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The effects of gender and Catechol O-Methyltransferase (COMT) Val108/158Met polymorphism on emotion regulation in Velo-Cardio-Facial Syndrome (22q11.2 Deletion Syndrome): a fMRI study

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Abstract

Velocardiofacial syndrome (VCFS) is caused by a micro-deletion of over 40 genes at the q11.2 locus of chromosome 22 and is a risk factor for the development of schizophrenia and other psychiatric disorders. COMT, one of the genes located in the deleted region, has been considered as a major candidate gene for genetic susceptibility in psychiatric diseases. Its functional polymorphism Val108/158Met has been shown to affect prefrontal function and working memory and has been associated with emotional dysregulation. We utilized a functional magnetic resonance imaging (fMRI) event-related paradigm to asses COMT genotype and gender-moderated effects on the neural activation that are elicited by viewing emotionally salient images charged with pleasant, unpleasant, and neutral content. Since estrogen down-regulates COMT activity resulting in lower COMT activity in women than men, we hypothesized an allele-by-gender interaction effect on neural activation. Participants included 43 VCFS individuals (Val/Male=9, Val/Female=17, Met/Male=9, Met/Female=8). We observed a gender effect on processing positive emotions, in that girls activated the cingulate gyrus more than boys. We further observed a significant gender-by-allele interaction effect on neural function specific to the frontal lobe during the processing of pleasant stimuli, and specific to limbic regions during the processing of unpleasant stimuli. Our results suggest that in VCFS, the effect of the COMT Val108/158Met polymorphism is moderated by gender during the processing of emotional stimuli and could contribute to the understanding of the way in which this COMT polymorphism affects vulnerability to neuropsychiatric disorders.

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1. Introduction

Velocardiofacial syndrome (VCFS) is caused by a micro-deletion of over 40 genes at the q11.2 locus of chromosome 22. The 22q11.2 micro-deletion occurs with a frequency of about 1 in 4000 live births and is therefore the most common micro-deletion syndrome (Botto, L.D. *et al*. 2003). VCFS is characterized by a seemingly heterogeneous set of symptoms which frequently include cardiac anomalies, cleft palate, learning disabilities, and mental retardation (Shprintzen, R.J. *et al*. 1978). Additionally, VCFS confers a significantly higher risk, relative to the general population, for the development of schizophrenia and other psychiatric disorders, including ADHD, anxiety, depression, and obsessive compulsive disorder. The prevalence of schizophrenia in the VCFS population is estimated at between 20 to 30 percent, as compared to a 1 percent incidence in the general population (Murphy, K.C. *et al*. 1999; Green, T. *et al*. 2009). Although the mechanism behind the development of schizophrenia remains unclear, a number of genes in the 22q11.2 region have been implicated as possible susceptibility loci believed to play a role (Berrettini, W.H. 2000; McGuffin, P. *et al*. 2003; Owen, M.J. *et al*. 2004).

Catechol O-Methyltransferase (COMT) is one such candidate gene. COMT is an enzyme responsible for the synaptic catabolism of catecholamines, including dopamine, epinephrine, and norepinephrine. Two distinct functional forms of COMT exist as a result of a single nucleotide polymorphism (SNP) at codon 108/158. The functional polymorphism arises as a result of a G to A missense mutation. This SNP results in the substitution of Methionine for Valine (Val108/158Met). While the Val108/158 allele is stable at normal body temperatures, the Met108/158 allele is thermolabile and is therefore only about one-fourth as enzymatically active. Accordingly, the Val108/158 allele is more efficient than the Met allele, which degrades dopamine more slowly and thus allows the dopamine to remain active, in its signaling form, for a longer period of time within neural synapses (Lotta, T. *et al*. 1995). We know less about the effect of the Val108/158Met polymorphism on the noradrenergic (as opposed to dopaminergic) system (DeRosse, P. *et al*. 2006). However, it has been demonstrated that variability in this polymorphism affects response to psychoactive substances that target the noradrenergic system (Szegedi, A. *et al*. 2005). Noradrenergic neurons project to numerous brain regions involved in processing affective stimuli (Moore, R.Y. and Bloom, F.E. 1979; Heinz, A. and Smolka, M.N. 2006) such as the amygdala, hippocampus, and cingulate, and norepinephrine is strongly implicated in emotion memory and regulation (Berridge, C.W. and Waterhouse, B.D. 2003; Hurlemann, R. *et al*. 2005). Patients with VCFS have only one copy of the COMT gene and, therefore, may have higher baseline levels of catecholamines than the general public. Although several linkage and association studies have demonstrated a relationship between COMT and psychiatric diseases, these studies as a whole have been short of conclusive. Investigations into the relationship between COMT genotype and cognitive functioning have proven to be more successful in generating consistent results.

