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Author: Hidding, Elske
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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>
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</thead>
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<tr>
<td></td>
<td>FSIQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face Recognition</td>
<td>.270*</td>
<td>-.300*</td>
<td>.156</td>
</tr>
<tr>
<td>Reaction Time</td>
<td></td>
<td></td>
<td>-.195</td>
</tr>
<tr>
<td>Accuracy</td>
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<td>.193</td>
<td>.218</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-.189</td>
</tr>
<tr>
<td>Emotion Recognition (positive)</td>
<td>.165</td>
<td>-.086</td>
<td>.034</td>
</tr>
<tr>
<td>Reaction Time</td>
<td></td>
<td></td>
<td>-.289*</td>
</tr>
<tr>
<td>Accuracy</td>
<td>.310*</td>
<td>.053</td>
<td>.095</td>
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<td></td>
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<td></td>
<td>-.268*</td>
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<td>Emotion Recognition (negative)</td>
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<td>-.326*</td>
<td>.123</td>
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<tr>
<td>Reaction Time</td>
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<td></td>
<td>.039</td>
</tr>
<tr>
<td>Accuracy</td>
<td>.359**</td>
<td>.080</td>
<td>.198</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>.523**</td>
</tr>
</tbody>
</table>

Partial correlations, controlling for COMT status

|                      | ASD total |             |         |
| Face Recognition     | .186      |             |         |
| Reaction Time        | .069      |             |         |
|                      |           |             |         |
| Emotion Recognition (positive) | .145 |         |         |
| Reaction Time        | .350*     |             |         |
|                      |           |             |         |
| Emotion Recognition (negative) | .039 |         |         |
| Reaction Time        | .354*     |             |         |
|                      |           |             |         |

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

Many children with 22q11DS experience cognitive and behavioral problems consistent with the two major neurodevelopmental disorders ASD and ADHD (Schneider et al. 2014a; Baker & Vorstman 2012; Green et al. 2009; Niklasson et al. 2009). The studies described in this thesis aimed to provide a better understanding of the mechanisms that result in vulnerability to autism and ADHD symptomatology in individuals with 22q11DS. For this purpose neurocognitive functioning was assessed in a sample of 102 children and adolescents (aged 9-18.5 years) with 22q11DS. Neurocognitive functions can be seen as the expression of the functioning of the brain at an endophenotypic level, by which the association between the genotype (genetic syndrome) and the phenotype (autism and ADHD symptomatology) is mediated. The objective of the current thesis was to investigate the association between neurocognitive functioning and severity of autism and ADHD symptomatology in individuals with 22q11DS. Insight into this association in this specific population is relevant for our understanding of the different trajectories in neurodevelopmental disorders like ASD and ADHD. This knowledge can be used as a starting point for the development and adjustment of preventive interventions and for treatments of children and adolescents with 22q11DS who are at risk of these developmental problems.

Main findings

Neurocognitive functioning in 22q11DS

The studies presented in this thesis provide a profile of neurocognitive strengths and weaknesses that can be viewed as the cognitive phenotype of children and adolescents with 22q11DS. The intelligence profile that was presented in the first study (chapter 2) emphasizes the relevance of investigating subdomains of intelligence. When looking at cognitive strengths and weaknesses in our sample we found processing speed and short term attention and memory as relative strengths, which is in line with other studies (Duijff et al. 2012; Niklasson & Gillberg 2010). Relative weaknesses in the intelligence profile of children and adolescents with 22q11DS were perceptual organization, sustained attention or concentration, vocabulary, and long term memory. These specific cognitive strengths and weaknesses emphasize the importance of focusing on multiple and more detailed levels of cognitive functioning in this population when evaluating the developmental impact of the syndrome.

Since processing speed proved to be a relative strength in our first study, the outcome that the majority of deficits in executive functioning (EF) were found in accuracy and not in reaction time was a consistent result (chapter 3). Research on EF in children and adolescents with 22q11DS presents consistent evidence for problems in cognitive
control as reflected by the deficits in accuracy of EF (Gur et al. 2014; Campbell et al. 2010). By evaluating a wide range of EF our study provides a profile of the major strengths and weaknesses in EF in children and adolescents with 22q11DS. The profile revealed that this group failed to perform accurately on tasks that demand cognitive flexibility, resistance against distraction, inhibition and sufficient working memory capacity. We also saw that our group experienced difficulties with planning and sustained attention, from which we conclude that severe impairments in EF form a major characteristic of the neurocognitive phenotype of the syndrome. Since in our study age was associated with poorer quality of EF, and other studies also found similar differences in degree of impairments at different ages, it seems very important to monitor the cognitive development of individuals with 22q11DS and its impact on the developmental outcome of this syndrome. 

