

## Segregated and Integrated Coding of Reward and Punishment in the Cingulate Cortex

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<sup>1</sup>Division of Systems Neuroscience, Tohoku University Graduate School of Life Sciences, Sendai; <sup>2</sup>Advanced Research Institute for the Sciences and Humanities, Nihon University; <sup>3</sup>Division of Applied System Neuroscience, Nihon University Graduate School of Medical Science, Tokyo, Japan; and <sup>4</sup>Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, United Kingdom

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**Fujiwara J, Tobler PN, Taira M, Iijima T, Tsutsui K-I.** Segregated and integrated coding of reward and punishment in the cingulate cortex. *J Neurophysiol* 101: 3284–3293, 2009. First published April 1, 2009; doi:10.1152/jn.90909.2008. Reward and punishment have opposite affective value but are both processed by the cingulate cortex. However, it is unclear whether the positive and negative affective values of monetary reward and punishment are processed by separate or common subregions of the cingulate cortex. We performed a functional magnetic resonance imaging study using a free-choice task and compared cingulate activations for different levels of monetary gain and loss. Gain-specific activation (increasing activation for increasing gain, but no activation change in relation to loss) occurred mainly in the anterior part of the anterior cingulate and in the posterior cingulate cortex. Conversely, loss-specific activation (increasing activation for increasing loss, but no activation change in relation to gain) occurred between these areas, in the middle and posterior part of the anterior cingulate. Integrated coding of gain and loss (increasing activation throughout the full range, from biggest loss to biggest gain) occurred in the dorsal part of the anterior cingulate, at the border with the medial prefrontal cortex. Finally, unspecific activation increases to both gains and losses (increasing activation to increasing gains and increasing losses, possibly reflecting attention) occurred in dorsal and middle regions of the cingulate cortex. Together, these results suggest separate and common coding of monetary reward and punishment in distinct subregions of the cingulate cortex. Further meta-analysis suggested that the presently found reward- and punishment-specific areas overlapped with those processing positive and negative emotions, respectively.

### INTRODUCTION

Successful adaptive behavior, including learning and decision making, requires accurate evaluation of actions and choices. Reward and punishment provide positive and negative evaluative information, based on which behavior can be adapted. The cingulate cortex is involved in processing the expectation and occurrence of reward and punishment. Reward and punishment processing have usually been studied separately.

Single-unit recording studies in monkeys demonstrated that the anterior and posterior regions of the cingulate cortex contain some neurons that show increased firing in response to reward delivery (Amiez et al. 2006; McCoy et al. 2003; Niki and Watanabe 1979) and others that show sustained firing toward the anticipated time of reward delivery (Amiez et al.

2006; Niki and Watanabe 1979; Shidara and Richmond 2002). Human functional magnetic resonance imaging (fMRI) studies using monetary reward have confirmed increased anterior and posterior cingulate activation in relation to reward receipt (Izuma et al. 2008; Nieuwenhuis et al. 2005; O'Doherty et al. 2001) or anticipation (Ernst et al. 2004; Marsh et al. 2007; Tom et al. 2007). Lesion studies suggest that the cingulate sulcus is involved in the integration of previous reward history with current action choice (Kennerley et al. 2006). Thus a considerable body of evidence implicates the cingulate region in reward processing.

Human event-related potential studies have revealed the source of a punishment-related potential in the midventral part of anterior cingulate cortex (Gehring and Willoughby 2002). Human fMRI studies have reported increased activation with decreased reward (Bush et al. 2002) or with receipt of punishment (Liu et al. 2007) and decreased activation with anticipation of punishment (Tom et al. 2007). Single-neuron studies of explicit punishment (e.g., pain or aversive liquid) processing in the cingulate are less common. However, psychological theories suggest omission or reduction of an expected reward as a higher-order form of punishment (e.g., Amsel 1992). Also behavioral errors may provide instances of punishing outcomes because they are usually accompanied by reward omission, time-out periods, and error-specific auditory or visual feedback. A group of cingulate neurons shows increased firing in relation to reward omission, reward decrease, and errors in monkeys (Amiez et al. 2005; Brooks 1986; Ito et al. 2003; Matsumoto et al. 2007; Michelet et al. 2007; Niki and Watanabe 1976, 1979; Quilodran et al. 2008; Shima and Tanji 1998). Cingulate neurons in humans also code unexpected reductions of reward (Williams et al. 2004). Taken together, the evidence suggests higher-order punishment processing by cingulate cortex in both human and nonhuman primates.

Despite substantial experimental evidence implicating the cingulate cortex in the processing of affective value, reward and punishment have usually been studied separately and a direct comparison of reward and punishment processing has been made in only a few studies (Ito et al. 2003; Matsumoto et al. 2007; Quilodran et al. 2008; Sallet et al. 2007). Therefore it is largely unclear whether the same or different cingulate neurons and regions code reward and punishment information and whether previously reported activations would code reward and punishment specifically or in an integrated fashion. Because reward and punishment elicit different types of emotion (positive and negative, respectively) and induce different

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types of behavior (approach and avoidance, respectively), it may be useful for the neural system to maintain distinct representations. On the other hand, it may also be necessary to integrate reward and punishment information, for example, to compare the value of risky options that can result in both rewards and punishments.

In this study, we investigate reward and punishment processing in the cingulate cortex, with special interest in whether the representation of reward and punishment information is segregated or integrated. Therefore we compared cingulate activations for different levels of monetary reward and punishment. A reward- and punishment-specific region would show increasing activity only with increasing gains and losses, respectively. On the other hand, a region involved in integrated coding would show increasing or decreasing activity throughout the full range of losses and gains.

## METHODS

### *Participants*

Seventeen right-handed adults (12 males and 5 females, ages 20–29 yr) with no history of neurological, psychiatric, or auditory symptoms participated in the imaging study. Written informed consent was obtained from each participant. This experiment was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of the Nihon University School of Medicine.

