



Reduced sensitivity to delayed time and delayed reward of the post-operative insular glioma patients in delay discounting

Wenjin Fu^{a,1}, Zhenxing Huang^{b,d,g,1}, Jun Li^a, Qi Dong^a, Yang Li^a, Gen Li^{b,d}, Yaokai Xu^{b,d}, Bowen Xue^{b,d}, Zhenye Li^{b,d}, Chuansheng Chen^c, Shengjun Sun^{d,e}, Yazhuo Zhang^{d,f}, Zonggang Hou^{b,d,*}, Jian Xie^{b,d,*}

^a State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing 100875, PR China

^b Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China

^c Department of Psychology and Social Behavior, University of California, Irvine CA 92697, United States

^d National Clinical Research Center for Neurological Diseases (China), Beijing 100070, China

^e Neuroimaging Center, Beijing Neurosurgical Institute, Capital Medical University, Beijing 100070, China

^f Beijing Neurosurgical Institute, Capital Medical University, Beijing 100070, China

^g Department of Critical Care Medicine, Qilu Hospital of Shandong University, Jinan 250012, China

ARTICLE INFO

Keywords:

Decision making

Delay discounting

Insula

Insular glioma

ABSTRACT

Previous studies have shown that the insula is closely related to addiction, and the structure's role in delay discounting can be measured by a specific task, but the specific role of the insula has been less studied. In this study, we first conducted a lesion study in which we recruited healthy controls ($n = 30$) and patients with unilateral insula injury ($n = 16$) to complete a behavioral delay discounting task. Then we conducted a functional magnetic resonance imaging (fMRI) study, and a separate group healthy volunteers ($n = 51$) completed a delay discounting task during the fMRI scan. The lesion study showed a significant difference between the two groups in the delay discounting task, which revealed that insula injury was associated with impaired decision making. The fMRI study revealed choice-sensitive insula activation that was modulated by delayed time and delayed reward, indicating an important role of the insula in delay discounting. Overall, our results provide evidence for a role of the insular lobe in delay discounting and suggests that this structure may be considered an important factor in the future treatment and diagnosis of addiction disorders.

1. Introduction

The insula is a triangular cortical structure, located deep to the Sylvian fissure and covered by the fronto-parieto-temporal operculum. This hidden cortex is rarely studied, so its function is far from clear, but studies have consistently reported that patients with insula cortex damage were more likely to withdraw from both substance based (e.g. smoking) (Abdolahi et al., 2015; Naqvi et al., 2007) and non-substance based (e.g. gambling) addiction (Clark et al., 2014). However, the exact mechanism underlying this clinically observed phenomena remains unclear.

The decision-making process is a diagnostic feature of addiction and may be a possible cognitive mechanism through which the insular

contributes to addiction. The relationship between addiction and decision making under either uncertainty (known outcome) or certainty (unknown outcome) has been established by previous research (Claus et al., 2018; Lee et al., 2016). The importance of decision making during in certainty conditions has recently attracted increasing attention because it is very similar to the state of addiction (addicts know there will be serious consequences in the future) (Miedl et al., 2015). Unfortunately, although a large body of evidence has consistently implicated the insular cortex in decision making under uncertainty (Kohno et al., 2017; Weller et al., 2009; Zhang et al., 2019), the contribution of the insula to decision making under certainty conditions has been rarely studied (Zhang et al., 2018).

Delay discounting refers to a psychological phenomenon when the

* Corresponding authors at: Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, No.119 of south 4th ring road, Fengtai District, Beijing 100070, China.

E-mail addresses: houzg2006@163.com (Z. Hou), xiejian0630@126.com (J. Xie).

¹ Both authors contributed equally to this work.

subjective value of future reward decreases with time and has been identified as a fundamental element of decision making (Matta et al., 2012). In a typical delay discounting task (DDT), participants are required to make choices between smaller, sooner rewards and larger, delayed rewards (Mitchell et al., 2005). Choosing smaller, sooner rewards indicates a high rate of delay discounting. Previous studies using this paradigm observed that subjects craving for alcohol (Mitchell et al., 2005), methamphetamine (Hoffman et al., 2008), tobacco (Ohmura et al., 2005), heroin and cocaine (Kirby and Petry, 2015), and gambling (Ledgerwood et al., 2009) discounted delayed rewards faster than healthy volunteers. A high rate of delay discounting has been considered to predict relapse to addiction (Sheffer et al., 2012; Sheffer et al., 2014).

Conversely, a limited number of studies did not find consistent results on the role of the insular cortex in the process of delay discounting. For example, patients with lesions predominantly within the insula were prone to select larger, delayed rewards relative to smaller, sooner rewards (Sellitto et al., 2015). However, an animal study found that selective damage to the insular cortex did not affect the choice between the two types of rewards (Ishii et al., 2012). Wittmann et al. performed two functional magnetic resonance imaging (fMRI) studies that reached conflicting conclusions. In the first study, the insula was less activated when subjects chose smaller, sooner rewards (Wittmann et al., 2007); however, their second study did not find an insular activation difference between smaller, sooner rewards and larger, delayed rewards (Wittmann et al., 2010a).

Discrepancies among the above-mentioned studies indicated that the role of insula in delay discounting process could be affected by several factors. The delayed time and reward amount may be candidate modulators because they are important variables for delay discounting (Dennis et al., 2020) and the insula participates in time and value processing (Tanaka et al., 2004; Von Siebenthal et al., 2020). In this study, we tested the contributions of both delayed time and reward amount to insular function during a DDT. We first performed behavioral analysis in patients with insular damage ($n = 16$) and healthy volunteers ($n = 30$) to see if insular damage affected the relationship between choice (smaller, sooner rewards relative to larger, delayed) and delayed time or reward amount. Next we carried out fMRI analysis in healthy volunteers ($n = 51$) to see if delayed time or reward amount affected insular activation. We hypothesized that the role of the insular cortex in delay discounting process varied with the delayed time or reward amount.

2. Materials and methods

This study was approved by the Institutional Review Boards of Beijing Tiantan Hospital and the Institute of Cognitive Neuroscience and Learning at Beijing Normal University. All subjects gave written informed consent for this study.

2.1. Study I: The lesion study

2.1.1. Subjects

The sample consists of 16 patients (10 males and 6 females) with focal insula lesions and 30 healthy controls (18 males and 12 females). The patients were recruited from May 2019 to December 2019 from Beijing Tiantan Hospital. All patients were diagnosed with insular gliomas and had recovered from insular resection. All lesions were unilateral (7 subjects with left lesions; 9 subjects with right lesions). Healthy controls were recruited through advertisements in Beijing and were interviewed by experienced clinicians to exclude any personal or family history of mental disorders. It should be noted that a previous study provided evidence that patients who underwent insular glioma surgery could exhibit small differences in attention, executive function, and memory compared to healthy individuals (Wu et al., 2011). Therefore, we did not perform these cognitive tests in the present study. All subjects were right-handed and had normal or corrected-to-normal vision.

