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Neural circuitry involved in quitting after repeated failures: role of the cingulate and temporal parietal junction

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The more times people fail the more likely they are to give up, however little is known about the neural mechanisms underlying this impact of repeated failure on decision making. Here we have used a visual shape discrimination task with computer-controlled feedback combined with functional magnetic resonance imaging (fMRI) to investigate the neural circuits involved. The behavioral task confirmed that the more times subjects experienced failure the more likely they were to give up, with three successive failures being the key threshold and the majority of subjects reaching the point where they decided to quit and try a new stimulus set after three or four failures. The fMRI analysis revealed activity changes in frontal, parietal, temporal, limbic and striatal regions, especially anterior cingulate cortex (ACC), posterior cingulate cortex (PCC) and temporal parietal junction (TPJ) associated with the number of previous failures experienced. Furthermore, their parameter estimates were predictive of subjects' quitting rate. Thus, subjects reach the point where they decide to quit after three/four failures and this is associated with differential changes in brain regions involved in error monitoring and reward which regulate both failure detection and changes in decision-making strategy.

Reinforcement learning (RL) is a process whereby the estimation of state/action values is improved through trial and error so that behavior becomes more advantageous¹. The detection and evaluation of behavioral feedback are thus of critical importance to allow adjustment of subsequent choices efficiently^{2–6}. For example, failure (negative feedback) is common and can be used to shift from one set of stimulus-response translation rules to another⁷. In many situations optimal behavior requires the selection of actions based on the expected value that is derived from an individual's recent history of failures^{8,9}. Thus, feedback on failure is important for making subsequent choices and plays a key role in influencing behavioral decision making. For example, learned helplessness is suggested to occur when an individual's desire to learn is destroyed because of unpleasant and uncontrollable events.

To behave adaptively, animals and humans need the capacity for reinforcement learning to internally monitor responses and to evaluate external reinforcement or feedback¹⁰, and learn by trial and error to act in a manner that maximizes reward and minimizes punishment^{11,12}. This process applies to many different situations and appears to be supported by subcortical and cortical neural networks^{13–17}. Widespread neural systems are involved in encoding the value of outcomes received and responses related to monitoring or evaluation of a previously executed action. The main regions implicated include the anterior cingulate cortex (ACC), medial prefrontal cortex (MPFC), dorsolateral prefrontal cortex (DLPFC), amygdala, ventral striatum (VStr), posterior cingulate cortex (PCC) and temporal parietal junction (TPJ)^{18–21}. However, previous studies have focused on the effects of a single feedback given on a trial by trial basis^{4,21–23} rather than on how decision making, and associated neural mechanisms, are impacted by the more common experience of repeated failure during the performance of a task.

The “three strikes” phenomenon is well known and has often been reported in research related to decision making or sports psychology^{24,25}. This phenomenon relates to the so called “hot hand” belief in sport where a

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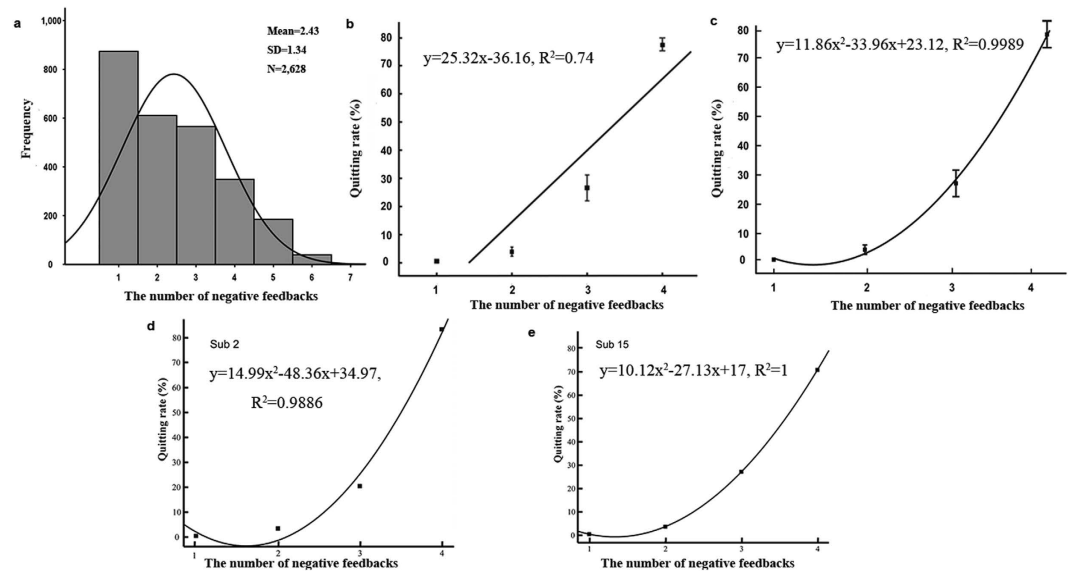


Figure 1. Behavioral results. (a) The coverage of choosing to continue. (b,c) A linear regression (b) and a quadratic polynomial (c) function between the number of negative feedbacks and quitting rate. (d,e) The relationship between the number of negative feedbacks and quitting rate using a quadratic polynomial function in two representative subjects.

player is considered to have a higher chance of making a shot after two or three successful shots than after two or three misses (resulting in “streaks”). However, in all these previous papers it is clear that the paradigms used resulted in subjects having an increased expectation of success after each failure. The current study aimed to identify more precisely what cognitive rules operate and which neural networks are involved in monitoring performance and predicting choice in order to regulate decision making in the face of repeated failures, and where each failure is not associated with a greater expectation of subsequent success. We used a novel feedback visual discrimination paradigm²⁶ with computer-controlled feedback, where the subject could either decide to continue (try again) or abort (quit and try a new discrimination) after failing on a trial. In the study we focused on the critical number of sequential trials on which subjects failed before deciding to quit and try a new stimulus set. Importantly, the paradigm deliberately minimized the potential for modulatory influences of situations where subjects could either achieve high gains (such as in gambling situations) or had other strong motivations (such as providing solutions to problems of significant intrinsic interest) for persisting with solving a task which might have resulted in an increased and highly variable tolerance of repeated failure. We hypothesized that subjects would reach a threshold after a specific number of failures when they would be more likely to change from persisting with the current stimulus set to giving up and trying a new stimulus set. We further hypothesized that the frontal and limbic brain regions specifically involved in decision making and controlling the effects of repeated failure would be involved, and exhibit changes in activity and functional connectivity associated with behavioral performance.

