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Developmental language trajectories: Differences between pre-schoolers with 22q11.2 Deletion Syndrome and typically developing pre-schoolers

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Abstract

The 22q11.2 Deletion Syndrome (22q11DS) is characterized by large phenotypic variation, but research suggests that the language development of children with 22q11DS is commonly delayed compared to typically developing (TD) children. However, little is known about the developmental language trajectories of children with 22q11DS. The aim of the current study is to investigate whether the language proficiency of pre-schoolers with 22q11DS develops differently compared to TD children by administering and analysing the standardized language measures (comprising different language domains) of children with 22q11DS aged 3;0-6;6 years old on two time points (six months apart). The children's scores were compared with a matched TD group at the first test moment, and with norm scores at both test moments. The results showed that children with 22q11DS have an overall lower language proficiency than their peers. Children with 22q11DS showed improvement for both receptive and expressive vocabulary and for sentence comprehension between T1 and T2. Furthermore, age corrected norm scores did not differ between T1 and T2, indicating that children with 22q11DS develop at a comparable rate as their TD peers on all subdomains. Exploratory analyses suggest that children with 22q11DS have more difficulty keeping up with the developmental pace of the norm group for expressive, than for receptive language skills. These findings indicate that developmental language trajectory is language domain dependent in this population. It is recommended to start speech-language therapy at a young age for children with 22q11DS and to monitor their language development throughout childhood.

1. Introduction

The 22q11.2 Deletion Syndrome (22q11DS) is the most common chromosomal microdeletion syndrome, with a heterogeneous clinical representation (McDonald-McGinn et al., 2015). The syndrome is generally associated with congenital heart defects, subtle facial abnormalities, cognitive impairments and an increased risk of developing psychiatric disorders (Kobrynski & Sullivan, 2007; Swillen & McDonald-McGinn, 2015). One of the characteristics of children with 22q11DS is that their language development lags behind relative to typically developing peers (Golding-Kushner, Weller, & Shprintzen, 1985). Based on the study of Van den Heuvel, Manders, Swillen and Zink (2018), it seems that the degree and domain of linguistic delay differs depending on the stage of development of the children with 22q11DS. However, longitudinal research on language development conducted among toddlers and children with 22q11DS in the early years of primary school is scarce. Previous longitudinal work mainly focused on intellectual functioning and suggests that a subgroup of children with 22q11DS showed a decreased IQ development compared to peers, leading to greater disparities as time progresses (Duijff, Klaassen, De Veye, Beemer, Sinnema, & Vorstman, 2012; Swillen & McDonald-McGinn, 2015). It is unclear whether language development in children with 22q11DS follows a similar pattern. The current paper aims to describe the changes in language skills of young children with 22q11DS as a function of age. The objective is to investigate whether the developmental language trajectory of pre-schoolers with 22q11DS differs from that of typically developing pre-schoolers, by comparing standardized language measures – comprising different language domains – at two time points with a time interval of six months.

Knowing the impact of a specific neurodevelopmental disorder on language functioning over time can help to identify a syndrome-specific profile with accompanying needs and potential interventions. Vice versa, a specific language profile and developmental trajectory may enable recognition of critical signals for children possibly suffering from this neurodevelopmental disorder. A delayed language development is a great burden for children, because communication is in general strongly linked to other cognitive skills, mental health and quality of life (e.g. Schoon, Parsons, Rush, & Law, 2010; Van Agt, Essink-Bot, Van der Stege, De Ridder-Sluiter, & De Koning, 2005). More insight in the language profile of children with 22q11DS can help provide prognosis for parents and

clinicians, and can help language interventions and therapy to focus on facilitating social and functional communication (verbal or non-verbal) (Solot et al., 2019).

This paper starts with a theoretical background about the characteristics of 22q11DS (section 2.1), the language problems observed in 22q11DS (section 2.2), the trajectory of language development in 22q11DS (section 2.3), and how this trajectory could relate to cognitive functioning in 22q11DS (section 2.4). Subsequently, the research questions and hypotheses of the current study are stated (section 3), the methodology is explained (section 4), and the results are presented (section 5). This paper ends with a discussion (section 6) and conclusion (section 7).

2. Theoretical framework

2.1 The 22q11.2 Deletion Syndrome

The 22q11.2 Deletion Syndrome (22q11DS) is a congenital, autosomal dominant micro-deletion syndrome, which is caused by a deletion at chromosome 22 at band q11.2. It is the most common microdeletion syndrome, with a prevalence estimated at 1 in 2000-4000 live births (McDonald-McGinn et al., 2015). Almost 85-95% of the cases are a result of a *de novo* deletion (McDonald-McGinn et al., 1999; McDonald-McGinn et al., 2001). Children with this syndrome may express many different physical and behavioural symptoms, however, the most common physical ones are: velopharyngeal insufficiencies, heart defects, and characteristic facial features. For this reason, the condition was previously known by the term velo-cardio-facial syndrome (VCFS). It is important to emphasize that the phenotype of the patients can vary widely, and to date it does not seem that a single clinical feature occurs in all cases. Due to the large variety in phenotype, the age of diagnosis of the syndrome may vary considerably: from around birth, all the way up to adulthood.

In addition to the physical symptoms, approximately 50% of the affected children also experience cognitive impairments, like learning disabilities, difficulty with visual spatial processing and attention deficits (DeBoer, Wu, Lee, & Simon, 2007; De Smedt, Devriendt, Fryns, Vogels, Gewillig & Swillen, 2007). Within the 22q11DS population, full-scale IQ ranges from around 50 to 110, with a normal distribution around a mean of 73 (De Smedt et al., 2007). Children with 22q11DS tend to have developmental delays (Shprintzen, 2000). Speech development of children with 22q11DS

can be influenced by the presence of velopharyngeal insufficiencies or a cleft palate (Persson, Lohmander, Jöhnsson, Óskarsdóttir, & Söderpalm, 2003). Moreover, children with 22q11DS seem to suffer from language impairments during infancy and childhood (Solot et al., 2000). Delays and impairments in socio-emotional development are also frequently observed (e.g. Shashi et al., 2012). Additionally, individuals affected by the syndrome have an increased risk of developing psychiatric disorders compared to the general population. 22q11DS is the strongest known (molecular) risk factor for developmental schizophrenia (Schneider et al., 2014).

2.2 Language problems in 22q11DS

Currently, research concerning language development of children with 22q11DS – and how this possibly deviates from typically developing children – is limited. Due to velopharyngeal insufficiencies (VPI) or palatal anomalies, a considerable amount of research and clinical work in the field of 22q11DS has focused on speech. Palatal anomalies frequently prevent a complete separation of the oral and the nasal cavities, with hypernasality and other vocal problems as a result (Solot et al., 2001). In contrast to speech issues, less attention has been paid to language problems in the research and clinical work about 22q11DS. Children with 22q11DS can have language problems that are independent of speech problems and intelligibility (Priester & Goorhuis-Brouwer, 2008; Solot et al., 2000).

Hitherto, the following is known about the language of children with 22q11DS. Roizen and colleagues (2007) used parental questionnaires to identify the early linguistic milestones of children with 22q11DS, including the production of their first words and sentences. The results revealed that children affected by 22q11DS start to lag behind their IQ- and age-matched peers and siblings sometime after the first year of life. This is indicated by slightly later achieved receptive language milestones than their siblings and community controls, but mainly by robust delays in expressive language milestones. These results are in line with an early descriptive study of Solot and colleagues (2000), in which 70% of the children with 22q11DS demonstrated a significant delay in language onset and did not speak or only used a few words at the age of 2. Contrarily, typically developing children produce their first words around their first birthday. In a subsequent study, Solot and

colleagues (2001) investigated the early communication profile of two age groups of children with 22q11DS with standardized speech and language tests. The general language score showed that 23% of the pre-school children with 22q11DS scored within one standard deviation from the mean – for which it was not specified whether this was above or below the mean. 49% scored one to two standard deviations below the mean, and 28% of the children scored more than two standard deviations below the mean of the scores of their peers. 90% of the tested children were non-verbal or only used one-word expressions at the age of 2 years old. For the 4-year-olds, this was still the case for 30% of the tested children. The researchers noted that the linguistic delay of most children (not defined how many) was more severe than their general cognitive delay. The main finding about the school-aged children with 22q11DS in this study, is that their language deficit persisted at group level. This is indicated by the scores for receptive, expressive and general language skills, which are at the average group level below two standard deviations from the mean norm scores. Two other studies found that the majority of toddlers and pre-schoolers with 22q11DS have a significant expressive language delay, beyond what might be expected based on their overall cognitive functioning, and seemingly unrelated to VPI (Gerdes, Solot, Wang, McDonald-McGinn, & Zackai, 2001; Solot et al., 2019). Van Wijngaarden (2015) adds that children with 22q11DS are in fact very eager to communicate. This retrospective study suggests that most children with 22q11DS try to use nonverbal communication or even use self-invented signs to express themselves. School-aged children with 22q11DS show a more severe deficit in their receptive language ability than their expressive language skills as compared to their peers (Glaser et al., 2002). However, this means that the development of language comprehension is still ahead of production, but the discrepancy between the two appears to be smaller than with typically developing children. Studies that looked at the language abilities of school-aged children with 22q11DS also investigated vocabulary acquisition. The early study of Golding-Kushner, Weller and Shprintzen (1985) reported a delay in receptive vocabulary skills of children with 22q11DS between 6-10 years old. Persson and colleagues (2006) reported that the mean scores of the children with 22q11DS on receptive vocabulary was moderately low; comparable to the findings of Golding-Kushner and colleagues (1985).

