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Human anterior cingulate neurons and the integration of monetary reward with motor responses

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The human dorsal anterior cingulate cortex (dACC) has been implicated in cognitive processes that have been proposed to play a role in integrating contextual information needed to select or modify appropriate motor responses. In humans, however, there has been little direct evidence tying the dACC to the integration of contextual information and behavioral response. We used single-neuron recordings from human subjects to evaluate the role of the dACC in reward-based decision making. Subjects undergoing planned surgical cingulotomy performed a task where they were instructed to make specific movements in response to changing monetary rewards. In many neurons, activity increased in response to a diminished reward, and was also predictive of the movement ultimately made. After dACC ablation, subjects made selectively more errors when they were required to change movement based on reward reduction. These findings suggest that the dACC in humans plays an important role in linking reward-related information with alternative actions.

The human dACC has been the subject of increasing scientific scrutiny because of its diverse connections and apparent role in a variety of higher cognitive functions. Recent studies have proposed that the dACC is involved in detecting errors, monitoring potential conflicts and performing new behaviors[1–7]. These tasks are believed to engage cognitive mechanisms that are important in linking relevant contextual information with subsequent actions[2,8]. Consistent with this hypothesis, there is also evidence to suggest that the dACC responds to decisional tasks involving monetary reward[9–11] and that these responses may play a role in modifying behavior[12]. Theories regarding dACC function in humans stem mainly from event-related brain-potential recordings and from functional imaging studies that reveal changes in blood flow, oxygenation and other metabolic indicators. Although these studies have been effective in identifying areas of the brain involved in a given task, they lack the resolution necessary to evaluate trial-by-trial changes in the activity of individual neurons[13–16]. Moreover, the precise role of the dACC in linking contextual information, such as reward, with a corresponding action remains the subject of some debate[1,9,12,17–19]. In this study, we took recordings of single neurons in the dACC of human subjects who were performing a structured behavioral task involving a monetary reward, and we identified relevant behavioral changes after focal dACC ablation.

Single-unit recordings in the dACC were taken from subjects undergoing planned cingulotomy (**Fig. 1a**, Methods). These patients were independently selected for surgery after being evaluated by a multidisciplinary cingulotomy assessment committee[20,21]. We elected to model the behavioral paradigm after a task known from human imaging and primate studies to be associated with increased dACC activity[9,22]. During surgery, subjects performed a sequential two-choice selection task that involved moving a joystick in one of two opposite directions in response to three possible visual cues (**Fig. 1b**). In each trial, the cue was presented for a 1,500-ms instruction interval, followed by a 1,500- to 3,000-ms delay interval, and finally by a 'go' cue indicating that the movement should start. In the majority of trials (80%), subjects were shown five dollar signs, indicating that they had received the standard reward and should move the joystick in the same direction as in the previous trial. On 10% of trials, subjects were shown three dollar signs, indicating that they had received a reduced reward and should switch the direction of joystick movement. These trials were presented infrequently so that subjects would base their responses on the current instruction rather than on a predictable change in reward (that is, so as to limit reward expectancy)[23]. In another 10% of the trials, to dissociate the effect of reward reduction from that of an instruction to switch movement direction, subjects were presented with a double-arrow cue, indicating that they had received the standard reward but should change the direction of movement.

We found that neuronal activity in the dACC increased when subjects were instructed to alter movement direction, and that the greatest response occurred when this instruction also signified a concomitant reduction in reward. Furthermore, the level of activity was predictive of whether or not the correct choice would ultimately be made. After dACC ablation, subjects selectively made more errors when they were required to change behavior based on reward reduction. These findings suggest that the dACC in humans is important in linking reward-related information to the selection of alternative actions, especially in the context of a diminished return.

RESULTS

Neuronal responses to reward value and motor instruction

The most prevalent response pattern was a significant increase in activ-

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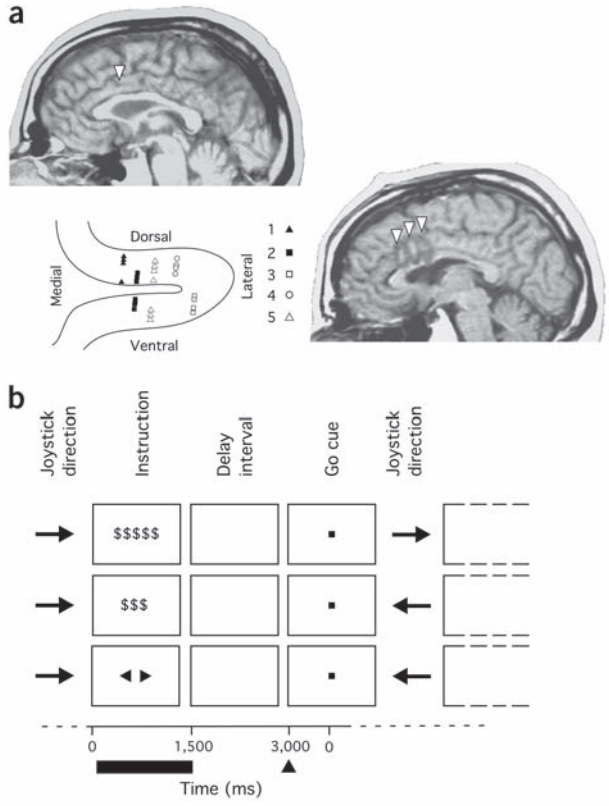

