The pituitary adenylate cyclase-activating polypeptide system as a sex-specific modulator of hippocampal response to threat stimuli

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ABSTRACT

Background: Pituitary adenylate cyclase-activating polypeptide (PACAP) receptor gene polymorphism has been postulated as a potential sex-specific diagnostic biomarker of trauma-related disorders. However, no research to date has evaluated whether the PACAPergic system may act as a vulnerability/resilience neuromechanism to trauma-induced psychopathology in healthy participants without heightened risk to experience traumatic events.
Methods: Here, we compared the amygdala and hippocampus response to fearful faces in participants with at-risk genotype versus non-risk participants from the Human Connectome Project (n = 991; 53.4% female).
Results: Increased hippocampal response to fearful faces in the female risk group emerged in sex by genetic risk interaction.
Conclusions: Our findings revealed the first sex-specific neurogenetic vulnerability factor to trauma-related disorders, and emphasize the importance of prevention-based strategies to ameliorate neuropsychiatric pathophysiology.

1. Introduction

Since it was first isolated from ovine hypothalamic extract over 30 years ago (Miyata et al., 1989), pituitary adenylate cyclase-activating polypeptide (PACAP) has emerged as a relevant neuromodulator and neurotrophic mediator (Sherwood et al., 2000) involved in fear and stress-regulating systems (Mustafa, 2013; Hammack and May 2015). The PACAPergic system acts as a main modulator of the hypothalamic-pituitary-adrenal (HPA) axis and, consequently, primarily stimulates corticotropin-releasing hormone (CRH) and corticosterone release (Lezak et al., 2014). However, besides its role as a master regulator of stress-related adaptive pathways, recent studies have suggested that exposure to chronic stress increases PACAP expression (Hu

et al., 2020), whereas PACAP deletion protects against the depressive effects of chronic stress (Lehmann et al., 2013). These findings therefore appear to suggest that PACAP is also likely to take part in shaping the characteristic maladaptive neuroplasticity that follows chronic stress exposure (Lutfy and Shankar, 2019), and places the PACAPergic system as a promising biomarker of trauma-related psychopathology.

From the three PACAP cognate receptors identified within this system, only PACAP receptor type 1 (PAC1R) has shown a high affinity for both PACAP27 and PACAP38, the most widely distributed PACAPs in the central nervous system (Shivers et al., 1991). Interestingly, a single nucleotide polymorphism (SNP) in the gene coding for PAC1R (ADCYAP1R1; rs2267735) has been consistently related to post-traumatic stress disorder (PTSD) diagnosis and symptomatology in

females exposed to trauma, but not in trauma-exposed males (Ressler et al., 2011; Wang et al., 2013; Almli et al., 2013). This polymorphism-by-sex interaction is thought to be explained by its specific location in mediating estrogen response. This interaction has recently been corroborated in a metanalysis featuring 9630 participants (Lind et al., 2017). In addition, PAC1R polymorphisms have also been identified as a potential transdiagnostic biomarker of anxiety (Ross et al., 2020) and depressive symptoms (Lowe et al., 2015) in females exposed to chronic stress. Specifically, these studies found that females carrying the risk genotype (CC) had worse somatic anxiety, insomnia, and depression symptoms.

This growing body of evidence correlating the ADCYAP1R1 polymorphism to dysfunctional response after exposure to stress and trauma in psychopathological samples raises questions on whether the effect of this specific risk genotype can be observed in healthy endophenotypes. Recent research in healthy females exposed to trauma suggests that CC alleles (i.e., the risk genotype) are associated with increased fear-potentiated startle responses (Jovanovic et al., 2020) and that this heightened response to threat stimuli coincides with greater activation in the amygdala and the hippocampus (Stevens et al., 2014). In addition, there is evidence suggesting that PAC1R polymorphisms appear to modulate hippocampus engagement during the acquisition of contextual fear conditioning in healthy participants with heightened risk to experience traumatic events (Pohlack et al., 2015). Interestingly, the impact of PAC1R SNP over neurocognitive hippocampal functions such as associative learning has been further supported by pre-clinical research in knockout mice (Hashimoto et al., 2002; Matsuyama et al., 2003; Yang et al., 2010). In this sense, past research suggests that PAC1R polymorphisms may be an important factor in vulnerability and etiopathology models of PTSD (Lambert and McLaughlin, 2019; Brewin, 2014) as a result of a hippocampal-dependent mnemonic modulation.