In an animal study (Gogos, J.A. *et al*. 1998), COMT knockout mice expressed a sexually dimorphic change in the amount of dopamine present in the frontal cortex. Male knockout mice experienced a 2-3 fold increase in the amount of dopamine present in the frontal cortex, whereas female mice of the same COMT genotype did not experience such an increase. This gender mediated alteration in dopamine levels was attributed to the hormonal down-regulation of COMT by estrogens (Cohn, C.K. and Axelrod, J. 1971). Sexually dimorphic behavioral phenotypes were also noted in that COMT knockout females behaviorally demonstrated an altered emotional reactivity, which speaks to the role of COMT in some aspects of emotionality in this animal model (Gogos, J.A. *et al*. 1998). Several human studies have strengthened the support for the effect of epigenetic determination of COMT activity by estrogen. A number of these studies impute the

Val108/158Met polymorphism in the increased incidence of anxiety and depression in females (Hosak, L. 2007; Harrison, P.J. and Tunbridge, E.M. 2008).

Although the direct association between COMT and schizophrenia has not been established definitively, dopaminergic and noradrenergic neurotransmission is of crucial importance to neural circuits involved in endophenotypes for schizophrenia, including disrupted affective arousal, working memory, and executive function. As such, it is more likely that the Val108/158Met polymorphism will have a more robust effect on the underlying neural functioning associated with psychosis, than with the psychiatric disease itself (Lewandowski, K.E. 2007). If COMT has a stronger relationship to neural activation than to observable behaviors, a fMRI investigation should prove to be an effective tool in understanding the genotypic effect of COMT on emotional processing (Hariri, A.R. and Weinberger, D.R. 2003).

Several imaging studies thus far have linked COMT genotype with differential neural activation elicited by emotional processing (Smolka, M.N. *et al*. 2005; Heinz, A. and Smolka, M.N. 2006). Heinz and Smolka (2005) have demonstrated that, in the general population, the Met108/158 allele is significantly positively correlated to the amount of reactivity displayed in the amygdala and other limbic locations. The same dose dependent Met allele interaction with limbic reactivity was replicated by Drabant *et al*. (2006). The hyper-activation of limbic structures was described, by both authors, as a possible contributing factor to the emotional dysregulation and lower emotional resilience that had been previously observed in those individuals who were homozygous for the Met108/158 allele.

A recent fMRI investigation of healthy subjects from the general population utilized a facial affect recognition task in order to further elucidate the interaction between gender and COMT genotype on brain activation during emotion processing (Kempton, M.J. *et al*. 2009). The study found that females showed a greater task-related activation in the left amygdala and temporal pole when compared with males. Additionally, the authors observed that Val homozygotes showed a larger magnitude of neural activation than Met homozygotes, particularly in females.

Previous findings from our work on children with VCFS have shown that the COMT Val108/158Met polymorphism also affects prefrontal tissue volumes in a gender-specific fashion (Kates, W.R. *et al*. 2006a). In this study, females hemizygous for the Met108/158 allele and males hemizygous for the Val108/158 allele were found to have larger dorsal prefrontal volumes and smaller orbital frontal volumes than females hemizygous for the Val108/158 allele and males hemizygous for the Met108/158 allele.

In the present study on VCFS patients, we utilize fMRI to asses COMT genotype and gender-moderated effects on the neural activation that are elicited by viewing emotionally salient images from the International Affective Picture System (IAPS) (Lang PJ *et al*. 1997). Based on previous findings in both functional and neuroanatomical imaging studies, we hypothesize that COMT genotype will have a sexually dimorphic effect on brain activation, especially in areas such as the amygdala and other limbic structures that have been previously shown to have differential activation during emotional processing in the general population.

2. Materials and Methods

2.1. Subjects

The procedures of this study were approved by the Institutional Review Board of the SUNY Upstate Medical University and all participants provided informed consent. The sample of 43 subjects on whom we have imaging and genetic data is a subsample of 80 adolescents with VCFS involved in a longitudinal study of biomarkers for psychosis in VCFS (Kates, W.R. *et al*. 2004; Antshel, K.M. *et al*. 2005a; Antshel, K.M. *et al*. 2005b; Kates, W.R. *et al*. 2005; Antshel, K.M. *et al*. 2006; Kates, W.R. *et al*. 2006a; Kates, W.R. *et al*. 2006b; Antshel, K.M. *et al*. 2007; Kates, W.R. *et al*. 2007a; Kates, W.R. *et al*. 2007b; Antshel, K.M. *et al*. 2008a; Antshel, K.M. *et al*. 2008b). The subjects for the larger, longitudinal study were recruited from the Center for the Diagnosis, Treatment, and Study of VCFS at SUNY Upstate Medical University. Families who have a child with VCFS who is actively followed through the Center were informed about the study by the center nurse practitioner. In addition, the study was posted on the VCFS Educational Foundation website. A deletion in the 22q11.2 region of the chromosome 22 was confirmed by fluorescence in situ hybridization (FISH) in all the subjects included in this study. Only children with ages between 9 and 15 years were included in the initial stage of the longitudinal study. Children with an identifiable genetic disorder other than VCFS, paramagnetic implants, or with a central nervous system (CNS) condition or conditions known to affect the CNS (i.e. intractable seizure disorder, traumatic brain injury, fetal alcohol syndrome or effects, elevated lead levels, or preterm birth (based on parent report)) were excluded from participation.