2.1.2. Lesion overlap

To clearly and directly visualize insula lesions, we collected the postoperative MRI scans for all patients. The resected brain area was segmented on T1- or T2-weighted images by an experienced neurosurgeon to generate a lesion mask via the Medical Imaging Interaction Toolkit (MITK) (www.mitk.org). Then the lesion masks and corresponding anatomical images were normalized into the standard Montreal Neurological Institute (MNI) space via SPM12. Next, the neurosurgeon performed a reconfirm procedure for more accurate matching to the original lesion range after normalization. Finally, the normalized and rechecked lesion masks were generated for lesion overlap using MRICroGL (<https://www.mccauslandcenter.sc.edu/mricrogl>).

2.1.3. Behavioral task

The DDT was revised from a previous version (Mitchell et al., 2005), which the author reported the demographic factors could have little effects on this task. The experiment consisted of 120 trials. Each trial began with the presentation of a 2-s fixation cross in the center of the screen. The subjects were then asked to choose one of the two hypothetical reward options (a full amount to be received at a delayed time point or a discounted amount to be received now) that were randomly presented on the left or the right side of the fixation for 5 s. They were required to press the left button if they selected the option on the left side or the right button if they selected the option on the right side (Fig. 1). The full amounts (delayed) of the rewards was ¥5, ¥10, ¥25, ¥50, ¥100, and ¥500. The delayed time points were 7, 14, 30, 90, and 180 days in the future. The discounted amounts (receive now) were 70%, 85%, 90%, or 95% of the full amounts. We calculated the early choice ratio (ECR, the ratio of immediate option selections to all selections) and used it as the behavioral index. The above-described task was defined as the want condition, which was only used in study I.

2.1.4. Statistical analysis

All statistical analyses were carried out using SPSS version 26.0. We first used one-way analysis of variance (ANOVA) to compare behavioral performance (ECR) between patients and controls. We also used repeated measures ANOVA to test if the delayed time or delayed reward amount had different effects on behavioral performance (ECR) of patients and controls. In this analysis, the delayed time (7 days vs. 14 days vs. 30 days vs. 90 days vs. 180 days) or delayed reward amount (¥5 vs. ¥10 vs. ¥25 vs. ¥50 vs. ¥100 vs. ¥500) served as a within-subject factor, and group (patient vs. control) served as a between-subject factor. If there was a significant interaction effect of either delayed time × group or delayed reward amount × group, we performed separate *post-hoc* analyses for patients and controls using repeated measures ANOVA (the delayed time or delayed reward amount served as a within-subject

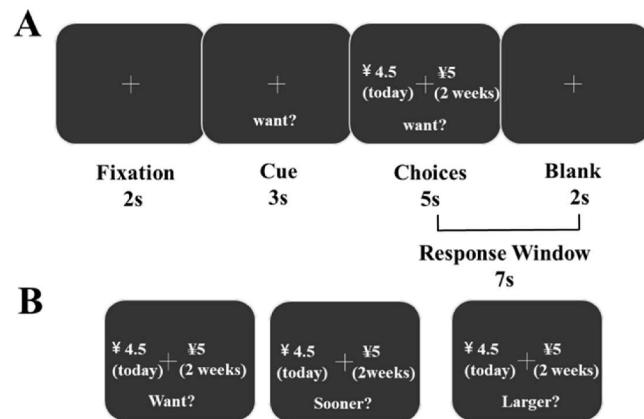


Fig. 1. Schematic diagram of the delay discounting task in this study. Panel A represents the process of trial, and Panel B represents the different conditions.

factor).

2.2. Study II: The fMRI study

2.2.1. Subjects

The sample consisted of 51 healthy volunteers (39 males and 12 females) who were recruited through advertisements in Beijing and were interviewed by experienced psychiatrists to exclude any personal or family history of mental disorders. All subjects were right-handed and had normal or corrected-to-normal vision. Three subjects were excluded from the final analysis for excessive head movement (>3 mm or 3°) or poor behavioral performance, so the final sample size in study II was 48 healthy volunteers. This number achieved acceptable statistical power for the within-subject design (Szucs and Ioannidis, 2020).

2.2.2. The fMRI task

The fMRI task included two conditions: want (60 trials) and control (20 trials) (Fig. 1). The want condition was similar to that of the behavioral task used in the lesion study. Subjects were required to make choices between the two reward options they preferred. The control condition did not involve any subjective evaluation; rather, subjects were required to assess the objective attributes of the choices (sooner or larger) and press the left or right button corresponding to the sooner time point or larger reward amount.

2.2.3. fMRI data acquisition

Image data was obtained at the Brain Imaging Center of Beijing Normal University. Subjects lay supine in a Siemens Trio 3 T scanner. Their heads were fixed with straps and foam pads to restrict movement. The fMRI images were obtained using an echo-planar imaging sequence with the following parameters: repetition time (TR), 2000 ms; echo time (TE), 30 ms; flip angle, 90° ; field of view (FOV), 200×200 mm; matrix size, 64×64 ; 31 axial slices; 4.0-mm thickness without gap section. The structural images were obtained using T1-weighted sagittal three-dimensional magnetization with rapid gradient-echo sequence and the following parameters: 176 slices; 1.0-mm thickness; TR, 2530 ms; TE, 3.45 ms; flip angle, 7° ; FOV, 256×256 mm; matrix size, 256×256 .

2.2.4. fMRI data preprocessing and analysis

Data preprocessing was implemented using Statistical Parametric Mapping software (SPM version 12.0, Wellcome Department of Cognitive Neurology, London, UK). Preprocessing included slice timing, realignment (correcting for head movement), normalization (to the MNI space), resampling (to a voxel size of $3 \times 3 \times 3$ mm 3), and spatial smoothing with 8-mm full-width at half maximum of the Gaussian smoothing kernel.

In the first-level analysis, we used task condition (want vs. control) as a predictor to assess brain activation for each subject. We also used trial-specific choice (larger delayed vs. smaller immediate) as a predictor to calculate choice-related brain activation for each subject. In these analyses, a high-pass filter at 128 s was used to remove noise associated with low-frequency confounds.

We further used a flexible factorial designed ANOVA to explore the effect of the delayed time on choice-related activation. This analysis included two within-subject factors. One factor is the choice (larger delayed vs. smaller immediate), and the other factor is the delayed time divided into two types: longer delay (i.e., 90 and 180 days) and shorter delay (i.e., 7, 14, and 30 days) according to the curve that described the change of ECR with the delayed time in healthy controls as indicated by the lesion study.

Similarly, we tested the effect of the delayed reward amount on choice-related activation. In this analysis, the factors were choice (larger delayed vs. smaller immediate) and the delayed reward amount that was divided into two types: larger reward (i.e., ¥100 and ¥500) and smaller reward (i.e., ¥5, ¥10, ¥25, and ¥50) according to the curve that described the change of ECR with the delayed reward amount in healthy controls

as indicated by the lesion study.

For all the imaging data described above, we first performed a region of interest (ROI)-based analysis, which limited our analyses within the bilateral insula. The bilateral insula ROI (Mask) was generated using the aal template within the DPABI (a toolbox for Data Processing & Analysis of Brain Imaging). For the clusters showing significant interaction of either choice \times delayed time or choice \times delayed reward amount, we extracted brain activations for each subject for *post-hoc* analysis using paired sample *t* tests in SPSS 26.0. We also performed whole-brain analysis to see if the result within insula ROI could withstand whole-brain correction and if there were other brain regions that showed similar patterns.

