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BJP 2014, 204:46-54.
Access the most recent version at DOI: 10.1192/bjp.bp.113.132324

References
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Maria Niarchou, Stanley Zammit, Stephanie H. M. van Goozen, Anita Thapar, Hayley M. Tierling, Michael J. Owen and Marianne B. M. van den Bree

Background
Children with 22q11.2 deletion syndrome (22q11.2DS) have been reported to have high rates of cognitive and psychiatric problems.

Aims
To establish the nature and prevalence of psychiatric disorder and neurocognitive impairment in children with 22q11.2DS and test whether risk of psychopathology is mediated by the children’s intellectual impairment.

Method
Neurocognition and psychopathology were assessed in 80 children with 22q11.2DS (mean age 10.2 years, s.d. = 2.1) and 39 sibling controls (mean age 10.9 years, s.d. = 2.0).

Results
More than half (54%) of children with 22q11.2DS met diagnostic criteria for one or more DSM-IV-TR psychiatric disorder. These children had lower IQ (mean 76.8, s.d. = 13.0) than controls (mean 108.6, s.d. = 15.2) (P < 0.001) and showed a range of neurocognitive impairments. Increased risk of psychopathology was not mediated by intellectual impairment.

Conclusions
22q11.2DS is not related to a specific psychiatric phenotype in children. Moreover, the deletion has largely independent effects on IQ and risk of psychopathology, indicating that psychopathology in 22q11.2DS is not a non-specific consequence of generalised cognitive impairment.

Declaration of interest
None.

Participants
As part of the Experiences of CHildren with cOpY number variants (ECHO) study, 80 children (50% females) with 22q11.2DS aged 6.6–14.1 years (mean 10.2, s.d. = 2.1) and 39 sibling controls (56% females) aged 6.3–14.3 years (mean 10.9, s.d. = 2.0) were recruited from 14 genetics clinics across the UK, the British 22q11 deletion syndrome charities Max Appeal! and The 22Crew, and our ECHO study website (http://medicine.cardiff.ac.uk/psychological-medicine-neuroscience/areas-research/copy-number-variant-research/research-projects/).

Table 1 provides a sociodemographic description of the sample. Numbers of children differ for different measures as five children with 22q11.2DS were not able to complete all the cognitive assessments. Furthermore, due to geographical considerations we did not conduct any neurocognitive testing in six children (in these cases psychiatric interviews were conducted using video-call).

Presence of the deletion was confirmed for all children with 22q11.2DS (87.5% of families were recruited from medical
conducted by trained psychologists, who were supervised by a
self-reports using the same instrument. All interviews were
headaches. Psychotic experiences were also assessed by children’s
spots/stripes before the eyes and sensory changes associated with
hallucinations occurring as part of a seizure or clouded sensorium,
imagery, elaborated fantasies, imaginary companions, illusions,
symptoms included hypnagogic/pompic hallucinations, eidetic
and delusional thinking. Phenomena not coded as psychotic
thought insertion and broadcast, thought echo and withdrawal
olfactory and tactile hallucinations. Questions were asked about
questions are included regarding content and location of auditory,
questions about the nature of possible symptoms. Specifically,
affirmatively, the interviewer continued with more detailed
processes. If these screening questions were answered
hallucinations, delusions or psychotic abnormalities of thought
probed for any evidence of perceptual disorders or
dealing with psychotic experiences, initial screening questions
interview with the primary caregiver. In the section of the interview
Psychiatric Assessment (CAPA)\textsuperscript{10} by means of semi-structured in-
Psychopathology was assessed with the Child and Adolescent
Psychopathology

Table 1  Sociodemographic information of sample
\begin{tabular}{|c|c|}
\hline
Family ethnic background & \% \\
\hline European & 91.25 \\
Mixed & 6.25 \\
Non-European & 2.5 \\
\hline Highest maternal educational qualification & \\
\hline Low: O-levels or GCSEs & 38.75 \\
Middle: A-levels/highers or vocational training & 40 \\
High: university degree and/or other higher postgraduate qualification & 20 \\
Unknown & 1.25 \\
\hline Family income, £ & \\
\hline \leq 19 999 & 16.25 \\
20 000–39 000 & 27.5 \\
40 000–59 000 & 18.75 \\
\geq 60 000 & 25 \\
Unknown & 12.5 \\
\hline
\end{tabular}

\textbf{Fig. 1}  Representation of possible relationships between
intellectual impairment and psychopathology and the 22q11.2

delletion.

