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Cannabinoid Receptor Genotype Moderation of the Effects of Childhood Physical Abuse on Anhedonia and Depression

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Context: The endocannabinoid system has been implicated in stress adaptation and the regulation of mood in rodent studies, but few human association studies have examined these links and replications are limited.

Objectives: To examine whether a synonymous polymorphism, rs1049353, in exon 4 of the gene encoding the human endocannabinoid receptor (*CNR1*) moderates the effect of self-reported childhood physical abuse on lifetime anhedonia and depression and to replicate this interaction in an independent sample.

Design, Setting, and Participants: Genetic association study in 1041 young US women with replication in an independent Australian sample of 1428 heroin-dependent individuals as cases and 506 participants as neighborhood controls.

Main Outcome Measures: Self-reported anhedonia and depression (with anhedonia).

Results: In both samples, individuals who experienced childhood physical abuse were considerably more likely to report lifetime anhedonia. However, in those with 1 or more copies of the minor allele of rs1049353, this pathogenic effect of childhood physical abuse was attenuated. Thus, in participants reporting childhood physical abuse, although 57.1% of those homozygous for the major allele reported anhedonia, only 28.6% of those who were carriers of the minor allele reported it ($P=.01$). The rs1049353 polymorphism also buffered the effects of childhood physical abuse on major depressive disorder; however, this influence was largely attributable to anhedonic depression. These effects were also noted in an independent sample, in which minor allele carriers were at decreased risk for anhedonia even when exposed to physical abuse.

Conclusions: Consistent with preclinical findings, a synonymous *CNR1* polymorphism, rs1049353, is linked to the effects of stress attributable to childhood physical abuse on anhedonia and anhedonic depression. This polymorphism reportedly resides in the neighborhood of an exon splice enhancer; hence, future studies should carefully examine its effect on expression and conformational variation in *CNR1*, particularly in relation to stress adaptation.

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ANHEDONIA, A CORE CLINICAL feature of major depressive disorder (MDD),[1] reflects loss of ability to experience pleasure or joy from activities normally considered pleasurable or, alternatively, lack of reactivity to pleasurable stimuli. Although anhedonia is not necessary for a diagnosis of depression, anhedonic depression, sometimes referred to as *melancholic subtype*, has been identified as one of the more severe forms of MDD.[2,3]

Animal models suggest that chronic unpredictable stress blunts hedonic capacity,[4] consequently producing a depression-like phenotype.[5] Similarly, in human studies, perceived stress has been found to increase negative affect and anhedonia[6] and to contribute to reduced reward responsiveness[7] even after controlling for depressed mood. Childhood exposure to physical abuse may be one such potent stressor. This form of stress, often perpetrated by a parent or caregiver, can be inescapable and have virulent short- and long-term effects on the physical and mental well-being of the child.[8,9] However, not all children exposed to childhood abuse and maltreatment develop problems. For in-

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stance, Caspi and colleagues[10] found that carriers of the high-activity allele of a polymorphism in the monoamine oxidase A (*MAOA*) gene were buffered from the pathogenic influence of severe childhood maltreatment on antisocial behavior and violence during early adulthood. Likewise, albeit controversially, multiple studies[11,12] have found that carriers of the short, putatively less functional, allele of the serotonin transporter gene (*SLC6A4*) are at greater risk for depression on exposure to stress, particularly childhood maltreatment.[13] Studies such as this point to the existence of possible biological and environmental mechanisms for stress adaptation.

Although the hypothalamic-pituitary-adrenal axis is central to stress adaption, in rodents the role of the endocannabinoid signaling system (eCBS) has been implicated in this process as well, both independently and in concert with the hypothalamic-pituitary-adrenal axis.[14] Specifically, the eCBS, which consists of the endocannabinoid receptors (CB1 and CB2) and the endogenous cannabinoids (eg, anandamide), is instrumental in moderating the effects of chronic unpredictable stress on anhedonia. Compared with wild-type mice, CB1 knockout mice subjected to chronic unpredictable stress demonstrate decreased intake of sucrose-sweetened water,[15] an experimental paradigm for anhedonia in rodents. Administration of CB1 inverse agonist rimonabant coupled with stress produces similar effects.[16] These experiments, along with other studies that show the impact of eCBS on hedonic tone[17,18] as well as modulations in eCBS attributable to stress,[19] have led preclinical researchers to posit that eCBS may be a vital contributor to the plasticity of the link between stress and depressionlike phenotypes.[20,21]

