Relationship between reaction time, fine motor control, and visual-spatial perception on vigilance and visual-motor tasks in 22q11.2 Deletion Syndrome

Sarah A. Howley[a,*], Sarah E. Prasad[a], Niall P. Pender[b], Kieran C. Murphy[a]

[a]Department of Psychiatry,Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont Hospital, Dublin 9, Republic of Ireland

[b]Department of Psychology, Beaumont Hospital, Dublin 9, Republic of Ireland

[*]Corresponding author at: Research Department of Clinical, Educational and Health Psychology, University College London, Gower Street, London, WC1E 6BT, United Kingdom; Tel: +44 751 262 1490; Fax: +44 207 916 1989;Email: sarah.howley.10@ucl.ac.uk.

Abstract

22q11.2 deletion syndrome (22q11DS) is a common microdeletion disorder associated with mild to moderate intellectual disability and specific neurocognitive deficits, particularly in visual-motor and attentional abilities. Currently there is evidence that the visual-motor profile of 22q11DS is not entirely mediated by intellectual disability and that these individuals have specific deficits in visual-motor integration. However, the extent to which attentional deficits, such as vigilance, influence impairments on visual motor tasks in 22q11DS is unclear. This study examines visual-motor abilities and reaction time using a range of standardised tests in 35 children with 22q11DS, 26 age-matched typically developing (TD) sibling controls and 17 low-IQ community controls. Statistically significant deficits were observed in the 22q11DS group compared to both low-IQ and TD control groups on a timed fine motor control and accuracy task. The 22q11DS group performed significantly better than the low-IQ control group on an untimed drawing task and were equivalent to the TD control group on point accuracy and simple reaction time tests. Results suggest that visual motor deficits in 22q11DS are primarily attributable to deficits in psychomotor speed which becomes apparent when tasks are timed versus untimed. Moreover, the integration of visual and motor information may be intact and, indeed, represent a relative strength in 22q11DS when there are no time constraints imposed. While this may have significant implications for cognitive remediation strategies for children with 22q11DS, the relationship between reaction time, visual reasoning, cognitive complexity, fine motor speed and accuracy, and graphomotor ability on visual-motor tasks is still unclear.

Key words:22q11.2 deletion syndrome; Intellectual disability; Visual-motor function; Reaction time; Vigilance

Introduction

22q11.2 Deletion Syndrome (22q11DS) is a genetic disorder associated with a 3 megabase microdeletion on the long (q) arm of chromosome 22 (Driscoll et al., 1992). It is the most common microdeletion disorder known to occur in humans (Shprintzen, 2005), with a prevalence rate ranging from 1 in 3900 live births (Goodship, Cross, Scambler, & Burn, 1995) to 1 in 7000 live births (Oskarsdottir, Fujic, &Fasth, 2004). Before the discovery of the microdeletion on chromosome 22, the syndrome was categorized into discrete conditions due to variable phenotypic expression, including (most commonly) DiGeorge syndrome, Shprintzen syndrome and velo-cardio-facial syndrome.

In order to confirm a 22q11.2 deletion, a cytogenetic technique known as *fluorescence in situ hybridization* (FISH) is used, in which a fluorescently labeled DNA or RNA probe is hybridized to immobilised metaphase chromosomes taken from a blood sample (Driscoll et al, 1992, Scambler et al, 1991). This method picks up 95% of individuals who have a deletion. The condition is associated with a range of physical health problems, including congenital heart defects (e.g. Ryan et al., 1997), craniofacial dysmorphology (e.g. Shprintzen, Goldberg, Young, & Wolford, 1981) and velopharyngeal insufficiency, particular palatal anomalies (e.g. Shprintzen, et al., 1981). It is also associated with a higher than average prevalence of psychiatric disorders, including schizophrenia in adults (Murphy, Jones & Owen, 1999) and, in children, prodromal features of psychosis (e.g., Baker &Skuse, 2005; Gothelf et al., 2007), attention deficit/hyperactivity disorder (e.g.,Antshel et al., 2006), depression (e.g., Swillen et al., 1999*b*) and autism spectrum disorders (e.g.,Vorstman et al., 2006).

Neuropsychological research over the last decade has successfully delineated a neurocognitive profile associated with 22q11DS, which indicates a range of deficits in spatial cognition (e.g., Simon, Bearden, McDonald-McGinn, &Zackai, 2005; Simon, 2008),

including motor abilities (Van Aken, Caeyenberghs, Smits-Engelsman, & Swillen, 2009; Van Aken et al., 2007) and visual-spatial and perceptual processing in adults (e.g., Henry et al. 2002). Impairments in sustained attention have also been widely reported (Campbell et al., 2010; Niklasson, 2006; Woodin et al., 2001) and one study reported sustained attention deficits after controlling for IQ (Lewandowski, Shashi, Berry, &Kwapil, 2007). However, the majority of studies of neurocognitive function in 22q11DS have not adequately controlled for the effects of intellectual disability, commonly reported to be in the borderline to moderate range in 22q11DS with a mean FSIQ of 70 and a prevalence of approximately 80% (e.g. Campbell et al., 2009; Lipson et al. 1991; Shprintzen et al., 1981; Swillen et al., 1997). De Smedt et al. (2007) reported a mean full scale IQ of 73.48 (range: 50-109) in a sample of 103 children with 22q11DS.

