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Pleiotropic locus for emotion recognition and amygdala volume identified using univariate and bivariate linkage

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Abstract

The role of the amygdala in emotion recognition is well established and separately each trait has been shown to be highly heritable, but the potential role of common genetic influences on both traits has not been explored. Here we present an investigation of the pleiotropic influences of amygdala and emotion recognition in a sample of randomly selected, extended pedigrees (N = 858). Using a combination of univariate and bivariate linkage we found a pleiotropic region for amygdala and emotion recognition on 4q26 (LOD = 4.34). Association analysis conducted in the region underlying the bivariate linkage peak revealed a variant meeting the corrected significance level ($p_{Bonferroni} = 5.01\times10^{-05}$) within an intron of *PDE5A* (rs2622497, $X^2 = 16.67$, $p = 4.4\times10^{-05}$) as being jointly influential on both traits. *PDE5A* has been implicated previously in recognition-memory deficits and is expressed in subcortical structures that are thought to underlie memory ability including the amygdala. The present paper extends our understanding of the shared etiology between amygdala and emotion recognition by showing that the overlap between the two traits is due, at least in part, to common genetic influences. Moreover, the present paper identifies a pleiotropic locus for the two traits and an associated variant, which localizes the genetic signal even more precisely. These results, when taken in the context of previous research, highlight the potential utility of PDE5-inhibitors for ameliorating emotion-recognition deficits in populations including, but not exclusively, those individuals suffering from mental or neurodegenerative illness.

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Introduction

The ability to successfully process and label the emotions of others is crucial to human social-interaction (1). Impaired emotion-recognition is a hallmark of a number of psychiatric disorders including schizophrenia, bipolar and major depressive disorder (2,3). Similarly emotion-recognition deficits also occur in neurodegenerative illness like Parkinson's and Alzheimer's disease (4,5). Furthermore, there is considerable evidence for individual differences in emotion recognition in healthy populations (6), and that a substantial portion of that variation appears to be under genetic influence (7). While multiple neural systems putatively sub-serve emotion recognition, the amygdala appears to have a preferential role in affect processing in both healthy and mentally ill individuals (1,8–10). As the structure of the amygdala is influenced by genetic factors (11,12), it is possible that the same genes that influence emotion recognition also influence amygdala volume and vice versa. However, it remains unclear whether the association between amygdala volume and emotion recognition is due to common genetic influences, and if so which genes in particular. Identifying genes with pleiotropic influence on both traits might reveal those molecular mechanisms that alter brain architecture and/or function, which in turn affect emotion-recognition performance. In an effort to further our understanding of the molecular underpinnings of emotion recognition the present paper aims to isolate genes that jointly influence emotion recognition and amygdala volume randomly selected, extended pedigrees.

Numerous neural systems are implicated in emotion recognition and in particular those systems reside in the frontal and temporal lobes, which together make up the neural pathways responsible for the interpretation of visual emotional stimuli (9,13). After a visual stimulus is processed via the lateral geniculate nucleus and V1, the amygdala becomes the focus of further processing in the brain, where it is the recipient of input from both cortical and sub-cortical streams (14). The amygdala was first implicated in emotional capacity by Brown and Shafer (15) who noted that monkeys with bilateral temporal lobe lesions were rendered tame and docile; and later this type of lesion was linked to emotion processing and more specifically fearful responses (16,17) Then later work in primates and rodents narrowed the region of interest for emotion processing down to the amygdala (18,19). The role of the amygdala in emotion recognition, and in particular the recognition of negative emotions, was confirmed in humans by lesion studies (20,21) as well as a number of functional imaging studies (10,22,23). While there is evidence that variation in the serotonin transporter gene influences the amygdala's response to emotive faces (24), the complete genetic architecture of amygdala function and structure is largely unknown (25).

There have been a handful of candidate gene studies with a focus on emotion-recognition ability (26,27) as well as amygdala volume in healthy and depressed individuals (28–32). A genome-wide linkage study isolated a significant QTL for emotion recognition on chromosome 1p36 in a sample selected for schizophrenia (33). However, there have been no genome-wide searches for amygdala volume, nor have there been attempts to disentangle the pleiotropic effects on the traits using multivariate analyses, where multivariate analyses are statistically more powerful than univariate ones if traits are genetically correlated (34–36).

