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Chapter 5
The role of COMT and plasma proline in the variable penetrance of social deficits in 22q11.2 Deletion Syndrome

Hidding, E., Swaab, H., de Sonneville, L.M.J., van Engeland, H., & Vorstman, J.A.S. The Role of COMT and plasma proline in the variable penetrance of social deficits in 22q11.2 Deletion Syndrome. Revised manuscript submitted.

Abstract

This paper examines how COMT<sup>158</sup> genotypes and plasma proline levels are associated with variable penetrance of social behavioral and cognitive problems in 22q11.2 deletion syndrome (22q11DS).

Quality of social functioning of 45 participants with 22q11DS (27 females) with a mean age of 13.3 (SD = 2.7, range 9-18.5) was assessed using the Autism Diagnostic Interview Revised. Quality of face and facial emotion processing was evaluated to examine social cognitive problems. Associations with COMT<sup>158</sup> genotypes and proline levels were examined.

High proline levels and poor face recognition in individuals with the COMTMET allele, together with poor facial emotion recognition, explained almost 50% of the variance in severity of autism symptomatology in individuals with 22q11DS.

High proline levels and a decreased capacity to break down dopamine as a result of the COMTMET variant are both relevant in the expression of the social phenotype in patients with 22q11DS. This epistatic interaction effect between the COMT<sup>158</sup> genotype and proline on the expression of social deficits in 22q11DS demonstrates how factors other than the direct effects of the deletion itself can modulate the penetrance of associated cognitive and behavioral outcomes. The findings of this study are not only relevant to our insight into 22q11DS, but also provide a model to better understand the phenomenon of variable penetrance in other pathogenic genetic variants.
Introduction

The 22q11.2 deletion syndrome (22q11DS) is characterized by a large variability in its phenotypic expression. The syndrome is associated with a high vulnerability to a variety of behavioral disorders with an onset in childhood or adolescence including anxiety disorders, mood disorders, attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder, and autism spectrum disorders (ASDs) in 30 – 50% of affected individuals (Schneider et al. 2014; Jolin et al. 2009; Baker and Vorstman 2012; Niklasson et al. 2009; Vorstman et al. 2006; Jonas et al. 2014). Most important, the 22q11.2 deletion is the highest known single genetic risk factor for schizophrenia (Murphy et al. 1999, Schneider et al. 2014). The deletion affects approximately 45 genes, many of which are involved in the development and functioning of the brain (Meechan et al. 2011, Mehta et al. 2014, Dennis and Thompson 2013). The study of individuals with 22q11DS thus provides an exceptional opportunity to elucidate how genetic variation can affect brain development and how interaction with additional factors influence the manifestation of cognitive and behavioral outcomes. This knowledge may also be valuable for other recurrent copy number variants (CNVs) since almost all of them are associated with variable penetrance of different brain-related phenotypes (Girirajan and Eichler 2010). This variable penetrance of phenotypes in genetic disorders poses a formidable challenge for clinicians and at present its mechanisms are still not fully understood.

One of the domains in which children with 22q11DS experience difficulties is the social domain. Most studies consistently report social problems, both cognitive and behavioral, as well as repetitive behavioral patterns that are considered by some as characteristic for autism symptomatology (Schneider et al. 2014, Baker and Vorstman 2012, Niklasson et al. 2001, Fine et al. 2005). Investigating which factors (stochastic, additional genetic or environmental) influence the developmental pathways associated with the 22q11.2 deletion, such that one child develops social problems while another child does not, may further enhance our understanding of the variability in penetrance of phenotypic expression. Here, we propose to examine the influence of two additional factors that may modulate the high vulnerability to social cognitive and behavioral deficits in children with 22q11DS: the genotype of the remaining allele of COMT and plasma levels of the amino acid proline.