Compared to other domains of cognitive functioning, there has been relatively little research to date on the development of motor skills in 22q11DS, particularly visual-motor integration, although more attention has been given to this area in recent times (e.g. Roizen et al., 2010; Van Aken et al. 2009, 2010). Lajiness-O'Neill et al. (2006) found that subjects were relatively more impaired on perceptual-motor tasks compared to fine motor and motor-free visual-spatial tasks, suggesting that the problem is at the level of visual-motor integration. Problems with dexterity have also been reported (Roizen, 2010; Sobin, Monk, Kiley-Brabeck, Khuri, &Karayiorgou, 2006; Van Aken et al., 2007, 2009). To date, intellectual ability is the only variable found to be associated with motor performance in 22q11DS. Neither gender nor presence of congenital heart defect (CHD) has been found to significantly influence motor skills in 22q11DS (Van Aken et al. 2007). A recent study (Van Aken et al., 2009) found that children with 22q11DS were significantly impaired relative to low-IQ controls on motor coordination, manual dexterity and visual perception tests. However, they did not differ from low-IQ controls on a putative visual-motor integration task, which

involved copying geometric shapes. In addition, Roizen et al. (2010) found that children with 22q11DS performed significantly worse on a graphomotor task compared to controls matched for full-scale IQ but did not differ from controls on a ball-catching task.

Therefore, the recent literature suggests a distinct visual motor profile associated with 22q11DS that is not entirely attributable to an overall reduction in intellectual functioning. However, the conclusion that impairment in visual-motor integration is the root of motor deficits in 22q11DS is not satisfactory, as the tasks on which 22q11DS groups *did not* differ from IQ-matched controls also required the ability to integrate visual and motor information (i.e. ball catching and drawing shapes). Also, there has been no attempt to control for attentional impairments on visual-motor tasks, nor has there been any research to date on the effects of task stimuli on visual motor ability e.g. whether the task is timed or untimed or the complexity of the task, such as drawing geometric shapes versus simple point accuracy (i.e., pointing to or touching the centre of a cross or other stimulus on screen). Investigating performance on simpler untimed tasks of visual-motor integration, such as point accuracy, would reduce the potential impact of attentional and other cognitive impairments and would arguably provide a purer measure of visual-motor integration.

The gaps in the current literature also suggested that it would be useful to compare 22q11DS and low-IQ control groups on a visual-motor task that taps into a specific component of attention, in order to directly compare the influence of attentional and psychomotor components on task performance. This may further elucidate whether the deficit in visual motor integration observed in 22q11DS is rooted in a difficulty integrating visual and motor information or whether it is a result of deficits in domains such as attention and fine motor control. For example, vigilance, as most commonly measured by reaction time, is taken to be a measure of the orienting component of visual attention (e.g., Dinges& Powell, 1985; Fleck, Sax &Strakowski, 2001) and has been found to differentiate more

accurately between clinical and non-clinical groups compared to traditional signal detection measures of perceptual sensitivity and response bias (*see* Fleck et al., 2001). Therefore, a reaction time test that requires both vigilance and visual-motor integration (by asking the participant to touch a stimulus on-screen) would provide a method of distinguishing between attentional and psychomotor components of a visual-motor task.

In light of the current gaps in the literature, the present study compared children with 22q11DS to a low-IQ and typically developing control group on three putative components of visual motor ability: visual motor integration, motor-free visual-spatial reasoning and psychomotor speed. A range of tasks were employed to assess visual motor abilities, including computerised tests of point accuracy and reaction time. A measure of vigilance was obtained by analysing independent measures of reaction time and psychomotor speed.

We hypothesised that the 22q11DS and low-IQ groups would perform significantly worse than TD controls on all neurocognitive tasks, demonstrating the global effects of reduced intellectual functioning in both groups. With reference to previous work (Lewandowski et al. 2007; Roizen et al. 2010;Van Aken et al. 2009), we hypothesised that the 22q11DS group would show significant impairments relative to low-IQ controls on tests of reaction time and psychomotor speed, reflecting their specific difficulties in attention and fine motor control when speed is required. Finally, we hypothesised that the 22q11DS and low-IQ groups would not differ significantly on untimed point accuracy tasks, nor would they differ on more complex visual-motor tasks, namely drawing shapes and visual-spatial reasoning, as these tasks would be more sensitive to global intellectual impairment.

Method

Recruitment

22q11DS participants were recruited through the National Centre for Medical Genetics based in Our Lady's Hospital for Sick Children (OLHSC) in Dublin and the Medical Genetics Department of Belfast City Hospital, Northern Ireland. Participants were also recruited through the national syndrome support group, 22q11 Ireland. Siblings of the 22q11DS participants were also recruited to form the typically developing (TD) control group. All participants received detailed information packs outlining the purpose of the study and informed consent was obtained from the parents or legal guardians. The low-IQ control group was recruited from one mainstream school and two special educational schools identified through the Irish Department of Education and Science. Information packs were disseminated to all potential study participants and informed consent was obtained from parents/legal guardians. All low-IQ control participants had prior assessments of intellectual function (WISC-IV) conducted within two years of their participation in the current study by a Clinical or Educational Psychologist and written consent was obtained from parents to access this data.