Of the eighty participants in the longitudinal study, twelve subjects with a full scale IQ less than 55 were excluded from the fMRI studies due to concern about performance. Three subjects experienced anxiety while in the scanner and refused to participate in the fMRI experiment. One subject was not scanned because of braces. Six subjects did not have genotype data. Complete scans could not be acquired on eight subjects due to technical difficulties during scanning. Finally, subjects with extensive interscan motion during the fMRI experiment (more than 2mm translation and/or more than 2 degrees rotation over the whole scan duration) were not included in the analysis (7 subjects, Val/Met=5/2).

The resulting subsample used for the current analyses (43 subjects), which did not significantly differ in IQ from the longitudinal study population, consisted of 25 adolescent girls (mean age = 15.4, SD=2.2, range 11-21; mean IQ=72.6, SD=9.9, range 55-92) and 18 adolescent boys (mean age = 14.8, SD=2.2, range 12-20; mean IQ=68.5, SD=11.2, range 52-92). Eight (32%) girls and nine (50%) boys were hemizygous for the Met allele. While the subjects hemizygous for the Val allele had significantly higher IQ scores than the Met allele carriers (p=0.008, two tail t-test), there were no significant differences in IQ between the female and male subjects. With the exception of two male subjects who were Asian (one hemizygous for Met, the other for Val), all adolescents were Caucasian. At the time of their participation, four (9.3%) subjects were taking anti-psychotic medication and eight (18.6%) were taking other psychotropic medications, primarily stimulants, anti-depressants, anti-anxiety, or mood stabilizers (see Table 1 for gender/allele breakdown). During the interviews, none of the subjects was found to have any drug or alcohol abuse. We conducted chi-square analyses to compare the medication usage and psychiatric status of our four groups, and found no significant differences for either set of analyses.

2.2. COMT Genotyping

Samples were genotyped in duplicate by sequencing or the ABI PRISM 5′ nuclease assay TaqMan®). For sequencing, PCR products spanning the Val108/158Met variant were

generated using the primers ValMet-F (5′ ctcatcaccatcgagatcaa) and ValMet-R (5′ gatgaccctggtgatagtgg) as previously described (Lachman, H.M. *et al*. 1996). For the ABI 5′ nuclease assay, TaqMan® primers and probes were designed using the Primer Express® Oligo Design software v2.0 (ABI PRISM) or using the ABI Assays-By-Design service. PCR amplification was carried out on 5–20 ng DNA using 1×TaqMan® universal PCR master mix (No Amp-erase UNG), 900 nM forward and reverse primers, 200 nM of the FAM labeled probe and 200 nM of the VIC labeled probe in a 5 ml reaction volume. Amplification conditions on an ABI 9700 dual plate thermal cycle (Applied Biosystems, Foster City, CA) were as follows: 1 cycle of 95°C for 10 min, followed by 50 cycles of 92°C for 15 sec and 58°C for 1 min.

2.3. Imaging Study

Stimuli—For emotion induction, the subjects were presented with a variety of pictures from the International Affective Picture System - IAPS (Lang, P.J. *et al*. 1993; Lang, P.J. *et al*. 1998), charged with neutral, negative, or positive emotional load. Pleasant, unpleasant, and neutral cues were taken from IAPS (Lang, P.J. *et al*. 1993), in which images were standardized across the dimensions of emotion, arousal, and valence (Lang, P.J. 1995). Each emotional valence category was represented by 26 pictures. The stimuli were arranged in a randomized order and were presented for 2500ms using an event-related design. During the fMRI scans, the participants were instructed to passively view the stimuli, to avoid the alteration of the brain activation pattern by the rating tasks (Taylor, S.F. *et al*. 2003). However, in order to optimize attention to the task, the subjects were asked to button-press when they saw an image that was upside down. The final image of the entire series was presented upside down. The stimuli were preceded and followed at the beginning and the end of the paradigm respectively by 20s resting periods with fixation crosses. Stimuli were visually cued with a mirror attached to the head coil on a front-projection screen in the scanner room. A laptop computer equipped with E-prime software (version 2) (Psychology Software Tools, Pittsburgh, PA) generated the visual stimuli and controlled the experimental parameters. After the fMRI acquisition, outside the scanner room, the subjects were asked to go through the same sequence of stimuli and rank them on a scale from 1 through 8, with 1 standing for ‘very unpleasant’, 4 for ‘neutral’, and 8 for ‘very pleasant’. The response time and the rating parameters were recorded for each stimulus.

fMRI acquisition—Each subject was imaged once while performing the above paradigm on a Philips Intera 1.5T MR scanner version release 11 (Philips Medical Systems, Best, The Netherlands) equipped with a Phillips quadrature head coil. For fMRI, 25 slices were acquired every 2.5s (4mm thickness, 1mm gap) using an FFE-EPI sequence (TR/TE = 2500ms/60ms, voxel size = 3.75×3.75, acq. matrix = 64×64×25 slices). A conventional 3D scan was obtained for anatomic localization.