In short, the literature on language ability in children with 22q11DS suggests that these children often demonstrate a significant delay in language onset and that they score lower on receptive vocabulary tasks than typically developing children. Although the studies described in this section differ with respect to age and quantity of participants, language domains and language measures, it seems that pre-schoolers with 22q11DS have a more apparent expressive language deficit, and that a receptive language deficit is more apparent in school years. The latter implies that school-aged children with 22q11DS show a smaller discrepancy between their receptive and expressive language abilities than their typically developing peers.

2.3 Trajectory of language development in children with 22q11DS

The studies discussed in the previous section do not clarify how the language skills of children with 22q11DS develop over time and whether their language development is atypical. Investigating the developmental language trajectory might define whether "late developers" will catch up with peers, whether their language ability continues to lag behind or whether their delay is increasing. To understand the trajectory of language development in children with 22q11DS, this trajectory can be related to patterns of change in typical language development (Hulme & Snowling, 2013). Although there are individual differences in the timing of language development, typically developing children acquire language in a remarkably similar order (Hoff, 2013; Luinge, Post, Wit, & Goorhuis-Brouwer, 2006). For an overview of the linguistic milestones in typically developing pre-schoolers, see Conti-Ramsden and Durkin (2012). Based on the research summarized in the current paper, the deletion at chromosome 22 seems to (directly or indirectly) influence this early language learning process.

The research by Scherer, D'Antonio and Kalbfleisch (1999) is one of the few longitudinal studies on language development in children with 22q11DS. They described the language development of four children between 6 and 30 months old on various language domains, every six months. From 12 months old, the children with 22q11DS performed significantly worse on the receptive and expressive language tasks than the typically developing children. The differences in receptive language scores between the 22q11DS group and the control groups of peers with palatal abnormalities and typically developing children, "persisted and widened" over the course of the test

moments (Scherer et al., 1999). This means that both peer groups developed faster than the children with 22q11DS. The differences became greater for receptive language ability than for expressive language ability. However, this study only included a small sample and - considering the large phenotypical variation in children with 22q11DS - it is difficult to say to what extent these findings can be generalized to the entire group of children with 22q11DS.

Another study that longitudinally investigated the language development of children with 22q11DS, is the study of Van den Heuvel, Manders, Swillen and Zink (2018). They used the same standardized language measurements as used in the current study to test the language development of children with 22q11DS between 6-12 years old, at two time points with 18-24 months in between. Results revealed that the overall language proficiency of the children with 22q11DS was profoundly impaired (with z-scores ranging from -0.80 to -3.00). The longitudinal data of this study indicated that the receptive language advantage over expressive language of the school-aged children with 22q11DS reduced over time. The authors suggest that this developmental language profile may be syndrome-specific, but that more research is required (Van den Heuvel et al., 2018). Regarding the trajectory of expressive language development, studies have shown that children with 22q11DS often show a significant increase in quantity and quality of expressive output between the ages of 3 and 10 years old (D'Antonio, Scherer, Miller, Kalbfleisch, & Bartley, 2001; Solot et al., 2001; Van den Heuvel et al., 2018).

The objective of the current study is to look at the general language development of pre-schoolers with 22q11DS and how this relates to that of typically developing peers. The development of receptive vocabulary is also examined, since the growth of vocabulary is widely recognized as a core feature of emerging linguistic abilities (Rice & Hoffman, 2014). Since the literature on longitudinal language studies in this field is limited, the next section elaborates on longitudinal studies about cognitive functioning in children with 22q11DS.

2.4 Trajectory of cognitive development in children with 22q11DS

There are several longitudinal studies available that focus on the cognitive development of children

with 22q11DS. Expectations in the relatively new field of language trajectories in 22q11DS may be partly based on studies about the (characteristic) cognitive developmental trajectory of these children.

Children with 22q11DS may show signs of a cognitive deterioration when they get older. Within the research field of this syndrome, the difficulty to keep up with peers is especially examined for intellectual abilities in terms of IQ scores. Duijff and colleagues (2012) described the cognitive development of 69 children aged 5;6-9;6 years old with 22q11DS. The authors measured the longitudinal changes in IQ scores of the children, in which they defined on group level a cognitive decline as a decrease in IQ scores by repeated measurements. Results showed that, on average, the children with 22q11DS exhibit a decline in Full Scale IQ scores by a mean of 9.7 IQ points between test moment 1 (5;6 years old), and test moment 3 (9;6 years old). This means that the children showed in general an inability to keep up with required age-related increases of raw scores (called 'growing into deficit'). Some of the children even showed a decline in raw scores. Note that the decrease in IQ scores emerged as an average group effect, but that not all children experienced an (equivalent) intellectual stagnation or decline.

The study of Solot and colleagues (2001) related the general language scores they had obtained from 79 children with 22q11DS with the children's intelligence scores. Although this study does not have longitudinal results, the relation between intelligence scores and language scores in this population might suggest that the developmental trajectory of intelligence could be a model for the developmental trajectory of language. In their sample, Solot and colleagues (2001) found a strong relationship between IQ and language scores. The average total language score (TLS) of the children with an average IQ (85-115) was 89 (+/- 11); the average TLS of the children in the moderately low IQ range (70-85) was 77 (+/- 8); and the average TLS of the children in the significantly low IQ range (<70) was 72 (+/- 12) – where the average score is 100 on both the TLS and the IQ-test.

The aim of the current study is not to compare intelligence and language scores, but rather to look at linguistic growth trajectories. It is examined whether linguistic trajectories of pre-schoolers with 22q11DS reflect normal developmental fluctuations or whether they show a different developmental pattern, possibly similar to what is observed in IQ scores.

3. The current study: Research questions and hypotheses

The current study is part of a larger study called 'Language Impairment in the 22q11.2 Deletion Syndrome'. This project aims to study the language development of children in the age of 3;0 to 7;6 years old at three time points, spread over a period of one year. The current sub-study investigates whether there are differences between the language scores of children with 22q11DS and typically developing (TD) children, and whether the language skills of children with 22q11DS and their peers develop differently over a period of six months.

The studies discussed in Chapter 2 suggest that the language development of children with 22q11DS is delayed. This is most clearly reflected by delayed linguistic milestones, a moderately low receptive vocabulary score, and a relatively smaller advantage for receptive language ability over expressive language ability with increasing age, compared to what is observed in typically developing peers (D'Antonio et al., 2001; Golding-Kushner et al., 1985; Persson et al., 2006; Scherer et al., 1999; Solot et al., 2001; Van den Heuvel et al., 2018). Section 2.3 describes that there is still no evident understanding of how the chromosomal deletion affects linguistic ability over time. To date, studies that map the linguistic trajectory in this population are scarce. The focus of the current study is language development in pre-school years; the period in which typically developing children make significant progress in learning language and attain (full) native competence of language (Conti-Ramsden & Durkin, 2012). The objective of this study is to investigate the development of the language proficiency in pre-schoolers with 22q11DS within a short time frame of six months. This will contribute to enhancing our knowledge about the prognosis of language outcomes of the population of children with 22q11DS. Learning more about the language development of individuals with 22q11DS will in turn improve recommendations for caretakers and speech-language therapists.

To investigate the linguistic development of pre-schoolers with 22q11DS, the first research question examines significant group differences between the language scores of pre-schoolers with 22q11DS and typically developing (TD, age/gender-matched) pre-schoolers at a baseline time point (T1). To compare the language level between the two groups of pre-schoolers, two standardized language measures are used (CELF-Preschool-CLS and PPVT). Subsequently, to map the course of linguistic development, the second research question is whether the developmental language

trajectories of pre-schoolers with 22q11DS and their TD peers differ during a time interval of six months using the same standardized measures. In addition to the latter question, we investigate how age and language level can influence individual growth. Due to a global pandemic (March-May 2020), it was not possible to obtain measures for all TD children at the second time point (T2). However, the use of standardized measures allows us to compare T2 scores of children with 22q11DS to age-referenced norm scores.

Regarding the first research question, based on the literature discussed, the hypothesis is that pre-schoolers with 22q11DS on average score significantly lower on standardized language tests than typically developing pre-schoolers. Given the phenotypic heterogeneity observed in previous work, large individual differences can be expected within the group of the children with 22q11DS. Concerning the second research question, it is expected that pre-schoolers with 22q11DS and TD pre-schoolers differ in their developmental language trajectory. It is hypothesized that pre-schoolers with 22q11DS show a slower growth trajectory than TD pre-schoolers. Because to date, little is known about the course of language development in pre-school children with 22q11DS, the hypothesis is based on longitudinal research with younger children in this population (Scherer et al., 1999), and longitudinal studies about intellectual ability in children with 22q11DS (Duijff et al., 2012).

