

Hemispheric differences in amygdala contributions to response monitoring

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The amygdala detects aversive events and coordinates with the rostral anterior cingulate cortex to adapt behavior. We assessed error-related activation in these regions and its relation to task performance using functional MRI and a saccadic paradigm. Both amygdalae showed increased activation during error versus correct antisaccade trials that was correlated with error-related activation in the corresponding rostral anterior cingulate cortex. Together, activation in the right amygdala and right rostral anterior cingulate cortex predicted greater accuracy. In contrast, the left amygdala activation predicted a higher error rate. These findings support a role for the amygdala in response monitoring. Consistent with proposed specializations of the right and left amygdala in aversive conditioning, we hypothesize that right amygdala–rostral anterior cingulate cortex interactions mediate learning to avoid errors, whereas left error-related amygdala activation underpins

Introduction

In humans, both the amygdala and rostral anterior cingulate cortex activate in response to aversive outcomes, and the amygdala response has been correlated with autonomic indices of conditioned fear [1]. Extensive evidence from both animal and human studies suggests that these structures mediate emotional- and reward-based learning and help organisms adapt to their environment (for review, see Refs [2–4]). Errors on a cognitive task are both salient (unexpected) and aversive (representing the nonachievement of a goal). As failures of performance, errors should prompt avoidance learning. Although the response of the rostral anterior cingulate cortex to errors is extensively documented (for review, see Ref. [5]), despite the similarities between errors and other events to which the amygdala responds, the response of the amygdala to errors has seldom been explored. Intracranial recordings from patients with epilepsy reveal error-related responses in the amygdala [6]. We previously reported the error-related activation in the rostral anterior cingulate cortex and amygdala that was related to error rate in healthy participants and those with schizophrenia [7]. These findings suggest that the amygdala is a component of the response monitoring circuitry that detects errors and adapts behavior to avoid their recurrence. Here, we examined the interactions of the amygdala and rostral anterior cingulate cortex during error commission and their relation to task performance.

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We expected these structures to interact during error commission based on evidence that ventromedial prefrontal cortex and, more specifically, rostral anterior cingulate cortex, modulates the amygdala response to salient events (e.g. [8–10]), an interchange that is supported by extensive reciprocal connections [11,12]. If amygdala–rostral anterior cingulate cortex interactions during error commission serve to adapt behavior, then they may correlate with task performance.

We used a saccadic paradigm and event-related functional magnetic resonance imaging to test our hypothesis of interactions between the amygdala and rostral anterior cingulate cortex during error commission that mediate task performance. Participants performed a pseudorandom sequence of prosaccade and antisaccade trials. Prosaccades require a gaze toward a suddenly appearing stimulus, whereas antisaccades require suppression of the prepotent prosaccade, and a gaze in the opposite direction. Analyses were restricted to antisaccades because only they produced sufficient errors. Given evidence of hemispheric specialization in amygdala responses (e.g. [1,13]), we considered activation in each hemisphere separately.

Methods

For greater methodological detail see Ref. [14].

Participants

Twenty-one healthy right-handed participants were recruited from the community. Data from two were excluded, one due to near perfect antisaccade performance (0.1% error rate) and the other one due to eye tracker malfunction. Analyses were conducted on the remaining 19 participants (12 male; mean age: 33 ± 11 years). In addition to a basic rate of pay, participants received a 5-cent bonus for each correct response. All participants gave written informed consent, and the study was approved by the Partners Human Research Committee.

Apparatus

Images were acquired with a 3.0 Tesla Siemens Trio, a whole-body high-speed imaging device equipped for echo planar imaging (Siemens Medical Systems, Erlangen, Germany). Task stimuli were generated by a Macintosh G4 Powermac using programs written in C++ on the Vision Shell programming platform (MicroML, St Hyacinthe, Quebec, Canada). Eye position was sampled at a rate of 60 Hz by ISCAN's RK-726PCI high-resolution pupil/corneal reflection tracker (Woburn, Massachusetts, USA).