Results

Relationship between negative feedback and quitting rate. Trial-by-trial analysis revealed that whether subjects decided to continue or quit discrimination of a specific stimulus set was influenced by the number of times they received negative feedback. We used a logistic regression model to predict whether subjects continued or gave up after receiving different numbers of negative feedbacks. This simplified model used one factor (the number of negative feedbacks) and could be expressed as

$$P(y = \text{quit}) = \frac{\exp(Am^*F)}{1 + \exp(Am^*F)} \quad (1)$$

with the following functions: $\text{Logit}(P) = Am^*F$, where F is the number of negative feedbacks, Am is the regression coefficient of negative feedback. The indices of the model were: Cox & Snell $R^2 = 0.286$, Nagelkerke $R^2 = 0.451$, accuracy of prediction = 84.2%. Based on the model, we drew a ROC curve with an area under the curve of $0.8 < S = 0.869 < 0.9$, suggesting that the model diagnosis was good ($S.E. = 0.008$, $p < 0.001$, 95% confidence interval is 0.854–0.884). Using Hosmer-Lemeshow analysis to test goodness of fit we found that there was no difference between the prediction result and initial data, which also indicated that the model was good ($\chi^2 < 0.001$, $df = 3$, $p > 0.05$). These results showed that whether to continue or to quit was indeed influenced by the number of times subjects received negative feedback.

Descriptive statistics showed that for the largest proportion of trials (91.33%) the decision to quit occurred between 1 and 4 failures, with most subjects doing so after 3 or 4 failures. Only 7.04% of quitting decisions occurred after 5 failures, 1.52% after 6 and 0.11% after 7 (see Fig. 1a). In the subsequent analyses we therefore combined trials where a 4th, 5th, 6th or 7th negative feedback was received. With respect to quitting rate, a repeated-measures ANOVA revealed a main effect of the number of negative feedbacks, $F_{(3,57)} = 206$, $p < 0.001$.

Post-hoc multiple Bonferroni-corrected comparison analyses indicated that there were significant differences between each of the different numbers of negative feedbacks received ($M1 = 0.57\%$, $SD1 = 1.26\%$, $M2 = 3.98\%$, $SD2 = 7.2\%$, $M3 = 26.61\%$, $SD3 = 20.48\%$, $M4 = 77.44\%$, $SD4 = 9.62\%$, all $p < 0.001$), other than between the first and second time ($p = 0.170$). These results showed that subjects reached the point where they started to change from continuing to quitting after the third time of receiving negative feedback. To further explore the relationship between the number of times negative feedback was received and quitting rate (percentage of quitting the item), we conducted a linear regression ($y = ax + b$) and a quadratic polynomial curve ($y = ax^2 + bx + c$) separately. The linear regression function was $y = 25.32x - 36.16$, $R^2 = 0.74$ (see Fig. 1b). The fit of the quadratic polynomial function was also good: $y = 11.86x^2 - 33.96x + 23.12$, $R^2 = 0.9989$, 95% confidence intervals (see Fig. 1c). To illustrate this finding, Fig. 1d,e show the quadratic polynomial function for quitting rate in individual trials as a function of the number of negative feedbacks in two representative subjects. Since the quadratic polynomial function was superior to the linear regression one we used it in all subsequent analyses. Overall, these results suggested that quitting rate was predicted by the number of negative feedbacks received and reached the point where subjects started to decide to quit rather than continue after a third failure with most quitting after 4 or more failures.

An analysis of confidence levels after each failure showed that they decreased following each successive failure (see supplementary information and Fig. S1). Importantly this confirmed that in our paradigm subjects did not experience an increased expectation of subsequent success after each failure.

Neural correlates of negative feedback. To investigate which brain regions showed activity changes associated with negative feedback in the task, we first performed a whole-brain analyses on fMRI data collected during the feedback stage. Since there were too few trials where subjects had more than 4 failures to perform an effective analysis of fMRI data we only analyzed neural changes following 1, 2, 3 and 4+ failures. This analysis revealed that a number of middle and superior frontal, temporal and occipital cortical regions and the ventral striatum showed increased activity whereas medial and dorsolateral frontal regions showed decreased activity. These neural activity changes were significantly associated with the number of times negative feedback was received (see Table 1 and Fig. 2a). A number of frontal regions also showed activation differences in the contrast between positive and negative feedback (Table 1 and Fig. 2b). Greater activation changes during the receipt of negative feedback that were associated with the subsequent decision to quit as opposed to continue only occurred in dACC/MPFC (Table 1 and Fig. 2c), whereas in other frontal and temporal regions greater activation changes associated with the decision to quit rather than to continue only occurred during the actual choice stage (Table 1 and Fig. 2d).

Neural correlates of number of negative feedbacks received and quitting rate. To explore how activity changes in the different brain regions related to the number of times negative feedback was received and quitting rate, we used the same quadratic polynomial function as for analysis of the behavioral data. Brain activations were extracted from 8 mm diameter spheres in the following ROIs: MPFC (0, 47, 21), bilateral dACC (0, 26, 29), left insula (-36, 23, 0), right DLPFC (39, 53, 19), left and right VStr (-24, 2, 7/27, -4, 10), left PCC (-9, -22, 43), right precuneus (12, -49, 55), right amygdala (23, -11, -27), left middle temporal gyrus (MTG, -51, -13, -14) and right TPJ (66, -49, 1).