For the imaging data analysis, the significance level was set at voxel-level $P < 0.05$ family-wise error (FWE) correction with a spatial extent threshold of 20 voxels. For non-imaging data, two-tailed $P < 0.05$ was considered significant.

3. Results

3.1. Study I: The lesion study

The lesion overlap is shown in Fig. 2, and all lesions were insula centered. Although the DDT we used has less association with demographic factors, we still compared differences between the two groups. Patients and controls did not show any differences in demographic factors ($P_s > 0.05$, Table 1). However, age showed a trend toward a statistically significant difference between groups, so we also considered age as a covariate in the subsequent one-way ANOVA analysis, which showed no significant difference between patients and controls ($F = 0.209$, $P = 0.649$; Fig. 3).

When we performed repeated measures ANOVA to assess the effect of delayed time on the group difference at the ECR, we observed a significant interaction effect of group \times delayed time ($F = 4.636$, $P = 0.012$) and a significant main effect of delayed time ($F = 3.658$, $P = 0.029$). The main effect of the group was not significant ($F = 0.785$, $P = 0.380$). The subsequent *post-hoc* analysis showed a significant simple effect of delayed time on the ECR for controls ($F = 4.208$, $P = 0.025$) but not patients ($F = 0.859$, $P = 0.495$; Fig. 4A). The ECR of the control group increased significantly with longer delayed time, which is consistent with a previous study (Mitchell et al., 2005). In contrast, the ECR of the patients with insular damage did not change with the delayed time. Additionally, when the delayed time was ≤ 30 days, there was a rapid increase in the preference for immediate rewards in healthy controls with longer delayed time, but when the delayed time was > 30 days, the preference for immediate rewards slowly increased. Notably, patients with insular injury did not show this pattern, which indicated that the lesion affected processing time during the DDT.

We performed a similar repeated measures ANOVA to examine the effect of the delayed reward amount on the group difference at the ECR. This analysis also revealed a significant interaction effect of group \times delayed reward amount ($F = 3.988$, $P = 0.009$) and a significant main effect of the delayed reward amount ($F = 4.710$, $P = 0.003$). The main effect of the group was still not significant ($F = 0.953$, $P = 0.334$). The *post-hoc* analysis again showed significant a simple effect of the delayed reward amount on the ECR in controls ($F = 4.403$, $P = 0.008$) but not patients ($F = 2.580$, $P = 0.068$; Fig. 4B). Similar to a previous report (Mitchell et al., 2005), the ECR of the control group significantly decreased with the increase of the delayed reward amount. However, the ECR of the patients with insular damage did not change with the delayed reward amount. Moreover, when the delayed reward was $\leq ¥50$, there was a rapid decrease of the preference for immediate rewards in healthy controls with a higher delayed reward, but when the amount was $> ¥50$, the preference for immediate rewards decreased slowly. Again, patients with insular lesion did not show this pattern, indicating that insular damage affecting the processing of reward in the DDT.

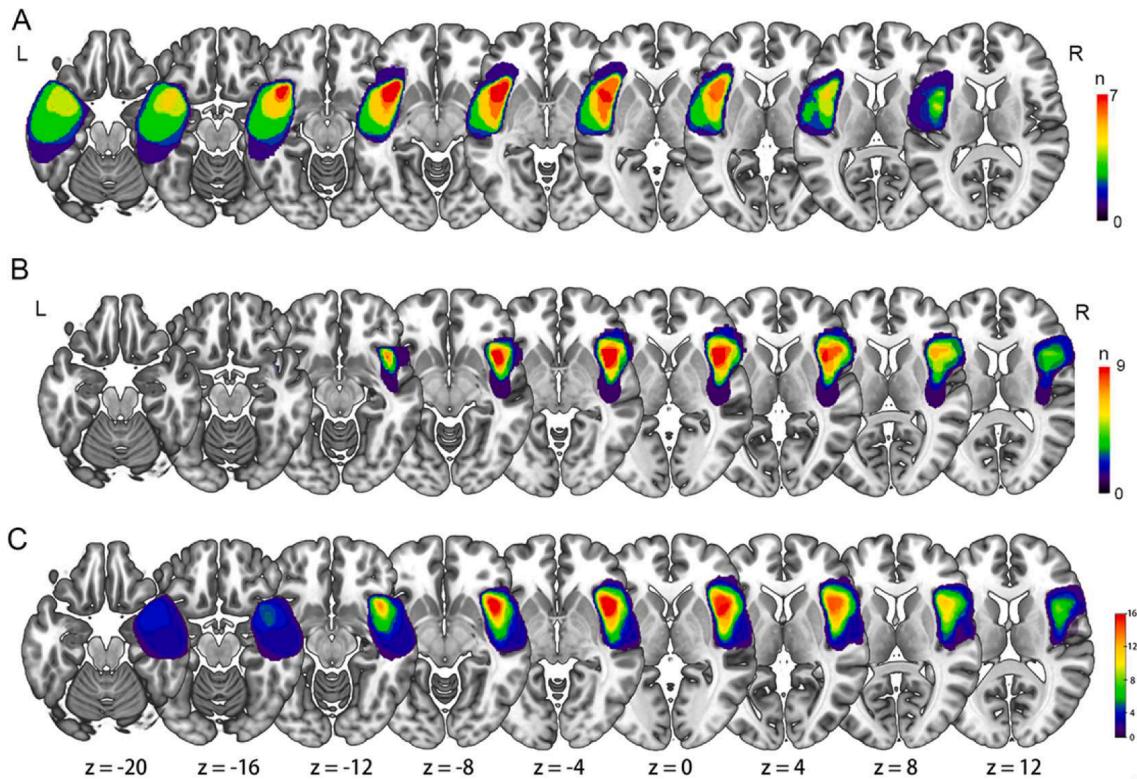


Fig. 2. Lesion overlap for patient group. The color represents the number of subjects with alesion in this area. For the patients ($n = 16$), nine subjects were injured in the right insula (A), seven subjects were injured in the left insula (B). And all lesions are normalized to the hemisphere for comparison (C). Mean lesion volume was 23.7 cm^3 and maximal lesion overlap (100%) was in anterior insula cortex.

Table 1
Demographic variables across groups in the lesion study.

	Mean \pm SD		F or χ^2	P
	Patients	Controls		
Number of subjects	16	30	—	—
Gender(male/female)	10/6	17/13	0.146 ^a	0.702
Age(years)	41.25 ± 10.93	36.17 ± 8.08	3.218	0.080

^a Chi-square test.

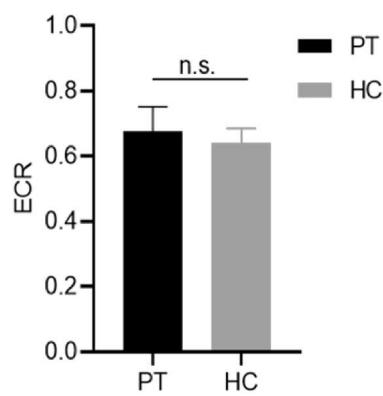


Fig. 3. Comparison between patient group and healthy control group in ECR. No statistically significant differences were found.