Here, we report on bivariate linkage and association analysis in a sample of 897 Mexican-American individuals from extended pedigrees. We identify a region of chromosome 4 as being truly pleiotropic for bilateral amygdala volume and emotion-recognition ability using bivariate linkage analysis. Using association analysis of common variants within that linkage region we identify a gene, *PDE5A*, as being influential on both traits.

Methods

Participants

The sample comprised 858 Mexican American individuals from extended pedigrees (115 families, average size 7.53 people, range = 1–89). The sample was 63% female and had a mean age of 44.78 (SD = 15.19; range = 18–97). Individuals in this San Antonio Family Study cohort have actively participated in research for over 18 years and were randomly selected from the community with the constraints that they are of Mexican American ancestry, part of a large family, and live within the San Antonio region (see (37)) for recruitment details).

All participants provided written informed consent on forms approved by the institutional review board at the University of Texas Health Science Center of San Antonio.

Neuropsychological Assessment

As part of the “Genetics of Brain Structure and Function” protocol, each participant completed a 90-minute neuropsychological test battery consisting of standard and computerized measures (38,39), including the Penn Emotion Recognition Task (40). This computer-based emotion recognition task consists of 40 color photographs of facial expression of emotions including: happy, sad, angry, fearful and neutral (see Figure 1 for examples of the stimuli). The stimuli are balanced for the poser’s gender and ethnicity across emotions. During the task participants are required to identify which emotion (happy, sad, angry, fearful or neutral) best describes each face stimulus. The emotion recognition phenotype in the present study is a summed score across all stimuli.

MRI Acquisition

All images were acquired on a research-dedicated, Siemens 3T TIM Treo MR scanner and a high-resolution phase array head coil housed in the Research Imaging Institute, UTHSCSA. Seven high-resolution T1-weighted 3D turbo-flash sequences with an adiabatic inversion contrast pulse were acquired in each subject using the following parameters: TE/TR/TI = 3.04/2100/785 ms, flip angle=13°, 800μm isotropic resolution (41).

Image Processing

The freely available software package FreeSurfer (http://surfer.nmr.mgh.harvard.edu/, (42,43), as implemented in our group (12), was used to extract amygdala volume for subsequent genetic analyses. These methods were described previously (44,45). Briefly, Fischl and colleagues developed a procedure for automatically and accurately labeling each voxel in the brain as one of 40 subcortical structures (e.g., thalamus, hippocampus, amygdala, etc.). This procedure is based on modeling the segmentation as a nonstationary

anisotropic Markov Random Field (MRF), in which the probability of a neuroanatomic label is modulated by that of its neighbors. Probabilities were computed separately at each position in an atlas resulting in a maximum *a posteriori* estimation of each voxel's label in each image. Amygdala volume was averaged across hemispheres, yielding an average volume phenotype for each subject.

Data Analysis

Genotyping

Subjects were genotyped for approximately one million SNPs using Illumina HumanHap550v3, HumanExon510Sv1, Human1Mv1 and Human1M-Duov3 BeadChips, according to the Illumina Infinium protocol (Illumina, San Diego, CA). SNP loci were checked for Mendelian consistency utilizing SimWalk2 (46). SNPs or samples exhibiting high calling rate failures or requiring excessive blanking (i.e., if <95% of the genotypes are retained) were eliminated from analyses. Missing genotypes were imputed according to Mendelian laws based on available pedigree data using MERLIN (47). Maximum likelihood techniques, accounting for pedigree structure, were used to estimate allelic frequencies (48). For linkage analyses, multipoint identity-by-descent (IBD) matrices were calculated based on 28,387 SNPs selected from the 1M GWAS panel as follows. Using genotypes for 345 founders, SNPs on each chromosome were selected to be at least 1kb apart, MAF >= 5%, and LD within a 100kb sliding window not exceeding |rho| = 0.15. The resulting selection averaged 7–8 SNPs/centimorgan. For each centimorgan location in the genome, multipoint IBD probability matrices were calculated using a stochastic Markov Chain Monte Carlo procedure implemented in the computer package, LOKI (49).

