

Abstract

22q11.2 deletion syndrome (22q11DS) has a complex phenotype with more than 180 characteristics, including cardiac anomalies, cleft palate, intellectual disabilities, a typical facial morphology, and mental health problems. However, the variable phenotype makes it difficult to predict clinical outcome, such as the high prevalence of psychosis among adults with 22q11DS (~25-30% vs. ~1% in the general population). The purpose of this study was to investigate whether subtypes exist among people with 22q11DS, with a similar phenotype and an increased risk of developing mental health problems. Physical, cognitive and behavioural data from 50 children and adolescents with 22q11DS were included in a *k*-means cluster analysis. Two distinct phenotypes were identified: Type-1 presented with a more severe phenotype including significantly impaired verbal memory, lower intellectual and academic ability, as well as statistically significant reduced total brain volume. In addition, we identified a trend effect for reduced temporal grey matter. Type-1 also presented with autism-spectrum traits, whereas Type-2 could be described as having more 22q11DS-typical face morphology, being predominately affected by executive function deficits, but otherwise being relatively high functioning with regards to cognition and behaviour. The confirmation of well-defined subtypes in 22q11DS can lead to better prognostic information enabling early identification of people with 22q11DS at high risk of psychiatric disorders. The identification of subtypes in a group of people with a relatively homogenous genetic deletion such as 22q11DS is also valuable to understand clinical outcomes.

Key words

Velo-cardio-facial syndrome (VCFS); 22q11.2 deletion syndrome (22q11DS); DiGeorge Syndrome; cluster analysis; k-means; subtype; behavioural phenotype.

1. Introduction

It is evident that the genetic basis of many psychiatric disorders is heterogeneous. However, there is growing consensus that the study of well-defined genetic disorders with unusually high rates of psychiatric disorders can be used as models to increase understanding of pathways to psychopathology not only in the disorder itself but also in the general population (Murphy & Owen, 2001). One such disorder is 22q11.2 deletion syndrome (22q11DS), a relatively common genetic disorder associated with a spontaneous or inherited single interstitial deletion of ~40 genes on chromosome 22q11.2 (Shprintzen, 2005). This microdeletion disorder occurs *de novo* in ~85% of cases, and is otherwise inherited. The prevalence of 22q11DS is 1 in 4,000 live births (Óskarsdóttir, Vujic, & Fasth, 2004). However, the incidence of 22q11DS is likely to be higher due to the fatality of some associated sequences such as Potter sequence (Devriendt, Moerman, & Van Schoubroeck, 1997; Wraith, Super, Watson, & Phillips, 1985).

People with 22q11DS often have a typical facial morphology and a high frequency of congenital physical defects including cardiac and palatal anomalies. In addition it has been argued that people with 22q11DS have a specific behavioural phenotype, defined as "... the characteristic behavioural, psychiatric, neuropsychological and linguistic components of a genetic disorder" (Murphy, 2004). In particular, people with 22q11DS have mild intellectual disabilities and specific impairments in areas such as numeracy, visuo-spatial processing, and executive function. Having 22q11DS also constitutes a very significant risk factor for a number of psychiatric disorders. For example, the risk of developing schizophrenia-like psychotic disorders in 22q11DS is second only to the risk experienced by having two parents or a monozygotic co-twin with schizophrenia (Murphy, Jones, & Owen, 1999). The syndrome is also associated with a high prevalence of anxiety, autistic spectrum, obsessive-compulsive, mood, and attention-deficit/hyperactivity disorders (Campbell et al., 2010; Fine et al., 2005; D Gothelf et al., 2004; D Gothelf, Schaer, &

Eliez, 2008; Green et al., 2009; Swillen, 2001}. The behavioural phenotype in 22q11DS is increasingly being linked with brain morphology and volumetric differences (Campbell et al., 2006; Chow, Robert, Zipursky, Mikulis, & Bassett, 2002; Eliez, Schmitt, White, & Reiss, 2000; D Gothelf, Penniman, Gu, Reiss, & Eliez, 2007; W. Kates et al., 2004; W. Kates et al., 2001; Sundram et al., 2010; van Amelsvoort et al., 2004). People with 22q11DS have an overall smaller brain volume compared with age-matched typically developing peers, with a disproportionate loss of volume in the posterior part of the brain (Campbell, et al., 2006; Eliez, et al., 2000). In addition, white matter loss is more pronounced than grey matter loss (Campbell, et al., 2006; W. Kates, et al., 2001). Regional brain changes and function, especially in the fronto-striatal and fronto-parietal networks, have been linked with cognitive deficits such as working memory (Azuma et al., 2009), emotional problems, atypical pro-social behaviours and schizotypal traits (Campbell, et al., 2006; Sundram, et al., 2010).