Despite this accumulating preclinical and emerging human association evidence,[22,23] the moderating effects of eCBS on the link between chronic uncontrollable stress, such as exposure to childhood physical abuse, and anhedonia remains largely unexamined. The goal of this study was to conduct the first investigation of whether rs1049353 in *CNR1* (NCBI Entrez Gene 1268) is involved in stress adaption of this nature. We (1) examined whether carriers of the minor allele (AA/AG) of rs1049353, a synonymous polymorphism in *CNR1*, who were exposed to childhood physical abuse have a differential likelihood of self-reported lifetime anhedonia compared with those who were homozygous for the major allele (GG); (2) examined whether this effect extended to a diagnosis of MDD with anhedonia; (3) examined whether our results were specific to childhood physical abuse; and (4) replicated this finding in an independent sample.

METHODS

SAMPLES

Primary Sample

The primary sample was drawn from a large prospective cohort study of women born in Missouri. The Missouri Adolescent Female Twin Study (MOAFTS) consists of a cohort of female same-sex twin pairs born between July 1, 1975, and June 30, 1985, who were identified from birth records.[24] Twins were eligible to participate if both members of the twin pair had survived past infancy and were not adopted and if their biological parents were Missouri residents at the time of the twins' birth. Using a cohort-sequential sampling design, twins and at least 1 biological parent (typically the mother) were invited to participate in the baseline interviews during 1994 to 1999, when the twins were 13, 15, 17, or 19 years old. Recruitment of additional 13-year-old twins continued during a 2-year period as they became age eligible. A telephone diagnostic interview was administered, first to the parents and, after obtaining parental permission, to the twins (minors). Further details regarding sample recruitment and characteristics of this first wave of interview data, which were not used in the current study, are given elsewhere.[25] Subsequently, participants were invited to take part in several full-length and short follow-up interviews and respond to mailed questionnaires.

During 2002 to 2005, the first full-length follow-up interview was completed, which included assessments of childhood experiences (including physical abuse) and mental health (including anhedonia and depression).[26] All eligible twins, including those who may not have completed a baseline assessment, were invited to participate in the follow-up provided that they or their parents had not previously indicated an unwillingness to participate in future studies. A total of 3787 twins (14% African American) aged 18 to 29 years completed follow-up interviews. Twins were also invited during this period to provide permission for future DNA collection for genomic studies.[27] In a subsequent effort, of those contacted, 1191 individuals, including one or both members of monozygotic and dizygotic twin pairs, provided a sample. Collection of samples from the remaining participants is ongoing; this study reports on genotyping efforts completed on 1188 participants (with 3 withdrawn owing to genotyping problems). Genotyping was conducted (GoldenGate; Illumina, Inc) with an array of 1536 single-nucleotide polymorphisms (SNPs) in genes associated with addictions[28] and those for population admixture.[29] For this study, data from 1041 women of European-American descent (designated using birth record data) with both phenotypic and genetic data were used; as noted in a previous study,[27] these women are representative of the larger cohort and do not vary on key sociodemographic or psychiatric assessments from the remainder of the cohort.

Replication Sample

We also used data from an independent sample for replication. The Comorbidity and Trauma Study (CATS)[30-34] recruited heroin-dependent individuals to serve as cases from opioid replacement therapy clinics in the greater Sydney region in New South Wales, Australia. Inclusion criteria were being age 18 years or older, having an adequate understanding of English, and current or past participation in opioid replacement therapy for heroin dependence. Participants reporting recent suicidal intent or known to be currently experiencing psychosis were excluded. Neighborhood controls were recruited from geographic areas in proximity to opioid replacement therapy clinics. The use of opioids recreationally more than 10 times in a person's lifetime was an exclusion criterion for the control group; the inclusion and exclusion criteria, except for opioid replacement therapy participation, were otherwise identical to those of the case group. Genotyping was conducted using established technology (GoldenGate; Illumina Inc); however, the array was custom designed. For the current analysis, phenotypic and genetic data were drawn for replication from 1428 cases and 506 neighborhood controls. Principal components (created in SmartPCA[35]) from all SNPs were used to control for ethnic admixture. For each outcome (anhedonia, depression, and anhedonic depression), one principal component was identified as significant ($P = .03$-$.04$); consequently, all logistic regression analysis included this principal component as a covariate.