Inclusion criteria for the 22q11DS group were (i) a confirmed deletion at chromosome 22q11.2, as determined by the cytogenetic test, FISH (ii) FSIQ above 40 (iii) age range between 6 and 16 years. Inclusion criteria for the TD sibling control group included (i) no known genetic disorder (ii) no known neurological or psychiatric conditions (iii) intellectual functioning within the average range (FSIQ score over 80) (iv) age range between 6 and 16 years. Inclusion criteria for the low-IQ control group included (i) no identified major neurologicalor psychiatric conditions (ii) FSIQ above 40 (iii) age range between 6 and 16 years. The study was approved by the Beaumont Hospital Ethics (Medical Research)

Committee, the OLHSC Research Ethics Committee and the Office for Research Ethics Committees Northern Ireland.

Participants

Participants were children and adolescents with 22q11DS (N = 31, 15 male, 16 female, M_{age} = 11.4 years, age range: 6-16 years), typically developing (TD) sibling controls (N = 26, 12 male, 14 female, M_{age}= 11.9 years, age range: 6-16 years) and low-IQ community controls (N = 17, 6 male, 10 female, M_{age}= 12.1 years, age range: 8-16 years). As shown in Table 1, the low-IQ control group did not differ significantly from the 22q11DS group on any of the following indices of the Wechsler Intelligence Scale for Children (WISC-IV): Full-Scale IQ (FSIQ), Verbal Comprehension Index (VCI) and Perceptual Reasoning Index (PRI). The three groups did not differ significantly from one another in terms of age (F [2, 76] = 0.92, p = 0.40) or gender distribution (χ^2 [2, N = 177] = 1.06, p= 0.59). All participants were from White Irish or White British ethnic backgrounds. The number of participants in the 22q11DS and TD control groups varied across the neurocognitive tests due to factors such as non-compliance with testing and participant attrition. The number in each group for each neurocognitive test is displayed in Table 2.

Materials and Procedure

The *Wide Range Assessment of Visual Motor Abilities* (WRAVMA; Adams &Sheslow, 1995) is a well-standardised tool that provides a reliable, accurate evaluation of visual-motor skills of children and adolescents ages 3-17 years. Completion of the battery provides a Visual Motor Abilities (VMA) composite score, which is an average of the standard scores of the three separate subtest assessments: (i) visual-motor integration (Drawing test) (ii) visual-spatial reasoning (Matching test) and (iii) fine motor control (Pegboard test). Standard scores have a mean of 100 and a standard deviation of 15. The Drawing subtest involves participants copying line drawings which are developmentally

arranged in order of increasing difficulty. The test is discontinued after 3 consecutive failed items. The outcome measure is the number of drawings rendered with reasonable accuracy as per manual instructions. The Matching subtest requires participants to view target items and choose which of 4 options underneath matches the target item. The test is discontinued after 5 consecutive failed items. The outcome measure is the number of items correctly matched. The Pegboard test requires participants to place plastic pegs in holes on a board using their dominant hand[1] as quickly as possible. The outcome measure is the number of pegs placed correctly in the holes in 90 seconds with the dominant hand.

The norms for each WRAVMA subtest were derived from the same standardization sample of 2,600 children, permitting a psychometrically sound comparison of a child's overall visual-motor ability (Adams &Sheslow, 1995). Good levels of test-retest reliability are reported for WRAVMA subtests and composite with Cronbach's alpha ranging from 0.82 to 0.89. Good inter-rater reliability is reported for the Drawing test, which depends to some extent on the examiner's judgment (r = 0.97). Content validity was determined with a Rasch analysis for Drawing and Matching subtests, both of which obtained total sample item separation indices of 1.00. Finally, construct validity tests indicate that the three subtests are positively correlated to a moderate degree (correlation coefficients range from 0.28 to 0.38), suggesting that each subtest measures a related, but meaningfully different, aspect of visual motor ability.

The Motor Screening test and the Reaction Time test from the *Cambridge Neuropsychological Test Automated Battery* (CANTAB) were employed as measures of visual-motor integration (point accuracy), psychomotor speed (movement time) and vigilance (reaction time). The Reaction Time *child mode* was used in this study, which is a modified version of the task recommended for use with children between the ages of 4 and 16 years.

[1]The dominant hand was defined as the hand the child used to draw or write with (as per manual instructions). Corroboration of handedness was obtained from parents when assessing younger children

Both tests were administered using CANTAB *Eclipse* (Cambridge Cognition Ltd. 2005) software. Tests were presented on a touch-screen tablet PC (PacebladeSlimbook P110 series). The Reaction Time task was administered using a press pad (Cambridge Cognition 2-Button Press Pad Version 1.0).

The Motor Screening task requires participants to touch a flashing cross (X) in the centre as it appears in different locations on the screen. The test has an average duration of between 38.7 and 95.8 seconds, depending on the participant's speed of response. The outcome measures are (i) the time it takes for participants to touch the cross once it appears on the screen and (ii) the distance (measured in pixels) between the location touched by the participant and the centre of the cross.