The amygdala and hippocampus feature high concentrations of PAC1 receptors (Vaudry et al., 2009) and, interestingly, hyperreactivity in these brain regions has been consistently related to PTSD pathophysiology (Lee et al., 2021; Steward et al., 2020). However, no study to date has explored the neuroimaging and hippocampal-dependent neuropsychological endophenotypes of the ADCYAP1R1 polymorphism in healthy samples from the general population (i.e., without heightened risk to experience traumatic events). Exploring the role of ADCYAP1R1 polymorphism in healthy controls could reveal the neurobiological contributors of vulnerability/resilience to trauma-induced psychopathology and extend the field's models of how genetic vulnerability and neurobiology interact to lead to the onset of trauma and stress-related disorders.

Over the past decade, consortia-driven large-scale studies have provided multimodal neuroimaging, neuropsychological and genetic data acquired from healthy populations to characterize individual differences within a comprehensive range of human behavior. Among the most prominent efforts, the Human Connectome Project (HCP) by the WU-Minn consortium (Glasser et al., 2016) includes the responses of nearly 1000 healthy young adults to an emotional processing paradigm (Hariri et al., 2002) along with extensive genotyping (dbGaP, 2021) comprising ADCYAP1R1 SNP (rs2267735) and a comprehensive hippocampal-dependent neuropsychological evaluation. In this study, we evaluated HCP data to explore whether ADCYAP1R1 SNP mediates a significant effect in healthy adults' response to threatening and mnemonic stimuli. In line with previous results in PTSD and traumatized populations (Ressler et al., 2011; Stevens et al., 2014; Lambert and McLaughlin, 2019; Brewin, 2014), we hypothesize that PAC1R SNP will impact amygdala and hippocampus activation alongside neuropsychological hippocampal-dependent measures accounting for different neurocognitive subdomains of memory in females but not males.

2. Methods and materials

Human Connectome Project (HCP) is a consortium effort for the

mapping of brain function that provides multimodal neuroimaging and behavioral data for biomedical research, including comprehensive genotyping of SNP available through the database of Genotypes and Phenotypes (dbGaP).

2.1. Participants

From an initial pool of 1206 healthy young adults, 1044 had completed an emotional matching functional magnetic resonance imaging (fMRI) paradigm and 991 of those had available information regarding the ADCYAP1R1 SNP (age range = 22–35 years; age mean = 28.74; SD = ±3.69). The sex distribution was roughly balanced, with 462 males (46.6%) and 529 females (53.4%), while self-reported racial identity was predominantly White (76%; 11% Hispanic/Latino), followed by Black/African American (14%) and Asian/Hawaiian (5%). Regarding socioeconomical status, the household income of our participants was centered around the USA national average (Federal Reserve Bank of St.Louis, 2022). The genomic distribution of the ADCYAP1R1 genotype followed the expected pattern (Phan et al., 2020), with a quarter of the sample (24.9%) expressing the risk alleles CC. The risk genotype was defined following a dominant/recessive model (CC vs. CG/GG) in order to maximize comparability with prior research. Nevertheless, recent metanalytic findings suggested that no significant differences should be expected in the estimated effect sizes of the models (Lind et al., 2017).

2.2. Neuroimaging analyses

To evaluate reactivity to fearful stimuli, we selected task-based fMRI data derived from an adaptation of a well-validated emotion processing paradigm (Hariri task (Hariri et al., 2002; WU - Minn Consortium Human Connectome Project, 2017)). Briefly, the participants were asked to signal via a controller which of two stimuli (left/right) matched a third stimulus presented at the top of the screen, alternating between blocks of trials with either angry/fearful face expressions or neutral shapes. Measures of accuracy (percent correct match) and mean reaction time (milliseconds) were collected.