According to Model A, psychopathology is a direct consequence of the deletion, whereas according to Model B, psychopathology can be better explained by the intellectual impairment caused by the 22q11.2 deletion. The mediation model examines the role of group status (children with 22q11.2DS v. sibling controls) on psychiatric diagnosis through IQ, del. deletion.

Table 1 Sociodemographic information of sample

<table>
<thead>
<tr>
<th>Family ethnic background</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>European</td>
<td>91.25</td>
</tr>
<tr>
<td>Mixed</td>
<td>6.25</td>
</tr>
<tr>
<td>Non-European</td>
<td>2.5</td>
</tr>
<tr>
<td>Highest maternal educational qualification</td>
<td></td>
</tr>
<tr>
<td>Low: O-levels or GCSEs</td>
<td>38.75</td>
</tr>
<tr>
<td>Middle: A-levels/highers or vocational training</td>
<td>40</td>
</tr>
<tr>
<td>High: university degree and/or other higher postgraduate qualification</td>
<td>20</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.25</td>
</tr>
<tr>
<td>Family income, £</td>
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<td>≤ 19 999</td>
<td>16.25</td>
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</tr>
<tr>
<td>40 000–59 000</td>
<td>18.75</td>
</tr>
<tr>
<td>≥ 60 000</td>
<td>25</td>
</tr>
<tr>
<td>Unknown</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Psychopathology

Psychopathology was assessed with the Child and Adolescent Psychiatric Assessment (CAPA)\textsuperscript{10} by means of semi-structured interview with the primary caregiver. In the section of the interview dealing with psychotic experiences, initial screening questions probed for any evidence of perceptual disorders or hallucinations, delusions or psychotic abnormalities of thought processes. If these screening questions were answered affirmatively, the interviewer continued with more detailed questions about the nature of possible symptoms. Specifically, questions are included regarding content and location of auditory, olfactory and tactile hallucinations. Questions were asked about thought insertion and broadcast, thought echo and withdrawal and delusional thinking. Phenomena not coded as psychotic symptoms included hypnagogic/pompic hallucinations, eidetic imagery, elaborated fantasies, imaginary companions, illusions, hallucinations occurring as part of a seizure or clouded sensorium, spots/stripes before the eyes and sensory changes associated with headaches. Psychotic experiences were also assessed by children’s self-reports using the same instrument. All interviews were conducted by trained psychologists, who were supervised by a consultant child and adolescent psychiatrist. Interviews were audiotaped for monitoring and assignment of DSM-IV-TR diagnoses by the child and adolescent psychiatrist. We did not regard ADHD, ODD, pervasive developmental disorder and mood and anxiety disorders as mutually exclusive diagnoses.

Fig. 1 Representation of possible relationships between intellectual impairment and psychopathology and the 22q11.2 deletion.

Autistic behaviour was assessed using the Social Communication Questionnaire (SCQ),\textsuperscript{12} which was completed by the primary caregiver. Total scores can range from 0 to 39. The cut-off of 15, which is suggestive of autism spectrum disorder (ASD), was used in our analyses.

With regard to psychotropic medication, one child with 22q11.2DS and one sibling were receiving oral methylphenidate for ADHD.

Cognition

Neurocognitive assessments were conducted by trained raters. An estimate of general intelligence (IQ) was obtained by administering the Wechsler Abbreviated Scale of Intelligence (WASI; four subtests).\textsuperscript{13} Processing speed was assessed with the Reaction Time (RT) (child mode) test; attention and vigilance were examined with the Match to Sample visual search (MTS) and the Rapid Visual Information Processing (RVP) (child mode) tests, from the CANTAB (Cambridge Neuropsychological Automated Battery eclipse version 3 software, Cambridge, 2006); executive function was assessed with the Spatial Working Memory (SWM) and the Stockings of Cambridge (SOC) tests from the CANTAB. To obtain a global assessment of executive function we also administered the Wisconsin Card Sorting Test (WSCST).\textsuperscript{14}

Data analysis

Data analysis was conducted using Stata (version 11) for Windows XP.