### *Experimental design and task*

Participants were asked to compete with a computer in a free-choice task in which they had to choose between two decks of cards in every trial. Prior to the experiment, they were given the following instructions: 1) the outcome of each chosen card would be added to, or subtracted from, the basic payment of 3,000 yen (100 Japanese yen correspond to about 1 dollar US); 2) before starting every trial, the computer would see the front side of the top card of each deck and decide which deck to put on which location (left or right), aiming to minimize the income of participants; and 3) the participants had to compete with the computer by trying to pick the card yielding the higher outcome in every trial, thereby maximizing their income as a whole. However, unrevealed to participants, the outcome sequence was fully predetermined by the experimenter before the start of the experiment (see following text). Questioning of participants after the experiment revealed that all participants except one (data discarded) believed that they were competing with a computer. During a practice session, participants had to learn the properties of the decks by trial and error and were not given any information about the distribution and size of outcomes of the two decks. Each deck contained the same cards, which were associated with 0 yen or a gain or loss of 200, 400, or 800 yen. Both decks also contained blank control cards. At the beginning of each trial, the two decks were presented until participants made their choice, but for a maximum of 4 s. If no response occurred during that interval, the computer randomly chose one of the decks, which happened very rarely (0–1 trial for each participant). Reported results correspond only to trials in which participants responded in time. Once a choice was made, the chosen deck was highlighted (1 s). After a variable delay of 3–4 s, the outcome of the chosen deck (chosen outcome) was presented for 2 s. After a second delay of 3–4 s, the outcome of the unchosen deck (unchosen outcome) was presented for 2 s, followed by an intertrial interval of 3–4 s. Although participants were instructed to compete with the computer in the task to try to earn more money, the whole outcome sequence was predetermined and the choices made by the participants had no influence on the sequence. The outcome sequence was designed so that losses and gains incurred from the chosen outcome ranged within –800 to +800

yen (–800, –400, –200, 0, +200, +400, +800 yen) and a mean of 0 yen. Relative gains and losses, defined as the difference between chosen and unchosen outcomes, ranged within –800 to +800 yen with a mean of 0 yen (0,  $\pm 200$ ,  $\pm 400$ ,  $\pm 600$ , or  $\pm 800$ ). Absolute and relative values were completely counterbalanced experimentally. In other words, the probability of the unchosen outcome being lower, the same as, or higher than the chosen outcome was constant ( $P = 1/3$ ). The task was designed such that the experienced gains and losses from the chosen option were the same in relative gain and relative loss trials. To adhere to these boundary conditions for outcomes, the trial sequence was predetermined for each participant but varied across participants.

Each participant started the task with 3,000 yen and was told that any losses they incurred during the experiment would be subtracted from this total, whereas any gains would be added to the total. Thus participants knew that their eventual payments at the end of the experiment would consist of a base amount of 3,000 yen plus or minus a variable amount earned during the experiment. The actual payoff of the variable amount earned and lost during the experiment was zero in all participants. This was ensured by predetermining the sequence of chosen outcomes such that the actual mean payoff corresponded to the theoretical mean payoff of 0 yen after every 11 or 12 trials. However, for ethical reasons, each participant received 5,000 yen (about 50 dollars US), according to the duration of their participation, about 3 mo after scanning. Participants were not informed of this before the experiment. The experiment comprised a training phase (20 trials), a scanning phase (122 trials), and a behavioral testing phase (122 trials). Earnings of the training phase did not contribute to the total earnings of participants. In the behavioral testing phase participants were required to indicate how happy or unhappy the chosen outcomes of each trial made them, on a scale from 1 (very happy) to 9 (very unhappy). To avoid cumulative wealth effects (Kahneman and Tversky 1979), accumulated earnings were not displayed and both gains and losses were counterbalanced such that the cumulative wealth of all participants was 0 yen after every 11 or 12 trials. Participants reported that they did not try to add their earnings during the experiment.

### *Analysis of outcome-dependent responding*

We studied the effects of gains and losses on subsequent behavior in several different ways. First, we split the data according to whether participants experienced a gain or loss in the previous trial and used a  $\chi^2$  test to assess whether this influenced the proportion of option choices in the current trial. Second, response time in the current trial was linearly regressed against absolute or relative value of the previous trial. Third, individual propensity to follow a win-stay/lose-shift strategy was calculated by comparing the number of instances in which participants chose the same option as the one that resulted in a gain in the previous trial (win-stay) and the number of instances in which they switched after a loss (lose-switch) with the number of instances in which participants switched after a gain (win-switch) and perseverated after a loss (lose-stay). This corresponds to (win-stay + lose-switch):(win-switch + lose-stay). Deviation of this ratio from 1:1 was tested with a  $\chi^2$  test. Finally, we z-transformed the individual propensity to follow a win-stay/lose-shift strategy and regressed it against gain- and loss-related brain activation (Fig. 3).

### *Image acquisition*

All images were acquired using a 1.5-T Siemens Symphony magnetic resonance imaging (MRI) scanner (Siemens, Erlangen, Germany) at Nihon University. Gradient-recalled echo planar imaging (EPI) was used for the fMRI sequence to obtain blood oxygen level-dependent (BOLD) contrast. In all, 976 functional scans per participant were acquired using a gradient EPI sequence (20 axial slices in the anterior commissure–posterior commissure plane; repe-

tition time [TR] = 2,000 ms, echo time [TE] = 50 ms, flip angle = 90°, field of view [FOV] = 192 mm, 64 × 64 matrix, voxels size = 3 × 3 × 5 mm, slice thickness = 4 mm, gap = 1 mm). A T1 anatomical scan of each participant was obtained (192 sagittal slices; TR = 2,000 ms, TE = 3.93 ms, flip angle = 15°, FOV = 256 × 224 mm, in-plane resolution = 1 × 1 mm, slice thickness = 1 mm).

### fMRI analysis

Preprocessing and data analysis were performed using SPM2 software. The first two functional scans were discarded to allow for magnetic saturation. The individual slices of a functional volume were temporally corrected for their acquisition time difference, with reference to the middle (tenth) slice. The functional images of each participant were realigned with reference to the first image to correct for head motion. The anatomical images were coregistered with the mean functional images and normalized to the Montreal Neurological Institute (MNI) brain template. Functional data were then normalized using the same transformation parameters and smoothed in the spatial domain (isotropic Gaussian kernel of 8 mm at full width half-maximum).