However, one of the complicated features of 22q11DS is its phenotypic heterogeneity. There is a significant variability between the expressed phenotype in affected individuals within the same family (Driscoll et al., 1992; Leana-Cox, Pangkanon, Supovitz, Curtin, & Wulfsberg, 1995; McLean, Saal, Spinner, Emanuel, & Driscoll, 1993) and even between monozygotic twins with the deletion (Singh, Murphy, & O'Reilly, 2002). In some cases, one individual can be very severely affected whilst a sibling, parent or child is much less affected by the deletion. The variability in both the type and severity of symptoms is problematic for the families and the healthcare professionals involved in the care of people with the syndrome. While some characteristics of 22q11DS can have a causal relationship, for example the presence of cleft palate and velopharyngeal insufficiency, others appear unrelated. Curiously, until the deletion was identified in 1992 (Scambler et al., 1992), children with the syndrome were usually given more clinically homogenous diagnoses such as velo-cardio-facial syndrome (VCFS) or Di George syndrome (sequence) depending on the clinical features present. Children with VCFS were usually diagnosed

due to the co-occurring palatal anomalies with cardiac defects and a typical facial morphology, whilst children with Di George syndrome more typically had severe cardiac anomalies with co-occurring immunological deficiencies. However, since the deletion was identified nearly twenty years ago, all children with the deletion are recognised as having the same syndrome regardless of how many symptoms they share; hence the syndrome may be an example of multiple phenotypes arising from one deletion.

In the last couple of years, longitudinal studies of people with 22q11DS have outlined specific risk factors for the development of psychosis (Antshel et al., 2010; D Gothelf et al., 2005; D Gothelf et al., 2007; Doron Gothelf et al.; W. R. Kates, Antshel, et al., 2011; W. R. Kates, Bansal, et al., 2011; Schaer et al., 2009). Debbané and colleagues report that auditory hallucinations can be present as early as the age of 9 among children with 22q11DS, these hallucinations may be a risk factor for later psychosis or may indeed, represent a prodrome (Debbane, Glaser, David, Feinstein, & Eliez, 2006). Further, a decrease of verbal IQ has been found to be linked to more psychotic symptoms among adolescents with 22q11DS (D Gothelf, et al., 2005; W. R. Kates, Antshel, et al., 2011) whilst longitudinal volumetric grey matter reductions in the temporal cortex are associated with a higher prevalence of positive symptoms (W. R. Kates, Antshel, et al., 2011). However, despite our rapidly increasing knowledge of the risk factors for developing psychosis, it is not currently possible to predict the types of cognitive impairments or psychiatric disorders that an individual child with 22q11DS will experience. This makes it difficult to implement early intervention strategies to improve quality of life and reduce the burden of disease. In order to identify reliable precursors (of severe psychiatric disorders) and to improve care, it would be useful to identify homogenous phenotypic subtypes. This would enable more targeted investigations of the genetic influences on the phenotypic variability in 22q11DS as well as enabling the syndrome to be utilised as a genetic model to understand the ontogeny of psychosis, obsessive-compulsive disorder and other psychiatric disorders in the general population.

Hence, the objective of the current study was to investigate the presence of subtypes, based on clinical features, in order to refine the extensive phenotypic spectrum in 22q11DS so as to improve clinical diagnosis. We analysed an existing dataset pertaining to a large cohort of children and adolescents with 22q11DS. To identify homogenous phenotypes within the cohort, we used cluster analysis, which separates participants into a small number of discrete categories, based on similarity. This method has a long history of success, and is particularly well-suited to exploratory efforts such as ours.

2. Material and methods

2.1. Participants

In the current study, 50 children (22 male, 28 female; aged 6 to 17 years, mean age = 11 years, SD = 2.9) who had a clinical and genetic diagnosis of 22q11DS were included. The study was approved by local ethics committees. Participants had previously been recruited from a VCFS (UK) support group and from various clinical geneticists to minimise ascertainment bias. All were volunteer participants in a comprehensive study of the biological and behavioural phenotype of children with 22q11DS at the Institute of Psychiatry, London, UK (Campbell, 2006). Three-dimensional facial analysis was undertaken at the University College London, UK (P Hammond et al., 2005; P Hammond et al., 2004). The number of participants (50) was limited, but due to the large number of data contributed by each participant (180), this still affords appropriate statistical power for the analysis of clustering solutions with up to four clusters, using k-means clustering. This is because the critical aspect of sample size for k-means clustering is the number of participants compared with the number of clusters – not the number of dependent variables compared with the number of participants. For an in-depth description of these issues, including a

simulation study that corresponds closely to our data structure, see (Maitra, Peterson, & Ghosh, in press).

