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# Inhibition of Attention for Affective Material: Contributions by *HOMER1* Gene Variation

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## Abstract

Failure to inhibit attention to irrelevant affective information has been linked to depression and rumination. However, few studies have investigated the biological bases of this process. Variation in the *HOMER1* gene was identified in a genome-wide association study as associated with major depressive disorder and is associated with executive functioning inefficiency. Several studies have linked variation in the *BDNF* gene with emotional and cognitive processes such as rumination. The current study examined the association between these two auspicious genetic variants and inhibition of attention for affective information. In Study 1, 60 psychiatrically healthy community participants completed a negative affective priming task with positive and negative words. *HOMER1* variation, but not *BDNF* variation, was associated with difficulty inhibiting irrelevant negative information. These results were replicated in a second study utilizing a sample of 97 psychiatrically healthy young adults. Implications for the current literature and future directions are discussed.

### Keywords

inhibition; negative priming; genes; genetics

Both theory and empirical evidence suggest that biased information processing is important in the pathogenesis and maintenance of depression (Ingram, 1984; Mathews & MacLeod,

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2005). In particular, there is growing evidence that difficulty disregarding or inhibiting attention toward irrelevant negative information contributes to the development and maintenance of depression. Several studies have demonstrated an association between current depression and difficulty inhibiting attention for negative information (Goeleven, De Raedt, Baert, & Koster, 2006; Joormann & Gotlib, 2010). Similarly, rumination, a cognitive process strongly implicated in depression risk and maintenance, is thought to arise due to difficulty disregarding irrelevant negative information and has been associated with difficulties with inhibition in laboratory tasks (Joormann, 2010).

Despite the accumulating evidence suggesting the importance of inhibiting attention to negative information in depression, few studies have examined genetic contributions to this process. Identifying the genetic bases of cognitive processes associated with depression may increase our knowledge of vulnerability and thereby guide theory and treatment. Two genetic variants that represent intriguing candidates for contribution to inhibitory process in depression are the G/A polymorphism (SNP rs7713917) of the *HOMER1* gene and the rs6265 Val66Met polymorphism of the *BDNF* gene.

Variation in the *HOMER1* gene is associated with depression risk in animal models (Orsetti, Di Brisco, Canonico, Genazzani, & Ghi, 2008) and in humans (Rietschel et al., 2010). The *HOMER1* gene is involved in glutamatergic neurotransmission, which is commonly disrupted in major depression (Ango et al., 2000), and deletion of *HOMER1* in mice leads to depression-related behaviors (Grinevich et al., 2011; Grinevich, Seeburg, Schwarz, & Jezova, 2012). In humans, a recent genome-wide association (GWA) study of 604 patients with Major Depressive Disorder (MDD) and 1,364 controls identified a single nucleotide polymorphism (SNP) rs7713917, located in a putative regulatory region of the *HOMER1* gene, was significantly associated with MDD. This association was confirmed in a replication sample of 409 patients and 541 control subjects (Rietschel et al., 2010)[1]. Individuals with the AA genotype, compared to individuals with at least one G allele, were at greater risk for MDD.

This same study (Rietschel et al., 2010) also examined whether rs7713917 variation was associated with altered executive control measured with an N-back task, which requires participants to maintain and manipulate information in working memory. Using fMRI to measure neural activity, they found that A allele homozygotes had reduced efficiency (greater activation with poorer behavioral performance) in the dorsolateral prefrontal cortex compared to G-allele carriers. Importantly, prior research indicates that dorsal lateral prefrontal cortex activity is critical to performance on negative priming tasks used to measure inhibition (Egner & Hirsch, 2005). Thus, variation in *HOMER1* may impact depression through dysregulated executive control, such as difficulty with inhibition of attention to irrelevant affective information. The association between *HOMER1* variation and both depression and executive cognition makes polymorphism rs7713917 a good

[1]It should be noted that there is variability in the genes and alleles associated with MDD between different GWA studies. The current studies used the Rietschel et al. (2010) GWA results as a starting point to identify auspicious candidate genes because it was the largest and best-conducted GWAS at the time the present studies were undertaken. The discussion of reliability between GWA studies is beyond the scope of this paper. See the discussion of Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium (2013) for hypotheses regarding issues of variability and reliability between MDD GWA studies.

candidate for the study of inhibition of attention to affective information. In particular, the identification of *HOMER1* rs7713917 through a GWA study provides a strong rationale for examining the relationship between the SNP and specific processes associated with depression.

Variation in the Val66Met polymorphism (rs6265) of the BDNF gene has likewise been associated with both depression and cognitive processes relevant for inhibition of attention to affective information. There is equivocal evidence regarding a direct association between Val66Met variation and major depressive disorder, although this may be explained by recent findings which suggest that this relationship occurs only in males (Verhagen et al., 2010). Regardless, there is now evidence that variation in Val66Met is associated with rumination in healthy (Beevers, Wells, & McGeary, 2009; Clasen, Wells, Knopik, McGeary, & Beevers, 2011) and clinically depressed samples (Hilt, Sander, Nolen-Hoeksema, & Simen, 2007) with the Met allele associated with increased rumination compared to individuals homozygous for the Val allele. Research suggests that rumination may be caused or maintained by difficulty inhibiting or disregarding negative information (Joormann, 2004). Indeed, studies using affectively modified versions of Sternberg and negative priming tasks demonstrated a relationship between rumination and difficulty inhibiting depression-relevant information (Joormann & Gotlib 2008; 2010). This link between rumination and inhibition raises the question as to whether Val66Met variation may play a role in the inhibition of attention to emotional material. Further suggesting that Val66Met plays a role in the disinhibition of dysphoric information, the Met allele has been associated with greater activity in dorsolateral and dorsomedial prefrontal cortical areas for sad distractors, suggesting less efficient inhibition of attention, and diminished activity in these regions for attentional targets in an oddball task (Wang, Ashley-Koch, Steffens, Krishnan, & Taylor, 2012). Taken together, these findings implicate the Met allele of the Val66Met polymorphism as a likely candidate for difficulty in inhibiting negative affective information.