Pre-processed fMRI images were obtained (please see Glasser et al., 2013 for a detailed explanation of the specific preprocessing steps) from the S1200 open access release of the HCP Young Adult study (WU - Minn Consortium Human Connectome Project, 2017; Glasser et al., 2013). Using Statistical Parametric Mapping (SPM12) software (Penny et al., 2006), pre-processed fMRI images were additionally smoothed with an 8-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel to increase signal-to-noise ratio. First-level contrast images were calculated for each participant. Specifically, emotional reactivity was assessed by contrasting fearful faces trials to neutral stimulus trials. Motion parameters previously estimated from a rigid-body transformation to the first image acquired (original and temporal derivatives) were also added as regressors to correct for movement during the scanning. In addition, the Blood Oxygenation Level Dependent (BOLD) signal was convolved with the SPM12 canonical hemodynamic response function, and a 128-s high-pass filter was used to remove low-frequency drifts.

First-level contrast images for each participant were included in second-level (group) analyses. We initially estimated one two-sample *t*-test model per each sex in order to compare responses to emotional stimuli between risk versus non-risk ADCYAP1R1 genetic groups (i.e., CC as the at-risk group and CG/GG as a non-risk group) in each sex. Specifically, region of interest (ROI) analyses were performed using two bilateral anatomical masks from our *a priori* regions of interest, the amygdala and the hippocampus, as defined by the WFU_Pickatlas toolbox (Maldjian et al., 2003). From these analyses, we created one additional functional mask (combining significant results from both sex groups), within which we investigated a hypothetical genotype-by-sex interaction using a full factorial design. Voxels surviving a family-wise error (FWE) small-volume corrected significance threshold of $p < 0.05$

were deemed significant after Bonferroni correction for multiple comparisons (i.e., number of masks).

2.3. Behavioral analyses

We assessed in-scanner task performance data regarding accuracy (percent of correct matching of stimuli) and reaction times (milliseconds) during both conditions of the emotional processing task (faces and shapes), as well as measures of the differential task performance (faces-shapes). Additionally, we also evaluated the neuropsychological hippocampal-dependent measures available in the HCP dataset accounting for different subdomains of memory: verbal episodic memory (Penn Word Memory Test (Moore et al., 2015)), non-verbal episodic memory (Picture Sequence Memory (Dikmen et al., 2014)), and working memory (List Sorting (Tulsky et al., 2014)).

R software (R Core Team R Foundation for Statistical Computing, 2021) was employed to perform two-sample t-tests in order to compare task performance and neuropsychological scores between ADCYAP1R1 genotypes in females and males. Cohen's d was computed to measure the effect size of our results. Moreover, linear regression models were built to test genotype-by-sex interactions.

3. Results

Participants were clustered according to their genotype (i.e., CC as the at-risk group and CG/GG as a non-risk group) and sex, resulting in 139 females in the at-risk group, 390 females in the non-risk group, 108 males in the at-risk group, and 354 males in the non-risk group.

3.1. Neuroimaging results

3.1.1. fMRI responses to fearful stimuli

All analyses were performed using the fearful > neutral stimuli contrast, which showed a robust engagement of the fusiform gyrus, the inferior occipital lobe, the amygdala, and the hippocampus in the whole sample (Fig. 1). Specifically, the female risk group showed significantly higher activation, compared to the female non-risk group, in the hippocampus (pFWE = 0.001; t = 4.51; x, y, z = 34, −14, −20), but not in the amygdala (Fig. 2). In addition, an exploratory analysis of the male sample found a lower activation within the amygdala in the risk group in comparison with the non-risk group (pFWE = 0.044; t = 3.13; x, y, z = 20, 0, −12) (Fig. 3). However, this finding did not survive Bonferroni correction for multiple comparisons (i.e., two regions of interest: hip-
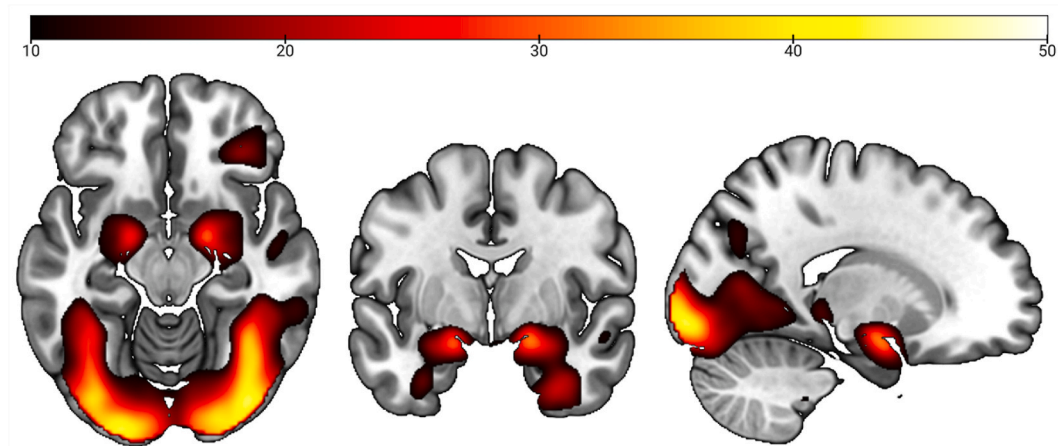