Confirmatory Factor Analysis

Given that the aim of the present study was to identify genes with pleiotropic effects on both amygdala volume and emotion recognition it was important to be able to conduct multivariate analyses beyond bivariate linkage. To this end a simple one-factor confirmatory factor model was built using two items, amygdala volume and emotion recognition, where, in order to ensure that each trait contributed to the factor score equally, factor loadings were constrained to be equal which is also requirement of the model being identified. This model was built using Mplus (50) where family structure was taken into account using the *cluster* command.

Quantitative Genetic Analyses

All genetic analyses were performed in SOLAR (34). SOLAR implements a maximum likelihood variance decomposition to determine the contribution of genes and environmental influence to a trait by modeling the covariance among family members as a function of expected allele sharing given the pedigree. In the simplest such decomposition, the additive genetic contribution to a trait is represented by the heritability, or h^2, index. First, univariate variance decomposition analysis was applied to both bilateral amygdala volume and emotion recognition performance. Both traits were normalized using an inverse Gaussian transformation. Age, age^2, sex and their interactions were included as covariates. Second, bivariate analysis was applied to the two variables where the phenotypic covariance between

the traits was decomposed into its genetic and environmental constituents to determine the extent they are influenced by shared genetic effects (e.g. genetic correlation, r_g).

Linkage and Association Analyses

Quantitative trait linkage analysis was performed to localize specific chromosomal locations influencing amygdala volume and emotion-recognition ability (34). Initially this was done under a univariate model for each trait. Model parameters were estimated using maximum likelihood. The hypothesis of significant linkage was assessed by comparing the likelihood of a classical additive polygenic model with that of a model allowing for both a polygenic component and a variance component due to linkage at a specific chromosomal location (as evidenced by the location-specific identity-by-descent probability matrix). The LOD score, given by the log10 of the ratio of the likelihoods of the linkage and the polygenic null models, served as the test statistic for linkage. Genome-wide thresholds for linkage evidence were computed for this exact pedigree structure and density of markers, using a method derived from (51): a LOD of 1.69 is required for suggestive significance (likely to happen by chance less than once in a genome-wide scan) and a LOD of 2.9 is required for genome-wide significance. Regions showing potential pleiotropy were subjected to bivariate linkage analysis; for comparison to the univariate results, the resulting LOD was converted to a 1df equivalent based on the p-value for the 2df test (linkage to both traits vs. linkage to neither) (52). To ensure that the bivariate LOD scores were truly driven by both and not one of the traits we tested the null hypothesis of the absence of pleiotropy (i.e., co-occurrence of linkage is by chance) versus the alternative of complete pleiotropy by comparing the likelihoods of the relevant nested models. To this end we maximized two models, one where the genetic correlation between linkage peaks was allowed to vary freely and a null where this correlation was constrained to be zero; the likelihoods of these two models were then compared, twice the difference between these two log-likelihoods being distributed as a chi-square with 1 degree of freedom. This method has been established as powerful approach for detecting pleiotropic effects (53).

Genomic regions meeting bivariate genome-wide significance for linkage were investigated in greater detail using association analysis of the emotion and amygdala confirmatory factor score and the genetic variants encapsulated by the linkage peak. Statistical significance levels were established according to the effective number of tested variants given the linkage disequilibrium (LD) structure in the region, to this end the pairwise genotypic correlations are calculated in an effort to establish the effective number of independent tests carried out during association analysis. This method, by Moskvina and Schmidt (54), is considered to be conservative and entails computing the eigenvalues of the genotypic correlation matrix. A corrected *P*-value is obtained from a Bonferroni correction based on the nominal alpha (=0.05) and the total number of independent tests.

Results

Heritability and Linkage Analysis

Both amygdala volume (h^2 = 0.72, s.e. = 0.07, $p = 4.95\times10^{-05}$, *mean* = 3066.72, *s.d.* = 434.47) and emotion recognition (h^2 = 0.32, s.e. = 0.06, $p = 5.12\times10^{-10}$, $mean_{happy}$ = 7.78,

$s.d._{happy}$ = 1.47, $mean_{sad}$ = 6.15, $s.d._{sad}$ = 1.40, $mean_{fear}$ = 6.61, $s.d._{fear}$ = 1.36, $mean_{anger}$ = 5.56, $s.d._{anger}$= 2.21, $mean_{neutral}$ = 5.58, $s.d._{neutral}$ = 4.37) were highly heritable and a bivariate model indicated significant genetic overlap between the two traits (r_g = 0.25, s.e. = 0.13 p = 0.048). For amygdala volume and emotion recognition age and sex were significant covariates (Table S1) and as such the effect of age and sex was covaried for in all subsequent analyses. The factor score derived for emotion recognition and amygdala volume was also highly heritable (h^2 = 0.45, se = 0.06, $p = 5.68\times10^{-22}$) and the factor loadings for both traits were deemed to be significant at the $p<0.001$ level, goodness of fit statistics were not available due to saturation of the model.

