More than words

The 22q11.2 deletion syndrome as a genetic model for understanding variability in neuropsychiatric symptoms of children with Developmental Language Disorder

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Meer dan Woorden
Het 22q11.2 deletiesyndroom als genetisch model om variatie in neuropsychiatrische symptomen bij kinderen met een taalontwikkelingsstoornis te begrijpen
(met een samenvatting in het Nederlands)

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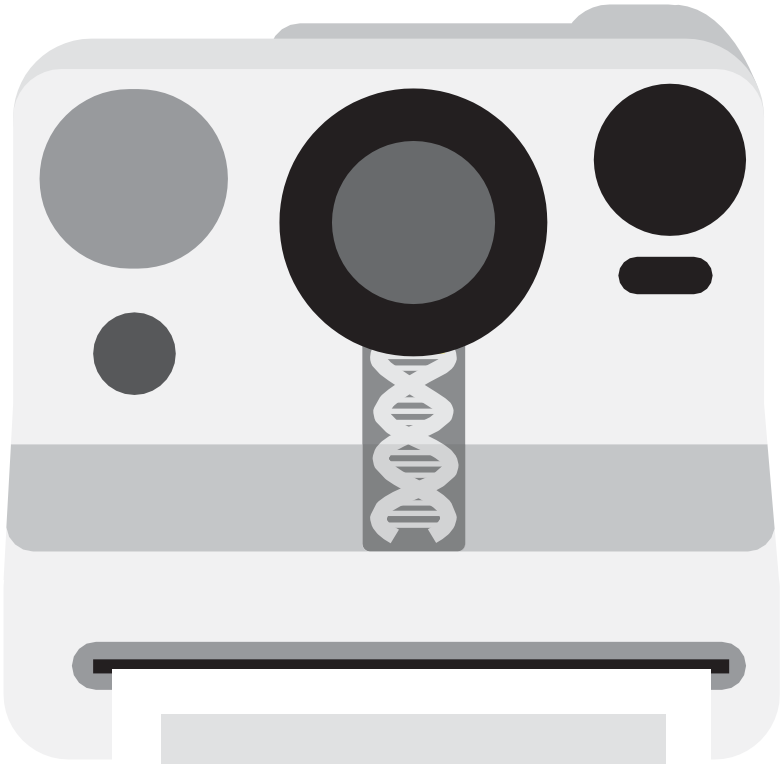

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General Introduction

General introduction

The acquisition of language is essential for developing children, because language is their primary tool to communicate with their caregivers, peers, and teachers, and is crucial for successful social and educational functioning (Bleses et al., 2016; Durkin et al., 2017). Primary language acquisition means that children learn the sounds of their native language, the meaning and the use of words and sentences in that language, and the rules to compose and combine those words and sentences. Moreover, using language encompasses implicit rules for communication and conversation. Language learning is therefore a complex task, but nevertheless, most children acquire their native language, or languages, effortlessly and successfully in the first years of life. This, however, does not hold for all children.

Approximately 3-7% of the children in the general population experience persistent language difficulties that cannot be explained by a known cause, and thereby meet diagnostic criteria of Developmental Language Disorder (Bishop, Snowling, Thompson, Greenhalgh, & and the CATALISE-2 consortium, 2017; Norbury et al., 2016). Previously, the term Specific Language Impairment (SLI) was used to refer to children who would presently be diagnosed with DLD. The adjective '*specific'* implied that impaired language development was considered to be an isolated symptom that occurred in absence of difficulties in other developmental domains. However, this terminology has been recently adapted (Bishop et al., 2017). It is now widely acknowledged that, whereas impaired language development is the primary clinical characteristic of DLD, subtle developmental difficulties in multiple developmental domains, other than language, are also associated with DLD. For example, such difficulties may include subtle deficits in nonverbal cognitive functioning (Gallinat & Spaulding, 2014; Kapa & Erikson, 2019) and below average development of motor skills (Blom & Boerma, 2019; Gallinat & Spaulding, 2014). In addition, DLD is associated with increased rates of neurodevelopmental and psychiatric symptoms, hereafter referred to as neuropsychiatric symptoms, that comprise behavioral problems and socio-emotional difficulties (Yew & O'Kearney, 2013).

Gaining insight in the occurrence of neuropsychiatric symptoms in DLD is highly relevant, because having neuropsychiatric symptoms negatively affects the wellbeing of children with DLD and their families, warranting timely and targeted intervention (Durkin et al., 2012). Not only is DLD characterized by an increased prevalence of neuropsychiatric symptoms; the extent to which children with DLD develop such symptoms is highly variable (Bishop et al., 2017; Toseeb et al., 2022). These individual differences pose a tremendous

challenge for current scientific research, as improving our understanding in this regard may have important implications for managing individual expectations, and designing prevention and (early) intervention.

Previously, it has been hypothesized that the variability in the severity and type of language difficulties is a factor that contributes to the observed inter-individual differences in the occurrence of neuropsychiatric symptoms in children with DLD (Bornstein et al., 2013; Im-Bolter & Cohen, 2007). However, studies reported mixed results regarding the strength of this association, with some studies not providing evidence for the existence of such an association (Maggio et al., 2014; Snowling et al., 2006). Consequently, it remains unclear to what extent an association exists between early language difficulties and co-occurring neuropsychiatric symptoms in DLD.

As will be further explained in this introduction chapter, it is proposed in this dissertation that the etiological heterogeneity that characterizes DLD, referring to the inter-individual variation in risk factors for DLD, contributes to the mixed results in the literature. Therefore, we hypothesize that studying a group of children who have a shared genetic etiology of their developmental language difficulties, may increase our ability to identify meaningful associations between language difficulties and co-occurring neuropsychiatric symptoms, if these exist. **The overall objective of this dissertation is to improve our understanding of the inter-individual differences in the occurrence of neuropsychiatric symptoms in children with DLD. The central approach that is examined in this dissertation is the comparison of children with DLD to a such an etiologically homogeneous group: children with the 22q11.2 deletion syndrome** (22q11DS; McDonald-McGinn et al., 2015). If associations between language difficulties and co-occurring neuropsychiatric symptoms exist, it is expected that the decreased etiological heterogeneity in 22q11DS will allow to uncover such associations.

What is Developmental Language Disorder (DLD)?

With a prevalence rate of 3-7% in the general population, the prevalence of DLD is relatively high compared to that of other neurodevelopmental or neuropsychiatric disorders (*see table 1 for prevalence rates of neuropsychiatric conditions in the general population*). The diagnostic criteria for DLD are described in an expert consensus document (Bishop et al., 2017), and correspond to the classification 'language disorder' in the Diagnostic and Statistical Manual for Mental Disorders (DSM-5: 315.32, F80.2; American Psychiatric Association, 2013), as well as to the classification 'developmental language disorder' in the International Classification of Diseases (ICD-11;

6A01.2; World Health Organization, 2019). The first criterion for DLD is that a child needs to have developmental language difficulties that are persistent and interfere with their daily life functioning. In addition, the diagnostic criteria of DLD stipulate that language problems of children with DLD cannot be explained by a known cause, such as a physical condition, hearing loss, intellectual disability or lack of environmental exposure to language.

Etiological heterogeneity

Despite the fact that the cause of DLD in an individual child is per definition unknown, on a group-level, a large variety of genetic and environmental risk factors for DLD have been identified, such as male sex, difficulties at birth as indicated by a low Apgar score 5 minutes after delivery, a younger maternal age, low maternal education level and a younger position in the birth order (Diepeveen et al., 2017; Harrison & McLeod, 2010; Rudolph, 2017; Whitehouse et al., 2014). The exact individual combination and interaction of factors that causes DLD varies from child to child, which means that DLD is characterized by large etiological heterogeneity.

Language in DLD

Language is a multi-faceted construct, that comprises different domains, for instance phonology (*sounds and sound structure*), morphology and syntax (*grammatical skills*), semantics (*meaning of words*) and pragmatics (*knowledge of language use*). The large majority of children with DLD has difficulties with appropriate use of the grammatical rules of their language, which is therefore seen as a hallmark feature of the disorder. That is, children with DLD often have weak development in the language domains morphology and syntax, most prominently with correctly inflecting verbs (Leonard, 2014). Although vocabulary is sometimes reported as a relative strength, children with DLD also tend to have a smaller lexicon than their typically developing peers (Rice & Hoffman, 2015). Moreover, given that the development of pragmatic language abilities relies on the development of language skills in other domains, it is not surprising that many children with DLD also experience difficulties with pragmatic language (Matthews et al., 2018). The development of narrative skills, i.e., telling and understanding stories, is often used to measure pragmatic language skills (Botting, 2002; Fey et al., 2004) . Many children with DLD produce narratives with lower grammatical complexity and with lower informative content (Blom & Boerma, 2016; Zwitserlood et al., 2015), and their ability to understand the narratives of others is also weaker than that of their typically developing peers (Blom & Boerma, 2016).

Of note, the diagnostic criteria for DLD do not specify to which extent children need to present with difficulties in certain language domains or modalities (e.g.,language production and comprehension). Consequently, despite having the same clinical diagnosis, children with DLD may vary from each other in the type and severity of their language difficulties. This variability is for example illustrated by the observation that around 50% of the children with DLD present mainly with problems in expressive language (i.e. language production), with relatively stronger receptive language abilities, while others have severe problems in both expressive and receptive language (i.e. language comprehension; Boyle et al., 2009; Leonard, 2014; Tomblin et al., 1997). In practice, DLD is to be considered an umbrella term describing children with different constellations of language difficulties (i.e. language phenotype Calder et al., 2022; Lancaster & Camarata, 2019).

Neuropsychiatric symptoms in DLD

Compared to children in the general population, children with DLD have an increased risk to also develop co-occurring neuropsychiatric disorders (see table 1). Each of these disorders is conceptualized as a different diagnostic category that comprises a set of different neuropsychiatric symptoms (Kraemer, 2007). These symptoms include externalizing behaviors (e.g., inattention/aggression), internalizing behaviors (e.g., withdrawn/anxious) as well as socio-emotional difficulties (e.g.,Yew & O'Kearney, 2013). In addition to the language problems related to DLD, having co-occurring neuropsychiatric symptoms may severely interfere with the daily functioning of a child with DLD, and may negatively affect academic or occupational outcomes (Bishop et al., 2017; Durkin et al., 2012). Similar to the language phenotype, the extent to which children with DLD develop neuropsychiatric symptoms is highly variable, as indicated by the varying prevalence rates of the different neuropsychiatric disorders. This highlights the need to improve our understanding of the factors that contribute to the inter-individual differences in development of neuropsychiatric symptoms in DLD, as this could enhance our ability to identify those children with DLD who have the highest risk to develop such problems, and therefore potentially most benefit from targeted intervention (Toseeb et al., 2022).

Table 1. *Overview of Prevalence Rates of Different Neuropsychiatric Disorders in Children in the General Population, Children with DLD, and Children with 22q11DS*

Neuropsychiatric Disorder	General Population	DLD	22q11DS
ADHD	5%	14-50%	~30%
ASD	1.85%	4-11%	~30%
Anxiety disorder	3-15%	26%	~30%
Depression**	7.5%	13%	20%
Schizophrenia**	~0.75%	3.8%	25%

Abbreviations. ADHD = attention deficit hyperactivity disorder. ASD = Autism Spectrum Disorder
**adolescence (depression) & adulthood (schizophrenia)
References. **General Population -** ADHD: (Posner et al., 2020)| ASD: (Redfield et al., 2014) | Anxiety: (Beesdo-Baum & Knappe, 2012) | Depression: (Avenevoli et al., 2015) | Schizophrenia: (Moreno-Küstner et al., 2019).
DLD - ADHD: (Mueller & Tomblin, 2012) | ASD: (Conti-Ramsden et al., 2006; Mouridsen & Hauschild, 2009) | Anxiety & depression: (Beitchman et al., 2001) | Schizophrenia: (Mouridsen & Hauschild, 2008).
22q11DS - (Schneider et al., 2014).

The association between language and neuropsychiatric symptoms in DLD

Several explanations have been proposed for the increased prevalence of neuropsychiatric symptoms in children with DLD. Firstly, it has been suggested that having language difficulties may (in and of itself) pose a child at risk for the development of neuropsychiatric symptoms (Bornstein et al., 2013; Im-Bolter & Cohen, 2007; Salmon et al., 2016). A frequently used example is that children who are less able to express their thoughts and wishes verbally, are more likely to use aggressive behavior to gain control in social situations (Bornstein et al., 2013). Another example is that language problems may cause problematic behavior in the school context, because children with low language comprehension are more likely to have difficulties in sustaining their attention, withdraw from doing their tasks, or show oppositional behavior (Chow & Wehby, 2018; Im-Bolter & Cohen, 2007). It could thus potentially be of clinical relevance to identify whether certain characteristics in the early language profile of children with DLD might support the identification of those children who are most at risk for developing neuropsychiatric symptoms. As such, it has been recommended to investigate to what extent different aspects of language in DLD (e.g., receptive/expressive) are associated with the development of different types of co-occurring neuropsychiatric symptoms (Chow & Wehby, 2018; Conti-Ramsden et al., 2013).

To date, studies addressing this issue provided mixed results. Some studies found the association between language difficulties and co-occurring neuropsychiatric symptoms to be significant (Conti-Ramsden et al., 2013;

Snowling et al., 2006; Toseeb et al., 2022), whereas others did not (Conti-Ramsden et al., 2006; Leyfer et al., 2008; Lindsay & Dockrell, 2012; Maggio et al., 2014). Furthermore, the results of the studies that did observe a significant association between language difficulties and neuropsychiatric symptoms in DLD pointed in different directions. Having weaker receptive language skills was found to be associated with increased levels of internalizing problems (Toseeb et al., 2022) and having expressive language difficulties was reported to be related to increased rates of externalizing problems and hyperactivity (Conti-Ramsden et al., 2013; Snowling et al., 2006). Some other studies concluded that language deficits did not differently affect development of either externalizing, internalizing or social problem behaviors (Chow & Wehby, 2018; Curtis et al., 2018; Snowling et al., 2006). Taken together, while the co-occurrence between language difficulties and neuropsychiatric symptoms is clearly established in DLD, it remains unclear to what extent the variable occurrence of neuropsychiatric symptoms in DLD is a consequence of inter-individual variation in severity and type of language difficulties that exists in this population.

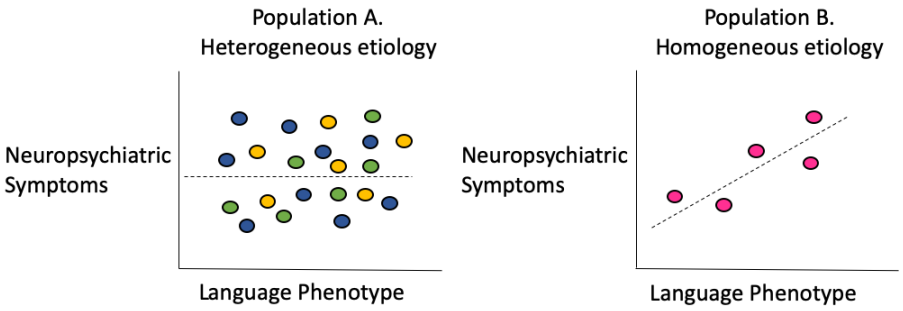
In addition to proposing that language difficulties are indirectly associated with the occurrence of neuropsychiatric symptoms in DLD, an alternative explanation for the association of neuropsychiatric symptoms and language difficulties in DLD, is that both are consequences of a shared underlying cause. Some of the genetic risk factors for DLD could affect brain development in such a way, that a child is posed at risk for having both language difficulties and neuropsychiatric symptoms, and that the two unfold in tandem over the course of development (Mountford et al., 2022). Consequently, it is highly probable that the etiological heterogeneity that characterizes DLD may at least in part explain the diverging results of previous studies regarding the association between language difficulties and co-occurring neuropsychiatric symptoms. That is, it may be that the development of co-occurring neuropsychiatric symptoms in DLD varies as a function of the etiology underpinning DLD. Additionally, different etiologies of DLD may differently impact the association between language abilities and co-occurring neuropsychiatric symptoms in DLD. If this is the case, the presence and the strength of this association would vary considerably within the population of children with DLD (see figure 1). As a consequence, this would hamper our ability to statistically detect an association between language difficulties and the occurrence of neuropsychiatric symptoms in the population of children with DLD as a whole.

Against this background, we propose that it may be more effective to investigate such associations, if these exist, in a population of children with developmental language difficulties that is etiologically homogeneous (Bathelt et al., 2016; Newbury et al., 2021; see figure 1). Such an etiology could be a shared genetic origin, as advances in genetic technology have led to the identification of several genetic factors that play a role in language disorders (Barnett & van Bon, 2015). Of particular interest here are Copy Number Variants (CNV) that are associated with child language disorders (Barnett & van Bon, 2015; Mountford et al., 2022). A CNV refers to a deletion or duplication of genetic material on a specific region of a child's genome, often encompassing more than one gene (Sønderby et al., 2021). Some of the CNVs are pathogenic, meaning that they are disease-causing, and a subset of these pathogenic CNVs is associated with a range of cognitive and psychiatric problems, including both developmental language difficulties and a high incidence of psychiatric disorders (Mountford et al., 2022; Sønderby et al., 2021). A prime example of such a genetic syndrome resulting from a pathogenic CNV that is associated with early language difficulties, is the 22q11.2 deletion syndrome (22q11DS).

What is the 22q11.2 Deletion Syndrome?

The 22q11.2 deletion syndrome (22q11DS; OMIM #188400, #192430) is one of the most common chromosomal micro-deletion syndromes, and is identified in every 1 in 2000-4000 live births (Blagojevic et al., 2021). In around 90% of the identified patients with 22q11DS, the condition is de novo, which indicates that the deletion is not inherited (McDonald-McGinn et al., 2015a). 22q11DS is caused by a missing region of DNA on the long arm (q) at locus 11.2 on chromosome 22, hence the name 22q11.2 deletion syndrome. Most typically, 22q11DS is associated with a 3MB range of missing genetic information, comprising the four low copy repeat regions A-D (LCR22-A, LCR22-B, LCR22-C and LRC22-D). In addition, cases with nested deletions (e.g., deleted regions from B-D) have also been identified (McDonald-McGinn et al., 2015a; Morrow et al., 2018).

Figure 1. *Illustration to what extent the study of a population with a homogeneous etiology, rather than an etiologically heterogeneous population, may facilitate detecting associations between language difficulties and neuropsychiatric symptoms.*



Explanation. Each dot represents an individual child; the different colors of the dots each represent a different etiology. The dotted lines represent a hypothetical association between language difficulties and neuropsychiatric symptoms.
Left panel: In an etiologically heterogeneous population (population A; e.g., DLD), it is difficult to detect a statistically significant association between the language phenotype and neuropsychiatric symptoms, because this association may be absent in some individuals and vary in strength in other individuals, who all have different etiologies.
Right panel: in a population with a homogeneous etiology (Population B; e.g., 22q11DS), the association between language difficulties and co-occurring neuropsychiatric symptoms is likely less variable, and can therefore be more readily detected. In this example, the positive association in the etiologically homogeneous population is identical to the association that can be observed in a subset of individuals in the etiologically heterogeneous population (the green dots).

The 22q11DS has also been called Di-George syndrome, Sphrintzen syndrome, or Velo-Cardio-Facial-Syndrome (VCFS), especially before the exact genetic cause was known. These early names refer to the different clusters of common physical manifestations that we now know are associated with the same deletion of 22q11.2, including palatal abnormalities and velopharyngeal insufficiency (VPI), congenital heart defect, hypocalcaemia, immune deficits and subtle dysmorphic facial features (McDonald-McGinn et al., 2015a). 22q11DS is associated with a heterogeneous clinical presentation of these and other features. For instance, 75% of individuals have congenital heart defects, but 25% do not. Likewise, it has been reported that around 50% of children with 22q11DS develop scoliosis, making this another physical feature that is common in 22q11DS (Homans et al., 2018).

Several genes encoded in the deleted region are expressed in the brain (Jonas et al., 2014), and therefore 22q11DS has profound effects on the development of brain structures, functions and connectivity (Zinkstok et al., 2019). Consequently, 22q11DS is associated with cognitive and behavioral symptoms resulting from these alterations in brain development (Sønderby et al., 2021). These may include a range of deficiencies in cognitive functions, such as attention, working memory or inhibition (see Everaert et al., 2021 for an overview). Furthermore, on average, an Intelligence Quotient (IQ) of 70 points is reported in 22q11DS, indicating that mild intellectual impairment is common in individuals with 22q11DS. However, the range of IQ scores is normally distributed in this population, meaning that individuals with 22q11DS may present with severe intellectual impairment but also with a level of intellectual functioning in the average range (Fiksinski et al., 2022).

Language in 22q11DS

Speech-language problems are reported in around 95% of children with 22q11DS (Solot et al., 2019a), making this one of the most prevalent clinical symptoms. Speech problems associated with 22q11DS include articulation problems, hypernasality and motor speech disorders (Baylis & Shriberg, 2019; Solot et al., 2019a). Difficulties in the development of language skills are often noted at an early age, as the onset of the first words and sentences in the majority of children with 22q11DS is delayed (Roizen et al., 2007; Scherer et al., 1999). Generally, although receptive language is also impaired, difficulties with expressive language specifically stand out in preschool-aged children with 22q11DS (Gerdes et al., 1999; Solot et al., 2001). Language skills of school-aged children with 22q11DS (6-12yo) have been described in more detail than those of younger children. School-aged children with 22q11DS frequently experience difficulties in both language modalities and in different language domains, including sentence comprehension and expressive syntax. In contrast to what has been reported for younger children with 22q11DS, it appears that receptive language is on average more impaired than expressive language (Solot et al., 2019a; Van Den Heuvel et al., 2018). Of note, even if children with 22q11DS present with severely impaired language skills, they formally do not meet diagnostic criteria for DLD, as their language difficulties occur in the context of a known etiology.

Neuropsychiatric symptoms in 22q11DS

22q11DS is associated with increased rates of a variety of neuropsychiatric disorders, including ADHD, ASD and anxiety in childhood, and depression and

psychosis spectrum disorders in adolescence and early adulthood (see table 1 for a summary of the prevalence rates). In addition, the prevalence of disruptive behavioral disorders and substance abuse are relatively low in 22q11DS (Fiksinski et al., 2018a; Vingerhoets et al., 2019). Thus, despite a shared genetic risk factor (i.e., the 22q11 deletion), 22q11DS is characterized by a variable presentation both with regard to the nature and the severity of neuropsychiatric symptoms. This implies that factors other than the 22q11 deletion contribute to the inter-individual differences in the expression of neuropsychiatric symptoms in this population. Currently our knowledge of these factors is limited, including the impact of early language difficulties, whereas such knowledge may have important implications to design and implement clinical care for individuals with 22q11DS.

22q11DS as genetic model for DLD

The genetic risk for developing neuropsychiatric symptoms that is shared by all individuals with 22q11DS, provides a unique opportunity to study the factors that impact the pathway from genetic susceptibility to clinical expression of neuropsychiatric symptoms (Fiksinski et al., 2021; Zinkstok et al., 2019). This thus also includes the association between language and co-occurring neuropsychiatric symptoms that is the focus of this dissertation. Moreover, it has been suggested that 22q11DS could function as a genetic model that may contribute to a better understanding of the factors and mechanisms that play a role in the development of idiopathic conditions, including scoliosis and psychosis spectrum disorders (de Reuver et al., 2021; Sanders et al., 2019; Zinkstok et al., 2019). To illustrate, it was demonstrated that both a lower level of intellectual functioning and a decline in verbal intellectual functioning were associated with an increased risk to develop psychosis in individuals with 22q11DS (Vorstman, et al., 2015). This strengthened the hypothesis that these factors are also associated with development of schizophrenia in the general population (e.g.,Kahn, 2020). Against this background, here it is be proposed that studying the association between early language difficulties and neuropsychiatric symptoms in 22q11DS may be relevant to our understanding of this association in not only children with 22q11DS, but also in children with DLD.

The present dissertation

To date, it remains uncertain to what extent the inter-individual variation in language difficulties in DLD contributes to the highly variable development of co-occurring neuropsychiatric symptoms in this population. To enhance our

ability to detect meaningful associations between language difficulties and the occurrence of neuropsychiatric symptoms, this dissertation studies these associations in children with 22q11.2 deletion syndrome, who have a shared genetic cause and who also experience language difficulties. It will be investigated to what extent 22q11DS may serve as a genetic model to increase our understanding of the inter-individual differences in neuropsychiatric symptoms in DLD.

Aim 1

A requirement for 22q11DS to function as a genetic model, is that the condition of interest has similar clinical signs and symptoms as well as underlying neurocognitive deficiencies in 22q11DS as compared to this condition in the general population (Bassett & Chow, n.d.; de Reuver et al., 2021). Given the scientific evidence reviewed in this chapter, and as indicated by previous studies (e.g.,Goorhuis-Brouwer et al., 2003; Kambanaros & Grohmann, 2017; Solot et al., 2000), 22q11DS appears to share important clinical features with DLD. However, there are gaps in previous descriptions of 22q11DS that hamper a thorough comparison between these two groups. Therefore, the first aim of this study is to address these research gaps. Below, the most important gaps with respect to the neuropsychiatric symptoms and language difficulties in 22q11DS are briefly reviewed.

Neuropsychiatric symptoms. To date, the profile of neuropsychiatric symptoms associated with 22q11DS has been described using the prevalence rates of different diagnostic classifications, each representing a different neurodevelopmental disorder (see table 2). However, to capture the full spectrum of inter-individual variation in the severity and the type of neuropsychiatric symptoms associated with 22q11DS, descriptions on a symptom level are warranted. Such descriptions are expected to contribute to improving clinical care for this population and would spur further studies aiming to detect the mechanisms that can explain inter-individual variation in neuropsychiatric symptoms among individuals with 22q11DS. Moreover, descriptions of neuropsychiatric symptoms in 22q11DS on a symptom level would allow for a more detailed comparison of 22q11DS to other clinical groups, such as DLD (Jacquemont et al., 2022).

Language phenotype. Reports describing the severity of the language impairment of preschool-aged children with 22q11DS, specifically those including inter-individual differences in the degree of impairment on different

language domains, are currently lacking. The majority of children with 22q11DS has complex speech disorders, which negatively impact their speech production ability (Solot et al., 2019a). Thus, an open question is to what extent the difficulties in expressive language at this young age might be explained by the fact that so many young children with 22q11DS have difficulties producing (intelligible) speech (Gerdes et al., 1999; Solot et al., 2001).

In school-aged children with 22q11DS, the development of narrative language abilities has received limited attention. As these are an important component of pragmatic language skills, altered development of narrative skills may particularly impact a child's daily life functioning (Matthews et al., 2018). To our knowledge, only two studies have directly assessed the narrative skills of school-aged children with 22q11DS (Persson et al., 2006; Van Den Heuvel et al., 2017b). These studies showed that children with 22q11DS had more difficulty with producing grammatically correct sentences, as well as with transferring essential information in their stories as compared to their typically developing peers. Narrative comprehension of children with 22q11DS has not received much attention in previous research. Together, these findings highlight the need for a more detailed report of standardized language outcomes in preschool-aged children with 22q11DS, including the association between speech and language, as well as a description of narrative skills in school-aged children with 22q11DS. Finally, such descriptions of 22q11DS enable a comparison between the strengths and weaknesses in the language profile of children with 22q11DS and children with DLD.

Aim 1. Address knowledge gaps regarding the profile of neuropsychiatric symptoms and language difficulties in 22q11DS.

Aim 2

Previous studies directly comparing 22q11DS to DLD are scarce, which limits the ability to determine the differences and similarities between DLD and 22q11DS. As mentioned previously, a better view on similarities and differences between both groups, both on a behavioral and a neurocognitive level, is highly relevant to gain insight into the extent to which 22q11DS could function as a genetic model to understand DLD. The second aim of the current dissertation aims to address this gap.

To our knowledge, there are only two studies directly comparing children with 22q11DS to children with DLD. The first is a single case study,

comparing a broad range of language skills of a boy with 22q11DS, measured at ages 6 and 10 years, to age-matched peers with DLD (Kambanaros & Grohmann, 2017). On two aspects of language that were measured, one at age 6 and the other at age 10, significant differences between the boy with 22q11DS and the children with DLD were observed. However, the vast majority of the language tasks did not differentiate the boy with 22q11DS from the children with DLD, neither at age 6 nor at age 10. The second study has directly compared neuropsychiatric symptoms between 31 preschool-aged children with 22q11DS and 24 peers with a
language disorder in the context of mild intellectual impairment (Swillen et al., 2001). The severity of neuropsychiatric symptoms was largely similar between these two groups of children, although teachers reported relatively more oppositional behavior in DLD and relatively more withdrawn behavior in 22q11DS. In addition to these two studies, other research has hinted at overlapping features of 22q11DS and DLD without explicitly testing them, for instance with regards to the severity of language impairment (Solot et al., 2000), the weakness in production of narratives (Persson et al., 2006) and the weaker language skills than what would be expected for the level of intellectual functioning (Goorhuis-Brouwer et al., 2003). Together, this work tentatively suggests that 22q11DS could function as a genetic model for DLD, given the suggested overlapping behavioral features. However, direct comparisons of larger samples of children with 22q11DS and children with DLD are required to gain insight into the behavioral similarities and differences between these groups.

In addition, as mentioned previously, both the genetic factors associated with DLD, as well as the 22q deletion, have an impact on prenatal brain development. Thus, for 22q11DS to function as a genetic model for DLD, it is relevant to gain insight in the extent to which these different genetic factors similarly influence the functioning of the neural language network. Alterations in both structure and function of language-related brain areas have been previously observed in DLD (Badcock et al., 2012; Mayes et al., 2015). However, language-related brain functioning has not been subject of study in children with 22q11DS. Thus, next to direct comparisons on the behavioral level, such comparisons are also necessary at the level of neural processing.

Aim 2. Compare 22q11DS to DLD on the level of behavioral manifestations and neural language processing, using both existing literature as well as results from studies in this dissertation.

Aim 3

The third aim of the current dissertation is to investigate the association between language skills and neuropsychiatric symptoms in children with 22q11DS and children with DLD. This final step is necessary because without such insight, it is impossible to know if 22q11DS could function as a genetic model to understand inter-individual differences in neuropsychiatric symptoms in DLD. In 22q11DS, weaker language skills in childhood have been associated with the occurrence of psychosis spectrum symptoms in adolescence (Solot et al., 2020). As of yet, the association between language and neuropsychiatric symptoms in 22q11DS has not been further explored. Further investigation of this association, including a comparison to DLD, is needed to determine to what extent the genetic homogeneity of 22q11DS allows to statistically detect such associations, while the heterogeneity in DLD may hinder our ability to do so.

Aim 3. Compare the strength of the association between language skills and neuropsychiatric symptoms between children with 22q11DS and DLD.

Data

To address these three research aims, we have initiated two studies, being: (1) the 3T-study and (2) the EPISODE-study. Furthermore, we have used data from two cohorts of children that participated in other, partly related research projects. These were (3) the CoDEmBI-study and (4) the 22q11DS psychiatry cohort study. The boxes below shortly introduce each of these studies.

(1) The 3T study

Research Aims: 1) to investigate the language development of children with 22q11DS in comparison to children with DLD. 2) To study the associations between language development, cognitive development and neuropsychiatric symptoms in these populations.

Design:	Longitudinal cohort study
Participants:	22q11DS (n=44); DLD (n=65); Typically Developing (n=81)
Age range:	3,5-6 years at inclusion
Measures used in this dissertation:	Language, neuropsychiatric symptoms, intellectual functioning

(2) EPISODE-study
Research Aims: 1) to investigate neurophysiological functioning during spoken language processing in children with 22q11DS and children with DLD. 2) To investigate narrative abilities of children with 22q11DS and children with DLD.

Design:	Cross-sectional study
Participants:	22q11DS (n=14); DLD (n=14); chronologically age-matched typically developing (n=25).
Age range:	chronological age 6-10 years
Measures used in this dissertation:	Functional MRI, language

(3) the CoDEmBI-study
Original research aim: to investigate language and cognitive development in cultural minority children in the Netherlands

Design:	Longitudinal cohort study
Participants:	bilingual children with (n=33) and without DLD (n=74); monolingual children with (n=96) and without DLD (n=45).
Age range:	chronological age 5-6 years at inclusion
Measures used in this dissertation:	Narrative abilities of monolingual children without DLD

(4) the 22q11DS psychiatry cohort study
Original research Aim: to describe and understand psychiatric and cognitive outcomes in adolescents and young adults with 22q11DS

Design:	Clinical cohort study – this study is still ongoing
Participants:	22q11DS (n=208)
Age range:	11-25 years
Measures used in this dissertation	Neuropsychiatric symptoms, intellectual functioning

Chapter outline

In chapter 2, data from the psychiatry cohort study is used to address the current knowledge gaps regarding the occurrence of neuropsychiatric symptoms in individuals with 22q11DS (Research Aim 1). Complementary to descriptions in terms of diagnostic categories, this chapter gives a

comprehensive overview of the expression of neuropsychiatric symptoms in a large sample of adolescents with 22q11DS, using a dimensional perspective.

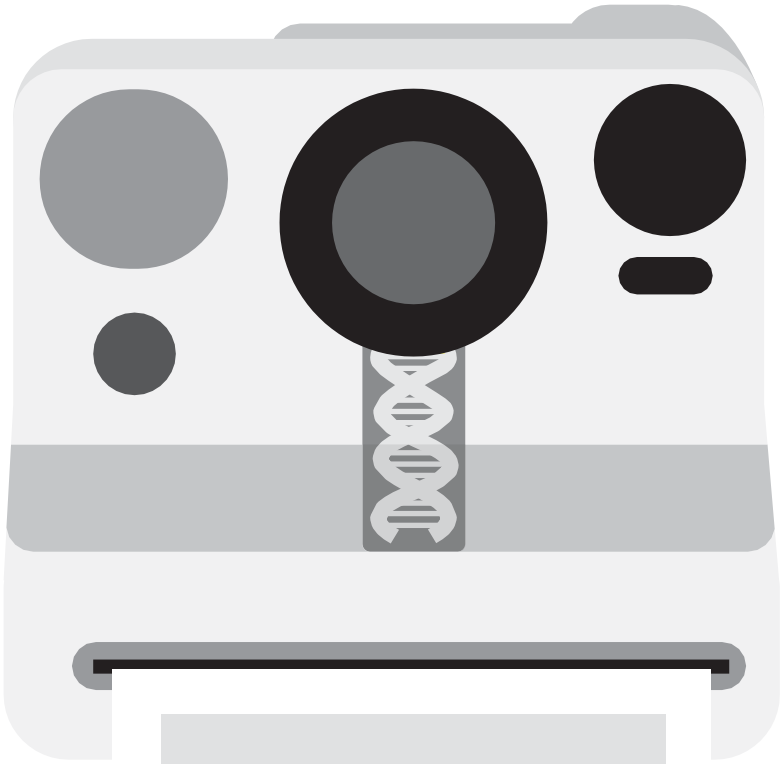
In chapter 3, data from the 3T-study is used to address the current knowledge gaps regarding the profile of language difficulties that is associated with 22q11DS (Research Aim 1). This chapter provides a detailed report on the language skills of preschool-aged children with 22q11DS, including the degree of inter-individual variation in children's development in different language domains and modalities. In addition, this chapter reports on the association between language abilities of preschool-aged children with 22q11DS and their speech intelligibility.

*In chapter 4, data from the EPISODE-study and the CoDEmBI-study were used to address Research Aim 1, and to draw a direct comparison between 22q11DS and DLD (Research Aim 2). This chapter d*irectly compares the ability to produce and comprehend narratives in three groups of children: children with 22q11DS children with DLD and typically developing children who were matched on mental age. Not only does this add information on a linguistic domain that did not receive much attention in 22q11DS, it also allowed to study to what extent narrative abilities in 22q11DS are associated with their level of intellectual functioning.

In chapter 5, data from the EPISODE project was used to address Research Aim 2. This chapter reports on the level of brain activation during spoken language processing in children with 22q11DS, age-matched children with DLD and age-matched typically developing children.

In chapter 6, data from the 3T project was used to compare the strength of the association between language skills and neuropsychiatric symptoms between children with 22q11DS and DLD (Research Aim 3). In this chapter the association between language difficulties and the occurrence of behavioral symptoms associated with Autism Spectrum Disorder (ASD) is studied. The strength of this association is compared between children with 22q11DS and children with DLD, and with a group of typically developing age-matched peers (TD). This allows to directly address the question, whether studying a homogeneous subgroup (22q11DS) enables to expose a relationship that is not, or only weakly, detected in a heterogeneous group (DLD).

Chapter 7 provides a summary of our findings. In addition, the scientific and clinical implications and directions for future research will be discussed. This chapter ends with a general conclusion of this dissertation.



2

A Comprehensive Overview of Neuropsychiatric Symptoms in Adolescents with 22q11.2 Deletion Syndrome: A Dimensional Approach

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Background. The 22q11.2 deletion syndrome (22q11DS) is associated with a variety of neuropsychiatric outcomes, including neuropsychiatric disorders, that vary across deletion carriers. In-depth descriptions of neuropsychiatric symptoms in 22q11DS are crucial to further our understanding of the mechanisms that can explain such phenotypical heterogeneity. In addition to diagnostic classifications, we adopt a dimensional approach to provide a comprehensive overview of neuropsychiatric symptom expression in adolescents with 22q11DS. **Methods**. Participants were 208 adolescents (59% female) with 22q11DS, between 10-19 years old (M=13.6, SD=1.9). Participants' scores on semi-structured clinical interviews (DSM-IV interview, ADI-R, K-SADS) and IQ-tests were used to quantify symptom expression on multiple symptom dimensions, some reflecting DSM-IV diagnostic classifications. We compared the distribution of neuropsychiatric symptoms between and within symptom dimensions. We investigated symptom expression of individuals without a formal DSM-IV diagnosis. We used correlation analyses to explore associations between different symptom dimensions. **Results.** We demonstrated inter-individual differences in symptom expression, both between and within neuropsychiatric symptom dimensions. On most symptom dimensions, more than 50% of adolescents expressed at least one clinically relevant symptom; a significant proportion of youth without a formal DSM-IV diagnosis reported clinically relevant symptoms in the corresponding domain (e.g., >85% of those without an ADHD diagnosis reported ADHD symptoms). The exploratory correlation analysis indicated mostly positive correlations between minor symptom dimensions. **Conclusions.** The finding that most adolescents with 22q11DS express neuropsychiatric symptoms, even in the absence of a DSM-IV classification, has substantial ramifications for guiding adequate support. Future studies adopting a dimensional perspective are recommended to elucidate the mechanisms that contribute to symptom expression in 22q11DS. Ultimately, a better understanding of such mechanisms may be relevant not only to improve clinical care for 22q11DS, but also to understand phenotypical variation in other high-risk genetic variants or the general population.

Introduction

The 22q11.2 deletion syndrome (22q11DS; OMIM #188400, #192430) is a genetic syndrome, caused by a hemizygous microdeletion of 0.7-3 million base pairs on chromosome 22. Among a rapidly growing list of genetic variants associated with high-risk for the expression of neurodevelopmental or psychiatric disorders, 22q11DS is relatively common, with an estimated prevalence of 1 in 2,000-4,000 live births (Blagojevic et al., 2021). Additionally, 22q11DS is genetically well-described, and increasingly, the genetic diagnosis is made early in life. Together, this makes 22q11DS a promising model to understand the mechanisms that may contribute to the development of idiopathic conditions, but also to explain phenotypical variability, both in other rare genetic variants and in the general population (Fiksinski et al., 2023; Insel, 2010; Zinkstok et al., 2019).

Despite sharing the same genetic risk factor, individual presentations of 22q11DS are characterized by a high degree of heterogeneity of clinical manifestations, including a range of physical symptoms, such as congenital cardiac and palatal abnormalities (McDonald-McGinn., 2015), none of which is present in every individual with 22q11DS. The same clinical heterogeneity is observed for the expression of neurodevelopmental and psychiatric symptoms, hereafter referred to as neuropsychiatric symptoms, that comprise varying degrees of intellectual impairment and various psychiatric disorders (Fiksinski et al., 2018; Schneider et al., 2014). Despite recent progress (e.g.,Davies et al., 2020), our understanding of factors contributing to the diversity and variable penetrance of neuropsychiatric symptoms in 22q11DS remains limited. This poses a significant challenge for clinical practice, in particular regarding the management of individual expectations and planning (early) treatment strategies (Fiksinski et al., 2021). A better understanding of the underlying mechanisms driving neuropsychiatric symptom expression in 22q11DS is needed to further both research and clinical practice. To achieve this objective, obtaining a more a fine-grained phenotypic description of neuropsychiatric symptoms in 22q11DS is essential (Jacquemont et al., 2022; Michelini et al., 2021).