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Table 1. Characteristics of the Primary Sample and the Replication Sample[a]

Characteristic	Primary Sample, MOAFTS (n = 1041)	Replication Sample, CATS: Heroin-Dependent Cases (n = 1428)	Replication Sample, CATS: Neighborhood Controls (n = 506)
Female sex, %	100	39.1	55.5
Age, mean (range), y	21.7 (18-27)	36.4 (18-61)	34.6 (18-65)
Anhedonia, %	22.0	63.9	51.2
MDD, %	18.4	59.9	51.3
MDD + anhedonia, %[b]	81.8	96.6	89.2
Childhood physical abuse, %	9.4	51.6	34.0
Minor allele frequency of rs1049353, %	30.4	25.7	23.7
Hardy-Weinberg *P* value	.86	.64	.24

Abbreviations: CATS, Comorbidity and Trauma Study; MOAFTS, Missouri Adolescent Female Twin Study; MDD, major depressive disorder.
[a] Unless noted otherwise, percentages are based on the group numbers given in the column headings.
[b] Denominators for MDD + anhedonia were 192 for the primary sample and, in the replication sample, 854 for the heroin-dependent cases and 259 for the neighborhood controls.

All participants provided written informed consent as part of the individual studies, which received approval from institutional review boards.

MEASURES

Both studies used modified versions of the Semi-Structured Assessment for the Genetics of Alcoholism[36] for interview-based data collection. Reliability[36] and validity[37] for this tool are good.

ANHEDONIA

Anhedonia was coded using 1 or more self-report items querying a person's inability to experience pleasure from daily activities, which is a component of the depression diagnosis. All participants were queried about anhedonia (ie, no skip-outs). Specifically, in MOAFTS, individuals were asked whether there had ever been a time when they were a lot less interested in most things or unable to enjoy the things they usually enjoyed or felt unable to care about things or other people most of the day and nearly every day for 2 weeks or longer. In CATS, anhedonia was coded from an item asking about a time when, for at least 1 week, the respondent lost interest/enjoyment in almost everything or in things they usually enjoyed.

MAJOR DEPRESSIVE DISORDER

A lifetime diagnosis of MDD was coded using *DSM-IV* diagnostic criteria. Self-reported items were used to ascertain diagnostic criteria. Major depressive disorder was further classified by the presence or absence of anhedonia.

CHILDHOOD PHYSICAL ABUSE

Assessed via self-report, exposure to childhood physical abuse in MOAFTS was coded dichotomously: individuals were coded as being exposed to childhood physical abuse if they reported either being "physically abused as a child" or "ever physically injured or hurt on purpose by any adult" or responded that they were often "hit with a belt or stick or something like that" or "physically punished so hard you hurt the next day" by a parent or parent figure. In CATS, 9 items assessing childhood (ie, younger than 18 years) physical abuse were drawn from a longitudinal cohort study from New Zealand.[38] Items included being severely beaten, kicked, choked, throttled, burned with hot objects for punishment, or bruised by a parent or parent figure. These items were combined to create a continuous factor that was used for analysis. In both studies, physical punishment, such as occasional spanking or slapping, were excluded from the definition of abuse.

GENOTYPE

The polymorphism rs1049353 was coded dichotomously as carriers of the minor allele (AA/AG) and those homozygous for the major allele (GG). Secondary analyses compared AA and AG genotypes separately. We selected this SNP because it (1) is widely studied in the context of mood, (2) is exonic, and (3) was typed in both samples with high quality. No other SNPs in *CNR1* or any other gene were examined.

STATISTICAL ANALYSIS

Analyses were performed using commercial software (SAS, version 9; SAS Institute, Inc)[39] and logistic regression. The model used to test the statistical significance of b4 was anhedonia = b0 + (b1 × covariate) + (b2 × rs1049353) + (b3 × physical abuse) + (b4 × rs1049353 × physical abuse) + e.

Covariates were study specific and included age, sex, and case-control or ascertainment status and a principal component reflecting ethnic variation. For MOAFTS, survey options that allow for adjustment of standard errors for familial clustering of twin data were used.

RESULTS

SAMPLE CHARACTERISTICS

Table 1 reports the characteristics of the primary and replication samples. The primary (MOAFTS) sample consisted of women aged 18 to 27 years from the general population. Rates of anhedonia (22.0%), MDD (18.4%), and abuse (9.4%) are representative of young female populations and generalize to the full sample (including nongenotyped individuals). Not surprisingly, rates of anhedonia (cases, 63.9%; controls, 51.2%), MDD (cases, 59.9%; controls, 51.3%), and abuse (cases, 51.6%; controls, 34.0%, reporting ≥1 form of abuse) were considerably higher in CATS. Rates were high in the controls, presumably because they were matched with the heroin-dependent cases for neighborhood characteristics.