For amygdala volume, one genome-wide significant locus was observed on chromosome 4 at 120cM (LOD = 4.065). A LOD of 2.175 was observed for the emotion-recognition task on chromosome 2 at 71cM, meeting criteria for suggestive significance, while the chromosome 4 locus showed some evidence for linkage to emotion recognition (LOD = 1.217; see Figure 2). Bivariate linkage revealed a genome-wide significant QTL for both amygdala and emotion recognition on chromosome 4 at 122cM (1df-equivalent LOD = 4.399), which suggests that this region of chromosome 4 mediates both amygdala volume and performance on the emotion recognition task. The test for pleiotropy vs. coincident linkage confirmed the presence of pleiotropy for the two traits at this locus (X^2 = 20.12, df=1, $p = 3.6\times10^{-06}$). The factor score, derived from the one-factor model of emotion recognition and amygdala volume, showed genome-wide significant linkage at precisely the same region on chromosome 4 at 122cM (LOD = 3.336).

The possible confounding role of intracranial volume at this locus was investigated using trivariate linkage. Univariate linkage revealed a QTL of suggestive significance for intracranial volume on chromosome 16 at 37cM (LOD = 2.65) with little evidence for genetic influence on this trait on chromosome 4 at 122cM (LOD = 0.47). Moreover, in a trivariate linkage model of the emotion-recognition task, amygdala volume and intracranial volume on chromosome 4 at 122cM showed genome-wide significance (1 df-equivalent LOD = 3.546), and even within this trivariate model (which takes into account the influence of intracranial volume) the pleiotropy test supported complete pleiotropy between amygdala and emotion recognition (X^2 = 7.74, $p = 2.7\times10^{-03}$). Furthermore, the possibility that the right or left amygdala might be driving the result was addressed by running univariate and bivariate linkage in the same region. Left amygdala (h^2 = 0.7019, s.e. = 0.0788, $p = 2.03\times10^{-21}$) had a univariate LOD of 3.315 on chromosome 4 at 120cM and right amygdala (h^2 = 0.6958, s.e. = 0.0754, $p = 1.43\times10^{-23}$) had a univariate LOD of 3.103 in the same location. Moreover, bivariate linkage analysis with left amygdala and emotion recognition (rho_g = 0.24) revealed a bivariate LOD of 3.282 on chromosome 4 at 122cM, while bivariate linkage analysis with right amygdala and emotion recognition (rho_g = 0.27) revealed a bivariate LOD of 3.6812 on chromosome 4 at 122cM. These results support the idea that the shared genetic influence on amygdala volume and emotion recognition is not lateralized to either the left or right amygdala.

Association Analysis

Association analysis was conducted for all genetic variants under the 1-LOD confidence interval of the bivariate linkage peak (defined as 120–124cM) and a factor score derived from amygdala volume and emotion recognition. In total there were 2053 SNPs in this region but after taking into account LD (54) there were 1023 effective SNPs, necessitating a Bonferroni corrected alpha of 5.01×10^{-05}. One variant, rs2622497 ($p = 4.40 \times 10^{-05}$) met the adjusted-significance level and was located within an intron of the gene *PDE5A* (*phosphodiesterase 5A, cGMP-specific*). Several other variants met a suggestive-level of significance that also fell within *PDE5A* in addition to a number of variants downstream of the gene, all of which were in varying degrees of LD with the top-ranked variant (see Table 1 and Figure 3). Univariate association analysis for each individual trait for rs2622497 did not reach significance either for the amygdala ($p = 1.0\times10^{-03}$) or for emotion recognition ($p = 4.1\times10^{-03}$).

If the SNP rs2622497 is included as a covariate in the linkage analysis of the factor score derived from emotion recognition and amygdala volume the LOD score observed without the covariate (LOD = 3.336) was reduced (LOD = 2.506) and no longer significant. This linkage conditional on association test gives additional support for the association between rs2622497 and emotion recognition and amygdala.