In the current literature, the neuropsychiatric symptoms associated with 22q11DS have been predominantly described from a categorical perspective (e.g., Schneider et al., 2014). This approach relies on diagnostic categories, each representing a separate psychiatric disorder, to classify patterns of neuropsychiatric symptoms (Borsboom et al., 2016; Kraemer, 2007; Potuzak et al., 2012). Studies reporting the prevalence rates of diagnostic categories in 22q11DS, indicate that Autism Spectrum Disorder (ASD),

Attention Deficit Hyperactivity Disorder (ADHD) and anxiety disorders are relatively prevalent in childhood, each affecting around 30% of the children with 22q11DS. Mood and psychosis spectrum disorders increase over the course of adolescence; around 25% of the individuals with 22q11DS will have a psychotic disorder in (young) adulthood (Fiksinski et al., 2018; Jhawar et al., 2021; Schneider et al., 2014). The prevalence rates of conduct behavior and substance abuse are relatively low in individuals with 22q11DS (Fiksinski et al., 2018; Vingerhoets et al., 2019). Taken together, these categorical descriptions indicate that the 22q11.2 deletion is associated with a heterogeneous presentation of neuropsychiatric disorders, increasing the risk for some, but not all.

Despite shedding light on inter-individual variability, such categorical descriptions may not fully capture the variation in neuropsychiatric symptom expression that may exist among individuals with 22q11DS. Firstly, a categorical approach classifies individuals in binary categories (i.e., an individual does or does not have a neuropsychiatric disorder), whereas multiple studies show that symptoms within many diagnostic categories are continuously distributed in the general population (Haslam et al., 2020 for a meta-analysis; Lilienfeld & Treadway, 2016). In addition, this categorical approach does not capture possible variation in the degree of expression of different core symptoms within each diagnostic category (Borsboom et al., 2016; Lilienfeld & Treadway, 2016). Consequently, an exclusively categorical approach falls short in describing the type and severity of symptoms that are most frequently expressed in 22q11DS, and may overlook potentially relevant symptoms in those individuals without a clinical diagnosis (Baker & Vorstman, 2012).

To address these issues, a dimensional approach has gained increased interest, complementing the categorical approach, to describe neuropsychiatric symptoms in the general population (Michelini et al., 2021; Sanislow et al., 2010), as well as in 22q11DS (Fiksinski et al., 2021; Niarchou et al., 2017). Here, neuropsychiatric symptoms are considered quantitative traits, or symptom dimensions, on which individuals vary in terms of severity (Kraemer, 2007). Most commonly, the range of intellectual impairment is described both categorically and dimensionally in 22q11DS. The former approach has demonstrated that, on average 45% of the adults with 22q11DS has an intellectual disability (as indicated by Intelligence Quotient (IQ) < 70). The latter approach demonstrated that IQ-scores in 22q11DS are normally distributed around a mean of 70 points (Swillen et al., 2018) . As this example demonstrates, a dimensional approach allows to provide a more detailed

description of the 22q11DS associated symptom profile (Baker & Vorstman, 2012; Chawner et al., 2021; Niarchou et al., 2015, 2017). To further our insight into the neuropsychiatric phenotype associated with 22q11DS, here we aim to provide an overview of neuropsychiatric symptoms in 22q11DS from a dimensional perspective, including multiple major neuropsychiatric domains.

Methods

Participants

A total of 208 adolescents with 22q11DS who visited the outpatient clinic at the psychiatry department of the University Medical Center Utrecht (UMCU) between 2002 and 2018 were included in the study. As part of the routine clinical care (Bassett et al., 2011), all patients with 22q11DS were offered to take part in a developmental and psychiatric assessment, regardless of having immediate developmental or psychiatric concerns. Inclusion criteria for participation in the study were: 1) A genetically confirmed 22q11.2 deletion; 2) Absence of an acquired brain trauma unrelated to 22q11DS; and 3) age at enrollment between 10 and 19 years old. Participants and, where relevant, their parents or legal guardians, provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013) and was approved by the Medical Ethical review board of the UMC Utrecht.

Instruments

As part of the standard clinical assessment, three semi-structured interviews were administered to all patients' parents or legal guardians to evaluate the presence of neuropsychiatric symptoms. The mood and psychosis sections of the Kiddie-Schedule for Affective Disorders and Schizophrenia were used to measure symptoms associated with Mood Disorders and Psychotic Disorders (Kiddie-SADS; Ambrosini, 2000). A semi-structured assessment of DSM-IV Symptoms was used to assess the presence of symptoms associated with ADHD, Anxiety Disorder, Disruptive Behavior Disorders and Eating Disorders. The Autism Diagnostic Interview-Revised was used to measure symptoms associated with ASD (ADI-R; Lord et al., 1994). A trained clinician rated for each symptom if it was absent (score 0), doubtfully present (score 1), mildly/moderately present (score 2) or strongly present (score 3). In the same assessment, the patients' level of intellectual functioning was assessed with an age-appropriate version of the standardized Wechsler scales of intelligence (Wechsler, 1997, 2008; Weschler, 2014; Weschler & Naglieri, 2006; Appendix S1 table S1). These tests provide scores for Full Scale IQ (FSIQ), Verbal IQ (VIQ),

and Performance IQ (PIQ), all normally distributed with a mean = 100 and SD = 15 in the general population. All instruments were administered and/or scored by trained clinicians and diagnostic classifications were made in accordance with DSM-IV TR criteria, based on all available information (American Psychiatric Association, 2000).

Symptom dimensions and standardized scores

We aimed to study the inter-individual differences in the severity of symptom expression, beyond a categorical distinction (i.e. having or not having a clinical diagnosis). As such, our approach was to define different symptom dimensions, that correspond to different neuropsychiatric domains, and subsequently, to quantify the expression of symptoms for each individual on each symptom dimension. Based on the structure of the clinical interviews and the intelligence assessments, we were able to define eight major symptom dimensions, as well as multiple minor symptom dimensions within each major symptom dimension (see table 1 for a complete overview of the major and minor symptom dimensions, and the instruments used for their operationalization).

For the dimensions measured with any of the clinical interviews, we quantified symptom expression by computing the sum score of the items that belonged to each major symptom dimension and each minor symptom dimension. We used the outcomes of the intelligence measures (IQ-scores) as quantification of the expression of symptoms on the dimension intellectual functioning. Specifically, we used the FSIQ scores for the major symptom dimension and the Verbal and Performance IQ scores for the minor symptom dimensions. To allow for comparison of the distributions of expressed symptoms across the different symptom dimensions, we standardized all sum- and IQ-scores by computing percentage scores. For sum scores derived from the clinical interviews, we used the formula [(participant sum score on symptom dimension / the maximum possible sum score on that symptom dimension) * 100]. To transform the IQ-scores to percentage scores, we first transformed all IQ scores >100 as a score of 100, and all scores < 55 as a score of 55, so that the range of possible IQ scores only covered the level of 'severely impaired' to 'average' intellectual functioning. Then, we converted all IQ scores into percentage scores using the formula: [100 - ((IQ-score -55)/45) *100)]. We inverted this percentage score to align it with the symptom distributions, such that a lower IQ score corresponds to more severity, i.e., a higher percentage score. Hence, all symptom dimensions ranged from low percentage scores (i.e. few symptoms/problems) to high percentage scores

(i.e. many symptoms/problems). In this study, we refer to these percentage scores as standardized scores.

Cut-off scores and severity ranges

To support the interpretation of the distribution of standardized scores within each symptom dimension we computed two different cut-off values for each symptom dimension, that enable us to divide each symptom dimension into three severity ranges.

First, the 'Symptom Cut-off score (SC)' corresponds to the standardized score that represents the expression of one symptom on a given dimension. For the symptom dimensions that were measured with the clinical interviews, a symptom was considered present if an item was rated with a minimum score of 2. The SC was computed with the formula: [(2 / total number of items in that dimension)*100]. For the symptom dimensions reflecting intellectual functioning, the SC corresponds with the standardized score that reflects an IQ score of 85 (i.e., >-1SD).

Additionally, we computed for each major and minor symptom dimension a 'Diagnostic cut-off score' (DC), but different approaches were taken to compute this score. Some of our major dimensions or minor dimensions directly mirror DSM-IV categories. For instance, the major dimension 'Attention Deficit and Hyperactivity' resembles the diagnostic classification 'ADHD'. In these instances, the DC corresponds to the standardized score that reflects the minimum number of symptoms that is required to meet the DSM-IV diagnostic criteria, using the formula: [((minimum number of symptoms required for DSM-IV diagnosis * 2) / total number of items in corresponding symptom dimension))*100]. To calculate the DC for those symptom dimensions that did not directly resemble a DSM-IV diagnostic category, we used a slightly different procedure. For the minor dimensions that reflect a core symptom domain within a diagnostic category (e.g.,'Attention-deficit' within 'ADHD'), we adopted the cut-off criteria provided by the DSM-IV if these were provided. For the major dimensions that by themselves did not mirror a DSM-IV diagnostic category (e.g.,"Disruptive Disorder" that comprises Oppositional Defiant Disorder and Conduct Disorder), we defined the DC as sum of the items that is needed for a DSM-IV diagnosis for their corresponding minor symptom dimensions (see table 1). For the symptom dimensions reflecting intellectual functioning the DC corresponds to the standardized score that reflects an IQ score of 70 (i.e. >-2SD).

We further refer to the range of standardized scores below the SC as the 'normal range', the range of standardized scores in between the SC and

the DC as the 'subthreshold range' and the range of scores above the DC as the 'clinical range'.

Analyses

Data manipulation, visualization and analysis was done in RStudio version 4.0.2 (R Core Team, 2017). First, we calculated and visualized the distribution of standardized scores on both the major and minor symptom dimensions. In addition, we calculated the proportion of individuals within the normal, subthreshold and clinical range respectively for all of these symptom dimensions. To shed light on the range of expressed symptoms among individuals without a diagnosis, we described the distribution of standardized scores on each symptom dimension that corresponds to a clinical DSM-IV diagnosis, for the individuals without a clinical diagnosis. Finally, we used correlation analyses to explore the interrelationships between the different minor symptom dimensions.

Results

Dimensional overview of neuropsychiatric symptom expression in 22q11DS

Participants were on average 13.6 years old (SD=1.90), and the total sample of 208 adolescents included 123 girls (59%) and 85 boys (41%). Figure 1 displays the distribution of the standardized scores of the adolescents with 22q11DS, within each of the eight major symptom dimensions and their corresponding minor symptom dimensions (see also Appendix S1 table S2).

Major symptom dimensions

The range of standardized scores varied between the different major symptom dimensions, with especially the dimensions 'Intellectual Functioning', 'Attention Deficit & Hyperactivity' and 'Autism Spectrum' having a relatively large proportion of adolescents with high standardized scores, reflecting higher levels of symptom expression, as compared to other major symptom dimensions. Furthermore, standardized scores of the adolescents with 22q11DS varied within most major symptom dimensions, ranging from low to high levels of symptom expression. The data revealed that most adolescents had a standardized score that fell in the subclinical range on the majority of major symptom dimensions.

Table 1. *Overview of the eight Major Symptom Dimensions (**bold**) and corresponding Minor Symptom Dimensions (italics) and the Measures Used to Quantify Participants' Standardized Score for Each Symptom Dimension, Including the Total Number of Items for Each Measure and the Number of Items Needed for a Score to Fall in the Clinical Range (>DC).*

Symptom dimension	Instrument	N items Total	N items clinical range
Intellectual functioning	IQ test - Full Scale IQ score	-	IQ < 70
Verbal Intelligence	verbal IQ score	-	IQ < 70
Performance Intelligence	Performance IQ score	-	IQ < 70
Attention deficit and hyperactivity	DSM-IV interview – Main section: ADHD	18	12
Attention Deficit	subsection: Inattention	9	6
Hyperactivity & impulsivity	subsection: Hyperactivity and Impulsivity	9	6
Autism Spectrum	ADI-R	37	21
Social Interaction problems	Subsection: Social interaction	16	10
Communication problems	Subsection: Communication	13	8
RRBI	Subsection: RRBI	8	3
Mood	KSADS - Main section: Mood	30	8
Depressive Behavior	Subsection: Depression	24	5
Manic Behavior	Subsection: Mania	6	3
Anxiety	DSM-IV interview - Main section: Anxiety	25	13
Generalized Anxiety	Subsection: Generalized Anxiety	8	5
Separation Anxiety	Subsection: Separation Anxiety	8	3
Obsessive Compulsive Behavior	Subsection: Obsessive Compulsive Disorder	9	5
Psychosis spectrum	KSADS - Main section: Psychosis	50	3
Positive psychotic symptoms	Subsection: Hallucinations &Delusions	41	1
Other psychotic symptoms	Subsection: Other psychotic symptoms	9	2
Disruptive Behavior	DSM-IV interview - Main section: Behavioral disorders	24	7
Oppositional Defiant Behavior	Subsection: Oppositional Defiant Disorder	8	4
Conduct Behavior	Subsection: Conduct Disorder	16	3
Eating behavior	DSM interview - Main section: Eating disorders	16	11
Anorexic Behavior	Subsection: Anorexia	4	4
Bulimic Behavior	Subsection: Bulimia	6	6
Other Eating Problems	Subsection: Other	6	1

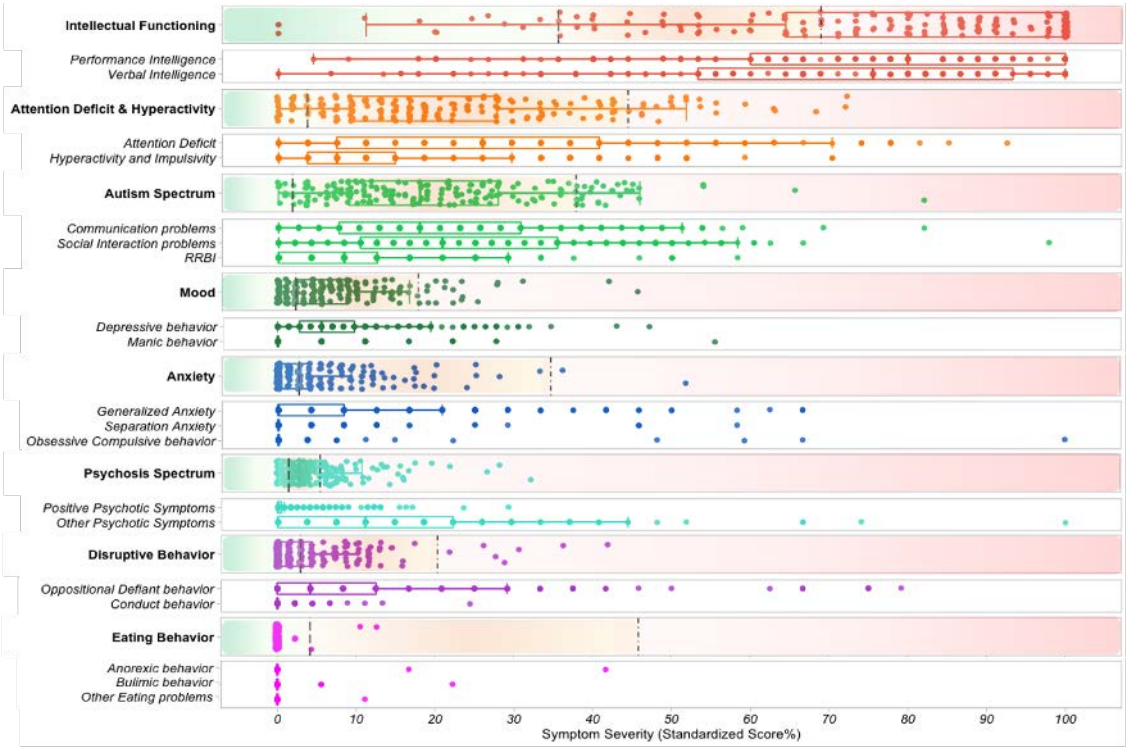
Abbreviations. ADHD = Attention Deficit Hyperactivity Disorder. ADI-R = Autism Diagnostic Interview – Revised. RRBI = Repetitive Restricted Behaviors and Stereotyped Interests. KSADS= Kiddie – SADS. IQ = Intelligence Quotient.

Exceptions are the major dimension Intellectual Functioning, in which most scores fell in the clinical range, and the major dimension Eating Behavior, in which most scores fell in the normal range. Of note, only 4% of scores fell in the normal range for the major dimension Autism Spectrum, indicating that 97% of the adolescents expressed at least one symptom on this dimension. In the major dimension Psychosis Spectrum, a relatively large proportion of the adolescents had a score in the clinical range, whereas, on average, standardized scores were relatively low on this dimension. Of note here is that the presence of one symptom was enough to exceed cut-off for the clinical range for the minor symptom dimension positive symptoms.

Minor symptom dimensions

Similar to observations of the major symptom dimensions, standardized scores of the adolescents with 22q11DS varied both between and within the minor symptom dimensions. The distribution of expressed symptoms varied between some minor symptom dimensions that belong to the same major symptom dimension. More specifically, within the major symptom dimensions Attention Deficit and Hyperactivity, Autism Spectrum, Mood, Anxiety and Disruptive behavior, we observed that the proportion scores that fell in the clinical range was much larger for one of the minor symptom dimensions. Exceptions were the two minor symptom dimensions within Intellectual Functioning, with a comparable proportion of adolescents with severity scores in the subclinical and clinical range. Additionally, the minor dimensions reflecting Eating Behavior revealed little variation, and most of the adolescents had a standardized score of 0, indicating no symptom expression.

Figure 1. *Boxplot Presenting the Standardized scores (%) on the Major Symptom Dimensions (**bold**) and Minor Symptom Dimensions (italic) for Adolescents with 22q11DS. Individual Dots Represent Individual Participants. Participants With the Same Score Share Overlapping Dots.*



Abbreviations. RRBI = repetitive restricted behaviors and stereotyped interests. *Note*. Area to the left of the striped line = normal range; area between striped and dotted line = subthreshold range; area to the right of the dotted line = clinical range

Table 2. *Overview of the Distribution of Standardized Scores on Each Major Symptom Dimension (**bold**) and Minor Symptom Dimension (italics), Only Including the Standardized Scores of Adolescents With 22q11DS who do not Have a Corresponding DSM-IV Diagnostic Classification.*

Symptom domains	DSM-IV [c]	%[d]	Median	IQR	%normal	% sub-threshold	% clinical
Attention deficit	ADHD	92.5	**16.7**	**20.8**	**11.4**	**77.7**	**10.9**
Inattention	-	-	25.9	29.6	19.0	57.1	23.9
Hyperactivity and impulsivity	-	-	11.1	18.5	31.7	61.2	7.10
Autism spectrum	ASD	55.6	**16.2**	**19.9**	**6.42**	**77.1**	**16.5**
Social interaction problems	-	-	18.8	27.0	9.17	69.7	21.1
Communication problems	-	-	18.0	23.0	17.4	67.0	15.6
RRBI	-	-	4.17	12.5	50.9	35.2	13.9
Mood[a]	-	92.9	5.56	6.94	18.5	71.2	10.3
Depressive behavior	MDD	92.9	**6.94**	**8.33**	**20.7**	**59.2**	**20.11**
Manic behavior[b]	-	92.9	0	0	90.8	8.70	0.54
Anxiety[a]	-	92.4	**2.67**	**6.67**	**48.1**	**50.8**	**1.10**
Generalized anxiety	GAD	99.5	0	16.7	57.9	35.5	6.60
Separation anxiety	SAD	99.5	0	0	87.2	9.18	3.58
Obsessive compulsive behavior	OCD	97.8	0	0	95.3	3.12	1.55
Psychosis spectrum	PD	86.7	**2.67**	**4**	**28.5**	**47.7**	**28.8**
Other psychotic symptoms	-	-	7.41	18.5	35.9	23.5	40.6
Positive psychotic symptoms	-	-	0	0.81	77.2	19.9	2.92
Disruptive behavior[a]	-	99	**1.45**	**7.25**	**53.0**	**43.4**	**3.54**
Oppositional defiant behavior	ODD	99	4.17	16.7	54.5	34.3	11.1
Conduct behavior	CD	100	0	0	94.5	4.50	1.00
Eating behavior[a]	-	100	**0**	**0**	**98.5**	**1.52**	**0**
Anorexic behavior	AN	100	0	0	99.0	1.01	0
Bulimic behavior	BN	100	0	0	99.5	0.51	0
Other eating problems	-	100	0	0	99.5	0	0.51

Abbreviations. RRBI = Restricted Repetitive Behaviors and Stereotyped Interests. ADHD = Attention Deficit Hyperactivity Disorder. ASD= Autism Spectrum Disorder. RRBI = repetitive restricted behaviors and stereotyped interests. MDD=Major Depressive Disorder. GAD=Generalized Anxiety Disorder. SAD=Separation Anxiety Disorder. OCD=Obsessive Compulsive Disorder. PD=Psychotic Disorder. ODD=oppositional defiant disorder. CD=Conduct Disorder. An=Anorexia Nervosa. BN=Bulimia Nervosa. Normal = normal range. Subthreshold = subthreshold range. Clinial = clinical range. [a]For the major dimensions Mood, Anxiety, Disruptive Behavior and Eating Behavior, only scores of participants without a DSM-IV diagnosis in any of the corresponding diagnostic classifications were used. [b]There was no registration of participants with a DSM-IV diagnosis of bipolar disorder. We used scores of participants without a DSM-IV diagnosis of MDD. [c] This column indicates the DSM-IV diagnostic classifications that directly corresponds with a major or minor symptom domain. [d] Indicating the proportion of individuals without a diagnostic classification, out of the total individuals with a score (see table 2). Based on this information, the total number of individuals with a diagnostic classification can be computed. Example ADHD: 100% - 92.5% = 7.5% of the sample had a diagnosis of ADHD)

Dimensions in relation to categories

Table 2 provides an overview of the distribution of standardized scores on each major and minor symptom dimension, for the subset of adolescents with 22q11DS without a DSM-IV diagnostic classification corresponding to this symptom dimension.

This overview illustrates a degree of symptom expression that is comparable to the results for the total sample (Appendix S1 table S2). An exception seems the proportion of individuals with a standardized score exceeding the DC on the minor symptom dimension 'positive psychosis symptoms'. Here, it appears that individuals without a diagnostic classification of a psychotic disorder present with lower standardized scores (i.e., fewer symptoms), as compared to the total sample.

Correlations

Given the skewed distribution of our data, we used Spearman correlation analyses to investigate the associations between all minor symptom domains (see figure 2; Appendix S1 Table S3). Results mostly showed positive associations between minor symptom domains, indicating that higher levels of symptom expression on one minor symptom dimension were associated with higher levels of symptom expression on other minor symptom dimensions. We did not only observe such significant associations between minor symptom dimensions that belong to the same major symptom dimension (e.g., communication with social interaction in the Autism Spectrum dimension), but also significant cross-dimension associations (e.g., Autism Spectrum-communication with Attention Deficit Hyperactivity-inattention). Furthermore, we observed that some minor symptom dimensions were associated with multiple other minor symptom dimensions (e.g., Disruptive Behavior-oppositional behavior).

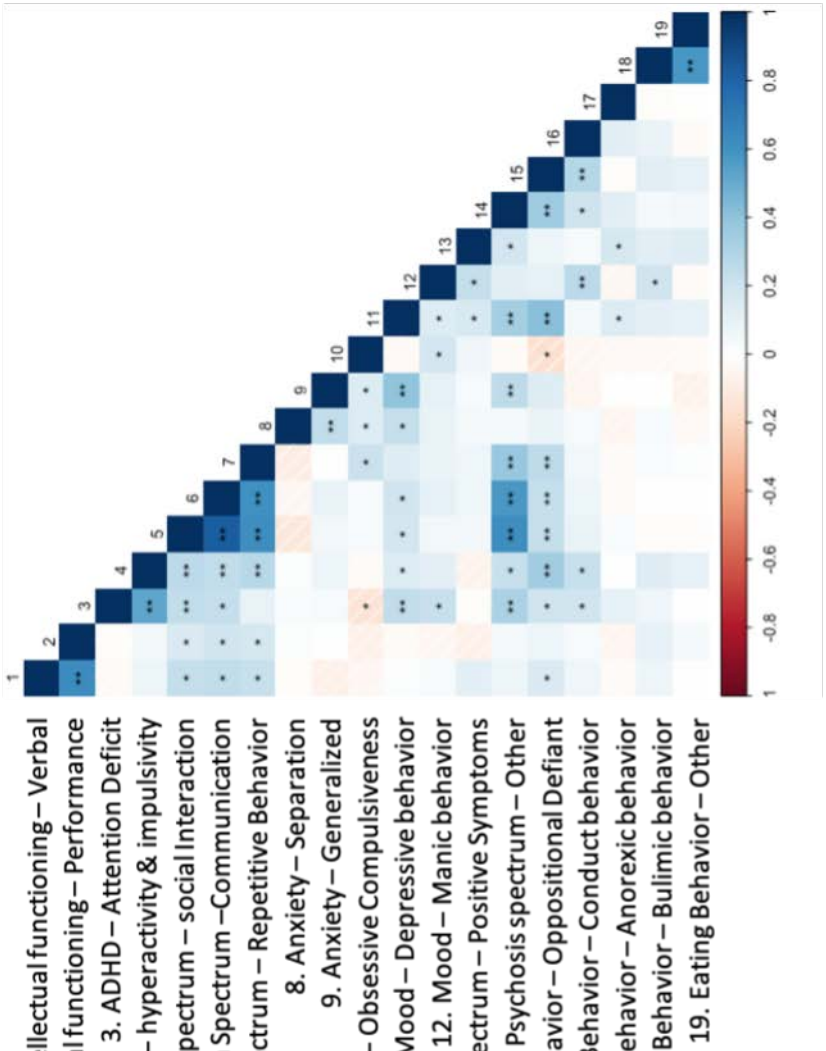


Figure 2. *Results of Spearman Correlation Analyses, Ranging from – 1 (dark red) to + 1 (dark blue), to Explore the Associations Between Scores on the Minor Symptom Dimensions (*p<.01, **p<.001)*

Discussion

We used a dimensional approach to provide a comprehensive overview of neuropsychiatric symptoms in adolescents with 22q11DS. To this end, we quantified symptom expression within eight major symptom dimensions and multiple minor symptom dimensions. We found that individuals with 22q11DS experience a wide range of neuropsychiatric symptoms, which often do not meet the criteria for a full clinical diagnosis of a neuropsychiatric disorder.

Results of the present study indicate that adolescents with 22q11DS express more symptoms on the major symptom dimensions "Intellectual functioning", "Attention deficits and hyperactivity", and "Autism spectrum" as compared to other major dimensions (e.g., "Eating behavior"), which is in keeping with the previously reported prevalence rates of the different categorical diagnostic classifications in adolescents with 22q11DS (Schneider et al., 2014). Previous descriptions indicated that none of the neuropsychiatric disorders was completely penetrant in 22q11DS (Fiksinski et al., 2021). Our present overview takes a dimensional perspective and complements those previous descriptions by demonstrating a broad range of inter-individual variation in the severity of neuropsychiatric symptom expression in most major and minor symptom dimensions. As suggested previously (Niarchou et al., 2017), the results of the present study indicate that neuropsychiatric symptom expression in 22q11DS, similar to the general population (Haslam et al., 2020), is distributed continuously, rather than discretely.

We demonstrate that a dimensional approach allows to describe the degree of expression on different core symptoms within each neuropsychiatric category. For instance, we observed that the major symptom dimension attention deficit hyperactivity is mainly driven by the expression of symptoms on the minor dimension attention deficits in adolescents with 22q11DS, in line with earlier work (Niarchou et al., 2015). In addition, results of the current study seem to indicate that symptoms associated with ASD seem more prominent in the domain of social communication and interaction seem than those in the domain of restricted and repetitive behaviors. On the one hand, this pattern may be characteristic for 22q11DS, as this is consistent with other earlier findings (Angkustsiri et al., 2014). On the other hand, in the present study the number of questions probing the repetitive domain was a lot lower than for the other two domains. As such, this may have influenced our results.

As has been demonstrated previously, individuals with 22q11DS present with subthreshold symptoms in multiple diagnostic categories, but most prominently involving psychosis (Schneider et al., 2019; Weisman et al., 2017), ASD (Chawner et al., 2021; Serur et al., 2019), ADHD (Klaassen et al.,

2013; Niarchou et al., 2015), and anxiety (Klaassen et al., 2013). Our findings broaden this observation by explicitly demonstrating that those adolescents with 22q11DS without a formal psychiatric diagnosis still display a wide range of symptoms, often across several symptom domains, with, in some instances, scores in the clinical range.

To further characterize the 22q11DS symptom profile, we explored the associations between different minor symptom dimensions. Our data revealed multiple significant associations between various minor symptom dimensions, including between those minor symptom dimensions that belong to a different major symptom dimension (e.g., between minor dimensions within attention deficit & hyperactivity and autism spectrum). Moreover, it appeared that in some instances, a single minor symptom dimension was associated with multiple minor dimensions that belonged to a variety of symptom dimensions (e.g., Mood- Depression). It could be that some of these observed correlations are (partly) due to overlapping symptoms between different minor symptom dimensions. A prime example of such a minor symptom dimension is other psychotic symptoms, containing symptoms associated with Autism Spectrum (e.g., difficulty connecting with others) and Depression (e.g., flattened affect). Nonetheless, the highly correlated symptom domains in 22q11DS resemble observations in the general population that individuals with clinically relevant symptoms that belong to a particular diagnostic category, are likely to present with increased rates of symptoms in other diagnostic categories (Lilienfeld & Treadway, 2016).

Strengths, limitations and future directions

A strength of the present study is that we measured the expression of neuropsychiatric symptoms in multiple major and minor symptom dimensions, in a large sample of adolescents with 22q11DS, which allowed us to give a comprehensive overview of neuropsychiatric symptom expression in this population. In this study, we used the sum of item scores within each symptom dimension as a means to indicate the severity of neuropsychiatric symptom expression for each of our participants. As a consequence, the symptom profile of individuals with the same sum score may differ. For instance, an individual having three items with the score 1, received the same sum score as an individual having one item with of the score 3. In addition, we chose the expression of one symptom as threshold for the subthreshold range, because we aimed to gain insight in the full range of inter-individual variation of individuals below the clinical range. A consequence of this rather lenient cut-off value is that our subthreshold range may not resemble the similar

range in standardized instruments (e.g.,those using a T-score distribution). Therefore, further research employing different quantification strategies might confirm our current results, and improve our insight into the profile of symptom expression of adolescents with 22q11DS.

Furthermore, it could be argued that results of this study are not representative for all individuals with 22q11DS, given that we used data that was collected at a psychiatry outpatient clinic. However, following the current international guidelines for care for individuals with 22q11DS (Bassett et al., 2011), all adolescents with 22q11DS were referred to this clinic regardless of having immediate psychiatric concerns, which may reduce recruitment bias. To confirm our suggestion that the study of 22q11DS could provide relevant insight into the inter-individual variability in neuropsychiatric symptom expression in the general population, or other populations with rare genomic diseases, future studies are needed to compare the dimensional symptom profile of 22q11DS to that of other populations.

In line with one previous study (Shankman et al., 2018), we showed that outcomes of clinical interviews can be used to quantify the expression of neuropsychiatric symptoms. This may be relevant for initiatives aiming to combine samples, and looking for clinically relevant neuropsychiatric outcomes (Jacquemont et al., 2022). Moreover, this approach directly relates to clinical practice, as the dimensional approach allows to complement a categorical diagnosis with a measure of severity, in line with suggestions of the diagnostic and statistical manual of mental disorders, 5th edition (DSM-5; (American Psychiatric Association, 2013; LeBeau et al., 2015). A limitation of the clinical interviews used for the current study was that these were all measures of psychiatrist report, and it would be interesting to study whether parent- or patient-reported measures would reveal a similar picture. Likewise, future descriptions of neuropsychiatric outcomes in 22q11DS are recommended to include measures of functional outcomes, such as adaptive functioning or quality of life.

Clinical and theoretical implications

Results of this study have some direct clinical implications. First, our approach highlights that there is a group of individuals with 22q11DS, who do not meet criteria for a formal diagnosis of a neurodevelopmental disorder, but that does experience a range of subthreshold symptoms. Even in the absence of such a clinical diagnosis, the presence of subthreshold symptoms may be associated with significant distress and impairment, particularly when these symptoms are expressed across several neuropsychiatric domains (Baker & Vorstman,

2012). Therefore, findings of the present study strongly support the clinical guidelines for 22q11DS (Bassett et al., 2011). These recommend a broad and repeated evaluation of both the level of cognitive functioning and presence of neuropsychiatric symptoms, for all children with 22q11DS, throughout development into early adulthood. Such repeated and thorough assessment might limit the likelihood of diagnostic overshadowing, which refers to the situation that a child's neuropsychiatric symptoms are overlooked or misinterpreted, due to the presence of a clinical diagnosis of a neurodevelopmental disorder (e.g., social problems as a result of an intellectual disability; Fiksinski et al., 2021)). A side-effect of such diagnostic overshadowing is that some neuropsychiatric symptoms may not receive adequate clinical attention. On an individual level, a dimensional approach, complementary to diagnostic categories, may therefore help reveal an individual profile of vulnerabilities on a symptom-level, that may have important implications for tailoring individual support. For instance, in addition to a formal diagnosis of 'intellectual disability and ADHD', a complementary dimensional approach would describe that this child may predominantly present with symptoms in the minor dimensions "Inattention", as well as with additional subthreshold symptoms on the dimensions "Generalized anxiety", and "Disruptive Behavior".

Our findings fit a general tendency in neuropsychiatric research to move away from traditional diagnostic categories, and to adopt a dimensional approach to study the factors that contribute to the development of neuropsychiatric symptoms (e.g.,Research Domain Criteria; Cuthbert, 2022). To further identify the risk factors that contribute to inter-individual variation of neuropsychiatric symptom expression in individuals with 22q11DS, it may be of interest to explore the use of a person-centered approach: a data-driven approach that can be used to cluster individuals based on similarities in their individual patterns of neuropsychiatric symptoms (Djelantik et al., 2020; Howard & Hoffman, 2018). Identification of such (transdiagnostic) symptom clusters in 22q11DS could thus pave the way for further studies to detect biological or environmental risk factors for these clusters. Ultimately, understanding such risk factors for neuropsychiatric symptom expression in 22q11DS may facilitate identification of neurobiological pathways of common mental disorders, and may guide research into novel targets for therapeutic intervention (Fiksinski et al., 2023; Zinkstok et al., 2019).

Conclusion

In this study, we used a dimensional approach to explore the expression of neuropsychiatric symptoms of adolescents with 22q11DS, complementary to a description in terms of diagnostic categories. This provides a fine-grained description of the inter-individual variation of neuropsychiatric symptom expression in this population. Our results are consistent with a body of research reporting on large phenotypic heterogeneity in individuals with 22q11DS, and demonstrate a wide range of neuropsychiatric symptom expression among those adolescents without a formal DSM-IV diagnostic classification. These findings may enhance our ability to manage clinical outcomes and to tailor clinical support and intervention for adolescents with 22q11DS. In addition, the presented dimensional overview may spur hypotheses for future studies aiming to investigate the biological and environmental mechanisms contributing to symptom expression in this genetic high-risk model for common mental disorders.

Supplementary Information

Appendix S1

Table S1. *Overview of the instruments to measure the level of intellectual functioning (IQ tests), together with the proportion of individuals that completed each test.*

Name instrument	n	%
WAIS-III	8	4.49
WAIS-IV	3	1.69
WISC-III	158	88.76
WISC-V	7	3.93
WNV	2	1.12

Abbreviations. WAIS III = Wechsler Adult Intelligence Scale – 3rd edition. WAIS IV = Wechsler Adult Intelligence Scale – 4th edition. WISC-III = Wechsler Intelligence Scale for Children – 3rd edition. WISC-V = Wechsler Intelligence Scale for Children – 5th edition. WNV = Wechsler NonVerbal intelligence scale. Note. The WNV does not make a differentiation between verbal IQ and performance IQ. For these two participants only the full scale IQ score was used.

Table S2. *Medians and interquartile ranges (IQR) of standardized scores of the adolescents with 22q11DS on each major symptom dimension (**bold**) and minor symptom dimension (italics), as well as the proportions of adolescents with a standardized scores in the different severity ranges.*

Symptom domains	N	Median	IQR	% normal range	% sub-threshold range	% clinical range
Intellectual Functioning	**178**	**84.4**	**35.6**	**3.50**	**23.0**	**45.5**
Performance Intelligence	175	80.0	40.0	16.6	28.6	54.9
Verbal Intelligence	174	75.6	40.0	10.3	28.7	60.9
Attention deficit & hyperactivity	**199**	**18.5**	**22.2**	**11.1**	**77.9**	**11.1**
Attention deficit	199	25.9	31.5	19.1	56.8	24.1
Hyperactivity and impulsivity	198	11.1	18.5	31.8	60.6	7.58
Autism spectrum	**196**	**18.0**	**19.4**	**3.57**	**79.8**	**16.3**
Social interaction problems	196	20.8	25.5	9.18	68.4	22.5
Communication problems	196	17.9	23.1	12.8	73.5	13.8
RRBI	195	8.3	14.6	46.2	40.0	13.9
Mood	**198**	**5.6**	**7.8**	**18.9**	**71.0**	**10.1**
Depressive behavior	198	6.9	8.3	20.7	58.7	20.6
Manic behavior	198	0	0	90.4	9.09	0.51
Anxiety	**198**	**2**	**6.7**	**50.0**	**49.0**	**1.01**
Generalized anxiety	198	0	16.7	58.1	35.4	6.57
Separation anxiety	197	0	0	87.3	9.14	3.55
Obsessive compulsive behavior	197	0	0	94.9	2.03	3.05
Psychosis spectrum	**198**	**3**	**5.2**	**25.3**	**42.4**	**32.3**
Other psychotic symptoms	196	11.1	22.2	33.7	20.9	45.4
Positive psychotic symptoms	197	0	1.63	68.5	20.81	10.7
Disruptive behavior	**200**	**4.2**	**7.2**	**52.5**	**44.0**	**3.50**
Oppositional defiant behavior	200	1.4	0	54.5	34.5	11.0
Conduct behavior	200	0	16.7	94.5	4.50	1.00
Eating behavior	**198**	**0**	**0**	**98.5**	**1.52**	**0.00**
Anorexic behavior	198	0	0	99.0	1.01	0.00
Bulimic behavior	198	0	0	99.5	0.51	0.00
Other eating problems	197	0	0	99.5	0.00	0.51

Abbreviations. RRBI = repetitive restricted behaviors and stereotyped interests

Note. Numbers of complete data vary due to practical reasons, including lack of time during the assessment, non-compliance of a participant, and not being able to obtain information from external sources (e.g., school).