Fig. 1. Entire sample brain activation to the fearful faces > shapes contrast. Pattern showing increased activation within the fusiform gyrus, the inferior occipital lobe, the amygdala and the hippocampus. The left hemisphere is depicted on the left. Color bar represent t values. For visualization purposes, the activation map was thresholded at t > 10. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
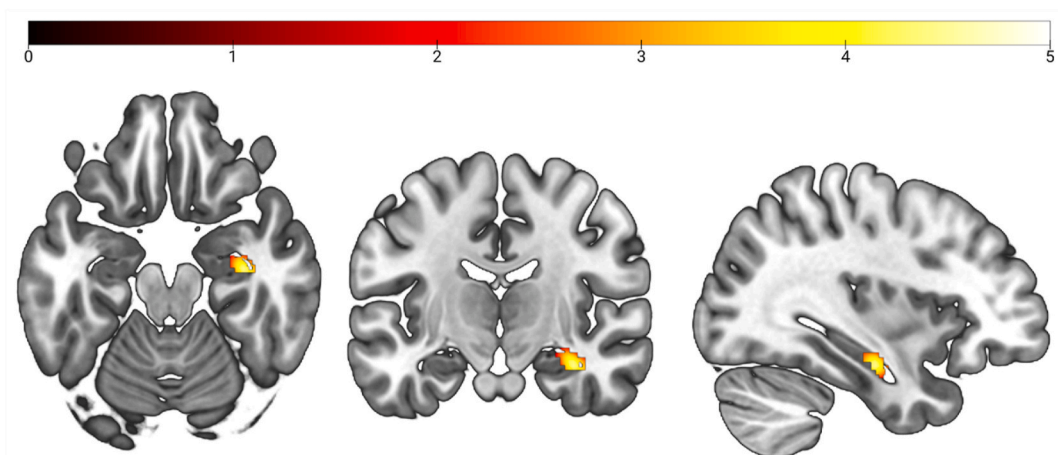

Fig. 2. Increased hippocampal activation to fearful stimuli contrasted to shapes in healthy females with the risk genotype (CC) in comparison with healthy females without the risk genotype (CG/GG). The left hemisphere is depicted on the left. Color bar represents t values. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fig. 3. Decreased amygdala activation to fearful stimuli contrasted to shapes in healthy males with the risk genotype (CC) in comparison with healthy males without the risk genotype (CG/GG). Exploratory result (p = 0.044) that did not survive Bonferroni correction. The left hemisphere is depicted on the left. Color bar represents t values. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
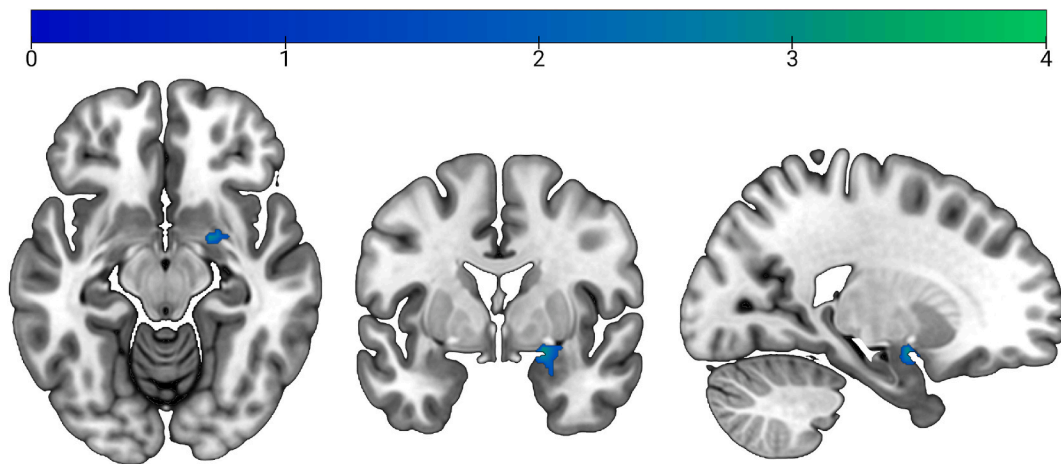
Table 1
In-scanner task performance findings during Hariri task.