The gene COMT is hemizygosely deleted in individuals with 22q11DS. This gene encodes Catechol-O-Methyltransferase, an enzyme involved in degradation of catecholamines, including dopamine (Philip and Bassett 2011; Williams 2011; Graf et al. 2001). A common polymorphism at codon 158 results in a decrease of COMT activity associated with the COMT^MET variant (Chen et al. 2004; Graf et al. 2001; Jonas et al. 2014). In individuals with 22q11DS, the functional effects of this polymorphism may be increased since only one copy of the gene is present. It is hypothesized that individuals with 22q11DS and the COMT^MET variant have a reduced capacity to eliminate dopamine, particularly in the prefrontal cortex (Simon et al. 2005). This could influence cognitive functioning, although findings in 22q11DS are inconsistent (Baker et al. 2005; Bearden et al. 2004; Campbell et al. 2010; Carmel et al. 2014; Furniss et al. 2011; Kates et al. 2006; Shapiro et al. 2014; Shashi et al. 2006). The COMT^{158} polymorphism is associated with functioning of the prefrontal cortex which
is necessary for processing of social relevant information (Azuma 2015; Coman et al. 2010; Kempton et al. 2009). Effects of the COMT<sup>158</sup> polymorphism on social cognition have been found in healthy subjects and patients with bipolar disorder (Lin et al. 2013; Soeiro-de-Souza et al. 2012; Weiss et al. 2007). However, thus far, no studies have investigated the relation between this polymorphism and social cognition in 22q11DS, even though abnormalities in this domain are reported often in patients with 22q11DS (e.g. Campbell et al. 2010; Campbell et al. 2009; Glaser et al. 2010; Gur et al. 2014; Jalbrzikowski et al. 2012).

Regarding social behavioral outcomes, the COMT<sup>MET</sup> variant is found to be associated with an increased vulnerability to several behavioral disorders including ADHD and obsessive compulsive disorder (Gothelf et al. 2007). However, despite the high prevalence of social cognitive and behavioral problems associated with ASD in the syndrome, only one study investigated the relation between COMT gene expression and ASD (Radoeva et al. 2014). This study included the PRODH gene which encodes proline dehydrogenase that catalyzes the conversion of proline into glutamate. Given the importance of glutamate signaling in visual information processing, PRODH variation may affect the vulnerability to visual processing deficits in 22q11DS (Magnee et al. 2011). Proline influences the quality of visual information processing that is necessary to deal with social stimuli while dopaminergic dysregulation influences higher cognitive processes and social cognition that, when impaired, underlie the deficits in social functioning observed in children with autism (Herba et al. 2008; Rump et al. 2009). Findings of several studies indicate an epistatic interaction between COMT and PRODH, suggesting that the phenotypic effect of one genetic variant depends on the variation in another gene (Jonas et al. 2014; Paterlini et al. 2005; Raux et al. 2007). For example high proline levels have been found associated with impaired visual processing in individuals with the COMT<sup>MET</sup> allele, but not in individuals with the COMT<sup>VAL</sup> allele (Magnee et al. 2011). The same interaction was also found in an eye-movement study (Vorstman et al. 2009) and another study showed that hyperprolinemia in individuals with the COMT<sup>MET</sup> allele was associated with the risk for psychosis (Raux et al. 2007). Recently, an epistatic interaction between COMT and PRODH genotypes on the probability of ASD was found in a group of individuals (aged 6-21 years) with 22q11DS (Radoeva et al. 2014). Here, we propose to expand these findings by examining the possible interaction of the COMT<sup>158</sup> genotype and variable plasma proline levels, which is the primary biological consequence of PRODH variation (Bender et al. 2005). Since social cognitive processes are involved in the emergence of social behavioral problems associated with ASD, we will study not only the effect of these factors on the risk of these social behavioral problems, but also on the child’s capacity of face and facial emotion recognition. We expect the relation between COMT genotype and social behavioral problems to be dependent of, or influenced by plasma proline level. Since COMT genotypes have been previously found to be associated with cognitive functioning in 22q11DS, we also hypothesize an impact of COMT genotypes on social cognitive processes and explore the possibility of an interaction between impairments in social cognition and COMT genotypes.
Method

In the present study, 27 females and 18 males with genetically confirmed 22q11DS participated ($M_{age} = 13.3, SD=2.7$, range 9-18.5; Full scale intelligence: $M= 66.3$, SD=12.6). The study was part of a nationwide study. Assessments took place at the Department of Psychiatry, Brain Center Rudolph Magnus of the University Medical Centre Utrecht (UMCU) and were carried out by an experienced child neuropsychologist and child psychiatrist. Patients were recruited via the website and newsletter of the 22q11DS parents’ network in the Netherlands or via referral by various medical services. Parents and participants were informed about the aims of the study and received a complete description of the study in writing before they decided on participation. Informed consent was obtained from participants and parents or caretakers. The assessment protocol was approved by the Dutch Central Committee on Research Involving Human Subjects.