Figure 1 Recording sites and behavioral task. (**a**) Preoperative sagittal T1-weighted MRI indicating the dACC recording site (left inset). Postoperative dACC lesion locations (with surrounding edema) indicated by the three arrowheads (right inset). Schematic illustration of the dACC in coronal section indicating the recording sites for each of the five subjects (bottom inset). In total, 80 cells were recorded in the dorsal bank and 54 cells in the ventral bank of the dACC. (**b**) Each row depicts the time line of events for the three trial types (first row, standard reward; second row, reduced reward; third row, double arrow). Reduced-reward and double-arrow cues indicate that the subject should move the joystick opposite the direction of the previous trial. Black bar, time during which the instructional cue was displayed; arrowhead, go cue.

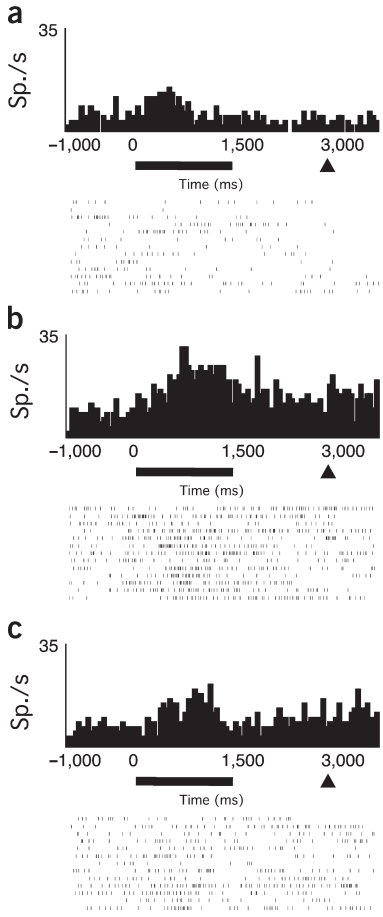

Figure 2 Neuronal responses of a single cell. (**a–c**) Peristimulus histograms and rasters during standard-reward (**a**), reduced-reward (**b**) and double-arrow trials (**c**). Horizontal black bar, time during which the instructional cue is shown; arrowhead, time at which the go-cue signal is first shown. Activity is aligned to instruction onset (time 0).

ity during reduced-reward trials compared to standard-reward trials. We recorded, from five subjects, a total of 134 dACC cells, of which 52 showed task modulation (repeated-measures ANOVA, $P < 0.05$). Task-modulated cells were obseved in all five subjects. Forty-three cells (32%) showed increased activity during reduced-reward trials (**Fig. 2**). To analyze the temporal nature of the modulation, the activity curve of each neuron was divided into 500-ms intervals and compared at each interval between the two trial types (two-tailed *t*-test, $P < 0.05$; single incremented comparisons). Most cells were modulated by the task during the instruction period and a few during the delay (χ^2 test, $P < 0.01$; **Fig. 3a** and **Table 1**). Averaged across the entire population of recorded cells, firing rates were significantly higher in reduced-reward trials than in standard-reward trials during the instruction interval (Kolmogorov-Smirnov (KS) test, $P < 0.00001$).

Double-arrow trials were compared to reduced-reward trials to determine whether the increased activity was dependent on the reduction in reward or on the instruction to change the motor response. A larger percentage of cells showed increased activity in reduced-reward trials than in double-arrow trials (32% versus 16%, respectively; **Figs. 2c** and **3b**). Among these cells, the proportion modulated by a reduced reward was consistently higher than that modulated by double-arrow trials (**Table 2**). Averaged across the entire population of cells, activity was significantly higher in reduced-reward trials than in double-arrow trials during the instruction period (KS test, $P < 0.001$). In contrast, there was no significant difference between double-arrow trials and standard-reward trials ($P > 0.05$). These findings suggest that, although some cells in the dACC showed modulation during instructions to switch motor response, the magnitude of the modulation depended significantly on the reward context.