We conducted two studies with psychiatrically healthy samples to investigate the relationship between *HOMER1* and *BDNF* variation and inhibition of attention to emotional information. Healthy samples were recruited to investigate the relationship between genetic variation and inhibition apart from any effects on inhibition due to psychopathology. While this potentially reduces some variability in emotionally-relevant inhibition associated with mood, it represents a more direct test of the relationship between genotype and inhibition by eliminating effects of psychopathology on inhibition of attention.

Consistent with prior research (Rietschel et al., 2010), we predicted that the AA *HOMER1* genotype would be associated with greater difficulty inhibiting attention for affective material compared to other genotype groups. Because prior research identified general executive functioning deficits associated with AA genotype, we did not make an *a priori* hypothesis regarding inhibition of negative or positive affective material. Consistent with the prior research on *BDNF* and rumination, we predicted that Met allele-carriers would demonstrate greater difficulty inhibiting attention for negative information compared to individuals homozygous for the Val allele.

# Study 1

## Participants

Participants were 60 adults recruited from the Austin, TX area community using radio, television, and internet advertisements. Participants did not have current or past major psychopathology as indicated by structured clinical interview, had low levels of depressive symptoms, and reported no current psychotropic medication use at the time of the study. Participants were paid $15 per hour for study participation. All procedures were approved by the University of Texas at Austin institutional review board and all participants provided written informed consent before participating in the study.

## Procedure

After providing informed consent, participants were administered the Structured Clinical Interview for DSM-IV (SCID). Presence of a current or past diagnosis of any Axis I disorder, except specific phobia and/or alcohol or substance abuse[2], excluded participants from the study. Furthermore, participants scoring greater than 12 on the Beck Depression Inventory-II (BDI-II) were excluded as were any participants reporting current psychotropic medication use. After completion of the SCID and BDI-II, participants provided buccal cells via a cheek swab and mouthwash for genotyping. Participants completed a negative affective priming task in individual testing sessions to assess inhibition of attention for emotional material. Participants were debriefed after completing the study.

## Assessments

**Structured Clinical Interview for DSM-IV—**To assess exclusion criteria, the patient version of the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995) was administered on the day of the laboratory session. Twenty percent of all interviews were rated by an independent assessor. Agreement on study inclusion/exclusion was excellent ($\kappa = 1.0$)

**Beck Depression Inventory – II—**The Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) is a 21-item questionnaire that assesses symptoms of depression. The BDI-II has demonstrated good to adequate internal consistency, test-retest reliability and construct validity (Dozois, Dobson, & Ahnberg, 1998).

## Inhibition Task

A negative affective priming (NAP) task was used to measure inhibition of attention to affective information. Negative priming refers to the process whereby response to an item is disrupted (usually indicated by increased latency to respond) if that item had been ignored in an immediately preceding trial. In a NAP task, the negative priming effect is examined using affectively-relevant stimuli. The present study used a NAP task that has been successfully

[2]Specific phobia, alcohol abuse, and substance abuse were not exclusionary criteria because they are not likely to influence the negative affective priming task. Our rates of these disorders in the sample were very low. Three participants endorsed current alcohol abuse and no participants endorsed substance abuse or specific phobia.

used to investigate NAP in depression and induced positive mood (Goeleven et al., 2006; Goeleven, De Raedt, & Koster, 2007).

In each trial of the NAP in the present study, participants were presented with two words and were instructed to indicate whether the target word was self-descriptive or not, while ignoring the distracter word. There are two types of trials in this task: a *prime trial* followed by a *probe trial*. In addition, there are two types of prime-probe trial pairs: *experimental* and *control* (see Supplementary Figure available in the online version of this article).

**Experimental Trial Pairs—**In experimental prime-probe pairs, both prime and probe trials contain one negatively-valenced and one positively-valenced word. In the prime trial of an experimental pair, the valence of the target stimulus is incongruent with the valence of the target stimulus in the subsequent probe trial. This results in negative priming for the probe trial due to participants inhibiting attention to a stimulus of a particular valence in the prime trial and then responding to that stimulus valence in the probe trial. For example, if the target word in the prime trial were positive, the target word in the probe trial would be negative. The participants would be inhibiting attention to a negative stimulus in the prime trial (while responding to the positive stimulus) and then would respond to a negative stimulus in the probe trial resulting in negative priming for the negative stimulus in the probe trial.

**Control Trial Pairs—**In control prime-probe pairs, the probe trials contained one negatively- and one positively-valenced word. However, the prime trials in control pairs were structured so that the distracter word valence was not congruent with the target word valence in the probe trial. Thus, no negative priming would occur for probe targets in control pairs. For example, if the target in the probe trial was negative, both words in the prime trial could be neutral, both could be positive, or one could be positive and the other neutral. In this way, participants are not inhibiting attention to a word of the same valence as the target word in a probe trial.

