Clinical neuroprediction: Amygdala reactivity predicts depressive symptoms 2 years later


Abstract

Depression is linked to increased amygdala activation to neutral and negatively valenced facial expressions. Amygdala activation may be predictive of changes in depressive symptoms over time. However, most studies in this area have focused on small, predominantly female and homogenous clinical samples. Studies are needed to examine how amygdala reactivity relates to the course of depressive symptoms dimensionally, prospectively and in populations diverse in gender, race and socioeconomic status. A total of 156 men from predominately low-income backgrounds completed an fMRI task where they viewed emotional facial expressions. Left and right amygdala reactivity to neutral, but not angry or fearful, facial expressions relative to a non-face baseline at age 20 predicted greater depressive symptoms 2 years later, controlling for age 20 depressive symptoms. Heightened bilateral amygdala reactivity to neutral facial expressions predicted increases in depressive symptoms 2 years later in a large community sample. Neutral facial expressions are affectively ambiguous and a tendency to interpret these stimuli negatively may reflect to cognitive biases that lead to increases in depressive symptoms over time. Individual differences in amygdala reactivity to neutral facial expressions appear to identify those at most risk for a more problematic course of depressive symptoms across time.

Key words: depression; amygdala; emotion; development; adolescence; facial expression

Introduction

Heightened amygdala reactivity during major depression is one of the most reliable findings in clinical neuroscience (Groenewold et al., 2013; Hamilton et al., 2014). Moreover, an important question is whether differences in amygdala reactivity precede changes in depression. A few recent studies are beginning to suggest that amygdala reactivity to emotional facial expression is predictive of depression over time. For example, prediction has been found across a yearlong span in a community sample enriched for familial history of depression (Swartz et al., 2015) and in the presence of stressful life events (Swartz et al., 2014), as well as across an 8-month period in response to treatment, in a clinically depressed sample (Canli et al., 2005). Beyond these few studies; however, this literature has been largely cross-sectional, i.e. brain activity is examined at the same time as symptoms or diagnosis of depression (or assessed retrospectively, i.e. before measures of neural functioning). For neuroimaging to have greater clinical and etiological significance, it must predict changes in behavior over time above and beyond what diagnostic assessments have already given at a single time point (e.g. Aharoni et al., 2013). Further, with mounting evidence for the dimensionality of mental...
illness (Clark et al., 1995; Ofirat and Krueger, 2012), neuroimaging must also predict changes in 'symptoms' over time to contribute our understanding of the etiology and course of these dimensional illnesses. Thus, in relation to depression, a critically important question is whether amygdala reactivity 'prospectively' predicts changes in future depressive symptoms over and above current levels of depressive symptoms (e.g. Morgan et al., 2013). Therefore, this study examined whether heightened amygdala reactivity during the transition to adulthood (age 20) was associated with 'increases' in depressive symptoms 2 years later while accounting for the age 20 depressive symptoms.

The amygdala plays an essential role in orienting and processing threat and affect (Davis and Whalen, 2001), and is implicated in behavioral anxiety (Taylor and Whalen, 2015). Amygdala reactivity may underpin the disruption in mood, increased anxiety, biased emotional processing and preferential representation of negative information typical of depression (Price and Drevets, 2010). It has been a central focus in neural investigations of depression, with many studies showing increased amygdala reactivity to fearful facial expressions in those with diagnoses of depression (Groenewold et al., 2013; Hamilton et al., 2014) and in community samples examining depressive symptoms (Swartz et al., 2015). However, growing evidence suggests that individuals with depression may show amygdala hyper-activation to not just fearful and angry facial expressions, but also happy facial expressions (Yang et al., 2010). Interestingly, heightened amygdala reactivity is also seen in response neutral facial expressions when they are interpreted negatively (Blasi et al., 2009). Consistent with a biased emotional processing of these ambiguous stimuli in depression, amygdala reactivity to neutral facial expressions has been associated with greater depressive symptom severity (Dannlowski et al., 2006). Depression is marked not only by heightened attention to negative information, but also biases toward negative interpretations of ambiguous information (Leppänen et al., 2004). Accordingly, studies of amygdala reactivity in depression would benefit from examining the relative contribution of amygdala reactivity to not only fearful facial expressions, but also other emotional and neutral facial expressions. Thus, this study focused primarily on neutral facial expressions as a predictor of change in symptom severity.