4. Methodology

4.1 Participants

Two groups of Dutch participants (N = 31 per group; 17 girls and 14 boys) were involved in this study: pre-schoolers with 22q11DS and typically developing (TD) pre-schoolers. The ages of the children at the first time point (T1) were between 3;0 and 6;6 years old (36 and 78 months). The second time point (T2) was on average six months after T1. As mentioned, we were only able to include T2 data from the children with 22q11DS.

The children with 22q11DS were individually matched to a typically developing peer, based on the following criteria: (1) age difference of no more than five months at T1, and (2) same sex. On a group level, there was no age difference between the two groups ($t(60) = -0.031$, $p = 0.96$). The age distribution of the participants at T1 is shown in Figure 1. It was not possible to match the children on

IQ level, because these data were not (yet) available. Exclusion criteria for this research project were a hearing loss of ≥ 35 dB and multilingualism. Extra exclusion criteria for the TD children were the presence of any speech, language or learning disorders, or a family history of any of these disorders. The children with 22q11DS were recruited via the national 22q11DS expertise centre of the Wilhelmina Children's Hospital Utrecht (WKZ) and via the national parent support group *Stichting Steun 22q11*. The TD children were recruited via regular primary schools and day-cares. Information about potential developmental abnormalities of the children was collected via parental questionnaires. Before T2, the parents/caregivers of the children with 22q11DS were asked whether significant events had occurred (concerning home situation, school and/or health) between T1 and T2. Notable events for the children with 22q11DS were that two children received tympanostomy tubes, one child appeared to have hearing loss (60 dB and 35 dB), and three children had frequent or severe ear/lung/throat infections during that time. Based on visual exploration of the data, the six children whose parents reported health related problems in the period between T1 and T2 do not appear to differ from the rest of the sample. Unfortunately, the analyses could not be performed again without these children, due to a lack of power.

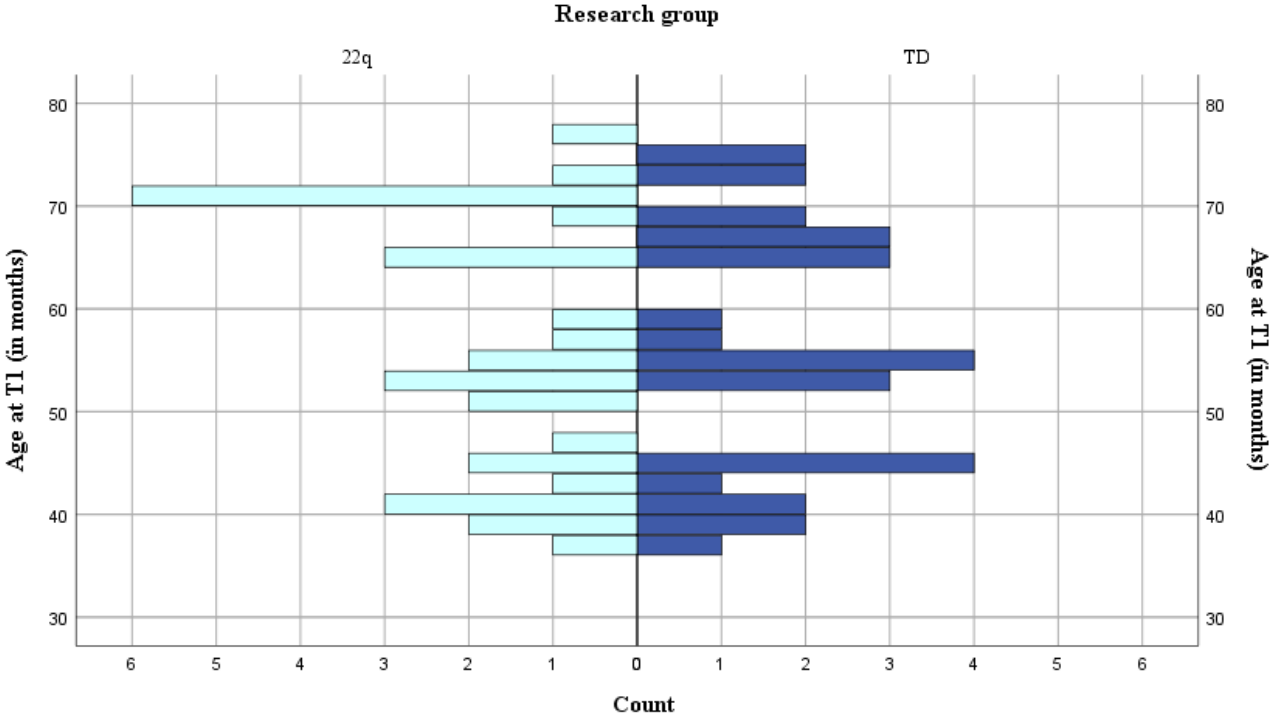

Figure 1. Spreading of age at T1 per participant group

4.2 Materials

The current study focused on the 'core language score' (CLS) of the CELF-Preschool-2-NL (Wiig, Secord, Semel, & De Jong, 2012), which includes expressive and receptive language tasks. This index score consists of the following three subtests: Word Structure (WS, expressive), to evaluate the child's knowledge of morpho-syntactic rules in a sentence completion task; Sentence Structure (SST, receptive), to evaluate the child's ability to interpret sentences of increasing complexity and length; and Expressive Vocabulary (EV, expressive), to evaluate the child's ability to label pictures with the correct name (Wiig et al., 2012). The CLS is a representative measure of the language skills of the tested pre-schooler and provides a quantification of their overall language performance (CELF-Preschool-2 Sample Report, 2005). The standardized scores of the CLS have a mean of 100 and a standard deviation of 15. The standardized score of the subtests of the CELF-Preschool have a mean score of 10, and a standard deviation of 3.

The second standardized language measure used is the Peabody Picture Vocabulary Test (PPVT-III-NL; Dunn, Dunn, & Schlichting, 2005); a widely used diagnostic instrument for receptive vocabulary (originally designed by Dunn, Dunn, Buheller, & Häcker, 1965). The PPVT consists of 204 test items, each with 4 images. The participant chooses the image that corresponds to the verbally presented word. The presented words increase in difficulty, and the task is terminated when the participant gives a predetermined number of incorrect answers. The standardized scores of the PPVT are normally distributed with an average score of 100 and a standard deviation of 15.

4.3 Procedure

Prior to T1, the parents/caregivers underwent a short screening by telephone to check whether the participants met the inclusion criteria and subsequently the parents gave informed consent. Additionally, the parents/caregivers were asked to fill in questionnaires to supply information about their own background and about the development and medical history of their children. Individual language assessments took place at the children's schools or day-care centres in a quiet room. The assessments at T1 consisted of two one-hour sessions within approximately one to two weeks. The assessments for the children with 22q11DS at T2 took place during a one-hour session, on average six

months and twelve days after T1 (range: 175-237 days). The test battery consisted of seven or eight linguistic and cognitive tasks per session. Four of the linguistic subtests are considered in the current study. All four of these tasks were administered at both T1 and (for the children with 22q11DS) T2. Audio recordings were obtained for the two expressive CELF subtests (WS and EV) and scored offline. The audio recordings were also checked and scored by another researcher. In case of discrepancies, agreement was reached by consensus. The research project 'Language Impairment in the 22q11.2 Deletion Syndrome' has received ethical approval from the Medical Research Ethics Committee (MREC, in Dutch: METC) of the University Medical Centre Utrecht.

4.4 Analyses

Prior to the statistical analyses, missing data was considered. The group of children with missing data was compared with the group of children with complete data sets. Subsequently, raw scores of the subtests of the CELF-Preschool (SST, WS and EV) were obtained per time point and converted into independent task norm scores, with averages and standard deviations per group. Norm scores of the three subtests of the CELF-Preschool were subsequently converted into the CLS, with corresponding CLS norm scores, with averages and standard deviations per group. Raw scores of the PPVT were also obtained per time point and converted into norm scores.

Statistical analyses were done with IBM SPSS Statistics 25 (2017). The norm scores of the PPVT, CELF subtests and CELF CLS were represented graphically per group (TD/22q11DS) at T1. The purpose of the visual representation of the data was to see how the groups of children scored compared to peers in the norm group, and to see whether the children had 'clinically relevant' scores. Norm-referenced scores were used here since they describe the subject's performance relative to his/her same-aged peers, and norm scores are comparable across tests of the CELF Preschool (Sullivan, Winter, Sass, & Svenkerud, 2014). The current study assumes a score to be 'clinically relevant' when the child achieves a CELF CLS of 85 (-1 SD) or lower, based on the recommendations of Siméa (2017). The same threshold is used for the PPVT norm score.