Repeated-measures ANOVA was used to test whether the parameter estimates of each target region were significantly different for each of the four frequencies of negative feedback (i.e. whether the pattern of each target region was similar to that observed in the behavioral results). The results showed there were main effects of negative feedback in dACC, PCC and TPJ [$F_{(3,76)} = 3.19$, $p = 0.028$; $F_{(3,76)} = 4.24$, $p = 0.008$; $F_{(3,76)} = 5.02$, $p = 0.003$], i.e. they showed the same trend as the behavioral results. Post-hoc, Bonferroni-corrected analysis results showed that the parameter estimate for the first negative feedback was significantly different from the second ($p = 0.048$), the third ($p = 0.01$) and fourth ($p = 0.005$) respectively in dACC ($M1 = -0.095$, $SD1 = 0.34$, $M2 = 0.045$, $SD2 = 0.43$, $M3 = 0.21$, $SD3 = 0.39$, $M4 = 0.26$, $SD4 = 0.43$). For PCC ($M1 = -0.071$, $SD1 = 0.25$, $M2 = -0.035$, $SD2 = 0.25$, $M3 = -0.15$, $SD3 = 0.12$, $M4 = -0.24$, $SD4 = 0.16$), there were no significant differences between the first, second and third feedbacks ($p > 0.05$) but there was for the fourth one ($p = 0.037$). For the TPJ ($M1 = -0.063$, $SD1 = 0.26$, $M2 = -0.21$, $SD2 = 0.28$, $M3 = -0.32$, $SD3 = 0.31$, $M4 = -0.39$, $SD4 = 0.29$) there were no differences between the first two times of negative feedback ($p = 0.119$) but there were between the first and the third and fourth times ($p = 0.007$, $p = 0.005$, see Fig. S2a,c,d).

We also explored how activity changes in dACC, PCC and TPJ related to the number of times negative feedback was received and quitting rate. First, we found that parameter estimates of dACC, PCC and TPJ fitted the same quadratic polynomial function ($R^2 = 0.98$, $R^2 = 0.93$, $R^2 = 0.99$, $p < 0.05$ in all cases). We next explored the relationship between parameter estimates of dACC, PCC and TPJ and quitting rate and obtained similar results ($R^2 = 0.93$, $R^2 = 0.94$, $R^2 = 0.89$, $p < 0.05$ in all cases, Fig. 3a–c).

For completeness we also investigated relationships between activity changes and number of feedbacks received and quitting rate using a linear regression. Results were broadly similar to those obtained using a quadratic polynomial function (see Supplementary information and Fig. S2b).

Interactions between neural systems. Having identified dACC, PCC and TPJ as the main regions associated with the number of times negative feedback was received, we next aimed to determine whether any of their functional connections showed a similar association. We therefore performed a set of generalized form of context-dependent psychophysiological interactions (gPPI) analyses using the dACC, PCC and TPJ as seed ROIs.

We contrasted the level of functional connectivity during the feedback stage with different numbers of times negative feedback was received. The analyses showed that there was significantly increased functional connectivity after ≥ 3 failures ($f3 + f4$) versus 1–2 failures ($f1 + f2$) for dACC-MTG (-45, 2, -26), TPJ-hippocampus

Brain Region	BA	No. Voxels	Peak t-value	x	Y	z
Negative feedback > baseline						
R. Superior Frontal Gyrus	10	19	7.47	39	53	19
R. Ventral Striatum		52	8.81	27	-4	10
R. Ventral Striatum		27	8.11	-24	2	7
R. Superior Temporal Gyrus	41/6	28	7.38	57	-19	7
R. Inferior Occipital Gyrus	18/19	142	10.50	30	-94	-11
Baseline > Negative feedback						
R. Medial Prefrontal Cortex	9/6	17	7.23	3	44	37
L. Dorsolateral Frontal Cortex	45	67	8.79	-45	29	7
L. Inferior Frontal Gyrus	13/47	22	7.55	-30	23	-8
R. Inferior Frontal Gyrus	13	11	7.44	42	26	10
R. Inferior Frontal Gyrus	47	35	9.22	27	26	-11
R. Thalamus		136	9.20	6	-16	-2
Positive feedback > Negative feedback						
R. Middle Frontal Gyrus	46/9/47	1638	19.61	51	26	31
Inferior Frontal Gyrus						
Ventral Striatum						
R. Medial Frontal Gyrus	8	18	7.19	3	32	46
L. Middle Frontal Gyrus	9/46	1039	14.34	-42	8	46
Inferior Frontal Gyrus						
L. Inferior Frontal Gyrus	13/47	45	9.79	-33	23	-5
L. Anterior Cingulate Cortex	32/24	73	7.89	-3	41	-2
R. Posterior Cingulate Cortex	31/23	100	9.55	6	-31	34
R. Precuneus	7	29	7.87	12	-67	40
L. Superior Temporal Gyrus	22	310	9.61	-57	-46	7
R. Middle Temporal Gyrus	21	191	9.16	54	-46	-11
L. Inferior Parietal Lobule	40/7	332	9.01	-42	-67	43
Superior Parietal Lobule						
R. Inferior Parietal Lobule	40/7	377	9.05	54	-58	43
Superior Parietal Lobule						
Feedback stage: Quit > continue						
R. Medial Frontal Gyrus	32/9	33	7.41	9	26	34
Anterior Cingulate Cortex						
Choice stage: Quit > continue						
R. Inferior Frontal Gyrus	47	97	9.32	36	20	-8
R. Middle Frontal Gyrus	10	35	8.84	39	50	1
R. Inferior Frontal Gyrus	9	224	10.11	51	14	25
R. Middle Frontal Gyru	46	142	8.84	48	32	22
L. Insula	13	29	7.31	-33	17	4
R. Middle Temporal Gyrus		13	7.06	54	-46	-5
R. Inferior Parietal Lobule	7	60	7.05	33	-61	40

Table 1. The table shows anatomical regions with significant activation changes, their laterality, and BA, Brodmann's areas. Areas of brain activation for negative feedback (MNI coordinates).

(-30, -19, -11), PCC-hippocampus/amygdala (-21, -10, -11) and PCC-inferior parietal lobule (IPL, -57, -43, 43/69, -37, 28) (all small volume corrected, $p < 0.001$; see Fig. 4).

Discussion

Using fMRI and a novel decision task paradigm the current study has elucidated how repeated negative feedback (failure) affects people's subsequent decision-making behavior. Our findings show that the more times subjects experience failure the more likely they are to give up, with three failures being the key threshold for subjects to start quitting and the majority of them doing so after a fourth failure. The brain areas most closely associated with the number of times negative feedback was received, and predictive of whether subjects gave up, were the dACC in particular but also the PCC and TPJ.