Functional data were analyzed in an event-related design. In general linear models (GLMs) we modeled each condition by the canonical hemodynamic response function and its temporal derivative. Participant-specific movement parameters were modeled as covariates of no interest. A high-pass filter with a cutoff period of 128 s was used to remove the low-frequency noise. Global scaling was not applied. The GLM served to compute trial-type-specific betas, reflecting the strength of covariance between the brain activation and the canonical response function for a given condition at each voxel for each participant (see Friston et al. 1995 for detailed descriptions).

In this study, we focused the analysis on cingulate activations related to the presentation of the chosen outcome. Brain activations related to the choice of action or the presentation of the unchosen outcome will be described separately. We modeled brain activations at the time of chosen outcomes with a stick (delta) function, convolved with the canonical hemodynamic response function. Importantly, we used different parametric modulators of the chosen outcome to search for monotonic changes in only the gain domain, only the loss domain (segregated representation), or the entire range of outcome gain and loss values (integrated representation). To identify regions coding gains (or losses), we first tested for increasing activation with increasing gain (or loss) setting a contrast of 1 on a parametric modulator that included only gains (or losses). To ensure a preferential relation of the activation to gains (or losses), parametric loss-related (or gain-related) activation increases and decreases were excluded (all masks:  $P < 0.05$ , uncorrected) and gain- and loss-related activation modulations were directly contrasted. To search for regions involved in monotonic coding throughout the full range of gains and losses, we used a parametric regressor that included all gain and loss values and tested for monotonic increasing or decreasing activation for decreasing loss and increasing gain by setting up a contrast of +1 or -1 to the parametric modulator. Finally, to locate common relations to gains and losses, we tested for significantly increasing activations to both the segregated gain and segregated loss modulators. A common relation to both gains and losses was then ensured with inclusive masking.

The effects of interest (betas, percentage of signal change) were calculated relative to an implicit baseline. Using random-effects analysis, the relevant contrasts of parameter estimates were entered into a series of one-way  $t$ -tests and simple ANOVAs with nonsphericity correction where appropriate. For each contrast, statistical parametric maps of the  $t$ -statistic were generated on a voxel-by-voxel basis and these  $t$ -values were transformed into  $z$ -scores of the standard normal distribution. We used thresholding strategy as described previously (O'Doherty et al. 2002, 2003) and used a threshold of  $P < 0.001$ , uncorrected within the cingulate cortex region of interest. The

same, anatomically defined region of interest was applied in all individuals. It included left and right anterior and mid and posterior cingulum as specified with the anatomical automatic labeling toolbox (Tzourio-Mazoyer et al. 2002) implemented in Pickatlas (Maldjian et al. 2003). Thus the present analysis did not attempt to account for fine-grained individual differences in anatomy. Reported voxels conform to MNI coordinate space, with the right side of the image corresponding to the right side of the brain.

### RESULTS

We used fMRI to investigate the neural coding of monetary gains and losses in the cingulate cortex. During scanning, participants were required to play a simple choice task, choosing between one of two options, each of which was associated with monetary gain or loss (Fig. 1A). For both options, gains and losses ranged from +800 to -800 yen (800 yen correspond to 8 dollars US). In each trial, the outcomes of the chosen and unchosen options were presented sequentially. A GLM was used to analyze brain activity at the time of the presentation of the chosen outcome in the cingulate cortex. Different levels of gain and loss were used as parametric modulators to search for regions showing gain- and loss-specific increase of activation as well as monotonic increase or decrease for decreasing loss and increasing gain throughout the full range of values used.

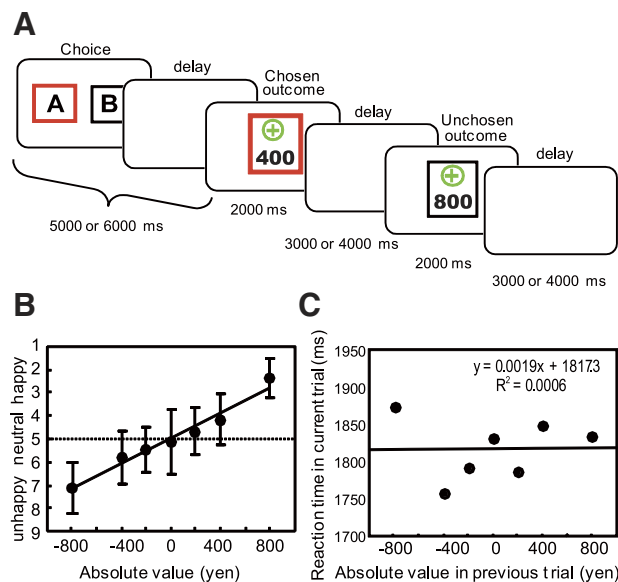


FIG. 1. Experimental design and behavior. A: behavioral task. In each trial, 2 decks were presented on the left and the right sides of a monitor and participants chose one of the 2 decks (by pressing button A for the deck on the left side and B for that on the right side). Each deck contained the same cards, which were associated with 0 yen or a gain or loss of 200, 400, or 800 yen (100 yen correspond to about 1 dollar US). Participants' choice was highlighted for 1 s and after a variable delay the outcome of the chosen deck was presented for 2 s. After a delay of 3–4 s the unchosen outcome was presented for 2 s, followed by an intertrial interval of 3–4 s. The likelihood of the unchosen outcome being higher, the same or lower than the chosen outcome remained constant and these 3 trial types were randomly interleaved. B: average happiness rating in all participants as a function of the absolute value of the chosen outcome (error bars represent SD). For each level of absolute gain or loss, ratings were pooled over different levels of relative gain or loss. The scale ranged from 1 (happy) to 9 (unhappy). Ratings were taken at the end of each trial. C: absence of relation between response time in current trial and absolute value in previous trial. Response times were measured from time of deck presentation.



### Behavioral performance

We regressed happiness/unhappiness ratings against the monetary value of the chosen outcome (pooling over different levels of unchosen outcomes). The rating varied as a function of the full range of chosen outcomes (Fig. 1*B*;  $r = 0.98$ ,  $P < 0.0001$ ). We regressed choice response time in the current trial to chosen gains and losses experienced in the previous trial and found no relation (Fig. 1*C*;  $r = 0.03$ ,  $P = 0.96$ ). These data suggest that, at least when evaluating the outcomes of their choices, participants processed gains and losses in a monotonic, integrated fashion.