The Reaction Time task requires participants to hold down a button on a press-pad whilst looking at the screen, until they see a yellow circle appear. They then have to let go of the button and touch the circle in the centre. The circle either appears in the centre of the screen (Predictable Condition) or in one of five possible locations (Unpredictable Condition). The Reaction Time task provides separate measures of reaction time and movement time. The outcome measures are (i) reaction time, calculated as the time elapsed between the circle appearing on the screen and the subject releasing the button on the press pad (ii) movement time, calculated as the time elapsed between the subject releasing the button and touching the circle and (iii) accuracy, calculated as the distance (number of pixels) between the centre of the circle and the location touched by the subject.

Although the CANTAB has been predominantly used with adult populations, there has been a surge of research using CANTAB in paediatric populations (e.g. Luciana, 2003; Luciana & Nelson, 2002) and across a range of developmental disorders including ADHD (Kempton et al., 1999) and autism (Hughes, Russell, & Robbins, 1994). Internal consistency and test-retest reliability have been established in samples of 50-60 children aged between

four and twelve years of age, with Cronbach's alpha ranging from 0.73 to 0.95 across subtests.

Procedure

The tests described above were administered in a set order and in accordance with instructions in the test manuals. Firstly participants completed the Motor Screening (Motor Screening) task, which provided an introduction to the use of the touch-screen tablet and gave a good indication of participants' abilities to understand verbal instructions and produce motor responses. No time limit was imposed on this test.Secondly, participants completed the WRAVMA battery (Drawing, Matching and Pegboard subtests) and then the reaction time task. A practice phase was completed before participants attempted the reaction time test, which ensured competence at each component of the test. Overall, the testing lasted approximately one hour,

Statistical analysis

Data in this study were analysed using SPSS version 17. All data were investigated in a preliminary data analysis to confirm appropriateness of statistical procedures. All data sets were normally distributed with the exception of data obtained from the CANTAB Reaction Time test (as assessed by Kolmogorov-Smirnoff test and visual inspection of data distribution). This data was analysed with non-parametric tests. The three groups were compared on each independent variable using a one-way analysis of variance (ANOVA) or Kruskal-Wallis test and appropriate post-hoc tests with adjustment for multiple comparisons. Adjustments for multiple comparisons were either done automatically by SPSS Tukey HSD test or done manually for non-parametric analyses (i.e.,$\acute{\alpha} = .05 \div$ number of comparisons). For analyses in which sample sizes differ (WRAVMAsubtests), the Gabriel post-hoc test is used instead of the Tukey HSD test. Homogeneity of variance was confirmed for all

parametric analyses. Effect sizes are reported as *eta squared* (η^2) for parametric analyses and as *r* values for non-parametric analyses.

Results

Table 2 displays the mean scores of each group onall cognitive tests. A statistically significant effect of group membership was observed for overall visual motor ability as indicated by the WRAVMA composite score, $F(2, 74) = 45.0$, $p<0.001$, $\eta^2 = 0.56$. Post hoc comparisons showed that the mean difference between the 22q11DS groupthe TD groupwas statistically significant ($M_{diff} = 27.0$, $p<0.001$) as was themean difference between the TD group and the low-IQ group ($M_{diff} = 28.8$, $p <0.001$). The mean difference between the 22q11DS and low-IQ groups was not significant ($M_{diff} = 0.86$,$p = 0.97$).

On the Drawing subtest, a statistically significant effect of group membership was observed, $F (2, 74) = 19.2$, $p<0.001$, $\eta^2 = 0.35$. Post hoc comparisons indicated that the mean difference between the 22q11DS group and the TD control group was statistically significant ($M_{diff} = 14.0$, $p<0.001$), as was the mean difference between the TD and low-IQ groups, $M_{diff} = 23.7$, $p <0.001$. The mean difference between the 22q11DS and low-IQ control group was also statistically significant, with the 22q11DS group obtaining a significantly higher mean score than the low-IQ group ($M_{diff} = 9.6$, $p = 0.025$).

On the Matching subtest, there was a statistically significant effect of group membership, $F (2, 74) = 22.1$, $p<0.001$, $\eta^2 = 0.38$. Post hoc comparisons indicated that the TD control group obtained a significantly higher mean score than both the 22q11DS group ($M_{diff} = 23.7$, $p<0.001$) and the low-IQ group($M_{diff} = 26.6$, $p <0.001$). The 22q11DS group did not differ significantly from the low-IQ control group ($M_{diff}= 2.9$, $p= 0.80$).

On the Pegs subtest, a statistically significant effect of group membershipwas observed, $F (2, 74) = 23.6$, $p<0.001$, $\eta^2 = 0.40$.Post hoc comparisons indicated that the

22q11DS groupobtained a significantly lower mean score than both the TD control group (M_{diff} = 27.5, p<0.001) and the low-IQ control group (M_{diff}= 11.0, p = 0.042). The mean difference between the low-IQ control group and the TD control group was also statistically significant, M_{diff} = 16.3, p = 0.004.