In the current study, we found activity and functional connectivity changes in the dACC, PCC and TPJ were associated with receiving negative feedback, which is consistent with previous studies^{18,27}. Neural activity changes have also been described which are related to this effect of negative feedback, such as encoding the value of outcomes²⁸, expectation of the value of the available actions²⁹ and monitoring or evaluation of previous actions³⁰.

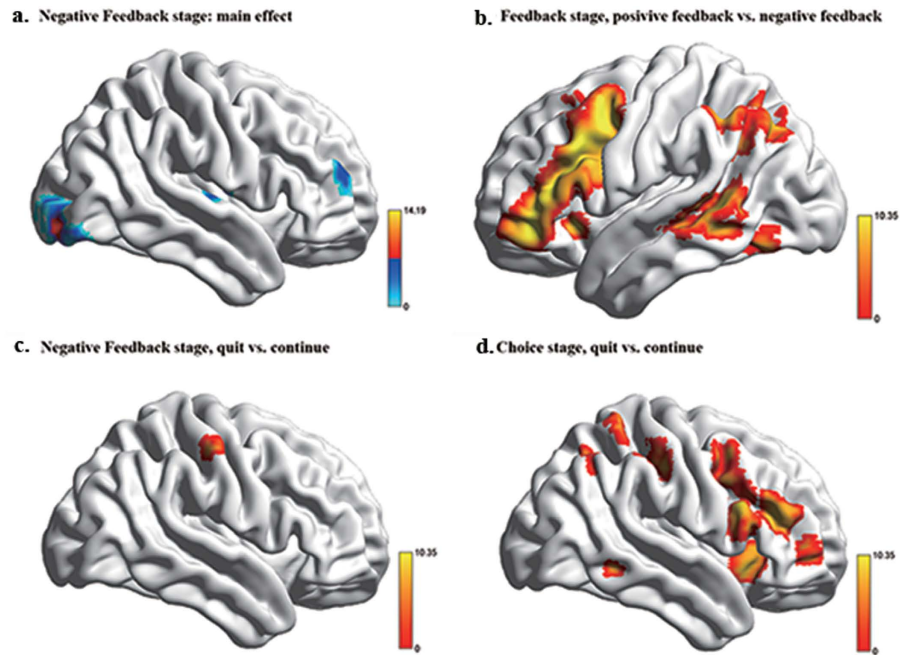


Figure 2. Whole-brain analysis results. (a) Neuroanatomical location of brain regions during the feedback stage. (b,c) Brain regions exhibiting significant increased activation in the contrast between positive and negative feedback (b) and between quitting and continuing with a stimulus set (c) during the feedback stage, and the latter contrast during the choice stage (d). FWE, $p < 0.05$ corrected and > 10 voxels.

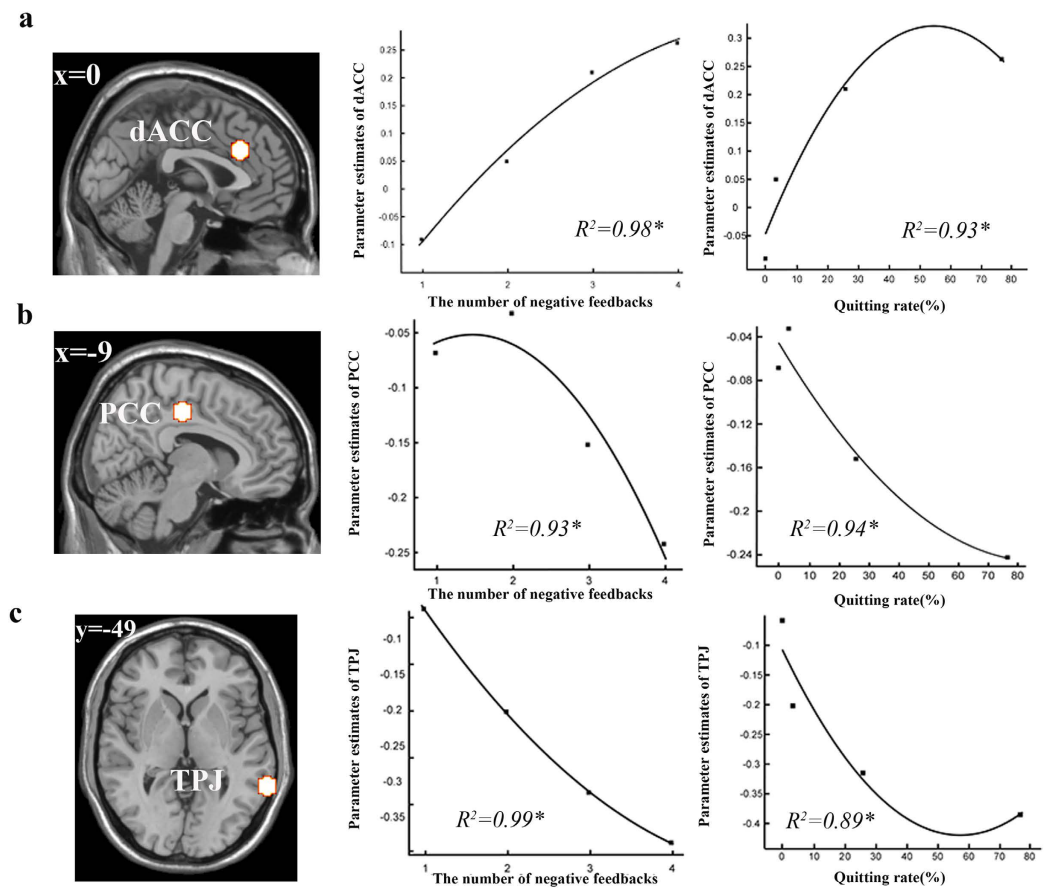


Figure 3. ROI results. (a–c) Brain activations were extracted from an 8 mm diameter spherical dACC, PCC, TPJ ROIs. The relationship between parameter estimates of dACC (a), PCC (b), TPJ (c) and the number of negative feedbacks or quitting rate is a quadratic polynomial function.