2.2. Procedure

The analysis included previously-collected data pertaining to facial dysmorphology, brain morphology, intellectual functioning, and cognitive abilities as collected using previously published methodologies (Campbell, et al., 2010; Campbell, et al., 2006; Campbell et al., 2009; Campbell et al., 2011).

2.2.1. Three-Dimensional (3D) dense surface analysis of facial images

Following manual landmarking of the 3D face surfaces, ‘Dense Surface Models’ (DSM) were computed. To build a DSM, the Procrustes algorithm was used to compute mean landmarks to which all surfaces are warped using thin-plate splines so the face surfaces were closely aligned. The points on a selected face were mapped to the closest points on each face to produce a dense correspondence of tens of thousands of points across all image surfaces. An average face surface of the set was then computed. The differences between the positions of the densely corresponded points on each face surface and those on the overall average face were subjected to a principal component analysis (PCA). Each face surface was re-synthesised as a weighted linear sum of the principal components. For this dataset, 98% of shape variation was accounted for by 49 PCA modes. Similarity between two individual face surfaces, or between a face surface and the average face of a subset, was computed using the Euclidean metric on the DSM weightings. We calculated shape similarity or proximity of an individual’s face, or the mean face of one subset, to another individual, or to the mean of another subset, respectively.

2.2.2. Brain Morphology

All structural magnetic resonance imaging data was obtained using a GE Signa 1.5T Neuro-optimised MR system (General Electric, Milwaukee WI, USA) at the Maudsley Hospital, London, UK. Each scan was analysed using Measure, a manual tracing methodology (Barta, Dhingra, Royall, & Schwartz, 1997) (Johns Hopkins University, Baltimore, MD, USA), using previously published anatomical definitions (van Amelsvoort et al., 2001). All inter- and intra-rater reliabilities (range: 0.89 – 0.92) were highly significant (Bartko & Carpenter, 1976). The cortical and subcortical regions measured included total intracranial space and bulk tissue volume (i.e., grey + white matter) of right and left cerebral hemispheres; frontal, parietal, temporal, and parietal-occipital lobes; the cerebral ventricles; hippocampus; caudate nucleus; putamen; and cerebellum (for more details see (Campbell, et al., 2006)).

2.2.3. Cognitive Measures

The study included measures of general intellectual functioning, academic achievement, general memory, executive function, social cognition, perception, and motor skills (for further information on specific tests, see supplementary material A).

2.2.4. Behavioural and clinical measures

The behavioural measures included clinical rating scales of psychological adjustment, adaptive behaviour, and social reciprocity (see supplementary material B). Furthermore, non-diagnostic dimensional parental rating scales included measures of Attention-Deficit/Hyperactivity Disorder (ADHD), anxiety, autism, and schizotypy (see supplementary material A).

2.3. *Statistical analysis*

We used *k*-means cluster analysis (Hartigan & Wong, 1979) as implemented in the R statistical language (v2.14.1: R Development Core Team, 2011). For each cluster analysis, we used 100 iterations of the search algorithm, and repeated this 200 times with different (random) starting points. Each cluster analysis included data from the PCA modes from the facial DSM analysis; cognitive, behavioural and physical variables; and an age variable. Before analysis, missing values were replaced by the group mean, which ensures that the imputed data provide no information that can bias the cluster assignments. There was an average of 29 missing values per participant, but the rate of missing data was not different between the two clusters finally identified ($t(48) = .04, p = .97$). Additionally, because *k*-means clustering is sensitive to differences between the absolute magnitudes of different variables, each variable was standardised to a mean of zero and a standard deviation of one. A large number of t-tests were used to investigate between-cluster differences, increasing the risk of a false positive (Type-1 error). This effect was attenuated by using an alpha-level of .01. The high probability that at least one of the tests was a false positive (at $\alpha = .01$) with 180 t-tests, means there is a 90% chance of making four or fewer Type I errors; however, the chance that all of the 30 observed significant results were false positives is vanishingly small (less than 10^{-10}). This means that the global difference between the clusters was very reliable, even though the precise make-up of the list variables which contribute to that global difference is subject to some error.