Saccadic paradigm

Each task run consisted of a pseudorandom sequence of prosaccade and antisaccade trials, balanced for right and left movements, and fixation intervals of 2, 4, or 6 s. Participants performed six runs of 5 min 22 s each, generating a total of 211 prosaccade, 211 antisaccade, and 80 fixation trials. Saccadic trials lasted 4000 ms and began with an instructional cue, indicating a prosaccade or antisaccade, at screen center. After 300 ms, the cue was replaced by a white fixation ring. At 2000 ms, the ring shifted to the right or left. This was the stimulus to which the participant responded. The white ring remained in the peripheral location for 1000 ms, and then returned to the center for 1000 ms.

Image acquisition

Two high-resolution structural images were acquired using a three-dimensional magnetization prepared rapid gradient echo (MPRAGE) sequence (repetition time/echo time/flip angle = 7.25 ms/3 ms/7°; voxel size: $1.3 \times 1.3 \times 1$ mm). Functional magnetic resonance images were collected using a gradient echo T2*-weighted sequence (repetition time/echo time/flip angle = 2000 ms/30 ms/90°). Twenty contiguous horizontal slices parallel to the intercommissural plane (voxel size: $3.13 \times 3.13 \times 5$ mm) were acquired interleaved. The functional sequences included prospective acquisition correction (PACE) for head motion [15].

Analysis of imaging data

All analyses were conducted using FreeSurfer [16] and FreeSurfer Functional Analysis Stream software [17].

Functional scans were corrected retrospectively for motion, intensity normalized, smoothed using a three-dimensional 8-mm full-width, half-max Gaussian kernel, and aligned to the averaged MPRAGE scans. The averaged MPRAGE scans were also used to construct inflated (two-dimensional) models of individual cortical surfaces that were also spatially normalized for averaged group analyses. Finite impulse response estimates of the event-related hemodynamic responses for each of four trial types (correct prosaccades, error prosaccades, correct antisaccades, and error antisaccades) were calculated for each participant at 12 time points with an interval of 2 s (corresponding to the repetition time) ranging from 4 s before the start of a trial to 18 s after the start. Analyses focused on the 6-s time point at which error-related activation is maximal [14].

Regions of interest definition

The left and right amygdalae were defined using an automated subcortical parcellation program [18]. The left and right rostral anterior cingulate cortex were defined using an automated surface-based parcellation system that provided an anterior cingulate cortex label [19], which was then divided into dorsal and rostral regions in each participant by placing a line at the anterior boundary of the genu of the corpus callosum that was perpendicular to the intercommissural plane [12]. Each of the region of interest (ROI) labels was visually inspected for accuracy either in the volume (amygdalae) or on the inflated cortical surface (rostral anterior cingulate cortex) for each participant. ROI activation in each of the contrasts of interest (error vs. correct, correct vs. fixation, and error vs. fixation) was examined for outliers based on individual participants' z -scores (≥ 3), their effect on normality [i.e. skewness ($> |1.5|$) and kurtosis ($> |3|$)], and on leverage ($> 4/n$). The one participant who exceeded all three cut-offs for non-normality was excluded from the analyses.

Quantification of error-related amygdala activation

Activation for error and correct antisaccades was computed by averaging across all voxels in the anatomically defined ROIs and compared across participants using paired t -tests. We also examined activation in each condition relative to the fixation baseline using one-sample t -tests.

Relation of error-related amygdala and rostral anterior cingulate cortex activation

We regressed error-related amygdala activation onto estimates of raw blood oxygenation level dependent (BOLD) signal in the error versus correct contrast at 6 s at each vertex of the cortical surface in each hemisphere separately. We quantified error-related activation in the amygdala as percent signal change averaged across all voxels showing a positive sign in the error versus correct contrast at 6 s. To correct for multiple comparisons, we

ran 10 000 Monte Carlo simulations of synthesized white Gaussian noise using a probability value of less than 0.01 and the smoothing, resampling, and averaging parameters of the functional analyses. We restricted the simulations to our *a priori* rostral anterior cingulate cortex ROIs. This determines the likelihood that a cluster of a certain size in the rostral anterior cingulate cortex would be found by chance (cluster-wise probability value, CWP). To facilitate comparison with other studies, approximate Talairach coordinates were derived by mapping the surface-based maxima back to the original structural volume for each participant, registering the volumes to the Montreal Neurological Institute (MNI305) atlas [20], and averaging the coordinates that corresponded to the surface maxima across participants. The resulting coordinates were transformed to standard Talairach space using an algorithm developed by Matthew Brett (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>).