Social cognition as underlying mechanism of social functioning is an important element for understanding the behavioral disturbances in the social domain that are often found in 22q11DS. We found impairments in both face and facial emotion recognition in our sample with 22q11DS compared to the norm (chapter 4). Recognition of positive emotions was relatively less impaired as compared to the recognition of negative emotions. We further observed that quality of abstract visual information processing was also impaired, especially the processing of more complex, featural (nonsocial), information. These findings suggest that children and adolescents with the syndrome experience difficulties in the processing of complex abstract and social visual information. Further analyses gave reason to believe that the deficit in social information processing may at least partly originate from a general impairment in the processing of visuospatial information.

**Associations with autism and ADHD symptomatology**

The central aim of the research in this thesis was to discover possible mediating mechanisms that are associated with the vulnerability to ASD and ADHD symptomatology in children and adolescents with 22q11DS. Therefore, associations between the profiles of neurocognitive functioning and severity of ASD and ADHD symptomatology, as evaluated in this study, were examined. We first started by looking at differences in intelligence profiles between subgroups with and without symptoms of ADHD and ASD. However, these profiles did not differentiate between participants with and without ASD and/or ADHD. This raises the question whether looking at subgroups based on diagnostic criteria is sensitive enough in this population. It is a clinical reality that children with 22q11DS do have an increased vulnerability to both ASD and ADHD symptomatology. This can be seen as a first argument to investigate both symptom domains instead of following the DSM-IV criteria that, at least formally, do not allow a concurrent diagnosis of both ADHD and ASD in the same individual. Secondly, looking at symptoms that are severe enough to be categorized as a problem score, based on the cut-off criteria of questionnaires or diagnostic criteria, may also not be the most optimal strategy, since a lot of these children experience problems in those domains even when these problems are not severe enough to yield scores in the clinical range.

To overcome these restraints of diagnostic criteria, we decided to use continuous measures of severity on both the ASD and ADHD symptom domains. On the
subdomains of intelligence we found poorer performances on tasks that require perceptual motor integration, visual information processing, comprehension or verbal expression to be associated with more severe ASD symptomatology (chapter 2). Our second study demonstrated impairments in cognitive flexibility, inhibition and distractibility to be associated with more severe ASD symptoms (chapter 3). Regarding social cognition, poorer accuracy of emotion recognition was associated with more severe ASD symptoms. This association could not be explained by the poorer quality of processing of abstract visual information (chapter 4). Weaker quality of visuospatial information processing and poorer numerical reasoning, concentration and attention were associated with more severe ADHD symptomatology (chapter 2). More difficulties with sustained attention and a higher distractibility were also associated with more severe ADHD symptomatology (chapter 3). Poorer accuracy of emotion recognition was found to be associated with more severe ADHD symptomatology. However, when using quality of featural processing as a covariate, this association between emotion processing and ADHD symptomatology no longer existed (chapter 4). This could indicate that poorer emotion recognition in children with more severe ADHD symptoms is at least partly explained by poorer visual information processing strategies. The associations between neurocognitive functioning and ASD and ADHD symptomatology in our sample differs from those in other clinical groups with ASD and ADHD without 22q11DS. This suggests that in the 22q11DS population specific mechanisms are involved in the development and expression of ASD and ADHD symptoms as compared to idiopathic, and therefore highly heterogeneous, ASD and ADHD populations.

Variability in expression of social deficits
In the last chapter we investigated the influence of two additional factors as possible modulating mechanisms of the high vulnerability to social cognitive and behavioral deficits in the 22q11DS population (chapter 5). The contribution of the genotype of the remaining allele of COMT and plasma levels of the amino acid proline to the variability in expression of social deficits was examined. This study demonstrated that individuals with the COMT<sub>MET</sub> genotype who also displayed high plasma proline levels presented with more severe social behavioral problems. Additionally, in individuals with the COMT<sub>MET</sub> variant poorer quality of face recognition was associated with more severe social behavioral problems, while in individuals with the COMT<sub>VAL</sub> variant this association was absent. Lastly, the association between poorer quality of emotion recognition and severity of social behavioral problems that was described in chapter 4 appeared to be independent from COMT<sub>150</sub> genotype and plasma proline level.