Controls for change in reward value and novelty

We used an increased-reward control task to determine whether the observed activity stemmed from the reduction in reward or simply from a change in reward in any direction. Thirty-two cells were recorded in one subject during a task in which seven dollar signs were presented on 10% of trials. Similar to reduced-reward trials, the subject was instructed to move in the direction opposite to that of the previous trial, but would this time receive a higher reward. Within this group of cells, only 13% showed enhanced activity, as compared to 38% in reduced-reward trials. The average activity was also significantly higher in reduced-reward trials than in increased-reward trials (KS test; $P < 0.01$). Thus, the dACC responded more strongly to a decrease in reward than to an increase of

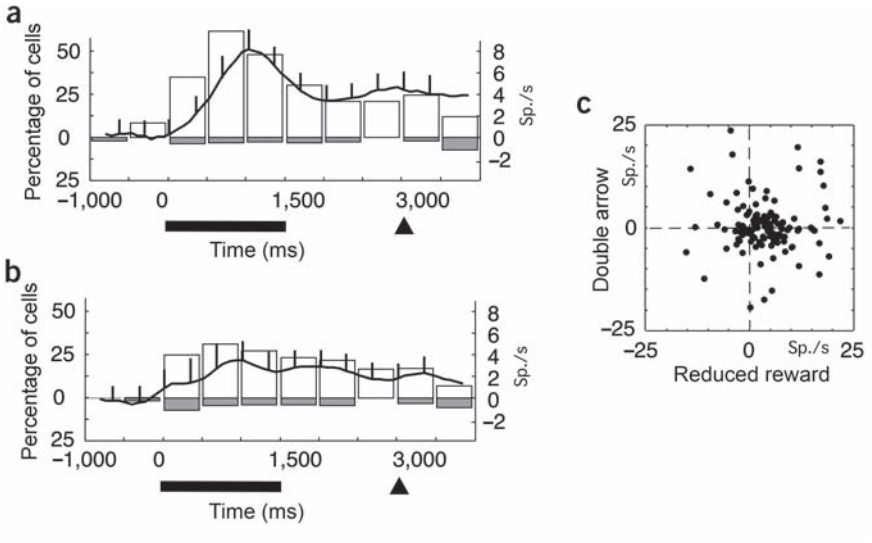

Figure 3 Time course of neuronal activity. (**a**) Activity as a function of time, binned into 500-ms intervals, for all recorded dACC neurons comparing reduced-reward trials to standard-reward trials. White bars, cells with significantly higher activity on reduced-reward trials relative to standard-reward trials; gray bars, cells with significantly lower activity; black curve, average firing rate of all recorded cells on reduced-reward trials minus average firing rate on standard-reward trials. Error bars, s.e.m. (**b**) Activity as a function of time comparing double-arrow trials to standard-reward trials (same convention as above). Black bar, time during which instructional cue is shown; arrowhead, time at which go-cue signal is first shown. Activity is aligned to instruction onset (time 0). (**c**) Scatterplot comparing change in activity for individual cells on reduced-reward and double-arrow trials minus activity on standard-reward trials during instruction.

comparable magnitude.

We also examined activity when standard-reward trials were immediately preceded by a reduced-reward trial. Such trials represented a relative increase in reward compared to the prior trial, but did not require a specific reward-related change in movement direction. In these cases, only 9% of the cells demonstrated enhanced activity. Similarly, 6% of the cells demonstrated enhanced activity in standard-reward trials when preceded by an increased reward, suggesting that most neurons in the dACC did not respond to an expected reduction in reward without the need to make an appropriate change in motor response.

Finally, because reduced-reward and double-arrow trials were presented infrequently, an additional control task was used to determine whether enhanced activity during these trials was partly dependent on stimulus novelty[24]. In a different subject, 23 cells were recorded using a task in which a filled circle appeared 10% of the time. In these trials, the subject received the standard reward and was instructed to move the joystick in the same direction as the previous trial. Only 4% of the cells showed increased activity in these control trials, whereas 39% did so in reduced-reward trials and 26% in double-arrow trials, suggesting that stimulus novelty in itself did not account for the observed effects.

Predictive neuronal activity

These findings suggest that neurons in the dACC respond to the instruction to alter movement, and that the magnitude of the response depends on the instructions' motivational reward value. However, it remained unclear whether this activity correlated with the subjects' behavior. Therefore, choice probability (CP) analysis was performed to determine whether neuronal activity during the instruction period accurately predicted whether the subject would subsequently perform the correct movement[25,26] (Methods). Overall, subjects made errors on 7%, 4% and 1% of reduced-reward, double-arrow and standard-reward trials, respectively. All three trial types had comparable mean significance thresholds ($CP = 0.62 \pm 0.01$; bootstrap test, 95% confidence limit, H_0: $CP = 0.5$).

