PACAP receptor gene polymorphism impacts fear responses in the amygdala and hippocampus

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We have recently found higher circulating levels of pituitary adenylate cyclase-activating polypeptide (PACAP) associated with posttraumatic stress disorder (PTSD) symptoms in a highly traumatized cohort of women but not men. Furthermore, a single nucleotide polymorphism in the PACAP receptor gene (ADCYAP1R1), adenylate cyclase activating polypeptide 1 receptor type 1, was associated with individual differences in PTSD symptoms and psychophysiological markers of fear and anxiety. The current study outlines an investigation of individual differences in brain function associated with ADCYAP1R1 genotype. Forty-nine women who had experienced moderate to high levels of lifetime trauma participated in a functional MRI task involving passive viewing of threatening and neutral face stimuli. Analyses focused on the amygdala and hippocampus, regions that play central roles in the pathophysiology of PTSD and are known to have high densities of PACAP receptors. The risk genotype was associated with increased reactivity of the amygdala and hippocampus to threat stimuli and decreased functional connectivity between the amygdala and hippocampus. The findings indicate that the PACAP system modulates medial temporal lobe function in humans. Individual differences in ADCYAP1R1 genotype may contribute to dysregulated fear circuitry known to play a central role in PTSD and other anxiety disorders.

Significance

Higher circulating pituitary adenylate cyclase-activating polypeptide (PACAP) and a polymorphism in its receptor gene ADCYAP1R1, adenylate cyclase activating polypeptide 1 receptor type 1, have recently been linked with posttraumatic stress disorder (PTSD) in women and not men. The current study examined the influence of ADCYAP1R1 genotype on brain function among traumatized women. In individuals with the risk genotype, the amygdala showed greater reactivity to threat stimuli and decreased functional connectivity with the hippocampus. ADCYAP1R1 genotype had larger effects on PTSD diagnosis, suggesting that amygdala reactivity is an intermediate phenotype for anxiety-related psychopathology. Amygdala reactivity has been identified as a possible predisposing risk factor for PTSD, and the current findings indicate a possible genetic mechanism. Findings also point to a neurological explanation for increased PTSD prevalence in women.


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sample of adult women who have experienced moderate to high levels of civilian trauma. To disentangle genetic effects from the complex effects of PTSD and other psychiatric symptoms, genotype groups were matched for childhood and adult trauma levels and PTSD and depression symptom severity.

Our primary hypotheses focused on the amygdala because of its role in regulating emotional arousal and as a possible predisposing factor in PTSD. We also examined the hippocampus, another brain region that plays a central role in PTSD (22), where PACAP binding sites are particularly dense (23) and where PACAP has been shown to act in a neuroprotective or neurotrophic manner (24–26) and may facilitate synaptic plasticity (25, 27). We predicted that individuals with the risk polymorphism would show exaggerated amygdala responses to threat stimuli and decreased functional connectivity between the amygdala and the hippocampus, the anterior cingulate cortex, and the medial prefrontal cortex, regions that regulate amygdala reactivity (28, 29).

**Results**

Twenty-two participants with the CC genotype formed the risk group, and 27 participants with GC or GG genotypes formed the nonrisk group. Participants in the risk (CC) group did not differ from participants in the nonrisk (GC/CC) group in age, education, income, amount of trauma experienced, PTSD symptoms, depression symptoms, trait anxiety, or state anxiety immediately before the scan, as shown in Table 1.

**fMRI Responses to Fearful Face Stimuli.** All analyses were performed using the contrast of fearful > neutral face stimuli. In the amygdala region of interest (ROI), the risk group showed significantly greater activation than the nonrisk group (Fig. 1A; \( p_{\text{corr}} < 0.05 \)). When each group was examined separately, the risk group showed bilateral amygdala activation \( p_{\text{corr}} < 0.05 \); left: \( Z = 3.52, k = 75, x, y, z = -32, -8, -16 \); right: \( Z = 3.12, k = 62, x, y, z = 24, -4, -28 \), whereas the nonrisk group showed no significant amygdala activation. In the hippocampus ROI, the risk group showed significantly greater activation than the nonrisk group (Fig. 1B; \( p_{\text{corr}} < 0.05 \)). When groups were examined separately, the risk group showed significant hippocampal activation bilaterally (\( p_{\text{corr}} < 0.05 \); left: \( Z = 3.23, k = 148, x, y, z = -24, -12, -12 \); right: \( Z = 2.56, k = 136, x, y, z = 36, -8, -20 \), whereas the nonrisk group showed no significant cluster of activation.