On the Motor Screening test, no statistically significant effect of group membership was observed for either response latency (F[2, 75] = 1.30, p = 0.28) or point accuracy (F[2, 75] = 0.40, p = 0.67). In the predictable condition of the Reaction Time test, there was no statistically significant group effect observed for reaction time (χ^2[2] = 0.13, p = 0.94), movement time (χ^2[2] = 5.80, p = 0.06) or point accuracy (χ^2[2] = 4.21,p = 0.12). In the unpredictable condition, there was no statistically significant group effect observed for reaction time (χ^2[2] =1.75, p = 0.42)or point accuracy (χ^2[2] =3.01, p = 0.22). However there was a statistically significant group effect observed on movement time (χ^2 [2] = 7.70, p = 0.021). Post hoc tests indicated a statistically significant difference between the 22q11DS and TD control group (Z = -2.6,p =0.08, r = 0.52) but no significant difference between the 22q11DS and the low-IQ control group (Z = 0.88, p = 0.95) or the low-IQ and TD control groups after correction for multiple comparisons (i.e., $\acute{\alpha}$ = 0.05 ÷ 3 = 0.017),Z = 2.28, p = 0.023.

Discussion

This study investigated visual-motor abilities in children with 22q11DS compared to a low-IQ control group and a typically developing control group. The results of this study suggest the presence of a distinct visual-motor profile in the 22q11DS group that is not entirely mediated by reduced intellectual function or impairments in reaction time. These results suggest a profile characterised by relatively intact visual-motor ability when tasks are untimed and less cognitively demanding and impairment in fine motor control that is disproportionate to their level of intellectual functioning. Contrary to our first hypothesis, that

group differences would be observed on all tasks, there were no statistically significant group differences on the computerised visual-motor tests, with the exception of a significant impairment in the 22q11DS on the psychomotor speed component of the reaction time test. The absence of impairment in reaction time and point accuracy, along with the pronounced impairment on the Pegs test, suggests that the coordination of a motor response was the core difficulty in the 22q11DS group, which may be due to difficulties with visual-motor integration and fine motor control when speed of movement is required. This is also supported by the absence of statistically significant group differences on the Motor Screening test, which is an untimed test of point accuracy. This pronounced deficit in fine motor control partially supports our second hypothesis, which stated that the 22q11DS would perform worse than low-IQ controls on psychomotor speed and reaction time tests.

However, contrary to our second hypothesis, there were no statistically significant differences between the 22q11DS and low-IQ groups in reaction time latencies. Because 22q11DS is associated with significant impairments in sustained attention (e.g. Campbell et al., 2009; Lewandowski et al., 2007; Swillen et al., 1997), one component of which is vigilance (Matthias et al., 2010), we hypothesised that reaction time on a vigilance task, such as the CANTAB reaction time test, would be significantly impaired. One interpretation of this result is that the orienting and intrinsic alertness components of visual attention were relatively intact within the 22q11DS group (Posner & Petersen, 1990; Sturm et al., 1999). It may be that attention deficits in 22q11DS are located in processes which place more demands on executive functions such as selectivity, inhibition or processing capacity (Posner & Peterson, 1990; Rossi, Pessoa, Desimone&Ungerleider, 2009). This would fit with previous findings of poor executive functioning in 22q11DS (e.g., Campbell et al., 2009; Woodin et al., 2001). Therefore, it cannot be concluded from these results that there were no differences in attention between the groups, rather that there were no differences in vigilance as

measured by reaction time. Group differences in attention may have been observed on a more cognitively demanding task with multiple salient stimuli.It may be useful for future studies to compare performance on a reaction time test and more complex tests of perceptual sensitivity and response bias in a larger group of children with 22q11DS, in order to more fully explore the mechanisms underlying vigilance and sustained attention deficits reported to exist in this population.

In support of our final hypothesis, the 22q11DS and low-IQ groups did not differ significantly from one another on the Matching subtest of the WRAVMA or the untimed point accuracy tests. The absence of a significant difference between the groups on the Matching subtest of the WRAVMA suggests that visual-spatial ability is perhaps more sensitive to the effects of global intellectual impairment.Contrary to our final hypothesis, the 22q11DS group performed significantly better than low-IQ controls on the more complex drawing test. This suggests that drawing ability may be relatively better in the 22q11DS group than would be expected for their overall intellectual abilities, as they obtained significantly higher scores than the low-IQ group on the Drawing subtest, despite being matched to this group on Full-Scale IQ and Perceptual Reasoning indices of the WISC-IV. Thus, although drawing is still impaired compared to TD children, it may represent an area of relative strength for the 22q11DS group compared to their other visual-motor abilities and compared to a low IQ control group.This may have implications for cognitive remediation strategies in this population, such as, for example, increasing emphasis on computer-assisted learning, which has become prominent in neurobiological disorders, such as ADHD (e.g. Steiner, Sheldrick, Gothelf, & Perrin, 2011).

However, the difference between the 22q11DS and low-IQ groups in drawing shapes may be related to poorer grip strength, higher levels of impulsivity or other personality factors in the low-IQ group. Therefore, it would be useful in future studies to

incorporatemeasures of grip strength, impulsivity and other behavioural indices into the testing procedure to allow control of other factors potentially affecting test performance.

The results of this study further highlight the importance of controlling for intellectual disability when investigating specific aspects of the 22q11DS neurocognitive profile. Although visual-motor impairments, such as graphomotor and motor speed deficits, are also common in children with other neurodevelopmental disorders, such as ADHD and behavioural disorders (e.g., Mayes & Calhoun, 2007) and autism spectrum disorders (e.g., Kushki, Chau, &Anagnostou, 2011), the results of the current study suggest that two groups with equivalent levels of intellectual impairment showed differing profiles of strength and weakness on visual-motor tasks. This supports the idea that the 22q11DS phenotype contributes in some way to the development of visual motor skills.