Although the focus of the present study is on the processing of absolute gains and losses of chosen outcomes, we briefly mention behavioral results related to relative gains and losses and to behavioral strategies (Fujiwara et al. 2009). Relative gains and losses are defined as positive and negative differences between chosen and unchosen outcomes. For example, if the chosen outcome is  $-200$  and the unchosen outcome is  $-800$ , a relative gain of  $+600$  ensues. Happiness ratings also increased as a function of relative value (pooling over different levels of absolute value) ( $r = 0.96$ ,  $P < 0.0001$ ). Correlations for absolute and relative values did not differ significantly from each other ( $P = 0.32$ ,  $z$ -test). Response times were shorter in the current trial with increasing relative value experienced in the previous trial ( $r = -0.71$ ,  $P = 0.03$ ). In the present experimental situation, experiencing an absolute or relative loss or gain in the previous trial appeared not to significantly influence the proportion of option choice on the current trial by individual participants (all  $P$  values  $\geq 0.093$ ,  $\chi^2$  test). Although care should be taken when interpreting negative results, one reason for relatively little evidence of previous outcomes influencing subsequent choice may be that participants were pretrained on the task and thus may have learned that the options did not differ significantly in terms of reward prediction. To test whether participants made random choices, we

performed a runs test on the sequence of each participant's choices of the two options. Out of 16 participants, 8 showed significant deviations from randomness in choosing the two options ( $P < 0.05$ ), without showing simple left–right biases ( $\chi^2$  test for proportion of choosing left or right: all  $P$  values  $> 0.1$ ). Of the remaining 8 participants, one showed a left–right bias ( $P < 0.001$ ,  $\chi^2$  test) and 3 used win-stay/lose-shift or lose-stay/win-shift strategies ( $P < 0.05$ ,  $\chi^2$  test). These strategies were not detected by the runs test because they depend on the outcome in the previous trial, whereas the runs test considers patterns only in choice sequence, irrespective of outcomes. Taken together, these data suggest that participants processed both absolute and relative values, they usually made nonrandom choices, and that relative gains in the previous trial accelerated responses in the next trial, whereas absolute gains from the chosen option in the previous trial did not.

### Segregated and integrated gain- and loss-related activation within cingulate cortex

To localize regions in cingulate cortex coding gains and losses in a segregated or integrated fashion, we used either gain- and loss-specific or full-range parametric modulators in two separate GLMs (see METHODS for details). Figure 2*A* shows a series of sagittal sections ( $x = 0$ ,  $\pm 7$ , and  $\pm 14$  mm) displaying the regions involved in segregated and integrated coding of gain and loss in cingulate cortex. Gain-specific regions were located mainly in the anterior part of the cingulate cortex (ACC; Brodmann's Area [BA] 32; Fig. 2*A*, red, Table 1), and the posterior cingulate cortex (PCC; BA 23 and 31; Table 2 for regions outside the cingulate cortex). Figure 2*B* shows outcome-induced activations in the gain-specific region in the PCC ( $P < 0.001$ ;  $6/-32/40$ , BA 31). In these regions, activations increased primarily across the range of positive outcome values rather than across negative outcome values and accordingly, when directly compared, the relation

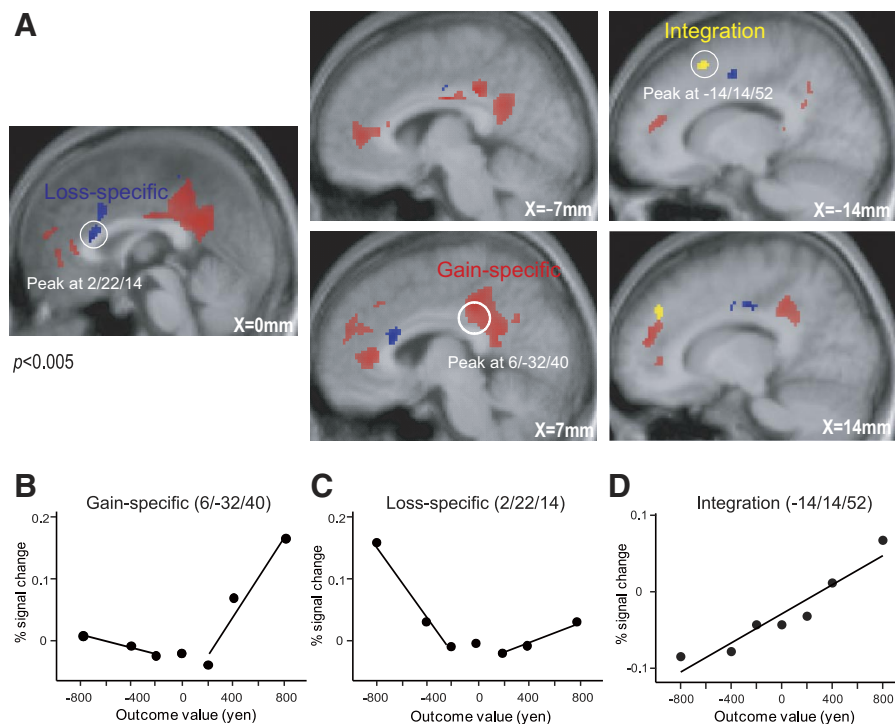


FIG. 2. Cingulate and medial prefrontal regions involved in segregated and integrated coding of gain and loss ( $x = 0$ ,  $\pm 7$ , and  $\pm 14$  mm). *A*: locations in cingulate cortex showing preferential increase of activation with increasing gain rather than loss (red); preferential increase with increasing loss rather than gain (blue); or monotonic increase of activation with decreasing loss and increasing gain (yellow). To show the extent of activations as well as their foci, we applied a threshold of  $P < 0.005$  for producing this figure. Note that all indicated activation peaks survived the threshold of  $P < 0.001$ . *B*: activation change of gain-specific region in posterior cingulate cortex (6/-32/40). *C*: activation change of loss-specific region in anterior cingulate cortex (peak at 2/22/14). *D*: activation change of integrated region in dorsal middle cingulate cortex (-14/14/52).