**Task Structure—**The task was programmed and presented in E-Prime 2.0. Each trial in the NAP consisted of two words presented on the top and bottom halves of the screen. One word was presented in a green font while the other was presented in a red font. Participants were instructed to indicate, as quickly and accurately as possible, whether the word in green described them or not and to ignore the word in red. Participants responded by pressing keys on a response box labeled “yes” and “no” with their index and middle fingers, respectively. We recorded participants’ response to each target word and the latency to respond.

Each trial began with a fixation cross for 500 ms followed by the word pair, which remained on screen until the participant responded indicating whether the target word was self-descriptive. Following offset of the word stimuli, there was a blank screen intertrial interval of 500 ms. Participants completed 128 trials: 32 experimental trial pairs and 32 control trial pairs. Participants completed 16 experimental probe trials with a negative target word and 16 with a positive target word. Participants completed an equal number of trials with the target word in the top and bottom position and the order of presentation of stimuli was randomized for each participant. Position of the target word across prime and probe trials

was randomized and counterbalanced. Words were presented in 30-point, Arial font. Letters were approximately 0.8 cm tall and were presented 1.6 cm apart. Thus, the words were separated by a visual angle of 1.5°.

**Task Stimuli—**Stimuli were English words selected from the Affective Norms for English Words (ANEW; Bradley & Lang, 1999) database. Thirty-two positive-negative word pairs were selected for the probe trials. Sixteen positive-negative pairs were selected for prime trials in experimental trial pairs. Prime trials that preceded probe trials with a negative target in control trial pairs selected from 5 neutral-neutral pairs, 2 neutral-positive pairs, and one positive-positive pair. Prime trials that preceded probe trials with a positive target in control trial pairs selected from 5 neutral-neutral pairs, 2 neutral-negative pairs, and one negative-negative pair. Each word pair was presented twice during the task. Word pairs were matched for number of letters and frequency of use. Words included both adjectives (e.g., stupid, loyal) and nouns (e.g., victim, woman) and were counterbalanced across valence.

**Inhibition score—**To calculate an inhibition score, latency to respond on a probe trial in a control trial pair was subtracted from latency to respond to an experimental probe trial for each stimulus type (positive and negative). Thus, higher scores represent greater inhibition (i.e., a stronger negative priming response).

## Genotyping

Genomic DNA were isolated from buccal cells using a modification of published methods (Lench, Stanier, & Williamson, 1988; Meulenbelt, Droog, Trommelen, Boomsma, & Slagboom, 1995; Spitz et al., 1996; Freeman et al., 1997). The cheeks and gums were rubbed for 20 s with three sterile, cotton-tipped wooden swabs. The swabs were placed in a 50-ml capped polypropylene tube containing lysis buffer (500 μl of 1 *M* Tris-HCl; pH 8.0; 500 μl of 10% sodium docecyl sulfate; and 100 μl of 5 *M* sodium chloride). The subjects then rinsed out the mouth vigorously with 10 ml of distilled water for 20 sec and this was added to the 50-ml tube. The tubes were stored at 4°C until the DNA was extracted.

**HOMER1—**The G/A polymorphism (rs7713917) was genotyped using Taqman assay C___1988008_20 (Applied Biosystems) using an ABI 7300 Real time PCR system. The frequency of the HOMER1 alleles (G/G, $n = 11$; G/A, $n = 31$; A/A, $n = 18$) did not differ from the Hardy-Weinberg equilibrium ($\chi^2 = 0.14$, $p = 0.71$).

**Brain derived neurotrophic factor (BDNF)—**The Val66Met polymorphism (rs6265) was genotyped using Taqman assay C___11592758_10 (Applied Biosystems) using an ABI 7300 Real time PCR system. The frequency of the BDNF alleles (Val/Val, $n = 25$; Val/Met, $n = 30$; Met/Met, $n = 5$) did not differ from the Hardy-Weinberg equilibrium ($\chi^2 = 0.94$, $p = 0.33$). Due to the low number of participants in the Met/Met group, and consistent with prior research (e.g., Beevers et al., 2009), we combined the Met/Met and Val/Met groups to form a Met-carrier group.[3]

[3]Analyzing the Val/Met and Met/Met groups separately did not change the results reported below for BDNF genotype groups.

## Results

**Sample Characteristics—**Descriptive statistics for the sample are presented in Table 1. There were no significant differences between *HOMER1* allele groups in age, $F(2, 59) < 1$, $p = .58$, gender, $\chi^2(2, N = 60) = 5.05$, $p = .08$, self-reported race, $\chi^2(2, N = 59) < 1$, $p = .47$, depression symptoms, $F(2, 59) = 1.42$, $p = .25$, endorsement of positive words in the NAP task, $F(2, 59) = 1.37$, $p = .26$, or endorsement of negative words, $F(2, 59) = 2.19$, $p = .12$. Similarly, there were no significant differences between *BDNF* allele groups in age, $t(58) < 1$, $p = .98$, self-reported race, $\chi^2(1, N = 59) < 1$, $p = .89$, depression symptoms, $t(58) = 1.63$, $p = .11$, endorsement of positive words in the NAP task, $t(58) = 1.41$, $p = .17$, or endorsement of negative words, $t(58) < 1$, $p = .39$. There was a marginally significant difference between groups for gender, $\chi^2(1, N = 60) = 3.24$, $p = .07$, with slightly more men in the Met-carrier group.