3. Results

3.1. *Cluster analyses*

To identify subgroups, *k*-means cluster analyses were performed four times, varying the number of clusters between two and five, producing a measure of mis-fit based on the residual sum

of squares within clusters, summed across clusters. These values were then plotted on a “scree plot”, which revealed that the 22q11DS participants were best described as belonging to one of two clusters. For exposition, these groups are labelled “Type-1” and “Type-2” (see Table 1).

Independent samples t-tests showed that the two subtypes significantly differed on 30 variables (at $\alpha = .01$; see Tables 2 and 3 for a summary).

3.2. Stability and Validity of differences between Type-1 and Type-2

There was a significant difference in mean age between Type-1 and Type-2 ($t(31.94) = -4.47, p < .01$). To check that the identification of the subgroups was not simply based on age, the cluster analyses were recalculated omitting age information. The result confirmed previous group membership.

Our results predict differences in mental health outcomes between Type-1 and Type-2 participants, which might be an important new tool in managing 22q11DS patients. We wanted to test the validity and stability of these differences, to make sure that the cluster analysis was not simply separating clusters on the basis of pre-existing mental health outcomes. To this end, we removed all 16 variables that measured mental health outcomes, and re-calculated the two-cluster solution. The variables removed were those that measured depression, anxiety, emotional symptoms, ADHD symptoms (rated by teachers and parents), schizotypy, peer problems, poor daily living skills, oppositional behaviour (rated by teachers and parents), and cognitive inattention. The new cluster analysis on the reduced data set produced almost exactly the same assignment of individuals to Type-1 and Type-2 classes: only two of the 50 participants were assigned differently than in the original analysis. This analysis provides an out-of-sample test of the validity of our mental health outcomes, because the Type-1 and Type-2 groups still differ on mental health outcomes, even when the clusters were identified without the mental health data.

3.3. Classification of participants to subtypes

We used nearest means analysis to investigate how accurately participants could be classified into subtypes on the basis of their individual data (Duda, Hart, & Stork, 2001). The nearest means analysis began with the two identified subtypes and summarised them using the mean value of each variable across all participants in each subtype. Individual participants were then classified as Type-1 or Type-2 according to how close their scores fell to the mean score of each subtype (we defined “closest” using a Euclidean metric on the standardised data).

We examined the accuracy of this technique for assigning individuals to subtypes using a cross validation analysis. We randomly selected five participants as a “test group”, and designated the other 45 participants as the “training group”. We then used k-means clustering to identify two subtypes in the training group, and found the means for each variable within those two groups. Next, we classified each person from the test group into one of the two subtypes identified in the training group, using nearest means analysis. The classifications of the test group were evaluated against the classifications of those same people in the overall (50-participant) cluster analysis reported above, in order to determine the accuracy of the procedure. This process was repeated 500 times, with different test groups each time.

To identify the influence of different input variables, the entire process was repeated three times: 1) including facial data only (no behavioural, cognitive, or physical data); 2) including all variables; and 3) including all variables *except* for the facial data. Results showed that the behavioural, cognitive, and physical data were more accurate than the facial measurements. Namely, classification of the test group was least accurate when using only facial data (82% for Type-1 and 31% for Type-2), followed by the use of all data (facial, behavioural, cognitive, and physical data; 86% for Type-1 and 94% for Type-2), and was most accurate when using all but the facial data (cognitive, behavioural, and physical data only; 99% for Type-1 and 94% for Type-2).

4. Discussion

4.1. *Identification of subtypes*

The purpose of the current study was to investigate the presence or absence of subtypes among children with 22q11DS. The current study identified two distinct subtypes (Type-1 and Type-2). To our knowledge, this is the first study to present evidence supporting the idea that the variable phenotype in 22q11DS may be expressed as subtypes independent of age and gender. Type-1 was characterised by reductions in total brain volume; lower intellectual functioning; poorer mathematical ability, verbal skills, and verbal memory; and increased autistic-like traits, including poor social skills. Type-2 had fewer behavioural problems but more significant executive function deficits and more typical 22q11DS facial features. The phenotypic pattern in the two subtypes suggests that the data do represent two specific subtypes rather than just representing the top and bottom half of the 22q11DS phenotypic continuum in terms of intellectual functioning.