Table S3. *Results of Spearman correlation analyses, to explore the associations between scores on the minor symptom domains*

	IF_V	IF_P	ADH_A	ADH_H	AS_I	AS_C	AS_R	AS_D	Anx_S	Anx_G	Anx_O	Mood_D	Mood_M
IF_V	1												
IF_P	0.87**	1											
ADH_A	-0.24	-0.22	1										
ADH_H	-0.09	-0.09	0.73**	1									
AS_I	0.26*	0.17*	0.28**	0.31**	1								
AS_C	0.28*	0.2*	0.25**	0.28**	0.98**	1							
AS_R	0.29*	0.2*	0.08**	0.27**	0.86**	0.85**	1						
AS_D	0.33*	0.26*	0.21*	0.19*	0.74**	0.76**	0.72**	1					
Anx_S	-0.28	-0.21	-0.16	-0.23	-0.47	-0.41	-0.46	-0.44	1				
Anx_G	-0.36	-0.26	-0.07	-0.1	-0.11	-0.09	-0.2	-0.29	0.4**	1			
Anx_O	-0.23	-0.24	-0,43*	-0.32	-0.13	-0.12	0.09*	-0.15	0.18*	0.15*	1		
Mood_D	-0.33	-0.35	0.24**	0.08*	0.06*	0.05*	-0.07	-0.09	0.25*	0.55**	-0.26	1	
Mood_M	-0.25	-0.34	0.17*	-0.01	-0.17	-0.14	-0.15	-0.12	0.05	0.03	0.18*	0*	1
Psy_P	-0.09	-0.3	-0.25	-0.4	-0.18	-0.18	-0.18	-0.18	-0.04	-0.07	0.02	0.07*	0.22*
Psy_O	-0.06	-0.12	0.39**	0.28*	0.8**	0.78**	0.57**	0.55**	-0.27	0.16**	-0.27	0.36**	-0.08
DB_O	0.02*	-0.05	0.31*	0.46**	0.27**	0.26**	0.22**	0.11	-0.07	0.09	-0.51*	0.51**	-0.05
DB_C	-0.09	-0.13	0.29*	0.27*	-0.01	-0.05	-0.08	0.04	-0.13	-0.26	-0.28	-0.11	0.29**
EB_A	-0.24	-0.27	0.04	-0.16	-0.16	-0.23	-0.27	-0.29	-0.16	-0.09	-0.17	0.09*	-0.19
EB_B	-0.1	-0.03	-0.11	-0.02	-0.35	-0.35	-0.3	-0.18	-0.09	-0.24	-0.22	-0.09	0.09*
EB_N	-0.14	-0.07	-0.17	-0.05	-0.27	-0.28	-0.23	-0.12	-0.17	-0.27	-0.19	-0.07	-0.18

	Psy_P	Psy_O	DB_O	DB_C	EB_A	EB_B	EB_N
IF_V							
IF_P							
ADH_A							
ADH_H							
AS_I							
AS_C							
AS_R							
AS_D							
Anx_S							
Anx_G							
Anx_O							
Mood_D							
Mood_M							
Psy_P	1						
Psy_O	-0.03*	1					
DB_O	-0.14	0.44**	1				
DB_C	-0.13	0.11*	0.32**	1			
EB_A	0.21*	-0.01	-0.16	0.08	1		
EB_B	0.06	-0.32	-0.03	-0.06	-0.16	1	
EB_N	0.11	-0.23	-0.02	-0.19	-0.11	0.82**	1

*p<.01, **p<.001 . Abr. IF_V = Intellectual Functioning – Verbal intelligence. IF_P = Intellectual Functioning – Performance intelligence. ADH_A = attention deficit hyperactivity – attention deficit. ADH_H = attention deficit hyperactivity – hyperactivity & impulsivity. AS_I = Autism Spectrum – Social Interaction problems. AS_C = Autism Spectrum –Communication problems. AS_R = Autism Spectrum – Restricted Repetitive Behaviors & Stereotyped Interests. AS-D = Autism Spectrum – Developmental Delay. Anx_S = Anxiety – Separation anxiety. Anx_G = Anxiety – Generalized anxiety. Anx_OC = Anxiety – Obssessive Compulsive behavior. Mood_D = Mood – Depressive behavior. Mood_M = Mood – Manic behavior. Psy_P = Psychosis spectrum – Positive Symptoms. Psy_O = Psychosis spectrum – Other symptoms. DB_O = Disruptive Behavior – Oppositional Defiant behavior. DB_C = Disruptive Behavior – Conduct behavior. EB_A = Eating Behavior – Anorexic behavior. EB_B = Eating Behavior – Bulimic behavior. EB_N = Eating Behavior – other eating problems

Table S4. *Author contributions*

Contribution	**Author**
Conceptualization	Iris Selten; Jill Blok; Janneke Zinkstok; Jacob Vorstman; Ania Fiksinski
Methodology	Iris Selten; Jill Blok; Jacob Vorstman; Ania Fiksinski
Formal analysis	Iris Selten; Jill Blok
Investigation	Iris Selten; Janneke Zinkstok; Jacob Vorstman; Ania Fiksinski
Data Curation	Iris Selten; Jill Blok; Ania Fiksinski; Janneke Zinkstok; Jacob Vorstman
Writing-original draft	Iris Selten; Jill Blok; Ania Fiksinski
Writing-review and editing	Iris Selten; Tessel Boerma; Manik Djelantik; Michiel Houben; Frank Wijnen; Janneke Zinkstok; Jacob Vorstman; Ania Fiksinski
Visualization	Iris Selten; Jill Blok
Supervision	Jacob Vorstman; Ania Fiksinski
Project administration	Iris Selten; Janneke Zinkstok; Jacob Vorstman; Ania Fiksinski

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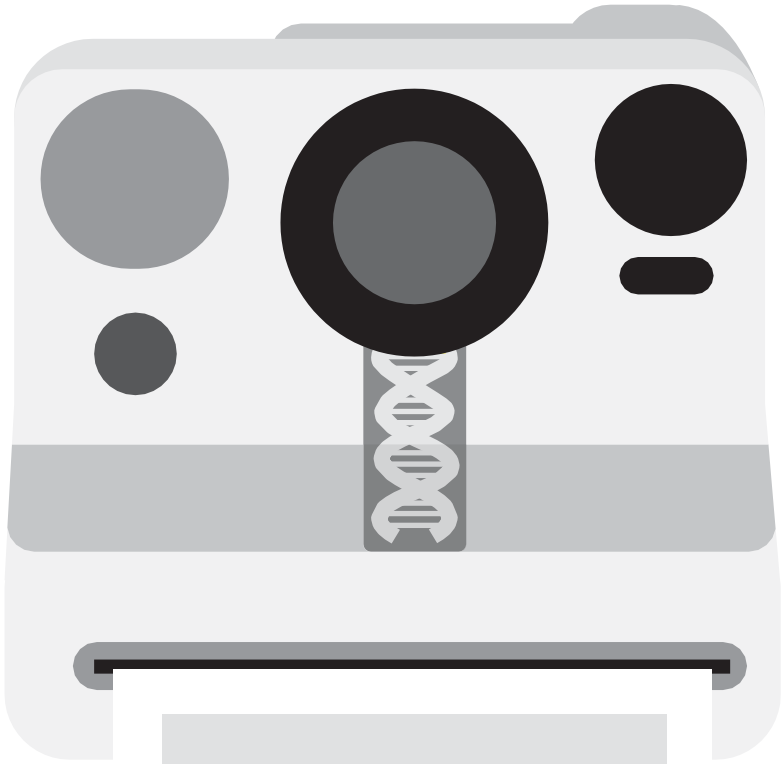

3

The Language Profile of Preschool Children with 22q11.2 Deletion Syndrome and the Relationship with Speech Intelligibility

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Purpose. Young children with 22q11.2 Deletion Syndrome (22q11DS) often have impaired language development and poor speech intelligibility. Here we report a comprehensive overview of standardized language assessment in a relatively large sample of preschool-aged children with 22q11DS. We furthermore explored whether speech ability explained variability in language skills. **Method.** Forty-four monolingual Dutch preschoolers (3-6 years) with a confirmed genetic 22q11DS diagnosis participated in this prospective cohort study. Standardized tests (CELF Preschool-2-NL and PPVT-III-NL) were administered. Speech intelligibility was rated by two expert speech and language therapists, using a standardized procedure. **Results.** Most children had impaired language skills across all tested domains. The composite score for expressive language was significantly lower than that for receptive language, but the two were strongly correlated. Only small differences between the mean scores on the various subtests were observed, with the lowest scores for expressive morpho-syntactic skills. Language scores showed a moderate positive relation with speech intelligibility, but language abilities varied greatly among the children with intelligible speech. **Conclusions.** We show that the majority of preschool children with 22q11DS have a broad range of language problems. Other than the relatively larger impairment in expressive than in receptive language skills, our results do not show a clearly delineated language profile. As many of the children with intelligible speech still had below-average language scores, we highlight that language problems require a broad assessment and care in all young children with 22q11DS. Future research using spontaneous language and detailed speech analysis is recommended, to provide more in-depth understanding of children's language profile and the relationship between speech and language in 22q11DS.

Introduction

The 22q11.2 Deletion Syndrome (22q11DS; OMIM #192430, #188400, #611867), previously called DiGeorge or Velo-Cardio-Facial syndrome, is the most common microdeletion syndrome with an estimated incidence of 1 per 2,148 live births (Blagojevic et al., 2021). 22q11DS is characterized by large phenotypical variation. The most common physical symptoms include congenital heart disease and palatal abnormalities (McDonald-McGinn et al., 2015). With regard to the cognitive phenotype, most children with 22q11DS have intellectual abilities in the borderline range (Intelligence Quotient; IQ: 70-85) or mild intellectual disability (IQ: 55-70; De Smedt et al., 2007; Swillen et al., 2018). Additionally, 22q11DS is associated with an increased risk for neurodevelopmental disorders or psychiatric disorders, such as anxiety disorders, attention deficit hyperactivity disorder, and autism spectrum disorder in childhood, and schizophrenia in adolescence and early adulthood (Fiksinski et al., 2018). Speech-language problems are reported in ~95% of children with 22q11DS (Solot et al., 2019a), making this one of the most prevalent symptoms in early childhood. The negative effect of early language impairment on social interactions, socio-emotional development, and wellbeing has been widely acknowledged (Bleses et al., 2016; Conti-Ramsden et al., 2018; Durkin et al., 2017; Le et al., 2021; Longobardi et al., 2016; McKean et al., 2017). In the present study, we therefore first comprehensively describe the language profile of young children with 22q11DS to extend the knowledge on the language abilities of these children at an early age, using standardized language assessments that are frequently used in clinical practice. Second, we explore the relationship between children's language skills and their speech intelligibility.

Language abilities of children with 22q11DS

School-aged children with 22q11DS (i.e., 6- to 12-year-olds) experience difficulties with semantics, syntactic accuracy and complexity, and narrative production and comprehension (Glaser et al., 2002; Moss et al., 1999; Persson et al., 2006; Rakonjac et al., 2016; Selten et al., 2021; Van Den Heuvel et al., 2018). Studies with participants in this age range typically report that children's receptive language impairment is more pronounced than the expressive language impairment, although both receptive and expressive language abilities lag behind age-adequate levels (Glaser et al., 2002; Marden, 1999; Van Den Heuvel et al., 2018). Language skills of children with 22q11DS are also below what is expected given their level of intellectual functioning (Persson et al., 2006; Scherer et al., 1999; Selten et al., 2021; Van Den Heuvel

et al., 2018).

The delays in expressive language are often one of the first behavioral symptoms that are noted by parents of children with 22q11DS. Studies on the language abilities of toddlers and preschoolers with 22q11DS have primarily used parental report to describe children's expressive language milestones. The onset of the first words and sentences is reported to be delayed in over 90% of young children with 22q11DS Solot et al., 2000). Children with 22q11DS are on average 23-26 months old when they produce their first words and start to produce two-word combinations (Roizen et al., 2007). However, 69% of children with 22q11DS have been reported to still be non-verbal at the age of 24 months (Solot, et al., 2000). Three studies with relatively large sample sizes have used standardized language assessments to evaluate language skills of preschool-aged (1-5,5 years old) children with 22q11DS; they reported impairments on composite measures of global, receptive, and expressive language abilities (Gerdes et al., 1999, 2001; Solot, et al., 2000). Both parental report and standardized language assessment suggest a larger delay in expressive than receptive language abilities in preschool children with 22q11DS (Gerdes et al., 1999; Scherer et al., 1999; Shprintzen, 2000; Solot et al., 2001), which stands in contrast with research with school-aged children with 22q11DS for whom the opposite has been observed. These contrasting findings may stem from differences in the types of measures used, but most likely also reflect differential developmental trajectories for receptive and expressive language abilities.

Additionally, in school-aged children, a profile of relatively weak receptive semantic abilities and strong expressive syntactic abilities has been described, based on the evaluation of different subtests that are part of standardized language assessments (Glaser et al., 2002; Van Den Heuvel et al., 2018). Such specific knowledge of the language profile in 22q11DS can support the development of targeted intervention, as well as spur research investigating factors that may influence impaired development in specific language domains. Currently, such a specific language profile is lacking for preschool-children with 22q11DS, as none of the previous studies using standardized assessment
have reported subtest outcomes.

The relationship between speech and language in 22q11DS

Speech problems, such as hypernasality, are common in 22q11DS (Baylis & Shriberg, 2019; Solot et al., 2019a). Especially below the age of 5 years, the majority of children with 22q11DS have poor speech intelligibility (Antshel et

al., 2009; Persson et al., 2003; Solot, et al., 2000). The exact cause of poor intelligibility in 22q11DS often remains unclear, as it may be the result of a variety of neurological problems, such as dyspraxia or a speech sound disorder, and/or anatomical abnormalities, including velopharyngeal insufficiency in the absence of a cleft palate (Baylis & Shriberg, 2019; Gerdes et al., 1999; Golding-Kushner, 2005; Persson et al., 2003; Solot et al., 2019a, 2019a).

The number of studies that address the relationship between speech and language in children with 22q11DS is limited. A study by Gerdes et al. (1999) found no difference between children with 22q11DS with and without palatal abnormalities on standardized language outcomes. This is supported by findings from Solot et al. (2001), who mention that there are no correlations between language, speech, and palatal abnormalities in their sample of school-aged children with 22q11DS. A study by Fritz (2005) compared nine 4- to 6-year-old children with 22q11DS to children with an idiopathic cleft palate, and found that the latter group obtained age-adequate standardized language scores, whereas children with 22q11DS scored significantly below the norm for their age. However, they did not report the prevalence of palatal abnormalities in their 22q11DS sample. Together, these results suggest that palatal abnormalities may not influence language outcomes in 22q11DS. However, it has been suggested that poor speech intelligibility rather than anatomical abnormalities may negatively affect language development in children with 22q11DS (Shprintzen, 2000). This is supported by the finding that in children with an idiopathic cleft palate and lip, low intelligibility is associated with weak language ability (Særvold et al., 2019). The etiology of the association between speech intelligibility and language difficulties is unclear. It may be that the presence of language difficulties affects children's speech intelligibility, as it has been observed that impaired language development also affects articulatory processes (Mahr et al., 2020; Vuolo & Goffman, 2018). On the other hand, children with relatively poor intelligibility have been shown to be less assertive conversation partners (Frederickson et al., 2006; Hardin-Jones & Chapman, 2011), which could negatively affect parent-child interactions (Kuehn & Moller, 2000). For children with 22q11DS, it has indeed been suggested that parents may be less likely to reinforce early speech attempts if their child has poor speech intelligibility (Shprintzen, 2000). Poor speech intelligibility may thus hamper language development in young children with 22q11DS, as poor intelligibility can negatively affect interactions, thereby reducing their exposure to linguistic input, as well as limit opportunities to practice their language skills (Antshel et al., 2009).

The current study

Research describing standardized language outcomes in preschool-aged children with 22q11DS is scarce. Standardized language assessments are frequently used by speech-language pathologists (SLPs) as they are typically required for a diagnosis and access to specialized education and care. Therefore, a more detailed description of standardized language scores may be particularly relevant to SLPs working with children with 22q11DS. Moreover, a more detailed description of standardized language scores can aid the identification of strengths and weaknesses in the early language profile of children with 22q11DS, supporting targeted intervention. The current study therefore aims to provide a comprehensive overview of the language profile of 3- to 6-year-old children with 22q11DS using standardized instruments, the Clinical Evaluation of Language Fundamentals (CELF Preschool-2-NL) and the Peabody Picture Vocabulary Test (PPVT-III-NL). Additionally, we asked parents about the age at which their child produced their first word and sentence. Based on previous research, we expect children with 22q11DS to have impaired language abilities as indicated by norm-scores in the below-average range (Gerdes et al., 1999, 2001; Solot et al., 2001). We furthermore expect expressive abilities to be more impaired than receptive abilities (Gerdes et al., 1999; Scherer et al., 1999; Shprintzen, 2000; Solot et al., 2001). We do not have hypotheses with regard to specific language domains, as previous studies with children in this age range have not reported outcomes of subtests measuring specific language domains.

Speech intelligibility rather than the presence of anatomical abnormalities could impact early language development, by negatively impacting parent-child interactions thereby affecting the quantity and quality of language input and practice a child gets (Antshel et al., 2009; Særvold et al., 2019; Shprintzen, 2000). To explore this relationship, we investigated whether speech intelligibility, as rated by two expert SLPs, could explain variability in language skills of preschool children with 22q11DS.

Method

Participants

Forty-four children with 22q11DS participated in a larger prospective cohort study ('3T project') investigating children's language, cognitive, and behavioral development. The children were recruited and assessed for eligibility in the span of one year (November 2018 to November 2019) through the national multidisciplinary outpatient clinic for children with 22q11DS (University Medical Centre Utrecht, the Netherlands), four other medical

centers in the Netherlands, and the Dutch 22q11DS patient support group (Stichting Steun 22Q11) (see appendix A). Inclusion criteria were: 1) a genetically confirmed diagnosis of 22q11DS, 2) monolingual Dutch, 3) aged between 3,0 and 6,5 years, and 4) absence of bilateral permanent hearing loss (> 35 dB) as reported by parents. Parents are considered reliable informants regarding hearing loss of this severity, given that multiple standardized hearing assessments are part of the routine clinical follow-up for all infants (otoacoustic emissions tests) and preschoolers (pure tone/tonal audiometry test) in the Netherlands. Demographic characteristics of our participants are described in Table 1.

Procedure

The study was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013) and was approved by the Medical Ethical review board of the University Medical Center Utrecht (CCMO registry nr. NL63223.041.17). All parents provided written informed consent.

Parents filled in online questionnaires regarding demographic information and their child's language development. Language assessment took place at the child's school or day-care center and was part of two 45-minutes sessions conducted by a trained researcher. All researchers had at least a Master's degree in the field of cognitive psychology, developmental psychology, or linguistics and had extensive previous experience working with young children in a research and/or clinical context. Language tests were mixed with cognitive tasks and administered in a fixed order. Children's responses to expressive language subtests of the CELF were recorded and were also scored by a second researcher. In case of discrepancies, final scores were determined through a consensus procedure.

Table 1. *Participant Characteristics of the Total Sample (N = 44).*

	N	***M***	***SD***	***Range***
Female/Male	19/25			
Average age in months	44	58.8	12.4	37 – 77
IQ [a]	42[a]	80.0	12.1	50 – 103
Parental education [b]	44	6.4	1.8	2 – 9

	Yes		***No***		***Unclear***	***Missing***
	N	*%*	*N*	*%*	*N*	*N*
Speech-language therapy	41	93	3 [c]	7	-	-
Suspected VPI [d]	21	48	9	20	12	2
Cleft palate [e]	3	7	41	93	-	-
Congenital heart defect [f]	25 [g]	57	19	43	-	-
Tympanostomy tubes	15	34	29	66	-	-
Ear infections	26		18		-	-

Frequency (n)	Never	1-3 times in life	A few times	Very frequently
	18	7	6	13

Abbreviation: IQ: Intelligence Quotient VPI = Velopharyngeal Insufficiency

a. Intelligence quotient (IQ) scores were obtained from medical records or schools. These IQ tests were administered by a licensed psychologist in the context of formal cognitive assessments and included the Bayley Scale of Infant Development (BSID-III-NL; *n* = 3), age-appropriate Wechsler tests (*n* = 19) or SON-R[1] (*n* = 18). Two children with 22q11DS had no recent IQ scores. For one of these children, a trained researcher from the current study administered the shortened version of the Wechsler Non-Verbal (Weschler & Naglieri, 2006). No IQ data could be obtained for the other child due to restrictions regarding the COVID-19 pandemic. The IQ score of a third child could not be obtained due to a developmental age that was too low for the BSID-III-NL. In total, 8 children had an intellectual disability as represented by an IQ score of < 70.

b. Parental education was indexed by the average education level of both parents, ranked on a 9-point scale reflecting the Dutch educational system (ranging from 1 'no education' to 9 'university degree'), see appendix B for more detailed information.

c. One of these children started therapy for hypernasality after the start of this project, another one of these children did have yearly check-ups with a speech-language pathologist (SLP) at the local hospital.

d. Suspicion of VPI was based on the judgement of the same SLPs who performed the intelligibility ratings (see Measures below) using the same audio recordings. No nasometry, scoping or other procedures to measure VPI were performed.

e. Based on parent-report and medical records. All three cases are submucous clefts.

f. The presence of any type of congenital heart defect was assessed by a pediatric cardiologist based on the review of medical records.

g. Of these, 16 (64%) were hemodynamically significant, 18 (72%) were corrected by means of surgical intervention. Thirteen cases presented in isolation, while 12 cases presented with more than one type of cardiac defect. The most common cardiac defect in our sample was Ventricular Septal Defect (*n* = 16).

Measures

Language. We used the Dutch version of the Clinical Evaluation of Language Fundamentals Preschool (CELF Preschool-2-NL; Wiig et al., 2012). This standardized language test for children between ages 3;0 and 6;11 (years; months) comprises seven subtests that measure language abilities in various domains, both receptively (syntax and semantics) and expressively (morphosyntax, syntax, and semantics). The CELF subtest scores for each task can be transformed into age-corrected norm-scores (M = 10, SD = 3). Combining norm-scores of different subtests results in three age-corrected index scores (M = 100, SD = 15). The Core Language Index (CLI) reflects overall language level and is composed of one receptive and two expressive subtests. The Receptive Language Index (RLI) and Expressive Language Index (ELI) are composed of the three receptive and the three expressive subtests, respectively. The reliability kappa's of the CELF Preschool-2-NL vary between 0.73 and 0.96 for the various subtest and index scores. Regarding validity, the CELF Preschool-2-NL shows sufficient correlation with other measures: .71 with the verbal IQ component of the WPPSI and 0.66 to 0.74 with the CELF 4 (in a group of children in the age range that overlaps between the CELF Preschool and the CELF 4). Sensitivity with clinical groups is 0.89 and specificity is 0.83.

We also administered the Dutch version of the Peabody Picture Vocabulary Test (PPVT-III-NL; Schlichting, 2005), a standardized measure for receptive vocabulary, resulting in age-corrected norm-scores (M = 100, SD = 15). The reliability of the PPVT-III-NL is good, with a Lamda-2 coefficient between 0.89 and 0.97 and correlation of 0.94 for test-retest reliability. For a detailed description of the instruments (including the different subtests of the CELF), see appendix C.

Parents reported the approximate age of onset of their child's first word and sentence by choosing one of five age categories, which were based on the Van Wiechen-Developmental screening instrument (Laurent de Angulo et al., 2005; see appendix D).

Speech intelligibility. Speech intelligibility was scored based on recordings of spontaneous speech of each child. The spontaneous speech was recorded during a play break between standardized language tasks. Speech was recorded in Audacity 2.3.0 using a Samson Go Mic portable USB condenser microphone. During this 15-minute play break, all children were given the same set of toys and coloring materials. Researchers were trained and used a

standardized protocol. They were instructed to let the child determine the narrative of the play situation and to ask as few questions as possible, and if doing so to use open-ended questions. The 3 minutes of audio with the most speech uttered by the child from this play-break were selected for analysis.

Two speech-language pathologists (SLPs) affiliated with the 22q11DS outpatient clinic, who have extensive experience working with children with 22q11DS, individually performed blind ratings of children's speech intelligibility based on the 3-minute audio recordings of spontaneous speech. The SLPs rated speech intelligibility according to the intelligibility scale from the Cleft Audit Protocol for Speech (CAPS-A; Sell et al., 2009). Prior to assessing the speech data, the SLPs did a consensus training using audio recordings of children with 22q11DS who were not taking part in this study. Recordings were scored in the same order by both SLPs. Original scores were inverted, so that the scale ranged from 1 (impossible to understand) to 5 (normal speech intelligibility). The ratings of the two SLPs never differed more than two points. For cases in which there was a 2-point difference (n = 4), a final rating was determined by consensus. Final ratings thus never differed more than 1 point. The average of both ratings was used for further analyses.

Data Analyses

The first aim of the current study was to provide a detailed overview of the language profile of young children with 22q11DS. We report the composite index scores and subtest norm scores of the language measures. If children did not complete one or more CELF subtests, this resulted in missing index scores. Analyses always included the maximum number of available participant scores. We used χ^2- or t-tests to check for differences between the groups of children with and without CELF index scores in sex, age, intelligence quotient (IQ), speech intelligibility, and parental education. Next, we conducted a paired samples t-test to determine whether there was a difference between the CELF RLI and the ELI. In addition, we explored intra-individual variability by means of a correlation between CELF RLI and ELI. We did not statistically analyze differences between subtest scores, as the large number of comparison relative to our sample size would likely result in type-I errors. We report the number of children with a score more than -1 Standard Deviation (SD) below the normed mean, as this is a clinically relevant cut-off score according to the CELF manual . Additionally, we present parent-report of early language milestones.

The second aim was to investigate the relationship between children's language abilities and speech intelligibility. As speech intelligibility scores

were an ordinal variable, we used Kendall's tau correlation to determine the correlation with the CELF index scores (CLI, RLI, ELI) and PPVT score. In case of significant correlations, we subsequently conducted regression analyses with each of these four language scores as dependent variable and intelligibility score as a predictor. We only corrected for age in these analyses if age and speech intelligibility were significantly correlated. Lastly, to explore the possible relationship between speech intelligibility and language abilities beyond the group-level, we visually inspected the data by means of scatterplots using the CELF index scores and speech intelligibility score.

All analyses were performed in R version 4.0.2 (R Core Team, 2020), using the tidyverse (v1.3.0; Wickham et al., 2019), rstatix (v0.6.0; Kassambara, 2020), e1071 (v1.7.3; Meyer et al., 2019), pastecs (v1.3.21; Grosjean et al., 2018), expss (v0.10.6; Demin & Jeworutzki, 2020), and the effectsize (v0.4.4-1; Ben-Shachar et al., 2020) packages. Figures were made using IBM SPSS 27.0 (2020) and MS Powerpoint. Effects sizes were interpreted following Lovakov & Agadullina, (2021). Parametric results are reported unless non-parametric tests were required and showed different outcomes than parametric tests.

Results

Task completion data

Not all participants could complete the PPVT or all CELF subtests, resulting in one or more missing CELF index scores. Experimenter observations suggest that incomplete task data was predominantly the result of limited task compliance and insufficient expressive language skills. Intelligibility scores of two children could not be determined because these children produced insufficient spontaneous speech.

Children who could not complete one or more tasks required to calculate CELF index scores were significantly younger (n = 13; M_{age} = 52 months, SD = 12.2) than children who completed all tasks (n = 31; M_{age} = 62 months, SD = 11.6; $t(21.62) = -2.31$, $p = .031$, $d = 0.78$, 95% CI [-17.43 – -0.93]) and had lower intelligibility scores (M = 2.64, SD = 0.67) than children with complete data (M = 3.16, SD = 0.90; $U = 98.5$, $p = .036$, $r = -0.42$, 95% CI [-1.0 – -6.46]). There was no difference between these groups in sex distribution ($\chi^2(1) = 0.01$, $p = .940$, $V = 0.06$), parental education ($t(20.95) = -1.14$, $p = .269$, $d = 0.39$, 95% CI [-1.94 – 0.57]), or IQ scores ($t(14.52) = -1.59$, $p = .134$, $d = 0.64$, 95% CI [-19.27 – 2.86]).

Language profile of young children with 22q11DS

Group mean scores for the three CELF index scores and the PPVT were all in

the below-average range (< -1 SD). Most children obtained below-average scores on the CELF CLI (83%), RLI (76%), and ELI (83%). On the PPVT, 50% of the children scored in the below-average range (see Figure 1 and appendix E). On average, the children obtained significantly higher scores on the CELF RLI than on the CELF ELI ($t(30) = 3.22$, $p = .003$, g = 0.58, 95% CI[1.97 –8.81]). Scores on the CELF RLI and ELI were strongly correlated ($r(31) = 0.75$, $p < .001$, 95% CI [0.55 – 0.88]).

Similar to the CELF index scores, we found that most children scored in the below-average range on each of the CELF subtests norm scores (see Table 2). One child had a single subtest norm score that was more than + 1 SD above the normed mean; all subtest norm scores of all other children were in the average to below-average range. At group-level, there were no clear differences between subtests norm scores. The lowest mean norm score was obtained for Word Structure, which measures expressive morphosyntax. The highest mean norm scores were found for the subtests Basic Concepts (subtest for 3-year-olds) and Word Categories-Receptive (subtest for 4- to 6-year-olds), which are both designed to gauge receptive semantics. Basic Concepts was only completed by 50% of children in the appropriate age range; outcomes should therefore be interpreted with caution.

Lastly, parents reported a delayed production of the first word and sentence in 23 (52%) and 34 (78%) children, respectively (see Figure 2).

Table 2. *Norm Scores of the CELF Subtests for the Expressive and Receptive Language Index*

	Task Completion[a] *(n)*	*M*[b]	*SD*	*Range*	*% scores < -1 SD*
Expressive Language Index					
Expressive Vocabulary [c]	39	5.2	2.3	1 – 10	74
Word Structure [c]	36	4.3	3.1	1 – 12	69
Recalling Sentences	35	4.8	2.3	1 – 11	83
Receptive Language Index					
Sentence Comprehension [c]	40	5.7	2.6	1 – 10	63
Concepts and Following Directions	36	5.5	3.2	1 – 15	64
3-year-olds [d] Basic Concepts	6	8.8	2.3	6 – 12	17
4- to 6-year-olds [d] Word Categories-Receptive	28	6.1	2.6	2 – 12	54

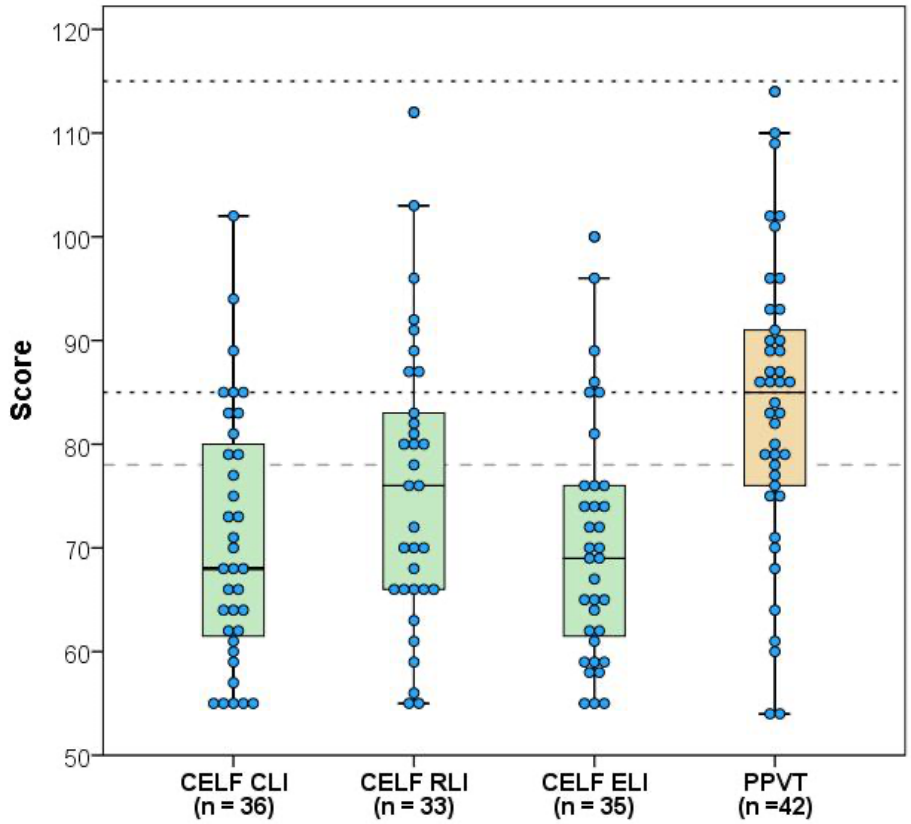
a. $N = 44$

b. CELF subtest norm scores can range from min. 1 to max. 19 with a mean of 10 and SD of 3

c. These subtests comprise the Core Language Index.

d. Basic Concepts ($n = 12$) is administered to children between 3;0 and 3;11, while Word Categories-Receptive ($n = 32$) is administered between 4;0 and 6;11

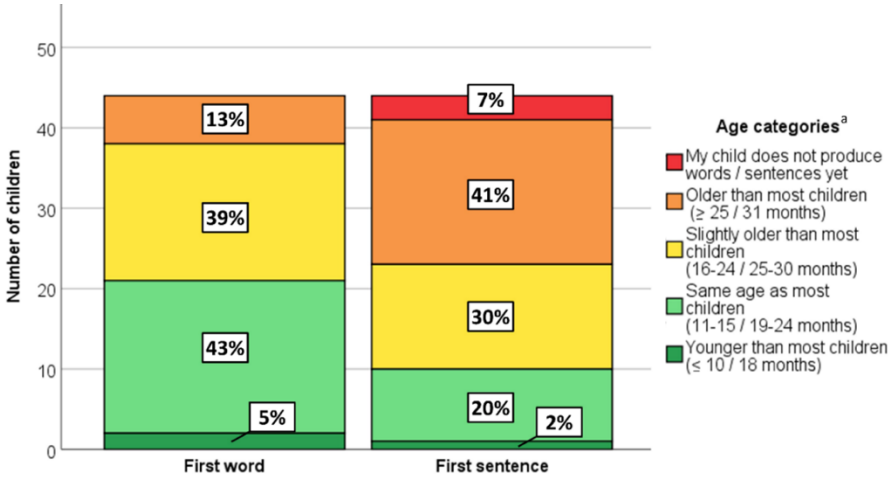
Figure 1. *Box and Whisker Plot (boxplot with individual data points) for the Three CELF Index Scores (green) and the PPVT (orange)*[a]



Abbreviations: CLI: Core Language Index. RLI: Receptive Language Index. ELI: Expressive Language Index. PPVT: Peabody Picture Vocabulary Test

a. Dotted lines indicate + / - 1 SD around the normed mean. The dashed line indicates -1,5 SD below the normed mean. Blue dots represent individual data points.

Figure 2. *Stacked Bar Chart With Percentages of Children in a Specific Age Category During Which the First Word or Sentence was Produced Based on Parental Report* [a]



a. Answer-categories were based on three parameters from the Van Wiechen-Developmental screening instrument (Laurent de Angulo et al., 2005; see appendix D). The ages between the brackets indicate the cut-off for words before the slash and for sentences after the slash.

Language abilities and speech intelligibility

The intelligibility scores ranged between 1.5 to 4.5, with a mean score of 3.0 (SD = 0.9). A total of 30 children (70%) had a score of 3 or higher, indicating minor to no speech intelligibility problems. Speech intelligibility scores were not significantly correlated with age (τ_b = -0.03, p = .798).

Intelligibility scores were weakly to moderately correlated with language outcomes (CELF CLI: τ_b = 0.35, p = .005; CELF RLI: τ_b = 0.33, p = .016; CELF ELI: τ_b = 0.32, p = .012; PPVT: τ_b = 0.32, p = .007). Additional regression analyses showed that speech intelligibility was significantly related to all CELF index scores and the PPVT, but that intelligibility ratings shared only a moderate amount of the variance in language scores (see Table 3).

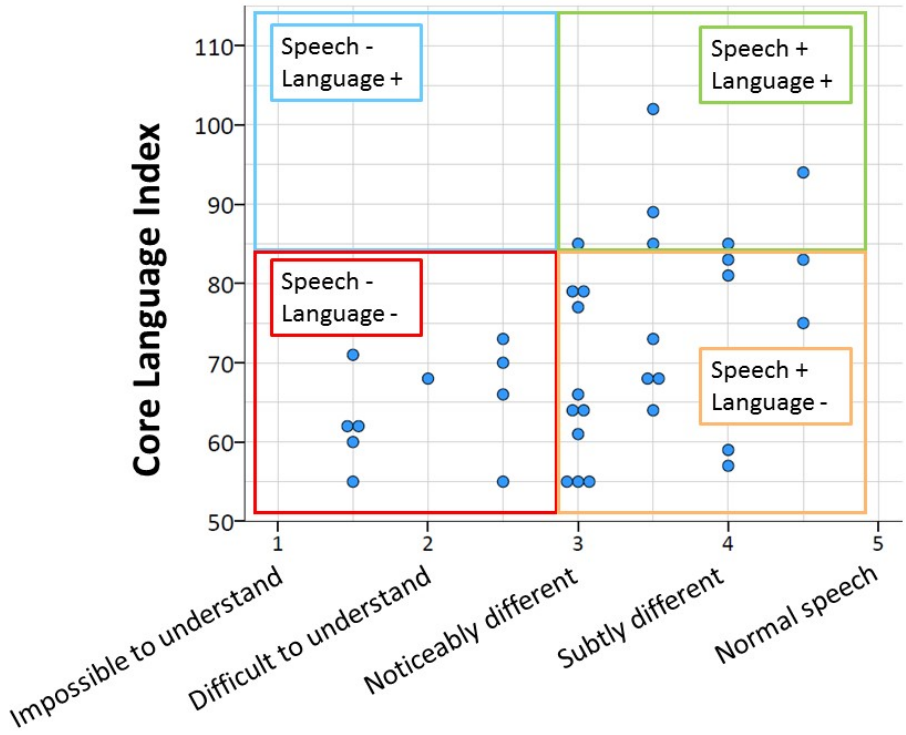
Table 3. *Outcomes of the Regression Analyses for CELF Index and PPVT Scores with Speech Intelligibility Scores as a Predictor.*

	N	β	95% CI	*F*	*df*	*p* [a]	*Adjusted* R^2
Core Language Index	36	6.61	2.31 – 10.90	9.75	1, 34	.004**	0.20
Receptive Language Index	32	6.67	1.66 – 11.67	7.40	1, 30	.011*	0.17
Expressive Language Index	35	5.79	1.58 – 9.99	7.84	1, 33	.008**	0.17
PPVT	41	6.83	1.99 – 11.68	8.13	1, 39	.007**	0.15

Abbreviations: PPVT: Peabody Picture Vocabulary Test.
a. * significant at two-sided $p = .050$, ** significant at $p = .010$

Visual inspection and exploratory descriptive analyses of CELF CLI data in relation to speech intelligibility scores provided more insight into the within-group variability (see Figure 3). Most children (n = 20; 56%) had CELF CLI scores in the below-average range (< -1 SD) with relatively high speech intelligibility ratings of 3 or more. Around a quarter of children (n = 10; 28%) had CELF CLI scores in the below-average range and a low (below 3) speech intelligibility score. A few children (n = 6; 17%) had CELF CLI scores in the average range and speech intelligibility scores of higher than 3. None of the children had CELF CLI scores in the average range combined with intelligibility scores lower than 3. Similar distributions were observed for the CELF RLI, CELF ELI, and PPVT.

Figure 3. *Core Language Index scores [a] in Relation to Speech Intelligibility Scores [b] and Classification of Individuals Based on These Scores Into Different Categories*



a. Dots represent individual data points
b. Labels used on the x-axis reflect shortened versions of the labels used in the CAPS-A. The labels as provided by the CAPS-A are (using our inverted scoring): 5 = Normal; 4 = Different from other children's speech, but not enough to cause comment; 3 = Different enough to provoke comment, but possible to understand most speech; 2 = Only just intelligible to strangers; 1 = Impossible to understand.
c. Colored squares indicate categories based on CLI score low (-; < 85) or high (+; ≥ 85) and speech intelligibility, low (-; < 3) or high (+; ≥ 3).

Discussion

This study shows that 3- to 6-year-old children with 22q11DS have impaired language skills. Our results from standardized language assessment are in line with previous research (Gerdes et al., 1999, 2001; Solot et al., 2001), and we add to the existing knowledge of language development in children with 22q11DS by providing a more detailed profile of language skills during the preschool-years. Our findings indicate that impairment was apparent across all tested language domains, including morphology, syntax, and semantics, at

the sentence- as well as the word-level. In line with previous research, we also found that most parents reported a delayed onset of their child's first word and sentence (Gerdes et al., 1999; Goorhuis-Brouwer et al., 2003; Solot et al., 2001; Solot et al., 2000). Despite the inter-individual variation present in the language scores, we observed that only a small number of children achieved age-expected language outcomes; the majority ranged from mildly impaired to severely impaired. Thus, we add to the body of research that shows that language impairment is a core phenotypic characteristic of 22q11DS.

Both expressive and receptive language abilities were impaired in our sample of preschool children with 22q11DS. In line with previous research in this age group (Gerdes et al., 1999, 2001; Solot et al., 2001), we found that expressive language abilities were more severely impaired than receptive language abilities. Children's receptive and expressive language skills were strongly correlated; children with the most severe receptive language problems also had severe expressive language problems.

With respect to the results on the different subtests, we observed that overall expressive morpho-syntactic skills seemed relatively weak (subtests Repeating Sentences and Word Structure), whereas receptive word-knowledge seemed least impaired (subtest Word Categories-Receptive and the PPVT). This stands in contrast with previous research in older children with 22q11DS that showed the highest subtest scores for expressive morpho-syntactic skills (Word Structure and Recalling Sentences), and the lowest subtest scores for receptive semantics (Sentence Structure and Word Categories-Receptive) (Glaser et al., 2002; Van Den Heuvel et al., 2018). This suggests that the level of language impairment may vary across language domains during childhood, further emphasizing the need to monitor children's language abilities over a prolonged period of time.

While in the present study we found the lowest scores on expressive morpho-syntactic skills, the observed differences between the mean scores on the various subtests were small, all indicating a below average performance. This may indicate that the subtests of the CELF are not sensitive enough to reveal specific strengths or weaknesses. On the other hand, it may also be that the language profile of young children with 22q11DS is not characterized by differences between specific language domains (e.g., morphology, semantics), but rather by a profile of more severe impairment in expressive than receptive abilities across all language domains.

We investigated whether variability in speech intelligibility was related to the observed variability in children's language abilities. In line with our expectations, our results show that speech intelligibility is related to children's

language abilities. Unlike suggested by previous research (Antshel et al., 2009; Shprintzen, 2000), intelligibility problems were not only related to expressive language abilities but also to receptive languages skills. If intelligibility had only been related to expressive language abilities this could have suggested that poor speech intelligibility hindered assessment and scoring of the language tests rather than reflecting impaired language abilities. The fact that intelligibility was also related to specifically receptive language abilities, thus supports the hypothesis that intelligibility may affect quantity and quality of children's socio-communicative interactions, thereby impacting language development. However, it should be noted that our data does not allow us to determine the direction of this relationship. Additionally, speech intelligibility and language abilities only share a moderate amount of variance, indicating that other factors are also at play. Children whose speech was judged as intelligible showed a large amount of individual variation in their language abilities (ranging from severely impaired to age-adequate), while this variation was not observed in children with poor intelligibility, all of whom had impaired language abilities.

Implications

Based on our findings, we reiterate the recommendation of previous research (Solot et al., 2019a) that language assessment should be included in routine clinical care for children with 22q11DS from a young age onward. Based on the small intra-individual variability we observed in our CELF results, we conclude that a low score on the core language index of the CELF (Wiig et al., 2012), or an equivalent short language assessment, can sufficiently inform professionals about whether a child might require more extensive assessment and care.