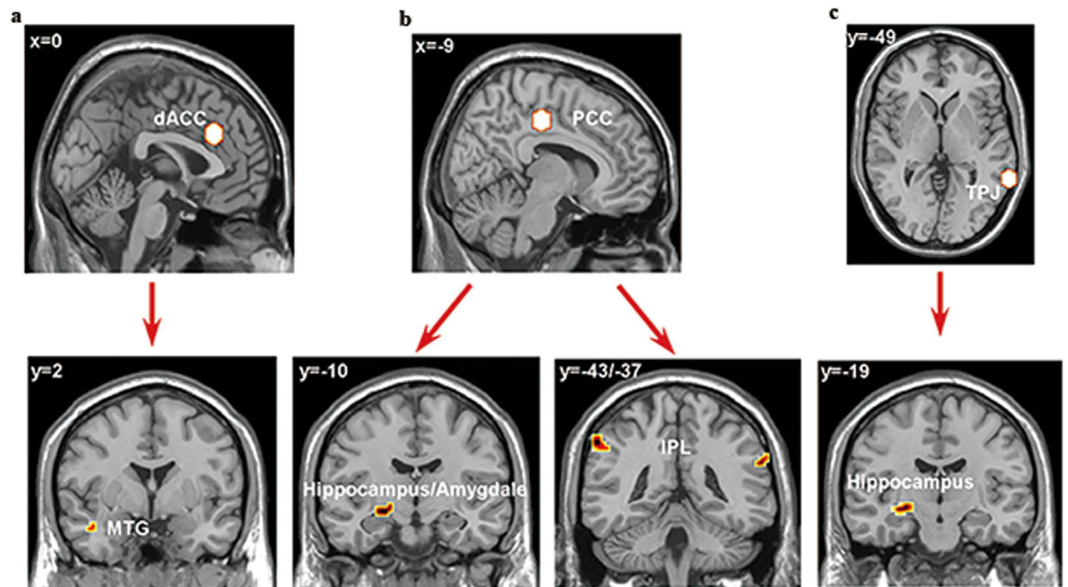


Figure 4. gPPI results. (a) The dACC seed had increased functional connectivity with MTG for the f3 + f4 condition. (b) The PCC seed had increased functional connectivity with bilateral IPL and hippocampus/amygdala for f3 + f4 condition. (c) The TPJ seed had increased connectivity with hippocampus for f3 + f4 condition ($p < 0.001$, small volume corrected).

These changes have been found in diverse brain regions including the ACC, MPFC, DLPFC, amygdala, and striatum¹⁸. Although behavioral decisions are likely to depend on information computed in this network of brain regions, it is not yet known which components are of specific importance for decision making which guides the selection of action¹⁸. Our finding from the contrast between the decision to quit or continue that the ACC is activated during receipt of negative feedback, rather than during the actual choice stage, suggests it is particularly involved in error detection and monitoring of behavioral responses.

Our behavioral results showed that the more times subjects experienced failure the more likely they were to give up. Three failures appeared to be point at which there was a clear increase in quitting behavior, indicating that this was a key threshold. However, the greatest proportion of subjects decided to quit after four failures. The relationship between the number of times negative feedback was received and quitting rate fitted a quadratic polynomial function. Based on this we extracted the parameter estimates from regions of interest that fitted the same function. The “three strikes” phenomenon is well known and relates to the “hot hand” belief^{24,25}. However, in all previous studies it is clear that the paradigms used resulted in subjects having increased expectation of success after each failure. In our study, we also asked subjects to report their confidence level after each round and this showed that their confidence in success decreased with successive failures and confidence level was negatively correlated with the number of negative feedbacks received (see Supplementary Information and Fig. S1). Thus in this paradigm subjects had a progressively higher expectation of failure (not success) after each failed trial.

In our study changes in BOLD activity were only found during the feedback stage and not during the choice one and thus primarily reflect changes occurring following decision making. We also found that dACC activation could predict behavioral choice when subjects received a second and third negative feedback (see Supplementary Information and Fig. S2b). The ACC, as a component of cognitive control network (CCN), engages multiple processes, including task switching, response inhibition, error detection, response conflict and working memory^{31–36}. On the other hand, the ACC may play a central role in decision making due to its involvement in both learning and using extended action-outcome histories to optimize choice behavior^{3,37,38}. Reinforcement learning theory postulates that the ACC is involved in learning after obtaining an outcome that is worse than expected, i.e., a reward prediction error^{38,39}. Importantly, in our current study activity in dACC could reliably predict whether subjects continued or gave up. The ACC has also been implicated in reward-action associations, average expected values and negative reward prediction errors^{3,40–43}. It is likely that the key role of the ACC in these processes is due in part to its position within the reward system, and also on its use of outcome information for action value adjustments and behavioral regulation⁴⁴. In humans, ACC lesions promote response slowing and variability⁴⁵ but the ability to learn from feedback is spared^{46,47}. Thus, the function we can attribute to the dACC activity changes we have found may be not only to evaluate feedback but also to participate in monitoring the different steps of the task at hand to optimize action adaptation and valuation⁴⁴.

The PCC is also an important region linking reward processing, attention, memory and motor control systems, and mediates the integration of variables such as reward, uncertainty, errors and option switching across multiple trials⁴⁸. Recent nonhuman primate work provides evidence for a more active role in the control of cognition through signaling an environmental change and the need to alter behavior²⁰. In this probabilistically rewarded choice task, monkeys’ behavior followed a win-stay or lose-shift heuristic. After choosing the risky option, monkeys were more likely to choose it again if they received a larger reward but switched to the safe

option if they received a smaller one. Firing rates of PCC neurons were correspondingly higher following smaller rewards than large ones, and variability in responses predicted the likelihood monkeys would switch their choice on the next trial²⁰. Thus the PCC, as well as dACC, is a key node responsible for environmental change detection and subsequent alterations in behavioral strategy.

The right TPJ is also activated by unexpected stimulus events of behavioral relevance¹⁹. The TPJ is involved in stimulus-driven representation of task-relevant information that can be used to engage an appropriate behavioral response^{19,49}. Although implicated in stimulus detection, the TPJ serves critical social cognitive and regulatory roles subserving higher order cognitive processes (e.g. perspective taking, mentalizing, theory of mind)^{50,51}. In summary therefore, dACC, PCC and TPJ are all associated with valuation, reward learning and decision-making functions.