Although findings with clinical samples support the amygdala as a potential indicator of depression severity, most clinical and community studies have focused primarily on samples from high socioeconomic background, samples of women and samples that are primarily European-American. Males have lower overall depression rates (Blazer et al., 1994; Kessler et al., 2003; Pratt and Brody, 2008). However, a notable percentage of men suffer from depression. For example, recent results from the National Comorbidity Survey (Kessler et al., 2012) found that 14.4% of men met criteria for major depressive disorder in their lifetime. Depression research using neuroimaging has also largely ignored men from diverse racial backgrounds (Falk et al., 2013). Moreover, we know little about the neural predictors of the course of depression symptoms in individuals living in low-income, urban environments, who face greater numbers of life stressors (Spence et al., 2002; Najman et al., 2010). Finally, as the transition to adulthood marks a period of major social, economic and neural change (Arnett, 2000; Cohen et al., 2003; Taber-Thomas and Perez-Edgar, 2015), it is an important developmental period for understanding the course of depressive symptoms. Thus, we examined the prospective prediction of depression symptoms at the transition to adulthood in a racially diverse sample of young men from low-income urban backgrounds (Shaw et al., 2003, 2012)

The goal of this study was to examine the relationship between amygdala activation during the transition to adulthood and depression symptomatology 2 years later. We hypothesized that greater amygdala reactivity to emotional facial expressions at age 20 would predict more depressive symptoms at age 22. We also examined whether these results remained after controlling for depressive symptoms at age 20. We anticipated that predictive effects would be strongest for neural response to neutral facial expressions, as these ambiguous expressions are likely to tap biases in negative emotion processing. The relative predictive strength of each facial expression allowed for examination of the specificity of particular emotional expressions to later depressive symptoms. By better understanding the association between amygdala reactivity at the transition to adulthood and later outcomes in a large and diverse sample, we can begin to identify potential mechanisms governing who goes on to develop problematic courses of depressive symptoms.

Methods
Participants
The current sample is part of the Pitt Mother and Child Project, an ongoing longitudinal study of child vulnerability and resiliency in low-income families. This study includes 310 young men and their mothers who were recruited when they were infants from Allegheny County Women, Infant and Children Nutritional Supplement Clinics. Participants were recruited between 1991 and 1992 when the men were between 6- and 17-months old and have been followed over 22 years (Shaw et al., 2003, 2012). Retention rates were high at each assessment from ages 1.5 through 20. For the fMRI component of the study, data were available on 167 participants. Although attrition to the age 20 visit was quite low for such a long-term study (i.e. 256 young men participated at age 20; 83% retention across 19 years), the fMRI component introduced several sources of data loss because of participants who did not want to take part in the MRI portion, had a history of head injury, had bullet or metal fragments in their body, or whose fMRI data did not meet quality standards. A total of 11 of these subjects did not complete the BDI at age 22. See Supplementary Table S1 for a summary of data attrition and Table 1 for a description of the demographic and behavioral characteristics of the final sample. Based on parent report when children were 18-months old, of those included in the present analyses 79 participants (50.6%) were European American, 64 (41.0%) were African American and 13 (8.3%) were identified by their mothers as of other races (a similar racial/ethnic composition to the overall sample). At child age 18 months, mothers in the final sample had spent a mean of 12.66 years in school (SD = 1.57) and families had a monthly income of $1108.19 (SD = 889.20) and a mean rating of 23.66 (SD = 6.81) on the Hollingshead four factor index of social status (Hollingshead, 1975), indicating that this is a working-class to impoverished sample. Simple t-tests revealed no differences between European American and other race/ethnic categories in amygdala reactivity, Ps = 0.37–0.91, or depressive symptoms at age 20 or age 22, Ps = 0.35–0.76. Race/ethnic categories did not moderate amygdala reactivity in subsequent linear regressions predicting age 22 BDI scores, Ps = 0.32–0.96. Additionally, a comparison between those included in the final sample for this study, and those participants lost to attrition, revealed no significant differences between subjects retained and those not on...
the Child Behavior Checklist (Achenbach, 1992) at 24, 42 or 60 month of age on the Anxious/Depressed, Ps 0.16–0.58, Internalizing Problems, Ps 0.17–0.58, or Externalizing Problems subscales, Ps 0.09–0.66. Though our focus was on a dimension of self-reported symptomatology over time, the sample did contain a substantial portion of participants that met criteria for major depression: In the final sample 9.00% (n = 14) at age 20 and 12.00% (n = 20) at age 22 were identified on the Structured Clinical Interview for DSM-IV-TR (First et al., 2002) as having major depressive disorder. Participants were reimbursed for their time at the end of each assessment and all procedures have been approved by the Institutional Review Board (IRB) of the University of Pittsburgh.

Measures

Demographic variables. At 1.5 years, mothers reported on their child’s race/ethnicity, years of education, family income and socioeconomic status (Hollingshead, 1975).