Given the significant effect of age and sex on amygdala volume the interactive effect of genotype and sex and age were included as covariates in the association analysis. For our top SNPs there was a significant interaction with sex (sex*snp_rs2622497, $\beta = 0.9823664$, $p = 0.0032331$; sex*snp_rs2715021, $\beta = 0.9887387$, $p = 0.0032051$; sex*snp_rs9884801, $\beta = 0.9857738$, $p = 0.0038682$; Figures S1–3) but not with age. In each case the sex*snp interactions indicated that the effect was marginally more pronounced in men than in women however the direction of the effect was the same in both groups. Consequently an interaction term for sex*genotype was included in all association analysis.

Discussion

While numerous studies highlight an association between the amygdala and emotion recognition (10,20–23), the present study extends this finding by providing evidence for a pleiotropic locus on chromosome 4 using bivariate linkage. Furthermore, by examining variants within the quantitative locus, we identify a variant (rs2622497) within the intron of *PDE5A* that appears to jointly influence amygdala volume and emotion recognition. To our knowledge this is the first study to formally test the common genetic influences on amygdala volume and emotion-recognition ability using a bivariate model. It is well established that the implementation of a bivariate versus a univariate model is beneficial as the joint analysis of multiple traits confers greater power and precision in the mapping of a QTL (34,55,56).

The cyclic nucleotide phosphodiesterases (PDE) are a family of enzymes with two main subtypes, cAMP- and cGMP-specific nucleotides. The *PDE5A* gene codes for PDE5, a cGMP-specific PDE (57). Cyclic guanosine monophosphate (cGMP), a second messenger, is crucial to signal transduction between cells as well as synapse communication and

synaptic plasticity (58), as such PDEs are important for effective cell-to-cell communication in the central nervous system and in the brain (57). Indeed, there is widespread expression of *PDE5A* throughout the body and it is also expressed in various regions of the brain, including in the amygdala (59), the pyramidal cells of the hippocampus, Purkinje cells in the cerebellum and in some areas of the cortex (60,61). As such PDE5 has emerged as a potential drug target for treating cognitive deficits (57,62). Through the use of mouse models it has emerged that administration of PDE5-inhibitor sildenafil (more commonly known as Viagra; Pfizer) improves memory, including recognition memory as well as spatial and fear-conditioning memory, in aged rats (63,64) and also ameliorates cognitive deficits associated with Huntington's Chorea and Alzheimer's Disease, by increasing the levels of cGMP in the hippocampus (65–67). Thus given that the present study shows an association between *PDE5A* and emotion recognition, which can be regarded as a type of recognition memory insofar as participants are required to access information stored in long-term memory of emotional subtypes (68), and that previous research has shown an association between PDE5-mediated levels of cGMP in the hippocampus it seems that the findings of the present study are in line with previous literature in the field.

Recognition necessitates knowledge retention, which is enhanced by contextual association. In the case of emotion recognition, this might include associations formed by previous experiences whereby a particular facial configuration has come to be associated with a particular emotion. Such examples might include life events which precede or co-occur with the expression of a particular emotion, with what that person said while experiencing that emotion or what was said about them during that time, with how one felt upon seeing the expression and so on (68). If this were the case then emotion recognition should require access to long-term memory, even when the emotional stimulus is portrayed by a stranger, and so it seems plausible that emotion recognition is supported by a distributed neural network that includes those brain regions typically implicated in memory performance in addition to the amygdala (10,69). In this context, *PDE5A*, a gene expressed particularly in the cerebellum and hippocampus, is especially interesting. Indeed, the cerebellum and the hippocampus, and for that matter the amygdala, have been implicated in long-term memory activation in humans (70). It is of note that in the present sample there exists significant genetic correlation between amygdala and both cerebellum ($rho_g = 0.30$, $p = 2.5\times10^{-03}$) and hippocampus ($rho_g = 0.66$, $p = 2.15\times10^{-14}$). A tentative hypothePsis from the results of the present study is that emotion recognition might be improved with the administration of PDE5-inhibitor, which would be in line with research outlined above (63,64) and would have substantial implications for those individuals for whom emotion recognition proves difficult, for example, those people that suffer from schizophrenia (2).