2.4. Data Analysis

Following image reconstruction and after discarding the first eight frames to allow for stabilization of the magnetic field, the image data was transferred from the MRI scanned to IBM compatible PC workstations via existing network connections. fMRI data were analyzed offline using the Statistical Parametric Mapping-SPM5 software package (Wellcome Department of Cognitive Neurology, 2005, London, UK, http://www.fil.ion.ucl.ac.uk/spm/), running under a Windows version of Matlab2007b (Mathworks, Inc., Natick, MA) on Centrino Duo based Dell computers. Statistical analysis for behavioral data was conducted using the statistics analysis software package PASW Statistics 17 (www.SPSS.com).

Preprocessing of fMRI data—Images were visually inspected at intermediate stages of the preprocessing to ensure the absence of ghosting, significant signal dropout, and any other image processing artifacts. Preprocessing steps included: (1) Motion correction using INRIalign, a motion correction algorithm unbiased by local signal changes (Freire, L. and Mangin, J.F. 2001). (2) Spatial normalization of motion-corrected images into the standard Montreal Neurological Institute space (Friston, K.J. *et al*. 1995), using a hybrid algorithm of affine transformation and nonlinear warping, and the voxels were resampled at a resolution of 3×3×3 mm^3 using trilinear interpolation. (3) Gaussian spatial filtering with a full-width, half maximum (FWHM) of 6 mm for group analysis.

First-level parametric fMRI analysis—We carried out first-level parametric analyses individually for every subject utilizing the general linear model (GLM) in SPM5. The fMRI data were analyzed as a time series modeled by a sine wave shifted by an estimate of the hemodynamic response. A temporal smoothing kernel of 256 seconds was applied to improve the signal-to-noise ratio of the data. Individual subject maps were created by using one-sample t tests. We estimated parameters that reflected activation as (1) a contrast between the tasks of viewing images with pleasant content and the ones with neutral content ('pleasant – neutral') and (2) a contrast between the tasks of viewing images with unpleasant content and the ones with neutral content ('unpleasant – neutral').

Second-level analysis—The parameter estimates from the first-level analysis were entered into a second level (random effects) full factorial analysis to test inferences about differential activations between the two genotype groups and the gender interaction (Val_{Male}, Val_{Female}, Met_{Male}, Met_{Female}). The three effects generated were: for main effect of genotype [eg., 1 1 −1 −1], for main effect of gender [eg., 1 −1 1 −1], and for gene × gender interaction [eg., 1 −1 −1 1]. Guided by the results of previously published studies (Smolka, M.N. *et al*. 2005; Kempton, M.J. *et al*. 2009) we performed ROI specific analyses (Left/Right amygdala, Brodmann Areas (BA) 9, 24, 35, 36, 44 and 46) and we used an uncorrected threshold of p=0.01 (voxelwise) to identify the regionally specific differences. The ROIs were generated using WFU PickAtlas Tool Version 2.3 software (Maldjian, J.A. *et al*. 2003) that generates ROI masks based on the Talairach Daemon database (Lancaster, J.L. *et al*. 1997; Lancaster, J.L. *et al*. 2000). The resultant statistical maps were rendered onto a three-dimensional standard brain. Statistically significant group differences (Tables 2 and 3) were reported as voxel-intensity t-values only for the voxels with a FDR (Benjamini, Y. and Hochberg, Y. 1995) corrected p value less than 0.05 or those approaching significance (<0.1). The coordinates reported for statistical maxima of neural activation are in MNI(SPM) coordinate system. For anatomical label localization, statistical maxima of activation were converted from the MNI(SPM) coordinates to conform to the standard Talairach space (Talairach, J. and Tournoux, P. 1988) using BrainMap GingerALE (www.brainmap.org) and Talairach Client (www.talairach.org).

3. Results and Discussion

3.1. Behavioral performance

ANOVA of the average pleasant ratings and neutral ratings indicated no significant differences (p<0.05) by COMT, gender, or COMT-by-gender interaction. However, the effect of COMT genotype (Val > Met) on unpleasant ratings approached significance (F [1,1,1,31] = 3.58; p=0.068). We also observed a significant effect of COMT genotype (Val > Met) on IQ scores (F [1,1,1,39] = 4.84; p=0.034), but no significant gender effect or COMT-by-gender interaction.

3.2. fMRI

The genotype and gender distribution of the 43 subjects included in this experiment were as follows: Val_{Male}: N=9, Val_{Female}: N=17, Met_{Male}: N=9, and Met_{Female}: N=8 (see Table 1). We performed second-level (random effects) full factorial analyses across gender-by-COMT levels.

Genotype Effect—In the 'Unpleasant-Neutral' contrast we observed an overall genotype effect, where Met allele carriers exhibited significantly higher neural activation (p_{FDR}=0.04) in the left posterior mid-cingulate cortex (pMCC; BA posterior 24a', posterior 24b', 24d) than Val allele carriers (see Table 3). No significant genotype effects (at p_{FDR}<0.05) were observed in the 'Pleasant – Neutral' contrast.