Psychopathology (Goal 1)

The prevalence of psychiatric problems in children with 22q11.2DS compared with their siblings was examined using a $\chi^2$-test. Associations between age and psychiatric diagnoses were examined using Spearman’s rank correlations, and association between gender and psychiatric diagnoses were examined using $\chi^2$-tests. To examine whether any of the comorbid diagnoses occurred more frequently than others, $\chi^2$-tests were used.

Nature and prevalence of cognitive impairments (Goal 1)

All neurocognitive measures were standardised to have a mean of zero and a standard deviation of one, apart from the ‘failure to
maintain set’ variable of the WCST (which is categorical) and IQ score. Apart from IQ, all other cognitive variables were not normally distributed. To compare the mean differences in cognitive performance of the children with 22q11.2DS with their siblings, t-tests or, in the case of non-normally distributed cognitive variables, Mann–Whitney U-tests were conducted. Spearman’s rank correlations were used to estimate the correlations between IQ and age, and IQ and gender. A t-test was used to examine whether the average verbal IQ in children with 22q11.2DS was different from the average performance IQ.

IQ in relation to other cognitive measures and patterns of associations (Goal 1)

Spearman’s rank correlations were used to estimate the correlations between IQ and other neurocognitive measures. A comparison of the magnitudes of the correlations of the neurocognitive tests for children with 22q11.2DS v. sibling controls was conducted following Fisher’s r-to-z transformation. A two-group variance-comparison test using the sdtest command was employed to examine whether there was greater variation in neurocognitive performance in the children with 22q11.2DS in relation to their siblings.

Psychopathology and cognition (Goal 2)

In order to determine whether the differences in psychiatric diagnoses between the children with 22q11.2DS and their sibling controls could be explained by IQ, we performed the following analyses. Independent regressions were performed in the total sample to determine whether the independent variable (i.e. IQ score) predicted presence of psychiatric diagnosis (0 = no diagnosis, 1 = present diagnosis). From these regressions we derived odds ratios (ORs) and 95% confidence intervals (CIs). To facilitate interpretation of the results, IQ score was standardised to have a mean of 0 and a standard deviation of 1 and recoded so that higher score indicated worse performance. These analyses were conducted only for the psychiatric diagnoses that were significantly different between the two groups: 1. ADHD (absent (0) v. present (1)); 2. any anxiety disorder (absent (0) v. present (1)); 3. ODD (absent (0) v. present (1)); 4. ASD screening (0 = SCQ score <15, 1 = SCQ score ≥15). To test the assumption that the relationship between IQ and psychopathology was similar in children with 22q11.2DS and siblings and that combining the two groups for subsequent analysis was therefore appropriate, we assessed homogeneity of ORs using the $\chi^2$-test of homogeneity. Odds ratios and 95% confidence intervals for the associations between IQ and psychopathology after adjusting for group status (22q11.2DS v. siblings) were estimated using the Mantel–Haenszel method.

Mediation analysis was also conducted to examine the extent to which IQ score mediated the associations between group status and psychiatric diagnosis. Figure 1 (Model B) illustrates a representation of the model tested. The binary_mediation command was used to estimate the indirect effect of IQ on psychopathology, using the product of coefficients approach, which is considered to have good power and low type I error. Standard errors and biased-corrected confidence intervals were also calculated using bootstrapping with 5000 replications. We repeated these analyses to explore whether the other cognitive measures mediated the relation between the deletion and psychiatric problems. To limit the number of statistical comparisons we examined only the primary scores of these cognitive tests (i.e. MTS total correct; RTI 5-choice reaction time; RVP A; SOC problems solved in minimum moves; and SWM between errors score, number of perseverative errors).