Task type appeared to contribute significantly to performance in the present study, particularly in the 22q11DS and low-IQ groups who displayed no impairment relative to TD controls on most computerised tests. This may be because the computerised tasks required minimal verbal instruction, allowed for some demonstration by the experimenter and the reaction time test was preceded by a "practice phase" which broke the task down into a number of steps and mastery of all steps was required before participants could move on to the testing phase. Similarly, the motor screening test was arguably a test of visual-motor integration in the absence of other cognitive demands, such as verbal comprehension, working memory and, to a certain extent, sustained attention (the task was never longer than 96 seconds in duration). Task instructions were simple ("touch the flashing X when it appears on the screen") so, therefore, even children at the lower end of the FSIQ range and those with verbal comprehension difficulties were able to complete this task. Furthermore, all computerised tests were relatively short in duration (2-10 minutes) and were presented in a game-like format, which tended to appeal to participants and may have increased motivation,

compliance and interest (e.g. Luciana & Nelson, 1998, 2002). Therefore, the lack of statistically significant differences between the groups on most of the computerised visual motor tests may be due to the reduction in (or control of) other cognitive demands, such as verbal comprehension and sustained attention.

Methodological strengths and weaknesses

A major strength of this study was controlling for intellectual disability through the recruitment of a control group matched to the 22q11DS group on three indices of intellectual ability, that is, Full-Scale IQ, Verbal Comprehension and Perceptual Reasoning. Another strength of this study was the use of basic computerised tests of visual motor integration (point accuracy) and psychomotor speed alongside a standardised battery of more complex visual-motor tasks. The CANTAB tasks potentially reduced the effects of cognitive deficits in executive and verbal domains, both of which possibly made performance on the WRAVMA more difficult for children with intellectual disability. In addition, the CANTAB Reaction Time test provided separate measures of reaction time and psychomotor speed, which arguably allowed for the separation of attentional factors (i.e., vigilance) from visual-motor ability.A primary limitation of the current study was the relatively small sample sizes of the study groups. On the reaction time test in particular, this led to an increased risk of Type II error.Another limitation is the fact that the majority of the low-IQ control group were recruited primarily from schools for special educational needs (n = 11; 64%), whereas the majority of 22q11DS children (n = 27; 87%) were attending mainstream schools with assistance from special educational needs staff. Therefore, although their mean IQ index scores were equivalent, it is possible that different learning environments may have contributed to the differences observed between the groups.

Conclusions

Taken together, the findings of the current study are consistent with previous findings of fine motor control and accuracy deficits in children with 22q11DS (e.g., Roizen et al., 2010, Van Aken et al., 2009). However, contrary to previous findings, this study suggests that visual-motor integration is not necessarily a core cognitive impairment in 22q11DS but rather that impairments in visual-motor abilities are mediated by task type, the presence of other cognitive or executive demands, such as attention and working memory, and perhaps even motivational factors such as the game-like appearance of the tests (e.g., Luciana & Nelson, 1998, 2002). Further investigation with larger numbers of participants and a more homogeneous low-IQ control group is required to further investigate the extent of the influence of task effects and executive demands on visual motor abilities in 22q11DS.

Acknowledgments

Our thanks to our colleagues in the Beaumont Department of Psychology who provided training in cognitive assessment; to Ms Anne Lawlor and the 22q11 Ireland support group who publicised our research and disseminated our recruitment requests and information leaflets among their members; to our colleagues in the education sector who assisted us with recruitment and allowed us to conduct testing at their facilities; and most of all, to all the participants and their families who gave us their time and put in a great deal of effort in taking part in the study.

References

Antshel, K., Fremont, W., Roizen, N., Shprintzen, R., Higgins, A., Dhamoon, A., &Kates, W.R. (2006). ADHD, major depressive disorder, and simple phobias are prevalent psychiatric conditions in youth with velocardiofacial syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry*, *45*, 596-603. doi:10.1097/01.chi.0000205703.25453.5a

Baker, K., &Skuse, D. (2005). Adolescents and young adults with 22q11.2 deletion syndrome: psychopathology in an at-risk group. *British Journal of Psychiatry, 186*, 155–120. doi:10.1192/bjp.186.2.115

Driscoll, D., Spinner, N., Budarf, M., McDonald-McGinn, D., Zackai, E., & Goldberg, R., Shprintzen, R., ... Jones, M.C. (1992). Deletions and microdeletions of 22q11 in velo-cardio-facial syndrome. *American Journal of Medical Genetics, 44*, 261–68.doi:10.1002/ajmg.1320440237

Campbell, L., Stevens, A., Daly, E., Toal, F., Azuma, R., Karmiloff-Smith, A., … Murphy, K.C.(2009). A comparative study of cognition and brain anatomy between two neurodevelopmental disorders: 22q11.2 deletion syndrome and Williams syndrome. *Neuropsychologia*, *47*, 1034–44.doi:10.1016/j.neuropsychologia.2008.10.029

Campbell, L.E., Azuma, R., Ambery, F., Stevens, A., Smith, A., Morris, R.G.,… Murphy, K.C. (2010). Executive functions and memory abilities in children with 22q11.2 deletion syndrome, *Australian and New Zealand Journal of Psychiatry*, *44*, 364-371. doi:10.3109/00048670903489882