Measures

Psychiatric classifications were made according to DSM-IV criteria (American Psychiatric Association 2000) resulting from a multidisciplinary consensus meeting headed by an experienced child psychiatrist. The assessment protocol has been described elsewhere (Hidding et al. 2015; Vorstman et al. 2006) and included the Autism Diagnostic Interview-Revised (ADI-R; Rutter et al. 2003), scored by certified interviewers. The ADI-R provided scores for the three domains in which children with autism spectrum disorders (ASD) experience difficulties, i.e. reciprocal social interaction, communication impairment, repetitive and stereotyped behaviors. These domains were used as a measure of severity social behavioral problems. Table 1 provides the means and distribution of the severity scores.

Table 1 Severity scores of social behavioral problems.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>M</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADI-total</td>
<td>45</td>
<td>26.1</td>
<td>13.9</td>
<td>0-49</td>
</tr>
<tr>
<td>Reciprocal social interaction</td>
<td>45</td>
<td>11.6</td>
<td>7.2</td>
<td>0-26</td>
</tr>
<tr>
<td>Communication impairment</td>
<td>45</td>
<td>8.3</td>
<td>5.4</td>
<td>0-19</td>
</tr>
<tr>
<td>Repetitive and stereotyped behaviors</td>
<td>45</td>
<td>2.8</td>
<td>2.0</td>
<td>0-8</td>
</tr>
</tbody>
</table>

Social information processing

Social information processing was assessed with the use of the Amsterdam Neuropsychological Tasks (ANT) program (De Sonneville 1999, 2005). Test-retest reliability, construct-, criterion, and discriminant validity of the computerized ANT-tasks are satisfactory and have extensively been described elsewhere (De Sonneville 2014; Gunther et al. 2005; Huijbregts et al. 2002; Rowbotham et al. 2009). The ANT tasks, used in this study, will be briefly described, for detailed descriptions see e.g. De Sonneville et al. (2002).
Face recognition (FR) With this task speed and accuracy of recognizing (neutral) faces was measured. From a set of 20 pictures of different persons (boys, girls, men and women) a probe, the to-be-recognized face, is presented on a monitor for 2.5 seconds, prior to the imperative signal which consists of four digitized high-quality color photos of human faces. Gender and age category (children, adults) of signal and probe always match. A ‘yes’- response is required when the probe is present (20 trials) by pressing the mouse button below the index finger of the preferred hand, and a ‘no’-response when the probe (20 trials) is not present, by pressing the mouse key below the index finger of the non-preferred hand. Main outcome variables were mean reaction time and number of errors.

Identification of Facial Emotions (IFE) This task examined the ability to identify emotions from facial expression. Participants were asked to judge whether a face showed a specific expression by pressing the ‘yes’- key or another non target emotion by pressing the ‘no’- key. The total stimulus set consisted of 32 pictures from four different persons, each showing the eight emotions: happy, sad, anger, fear, disgust, surprise, shame, and contempt. The task consists of eight parts of 40 trials in which half of the trials contain the target emotion, whereas in the other half a random selection of the other emotions is presented. Four task parts were administered to measure the recognition of the basic emotions happy, sad, anger, and fear, respectively. Main outcome variables were mean reaction time and number of errors per part. To reduce the number of analyses, it was decided to lump the results of the three negative parts together.

COMT^{158} genotyping and proline measurement
COMT^{158} genotyping was carried out using allele-specific TaqMan probes (Applied Biosystems, Foster City, CA). Methodological details of PCR and sequence detection have been published in detail elsewhere (Vorstman et al. 2009). Plasma proline levels were assessed by automated ion exchange chromatography with post-column ninhydrin derivatization, using JEOL AminoTac (JEOL AminoTac JLC-500/V, Tokyo, Japan) following AM blood draw. Methodological details of the plasma proline measurement protocol have also been published in detail elsewhere (Vorstman et al. 2009).