Gender Effect—In the 'Pleasant-Neutral' contrast we observed an overall gender effect, where the female subjects showed increased cortical activation in the left anterior mid-cingulate gyrus (aMCC; BA anterior 24a', b', c') (see Table 2). The analysis didn't indicate any significant gender effects (at p_{FDR}<0.05) in the 'Unpleasant – Neutral' contrast.

Genotype-by- Gender interaction—When we contrasted neural activation for pleasant (vs. neutral) stimuli, we observed a gender-by-allele effect in the frontal system, specifically the right pars opercularis (BA 44), where the female Val and the male Met subjects showed significantly increased activation compared to the male Val and female Met subjects (see Table 2 and Figure 1).

When we contrasted neural activation for unpleasant (vs. Neutral) stimuli, we observed a gender-by-allele effect in the limbic system, where the Val male and the Met female subjects demonstrated greater activation than Val female and Met male subjects (see Table 3 and Figure 2) in the left amygdala, right parahippocampal gyrus (BA 35), and the left posterior mid-cingulate cortex (pMCC; BA 24) (see Table 3).

3.3. Discussion

To our knowledge, this is the first fMRI study to investigate the effect of the COMT Val108/158Met polymorphism and gender on emotion induction in VCFS. We observed a significant gender-by-allele interaction in neural function associated with processing both pleasant and unpleasant stimuli. This suggests that in VCFS, the effect of the COMT Val108/158Met polymorphism is moderated by gender during the processing of emotional stimuli. These findings are consistent with our previous report of a gender-by-allele interaction effect on neuroanatomic volumes of the prefrontal cortex (Kates, W.R. *et al*. 2006a).

Our results suggest that in VCFS, processing positive stimuli may be a function of gender (as opposed to genotype) differences in that the combined group of girls activated the anterior mid-cingulate region significantly more than combined group of boys. These results are consistent with those of Hofer and colleagues who found gender-related neural responses to positive and negative emotional stimuli in the general population (Hofer, A. *et al*. 2006).

In contrast, we found a gender-by-genotype interaction specific to the frontal lobe during the processing of pleasant stimuli and specific to limbic and pMCC regions during the processing of unpleasant stimuli. That is, we observed that Val females and Met males recruited inferior frontal regions during the processing of pleasant stimuli, whereas Met females and Val males recruited limbic regions during the processing of unpleasant stimuli. This can be understood within the dual context of the hypothesized effect of COMT on brain function and the hypothesized effect of estrogen on COMT function.

In typical individuals, homozygosity for the Met allele is usually associated with optimal functioning during cognitive tasks that recruit the prefrontal cortex (Egan, M.F. *et al*. 2001; Malhotra, A.K. *et al*. 2002; Mattay, V.S. *et al*. 2003). Individuals with the Met-Met allele degrade dopamine more slowly, increasing its availability in prefrontal synaptic clefts (Lotta, T. *et al*. 1995), and optimizing efficiency during cognitive functioning. This is attributable to the inverted U-shaped relationship between dopamine activity, norepinephrine (NE) activity, and prefrontal function (Goldman-Rakic, P.S. *et al*. 2000; Arnsten, A.F. 2007), which in *typical* individuals places homozygosity for the Met allele at the top, "optimal point" of the inverted U. However, homozygosity for the Met allele in typical individuals is also associated with increased neural activation of limbic regions during emotion processing of negative stimuli (Smolka, M.N. *et al*. 2005), suggesting that dopamine signaling in response to emotionally negative stimuli is enhanced in the limbic regions of Met-homozygous individuals. Enhanced limbic signaling in Met-homozygous individuals may over-burden the capacity of the prefrontal cortex to regulate limbic function (Barnett, J.H. *et al*. 2007), putatively leading to decreased emotional resilience (Kempton, M.J. *et al*. 2009) in these individuals, despite their optimized cognitive efficiency.

Although previously published data on the effect of the COMT gene on cognitive function in VCFS are not consistent, it has been hypothesized that in VCFS, the presence of only one copy of the COMT gene results in greater cognitive vulnerability for individuals with the low – activity Met allele (Meyer-Lindenberg, A. and Weinberger, D.R. 2006). This hypothesis is based on the notion (Meyer-Lindenberg, A. and Weinberger, D.R. 2006) that the inverted U-shaped relationship described above is shifted to the right in individuals with VCFS, resulting in optimal functioning in VCFS individuals who are hemizygous for the Val allele, and suboptimal functioning in VCFS individuals who are hemizygous for the Met allele (since they are putatively exposed to relatively large amounts of dopamine in the prefrontal cortex). The potential vulnerability conferred by the Met allele in VCFS may extend to emotion processing as well (as is suggested by the findings by Gothelf, D *et al*. (Gothelf, D. *et al*. 2005), which indicate that VCFS individuals with the Met allele were more likely to exhibit severe psychiatric symptoms in late adolescence).