Similar results were obtained when ROI analyses were repeated using an additive model, examining voxels in which activation correlated linearly with the number of risk alleles (zero, one, or two C-alleles). Twenty-two participants had two risk alleles, 21 participants had one risk allele, and 6 participants had zero. The number of risk alleles correlated positively with activation in the amygdala bilaterally (\( p_{\text{corr}} < 0.05 \); left: \( Z = 3.12, k = 62, x, y, z = -28, -8, -12 \); right: \( Z = 2.67, k = 40, x, y, z = 28, 0, -16 \)) and in the hippocampus bilaterally (\( p_{\text{corr}} < 0.05 \); left: \( Z = 2.79, k = 112, x, y, z = -16, -36, -8 \); right: \( Z = 2.29, k = 53, x, y, z = 24, -36, -8 \)).

We then examined the effect sizes for group differences in amygdala activation associated with 

**Table 1. Group characteristics**

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>CC (n = 22), M (SD)</th>
<th>GCGG (n = 27), M (SD)</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>37.6 (11.5)</td>
<td>39.6 (13.2)</td>
<td>-0.6</td>
</tr>
<tr>
<td>No. different traumas (TEI)</td>
<td>5.7 (3.0)</td>
<td>6.8 (7.2)</td>
<td>-0.7</td>
</tr>
<tr>
<td>Childhood trauma (CTQ)</td>
<td>44.5 (19.1)</td>
<td>42.8 (15.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Emotional abuse</td>
<td>8.8 (4.0)</td>
<td>9.3 (3.7)</td>
<td>-0.5</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>7.9 (3.1)</td>
<td>7.7 (3.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>10.3 (6.4)</td>
<td>9.9 (6.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>PTSD symptoms (PSS)</td>
<td>14.6 (11.7)</td>
<td>16.3 (12.5)</td>
<td>-0.5</td>
</tr>
<tr>
<td>Intrusive</td>
<td>3.7 (3.3)</td>
<td>3.9 (3.7)</td>
<td>-0.2</td>
</tr>
<tr>
<td>Avoidance/numbing</td>
<td>5.5 (5.3)</td>
<td>7.0 (5.5)</td>
<td>-0.9</td>
</tr>
<tr>
<td>Hyperarousal</td>
<td>5.4 (4.4)</td>
<td>5.4 (4.2)</td>
<td>0.0</td>
</tr>
<tr>
<td>Depression symptoms (BDI)</td>
<td>12.4 (10.3)</td>
<td>13.7 (11.7)</td>
<td>-0.4</td>
</tr>
<tr>
<td>State anxiety (STAI)</td>
<td>34.1(10.4)</td>
<td>33.6(10.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Trait anxiety (STAI)</td>
<td>39.2(10.1)</td>
<td>36.1(9.3)</td>
<td>1.1</td>
</tr>
<tr>
<td>Years education, %</td>
<td>&lt;12th grade</td>
<td>9.5</td>
<td>7.4</td>
</tr>
<tr>
<td>12th grade/high school graduate</td>
<td>52.4</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td>General Educational Development</td>
<td>19.0</td>
<td>48.1</td>
<td></td>
</tr>
<tr>
<td>Some college/technical school</td>
<td>9.5</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>College/tech school graduate</td>
<td>9.5</td>
<td>14.8</td>
<td></td>
</tr>
<tr>
<td>Monthly income</td>
<td>$0–249</td>
<td>20.0</td>
<td>18.5</td>
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<tr>
<td>$250–499</td>
<td>10.0</td>
<td>11.1</td>
<td>0.4</td>
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<td>$500–999</td>
<td>30.0</td>
<td>40.7</td>
<td>0.7</td>
</tr>
<tr>
<td>$1,000–1,999</td>
<td>35.0</td>
<td>11.1</td>
<td>1.1</td>
</tr>
<tr>
<td>$2,000+</td>
<td>5.0</td>
<td></td>
<td>1.8</td>
</tr>
</tbody>
</table>