In addition, gPPI results showed increased dACC-MTG/TPJ -Hippocampus/PCC-Hippocampus/PCC-IPL functional connectivity after three or more failures compared to after only one or two. Attention-demanding, goal-directed behavior is mediated not only by distributed patterns of cerebral activation but, remarkably, also by concurrent suppression of activity in a distinct set of brain areas, such as fronto-parietal circuits (dACC/PCC/IPL/TPJ)^{49,52,53}. The PCC forms strong, reciprocal connections with the medial temporal lobe, especially the parahippocampal gyrus, which is important for associative learning and episodic memory²⁰. We also observed greater functional connectivity between right TPJ and a number of attentional and decision-making areas, including the right inferior frontal gyrus, MPFC and parahippocampal gyrus¹⁹.

Von der Gablentz *et al.*⁵⁴ used a modified Eriksen-Flanker task that required the participants to derive the correct stimulus-response association based on a feedback given after each flanker stimulus. Participants had to continuously monitor and adapt their performance as the stimulus-response contingency switched. The results showed that the switch was associated with activation of the precuneus, the cingulate cortex, the insula and brainstem regions. This brainstem system appears to interact with the cortical network and seems to be essential for performance monitoring and behavioral adaptation. One key difference is that in the reversal paradigm, stimulus-response contingencies were switched. In our study, we have used a visual shape discrimination task with computer-controlled feedback, where the subject could either decide to continue (try again) or abort (quit and try a new discrimination) after failing on a trial. We focused on the critical number of sequential trials on which subjects failed before deciding to quit and try a new stimulus set. The brain areas most closely associated with the number of times negative feedback was received, and predictive of whether subjects give up, are the dACC, PCC and TPJ, especially the dACC. It appears that in the human brain computation of both error monitoring and reward outcome to guide decision making is associated with integrated changes in frontal, parietal, temporal and limbic circuitry. While, the two tasks have in common that the same stimulus display is shown repeatedly, so that participants can also effectively “try again” in the reversal task, an important difference is that in the reversal task repeated failures are not guaranteed to occur in immediate succession.

According to principles of reinforcement learning, our results can be interpreted as a reward prediction error signal sent from posterior regions (PCC, TPJ) to more anterior circuitry (dACC) involved in behavioral adaptation, with the dACC monitoring how behavior is adjusted in the future^{7,23,38,47}. However, some limitations in our current study need to be taken into account. A major source of difficulty in interpreting our findings concerns the nature of stay/switch decision making. In our paradigm making the decision to switch was easier than deciding to continue and uncertainty has a clear influence on decision making (1–2 feedbacks = my decision to stay is clear, 3–4 feedbacks = greater uncertainty). Thus it is difficult to determine from our paradigm and results what influence uncertainty may have played. In addition, the paradigm deliberately made it hard for subjects to learn anything about the stimuli in order to investigate pure negative feedback effects and exclude learning, and increasing expectations of success, as potential confounding factors. As such the paradigm may be less ecologically relevant compared with one in which a behavioral strategy can at least implicitly be learned and adapted to in accordance with feedback received.

In summary, the present study has provided new insights into both patterns of behavior and changes in associated neural circuitry during the experience of repeated failure in a visual discrimination task. Behaviorally, the more times subjects experienced failure the more likely they were to give up, with three failures being the key threshold for starting to adopt quitting and the majority of subjects actually quitting after receiving a fourth negative feedback. Changes in the activity and functional connectivity of dACC, PCC and TPJ were particularly associated with the number of previous failures and also predictive of subjects giving up. Both the pattern of behavior and that of activity changes in these three regions fitted a quadratic polynomial regression model. The current findings therefore provide new evidence for an association between the experience of repeated failures and adaptive changes in decision making. It appears that in the human brain the decision to quit after three/four failures is associated with integrated changes in frontal, parietal, temporal and limbic circuitry, which serve to compute both error monitoring and reward outcome to guide decision making.

Methods

Participants. 20 healthy right-handed undergraduate Han Chinese subjects with no history of neurological or psychiatric disorder ($M_{age} = 22.0$, $SD = 2.07$; 9 males) were recruited to participate in the experiment. All subjects provided written informed consent and were paid according to their performance in the experiment. The study was approved by the ethics committee of Southwest University (China) and the Institutional Human Participants Review Board of the Southwest University Imaging Center for Brain Research. The methods were carried out in accordance with approved guidelines.

Experimental procedures and stimuli. Before the fMRI session, subjects participated in 5 training trials after being given detailed instructions. In the task, subjects were asked to play a game where they were required to determine from ten stimuli comprising two different colored areas which had the largest overall area and with