TABLE 1. *Gain-specific regions in the cingulate*

Anatomical Region	Side	x	y	z	z-Score	Voxels	
Anterior cingulate cortex	L	-10	42	6	3.64	57	***
	R	14	52	18	3.50	72	***
	R	4	32	6	3.45	52	***
Posterior cingulate cortex	L	-6	-12	30	3.99	876	****
	L	-10	-30	32	4.40		****
	L/R	0	-48	26	3.79		****

\*\*\* $P < 0.001$ ; \*\*\*\* $P < 0.0001$ .

with gains was significantly stronger than that with losses. Loss-specific regions were located mainly in the middle and the posterior part of the ACC (BA 24 and 33; Fig. 2A, blue, Table 3; Table 4 for regions outside the cingulate cortex). Figure 2C shows activations in the loss-specific region of the middle ACC ( $P < 0.001$ ; 2/22/14, BA 24) over different outcome values. In these regions, activations increased primarily across the range of negative outcome values rather than across positive outcome values, resulting in a significantly stronger relation of activation with losses than with gains. The cingulate regions showing an integrated value signal located in the dorsal part of the ACC (BA 32; Fig. 2A, yellow), around the border with medial prefrontal cortex (MPFC) in the cingulate gyrus. Figure 2D shows the activation change in the integration region ( $P < 0.001$ ; -14/14/52; although this peak was in the MPFC, the activation extended into BA 32; the number of activated voxels in MPFC was 12 and that in BA 32 was 8). The activation increased across the entire range of negative and positive outcome values and showed significantly better relation to a fully integrated signal than segregated gain or loss signals. Outside the cingulate cortex, the main region showing integrated value signals was in the dorsolateral prefrontal cortex ( $P < 0.001$ ; 36/36/44). At the chosen threshold ( $P < 0.001$ ), no cingulate region showed decreasing activation across the full range of outcomes. Taken together, distinct regions in anterior cingulate appear to process gains and losses in a segregated or integrated fashion.

#### *Relation of cingulate activity to outcome-dependent response strategy*

Information about the outcomes of previous choices appears to be integrated by the cingulate into current behavior. To test one possible relation of outcome processing and

TABLE 2. *Gain-specific regions outside the cingulate*

Anatomical Region	Side	x	y	z	z-Score	Voxels	
Superior frontal gyrus	L	-14	14	52	4.22	36	****
	L	-14	48	36	3.79	61	****
	R	14	48	40	3.34	32	***
Inferior operculum	L	-48	20	4	3.38	11	***
Insula	R	46	32	-4	3.43	23	***
Midbrain	L/R	0	-18	-14	3.61	34	***
Inferior temporal gyrus	R	50	-26	-22	3.59	19	***
	R	58	-36	-10	3.80	104	****
Inferior parietal lobule	R	38	-58	40	3.95	302	****
	R	60	-54	20	3.42		***
	R	64	-44	30	3.56		***
Cerebellum	L	-20	-72	-36	3.67	30	***

\*\*\* $P < 0.001$ ; \*\*\*\* $P < 0.0001$ .TABLE 3. *Loss-specific regions in the cingulate*

Anatomical Region	Side	x	y	z	z-Score	Voxels	
Anterior cingulate cortex	R	10	26	16	3.51	26	***
	L/R	0	24	10	3.41		***
	L	-18	-6	44	3.48		***

\*\*\* $P < 0.001$ .

subsequent choice, we calculated for each participant the degree to which he or she followed a win-stay/lose-shift strategy (win-stay/lose-shift propensity index) and correlated this measure to gain- and loss-specific activity (Fig. 3). Distinct regions in PCC showed stronger gain coding with decreasing individual propensity of following win-stay/lose-shift strategy (i.e., increasing individual propensity of following win-shift/lose-stay strategy) and stronger loss coding with increasing individual propensity of following win-stay/lose-shift strategy ( $P < 0.001$ ). The strategy-sensitive gain- and loss-related regions tended to be more posterior and ventral, respectively, than the general gain-related regions reported earlier (Fig. 2). Taken together, individual differences in integrating previous outcomes with current behavior are reflected by differences in outcome-related activations in the cingulate cortex. At the chosen threshold, no cingulate regions showed the opposite relations (positive correlation of propensity to follow win-stay/lose-shift with gains and negative correlation with losses). Incidentally, following a strict win-stay/lose-shift strategy is equivalent to choosing options according to a standard reinforcement learning algorithm (e.g., Rescorla and Wagner 1972), with a learning rate parameter of 1. Accordingly, the relations of win-stay/lose-shift propensity with gain- and loss-related activations may reflect a basic involvement of the posterior cingulate in individual learning about gains and losses.

#### *Common gain- and loss-related activation within cingulate cortex*

The cingulate cortex has been implicated not only in processing reward and punishment but also in other functions, such as attention and arousal (Critchley et al. 2001; Ng et al. 2007; Oliveira et al. 2007). Perhaps because of their relevance for survival, both reward and punishment induce attention and arousal (e.g., Lang and Davis 2006; Löw et al. 2008). The combined study of reward and attention allows at least a partial dissociation of value from attentional functions of the cingulate cortex. Attentional accounts would predict similar activation increases, resulting in U-shaped activation patterns, with increasing reward and punishment. Conversely, as argued and shown earlier, value accounts would predict specific or fully integrated reward and punishment processing. In a next step, we therefore localized regions in cingulate cortex showing common coding of gains and losses. Activations increased with

TABLE 4. *Loss-specific regions outside the cingulate*

Anatomical Region	Side	x	y	z	z-Score	Voxels	
Inferior operculum	R	36	6	28	3.69	22	***
Insula	L	-28	22	8	3.64	38	***

\*\*\* $P < 0.001$ .