Note that the use of a large anatomically defined ROI created a conservative estimate of effect size.
group. When examined separately, each group showed activation of regions typically involved in processing face stimuli (31), but the risk group engaged medial temporal, orbitofrontal, and striatal regions, whereas the nonrisk group engaged lateral temporal and occipital regions and the insula.

**Amygdala Functional Connectivity.** Connectivity with the hippocampus.

Functional connectivity results represent voxels showing increased covariance with the amygdala in the contrast of fearful > neutral stimuli. Analyses were performed using separate seed regions for the left and right amygdala, and target voxels were restricted to a bilateral mask of the hippocampus. The results are shown in Fig. 2. Amygdala–hippocampal connectivity was significantly decreased in the risk group, relative to the nonrisk group: the left amygdala showed decreased connectivity with the right anterior hippocampus ($p_{corr} < 0.05$, $Z = 2.95, k = 17, x, y, z = 32, −8, −32$), and the right amygdala showed decreased connectivity with the left posterior hippocampus ($p_{corr} < 0.05$, $Z = 2.77, k = 19, x, y, z = −12, −40, 4$). When examined individually, the risk group showed no significant amygdala–hippocampal connectivity for fearful relative to neutral stimuli. In contrast, the nonrisk group showed significant connectivity between the left amygdala and right anterior hippocampus ($p_{corr} < 0.05$, $Z = 2.94, k = 20, x, y, z = 32, −12, −28$) and between the right amygdala and left hippocampus ($p_{corr} < 0.05$; anterior cluster: $Z = 3.59, k = 23, x, y, z = −20, −12, −28$; posterior cluster: $Z = 2.56, k = 18, x, y, z = −12, −40, 4$).

**Connectivity with the prefrontal cortex.** Analyses were performed using seed regions for the left and right amygdala, and target voxels restricted to a bilateral mask of anterior cingulate and medial prefrontal cortex, in Brodmann area (BA) 24, 25, and 32. Genotype did not significantly influence amygdala–prefrontal connectivity.

**Exploratory whole-brain connectivity.** Connectivity between amygdala seed regions and all voxels within the brain is presented in Table S2. The risk group showed less connectivity than the nonrisk group in lateral temporal regions, an anterior medial prefrontal cluster in the right superior frontal gyrus, left caudate, and sensorimotor cortex. There was no region of increased amygdala connectivity for the risk relative to the nonrisk group.

**Discussion**

In the current study we investigated individual differences in amygdala and hippocampal function associated with the *ADCYAP1R1* polymorphism previously linked with PTSD in women. Consistent with our hypotheses, the *ADCYAP1R1* risk genotype (CC) was associated with increased responses to fearful stimuli in the amygdala and hippocampus. Exaggerated neural responses to fearful stimuli are also characteristic of PTSD relative to traumatized control participants, particularly within the amygdala (30, 32, 33). In addition, individuals with the risk genotype showed reduced functional connectivity between the amygdala and hippocampus relative to the nonrisk genotype. The genotype groups were matched for childhood trauma, lifetime trauma, PTSD symptoms, and depression symptoms. Therefore, the current findings reflect independent effects of the polymorphism on brain function, in the context of a heavy trauma load.

Many previous studies have observed that hyperarousal symptoms in PTSD and other anxiety disorders are linked with increased amygdala reactivity (30, 33), and it has been suggested that amygdala hyperreactivity may predispose individuals for pathological responses to traumatic stress (12). Here we observed increased amygdala reactivity in individuals with the *ADCYAP1R1* risk genotype as compared to the nonrisk group.
risk genotype. These findings are consistent with previous evidence that *ADCYAP1R1* influences the startle reflex, an amygdala-modulated physiological response, producing exaggerated fear responses and a defect in safety signal learning (5, 10). The risk genotype appears to be associated with decreased expression of the PACAP receptor because females with the risk polymorphism showed less *ADCYAP1R1* mRNA than those who did not have the risk polymorphism (5). The current findings point to one possible risk pathway for PTSD, in which the risk genotype predisposes individuals to increased fear reactivity through up-regulated amygdala responses related to decreased expression of the PACAP receptor.

