Published in final edited form as:

Schizophr Res. 2012 March ; 135(0): 202–203. doi:10.1016/j.schres.2011.12.011.

A second look: No effect of the *COMT* Val158Met polymorphism on conflict adaptation in youth with chromosome 22q11.2 deletion syndrome

Joel Stoddard,

Mood and Anxiety Disorders Branch, National Institute of Mental Health, United States

Department of Psychiatry and Behavioral Sciences, Medical Investigation of Neurodevelopmental Disorders (MIND) Institute, University of California at Davis Health System, United States

Yukari Takarae, and

Center for Mind and Brain, University of California at Davis, United States

Tony J. Simon

Department of Psychiatry and Behavioral Sciences, Medical Investigation of Neurodevelopmental Disorders (MIND) Institute, University of California at Davis Health System, United States

1. Introduction

The catechol o-methyltransferase gene (*COMT*) gene is located at chromosome 22q11.2, where the most common human genetic microdeletion occurs. The resultant syndrome (22q11.2DS) confers both a high risk of psychotic disorder (~25 fold) and schizophrenia-related executive dysfunction (e.g. Murphy et al., 1999). Therefore, 22q11.2DS has been a model population in which to study *COMT* behavioral phenotypes, specifically executive function and clinical psychosis (e.g. Tunbridge et al., 2004). However, in 22q11.2DS, neither allele of the codominant, functional *COMT* Val108/158Met polymorphism (rs4680) has been reliably associated with clinical psychosis (Murphy et al., 1999; Gothelf et al., 2005; Bassett et al., 2007; Boot et al., 2011) or executive function (Bearden et al., 2004; Glaser et al., 2006; Shashi et al., 2010). We have previously reported an association between the rs4680 Met allele and conflict adaptation (Takarae et al., 2009) but not to flanker interference (Stoddard et al., 2011) within the same task. To resolve this discrepancy, we re-examined the association between rs4680 and impairment in conflict adaptation in the larger sample (Stoddard et al., 2011) using the same method as before (Takarae et al., 2009).

2. Methods

We tested 53 participants with 22q11.2DS, 49 of whom participated in a prior study (Stoddard et al., 2011) and 27 of whom participated in our previous report (Takarae et al., 2009). We used the same selection criteria and tasks as described in that report. All youth were aged 6–15 years, and were tested with an Attention Networks Test, which includes a flanker task. Typically developing youth (TD; $n=34$) served as a positive control group. Of

those with 22q11.2DS, 31 had the rs4680 Met allele and 22 the Val allele. Groups did not differ by age or sex. We compared adaptation to flanker interference by studying prior trial effects on current trial performance using the same analytic method as before, but current data processing used a MatLab v. 7.10 script rather than a Microsoft Excel 2004 macro. In addition, trial condition mean and variance were used for trial exclusion rather than grand mean and variance. We replicated the prior analysis with these changes with no differences in results (data not shown). Significance tests were by repeated measures ANCOVA with polynomial tests for flanker sequence contrasts. Age was included as a covariate because of its significant effect. Degrees of freedom were corrected by the Huynh–Feldt method for violations of the sphericity assumption.

3. Results

Results are presented in Table 1, where only the previously reported (Stoddard et al., 2011) overall effects of flanker interference were significant. Within each group, none of the flanker sequence effects on reaction time or error were significant when modeled as linear or quadratic trends. When considering the 22q11.2DS groups only, we did not find that the COMT SNP significantly affected overall performance ($F=0.268$, $p=0.607$ for RT; $F=0.247$, $p=0.621$ for error rate) or interacted with adaptation to flanker interference ($F=1.24$, $p=0.288$ for RT; $F=0.179$, $p=0.817$ for error rate).

4. Discussion

By increasing our sample size we found no differences in conflict adaptation between either allele of rs4680 in youth with 22q11.2DS. Post hoc power analysis suggests that future studies will require larger samples. Until that occurs, we propose that great caution should be taken when considering the role of the *COMT* SNP rs4680 in cognitive control and psychiatric outcomes in those with 22q11.2DS.