Dinges, D.F. & Powell, J.W. (1985). Microcomputer Analyses of performance on a portable, simple visual RT task during sustained operations. *Behaviour Research Methods, Instruments and Computers, 17*, 652-655.doi:10.3758/BF03200977

Driscoll, D., Spinner, N., Budarf, M., McDonald-McGinn, D., Zackai, E., & Goldberg, R., ...Emanuel, B.S. (1992). Deletions and microdeletions of 22q11 in velo-cardio-facial syndrome.*American Journal of Medical Genetics, 44*, 261–68.doi:10.1002/ajmg.1320440237

Fleck, D.E., Sax, K.W. &Strakowski, S.M. (2001).Reaction time measures of sustained attention differentiate bipolar disorder from schizophrenia. *Schizophrenia Research*, *52*, 251-259. doi:10.1016/S0920-9964(01)00170-0

Goodship, J., Cross, I., Scambler, P., & Burn, J. (1995). Monozygotic twins with chromosome 22q11.2 deletion and discordant phenotype. *Journal of Medical Genetics, 32,* 746-748. doi:10.1136/jmg.32.9.746

Gothelf, D., Hoeft, F., Hinard, C., Hallmayer, J., Van Dover Stoecker, J., Antonarakis, S., Morris, M., & Reiss, A. (2007). Abnormal cortical activation during response inhibition in 22q11.2 deletion syndrome. *Human Brain Mapping*, *28*, 533–542.doi:10.1002/hbm.20405

Henry, J., van Amelsvoort, T., Morris, R., Owen, M., Murphy, D., & Murphy, K.C. (2002). An investigation of the neuropsychological profile in adults with

velocardiofacialsyndrome (VCFS).*Neuropsychologia, 40*, 471–478.doi:10.1016/S0028-3932(01)00136-1

Hughes, C., Plumet, M.H., &Leboyer, M. (1999). Towards a cognitive phenotype for autism: Increased prevalence of executive dysfunction and superior spatial span amongst siblings of children with autism. *Journal of Child Psychology and Psychiatry*, *40*, 705–718.doi:10.1111/1469-7610.00487

Kempton, S., Vance, A., Maruff, P., Luk, E., Costin, J., &Pantelis, C. (1999). Executive function and attention deficit hyperactivity disorder: Stimulant medication and better executive function performance in children. *Psychological Medicine*, *29*, 527–538.doi:10.1017/S0033291799008338

Lajiness-O'Neill, R., Beaulieu, I., Asamoah, A., Titus, J., Bawle, E., Ahmad, S., … Pollack, R. (2006). The neuropsychological phenotype of velocardiofacial syndrome (VCFS): Relationship to psychopathology. *Archives of Clinical Neuropsychology, 21*, 157–184. doi:10.1016/j.acn.2005.09.001

Lewandowski, K.E., Shashi, V., Berry, M.N., &Kwapil, T.R. (2007). Schizophrenic-like neurocognitive deficits in children and adolescents with 22q11 deletion syndrome.*American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics, 144*, 27-36. doi:10.1002/ajmg.b.30379

Lipson, A., Yuille, D., Angel, M., Thompson, P., Vandervoord, J. &Beckenham, E.(1991).Velo-cardio-facial (Shprintzen) syndrome: An important syndrome for the

dysmorphologist to recognise. *Journal of Medical Genetics, 28*, 596–604.doi:10.1136/jmg.28.9.596

Luciana, M. & Nelson, C. (1998).The functional emergence of prefrontally-guidedworking memory systems in four- to eight-year-old children.*Neuropsychologia*, *36*, 273–93.doi:10.1016/S0028-3932(97)00109-7

Luciana, M. and Nelson, C. (2002). Assessment of neuropsychological function through use of the Cambridge Neuropsychological Testing Automated Battery: Performance in 4- to 12-year-old children. *Developmental Neuropsychology*, *22*, 595–624.doi:10.1207/S15326942DN2203_3

Luciana, M. (2003) Practitioner Review: Computerised assessment of neuro-psychological function in children: clinical and research applications of the Cambridge Neuropsychological Testing Automated Battery (CANTAB) . *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *44*, 1-15.doi:10.1111/1469-7610.00152

Matthias, E., Bublak, P., Muller, H.J., Schneider, W.X., Krummenacher, J., & Finke, K. (2010). The influence of alertness on spatial and nonspatial components of visual attention.*Journal of Experimental Psychology and Human Perception and Performance, 36,* 38-56. doi:10.1037/a0017602

Murphy, K.C., Jones, L., & Owen, M. (1999).High rates of schizophrenia in adults with velo-cardio-facial syndrome.*Archives of General Psychiatry, 56*, 940-945. doi:10.1001/archpsyc.56.10.940

Oskarsdottir, S., Fujic, M., &Fasth, A. (2004). Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in Western Sweden. *Archives of Disease in Childhood, 89*, 148-151. doi:10.1136/adc.2003.026880

Posner, M.I. & Peterson, S.E. (1990). The attention system of the human brain.*Annual Review of Neuroscience, 13*, 25-42. doi:10.1146/annurev.neuro.13.1.25