We found that neuronal activity across the population significantly predicted whether the subjects would select the correct movement in reduced-reward trials as early as 2,800 ms before execution of the motor response ($CP = 0.65$; **Fig. 4**). Activity peaked at the end of the instruction period and declined shortly after movement. Neuronal activity was not predictive, however, of correct versus incorrect responses in either the standard-reward or the double-arrow trials ($CP = 0.49$ and 0.52, respectively). It was also not predictive of the direction of movement ($CP = 0.50$). This suggests that the predictive activity selectively present in reduced-reward trials did not reflect either the movement direction or the presence or absence of a change in direction. It also did not signal the occurrence of reward reduction alone, as reward values were identical in both correct and incorrect trials. Rather, it appeared that dACC activity was directly linked with the act of correctly choosing a change in movement direction, before the execution of the motor response, especially in the context of a diminished reward.

Effect of dACC ablation on subject performance

Given the above findings, we hypothesized that dACC ablation would lead to a deficit in changing movement directions, particularly when associated with reward reduction. We therefore compared task performance before and after cingulotomy in three of the five subjects. Before ablation, mean error rates for this group were 5%, 3% and 0.4% on reduced-reward, double-arrow and standard-reward trials, respectively. After ablation, the error rate increased to 62% ± 8% on reduced-reward trials and to 28% ± 9% on double-arrow trials (**Fig. 5a**). This constituted a significant difference between the two trial types (χ^2 test, $P < 0.001$). The mean error rate for standard-reward trials changed only from 0.4% to 1.0%.

After ablation, variability of both reaction time and movement time increased in all trial

Table 1 Task modulation

$n = 134$	Reduced reward only	Double arrow only	Both reduced reward & double arrow	Total
Instruction only	23 (17%)	4 (3%)	9 (7%)	36 (27%)
Delay only	1 (1%)	3 (2%)	4 (3%)	8 (6%)
Both instruction & delay	6 (5%)	2 (2%)	0 (0%)	8 (6%)
Total	30 (22%)	9 (7%)	13 (10%)	52 (39%)

Number and percentage of all recorded cells with significantly increased activity in either reduced-reward or double-arrow trials or both, compared to standard-reward trials. Total in the reduced-reward only column indicates percentage of cells from all recorded neurons that responded to reduced-reward trials only during either the instruction interval, delay interval or both. Cumulative total from the "Reduced reward only and the "Both reduced reward & double arrow" categories represents all cells with significant response to reduced-reward trials.

Table 2 Task modulation for individual subjects

Patient (n = 52)	1 (n = 12)	2 (n = 13)	3 (n = 6)	4 (n = 14)	5 (n = 7)
Diagnosis	OCD	BAD	Major depression	Major depression	Major depression
Duration (years)	35	27	26	11	30
Severity score	Y-BOCS = 36	BDI = 46	BDI = 42	BDI = 36	BDI = 46
Reduced reward	10 (83%)	9 (69%)	5 (83%)	13 (92%)	6 (86%)
Double arrow	5 (42%)	6 (46%)	3 (50%)	5 (36%)	3 (43%)
Control trials	Ablation	Novelty + ablation		Increased reward + ablation	

Number of cells, recorded from each subject, with significantly increased activity in reduced-reward or double-arrow trials compared to standard-reward trials are indicated in the first row. The number and percentage of cells modulated by reduced-reward or double-arrow trials are indicated in the bottom rows. Subjects are identified by the same numbers used in **Figure 1a**, along with their diagnosis, disease duration and severity and the types of additional control trials used.

types (F-test, $P < 0.001$; **Fig. 5b,c**). There was no significant difference between double-arrow and reduced-reward trials, however, in the mean (Wilcoxon rank-sum test, $P > 0.05$) or variability (F-test, $P > 0.05$) of these time measures, either before or after ablation. In fact, mean reaction time was slightly shorter in reduced-reward trials. This suggests that the observed difference in performance was not attributable simply to an inherent difference in task difficulty or in stimulus-response conflict[6,27]. Furthermore, there was no significant difference in reaction time or movement time between correct and incorrect movements after ablation ($P > 0.05$), suggesting that the increase in errors did not reflect a selective change in motor performance on incorrect trials. Finally, there was no correlation between error rates and session progression before ablation in either trial type (linear regression, $r^2 = 0.002$), indicating that increased errors after ablation did not reflect a trend toward worsening performance as sessions progressed. The above findings were consistent with the physiologic data suggesting that the dACC plays a role in signaling alternative actions, especially in the context of a diminished reward.

DISCUSSION

Although the present observations have some parallels with previous imaging and event-related brain potential studies, they cannot be completely explained by existing theories. For example, some studies show that the ACC generates negative scalp potentials shortly after the execution of an incorrect motor response[4,7]. It could be argued that reduced-reward and double-arrow cues are perceived as behavioral errors indicating a need to modify an 'incorrect' behavior. However, neither the double-arrow nor the reduced-reward cues appeared as a consequence of incorrect actions. Furthermore, the finding that reduced-reward trials demonstrated significantly higher activity than did double-arrow trials argues against this being a simple error response. Other studies also suggest that the dACC is involved in monitoring conflicting behavioral responses[1,6,17]. From that perspective, it may be that reduced-reward and double-arrow trials represented a greater degree of conflict than standard-reward trials. However, there is little evidence to suggest that reduced-reward trials were associated with more conflict than double-arrow trials, as both required switching directions and both elicited similar reaction times and errors. Hence, greater activity in reduced-reward trials cannot be completely attributed to conflict monitoring[27]. Further support for our findings is provided by event-related brain potential recordings in humans suggesting that the ACC is activated by perceived monetary losses rather than by perceived errors[12] and by functional imaging studies demonstrating a stronger dACC response to monetary losses when associated with a behavioral choice[10].