The majority of children in this study had impaired language abilities in the absence of poor speech intelligibility. It has been shown that specifically children with language impairment early in life have poorer academic and occupational outcomes than children with pure speech problems (Johnson et al., 2010), underscoring the need for separate assessment and monitoring of language problems in all preschool children with 22q11DS. Such assessment should be carried out regardless of their speech intelligibility problems, as these two appear to be interrelated but separate issues. This is supported by research on other neurodevelopmental or genetic conditions that are associated with speech-language difficulties, including Down Syndrome, Cerebral Palsy, SATB2-associated syndrome, and Pheland-McDermid syndrome, which has shown that children's impaired language abilities are not

or only weakly related to speech problems or low speech intelligibility (Brignell et al., 2021; Cleland et al., 2010; Nyman et al., 2021; Snijders Blok et al., 2021). Moreover, our findings highlight that it is crucial to inform professionals outside the field of speech-language pathology, such as genetic counselors and general pediatricians, about the necessity to differentiate between language problems and speech problems in children with 22q11DS, especially among those with intelligible speech. Nevertheless, we recognize that impaired language is not an isolated symptom in 22q11DS and should not be evaluated as such, given the multisystemic nature of the syndrome (McDonald-McGinn et al., 2015).

Children with 22q11DS have an increased risk for developing social-communicative problems and neurodevelopmental disorders (Fiksinski et al., 2018; McDonald-McGinn et al., 2015; Norkett et al., 2017), and this may be related to their language problems. A recent study showed that language difficulties in school-aged children with 22q11DS might be an early marker of an increased risk for the development of psychotic symptoms later in life (Solot et al., 2020), although the exact relation of childhood language difficulties to the development of psychosis warrants further research. A crucial factor in preventing psychiatric problems in children with 22q11DS may be maintaining a balance between a child's capabilities and environmental demands (Fiksinski et al., 2018). Although our results show that expressive problems are more severe in early childhood, we think awareness of especially receptive language problems, which become more prominent in school-age years (Glaser et al., 2002; Van Den Heuvel et al., 2018), is key to ensuring that environmental demands do not exceed the child's capabilities. These receptive language problems, such as difficulties in understanding stories and instructions, are already present at this young age and may be more easily overlooked by caretakers and teachers, especially in the absence of major speech problems (Nyman et al., 2021). Therefore, we urge professionals to monitor receptive language abilities and to raise awareness of the implications of these receptive problems in parents and other professionals working with the child.

Strengths, limitations, and future directions

A strength of this study is our relatively large sample of children with 22q11DS within a narrow age range, allowing for more reliable generalization of our results. Although most participants were recruited through a specialized outpatient clinic and may therefore consist of those children with more severe phenotypic characteristics, our sample presents with similar population

characteristics as reported in the literature (McDonald-McGinn et al., 2015). We did not collect data regarding race and/or ethnicity of our sample, which could limit the representativeness of our sample and the generalizability of the results. A limitation of the current results is that some children could not complete all subtests of the standardized language assessment and are missing in some of the analyses. The fact that some children could not complete certain tests is informative in and of itself, and our observations suggest that these children also had below-average language abilities. Nevertheless, the incomplete task data limits us in describing the language profile of these children.

Our findings confirm earlier suggestions that the expressive-receptive language profile of young children with 22q11DS differs from that of older children, but longitudinal research is needed to determine when this shift occurs. Moreover, although standardized tasks are useful from a clinical point of view, future research could use spontaneous language assessment to further investigate linguistic abilities of preschoolers with 22q11DS in more detail, such as grammatical complexity and error patterns. Spontaneous language analysis might aid the characterization of the language profile of children with low language levels, as this type of assessment has a higher ecological validity and can be administered to children with an even wider range of language levels. This can benefit both theory with regards to our understanding of the pathway from genes to neurological development to the development of specific linguistic abilities, as well as clinical practice with regards to targets for intervention.

We consider the most important strength of this study that we used an instrument to evaluate the language skills of the children with 22q11DS that is commonly used, available in various languages, and can easily be integrated into clinical practice. The same holds for the speech intelligibility rating, as performed by speech and language pathologists who work with children with 22q11DS. However, the validity of the intelligibility subscale of the Cleft Audit Protocol for Speech has not consistently been evaluated as good (Chapman et al., 2016; Sell et al., 2009) and judgement of intelligibility may be subject to bias. We showed that intelligibility explained some of the variability observed in the language abilities of children with 22q11DS. Given that previous research did not detect a relationship between palatal abnormalities and language outcomes in 22q11DS (Gerdes et al., 2001; Solot et al., 2001), our findings may prompt future research to investigate how the complex and multifactorial speech and intelligibility problems in 22q11DS contribute to their impaired language abilities. It has been shown that children

with 22q11DS frequently have articulation disorders (Solot et al., 2000) and have heightened incidence of apraxia of speech as compared to children with non-syndromic cleft palate (Kummer et al., 2007). Therefore, a more detailed investigation of the underlying mechanisms of the speech errors and their relationship with intelligibility and language may be relevant to further inform our understanding of the interrelated development of speech and language abilities in the 22q11DS population. In addition, future studies are needed to investigate other factors that may affect language development, such as cognitive level or interrelations with other phenotypic characteristics of 22q11DS, such as socio-communicative difficulties (Angkustsiri et al., 2014; Campbell et al., 2011; Norkett et al., 2017; Van den Heuvel et al., 2017a).

Finally, it has been suggested that children with 22q11DS may be similar to children with Developmental Language Disorder (DLD; Goorhuis-Brouwer et al., 2003; Kambanaros & Grohmann, 2017; Swillen et al., 2001; Vansteensel et al., 2021). As children with 22q11DS frequently are treated by speech-language pathologists who also work with children with DLD, future research could investigate to what extent the language profile of children with 22q11DS overlaps with or differs from that of children with DLD. This would be helpful in determining whether these children may benefit from the same interventions and therapies.

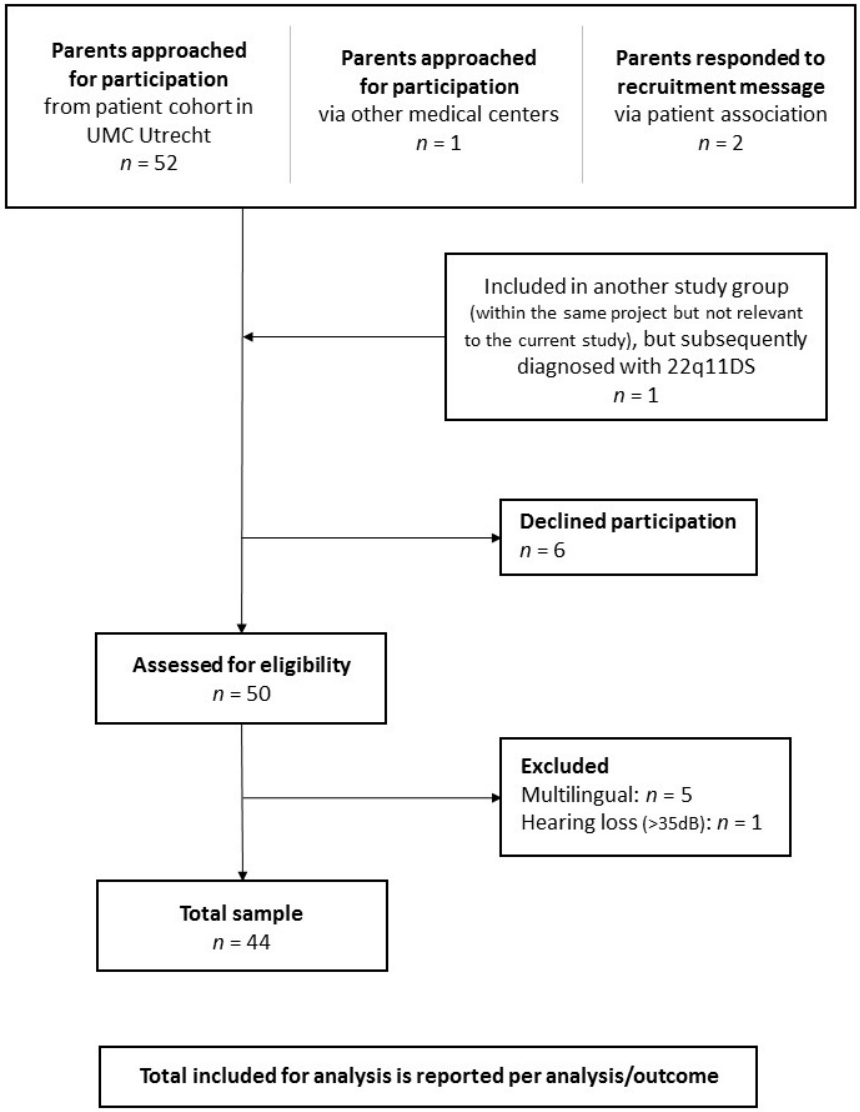
Conclusion

This study shows that most 3- to 6-year-old children with 22q11DS have impaired language skills in all tested language domains. Expressive abilities are relatively more impaired than receptive language abilities. We reiterate the importance of incorporating language assessment into routine clinical care, as our results contrast with findings in older children, thus suggesting the degree of impairment may vary across language domains during childhood. Speech intelligibility explains some of the variability in language outcomes, but the pathways underlying this relationship are currently unknown. Future research is warranted to further investigate the interrelatedness of speech and language impairment in these children.

Supplementary information

Appendix A.

Figure 1. *Flowchart of participant enrollment and inclusion*



Note. The patient cohort is based at the national multidisciplinary outpatient clinic for children with 22q11DS at the University Medical Utrecht. The national patient association (Stichting Steun 22Q11) posted two messages on their website and one message in the yearly magazine. Four other medical centers in the Netherlands that regularly treat and refer 22q11DS patients were also approached to assist in recruitment. One center provided study information to the parents of one patient, but the other three centers indicated that there were no patients known that met the inclusion criteria and were not already known at the University Medical Center Utrecht.

Appendix B.

Table 1. *The highest attained educational level [a] for both mother and father as compared to the average Dutch population [b].*

	Mother		*Father*		*Dutch population*
Category	N	%	N	%	%
2	1	2,3	1	2,5	7
3	3	7	2	5	9,3
4	2	4,7	3	7,5	8,1
5	5	11,6	4	10	12,7
6	12	27,9	13	32,5	13,5
7	1	2,3	0	0	9,7
8	11	25,6	9	22,5	22
9	8	18,6	8	20	13,2

a. Parental education was indexed a 9-point scale (ranging from 1 'no education' to 9 'university degree'). This scale is based on the International Standard Classification of Education (ISCED; 2011) as adapted for the Dutch educational system by the Dutch National Bureau of Statistics (CBS). Similarly, the categories can be roughly divided into three levels: low (1-3), medium (4-6) high (7-9). There were no parents in category 1. Four children came from a single parent household, all of which were single mothers. For one other child, only the education level of father was known, as mother declined to answer this question.
b. Based on statistics by the CBS (retrieved from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/82275NED/table?fromstatweb).

Appendix C.

A description of the standardized language tasks used in this study can be found below.

Peabody Picture Vocabulary Test III-NL (PPVT; Schlichting, 2005)

The PPVT is an age-normed task that measures receptive vocabulary and can be used with children from 2;3 (years; months) up into adulthood. The child is asked to point to one out of four pictures that corresponds to a word orally presented by the examiner.

Clinical Evaluation of Language Fundamentals (CELF) Preschool-2-NL (Wiig et al., 2012)

The CELF is an age-normed task for children between 3;0 and 6;11 (years; months). Six subtest scores can be used to calculate composite index scores. An overview of the CELF subtests can be found in Table 7.

- The Core Language Index (CLI) reflects global language abilities and consists of Sentence Comprehension, Word Structure, and Expressive Vocabulary.
- The Receptive Language Index (RLI) reflects expressive language abilities, or language production, and consists of Sentence Comprehension, Concepts and Following Directions, and either Word Categories-Receptive or Basic Concepts, depending on the age of the child. Basic Concepts is normed for children from 3;0 to 3;11, while Word Categories-Receptive is normed for children from 4;0 to 6;11.
- The Expressive Language Index (ELI) reflects receptive language abilities, or language comprehension, and consists of Word Structure, Expressive Vocabulary and Recalling Sentences.

Table 1. *Description of the CELF Preschool-2-NL subtests*

Receptive language Index		
Task	*Language domain*	*Description*
Sentence Comprehension	Receptive syntax	The child is asked to point to one out of four pictures that corresponds to a sentence read by the examiner. This subtest has 22 items, and each correct answer is rewarded with 1 point.

Concepts and Following Directions	Receptive semantics and syntax	The child sees pictures displaying different animals of different sizes and is asked to follow instructions given orally by the examiner with regards to the order and size of the animals the child should point to. This subtest has 22 items, and each correct answer is rewarded with 1 point.
Basic Concepts (for ages 3;0-3;11)	Receptive semantics	The child is asked to point to the item in the picture that belongs to the semantic category given by the examined (e.g., *which one is last / cold / long*). This subtest has 18 items, and each correct answer is rewarded with 1 point.
Receptive Word Categories (for ages 4;0-6;11)	Receptive semantics	The child is asked to point to the two pictures that belong together out of a set of three or four pictures. This subtest has 20 items, and each correct answer is rewarded with 1 point.

Expressive language Index		
Task	*Language domain*	*Description*
Word Structure	Expressive morpho-syntax	The child is asked to finish a sentence read by the examiner accompanied by one or more pictures (e.g., *this is one cat, and these are two …*, where the second picture depicts two cats). This subtest includes items related to verb conjugation, adjectives, plurals, diminutives, possessives and more. It has 23 items, and each correct answer is rewarded with 1 point.
Expressive Vocabulary	Expressive semantics	The child is asked to name an object or action depicted in a picture. This subtest has 20 items, and each correct answer is rewarded with 2 points, some items having answers worth 1 point.
Recalling Sentences	Expressive syntax	The child is asked to repeat sentences increasing in length and complexity read by the examiner. There are 13 sentences and repeating the sentence without mistakes or alterations is rewarded with 3 points, one mistake/alteration is rewarded with 2 points, and two or three mistakes/alterations is rewarded with 1 point. When the child makes four or more mistakes or alterations, they receive 0 points.

Appendix D.

Answer-categories were based three parameters from the Van Wiechen-Developmental screening instrument (Laurent de Angulo et al., 2005):

- Parameter 37: 90% of the children will have a productive vocabulary of at least 2 words by the age of 15 months
- Parameter 41: 90% of the children will be able to combine 2 words in a short sentence by the age of 24 months
- Parameter 45: 90% of the children will be able to combine 3 words in a sentence by the age of 36 months

Therefore, answer categories 'slightly older than most children', 'older than most children', and 'my child does not produce words / sentences yet' were grouped together as indicating a delayed onset of the first word or sentences.

Appendix E.

Table 1. *Task completion, mean scores, standard deviations, range of scores and percentage of children with a clinically significant score (< -1 or -1.5 SD) of the total sample of children with 22q11DS (N = 44) on each of the CELF index scores and the PPVT* [a].

	Task Completion (n)	*M*	*SD*	*Range*	*Score <-1 SD (%)*	*Score <-1.5 SD* [b] *(%)*
Core Language Index	36	70.8	12.2	55 – 102	83	69
Receptive Language Index	33	75.8	13.8	55 – 112	76	56
Expressive Language Index	35	70.4	11.6	55 – 100	83	80
PPVT	42	83.7	14.1	55 – 114	50	29

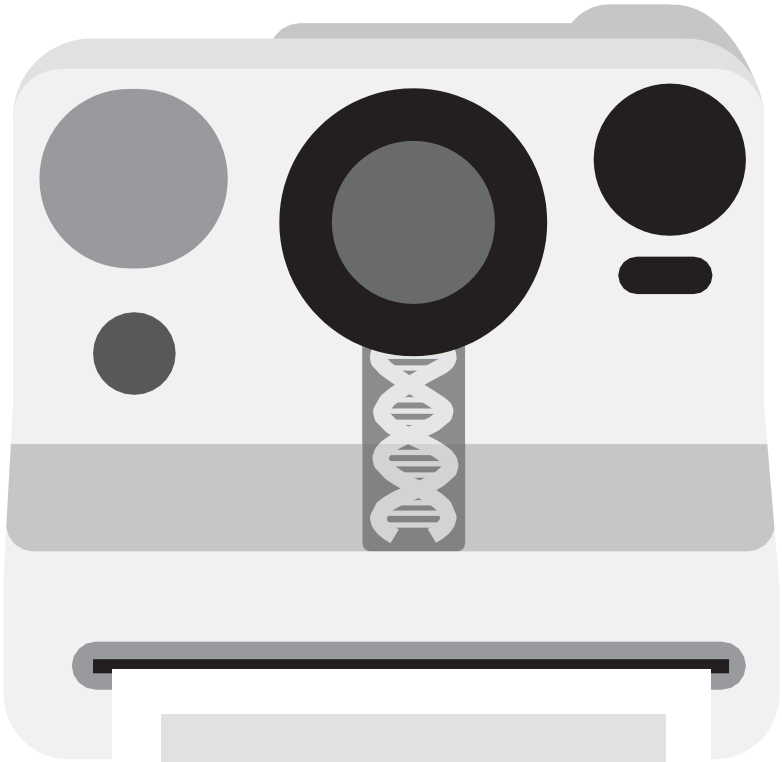
Abbreviations: PPVT: Peabody Picture Vocabulary Test.

a. CELF index and PPVT scores range from min. 55 to max. 145 with a mean of 100 and SD of 15.

b. In some contexts or countries, -1.5 SD is taken as the cut-off for clinical relevance for these index scores. We therefore also report these proportions.

Appendix F. *Author Contributions*

Contribution	**Author**
Conceptualization	Emma Everaert; Iris Selten; Tessel Boerma; Jacob Vorstman; Frank Wijnen; Ellen Gerrits
Formal analysis	Emma Everaert; Iris Selten
Investigation	Emma Everaert; Iris Selten; Tessel Boerma
Resources	Michiel Houben
Data Curation	Emma Everaert; Iris Selten; Tessel Boerma; Hester de Wilde; Desiree Derksen; Sarah Haverkamp
Writing-original draft	Emma Everaert; Iris Selten
Writing-review and editing	Emma Everaert; Iris Selten; Tessel Boerma; Michiel Houben; Jacob Vorstman; Hester de Wilde; Desiree Derksen; Sarah Haverkamp; Frank Wijnen; Ellen Gerrits
Visualization	Emma Everaert; Iris Selten
Supervision	Tessel Boerma; Michiel Houben; Jacob Vorstman; Frank Wijnen; Ellen Gerrits
Project administration	Emma Everaert; Iris Selten; Tessel Boerma
Funding acquisition	Frank Wijnen



4

Narrative Comprehension and Production Abilities of Children with 22q11.2 Deletion Syndrome

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Background. The 22q11.2 Deletion Syndrome (22q11DS) is associated with language deficits and weak intellectual functioning. In other clinical groups, linguistic and cognitive difficulties have been associated with impaired acquisition of narrative abilities. However, little is known about the narrative abilities of children with 22q11DS. ***Aims.*** To describe the ability of children with 22q11DS to produce and comprehend narrative macrostructure. Additionally, to examine the role of intellectual functioning in explaining their narrative difficulties. ***Methods and Procedures.*** Narrative skills of 14 school-aged children with 22q11DS were compared to those of younger typically developing (TD) children matched on mental age and same-aged peers with Developmental Language Disorder (DLD). ***Outcomes and Results.*** Children with 22q11DS had significantly lower scores on narrative comprehension than younger TD children. No significant differences emerged on narrative production. Children with 22q11DS and children with DLD did not differ significantly on any of the narrative measures. ***Conclusions and Implications.*** Narrative comprehension in children with 22q11DS seems more affected than production. Narrative comprehension difficulties cannot be entirely explained by a low level of intellectual functioning. Narrative comprehension and production abilities in 22q11DS require further consideration.

Introduction

The acquisition of narrative abilities, the abilities to use language to tell and understand stories, is difficult for children who experience language problems (Fey et al., 2004). Difficulties in narrative development may negatively affect a child's daily functioning, as narrative abilities are essential to communicate with peers and family, and to interact in a school context (Boudreau, 2008). The 22q11.2 deletion syndrome (22q11DS) is a genetic disorder that is, amongst others, associated with severe difficulties in language development (for an overview, see Solot et al., 2019). Many children with 22q11DS also experience problems in social interaction as well as learning difficulties (Swillen & McDonald-McGinn, 2015). Weak narrative abilities may play a role in the occurrence of such problems in 22q11DS. Therefore, the first aim of the present study is to investigate the narrative production and comprehension abilities of children with 22q11DS.

We compare the narrative abilities of children with 22q11DS with those of typically developing (TD) children matched on mental age. Hereby, we investigate whether narrative abilities of children with 22q11DS lag behind the level of what can be expected for their level of cognitive development, as a below average level of intellectual functioning is characteristic for 22q11DS. In addition, we compare the narrative abilities of children with 22q11DS to those of chronologically age-matched children with a Developmental Language Disorder (DLD). This comparison allows us to study the role of intellectual functioning in the narrative abilities of children with 22q11DS, as, in contrast to 22q11DS, DLD is mostly associated with an average level of intellectual functioning (Bishop et al., 2017; Swillen & McDonald-McGinn, 2015).

The 22q11.2 Deletion Syndrome

22q11DS is caused by a micro-deletion on the long arm of chromosome 22 and is estimated to occur in 1 in 3,000 to 6,000 (live) births (Swillen & McDonald-McGinn, 2015). The syndrome has many possible symptoms, which can vary in their expression across individuals and affect almost any part of the body. Common symptoms include congenital heart defect, palatal abnormalities and intellectual impairment. Most children with 22q11DS function on a level of borderline intelligence (IQ between 70-85) or mild intellectual disability (IQ between 55-70; (De Smedt et al., 2007; Swillen et al., 2018). Additionally, children with 22q11DS are at increased risk for psychopathology, especially Autism Spectrum Disorder, Attention Deficit

Hyperactivity Disorder, and Anxiety Disorders in childhood, and schizophrenia in young adulthood (Fiksinski et al., 2018).

One of the earliest developmental symptoms noted by parents of children with 22q11DS and clinicians is the delayed achievement of language milestones (Solot et al., 2019a). Over 90% of children with 22q11DS do not become verbal within the typical age limits (Gerdes et al., 1999; Mills et al., 2006; Solot et al., 2000). Over the course of childhood, the majority of children with 22q11DS continue to have difficulties across various language domains, such as vocabulary and grammar (Glaser et al., 2002; Solot et al., 2019a; Van den Heuvel et al., 2018). In addition, while typically developing (TD) children generally have better receptive language skills (understanding language) compared to expressive language skills (producing language; (Bates, 1993), this advantage of receptive language skills seems smaller in school-aged children with 22q11DS (Van Den Heuvel et al., 2018). This suggests that monitoring receptive language skills in these children may thus be particularly important.

Finally, children with 22q11DS often struggle to effectively use language in a social context, as is evident from problems in communication, interaction and peer relations in children with 22q11DS (Angkustsiri et al., 2014; Persson et al., 2006; Van den Heuvel et al., 2017a). One aspect of language that is especially important for language use in everyday life is the development of narrative abilities (Botting, 2002), which is the focus of the current study.

Development and assessment of narrative abilities

A narrative is a story that is used to inform others about a sequence of personal or fictional events in a coherent and structured way. Both our ability to understand and to produce narratives is vital, given their prominent role in social interactions in personal, school and formal settings. Moreover, the development of narrative abilities is related to the development of literacy skills and academic success (Botting, 2002; Johnston, 2008; Westerveld & Gillon, 2010). Studies in the general population show that children's narrative development starts around the age of 2 years and continues into adolescence. Around the age of 9 years old, most children are able to tell a story that connects a series of actions and events, contains a coherent plot, and involves character descriptions (Pinto et al., 2019; Roelofs-Brogers, 1998).

To assess story generation abilities, a child is usually requested to tell a story using a set of pictures as prompts. The produced narrative can be analyzed globally at the level of narrative macrostructure by evaluating

organizational aspects of the narrative that support transfer of story content, such as the use of an episodic structure. In addition, narrative production can be analyzed locally at the level of narrative microstructure by evaluating the linguistic aspects of the narrative, such as lexical diversity and grammatical complexity. To assess narrative comprehension, a child is requested to answer a set of comprehension questions about the story events and emotional states of the characters (Botting, 2002; Norbury & Bishop, 2003).

Narrative problems and associated mechanisms

For some children, the development of narrative production and comprehension lags behind in comparison to their peers. A well-known group that experiences persistent narrative difficulties are children with a diagnosis of Developmental Language Disorder (DLD). Around 5-7% of children in the general population receive this diagnosis, because they have severe problems in language acquisition in absence of intellectual disability and without an evident physical, neurological or environmental cause (Bishop et al., 2017). Research on the narrative abilities of children with DLD has shown that their difficulties in narrative production and comprehension are associated with impairments in (a combination of) linguistic, cognitive and/or social functions (Blom & Boerma, 2016; Duinmeijer et al., 2012; Lindgren, 2019; Lynch et al., 2008; Matthews et al., 2018), depending on which specific narrative skills are evaluated (Duinmeijer et al., 2012). Difficulties in the organization of plot structure and transfer of story content (i.e., in production of narrative macrostructure) are reported to be relatively independent of language ability, including receptive vocabulary size and grammar knowledge (Blom & Boerma, 2016; Boerma et al., 2016). Rather, weak production of narrative macrostructure is associated with impairments in cognitive functions, such as attention, working memory and the use of real-world knowledge to understand a (social) situation (Blom & Boerma, 2016; Duinmeijer et al., 2012; Ketelaars et al., 2012). This contrasts with weak performance on measures of narrative microstructure, which is often associated with lower language skills in children with DLD (Botting, 2002). Finally, problems with narrative comprehension in these children have been related to poorer receptive vocabulary, weaker sustained attention and inference problems (Blom & Boerma, 2016; Boerma et al., 2016).

Narrative skills of children with 22q11DS

Children with 22q11DS may be specifically vulnerable to develop difficulties in production of narrative macrostructure and narrative comprehension, given

that 22q11DS is associated with language problems as well as impairments in the cognitive and social skills that have been associated with narrative difficulties in DLD. Solot and colleagues (2019) summarized the following narrative difficulties in children with 22q11DS: "*Extracting salient points from verbal or written narrative, understanding implications, making inferences and predictions, and use of disorganized, terse, ambiguous, or verbose narratives*" (p.988). To our knowledge, only two studies have directly assessed the narrative skills of children with 22q11DS (Persson et al., 2006; Van Den Heuvel et al., 2017b). Persson and colleagues (2006) used the Bus Story retelling task with 19 school-aged children with 22q11DS. The children did not make more grammatical errors compared to TD children of the same age, but produced shorter and fewer grammatically complex sentences. In addition, children with 22q11DS needed more encouragement to take initiative and they transferred less essential information in their stories. Van Den Heuvel and colleagues (2017b) assessed 27 children with 22q11DS between 6 and 14 years old with a perspective taking task, in which children were asked to describe a picture and ascribe feelings and thoughts to the characters. They report that children with 22q11DS provided much information about irrelevant visual details, resulting in a chain of unconnected utterances. The authors conclude that children with 22q11DS transferred less essential information than TD children. Taken together, emerging evidence suggests that children with 22q11DS indeed experience problems in the production of narratives. However, more research is warranted, in particular with regard to the comprehension aspect of narrative skills and whether narrative abilities of children with 22q11DS are in line with what can be expected for their level of cognitive development.

Research aims and hypotheses

Given that the development of narrative abilities is critical for communicating personal experiences, social interaction and academic functioning, a better understanding of the narrative production and comprehension abilities in 22q11DS is important. Narrative skills have been shown to build on linguistic and cognitive functions (Johnston, 2008; Matthews et al., 2018); this holds especially for production of narrative macrostructure and narrative comprehension (Blom & Boerma, 2016). Consequently, children with 22q11DS are at a high risk of impairment in these domains, as this syndrome is associated with an increased risk for both intellectual and linguistic difficulties. Therefore, the first aim of the present study is to describe the narrative abilities of children with 22q11DS. Subsequently, we compare the narrative abilities of children with 22q11DS with those of a group of younger TD children matched

on mental age. This comparison will show if their narrative abilities are keeping with, or impaired beyond, what may be expected for their developmental level. We expect children with 22q11DS to perform on par with their younger, mentally age-matched peers on the measures for production of narrative macrostructure and narrative comprehension. If confirmed, this would indicate that their delay in narrative development is in keeping with their global cognitive development.

Furthermore, we compare the narrative abilities of children with 22q11DS with a group of same-aged peers with a diagnosis of DLD. We may expect that children with 22q11DS perform on par with the children with DLD, despite the overall higher level of intellectual ability in the DLD group, as we know that children with DLD can demonstrate weak language skills in the absence of intellectual problems. If confirmed, this may indicate that narrative difficulties of children with 22q11DS cannot entirely be attributed to a lower level of intellectual functioning However, it could also be that such a discrepancy between intellectual ability and language skills is a unique feature of DLD. Alternatively, the children with DLD could perform better than the same-aged children with 22q11DS on the narrative tasks, given that the latter group has both intellectual and linguistic difficulties. This could suggest a role of specific language difficulties in addition to low intellectual ability in narrative abilities in 22q11DS.

Method

Participants

Our participants took part in a larger project which aimed to measure brain activation during language processing by using brain scans (fMRI; Vansteensel et al., 2021). A total of 14 children with 22q11DS and 15 children with DLD, all between 6 to 10 years old, were included in this study. For both groups, we only included children who did not present with intellectual disability (verbal or non-verbal IQs were higher than 70), hearing loss (>35dB) and a diagnosis of Autism Spectrum Disorder. Parents of all participants gave written informed consent for their child to participate in the study. The study was approved by the Ethical Review Board of the University Medical Center Utrecht, and was performed in accordance with the Declaration of Helsinki (World Medical Association, 2013).

Narrative task results of children with 22q11DS and children with DLD were compared with data from 14 younger TD children, who were selected from a larger pool of children that participated in an earlier study (Boerma et al., 2016). We matched the TD children to our participants with 22q11DS based

on their nonverbal mental age, since we aimed to investigate whether narrative abilities of 22q11DS children were in line with their developmental level. For all TD children, intelligence scores of the short version of the Wechsler Nonverbal-NL (WNV; Weschler & Naglieri, 2006) were available. For both children with 22q11DS and children with DLD, we collected intelligence scores from standardized intelligence measures (mostly Wechsler tests) obtained from either medical or school records. If intelligence was assessed more than two years prior to the study, we administered the short version of the WNV-NL at the start of the test session. We calculated the mental age of all participants using the formula: *[(full scale IQ score * participants chronological age) / 100]* (Caplan et al., 2015). Participant characteristics are presented in the results section (see Table 1).

Measures

Language abilities**.** We used two measures to collect background information on the language abilities of our participants with 22q11DS and DLD: 1) To assess children's grammatical language skills*,* we used the sentence repetition subtest of the Dutch adaptation of the Clinical Evaluation of Language Fundamentals (CELF-IV-NL; Kort et al., 2010). For this task, children are asked to repeat sentences of increasing difficulty, read to them by a researcher. This task is often used to identify children with DLD (Klem et al., 2015). We used children's chronological age to convert raw scores into age-corrected standard scores (M = 10; SD = 3) with a higher raw score indicating better grammatical skills and a standard score below 7 indicating "below average performance"; 2) to assess receptive vocabulary, we used the Dutch adaptation of the Peabody Picture Vocabulary Test (PPVT-III-NL; Schlichting, 2005). During this task, children are shown four different pictures and are requested to point to the picture that corresponds to the target word that is read out loud by the researcher. Performance on the PPVT is measured as a quantitative score with higher raw scores indicating better word comprehension skills. We converted raw scores into age-corrected standard scores (M = 100; SD = 15). PPVT scores were also available for the group of TD children.

Narrative abilities. Children's abilities to produce and comprehend narrative macrostructure were measured with the Multilingual Assessment Instrument for Narratives (MAIN; Gagarina et al., 2012). The MAIN was developed within the framework of the COST Action IS0804 *Language Impairment in a Multilingual Society: Linguistic Patterns and the Road to Assessment* and can be used to assess different aspects of narrative comprehension and

production of (bilingual) children from 3 to 10 years old. For the purpose of the current study, we used a *model story* and a *production story* from the MAIN stimulus set. Both stories are depicted by a sequence of six pictures and contain three story episodes. In each episode, elements of the time and place of the story and story characters are introduced. Furthermore, each story episode contains a goal (e.g., cat wanted to catch baby birds), an attempt to reach that goal (e.g., cat tried to climb the tree) and an outcome of that attempt (e.g., cat was chased away by the dog). In addition, each story episode includes elements that are related to the internal/mental state of the main characters (e.g., cat was scared).

All children first saw and heard the *model story* (Cat), which was read to them by the researcher, and were asked ten comprehension questions that targeted the story structure and internal states of the characters. Hence, the main goal of using the model story was to introduce the narrative assessment, and to evaluate narrative comprehension. Subsequently, all children were asked to generate their own story using the stimulus set that belongs to the *production story* (Baby birds) to assess production of narrative macrostructure. This was followed by a similar set of ten comprehension questions. Most children enjoyed this narrative task, which was administered as the final task of a test session of about 60 minutes in which children completed several language and cognitive tasks.

Scoring narrative abilities

We used the standard outcome measures for production and comprehension of narrative macrostructure offered by the MAIN: 1) Production. We counted how many story structure elements children incorporated during telling of the production story. The inclusion of these story elements is awarded points, resulting in a production score with a higher score indicating a better performance. The story elements included the setting (0, 1 or 2 points) and, for each episode, the internal state as initiating event, goal, attempt, outcome, and the internal state as reaction (each 0 or 1 point; max. 17 points). 2) Comprehension of the model story and production story. For each story, the MAIN provides ten comprehension questions to assess children's understanding of the story events and their consequences, and the goals of the main characters and their thoughts and feelings. For each story separately, children were awarded one point for each question that they answered correctly. Hence, a higher score indicates a better story comprehension (each story max. 10 points). A high quality microphone (Samson Go Mic) was used to record all narratives. The narratives were scored offline by a trained

researcher**.** Over 40% of the narratives from the TD group were scored by a second independent rater, resulting in acceptable inter-rater agreement (for exact numbers see Boerma et al., 2016)). The data of children in the two clinical groups were all scored using the same protocol. In case of uncertainties, a final score was awarded by consensus.

Data analyses

All analyses were performed in SPSS version 26. We confirmed our matching of the children with 22q11DS to TD children, based on mental age by using Univariate Analyses of Variance (ANOVA). In addition, we compared the three groups on chronological age, intelligence and gender distribution by using ANOVA and χ^2 tests. Given that significant differences in chronological age and intelligence are inherent to the design of this study, we only adjust for possible gender differences in our analyses. In addition, we evaluated the language abilities of children with 22q11DS and children with DLD using their raw and standard scores on the PPVT and the sentence repetition task.

The main aim of the current study was to compare narrative production and comprehension between children with 22q11DS, TD children and children with DLD. Since the MAIN narrative assessment does not provide age-corrected standard scores, we took the performance of the group of TD children as a reference to evaluate the narrative performance of children with 22q11DS and children with DLD. Given our limited sample size and the fact that we measured narrative abilities on an ordinal scale, we used three non-parametric Kruskal-Wallis tests with respectively the narrative production score, the comprehension score on the model story and the comprehension score on the production story as the outcome variables and with group (22q11DS, DLD, TD) as the independent variable. The Kruskal-Wallis test is a rank-based test, implying that scores of all children are ordered from lowest to highest and are assigned a rank. We therefore considered it insightful to display the median score for each group in our sample descriptives. If the Kruskal-Wallis test resulted in a significant group difference on any of the narrative measures, we used non-parametric Mann-Whitney tests for pairwise comparisons and applied Bonferroni correction for multiple testing. We additionally calculated the effect size *r*, by dividing the z-score of each pairwise comparison (as provided by SPSS) by the square root of the total number of observations. We visually inspected the frequency distribution of number of points that children received on these narrative measures.

Our limited sample size and choice of narrative measure prevent us from drawing meaningful conclusions regarding the associations between our

measures for linguistic and intellectual functioning and narrative abilities. We therefore included the results of these analyses as supplementary material (see appendix A).

Results

Matching procedure and participant characteristics

Table 1 shows the demographic information of the participants as well as their scores on intelligence and standardized language tests for each group and the statistics of these variables. We successfully matched the children with 22q11DS to the TD children based on their mental age (p = 1.00). IQ scores of the children with 22q11DS fell on average in the borderline range, significantly lower than those of the TD children and children with DLD (p < .001), implicating that chronological and mental age differed significantly between the three groups. That is, the children with 22q11DS had a significantly higher chronological age than the TD children (p = .001), but did not differ from the children with DLD in chronological age (p = 1.00). Moreover, the children with 22q11DS and TD children had a significantly lower mental age as compared to the children with DLD (p = .001). Finally, the children with DLD did not differ from children with 22q11DS with regard to their scores on the background language measures and both groups did not differ from the TD children on the raw score of the PPVT. Children with 22q11DS scored more than 1 standard deviation (SD) below the mean on the PPVT, whereas children with DLD performed within the average range on this task. For the sentence repetition task, both children with 22q11DS and children with DLD obtained on average a standard score lower than 7, indicating a below average performance.

Narrative Production

Table 2 shows the means, standard deviations, medians and range of participant scores per group on the narrative production task. The scores did not differ significantly between the children with 22q11DS, children with DLD and children in the TD group, indicating that we did not detect evidence for a difference between children in the number of story structure elements they produced [H(2) = 3.74, p = .154, η^2= .01; see Table 2].

Table 1. *Means and Standard Deviations for Age (in months), IQ Scores and Standardized Language Measures for the Children with DLD, Children with 22q11DS and TD Children.*

	TD			22q11DS			DLD			Comparison	
Variable	*N*	*M*	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*	χ^2/F	*p*
Gender (males)	7			8			8			0.14	.931
Chronological	14	77.2	14.7	14	104.2	19.1	15	98.4	20.6	8.40	.001
Mental age	14	76.6	14.2	14	76.7	14.6	14	104.7	23.9	11.2	<.001
Total IQ score	14	99.4	6.0	14	74.0	8.6	14	105.4	15.8	32.4	<.001
PPVT raw score	14	92.2	13.0	13	88.5	8.4	15	95.1	14.4	1.00	.376
PPVT standard	14	108.2	8.2	13	83.1	13.7	15	93.2	13.6	14.9	<.001
CELF raw score		-	-	14	33.2	10.1	15	25.1	12.1	3.80	.062
CELF standard score		-	-	14	5.2	2.2	15	3.9	2.0	-1.64	.113

Note. One girl with 22q11DS did not complete the PPVT. For one girl with DLD we were not able to compute her mental age, because we did not manage to obtain the IQ information from her school. *PPVT: Peabody Picture Vocabulary Test; *CELF: the sentence repetition task of the Clinical Evaluation of Language Fundamentals.

Table 2. *The Means, Standard Deviations (SD), Medians, and Ranges for the Score on the Production Task for the Children with 22q11DS, children with DLD, and TD Children.*

Group	*N*	*Mean*	*SD*	*Median*	*Range*
TD	14	8.6	2.2	8.5	5 - 12
22q11DS	14	7.0	2.6	7.0	2 - 12
DLD	15	7.2	2.5	6.0	4 - 13

Table 3. *The Means, standard Deviations (SD), Medians and Ranges for the Comprehension Score for the Model Story and the Production Story for the Children with 22q11DS, Children with DLD, and TD Children.*

	Model story					Production story				
Group	*N*	*Mean*	*SD*	*Median*	*Range*	*N*	*Mean*	*SD*	*Median*	*Range*
TD	14	9.6	0.5	10.0	9-10	14	9.0	1.2	9.5	7-10
22q11DS	14	8.4	1.4	9.0	6-10	13	6.5	1.9	6.0	4-10
DLD	15	8.6	1.4	9.0	5-10	14	7.4	1.9	8.0	5-10

Note. Comprehension data for the production story were not available for 1 child with 22q11DS and 1 child with DLD due to technical issues during data collection.

Narrative Comprehension

Significant differences between the three groups were observed for comprehension of both the model and the production story (see Table 3).

Model story. The Kruskal-Wallis test showed a significant main effect of group

for the comprehension score of the model story [H(2) = 6.58, p = .037, η^2= .06]. Additional pairwise comparisons did not survive Bonferroni correction. However, we found a medium effect size both for the comparison between children with 22q11DS and TD children (U = 52.00, p = .024, r = 0.43) and between children with DLD and TD children (U = 58.00; p = .027, r = 0.41). Finally, the observed small difference between 22q11DS and DLD was not statistically significant (U = 97.00; p = .717, r = 0.07). Figure 1 displays the distribution of scores per group on the comprehension task for the model story. Visual inspection of the data shows that the TD children performed at or near ceiling level, as eight children (57%) answered all questions correctly and six children (43%) only gave one incorrect answer. For the children with 22q11DS, only four children answered all questions correctly (29%) and six children provided more than one incorrect answer (43%). Similarly, only four children with DLD answered all questions correctly (27%) and five children provided more than one incorrect answer (33%; see Figure 1).

