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Hypothalamic-pituitary-adrenal axis genetic variation and early stress moderates amygdala function

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ABSTRACT

Early life stress may precipitate psychopathology, at least in part, by influencing amygdala function. Converging evidence across species suggests that links between childhood stress and amygdala function may be dependent upon hypothalamic-pituitary-adrenal (HPA) axis function. Using data from college-attending non-Hispanic European-Americans (n = 308) who completed the Duke Neurogenetics Study, we examined whether early life stress (ELS) and HPA axis genetic variation interact to predict threat-related amygdala function as well as psychopathology symptoms. A biologically-informed multilocus profile score (BIMPS) captured HPA axis genetic variation (*FKBP5* rs1360780, *CRHR1* rs110402; *NR3C2* rs5522/rs4635799) previously associated with its function (higher BIMPS are reflective of higher HPA axis activity). BOLD fMRI data were acquired while participants completed an emotional face matching task. ELS and depression and anxiety symptoms were measured using the childhood trauma questionnaire and the mood and anxiety symptom questionnaire, respectively. The interaction between HPA axis BIMPS and ELS was associated with right amygdala reactivity to threat-related stimuli, after accounting for multiple testing (empirical-p = 0.016). Among individuals with higher BIMPS (i.e., the upper 21.4%), ELS was positively coupled with threat-related amygdala reactivity, which was absent among those with average or low BIMPS. Further, higher BIMPS were associated with greater self-reported anxious arousal, though there was no evidence that amygdala function mediated this relationship. Polygenic variation linked to HPA axis function may moderate the effects of early life stress on threat-related amygdala function and confer risk for anxiety symptomatology. However, what, if any, neural mechanisms may mediate the relationship between HPA axis BIMPS and anxiety symptomatology remains unclear.

1. Introduction

It is undeniable that exposure to early life stress (ELS) predicts various forms of psychopathology (Green et al., 2010). However, the biological correlates contributing to this association are unclear. Research across species shows that ELS may, in part, promote psychopathology by influencing amygdala function (Lupien et al., 2009). The amygdala is critical for establishing the emotional significance of stimuli and enacting changes in physiological arousal and behavioral vigilance in response to provocation (Davis and Whalen, 2001). Nearly every form of psychopathology has been linked to abnormal amygdala function; most consistently, increased amygdala reactivity to threat has been found in stress-related disorders (Hariri, 2015; Shackman et al., 2016). ELS also predicts increased threat-related amygdala reactivity and amygdala-dependent behaviors (e.g., startle response, emotional memory, attentional bias toward threat; (Lupien et al., 2009; Tottenham and Sheridan, 2009)), suggesting that ELS-related differences in amygdala reactivity and related behavior are a promising mechanism through which ELS increases psychopathology risk.

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Table 1
Selected HPA Axis Polymorphisms, Associations with HPA Axis Function and Psychopathology, and Coding Scheme for HPA Axis Biologically-Informed Multilocus Profile Scores (BIMPS).

ne	SNP	Associations	Genotype (N)	Score
CRHR1	rs110402	**G allele**: increased cortisol response to the DEX/CRH test in severely maltreated individuals (Tyrka et al., 2009), especially in men (Heim et al., 2009), greater peak cortisol response to a psychosocial stress test and significant association of genotype x trait anxiety interaction with higher baseline cortisol levels (Mahon et al., 2013).	AA (73) AG (173) GG (78)	0- Low 1- Med 2- High
NR3C2	rs4635799/rs5522	**TC and CT haplotypes**: lower mineralocorticoid promoter activity and increased salivary and plasma cortisol, plasma ACTH, and heart rate in response to a psychosocial stress test (van Leeuwen et al., 2011; van Leeuwen et al., 2010); TT and TC were associated with nominally lowered AUC cortisol compared to CT (Klok et al., 2011b).	TT/TT (63) TC/TT (36) TT/CT (115) TC/TC (3) TC/CT (27) CT/CT (64)	0- Low 1- Med 1- Med 2- High 2- High 2- High
FKBP5	rs1360780	**T allele**: increased *FKBP5* expression leading to impaired negative feedback in the system due to decreased GR-cortisol sensitivity (Binder, 2009; Binder et al., 2004); lower AUC cortisol levels (Velders et al., 2011); impaired CORT recovery in response to a psychosocial stress test (Ising et al., 2008); significant interaction with ELS predicted decreases in methylation, thereby increasing FKBP5 responsiveness to activation (Klengel et al., 2013).	CC (165) CT (133) TT (27)	0- Low 1- Med 2- High