We did not replicate our previous findings showing an association between *ADCYAP1R1* and PTSD symptoms. The small effect sizes typically observed for associations between genetic polymorphisms and psychiatric pathology require large sample sizes to reliably detect an effect (34). Here we took the complementary approach of balancing the genotype groups for PTSD symptoms and observed a significant link between *ADCYAP1R1* and amygdala function. In addition, we found that the effect size for *ADCYAP1R1* genotype was larger than the effect size for PTSD in a previous study using a similar sample (30). Taken together, the findings support the idea that tracing individual differences from genes through neural circuits that underlie pathophysiology can provide a promising approach to investigating complex psychiatric disease. With larger sample sizes, future research should focus on linking all three levels of analysis (genes, neural systems, and symptoms) to address questions about the extent to which neural activation and connectivity might add additional predictive value, above and beyond genotype, in predicting PTSD.

We also observed that *ADCYAP1R1* genotype influenced the hippocampal response to fearful stimuli. The hippocampus is involved in supporting fear expression and the inhibitory memory traces that form during fear extinction (28, 35) and is less activated in PTSD than control participants during extinction recall (36). Synaptic plasticity in the hippocampus is also critical to the formation and retrieval of conscious memories of personal experiences (episodic memory (37)). Changes in hippocampal function are often observed in anxiety disorders, with several studies showing increased hippocampal activation in PTSD (38–41), hypothesized to reflect additional memory encoding or retrieval processes (38, 40). The hippocampus is particularly sensitive to stress hormones, which can impair plasticity (42, 43); significant early life stress, often in the form of childhood maltreatment, is closely linked to reductions in hippocampal plasticity (44). Individuals with posttraumatic stress symptoms often experience changes in declarative memory function, such as intrusive recall of trauma (45), and a general impairment in remembering specific details (46). In the current study, the risk and nonrisk groups experienced equivalent levels of environmental stressors in the form of child and adult trauma, but hippocampal reactivity was increased only in the risk group. This finding raises the possibility that the *ADCYAP1R1* risk polymorphism increases hippocampal vulnerability to the harmful effects of stress. This question would be best addressed by a prospective study examining genotype and hippocampal structure and function before and after stress. It is also notable that although the risk group showed heightened reactivity to fearful stimuli in the amygdala and hippocampus, the nonrisk group showed very little reactivity in either region. This contrasts with findings in healthy individuals showing robust amygdala and hippocampal responses to fearful vs. neutral face stimuli (47). This discrepancy may be explained by the idea of genetic resiliency. The current findings may point to a particularly resilient individual whose individual differences in *ADCYAP1R1* influence the “nonrisk” genotype. Resilient individuals may show less reactivity or may adapt more quickly to threat stimuli. Future studies should directly address this possibility.

The risk polymorphism was also associated with decreased functional connectivity between the amygdala and hippocampus. Interaction between these regions has been linked with multiple functions: pathways from amygdala to hippocampus are important for the modulatory effects of emotion on declarative memory encoding (48), whereas pathways from hippocampus to amygdala are necessary for contextual modulation of fear conditioning (49, 50). These are both cognitive mechanisms implicated in the maintenance of PTSD (38, 51). The *ADCYAP1R1* polymorphism did not influence interactions between the amygdala and ventromedial prefrontal cortex, despite the fact that dysregulated amygdala–prefrontal circuits are central neural features of PTSD (52, 53). Exploratory analyses showed the risk polymorphism was associated with decreased connectivity between the amygdala and a very anterior region of the medial prefrontal cortex, in BA 10, as well as other regions that may facilitate contextual modulation of amygdala activity including lateral temporal cortex and left caudate. However, *ADCYAP1R1* did not influence connectivity between the amygdala and several brain regions typically implicated in the pathophysiology of PTSD such as the anterior cingulate cortex and insula, suggesting that individual differences in the PACAP system may not explain all of the neural system changes associated with the disorder. It is important to note that the analyses used in the current paper cannot inform questions relating to the direction of interactions (e.g., whether one region influences the other).