Production story. The Kruskal-Wallis test showed a significant main effect of group for the comprehension score of the production story [H(2) = 12.02, p = .002, η^2 = 0.21]. Pairwise comparisons showed that scores of the children with 22q11DS differed significantly from those of the TD children, with a large effect size (U = 26.50, p = .001, r = 0.62), indicating that the children with 22q11DS gave fewer correct answers to the comprehension questions of the production story. Again, the comparison between the comprehension scores of the children with DLD and the TD children did not survive Bonferroni correction, although we found a medium effect size (U = 49.00, p = .020, r = 0.44). Finally, the comprehension score did not differ between the children with 22q11DS and children with DLD (U = 59.00, p = .114, r = 0.22). Figure 2 displays the distribution of scores per group on the comprehension task for the production story. Seven children of the TD group answered all comprehension questions correctly (50%), and the two weakest TD children provided three incorrect answers (14%). Only two children with 22q11DS (15%) answered all questions correctly and eight children provided more than three incorrect answers (62%). Only two children with DLD answered all questions correctly (14%) and four children provided more than three incorrect answers (29%; see Figure 2).

Figure 1.*The Proportion of Children per Group with Respectively 10 (=max), 9, 8, or Less than 8 Answers Correct on the Comprehension Questions of the Model Story.*

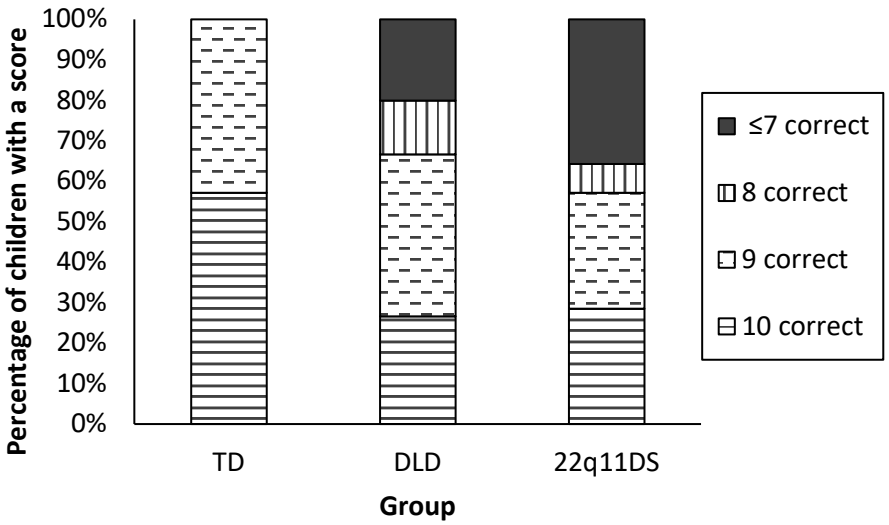
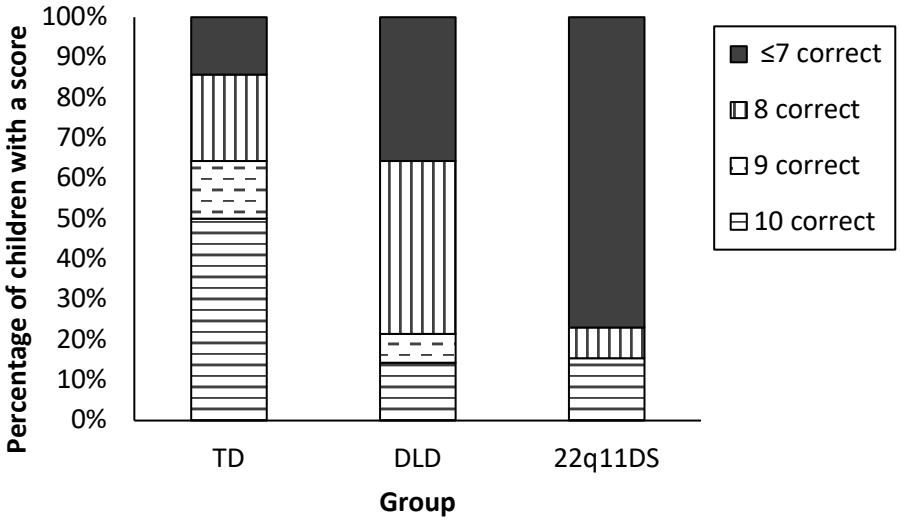


Figure 2. *The Proportion of Children with Respectively 10 (=max), 9, 8, or less than 8 Answers Correct on the Comprehension Questions of the Production Story.*



Discussion

In this study, we investigated the ability of school-aged children with 22q11DS to produce and comprehend narratives. We evaluated children's ability to produce narrative macrostructure by looking at the inclusion of story elements, such as the story setting, goals, attempts, outcomes, and internal states of the protagonists. We assessed children's narrative comprehension skills by asking comprehension questions about both a model story that was read to them and about the production story that they generated themselves. Furthermore, we addressed the role of level of intellectual functioning in relation to narrative abilities of children with 22q11DS. Through a comparison with a group of typically developing (TD) children who were younger in chronological age, but similar in terms of their mental age, we investigated whether children with 22q11DS display weaknesses in narrative development that go beyond what may be expected for their level of cognitive development. An additional comparison of the narrative abilities of children with 22q11DS with those of chronologically age-matched children with Developmental Language Disorder (DLD) allowed us to explore whether these two groups of children display comparable narrative difficulties, despite a significantly lower level of intellectual functioning of children with 22q11DS.

22q11DS in comparison to TD

Our results showed that children with 22q11DS experience difficulties in both production and comprehension of narrative macrostructure. Regarding the ability to produce narrative macrostructure, we did not detect evidence for a difference between children with 22q11DS and TD children, who were on average more than 2 years younger. Our limited sample size may have prevented us from establishing a difference in the narrative production skills of these two groups. However, if any such a difference exists, our raw data suggests a better performance of the younger TD children. Taken together, our results suggest a delay in the production of narrative macrostructure of children with 22q11DS. This would confirm previous findings regarding the story generation skills of children with 22q11DS (Persson et al., 2006; Van Den Heuvel et al., 2017b). Furthermore, the absence of a difference with mental-aged matched TD children, who were younger in age, could suggest that in children with 22q11DS, the ability to produce narrative macrostructure is roughly in line with what may be expected given their level of cognitive development. Consequently, we may tentatively infer that the development of narrative production skills in 22q11DS is associated with their level of intellectual functioning.

The present study is the first to examine narrative comprehension in children with 22q11DS. Our findings indicate that children with 22q11DS have more difficulty understanding the production story than the younger TD children. We cannot draw a firm conclusion regarding the comprehension of the model story. However, we believe that our approach may have underestimated the difference between the children with 22q11DS and the TD children, given that the latter group performed at ceiling on the comprehension task of the model story and we observed a medium effect size. This finding may indicate that the level of narrative comprehension of children with 22q11DS is weaker than what is expected based on their cognitive developmental level. In contrast to narrative production, this may imply that the deficit in narrative comprehension in 22q11DS cannot be completely attributed to the overall lower level of intellectual functioning in this population. Plausibly, our finding suggests that other factors besides low intellectual functioning may be contributing to the difficulties in narrative comprehension in 22q11DS.

Taken together, these findings indicate that children with 22q11DS show global weaknesses in narrative skills, with narrative comprehension more affected than narrative production. This is an interesting finding in light of earlier research suggesting that receptive language problems in 22q11DS increase over the course of childhood, leading to a smaller receptive over expressive language advantage in these children in comparison to TD peers (Glaser et al., 2002; Van den Heuvel et al., 2018).

22q11DS in comparison to DLD

We did not detect significant differences between the narrative abilities of the children with 22q11DS and the children with DLD, despite the difference in level of intellectual functioning between these groups. Again, while our study would have identified such differences if these were truly substantial in the general population, our limited sample size may have prevented us from detecting smaller group differences. Alternatively, and in line with our expectations, it is likely that we did not detect a difference in narrative performance between children with 22q11DS and children with DLD, because children with DLD often present narrative difficulties irrespective of their level of cognitive functioning (Fey et al., 2004; Norbury et al., 2016a; Pearce et al., 2010). Similarly, our observation that the children with 22q11DS did not differ from the children with DLD, despite a lower level of intellectual functioning of children with 22q11DS, may indicate that the difficulties in narrative production and comprehension cannot entirely be attributed to the low level

of intellectual functioning in 22q11DS. This is an interesting observation, considering the previously reported overlapping characteristics in the language and behavioral profiles of children with 22q11DS and children with DLD (Goorhuis-Brouwer et al., 2003; Swillen et al., 2001).

Possible mechanisms associated with narrative difficulties in 22q11DS

The observed similarities between children with 22q11DS and children with DLD suggest that we can apply our knowledge of mechanisms that are associated with narrative difficulties in DLD to understand narrative difficulties in 22q11DS. Previous studies on children with DLD show that a combination of deficiencies in linguistic, cognitive and social functions may be associated with difficulties in narrative production and comprehension (Blom & Boerma, 2016; Duinmeijer et al., 2012). Linguistically, our participants with 22q11DS demonstrated below average grammatical skills as indicated by their performance on the sentence repetition task. Knowledge of the grammar of a language is important to describe and understand causal connections between story events and episodes (Botting, 2002). Hence, the problems of children with 22q11DS with formulating and understanding grammatical structures may therefore have interfered with their narrative production and comprehension. Furthermore, children with 22q11DS had a similar level of vocabulary comprehension as the younger TD children, which can thus not explain the difference in narrative comprehension between the two groups. However, the understanding of complex sentences and instructions has been reported to be weak in children with 22q11DS (Van den Heuvel et al., 2018). Although we did not measure complex sentence comprehension, it is possible that problems in understanding the sentences that built up the narrative, as well as problems in understanding the questions that were used to assess narrative comprehension may have contributed to the difference in narrative comprehension between children with 22q11DS and younger TD children.

Our findings of the comparisons of narrative comprehension abilities of children with 22q11DS to those of both mental-aged matched TD children and children with DLD are consistent, suggesting that difficulties in narrative comprehension skills cannot entirely be attributed to the weaker intellectual abilities in 22q11DS. With respect to narrative production, our findings are less straightforward to interpret regarding the role of intellectual functioning, as we did not detect any significant group differences in the comparisons of narrative production abilities. This may indicate that, in reality, children with 22q11DS differ neither from younger mental age-matched TD children nor from children with DLD in their ability to produce narrative macrostructure.

Alternatively, differences in narrative production ability may actually exist, but our comparisons failed to demonstrate these at a significant test level, most likely due to a *priori* limited statistical power. Our results suggest that the difference in narrative production between children with 22q11DS and the TD children is larger compared to the difference between children with 22q11DS and children with DLD. Based on these observations, we tentatively speculate that similar to our findings for narrative comprehension, the observed difficulties in narrative production skills in 22q11DS may also not entirely be attributable to a weaker level of intellectual functioning. However, a study based on a larger sample size is required to examine this hypothesis.

In this study, we used IQ scores as a proxy of the level of cognitive functioning of children with 22q11DS. For a deeper understanding of the observed deficits in narrative comprehension as well as narrative production in 22q11DS, it is necessary to examine the narrative skills of children with 22q11DS in relation to broader cognitive abilities, as well as to social functions that have been associated with narrative problems in children with DLD, such as working memory, attention, and the ability to make (social) inferences (Blom & Boerma, 2016; Duinmeijer et al., 2012). In addition, future research with a larger sample could examine the types of errors that children make in the narrative comprehension and production tasks, enhancing our understanding of mechanisms underlying weak narrative functioning.

Implications

The deficits in narrative production and comprehension of children with 22q11DS have implications from both a research and a clinical perspective. Many children with 22q11DS experience difficulties in contact with peers and parents, as well as academic problems. Studying narrative difficulties of children with 22q11DS in relation to such functional outcomes is important, given that this may provide an opportunity for intervention. Previous work with low-income preschoolers suggests that narrative intervention may improve children's functioning in school and social settings (Johnston, 2008; Nicolopoulou et al., 2015).

Our findings tentatively suggest that the problems in narrative comprehension of children with 22q11DS exceed the severity of problems with narrative production and, moreover, indicate that these comprehension skills are weaker than expected for their level of cognitive development. If future studies replicate this observation, this highlights a challenge for people who interact with children with 22q11DS in a daily life, school or clinical setting with respect to matching their demands and expectations to a child's

capabilities (Fiksinski et al., 2018). Namely, the child's relatively stronger production abilities may hide the less readily observable weaker level of comprehension abilities. In addition, the overall level of intellectual functioning may often not reflect the level of language comprehension. Communication partners may overestimate the child's linguistic abilities due to these discrepancies. Therefore, the findings of this study underscore the importance of assessment of language comprehension abilities in children with 22q11DS (Van den Heuvel et al., 2018).

Conclusion

In summary, we found that children with 22q11DS experience difficulties in their ability to produce narrative macrostructure as well as in their ability to comprehend narratives. Our comparison of children with 22q11DS to younger TD children matched on mental age as well as to age-matched children with DLD, did not allow us to draw a firm conclusion regarding the extent to which narrative production difficulties can be entirely attributed to a low level of intellectual functioning. However, our findings do indicate that difficulties in narrative comprehension of children with 22q11DS were weaker than expected for their developmental level, and may not be solely explained by their overall lower level of intellectual functioning. The relatively weak narrative comprehension skills of children with 22q11DS as compared to their ability to produce a narrative, as well as the potential discrepancy between children's narrative skills and their level of intellectual functioning calls for further consideration from a research as well as a clinical perspective.

Appendix A.

Results of the Kendall tau (τ) correlation analyses between narrative comprehension scores on the model and production story on the one hand and IQ, PPVT and CELF scores on the other hand per group.

We performed a Kendall tau correlation analysis, that is most suited when analyzing associations in a small sample and data measured on an ordinal level. We only explored the relation between children's total IQ score and scores on the language measures on the one hand, and scores on narrative comprehension on the other hand, as we only found a significant group difference on our measures for narrative comprehension. Age did not significantly correlate with the outcomes of these measures of narrative comprehension, and therefore we did not correct for age in our correlation analyses ($\tau < 0.29$, $p > .168$). We report the results in the correlation table below per group (see Table 1). To summarize, we found a significant association between total IQ score and the comprehension score of the production story for the TD children ($\tau = -0.47$, $p = .036$) and a significant association between the PPVT score and the comprehension score of the model story for the children with DLD ($\tau = 0.55$, $p = .009$). We did not find any other significant correlations for TD children ($\tau < 0.36$, $p > .134$), children with 22q11DS ($\tau < 0.24$, $p > .251$) or children with DLD ($\tau < 0.25$, $p > .262$).

Table 1. *Results of the Kendall tau (τ) correlation analyses between narrative comprehension scores on the model and production story on the one hand and IQ, PPVT and CELF scores on the other hand per group.*

	22q11DS				DLD				TD			
	Model		Production		Model		Production		Model		Production	
	τ	p	τ	p	τ	p	τ	p	τ	p	τ	p
IQ	-0.25	.251	0.16	.486	-0.08	.725	0.00	1.00	0.36	.134	**-0.47**	**.036**
PPVT	-0.23	.309	-0.03	.900	**0.55**	**.009**	0.13	.564	0.00	1.00	0.00	1.00
CELF	0.05	.816	0.15	.525	0.25	.262	0.05	.814	-	-	-	-

Abbreviations. PPVT: Peabody picture vocabulary task. CELF: sentence repetition subtask of the Clinical Evaluation of Language Fundamentals.

Appendix B. *Author Contributions*

Contribution	**Author**
Conceptualization	Iris Selten; Tessel Boerma; Emma Everaert; Mariska J. Vansteensel; Jacob Vorstman; Frank Wijnen
Methodology	Iris Selten; Tessel Boerma; Mariska J. Vansteensel; Jacob Vorstman; Frank Wijnen
Formal analysis	Iris Selten
Investigation	Iris Selten; Tessel Boerma
Writing-original draft	Iris Selten; Tessel Boerma
Writing-review and editing	Iris Selten; Tessel Boerma; Emma Everaert; Mariska J. Vansteensel; Jacob Vorstman; Frank Wijnen
Project administration	Mariska J. Vansteensel
Funding acquisition	Mariska J. Vansteensel; Frank Wijnen

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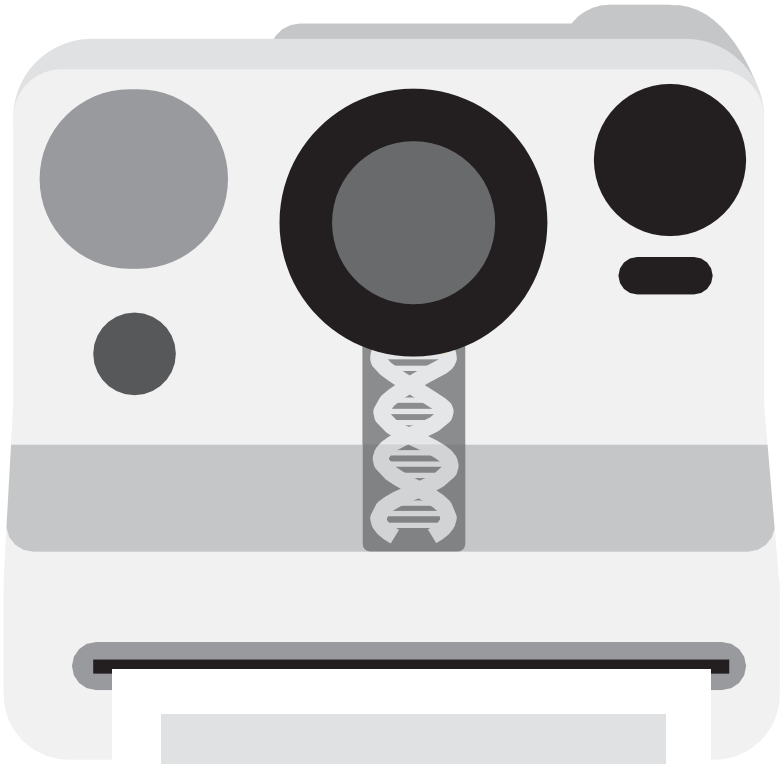

5

Reduced Brain Activation During Spoken Language Processing in Children with Developmental Language Disorder and Children with 22q11.2 Deletion Syndrome

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106 More than words

Language difficulties of children with Developmental Language Disorder (DLD) have been associated with multiple underlying factors and are still poorly understood. One way of investigating the mechanisms of DLD language problems is to compare language-related brain activation patterns of children with DLD to those of a population with similar language difficulties and a uniform etiology. Children with 22q11.2 deletion syndrome (22q11DS) constitute such a population. Here, we conducted an fMRI study, in which children (6-10yo) with DLD and 22q11DS listened to speech alternated with reversed speech. We compared language laterality and language-related brain activation levels with those of typically developing (TD) children who performed the same task. The data revealed no significant differences between groups in language lateralization, but task-related activation levels were lower in children with language impairment than in TD children in several nodes of the language network. We conclude that language impairment in children with DLD and in children with 22q11DS may involve (partially) overlapping cortical areas.

Introduction

Five to seven percent of children receive a diagnosis of Developmental Language Disorder (DLD), indicating they experience severe problems in language development that cannot be attributed to an obvious cause, such as known genetic or physical abnormalities, lack of exposure, hearing loss or low intellectual functioning (Bishop et al., 2017; Norbury et al., 2016; Tomblin et al., 1997). A large variety of genetic and environmental risk factors, such as being male, a low 5-min Apgar score, low maternal education level and a younger position in the birth order, have been associated with DLD (Ganga et al., In preparation; Harrison & McLeod, 2010; Rudolph, 2017; Whitehouse et al., 2014), making it difficult to identify the underlying neurocognitive mechanisms that result in the language difficulties of DLD (Bishop, 2006a; Tomas & Vissers, 2018). However, to effectively tailor prevention and intervention strategies for DLD, we need to better understand these neurocognitive mechanisms and increase our insight in the pathways through which such risk factors cause alterations in the neural networks involved in language processing that, in turn, lead to impaired language development. A first step to address this aim is to carefully describe any alterations in the language-related brain activity patterns in DLD. A second step is a comparison of these brain activity patterns to those of a genetically uniform population that has a similar behavioral language phenotype as DLD. The rationale behind this comparison is that, if DLD and the genetically uniform population also share alterations at the level of neural activity, it can be surmised that the risk factors that are associated with DLD affect similar target points within the neural language processing network as the mutation in the genetically uniform population. A careful characterization of the genetically uniform population may then contribute to elucidating these target points for DLD and thereby increase our understanding of DLD (c.f. (Bathelt et al., 2016)). In the current study, we focus on children with 22q11.2 deletion syndrome as the genetically uniform population for comparison with children with DLD.

The 22q11.2 deletion syndrome (22q11DS) is caused by a micro-deletion on the long arm of chromosome 22 and is identified in an estimated one out of every 3000-6000 live births (McDonald-Mcginn et al., 2015). Children with 22q11DS may have various physical symptoms involving multiple organ systems. The most frequently occurring physical symptoms are congenital heart defects and palate abnormalities. Common developmental symptoms include delays in language and motor milestones, and low to borderline intellectual functioning. In addition, the deletion is associated with

elevated levels of psychopathology, in particular schizophrenia (Fiksinski et al., 2018; McDonald-McGinn et al., 2015; Vorstman, et al., 2015).

Many children with 22q11DS present with severe difficulties in language development, which overlap with those presented by children with DLD. Both children with 22q11DS and children with DLD show a delayed achievement of language milestones. Consequently, speech and language therapy is often indicated (Solot et al., 2019; Bishop et al., 2017). Even though language abilities of children with 22q11DS and children with DLD progress with increasing age, affected children do not seem to catch up with their typically developing peers and language difficulties therefore dominate concerns of parents of both groups (Conti-Ramsden et al., 2012; Norbury et al., 2016; Rice and Hoffman, 2015; Solot et al., 2000; Van Den Heuvel et al., 2018). In addition, for both populations, language difficulties may be present in all language domains, such as expressive and receptive grammar and vocabulary, as well as social communication, with wide inter-individual variability of affected language domains seen among both children with 22q11DS and children with DLD (Conti-Ramsden et al., 2012; Van Den Heuvel et al., 2017ab). Finally, it has been suggested that, similar to children with DLD, some children with 22q11DS have weaker language skills than expected for their level of intellectual functioning (Goorhuis-Brouwer et al., 2003; Norbury et al., 2016; Persson et al., 2006; Van Den Heuvel et al., 2018). Although there are phenotypical differences between 22q11DS and DLD (e.g.,heart defects, palate abnormalities and the occurrence of mental disorders such as schizophrenia (McDonald-McGinnn et al., 2015), the similarities in developmental language profiles are quite striking. Given these similarities, it is possible that the language difficulties in children with 22q11DS and children with DLD share a common underlying mechanism in that the genetic alterations of 22q11DS and the risk factors for DLD induce comparable changes in the neural networks involved in language processing that, in turn, lead to similar language problems. If that is the case, we would expect the language activation patterns in the brains of these groups of language-impaired children to be altered in a similar fashion, compared to those of their typically developing peers.

Language processing in the brain has historically been associated with two canonical language regions, Broca's area in the inferior frontal cortex and Wernicke's area in posterior temporal region (Broca, 1861; Wernicke, 1874), with a clear left hemispheric dominance in most people (Knecht et al., 2000). Over the past decades, however, advances in brain imaging technology, including functional magnetic resonance imaging (fMRI), and in the

conceptual understanding of language, have led to new insights in the neural substrate of language perception and production (Poeppel et al., 2012; Price, 2012). It is now widely accepted that language processing involves an extended network of peri-Sylvian brain areas and their connecting pathways (Poeppel et al., 2012; Price, 2012). Functional MRI studies in healthy children have revealed that brain areas activated during the performance of language tasks largely correspond with those observed in adults (Moore-Parks et al., 2010; Wood et al., 2004) and that the left-hemispheric specialization for speech processing emerges very early in life (Dehaene-Lambertz et al., 2002).

Importantly, current evidence on the language representation in DLD is scarce and results on whether or not this condition is associated with changes in language laterality and language-related activation levels in the brain have been inconsistent (Badcock et al., 2012; de Guibert et al., 2011; Ellis Weismer et al., 2005; Hugdahl et al., 2004; Pigdon et al., 2020). In addition, as far as we are aware, there are no published fMRI studies on language-related brain activity patterns in children with 22q11DS. Therefore, we here conducted an exploratory study to investigate language activation patterns in the brains of children with DLD and children with 22q11DS. We acquired 3T fMRI data from children of both groups while they performed a spoken language processing (story listening) task and compared language laterality and amplitude of fMRI activity with those of a group of typically developing (TD) children who performed the same task.

Methods

Participants

Children of 6-10 years old with a diagnosis of DLD were recruited via schools in the Utrecht area specialized in the education of children with language impairment. In the Netherlands, children with DLD enrolled in these schools have met one of the following criteria: 1) one score of at least 2 standard deviations below the mean on a comprehensive standardized language test, or 2) a score of at least 2 standard deviations below the norm on at least 2 subtests of a standardized language test addressing the language domains speech, pragmatics, grammar, semantics, respectively, or 3) a score of 1.5 standard deviations below the norm on at least two subtests of a standardized language test in at least two language areas, or 4) a score of 1.3 standard deviations below the norm on at least two subtests of a standardized language test in at least three language areas (Simea, 2017).

Children (6-10 years old) with a genetically confirmed diagnosis of 22q11DS were recruited via the 22q11DS childhood outpatient clinic at the Wilhelmina Children's Hospital (part of the University Medical Center Utrecht).

Exclusion criteria for both groups were low IQ (verbal and non-verbal IQ <70), moderate hearing impairment or worse (>35 dB), MRI-incompatible metal objects on or inside the body, anxiety in the scanner, and relevant comorbidities (e.g.,severe autism). In total, 16 children with DLD and 14 children with 22q11DS were included. For the DLD group, two children were not included in the analyses below, because of various reasons (left-handedness, diagnosis no longer valid). Here, we report on the remaining 14 right-handed children with DLD (7 male, 7 female) and 14 right-handed children with 22q11DS (8 male, 6 female). The fMRI data of these children were compared with those of a group of typically developing (TD) children of the same age range (control group, n=25, 11 male, 14 female, all right-handed, native Dutch speakers, one bilingual, one dyslexic), who were included in another fMRI study in which the same tasks were used (Charbonnier et al., 2020). All TD children attended regular schools and were not reported to have any relevant medical issues.

Parents of all participants gave written informed consent for their child to participate in the study. The studies were approved by the Medical Ethical Committee of the UMC Utrecht and performed in accordance with the Declaration of Helsinki (World Medical Association, 2013).

Hearing, IQ and Language performance

A trained member of the research team evaluated hearing in each child with 22q11DS or DLD. Pure tone audiometry was performed measuring the unmasked air conduction. Hearing loss was defined as an average hearing loss (average of 250, 1000 and 4000 Hz) of more than 35 dB. Children who had >35 dB hearing loss in both ears were excluded from the study. In addition, a shortened version of the Dutch version of the Wechsler Non Verbal intelligence scale of ability (WNV-NL; (Wechsler & Naglieri, 2008)) was used to examine intellectual function of children with DLD and children with 22q11DS. We report a composite IQ score, which was calculated based on performance on the subtasks Matrix Reasoning and Picture Recall or Spatial Orientation, dependent on a child's age.

As a measure of grammatical competence, the sentence repetition task of the Dutch adaptation of the Clinical Evaluation of Language Fundamentals (CELF 4-NL; (Kort et al., 2010)) was used. Below-average performance on sentence repetition tasks is an important characteristic of

language impairment, and such tasks are widely used in clinical settings (Klem et al., 2015). In this task, children were requested to exactly repeat sentences with increasing difficulty that were read by the experimenter. A higher score indicates a larger number of correctly repeated sentences. Raw scores were converted into standardized scores (M=10; SD=3).

To obtain a measure of receptive vocabulary, we used the Dutch version of the Peabody Picture Vocabulary Test (PPVT III-NL; (Schlichting, 2005)). The PPVT is a standardized vocabulary test that consists of 204 items that are divided over 17 sets. Children were visually presented with four pictures and were requested to point at the drawing that matched the target word that had been read out loud by the experimenter. Raw scores, which represent the number of correct responses, were converted to standardized scores (M=100; SD=15). For some participants, a recent audiogram, IQ test result and/or language test result was already available. In these cases, the respective tests were not repeated to avoid imposing unnecessary burden to the participants and potential confounds due to retesting. Notably, the TD children did not take part in the hearing, IQ or language tests, since their data was acquired within another study.

Participant preparation

All children were prepared for the fMRI scan in a dedicated room of the UMC Utrecht, which was equipped with a full-scale mock scanner. First, the Edinburgh Handedness Inventory (Oldfield, 1971) and an fMRI safety screening form were filled out by the participants or their parents on their behalf. Subsequently, participants practiced the fMRI tasks using a laptop computer. Finally, participants were acquainted with the MRI environment using the mock-scanner. Before and after the mock-scanner preparation, participants, their parents and the researcher filled out two Visual Analogue Scales (VAS), to indicate how much anxiety the participant felt about the fMRI experiment, and how enjoyable the participant considered participation. The VAS scales ran from 1 (not anxious, very enjoyable) to 10 (very anxious, not at all enjoyable). Three TD participants had had a prior fMRI scan. For them, mock-scanner preparation was not performed, but tasks were practiced before entering the real MRI scanner. Note that the VAS data of the TD children were included in a previous report of our group (Charbonnier et al., 2020).

Functional MRI Data Acquisition

Functional MRI data were acquired on a Philips Achieva (Best, the Netherlands) 3T scanner. To minimize the confounding effect of large blood vessels, we used a PRESTO pulse sequence, which involves a multi-shot 3D acquisition scheme (Neggers et al., 2008; Rutten et al., 1999; van Gelderen et al., 2012), and is routinely used in our institute for clinical, presurgical function mapping (Jansma et al., 2015, 2020). FMRI acquisition parameters were: TR = 22.5ms, TE = 31.22ms, flip angle 10 degrees, voxel size 4mm isotropic, 40 slices, FOV 224 x 256 x 160mm, prescribed sagittal, ear to ear, volume acquisition time 608ms. For each participant, a T1-weighted anatomical scan was acquired (1mm isotropic), while participants watched a video of their choice.

Tasks

While in the MRI scanner, participants performed a language task (Story task, SR) and/or a Hand-Movement task (HM).

Story task (SR)

The SR task (SR, duration 9.3 minutes, 921 volumes; (Charbonnier et al., 2020)) had a block design in which periods of spoken language processing (story listening, comprising speech comprehension and speech recognition) alternated with periods of rest. During the story listening blocks, participants listened to the voice of a female speech and language therapist who read a shortened version of a children's story (target age 5-8 years). To maximally attract the attention of the participants to the content of the story, children watched a colorful illustration that supported the narrative during each speech block (n=14 blocks, 8.7-38.6s in duration). During the rest conditions (reversed speech, n=14 blocks, 16.6-19.1s in duration), the illustration slowly turned to the next illustration (like turning a book page), which supported the narrative of the next story listening block, in which the story continued where it ended during the previous story listening block. Sound was delivered through an MRI-compatible audio system with in-ear plugs (MR Confon, Magdeburg, Germany). Children could press the alarm button if they needed adjustment of the audio volume. Note that the SR task data of the TD children have been reported on earlier (Charbonnier et al., 2020).

Hand-Movement task (HM)

A Hand-Movement (HM, duration ~4.5 minutes, 442 volumes) task was used in this study to assess the presence of any non-language related differences in brain-activation between TD and language-impaired children. During the

task, a red or green colored circle was visually presented (3s for first trial of a block, 0.5s for the remaining trials), which alternated with an illustration of a cartoon character (0.5-3s, 11 trials per block). During rest blocks, the circle was red, instructing the participants to relax and just watch the illustrations. During active blocks, the circle was green, instructing the participants to squeeze a response-balloon with their right hand every time they saw an illustration (i.e. a target). Each squeeze was rewarded with a colored line around the image. Response accuracy during this task was computed as the percentage of targets that was responded to with a balloon squeeze (true positives). Reaction time was defined as the time between the onset of target presentation and the balloon squeeze.

Analyses

Functional MRI Data Analysis

FMRI data analysis was performed offline with SPM12 (http://www.fil.ion.ucl.ac.uk/). Preprocessing involved realignment to the first functional scan, co-registration to the individual T1-weighted anatomical scan, normalization to standard, Montreal Neurological Institute (MNI), space and smoothing (Gaussian kernel, 8mm full width half max). Statistical analysis was performed by fitting a General Linear Model (GLM) to the data and the generation of contrast maps for each participant. Motion correction was performed by inclusion of two confound factors in the GLM, being 1) the six realignment parameters produced by SPM12 in the realignment preprocessing step and 2) a motion filter, as described before (Charbonnier et al., 2020). In short, the motion filter included a set of Finite Impulse Response Functions, which effectively remove images with excessive head motion from the analysis. To make sure that the motion filter did not result in an unacceptable decrease in statistical power (due to removal of large numbers of images), we computed the proportion of statistical power (PSP) remaining after the addition of the motion filter, and excluded datasets with PSP values of 0.4 or lower from further analyses. For the computation of the PSP, the following formula was used:

$$PSP = \frac{R_m^2 \times \sqrt{df_m}}{R^2 \times \sqrt{df}}$$

where and are the multiple correlation coefficients between the task and the remaining factors of the design matrix with the motion filter and the design

matrix without the motion-filter, respectively; df_m and df are the degrees of freedom of the design with and without motion filter.
Groupwise activity maps were obtained by entering the single subject contrast maps into a second level analysis (one sample t-test). We used the 3dClustSim tool in AFNI (version 16.2.07) to derive a cluster level threshold of $p<0.05$ (corrected for multiple comparisons) using Monte Carlo simulations (10.000 iterations) of random noise distribution (Cox, 1996; Forman et al., 1995). This approach combines an individual voxel probability threshold with a minimum cluster size to estimate the probability of a false positive, effectively taking into account both effect size and the spatial extent of the activity. We used the 3DFWHMx tool in AFNI (Auto-Correlation Function; ACF) to estimate noise smoothness values of the data. The resulting 2-sided threshold was obtained for an individual voxel threshold of $p<0.001$ (uncorrected) with a cluster extent and t-threshold varying with group and task. The existence of any differences between the activation patterns of the SR and the HM tasks of the three groups was investigated using second-level analyses according to the same procedures.

Regions of Interest
To specifically focus on the most relevant brain areas, most analyses were conducted on anatomically defined Regions of Interest (ROIs). Using the Brainnetome atlas (Fan et al., 2016), we generated a language-ROI that contained the peri-Sylvian language areas (i.e. Broca, Wernicke, Anterior Temporal and Auditory; Supplementary Table 1; Supplementary Figure 1A-D). For more detailed analyses of the language activation patterns, we also analyzed the language-sub-ROIs. In these analyses, we included, besides the peri-Sylvian language areas, also the caudate nucleus as an ROI (Supplementary Table 1; Supplementary Figure 1E), since that area has been indicated to show atypical structure and function in children with DLD (de Guibert et al., 2011; Dibbets et al., 2006) and in another speech disorder (orofacial verbal dyspraxia; (Vargha-Khadem et al., 1998). In addition, we investigated a motor-ROI. The motor-ROI was generated using the automated anatomical labeling atlas (AAL; (Tzourio-Mazoyer et al., 2002)) and included the precentral and postcentral gyri (Precentral, Postcentral; Supplementary Figure 1F).

Lateralization Index
We used a threshold-independent method to compute the Lateralization Index (LI; (Branco et al., 2006)). For each (sub-)ROI of both the left and right

hemisphere, the product between the height of the bins of the histogram of voxel's t-values (t-value range 0 – ∞, bin size 0.25) and the square of the index of the bins was computed. As such, voxels with higher t-values were assigned a heavier weight. The areas under the curve for the left and right hemisphere were subsequently used in the computation of the LI. LI differences between groups were tested for statistical significance using independent one-way ANOVAs and we used the Bonferroni method to correct for multiple comparisons.

Activation Levels: Mean Betas from GLM fit on fMRI data

Using the results of the GLM fit on the fMRI data, we computed, per participant and per task, the mean beta value (a measure of the size of the BOLD signal change induced by performing a task) for each of the language sub-ROIs and the motor-ROI. To match the dimensions, resolution and orientation of the fMRI data, the volume including the relevant regions of interest in MNI-space was resliced to the volumes containing the beta-coefficients, using nearest neighbor interpolation. Subsequently, a particular fixed percentage of voxels was selected, for each participant and task and within each ROI (i.e. 10% with the highest beta coefficients [i.e. strongest activation, top 10%], and 10% with the lowest beta coefficients [strongest de-activation, bottom 10%]), to avoid loss of power due to the inclusion of a large proportion of non-task-related voxels. By providing information about both the strongest activating and the strongest de-activating voxels, we aimed to offer a representation of the full range of beta values for each group, task and ROI. In earlier studies, the selection of a subset of voxels, based on their level of activity, as a basis for a single measure of task-related signal changes within an anatomically defined ROI, has been found to be a usable and valid approach (Buck et al., 2008; Buma et al., 2016; Mitsis et al., 2008; Tong et al., 2016). Using each of these two voxel selections, we subsequently calculated the mean (de-)activation per ROI. This resulted in a single (de-)activation estimate for each voxel selection, ROI, task, and participant. Differences between groups were tested for significance with independent one-way ANOVAs (Bonferroni correction for multiple comparisons).

Relation between Beta values and IQ and Language Scores

As a post-hoc analysis, we used ANCOVA to investigate the relationship between the beta values and the groups of participants by controlling for additional behavioral measures, such as IQ and language performance scores (sentence repetition and PPVT). A pairwise-interaction model was specified

per analysis, thus including modeling of the main effects per variable (group, IQ, sentence repetition and PPVT) and all their pair-wise interactions. We used the MATLAB implementation of ANCOVA (*anovan* with a combination of continuous and categorical variables) and used the type III sum of squares in estimating the main effects of the model given the previously observed interaction effects between the groups and the behavioral measures (IQ and PPVT in particular). The ANCOVA analyses were performed only for the ROIs with a significant group effect for the beta values from the previous analysis: left Anterior Temporal, Broca and Wernicke regions and using only the top 10% of beta values of the SR task. The results were corrected for multiple comparisons using a Bonferroni correction for the number of ROIs.

Results

VAS Scores

Children of the three groups reported comparable Visual Analogue Scale (VAS) scores for anxiety and enjoyment before and after the practice scan (Supplementary Table 2), and there were no significant differences between groups (anxiety: multivariate GLM, $F(6,92)=1.15$, $p=0.34$; enjoyment: multivariate GLM, $F(6,92)=2.0$, $p=0.10$). The practice scan itself mostly resulted in a decrease in the VAS scores for anxiety and enjoyment (i.e. a more positive perception), as reported by the participant, parent and researcher. For anxiety, this effect was significant for the DLD and the TD group, but not for the 22q11DS group (repeated measures GLM; DLD: $F(1,10)=10.75$, $p=0.01$; 22q11DS: $F(1,13)= 1.78$, $p=0.21$; TD: $F(1,20)=18.57$, $p<0.001$). Also for the levels of enjoyment, there was a significant effect of practice in the DLD and TD group, but not in the 22q11DS group (repeated measures GLM; DLD: $F(1,11)=13.55$, $p=0.004$); 22q11DS: $F(1,13)=0.17$, $p=0.69$; TD: $F(1,20)=11.39$, $p=0.003$). Two 22q11DS participants had high levels of anxiety after mock-scanner preparation and were excluded from further participation. No fMRI data were acquired for these participants and their results are not included in the analyses below. Also after the fMRI scan, there were no significant differences between groups for anxiety (one-way ANOVA, $F(2,44)=0.03$, $p=0.97$) and enjoyment (one-way ANOVA, $F(2,44)=0.72$, $p=0.49$).

Hearing, IQ and Language Performance

Participants with DLD and participants with 22q11DS had no hearing impairment (i.e. impairment levels of <25 dB in at least one ear; grade 0; (WHO, 1991)), except one 22q11DS participant, who had a slight hearing impairment in both ears (grade 1; (WHO, 1991)). Notably, this child had a cold

on the day of the hearing assessment. Both IQ and language were deviant for this participant compared to typically developing peers, but not compared to other children with 22q11DS. Demographic information of the participants and the results of the IQ and language tests are given in Supplementary Table 3. The three groups did not differ significantly in age (one-way ANOVA, $F(2,48)=0.76$, $p=0.48$). On average, the IQ of children with 22q11DS was 73 (SD=9; n=12), which is in the borderline impaired range and significantly lower than that of children with DLD, who had a mean IQ of 107 (SD=15; n=13; IQ data of one participant was missing), which is in the average range (Students t-test, $p<0.001$). Scores on the sentence repetition task were below the norm for their age for both children with DLD (M=4; SD=2; n=14) and 22q11DS (M=5; SD=2; n=12) and did not differ significantly between these two groups (Students t-test, $p=0.19$). Peabody Picture Vocabulary Test (PPVT) scores of children with 22q11DS (M=81; SD=13; n=12) were more than one standard deviation below the mean for their age and were significantly lower than for children with DLD, who reached scores that fell in the average range (M=95; SD=13; n=14; Students t-test, $p=0.01$). As noted in the Methods section, no hearing, IQ or language performance tests were performed by the TD children, as their data were acquired in a different study. All TD children attended regular schools.