3.2. Study II: The fMRI study

3.2.1. Want condition > control condition

The bilateral insula showed significant activation (left insula, cluster

size = 229 voxels, corrected $P = 0.001$, peak voxel MNI coordinate: $x = -30, y = 21, z = -3$; right insula, cluster size = 163 voxels, $P = 0.002$, peak voxel MNI coordinate: $x = 30, y = 24, z = 6$; Fig. 5) in the want condition relative to the control condition. This result remained after correcting for multiple comparisons across the whole brain (left insula, corrected $P < 0.001$; right insula, corrected $P < 0.001$). The whole-brain analysis revealed some other regions such as the frontal and parietal lobes and some basal ganglia structures (Table 2, Fig. 5), which is consistent with a previous report (Frost and McNaughton, 2017).

3.2.2. Delayed choices > Immediate choices

The bilateral insula also showed significant choice-related activation for the larger, delayed choices compared to the smaller, immediate choices (left insula, cluster size = 254 voxels, corrected $P = 0.001$, peak voxel MNI coordinate: $x = -30, y = 24, z = -6$; right insula, cluster size = 191 voxels, corrected $P = 0.002$, peak voxel MNI coordinate: $x = 33, y = 21, z = -3$; Fig. 6). This result could also withstand correction across the whole brain (left insula, corrected $P < 0.001$; right insula, corrected $P < 0.001$). In addition to the bilateral insula, some other regions such as the parietal, frontal, and orbitofrontal lobes, were also identified in this whole-brain analysis (Table 2, Fig. 6), which is also consistent with previous studies (Frost and McNaughton, 2017; Lv et al., 2020).

3.2.3. Choice \times delayed time

When we considered the effect of the delayed time on choice-related brain activation, our ROI-based, flexible factorial designed ANOVA showed a significant interaction effect of choice \times delayed time (left insula, cluster size = 176 voxels, corrected $P = 0.001$, peak voxel MNI coordinate: $x = -30, y = 18, z = -3$; right insula, cluster size = 160 voxels, corrected $P = 0.001$, peak voxel MNI coordinate: $x = 36, y = 24, z = -6$; Fig. 7). The insula results were still significant after correcting for multiple comparisons across the whole brain (left insula, corrected $P = 0.001$; right insula, corrected $P < 0.001$). Post-hoc analysis showed that

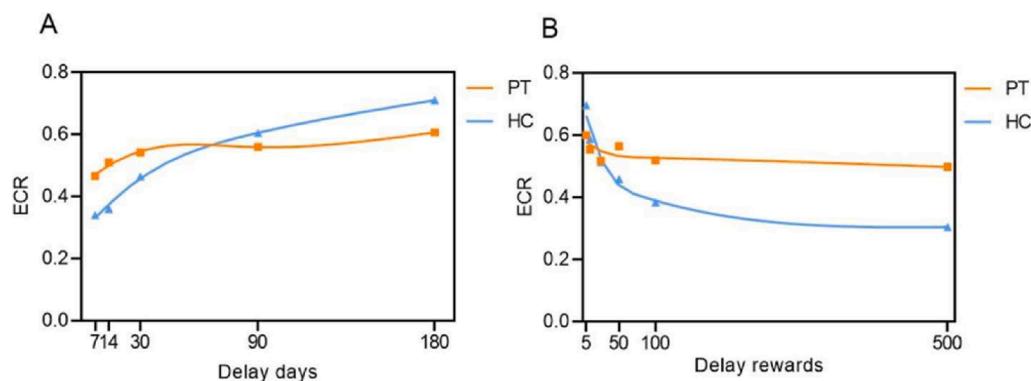


Fig. 4. Fitting curve plotting the ECR in different delay days and rewards. Panel A plotted a fitting curve of ECR in Various delay days. Panel B displayed fitting curve of ECR in different delay rewards. The patient group (orange line) and the healthy control group (blue line) showed different changes in different delay times and delay rewards. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

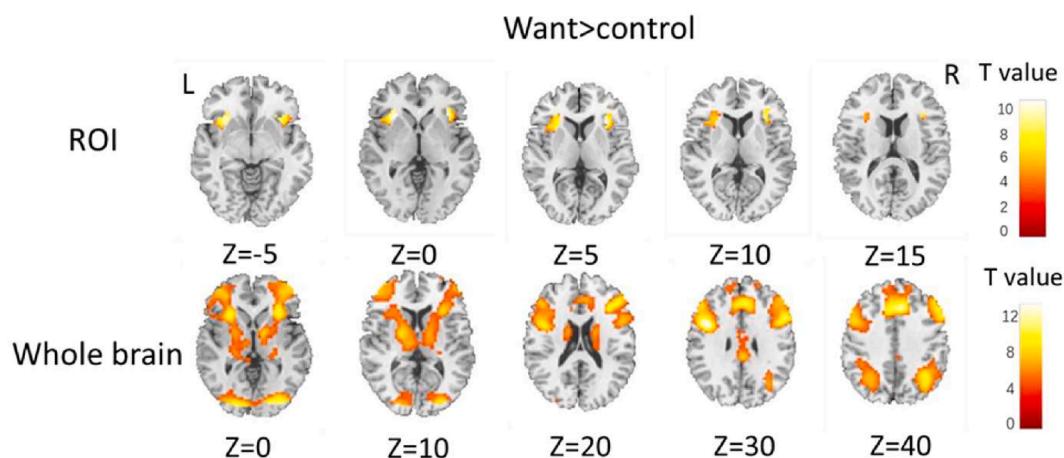


Fig. 5. Brain activation areas of the contrast between want condition and control condition. Compared with the Control condition, the want condition showed increased bilateral insula activation.

delayed choice activation was significantly higher than immediate choices for the longer delay ($t = -6.407, P < 0.001$), whereas no significant activation differences were found for the shorter delay ($t = -0.446, P = 0.659$; Fig. 7). In addition to the bilateral insula, some frontal lobe areas also showed significant activation in the interaction of choice \times delayed time (Table 2, Fig. 9).

3.2.4. Choice \times Delayed reward

Similarly, when we considered the effect of the delayed reward amount on choice-related brain activation, our ROI-based, flexible factorial designed ANOVA within the bilateral insula also showed a significant interaction of choice \times delayed reward amount (left insula, cluster size = 28 voxels, corrected $P = 0.030$, peak voxel MNI coordinate: $x = -30, y = 21, z = -3$; right insula, cluster size = 36 voxels, corrected $P = 0.022$, peak voxel MNI coordinate: $x = 36, y = 24, z = -6$, Fig. 8). Post-hoc analysis observed that brain activation for delayed choices was significantly higher than immediate choices for smaller rewards ($t = -4.183, P < 0.001$), but no significant activation differences were found for larger ones ($t = -1.701, P = 0.098$; Fig. 8). Unfortunately, the bilateral insula results were no longer significant in whole-brain analysis. We only observed activation of the left superior medial frontal gyrus (Table 2, Fig. 10).

4. Discussion

The current investigation consists of the lesion study and the fMRI

study. The first set of experiments revealed that patients with unilateral insular injury did not show significant changes in ECR with the change of delayed time and delayed reward, but the healthy controls did. The fMRI analysis in healthy volunteers found that insular activation during delay discounting was modulated by both delayed time and delayed reward. Consistently, both sets of results indicate an important role of the insula in the evaluation of delayed time and reward amount, which may be a possible mechanism for its involvement in delay discounting.