Posner, M. I., & Boies, S. J. (1971). Components of attention.*Psychological Review, 78,* 391–408.doi:10.1037/h0031333

Rossi, A.F., Pessoa, L., Desimone, R., & Ungerleider, G. (2009). The prefrontal cortex and the executive control of attention.*Experimental Brain Research, 192*, 489-97.doi:10.1007/s00221-008-1642-z

Ryan, A., Goodship, J., Wilson, D., Philip, N., Levy, A., Seidel, H., Schuffenhauer, S., … Scambler, P.J. (1997). Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *Journal of Medical Genetics, 34*, 798-804. doi:10.1136/jmg.34.10.798

Scambler, P.J., Carey, A.H, Wyse, R.K., Roach, S., Dumanski, J.P., Nordenskjold, M., & Williamson, R.(1991). Microdeletions within 22q11 associated with sporadic and

familial DiGeorge syndrome. *Genomics, 10*, 201–206.doi:10.1016/0888-7543(91)90501-5

Shprintzen, R., Goldberg, R., Young, D., & Wolford, L. (1981). The velo-cardio-facial syndrome: A clinical and genetic analysis. *Pediatrics, 67*, 167–72.

Shprintzen, R. (2005). Historical overview. In K.C. Murphy & P.J. Scambler (Eds.), *Velocardiofacial syndrome: A model for understanding microdeletion disorders* (pp.1 – 19). Cambridge University Press.

Simon, T., Bearden, C., McDonald-McGinn, D., &Zackai, E. (2005a).Visual-spatial and numerical cognitive deficits in children with chromosome 22q11.2 deletion syndrome.*Cortex, 41*, 131–141.doi:10.1016/S0010-9452(08)70889-X

Simon, T. (2008).A New Account of the Neurocognitive Foundations of Impairments in Space, Time and Number Processing in Children with Chromosome 22q11.2 Deletion Syndrome.*Developmental Disabilities Research Review, 14*, 52–58.doi:10.1002/ddrr.8

Sobin, C., Monk, S., Kiley-Brabeck, K., Khuri, J., &Karayiorgou, M. (2006). Neuromotor deficits in children with the 22q11 deletion syndrome.*Movement Disorders*, *12,* 2082–89.doi:10.1002/mds.21103

Steiner, N.J., Sheldrick, R.C., Gotthelf, D., & Perrin, E.C. (2011). Computer-based attention training in the schools for children with Attention Deficit/Hyperactivity Disorder: A preliminary trial. *Clinical Paediatrics, 50*, 615–622. doi:10.1177/0009922810397887

Sturm, W., de Simone, A., Krause, B. J., Specht, K., Hesselmann, V., Radermacher, I., ...Willmes, K.(1999). Functional anatomy of intrinsic alertness: Evidence for a fronto parietal-thalamic-brainstem network in the right hemisphere. *Neuropsychologia, 37,* 797–805. doi:10.1016/S0028-3932(98)00141-9

Sugama, S., Bingham, P.M., Wang, P.P., Moss, E.M., Kobayashi, H.,&Eto, Y. (2000). Morphometry of the head of the caudate nucleus in patients with velocardiofacial syndrome (del 22q11.2). *ActaPaediatrica, 89*, 546-9. doi:10.1111/j.1651 2227.2000.tb00335.x

Swillen, A., Devriendt, K., Legius, E., Eyskens, B., Dumoulin, M., &Gewillig, M. (1997).Intelligence and psychosocial adjustment in velo-cardio-facial syndrome: a study of 37 children and adolescents with VCFS. *Journal of Medical Genetics, 34*, 453–58.doi:10.1136/jmg.34.6.453

Swillen, A., Devriendt, K., Legius, E., Prinzie, P., Vogels, A., Ghesquiere, P., &Fryns, J.P.(1999). The behavioural phenotype in velo-cardio-facial syndrome: from infancy to adolescence. *Genetic Counselling, 10*, 79-88.

Van Aken, K., De Smedt, B., Van Roie, A., Gewillig, M., Devriendt, K., Fryns, J.P., …Swillen, A.(2007). Motor development in school-aged children with 22q11 deletion (velocardiofacial/ DiGeorge syndrome).*Developmental Medicine and Child Neurology, 49*, 210–13.doi:10.1111/j.1469-8749.2007.00210.x

Van Aken, K., Caeyenberghs, K., Smits-Engelsman, B., & Swillen, A. (2009).The Motor Profile of Primary School-Age Children with a 22q11.2 Deletion Syndrome (22q11.2DS) and an Age- and low-IQ-IQ Control Group.*Child Neuropsychology, 15*, 532-42. doi:10.1080/09297040902740678

Vorstman, J., Morcus, M., Duijff, S., Klaassen, P., Heineman-de Boer, J., Beemer, F., ...van Engeland, H. (2006). The 22q11.2 deletion in children: high rate of autistic disorders and early onset of psychotic symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry*, *27*, 1104-1113. doi:10.1097/01.chi.0000228131.56956.c1

Woodin, M., Wang, P., Aleman, D., McDonald-McGinn, D., Zackai, E., & Moss, E.(2001).Neuropsychological profile of children and adolescents with the 22q11.2 microdeletion.*Genetics in Medicine, 3*, 34–39. doi:10.1097/00125817-200101000-00008