Measure	Condition	Risk vs. non-risk (female)	Risk vs. non-risk (male)	Genotype-by-risk
Accuracy-percentage: Mean (SD)	*Faces*	98.44 (±2.64) vs. 98.52 (±3.55) p = 0.780	98.76 (±4.39) vs. 98.21 (±2.01) p = 0.068	p = 0.239
	Shapes	96.70 (±4.34) vs. 97.20 (±4.34) p = 0.231	96.32 (±4.52) vs. 96.13 (±5.19) p = 0.712	p = 0.303
	Faces-Shapes	1.73 (±4.24) vs. 1.31 (±3.96) p = 0.303	2.44 (±4.88) vs. 2.07 (±4.16) p = 0.484	p = 0.921
Reaction time-milliseconds: Mean (SD)	*Faces*	805.85 (±146.79) vs. 805.41 (±130.15) p = 0.975	747.76 (±122.17) vs. 775.41 (±127.41) p = 0.042*; t = 2.038; d = 0.219	p = 0.146
	Shapes	789.12 (±120.35) vs. 784.56 (±114.70) p = 0.698	742.14 (±107.01) vs. 750.40 (±110.69) p = 0.487	p = 0.444
	Faces-Shapes	16.72 (±78.86) vs. 20.84 (±85.65) p = 0.605	5.61 (±69.75) vs. 25 (±83.62) **p = 0.016**; t = 2.409; d = 0.240**	p = 0.210

SD, standard deviation.
*p < 0.05 uncorrected.
**p < 0.05 corrected for multiple comparisons (Bonferroni correction).

pocampus and amygdala). A positive polymorphism-by-sex interaction was found within the hippocampus (pFWE = 0.006; t = 3.65; x, y, z = 36, −14, −22) when using a factorial design that included all participants.

3.1.2. Emotion processing task performance

While there were no significant differences in either accuracy or reaction time measures between the female risk and non-risk groups, the mean reaction time for faces stimuli was slightly faster in the male risk group compared to the male non-risk group (t = 2.038; p = 0.042; d = 0.219). The male risk group showed a significantly lower reaction time

difference between faces and shapes trials in comparison to the male non-risk group (t = 2.409; p = 0.016; d = 0.240). These findings did not survive Bonferroni correction for multiple comparisons. The polymorphism-by-sex interaction was not statistically significant for any of the task performance measures (Table 1).

3.2. Hippocampal-dependent neuropsychological results

In the female sample, the risk group showed higher scores on the Penn Word Memory Test in comparison to the non-risk group (t = 1.973, p = 0.049, d = 0.185). However, this finding did not survive Bonferroni

Table 2
Neuropsychological hippocampal-dependent findings.

Measure	Risk vs. non-risk (female)	Risk vs. non-risk (male)	Genotype-by-risk
Penn Word Memory Test: Mean (SD)	36.34 (±2.65) vs. 35.81 (±2.96) p = 0.049*; t = 1.973; d = 0.185	35.2 (±3.09) vs. 35.3 (±2.90) p = 0.923	p = 0.188
Picture Sequence Memory Test: Mean (SD)	106.8 (±17.03) vs. 107.7 (±15.21) p = 0.547	102.4 (±17.52) vs. 102.3 (±16.88) p = 0.953	p = 0.649
List Sorting Working Memory Test: Mean (SD)	101.4 (±14) vs. 102.8 (±13.27) p = 0.284	103.2 (±13.20) vs. 104.4 (±12.88) p = 0.418	p = 0.880

SD, standard deviation.
*p < 0.05 uncorrected, none of the findings were significant after Bonferroni correction.

correction for multiple comparisons (Table 2). The same comparison did not reach an uncorrected significance in the male sample. The polymorphism-by-sex interaction was not significant either. In addition, the other neuropsychological hippocampal-dependent measures (the Picture Sequence Memory Test and List Sorting Working Memory Test) were not statistically different between risk vs. non-risk groups, in neither females nor males.