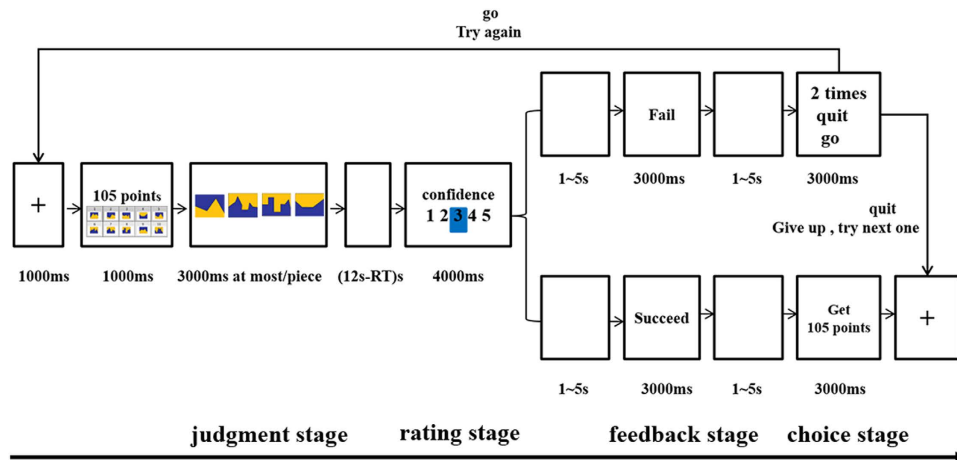


Figure 5. Visual shape discrimination task. Each trial in the task started with, a fixation point displayed in the center of the screen for 1000 ms. Next, ten pictures (each picture was divided into two colored areas) in a specific stimulus set, and the potential reward value, were shown for 1000 ms. Subjects were required to make judgments on which of the two colored areas was larger for four pictures, which were randomly selected from the ten pictures in the stimulus set (judgment stage). For each picture, subjects were given a maximum of 3 s to make their judgment and after the last decision was made the display screen went blank for the remainder of the 12 s. After subjects had made all decisions they gave their confidence level on their accuracy on a scale of 1 to 5 (rating stage – 4s). Subjects were told that if they accurately identified which colored part was larger in at least 3/4 stimuli then they would be informed on the screen after 3s (1–5 s jittered interval) that they had passed, otherwise they would be told that they had failed (feedback stage). After a further 3s interval (1–5s jittered) if the subjects passed they were informed they had gained the points on offer (3s) and then moved on to the start of another stimulus set. If subjects failed they were informed that they had won 0 points and how many times they had failed on that specific stimulus set (number displayed on the top of the screen). Subjects were then given the choice to either try again with the same stimulus set or to quit and try a new one (choice stage).

varying degrees of difficulty. After a decision round involving four (3 hard and 1 easy) out of the ten possible stimuli (8 hard and 2 easy) the subjects received feedback (succeed or fail) and when the feedback was negative they were given an alternative to either continue with same stimulus set again or to quit and try a new stimulus set. In this task, there are actually 112 different permutations for each stimulus set (i.e. $C_2^1 \cdot C_8^3 = 2 \cdot 8 \cdot 7 \cdot 6 / 3 \cdot 2 = 2 \cdot 56 = 112$). The subject is therefore unable to reach the conclusion that they cannot solve the condition after only 2 or 3 failures. Subjects could continue to try each stimulus set as many times as they wanted and so could receive as many negative feedbacks as they were prepared to accept. The monetary compensation subjects received depended on the total number of points they gained from stimulus sets where they successfully passed the discrimination test (Money (RMB) = points/1000). The visual discrimination task paradigm was written in E-prime 2.0 (<http://www.psnet.com/eprime.cfm>, Psychology Software Tools, USA) and the specific task flow is shown in Fig. 5.

One hundred and sixty pictures created by Computer Aided Design software (CAD) were used as stimuli in the perception task. Each picture (18 mm*10 mm) was subdivided into two irregular parts which were randomly colored either orange or blue and separated by a jagged line. To help avoid the subjects realizing that they were sometimes receiving false feedback and to keep them motivated by making sure the task was not too difficult, we used two different levels of difficulty ('easy' or 'hard'), although subjects were not informed about this before performing the task. Stimuli were divided into those which were 'easy' (32 pictures where subjects achieved $95\% \pm 5\%$ accuracy and the area size difference was $>30\%$) or 'hard' (128 pictures where subjects achieved $55\% \pm 5\%$ and the area difference was $<15\%$) based on the findings of a prior experiment. Stimuli were divided into those which were 'easy' (32 pictures where subjects achieved $95\% \pm 5\%$ accuracy and the area size difference was $>30\%$) or 'hard' (128 pictures where subjects achieved $55\% \pm 5\%$ and the area difference was $<15\%$) based on the findings of a prior experiment. In a pilot study, 22 healthy right-handed undergraduate Han Chinese subjects (11 females and 11 males, $M_{age} = 20.7$ years old) performed the study in order to assess the difficulty of the stimuli. Each picture was presented four times, making 640 pictures in total. In addition, subjects received false feedback (succeed or fail) calculated in terms of probability using permutation and combination functions (see Table 2). For example, where the probability of a correct feedback was $(C_4^3 + C_4^4) \cdot (1/2)^4 = 5/16 = 31\%$ then the number of times false correct feedback was given was $31\% \cdot 64 = 20$ (Permutation A). Where the subjects were wrong on the first occasion, and then succeeded on the next attempt, the probability was $(C_4^0 + C_4^1 + C_4^2) \cdot (1/2)^4 \cdot (C_4^3 + C_4^4) \cdot (1/2)^4 = 11/16 \cdot 5/16 = 21\%$. Thus the number of times false feedback was given for this permutation was $21\% \cdot 64 = 13$ (Permutation B), and so on for Permutations C, D, E, F and G. Using this approach we could systematically manipulate the number of failures each subject experienced and no subjects reported being aware of receiving false feedback.

Each trial had four stages: judgment, rating, feedback and choice. At the beginning of the trial a fixation cross was displayed in the center of the screen for 1000 ms. Next, the ten pictures in a specific stimulus set were shown

Permutation type	1	2	3	4	5	6	7	8	9	10	11	12	No. of false positive feedbacks
G	X	X	X	X	X	X	X	X	X	X	X	X	7
F	X	X	X	X	X	X	X	X	X	✓			6
E	X	X	X	X	X	X	X	✓					6
D	X	X	X	X	X	✓							6
C	X	X	X	✓									6
B	X	✓											13
A	✓												20

Table 2. The number of task outcome permutations. Every permutation type was included in the sequence and followed a random probability principle. “X” mean negative feedback presented. “✓” mean correct. The random possibility of Permutation type A is $(C_4^3 + C_4^4) * (1/2)^4 = 5/16 = 31\%$. The random possibility of Permutation type B is $(C_4^0 + C_4^1 + C_4^2) * (1/2)^4 * (C_4^3 + C_4^4) * (1/2)^4 = 11/16 * 5/16 = 21\%$. The random possibility of Permutation type C is $[(C_4^0 + C_4^1 + C_4^2) * (1/2)^4]^3 * (C_4^3 + C_4^4) * (1/2)^4 = (11/16)^3 * 5/16 = 10\%$.