To answer the first research question about group differences between the language scores of children with 22q11DS and their typically developing peers, independent samples *t*-tests were

conducted with the PPVT norm scores, the norm scores of the CELF subtests (SST, WS and EV), and with the CELF CLS. Because of multiple testing (5 times) on the same dataset, the significance level was adjusted to $\alpha = 0.01$. The mean scores, standard deviations and effect sizes were reported. The effect sizes were related to Cohen's (1988) conventions: $d = 0.2$ is a small effect, $d = 0.5$ is a medium effect, and $d = 0.8$ is a large effect. To check for assumptions of normality, histograms of the norm scores per group were plotted and two numerical measures of shape (skewness and kurtosis between -1 and 1) were used. When one of the variables did not follow a normal distribution, the groups were compared using non-parametric equivalents of the independent samples *t*-test (Mann-Whitney U test).

For the second research question, in which the development of the children with 22q11DS over a period of six months is examined, both norm scores and raw scores were used in the analyses to compare children's scores at T1 and T2. Raw scores can provide good insight into a child's development over time; it shows their relative growth at T2 compared to T1. It is important to note that the raw data can be compared within the subtests (T1 and T2), but not between the different subtests nor with the raw data of the PPVT. This is because the subtests differ with respect to the number of questions, the number of points awarded per correct answer and the point at which a test should be terminated. Norm scores can provide insight in development compared to the norm group, indicated by an equal growth rate (a flat line), faster growth rate (an upward trend), or a slower growth rate (a downward trend). The correlations between the scores at T1 and T2 are given per subtest, to indicate how stable children's scores are over time. In order to statistically test whether the norm scores of the children with 22q11DS changed over time, paired samples *t*-tests were conducted with the PPVT norm scores, CELF subtest norm scores (SST, WS, EV), and the CELF CLS. Because of multiple testing (5 times) on the same dataset, the significance level was adjusted to $\alpha = 0.01$. The mean scores, standard deviations and effect sizes are reported. The development of the children with 22q11DS over time was also analysed qualitatively: The number of children who had a positive, negative, or unchanged difference score was calculated to consider individual differences. Concerning the CELF subtests, an 'unchanged score' means the exact same norm score achieved at T1 and T2. Concerning the PPVT and CELF CLS, an 'unchanged score' means that the norm score of the children at T2 did not differ more than plus or minus five points from the score at T1. Subsequently, it was

tested how age and language score at T1 influenced the individual growth score of the children with 22q11DS. Pearson correlations were computed to assess the relationship between growth on the subtests (T2-T1) and both age and language scores at T1.

5. Results

5.1 Missing data

Not all children in the matched data set were included in the final data analyses, because some children with 22q11DS were unable to complete all the tasks. The flowchart in Figure 2 shows how many children were able to complete each task at T1 and T2. At T1, the exclusion of participants was due to (a combination of) the following reasons: developmental delay, task-orientation and lack of spoken language (only/mostly non-verbal communication). Figure 2 shows that a total of 23 pre-schoolers with 22q11DS completed all three subtests that together form the core language score (CLS) at T1, versus all 31 TD children. The eight children with 22q11DS who could not be included in the analyses of T1 were on average 3;10 years old (range: 3;1-4;8) and included five boys and three girls. The mean age of these children (M = 46.00, SD = 7.37; in months) is lower than the mean age of the children with 22q11DS who were included in analyses (M = 59.00, SD = 12.20; in months), which is a significant difference ($t(21) = -3.64$, $p = 0.004$). None of the excluded children have a cleft lip/palate, but 75% of these children have been reported by their parents/caregivers to be poorly understood by outsiders. Of the children with 22q11DS who were included in analyses, this is reported in 9% of the cases. One of the excluded children is suspected to have selective mutism. This means that an anxiety disorder underlies the inability to speak in the test situation, which is not related to the child's language development (Johnson & Wintgens, 2017).

The eight TD children matched (age/sex) to the excluded children with 22q11DS at T1, were not included in the analysis either. Per subtest, the largest number of pre-schoolers with 22q11DS who completed the task (with corresponding matched TD children) was included in the analysis. For the PPVT and CELF CLS, the descriptive statistics on age of the remaining children per analysis at T1

and T2 are given in Table 1. The mean ages of the CELF subtests were comparable to the CELF CLS and there were no age differences between the TD-group and the 22q11DS-group.

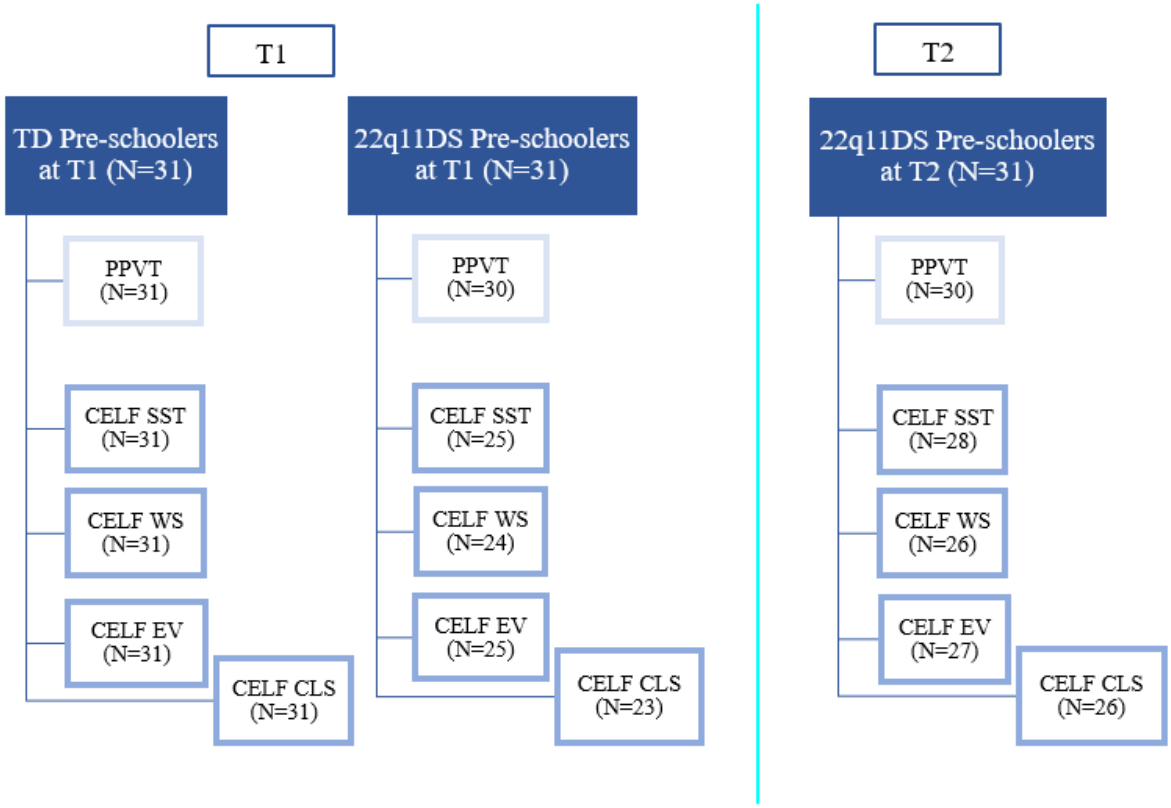

Figure 2. Flowchart for task completion per subtest at T1 and T2. PPVT = Peabody Picture Vocabulary Test; SST = Sentence Structure; WS = Word Structure, EV = Expressive Vocabulary; CLS = Core Language Score.

Table 1.

Descriptive statistics of age (in months) of the pre-schoolers included in the T1 and T2 analyses

	TD		22q11DS			
Subtest	*M*	*SD*	*M*	*SD*	*t*-test	*p*
PPVT						
T1: N = 30 (per group)	55.80	12.16	55.87	12.72	-.021	.98
T2: N = 30	N/A		62.13	12.99		
CELF CLS						
T1: N = 23 (per group)	59.22	12.29	59.26	12.20	-.013	.99
T2: N = 26	N/A		63.58	13.12		

Of the eight children who did not complete one or more tasks at T1, five could still not perform all tasks at T2 either. Thus, a total of 26 pre-schoolers with 22q11DS completed all three subtests that together form the CLS at T2. The three children who were not able to complete all the CELF subtests at T1 (but succeeded at T2) had norm scores on the CELF CLS of, respectively, 55, 64 and 55 at T2 – with 55 being the lowest attainable norm score on the CLS. Due to a missing T1 score, these children could not be included in the analysis for either research question. The child suspected to have selective mutism was the only case where a child could not perform a subtest at T2 (the EV task) but did so at T1 (with the use of gestures). In total, there are 23 children with 22q11DS whose linguistic development can be analysed over time.

