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Background

- Emotional dysfunction is a long-established and critical clinical feature of schizophrenia
- Neuroimaging studies of negative emotional processing in schizophrenia frequently report under-recruitment of the amygdala by patients
- However, many studies find intact or even over-recruitment of the amygdala by patients
- We carried out a meta-analysis of neuroimaging studies of amygdala activation during negative emotion processing in patients with schizophrenia, with two major goals:
  1. To determine whether patients show over-under- or over-recruitment of the amygdala during negative emotion processing
  2. To determine whether any task, imaging, demographic, or patient variables are acting as moderators of amygdala recruitment by patients

Methods

- Thirty-five functional Magnetic Resonance Imaging (fMRI) or Positron Emission Tomography (PET) studies of patients with schizophrenia and a healthy control group that used a negative emotional manipulation and used between-group statistical tests of activation in an amygdala region-of-interest (ROI) or in the whole-brain were included in the analysis
- Amygdala activations were defined as any activation or ROI within the Talairach coordinates of the amygdala according to the Talairach Daemon software (http://www.talairach.org)
- Reported statistics (t values, Z scores, F statistics, P values, or data from published figures) were converted to Hedges’ g using standard methods (see Van Snellenberg et al, 2006)
- Studies that carried out analyses in the amygdala but reported no findings in that region were included with an effect size of zero: exclusion of these studies would lead to a systematic “file-drawer” problem, and treating the effect as zero is the only approach guaranteed to be unbiased under the null hypothesis
- Effect sizes for studies reporting the peak activation within an ROI or activated cluster were corrected to have the same expected value as studies reporting mean activation
- Twenty-six putative moderator variables were sorted into five ‘families’ of moderators (see Table 1), and each family was corrected for multiple comparisons using False Discovery Rate correction (FDR; Benjamin & Hochberg, 1995)
- Effect size estimates and moderator regression parameter estimates were obtained using the framework of Hedges & Olkin (1985), but confidence intervals (CIs) and P values were obtained using the bias-corrected and accelerated bootstrap of Efron & Tibshirani (1993)
- Moderator regression models were selected using a step-forward procedure (see Figure 1)

Results

- A forest plot of effect sizes in all included studies is shown in Figure 2
- Across studies, patients exhibited significantly reduced activation of bilateral amygdala (mean = −0.22; 95% CI = −0.37 to −0.08; P = .002) and right amygdala (mean = −0.17; 95% CI = −0.37 to −0.03; P = .012), with the left amygdala showing a non-significant trend in the same direction (mean = −0.13; 95% CI = −0.31 to 0.04; P = .136); see Figure 3
- “Task contrast of interest” (i.e., whether a study used a direct between-group comparison in the emotional condition or an emotion – neutral interaction contrast) was the only significant moderator of bilateral amygdala activation after correction for false discover rate (FDR) (β = 0.35; 95% CI = 0.09 − 0.70; P = .009), demonstrating an estimated 0.35 standard deviations greater activation in patients when groups were compared in the emotional condition directly
- “Amygdala ROI used” was the only significant moderator of right amygdala activation after FDR correction (β = 0.34; 95% CI = 0.14 − 0.62; P < .001), indicating a 0.34 SD increase in right amygdala activation when an amygdala ROI was used
- An a posteriori follow up analysis of the mean effect-size data demonstrated that there is no difference in amygdala activation between patients and controls when groups are compared in the emotion condition directly (see Figure 4; mean = −0.04; 95% CI = −0.17 to 0.12; P = .689); in contrast, studies using an emotion – neutral contrast demonstrated reduced activation by patients (mean = −0.36; 95% CI = −0.54 to −0.23; P < .001)

Conclusions

- Patients with schizophrenia show under-recruitment of the amygdala during negative emotion processing only when an emotion – neutral contrast is used for statistical analyses
- This finding strongly suggests that amygdalar processing of negative emotion is intact in patients, consistent with a recent review (Kring & Moran, 2008), but that patients demonstrate abnormal amygdala activation to neutral stimuli, consistent with the neuroimaging results of Holt et al (2006)

Table 1

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<th>95% CI</th>
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<th>P value</th>
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<td>Task-related variables</td>
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<td>No</td>
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Figure 1

Schematic of Meta-Analysis and Moderator Analysis Procedure

- Literature search
- Selection criteria
- Moderator coding
- Amygdala effect size estimation
- Adjustment of effect sizes based on peak voxel reports
- Study-wise bootstrap resampling
- Calculation of weighted mean effect
- Calculation of bias corrected accelerated CIs and p values
- Multiple regression models calculated for all moderators

Figure 2

Amygdala Recruitment Across Studies

- Average effect size for bilateral amygdala: Mean = −0.22, 95% CI: −0.37 to −0.08, P < .001
- Average effect size for right amygdala: Mean = −0.17, 95% CI: −0.37 to −0.03, P < .012

Figure 3

Effect Sizes for Studies Using Direct Emotional Comparison or Interaction Contrast

- Task contrast of interest: β = 0.35, 95% CI = 0.09 − 0.70, P < .01
- Amygdala ROI used: β = 0.34, 95% CI = 0.14 − 0.62, P < .001

Figure 4

Effect Size for Studies Using Direct Emotional Comparison or Interaction Contrast

- Emotion condition: Mean = −0.04, 95% CI = −0.17 to 0.12, P = .689
- Emotion – neutral contrast: Mean = −0.36, 95% CI = −0.54 to −0.23, P < .001

Table 1 Descriptives

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