An important result of this study was that insula was involved in evaluating delayed time in delay discounting; this is supported by evidence from both the lesion and fMRI studies. Consistent with a previous report (Mitchell et al., 2005), we also found that with the increase of the delayed time (of the larger reward), healthy controls' preference for the smaller immediate reward increased and reached its asymptote when the delay time was > 3 months. The fact that patients with insular injury did not show this pattern indicated that insular injury damaged cognitive processing of the delayed time. This finding can be explained by our fMRI data, which showed that insular activation varied with the delayed time. In short, when the delay was > 3 months, the larger delayed reward activated the insula more than the smaller immediate reward, but this pattern disappeared when the delay time was < 3 months. It is possible that activation of the uninjured insular could not fully compensate the cognitive processing required for assessing different rewards (smaller immediate vs. larger delayed), especially when the delay was longer. As a result, patients with unilateral insular injury showed a relatively flat curve of ECR vs. delay time.

Table 2

Significant regions activated in whole-brain analysis (Voxel-level FWE corrected $P < 0.05$, cluster size > 20).

Brain area		Peak MNI coordinate X	Y	Z	Number of voxels	T value
Want > control						
Bilateral inferior occipital gyrus,	36	-84	-9		1307	11.76
Bilateral fusiform gyrus						
Bilateral insula, Bilateral middle frontal gyrus, Bilateral inferior frontal gyrus, Bilateral superior frontal gyrus, Left precentral gyrus, Bilateral thalamus, Bilateral anterior cingulum, Bilateral orbitofrontal lobe	-45	6	30		5624	13.45
Right inferior parietal lobe, Right angular	36	-57	42		627	9.83
Bilateral middle cingulum	0	-33	33		54	8.19
Left inferior parietal lobe, Left angular	-27	-60	45		484	8.63
Late > early						
Left middle temporal gyrus	-57	-33	0		156	6.29
Right middle temporal gyrus	63	-36	-9		106	7.16
Right insula, Right orbitofrontal gyrus, Right middle frontal gyrus, Right inferior frontal gyrus	45	54	-6		1243	7.79
Left insula, Left orbitofrontal gyrus, Left middle frontal gyrus, Left inferior frontal gyrus, Left precentral gyrus	-51	12	45		2989	9.47
Left inferior occipital gyrus	-24	-90	-3		162	6.70
Left fusiform	-48	-57	-15		92	6.89
Right inferior occipital gyrus	33	-87	-3		84	5.87
Left inferior parietal gyrus, Left angular	-54	-45	51		748	7.97
Right inferior parietal gyrus, Right angular	45	-60	45		600	8.65
Right caudate, Right pallidum	12	6	0		33	5.406
Left caudate, Left pallidum	-12	6	9		22	5.123
Bilateral middle cingulum						
Choice × delayed time						
Left insula	-30	18	-3		46	17.29
Right insula, Right inferior frontal gyrus	36	24	-6		93	19.15
Left middle frontal gyrus	-45	21	36		60	14.86
Left medial frontal gyrus,	-6	21	48		171	18.90
Left inferior parietal gyrus, Left angular	-42	-60	39		76	16.55
Choice × delayed reward						
Left superior medial frontal gyrus	-3	24	45		24	16.145

Craig (Craig, 2009) reported that the insula was involved in the time perception based on the observation that the insular cortex was significantly activated while subjects were instructed to report whether the moving speed of the stimuli increased or decreased (Üstün et al., 2017). In another study that required subjects to estimate tone duration, the bilateral insula showed an accumulating activation pattern and that peaked at the end of the stimulus (Wittmann et al., 2010b). In lesion studies, Monfort et al. reported that damage to the insular cortex would lead to impaired temporal performance in a visual time reproduction task (Monfort et al., 2014). More interestingly, Wittmann et al. used a temporal reproduction task and found that the posterior part of insula generated the representation of time while the anterior part maintained this representation and associated with impulsiveness (Wittmann et al., 2011). Hence, insular damage might lead to inappropriate time perception as reflected in the flat ECR curve vs. varied delay time.

Another important result of this study was that insula played an important role in evaluating the delayed reward during delay discounting, and this was supported by both the lesion and fMRI studies. With the increase of the delayed reward amount, healthy controls' preference for immediate reward decreased and reached its asymptote when the delayed reward was >¥100, which was consistent with a previous report (Mitchell et al., 2005). In contrast, patients with unilateral insular injury in our study did not show this pattern, indicating dysfunctional processing of delayed reward. Our fMRI findings showed that insula activation varied with delayed reward. That is, when the delayed reward was <¥100, the larger delayed reward activated the insula more than the smaller immediate reward, but this pattern disappeared when the delayed reward was >¥100. It is possible that the relatively flat curve between patients' ECR and delayed reward may be due to insular dysfunction. Following injury, activation of the damaged insula could not fully compensate to allow full cognitive processing of different rewards, especially when the delayed reward was smaller.

Previous reports hypothesized that the insula may be involved in reward processing. A previous fMRI study reported that the bilateral insula showed greater signals for high rewards than low rewards (Smith et al., 2009), which reflected the evaluation of insula-related reward size. In addition, a meta-analysis concluded that the insular cortex was sensitive to the size and difference of rewards (Wu et al., 2012). These findings are consistent with our fMRI results and demonstrate that insular cortex activation was associated with the amount of delayed reward. Moreover, Rochat and colleagues reported that insular lesion was associated with reward insensitivity and apathy (Rochat et al., 2013). Collectively, these lines of evidence could explain why individuals with unilateral insular cortex injury exhibited a flat ECR curve

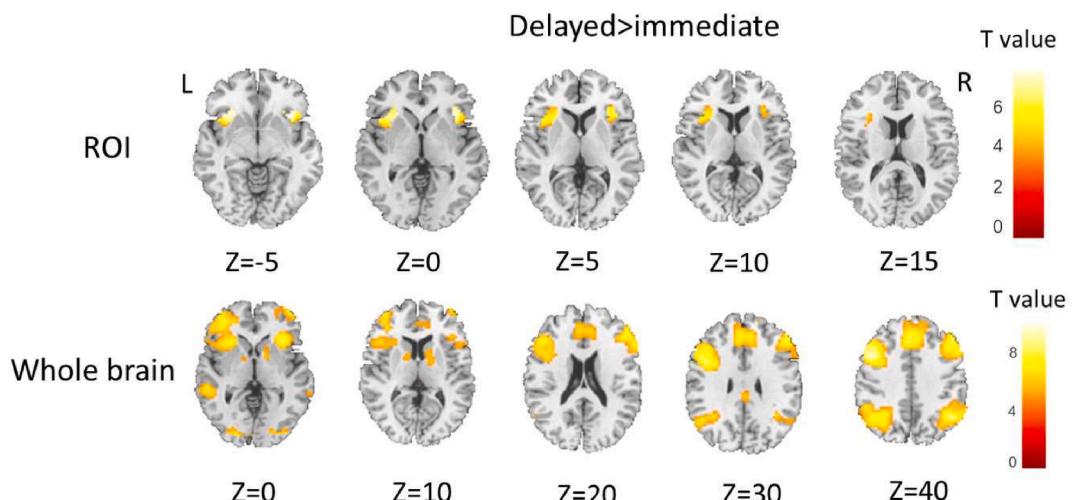


Fig. 6. Brain activation areas of the contrast between late choices and early choices Compared with the early trials, the late trials also showed increased bilateral insula activation.