Implications
The findings of this thesis contribute to our understanding of the mediating role of neurocognitive dysfunctions in the development of social and behavioral problems in 22q11DS. From the evidence presented in these studies we concluded that children
and adolescents with this syndrome present with specific cognitive and behavioral phenotypes. The associations between both phenotypes suggest the involvement of a developmental pathway in this syndrome that can be better identified as compared to the diversity of pathway’s in the idiopathic ASD and ADHD populations which are, by definition, genetically more heterogeneous. This implies that in children and adolescents with 22q11DS, partly different neurocognitive deficits are associated with the expression and variability of social behavioral problems as compared to children from heterogeneous ASD and ADHD populations. These findings support the idea of different pathways leading to the social behavioral problems reported in developmental disorders (de Zeeuw et al. 2012; Durston et al. 2011). Based on the outcomes of our last study it can be concluded that differences in developmental pathways are the result of a specific genetic etiology (Bruining et al. 2010). These differences are not only explained by the 22q11.2 deletion itself since variations in COMT gene expression and plasma proline level also play a role in the phenotypic outcome.

Clinical implications
In connection with the existing literature, the neurocognitive profiles described in this thesis emphasize the cognitive strengths and vulnerabilities in children and adolescents with 22q11DS aged 9 – 18.5 years. The results stress the importance to monitor the cognitive development of these children over time, in particular since longitudinal studies report a decline in cognitive functioning somewhere between the age of 7.5 and 15 in children with 22q11DS, with not all domains of functioning equally affected (Duijff et al. 2013; Antshel et al. 2010; Gothelf et al. 2007). How and to what extent the decline in cognitive functioning has an impact on developmental trajectories is not clear yet. Literature and our study suggest that the COMT*MET variant might be a risk factor of impairments in cognitive functioning and a unfavorable behavioral outcome (Radoeva et al. 2014; Magnee et al. 2011; Antshel et al. 2010; Gothelf et al. 2007; Lachman et al. 1996;).

Due to their relatively spared processing speed, short attention and memory, there is a risk of overestimating the cognitive capacities of these children. A child with 22q11DS may be seen to keep pace with the normal working tempo in classroom settings. Because of the cognitive difficulties it experiences however, this pace is mostly kept at the cost of quality of cognitive control. Since some of the cognitive dysfunctions identified in this developmental period are also associated with the severity of the social behavioral problems, an attentive focus on their cognitive abilities should be incorporated in protocols for preventive interventions, treatment and care. In view of this recommendation, it is interesting to note that a preliminary study already reported improvement in cognitive skills in adolescents with 22q11DS after following a cognitive remediation program (Harrell et al. 2013).

The observed difficulties with visual information processing and in particular with the processing of social relevant information provide important targets for clinical care of these children and adolescents. Especially in this age period (9-18.5 years) these impairments have a large impact on daily functioning. In their interaction with peers and others it is expected that young adolescents are capable of fast perceiving and interpreting visual and social stimuli. Non-verbal communication becomes
increasingly important and their impairment in both processing of abstract and social visual information may hamper social interaction with their peers. It is therefore important to monitor the social development in this age period and to be alert for signs of social exclusion, mood and anxiety problems as a consequence of these impairments.

Scientific implications and directions for future research

The findings presented in this thesis contribute to our understanding of the neurocognitive functioning of children and adolescents with 22q11DS, in particular by adding evidence about associations between quality of neurocognitive skills and severity of autism and ADHD symptomatology. Because of the cross-sectional design of the study we could not look at causal relations between the cognitive and behavioral outcomes. This is only possible by developing longitudinal study designs. For the interpretation and application of our findings in research and clinical settings it is also important to be aware of other limitations. First, although our total sample of \( N = 102 \) is relatively large, the sample size varies between the different studies. This complicates the generalization of findings, especially for the studies that include social cognition (\( N = 45 \)). Second, the age range (9-18.5 years) was relatively large and included the transition from childhood into adolescence, the sample being too small to look at the two developmental periods separately or to compare them. Our studies provide important new insights in the associations between the neurocognitive and behavioral phenotype within the syndrome. Because our data consisted of only one time-point we would recommend to investigate longitudinal changes in cognition and its associations with behavioral outcomes later in life. Lastly, the absence of a control group can also be seen as a limitation although it is difficult to determine what would constitute a suitable control group.