Task performance

Due to time constraints, the number of fMRI tasks performed varied across participants (Supplementary Table 3). Hand-Movement (HM) task performance was adequate in general. Mean response accuracies per group were 81% (SD=11; n=14; DLD), 81% (SD=17; n=12; 22q11DS) and 84% (SD=9; n=15; TD) correct, respectively. The corresponding mean reaction times were 618ms (SD=150; DLD), 576ms (SD=95; 22q11DS) and 578ms (SD=92; TD), respectively. There was no significant difference in accuracy (one-way ANOVA, $F(2,38)=0.30$, $p=0.74$), or in reaction time (one-way ANOVA, $F(2,38)=0.57$, $p=0.57$) between groups. Due to the nature of the SR task, quantification of performance during the scan was not possible.

Head Motion

The motion filter effectively removed 21% (SD=22; DLD), 30% (SD=28; 22q11DS), and 13% (SD=14; TD) of scans of the SR task, respectively, and 20% (SD=15; DLD), 23% (SD=24; 22q11DS) and 14% (SD=12; TD) of scans of the HM task (Figure 1A,B). There was no significant difference between groups in

the percentage of scans removed by the motion filter for either task (one-way ANOVAs; $F(2,43)=2.65$, $p=0.08$ and $F(2,38)=0.88$, $p=0.42$, respectively).

For the SR-task dataset of one DLD participant, the Proportion of Statistical Power (PSP) value was lower than 0.4, indicating that removal of the scans with excessive head motion resulted in an unacceptable loss of power, and this dataset was therefore excluded from further analysis (Supplementary Table 3). For the 22q11DS group, three datasets of the SR task, and one dataset of the HM task were excluded because the PSP value was lower than 0.4. For the control group, no dataset was excluded. The mean PSP values of the remaining datasets did not differ significantly between groups for both the SR and the HM task (Figure 1C,D; one-way ANOVAs; $F(2,39)=0.48$, $p=0.62$ and $F(2,37)=0.59$, $p=0.56$, respectively).

Group maps

Visual inspection of the SR group activity pattern of TD participants showed strongly left-lateralized activation in the inferior frontal gyrus, middle temporal gyrus and posterior temporal gyrus / angular gyrus (Figure 2). Anterior temporal cortex activation was largely bilateral, but somewhat stronger in the left hemisphere. Activity was also found in the superior frontal gyrus (more left than right) and in the bilateral posterior cingulate cortex. The group activation patterns of the children with DLD and children with 22q11DS showed activation in the left anterior temporal cortex, in a similar location as TD children (Figure 2). Notably, lowering the threshold in the group-map visualization revealed that both groups of language-impaired children showed an activation pattern that was highly similar to that of TD children (Supplementary Figure 2). Whole brain comparison of the group activation patterns did not reveal any significant differences between groups.

Figure 1. *Motion. Top panels: Boxplots indicating the percentage of removed scans of the SR task (A) and the HM task (B) for the three groups. Bottom panels: Boxplots for the proportion of statistical power (PSP) remaining after motion correction of the SR task (C) and the HM task (D). Note that only participants for whom the PSP value was larger than 0.4 (i.e. the participants used in further analysis) were included in these PSP plots.*

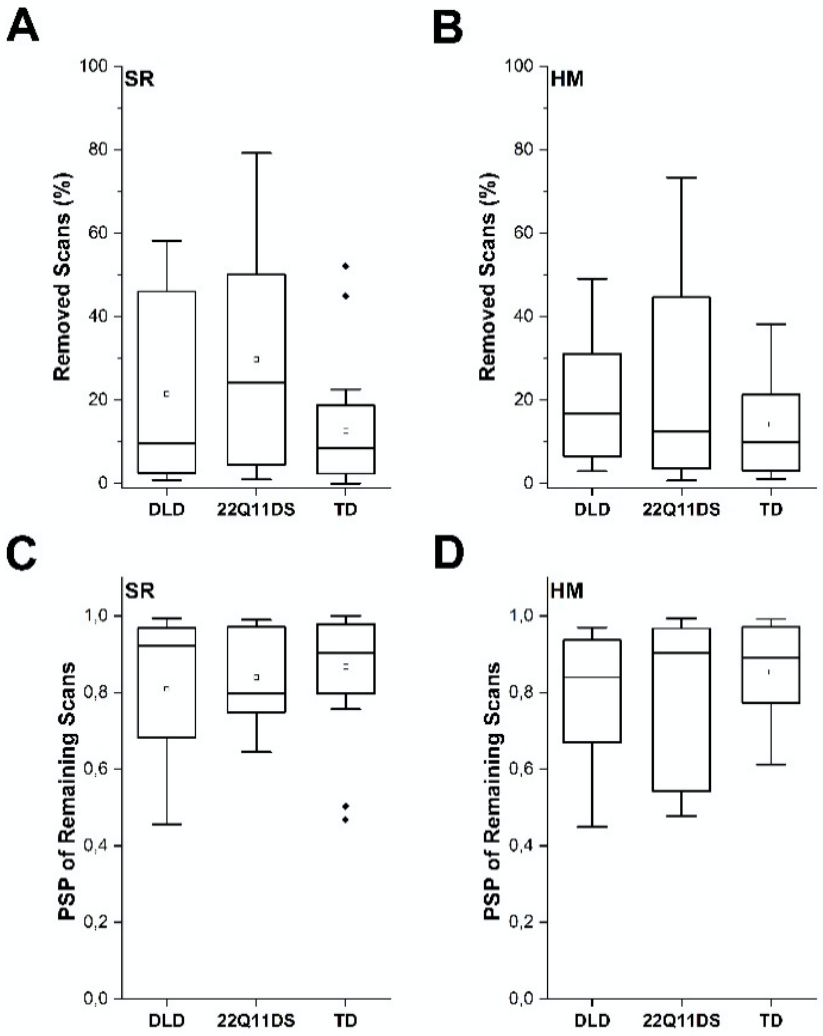


Figure 2. *SR task activation pattern. Group activation patterns of the SR task for children with DLD (n=13; T=3.93; p<0.001; threshold extent k≥37), 22q11DS (n=9; T=4.5; p<0.001; threshold extent k≥43) and TD children (n=20; T=3.58; p<0.001; threshold extent k≥35). The color scale indicates T-values.*

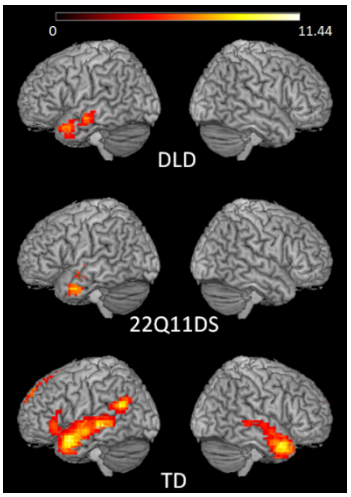
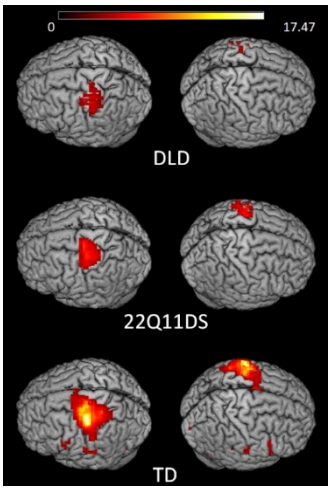


Figure 3. *HM activation. Group activation patterns of the HM task for children with DLD (n=14; T=3.85; p<0.001; threshold extent k≥43), 22q11DS (n=11; T=4.14; p<0.001; threshold extent k≥31) and TD children (n=15; T=3.79; p<0.001; threshold extent k≥39). The color scale indicates T-values.*



The HM activation pattern of TD children showed activation in the contralateral (left) precentral and postcentral sensorimotor hand area (Figure 3). In addition, hotspots of activated voxels were observed in the cerebellum (right more than left), the occipital lobe (visual cortex, mostly right), the temporo-occipital area (~brodmann area 37; more left than right), the left thalamus, two areas around the inferior part of the sensorimotor cortex bilaterally and in the supplementary motor area of the left hemisphere. In the group maps of the children with DLD and children with 22q11DS, clusters of activity were found in the right cerebellum and the left sensorimotor hand area, largely corresponding to the respective regions that showed activity in the TD children (Figure 3). Whole brain comparison of the group activation patterns revealed a cluster of voxels in the left sensorimotor hand area with a significant difference between the TD and DLD groups (TD > DLD; $p<0.001$, threshold extent $k\geq77$; Supplementary Figure 3). There were no significant differences in group activation patterns between the TD and the 22q11DS group or between children with DLD and children with 22q11DS.

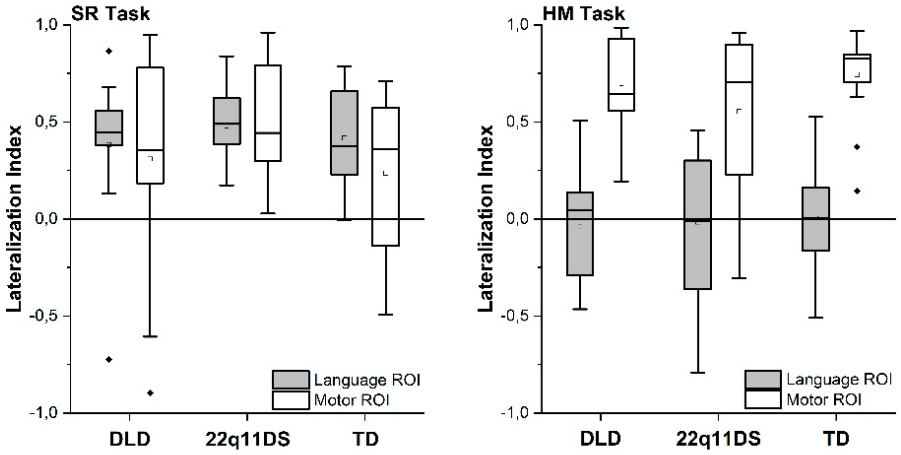
Lateralization index

For the SR task, mean Lateralization Indices (LIs) in the language-ROI were positive, indicating left-lateralized language-related activation in most participants of all groups (Figure 4; Supplementary Table 4). Interestingly, also within the motor-ROI, most LIs were positive and largely in the same range as values obtained for the language-ROI. There was no significant difference between groups in the SR task LIs in either of the two ROIs (one-way ANOVAs; language-ROI: $F(2,39)=0.30$, $p=0.75$; motor-ROI: $F(2,39)=0.99$, $p=0.38$).

The HM task resulted in left lateralized activation in the motor-ROI in all three groups, whereas LIs in the language-ROI were, on average, close to 0 (Figure 4; Supplementary Table 4). There were no significant differences in HM task LIs between the three groups in the two ROIs (one-way ANOVAs; language-ROI: $F(2,37)=0.06$, $p=0.94$; motor-ROI: $F(2,37)=1.25$, $p=0.30$).

To investigate potential differences between groups in the LIs of different sub-areas of the language network, we compared LIs of the SR task for each of the five different language sub-ROIs (Supplementary Table 5). There was no significant difference in the LIs across groups during performance of the SR task in any of the sub-ROIs, neither when all participants (with both positive and negative LIs) were taken into account, nor when only participants with positive (i.e. typical or left lateralized) LIs were included (see Supplementary Table 5 for values per sub-ROI and the results of the one-way ANOVAs).

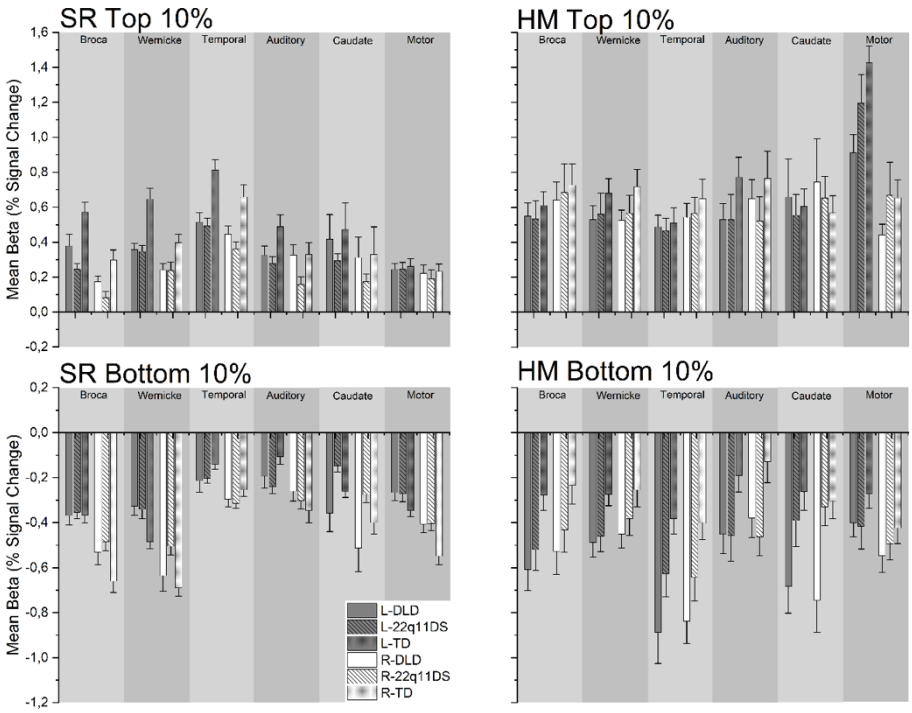
Figure 4. *Lateralization Index. Boxplots for the Lateralization Indices for the SR task (left) and the HM task (right) in the three groups. Grey boxes represent values for the language-ROI, white boxes for the motor-ROI.*



Activation Levels: Beta Values

We computed, per participant and per task, the mean beta value for each of the five language sub-ROIs and the motor-ROI (Figure 5), using either the 10% voxels with the highest beta value, or the 10% voxels with the lowest beta values. For the SR task, for the top 10% voxels, there were significant effects of group for the Anterior Temporal, Broca and Wernicke sub-ROIs of the left hemisphere (independent ANOVAs, $p<0.05$, Bonferroni corrected for 12 comparisons; Supplementary Table 6). Posthoc comparisons revealed that for left-Broca, SR-task-related activation in the TD group was significantly higher than in the 22q11DS group (post-hoc Bonferroni test, $p=0.002$). For left Anterior Temporal and left Wernicke, the TD group activation was significantly higher than that of both language-impaired groups ($p<0.01$ in all cases). Mean beta values did not differ between the two language-impaired groups in the left Anterior Temporal, Broca or Wernicke sub-ROI ($p>0.5$). Other differences between groups observed for the SR task (i.e. top 10% voxels: right Broca, right Wernicke, right Anterior temporal; bottom 10% voxels: left Wernicke, left Caudate, right motor) were significant in one-way ANOVA analyses (Supplementary Table 6), but none of these effects survived Bonferroni correction for multiple comparisons. Also for the HM task there were no significant differences between groups for either the top 10% or bottom 10% beta values after Bonferroni correction.

Figure 5. *Beta values. Upper panels: Mean (over participants; ±SEM) beta values, per sub-ROI, hemisphere and group, for the top 10% voxels of the SR task (left) and the HM task (right). Grey bars indicate values of the left hemisphere. White bars indicate values of the right hemisphere. Per sub-ROI and hemisphere, three bars are given, the left-most (without additional shading) represents the DLD group, the middle (striped bar) the 22q11DS group and the right (dotted bar) the TD group. Bottom panels: idem, but for the bottom 10% voxels. L=left hemisphere, R=right hemisphere.*



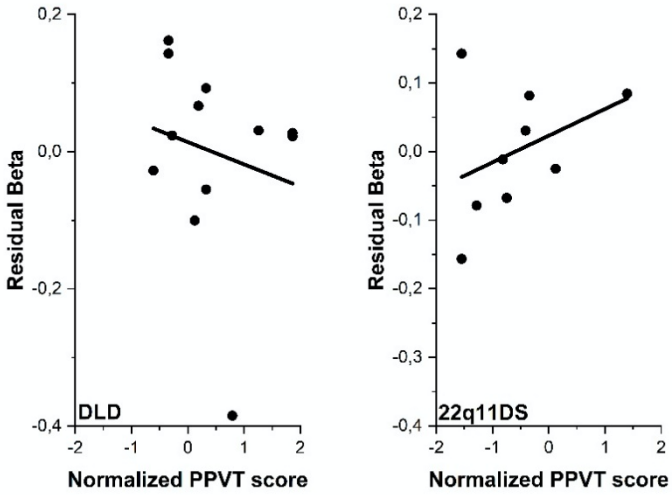
Relation between Beta values and IQ and Language Scores

For the left Anterior Temporal, Broca and Wernicke sub-ROIs (the three areas with a significant group effect for the beta values of the SR task), we investigated whether or not there was a relation between the mean beta values obtained in the SR task on the one hand and group, IQ, sentence repetition and PPVT score on the other. We only analyzed the relation for the top 10% of beta values since there was no significant group effect on the bottom 10% beta values in any ROI for the SR task. Notably, since IQ and language scores were not available for the TD children, this group was not

included in this analysis. This also applied to one DLD participant. The overall fit of the model using the group variable and the behavioral measures to predict the top 10% betas was only significant for the left Broca sub-ROI (F(10,1 per each variable)=4.92, p=0.009, adjusted R^2=0.66) In left Broca, the relationship between the sentence repetition scores and the top 10% beta values was significant at p<0.05. In addition, in the same area, there was a significant interaction effect of group*IQ, group*PPVT and IQ*PPVT scores (all significant at p<0.05, Supplementary Table 7). Notably, after correction for multiple (n=3 sub-ROIs) comparisons, only the effect of group*PPVT score remained significant. Other regions did not show a significant relation between the mean beta values and a combination of group (only 22q11DS and DLD included), IQ and language scores.

The analysis of the direction for the interactions between the group and the language scores showed opposite trends for the DLD and 22q11DS groups: for the DLD group, lower PPVT values were associated with higher betas, and higher PPVT values were associated with lower betas. The 22q11DS group showed the opposite relationship between the PPVT language scores and the beta values in the left Broca sub-ROI (Figure 6).

Figure 6. *Interactions between PPVT language scores, groups and betas in left Broca. The plots show the distribution of residual mean betas (based on top 10% voxels; y-axis) over the normalized PPVT language scores (x-axis)*



per group. The residual betas were obtained from first fitting the model on

*all variables and their pairwise interactions except for the interaction of interest (group*PPVT for top 10%). Because the model also fits the constant term, the residual betas appear to be zero-centered.*

Discussion

In this fMRI study, we investigated brain activation of two groups of language-impaired children, namely children with Developmental Language Disorder (DLD) and children with 22q11.2 Deletion Syndrome (22q11DS), and compared the results to data of a group of typically developing (TD) children acquired earlier within another study (Charbonnier et al., 2020). The data reveal that, during performance of a spoken language processing or a hand-movement task, both groups of language-impaired children showed activity in brain areas that were also found to be activated in TD children and lateralization values did not differ between the three groups. However, in language-impaired children, the level of language task-related activation (beta value) was lower than that of TD children in several nodes of the language network. Interestingly, in one of these nodes, left-Broca, the two language impaired groups showed an opposite relationship between beta values and language performance scores on the PPVT task.

IQ and Language performance

The data showed that the language-impaired participants were representative for children with either 22q11DS or DLD with regard to their intelligence and language skills. The sentence repetition task is a measure used by clinicians to identify children with a language impairment (Klem et al., 2015), and indeed participants with DLD obtained scores markedly lower than the age-adequate average (below the normal range for their age). In addition, absence of intellectual problems among the DLD participants of this study is in correspondence with the literature (Bishop et al., 2017). Interestingly, in our study, children with DLD scored in the average range on the PPVT. This may be explained by the fact that impaired language domains can differ across children with DLD and some children with DLD mainly have problems with expressive language (Bishop et al., 2017; Conti-Ramsden & Durkin, 2012). Moreover, average scores on a receptive vocabulary task have been previously reported in Dutch children with DLD (Blom & Boerma, 2016; Duinmeijer et al., 2012). As expected, children with 22q11DS in our sample presented, on average, with a level of borderline intellectual function (McDonald-McGinn et al., 2015a) and scored lower than the age-adequate range on the sentence repetition task and PPVT, which is in line with earlier studies reporting weak

vocabulary and grammatical skills in this population (Solot et al., 2019; Van Den Heuvel et al., 2018).

Brain Activation Patterns and Laterality

The brain activation patterns associated with the SR and the HM task of children with language impairment showed hotspots at locations that corresponded to those found in TD children. In addition, the data showed that both language-impaired groups had levels of motor and language lateralization that were not significantly different from that of TD children, in the motor- and language-ROI as well as in the language sub-ROIs. Taken together, we did not find evidence for fundamental spatial alterations in the motor or language networks of children with DLD and children with 22q11DS. As far as we are aware, there are no published studies on the language laterality of individuals with 22q11DS. For DLD, previous fMRI literature on language laterality has been inconsistent, with several studies showing decreased left-right asymmetry (Badcock et al., 2012; de Guibert et al., 2011) and others stating clear left-right asymmetry (Ellis Weismer et al., 2005; Hugdahl et al., 2004; Krishnan et al., 2021) in people with DLD. A recent twin study used functional transcranial Doppler ultrasound to assess language lateralization in large groups (n>100) of typically developing children and children with DLD, and found no evidence for atypical language laterality in children with DLD (Wilson & Bishop, 2018). Our findings, showing similar levels of language lateralization in children with DLD and TD children, are in agreement with that finding and add to it that also at a more spatially detailed level (i.e. in different sub-ROIs of the language network), language laterality is highly similar between these groups, and to that of children with 22q11DS. Perhaps surprisingly, in all three groups, the motor-ROI showed leftward lateralization during performance of the SR task. Although the group maps did not show supra-threshold activity in this area, the left-right asymmetry observed in the majority of the participants does indicate some level of involvement of the sensorimotor areas during the story listening task. This finding is in agreement with earlier reports on the involvement of the motor areas in language comprehension, which has been linked especially to the processing of action words (Buccino et al., 2005; Hauk et al., 2004; Vukovic et al., 2017).

Activation Levels

Children with DLD and children with 22q11DS had significantly lower language-related activation in several nodes of the language network than TD

children. Several phenomena should be considered for the interpretation of this observation. First, effects of head motion and task activity both predominantly occur at the lower end of the frequency power spectrum of the time-series, so that head motion is prone to affect task-beta estimates. These effects are random across subjects and thereby represent a source of noise in the second level analysis, attenuating the power of group-studies. In this study, head motion did not differ between groups, as indicated by the comparable number of scans excluded for excessive motion. Also the proportion of statistical power remaining after scan exclusion was not significantly different between groups. Based on these data, we consider it unlikely that differences in head motion caused the lower activation in the language areas of language impaired children. Second, task compliance may potentially affect activation patterns. The SR task was designed to keep the children attentive, but the nature of this task prohibited monitoring of task compliance during the scan. It should be noted, however, that levels of anxiety and enjoyment did not differ between groups, and also task performance (accuracy and reaction time) during the HM task was not significantly different between groups, indicating that all groups were similarly involved during the fMRI session at large. In addition, our finding that all groups showed clearly left-lateralized activation in language areas during the SR task, but not the HM task, suggests that, on average, children were actively processing the spoken language information during the SR task. A third factor to take into account is that children may have hearing loss that negatively affects their ability to hear the speech of the SR task. Indeed, previous research has shown a relationship between fMRI activation in the auditory cortex and sound volume (Bilecen et al., 2002; Röhl & Uppenkamp, 2012). Hearing impairment is quite common in children with 22q11DS (Van Eynde et al., 2016), but a diagnosis with DLD precludes hearing impairment as the cause of the language problems (Bishop et al., 2017). In our study, all but one of the participants (a child with 22q11DS) had hearing loss that was lower than 25dB, which corresponds to Grade 0 (no impairment), of the WHO grades of hearing impairment (WHO, 1991). Taking these three factors into account, we propose that the lower language activation in the brain of both groups of children with language impairment is of neurophysiological origin and is associated with their language problems, not with any language-external factor.

The lower levels of activity we observed in the left-Anterior Temporal and the left-Wernicke sub-ROI of children with DLD correspond to earlier reports on dampened language-related activity in peri-Sylvian regions of people with DLD (Badcock et al., 2012; de Guibert et al., 2011; Hugdahl et al.,

2004). Others did not find a significant difference in language activation patterns of TD children and children with DLD, but did report less detectable activity in cortical language areas of children with DLD (Pigdon et al., 2020). Interestingly, our finding that also children with 22q11DS demonstrate a decrease of language-related activity in the left-Anterior Temporal and the left-Wernicke sub-ROIs, suggests that similar brain areas are involved in the language impairment of 22q11DS and DLD.

Current views on language processing in the brain indicate that the Wernicke sub-ROI that we looked at in the current study, which encompasses (parts of) the posterior superior temporal gyrus, supramarginal gyrus and angular gyrus, is mainly associated with phonological (Binder, 2017; Middlebrooks et al., 2017) and semantic processing (angular gyrus; (Binder et al., 2009)). The anterior temporal areas, including the temporal pole, superior temporal gyrus/sulcus and middle temporal gyrus, on the other hand, are thought to play an important role in speech processing and speech comprehension (Price, 2012; Scott et al., 2000; Specht, 2014). Processing of both syntactic structure (word order) and semantics (word meaning) have been associated with the anterior and middle temporal regions, with a possible emphasis on syntactic processing in the superior temporal gyrus (Friederici, 2012; Humphries et al., 2006), whereas semantic processing seems to occur more in the middle temporal gyrus (Binder et al., 2009; Friederici, 2012). Given the size of the sub-ROIs used in the current study, it is difficult to draw conclusions about which aspect of spoken language processing is associated with the lower activation in the left-Anterior Temporal and the left-Wernicke sub-ROIs of language-impaired children. Consequently, we are not in a position to determine if the language difficulties in DLD and 22q11DS are due to a common underlying mechanism. Interestingly, the fact that both groups showed a decrease in fMRI activity levels in these areas, as well as below average sentence repetition scores, suggests that these measures are related. However, our post-hoc analysis did not reveal any significant relationship between group, IQ or language scores and the beta values in left-Wernicke and left-Anterior Temporal regions and this topic therefore deserves further investigation.

In children with 22q11DS, but not children with DLD, activation in the left-Broca sub-ROI was significantly lower than that of TD children. The findings for children with DLD are in agreement with a recent study on somewhat older children with DLD who performed a verb generation task (Krishnan et al., 2021). Notably, in our study, children with 22q11DS also scored lower on the PPVT than children with DLD, with most DLD children

scoring within the normal (or even above-normal in two cases) range, whereas most 22q11DS children scored below average on the PPVT. Our post-hoc analysis on the relation between beta values and behavioral scores revealed an interaction effect for group*PPVT in left-Broca, such that for children with DLD, smaller task-related neural activity changes (lower beta values) were associated with higher PPVT scores, whereas children with 22q11DS showed the opposite: larger task-related neural signal changes occurred in those with higher PPVT scores. This is interesting, since word comprehension plays an important role in both the SR task and in the PPVT. We hypothesize that (perceived) task difficulty may relate to this observation. In general, increasing language task difficulty has been associated with increased activation in language areas (Just et al., 1996; Keller et al., 2001; Yeatman et al., 2010). Interestingly, however, for working memory tasks, it has been demonstrated that the relation between task-load and fMRI activation has an inverted U-shape, in that with increasing task-load, fMRI activation increases up to a certain point, after which activation levels decrease with further increments in task difficulty (Callicott et al., 1999; Jansma et al., 2004; Van Snellenberg et al., 2015). Importantly, it has been proposed that the decreasing slope is not necessarily related to participants simply giving up on the task, but that this effect is caused by participants using alternative or additional cognitive processes. It could be speculated that this phenomenon is also present for language tasks and that children with DLD are on the rising phase of the inverted U-shape, whereas children with 22q11DS (most of whom have relatively low PPVT scores and therefore may perceive the SR as being more difficult to understand) are on the decreasing slope. Alternatively, the different relationship between language performance and fMRI activation may reflect a difference in developmental stage. Earlier research suggests that children and adults (Krishnan et al., 2015) and children with higher and moderate grammatical knowledge (Knoll et al., 2012) differ in their relationship between activity in frontal areas and language skills. Clearly, this topic deserves further investigation.

With respect to the HM task-related activity levels, we found it interesting that there was a cluster of voxels in the left sensorimotor hand area with a significant difference between TD children and children with DLD. Also, in the ROI analysis, the left motor-ROI showed a trend for less activation (lower top 10% beta values) in children with language impairment, compared to TD children, whereas de-activation in several language sub-ROIs seemed a bit stronger (lower bottom 10% beta values). These latter effects did, however, not survive Bonferroni correction for multiple comparisons. Yet, we do believe

that further investigation of motor-related activity patterns of children with DLD and with 22q11DS may be interesting, especially since for both groups, there are indications for the occurrence of motor-impairment (Oskarsdóttir et al., 2005; Preis et al., 1997).

Limitations

This study has several limitations. First, it cannot be excluded that one or more DLD participants of the current study also have 22q11 deletion syndrome. We consider this possibility highly unlikely, however, since the diagnosis of DLD is based on the exclusion of any physical and developmental symptoms in other domains than language, whereas such symptoms are associated with 22q11DS. Second, the sample sizes of the language-impaired groups were relatively limited, and smaller than that of the TD group. Although sample size differences prohibit proper comparison of the group activation patterns, they do not negatively affect the interpretation of the laterality indices and beta values, which were computed for each participant individually. Our observation of an interaction effect between beta values and PPVT scores, however, needs further validation in a follow-up study with larger sample sizes. Third, since this study focused on language-laterality and activation levels in relatively large ROIs, we used a conservative voxel size (4 mm isotropic) and smoothing kernel (8 mm). A more in-depth investigation on the detailed representation of language-sub-functions in these groups could benefit from a follow-up study where the acquisition and analyses parameters are geared towards higher spatial resolution. Fourth, hearing, IQ and language performance data was not available for the TD children because, for this group, we used data acquired for another study. All children of this group attended regular schools, however, and were not reported to have any relevant medical issues. Overall, we believe this group can therefore be considered as typically developing. Of note, one TD participant was dyslectic. Since dyslexia has been associated with hypo- and hyperactivation in several brain regions (Hancock et al., 2017), we checked whether or not leaving out this child from the statistical analysis of the SR task would affect the results. Importantly, the findings on SR lateralization index and beta values did not change by excluding this child and we therefore decided not to exclude this participant from the manuscript.

Conclusions

Our observation that children with DLD and children with 22q11DS show decreased levels of activity in the Anterior Temporal and Wernicke sub-ROIs

suggests that the language impairment of both groups involves similar cortical areas. The difference between the two groups in the relationship between fMRI activity in Broca's area and PPVT scores may be indicative of a difference in the severity of the impairment, but it cannot be excluded that the two groups differ in a more fundamental level in this respect. Our findings do not exclude the existence of (partially) overlapping neural mechanisms underlying the language impairment of children with 22q11DS and children with DLD, and therefore suggest that further characterization of 22q11DS may also be informative for understanding DLD. However, a definitive answer to this question requires further an in-depth investigation of the relationship between neural activity and language performance in these two groups.

Supplementary Information

Supplementary figures 1, 2 and 3 can be found online via:
https://www.sciencedirect.com/science/article/pii/S0028393221001585

Supplementary Figure 1. *Visualization of the five language sub-ROIs and motor-ROI used in this manuscript. Projections of the different sub-ROIs on one hemisphere of a template brain. ROIs were made for both hemispheres. A) Broca, B) Wernicke, C) Anterior Temporal, D) Auditory, E) Caudate, F) Motor-ROI. The combination of sub-ROIs A-D is referred to as 'language-ROI'.*

Supplementary Figure 2. *SR task activation pattern. Group activation patterns of the SR task for children with DLD (n=13) and 22Q11DS (n=9). For these images, we used a low T-threshold. The color scale indicates T-values between 1.5 and 7.*

Supplementary Figure 3*. Cluster of voxels in the left sensorimotor hand area with a significant difference for the HM task between TD children and children with DLD (T=3.42; p<0.001; threshold extent k≥77).*

Supplementary Table 1. *Language (sub-)ROI(s). Brainnetome areas included in the language-ROI and each of the language sub-ROIs. The large language-ROI contained the first four rows of the table (the sub-ROIs marked with an asterisk). Note that area A41/A42, an area typically associated with auditory perception, was included in the Wernicke ROI as well, to avoid this ROI being discontinuous.*

Language sub-ROI	Brainnetome areas
Broca*	A44d, A44op, A44v, A45c, A45r, IFS
Wernicke*	A39rv, cpSTS, A40rd, A40c, A40rv, A41/42, A22c
Anterior Temporal*	A22r, A21c, A21r, A38m, A38l, aSTS, rpSTS
Auditory*	A41/42, TE1.0/TE1.2
Caudate	vCa, dCa

Supplementary Table 2. *Anxiety and enjoyment. Visual Analogue Scale scores for anxiety and enjoyment experienced by the participants (mean ± SD), as rated by the participants themselves, their parent and the researcher, before and after the mock-scan preparation, and by the participant after the real fMRI scan.*

	Anxiety			Enjoyment		
	DLD	22q11DS	TD	DLD	22q11DS	TD
Participant Before Preparation	4.2±2.6	3.5±3.2	3.7±1.9	2.9±2.6	3.6±3.6	2.9±1.8
Participant After Preparation	1.9±1.0	2.9±3.3	2.1±1.6	1.7±0.9	3.5±3.0	1.9±1.1
Participant After MRI	2.1±1.4	2.3±2.8	2.1±1.2	1.5±0.6	2.1±2.1	1.9±1.3
Parent Before Preparation	4.6±2.0	4.4±2.5	3.8±1.8	3.0±1.9	3.8±2.4	2.8±1.7
Parent After Preparation	3.0±2.0	3.4±2.3	2.7±1.8	2.4±1.4	2.9±2.1	2.0±1.0
Researcher Before Preparation	4.3±1.6	4.4±1.7	3.7±1.4	2.6±0.8	2.9±1.0	3.3±1.2
Researcher After Preparation	2.7±1.2	3.9±2.4	2.6±1.2	1.8±0.8	3.1±1.5	2.4±1.2

Supplementary Table 3. *Demographics of all groups of participants, results of the IQ and language tests and acquired scans per participant. DLD = developmental language disorder, 22q11DS = 22q11 deletion syndrome, TD = typically developing. Scores for the sentence repetition and PPVT language tasks are standardized scores. 1=scan/task acquired, n/a = scan/task not acquired, excl = data excluded due to excessive head motion and resulting PSP values <0.4, *785 dynamics acquired, **239 dynamics acquired, ***598 dynamics acquired, ****440 dynamics acquired.*

Group	Nr	Age	Gender	TIQ	Sentence repetition	PPVT	Anatomy	SR	HM
DLD	1	6,1	f	-	1	78	1	1	1
DLD	2	6,12	m	111	5	117	1	1	1
DLD	3	6,32	f	131	6	108	1	1	1
DLD	4	6,51	f	107	2	80	1	1	1
DLD	5	6,63	f	127	7	117	1	1	1
DLD	6	7,09	f	97	2	101	1	excl	1
DLD	7	7,1	m	94	1	92	1	1	1
DLD	8	7,63	m	94	1	85	1	1	1
DLD	9	8,44	m	92	5	84	1	1	1
DLD	10	8,95	f	94	4	101	1	1	1
DLD	11	9,32	m	109	5	84	1	1	1
DLD	12	9,47	m	100	4	94	1	1	1
DLD	13	10,26	m	136	6	91	1	1	1
DLD	14	10,69	f	98	5	94	1	1	1
22Q11DS	1	6,50	m	88	5	110	1	1	1
22Q11DS	2	6,92	f	94	1	82	1	excl	1
22Q11DS	3	6,96	m	67	8	96	1	excl	excl
22Q11DS	4	7,39	m	70	7	91	1	1	1
22Q11DS	5	7,85	m	68	3	84	1	1*	1
22Q11DS	6	8,09	m	73	6	70	1	1	1**
22Q11DS	7	8,22	m	68	5	78	1	1	1
22Q11DS	8	8,33	m	69	6	74	1	excl	1
22Q11DS	9	9,65	m	76	8	77	1	1	1
22Q11DS	10	9,73	f	70	2	66	1	1	1
22Q11DS	11	10,61	f	73	5	83	1	1	1
22Q11DS	12	10,83	f	64	4	66	1	1	1
TD	1	6,1	f	-	-	-	1	1	1
TD	2	6,15	f	-	-	-	1	n/a	n/a
TD	3	6,7	f	-	-	-	1	1	1
TD	4	6,78	f	-	-	-	1	1	1
TD	5	6,83	m	-	-	-	1	1	1

TD	6	6,89	f	-	-	-	1	1	n/a
TD	7	7,34	f	-	-	-	1	1	1
TD	8	7,7	f	-	-	-	1	1	n/a
TD	9	7,93	m	-	-	-	1	1	1
TD	10	8,18	m	-	-	-	1	n/a	n/a
TD	11	8,24	f	-	-	-	1	1	1
TD	12	8,52	m	-	-	-	1	1	n/a
TD	13	8,61	f	-	-	-	1	1	1
TD	14	8,71	m	-	-	-	1	1	1
TD	15	9,02	f	-	-	-	1	1***	n/a
TD	16	9,07	f	-	-	-	1	n/a	1
TD	17	9,19	f	-	-	-	1	1	1
TD	18	9,35	m	-	-	-	1	1	n/a
TD	19	9,39	f	-	-	-	1	1	n/a
TD	20	9,62	m	-	-	-	1	1	n/a
TD	21	9,65	m	-	-	-	1	1	n/a
TD	22	10,21	f	-	-	-	1	n/a	1
TD	23	10,4	m	-	-	-	1	1	1
TD	24	10,7	m	-	-	-	1	1	1
TD	25	10,95	m	-	-	-	1	n/a	1****

Supplementary Table 4. *Average LIs for the SR task and the HM task in the language- and motor-ROI. Values represent M±SD. The number of participants contributing to each value is indicated between brackets.*

	Lateralization Index - SR Task			**Lateralization Index - HM Task**		
	DLD	**22Q11DS**	**TD**	**DLD**	**22Q11DS**	**TD**
Language - ROI	0.38±0.38 (13)	0.48±0.21 (9)	0.42±0.26 (20)	-0.04±0.28 (14)	-0.02±0.40 (11)	0.00±0.30 (15)
Motor-ROI	0.31±0.55 (13)	0.49±0.35 (9)	0.24±0.40 (20)	0.68±0.25 (14)	0.55±0.44 (11)	0.7 ±0.22 (15)

Supplementary Table 5. *Lateralization Indices (LIs) of the SR task and results of independent one-way ANOVAs. Numbers between brackets indicate the number of participants included in the mean. In the upper part of the table, numbers are based on all participants conducting the SR task The bottom half of the table represents averages based on only participants with positive (i.e. typical left lateralized) values.*

All participants				**One-way ANOVA**
Language sub-ROI	**DLD**	**22Q11DS**	**TD**	
Broca	0.61±0.48 (13)	0.79±0.20 (9)	0.63±0.30 (20)	$F(2,39)=0.81$, $p=0.45$
Wernicke	0.51±0.33 (13)	0.48±0.40 (9)	0.52±0.31 (20)	$F(2,39)=0.05$, $p=0.95$
Anterior Temporal	0.33±0.41 (13)	0.49±0.35 (9)	0.36±0.25 (20)	$F(2,39)=0.72$, $p=0.49$
Auditory	0.30±0.62 (13)	0.67±0.30 (9)	0.50±0.43 (20)	$F(2,39)=1,76$, $p=0.19$
Caudate	0.21±0.56 (13)	0.49±0.45 (9)	0.33±0.60 (20)	$F(2,39)=0.66$, $p=0.52$
Only participants with positive LI values				**One-way ANOVA**
Language sub-ROI	**DLD**	**22Q11DS**	**TD**	
Broca	0.73±0.21 (12)	0.79±0.20 (9)	0.68±0.21 (19)	$F(2,37)=0.86$, $p=0.43$
Wernicke	0.58±0.21 (12)	0.58±0.30 (8)	0.56±0.29 (19)	$F(2,36)=0.03$, $p=0.97$
Anterior Temporal	0.42±0.26 (12)	0.58±0.26 (8)	0.36±0.25 (20)	$F(2,37)=2.13$, $p=0.13$
Auditory	0.60±0.24 (10)	0.67±0.30 (9)	0.64±0.27 (17)	$F(2,33)=0.16$, $p=0.85$
Caudate	0.49±0.33 (9)	0.66±0.34 (7)	0.67±0.39 (11)	$F(2,26)=0.74$, $p=0.49$