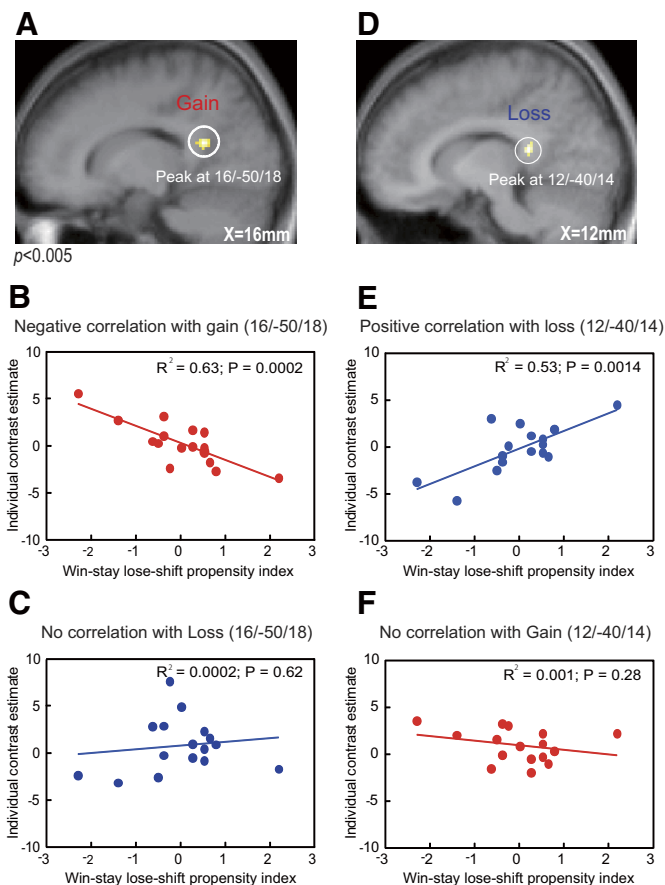


FIG. 3. Cingulate and paracingulate regions processing gain and loss dependent on individuals' propensity for following outcome-dependent choice strategies. *A*: location in cingulate cortex showing stronger absolute gain coding with decreasing individual propensity of following win-stay/lose-shift strategy (i.e., increasing individual propensity of following win-stay/lose-shift strategy). The activation extended into neighboring precuneus. *B* and *C*: negative relation of win-stay/lose-shift strategy implementation with gain (*B*) but no relation with loss (*C*). *D*: location in cingulate cortex showing stronger absolute loss coding with increasing individual propensity of following win-stay/lose-shift strategy. *E* and *F*: positive relation of win-stay/lose-shift strategy implementation with loss (*E*) but no relation with gain (*F*). The significant correlations of this figure (*B*, *E*) were also significant with outlier-resistant nonparametric tests for correlation (all  $P < 0.05$ , Spearman and Kendall tests).

both gains and losses in a posterior part of the ACC and in PCC (BA 24 and 23, Fig. 4, Table 5; Table 6 for regions outside the cingulate cortex). Figure 4*B* shows activations in the common

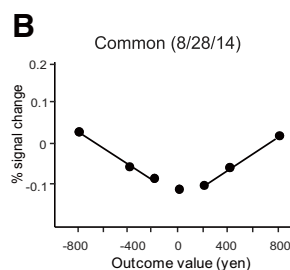
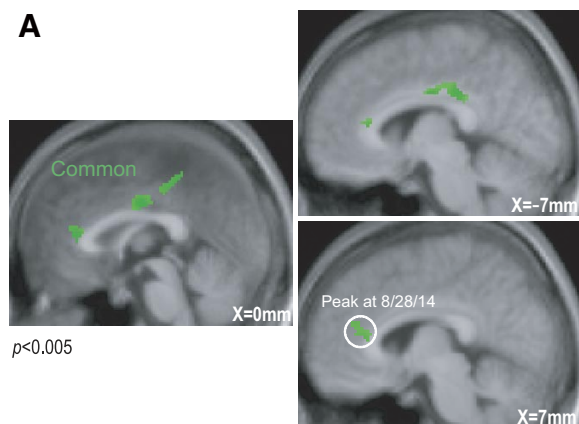


FIG. 4. Common activations to gains and losses in cingulate cortex ( $x = 0, \pm 7$  mm). *A*: anterior and posterior parts of the cingulate cortex showed similar changes in activation to gains and losses. To show the extent of activations as well as their foci, we applied a threshold of  $P < 0.005$  for producing this figure. Note that the indicated activation peak survived the threshold of  $P < 0.001$ . *B*: activation change of commonly activated region in anterior cingulate cortex (8/28/14). Activation increases to losses differed insignificantly from activation increases to gains.

TABLE 5. Common gain and loss regions in the cingulate

Anatomical Region	Side	x	y	z	z-Score	Voxels	
Anterior cingulate cortex	L	-4	-12	30	4.12	44	****
	L	-2	30	8	3.70	60	***
Posterior cingulate cortex	L	-8	-30	32	4.48	43	****

\*\*\* $P < 0.001$ ; \*\*\*\* $P < 0.0001$ .

region of the anterior ACC ( $P < 0.001$ ; 8/28/14, BA 24) as a function of different outcome values. The activation showed common relations to both positive and negative values (inclusive masking, both  $P < 0.001$ ), without significant differences between relations to losses and gains ( $P > 0.05$ ). Thus regions in ACC and PCC, distinct from gain- and loss-specific regions reported earlier, showed activation patterns that are compatible with attentional functions. The proximity of some of these regions with segregated gain-related regions within the cingulate cortex suggests the possibility of gradients that our categorical statistical analysis could not reveal.

#### Relative gain and loss processing in the cingulate cortex

Finally, for a more complete description of the data, we briefly mention cingulate activations related to unchosen outcomes and to relative gains and losses. All of these analyses were performed for the later epoch of unchosen outcome presentation, rather than for the earlier, chosen outcome presentation reported so far. At the chosen threshold ( $P < 0.001$ ), activation in the cingulate cortex did not covary with the magnitude of unchosen positive or negative outcomes. Thus the results reported earlier appear not to simply track any outcome, but may reflect a more specific relation to the participant's gains and losses. In agreement with a previous report (Coricelli et al. 2005), the anterior cingulate showed increasing activations with increasing relative losses (10/24/34). Other anterior cingulate regions showed increasing activation to relative gains, usually coding both relative gains and losses (e.g., -14/42/12; 2/44/4). At the chosen threshold ( $P < 0.001$ ), no region in the cingulate cortex showed an integrated increasing or decreasing relative gain or loss signal. Taken together, these data suggest that relative value coding in the cingulate cortex tends to follow a common (U-shaped) activation pattern for gains and losses.