Rodent studies of PACAP show that it has neurotrophic effects (24, 26) and may facilitate synaptic plasticity (25, 27). Plasticity in the amygdala and hippocampus is crucial to multiple forms of memory, playing a central role in reinforcement learning and declarative memory. Relatively less mRNA expression of the PACAP receptor, previously associated with the risk polymorphism, may lead to a decrease in plasticity in the amygdala and hippocampus, creating a pattern of inflexible fear memories that are less sensitive to context and changing environmental circumstances. Such a pattern would be highly consistent with the symptoms of PTSD and may have implications for current therapeutic approaches that rely on neural plasticity for symptom improvement, such as prolonged exposure therapy. Future studies that specifically measure effects of *ADCYAP1R1* genotype on neural plasticity are needed.

Several limitations of the current study must be acknowledged. Because the *ADCYAP1R1* SNP, rs2267735, is located within a putative estrogen response element, PACAP may influence neural structure and function in an estrogen-dependent manner. Here we did not measure estrogen levels or estrous cycling. Future studies should investigate how the *ADCYAP1R1* polymorphism, may influence both the symptoms of PTSD and may have important implications for future research should also address the role of PACAP function in a nontraumatized sample and possible contributions to sex differences in healthy responses to threat stimuli (54). In addition, the current study does not allow us to determine whether enhanced amygdala and hippocampal responses are specific to threat stimuli or may be observed across a variety of emotionally arousing stimuli. In PTSD, enhanced reactivity to emotional stimuli appears to be specific to threatening stimuli (32). However, the *ADCYAP1R1* risk polymorphism may increase emotional reactivity more broadly. Future research is needed to determine whether the genotype effects are specific to threat stimuli. Finally, the current study cannot disentangle whether the results represent direct effects of the polymorphism on expression of the PACAP receptor or whether they are linked to differential gene methylation or differential interaction with estrogen because these have been previously associated with PTSD in a similar cohort (5).

Conclusions

The current study demonstrated that a polymorphism in the PACAP receptor gene *ADCYAP1R1* influences neural responses to threat stimuli. The risk polymorphism, previously shown to predict PTSD in women, was associated with exaggerated amygdala
and hippocampal reactivity. This study highlights the utility of neuroimaging methods in characterizing intermediate phenotypes for PTSD and other complex psychiatric disorders. Polymorphisms in the PACAP receptor gene and amygdala and hippocampal phenotypes provide biomarkers that indicate individuals who may be more or less resilient to pathological stress symptoms following trauma and indicate a neurobiological pathway that may contribute to the greater prevalence of PTSD in women than men. Findings may also point to potential new treatment avenues, through enhancing the function of PACAP receptor-mediated pathways.

Materials and Methods
Participants. Forty-nine African-American women ages 18–62 were recruited through an ongoing study of risk factors for PTSD. MRI data from a subset of this sample have been reported elsewhere in a study of fMRI networks associated with PTSD (30). Because ADCYAP1R1 has been linked to PTSD in women and not men (5, 7), the current investigation examined only women. Individuals who reported African-American race/ethnicity were recruited, to reduce effects of genetic admixture. Participants were approached in the general medical clinics of a large publicly funded hospital that serves economically disadvantaged individuals. High rates of childhood and adult trauma have previously been reported within this patient population (55, 56). Individuals reporting neurological disorder, current psychotropic medication, a history of bipolar disorder, schizophrenia or any current psychoses, or metal clips or implants were excluded. Participants had normal or corrected-to-normal vision. Urine tests for pregnancy and illegal drug use (cocaine and marijuana) were negative. Participants conducted 24 h before the MRI scan, and individuals who showed positive results were excluded. Participants received monetary compensation for their time. All participants provided written informed consent before participating. The institutional review board of Emory University approved the study procedures, and testing took place at Grady Memorial Hospital and the Biomedical Imaging Technology Center at Emory University Hospital.