As noted above, however, it has also been shown that estrogen down-regulates COMT activity (Gogos, J.A. *et al*. 1998; Xie, T. *et al*. 1999; Jiang, H. *et al*. 2003), resulting in lower COMT activity in women than men, despite the fact that both sexes have similar levels of COMT protein and mRNA (Chen, J. *et al*. 2004; Tunbridge, E. *et al*. 2004) or higher in women (Dempster, E. *et al*. 2006). Because estrogen inhibits COMT, the lowest catecholamine (norepinephrine and dopamine) levels would be expected in Val108/158 males (whose male status and Val status together confer the highest level of COMT activity), followed by intermediate catecholamine levels in Val108/158 females or Met108/158 males (who possess either the higher activity COMT allele or lower estrogren levels, but not both), and the highest catecholamine levels would be found in Met108/158 females (who possess both the low activity COMT allele and high estrogen levels). (See Figure 3, which depicts the proposed shift in the inverted U for individuals with VCFS when COMT genotype is considered).

As reviewed by Arnsten, the different levels of catecholamines that these gender-genotype states produce can lead to disruption of cognitive processes, due to selective actions on adrenergic alpha 1 and 2 receptors and dopaminergic D1 receptors (Arnsten, A.F. 2007). Specifically, lower levels of norepinephrine are thought to "sharpen" the signals in brain areas with high-affinity adrenergic alpha 2A receptors. Because alpha 2A receptors are coupled to inhibitory G proteins, activation of these receptors inhibits the production of cyclic AMP (cAMP) and reduces excess activity. In contrast, chronically high levels of norepinephrine or dopamine (e.g., found in Met108/158 females) would increase binding to

lower-affinity alpha 1 and beta 1 receptors as well as D1 receptors (all of which are coupled to stimulatory G proteins and increase cAMP production). As Arnsten (2007) points out, this excessive cAMP production and cellular activation actually impairs prefrontal cortical function because the window of optimal dopamine stimulation is somewhat narrow (Goldman-Rakic, P.S. *et al*. 2000; Takahashi, H. *et al*. 2005; Williams, G.V. and Castner, S.A. 2006). Based on Arsten's reasoning, we would predict that VCFS Val158 males exhibit a lower efficiency for cognitive processing.

In contrast to the effects of high catecholamine levels on prefrontal cortical function, the high cAMP levels and cellular activation produced by D1 activation, and alpha 1 and beta 1 activation are predicted by Arnsten (2007) to promote amygdala function. Thus, subjects with higher catacholamines would be expected to perform better at determining the salience or valence (positivity or negativity) of emotional stimuli and show greater amygdala activation.

Related to these points, a particularly noteworthy observation in the present study was the shift in localization from anterior mid-cingulate cortex (aMCC) to posterior mid-cingulate cortex (pMCC) activations when we probed for Gender specific effects in the Pleasant – Neutral condition and Genotype specific effects (and Gender-by-Genotype interactions) in the Unpleasant – Neutral condition. As already discussed, one inference from Arnsten's (2007) model is that the levels of catacholamines enhance activation of different receptor subtypes (and thus potentially different cell populations and brain regions) in our paradigm. Thus, the question arises whether the aMCC and pMCC express different adrenergic and dopaminergic receptors which could account for the shift in activation in different states. Support for this possibility comes from recent work mapping the alpha 1, alpha 2, and D1 receptor densities along the cingulate gyrus in postmortem human brain tissue (Palomero-Gallagher, N. and Zilles, K. 2009). Interestingly, the pMCC was reported to contain 15% more alpha 2 adrenergic receptors and 30% less D1 receptors than the aMCC. Thus, based on Arnsten's model, one might expect preferential activation of the pMCC in conditions of low catecholamine drive, and preferential aMCC activation in conditions of high catecholamine drive.

Another possibility that might contribute to our observation of differential activation of cingulate gyrus subregions, is the observation that previous functional imaging studies have shown aMCC activation during elicitation of fear responses, while pMCC activation is enhanced during elicitation of anger responses (reviewed in (Vogt, B. and Lane, R. 2009)). Vogt and Lane (2009) further suggested that the patterns of differential activation were a direct result of the differences in the relative strengths of connections that the aMCC and pMCC have with the amygdala and subcortical noradrenergic nuclei. Based on the available data, these authors concluded that the aMCC is involved in fear and avoidance behaviors, while the pMCC is involved in coordinating skeletomotor and autonomic responses to emotional stimuli. It is along these two dimensions that our subjects of different genotypes and genders would be expected to differ (i.e., fear and anger responsiveness). Interestingly structural anomalies of the cingulate gyrus have also been implicated in VCFS. Specifically, individuals with VCFS demonstrate bilateral volumetric reductions in the anterior cingulate (DuFour et al, 2008), as well as cortical thinning in anterior and posterior cingulate (Bearden et al., 2008). However, the extent to which these findings are moderated by either gender or genotype status has not been explored.