There are some limitations of our data set, and our approach, which provide natural directions for future research – some of which we are already pursuing. In particular, our sample size was not large enough to support the most stringent analyses of cluster stability and validity. This is likely to be a problem in all studies of this sort, due to limitations in the collection of clinical data, and availability of patients. Another limitation due to the sample size is the lack of inferential statistics available for *k*-means clustering. This means that we were unable to probabilistically test the hypothesis that the two-cluster solution provided the best description of the data structure. This problem might be addressed by using structure discovery algorithms that *do* provide inferential frameworks, such as Kemp and Tenenbaum's (2008) structural forms algorithm, but these approaches invariably require many more data than are available for 22q11DS patients. Nevertheless, the two-cluster solution we discovered satisfies a more important criterion than a null hypothesis test: it

appears to provide a coherent and clinically relevant separation of sub-types. The best way to test any proposed clustering is not through the application of more sophisticated algorithms or inferential tests, but rather to see whether the structure and associated predictions hold up in other data. Nevertheless, we are encouraged at the initial success the clustering solution has shown in predicting mental health outcome, even when those data were not used to inform the analysis.

4.2. *Structural brain anatomy*

Studies of structural brain anatomy in people with 22q11DS have typically found global volumetric reductions including, for example, cortical regions such as the occipital and parietal lobes, and the cerebellum (for a review see [Tan, Arnone, McIntosh, & Ebmeier, 2009](#)). With regards to differences in structural brain anatomy between the two subtypes, Type-1 showed a statistically significant smaller total brain volume including a disproportionate reduction of the left temporal cortex (trend level effect). Consistent with the findings of reduced total brain volumes in Type-1, there was a trend level effect for larger lateral ventricles in the Type-1 subgroup. With regards to temporal cortex abnormalities, findings in the general 22q11DS population are less conclusive and dependent on the sample composition. However, three studies with different sample compositions of adults with 22q11DS have focussed the attention on temporal lobe morphology and, in particular, volumetric reductions as a plausible risk factor for the development of psychosis ([Chow, et al., 2002](#); [van Amelsvoort, et al., 2004](#); [van Amelsvoort, et al., 2001](#)). Indeed, volumetric temporal grey matter reductions have been linked with a higher prevalence of positive symptoms of psychosis in children with 22q11DS ([W. R. Kates, Antshel, et al., 2011](#)). Hence, it may be the case that temporal lobe volume progressively changes in those individuals with 22q11DS who develop psychosis. Whether this change is prodromal or occurs in relation with the onset, or course, of the schizophrenia is not known. Indeed, Eliez and colleagues reported an inverse correlation between temporal lobes volume and age among children with 22q11DS, while a control group showed a

positive correlation, thus indicating a differential developmental trajectory of the temporal lobes in 22q11DS (Eliez et al., 2001). Recently, Tan and colleagues concluded that specific volumetric reductions of the fronto-temporal regions of the brain may make people with 22q11DS more vulnerable to developing psychotic symptoms (Tan, et al., 2009). Similarly, in the general population, it has been suggested that young people with schizotypal traits (Takahashi et al., 2010), and young people at ultra-high risk of developing psychosis, have volumetric reductions in the superior temporal gyrus (Pantelis et al., 2003; Witthaus et al., 2009) and these such reductions may precede the onset of florid psychosis (Takahashi et al., 2009).

Temporal lobe abnormalities have also been linked with autism-spectrum disorders (ASDs) (Raznahan et al., 2010; Toal et al., 2010), particularly to the language, social, and emotional characteristics of ASDs (Baron-Cohen & Belmonte, 2005; Schultz, 2005). Adults with ASDs have been reported to have medial temporal grey matter reductions (McAlonan et al., 2005), and similar findings of reductions in the superior temporal gyrus have been reported in children with ASDs (Boddaert et al., 2004). Within the 22q11DS literature there has (to the authors knowledge) so far been no reports linking temporal lobe abnormalities with autistic-like traits such as social deficits.

4.3. Prevalence of autistic-like traits and psychosis

A key between-subtype difference was the increased presence of autistic-like traits, such as social dysfunction in Type-1. Over the last few years, there have been several reports of autistic-like traits, such as self-directed behaviours and poor social skills, among children with 22q11DS (Gerdes, Sobot, Wang, McDonald-McGinn, & Zackai, 2001). However, it was not until Niklasson and colleagues (Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2001) included specific assessments for autism that it was reported that as many as 30% of children with 22q11DS have ASDs. More recently, studies have reported that between 14-50% of children with 22q11DS have

ASDs; however, there may be a larger proportion of children with 22q11DS who have some autistic-like features not warranting a clinical diagnosis of an ASD due to the absence of stereotypic repetitive behaviours (Fine, et al., 2005; Gerdes, et al., 2001; Glaser et al., 2007; Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2008; Vorstman et al., 2006). The presence of a subtype characterised by a higher prevalence of autistic-like symptoms is interesting since it has been suggested that autistic traits in 22q11DS may overlap with prodromal schizophrenia rather than true autism, and may be a reflection of underlying neurodevelopmental abnormalities (Vorstman, et al., 2006). Additionally, it has been reported that premorbid social impairments is one of the most prominent (present in 50-87% of cases) features in childhood onset schizophrenia (Sporn et al., 2004). It is worth noting, however, that although some children with 22q11DS appear to have co-morbid psychotic symptoms and ASDs, in the recent study by Vorstman and colleagues (Vorstman, et al., 2006), only 5 of 30 children with 22q11DS and ASDs had an additional diagnosis of psychotic disorders. However, the children in the study were young and it is possible that more of these participants have since transitioned to a psychotic illness.