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Table 2. Rates of Lifetime Anhedonia Stratified by rs1049353 Genotype and Lifetime Exposure to Childhood Physical Abuse

	No. (%)[a]				
	Primary Sample, MOAFTS		Replication Sample, CATS		
Genotype	Unexposed	Exposed	Low Exposure, Bottom Quartile	Intermediate	High Exposure, Top Quartile
GG	459 (20.7)	42 (57.1)	273 (42.9)	559 (60.0)	264 (74.6)
AA/AG	484 (19.4)	56 (28.6)	210 (51.4)	409 (65.5)	219 (66.1)
AG	402 (19.9)	11 (31.1)	180 (53.0)	335 (66.3)	187 (66.1)
AA	82 (17.1)	45 (18.2)	30 (41.9)	74 (62.2)	32 (65.6)
Total	**943** (20.1)	**98** (40.8)	**483** (46.6)	**968** (62.3)	**483** (70.8)

Abbreviations: CATS, Comorbidity and Trauma Study; MOAFTS, Missouri Adolescent Female Twin Study.
[a]The number in parentheses represents the percentage with anhedonia.

PHYSICAL ABUSE AND ANHEDONIA IN MOAFTS

First, we conducted univariate analyses between anhedonia, rs1049353, and childhood physical abuse. Childhood physical abuse was strongly associated with anhedonia (odds ratio [OR] 2.75; 95% CI, 1.78-4.24); 40.8% of those with a history of childhood physical abuse reported anhedonia compared with 20.1% of those without a history of abuse. Genotype (rs1049353) was not associated with anhedonia (OR, 0.82; 95% CI, 0.61-1.10) or with exposure to childhood physical abuse (OR, 1.26; 95% CI, 0.83-1.92).

Next, we examined the association between anhedonia and childhood physical abuse stratified by genotype (coded AA/AG or GG). In GG individuals, there was a significant association between anhedonia and abuse (OR, 5.09; 95% CI, 2.66-9.77). As listed in **Table 2**, 57.1% of GG individuals with a history of childhood physical abuse reported anhedonia compared with 20.7% of GG individuals who were not abused (**Figure**). In contrast, in AA/AG individuals, there was no significant association between anhedonia and abuse (OR, 1.66; 95% CI, 0.89-3.09), with 28.6% and 19.4% of abused and nonabused participants reporting anhedonia, respectively. We also examined all 3 genotype groups separately (GG, AG, and AA). However, given the small number of AA individuals exposed to abuse, estimates for AA and AG genotypes could be statistically equated, allowing us to combine the AA and AG groups.

To formally test the interaction effect, we conducted a logistic regression that included genotype (AA/AG vs GG), abuse (exposed/unexposed), and their interaction as well as age. As reported in **Table 3**, the interaction OR (OR, 0.31; 95% CI, 0.12-0.79) confirmed that, in carriers of the minor allele (AA/AG), the effect of childhood physical abuse on anhedonia was buffered.

PHYSICAL ABUSE AND MDD IN MOAFTS

Childhood physical abuse (OR, 2.93; 95% CI, 1.88-4.57), but not genotype (OR, 0.91; 95% CI, 0.67-1.25), was associated with a diagnosis of lifetime MDD. Genotype interacted with childhood physical abuse to predict lifetime MDD (Table 3, interaction OR, 0.34; 95% CI, 0.14-0.85). However, the effect of the interaction was largely attributable to the presence of anhedonia in the context of MDD. The interaction between rs1049353 and childhood physical abuse influenced anhedonic MDD in a manner similar to its effect on anhedonia alone, suggesting that the stress-adaptive effects of rs1049353 on MDD are attributable to anhedonia (Table 3).