Rare variation is a likely source of family-based linkage signals associated with complex traits (71,72). Therefore, it is unsurprising that those SNPs showing strongest association with amygdala volume and emotion recognition in the present study are relatively rare (Table 1). The use of extended pedigrees, such as those presented in the current study, improve the chance of detecting association to rare variants. This is because pedigree-based studies represent an implicit enrichment strategy for identifying rare variants. Mendelian transmissions from parents to offspring maximize the chance that multiple copies of rare

variants exist in the pedigree. Thus, pedigree-based studies have optimal power to detect effects of rare variants and so it is unlikely that the associations shown in the present study are false-positives, particularly given that the variants in question do not show a significant departure from the Hardy-Weinberg Equilibrium (Table 1). Our top-ranked variant (rs2622497) appears to be similarly rare across populations (Table S2, (73))

The results of the present study could be called into question if the genetic effects detected were in fact univariate in nature (e.g. driven by only one of the phenotypes, perhaps in particular by the amygdala). However, the linkage signal was subject to a pleiotropy test and was shown to be truly pleiotropic. Furthermore, the factor score derived from the factor model can be said to be driven by both traits equally as the factor loadings, which are used to determine each individuals factor score, were constrained to be equal. Although, it is the case that no formal test can be applied to the association analysis to further underscore the bivariate underpinnings of the signal.

There is some evidence from previous research that is suggestive of a modulatory effect of age on amygdala volume and emotion recognition (74–76) as well as interactions between sex and genotype on amygdala volume (77). As such, in the present study the effects of age and sex were controlled for in all analyses, including in the association analysis where an additional interaction covariate (sex*snp) was included. A significant sex*snp interaction was evident for amygdala volume for our top three SNPs (Figure S1–3) such that the effect of genotype was slightly more pronounced in men than in women but the direction of effect of was the same.

Patients with schizophrenia exhibit substantial and robust impairments in emotion-recognition ability (40,78). It is interesting then that the gene implicated in the present paper, *PDE5*, codes for a member of the phosphodiesterase enzyme family as phosphodiesterase genes, and in particular cAMP-specific *PDE4*, have been implicated in schizophrenia risk (79,80). Moreover, administration of rolipram (a PDE4-inhibitor) reduces phencyclidine induced cognitive impairments in humans, where phencyclidine is an established pharmacological model of schizophrenia symptomatology (81). Phosphodiesterases have also been shown to have potential utility in the treatment of Alzheimer's Disease and in particular the associated cognitive impairment (82,83). Furthermore, the administration of a PDE5-inhibitor has been shown to reduce symptoms of depression and cognitive impairment in a recent placebo-controlled study (84). The established role of phosphodiesterases in psychopathology and cognitive impairment in psychiatric illness, taken together with the results of the present study, highlight the potential utility of PDE5-inhibitors in the treatment of emotion-recognition impairments in schizophrenia, depression and Alzheimer's disease.

In summary, the linkage and association findings presented in the current study highlight a pleiotropic gene, *PDE5A*, for amygdala volume and emotion-recognition ability. This is the first paper to identify a common genetic locus that influences these two traits. Although this study is conducted in healthy individuals, when taken in the context of previous research, which has shown the potential utility of PDE5-inhibitors as cognitive enhancers, it suggests that *PDE5A* may be an important target for ameliorating emotion-recognition deficits in

certain populations including, but not exclusively, those individuals suffering from mental or neurodegenerative illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Examples of facial emotion stimuli taken from the Penn Emotion Recognition Task (40). The emotions depicted, from left to right (where the upper image is a mild expression of emotion and the lower is intense), are as follows: angry, disgusted, surprised, happy, neutral, and sad.