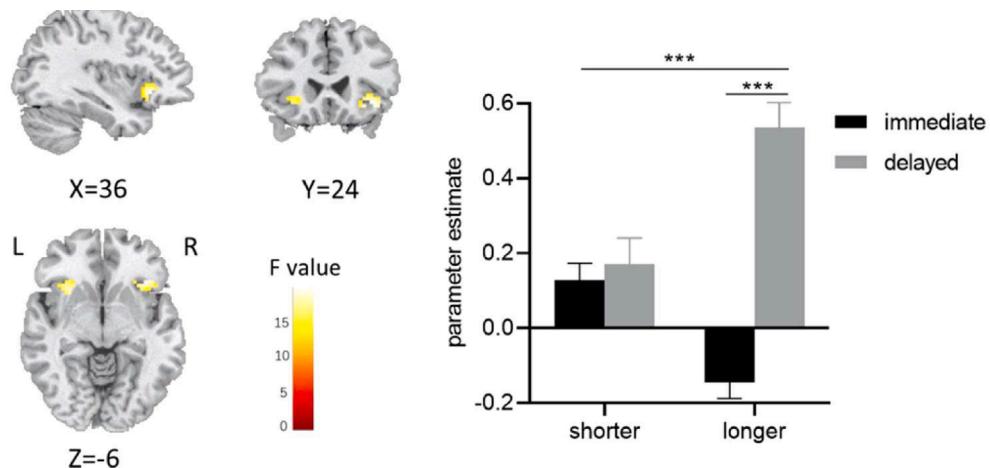


Fig. 7. ROI analysis results of insula showed significant interaction between choice and delay time. The bar graph showed the mean activation of the significant clusters in insula. Errors bars indicate the standard error of mean.

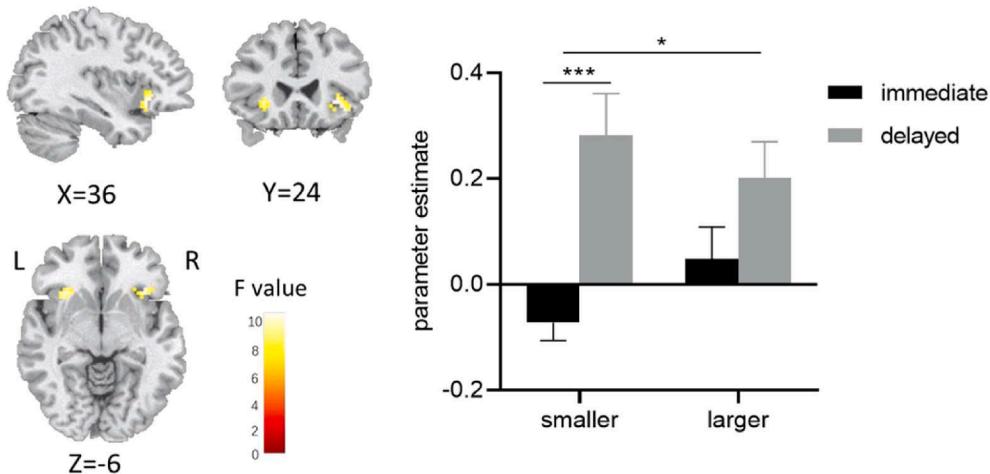


Fig. 8. ROI analysis results of insula showed significant interaction between choice and delay reward. The bar graph showed the mean activation of the significant clusters in insula. Errors bars indicate the standard error of mean.

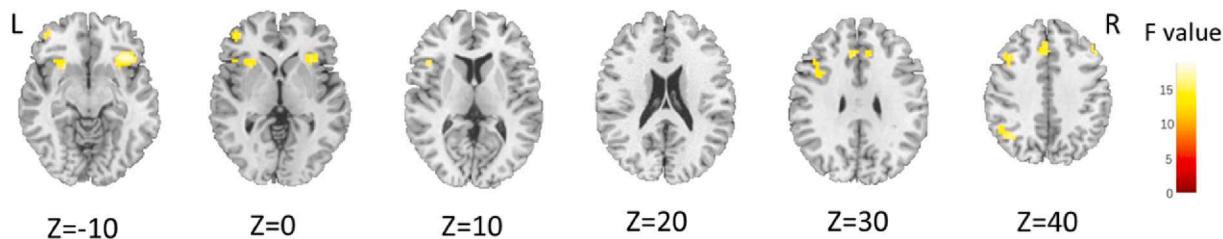


Fig. 9. Whole brain analysis showed significant interaction between choice and delay time.

as the delayed larger reward changed.

In conclusion, impaired time and reward perception may have caused the flat ECR curve in our patient group. Time or reward perception seems to require separate mental processing embedded in the insular cortex. This corresponds to the functions of the insula described in previous studies. It is widely accepted that the insular cortex receives internal feelings from our body (e.g. visceral, hormonal, autonomic), which is termed interoception. These innervations enable us to generate self-awareness and emotion (Craig, 2002; Critchley and Garfinkel, 2017), all of which contribute to subjective feeling. In healthy individuals, this subjective feeling is used to evaluate two choices in the DDT and choose what they want. However, Wang et al. found that

damage to the insular cortex disrupted the accuracy and sensitivity of interoception (Wang et al., 2019), which could further influence emotional awareness, and lead to a state where one could not perceive their preference among numerous stimuli (Ho et al., 2017). Another way to describe this is the loss of subjective feelings. From this perspective, we could infer that patients with insular damage in our study might have impaired subjective feelings in both time and reward dimensions, so they were unable to perceive which choice would satisfy them in the DDT task.

In fact, subjective feeling is important in decision making (Dunn et al., 2010), including decisions under certainty (Delay discounting) and uncertainty (Risky discounting). In a risky decision study performed

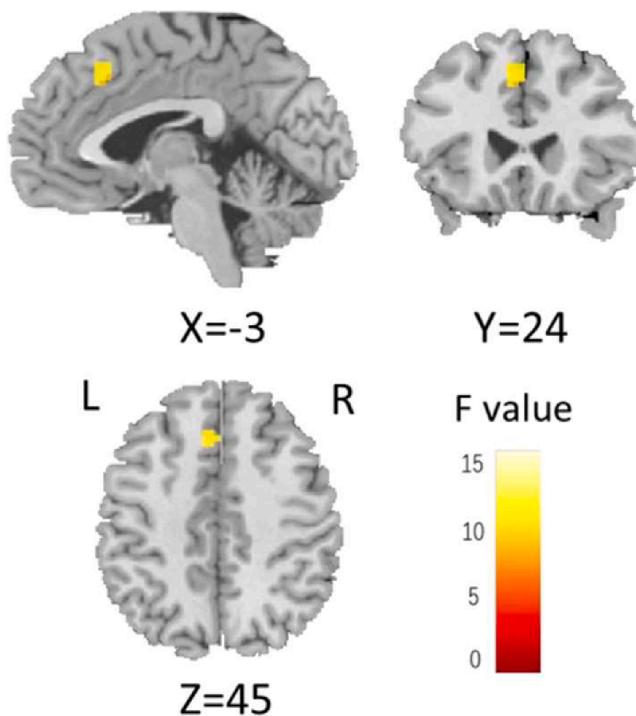


Fig. 10. Whole brain analysis showed significant interaction between choice and delay reward.

by Weller et al., insula infarction patients and healthy controls were instructed to maximize monetary earning by making a decision between risky and certain choices, and they found that the number of risky choices in insula patients did not change as risk level varied, indicating insensitivity to risk magnitude (Weller et al., 2009). The authors considered that this result was associated with emotion bluntness following insula damage. Their results mirror ours, but for another type of decision making. It seems that the insular cortex generates emotional subjective feelings by perceiving interoception, which contributes to estimating decision-making outcomes (Weber and Johnson, 2009). Damage to the insula, which represents and regulates body signals, would result in deficits in feelings and emotions, then lead to impaired decision making (Bechara and Damasio, 2002; Dunn et al., 2006).