4. Discussion

In this study, we aimed to evaluate the neurofunctional endophenotypes of the ADCYAP1R1 polymorphism in healthy participants. Specifically, we assessed hippocampal and amygdala response to fearful stimuli, which had been previously identified as potential neurogenetic biomarkers in patients with PTSD and trauma-exposed populations (Lee et al., 2021). In sum, we found a significant interaction of sex by genetic risk on hippocampus reactivity to fearful stimuli, revealing increased hippocampal activity to threatening stimuli in healthy females with a genetic risk profile. These findings are in agreement with previous reports (Stevens et al., 2014) and support the hypothesis that the ADCYAP1R1 risk genotype may impact subcortical responses to fearful stimuli in females. Importantly, our results highlight that the effects of ADCYAP1R1 polymorphism on stress circuitry functioning in females may be present prior to trauma exposure. This finding adds value to current knowledge about the PAC1R SNP and reinforces its role as a potential sex-specific vulnerability endophenotype to trauma-related disorders.

Although traditional conceptualizations of trauma-related disorders emphasize structural hippocampus alterations (i.e., decreased hippocampal volume (Wingenfeld and Wolf, 2014)) as a consequence of the neurotoxicity induced by the glucocorticoid cascade resulting from stress exposure (Sapolsky et al., 1986), more recent studies report that these hippocampal abnormalities are found both in trauma-exposed PTSD patients and their non-exposed healthy twins (Gilbertson et al., 2002; Pitman et al., 2006). Interestingly, these findings suggest that hippocampal reactivity may predate psychopathology (Morey et al., 2020). In this sense, and as highlighted in our findings, the focus placed on the hippocampal neural response within trauma-related pathology is shifting from being considered as a consequence of allostatic load towards its role as an endophenotype of vulnerability. In addition, recent pre-clinical results do not fully support the glucocorticoid cascade hypothesis as a causal factor of the hippocampal atrophy and dysfunction in PTSD (Kim et al., 2015; Szeszko et al., 2018). Although these molecular hypotheses are beyond the scope of this study, our findings support current evidence endorsing this system as a relevant actor in the susceptibility to develop maladaptive stress responses (Lutfy and Shankar, 2019). Indeed, rs2267735 polymorphism has been found to modulate a wide variety of psychological processes involved in trauma-related disorders such as fear conditioning discrimination (Ressler et al., 2011), contextual fear acquisition (Pohlack et al., 2015), and dark-enhanced and fear-potentiated startle responses (Jovanovic et al., 2020). Likewise, patients with PTSD consistently present diminished fear extinction learning and an over-expression of fear when facing conditioned stimuli (Seligowski et al., 2019; Norrholm and Jovanovic, 2018).

Furthermore, the abnormal hippocampal reactivity to fearful stimuli identified in this study is consistent with the excessive subcortical neural responses observed in patients with PTSD (Kunimatsu et al., 2020). In addition to its central role in contextual fear acquisition and extinction (Lacagnina et al., 2019) and susceptibility to acute and chronic stress (Kim et al., 2015), hippocampal reactivity has also been closely related to episodic memory performance (Moscovitch et al., 2016) alterations which, in turn, have been suggested as a vulnerability factor for PTSD (Lambert and McLaughlin, 2019). Females with the risk genotype showed a better performance in a verbal episodic memory task (non-significant after Bonferroni correction). This exploratory result

dovetails with the rs2267735 polymorphism modulation of the hippocampus observed in our main findings accounting the critical involvement of the hippocampus in episodic memory (Moscovitch et al., 2016). However, the directionality of this result does not align with prevalent PTSD models suggesting that alterations in associative learning before trauma constitute an essential vulnerability factor (Lambert and McLaughlin, 2019). Instead, this exploratory result would lean more towards other models suggesting phenomena such as over-consolidation act as predictors of trauma-related disorders (Kida, 2019; Colucci et al., 2020). In this sense, although the involvement of the hippocampus in the pathophysiology of PTSD has been repeatedly postulated in different models and has been supported by extensive evidence (Wingenfeld and Wolf, 2014; Harnett et al., 2020), further research is warranted to ascertain the specific role of premorbid differences in episodic memory as risk factors of PTSD.