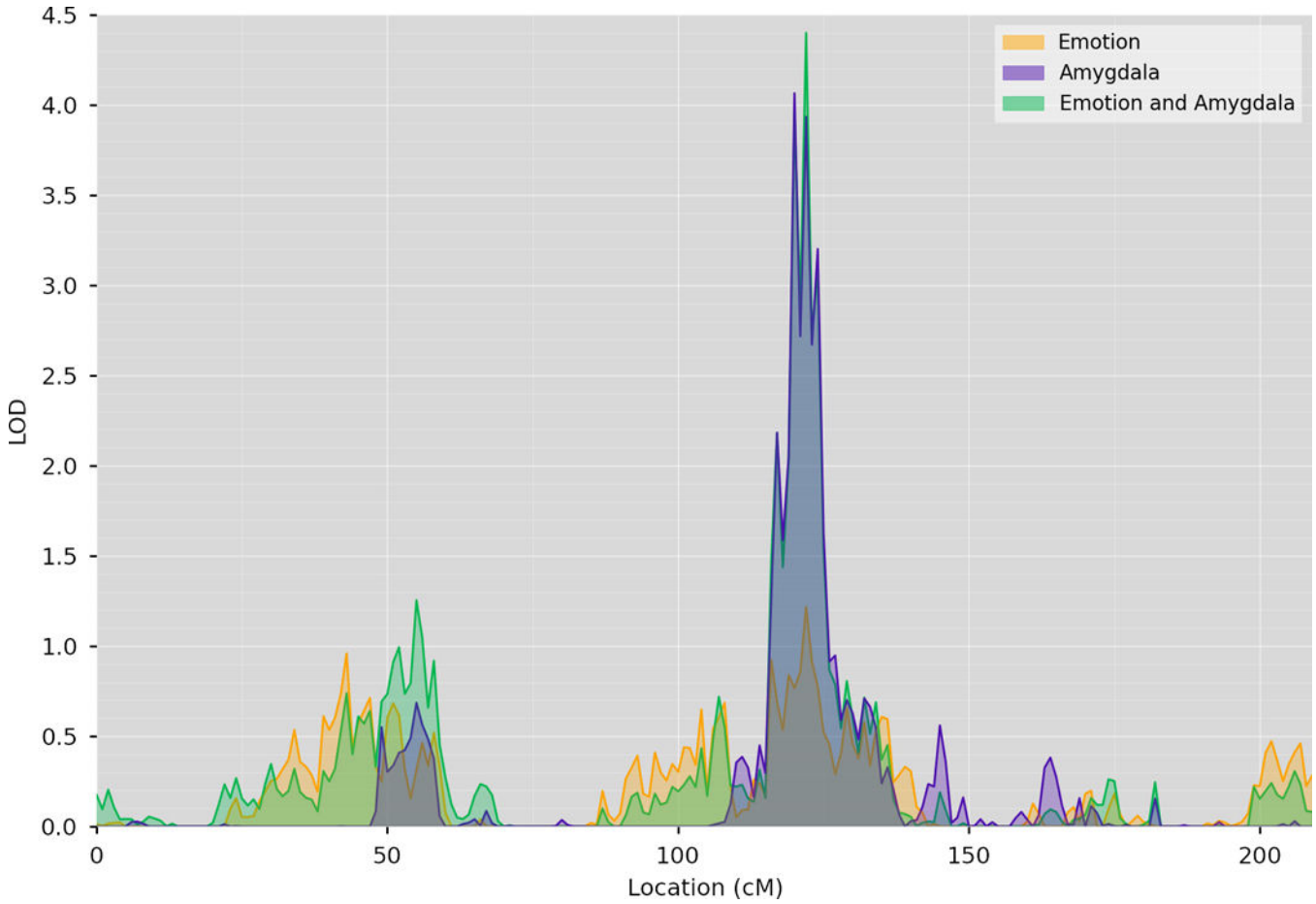

Figure 2.

Linkage analysis. Chromosome 4 multipoint plot for univariate and bivariate analyses where univariate analysis revealed a genome-wide significant QTL for amygdala volume (purple) and near suggestive significance for emotion recognition (orange), and bivariate analysis revealed a genome-wide significant linkage signal for both traits.