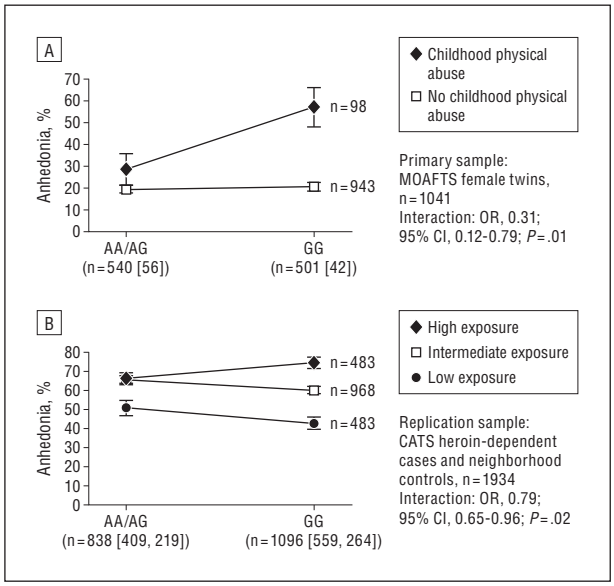

Figure. The association between childhood physical abuse and anhedonia as a function of rs1049353. A, Exposure in the Missouri Adolescent Female Twin Study (MOAFTS) sample. B, Exposure in the Comorbidity and Trauma Study (CATS) sample. The total number of subjects with each genotype is listed on the x-axis. The number in brackets beside each total reflects, for A, the number of subjects with the genotype who were exposed. For example, of 501 GG subjects, 42 were exposed. Similarly, for B, it reflects the number of subjects with the genotype who were also in the intermediate- and high-exposure groups. For example, of 1096 GG subjects, 559 and 264 were in the intermediate- and high-exposure categories, respectively.

REPLICATION

We successfully replicated the significant effects of the interaction between genotype and childhood physical abuse on anhedonia and on anhedonic MDD in the CATS sample of heroin-dependent individuals and neighborhood matched controls. The continuously distributed abuse factor (mean, 0; SD, 1) had a strong main effect on anhedonia, resulting in 1.48 increased odds of anhedonia for every unit of standard deviation increase in exposure. Next, we compared rates of anhedonia as a function of genotype and exposure to abuse. Childhood physical abuse was derived as a con-

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Table 3. Association Between rs1049353 Genotype, Childhood Physical Abuse, and Anhedonia as Well as Depression[a]

Sample	OR (95% CI)				
	rs1049353	Abuse	Interaction	Δ AIC[b]	Other Covariates
Primary: MOAFTS (n = 1041)					
Anhedonia	0.94 (0.67-1.33)	4.99 (2.69-9.26)	0.31 (0.12-0.79)	−28.78	Age, 1.09 (1.03-1.16)
P value			.01		
MDD	1.05 (0.74-1.51)	4.99 (2.68-9.31)	0.34 (0.14-0.85)	−25.96	
P value			.02		
MDD + anhedonia	0.95 (0.67-1.35)	3.99 (2.17-7.34)	0.34 (0.13-0.89)	−25.44	
P value			.03		
Sample	**rs1049353**	**Abuse Factor Score**	**Interaction**	**Δ AIC[b]**	**Other Covariates**
Replication: CATS (n = 1934)					
Anhedonia	1.04 (0.86-1.26)	1.59 (1.39-1.83)	0.79 (0.65-0.96)	−91.88	Age, 1.00 (0.99-1.01) Sex, 1.51 (1.24-1.83) Case, 1.51 (1.24-1.92) Ethnicity, 0.01 (0-0.71)[c]
P value			.02		
MDD	0.96 (0.80-1.16)	1.58 (1.38-1.82)	0.83 (0.68-1.01)	−85.99	
P value			.06		
MDD + anhedonia	0.99 (0.82-1.19)	1.59 (1.39-1.82)	0.77 (0.64-0.93)	−92.49	
P value			.008		

Abbreviations: AIC, Akaike information criterion; CATS, Comorbidity and Trauma Study; MDD, major depressive disorder; MOAFTS, Missouri Adolescent Female Twin Study; OR, odds ratio.

[a] The single-nucleotide polymorphism rs1049353 was coded as AA/AG, 1; GG, 0. Abuse was coded as 0/1 in MOAFTS and as a continuously distributed factor score in CATS, with a mean (SD) of 0 (1.0). Note that interaction terms for CATS are significant even when 95% CIs approach 1 because the abuse measure is continuously distributed.

[b] Δ AIC is a measure of relative model fit. It reflects the difference in the AIC between an intercept-only model and the current model with all covariates included.