Statistical analyses
Main outcome parameters for analyses of the social information processing tasks are z-scores, which are automatically computed by means of nonlinear regression functions that describe the relation between test age and task performance. These functions are fully implemented in the ANT program and based on norm samples varying in size between 3,100 to 6,700 subjects, depending on the task (De Sonneville 2014), and are therefore considered to be reliable estimates of performance level. Results were examined for extreme values. As extreme values are a clinical reality in this population, z-scores ≥ 6 were set to 6 to keep these subjects in the analyses. One subject with an error rate >50% was excluded from statistical analysis as this rate is worse than chance level. In addition, missing values in the final sample are the consequence of an inability of the subject to complete difficult task parts, or skipping
parts because of running out of time. As a result, degrees of freedom will slightly vary between analyses.

Prior to analysis, normality of the data was examined using skewness and kurtosis measures and the Shapiro-Wilk tests ($\alpha=.01$). Since the outcome parameter proline and two of the social information processing outcome parameters appeared to be skewed, Log transformations were applied to proline and all social information processing outcome parameters.

To examine the relation between severity of social behavioral problems and COMT$^{158}$ allele status as well as the influence of proline level, multiple regression analyses were performed with severity of social behavioral problems (separate analyses for sum score and scale scores) as dependent measures, COMT$^{158}$ allele status as fixed factor and proline level as covariate. Since we expect proline to interact with COMT$^{158}$ allele status, moderation analyses using the method of Aiken and West (1991) were performed to investigate the interaction between COMT$^{158}$ allele status and proline level.

To investigate the association of social cognition and severity of social behavioral problems as well as with COMT$^{158}$ allele status and proline levels, zero order correlations between social cognition (face and facial emotion recognition) and severity of autism symptoms were explored, followed by partial correlations with COMT$^{158}$ allele status and proline levels as covariates, respectively (small effect size: $r = 0.1-0.23$; medium: $r = 0.24-0.36$; large: $r \geq 0.37$; Cohen 1992).

Based on these exploratory correlational analyses, relevant social cognition parameters were included in moderation analyses with social behavioral problems as dependent measures, social cognition as fixed factor and COMT$^{158}$ allele status/proline levels as moderating covariate.

Finally, to obtain an integrative model acknowledging the influence of all identified factors on severity of social behavioral symptoms, a backward regression analysis was performed.

Results

Severity of autism symptoms was correlated with COMT status ($r=-.345$, $p=.013$ 1-tailed) indicating that the COMT$^{\text{MET}}$ allele was associated with more severe symptoms, but not with proline level ($p=.475$). However, the moderated regression model was significant [$F(3,35)=4.375$, $p=.010$] which revealed a COMT*proline interaction for the (total) severity score (Table 2), indicating that higher problem scores were only seen in individuals with the COMT$^{\text{MET}}$ allele who also showed high proline levels (Figure 1). Moderation analyses with the three autism domains revealed comparable COMT*proline interactions for the domains reciprocal social interaction ($p=.009$) and communication impairment ($p=.049$), while the effect was not significant for the domain of repetitive and stereotyped behaviors ($p=.510$).
Table 2 Moderation analysis with COMT status and severity of autism symptomatology for testing COMT*Proline interaction.

<table>
<thead>
<tr>
<th>Criterion variable</th>
<th>Predictor/covariate</th>
<th>F(df)</th>
<th>$R^2$</th>
<th>$\beta$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism severity (total)</td>
<td>COMT status</td>
<td>4.375 (3,35)</td>
<td>.273</td>
<td>-.369</td>
<td>.015</td>
</tr>
<tr>
<td></td>
<td>Proline</td>
<td></td>
<td>.085</td>
<td>.577</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COMT*Proline</td>
<td></td>
<td></td>
<td>-.367</td>
<td>.020</td>
</tr>
</tbody>
</table>

Figure 1 Interaction of COMT*Proline for severity of total severity autism symptomatology.

Speed of face recognition and accuracy of facial emotion recognition were correlated with the total severity score (Supplemental Table 1), with poorer quality of social cognition in individuals with more severe social behavioral problems. Using COMT status as covariate, the correlation remained significant for facial emotion recognition, however the relation between face recognition and total severity was no longer significant (Supplemental Table 1). This suggests that poorer quality of emotion recognition is associated with more severe social behavioral problems, independent of COMT genotype.