**Manipulation Check—**To determine whether we achieved the expected negative priming effect we conducted a paired samples t-test comparing prime and probe trials across valence and genotype groups. There was a significant difference in mean reaction time for prime ($M = 1034$ ms; $SD = 146$ ms) and probe ($M = 1054$ ms; $SD = 147$ ms) trials in experimental pairs, $t(59) = 2.61$, $p = .012$, Cohen's $d = .14$, indicating a negative priming effect regardless of stimulus valence or genotype group. Probe trials for experimental pairs were also significantly slower than probe trials for control pairs ($M = 1001$ ms; $SD = 160$ ms), $t(59) = 5.02$, $p < .001$, Cohen's $d = .34$, again indicating a significant negative priming effect regardless of valence.[4] Furthermore, prime trials for control pairs ($M = 1007$ ms; $SD = 153$ ms) did not differ from probe trials for control pairs, $t(59) < 1$, $p = .66$.

**Inhibition of Attention for Affective Material—**A 3 (*HOMER1* genotype: GG, GA, AA) x 2 (stimulus valence: negative, positive) ANOVA revealed no significant main effects for *HOMER1* genotype or valence on inhibition of attention, $F(2, 57) = 2.36$, $p = .1$, and $F(1, 57) < 1$, $p = .69$, respectively. However, there was a marginally significant interaction with a medium effect size between *HOMER1* genotype and valence for inhibition of attention, $F(2, 57) = 3.02$, $p = .056$, $\eta_p^2 = .1$. Exploratory post-hoc analyses indicated an effect for *HOMER1* genotype on inhibition of attention for negative stimuli, $F(2, 57) = 3.64$, $p = .032$, $\eta_p^2 = .1$, but not for positive stimuli, $F(2, 57) < 1$, $p = .79$. Further post-hoc analyses revealed that differences between *HOMER1* genotype in inhibition of attention for negative words was driven by differences between the GG and GA genotype groups, $t(40) = 2.67$, $p = .011$, Cohen's $d = .84$. There were no significant differences between GG and AA, $t(27) = 1.76$, $p = .09$, or GA and AA, $t(47) < 1$, $p = .42$, groups. These results can be seen in Figure 1. Single sample t-tests were conducted to determine if the inhibition demonstrated for each genotype group significantly differed from zero. The GA group demonstrated an inhibition score significantly less than zero, $t(30) = 3.15$, $p = .004$, Cohen's $d = 1.15$, but the GG, $t(10) = 1.15$, $p = .28$, and AA, $t(17) = 1.30$, $p = .21$, groups did not differ from zero.

[4]An anonymous reviewer enquired as to whether endorsement or rejection of words a self-descriptive would affect the NAP task. To our knowledge, prior studies have not examined this in the NAP task. We found that there was not a significant 3-way interaction between trial type, stimulus valence, and endorsement (Study 1 $p = .29$, Study 2 $p = .30$) suggesting that endorsing or rejecting the target word as self-descriptive did not affect the negative priming effect. We report the full results of these analyses in the online supplementary material.

A 2 (*BDNF* genotype: Val/Val, Met-carrier) x 2 (stimulus valence: negative, positive) ANOVA revealed no significant main effects for *BDNF* genotype or valence on inhibition attention, $F(1, 58) = 1.16$, $p = .29$, and $F(1, 57) = 2.55$, $p = .12$, respectively. The interaction between *BDNF* genotype and valence was also not statistically significant, $F(1, 58) = 1.51$, $p = .22$.[5] Due to the lack of even marginally significant main effects or interaction, we did not conduct post-hoc analyses.

### Study 1 Discussion

Study 1 demonstrated a relationship between *HOMER1* genotype variation and inhibition of attention to negatively valenced emotional material. Specifically, the GA allele group was associated with reduced inhibition compared to the GG group. The inhibition score for the GA allele group was statistically different from zero in the negative direction indicating *facilitation* (i.e. faster responding) to negative targets after ignoring a negative word in the previous trial.

The results of Study 1 are partially consistent with previous work that found *HOMER1* variation was associated with altered executive functioning (Rietschel et al., 2010). However, we found the strongest effects for the GA genotype compared with the GG genotype, whereas prior work found significant effects for the AA genotype compared to G allele-carriers. Furthermore, our results were specific to negative affective material, which was unexpected.

The results of Study 1 suggest a relationship between *HOMER1* variation and inhibition of affective information. However, given our small sample size and the unexpected findings that the strongest effect was for the GA genotype compared with the GG genotype and that the effect was limited to negative affective material, there is a possibility that these results represent a spurious association. As such, we sought to replicate these results in an independent sample. We also examined *BDNF* variation again to increase our confidence in the lack of significant results found in Study 1. Furthermore, because allele frequencies vary between ethnic populations due to the unique environmental and genetic histories of different ethnic groups (i.e. population stratification), there is the possibility that ethnic differences related to unmeasured genetic variation or to culture may influence the relationships in gene association studies. This potential confound could have attenuated or eliminated genuine genetic associations. To address this potential confound, we restricted analyses to an ethnically homogenous (Caucasian) sample for Study 2.