### Results

#### Psychopathology (Goal 1)

More than half (54%) of the children with 22q11.2DS met diagnostic criteria for one or more DSM-IV-TR psychiatric disorders, compared with 10% of the siblings, $P<0.001$ (Table 2). Children with 22q11.2DS exhibited higher rates of ADHD, ODD and anxiety disorders in relation to their siblings. Furthermore, more children with 22q11.2DS (26%) met the cut-off for probable ASD diagnosis in relation to their siblings (5%). Psychiatric diagnoses were not related to age or gender in the children with 22q11.2DS (data not presented). High rates of comorbidity were observed for children with 22q11.2DS (Fig. 2): 12 (37.5%) children with ADHD also had at least one anxiety disorder; 12

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Children with 22q11.2DS</th>
<th>Siblings</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diagnosis</td>
<td>43 (54.5)</td>
<td>4 (10.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>21 (26.3)</td>
<td>2 (5.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Generalised anxiety disorder</td>
<td>5 (6.3)</td>
<td>0</td>
<td>0.12</td>
</tr>
<tr>
<td>Panic disorder without agoraphobia</td>
<td>1 (1.3)</td>
<td>0</td>
<td>0.48</td>
</tr>
<tr>
<td>Panic disorder with agoraphobia</td>
<td>2 (2.5)</td>
<td>0</td>
<td>0.33</td>
</tr>
<tr>
<td>Agoraphobia without history of panic disorder</td>
<td>1 (1.3)</td>
<td>0</td>
<td>0.49</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>12 (15.2)</td>
<td>1 (2.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Social phobia</td>
<td>14 (17.5)</td>
<td>2 (5.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Obsessive–compulsive disorder</td>
<td>3 (3.8)</td>
<td>0</td>
<td>0.23</td>
</tr>
<tr>
<td>Separation anxiety disorder</td>
<td>2 (9.1)</td>
<td>0</td>
<td>0.41</td>
</tr>
<tr>
<td>Attention-deficit hyperactivity disorder</td>
<td>32 (40.5)</td>
<td>2 (5.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
<td>15 (18.8)</td>
<td>1 (2.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Tic disorder</td>
<td>6 (7.5)</td>
<td>0</td>
<td>0.31</td>
</tr>
<tr>
<td>Delusional disorder</td>
<td>2 (2.5)</td>
<td>0</td>
<td>0.33</td>
</tr>
<tr>
<td>Selective mutism</td>
<td>1 (1.3)</td>
<td>0</td>
<td>0.49</td>
</tr>
<tr>
<td>Autism spectrum disorder screening</td>
<td>20 (26.0)</td>
<td>2 (5.3)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

22q11.2DS, 22q11.2 deletion syndrome.

| a. Insufficient information to confirm diagnosis for one participant.

(37.5%) had ODD; and 12 (41.2%) screened positive for probable ASD. Among children with an anxiety disorder, 7 (33.3%) also had ODD and 11 (52.4%) screened positive for probable ASD. Among children with ODD, 6 (30%) also screened positive for probable ASD. None of the comorbid diagnoses occurred more frequently than others (P > 0.2). Overall, psychotic experiences (parent and self-report combined) were reported by 10% of children with 22q11.2DS, and 8% of their siblings. Parents reported psychotic experiences for 5% of the children with 22q11.2DS and none of their siblings. Whereas 6% of the children with 22q11.2DS and 8% of their siblings self-reported psychotic experiences. Parental and child reports were in agreement for only one child (who had 22q11.2DS).

Nature and prevalence of cognitive impairments (Goal 1)

Children with 22q11.2DS had a lower estimated total IQ and performed worse than their siblings on all cognitive tests (Table 3). The IQ distribution of the children with 22q11.2DS was shifted over 30 points to the left compared with the siblings (Fig. 3). Of the children with 22q11.2, 30.6% had mild intellectual disability (IQ range 53–69), 30.6% had a borderline IQ score (70–79) and 38.9% had an average IQ score (81–109). Older children with 22q11.2DS had lower IQs than younger children (r = −0.32, P = 0.01) but this was not the case for siblings (r = −0.09, P = 0.61). No gender differences were found for IQ between children with 22q11.2DS and their siblings. There were no differences between verbal and performance IQ for children with 22q11.2DS (r = −0.24, P = 0.82).

We found 22% of children with 22q11.2DS had higher verbal (>10 points) than performance IQ, but equally 22% had higher performance (>10 points) than verbal IQ. Children with 22q11.2DS were also found to perform worse than their siblings on all other neurocognitive tests (Table 3).