Beck depression inventory: second edition (BDI-II). Self-reports of depression symptoms were gathered at age 20 and 22 using the BDI-II and calculated as a total score of the 21 items for each individual. The BDI-II has been shown to exhibit high internal consistency, x = 0.91 (Beck et al., 1996). Within the current sample the BDI showed good internal consistency at both age 20, x = 0.86, and age 22, x = 0.86.

Amygdala reactivity paradigm. A canonical face processing task (Hariri et al., 2000) was collected at age 20 (see Supplementary Figure S1). The experimental task included four face processing blocks interleaved with five sensorimotor control blocks (Manuck et al., 2007; Carré et al., 2012; Hyde et al., 2014, 2015). In the face processing block participants viewed one face in the upper half of the screen and two faces in the bottom half of the screen. Participants were asked to identify which of the two bottom faces matched the upper face. Each face processing block contained a different set of six matching images of a single emotional facial expression (anger, fear, surprise and neutral). Participants were randomly assigned to one of four block orders. Facial expression images were a subset of stimuli from the pictures of facial affect set (Ekman and Friesen, 1976), balanced for gender. In the sensorimotor control blocks participants viewed a geometric shape (circles, vertical ellipses or horizontal ellipses) in the upper half of the screen and two shapes in the bottom half of the screen. All blocks were preceded by brief instructions (‘Match Faces’ or ‘Match Shapes’) lasting 2 s. In the face processing blocks, each of the six face trios was presented for 4 seconds with a variable interstimulus interval of 2–6 s (mean = 4 s) for a total block length of 48 s. A variable interstimulus interval was used to minimize expectancy effects and resulting habituation, as well as to maximize amygdala reactivity throughout the paradigm. In the sensorimotor control blocks, each of the six shape trios was presented for 4 s with a fixed inter-stimulus interval of 2 s for a total block length of 36 s. Total task time was 390 s. Subject performance (accuracy and reaction time) was monitored during all scans.

Blood oxygenation level-dependent fMRI acquisition. Each participant was scanned with a research-dedicated Siemens 3-T Tim Trio. Blood oxygenation level-dependent (BOLD) functional images were acquired with a gradient-echo echoplanar imaging (EPI) sequence (repetition time/echo time = 2000/29 ms, field of view = 200 × 200, matrix size = 64 × 64, flip angle = 90°), which covered 34 interleaved axial slices (3-mm slice thickness, voxel size 3 × 3 × 3 mm) aligned with the AC-PC plane and encompassing the entire cerebrum and most of the cerebellum to maximum coverage of limbic structures. All scanning parameters were selected to optimize the quality of the BOLD signal while maintaining a sufficient number of slices to acquire whole-brain data. Before collecting fMRI data for each participant, a reference EPI scan was acquired and visually inspected for artifacts (e.g. ghosting) and good signal across the entire volume of acquisition, including the amygdala. Additionally, an autoshimming procedure was conducted before the acquisition of BOLD data in each participant to minimize field inhomogeneities. Higher-order shimming was implemented as needed.

Data analysis

Frequency distributions and normality. IBM SPSS Statistics version 22 was used to examine the distribution of study variables. BDI-II total scores at age 20 (M = 5.16, SD = 6.14, Kurtosis = 4.84) and age 22 (M = 4.90, SD = 5.93, Kurtosis = 4.00) and extracted amygdala activation (M = 0.024–0.36, SD = 0.53–0.58, Skew = −0.29 to 0.88, Kurtosis = −0.30 to 5.33) met reasonable assumptions of normality.

Image processing and analysis. Whole-brain image analysis was completed using the general linear model (GLM) of SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Images for each participant were grey matter segmented, realigned to the mean volume in the time series and unwarped to correct for head motion, co-registered to high resolution structural scans, spatially normalized into a standard stereotactic space (Montreal Neurological Institute template) using a 12-parameter affine model, and smoothed to minimize noise and residual difference in gyril anatomy with a Gaussian filter set at 6-mm Full-Width Half-Maximum (FWHM). Voxelwise signal intensities were ratio-normalized to the whole-brain global mean. After pre-processing, the Artifact detection Tools software package (http://www.nitr. org/projects/artifact_detect/) was used to detect global mean intensity and translation or rotational motion outliers (>4.5 SD from the mean global brain activation, >2 mm movement or 2° translation in any direction) within each participant’s data and created a regressor identifying each outlier volume to account for the possible confounding effects of volumes with large motion or intensity deflections. Additionally, because of the relatively extensive signal loss typically observed in the amygdala, single-subject BOLD fMRI data were only included in subsequent analyses if there was a minimum of 90% signal coverage in the amygdala bilaterally using our amygdala Region of interest (ROI) (Carré et al., 2012). A total of seven subjects were excluded due to poor signal coverage (see Supplemental...
Materials for details on these quality procedures and Supplementary Table S1).