Results

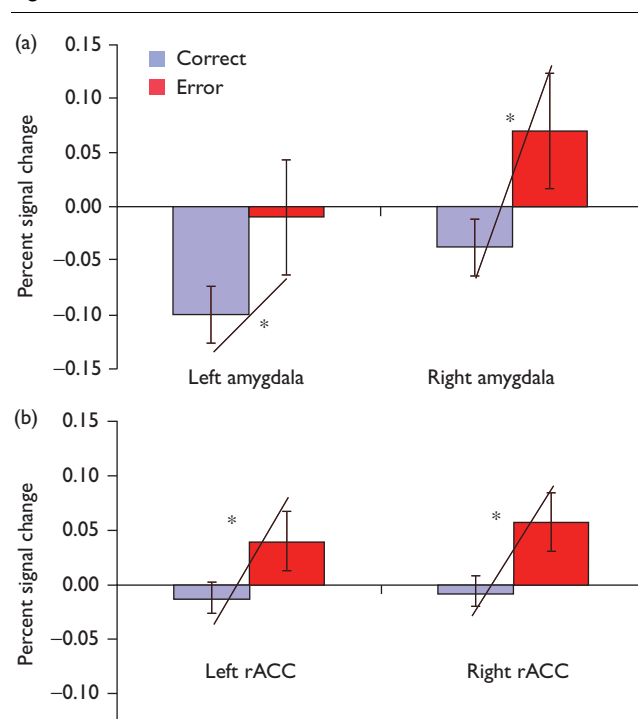
Error-related amygdala activation

Antisaccade error rate was $9 \pm 6\%$. Error versus correct antisaccades were associated with increased amygdala [left hemisphere: $t(18) = 2.29$, $P = 0.04$; right hemisphere: $t(18) = 2.87$, $P = 0.01$] and rostral anterior cingulate cortex [left hemisphere: $t(17) = 2.26$, $P = 0.05$; right hemisphere: $t(17) = 2.72$, $P = 0.01$] activation bilaterally (Fig. 1). The source of increased error-related activation differed by hemisphere. In the left amygdala, it was due to deactivation during correct trials [$t(17) = -3.77$, $P = 0.002$], rather than an increase during error trials [$t(17) = 0.59$, $P = 0.85$]. In contrast, in the right amygdala the increase was primarily due to increased activation during error trials [trend: $t(17) = 1.93$, $P = 0.07$], rather than deactivation during correct trials [$t(17) = 1.38$, $P = 0.18$]. The rostral anterior cingulate cortex showed significant error-related activation in both hemispheres that was primarily due to greater activation for errors [left hemisphere: $t(17) = 1.51$, $P = 0.15$; right hemisphere: $t(17) = 2.38$, $P = 0.03$], rather than deactivation during correct trials [left hemisphere: $t(17) = -0.88$, $P = 0.40$; right hemisphere: $t(17) = -0.62$, $P = 0.54$].

Relation of error-related amygdala and rostral anterior cingulate cortex activation

Error-related activation in both amygdalae was positively correlated with activation in the corresponding rostral anterior cingulate cortex (Fig. 2). For right amygdala, as expected, the maximum fell in rostral anterior cingulate cortex (13, 47, 12, $R^2 = 0.59$, $P < 0.001$; CWP < 0.001). For left amygdala, the maximum fell in orbitofrontal cortex and extended into subgenual rostral anterior cingulate cortex (-7, 44, -6). This region met cluster-wise correction based on the entire cortical surface ($R^2 = 0.63$, $P < 0.001$; CWP = 0.01).

Fig. 1



Percent signal change with standard error bars for error and correct antisaccades in the left and right (a) amygdalae and (b) rostral anterior cingulate cortex (rACC) regions of interest. * $P < 0.05$.