## Study 2

### Method

**Participants—**Participants were 97 young adults recruited from introductory psychology classes at the University of Texas at Austin. As in Study 1, participants in Study 2 did not have current or past major psychopathology as indicated by structured clinical interview,

[5]Due to evidence that the association between *BDNF* variation and depression-relevant phenotypes may differ by gender (Verhagen et al., 2010) we also conducted these analyses separately by gender. Results were not statistically significant for males or females and the pattern of results was very similar to those combining genders.

had low levels of depressive symptoms, and reported no current psychotropic medication use at the time of the study. As noted above, in order to rule out potential population stratification effects, we restricted analyses to an ethnically homogenous (Caucasian) sample[6]. Participants partially fulfilled a research requirement by completing this study. All procedures were approved by the University of Texas at Austin institutional review board and all participants completed written informed consent before participating in this study.

**Procedure—**Mass pre-testing identified participants who scored less than 4 on the short-form of the Beck Depression Inventory (BDI-SF; Beck, Rial, & Rickels, 1974). After providing informed consent, participants were administered the SCID to determine study eligibility. As in Study 1, the presence of current or past DSM-IV Axis I diagnoses, excepting specific phobia and/or alcohol abuse, excluded individuals from study participation. Eligible participants completed a demographic form, BDI-II, and computer-administered NAP task in individual sessions. Participants provided buccal cells via a cheek swab and mouthwash for genotyping. After study participation participants were debriefed.

**Assessments—**Structured clinical interview (SCID; First et al., 1995) and depression symptom severity (BDI-II; Beck et al., 1996) measures were identical to Study 1. As in Study 1, 20% of interviews were reviewed by an independent assessor and agreement on inclusion/exclusion by the SCID was excellent ($\kappa = 1.0$). The negative affective priming task to measure inhibition of attention for negative and positive emotional words was identical to Study 1 as were genotyping methods for *HOMER1*. The frequency of the *HOMER1* alleles (G/G, $n = 32$; G/A, $n = 47$; A/A, $n = 18$) and *BDNF* alleles (Val/Val, $n = 58$; Val/Met, $n = 34$; Met/Met, $n = 5$) did not differ from Hardy-Weinberg equilibrium ($\chi^2 = 0.01$, p = 0.92 and $\chi^2 = 0.00004$, $p = 0.99$, respectively). As in Study 1, *BDNF* Val/Met and Met/Met groups were combined to form a Met-carrier group.[7]

## Results

**Sample Characteristics—**Descriptive statistics for the sample are presented in Table 2. There were no significant differences between *HOMER1* allele groups in age, $F(2, 96) < 1$, $p = .94$, depression symptoms, $F(2, 96) < 1$, $p = .59$, endorsement of positive words in the NAP task, $F(2, 97) < 1$, $p = .51$, or endorsement of negative words, $F(2, 97) < 1$, $p = .59$. However, there was a marginally significant difference between *HOMER1* groups in gender, $\chi^2(2, N = 95) = 5.67$, $p = .059$. There were no significant differences between *BDNF* allele groups in age, $t(95) < 1$, $p = .91$, gender, $\chi^2(1, N = 95) < 1$, $p = .99$, depression symptoms, $t(95) < 1$, $p = .97$, endorsement of positive words in the NAP task, $t(95) < 1$, $p = .60$, or endorsement of negative words, $t(95) < 1$, $p = .71$.

**Manipulation Check—**As in Study 1, we tested whether we achieved the expected negative priming effect across stimulus valence and genotype group. As with Study 1, a paired-samples t-test indicated a significant difference in mean reaction time for prime ($M =$ 905 ms; $SD = 131$ ms) and probe ($M = 920$ ms; $SD = 146$ ms) trials for experimental pairs,

[6]Analyses using the larger, ethnically heterogeneous sample are reported in Online Supplementary Material and were nearly identical to the analyses using the restricted sample.
[7]As in Study 1, analyzing the data with the Val/Met and Met/Met groups separately did not change the results.

$t(96) = 2.58$, $p = .011$, Cohen's $d = .11$, indicating a negative priming effect regardless of stimulus valence or genotype group. Probe trials for experimental pairs were also significantly slower than probe trials for control pairs ($M = 870$ ms; $SD = 136$ ms), $t(96) = 4.49$, $p < .001$, Cohen's $d = .35$, again indicating a significant negative priming effect regardless of valence. Furthermore, prime trials for control pairs ($M = 884$ ms; $SD = 130$ ms) did not differ from probe trials for control pairs, $t(59) = 1.33$, $p = .19$.