In addition to the insula, we also observed activation in some areas of the lateral or medial frontal and orbitofrontal cortices, temporal and partial lobes, cingulum, and basal ganglia structures during the fMRI study. These findings are consistent with previous studies that found that these brain areas were also associated with delay discounting (Frost and McNaughton, 2017; McClure et al., 2004; Sellitto et al., 2010; Tanaka et al., 2004; Weber and Huettel, 2008; Wittmann et al., 2010a). However, their roles in delay discounting require further research.

The originality of this work lies in the combination of lesion and fMRI studies. The combined results allow a stronger level of inference, so we were able to explore the regulatory effects of delayed time and delayed reward on delay discounting. However, the findings should be considered in the context of some limitations. First, the sample size of patients with brain injury was relatively small, and subsequent investigations should expand the sample size. Secondly, patients with damage in other brain areas outside the insula should be added as brain damage controls to explore the specific impact of insular damage on delay discounting processing. Future research may also examine patients with insular injury to see if compensatory effects occur in other brain regions. Finally, the random option side for behavior testing might introduce some bias, and the interactive effect between option side and choice strategy could be assessed in future studies.

5. Conclusions

This lesion/fMRI study provides direct evidence for a role of insula in delay discounting. Specifically, insular injury leads to insular dysfunction in delay discounting, and the effect of the insula on delay discounting is also regulated by delayed time and delayed reward. Our findings extend the literature regarding the role of the insula in delay discounting and clarifies how insula activation is affected by delayed time and delayed reward.

Ethical approval

This study was approved by the Institutional Review Boards of Beijing Tiantan Hospital and the Institute of Cognitive Neuroscience and Learning at Beijing Normal University. All subjects gave written informed consent for this study.

CRediT authorship contribution statement

Wenjin Fu: Data curation, Software, Formal analysis, Investigation, Writing – original draft. **Zhenxing Huang:** Methodology, Data curation, Investigation, Writing – original draft. **Jun Li:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Qi Dong:** Supervision. **Yang Li:** Data curation, Formal analysis. **Gen Li:** Data curation, Formal analysis. **Yaokai Xu:** Data curation, Formal analysis. **Bowen Xue:** Data curation, Formal analysis. **Zhenye Li:** Supervision. **Chuansheng Chen:** Supervision. **Shengjun Sun:** Supervision. **Yazhuo Zhang:** Supervision, Funding acquisition. **Zonggang Hou:** Supervision, Investigation. **Jian Xie:** Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (ID: 81771792) and the Beijing Municipal Science & Technology Commission (Z171100000117002).

References

- Abdolah, A., Williams, G.C., Benesch, C.G., Wang, H.Z., Spitzer, E.M., Scott, B.E., Block, R.C., van Wijngaarden, E., 2015. Smoking cessation behaviors three months following acute insular damage from stroke. *Addictive Behaviors* 51, 24–30.
- Bechara, A., Damasio, H., 2002. Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. *Neuropsychologia* 40 (10), 1675–1689.
- Clark, L., Studer, B., Bruss, J., Tranel, D., Bechara, A., 2014. Damage to insula abolishes cognitive distortions during simulated gambling. *Proceedings of the National Academy of Sciences of the United States of America* 111 (16), 6098–6103.
- Claus, E.D., Feldstein Ewing, S.W., Magnan, R.E., Montanaro, E., Hutchison, K.E., Bryan, A.D., 2018. Neural mechanisms of risky decision making in adolescents reporting frequent alcohol and/or marijuana use. *Brain Imaging Behav* 12 (2), 564–576.
- Craig, A.D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neuroscience* 3 (8), 655–666.
- Craig, A.D., 2009. Emotional moments across time: a possible neural basis for time perception in the anterior insula. *Philosophical Transactions of the Royal Society B* 364 (1525), 1933–1942.
- Critchley, H.D., Garfinkel, S.N., 2017. Interoception and emotion. *Curr Opin Psychol* 17, 7–14.
- Dennis, L.E., Kohno, M., McCready, H.D., Schwartz, D.L., Schwartz, B., Lahna, D., Nagel, B.J., Mitchell, S.H., Hoffman, W.F., 2020. Neural correlates of reward magnitude and delay during a probabilistic delay discounting task in alcohol use disorder. *Psychopharmacology (Berl)* 237 (1), 263–278.
- Dunn, B.D., Dalgleish, T., Lawrence, A.D., 2006. The somatic marker hypothesis: a critical evaluation. *Neurosci Biobehav Rev* 30 (2), 239–271.
- Dunn, B.D., Galton, H.C., Morgan, R., Evans, D., Oliver, C., Meyer, M., Cusack, R., Lawrence, A.D., Dalgleish, T., 2010. Listening to your heart. How interoception