5.2 Group comparisons

To answer the first research question of this study, the scores of the language tests administered at T1 of children with 22q11DS were compared with those of the matched TD children. Figure 3 represents the average norm scores and individual data points of the PPVT, per participant group. Concerning the PPVT norm scores, the children with 22q11DS scored on average lower (M = 82.83, SD = 12.21) than the TD children (M = 109.40, SD = 12.14). This difference was significant and showed a large effect ($t(58) = 8.11$, $p < 0.001$, $d = 1.45$). The PPVT norm score of 57% of the children with 22q11DS (17 out of 30) is clinically relevant, compared to 3% of the PPVT norm scores of the TD children (1 out of 30).

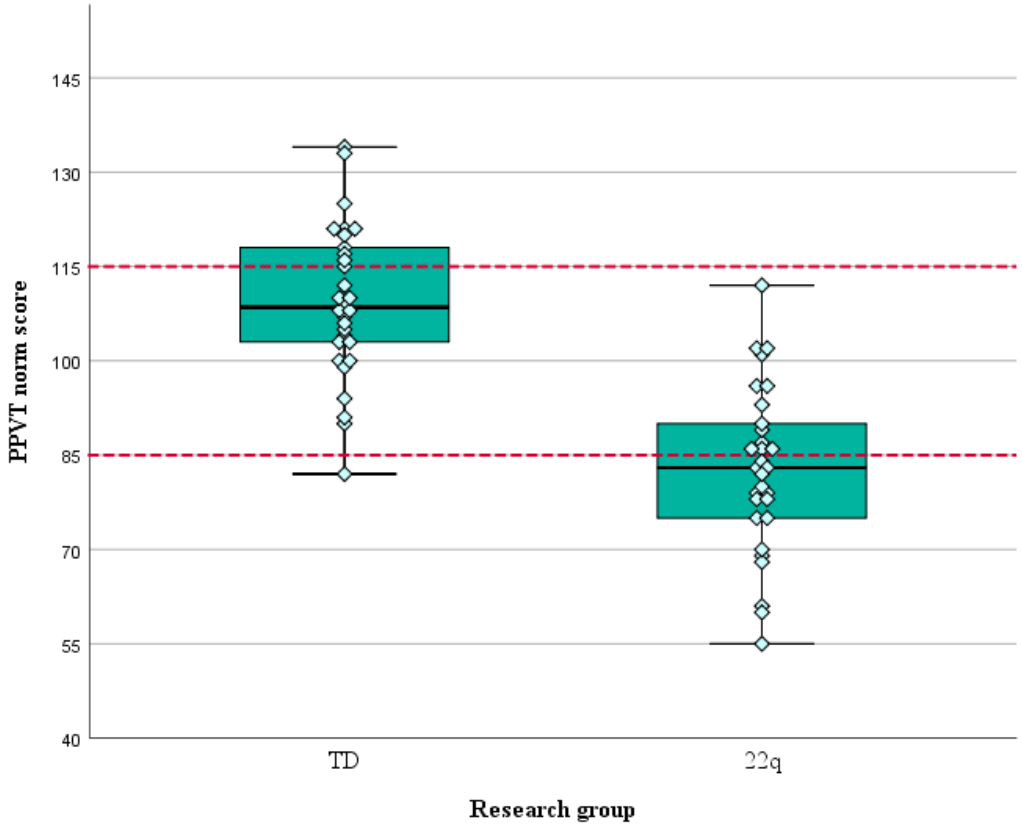

Figure 3. PPVT norm scores per participant group, including individual datapoints. Dashed red lines represent +/- 1 SD of the mean.

Figures 4, 5, and 6 represent the average norm scores and individual data points of the subtests of the CELF-Preschool, per participant group. On average, the TD children scored higher on the SST subtest (M = 11.52, SD = 2.28) than the children with 22q11DS (M = 5.56, SD = 2.45). This difference was significant and showed a large effect ($t(48) = 8.91$, $p < 0.001$, d = 1.56). Furthermore, the TD children scored on average higher on the WS subtest (M = 12.08, SD = 2.81) than the children with 22q11DS (M = 4.54, SD = 2.89). This difference was significant and showed a large effect ($t(46) = 9.17$, $p < 0.001$, d = 1.59). On average, the typically developing children also scored higher on the EV subtest (M = 11.64, SD = 2.91) than the children with 22q11DS (M = 5.60, SD = 1.94). This difference was significant and showed a large effect ($t(48) = 8.63$, $p < 0.001$, d = 1.54). Because Levene's test for equality of variance was found to be violated for the analysis of the EV subtest, a nonparametric test was performed as well, showing the same results.

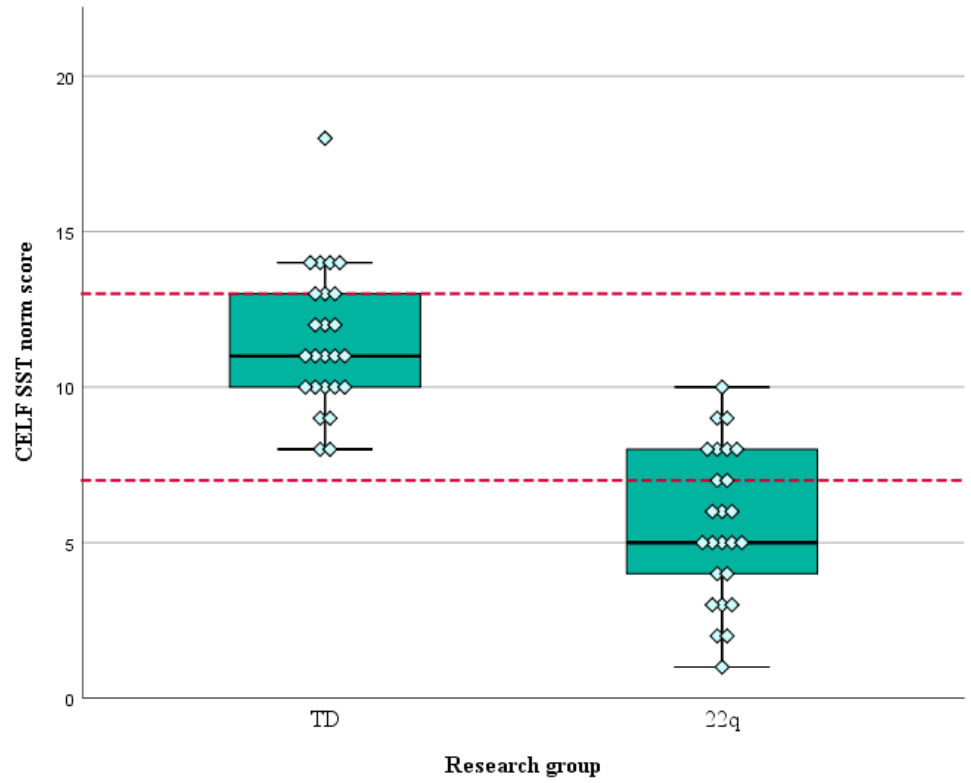

Figure 4. Sentence Structure (SST) norm scores per participant group, including individual datapoints. Dashed red lines represent +/- 1 SD of the mean.

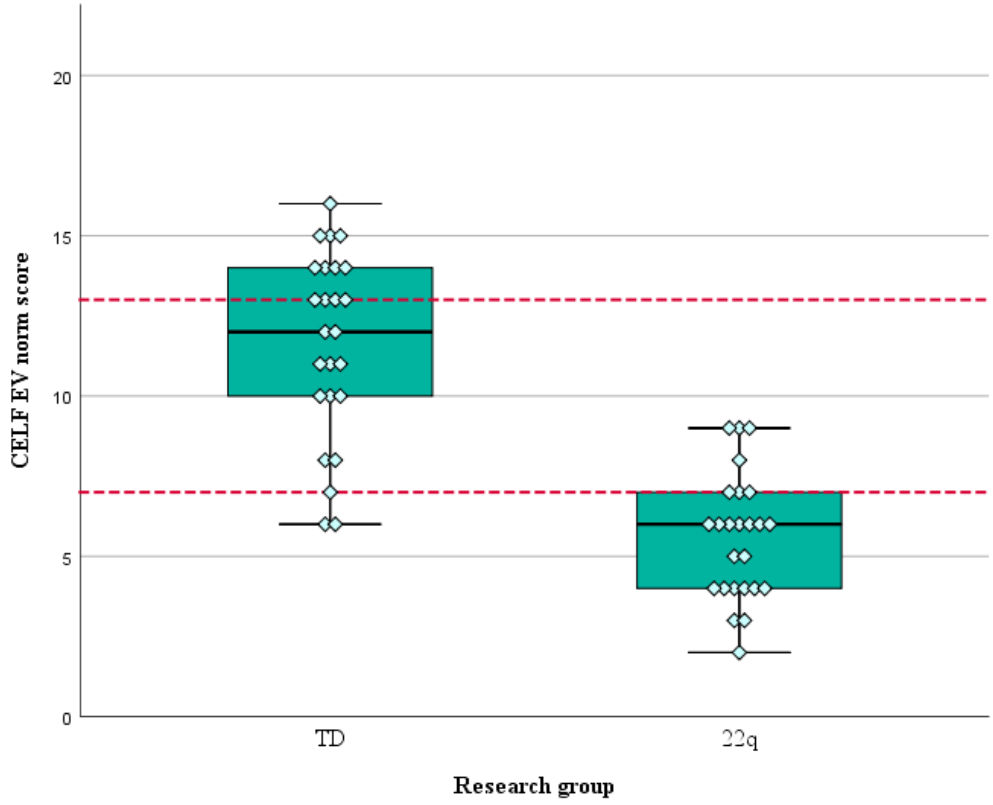

Figure 5. Word Structure (WS) norm scores per participant group, including individual datapoints. Dashed red lines represent +/- 1 SD of the mean.