**Inhibition of Attention for Affective Material—**A 3 (*HOMER1* genotype: GG, GA, AA) x 2 (stimulus valence: negative, positive) ANOVA revealed a significant main effect for valence on inhibition of attention, $F(1, 94) = 17.45$, $p < .001$, $\eta_p^2 = .16$, but no significant main effect for *HOMER1* genotype $F(2, 94) = 2.05$, $p = .14$. The main effect for valence was driven by greater inhibition of attention for positive words ($M = 59.6$, $SD = 120.4$) compared to negative words ($M = -24.8$, $SD = 116.4$). There was also a significant interaction between *HOMER1* genotype and valence on inhibition of attention, $F(2, 94) = 3.24$, $p = .044$, $\eta_p^2 = .06$. Post-hoc analyses indicated an effect for *HOMER1* genotype on inhibition of attention for negative stimuli, $F(2, 96) = 5.37$, $p = .006$, $\eta_p^2 = .1$, but not for positive stimuli, $F(2, 96) < 1$, $p = .78$. Further post-hoc analyses revealed that differences between *HOMER1* genotype in inhibition of attention for negative words was driven by differences between the GG and GA genotype groups, $t(77) = 3.07$, $p = .003$, Cohen's $d = .7$. There were no significant differences between GG and AA, $t(48) < 1$, $p = .37$, or GA and AA, $t(63) = -1.7$, $p = .1$, groups. These results can be seen in Figure 1. Single sample t-tests were conducted to determine if the inhibition demonstrated for each genotype group significantly differed from zero. The GA group demonstrated an inhibition score significantly less than zero, $t(47) = 3.27$, $p = .002$, Cohen's $d = .95$, but the GG, $t(32) = 1.21$, $p = .24$, and AA, $t(17) < 1$, $p = .82$, groups did not differ from zero.

A 2 (*BDNF* genotype: Val/Val, Met-carrier) x 2 (stimulus valence: negative, positive) ANOVA revealed a significant main effect for valence on inhibition of attention, $F(1, 95) = 23.7$, $p < .001$, $\eta_p^2 = .20$, but not for *BDNF* genotype, $F(1, 95) < 1$, $p = .93$. The interaction between *BDNF* genotype and valence was also not statistically significant, $F(1, 95) < 1$, $p = .38$.[8] Due to the lack of even marginally significant main effects or interaction, we did not conduct post-hoc analyses.

## General Discussion

Results from these two studies indicate that *HOMER1* variation is associated with differences in inhibition of attention to negative emotional material in psychiatrically healthy samples. Both studies demonstrated that the GA genotype is associated with facilitation of response to a negative word on a target trial when a negative word was ignored in the previous trial. The implication of the heterozygous variant was unexpected given previous research which has suggested that the AA variant conveys vulnerability for depression (Rietschel et al., 2010). It is important to note that in both of the current studies the AA group demonstrated inhibition scores which, although not statistically significant,

[8]Again, we conducted these analyses separately by gender and results were not statistically significant for males or females and the pattern of results was very similar to those combining genders.

were in the hypothesized direction. Additional research is needed to resolve this discrepancy and to examine whether *HOMER1* variation plays a role in other cognitive processes associated with psychopathology.

These results add to the literature implicating *HOMER1* gene variation (e.g., Rietschel et al., 2010) or HOMER1 protein expression (e.g., Yang et al., 2013) in cognitive processes, in particular, cognitive processes involving attention. However, it was unexpected that the GA *HOMER1* genotype demonstrated an association specifically with difficulty inhibiting attention for negative information as opposed to with difficulty inhibiting information more generally. Prior research implicated *HOMER1* variability in altered executive functioning but did not find a specific association with negative emotional stimuli (Rietschel et al., 2010). Our findings suggest the potential for a subtle gene by environment (GxE) interaction where the association between *HOMER1* genotype and inhibition of attention is dependent on environmental factors such as the emotional valence of the stimulus. There is a growing interest in whether and how GxE effects play an important role in psychiatric and neuroscientific outcomes (see, for example, Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). The current studies contribute to this burgeoning GxE literature, though these effects should be treated with caution until replicated in larger samples given concerns about low power and replicability of GxE studies (Dick et al., 2015; Duncan & Keller, 2011).

These results have interesting implications in the context of dual process models of cognition, which distinguish between processes that are associative/automatic and those that are reflective/deliberative (for a review see Evans, 2008). The association of HOMER1 variation with attention for negative information (an associative process) but not with differential endorsement of negative words (a reflective process) suggests that HOMER1 variation may exert its effects in more associative contexts than reflective contexts. While speculative, this may reflect an evolutionarily conserved process to attend to negative information. Associative cognitive processes are often considered evolutionarily old (compared to reflective processes) and are shared with other animal species (Evans, 2008), and attention to negative information or threat is an associative cognitive process that is likely evolutionarily adaptive and has been evolutionarily conserved (Öhman, 1997). Such a process could have beneficial effects (e.g., being better able to notice and adaptively respond to negatively-valences socially-relevant information) as well as effects detrimental to wellbeing (e.g., a focus on negative information to the exclusion of positive information leading to negative mood states such as anxiety or depression) while being evolutionarily adaptive on the whole. Continued research in both humans and animals could help explicate these potential evolutionarily conserved processes.

*HOMER1* gene variation has been associated with increased risk for depression in adults (Rietschel et al., 2010) and increased risk of mood disorders in children (Strauss et al., 2012). Our results do not directly link *HOMER1* variation and depression vulnerability, but they do raise the possibility of a mechanism by which *HOMER1* may contribute to depression vulnerability; specifically, that individuals with the GA genotype may have difficulty inhibiting attention to negative affective material. However, it should be noted that the samples from the current studies were psychiatrically healthy without a history of depression. It is possible that these samples are comprised of particularly resilient

individuals. Additional research is needed to examine whether these findings extend to depression vulnerable or currently depressed individuals.