(easy or hard discrimination difficulty) and the potential reward value (100–120 points in increments of 5) for 1000 ms. Here, the reward was just to motivate subjects to take part in the experiment seriously. The range of reward values was very small (100–120) and was varied slightly just to help increase subjects’ attention. Subjects were then required to make judgments on a random selection of four out of the ten pictures in the stimulus set for which color had the largest overall area (judgment stage). In each case the subjects were given a maximum of 3 s to make their judgment and after the last decision was made the display screen went blank for the remainder of the 12 s. After subjects had made all their decisions they gave their confidence level on their accuracy on a scale of 1 (no confidence) to 5 (very high confidence) (rating stage – 4s). Subjects were told that if they accurately identified which colored part was larger in at least 3/4 stimuli (i.e. 3/4 or 4/4) then they would be informed on the screen after 3s (1–5 s jittered interval) that they had passed, otherwise they would be told that they had failed (feedback stage). In fact, as described above, all feedback given was computer controlled and calculated in terms of probability, making it hard for subjects to learn anything about the picture sets from either their successes or failures. After a further 3s interval (1–5s jittered), if the subjects had passed they were informed that they had gained the points on offer (3s) and then moved on to the start of another stimulus set. If the subjects had failed they were informed that they had won 0 points and how many times they had failed on that specific stimulus set (number displayed on the top of the screen). Subjects were then given the choice to either try again with the same stimulus set or to quit and try a new one (choice stage). In all cases where decisions were made the response time to press the button was recorded. Overall the task included 160 different stimulus sets presented in a random sequence of three difficult and one easy. Since we wanted to reveal subjects’ normal decision making strategies no limit was placed on the number of times they could fail and choose to continue with a specific stimulus set. Mean monetary compensation subjects received was 60 RMB.

fMRI data acquisition. During each fMRI scan an Echo-Planar imaging (EPI) sequence was used for data collection, and T2*-weighted images were recorded per run using a Siemens TRIO 3.0T MRI scanner [repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle = 90°; FoV = 220 × 220 mm²; matrix size = 64 × 64; 32 interleaved 3 mm-thick slices; in-plane resolution = 3.4 × 3.4 mm²; inter slice skip = 0.99 mm]. Additionally, anatomical images (256 × 256 × 176) with 1 × 1 × 1 mm³ resolution were obtained by a T1-weighted three-dimensional magnetization prepared rapid gradient echo (MPRAGE) sequence (inversion time = 900 ms; TR = 1900 ms; TE = 2.52 ms; flip angle = 9°).

fMRI data analyses. Statistical analyses were performed using the general linear model in SPM8⁵⁵. Slice timing was used to correct slice order, the data was realigned to estimate and modify the six parameters of head movement and the first three images were discarded to achieve magnet-steady images. These images were then normalized to MNI space in 3 × 3 × 3 mm³ voxel sizes. The normalized data were spatially smoothed with a Gaussian kernel; the full width at half maximum (FWHM) was specified as 8 × 8 × 8 mm³. After pre-processing, the ten regressors from each run [i.e., judgment stage (stimulus/judgment), rating stage (rating), feedback stage (correct, 1, 2, 3, 4 or more failures – correct, f1/f2/f3/f4), choice stage (continue/quit)] were modeled to create the design matrix. The regressors were then convolved with the Canonical Hemodynamic Response Function and the six realignment parameters for each subject were also included as confounding factors.

Whole-brain analyses. Our results primarily relate to feedback processing. We investigated brain regions whose activation was associated with the process of negative feedback using one-sample t-tests. Moreover, we also investigated the contrast between positive (correct and get points) and negative feedback (f1 + f2 + f3 + f4). In addition, the contrast between the decision to stay or shift after negative feedback during both the negative feedback and choice stages was conducted. The image threshold for fMRI data significance was set to, $p < 0.05$ FWE corrected, with clusters of ≥ 10 contiguous voxels.

Region of interest analyses (ROI). We used the MarsBar toolbox⁵⁶ for use with SPM8 to perform ROI analyses to further characterize patterns of activation which matched behavioral decision making performance. Brain activation was extracted from 8 mm diameter spheres centered on co-ordinates identified in previous research. ROIs included the MPFC (0, 47, 21), dACC (0, 26, 29), insula (-36, 23, 0), amygdala (23, -11, -27), DLPFC (39, 53, 19), VStr (-24, 2, 7/27, -4, 10), PCC (-9, -22, 43), precuneus (12, -49, 55), TPJ (66, -49, 1) and MTG (-51, -13, -14)^{6,18,57} using MarsBar software. Repeated-measures ANOVA was used to test whether the parameter estimates for each of the target regions were significantly different across the four frequencies (1–4 times) of negative feedback. Quadratic polynomial function analysis was conducted to explore the relationship between ROI parameter estimates and quitting rate at different frequencies of negative feedback.

Functional connectivity analyses. Based on behavioral results, we could infer that subjects tended to continue with the same stimulus set after up to 2 failures ($f_1 + f_2$) but would quit after ≥ 3 failures ($f_3 + f_4$). Functional connectivity strengths were then analyzed to investigate changes between regions associated with behavioral choice (i.e. continue or quit). We measured functional connectivity using gPPI analysis^{55,58,59}. For the gPPI analysis, we extracted the de-convolved time-course of each seed region (dACC, PCC, TPJ) in each subject, based on an 8 mm radius sphere centered on the peak-activation voxel from the ROI. We calculated the product of this activation time-course and the vector of the psychological variable of interest to create the psychophysiological interaction term. New SPMs were computed for each subject, including the interaction term, the physiological variable (i.e. the ROI activation time course) and the psychological variable as regressors. We then identified areas where activation was predicted by the psychophysiological interaction term, with ROI activity and the psychological regressor treated as confound variables. These analyses were carried out separately for both $f_1 + f_2$ and $f_3 + f_4$ conditions. Individual PPI SPMs were entered into a random-effects group analysis contrasting connectivity patterns between $f_1 + f_2$ and $f_3 + f_4$ conditions with a one-sample t-test, threshold at $p < 0.001$, small volume corrected, with a minimum cluster size of 10 voxels.

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Author Contributions

W.H.Z., F.C., T.Y. and H.L. designed the experiments; W.H.Z. and F.C. conducted the experiments; W.H.Z., F.C., K.K. and T.Y.F. analyzed the data; W.H.Z., K.K. and T.Y.F. wrote the paper. All authors reviewed the manuscript.

Additional Information

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