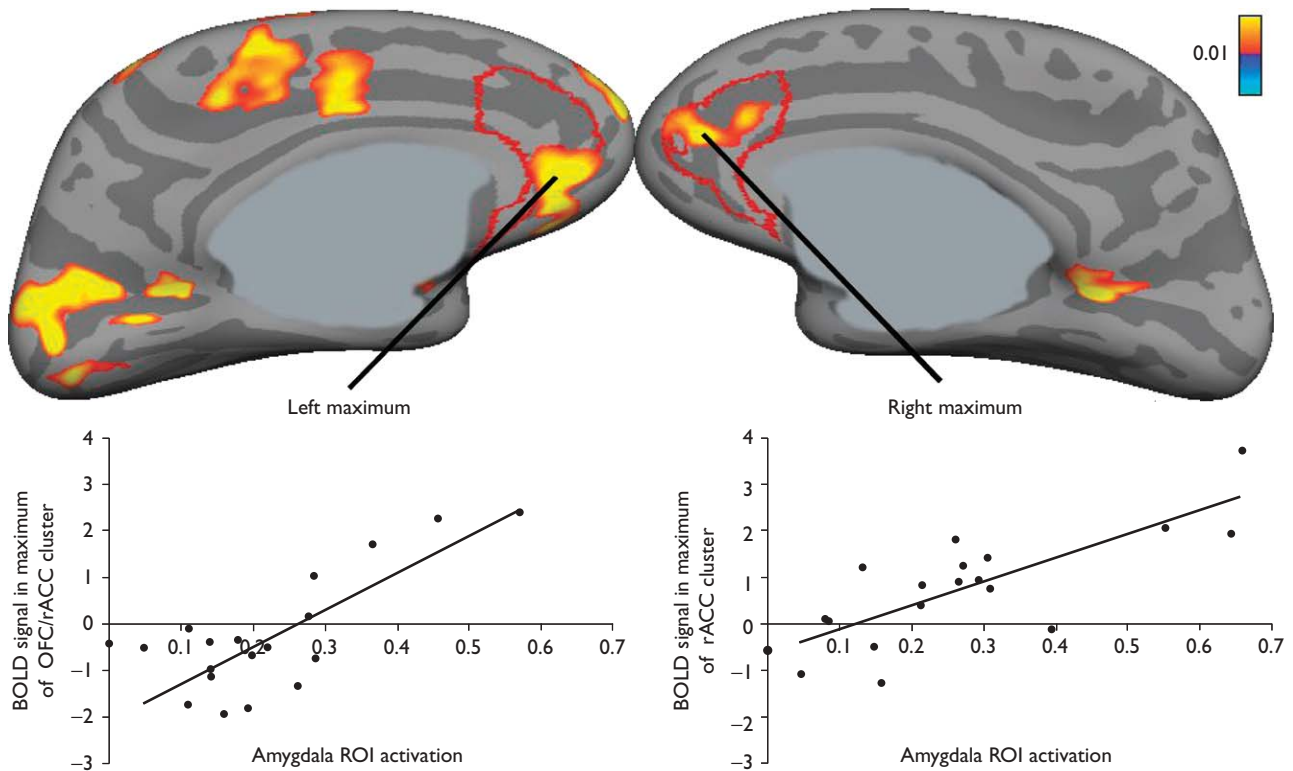
Relation of error-related amygdala and rostral anterior cingulate cortex activation to performance

To examine whether error-related amygdala and rostral anterior cingulate cortex activation and their interactions predicted antisaccade performance, we performed a standard linear regression, which tests the unique variance contributed by each component after removing the shared variance, using error rate as the dependent variable. The model had eight terms (Table 1) and accounted for 51% of the variance in error rate after adjusting for the number of parameters ($P = 0.05$). Although greater error-related activation of the left amygdala significantly predicted a higher error rate, the right amygdala showed a trend to improve accuracy that was augmented by the right rostral anterior cingulate cortex, and counteracted by the left rostral anterior cingulate cortex as indicated by the significant interactions. To summarize, together, right rostral anterior cingulate cortex and right amygdala error-related activation predicted better performance, whereas error-related activation in the left amygdala was associated with worse performance.