ROI analyses and data extraction. The GLM of SPM8 was used to conduct fMRI data analyses of the main effects of the task. Linear contrasts employing canonical hemodynamic response functions were used to estimate condition-specific (i.e. fear > shapes) BOLD activation for each individual and scan. These individual contrast images (i.e. weighted sum of the beta images) were then used in second-level random effects models that account for both scan-to-scan and participant-to-participant variability to determine mean expression-specific reactivity using one-sample t-tests.

Our major hypothesis focused on amygdala response to neutral facial expressions vs shapes; however, we included two additional negatively valenced contrasts, anger vs shapes and fear vs shapes, given their importance in the previous literature. Contrast-specific BOLD parameter estimates were extracted from activation clusters within our amygdala ROIs surviving a threshold of $P < 0.05$, corrected for multiple comparisons across a bilateral amygdala ROI using the FWE correction across the small volume within SPM8. Automated Anatomical Labeling (AAL) ROIs for the whole amygdala were selected using the WFU PickAtlas Tool, version 1.04. Significant peak activation in both left and right amygdala ROIs was observed for the fear vs shapes, anger vs shapes and neutral vs shapes contrasts [see Table 2 and Figure 1]. Significant peak activation values were extracted for each subject to be used in subsequent analyses within SPSS.

Results

Linear regressions were constructed using amygdala reactivity to predict BDI scores at age 22. Separate regression were generated for each of three contrasts (neutral vs shapes, fear vs shapes and anger vs shapes), employing a Bonferroni correction for two extracted regions for each contrasts ($\alpha = 0.008$). See Table 3 for a summary of these results. The neutral vs shapes contrasts for left and right amygdala ROIs revealed a significant prediction of BDI scores at age 22, indicating that this predictive effect was bilateral and that greater depression symptoms at age 22 were predicted by greater amygdala reactivity to neutral facial expressions at age 20. The fear vs shapes contrast for left and right whole amygdala did not predict BDI scores at age 22 following Bonferroni correction, but showed a non-significant trend ($P$ value 0.01, greater than the adjusted $\alpha$ of 0.008). The anger vs shapes for left and right whole amygdala contrasts did not predict BDI scores at age 22.

We then examined whether the prediction from neutral vs shapes contrasts for the left and right amygdala remained significant after controlling for BDI scores at age 20. The results revealed that bilateral prediction of BDI scores remained significant for the left, $B = 2.09$, SE $= 0.75$, $t$ (153) = 2.77, $P = 0.006$, and right amygdala, $B = 1.93$, SE $= 0.70$, $t$ (153) = 2.77, $P = 0.006$.

Additional analyses were conducted to rule out associations with other covariates as driving the association between amygdala reactivity and depressive symptoms at age 20. When included as an additional predictor in linear regressions, socioeconomic status, as assessed by the Hollingshead, was not a significant predictor of age 22 BDI scores, $Ps = 0.13$–0.38. Similarly
Table 2. Amygdala activation to face stimuli

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Peak activation ((t, k))</th>
<th>P value</th>
<th>Montreal Neurological Institute coordinates ((x, y, z))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left amygdala ROI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger vs shapes</td>
<td>8.80 ((k = 155))</td>
<td>&lt;0.001</td>
<td>–22, –4, –16</td>
</tr>
<tr>
<td>Fear vs shapes</td>
<td>9.22 ((k = 143))</td>
<td>&lt;0.001</td>
<td>–18, –6, –18</td>
</tr>
<tr>
<td>Neutral vs shapes</td>
<td>6.19 ((k = 124))</td>
<td>&lt;0.001</td>
<td>–20, –6, –16</td>
</tr>
<tr>
<td>Right amygdala ROI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger vs shapes</td>
<td>8.21 ((k = 130))</td>
<td>&lt;0.001</td>
<td>24, –4, –16</td>
</tr>
<tr>
<td>Fear vs shapes</td>
<td>8.38 ((k = 133))</td>
<td>&lt;0.001</td>
<td>22, –4, –16</td>
</tr>
<tr>
<td>Neutral vs Shapes</td>
<td>7.54 ((k = 119))</td>
<td>&lt;0.001</td>
<td>20, –4, –16</td>
</tr>
</tbody>
</table>

Note: Contrasts marked with an * were below the Bonferroni corrected alpha level for the number of contrasts \((n = 0.008)\). Contrasts marked with a † were above the Bonferroni corrected alpha level for the number of contrasts \((n = 0.008)\) but below P < 0.05.