Regarding face recognition, the COMT*proline interaction resulted in a non-significant model ($p=.266$). However, a moderated regression analyses revealed a significant interaction between COMT status and face recognition [$F(3,34)=4.517$, $p=.009$] (Table 3), indicating that the association of slower face recognition with more severe symptoms holds only for individuals with the COMT$^{M}$E allele (Figure 2), while no interaction effects with proline were found.

Figure 2 Interaction of speed of Face Recognition* COMT for severity of total severity autism symptomatology.

A final multiple regression analysis, attempting to integrate the previous findings, resulted in a significant model [$F(4,28)=6.765$, $p=.001$], explaining 49.1% of the variance in severity of social behavioral problems, using COMT status, accuracy of positive emotion recognition, the COMT*proline interaction and the COMT*Face recognition interaction as contributing predictors.

The COMT$^{M}$E variant was associated with more severe problems, and this association was strongest for those individuals with higher proline levels. Accuracy of positive emotion recognition independent of COMT status and quality of face recognition were associated with more severe problems. For face recognition this association only existed in those individuals with the COMT$^{M}$E variant (Table 4).
A final multiple regression analysis, attempting to integrate the previous findings, resulted in a significant model \( F(4,28) = 6.765, p = .001 \), explaining 49.1% of the variance in severity of social behavioral problems, using COMT status, accuracy of positive emotion recognition, the COMT*proline interaction and the COMT*Face recognition interaction as contributing predictors.

The COMT\textsuperscript{MET} variant was associated with more severe problems, and this association was strongest for those individuals with higher proline levels. Accuracy of positive emotion recognition independent of COMT status and quality of face recognition were associated with more severe problems. For face recognition this association only existed in those individuals with the COMT\textsuperscript{MET} variant (Table 4).
Table 4 Multiple regression model (backward): predictors of autism symptom severity.

<table>
<thead>
<tr>
<th>Criterion variable</th>
<th>Predictor/covariate</th>
<th>F(df)</th>
<th>R²</th>
<th>β</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism severity (total)</td>
<td>COMT status</td>
<td>6.765 (4,28)</td>
<td>.491</td>
<td>-.405</td>
<td>.007</td>
</tr>
<tr>
<td>Emotion Recognition¹</td>
<td></td>
<td></td>
<td></td>
<td>.295</td>
<td>.045</td>
</tr>
<tr>
<td>COMT*Proline</td>
<td></td>
<td></td>
<td></td>
<td>-.365</td>
<td>.016</td>
</tr>
<tr>
<td>COMT*Face Recognition</td>
<td></td>
<td></td>
<td></td>
<td>-.271</td>
<td>.062</td>
</tr>
</tbody>
</table>

¹Accuracy of recognition of positive emotions

Discussion

The influence of the COMT¹⁵⁸ genotype on variable penetrance of social deficits as well as the possible epistatic interaction of COMT¹⁵⁸ genotype and plasma proline level were examined in 45 participants with 22q11DS. Outcomes revealed both a main effect of COMT¹⁵⁸ genotype on severity of social behavioral problems and an interaction between the COMT genotype and proline levels. Individuals with the COMTMET genotype and high proline levels were more likely to present with severe social behavioral problems. In participants with the COMTMET variant poorer quality of face recognition appeared to be associated with more severe social behavioral problems while for individuals with the COMTVAL variant the relation between quality of face recognition and severity of those problems was not present. Poorer quality of emotion recognition, however, was associated with more severe social behavioral problems, independent of COMT¹⁵⁸ genotype and plasma proline level. An integrative regression model showed that COMT¹⁵⁸ genotype and its interaction with both proline and quality of face recognition, together with quality of facial emotion recognition accounted for almost 50% of the variance in social behavioral problems.

Although these outcomes need to be interpreted with some caution given the relative small sample size of the study, these findings add to the growing body of research investigating the phenotypic variability in CNVs such as 22q11DS. Elucidating which factors modulate the risk of social cognitive and behavioral problems in 22q11DS may improve our understanding of mechanisms involved in the variable penetrance of phenotypes observed in many CNVs (Jonas et al. 2014; Vorstman et al. 2013). Therefore, ideally our findings should not only be replicated in a larger sample of 22q11DS patients, but also in carriers of other pathogenic CNVs.