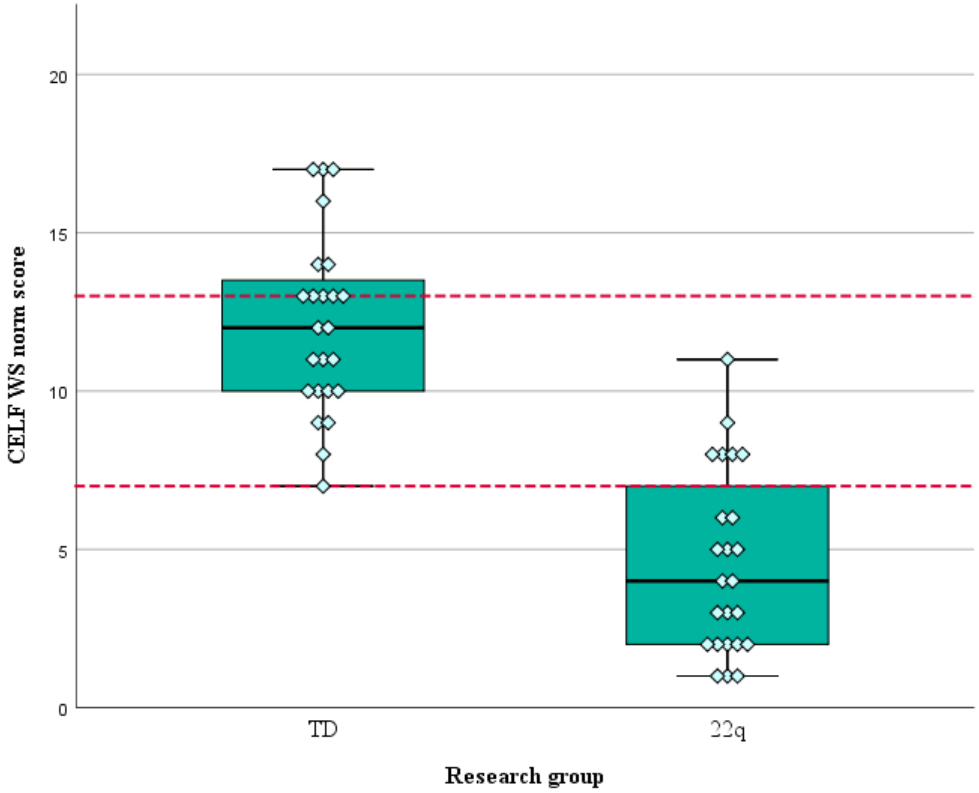

Figure 6. Expressive Vocabulary (EV) norm scores per participant group, including individual datapoints. Dashed red lines represent +/- 1 SD of the mean.

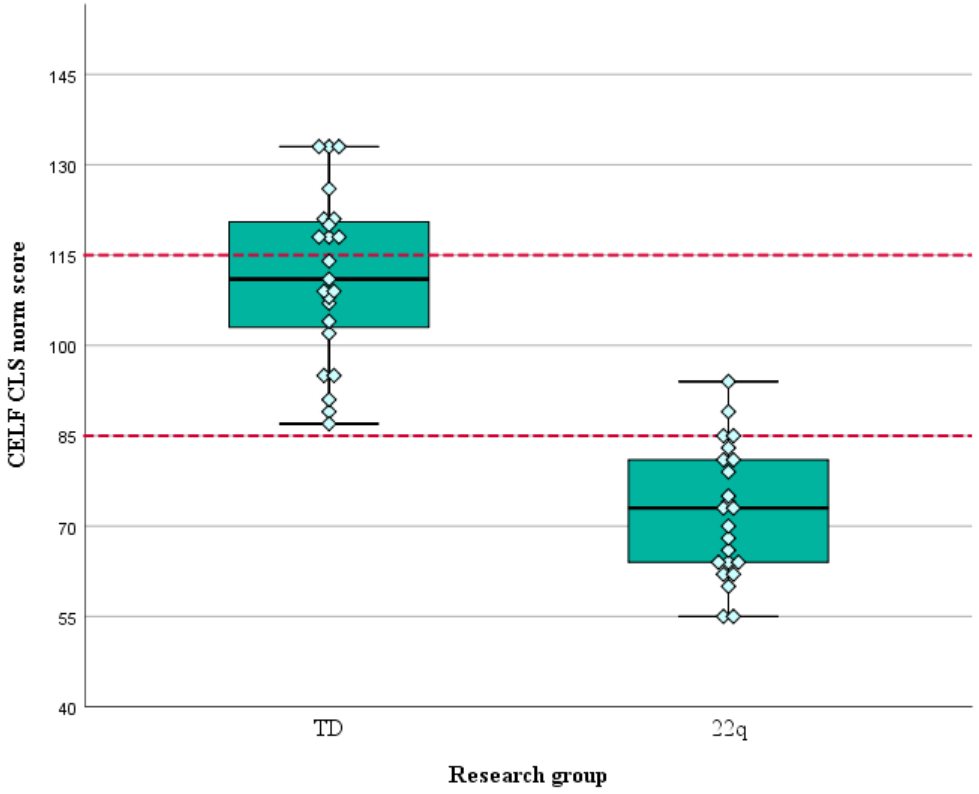

Figure 7. CELF CLS norm scores per participant group, including individual datapoints. Dashed red lines represent +/- 1 SD of the mean.

Figure 7 shows the average norm scores and individual data points of the CLS, per participant group. On average, the TD children scored higher on the CLS index of the CELF-Preschool (M = 111.39, SD = 13.89) than the children with 22q11DS (M = 72.26, SD = 10.93). This difference was significant and showed a large effect ($t(44) = 10.62$, $p < 0.001$, d = 1.68). The CELF CLS of 91% of the children with 22q11DS (21 out of 23) is clinically relevant, compared to none of the CELF CLS scores of the TD children.

5.3 Developmental language trajectories

To answer the second research question of this study, the scores of the language tests obtained at T1 of the children with 22q11DS were compared with their scores at T2, six months thereafter. The results of the Pearson correlations between the children's scores at T1 and at T2 (on the same test) are given in Table 2. The significant correlations show stability in children's language scores over time. In order to statistically test the growth over the six-month period, paired samples t-tests between the language scores at T1 and T2 (raw and norm scores) were conducted. The results are shown in Table 2. The significant positive difference in raw scores between T1 and T2 on the PPVT, SST and EV reflect growth on group level, relative to the scores on this specific task six months earlier. The number of clinically relevant scores in the group of children with 22q11DS decreased at T2 compared to T1. At T2, 37% of the scores on the PPVT are clinically relevant (11 out of 30), whereas this was 57% at T1. 74% of the scores on the CLS are clinically relevant at T2 (17 out of 23), whereas this was 91% at T1.

Table 2.

Relative differences between the subtest scores at T1 and T2 of the pre-schoolers with 22q11DS on group level. Mean scores (M), standard deviations (SD), dependent samples t-test results (t-test and p), effect sizes (d) and correlations between T1 and T2 scores (r) are reported.

Subtest	T1 *M (SD)*	T2 *M (SD)*	Relative difference	*t*-test	*p*	*d*	Correlation subtest T1-T2 *(r)*
PPVT (N=30)							
Raw score	52.75 *(16.68)*	62.14 *(17.45)*	9.39	-4.62	< .001**	.87	0.80**
Norm score	82.83 *(13.21)*	87.93 *(14.72)*	5.10	-1.99	.056	.36	0.50**
CELF SST (N=25)							
Raw score	11.36 *(4.58)*	14.16 *(3.61)*	2.80	-4.54	< .001**	.91	0.74**
Norm score	5.56 *(2.45)*	6.32 *(2.78)*	.76	-1.56	.13	.31	0.57**
CELF WS (N=24)							
Raw score	10.00 *(4.32)*	11.65 *(5.29)*	1.65	-2.49	.021	.52	0.80**
Norm score	4.65 *(2.90)*	5.09 *(3.79)*	.44	-.81	.43	.17	0.74**
CELF EV (N=25)							
Raw score	18.38 *(7.67)*	21.29 *(6.94)*	2.92	-3.22	.004**	.66	0.82**
Norm score	5.75 *(1.82)*	5.75 *(2.64)*	.00	.00	1.00	.00	0.63**
CELF CLS (N=23)							
Norm score	72.26 *(10.93)*	74.09 *(15.71)*	1.83	-.87	.34	.18	0.77**

**$p < .01$

To identify how the language development of the children with 22q11DS relates to typically developing children, it was examined how the norm scores of the children with 22q11DS differ between T1 and T2. The finding that none of the subtests showed a significant (positive or negative) difference in norm scores between T1 and T2 suggests that on a group level, the pre-schoolers showed the same developmental pace as the norm group. Figure 8 represents the average norm scores of the PPVT and CELF CLS at T1 and T2. The development of the norm scores on the CELF subtests are not shown, but were comparable to the CLS, as presented in Figure 8.