Given the overall diversity of these findings, it is important to note that a complex relationship exists between the activity of single neurons and the activity observed in functional magnetic resonance imaging[15,16], positron emission tomography[14] and electroencephalographic recordings[7,13]. Furthermore, the ACC is known to show considerable functional and anatomical heterogeneity[2,28,29]. Hence, it may be that different types of signals are conveyed by adjacent or overlapping groups of neurons.

Although the subject population in the present study had major depression, obsessive-compulsive disorder (OCD) and/or bipolar affective disorder (BAD), our main observations are consistent with those made of individuals in the general population using noninvasive techniques. Functional imaging studies have demonstrated selective enhancement of dACC activity in response to diminished reward in a motor selection paradigm[9] and in response to monetary losses in a risk-reward based decisional task[10]. These findings are also in agreement with nonhuman primate recordings demonstrating increased activity in the rostral cingulate motor area when movements are instructed by a reduction in juice reward[22]. Furthermore, we found that all subjects in our study demonstrated significant neuronal responses to the task irrespective of their diagnoses. Last, functional imaging studies do not reveal consistent differences in metabolic activity in the ACC of patients with major depression or OCD as compared to normal controls. Indeed, such studies demonstrate both increases and decreases, and often no change in activity[30,31]. Given these considerations, we believe it is unlikely that the qualitative nature of the responses observed in the present study would significantly differ from that expected in the general population. However, it remains possible that the relative degree

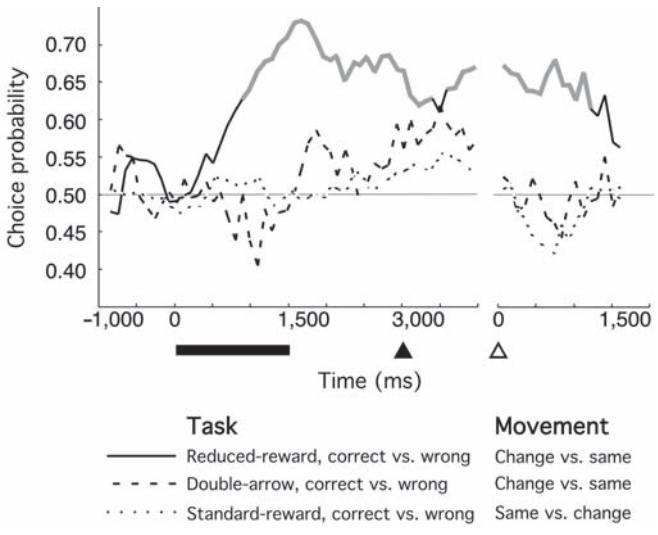

Figure 4 Choice probability as a function of time. CP was calculated by comparing the neuronal responses for correct and incorrect movements in each of the three trial types. Gray areas along the curves indicate intervals during which neuronal activity significantly predicted the subjects' upcoming response. A CP of 0.5 indicates an equal probability of predicting a correct versus incorrect choice. Horizontal black bar, time during which instructional cue is shown; solid arrowhead, time the go cue first appeared, with movement occurring on average at 3,700 ± 50 ms. Activity is aligned to instruction onset (time 0) on the left, and to the corresponding movement onset (open arrowhead, time 0) on the right.