If autistic-like features constitute a psychosis-prodrome among children with 22q11DS, as suggested by Vorstman and colleagues (Vorstman, et al., 2006), it will be important to investigate if children in Type-1 have a higher risk of developing schizophrenia-like psychotic disorders. With an early diagnosis and subsequent early intervention, it may be possible to improve the quality of life and clinical outcome for young adults with 22q11DS and psychosis. With regards to the currently reported sample, 17 of the participants have been followed up 5-6 years after the initial assessment and assessed for the presence of psychiatric disorders. When re-running a preliminary cluster analyses (bearing in mind the small sample size), it was found that whilst three participants changed from the more severe Type-1 to Type-2, no one had changed category from Type-2 to Type-1. Those participants remaining in Type-1 scored lower on general adaptive functioning scores (GAF) and higher on negative symptoms, such as alogia, anhedonia, and avolition. In

addition, one of the participants in Type-1 had a clinical diagnosis of schizophrenia. However, it is likely that many factors influence whether a person with 22q11DS develops psychosis and as yet it is unknown what these moderating factors may be.

4.4. *Intellectual functioning*

Other features of Type-1 identified in the current study, such as lower verbal intelligence, verbal memory, and language problems, have also been identified as risk factors for psychosis in the general population (David, Malmberg, Brandt, Allebeck, & Lewis, 1997) and among children with early-onset schizophrenia (Sporn, et al., 2004). Studies have consistently reported that children with 22q11DS have intellectual disabilities and/or learning problems. A recent study found that approximately 60% of children with 22q11DS have a borderline-average intelligence (FSIQ>70), while 40% have an intellectual disability (FSIQ<70) (De Smedt, Devriendt, et al., 2007). In the current study only 30% of the sample had a FSIQ score ≥ 70 whilst 70% had a FSIQ ≤ 69 . However, our analyses also revealed that general intellectual impairments in Type-1 were more profound than for Type-2. This is consistent with suggestions by De Smedt and colleagues' (2007) that children with co-occurring 22q11DS and ASD have lower intellectual functioning compared to those without the comorbid diagnosis. However, contrary to their findings that this lowered intellectual functioning in children with 22q11DS and ASD was due to lowered performance IQ, our data suggest that the difference in general intellectual ability was driven by verbal IQ impairments accompanied by poorer receptive language, verbal delayed recognition memory, and a trend level effect for verbal immediate memory. Verbal abilities, such as reading, spelling, and verbal rote memory, are often reported as strengths among children with 22q11DS (Antshel, Fremont, & Kates, 2008). However, it has been reported that verbal IQ scores progressively decline in individuals with 22q11DS who develop psychosis, and that this decrease is correlated with a decrease in left hemispheric cortical grey matter (D Gothelf, Penniman, et al., 2007). There was also a difference in

mathematical reasoning in Type-1 compared to Type-2. Numerical difficulties are well established in 22q11DS (De Smedt, Swillen, et al., 2007; Moss et al., 1999; Simon, Bearden, McDonald-McGinn, & Zackai, 2005; Woodin et al., 2001) and although it has been found that the verbal subsystem underlying arithmetical skills is relatively preserved in 22q11DS, it is not unlikely that the poorer verbal skills in Type-1 would have implications for their mathematical reasoning skills.

4.5. *Executive function*

One curious finding in the current study was that Type-2 people had more significant executive function deficits, particularly with regards to planning ability, and also had more typical 22q11DS facial features compared with Type-1. Executive dysfunction is frequently reported in both ASDs and schizophrenia. Indeed, a recent study of predictors of psychosis among adolescents with 22q11DS reports that performance on executive functioning tasks, together with parentally-rated odd/eccentric symptoms, were the best predictors of prodromal psychotic symptoms (Antshel, et al., 2010). However, the current study included several executive function tasks (see Table 2 and supplementary material) and only three tests differentiated between the two groups: The IntraDimensional/ExtraDimensional (ID/ED) set shifting (rule acquisition and reversal); the Stockings of Cambridge (SOC; spatial planning); and a Go-NoGo (inhibition) task. Although, the ID/ED is considered a computerised analogue of the Wisconsin Card Sorting test, Type-1 and Type-2 only differed on the intradimensional components which indicated that the Type-2 subtype were slower to learn initially but once understanding the rules, they may perform similarly well compared to Type-1. In the Go-NoGo task, reaction time rather than inhibitory skills differed between the two groups; this is again apparent in the SOC tasks where Type-2 were slower at both initiating and completing spatial problems, and also made poorer choices. These findings highlight the phenotypic variability among children with 22q11DS and also emphasise that poorer