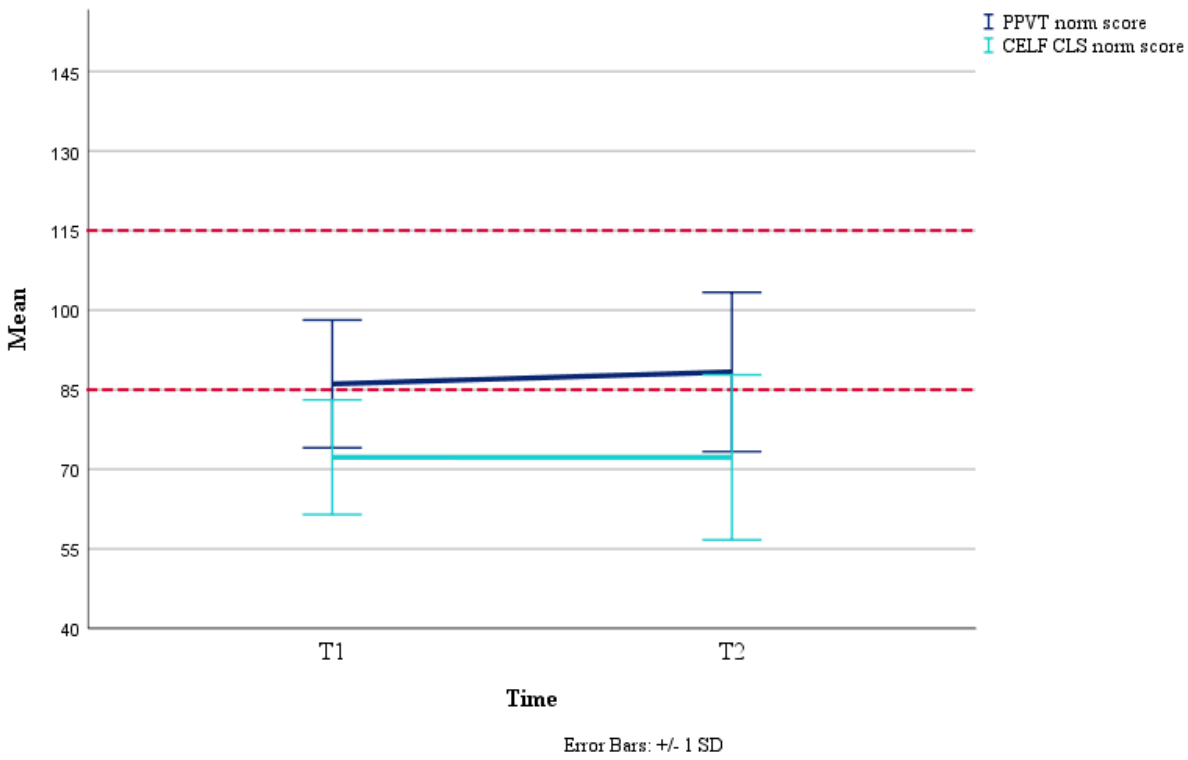

Figure 8. CELF CLS norm score and PPVT norm score of the pre-schoolers with 22q11DS at T1 and T2. Dashed red lines represent +/- 1 SD of the mean.

To provide more insight into the individual differences of the development of pre-schoolers with 22q11DS, Figure 9 shows the percentage of children who had a positive, negative or 'unchanged' difference norm score between T1 and T2 per test. Most children increased on the norm score of the PPVT and SST. For the WS and EV, the largest percentage of children showed a decrease in norm score. For the CLS, the percentages of children who decline, increase or remain the same in norm score are comparable.

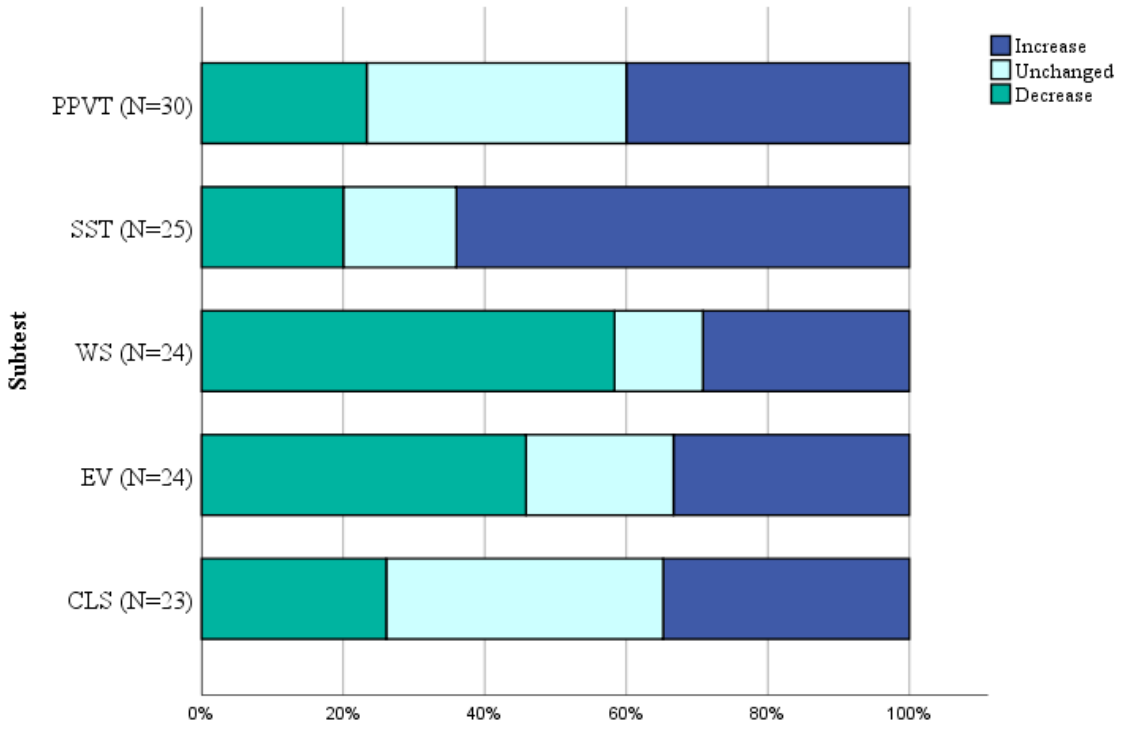

Figure 9. Percentage of children with 22q11DS with a decreased, unchanged or increased subtest norm score at T2, relative to T1.

To gain more insight into what factors are related to the individual differences in language development in children with 22q11DS, their individual growth was related to age and language level. The difference in norm scores of the CELF subtests (T2-T1) was associated with the age (at T1) and language level (per subtest at T1) of the children. The results of the Pearson correlations are given in Table 3. In most cases, no significant relation ($p > 0.05$) was found between the growth on the subtests and language level at T1. Notably, with regard to the PPVT, the results indicate that children with 22q11DS who already had a higher score at T1, showed less growth than the children with a lower score at T1 (negative correlation). The results also showed that children with 22q11DS with a higher WS score at T1, seem to experience more growth than the children with a lower WS score at T1 (positive correlation). For all subtests, no significant relation was found between the growth on the subtest and age at T1.

Table 3.

Correlations between growth on the subtest's norm scores (T2-T1) and age (at T1) and language level per subtest (at T1)

Subtest		Age at T1	Subtest norm score at T1
PPVT (N=30)	Pearson's *r*	-0.23	-0.42
(Δ norm score T1-T2)	*p*-value	.23	.02*
CELF SST (N=25)	Pearson's *r*	-0.08	-0.35
(Δ norm score T1-T2)	*p*-value	.69	.08
CELF WS (N=23)	Pearson's *r*	-0.10	0.56
(Δ norm score T1-T2)	*p*-value	.63	.006**
CELF EV (N=24)	Pearson's *r*	-0.19	-0.08
(Δ norm score T1-T2)	*p*-value	.38	.71
CELF CLS (N=23)	Pearson's *r*	-0.12	0.12
(Δ norm score T1-T2)	*p*-value	.60	.60

*$p < .05$; **$p < .01$

6. Discussion

The current study investigated the developmental language trajectories of pre-schoolers with 22q11DS in relation to typically developing (TD) pre-schoolers, on two time points (six months apart). We therefore administered and analysed the standardized language measures CELF Preschool and Peabody Picture Vocabulary Test (PPVT). Regarding the CELF, three subtests and the Core Language Score (CLS) were used, comprising different language domains. For this study, it was of interest to further investigate the language profile of children with 22q11DS, which can help provide prognosis, language interventions and therapy.