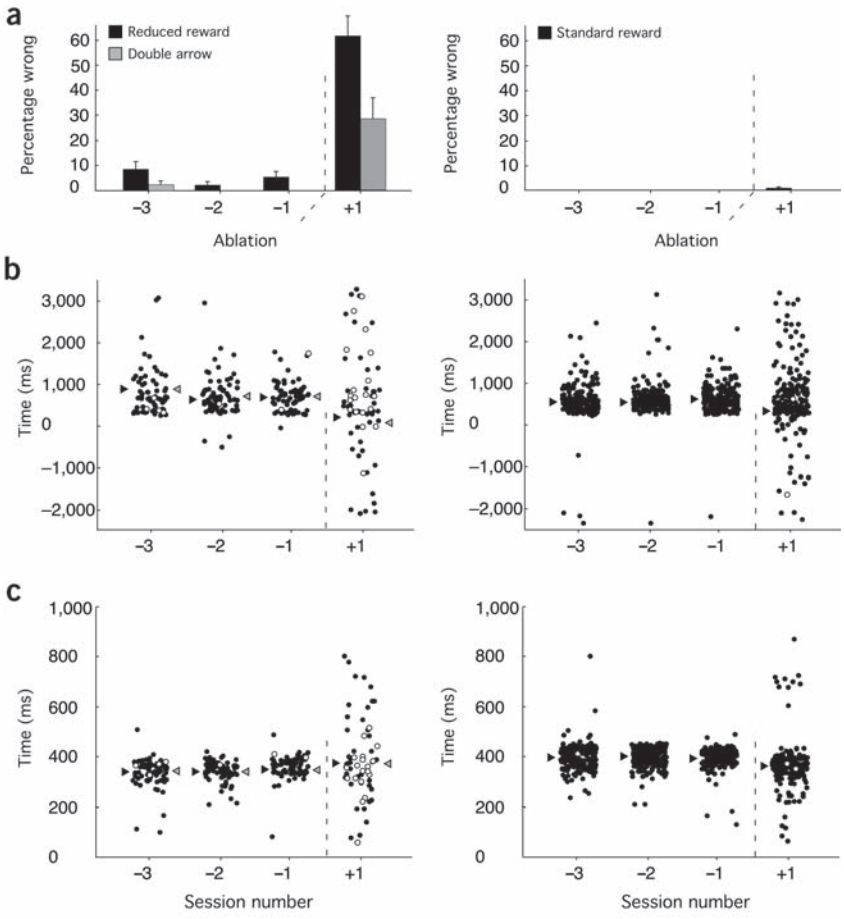

Figure 5 Subject performance before and after dACC ablation. The abscissa denotes the session number before (–3, –2, –1) and after ablation (+1). Each session represents 450 trials grouped from the three subjects. Sessions were spaced approximately ten min apart (30 min between –1 and +1). Three graphs to the left, performance on reduced-reward and double-arrow trials (grouped together); three to the right, performance on standard-reward trials. (**a**) Percentage of trials in which the subject moved the joystick in the wrong direction. Black and gray bars indicate the percentage of errors made on reduced-reward and double-arrow trials, respectively. Error bars, s.e.m. (**b**) Distribution of reaction times. The *y*-axis denotes the onset of joystick movement before or after presentation of the go cue (time 0). Each circle represents performance on a single trial. Filled circles indicate trials in which the subject moved the joystick in the correct direction and open circles those moved in the incorrect direction (including premature movements). (**c**) Distribution of movement times with time 0 denoting onset of movement. The black and gray arrowheads indicate the mean reaction times or movement times during reduced-reward and double-arrow trials, respectively.

of modulation may differ between subjects.

The current findings demonstrate that neuronal activity in the human dACC has a role in linking reward-related information with appropriate actions, especially when reward is reduced. That is, neurons in the dACC not only responded to the individual contextual components of the task, but also reflected their associative relationship with the corresponding behavior. This view is supported by our present observations demonstrating predictive activity before motor response execution and selective changes in subject performance after ablation. Together, these findings support indirect studies that have implicated the dACC in cognitive mechanisms believed to be important in appropriately modifying or altering behavior[1,3,5,9,32]. In particular, changes in activity reflected in functional imaging and electroencephalographic recordings of individuals carrying out risk-based decisional tasks have been posited to be responsible for the modification of subsequent behavior[10–12]. In the context of a monetary reward, the dACC may thus serve an adaptive function that provides the signal to change or to 'try something new,' especially when a previously productive behavior results in a perceived loss.

METHODS

Subject population. Five subjects were enrolled in this study after signing an informed written consent under a protocol approved by the Institutional Review Board and the cingulotomy assessment committee at Massachusetts General Hospital. Patients were considered for surgery by an independent multidisciplinary committee composed of psychiatrists, neurologists and neurosurgeons. The decision to offer surgery bore no relation to the current study, and adhered to the same evaluative and ethical guidelines used for all prior cingulotomy patients[20]. Once a decision had been made to proceed with the operation and the patient had signed an informed surgical consent, the subject was approached by an independent member of the team for possible inclusion in the study. The full details of the surgery and possible tasks were discussed with the patients and their families. To ensure that the patients were comfortable performing the task, they practiced it before surgery. At all time points before and during surgery, the patients had the understanding that their participation bore no relation to the surgical outcome, and that they could withdraw from the study at any time.

Each subject met DSM-IV-R criteria for axis I diagnosis of major depression, OCD or BAD, and had exhausted standard medical therapy. Standardized assessment techniques included the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Beck Depression Inventory (BDI) and Sickness Impact Profile. Three of the subjects enrolled in the study had major depression, one had OCD and one had BAD.