As noted in the discussion of Study 1, the results of these studies did not support a relationship between *BDNF* Val66Met variation and inhibition of attention for emotional information. This was somewhat surprising given that there is an association between Val66Met variation and rumination (Beevers et al., 2009; Clasen et al., 2011) and between difficulty inhibiting attention to emotional material and rumination (Joormann & Gotlib 2008; 2010). Prior work has found that interaction between *BDNF* and serotonin transporter gene variation is associated with cognitive aspects of psychopathology (e.g., Bredemeier, Beevers, & McGeary, 2014; Stone, McGeary, Palmer, & Gibb; Wells, Beevers, & McGeary, 2010) raising the question as to whether examining gene-gene interactions with *BDNF* may reveal important effects obscured by examining BDNF variation in isolation. Additional research is needed to examine other potential mechanisms of the relationship between Val66Met and rumination as well as possible gene-gene interactions.

The use of a non-clinical sample represents both a limitation and an advantage. As noted above, a direct relationship between *HOMER1* and depression cannot be inferred from the current results. However, the results were observed without the confounding influence of psychopathology, which increases our confidence in the association between *HOMER1* variation and difficulty inhibiting attention for negative emotional material.

Future studies are needed to evaluate these SNPs using other measures of affective inhibition, such as recall for previously suppressed affective words (see Joormann, Hertel, LeMoult, & Gotlib, 2009). Variations of the NAP task may clarify whether *HOMER1* variation is associated with inhibition of negative visual material, such as faces (see Goeleven et al., 2006). Additionally, other paradigms may be used to investigate related cognitive processes implicated in depression, such as use of the Sternberg task to evaluate the filtering of negative emotional material from working memory (see Joormann & Gotlib, 2008). Other research may examine whether *HOMER1* variation plays a role in processes theoretically related to inhibition and deficits in cognitive control, such as rumination and emotion regulation.

Some limitations must be considered in the interpretation of these data. Analyses considered two candidate genes and did not assess how *HOMER1* or *BDNF* may interact with each other or other genes associated with attention to emotional material. Given the relationship between inhibition of attention and rumination (e.g., Joormann & Gotlib 2010) and BDNF variation and rumination (e.g., Beevers et al., 2009), it would have been beneficial to have directly measured rumination in the current studies. Future research would do well to integrate multiple measures at multiple levels of analysis (e.g., self-report, cognitive, neural) when examining similar gene-phenotype relationships. Additionally, an alternative explanation of the significant results is that there may be a nonrandom association between the *HOMER1* and another functional gene (i.e. linkage disequilibrium). That is, it may be the other (unknown) functionally associated gene that is responsible for the observed results. This is a limitation that is common to candidate gene studies. As noted in the discussion for Study 1, population stratification may be a threat to internal validity in gene association

studies. However, Study 1 did not contain statistically significant differences in allele frequencies across demographic variables, and Study 2 examined a racially homogenous sample, which mitigates this threat to the associations reported here. Both of our studies had small sample sizes, which provides low power to detect small effect sizes. The fact that we found the same pattern of results across two independent samples helps mitigate concerns regarding Type I error for the *HOMER1* findings and Type II error for the nonsignificant *BDNF* findings. Nevertheless, given the inconsistency often found in the field of psychiatric genetics, examining these associations in larger samples will be important in order to increase confidence in the stability and veracity of the effects reported here (see, for example, Ioannidis, 2013).

Overall, the current findings contribute to our knowledge of the relationship between *HOMER1* variation and inhibition of attention. Specifically, these data advance our understanding of contributions of genetic variation to inhibition of negatively valenced affective material. These results expand our knowledge of the potential psychological phenotypic expression of *HOMER1* variation. Future work would do well to replicate these effects in larger samples while examining potential epistatic interactions between *HOMER1* and other genetic variants.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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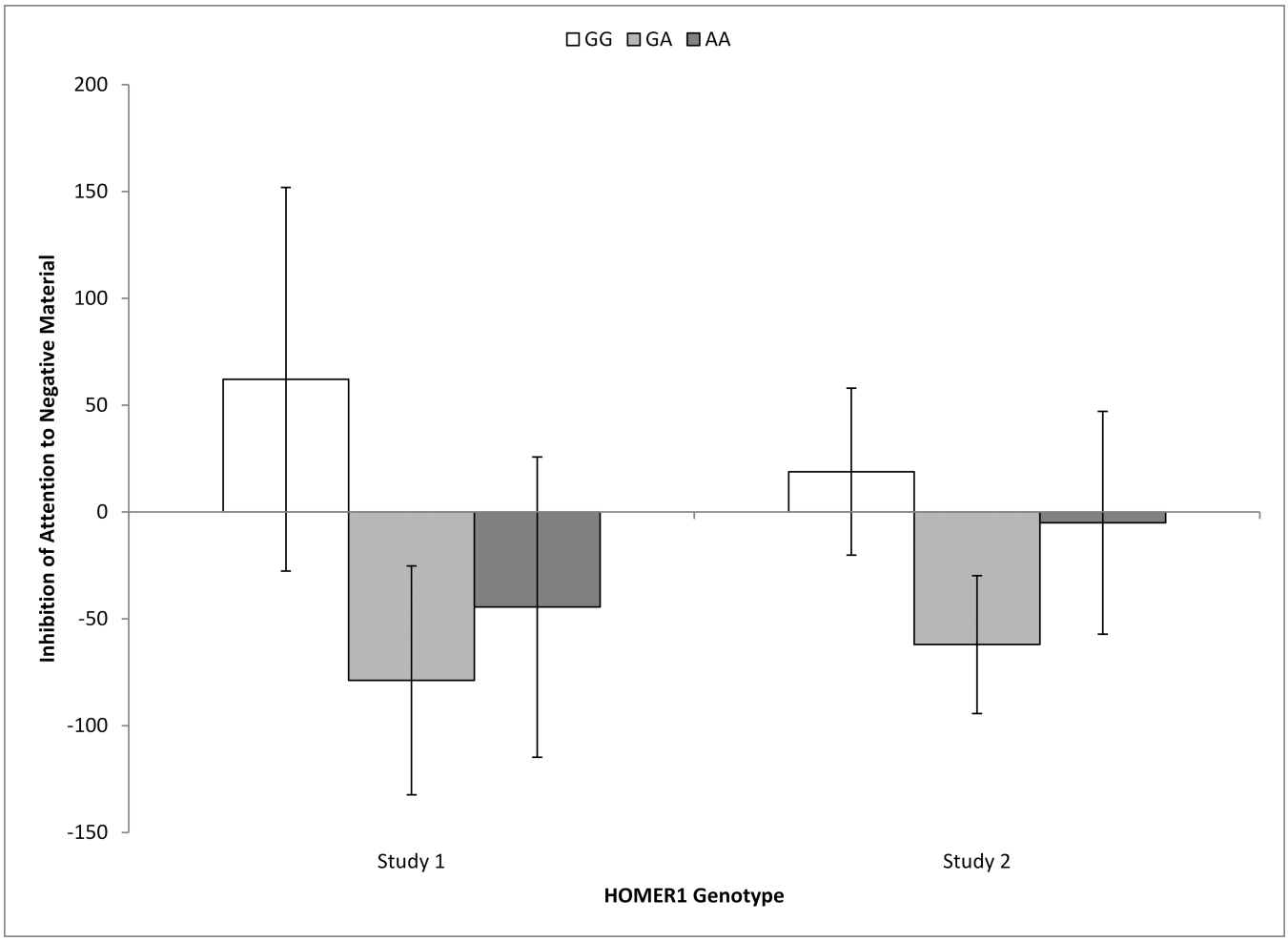