Supplementary Table 6. *Mean beta statistics. Results of the independent one-way ANOVAs, per task, sub-ROI and hemisphere, testing for an effect of group, using the mean beta values of the top 10% voxels (upper half of the table) and the bottom 10% voxels (bottom half of the table), respectively. Results marked with an asterisk were significant after Bonferroni correction for multiple comparisons.*

TOP 10% voxels				
ROI	***SR Task***		***HM Task***	
	Left	***Right***	***Left***	***Right***
Broca	$F(2,39)=7.4$, $p=0.002$*	$F(2,39)=4.11$, $p=0.02$	$F(2,37)=0.25$, $p=0.78$	$F(2,37)=0.13$, $p=0.88$
Wernicke	$F(2,39)=10.3$, $p<0.001$*	$F(2,39)=3.97$, $p=0.03$	$F(2,37)=0.82$, $p=0.45$	$F(2,37)=1.47$, $p=0.24$
Ant. Temp.	$F(2,39)=9.68$, $p<0.001$*	$F(2,39)=6.02$, $p=0.005$	$F(2,37)=0.07$, $p=0.93$	$F(2,37)=0.36$, $p=0.70$
Auditory	$F(2,39)=3.19$, $p=0.05$	$F(2,39)=1.66$, $p=0.20$	$F(2,37)=1.53$, $p=0.23$	$F(2,37)=0.75$, $p=0.48$
Caudate	$F(2,39)=0.32$, $p=0.73$	$F(2,39)=0.27$, $p=0.77$	$F(2,37)=0.10$, $p=0.90$	$F(2,37)=0.28$, $p=0.76$
Motor	$F(2,39)=0.06$, $p=0.94$	$F(2,39)=0.17$, $p=0.84$	$F(2,37)=5.25$, $p=0.01$	$F(2,37)=1.19$, $p=0.32$

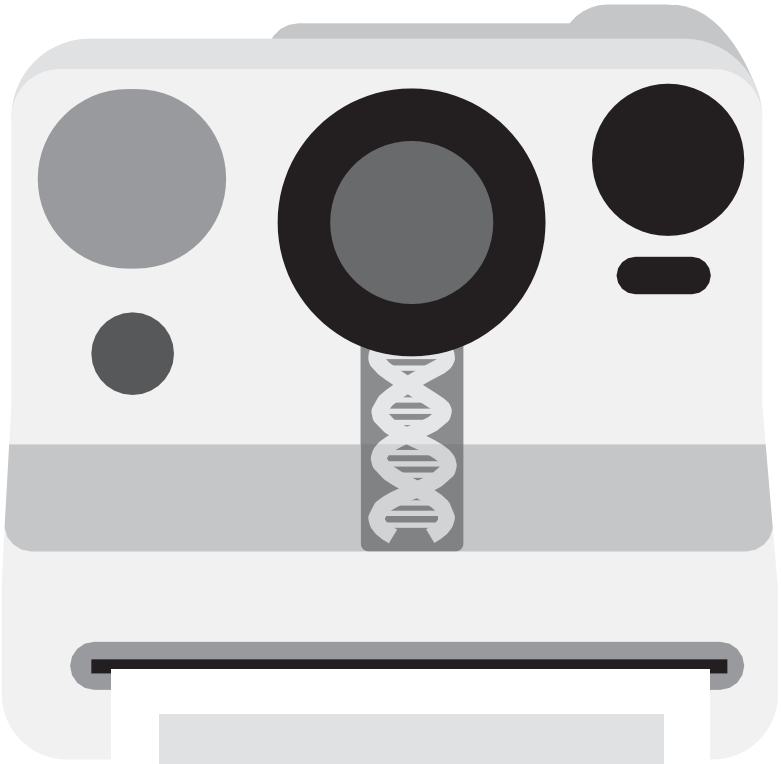
BOTTOM 10% voxels				
ROI	***SR Task***		***HM Task***	
	Left	***Right***	***Left***	***Right***
Broca	$F(2,39)=0.03$, $p=0.97$	$F(2,39)=2.91$, $p=0.07$	$F(2,37)=4.52$, $p=0.02$	$F(2,37)=2.66$, $p=0.08$
Wernicke	$F(2,39)=6.03$, $p=0.005$	$F(2,39)=2.96$, $p=0.06$	$F(2,37)=3.82$, $p=0.03$	$F(2,37)=2.12$, $p=0.13$
Ant. Temp.	$F(2,39)=1.54$, $p=0.23$	$F(2,39)=0.98$, $p=0.38$	$F(2,37)=6.10$, $p=0.005$	$F(2,37)=6.15$, $p=0.005$
Auditory	$F(2,39)=2.54$, $p=0.09$	$F(2,39)=0.78$, $p=0.47$	$F(2,37)=3.15$, $p=0.06$	$F(2,37)=3.78$, $p=0.03$
Caudate	$F(2,39)=3.34$, $p=0.05$	$F(2,39)=2.08$, $p=0.14$	$F(2,37)=4.46$, $p=0.02$	$F(2,37)=5.31$, $p=0.009$
Motor	$F(2,39)=2.15$, $p=0.13$	$F(2,39)=4.54$, $p=0.02$	$F(2,37)=1.19$, $p=0.32$	$F(2,37)=0.79$, $p=0.46$

Supplementary Table 7. *Results of ANCOVA analysis aimed to investigate the main effects of the group and behavioral measures on predicting the mean beta values per ROI, as well as all pairwise interactions of the predictor variables. The results are shown for the model predicting the top 10% mean betas per ROI. The result marked with an asterisk remained significant after Bonferroni correction for multiple comparisons.*

	Left Anterior Temporal	**Left Broca**	**Left Wernicke**
Group	F=0.42, p=0.53	F=2.73, p=0.13	F=0.22, p=0.65
IQ	F=0.15, p=0.71	F=0.82, p=0.39	F=0.21, p=0.66
Sentence Repetition	F=0.6, p=0.46	F=8.23, p=0.02	F=0.94, p=0.36
PPVT	F=0, p=1	F=4.09, p=0.07	F=0.19, p=0.68
Group*IQ	F=0, p=0.96	F=5.75, p=0.04	F=0.33, p=0.58
Group* Sentence Repetition	F=0.79, p=0.39	F=0.34, p=0.58	F=0.93, p=0.36
Group*PPVT	F=0.26, p=0.62	F=11.28, p=0.007*	F=0.60, p=0.46
IQ* Sentence Repetition	F=0.29, p=0.6	F=0.96, p=0.35	F=0.04, p=0.84
IQ*PPVT	F=0.75, p=0.41	F=7.7, p=0.02	F=0.42, p=0.53
Sentence Repetition *PPVT	F=0.08, p=0.79	F=0.26, p=0.62	F=0.04, p=0.84

Supplementary Table 8. *Author Contributions*

Contribution	**Author**
Conceptualization	Mariska J. Vansteensel; Frank Wijnen
Methodology	Mariska J. Vansteensel; Iris Selten; Lisette Charbonnier
Software	Lisette Charbonnier
Formal analysis	Mariska J. Vansteensel; Iris Selten; Lisette Charbonnier; Julia Berezutskaya; Mathijs A.H. Raemaekers
Investigation	Mariska J. Vansteensel; Iris Selten; Lisette Charbonnier
Data Curation	Iris Selten; Lisette Charbonnier
Writing-original draft	Mariska J. Vansteensel; Iris Selten; Julia Berezutskaya; Mathijs A.H. Raemaekers
Writing-review and editing	Mariska J. Vansteensel; Iris Selten; Lisette Charbonnier; Julia Berezutskaya; Mathijs A.H. Raemaekers; Nick F. Ramsey; Frank Wijnen
Visualization	Mariska J. Vansteensel; Iris Selten
Supervision	Nick F. Ramsey; Frank Wijnen
Project administration	Mariska J. Vansteensel
Funding acquisition	Mariska J. Vansteensel; Frank Wijnen



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Behaviors Related to Autism Spectrum Disorder in Children with Developmental Language Disorder and Children with 22q11.2 Deletion Syndrome

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Background and Aims: Children with Developmental Language Disorder (DLD) are at an increased risk to develop behaviors associated with Autism Spectrum Disorder (ASD). The relationship between early language difficulties and ASD-related behaviors in DLD is poorly understood. One factor that may hinder progress in understanding this relationship is the etiological heterogeneity of DLD. We therefore study this relationship in an etiologically homogeneous group of children: children with the 22q11.2 Deletion Syndrome (22q11DS). We also included a group of age-matched typically developing children (TD). **Method:** 44 children with 22q11DS, 65 children with DLD and 81 TD children, between 3,0-6,5 years old, participated in a longitudinal cohort study with a 1-year interval. A parental questionnaire (SRS-2) was used to measure the incidence of behaviors in two key behavioral domains associated with ASD. At baseline, we assessed children's language abilities and level of intellectual functioning with standardized tests. We compared the distribution of ASD-related behaviors and used regression analyses to investigate whether language abilities at baseline predict ASD-related behavior at follow-up. **Results:** Both the children with 22q11DS and the children with DLD displayed significantly more ASD-related behaviors than the TD children. Both in 22q11DS and DLD, baseline receptive language scores were negatively correlated with ASD-related behaviors one year later, when controlling for baseline SRS-scores. However, this association was statistically significant only in children with 22q11DS, even when controlled for IQ-scores, and it was significantly stronger as than in the TD group. The strength of the association did not differ significantly between 22q11DS and DLD. **Conclusion:** Only in children with 22q11DS we observed that weaker receptive language skills were related to increased behavioral problems in the domain of social communication and interaction one year later. **Implications:** Relationships between early language impairment and other behavioral phenotypes may be more feasible to detect in a subgroup of children with a homogeneous etiology, than in a group of children with a heterogeneous etiology (such as children with DLD). Our results in 22q11DS reveal that receptive language might be especially important in predicting the occurrence of ASD-related behaviors. Future research is needed to study the occurrence of ASD-related behaviors in those children with DLD with the weakest receptive language. Screening for ASD-related behaviors in children with developmental language difficulties is recommended from a young age, especially among children with receptive language difficulties.

Introduction

Children with Developmental Language Disorder (DLD) not only present with a variety of language problems, but also display elevated rates of behaviors that are typically observed in children with Autism Spectrum Disorder (ASD). However, the extent to which children with DLD develop these ASD-related behaviors varies greatly (e.g., Conti-Ramsden et al., 2006), highlighting the need to understand the mechanisms that contribute to such inter-individual variability in DLD. Previous research suggests that that individual differences in the language skills of children with DLD could not explain this variability in the occurrence of ASD behaviors (Conti-Ramsden et al., 2006; Leyfer et al., 2008). However, it is possible that this research was hindered to detect an association between language and ASD-related behaviors, by the etiological heterogeneity of DLD. That is, a wide range of biological and environmental risk factors, which may vary from child to child, is known to contribute to the development of DLD (Conti-Ramsden & Durkin, 2017). It could be that some of these etiological factors are more strongly associated with the development of ASD-related behaviors than others, and that different etiologies may differently impact the association between language skills and the occurrence of ASD-related behaviors in DLD. As a result, wide inter-individual variation in the strength of the relationship between language and ASD may exist among the group of children with DLD, which makes it difficult to elucidate such a relationship. The aim of the present study is therefore to investigate if we can more readily detect this relationship within a group of children who all share the same genetic etiology: The 22q11.2 deletion syndrome (22q11DS; McDonald-McGinn et al., 2015). 22q11DS is a relatively frequently occurring genetic disorder that is, like DLD, associated with developmental language difficulties (Solot et al., 2019a) and ASD-related behavior (Fiksinski et al., 2018). Here, we report on findings of our comparative study of children with 22q11DS, children with DLD, and typically developing (TD) age-matched peers.

What is Developmental language Disorder

Developmental Language Disorder (DLD) is a neurodevelopmental condition, with an estimated prevalence of 3-7% of the children in the general population (Bishop et al., 2017; Norbury et al., 2016). Children with DLD have severely impaired language skills, which negatively affects their functioning in other domains, such as academic and occupational achievement. The diagnostic criteria of DLD stipulate that the language difficulties of children with DLD are not explained by a known physical, neurological, intellectual or

environmental cause (Bishop et al., 2017). Nevertheless, various biological and environmental risk factors have been associated with DLD that may differ from child to child (Conti-Ramsden & Durkin, 2017; Rudolph, 2017), indicating that the etiology of DLD is highly heterogeneous.

This etiological heterogeneity may be reflected in the phenotypical heterogeneity that characterizes DLD (Bishop, 2006). Children with DLD vary from each other with respect to their level of impairment in the different modalities of language (i.e., receptive and expressive), as well as in the different language domains, including phonology, morphosyntax, semantics and pragmatics (Lancaster & Camarata, 2019; Williams et al., 2008). Furthermore, DLD is not only heterogeneous in terms of its linguistic profile, but also with respect to co-occurring features, including socio-emotional and behavioral difficulties (Chow et al., 2018; Curtis et al., 2018). Of particular relevance to the study presented here is that the prevalence of ASD, and therefore the behavioral symptoms that are associated with ASD, is increased among children with DLD, which appears to be a consistent finding across multiple independent studies (Conti-Ramsden et al., 2006; Leyfer et al., 2008; Loucas et al., 2008; Miniscalco et al., 2018; Mouridsen & Hauschild, 2009).

Autism Spectrum Disorder in children with DLD

ASD is characterized by impairments in two core behavioral domains, that are described in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013). The first involves difficulties in Social Communication and Interaction (SCI) and the second is related to the presence of Restricted and Repetitive Behaviors and Interests (RRB). In the present study, we use the term ASD-related behaviors to refer to symptoms in these two domains. Experiencing ASD-related behaviors negatively impacts friendship quality, independence and early work experience in adolescents with DLD, beyond the impact of their language difficulties (Durkin et al., 2012).

Problems with pragmatic language, which refers to the use of language in a social context, are part of the diagnostic criteria for both ASD and DLD. But additional ASD related behaviors have been observed in children with DLD, including weak social competence, difficulties in peer relationships (Howlin et al., 2000; Loucas et al., 2008; McCabe, 2005; Mok et al., 2014) and presentation of repetitive behaviors (Honey et al., 2008; Howlin et al., 2000; Ozyurt & Dinsever Elikucuk, 2017). Previous studies (summarized in table 1), indicate high variability in the extent to which children with DLD develop ASD-related behaviors. Some children may be meeting full criteria for ASD, whereas

others develop subthreshold levels of ASD-related behaviors, while yet another subgroup of children with DLD does not present with any ASD-related behaviors. Overall, previous findings suggest that DLD is associated with an increased probability to develop ASD or ASD-related behaviors, in particular those involving problems in communication and interaction, but to a varying extent. Understanding the factors that impact this variability could enhance our ability to early identify those children with DLD who are most liable to develop ASD behaviors, and ultimately, explore the potential of early interventions (Williams et al., 2008).

Relation between language and ASD-related behaviors in DLD

It has been suggested that difficulties in understanding others and expressing oneself may pose a risk for the development of a range of socio-emotional and behavioral difficulties (Bornstein et al., 2013; Salmon et al., 2016). In a meta-analysis of longitudinal studies in TD children, Chow and colleagues (2018) empirically confirmed this suggestion, and even showed that receptive language appeared more important in predicting later behavioral outcomes than expressive language. However, this meta-analysis did not include specific measures of ASD, therefore the observed socio-emotional and behavioral difficulties cannot be considered as equivalent to ASD.

Given that language development is of critical importance for a child's social and behavioral functioning (Conti-Ramsden et al., 2018), one could hypothesize that the variation in language difficulties among children with DLD partly explains the observed variation in the prevalence of ASD and ASD-related behaviors in this population. The existing evidence for this hypothesis is mixed, but appears to tend towards no or at most a weak correlation between language difficulties and ASD-related behaviors in DLD. First, and in contrast to the hypothesis mentioned above, a vast number of studies did not detect a relationship between the language abilities and the development of ASD or subthreshold ASD-symptoms in children with DLD (Conti-Ramsden et al., 2006; Howlin et al., 2000; Leyfer et al., 2008; Mouridsen & Hauschild, 2009), nor between language ability and difficulties with peer relationships (Mok et al., 2014). One study showed that receptive language deficits appeared to be negatively associated with the domain measuring 'communication and language' in the Autism Diagnostic Interview (ADI-R), in children with a mixed receptive/expressive language disorder (Mildenberger et al., 2001). Furthermore, expressive language deficits of children with DLD were shown to be associated with social interaction problems in the school context and weaker receptive language skills in children with DLD were associated with

increased repetitive behaviors (Gibson et al., 2013). However, both these latter studies were limited by a small sample size, and one used only cross-sectional data (Gibson et al., 2013).

On the one hand, this evidence may suggest that early language difficulties do not impact the development of ASD-related behaviors in children with DLD. On the other hand, if a relationship between language and ASD-related behaviors exists in some children with DLD, the etiological heterogeneity that characterizes DLD poses a challenge to elucidate this relationship. Given the etiological variability of DLD, it is possible that the co-morbidity of ASD-related behaviors in DLD varies as a function of the specific etiology underpinning DLD. This would also imply that different etiologies of DLD may differently impact the relationship between language abilities and the development of ASD-related behaviors. Against this background, it may therefore be relevant to study the relationship between language and ASD in a group of children who are phenotypically similar to DLD, but who have a more homogeneous etiology.

22q11.2 deletion syndrome

In the present study, we therefore compare children with DLD to children with the 22q11.2 deletion syndrome (22q11DS; OMIM #188400, #192430). 22q11DS is a neurodevelopmental condition, that is resulting from a Copy Number Variant (CNV; McDonald-McGinn et al., 2015). A CNV refers to a deletion or duplication of genetic material on a specific region of a child's genome, often encompassing more than one gene (Smajlagić et al., 2021). In this case, 22q11DS is caused by a by a hemizygous microdeletion of 0.7-3 million base pairs on the long arm of chromosome 22 (McDonald-McGinn et al., 2015). Some of the CNVs, are pathogenic, meaning that they are disease-causing. A subset of these pathogenic CNVs, among others 22q11DS, are associated with a range of neurodevelopmental problems, including both developmental language difficulties and a high incidence of ASD (Barnett & van Bon, 2015; Sønderby et al., 2021).

Table 1. *Overview of Empirical Studies That Reported Prevalence Rates of ASD-diagnoses and the Incidence of ASD-related Behaviors in Children that were Diagnosed with or Referred for DLD, and in whom Presence of ASD or Suspected ASD was Excluded.*

Outcome measure of ASD-related behavior	N	Mean Age baseline (years)	Mean Age follow-up	Instrument to assess ASD-related behavior	% of individuals with this behavior at follow-up	Study
Full criteria for ASD on	76	7	14	ADOS & ADI	4%	(Conti-Ramsden et al., 2006)
two instruments or	108	2.5 – 3.5	5	Review of clinical records	11%	(Miniscalco et al., 2018)
diagnostic classification of ASD	469	5	35.8	Review of clinical records	2.1%	(Mouridsen & Hauschild, 2009)
Full criteria for ASD on one instrument only	76	7	14	ADOS or ADI	26%	(Conti-Ramsden et al., 2006)
ASD-related behaviors	108	2.5 – 3.5	5	Review of clinical records	12%	(Miniscalco et al., 2018)
on both SCI and RRBII	93	2.5	9 -11	SRS-2	20%	(Roy & Chiat, 2014)
ASD-related behaviors	44	11.1	cross-sectional[a]	ADI or ADOS or Both	41%	(Leyfer et al., 2008)
on SCI only				*ADI Social Interaction*	*14%*	
				ADI communication	*11%*	
				ADOS Social Interaction	*18%*	
				ADOS communication	*25%*	
ASD-related behaviors on RRBI only	44	11.1	cross-sectional[a]	ADI ADOS	25% 10%	(Leyfer et al., 2008)

Abbreviations. ADOS = Autism Diagnostic Observation Schedule . ADI = Autism Diagnostic Interview. SCI = social communication and interaction. RRBI = restricted repetitive behaviors and interests. SRS-2 = Social Responsiveness Scale

[a].Presence of ASD was explicitly excluded

22q11DS has a prevalence of 1:2000 live births (Blagojevic et al., 2021) and is characterized by a heterogeneous phenotype, including varying physical, cognitive and psychiatric difficulties. The level of intellectual functioning in 22q11DS is variable, and is normally distributed around a full-scale IQ-score of 70 in adulthood (De Smedt et al., 2007). Speech-language difficulties are reported in 95% of children with 22q11DS, making this one of the primary developmental concerns that manifest early in life (Solot et al., 2019a). Similar to what is reported in DLD, 22q11DS is associated with impaired language development across modalities and domains (Everaert, 2023; Solot et al., 2019b; Van den Heuvel et al., 2018), it has been shown that the language skills of children with 22q11DS are impaired beyond what can be expected given their overall cognitive level, which also corresponds to what is observed in many children with DLD (Goorhuis-Brouwer et al., 2003; Norbury et al., 2016b; Selten et al., 2021; Solot et al., 2001). One previous study investigated neurophysiological functioning during language processing and did not detect differences between children with 22q11DS and children with DLD (Vansteensel et al., 2021). Others concluded that children with 22q11DS have a largely overlapping profile of behavioral difficulties with children with both a language impairment and a learning disability (Swillen et al., 2001). Together this indicates that 22q11DS and DLD share significant overlap. Of note is that the current diagnostic criteria for DLD differentiate children with 22q11DS from children with DLD, based on the presence of a genetic condition (i.e., 22q11DS), which underlies the developmental language difficulties that are observed in virtually all children with 22q11DS.

In addition, 22q11DS is associated with an elevated prevalence of a variety of neurodevelopmental disorders in childhood, as well as schizophrenia in young adulthood. The prevalence of ASD varies across studies and is typically reported between 10-40% (Fiksinski et al., 2018; Schneider et al., 2014). It has been observed that early language difficulties are associated with the development of subsequent psychosis in 22q11DS (Solot et al., 2020). However, the relationship between early language difficulties and the development of ASD and ASD-related behaviors has not been studied in 22q11DS.

Aim of the present study

The aim of the present study is to enhance our understanding of the relationship between language difficulties and the occurrence of ASD-related behaviors in children with developmental language difficulties. To this end, we will investigate the relationship between language skills and ASD-related

behaviors in children with 22q11DS, and compare these observations to children with DLD and TD children.

Moreover, we use a longitudinal design, which allows us to study the influence of language on the emergence of ASD-related behaviors, while controlling for initial levels of ASD-related behaviors. We use a continuous measure of ASD-related behaviors, which contributes to gaining insight into the severity of both core behavioral symptoms associated with ASD (i.e., problems in social communication and interaction and repetitive restricted behaviors and interests). In addition, we assess the influence of both expressive and receptive language on the occurrence of ASD-related behaviors, as they may be differentially related to behavioral development (Conway et al., 2017). Given that children with 22q11DS on average have a lower level of intellectual functioning than children with DLD, we will account for the potential confounding effect of IQ-scores. We hypothesize that children with 22q11DS and children with DLD present with increased rates of ASD-related behaviors in comparison to TD children, in both domains. Additionally, if a relationship between language and ASD-related behaviors exists, we hypothesize that the etiological homogeneity in the 22q11DS sample will enable us to more readably detect this relationship, while the etiological heterogeneity in DLD hampers our ability to do so.

Method

Participants

The participants were children taking part in the "3T-study", a longitudinal cohort study on the linguistic, cognitive and psycho-social development of children with 22q11DS and children with DLD, in comparison to TD age-matched peers (Everaert, 2023). Parents or caregivers provided written informed consent, the study was approved by the Ethical Review Board of the University Medical Center Utrecht, The Netherlands, and was performed in accordance with the Declaration of Helsinki (World Medical Association, 2013). Inclusion criteria were 1). Aged between 3 and 6,5 years old. 2). Being monolingual Dutch and 3). Absence of hearing loss (dB>35). A child was considered monolingual Dutch if 80% of their life-time daily language input was in the Dutch language. This information was retrieved through a short, standardized phone interview with a child's parents or legal guardians. In the same interview, parents were asked if there had ever been any concerns regarding their child's hearing. In the Netherlands, hearing is assessed during newborn screening and is repeated several times in the first two years of life. We therefore included all children whose parents did not indicate any

concerns about their child's hearing. In case of hearing concerns, we asked for the results of standardized hearing tests, which allowed us to decide whether a child could participate in the study.

In the 22q11DS group, the genetic deletion was confirmed with a molecular genetic test. Children with DLD met one of the following criteria prior to participation in the study, in accordance with the Dutch criteria for admission to special care or education for children with DLD: a) a standardized global language test score of 2 standard deviations or more below the age-adequate mean, b) two separate standardized test scores of 2 SDs or more below the age-adequate mean for at least one important language domain, c) standardized single test scores of 1.5 SDs or more below the mean for at least *two* of these domains, or d) standardized single test scores of 1.3 SDs or more below the mean for at least *three* of these domains (Stichting Siméa, 2017). Prior to inclusion, children in the TD group were screened for the absence of concerns of developmental language problems or neurodevelopmental disorders. Children with 22q11DS were recruited via the national outpatient clinic for 22q11DS at the University Medical Center Utrecht, or via the national patient organization. Children with DLD were recruited via national expertise centers for children with severe language problems. TD children were recruited via daycare centers or primary schools for regular education. The final cohort consisted of 44 children with 22q11DS, 65 children with DLD and 81 TD children.

Measures

ASD-related behaviors. Parents or legal caregivers filled out the second version of the Social Responsiveness Scale about their child (SRS; Roeyers et al., 2011). The SRS is a questionnaire consisting of 65 items, with each item describing a behavior that is associated with ASD. Each item was scored on a 4-point likert-type scale ranging from 0 (=never) to 3 (=often), indicating whether the child displays that type of ASD-related behavior. Each item belongs to one of two scales that matches with either of the two core domains of ASD as described in the DSM-5, being *difficulties with Social Communication and Interaction (SCI-scale, 53 items)* and *Repetitive and Restricted Behaviors and interests (RRB-scale, 12 items).*

Depending on the age of their child, parents filled out the SRS-version for 2- and 3-year-old children, or 4- to 18-year-old children, which are comparable both in the number and content of items. The SRS is normed on the Dutch population for children aged 2 and 3 years old and children aged 4 to 18 years old, as well as for different sexes. Based on procedures described

in the SRS manual, we transformed the raw scores on the SCI-scale and the RRB-scale into age- and sex-corrected normed T-scores for each participant. We used these two T-scores as variables in our analyses (i.e., T-SCI and T-RRB). A T-score lower than 60 indicates behavior in the normal range, a T-score of 60-65 indicates mild to moderate deficiencies in social behavior, T-scores between 66-75 indicate moderate social deficits and T-scores >76 indicate severe deficits in social functioning.

Receptive and Expressive language. The Dutch version of the Clinical Evaluation of Language Fundamentals – Preschool version (CELF; Wiig et al., 2012) was administered to measure children's language abilities. The CELF consists of different subtests to assess the level of functioning in different language domains. For the present study, we used children's scores on the three subtests that measured receptive language abilities (*sentence comprehension, following directions, and basic concepts or word classes*) and three subtests that measured expressive language abilities (*word structure, expressive vocabulary, and recalling sentences*). The CELF provides normed scores for the Dutch population, which allowed us to transform the raw scores on each subtest into age-corrected normed scores. Subsequently, by taking the sum of these normed scores, we could compute both a Receptive Language Composite score (CELF RLC) and an Expressive Language Composite score (CELF ELC), according to procedures described in the CELF manual. These composite scores have a mean score of 100 and a standard deviation of 15.

Intelligence. Results of children's intelligence assessments (i.e., IQ-scores) were collected via medical or school records. If this data were not available, which was the case for all TD participants, we administered a shortened version of the Wechsler Non Verbal (WNV; Wechsler & Naglieri, 2008). We used the full-scale IQ scores (FSIQ) in our analyses. These IQ scores have a mean score of 100 and a standard deviation of 15.

Procedure

Data collection consisted of a baseline measurement and a follow-up measurement after 12 months. The language assessment took place at a child's daycare facility or school by a trained researcher. Parents were asked to fill out online questionnaires regarding the linguistic and behavioral development of their child. Due to the COVID-19 pandemic, follow-up visits at schools and daycares were not possible. Consequently, ASD-related

behaviors were measured at both baseline and follow-up, whereas language skills were measured at baseline only. The tasks measuring expressive language were recorded and subsequently scored by the researcher who administered the task and, independently, by a second researcher. In case of discrepancies, a final score was reached by consensus.

Data processing and analyses

All analyses were conducted in RStudio version 4.0.2 (RStudio Team, 2020). We provide a visual overview of the distribution of T-SCI scores and T-RRBI scores for all three participant groups (22q11DS, DLD, TD). In addition, using Analyses of Variance (ANOVA), we compared the distribution of ASD-related behaviors (T-SCI scores or T-RRBI scores) in our three participant groups. We also used Chi-Square tests to compare the proportion of children in each participant group with T-SCI scores or T-RRBI scores in the mildly impaired range or higher (T>60). Overall, we used an alpha-level of .05 to indicate statistically significant main effects. For post-hoc analyses, we applied Bonferroni corrections to correct for multiple comparisons. Given that we compared three groups, and investigated group differences on the two SRS-scales separately, our alpha level indicating statistically significant group differences is: 0.05/3 = 0.017. We report effect sizes and follow Ferguson (2009) for the interpretation.

We took several steps to examine the relationship between early language skills and the occurrence of ASD-related behaviors. First, we conducted, per group, four sets of partial correlations, each time correlating either scores on the CELF RLC or the CELF ELC with either T-SCI or T-RRB measured at follow-up, controlling for the baseline T-scores on that SRS-scale (e.g., "CELF ELC **T-SCI at follow-up, controlled for baseline T-SCI*"). Subsequently, for those partial correlations indicating a significant association, we conducted a multiple regression analysis to investigate to what extent the scores on the relevant language variable predict the scores on the relevant SRS-scale at follow-up, accounting for other relevant variables, including baseline SRS-scale, parental education and intellectual functioning (*e.g., T-SCI at follow-up predicted by parental education + FSIQ + baseline T-SCI + CELF ELC*).

Finally, we conducted a second multiple regression analysis to investigate whether the strength of the association between the relevant language variable and SRS-scale differed between the participant groups, accounting for the effects of demographic variables and FSIQ. Our outcome variable was the relevant measure of ASD-related behavior (T-SCI or T-RRB).

Our full model included age, sex, level of parental education, FSIQ, and baseline ASD-related behavior as predictors. In addition, we added the interaction term for group*language (*e.g., group*CELF ELC*) as predictor variable. In all our regression analyses, we centered all continuous variables to avoid multi-collinearity.

Results

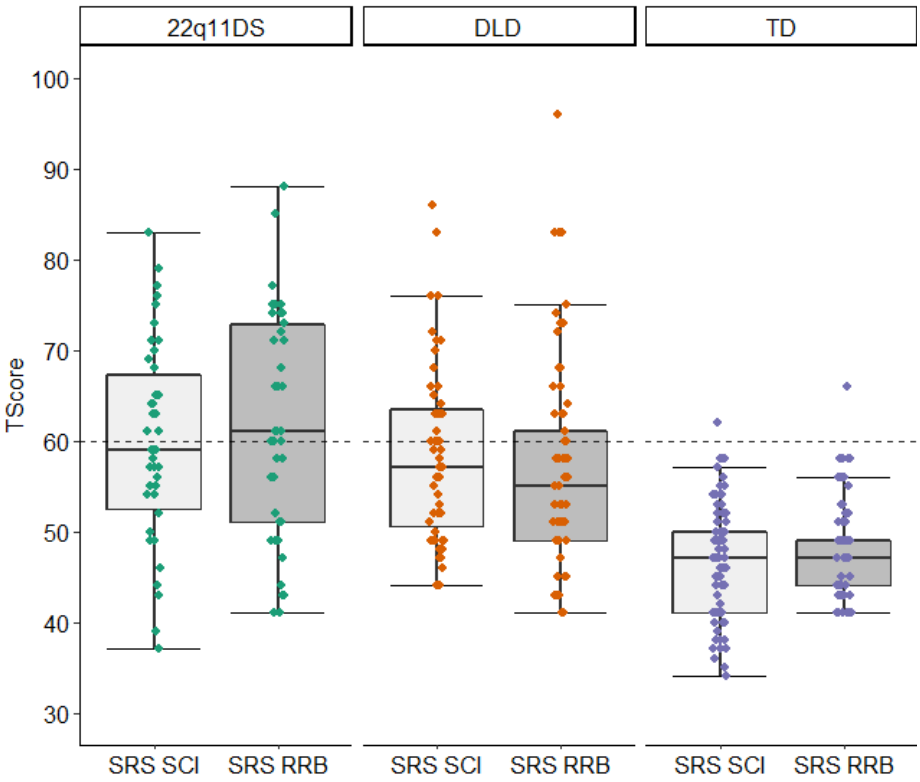
Data attrition and sample description

Some parents did not complete the SRS at the follow-up measure, resulting in missing data for children with 22q11DS (n=2), DLD (n=8) and TD children (n=3; see table 1 in appendix A). In addition, three children from the TD group had a score on the language assessment indicating below average language performance (i.e., CELF core language composite score <-1 SD), and were therefore excluded from further analyses. In comparison to the other two groups, the final sample of children with DLD consisted of more boys than girls ($22q11_{male}$=55%, DLD_{male}=77%, TD_{male}=44%, [$\chi 2(2)=16.64$, $p<.001$]). In addition, significant group differences were found for level of parental education and IQ scores (see table 2 for sample descriptives).

ASD-related behaviors at follow-up

Figure 1 displays the distribution of T-scores at follow-up on both SRS scales (SRS SCI and SRS RRB). Results of the ANOVA showed a main effect of group for both T-SCI scores [$F(2,171)=41.45$, $p<.001$, $\eta^2 = .033$] and T-RRB scores [$F(2,171)=30.31$, $p<.001$, $\eta^2 = 0.26$]. Pairwise comparisons showed that TD children, on average, had lower T-scores on both SRS-scales ($p_{SCI}<.001$; $p_{RRB}<.001$) than the children with 22q11DS or the children with DLD, who did not differ from each other ($p_{SCI} = 1$, $p_{RRB} = .160$). Table 3 shows the proportion of children within each group with a T-score in the mildly impaired range or higher (T>60). Pairwise comparisons showed that the proportion of children with a mildly impaired score or higher did not differ significantly between the children with 22q11DS and the children with DLD in the SCI-scale [$\chi^2(2)=0$, $p = >.999$]. The proportion of children with a score in this range on the RRB-scale was significantly larger in the 22q11DS group than in the DLD group ($\chi^2(2)=4.88$, $p=.027$), but the effect did not survive Bonferroni correction.

Figure 1. *Distribution of T-scores on the Two Subscales of the SRS (SRS SCI and SRS RRB) for Children with 22q11DS (n=42), Children with DLD (n=57), and TD Children (n=75). Each dot Indicates the Score of an Individual Participant.*



Abbreviations. SCI = Social communication and Interaction. RRBI = Restricted Repetitive Behaviors and Interests.

Note. A higher T-score on the SRS indicates more ASD-related behaviors. The horizontal dotted line reflects the cut-off score for the subclinical range (T=60). Each box represents the middle 50% of T-scores ranging from the 25th percentile to the 75th percentile. Black bar in each box represents the median. Whiskers represent the 2,5th percentile and 97,5th percentile.

Table 2. *Sample Characteristics of Children with SRS Data at the Follow-Up Measurement Point*

Variable	Group									Statistics			
	22q11DS (n=42)			**DLD (n=57)**			**TD (n=75)**						
	M	SD	Range	M	SD	Range	M	SD	Range	(df)F	*p*	η^2	post-hoc
Age baseline (months)	58.5	12.2	37-77	57.0	10.2	36-74	55.8	11.0	36-78	(2,171)=0.76	.468	.00	-
Age follow-up (months)	71.3	12.2	50-90	70.0	10.2	49-87	68.6	11.0	49-91	(2,171)=0.81	.446	.00	-
Parental education[a]	6.44	1.8	2-9	6.5	1.6	3.5-9	7.9	1.2	4-9	(2,170)=19.7	<.001	.19	TD>DLD=22q11
FSIQ[b]	79.6	12.1	50-103	97.0	12.8	69-124	107	13.0	81-139	(2,166)=59.5	<.001	.42	TD>DLD>22q11

a. Parental education was indexed by the average education level of both parents, ranked on a 9-point scale reflecting the Dutch educational system (ranging from 1 'no education' to 9 'university degree'). This information was missing for 1 TD child
b. Full-scale Intelligence Quotient. This information was missing for 2 children with 22q11DS, 2 children with DLD and 1 TD child.

Table 3. *Percentages Indicating the Proportion of Children with 22q11DS, DLD or TD with a T-score >60 on the SRS-scales*

SRS scale	Group			Statistics		
	22q11DS (n=42)	**DLD (n=57)**	**TD (n=75)**	χ^2	p	Post-hoc
SCI	45.2%	43.9%	1.33%	41.39	<.001	TD<22q11DS=DLD
RRBI	59.5%	35.0%	1.33%	50.14	<.001	TD<22q11DS=DLD
SCI and RRBI	42.9%	24.6%	0%	36.24	<.001	TD<22q11DS=DLD

Abbreviations. *SCI = T-score on SRS-scale Social Communication and interaction. RRBI = T-score on SRS-scale* Restricted Repetitive Behaviors and Interests.

The relation between ASD-related behaviors and language

There was missing data in all three participant groups, leaving a subsample of 28 children with 22q11DS (46% male), 54 children with DLD (76% male) and 72 TD children (46% male) who could be included in the analyses investigating the relationship between language difficulties and the occurrence of ASD-related behaviors at follow-up. As a substantial number of children with 22q11DS could not be included in the regression analyses, we compared those children to the children with 22q11DS with complete data. The main reason for exclusion in 22q11DS was missing data on the language measures (see appendix A for type of missing data). It appeared that children with and without missing data did not differ significantly in on the distributions on age, sex or T-RRB scores (see appendix A). However, in the group of children with 22q11DS, the comparison of SCI scores between children with and without missing data resulted in a borderline significant difference (p = .052), suggesting that the children with missing data may have had somewhat higher scores on the SCI-scale (indicating more problems) than the children without missing data. Given the small number of children with missing data in both the TD and DLD group, we did not statistically compare the children in these groups to children with complete data.

The descriptive statistics and group comparisons of the subsample that could be included in the regression analyses are reported in table 4. Again, the gender distribution differed significantly between the three groups [$\chi 2(2)=15.08$, p <.001], as there were more boys in the DLD group (79% male) than in the TD group (46% male) or 22q11DS group (46% male). On all measures of ASD-related behaviors and language, TD children had on average higher scores than children with DLD or children with 22q11DS, who often did not differ. Children with DLD only differed from the children with 22q11DS on their IQ score and score of receptive language, with higher scores of the DLD group.

Partial correlations

Table 5 shows the results of partial correlations for each group. We observed a significant negative correlation with a large effect size between baseline CELF RLC scores and T-SCI scores at follow-up in the 22q11DS group. This indicates that weaker receptive language skills were associated with higher rates of ASD-related behaviors in the domain of SCI at follow-up in the children with 22q11DS, while controlling for baseline T-SCI scores.