- shapes emotion experience and intuitive decision making. *Psychol Sci* 21 (12), 1835–1844.
- Frost, R., McNaughton, N., 2017. The neural basis of delay discounting: A review and preliminary model. *Neurosci Biobehav Rev* 79, 48–65.
- Ho, Namkung, Sun-Hong, Kim, Akira, Sawa, 2017. The Insula: An Underestimated Brain Area in Clinical Neuroscience, Psychiatry, and Neurology. *Trends in Neurosciences*.
- Hoffman, W.F., Schwartz, D.L., Huckans, M.S., McFarland, B.H., Meiri, G., Stevens, A.A., Mitchell, S.H., 2008. Cortical activation during delay discounting in abstinent methamphetamine dependent individuals. *Psychopharmacology* 201 (2), 183–193.
- Ishii, H., Ohara, S., Tobler, P.N., Tsutsui, K.-I., Iijima, T., 2012. Inactivating anterior insular cortex reduces risk taking. *J Neurosci* 32 (45), 16031–16039.
- Kirby, K.N., Petry, N.M., 2015. Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. *Addiction* 99, 461–471.
- Kohno, M., Morales, A.M., Guttman, Z., London, E.D., 2017. A neural network that links brain function, white-matter structure and risky behavior. *Neuroimage* 149, 15–22.
- Ledgerwood, D.M., Alessi, S.M., Phoenix, N., Petry, N.M., 2009. Behavioral assessment of impulsivity in pathological gamblers with and without substance use disorder histories versus healthy controls. *Drug and alcohol dependence* 105 (1-2), 89–96.
- Lee, D., Lee, J., Yoon, K.J., Kee, N., Jung, Y.C., 2016. Impaired anterior insular activation during risky decision making in young adults with internet gaming disorder. *Neuroreport* 27, 605–609.
- Lv, C., Wang, Q., Chen, C., Xue, G., He, Q., 2021. Activation patterns of the dorsal medial prefrontal cortex and frontal pole predict individual differences in decision impulsivity. *Brain Imaging Behav* 15 (1), 421–429.
- da Matta, A., Gonçalves, F.L., Bizarro, L., 2012. Delay discounting: concepts and measures. *Psychology and Neuroscience* 5 (2), 135–146.
- McClure, S.M., Laibson, D.I., Loewenstein, G., Cohen, J.D., 2004. Separate neural systems value immediate and delayed monetary rewards. *Science* 306 (5695), 503–507.
- Miedl, S.F., Wiswede, D., Marco-Pallarés, J., Ye, Z., Fehr, T., Herrmann, M., Münte, T.F., 2015. The neural basis of impulsive discounting in pathological gamblers. *Brain Imaging Behav* 9 (4), 887–898.
- Mitchell, J.M., Fields, H.L., Desposito, M., Boettiger, C.A., 2005. Impulsive Responding in Alcoholics. *Alcoholism: Clinical and Experimental Research* 29, 2158–2169.
- Monfort, V., Pfeuty, M., Klein, M., Collé, S., Brissart, H., Jonas, J., Maillard, L., 2014. Distortion of time interval reproduction in an epileptic patient with a focal lesion in the right anterior insular/inferior frontal cortices. *Neuropsychologia* 64, 184–194.
- Naqvi, N.H., Rudrauf, D., Damasio, H., Bechara, A., 2007. Damage to the Insula Disrupts Addiction to Cigarette Smoking. *Science* 315 (5811), 531–534.
- Ohmura, Y.u., Takahashi, T., Kitamura, N., 2005. Discounting delayed and probabilistic monetary gains and losses by smokers of cigarettes. *Psychopharmacology* 182 (4), 508–515.
- Rochat, L., Van der Linden, M., Renaud, O., Epiney, J.-B., Michel, P., Sztajzel, R., Spierer, L., Annoni, J.-M., 2013. Poor reward sensitivity and apathy after stroke: implication of basal ganglia. *Neurology* 81 (19), 1674–1680.
- Sellitto, M., Ciaramelli, E., di Pellegrino, G., 2010. Myopic discounting of future rewards after medial orbitofrontal damage in humans. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 30 (49), 16429–16436.
- Sellitto, M., Ciaramelli, E., Mattioli, F., di Pellegrino, G., 2015. Reduced Sensitivity to Sooner Reward During Intertemporal Decision-Making Following Insula Damage in Humans. *Front Behav Neurosci* 9, 367.
- C. Sheffer J. MacKillop J. McGahey R. Landes L. Carter R. Yi B. Jones D. Christensen M. Stitzer L. Jackson W. Bickel Delay discounting, locus of control, and cognitive impulsiveness independently predict tobacco dependence treatment outcomes in a highly dependent, lower socioeconomic group of smokers 21 3 2012 221 232.
- Sheffer, C.E., Christensen, D.R., Landes, R., Carter, L.P., Jackson, L., Bickel, W.K., 2014. Delay discounting rates: a strong prognostic indicator of smoking relapse. *Addict Behav* 39 (11), 1682–1689.
- SMITH, B., MITCHELL, D., HARDIN, M., JAZBEC, S., FRIDBERG, D., BLAIR, R., ERNST, M., 2009. Neural Substrates of Reward Magnitude, Probability, and Risk During a Wheel of Fortune Decision-Making Task. *Neuroimage* 44 (2), 600–609.
- Szucs, D., Ioannidis, J.P.A., 2020. Sample size evolution in neuroimaging research: An evaluation of highly-cited studies (1990–2012) and of latest practices (2017–2018) in high-impact journals. *Neuroimage* 221, 117164. <https://doi.org/10.1016/j.neuroimage.2020.117164>.
- Tanaka, S.C., Doya, K., Okada, G.o., Ueda, K., Okamoto, Y., Yamawaki, S., 2004. Prediction of immediate and future rewards differentially recruits cortico-basal ganglia loops. *Nat Neurosci* 7 (8), 887–893.
- Üstün, S., Kale, E.H., Çiçek, M., 2017. Neural Networks for Time Perception and Working Memory. *Front Hum Neurosci* 11, 83.
- Von Siebenthal, Z., Boucher, O., Lazzouni, L., Taylor, V., Martinu, K., Roy, M., Rainville, P., Lepore, F., Nguyen, D.K., 2020. Expected value and sensitivity to punishment modulate insular cortex activity during risky decision making. *Sci Rep* 10, 11920.
- Wang, X., Wu, Q., Egan, L., Gu, X., Liu, P., Gu, H., Yang, Y., Luo, J., Wu, Y., Gao, Z., Fan, J., 2019. Anterior insular cortex plays a critical role in interoceptive attention. *Elife* 8.
- Weber, B.J., Huettel, S.A., 2008. The neural substrates of probabilistic and intertemporal decision making. *Brain Res* 1234, 104–115.
- Weber, E.U., Johnson, E.J., 2009. Mindful Judgment and Decision Making. *Annual Review of Psychology* 60 (1), 53–85.
- Weller, J.A., Levin, I.P., Shiv, B., Bechara, A., 2009. The effects of insula damage on decision-making for risky gains and losses. *Soc Neurosci* 4 (4), 347–358.
- Wittmann, M., Leland, D.S., Paulus, M.P., 2007. Time and decision making: differential contribution of the posterior insular cortex and the striatum during a delay discounting task. *Exp Brain Res* 179 (4), 643–653.
- Wittmann, M., Lovero, K.L., Lane, S.D., Paulus, M.P., 2010a. Now or later? Striatum and insula activation to immediate versus delayed rewards. *J Neurosci Psychol Econ* 3 (1), 15–26.
- Wittmann, M., Simmons, A.N., Aron, J.L., Paulus, M.P., 2010b. Accumulation of neural activity in the posterior insula encodes the passage of time. *Neuropsychologia* 48 (10), 3110–3120.
- Wittmann, M., Simmons, A.N., Flagan, T., Lane, S.D., Wackermann, J., Paulus, M.P., 2011. Neural substrates of time perception and impulsivity. *Brain Research* 1406, 43–58.
- Wu, A.S., Witgert, M.E., Lang, F.F., Xiao, L., Bekele, B.N., Meyers, C.A., Ferson, D., Wefel, J.S., 2011. Neurocognitive function before and after surgery for insular gliomas. *J Neurosurg* 115 (6), 1115–1125.
- Wu, C.C., Sacchet, M.D., Knutson, B., 2012. Toward an Affective Neuroscience Account of Financial Risk Taking. *Frontiers in Neuroscience* 6, 159.
- Zhang, X., Li, S., Liu, Y., Chen, X., Shang, X., Qi, F., Wang, X., Guo, X., Chen, J., 2019. Gain-loss situation modulates neural responses to self-other decision making under risk. *Sci Rep* 9, 632.
- Zhang, Y.-Y., Xu, L., Liang, Z.-Y., Wang, K., Hou, B., Zhou, Y., Li, S., Jiang, T., 2018. Separate Neural Networks for Gains and Losses in Intertemporal Choice. *Neurosci Bull* 34 (5), 725–735.