Discussion

Our findings support the hypothesis that the amygdala interacts with the rostral anterior cingulate cortex to participate in response monitoring. Both amygdalae

Fig. 2



Statistical maps of regressions of error-related amygdala activation onto error-related activation displayed on the inflated medial cortical surfaces. Scatter plots show percent signal change in the amygdala plotted against raw blood oxygenation level dependent (BOLD) signal on the surface. Gray masks cover noncortical regions in which any activation is displaced. OFC, orbitofrontal cortex; rACC, rostral anterior cingulate cortex; ROI, region of interest. Left hemisphere $R^2=0.63$, right hemisphere $R^2=0.59$.

Table 1 P and t values of parameter estimates in regression of error-related amygdala and rACC activation on error rate

	t value	P value
LH amygdala	2.58	0.03*
RH amygdala	-1.96	0.08
LH rACC	-1.19	0.26
RH rACC	-0.05	0.61
LH amygdala × LH rACC	-1.42	0.19
RH amygdala × RH rACC	-2.31	0.05*
LH amygdala × RH rACC	1.93	0.09
RH amygdala × LH rACC	2.34	0.04*

LH, left-hemisphere; rACC, rostral anterior cingulate cortex; RH, right-hemisphere.

* $P \leq 0.05$.

showed greater activation during error than correct trials that correlated with error-related activation in the corresponding the rostral anterior cingulate cortex, a region that is functionally and structurally connected with amygdala [11,12,21] and that modulates the response of the amygdala to salient events (e.g. [8–10]). Interestingly, the source of error-related amygdala activation and its interactions with the rostral anterior cingulate cortex in predicting error rate differed by hemisphere. In the right hemisphere, error-related activation of the amygdala was primarily due to increased

activation during error trials and it correlated with error-related activation in a right perigenual rostral anterior cingulate region that also showed significantly increased error-related activation (reported elsewhere, [14]). Together with the right rostral anterior cingulate cortex, the right amygdala predicted fewer errors. Given the hypothetical role of rostral anterior cingulate cortex in appraising the affective or motivational significance of errors [22,23], these findings suggest that the right amygdala and right rostral anterior cingulate cortex work together to modulate affective responses to errors and to learn to prevent their occurrence. They are consistent with animal and human studies that suggest a right amygdala dominance for aversive conditioning (e.g. [1,13]). Here, learning is presumably in the service of avoiding errors.

In contrast, error-related activation in the left amygdala was not due to greater activation on error trials, instead it primarily reflected deactivation from baseline during correct responses. It was correlated with error-related activation in orbitofrontal cortex, extending into subgenual rostral anterior cingulate cortex. Both of these regions are reciprocally interconnected with amygdala

[11,24], and are involved in autonomic control and emotional expression [3,25]. Although error-related activation in left orbitofrontal cortex and subgenual rostral anterior cingulate cortex was *correlated* with that in left amygdala, neither of these regions showed significant error-related activation (reported elsewhere, [14]). Finally, in contrast to the right amygdala/rostral anterior cingulate cortex interaction, error-related activation in left amygdala predicted more, not fewer, errors. In humans, cerebral blood flow and metabolism in the amygdala, subgenual rostral anterior cingulate cortex, and orbitofrontal cortex of the left hemisphere are abnormally elevated in major depression, and left amygdala activity positively correlates with depression severity and normalizes with effective treatment (for review, see Ref. [26]). Thus, a speculative interpretation of the differential response to error versus correct responses in left amygdala, and its association with activation in orbitofrontal cortex and subgenual rostral anterior cingulate cortex, is that it reflects negative affect that interferes with performance. Thus, only the right amygdala appeared to function in a way that was consistent with our prediction that the amygdala would detect errors as aversive events and act with the rostral anterior cingulate cortex to adapt behavior. The apparently different contributions of the right and left amygdalae to task performance are consistent with their proposed specializations: right amygdala may be dominant for fear conditioning (e.g. [1,13]), whereas the left amygdala may mediate negative affect [26].

Conclusion

During response monitoring, the right amygdala and rostral anterior cingulate cortex seem to mediate aversive conditioning to errors, whereas the left amygdala may underpin detrimental negative affect concerning performance. Optimal activity in these structures may help you learn from your mistakes, and not get too upset about them.

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