Last, since our findings were not paired with hyperactivation of the amygdala, as observed in healthy females exposed to trauma (Stevens et al., 2014), our research favors the hippocampus as the key structure being modulated by ADCYAP1R1 polymorphism prior to trauma, while the amygdala hyperreactivity may be a result of the trauma exposure itself. These findings are also in agreement with previous studies evaluating the modulation that the PACAP system exerts over the hippocampus and the amygdala functioning (Johnson et al., 2020). Specifically, Schmidt et al. (2015) reported that an infusion of PACAP into the hippocampus enhances the retention of contextual fear memories (Schmidt et al., 2015) and Otto et al. (2001) found that PAC1R knockout mice show specific deficits in the same task while amygdala-dependent cued fear remain preserved (Otto et al., 2001). Notwithstanding, our analyses also revealed that lower amygdala reactivity may be displayed in conjunction with a lower reaction time difference in males with the risk alleles. These exploratory findings appear to suggest that, although ADCYAP1R1 polymorphism showed a mild impact over reactivity to threat stimuli in males, it may be still playing a relevant role as a potential protective factor.

Altogether, our research suggests that the PAC1 receptor polymorphism, rs2267735, is closely related to hippocampal hyperreactivity to threatening stimuli in healthy females, an endophenotype that, based on previous research involving PACAP to PTSD, could constitute a sex-specific mechanism of vulnerability to trauma-related disorders. Most importantly, as the first sex-based biomarker of risk for the development of trauma-related disorders in a healthy population, our findings both provide significant insights into the aetiology of sex differences in mental disorders (Christiansen and Berke, 2020) and push towards an increasingly personalized psychiatry that is capable of delivering sex-specific treatments (Riecher-Rössler, 2017).

4.1. Limitations

Further research is needed to evaluate the test-retest reliability of our task functional MRI measures. Likewise, other tasks may be needed to fully grasp the effect of ADCYAP1R1 polymorphism in fear processing before the trauma. Human Connectome Project data did not comprehensively characterize prior history of trauma in their sample; therefore, caution is required when concluding our findings as risk or vulnerability biomarkers. Nevertheless, we have no reason to expect higher trauma exposure rates than in the general population of young adults in this sample. In addition, clinical variables regarding psychological trauma, such as child maltreatment or history of sexual abuse, would enable the assessment of a gene-by-environment interaction within the general population, though the collection and sharing of such sensitive data pose a challenge for current open access methods. It is also worth noting that, while being one of the genes most prominently associated with PTSD, ADCYAP1R1 SNP has not yet survived GWAS level of statistical significance (Sharma and Ressler, 2019). Finally, as with other research evaluating vulnerability to trauma, the hypotheses made in this publication would be better addressed by longitudinal studies capable of

disentangling vulnerability factors and neural consequences of trauma and PTSD.

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Data and materials availability

Data were provided by the Human Connectome Project as part of the Young Adult release. Genetic data is available in the dbGaP: accession number phs001364.v1.p1 after approval of a legitimate research interest request.

CRediT authorship contribution statement

Daniel Porta-Casteràs: Investigation, Visualization, Writing – original draft. **Marta Cano:** Methodology, Investigation, Project administration, Supervision, Writing – review & editing. **Trevor Steward:** Methodology, Project administration, Writing – review & editing. **Raül Andero:** Conceptualization, Methodology, Funding acquisition, Project administration, Writing – review & editing. **Narcís Cardoner:** Conceptualization, Methodology, Funding acquisition, Project administration, Writing – review & editing.

Declaration of competing interest

Authors declare that they have no competing interests.

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