TABLE 6. Common gain and loss regions outside the cingulate

Anatomical Region	Side	x	y	z	z-Score	Voxels	
Postcentral gyrus	R	18	-32	56	3.38	13	***
Inferior operculum	R	50	24	4	3.63	88	***
	R	46	30	-2	3.52		***
	R	38	14	32	3.28		***
Insula	L	-34	16	-18	3.71	22	***
	L	-46	20	4	3.33	10	***
Midbrain	L	-10	-10	-10	4.03	32	****
Middle temporal gyrus	R	54	-20	-14	3.94	112	****
	R	58	-34	-10	3.86	13	****
	R	58	-42	20	3.35	26	***

\*\*\* $P < 0.001$ ; \*\*\*\* $P < 0.0001$ .

## DISCUSSION

In this fMRI study, we tested cingulate cortex activations related to the outcome value of a chosen option in a free-choice task and found both segregated and integrated reward and punishment coding in distinct cingulate regions. To analyze the type of value coding, we used a parametric experimental design with segregated monetary gain (reward) and loss (punishment) modulators or with an integrated full-range modulator. The parametric experimental design with monetary gain and loss enabled a direct and quantitative comparison of the reward- and punishment-related activations. Such comparisons would be difficult if stimuli from different modalities (e.g., food and electrical shock) were used for reward and punishment because activation differences could be attributable to differences in sensory properties and intensities of stimuli rather than differences in outcome value itself. The presently used parametric experimental design took full advantage of the quantitative and well-controlled nature of money.

The cingulate may play a role in the processing of emotions. For example, recalled and reexperienced sadness and happiness result in distinct cingulate activations (Damasio et al. 2000). Processing the outcome of a choice not only may comprise the evaluation of outcomes and the future action planning based on the outcomes, but also involve the induction of emotions (e.g., Berridge and Robinson 2003). The behavioral data of the current study suggest that, with the present

task design, the chosen outcome itself has less influence on future choice than the relative outcome, the difference between unchosen and chosen outcomes. In agreement with this notion, we hypothesized that the observed activation elicited by chosen outcomes in this study is mainly related to a passive induction of simple emotions such as joy or disappointment. To test this hypothesis with reference to previous findings, we performed a meta-analysis on 51 studies that reported cingulate activation with positive and negative emotion or physical pain. For the meta-analysis of emotions, we referred to those studies that presented pictures of faces or words for inducing emotions without requiring generation of an action based on that information ( $n = 24$ ). For the meta-analysis of pain, we referred to those studies that applied thermal noxious stimulation for inducing pain ( $n = 27$ ). For each study, we plotted the reported peak of activation (coordinates in MNI space) related to positive and negative emotion or physical pain (see Supplemental Data for the references used for the analysis).<sup>1</sup> Figure 5 shows the summary of the result of this study (Fig. 5, A and B) and that of the meta-analysis (Fig. 5, C–E). In the meta-analysis, we plotted the centers of activation elicited with positive emotions such as happiness and joy (Fig. 5C) and those of the activation elicited with negative emotions such as anger, sadness, and fear (Fig. 5D). We also plotted pain-related activations in cingulate cortex (Fig. 5E). By comparing the results of our study with those of the meta-analysis, we detected a common trend. The locations of gain-specific regions in the anterior part of ACC and in the posterior part of PCC (Fig. 5A) correspond to previously reported foci of activation for positive emotions (happiness, red circles in Fig. 5C). On the other hand, the locations of loss-specific regions in the middle and the posterior part of ACC (Fig. 5B) correspond to previously reported foci of activation for negative emotions (anger, sadness, and fear, represented with circles of light blue, blue, and green, respectively, in Fig. 5D) and pain (purple circles in Fig. 5E), respectively. The pain-related activations of the cingulate cortex are considered to be affective rather than sensory in nature because they can be elicited by psychological and hypnosis-induced pain (Derbyshire et al. 2004; Raij et al.

<sup>1</sup> The online version of this article contains supplemental data.

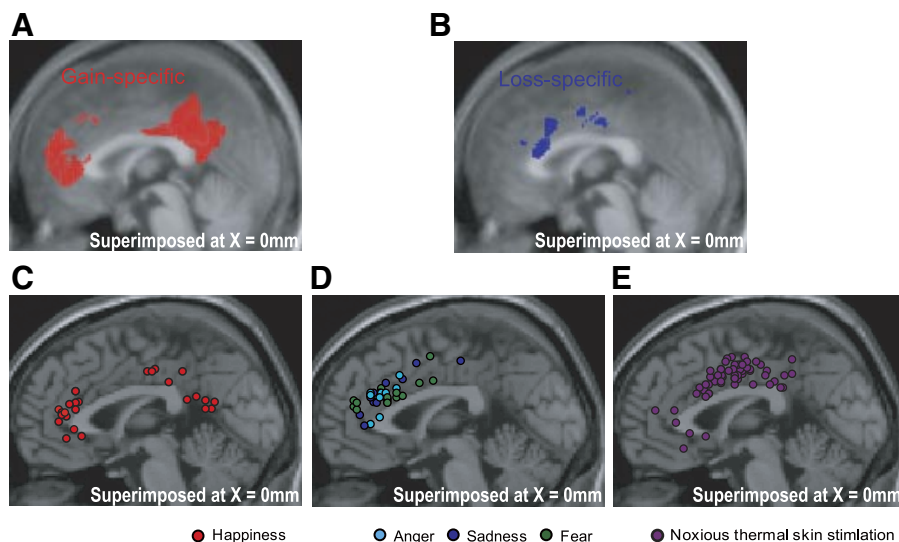


FIG. 5. Summary of the results of this study and meta-analysis. Gain-specific (A) and loss-specific (B) regions identified by this study. To facilitate comparison with meta-analysis, A and B are reproduced from Fig. 2 by superimposing the activation from  $x = -14$  to  $x = 14$  mm on  $x = 0$  mm. C: summary of the peak-activation sites in the cingulate cortex for positive emotion of happiness in 15 previous studies. D: summary of the peak-activation sites in the cingulate cortex for negative emotion of anger/sadness/fear in 22 previous studies. Light blue: anger; blue: sadness; green: fear. E: summary of the peak-activation sites in the cingulate cortex during noxious thermal stimulation of the skin in 27 previous studies. Activation peaks identified by meta-analysis were all superimposed at  $x = 0$  mm.