IQ in relation to the other cognitive measures and patterns of associations (Goal 1)

Correlation analysis (Table 4) indicated that the CANTAB measures and the WCST did tap into neurocognitive domains that were independent of IQ in children with 22q11.2DS. As a sensitivity analysis, we reran the analyses comparing cognitive performance in children with 22q11.2DS and sibling controls, including only children with 22q11.2DS with IQ > 70 and results remained substantially the same, suggesting the findings were not driven by the subgroup with mild intellectual disability. The pattern of associations between the neurocognitive tests ranged from low to modest in strength (Table 5), indicating that these cognitive tests do measure different cognitive abilities in both groups of children. Although the correlations between the tests tended to be somewhat higher for children with 22q11.2DS (range 0.15 to 0.55) compared with sibling controls (−0.17 to 0.44), formal comparison indicated the magnitude of associations was higher in children with 22q11.2DS for only 2 out of 15 correlations: RVP test with both the RTI test and perseverative...
Discussion

Psychopathology

More than half (54%) of children with 22q11.2DS met diagnostic criteria for one or more DSM-IV-TR psychiatric disorder. They had higher rates of ADHD, ASD, ODD and anxiety disorders compared with sibling controls. These rates are broadly similar to those reported in previous studies of children with 22q11.2DS (e.g. Green et al\(^4\)) and to population studies of children with intellectual disabilities (e.g. Emerson\(^7\)), indicating that in childhood, 22q11.2DS does not seem to be related to a specific psychiatric phenotype,\(^7\) at least as captured by current diagnostic systems.\(^20\) It also suggests that these disorders can share underlying pathogenic mechanisms with intellectual disability. Comorbidity was also substantial, providing further evidence that the effect of the deletion is widespread across a range of neuro-developmental syndromes. This is in keeping with previous studies of children with 22q11.2DS (e.g. James et al\(^3\)), studies of rare CNVs and single-gene disorders which similarly tend to be associated with increased risk of many different types of psychopathology (e.g. Miller et al\(^23\)).

The frequency of psychotic-like experiences was similar between children with 22q11.2DS and their siblings, indicating that at this age children with 22q11.2DS are too young to exhibit the higher rates of psychotic experiences robustly seen in late adolescence and adulthood. Interestingly, parent and child reports were in agreement only for one child with 22q11.2DS and none of the siblings for whom any psychotic experiences were only by self-report. This could be because children are not willing to share these symptoms with their parents or due to difficulties associated with obtaining reliable data on psychotic experiences in children of this age.

Cognition

Our findings demonstrate that the IQ distribution of the children with 22q11.2DS is shifted over 30 points to the left in relation to
their siblings. This is in agreement with previous studies in 22q11.2DS as well as the literature on single-gene disorders (e.g. fragile-X syndrome\textsuperscript{23}) and other neurodevelopmental syndromes (e.g. ASD and ADHD\textsuperscript{24}). Even though performance on the neurocognitive tests was generally impaired in the entire sample of children with 22q11.2DS, it was also variable. That is, performance on IQ was unrelated to performance on most neurocognitive tests, a finding in accordance with reports in other single-gene disorders (e.g. ADHD\textsuperscript{25}). Furthermore, there has been disagreement on whether there is a relationship between IQ score and the other neurocognitive measures of children with 22q11.2DS, 22q11.2 deletion syndrome; MTS, Match to Sample Visual Search; RTI, Reaction Time; RVPA, Rapid Visual Information Processing; SOC, Stockings of Cambridge; SWM, Spatial Working Memory; WCST, Wisconsin Card Sorting Test.