Stress- and psychopathology-related differences in amygdala function may be partially driven by associated hypothalamic-pituitary-adrenal (HPA) axis dysfunction (de Kloet et al., 2005). Indeed, amygdala reactivity is positively correlated with endogenous cortisol and pharmacologic agonism of the HPA axis potentiates amygdala reactivity in mouse and man (Bogdan et al., 2016). Collectively, these data suggest that variability in amygdala function may be related to ELS exposure, with independent converging lines of evidence suggesting that HPA axis function, which is highly heritable, (Federenko et al., 2004) temporally stable (Marquez et al., 2005), and disrupted by early life stress exposure (Essex et al., 2011) may be a key factor underlying this relationship. Lastly, multiple genetic association studies have identified polymorphisms coding for HPA axis-related proteins that are associated with functional consequences in the HPA axis (Table 1; Supplementary Material; (Derijk et al., 2008)) and predict stress-related psychopathology (Heim and Binder, 2012), as well as differences in amygdala function (Bogdan et al., 2016). These findings suggest that vulnerability to the effects of ELS may depend on genetically-conferred differences in HPA axis function.

Using data from the Duke Neurogenetics Study (DNS), which assesses a wide range of behavioral, experiential, and biological phenotypes among young adult college students, the present study examined whether a biologically informed multilocus profile score (BIMPS) reflecting functionally-relevant genetic variation in the HPA axis (Table 1) predicts amygdala function as well as psychopathology symptoms in the context of ELS. Our BIMPS approach aggregates genetic influence within the HPA axis that has previously been associated with HPA axis function, which may be more consistent with the resolution at which BOLD fMRI and behavioral genetics research is conducted than single SNP analyses. Such polygenic approaches are expected to provide more power by including polymorphisms of small effect that may only collectively significantly contribute to variance. Indeed, prior BIMPS approaches suggest that such profiles can significantly predict variability in neural and psychiatric phenotypes when individual polymorphisms do not (Nikolova et al., 2011; Pearson-Fuhrhop et al., 2014; Stice et al., 2012). Further, by using a biologically-informed approach with *a priori* rationale for including functional variants in the multilocus profile, as opposed to summary statistics reflecting relationships to a particular disorder, our results are more directly interpretable alongside other HPA axis-related research (Bogdan et al., 2016; Nikolova et al., 2011). Consistent with prior work evaluating single polymorphisms (White et al., 2012), we predicted that genetic variation associated with increased HPA axis activity would predict elevated threat-related amygdala reactivity and anxiety and mood symptomatology among those exposed to relatively elevated ELS.

2. Methods and materials

2.1. Participants

Non-Hispanic European/European-American participants (n = 325) of the Duke Neurogenetics Study (DNS) with fMRI and genetic data that were processed by January 2014 were available for analyses. Participants provided written informed consent to a study protocol approved by the Duke University institutional review board and were in general good health and free of DNS exclusions, including: 1) medical diagnosis of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease, or lifetime psychotic symptoms; 2) use of psychotropic, glucocorticoid, or hypolipidemic medication; 3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension); and 4) contraindications to MRI scanning. DSM-IV psychiatric disorders were assessed with the lifetime electronic Mini International Neuropsychiatric Interview (Sheehan et al., 1998) and Structured Clinical Interview for the DSM-IV Axis II (SCID-II (First et al., 1997). DSM-IV diagnosis was not exclusionary as the DNS seeks to establish broad variability in multiple psychiatrically-relevant behavioral phenotypes. Following quality control procedures (Supplementary Material), the final sample consisted of 308 non-Hispanic European/European-American participants (mean ± SD; age = 19.70 ± 1.24; 148 males; 63 with DSM-IV Axis I disorder; Table 2). We restricted our sample to non-Hispanic European/European-Americans because the variants included in our profile have been predominantly