Lastly, it should be noted that most of our participants are in mid-adolescence, a time during which both estrogens and prefrontal dopamine/norepinephrine levels are likely increasing, which may potentiate the effects of both estrogen and dopamine/norepinephrine on modulation of emotional responsivity. Accordingly, the genotype-by-gender interactions

that we have observed in brain function and brain structure (as our 2006 findings suggest (Kates, W.R. *et al*. 2006a)) can be understood in the context of an interplay between COMT, gender and development (Harrison & Tunbridge 2009).

3.4 Limitations

Since our study is limited to VCFS subjects, we cannot directly compare neuroactivation differences between hemizygous and homozygous subjects, as well as to quantify the differences in the ability to modulate emotions between hemizygous subjects with only one copy of the COMT gene compared with the ones with two copies. While in our subsample we did not find significant IQ differences between the female and male subjects, as reported in Antshel et al. 2005a (on the sample from where our subsample was drawn), we have found girls have slightly higher IQ. Accordingly, this can pose a potential limitation to our findings. Moreover, the small size of the samples prevents us from examining the effects of the presence of psychiatric disorder or the use of medication on the neural activation. Additionally, one has to consider the fact that repeated presentation of emotionally salient pictures could yield to habituation of activity of the ACC (Phan, K.L. *et al*. 2003) and the amygdala (Zald, D.H. 2003). Despite these limitations however, our findings elucidate the multifaceted interplay between the COMT polymorphism and gender that should be considered in future studies of not only individuals with VCFS but also typically developing youth and adults.

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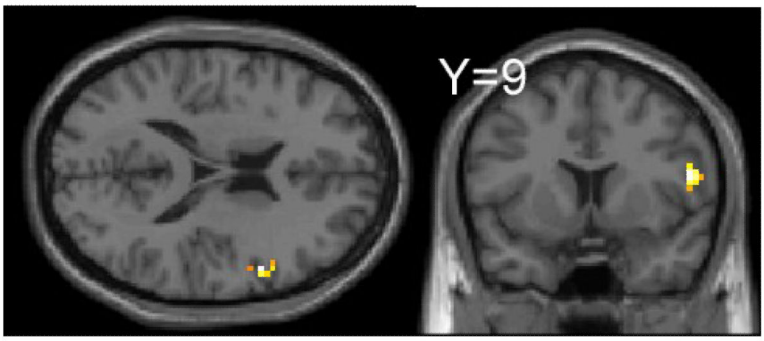

Figure 1.

Region of neural activation in the right BA 44 (Pars opercularis, MNI(x,y,z)= (54,9,18)) that presented significant (P_{FDR}= 0.011, T=3.88, cluster size=24 voxels) COMT-by-Gender interaction ('Val_{Female}' + 'Met_{Male}') - ('Val_{Male}' + 'Met_{Female}') during IAPS Emotion Regulation tasks between Val108/158 and Met108/158 VCFS subjects in the 'Pleasant-Neutral' contrast.

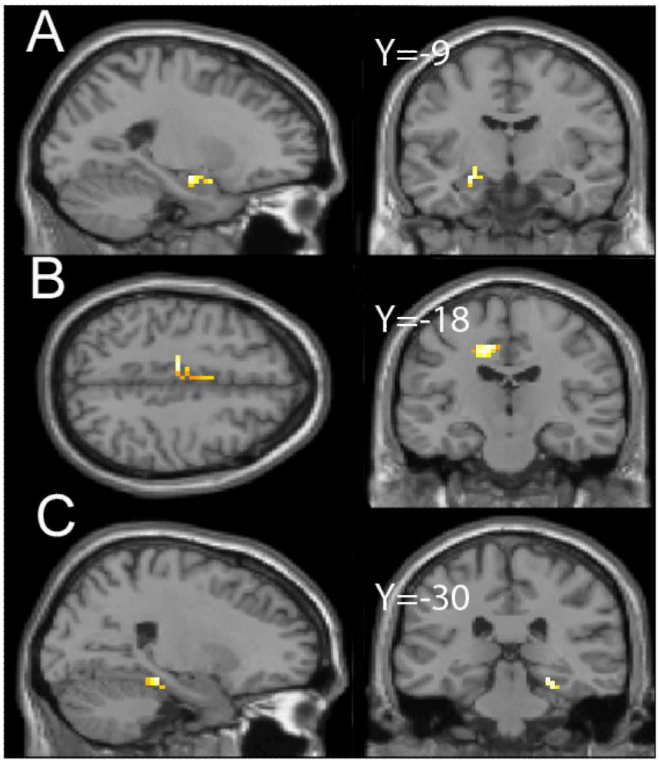

Figure 2.

Regions of neural activation that presented significant or approaching significance COMT-by-Gender interaction ('Val_{Male}' + 'Met_{Female}') - ('Val_{Female}' + 'Met_{Male}') during IAPS Emotion Regulation tasks between Val108/158 and Met108/158 VCFS subjects in the 'Unpleasant-Neutral' contrast. (A). Left Amygdala (MNI(x,y,z)= (−24, −9, −15), P_{FDR}=0.068, T= 3.1, cluster size=20 voxels); (B). Left BA 24 (Cingulate Gyrus, MNI(x,y,z)= (−12, −18, 45), P_{FDR}=0.043, T=3.6, cluster size=34 voxels); (C). Right BA 35 (Parahippocampal Gyrus, MNI(x,y,z)= (24, −30, −15), P_{FDR}=0.044, T=3.24, cluster size=16 voxels).