[c] Ethnicity reflects adjustment for a genetically determined principal component indexing continuous variation in ethnicity.

tinuously distributed factor score; for ease of visualization in Table 2 and the Figure, the continuous physical abuse measure is shown as the top and bottom quartile and the middle 50%. As reported in Table 2 and the Figure, rates of anhedonia, irrespective of genotype, were highest in participants in the top quartile for exposure to abuse (70.8%). However, in carriers of the A allele (ie, AA/AG individuals), rates of anhedonia (66.1%) were attenuated in those in the top quartile for physical abuse exposure. Unlike MOAFTS, there was no evidence in CATS for an additive increase in buffering with increasing copies of the A allele. We also examined whether the continuously distributed measure of abuse was associated with anhedonia in GG vs AA/AG individuals. Unlike MOAFTS, the continuous abuse measure was associated with anhedonia in both GG (OR, 1.65; 95% CI, 1.44-1.89) and AA/AG (OR, 1.31; 95% CI, 1.13-1.51) individuals.

Table 3 reports the corresponding logistic regression results, which were determined using the continuously distributed measure of childhood physical abuse. Consistent with the primary sample, even after controlling for sex, age, and heroin dependence, the interaction between continuously distributed physical abuse and rs1049353 was significant (OR, 0.79; 95% CI, 0.65-0.96).

Next, we examined whether the interaction between rs1049353 and the continuous measure of childhood physical abuse was a significant predictor of MDD. Again, consistent with the primary sample, an interaction significant at the trend level ($P = .06$) was noted (Table 3).

Finally, we examined whether the buffering effect of rs1049353 on MDD was observed only in participants with anhedonic depression. Consistent with the primary sample, rs1049353 interacted with the factor representing childhood physical abuse to predict anhedonic depression (Table 2; $P = .008$). Hence, the replication confirmed not only the stress-buffering effects of rs1049353 on the relationship between childhood physical abuse and anhedonia but also attributed any effect of this interaction on MDD to the presence of anhedonia.

SUICIDE ATTEMPTS

Rates of suicide attempt were considerably elevated in participants reporting both anhedonia and MDD. Showing remarkable across-study consistency, 20.4% of those reporting both anhedonia and MDD in MOAFTS and CATS reported suicide attempts. In participants reporting anhedonia but not meeting criteria for MDD, suicide attempts were reported by 8.4% and 8.3% of MOAFTS and CATS participants, respectively; in those meeting criteria for MDD without anhedonia, suicide attempts were reported by 6.1% to 7.0% (0%-1.4% in those with neither anhedonia nor MDD). Overall, 64.8% and 94.5% of suicide attempts reported in MOAFTS and CATS, respectively, aggregated in participants with both anhedonia and MDD.

SPECIFICITY ANALYSIS

To provide a framework for appropriate future replication, we examined whether this interaction would be captured when using other definitions of abuse. All analyses were conducted only in MOAFTS. Childhood sexual abuse was associated with increased likelihood of reporting an-

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hedonia (OR, 2.41; 95% CI, 1.52-3.83), but the interaction with rs1049353 was not significant (OR, 0.56; 95% CI, 0.23-1.43). We modified our childhood physical abuse measure to include physical punishment such as sometimes/often being slapped by a parent. Not only did the association between abuse and anhedonia attenuate (OR, 1.47; 95% CI, 1.08-2.01), the interaction was no longer significant (OR, 0.86; 95% CI, 0.46-1.62). An interaction with a dichotomous measure of exposure to adult (assaultive or nonassaultive) traumas was also not significant (OR, 0.49; 95% CI, 0.23-1.05). This series of analyses indicates that replication analyses are likely to be successful only when examining childhood physical abuse.

COMMENT

We sought to examine whether a synonymous polymorphism in the gene encoding the human cannabinoid receptor (*CNR1*) was involved in stress adaptation for anhedonia and depression. Highly consistent with findings from rodent models, our study replicates the buffering effect of the minor allele of rs1049353 (*CNR1*) on the pathogenic effects of childhood physical abuse on anhedonia. Furthermore, the protective effect of rs1049353 on MDD was attributable to the presence of anhedonia. Individuals who carried 1 or more copies of the minor allele (AA/AG) who reported being exposed to physical abuse during childhood were not at increased risk for anhedonia or for MDD.

ANHEDONIA AND DEPRESSION

Anhedonia is among the hallmark clinical features of MDD. However, a variety of epidemiologic and human experimental research demonstrates that melancholic (or anhedonic) depression varies from other forms of depression. In addition to the *DSM-IV* definition of melancholic depression, which requires pervasive anhedonic features, both psychometric[40-44] and laboratory-based experiments[7] have been used to examine hedonic capacity.[41] These studies concluded that anhedonia represents a unique and clinically important phenotype.