Electrophysiology and ablation. An array of three tungsten microelectrodes, set 2 mm apart, was placed in a parasagittal orientation and advanced ventrally with a motorized microdrive (Alpha Omega Engineering). Neuronal activity was band-pass filtered between 300 Hz and 6 kHz and sampled at 20 kHz. dACC localization and ablation were done as previously described[20,21]. Radiofrequency thermal ablative lesions were created using a 10-mm uninsulated tip electrode (Radionics) heated to 85 °C for 60 s. The lesions were spaced 7 mm apart in a parasagittal orientation. Postoperative magnetic resonance imaging (MRI) was used to confirm the location of all recording sites.

Behavioral task. The behavioral task was controlled by a Macintosh G4 computer (Apple Computer) using custom-made software. Spikes were stored and sorted off-line using a template-matching algorithm (Spike 2, Cambridge Electronics Design). During each recording session, subjects were asked to observe the computer monitor while performing the behavioral task. A joystick was mounted contralateral to the side of the recordings. Each trial began with the presentation of one of three pictorial instructional cues. Each represented at once both the amount of the financial reward and the direction in which the subject should move the joystick. On 'standard-reward' trials (80% of the total), five dollar signs were displayed, which indicated that the subjects had received 15 cents and should move the joystick in the same direction as in the previous trial. The other two trial types were each displayed 10% of the time. On 'reduced-reward' trials, three dollar signs were displayed, which

indicated that the subject had received 9 cents and should move the joystick in the direction opposite to that in the previous trial. On 'double-arrow' trials, two arrowheads were displayed, indicating that the subject had received the standard 15-cent reward but should move in the direction opposite to that in the previous trial. For the two patients in which control trials were introduced, standard-reward trials were presented 70% of the time and reduced-reward, double-arrow and control trials were each presented 10% of the time. In one patient we introduced increased-reward control trials. In these trials the reward was increased to seven dollar signs and the patient was instructed to maintain the same movement direction. In the other patient we introduced a novel control in which a filled circle was used as the instructional cue. The circle indicated a fixed reward and that the movement should be maintained in the same direction. The trial types were pseudo-randomly interleaved in blocks of ten, such that both the reduced-reward and double-arrow trials (and/or control trials) occurred once within each block. Subjects completed a total of 150 trials per recording run. Before surgery, subjects practiced the task until their performance exceeded 90% correct responses. Although subjects were told before performing the task that they would receive an amount of money commensurate with their performance, all were paid $100 after surgery. No form of anesthesia or sedating medication was given at any time immediately before, during or after dACC surgical ablation.

The instruction cue was displayed for 1,500 ms. To distinguish the effect of the instruction cue from that of the upcoming motor response, the instructional period was followed by an additional 1,500-ms delay interval in which a blank screen was displayed. At the end of the delay interval, a central square was displayed, indicating that the subject could move the joystick. The next instruction cue appeared immediately after the movement, and no feedback cue was given to indicate whether the movement was correct or incorrect. To minimize the potential effect of expectancy on motor responses, the delay interval lasted 3,000 ms in 10% of the trials. During all portions of the trials, the subjects were asked to maintain their gaze on the center of the screen.

Data analysis. Rasters and perievent histograms were constructed for all recorded neurons. A neuron was considered to have task modulation if it showed significantly different activity in either the reduced-reward or double-arrow trials compared to standard-reward trials during either the instruction or delay interval (repeated-measures ANOVA, $P < 0.05$). CP was calculated as previously described[25,26]. This approximates the ability of an ideal observer to predict the subjects' behavior from the neuronal activity. Neuronal firing rates during the trial were sorted according to whether a correct or incorrect corresponding movement was made. Because incorrect trials constituted a small percentage of the total, they were compared with an equal number of correct trials randomly selected from the same cells. Reaction times and movement times were each matched to within 100 ms (ref. 4). To determine whether CP was significantly different from chance, the spike counts were randomly shuffled 1,000 times into two groups and the CP recalculated for the shuffled data. If the CP was greater than 95% or less than 5% of the permuted data, the effect was considered to be significant. To define the timing of activity, this process was repeated in 500-ms windows that were advanced along the activity curve by increments of 100 ms. No significant difference was found in the shuffled distributions between the three trial types (one-way ANOVA, $P > 0.05$).