<table>
<thead>
<tr>
<th>Cognitive measure</th>
<th>IQ</th>
<th>rho</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTS, total correct</td>
<td></td>
<td>0.09</td>
<td>0.45</td>
</tr>
<tr>
<td>RTI 5-choice movement time</td>
<td></td>
<td>0.12</td>
<td>0.32</td>
</tr>
<tr>
<td>RTI 5-choice reaction time</td>
<td></td>
<td>0.07</td>
<td>0.59</td>
</tr>
<tr>
<td>RVPA</td>
<td></td>
<td>0.20</td>
<td>0.10</td>
</tr>
<tr>
<td>SOC Mean initial thinking time</td>
<td></td>
<td>−0.04</td>
<td>0.75</td>
</tr>
<tr>
<td>SOC Mean subsequent thinking time</td>
<td></td>
<td>0.08</td>
<td>0.54</td>
</tr>
<tr>
<td>SOC Problems solved in minimum moves</td>
<td></td>
<td>0.16</td>
<td>0.20</td>
</tr>
<tr>
<td>SWM Between errors</td>
<td></td>
<td>0.35</td>
<td>0.003</td>
</tr>
<tr>
<td>SWM Strategy</td>
<td></td>
<td>0.35</td>
<td>0.003</td>
</tr>
<tr>
<td>WCST Perseverative errors</td>
<td></td>
<td>0.25</td>
<td>0.04</td>
</tr>
<tr>
<td>WCST Non-perseverative errors</td>
<td></td>
<td>−0.13</td>
<td>0.29</td>
</tr>
<tr>
<td>WCST Failure to maintain set</td>
<td></td>
<td>−0.07</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Furthermore, children with 22q11.2DS had greater variation in cognitive performance in relation to their siblings, a finding in agreement with previous reports in 22q11.2DS.\textsuperscript{26} This variation could be due to the deletion having widespread effects in cognitive performance but we cannot exclude the possibility of other confounding factors, such as more attention or behavioural problems in children with 22q11.2DS in relation to their siblings, which might have influenced their performance in the cognitive tests. We did not find evidence of better verbal than non-verbal abilities in line with some\textsuperscript{27} but not all previous studies.\textsuperscript{28} Moreover, although previous studies have shown discrepancies between verbal and performance IQ (usually between 8 to 10 points\textsuperscript{29}), the number of children with better verbal than performance IQ (\(\geq 10\) points) in our study was similar to the number with better performance than verbal IQ (\(\geq 10\) points). Therefore our study does not support the hypothesis that 22q11.2DS is specifically associated with non-verbal intellectual disability.

### Lack of associations between cognitive impairment and psychopathology

There has been disagreement on whether there is a relationship between IQ and psychopathology in 22q11.2DS with some studies reporting relationships,\textsuperscript{30} while others do not.\textsuperscript{31} In line with our predictions, there was no relation between psychopathology and IQ in children with 22q11.2DS. The availability of a sample of sibling controls in which the same assessments were conducted as in the children with 22q11.2DS, in combination with a relatively large sample size, allowed us to conduct the first mediation analysis for this syndrome. The findings showed that psychopathology in 22q11.2DS is not explained by indirect effects, mediated by the children’s intellectual impairment.

We also explored the associations with other neurocognitive measures and our results indicated only an indirect effect of the deletion on probable ASD diagnosis through the SOC (an indicator of planning) test. This effect, however, was in the opposite direction than expected and therefore, given the exploratory nature of our analysis, we interpreted this result as

<table>
<thead>
<tr>
<th>Cognitive measure</th>
<th>MTS</th>
<th>RTI</th>
<th>RVPA</th>
<th>SOC</th>
<th>SWM</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTS, total correct</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTS, total correct</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>RTI 5-choice reaction time</td>
<td>0.28</td>
<td>0.07</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>RVPA</td>
<td>0.33</td>
<td>−0.07</td>
<td>0.55</td>
<td>0.14</td>
<td>1</td>
</tr>
<tr>
<td>SOC Problems solved in minimum moves</td>
<td>0.18</td>
<td>−0.12</td>
<td>0.35</td>
<td>0.35</td>
<td>0.28</td>
</tr>
<tr>
<td>SWM Between errors</td>
<td>0.15</td>
<td>−0.17</td>
<td>0.26</td>
<td>0.20</td>
<td>0.25</td>
</tr>
<tr>
<td>WCST, perseverative errors</td>
<td>0.16</td>
<td>0.02</td>
<td>0.25</td>
<td>0.09</td>
<td>0.27</td>
</tr>
</tbody>
</table>

22q11.2DS, 22q11.2 deletion syndrome; MTS, Match to Sample Visual Search; RTI, Reaction Time; RVPA, Rapid Visual Information Processing; SOC, Stockings of Cambridge; SWM, Spatial Working Memory; WCST, Wisconsin Card Sorting Test. Figures in italic type reflect differences in magnitude of the correlations between the two groups, at the level of \(P<0.05\) but \(P>0.01\). Figures in bold signify statistical significance.
lack of evidence for a mediated effect of the deletion through cognition.