References

- Bassett AS, Caluseriu O, Weksberg R, Young DA, Chow EW. Catechol-O-methyltransferase and expression of schizophrenia in 73 adults with 22q11 deletion syndrome. *Biol Psychiatry*. 2007; 61(10):1135–1140. [PubMed: 17217925]
- Bearden CE, Jawad AF, Lynch DR, Sokol S, Kanis SJ, McDonald-McGinn DM, Saitra SC, Harris SE, Wang PP, Zackai E, Emanuel BS, Simon TJ. Effects of a functional COMT polymorphism on prefrontal cognitive function in patients with 22q11.2 deletion syndrome. *Am J Psychiatry*. 2004; 161(9):1700–1702. [PubMed: 15337663]
- Boot E, Booij J, Abeling N, Meijer J, da Silva Alves F, Zinkstock J, Baas F, Linszen D, van Amelsvoort T. Dopamine metabolism in adults with 22q11 deletion syndrome, with and without schizophrenia- relationship with the COMT Val 108/158 Met polymorphism, gender and symptomatology. *J Psychopharmacol*. 2011; 25:888. [PubMed: 21447540]
- Glaser B, Debbané M, Hinard C, Morris MA, Dahoun SP, Antonarakis SE, Eliez S. No evidence for an effect of COMT Val158Met genotype on executive function in patients with 22q11 deletion syndrome. *Am J Psychiatry*. 2006; 163(3):537–539. [PubMed: 16513880]
- Gothelf D, Eliez S, Thompson T, Hinard C, Penniman L, Feinstein C, Kwon H, Jin S, Jo B, Antonarakis SE, Morris MA, Reiss AL. *COMT* genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. *Nat Neurosci*. 2005; 8(11):1500–1502. [PubMed: 16234808]

- Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Arch Gen Psychiatry*. 1999; 56(10):940–945. [PubMed: 10530637]
- Shashi V, Howard TD, Keshavan MS, Kaczorowski J, Berry MN, Schoch K, Spence EJ, Kwapil TR. COMT and anxiety and cognition in children with chromosome 22q11.2 deletion syndrome. *Psychiatry Res*. 2010; 178(2):433–436. [PubMed: 20488547]
- Stoddard J, Beckett L, Simon T. Atypical development of the executive attention network in children with chromosome 22q11.2 deletion syndrome. *J Neurodev Disord*. 2011; 3(1):76–85. [PubMed: 21475729]
- Takarae Y, Schmidt L, Tassone F, Simon TJ. Catechol-O-methyltransferase polymorphism modulates cognitive control in children with chromosome 22q11.2 deletion syndrome. *Cogn Affect Behav Neurosci*. 2009; 9(1):83–90. [PubMed: 19246329]
- Tunbridge E, Burnet PW, Sodhi MS, Harrison PJ. Catechol-O-methyltransferase (COMT) and proline dehydrogenase (PRODH) mRNAs in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and major depression. *Synapse*. 2004; 51(2):112–118. [PubMed: 14618678]

Table 1

Reaction time and accuracy by trial type.

	<u>22q11.2 DS</u>		<u>TD</u>	Comparison ^d
	COMT Met N=31	COMT Val N=22	N=34	
Reaction time (ms) ^a Mean (SD)				
Congruence				
IC ^b	802 (220)	872 (199)	778 (224)	Group: F=2.78, <i>p</i> =0.068
CC	830 (195)	901 (207)	791 (324)	Within subjects
CCC	796 (194)	811 (202)	772 (246)	Flanker: F=1.00, <i>p</i> =0.369 Group X Flanker: F=0.573, <i>p</i> =0.683
Interference				
CI	927 (264)	1008 (251)	887 (232)	Group: F=4.80, <i>p</i> =0.011
II	891 (315)	981 (320)	821 (211)	Within subjects
III	880 (396)	1038 (490)	825 (258)	Flanker: F=1.52, 0.224 Group X Flanker: F=0.532, <i>p</i> =0.679
Error rate ^c (%)Median (IQR)				
Congruence				
IC	0 (7)	7 (7)	0 (7)	Group: F=2.56, <i>p</i> =0.083
CC	0 (8)	0 (9)	0 (8)	Within subjects
CCC	0 (0)	0 (20)	0 (0)	Flanker: F=0.895, <i>p</i> =0.411 Group X Flanker: F=0.527; <i>p</i> =0.716
Interference				
CI	7 (17)	4 (8)	0 (7)	Group: F=3.23, <i>p</i> =0.044
II	0 (17)	0 (8)	0 (8)	Within subjects
III	0 (0)	0 (0)	0 (0)	Flanker: F=0.579, <i>p</i> =0.543 Group X Flanker: F=0.504; <i>p</i> =0.712

^a Group mean for median reaction times for a trial type (ms).^b Trial types are noted as follows: IC refers to a congruent trial preceded by incongruent trial; CC, a congruent trial preceded by single congruent trial; CCC, a congruent trial preceded by two successive congruent trials; CI, an incongruent trial preceded by congruent trial; II, an incongruent trial preceded by single incongruent trial; III, an incongruent trial preceded by two successive incongruent trials.^c Group median and IQR of raw error rates by trial type, error rate was transformed by taking their square root to improve normality for ANCOVA analysis.^d Compared with repeated measures flanker-sequence (abbreviated 'flanker') by group ANCOVA with age as a covariate. Degrees of freedom were corrected by the Huynh-Feldt method for violations of the sphericity assumption.