2005), empathy for the pain of a loved-one (Singer et al. 2004), or psychological pain of being socially excluded (Eisenberger et al. 2003). Taken together, these data suggest that within the ACC, anterior parts primarily process rewards and positive emotions, whereas posterior parts primarily process punishments, negative emotions, and pain. Moreover, the correspondences of localization of gain- and loss-specific regions and the foci of activation for positive and negative emotions suggest a close relation in the processes elicited by monetary gain and loss with those elicited by positive and negative emotions.

The behavioral data indicated that the outcome value influenced happiness/unhappiness ratings in an integrated fashion. That may imply that at least some brain regions should code reward and punishment in an integrated fashion. Strikingly, the only such region identified in the present study was in dorsal ACC, at the border of medial prefrontal and cingulate gyrus, suggesting that this region may have a preferential role in representing the full range of monetary reward and punishment as action outcome. This integrated coding of gains and losses cannot be directly related to a single type of emotion because gains and losses elicit emotions with opposite valence, positive and negative. Such integrated coding may be of a more cognitive rather than emotional nature and could be used for economic decision making. Indeed, it has been suggested that the cingulate cortex plays an important role in connecting emotional and cognitive processes and that the ventral part of ACC around the cingulate gyrus is more involved in emotional processes, whereas the dorsal part of ACC is more involved in cognitive processes (Bush et al. 2000; Marsh et al. 2007; Rushworth et al. 2007; Vogt 2005; Walton et al. 2007). This scheme is particularly noteworthy, given the connectivity of the cingulate with the rostral and ventral part of the ACC around the genu of the corpus callosum as well as the PCC receiving particularly strong connections from orbitofrontal cortex (OFC) (Carmichael and Price 1996). In this scheme, the processing of emotional aspects of gain and loss would arise from interplay between the cingulate cortex and the OFC. Human electrophysiology and fMRI studies (Bush et al. 2002; Holroyd et al. 2004; Mars et al. 2005; Walton et al. 2004) as well as monkey electrophysiology and neuropsychology (Kennerley et al. 2006; Matsumoto et al. 2007; Shima and Tanji 1998) indicate that the dorsal part of ACC around the cingulate gyrus and the adjacent MPFC are involved in action outcome monitoring and outcome-based action selection. It is conceivable that the presently observed integrated coding of losses and gains arises from combining the output of gain- and loss-specific areas within the cingulate cortex. Theoretically it is possible to produce linear coding across the entire range of loss and gain by combining the excitatory input from gain-specific regions with an inhibitory input from loss-specific regions. Taken together, the results suggest a role of dorsal ACC in general action outcome monitoring.

Although our task did not require approach or avoidance, gain and loss may elicit such behavior in the real world. The reward-processing regions of the cingulate cortex have strong connections with motor regions both within and outside the cingulate cortex (Morecraft and van Hoesen 1998; Wang et al. 2001). Thus the cingulate cortex may be particularly well suited to integrate reward and motor information (Rushworth et al. 2004; Shima and Tanji 1998). In agreement with this notion, the cingulate cortex may code reward history and

response information into action value (Holroyd and Coles 2008; Kennerley et al. 2006; Seo and Lee 2007). The present study adds to these previous findings by showing that outcome-related activation of the cingulate cortex also reflects individual differences in how previous outcomes influence subsequent choice.

Outside the cingulate cortex, we found strong gain- and loss-related activations in areas such as prefrontal cortex (dorsolateral [DLPFC], ventrolateral [VLPFC], medial [MPFC]), inferior parietal lobule, opercular/insular cortex, and midbrain. At a lower threshold ( $P < 0.05$ ) we also found activations in the OFC, amygdala, and striatum. These results replicate previous human fMRI findings of reward- and/or punishment-related activations (D'Ardenne et al. 2008; Ernst et al. 2004; Izuma et al. 2008; Knutson et al. 2001; Liu et al. 2007; Nieuwenhuis et al. 2005; O'Doherty et al. 2001; Tobler et al. 2007; Tom et al. 2007). It is noteworthy that integrated coding of reward and punishment also occurred in the DLPFC, which is well known to be involved in highly cognitive processes (Fuster 1997; Levin et al. 1991; Stuss and Benson 1986). Recently, a monkey single-unit recording study has shown integrated coding of reward and punishment in DLPFC (Kobayashi et al. 2006). Although we could clearly replicate reward- and punishment-related activations in many regions, we found relatively weak activations in OFC and striatum, regions that have been repeatedly related to processing reward and/or punishment. In our experimental design, exposure of chosen outcome value and unchosen outcome value were separated in time. Response-time data suggested that it was the difference between the chosen and unchosen outcome values—i.e., the relative outcome value, which was influencing the action-selection process in the next trial, whereas the chosen outcome value appeared to be of more purely emotional nature. Lack of relevance for the future choice process may have resulted in reduced reward- and punishment-related activations in striatum and OFC. Another reason would be that the activation was not detectable because of large interparticipant variability. In agreement with this notion, when we analyzed punishment activation in relation to personality, we found a substantial correlation of punishment processing with introversion and neuroticism in the lateral part of OFC (Fujiwara et al. 2008).

We found distinct reward and punishment coding along the anterior–posterior axis of the cingulate cortex. In OFC, reward and punishment information are represented separately, with the medial part being sensitive to reward and the lateral part being sensitive to punishment (Liu et al. 2007; O'Doherty et al. 2001, 2003). Separate representation of reward and punishment information is also found in the insular cortex (Liu et al. 2007) and the striatum (Seymour et al. 2007). On the other hand, some studies suggest integrated coding of reward and punishment. Monkey single-unit recording (Kobayashi et al. 2006) as well as human fMRI studies (Kim et al. 2006) reported that the rewarding value of avoiding punishment and that of obtaining reward are represented in the prefrontal cortex. Human fMRI studies using reward and punishment have suggested increasing and decreasing activation for reward and punishment, respectively, in the same striatal and prefrontal regions (Delgado et al. 2000; Tom et al. 2007). Taken together with the present findings, reward regions represent reward and punishment both in a segregated and integrated fashion. Future research may further elucidate how the segregated and inte-



grated value representations in cingulate cortex contribute to performing adaptive behavior such as incentive learning and decision making.

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