ANHEDONIA, DEPRESSION, AND STRESS

A wealth of studies demonstrate the pathogenic influence of childhood stressors, particularly maltreatment, on risk for depression.[9,45] In our study as well, individuals with a history of childhood physical abuse were at considerably increased odds of MDD. However, both preclinical and human clinical evidence indicate that anhedonia may be the "endophenotype" that connects childhood adversity to MDD. For instance, Bogdan and Pizzagalli[46] and Pizzagalli et al[6] have demonstrated that both acute and perceived stress, respectively, affect depression by impairing hedonic capacity.

GENOTYPE AND STRESS ADAPTATION

Not all individuals exposed to childhood adversity develop depression, and genotype may moderate the relationship between childhood adversity and mental health outcomes.[10,47] For instance, a polymorphism, rs1360780, in the *FKBP5* gene (which regulates glucocorticoid regulator sensitivity) reportedly enhances the risk for depression only in the presence of moderate to severe (but not mild) physical abuse.[48] Similarly, Cicchetti et al[49] found that maltreated individuals with the high-activity genotype of the *MAOA* gene reported fewer depressive symptoms in the presence of self-coping strategies, indicating that the high-activity allele produces a substrate, even in maltreated individuals, in which receptivity to coping strategies is enhanced. Our study demonstrates a similar stress-adaptive role for *CNR1* (rs1049353); this is important because the endogenous cannabinoid system in rodent paradigms has been found to afford stress buffering directly as well as indirectly via modulation of hypothalamic-pituitary-adrenal axis activity.

CONSISTENCY WITH THE PRECLINICAL ENDOCANNABINOID LITERATURE

Both eCBS and chronic stress are independently associated with hedonic capacity.[4,17] However, the link between chronic stress, anhedonia, and the endocannabinoid system is highly complex. Experimental manipulation of CB1 (via knockout or administration of an antagonist) produces phenotypes that mimic human melancholic depression.[21] For instance, studies have found that CB1 is associated with impaired cognition and neurodegeneration[21,50] and emotional processing (eg, positive affective memory),[51,52] which may be recruited in extinction of aversive memories[53] and in the inability to process emotions, which are features of melancholic depression. In addition, exposure to chronic stress reduces hippocampal CB1 receptor expression.[19] Prolonged exposure to elevated glucocorticoid levels, such as those induced by chronic stress conditions, also significantly reduces hippocampal CB1 receptor binding-site density.[54] In fact, a recent study[20] suggests that CB1 receptor deficiency may mimic the effects of chronic stress on emotional behavior. The most intriguing synergy of chronic stress and CB1 activity is its influence on anhedonia and depression.[55] Chronic stress also reduces anandamide (an endogenous cannabinoid) signaling in the corticolimbic circuit.[14]

The present study is remarkably consistent with these preclinical observations. We have shown that, in humans, *CNR1* genotype plays a stress-adaptive role in the etiologic characteristics of anhedonia and depression. When coupled with the rodent literature, our study suggests the possibility of a significant therapeutic role of the endocannabinoid system in depression.[56,57] However, which elements of the endocannabinoid system will need to be targeted remains to be examined. For instance, our work, consistent with animal experiments, focuses attention on the gene encoding the CB1 receptor, and many clinical studies of the CB1 inverse agonist rimonabant (for weight loss) have shown serious adverse effects of depression[58-62] and suicidality.[61,63] Thus, more research is required to understand the precise role of *CNR1*, specifically rs1049353, in this domain. Whether the adverse effects of rimonabant are moderated by rs1049353 or other *CNR1* genotypes may also be of distinct interest, particularly in drug development.

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CONSISTENCY WITH EMERGING HUMAN ASSOCIATION STUDIES

The role of the eCBS in humans is beginning to garner considerable interest. Congruent with the preclinical observation that CB1-deficient rodents exhibit melancholic features[21] and remarkably consistent with our findings, a study[22] of depressed patients found that those with the rs1049353 AA genotype were more likely to respond well to antidepressant treatment. Relatedly, GG individuals appeared to be resistant to treatment, particularly if they were female and had melancholic depression. Another study[64] identified 2.46 increased odds of patients with MDD carrying the A allele. Additionally, a study[65] of *FAAH* (fatty acid amide hydrolase, encoding the enzyme involved in hydrolysis of anandamide, and also a component of the eCBS) and reward-related human brain function noted that 385A (reduced enzymatic activity) carriers show decreased threat-related amygdala reactivity and increased reward-related reactivity in the ventral striatum, indicating its putative role in stress adaptation. One study has also explored the interaction between stress and *CNR1* in the development of mood-related conditions. Juhasz et al[23] found that a *CNR1* haplotype, including rs1049353, was associated with neuroticism, agreeableness, and depressive symptoms. Exposure to recent negative life events interacted with rs7766029; compared with carriers of the T allele, carriers of the CC genotype did not show an appreciable increase in vulnerability to depressive symptoms, even upon recent exposure to stressful life events. Evidence for an interaction with rs1049353 was noted but not considered to be significant when corrected for multiple testing. The authors also reported a strong mediating influence of childhood adversity, but interactions with it remained unexplored. Our study adds further support for the role of the endocannabinoid system in regulation of human mood, particularly in the context of stress adaptation.