performance on some tasks, or specific behavioural difficulties, does not necessarily mean that the child will have an overall poorer outcome.

4.6. Final note and conclusion

It is important to bear in mind that although people with 22q11DS share an etiological origin of the syndrome, there are many factors that can ensure that each individual is differentially affected both with regards to biological constraints, such as brain morphology, but also with regards to cognition and psychopathology. Potential mechanisms underlying this variability in 22q11DS include modifier genes that reside outside the deleted region, allelic variation of genes within the deleted region of the non-deleted chromosome, somatic mutations, epigenetic phenomena, individual characteristics (e.g., sex, race), environmental factors, and chance. Hence, the current study is a first step in identifying clinical subtypes; the next step will be to return to the genetic aetiology of the individuals in the two subtypes and investigate if there are differences that can account for the differential trajectory. In addition, it is important to follow-up the developmental course of the participants in the current study to see what future problems may be related to each specific subtype.

To conclude, for the first time we have identified two distinct phenotypes of people with 22q11DS. The presence of subtypes within the 22q11DS population can lead to better prognostic information enabling early identification of people with 22q11DS at high risk of, for example, schizophrenia-like psychotic disorders. The identification of subtypes in a group of people with a deletion at chromosome 22q11.2 is also valuable in designing research studies to understand the ontogeny of autism and schizophrenia in the general population.

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Table 1

Table 1
Demographic description of the two subtypes.

	Type-1	Type-2
Number	19	31
Male/Female	8/11	14/17
Mean age (<i>SD</i>)	12.9 (2.77)	9.9 (2.39)
Age range	8.5 – 16.8	6.0 – 15.8

Table 2

Table 2
Means, t-test score, and p-values for variables differentiating Type-1 and Type-2.

	Type 1 Mean	Type 2 Mean	t-test	p-value
Clinical scale				
ASQ	8.93	4.90	-3.31	<.001
Parental rating scales				
SDQ; Peer problems	5.56	2.62	-4.13	<.001
SDQ; Prosocial behaviour [#]	5.06	7.81	3.51	<.001
Social responsiveness scale	98.26	62.32	-3.20	<.001
Interactive sociability [#]	5.71	8.59	2.76	0.01
Cognition				
Full scale IQ (FSIQ)	61.06	68.47	2.99	<.001
Verbal IQ	64.83	73.81	3.00	<.001
WOND; Mathematical reasoning	70.33	77.47	3.02	<.001
WOLD; Oral language dimensions	70.22	83.59	4.38	<.001
WOLD; Receptive language	70.22	85.53	4.49	<.001
CMS; Verbal immediate memory	78.41	89.16	2.61	0.01
CMS; Verbal delayed recognition memory	78.41	89.35	2.79	<.001
ID/ED; Total errors	49.31	68.04	3.68	<.001
ID/ED; Pre-ED errors	6.31	12.07	3.47	<.001
SOC; Problems solved minimum moves	7.25	5.04	-4.51	<.001
SOC; Mean choices	16.17	18.52	3.96	<.001
SOC; Mean latency to first choice (seconds)	15.6	30.8	2.64	0.01
SOC; Mean latency to correct (seconds)	2.9	6.03	2.80	<.001
GNG; Reaction time to left signals (seconds)	361.3	445.1	3.29	<.001
GNG; Reaction time for no go errors (seconds)	273.8	362.8	3.25	<.001
BORB; Foreshortened view task	24.29	22.88	-3.40	<.001
BORB; Minimal features view task	24.53	23.47	-2.95	<.001
BORB; Associative matching	28.47	26.65	-2.54	0.01
Brain Volumes (mL)				