Psychological Assessment. The Modified PTSD Symptom Scale (PSS) (57) was used to assess PTSD symptoms, and the Traumatic Events Inventory (TEI) was used to assess types and severity of trauma experience. Childhood trauma was assessed using the Childhood Trauma Questionnaire (CTQ) (58, 59). Anxiety levels were assessed using the State Trait Anxiety Inventory (STAI) (60) and depression symptoms were indexed using the Beck Depression Inventory (BDI) (61). These measures have been used in our previous studies with this population (5, 34). Trauma was assessed using the TEI and CTQ during recruitment, and the additional psychological measures were administered during a laboratory visit 1 d before the MRI scan. All participants had experienced at least one trauma.

Genotyping and Analysis. Saliva was collected in Oragene tubes (DNA Genotek Inc.). A 500-μL aliquot was used for extraction using the DNeasy blood and tissue kit (Beckman Coulter Genomics). The resulting salivary DNA was quantified using a NanoDrop (NanoDrop2000) (Thermo Fisher Scientific Inc.) and then normalized to 10 ng/μL. A total amount of 15 ng of DNA per reaction was transferred to the genotyping plates and then dried down before the reactions. Reactions were performed on the Taqman Viia7 Real-Time PCR system using Taqman SNP Genotyping Assay Mix with Taqman GxPreme Master Mix (Life Technologies Inc.) and on the Sequenom SNP genotyping platform using iPlex gold reagents and the MassARRAY system (Sequenom Inc.). The ADCYAP1R1 variant rs2267735 was typed Hardy-Weinberg Equilibrium with a P value of 0.90. The call rates on both platforms were greater than 95%. Quality control measures, including within plate duplicates and nontemplate controls, were used. In addition, 25% of the samples were duplicated on both platforms. There were no discordant calls.

Following the group comparison strategy in ref. 5, participants were categorized into two groups on the basis of genotype: individuals with two copies of the C allele, previously associated with risk for PTSD, were assigned to the risk group (CC), whereas individuals with one or zero copies of the C allele (GC/GG) were assigned to the nonrisk group. To verify genotype effects, a secondary analysis was conducted using an additive model (the number of risk alleles: zero, one, or two C-alleles).

fMRI Threat-Processing Task. The task involved passive viewing of fearful and neutral face stimuli. This task has been shown to engage threat-processing networks in previous studies (32, 33, 62), and the specific procedures are described elsewhere (30). Fearful and neutral face stimuli (63) were presented in a block design. Trials included a face stimulus presented for 500 ms, followed by a 500-ms presentation of a fixation cross. Participants were instructed to pay attention to the faces and did not make any behavioral response, to minimize motion artifacts and neural activity unrelated to processing the visual stimulus.

Brain Imaging Acquisition and Analysis. Brain imaging data were acquired on a Siemens 3.0 Tesla Magnetom Trio (Siemens) using a 12-channel head coil. Functional images were acquired using the 16-channel pulse sequence (64) to maximize signal-to-noise ratio for functional images. Functional data and images were analyzed on Matlab (MathWorks Inc.) using statistical parametric mapping software (SPM8) (9). Whole-brain analyses were conducted for all participants. To identify regions with increased reactivity in PTSD (30, 52), the ROI included BA 24, 25, and 32, restricted to anterior cingulate and medial prefrontal cortex regions that are active with fearful relative to neutral face stimuli, such that results indicated increases in reactivity in PTSD relative to controls.

ROI analyses revealed a cluster-forming threshold of 0.01 was used to control for multiple comparisons. To address the a priori prediction that the ADCYAP1R1 polymorphism would influence amygdala and hippocampal activation, we conducted ROI analyses, with bilateral masks defined anatomically using the SPM Anatomy Toolbox (66). Exploratory whole-brain analyses were also conducted to examine the effect of ADCYAP1R1 genotype across a broader range of regions involved in processing emotional or social stimuli.
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