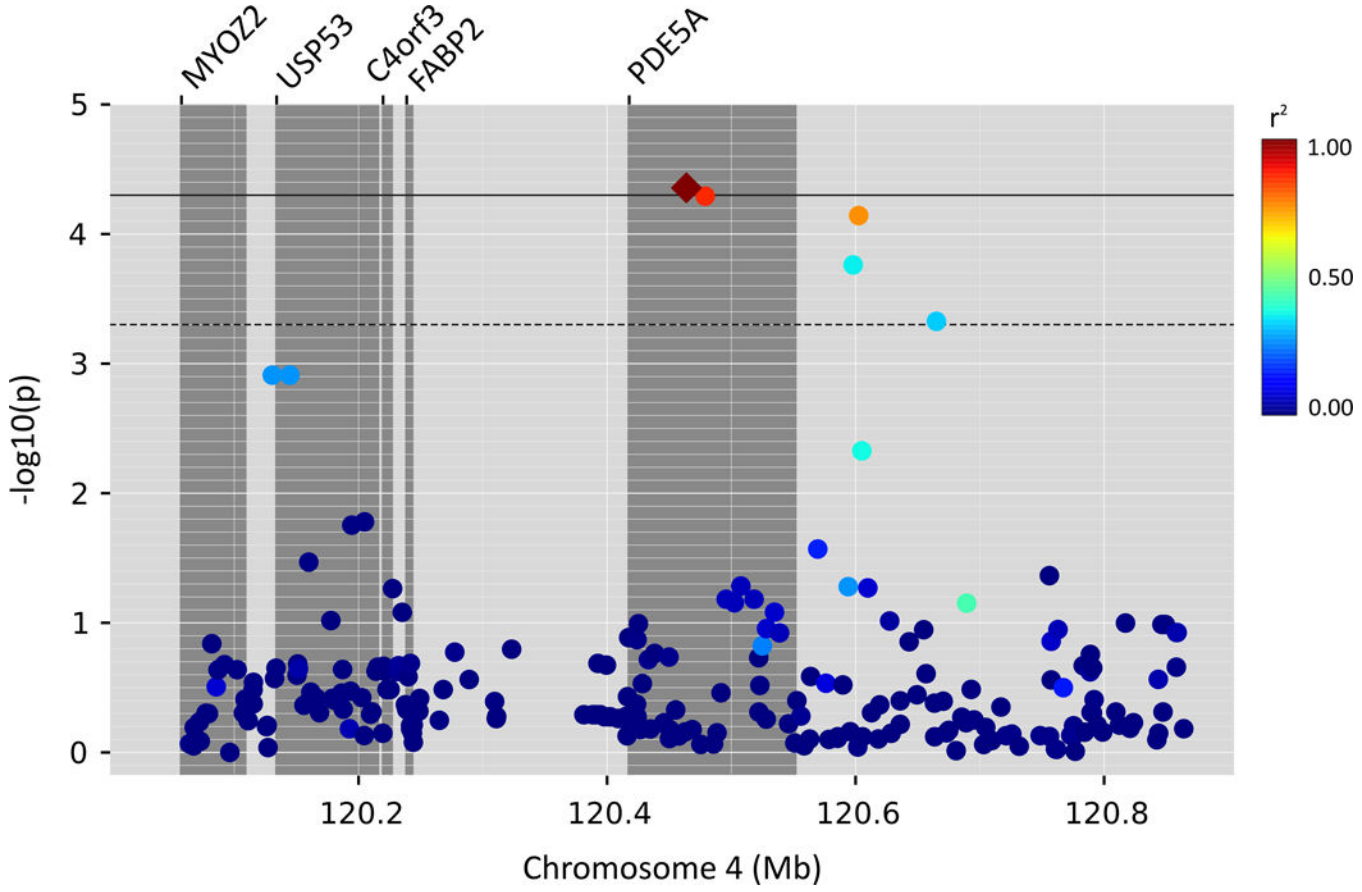

Figure 3.

QTL-specific association analysis for the genome-wide significant QTL region associated with amygdala volume and emotion recognition on chromosome 4. Intergenic regions are pale gray and genes are represented by dark grey bars with the gene name shown at the top of the plot. The top-ranked variant in this region is represented by a diamond and the degree of LD (r^2) with this variant is represented by the colour-scale shown on the far right.

Table 1

Estimates of X^2, size and direction of effect, variance explained, MAF and the HWE *p*-value for the top-five ranked SNPs from the QTL-specific association analysis for the bivariate emotion recognition and amygdala volume factor score.

SNP	X^2	*p-value*	β	Variance Explained	MAF	*p*-value HWE
rs2622497	16.67	0.000044	−0.07	0.02	0.008	0.84
rs2715021	16.42	0.000051	−0.07	0.02	0.008	0.73
rs9884801	15.76	0.000072	−0.07	0.02	0.006	0.88
rs2389894	14.10	0.000173	−0.05	0.01	0.014	0.13
rs2714982	12.22	0.000472	−0.05	0.01	0.015	0.62