rs1049353 AND *CNR1*

The polymorphism rs1049353 is exonic but synonymous, indicating that its effect on the activity of *CNR1* is not attributable to a coding change. However, synonymous SNPs can induce widespread modification in protein formation, and there is preliminary evidence that rs1049353 is in the region of an exon splice enhancer responsible for recruiting spliceosomes and other machinery necessary for accurate splicing of exons during translation.[66] Future studies should also explore whether the A/A (and A/G) genotypes of rs1049353 are associated with changes in endocannabinoid activity. Finally, rs1049353 is in high linkage disequilibrium (r^2=0.94) with rs4707436, which resides in the 3′ untranslated region of *CNR1*, resulting in potential regulatory effects. Similar untyped causal variants may also exist.

LIMITATIONS

Our results may be viewed with the following limitations in mind. First, these analyses were conducted in individuals of primarily European descent. This is an advantage in genetic studies in which population stratification can confound association signals and there is allelic variation in the frequency of rs1049353 across populations. Second, retrospective assessments of anhedonia and abuse were used, which may be subject to recall bias. Additionally, our measures of anhedonia were drawn from interview sections designed to assess depression—currently, independent questionnaires or laboratory assessments of anhedonia in detail are not available. Third, the majority of the sample that met criteria for MDD reported lifetime anhedonia, making the study of nonanhedonic MDD challenging. Fourth, although this is not a limitation, we used a dichotomous measure of childhood physical abuse in the primary sample and a continuous factor score in the replication sample. Because rates of childhood physical abuse were higher in the CATS replication sample and multiple indices of abuse were available, the factor score provides a more refined characterization of abuse exposure in that sample. Replication with a dichotomous and continuously coded environmental exposure measure indicates the robustness of these findings.[67] Finally, the replication sample included heroin-dependent participants serving as cases and controls matched for neighborhood (ie, high risk) exposure, and rates of anhedonia and abuse in this population exceeded those of the general population. Nonetheless, adjustment for case status did not influence our findings. However, it is possible that the mechanisms underlying the relationship between genotype, anhedonia, and physical abuse are different in this sample.

Two additional caveats regarding the replication are worth noting. First, although the AA genotype appeared to have a stronger protective influence than the AG genotype in MOAFTS, this effect was not statistically significant and was not replicated in CATS. Because of the smaller numbers in MOAFTS, it is not possible to discern whether this is an underpowered difference or a false-positive finding, and future studies should contrast these genotypes (AA vs AG) before combining them. Second, although there was no association between abuse and anhedonia in AA/AG individuals, this association was significant in CATS. This is likely the result of the higher rates of abuse in this sample and the power afforded by a continuous index of abuse. Nonetheless, future studies should examine the AA/AG subgroup carefully for these effects.

CONCLUSIONS

Despite widespread interest in the interface between biological contributors and environmental adversity,[11,13,68-71] this is one of few replicated examples of genotype × environment interaction. That genotype confers resilience to the pathogenic effects of childhood physical abuse underscores the plasticity of biological and environmental underpinnings of mental health.[72] Importantly, this study reinforces the need to examine depression from a fine-grained phenotypic perspective and highlights the role of anhedonia in depressive phenotypes. The role of anhedonia as a critical endophenotype is becoming increasingly apparent, particularly in genetic

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studies.[73] Hedonic capacity is heritable (46%), but the genetic correlation between anhedonia and depression is modest.[74] Thus, a composite measure such as MDD may attenuate genetic signals attributable to specific mechanisms underlying salient aspects of depression, such as anhedonia, and this may have contributed to the general failure of genome-wide association studies of depression.[75] Our study demonstrates that anhedonia may be the optimal target phenotype when examining the effect of childhood adversity on depression.

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