Whole brain	0.76	0.80	2.99	<.001
Right hemisphere	0.38	0.40	2.66	0.01
Left temporal cortex	0.04	0.05	2.70	0.01
Total temporal cortex	0.09	0.10	2.70	0.01
Total ventricular volume [*]	0.012	0.009	-.2.2	0.03
3D facial features				
Facial Size	-0.60	0.21	2.32	.01*
Nasal Profile	-0.57	0.34	3.24	<.001
Palpebral fissure	-0.40	0.44	2.69	.001
<p><i>Abbreviations:</i> ASQ: Autism Screening Questionnaire (now named Social Communication Questionnaire); SDQ: Strength and Difficulties Questionnaire; WOND: Wechsler's Objective Numerical Dimensions; WOLD: Wechsler's Objective Language Dimensions; ID/ED: IntraDimensional/ExtraDimensional task (CANTAB) measuring setshifting; SOC: Stockings of Cambridge (CANTAB) measuring planning; BORB: Birmingham Object Recognition Battery measuring object perception; GNG: GoNoGo task from the Maudsley Attention and Response Suppression Task Battery.</p> <p>* Trend level effect only # Reverse scale</p>				

Table 3

Table 3
 Summary of Type-1 phenotype as compared to Type-2.

Facial dysmorphology	Brain morphology	Cognition	Behaviour
Facial features more reminiscent of typically developing controls, including:	Reduced total brain volume**	Lower overall intellectual functioning including verbal IQ**	Poorer social interactive skills*
Smaller facial size *	Reductions of grey brain matter in the temporal lobes*	Poorer Mathematical reasoning skills **	More peer problems**
Less elongated nose**	Increased lateral ventricular volumes*	Poorer oral and receptive language skills**	Poorer prosocial behaviour**
Narrower basal base**		Poorer verbal delayed recognition** and immediate memory*	Poorer social reciprocity**
Shorter palpebral fissures*		Better executive functions, including planning and spatial working memory**	More autistic-like traits**
		Shorter reaction times in inhibition task**	

* $p < .03$, ** $p < .001$

Supplementary Material/Appendix A

Appendix A Summary of Cognitive measures

Test battery	Domains			
Wechsler Intelligence Scale for Children ⁷ – 3 rd edition UK ^[1]	Full Scale IQ	Verbal IQ	Verbal comprehension	Information, Similarities, Vocabulary, Comprehension
			Freedom from Distractibility	Digit span, Arithmetic
		Performance IQ	Perceptual organisation	Picture completion, Picture arrangement, Block design, Object assembly
			Processing Speed	Coding, Symbol search
Children's Memory Scale ^[2]	Auditory/Verbal	Verbal immediate, Verbal delayed, delayed recognition	Stories, Word pairs	
	Visual/Nonverbal	Visual immediate, Visual delayed	Faces, Dot locations	
	Attention/Concentration		Sequences, Numbers	
	Learning		Word pairs, Dot location	
Wechsler Objective Dimension Scales	Reading ^[3]	Reading, Reading comprehension, Spelling		
	Numerical ^[4]	Numerical operations, Mathematical reasoning		
	Language ^[5]	Oral expression, Listening comprehension		
Test of Reception of Grammar ^[6]	Grammar			
British Picture Vocabulary Scale ^[7]	Vocabulary			
Cambridge Neuropsychological Test Automated Battery ^[8]	Spatial Working Memory			
	Intra/Extra Dimensional Shift			

	Stockings of Cambridge			
Maudsley Attention and Response Suppression Battery ^[9]	Go-No-Go			
	Switch task			
Social cognition	Smarties Task ^[10]			
	Sally-Ann task ^[11]			
	Strange Stories ^[12]			
MRC Development of Face Processing Skills ^[13]	Expression			
	Facial speech			
	Gaze			
	Identity			
Birmingham Object Recognition Battery ^[14]	Object decision, Picture naming, Associative matching, Foreshortened and minimal features view			
Grooved Pegboard	Visual motor coordination			

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Appendix B Psychological adjustment, mental health and well being questionnaires

Scale	Domain	Sub items
Conners Rating Scales (Parent) ^[1]	ADHD index	Oppositional
		Cognitive problems/inattention
		Hyperactivity
Strengths & Difficulties Questionnaire ^[2]	Emotional symptoms	
	Conduct problems/inattention	
	Hyperactivity/inattention	
	Peer problem	
	Prosocial behaviour	
Vineland Adaptive Behavioural Scale ^[3]	Communication skills	
	Daily living skills	
	Socialisation	
	Motor Skills	
Social Responsiveness Scale ^[4]	Autistic traits	
Moods and Feelings Questionnaire ^[5]	Depression	
Anxiety Scale ^[6]	Anxiety	
Social Communication Questionnaire ^[7]	Autism screening questionnaire	
Schizotypy ^[8]		

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