One of the potential mechanism suggested to influence the clinical heterogeneity of 22q11DS are epistatic interactions (Jonas et al. 2014; Paterlini et al. 2005; Raux et al. 2007). Here we have investigated the interaction between COMT¹⁵⁸ genotypes and plasma proline levels. Our finding that more severe symptomatology in individuals with the COMTMET allele was associated with higher proline levels is in line with the interaction between the COMT and PRODH gene found by Radoeva et al. (2014).

Additionally, findings suggest that elevated plasma proline levels combined with the COMT¹⁵⁸ genotype, may have use as a biomarker for the risk of psychopathology
(Raux et al. 2007), including – as we show here- vulnerability to autism symptoms, in individuals with 22q11DS.
The results are in line with reports of increased vulnerability to psychiatric disorders in individuals with the COMT\textsc{Met} variant and a negative effect of high proline levels on cognitive and behavioral outcomes in individuals with this variant (Gothelf et al. 2007; Lachman et al. 1996; Magnee et al. 2011; Radoeva et al. 2014). Based on research thus far it seems justified to conclude that the co-occurrence of high proline levels and decreased capacity to break down dopamine as a result of carrying the COMT\textsc{Met} variant is associated with unfavorable cognitive and behavioral outcomes in 22q11DS. Our findings add to our understanding of the variable penetrance of cognitive and behavioral phenotypes in individuals with 22q11DS. The impact of the COMT genotype and variations in PRODH (or in their primary downstream effect on plasma proline) shows how variation, other than the deletion itself, can modulate the phenotypic outcome.

**Conclusion**
Patients with 22q11DS are at increased risk for a range of pathological outcomes, of which several are brain-related. As is the case in most pathogenic CNVs, the penetrance of these phenotypes is highly variable while the underlying mechanisms are poorly understood.
22q11DS, given its high occurrence in the population - i.e. relative to other CNVs- provides a model to examine the mechanisms contributing to variable penetrance. Against this background the reported epistatic interaction between the COMT\textsc{158} genotype and proline on the penetrance of social deficits within 22q11DS, provides valuable insight. We emphasize the importance of investigating these mechanisms in larger 22q11DS samples as well as in patients with other CNVs. Increasing the knowledge about the phenotypic pathway of the different CNVs and their developmental outcomes enables parents and clinicians to meet the challenges of these CNVs and helps to develop early interventions and improve developmental perspectives.
References


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Raux, G., Bumsel, E., Hecketsweiler, B., van Amelsvoort, T., Zinkstok, J., Manouvrier-Hanu,


Supplemental Table 1 **Pearson- and partial correlations between social cognition and severity of autism symptomatology controlling for COMT status, and Proline levels, respectively.**

<table>
<thead>
<tr>
<th></th>
<th>ASD total</th>
<th>COMT status</th>
<th>Proline</th>
<th>FSIQ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pearson Correlations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face Recognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time</td>
<td>.270*</td>
<td>-.300*</td>
<td>.156</td>
<td>-.195</td>
</tr>
<tr>
<td>Accuracy</td>
<td>-.002</td>
<td>.193</td>
<td>.218</td>
<td>-.189</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>.165</td>
<td>-.086</td>
<td>.034</td>
<td>-.289*</td>
</tr>
<tr>
<td>Emotion Recognition (positive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time</td>
<td>.310*</td>
<td>.053</td>
<td>.095</td>
<td>-.268*</td>
</tr>
<tr>
<td>Emotion Recognition (negative)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time</td>
<td>.078</td>
<td>-.326*</td>
<td>.123</td>
<td>-.128</td>
</tr>
<tr>
<td>ASD total</td>
<td></td>
<td>-.345**</td>
<td>.010</td>
<td>-.259*</td>
</tr>
<tr>
<td><strong>Partial correlations, controlling for COMT status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face Recognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time</td>
<td>.186</td>
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<td></td>
<td></td>
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<tr>
<td>Accuracy</td>
<td>.069</td>
<td></td>
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<tr>
<td>Emotion Recognition (positive)</td>
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<td></td>
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<tr>
<td>Reaction Time</td>
<td>.145</td>
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<tr>
<td>Accuracy</td>
<td>.350*</td>
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<td></td>
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<tr>
<td>Emotion Recognition (negative)</td>
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</tr>
<tr>
<td>Reaction Time</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>.354*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Correlation is significant at the 0.01 level (1-tailed), *Correlation is significant at the 0.05 level (1-tailed)**