The results presented in this thesis not only contribute to our knowledge about the cognitive and behavioral phenotype in 22q11DS, but may also help to understand the developmental pathways in ASD and ADHD. Additionally, our results on the role of genetic variation in the expression of cognitive and behavioral outcomes adds to our understanding of variability in expression of phenotypes in copy number variants (CNVs).

Since cognitive functioning is one of the mediating factors of variability in adaptive functioning of adults with 22q11DS, more insight into how cognitive functioning interacts with behavioral functioning during development may contribute to better adaptive skills later in life (Butcher et al. 2012; Schneider et al. 2014a). The association that was found between neurocognitive functioning and severity of the observed social behavioral problems explains some of the variability in the cognitive and behavioral phenotype of 22q11DS. Specific deficits in cognitive functioning are associated with more severe behavioral problems and this finding emphasizes the importance to further investigate the influence of cognitive deficits on the variability in phenotypic expressions. Thus far, research focused primarily on the risk of schizophrenia spectrum disorders within the syndrome. Studies have shown an association between impaired cognitive functioning and the presence of (premorbid) schizophrenic symptomatology (Antshel et al. 2010; Hooper et al. 2013; Schneider et al. 2014a; Schneider et al. 2014b). However, our findings suggest that it is similarly
important to monitor the cognitive development of children and adolescents with this syndrome in light of social behavioral problems that are part of developmental disorders. It is also important to take other factors into account that possibly influence the associations between neurocognitive functioning and social and behavioral outcomes in later life. For example medical complications, medication effects, interventions and education. Including these factors in the replication and further specification of the demonstrated associations is recommended, especially in longitudinal samples, to provide a better view of the developmental perspective of children and adolescents with 22q11DS.

A second implication concerns the differences in associations between neurocognitive functioning and severity of ASD and ADHD symptomatology as compared to findings in idiopathic groups with ASD and ADHD without 22q11DS. Our results suggest that those children with 22q11DS and ASD or ADHD symptomatology represent a genetic subgroup within the heterogeneous ASD and ADHD populations explaining some of the genetic variation within both developmental disorders (Vorstman & Ophoff 2013; Bruining et al. 2014). There might be specific neurocognitive pathways leading to ASD and ADHD symptomatology in individuals with 22q11DS that differ from pathways found in more heterogeneous groups (Durston et al. 2011; de Zeeuw et al. 2012), although these differences might also be (partly) explained by the previously mentioned factors influencing the association between the neurocognitive and behavioral phenotype in 22q11DS.

Lastly, our research contributes to our understanding of the role of CNVs in the variability of phenotypes of different genetic disorders. CNVs are associated with several neurodevelopmental disorders including autism and ADHD (Moreno-De-Luca & Cubells 2011; Grayton et al. 2012). Using 22q11DS as a model of how genetic, cognitive and behavioral factors are influenced by a specific CNV improves our knowledge about the mechanisms that causes variability in expression of phenotypes observed in many CNVs. The interactive effect of COMT\textsuperscript{158} genotypes and plasma proline level on the cognitive and behavioral phenotype in 22q11DS described in chapter 5 shows us how variation in genes within this specific CNV may be associated with the risk for psychiatric disorders.

In conclusion, this thesis shows the importance of assessing neurocognitive profiles in 22q11DS. Children and adolescents with the syndrome present with severe impairments on various domains of neurocognitive functioning. Some of these impairments are associated with the variable expression of social behavioral problems within the syndrome, underlining the importance of monitoring the cognitive development within this population. For clinical practice and future research it is important to be aware of the role of both genetic factors and neurocognitive functioning in the presence and severity of behavioral problems in 22q11DS and other CNVs. A better understanding of the mechanisms involved in the variable expression of phenotypes will facilitate improvement of clinical care and ultimately lead to a better prediction of developmental outcomes.
References


Harrell, W., Eack, S., Hooper, S.R., Keshavan, M.S., Bonner, M.S., Schoch,