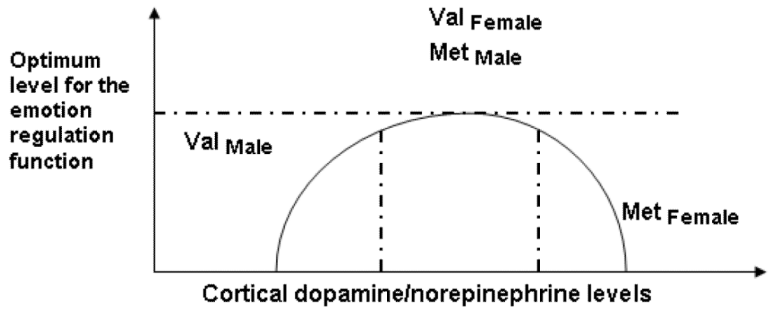

Figure 3.
The proposed shift in the inverted U-shaped curve representing the relationship between cortical dopamine/norepinephrine and emotion processing/regulation in individuals with VCFS.

Table 1

Number (percent) of participants with K-SADS-PL diagnoses or current medications, by genotype and gender

	Met Allele		Val Allele	
	Females (N=8)	**Males (N=9)**	**Females (N=17)**	**Males (N=9)**
Age (mean +/− SD)	15.9 (+/−1.9)	14.3 (+/−1.2)	15.2 (+/−2.4)	15.4 (+/−3)
Age range	13.1-18.2	12.6-16.3	11.6-21.6	12.3-19.9
Full scale IQ (mean, SD)	67.5 (+/−7.4)	65.4 (+/−9.8)	75 (+/−10.2)	71.5 (+/−12.2)
K-SADS-PL Diagnoses				
Depression or Anxiety*	4 (50)	1 (11)	2 (11.8)	1 (11)
ADHD	1 (12.5)	3 (33)	4 (23.5)	3 (33)
Psychotic Symptoms**	2 (25)	4 (44)	2 (11.8)	1 (11)
Medications †				
(Duration of treatment in years)				
Anti-psychotics	1 (12.5)	1 (11)	2 (11.8)	
				0
(Mean=3.5 years, SD=1.9)				
Other medications***	1 (12.5)	1 (11)	4 (23.5)	2 (22)
(Mean=2.5 years, SD=1.8)				

* Specific K-SADS-PL diagnoses from which this category was drawn includes major depressive disorder, generalized anxiety disorder, and obsessive compulsive disorder

** This category consists of endorsements of symptoms of hallucinations or delusions, at either the subthreshold or threshold level. Two of the nine participants endorsed lifetime, but not present, symptoms. Only four participants of the nine participants were under antipsychotic medication treatment.

*** Other medications include stimulants / atomoxotine, anti-depressants, anti-anxiety medications, and mood stabilizers

† No substance abuse was identified in this sample (i.e. alcohol, drugs).

Table 2

Regions of neural activation during IAPS Emotion Regulation Tasks that significantly differed between Val108/158 and Met108/158 VCFS subjects in the 'Pleasant-Neutral' contrast.

Pleasant - Neutral

Overall Gender Effect

Females: 1 Males : −1

System	Region	BA	Side	MNI coodinates x	y	z	T	P_{FDR}	cluster size
Limbic	Cingulate Gyrus	24	Left	−12	6	39	3.81	0.046	48
				−12	12	33	3.57	0.046	

Interaction Effect

Val F: 1 Met M: 1

Val M: −1 Met F: −1

System	Region	BA	Side	MNI coordinates x	y	z	T	P_{FDR}	cluster size
Frontal	Pars opercularis	44	Right	54	9	18	3.88	0.011	24

Table 3

Regions of neural activation during IAPS Emotion Regulation Tasks that significantly differed between Val108/158 and Met108/158 VCFS subjects in the 'Unpleasant'-'Neutral' contrast.

Unpleasant - Neutral									
Overall Genotype Effect									
Met: 1 Val: −1									
				MNI coordinates					**cluster size**
System	**Region**	**BA**	**Side**	**x**	**y**	**z**	**T**	P_{FDR}	
Limbic	Cingulate Gyrus	24	Left	−21	−18	42	3.78	0.042	7

Interaction Effect									
Val M: 1 Met F: 1									
Val F: −1 Met M: −1									
				MNI coordinates					**cluster size**
System	**Region**	**BA**	**Side**	**x**	**y**	**z**	**T**	P_{FDR}	
Limbic	Amygdala		Left	−24	−9	−15	3.1	0.068	20
	Parahippocampal Gyrus	35	Right	24	−30	−15	3.24	0.044	16
	Cingulate Gyrus	24	Left	−12	−18	45	3.6	0.043	34

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