**Strengths and limitations**

This is one of the largest studies to date to include children with 22q11.2DS with a relatively narrow age range as well as sibling controls, and one of the few studies to obtain detailed psychiatric as well as neurocognitive phenotyping. Moreover, this is the first study to use mediation analysis to further examine the relationships between IQ and psychopathology. Given that children with 22q11.2DS may have a risk of developing schizophrenia in adulthood in the order of 30%,2,3 follow-up will allow us to identify risk and protective factors for schizophrenia and to study potential mechanisms and markers of high risk that are unconfounded by reverse causation and medication effects.

On the other hand, even though this study is one of the largest to date, type II errors cannot be excluded. Also, although the age range of the children is narrow in comparison to previous studies in children with 22q11.2DS, we cannot exclude the possibility that significant developmental changes during that period might have influenced our findings.

**Theoretical implications**

Our findings raise a number of important issues. First, it is not yet known how the deletion can manifest itself in such a clinically variable manner. Various factors could contribute to this
variability, including the combined effect of reduced genetic dosage along with background genetic variation, in the 22q11.2 region, and elsewhere in the genome, as well as positional effects. For example, it has been hypothesised that dopamine dysregulation resulting from reduced gene dosage arising from the deletion could lead to brain dis connectivity and in turn to predisposition to the cognitive and psychiatric deficits for a subgroup of individuals with 22q11.2DS. Moreover, it is likely that environmental exposures also play a role.

These findings suggest that the 22q11.2 deletion has pleiotropic effects on IQ and psychopathology. In other words, the deletion has largely independent effects on IQ and risk of psychopathology. This implies that the associations seen more generally between impaired IQ and psychopathology might reflect the fact that cognitive impairments index genetic risk factors for psychiatric syndromes rather than that impaired cognition mediates the effects of risk. Indeed, there is accumulating evidence in support of this view from recent work on schizophrenia.

Clinical implications

The results indicate that the prevalence of psychopathology in children with 22q11.2 DS is high, with over half meeting DSM-IV-TR criteria. The prevalent diagnoses, which are often comorbid in children with 22q11.2DS, include ADHD, anxiety disorders, ODD and high rates of autistic traits. The prevalence of intellectual disability is also high, with 31% of children with the deletion having mild intellectual disability. Moreover, children with 22q11.2DS seem to exhibit a generally impaired cognitive performance, which is more variable than in the non-deleted population (as indicated by larger standard deviations in the performance of children with 22q11.2DS in relation to their siblings).

Furthermore, these findings underline the potential implications of childhood 22q11.2DS for parents and health services and indicate the importance of early detection and treatment. Our finding that psychopathology is not mediated by the children's intellectual impairment does not support the use of cognitive remediation for ameliorating the mechanisms underlying psychopathology in children with 22q11.2DS. However, our examination of general, rather than more specific cognitive functions, might have prevented the identification of relationships between specific cognitive deficits and psychiatric disorders.

These findings also provide no support for the suggestion that psychopathology in 22q11.2DS is a non-specific consequence of intellectual impairment reflecting mechanisms that differ from those operating in more typical cases. Rather, they are consistent with the conclusion that the mechanisms by which psychopathology is produced in 22q11.2DS might resemble those operating in more typical cases, and that 22q11.2DS might serve as a model in which mechanisms of childhood psychopathology might be studied.

In conclusion, we set out to determine the rate and nature of psychopathology and neurocognitive dysfunction, and the relationship between them, in children with 22q11.2DS. We found high rates of psychopathology and impairments across a wide range of neurocognitive functions compared with sibling controls. We found no evidence that the presence of psychopathology is correlated with neurocognitive impairment and it would appear that the former is not mediated by the latter. These findings have important clinical and theoretical implications. Further work is required to determine whether these findings can be extended to older age groups with 22q11.2DS, other CNVs and other high-risk samples.

References