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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1. Badre, D. & Wagner, A.D. Selection, integration, and conflict monitoring; assessing the nature and generality of prefrontal cognitive control mechanisms. *Neuron* **41**, 473–487 (2004).
2. Bush, G., Luu, P., Posner, M.I. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn. Sci*. **4**, 215–222 (2000).
3. Deiber, M.P. *et al*. Frontal and parietal networks for conditional motor learning: a positron emission tomography study. *J. Neurophysiol*. **78**, 977–991 (1997).
4. Holroyd, C.B., Dien, J. & Coles M.G. Error-related scalp potentials elicited by hand and foot movements: evidence for an output-independent error-processing system in humans. *Neurosci. Lett*. **242**, 65–68 (1998).
5. Jenkins, I.H., Brooks, D.J., Nixon, P.D., Frackowiak, R.S. & Passingham, R.E. Motor sequence learning: a study with positron emission tomography. *J. Neurosci*. **14**, 3775–3790 (1994).
6. Kerns, J.G. *et al*. Anterior cingulate conflict monitoring and adjustments in control. *Science* **303**, 1023–1026 (2004).
7. Miltner, W.H. *et al*. Implementation of error-processing in the human anterior cingulate cortex: a source analysis of the magnetic equivalent of the error-related negativity. *Biol. Psychol*. **64**, 157–166 (2003).
8. Paus, T. Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nat. Rev. Neurosci*. **2**, 417–424 (2001).
9. Bush, G., *et al*. Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proc. Natl. Acad. Sci USA* **99**, 523–528 (2002).
10. O'Doherty, J., Critchley, H., Deichmann, R. & Dolan, R.J. Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. *J. Neurosci*. **23**, 7931–7939 (2003).
11. Ernst, M. *et al*. Decision-making in a risk-taking task: a PET study. *Neuropsychopharmacology* **26**, 682–691 (2002).
12. Gehring, W.J. & Willoughby, A.R. The medial frontal cortex and the rapid processing of monetary gains and losses. *Science* **295**, 2279–2282 (2002).
13. Ahlfors, S.P. & Simpson, G.V. Geometrical interpretation of fMRI-guided MEG/EEG inverse estimates. *Neuroimage* **22**, 323–332 (2004).
14. Almeida, R. & Stetter, M. Modeling the link between functional imaging and neuronal activity: synaptic metabolic demand and spike rates. *Neuroimage* **17**, 1065–1079 (2002).
15. Logothetis, N.K., Pauls, J., Augath, M., Trinath, T. & Oeltermann, A. Neurophysiological investigation of the basis of the fMRI signal. *Nature* **412**, 150–157 (2001).
16. Sheth, S.A., *et al*. Linear and nonlinear relationships between neuronal activity, oxygen metabolism, and hemodynamic responses. *Neuron* **42**, 347–355 (2004).
w18. Ito, S., Stuphorn, V., Brown, J.W. & Schall, J.D. Performance monitoring by the anterior cingulate cortex during saccade countermanding. *Science* **302**, 120–122 (2003).
19. Mayr, U., Awh, E. & Laurey, P. Conflict adaptation effects in the absence of executive control. *Nat. Neurosci*. **6**, 450–420 (2003).
20. Dougherty, D.D., *et al*. Prospective long-term follow-up of 44 subjects who received cingulotomy for treatment-refractory obsessive-compulsive disorder. *Am. J. Psychiatry* **159**, 269–275 (2002).
21. Spangler, W.J., *et al*. Magnetic resonance image-guided stereotactic cingulotomy for intractable psychiatric disease. *Neurosurgery* **38**, 1071–1076 (1996).
22. Shima, K. & Tanji, J. Role for cingulate motor area cells in voluntary movement selection based on reward. *Science* **282**, 1335–1338 (1998).
23. Shidara, M. & Richmond, B.J. Anterior cingulate: single neuronal signals related to degree of reward expectancy. *Science* **296**, 1709–1711 (2002).
24. Downar, J., Crawley, A.P., Mikulis, D.J. & Davis, K.D. A cortical network sensitive to stimulus salience in a neutral behavioral context across multiple sensory modalities. *J. Neurophysiol*. **87**, 615–620 (2002).
25. Britten, K.H., Newsome, W.T., Shadlen, M.N., Celebrini, S. & Movshon, J.A. A relationship between behavioral choice and the visual responses of neurons in macaque MT. *Vis. Neurosci*. **13**, 87–100 (1996).
26. Williams, Z.M., Elfar, J.C., Eskandar, E.N., Toth, L.J. & Assad, J.A. Parietal activity and the perceived direction of ambiguous apparent motion. *Nat. Neurosci*. **6**, 616–623 (2003).
27. Zhang, H.H., Zhang, J. & Kornblum, S. A parallel distributed processing model of stimulus-stimulus and stimulus-response compatibility. *Cognit. Psychol*. **38**, 386–432 (1999).
28. Duncan, J. & Owen, A.M. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci*. **23**, 475–483 (2000).
29. Paus, T. *et al*. Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. *Cereb. Cortex* **6**, 207–214 (1996).
30. Ebert, D. & Ebmeier, K.P. The role of the cingulate gyrus in depression: from functional anatomy to neurochemistry. *Biol. Psychiatry* **39**, 1044–1050 (1996).
31. Saxena, S. & Brody, A.L., Schwartz, J.M. & Baxter, L.R. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *Br. J. Psychiatry* **35S**, 26–37 (1998).
32. Paus, T., Petrides, M., Evans, A.C. & Meyer, E. Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. *J. Neurophysiol*. **70**, 453–469 (1993).