Table 3. Prediction from bilateral amygdala ROI activation to age 22 depressive symptoms

<table>
<thead>
<tr>
<th>Contrast</th>
<th>B (SE)</th>
<th>t (df)</th>
<th>P value</th>
<th>(R^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left whole amygdala ROI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger vs shapes</td>
<td>–0.74 (0.81)</td>
<td>–0.91 (154)</td>
<td>0.36</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fear vs shapes</td>
<td>–1.68 (0.85)</td>
<td>–1.98 (154)</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>Neutral vs shapes*</td>
<td>2.58 (0.86)</td>
<td>2.94 (154)</td>
<td>&lt;0.01</td>
<td>0.06</td>
</tr>
<tr>
<td>Right whole amygdala ROI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger vs shapes</td>
<td>0.44 (0.88)</td>
<td>0.50 (154)</td>
<td>0.62</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fear vs shapes</td>
<td>–2.31 (0.90)</td>
<td>–2.55 (154)</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Neutral vs shapes*</td>
<td>2.24 (0.81)</td>
<td>2.78 (154)</td>
<td>&lt;0.01</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Note: Contrasts marked with an * were below the Bonferroni corrected alpha level for the number of contrasts \((n = 0.008)\). Contrasts marked with a † were above the Bonferroni corrected alpha level for the number of contrasts \((n = 0.008)\) but below P < 0.05.

There are several potential limitations to this study. The current sample consists of young men living in a predominantly low-income, urban environment. Although it is important to better understand these processes in groups under-represented in research and those who face greater numbers of stressors, the current sample limits the applicability of these findings to men from different socioeconomic status backgrounds or those across socioeconomic strata living in rural or suburban communities. Given that individuals with depression in the USA are more likely to be living in poverty (Kessler et al., 2003), the current sample might better represent the population of depressed individuals that need to be studied and provided effective treatments than a more general sample. Gender is also an important consideration—it is likely that young men and women follow different pathways to depression (Marcus et al., 2005; Essau et al., 2010). Gender differences in overall incidence are seen both in the USA (Kessler et al., 2003) and in diverse international studies (Andrade et al., 2003). This gap begins to emerge in adolescence (Wade et al., 2002), which likely affects how depression manifests in each gender. Although we did not examine amygdala reactivity’s relationship to depressive symptomatology in women, this study could be contrasted with results in a female or mixed sample. At the least, our results contribute to a better understanding of depression in men, who are less likely to be the focus of research on depression. Finally, it should be noted that the perception of faces from racial outgroups may lead to the perception of neutral facial expressions as negative—with a corresponding increase in amygdala reactivity (Hart et al., 2000; Hugenberg and Bodenhausen, 2003). Though we have seen race serve as a moderator of brain–behavior relationships in other reports from this sample (Hyde et al., 2015), when we examined whether the relationship between amygdala reactivity and depressive symptoms differed on the basis of participant race, we found no differences.

This study provides several avenues for future research. We specifically examined the association between amygdala reactivity and later depressive symptoms at the transition to...
adulthood. However it is crucial that we understand this association throughout development. Longitudinal observation of both behavior and brain function throughout adolescence and early adulthood would help to parse the degree of transaction that occurs between these two factors. There may be a peak of interactive influence between depressive symptoms and brain function during a particular period of development. Locating this peak of interaction would be integral to targeting intervention to maximize clinical impact. Moving the period of interest earlier in development may be fruitful as there may be influences in early or middle childhood that are antecedents for later differences in amygdala function—‘sleeper’ effects that do not manifest until adolescence and adulthood. During a relatively brief 2-year period from age 20 to age 22, heightened amygdala reactivity was a significant predictor of an increase depressive symptoms. Future research could expand on these findings with more frequent observations and a more comprehensive set of imaging tasks and assessments of depressive symptoms. This could identify if the transition to adulthood might represent a shift in symptoms or a single instance of an ongoing reciprocal relationship between brain function and symptomatology.

In summary, we report some of the first evidence for neuro-prediction of later depressive symptoms from amygdala reactivity. Activation to neutral facial expressions at age 20 predicted depressive symptomatology at age 22, over and above age 20 levels of depressive symptomatology. Moreover, we demonstrated these exciting predictive effects in a large sample incorporating typically underrepresented populations through high racial/ethnic and socioeconomic diversity.

Supplementary data
Supplementary data are available at SCAN online.

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Conflict of interest. None declared.

References