**Figure 1.**

Inhibition of attention to negatively-valenced affective words by *HOMER1* genotype group. Positive scores indicate greater inhibition while negative scores indicate facilitation. Error bars represent the 95% CI of the mean.

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**Table 1**

Demographic characteristics for Study 1. BDI-II = Beck Depression Inventory II.

| | Allele Status | | | | |
|---|---|---|---|---|---|
| | ***HOMER1*** | | | ***BDNF* Val66Met** | |
| **Demographic** | **GG** | **GA** | **AA** | **Val/Val** | **Met Carrier** |
| *n* | 11 | 31 | 18 | 25 | 35 |
| Age (Years) | 23.6 (2.1) | 25.2 (5.5) | 25.2 (4.5) | 24.9 (4.0) | 24.9 (5.2) |
| Gender | | | | | |
| Female | 7 | 13 | 14 | 17 | 17 |
| Male | 4 | 17 | 4 | 7 | 18 |
| Did not report | 0 | 1 | 0 | 1 | 0 |
| Race | | | | | |
| Asian | 5 | 17 | 8 | 11 | 19 |
| Black/African American | 0 | 1 | 4 | 4 | 1 |
| White/Caucasian | 6 | 10 | 2 | 7 | 11 |
| Multiple | 0 | 0 | 4 | 1 | 3 |
| Other* | 0 | 3 | 0 | 2 | 1 |
| Depressive symptoms (BDI-II) | 4.8 (3.9) | 3.2 (3.2) | 2.8 (2.9) | 2.5 (2.5) | 3.9 (3.7) |
| Positive Words Endorsed | 41.4 (6.9) | 44.6 (4.9) | 45.0 (7.6) | 45.5 (4.8) | 43.2 (7.0) |
| Negative Words Endorsed | 6.5 (7.8) | 3.4 (4.2) | 2.5 (4.5) | 3.0 (5.0) | 4.2 (5.4) |

*Includes American Indian, Native Hawaiian, and None/Did not report

**Table 2**

Demographic characteristics for Study 2. BDI-II = Beck Depression Inventory II.

| | Allele Status | | | | |
|---|---|---|---|---|---|
| | *HOMER1* | | | *BDNF* Val66Met | |
| **Demographic** | **GG** | **GA** | **AA** | **Val/Val** | **Met Carrier** |
| *n* | 32 | 47 | 18 | 58 | 39 |
| Age (Years) | 18.8 (0.8) | 18.7 (0.9) | 18.6 (0.8) | 18.7 (0.8) | 18.7 (0.8) |
| Gender | | | | | |
| Female | 12 | 19 | 11 | 30 | 20 |
| Male | 20 | 28 | 5 | 27 | 18 |
| Did not report | 0 | 0 | 2 | 1 | 1 |
| Depressive symptoms (BDI-II) | 3.2 (2.8) | 2.9 (3.3) | 3.5 (3.4) | 2.3 (3.1) | 3.1 (3.2) |
| Positive Words Endorsed | 45.5 (3.9) | 45.3 (4.9) | 46.7 (2.3) | 45.4 (4.7) | 45.9 (3.3) |
| Negative Words Endorsed | 2.4 (2.0) | 3.0 (4.4) | 2.1 (2.6) | 2.5 (3.1) | 2.8 (3.9) |