6.1 Main findings

The first aim was to investigate whether there were significant group differences between the language scores of pre-schoolers with 22q11DS and TD pre-schoolers at a baseline time point (T1). The results

showed that the age and gender matched TD children scored significantly higher than the children with 22q11DS on all subtests – comprising receptive and expressive vocabulary, sentence comprehension and morphosyntax. The group comparison at T1 also showed that almost all children with 22q11DS (91%) had a clinically relevant score on the CLS; the index score that presents a quantification of overall language performance. None of the studied TD children had a CLS score in the clinical range. These results support the hypothesis about the delayed language development in children with 22q11DS, in line with previous studies of D'Antonio and colleagues (2001), Golding-Kushner and colleagues (1985), Persson and colleagues (2006), Scherer and colleagues (1999), Solot and colleagues (2001), and Van den Heuvel and colleagues (2018).

The second aim was to investigate whether the developmental language trajectories of pre-schoolers with 22q11DS and their TD peers differ during a time interval of six months, with the use of standardized measures. In addition, it was examined whether age and language score (on T1) was related to individual development. The first finding is that the children with 22q11DS show improvement over the six-month period on three out of four subtests (PPVT, SST, EV), reflected in an increase in raw scores on a group level. These subtests include the domains of receptive vocabulary, expressive vocabulary and understanding sentences of increasing length and complexity. Only the raw scores on the WS subtest (tapping into morphosyntactic knowledge) showed no significant progress or decline on a group level. An additional finding is that children with 22q11DS show the same developmental pace as the norm group over the six-month period, on all subtests. This stems from the finding that the children's norm scores – which are corrected for age – do not differ between T1 and T2. This finding is not in line with the pre-formulated hypothesis that children with 22q11DS show a slower growth trajectory than their typically developing peers. This hypothesis was based on a small linguistic study with a younger population of children with 22q11DS (Scherer et al., 1999), and based on a study about IQ development in (slightly) older children with 22q11DS (Duijff et al., 2012). The results of the current study give reason to speculate that language development in this group of children does not follow the same pattern as their intellectual development. The children were (on a group level) able to keep up with the age-related increases of raw scores on the language tests; their delay on their TD peers did not increase. It can also be hypothesized that parallels with IQ

development might be reflected in other language domains than those tested in the current study. Duijff and colleagues (2012) speculate in their discussion that some children with 22q11DS decline in IQ because they cannot attain the level of abstract reasoning that is required as children grow older. Abstract reasoning is relevant in language development when generalizations need to be made from sparse data (Tenenbaum, Kemp, Griffiths, & Goodman, 2011). We speculate that a higher abstraction level is perhaps more present in other language domains than tested, such as semantics, pragmatics or understanding more complex syntactic structures. A second explanation for these findings might be that a pattern of 'growing into deficit' can only be seen if the language development of the children is observed over a longer time period. A longitudinal study with more than two test moments and/or with a larger time interval would be desirable for future work. However, the short time span of the current study also provides insight into rapid language development compared to the norm group, which is important knowledge when it comes to interventions - especially concerning this age range in which language develops at a rapid pace.

6.2 Exploratory findings

The results for developmental trajectory reflect the group as a whole, however, there were many individual differences. The heterogeneity of this population was already reflected on in the theoretical framework. With qualitative analyses, we attempted to gain more insight into the characteristics of the language development of children with 22q11DS. These analyses of the subtests showed that relatively more children had a decrease in norm scores on the expressive tasks (WS and EV), compared to the receptive tasks. This finding suggests that children with 22q11DS have more difficulty keeping up with the developmental pace of the norm group for expressive language skills, than for receptive language skills. This result ties in well with previous studies wherein most toddlers and pre-schoolers with 22q11DS have (mainly) an expressive language delay (Gerdes et al., 2001; Solot et al., 2019).

In order to see what might had influenced the individual differences within the group of children with 22q11DS, the relative development of the children was related to their age and language score at T1. In most cases, no relationship was found between the variables mentioned and relative

improvement score. The only significant correlations were between morphosyntactic score at T1 (WS subtest) and the growth score on this same test (positive relation), and between receptive vocabulary score at T1 (PPVT) and the growth score on this same test (negative relation). Although the sample in this study is rather small, these different results for expressive morphosyntax and receptive vocabulary indicate the need to further study developmental trajectories between different language domains. Future studies are recommended to look at the different language domains separately. The qualitative results of the current study also indicate that there may be differences in language trajectory based on language level in the group of children with 22q11DS. The latter gives reasons for separately analysing children with different language levels at T1. It is also recommended for future work to gain a better understanding of the heterogeneity and individual differences within the population of children with 22q11DS. This can be addressed by looking at factors that can explain individual differences, such as receiving speech-language therapy, attending regular or special (cluster-2) education, and socioeconomic status (SES). We know from previous research that these factors can influence individual differences in language development (e.g. Calvo & Bialystok, 2014; Thomas-Stonell, Oddson, Robertson, & Rosenbaum, 2009).

6.3 General considerations and limitations

There are some limitations to the current study that may have affected the outcomes. Our results may not be representative of the entire 22q11DS population, because some children in the matched data set were not included in the final analyses. On the one hand, excluding children who were not able to finish one or more of the tasks may have led to an overestimation of the average language score of the group of children with 22q11DS. On the other hand, it is also possible that the children with a mild phenotype are not included in the dataset because these children have not yet been diagnosed. Based on the previous two arguments, the distribution of the data may be different than expected in the 22q11DS group. However, this can also be the result of a floor effect, since the children cannot score lower than a certain norm score. The CELF Preschool is suited for the age range 3;0-6;11, however, some children with 22q11DS underperform a 3-year-old. Additionally, there were three children who had no CLS score at T1 but did succeed in all the CELF subtests at T2. These children could not be

included in the language development analyses, although they did improve themselves over the 6-month period. An additional aspect is that the eight children excluded from analyses at T1 are significantly younger than the children included in the analyses at T1. As a result, the age distribution over which we present our findings is smaller.

Previous studies show that deletion sizes can vary within this syndrome, and that children with a smaller chromosomal deletion have less cognitive impairments (Bartsch et al., 2003). This is a reason to include information about the size of the deletion in future studies. The only observation of an atypical small deletion in the current study (distal C-D) appears to be consistent with these previous findings. Another shortcoming of the study is that it was not possible to include IQ-scores. This is important to note since Solot and colleagues (2001) found, as described in section 2.4, that the development of receptive language may be related to intellectual abilities in this population. This is in line with observations from a study about the chromosomal 16p11 deletion (Hanson et al., 2015). In the study of Duijff and colleagues (2012), the decrease in IQ-score was only seen in a subset of the tested children, and in the current study, the decrease in CLS was seen in a (small) subset of the children – this may indicate that these two developmental trajectories coincide in this population. When information about the children's IQ-scores can be included in future research, it may provide more insight into the relationship between language (receptive and/or expressive) and intellectual functioning within the population of children with 22q11DS.

6.4 Implications of findings

Understanding cognitive trajectories is important for the care and support of children with 22q11DS and for further research purposes (Swillen, 2016). This certainly also applies to the language trajectories of these children. Knowledge about language development can offer a better perspective for the caregivers of children with 22q11DS, it can support speech-language pathologists in diagnosis and treatment and provides insight into what must be considered in future (language) studies. For example, it is valuable for a speech-language therapist to be able to recognize and treat a child with 22q11DS at any developmental stage (Solot et al., 2019). Results of the current study show that children with 22q11DS between 3;0 and 6;6 years old have a considerable language delay compared to

typically developing children. This pattern became evident for all sub language domains tested. The high percentage of clinically relevant scores stresses the importance of early screening and monitoring of the language ability of children with 22q11DS. Based on this study, it is also recommended to start early with speech-language therapy in children with 22q11DS.

Regarding language trajectories, the language delay in children with 22q11DS does on a group level not seem to increase or decrease in relation to typically developing children. However, the number of clinically relevant scores at T2 within the 22q11DS group has decreased compared to T1. This means that some children have caught up their language proficiency in the six-months period. Follow-up studies may reveal whether this improvement is related to, for example, receiving speech-language therapy. Based on this study, it can be speculated that it is important to focus on the expressive language skills of young children with 22q11DS, since this shows a slower development in the tested group of pre-schoolers (compared to receptive language skills).

7. Conclusion

The results of the current study contribute to a growing body of research on the language abilities of children with 22q11DS. Although this population is heterogeneous, the findings of this study show that pre-schoolers with 22q11DS have an overall lower language proficiency than their peers. However, they show on a group level a comparable developmental pace as typically developing children over a six-month period. This indicates that on average they do not ‘grow into their deficit’ or show an absolute decline when it comes to expressive and receptive vocabulary, sentence comprehension and morphosyntax. Next steps for future research are to further map the language trajectories with longitudinal studies and to delve more into the individual differences of this population. This is recommended because an increasing understanding of language development (and related fields) in children with 22q11DS contributes to improving treatment, care and individual follow-up, and will in turn also have an impact on the quality of life of this group of children.

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