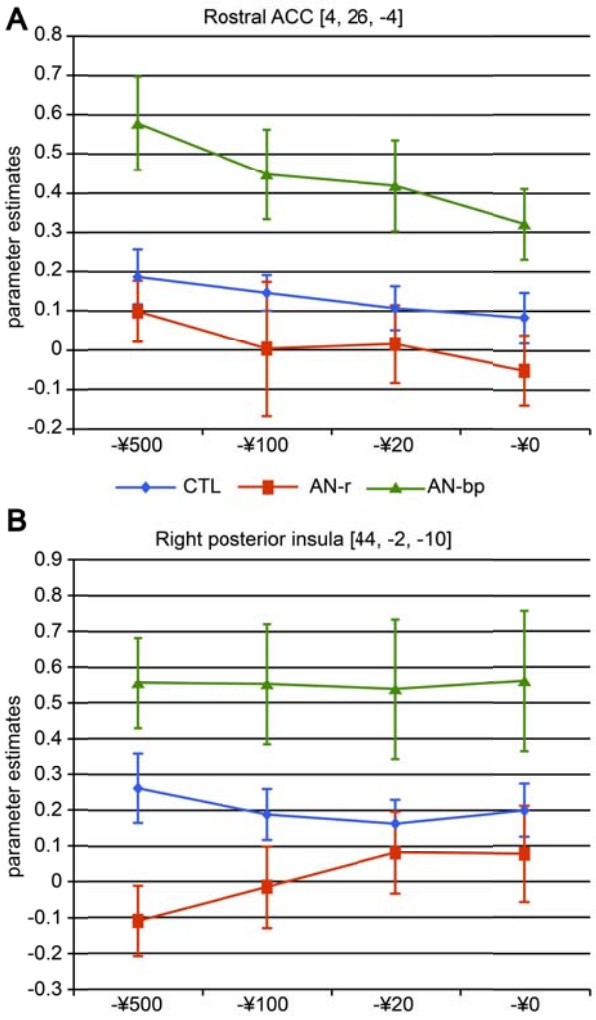



Figure 3. The activation of peak voxels by group in the rostral anterior cingulate cortex and the right posterior insula during the monetary incentive delay task

Relative levels of activation within the rostral ACC (A) and the right posterior insula (B) plotted against each monetary loss. ¥ = potential amount lost per trial; ACC = anterior cingulate cortex; AN-bp = binge eating/purging-type anorexia nervosa; AN-r = restricting-type anorexia nervosa; CTL = healthy control participants. Mean ± SD is shown.



**List of supporting information**

1. Table_S1_ Figure_S1_Suppinfo.docx

**Table 1.** Demographic and clinical information and behavioral results of the monetary incentive delay task

| | CTL (N = 20) Mean ± SD | AN-r (N = 11) Mean ± SD | AN-bp (N = 12) Mean ± SD | ANOVA F | p | $\eta^2$ | post-hoc test (Tukey HSD) comparison |
|---|---|---|---|---|---|---|---|
| Age (years) | 33.2 ± 8.8 | 30.9 ± 10.1 | 39.3 ± 7.0 | 3.04 | 0.06 | 0.13 | |
| Education (years) | 14.9 ± 1.9 | 13.5 ± 2.7 | 15.1 ± 1.8 | 2.25 | 0.12 | 0.10 | |
| BMI ‡ | 21.4 ± 3.4 | 12.0 ± 1.3 | 16.4 ± 2.4 | 44.97 | < 0.001 | 0.69 | AN-r < CTL*, AN-bp < CTL*, AN-r < AN-bp* |
| Duration of AN (years) | N/A | 11.7 ± 7.0 | 17.3 ± 6.3 | N/A | 0.06 | 0.16 | |
| EDE-Q ‡ | 0.85 ± 0.77 | 1.23 ± 0.96 | 3.51 ± 1.51 | 24.71 | < 0.001 | 0.55 | CTL < AN-bp*, AN-r < AN-bp* |
| BDI-II § | 6.8 ± 4.6 | 23.8 ± 12.7 | 29.1 ± 11.9 | 24.40 | < 0.001 | 0.55 | CTL < AN-bp*, CTL < AN-r* |
| STAI trait § | 38.8 ± 10.4 | 46.6 ± 15.0 | 62.9 ± 14.7 | 12.95 | < 0.001 | 0.39 | CTL < AN-bp*, AN-r < AN-bp* |
| Total earnings (¥) | 2849 ± 521 | 2998 ± 773 | 3163 ± 502 | 1.08 | 0.35 | 0.05 | |
| Hit rate (% overall) | 45.5 ± 2.6 | 44.5 ± 4.9 | 45.3 ± 3.0 | 0.35 | 0.71 | 0.02 | |
| RT (ms overall) § | 232.8 ± 16.0 | 239.7 ± 40.0 | 229.8 ± 34.7 | 0.35 | 0.71 | 0.02 | |

AN-bp = binge eating/purging-type anorexia nervosa; AN-r = restricting-type anorexia nervosa; BDI-II = Beck Depression Inventory Second Edition; BMI = body mass index; CTL = healthy control participants; EDE-Q = global score of the Eating Disorder Examination Questionnaire 6.0; N = numbers; STAI trait = trait anxiety score of State-Trait Anxiety Inventory, form JYZ; RT = reaction time

*Significant p value ($p < 0.05$) for the Tukey HSD post-hoc test.