Table 4. *Sample Characteristics of the Children who were Included in the Regression Analyses.*

Variable	Group									Statistics			
	22q11DS (n=28)			**DLD (n=52)**			**TD (n=72)**						
	M	SD	Range	M	SD	Range	M	SD	Range	(df)F	p	η^2	post-hoc
Age Follow-up (months)	73.4	12.0	52.1-88.7	70.3	10.3	49.9-87.4	68.9	10.8	48.7-90.9	(2,149)1.7	.184	.02	-
FSIQ	83.0	10.3	62-103	96.5	12.8	69-124	107.0	13.6	81-139	(2,149)38.3	<.001	.34	TD>DLD >22q11
Language *(Baseline)*													
CELF ELC	72.7	11.5	55-100	71.6	9.8	56-98	103.0	13.3	77-132	(2,149)129.1	<.001	.63	TD>DLD =22q11
CELF RLC	76.7	14.3	55-112	85.3	13.8	56-115	108.0	12.3	84-139	(2,149)75.9	<.001	.50	TD>DLD >22q11
ASD-related behavior													
T-SCI *Baseline*	59.3	12.2	38-83	60.9	10.7	43-85	48.8	7.81	34-79	(2,149)26.7	<.001	.26	TD<DLD =22q11
T-RRBI *Baseline*	62.3	13.5	43-99	59.8	11.9	43-91	48.8	7.3	39-72	(2,149)25.6	<.001	.26	TD<DLD =22q11
T-SCI *Follow-up*	57.3	11.4	37-77	58.6	8.9	44-83	47.0	6.4	34-62	(2,149)35,8	<.001	.32	TD<DLD =22q11
T-RRBI *Follow-up*	60.8	13.1	41-85	58.1	11.5	41-96	48.2	5.3	41-66	(2,149)25.7	<.001	.26	TD<DLD =22q11

Abbreviations. FSIQ = full scale Intelligence Quotient. CELF ELC = expressive language composite score. CELF RLC = receptive language composite score. SCI = T-score on SRS-scale Social Communication and interaction. RRBI = T-score on SRS-scale Restricted Repetitive Behaviors and Interest

Table 5. *Results of the Partial Correlations Between the Measures of Language and ASD-Related Behaviors at Follow-Up, while Controlling for ASD-Related Behaviors at Baseline.*

Correlation model	Group					
	22q11DS (n=28)		**DLD (n=52)**		**TD (n=72)**	
	r	*p*	*r*	*p*	*r*	*p*
T-SCI – CELF ELC	-0.23	.239	-0.14	.326	-0.09	.460
T-SCI – CELF RLC	**-0.59**	**.001**	-0.18	.197	-0.01	.936
T-RRBI – CELF ELC	0.12	.552	-0.08	.594	0.01	.919
T-RRBI – CELF RLC	-0.22	.260	-0.04	.807	-0.04	.767

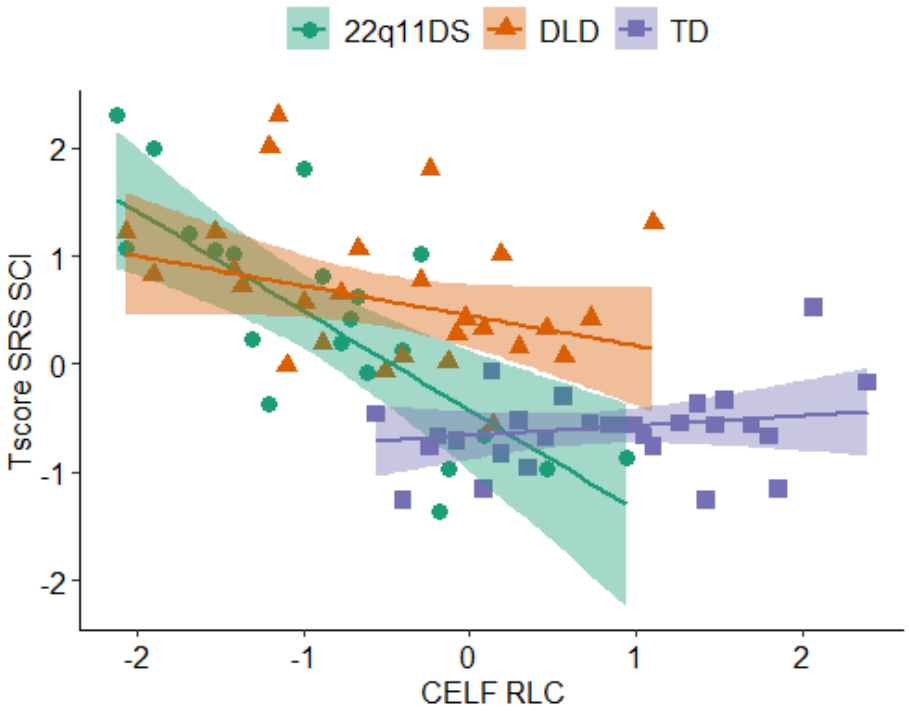
Abbreviations. T-SCI = T-score on social communication and interaction (SRS-scale SCI)
T-RRBI = T-score on Restricted Repetitive Behaviors and Interests. (SRS-scale RRBI)
CELF ELC = expressive language composite score (CELF)
CELF RLC = receptive language composite score (CELF)

Regression analysis

We conducted a regression analysis to explore the strength of the association between CELF RLC and T-SCI scores at follow-up in the group of children with 22q11DS. Given that the 22q11DS group is characterized by low FSIQ-scores, we added FSIQ as predictor in this model, together with baseline T-SCI and CELF RLC. The regression model was significant, with a large effect size [$F(3,24)=22.38$, $p < .001$, R^2-adj = 0.70]. Model estimates showed that CELF RLC scores at baseline significantly predicted T-SCI scores at follow-up, taking into account FSIQ and baseline T-SCI scores (see table 6).

Subsequently, we investigated if the relationship between CELF RLC and T-SCI differed between the three groups, when accounting for variation in demographic variables and FSIQ. We therefore conducted a final regression model, including age, sex, parental education, FSIQ and baseline T-SCI scores as predictors, as well as adding the interaction term of 'group*CELF RLC'. The full regression model using the TD group as the reference group was significant with a large effect size [$F(10,141)=41.31$, $p < .001$, R^2-adj = 0.73]. Results showed that receptive language scores at baseline were significantly more strongly associated with T-SCI at follow-up in children with 22q11DS than in TD children, whereas this difference was not significant in the comparison between the TD and DLD groups nor in the comparison between the 22q11DS and DLD groups (see Table 7 and Figure 2).

Figure 2. *Plot Presenting the Relationship between Receptive Language and ASD-Related Behaviors in the Domain of Social Communication and Interaction in Children with 22q11DS (n=28), Children with DLD (n=52) and TD-Children (N=72), Using the Predicted Values Resulting From the Regression Model.*



Abbreviations. SRS SCI = Social Communication and Interaction (SRS-scale SCI). CELF RLC = Receptive Language Composite score (measured with the CELF) Note. Individual dots represent data points of individual participants. Solid line is predicted mean per group.

Table 6. *Results of the Regression Analysis for the 22q11DS Group (n=28), Predicting T-scores on Social Communication and Interaction at Follow-Up, Using Receptive Language as Predictor, Accounting for Full Scale IQ-scores and T-scores on Social Communication and Interaction at Baseline*

Variable	Beta	Std-error	t	*p*
Intercept	-0.33	0.22	-1.48	.152
FSIQ	0.06	0.21	0.26	.796
Baseline T-SCI	0.65	0.12	5.55	<.001
CELF RLC	-0.61	0.19	-3.16	.004

Abbreviations: FSIQ = Full Scale Intelligence Quotient
T-SCI = T-score on social communication and interaction (SRS-scale SCI)
CELF RLC = receptive language composite score (CELF)

Table 7. *Results of the Interaction Model Predicting SRS SCI T-Scores at Follow-Up*

Variable	Beta	Std-error	t	*p*
Intercept	-0.29	0.11	-2.68	.008
Age follow-up	0.15	0.05	2.99	.003
Sex	0.15	0.09	1.57	.119
Parental education	-0.09	0.05	-1.63	.105
FSIQ	-0.06	0.06	-1.09	.280
Baseline T-SCI	0.67	0.06	11.70	<.001
CELF RLC: TD vs. 22q11DS	-0.50	0.17	-2.92	.004
CELF RLC: TD vs. DLD	-0.16	0.14	-1.15	.254
CELF RLC: 22q11DS vs. DLD[a]	-0.34	0.17	-1.97	.051

Abbreviations: FSIQ = full scale IQ score. T-SCI = T-score on social communication and interaction (SRS-scale SCI). CELF RLC = receptive language composite score (measured with CELF).
Note. We did not include main effects for group and RLC in this table as they cannot be interpreted in the presence of a significant interaction effect.
[a] The comparison between the 22q11DS and DLD groups comes from a different model using the 22q11DS group as the reference group. Full model statistics were [$F(10,141) = 41.31$, $p = .<001$, $R^2adj=0.73$]

Discussion

The goal of the present study was to investigate to what extent early receptive and expressive language difficulties are related to the occurrence of ASD-related behaviors in preschool-aged children with 22q11DS, children with DLD and TD children. We expected that the more homogeneous etiology of the 22q11DS group would increase the likelihood of detecting such a relationship, if it exists, compared to the etiologically more heterogeneous group of children with DLD.

Prevalence of ASD-related behaviors in 22q11DS and DLD

As expected, we observed that both young children with DLD and children with 22q11DS presented, on average, significantly more ASD-related behaviors than TD children. This was found in both key behavioral domains that are associated with ASD, including the domain of social communication and interaction (SCI) and the domain of Restricted Repetitive patterns of Behaviors and Interests (RRBI). To our knowledge, this is the first study reporting on prevalence rates of ASD-related behaviors in children with DLD in this age-range. Previous studies with older children and adolescents with DLD reported that around 30% of school-aged children with DLD present with ASD or ASD-symptoms, predominantly in the domain of SCI (see table 1). The results of the present study showed comparable prevalence rates of ASD-related behaviors, as well as a similar pattern of relatively more problems in the domain of SCI than in the domain of RRBI in young children with DLD. Of note, more than half of the sample of children with DLD did not have elevated rates of ASD-related behaviors, indicating that our measures of language and of ASD are not tapping into the same underlying construct. One previous study has specifically investigated the prevalence of ASD-related behaviors in a sample of young children with 22q11DS (Serur et al., 2019). These authors reported a similar level of problems in both the domain of SCI and RRBI, which is in line with the results of the present study, and which is in accordance with what is reported in school-aged children and adolescents with 22q11DS (Kates et al., 2007; J. A. S. Vorstman et al., 2006).

Relationship between language and ASD-related behaviors

Our analyses revealed that the level of receptive language skills of the children with 22q11DS was negatively associated with the level of ASD-related behaviors in the SCI-domain one year later. The design of the present study did not allow us to investigate the bidirectional relationship between language and ASD. However, as we corrected for baseline ASD-related

behaviors, the results of this study indicate that receptive language problems contribute to the occurrence of ASD-related behaviors in the domain of social communication and interaction. Moreover, and in line with previous observations (Van den Heuvel et al., 2018; Vorstman et al., 2006), intellectual functioning did not seem to contribute to the occurrence of ASD-related behaviors in children with 22q11DS. We had to exclude some children with 22q11DS in our analyses, because they had missing data on the language tasks. These children had relatively high SCI scores (indicating more problems), and, based on our own observations, had relatively low language levels (resulting in missing data on some of the language tasks). Hence, we expect that the inclusion of these individuals would most likely have strengthened, not weakened, the observed association.

We observed that the association between receptive language and SCI was stronger in the children with 22q11DS than in the group of TD children. A similar positive association was observed in the DLD children, but weaker and not reaching statistical significance. These observations confirm our hypothesis that such a relationship can be more easily detected in an etiologically homogeneous group (i.e., 22q11DS), than in an etiologically heterogeneous group (i.e., DLD). This supports the possibility that the inconsistent findings in the literature regarding the association between language ability and ASD-related behaviors are due, at least in part, to the etiological heterogeneity of the DLD population.

The strength of the association between receptive language and SCI did not significantly differ between the children with DLD and the children with 22q11DS, when accounting for important demographic variables, such as sex and FSIQ on which the groups differed significantly. The difference in sample sizes between the 22q11DS and DLD groups may have hindered to detect a statistical difference in the strength of the association between language and ASD-related behaviors (Aguinis et al., 2017), although a similar sample size difference existed between the 22q11DS and TD groups, for which our comparison of this relationship did result in a significant difference. Alternatively, our finding leads us to speculate that there may be a subgroup within the larger group of children with DLD, who behaves similarly as children with 22q11DS. The results of the present study seem to indicate that children with 22q11DS have on average weaker receptive language skills than children with DLD. Although prevalence rates of receptive language problems in DLD have not been frequently reported, also in other samples has been shown that around half of the children perform at an age-expected level (Boyle et al., 2009). Based on these observations, we may speculate that a relationship

between receptive language and SCI may exist only in those children with DLD with receptive language problems. As this has been previously observed in one study (Mildenberger et al., 2001), further research is needed to explore this hypothesis.

We did not observe any relationships between language and ASD-related behaviors in our TD group, which contrasts with research that did demonstrate such relationships (Larkin et al., 2017). However, other studies suggested that language is only predictive of problem behavior for children with very low language levels (Goh et al., 2021). As our TD children all had language scores in the normal range, this could explain why we did not detect a relationship between language and ASD-related behaviors in this group. In addition, we also did not detect significant associations between expressive language and ASD-related behaviors. This strengthens previous work suggesting that receptive language is more important for socio-emotional and behavioral development (Chow et al., 2018). Alternatively, it has been suggested that the impact of expressive language difficulties increases in a later developmental stage, when these skills are generally more developed (Conway et al., 2017). Future studies using a longer follow-up period or a larger age-range could answer such questions.

Implications

Our results may imply that the degree of receptive language impairment contributes to the occurrence of ASD-type behavior in children with developmental language disorders. It has been suggested that weak receptive language skills may especially be a risk factor for the development of problems in the domain of social interaction and communication, because children with weak receptive language skills may withdraw from their environment due to difficulties understanding parents, peers and teachers, thereby avoiding interactions with others. In turn, this leads to reduced opportunities to practice social skills (Angkustsiri et al., 2014; Bornstein et al., 2013; Salmon et al., 2016). As a next step, it would be interesting to study to what extent therapy targeting receptive language may also influence the development of ASD-related behaviors in children with language difficulties.

Besides ASD-related behaviors, DLD is associated with several other behavioral phenotypes, including Attention Deficit Hyperactivity Disorder (ADHD) and increased levels of anxiety and depressive symptoms. To elucidate to what extent early language difficulties contribute to the emergence of these different developmental phenotypes, future studies may copy the approach of the present study, by investigating these relationships

in an etiologically homogeneous group. It has been shown that a small number of children with different CNVs, other than 22q11DS, could be identified in a population of children who were initially diagnosed with DLD (Kalnak et al., 2018; Pettigrew et al., 2015; Plug et al., 2021). This indicates that, besides 22q11DS, there may be several other relevant subgroups with a shared genetic etiology and a phenotype corresponding to DLD. Examining interrelationships between language difficulties and other behavioral phenotypes in 22q11DS and such other subgroups may potentially provide leads for future studies aiming to investigate relationships between different behavioral phenotypes in DLD.

The results presented here likely have implications for clinical practice. The age of the youngest children in this study was three years. This is due to the fact that, in the Netherlands, a diagnosis of (suspected) DLD is often not given before this age. However, we know that ASD-related behaviors may be observed at an earlier age (Zwaigenbaum et al., 2015). Indeed, we found high rates of ASD-related behaviors in both children with 22q11DS and DLD in our sample at the baseline measure, which highlights the need for early awareness and screening of the presence of ASD-related behaviors, both in children with 22q11DS and DLD. It has been reported that receptive language problems tend to increase in children with 22q11DS during school-age (Van Den Heuvel et al., 2018). These problems may be easily overlooked by caregivers and professionals, particularly in the context of a broad range of physical symptoms that characterizes young children with 22q11DS. However, given the correlation with the occurrence of ASD-related behaviors, careful monitoring of receptive language development in children with 22q11DS is warranted.

Strengths, limitations and future directions

We used composite scores derived from a standardized language assessment, including measures of multiple language domains, which gives a broad indication of both a child's expressive and receptive language skills. A limitation of using such a standardized assessment is that a relatively large proportion of children with 22q11DS did not complete all tasks, and could therefore not be included in the final regression analyses. We therefore recommend future studies to include language measures that are more suitable for children with low language levels or intellectual disability. Such measures, especially spontaneous language measures, may even more strongly relate to daily life communication problems.

We aimed to test to what extent the homogeneous etiology of 22q11DS, would enable us to detect a stronger relation between language and ASD-related behaviors as compared to children with DLD. It is therefore a strength of this study that we accounted for the effect of the level of intellectual functioning, on which 22q11DS differed from both the DLD and TD children. However, besides weaker intellectual functioning, there are other factors that differ between DLD and 22q11DS. Specifically, 22q11DS is associated with physical manifestations, for which hospitalizations at an early age may be necessary, whereas this is not the case in DLD. In children with 22q11DS, these early physical manifestations may severely influence the early child-caregiver connection and communication (Swillen et al., 2018). As such, in line with our previous reasoning (Salmon et al., 2016), the physical manifestations of 22q11DS may impact future behavioral outcomes of children with 22q11DS, including the development of ASD-related behaviors. It would therefore be interesting for future studies to include the context of physical symptoms, and their association with the child-caregiver relationship, in models that predict later behavioral outcomes.

To our knowledge, this is the first study directly investigating the relationship between early language difficulties and the occurrence of ASD-related behaviors in children with 22q11DS. We consider it a strength of this study that we used a longitudinal design, including a measure of ASD-related behaviors, that was administered both at baseline and again at the 1-year follow-up assessment. This allowed us to demonstrate the impact of early language difficulties of children with 22q11DS and DLD on the occurrence of ASD-related behaviors one year later, while controlling for the initial level of ASD-related behaviors. To confirm our finding that receptive language difficulties are associated with the occurrence of ASD-related behaviors in children with 22q11DS, replication is necessary.

Such replication studies should take into account that other factors, besides early language difficulties, may influence the development of ASD-related behaviors in children. For instance, it has been suggested that the relationship between language and ASD-related behaviors could be mediated by cognitive factors that were not included in the present study, such as difficulties in emotion-recognition and theory of mind (Vissers & Koolen, 2016). Given that impaired development of these cognitive functions has been reported, both in 22q11DS (Milic et al., 2021) and in DLD (Vissers & Koolen, 2016), it would be interesting to test to what extent these factors play a role in understanding the relationship between receptive language and ASD-related behaviors in these two groups of children. Furthermore, factors such

as motor functioning or sensory processing may play a role in explaining the observed variation in the domain of repetitive and restricted behaviors (Berry et al., 2018). Impairments in these domains have been reported in children with DLD (Diepeveen et al., 2018) and in children with 22q11DS (Van Aken et al., 2009). Future studies would need to shed light to what extent the influence of such factors is on the development of ASD-related behaviors, in these groups of children.

Conclusion

We demonstrated that lower receptive language skills of children with 22q11DS, an etiologically homogeneous group with severe language difficulties, were associated with more ASD-related behaviors at a later age, specifically in the domain of social communication and interaction. This association was not significant in children with DLD, which corroborates with our hypothesis that the etiological heterogeneity within the DLD group may hinder our ability to detect such associations. This emphasizes the advantage of studying homogeneous subgroups to increase our understanding of phenotypical variability in DLD. Future research, for instance further comparing 22q11DS and DLD, is necessary to identify for which children with DLD receptive language difficulties play a role in the occurrence of ASD-related behaviors. Clinically, results of our study highlight the importance of screening for ASD-related behaviors in children with DLD and 22q11DS already at a young age, especially in those children with receptive language difficulties.

Supplementary information

Appendix A

Table 1. *Overview indicating the number of children with missing data for each variable, out of all children that were excluded from the regression analyses.*

Type of missing data	22q11DS (n=14)	DLD (n=5)	TD (n=3)
CELF ELC	8	2	1
CELF RLC	9	1	0
FSIQ	2	2	1
SRS Baseline	4	1	1

Abbreviatons. CELF ELC = Expressive language composite score. CELF RLC = CELF receptive language composite score. FSIQ = Full Scale IQ score. SRS baseline = baseline score on Social Responsiveness Scale.
Note. Total in 22q11D and DLD some children had missing data on multiple variables (e.g.,both CELF ELC and CELF RLC)
a. Parental education was indexed by the average education level of both parents, ranked on a 9-point scale reflecting the Dutch educational system (ranging from 1 'no education' to 9 'university degree'). This information was missing for 1 TD child

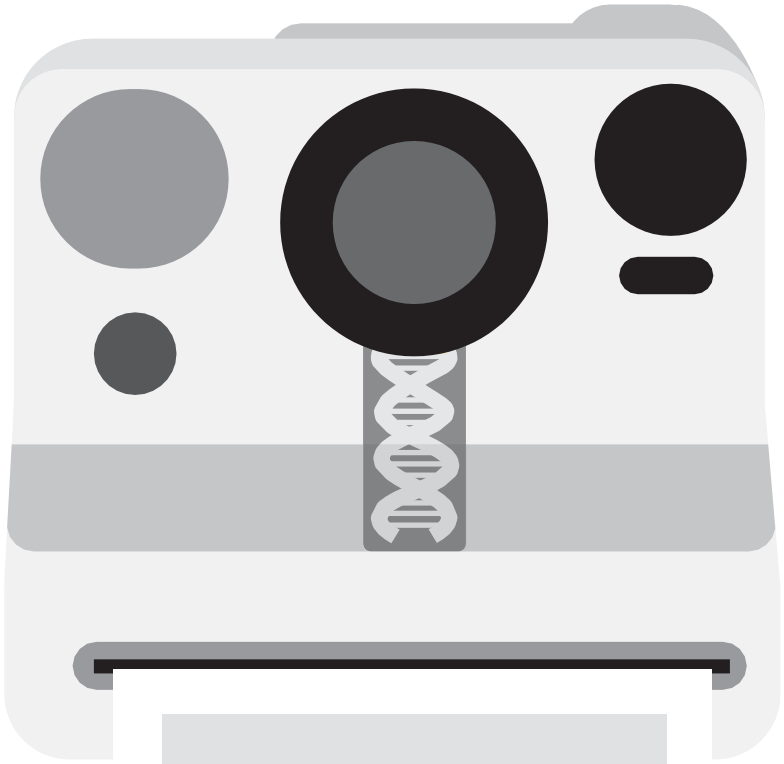
Table 2. *Results of independent t-tests, indicating whether scores on these variables differed between children with 22q11DS who could (n=28) and could not be (n=14) included in the regression analyses.*

Variable	Statistics	
	t/χ^2	*p*
Age follow-up	-1.57	.123
Sex	1.45	.228
T-RRB follow-up	0.63	.537
T-SCI follow-up	**2.02**	**.052**

Abr. T-SCI = T-score on social communication and interaction (SRS-scale SCI)
T-RRBI = T-score on Restricted Repetitive Behaviors and Interests. (SRS-scale RRBI). *Note.* Significant difference indicated higher rates of T-SCI scores for the children that did not take part in the regression analysi

Table 3. *Author Contributions*

Contribution	**Author**
Conceptualization	Iris Selten; Tessel Boerma; Emma Everaert; Jacob Vorstman
Methodology	Iris Selten; Tessel Boerma; Emma Everaert; Jacob Vorstman
Software	
Formal analysis	Iris Selten
Investigation	Iris Selten; Tessel Boerma; Emma Everaert
Data Curation	Iris Selten; Tessel Boerma; Emma Everaert
Writing-original draft	Iris Selten; Tessel Boerma; Jacob Vorstman
Writing-review and editing	Iris Selten; Tessel Boerma; Ellen Gerrits; Emma Everaert; Michiel Houben; Frank Wijnen; Jacob Vorstman
Visualization	Iris Selten
Supervision	Tessel Boerma; Frank Wijnen; Jacob Vorstman
Project administration	Iris Selten; Tessel Boerma; Emma Everaert
Funding acquisition	Ellen Gerrits; Frank Wijnen; Jacob Vorstman



7

General Discussion

The work presented in this dissertation aims to contribute to a better understanding of the inter-individual differences in the occurrence of neuropsychiatric symptoms in children with Developmental Language Disorder (DLD), by investigating the extent to which these differences are associated with the variable presentation of language difficulties that characterizes this population. Previous studies on this topic, discussed in the introduction chapter, have yielded mixed results regarding the presence and strength of this association. Such inconsistent results could, at least in part, be a consequence of the etiological heterogeneity that characterizes the population of children with DLD. Therefore the approach of the present dissertation was to focus on a genetically homogeneous group of children with language difficulties, with the goal to obtain a clearer picture of the association between language ability and neuropsychiatric symptoms. To this end, this dissertation focused on children with the 22q11.2 deletion syndrome (22q11DS). The current dissertation investigated whether 22q11DS could function as a genetic model to enhance our understanding of inter-individual differences in co-occurring neuropsychiatric symptoms in DLD. Three research aims were formulated (see *chapter 1*). In this final discussion chapter, the findings related to each of these three aims will be summarized. Subsequently, the scientific and clinical implications of these findings will be discussed, together with recommendations for future research. Finally, a conclusion will be drawn.

Summary of results

Aim 1

One requirement for 22q11DS to function as a genetic model for a given clinical condition in the general population, is that this condition in 22q11DS and in the general population share sufficient clinical characteristics (Bassett & Chow, 2008). The first aim of this dissertation was to contribute to a more complete overview of the 22q11DS linguistic and neuropsychiatric phenotype, enabling detailed comparisons with children with DLD.

Aim 1. Address knowledge gaps regarding the descriptions of neuropsychiatric symptoms and language difficulties in 22q11DS.

Neuropsychiatric symptoms associated with 22q11DS

Previously, the neurodevelopmental symptoms associated with 22q11DS have been largely described in terms of prevalence rates of diagnostic categories, including Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD) and schizophrenia. In *chapter 2*, a dimensional approach was adopted, which allowed describing neuropsychiatric phenotypic expression on a symptom level. An important observation in this sample of adolescents with 22q11DS was that neuropsychiatric symptoms had a continuous distribution in multiple major neuropsychiatric domains. This finding suggests that binary diagnostic categories may fall short in describing the full range of inter-individual variation in the expression of neuropsychiatric symptoms in 22q11DS. In most neuropsychiatric domains, more than 50% of the adolescents with 22q11DS expressed at least one clinically relevant symptom. For those adolescents without a formal DSM-IV diagnosis, the large majority expressed at least one clinically relevant neuropsychiatric symptom in the corresponding domain (*e.g., >85% had at least one ADHD symptom without a diagnosis of ADHD*). Together, the dimensional approach thus enables capturing the breadth and depth of the inter-individual variability in the expression of neurodevelopmental symptoms in all adolescents with 22q11DS, regardless of having a psychiatric diagnosis.

Language difficulties associated with 22q11DS

The existing descriptions of language abilities in preschool-aged children with 22q11DS were limited. Therefore, we undertook a study to provide a comprehensive overview of the language skills of preschool-aged children with 22q11DS. The results, described in *chapter 3,* showed that the vast majority of the preschool-aged children with 22q11DS had mildly impaired to severely impaired language skills in multiple major language domains, including syntax and semantics, both in expressive and receptive language. Despite a weak, positive association between speech intelligibility and language abilities (i.e., better intelligibility was associated with better language), a large part of the children with intelligible speech still had below-average language abilities. This led us to conclude that language difficulties in young children with 22q11DS should be considered a separate symptom, and should not to be conflated with speech problems in this population.

In contrast to preschool children, the language difficulties of school-aged children with 22q11DS had been relatively well-described, although descriptions of narrative abilities remained scarce. In *chapter 4,* we demonstrated that, on average, school-aged children with 22q11DS did not

differ from their typically developing peers with a similar mental age in their ability to tell a well-structured story (i.e., a narrative). However, the children with 22q11DS had more difficulties than the TD control group in correctly understanding a story told by the experimenter. This led us to conclude that, on average, both the narrative production and comprehension skills of school-aged children with 22q11DS lag behind what would be expected for their chronological age, with weak narrative comprehension standing out in particular.

Aim 2

Previous authors have suggested overlapping phenotypic characteristics between 22q11DS and DLD, but direct comparisons between the two populations were too limited to determine the differences and similarities between the two groups. In addition, the two populations have not been compared on measures of language-related brain functioning. The second aim of the current dissertation was to address these gaps.

Aim 2. Compare 22q11DS to DLD on the level of behavioral manifestations and brain activation during language processing, using both existing literature as well as results of this dissertation.

The language profile. Both 22q11DS and DLD are characterized by a delayed emergence of their first words and sentences (*chapter 3;* Bishop et al., 2017). Furthermore, the vast majority of young children with 22q11DS have below average language skills in multiple language domains that are likely to persist over the course of development (see *chapter 3*; Solot et al., 2019), which overlaps with the language difficulties that are associated with DLD (Bishop et al., 2017). Specifically, weak expressive grammatical skills have been reported as a hallmark deficit in DLD. Results in *chapter 3* showed that this was also the weakest language domain in the preschool-aged children with 22q11DS. Moreover, a recent study using the data from spontaneous language samples from the 3T project and the EPISODE study demonstrated that scores on spontaneous language measures of grammatical complexity and accuracy did not differentiate children with 22q11DS from those with DLD (Boerma, Everaert, et al., 2023). This is in line with the conclusions of the two studies that were discussed in the *chapter 1*, reporting a largely overlapping profile of grammatical skills in these populations (Kambanaros & Grohmann, 2017; Persson et al., 2006). Furthermore, in *chapter 4*, we demonstrated that children

with 22q11DS did not differ from children with DLD, neither in their ability to produce narrative macrostructure nor in their narrative comprehension skills.

However, only children with 22q11DS, and not the children with DLD, had weaker narrative *comprehension* than the younger TD children. This led us to suggest that, in line with others (Van den Heuvel et al., 2018), weak receptive language may be characteristic for children with 22q11DS. Although a comparison of the language skills of children with 22q11DS and children with DLD was not the primary aim of that chapter, further evidence for this remarkable delay in receptive language comes from our data in *chapter 6.* The CELF composite score for expressive language skills seemed comparable between the preschool-aged children with 22q11DS and their peers with DLD (22q11DS = 73, DLD = 72), whereas the CELF composite score for receptive language skills was lower in 22q11DS than in DLD (22q11DS = 76, DLD = 85). Moreover, post-hoc inspection of our data in *chapter 6* demonstrated that only around half of the children with DLD had below average receptive language, while a large majority of the children with 22q11DS scored consistently below age-expected levels on receptive language tasks. Taken together, this indicates that the severity and type of expressive language impairment seems to largely overlap in children with 22q11DS and children with DLD. However, almost all children with 22q11DS have receptive language impairment, whereas this is the case in only a subset of the children with DLD.

The role of intellectual functioning. The diagnostic criteria for DLD stipulate that a child's language difficulties cannot be attributed to a child's low level of intellectual functioning. The fact that children with 22q11DS had significantly weaker narrative comprehension abilities than typically developing children with a similar mental age (see *chapter 4*) may indicate that difficulties in narrative comprehension cannot be entirely explained by the level of intellectual functioning in 22q11DS. *Chapter 5* did not specifically aim to address the association between language skills and intellectual functioning in 22q11DS. However, considering the mean language and IQ scores in this sample of preschool-aged children with 22q11DS (expressive language = 73; receptive language = 77; intelligence = 83; *all measured with instruments that have M=100; SD=15 in the general population*), this indicates a discrepancy between the level of language skills and intellectual functioning in 22q11DS. As previously suggested, this implies that the language skills in children with 22q11DS are weaker than what would be expected based on their level of intellectual functioning (Goorhuis-Brouwer et al., 2003; Persson et al., 2006; Scherer et al., 1999), comparable to the diagnostic criteria for DLD.

Brain activation during neural language processing. In *chapter 5*, the brain activation during spoken language processing was compared between children with 22q11DS, children with DLD, and a group of typically developing age-matched peers. We observed that children with DLD and children with 22q11DS showed brain activation in similar areas as typically developing children during language processing. However, reduced brain activation was found in DLD and 22q11DS, as compared to their typically developing peers. This supported previous findings in DLD (Mayes et al., 2015), and led us to hypothesize that language difficulties in both groups may stem from similar alterations in the neural language network.

Neuropsychiatric symptoms. The prevalence rates of several neuropsychiatric disorders, in particular ADHD and Anxiety disorder, are comparable between 22q11DS and DLD (see table 1 in *chapter 1*). In addition, in both 22q11DS and DLD, ASD is a relatively frequently occurring condition, as compared to the other neuropsychiatric disorders. One previous study compared neuropsychiatric symptoms, as reported by parents and teachers, between children with 22q11DS and children with DLD, revealing a largely overlapping profile (see *chapter 1*; Swillen et al., 2001). The results in *chapter 6* corroborate this finding, as we found that children in both groups presented with similar rates of behaviors in two core symptom domains that are associated with ASD. However, while 22q11DS is associated with a pronounced risk to develop psychosis spectrum disorder or schizophrenia (Fiksinski et al., 2018) , this risk is much less pronounced in DLD. Furthermore, in comparison to other neuropsychiatric symptoms, severe externalizing behavior, such as oppositional behavior, is relatively frequently occurring in DLD (Pickles et al., 2016). In contrast, such symptoms are relatively weakly expressed by individuals with 22q11DS, as compared to symptoms in other neuropsychiatric domains (Fiksinski et al., 2018; *chapter 2*). Of relevance here are the results of *chapter 2*, demonstrating large inter-individual differences in the severity and type of neuropsychiatric symptoms in adolescents with 22q11DS. Likewise, inter-individual variation in the occurrence of neuropsychiatric symptoms has also been reported in DLD (Maggio et al., 2014). As such, despite differences on a group-level, overlap between the neuropsychiatric phenotypes of some children with DLD and some children with 22q11DS is very likely; there may be individuals with 22q11DS with a profile of neuropsychiatric symptoms that is characteristic for the group of DLD, and vice versa.

Summary. Both populations of children with 22q11DS and children with DLD are characterized by early and persistent language delays, with similar impairments in expressive morphosyntax, which is considered a hallmark deficit of DLD. Moreover, we found no evidence for a difference in the functioning of neural language networks between 22q11DS and DLD. That is, activation in these networks induced by spoken language processing was similarly reduced in both groups, as compared to age-matched TD peers. Next to these similarities, however, we also identified differences in the language profile of children with 22q11DS and children with DLD. Almost all children with 22q11DS have a receptive language impairment, whereas the presence and degree of receptive language impairment is more variable among children with DLD. Additionally, on a group-level, similarities and differences between the neuropsychiatric symptoms that are associated with 22q11DS and DLD could be identified. Given the inter-individual differences in the occurrence of neuropsychiatric symptoms in both populations, it seems likely that a subset of the individuals with 22q11DS presents with a DLD-like profile of neuropsychiatric symptoms, and vice versa.

Aim 3

A final step was to determine to what extent the genetic homogeneity of 22q11DS allows to statistically detect associations between language skills and neuropsychiatric symptoms, while the heterogeneity in DLD may hinder ability to do so.

Aim 3. Compare the strength of the association between language skills and neuropsychiatric symptoms between children with 22q11DS and DLD.

In *chapter 6,* this aim was addressed by studying preschool-aged children with 22q11DS, peers with DLD, and a comparison group of typically developing children with a similar age. The focus of interest was the association between expressive and receptive language difficulties on the one hand, and two core symptom domains that are associated with Autism Spectrum Disorder (ASD) on the other hand. These two core symptom domains were (1) problems in social communication and interaction, and (2) presence of repetitive and restricted behaviors and interests. The results showed one significant negative association, and only in the 22q11DS group. That is, having weaker receptive language skills was significantly associated with more problems in the domain of social communication and interaction in the children with 22q11DS. The

association between language problems and restricted behaviors was not significant in this group. In the DLD and TD groups, all associations between language skills and ASD-related behaviors were not significant.

In line with what we had hypothesized, we observed that the association between receptive language skills and communication difficulties was significantly stronger in the 22q11DS group than in the TD group. A significant difference in this association was not found between the DLD group and the TD group. Remarkably, even after controlling for important variables, e.g.,sex and intellectual functioning, the strength of this association did not differ significantly between the children with DLD and the children with 22q11DS.

Based on these findings the conclusion was drawn that investigating a genetically homogenous population, in this case 22q11DS, improves our ability to detect associations between language difficulties and co-occurring neuropsychiatric symptoms, whereas the etiologically heterogeneous etiology of DLD may interfere with our ability to do so. Secondly, given that a significant difference was not detected between 22q11DS and DLD, in the association between receptive language and communication difficulties, it was suggested that weaker receptive language problems could be associated with increased rates of ASD-related behaviors in children with DLD, but only in a specific subset of children who behave similarly as children with 22q11DS. Given the similarities and differences between 22q11DS and DLD, as mentioned in the discussion of aim 2, this subgroup may consist of those children with DLD with both expressive and receptive language impairment, as opposed to the children with DLD with age-appropriate receptive language skills.

Scientific implications, limitations and future directions

Differentiating between DLD subgroups

Results of this dissertation indicated that inter-individual differences in receptive language impairment explained some of the inter-individual variation of ASD-related symptoms in the domain of social communication and interaction in children with 22q11DS. Given that 22q11DS might function as a genetic model for the children with DLD, specifically those who have below-average receptive language skills, this finding may imply that this association also exists in this subset of children with DLD. It is therefore highly relevant to conduct a follow-up study to further explore this new hypothesis. This study should differentiate between the children with DLD who have low receptive language skills, and the children with DLD who have age-adequate

receptive language skills, and, subsequently, study whether the association between receptive language and ASD-related behaviors is indeed stronger in the first group than in the latter group. If this is the case, this would, first and foremost, enhance our understanding of inter-individual differences in the occurrence of ASD-related behaviors for the subset of children with DLD with low receptive language. Moreover, this would indicate that the association between language difficulties and the occurrence of ASD-related symptoms may vary between different subsets of children with DLD with different language phenotypes. In other words, the heterogeneity of this group would make it difficult to statistically detect such associations in the population of children with DLD as a whole. Consequently, differentiating between different subgroups of children with DLD, based on their language-phenotype, might be a promising approach for further research aiming to detect associations between language difficulties and ASD-related symptoms in DLD. Moreover, we could speculate that these different subgroups of children with DLD may be characterized by more similar combinations of genetic or environmental risk factors contributing to their DLD. Further studies are needed to explore these suggestions.

The suggestion that differentiating between subgroups of children with DLD might be relevant is not unique, as the interest in detecting subtypes of DLD already started more than two decades ago (e.g., Conti-Ramsden et al., 1997; Conti-Ramsden & Botting, 1999). Longitudinal research in DLD has shown that both a subgroup of children with expressive-receptive language impairment and a group with only expressive language impairment could be identified, and that the language profiles of children in those groups were relatively stable throughout development (Conti-Ramsden et al., 2012). However, others pointed out that empirical evidence is too limited to assume that valid subtypes exist within the population of children with DLD (Lancaster & Camarata, 2019; Reilly et al., 2014). This discussion about subgrouping in DLD can also be observed in the context of clinical practice. That is, whereas the classification 'language disorder' in the most recent version of the DSM, in contrast to the previous version, does not differentiate between subtypes of DLD (DSM-5; American Psychiatric Association, 2013), children can still be classified as having mixed expressive-receptive language disorder or expressive language disorder only according to the most recent version of the International Classification of Diseases (ICD-11; World Health Organization, 2019).

Results of this dissertation add to this discussion that, besides gaining insight into the inter-individual differences in language development, a

subgrouping approach may specifically contribute to a better understanding of the variability in the occurrence of neuropsychiatric problems of children with DLD. That is, regardless of the evidence that children with DLD may move from subgroup to subgroup over time (e.g., Conti-Ramsden & Botting, 1999), the results of *chapter 6* may imply that the identification of a child's subtype at a certain time point, in this case at preschool age, would be relevant. Specifically, the results of *chapter 6* may indicate that only for those children belonging to the expressive-receptive impaired subgroup at a young age, their degree of receptive language impairment predicts their risk to develop ASD-related behaviors. Longitudinal research is needed to investigate whether this subgroup of children, that may possibly be identified at a young age, is more likely to experience ASD-related behaviors at a later stage in development. To this end, studies are needed to investigate whether children whose receptive language skills strongly improve over time, and who may thus no longer belong to a subgroup characterized as having receptive-expressive impairment, also show improved ASD-related behaviors, or whether their ASD-related problems remain. Ideally such studies also take into account the effect of speech-language therapy.

The conclusion that a subgrouping approach to DLD might enhance our understanding of variability in the association between language difficulties and neuropsychiatric symptoms in this population is based on our finding that there might be a subgroup within the population of children with DLD that behaves similarly as children with 22q11DS. However, there are some limitations of our study design that are relevant for the interpretation of this finding. First, this conclusion was based on the comparison of these populations using a composite measure of receptive language derived from a standardized language test. It remains unknown if this measure is representative of these children's language comprehension in more naturalistic contexts. It is also unclear how these children would perform on more fine-grained measures of receptive language (e.g., grammaticality judgment or complex sentence comprehension). Furthermore, the present results were based on parent-report of ASD-related behaviors, and additional observational measures of ASD-related behaviors (e.g., using ADOS) would increase the validity of the present results. More generally, further (in-depth) comparisons of the development of language skills between children with 22q11DS and children with DLD, including the end-points of language development, are needed to establish similarities and differences between these populations. Future studies should therefore add to the few longitudinal descriptions of the language development of children with 22q11DS (see Van

Den Heuvel et al., 2018). This was one of the initial aims of the 3T project, however, due to the COVID-19 pandemic, it was not possible to complete the follow-up assessments of children's language abilities.

Receptive vs. expressive language difficulties

Theoretically, it has been hypothesized that children with weak receptive language skills are more likely to withdraw from their environment, thereby avoiding interactions with others, resulting in reduced opportunities to practice social skills. In turn, this may lead to increased symptoms in different neuropsychiatric domains, including social anxiety and communication difficulties associated with ASD (Bornstein et al., 2013; Salmon et al., 2016). In contrast, children with difficulties in expressive language, who are limited in expressing their thoughts and wishes, have been suggested to be more at risk for development of oppositional behaviors (Bornstein et al., 2013). This differential association between expressive and receptive language difficulties and the development of neuropsychiatric symptoms underscores the relevance of differentiating between the two language modalities when aiming to identify associations between language difficulties and the occurrence of neuropsychiatric symptoms in children with language difficulties. Results of this dissertation support this view, as was empirically demonstrated in children with 22q11DS that only the degree of receptive language impairment was related to the severity of ASD-related behaviors, specifically in the domain of social communication and interaction. As explained in *chapter 1*, the current literature is inconsistent as to what extent receptive and expressive language difficulties differently contributed to the occurrence of neuropsychiatric symptoms in children with DLD. As such, results of this dissertation highlight the value of studying a genetically homogeneous population, to shed light on theoretically assumed associations between language and neuropsychiatric symptoms.

Given that both 22q11DS and DLD are associated with increased prevalence of multiple neuropsychiatric disorders, future studies addressing the association between language and the occurrence of symptoms in various neuropsychiatric domains in these populations are warranted. Not only should such studies differentiate between receptive and expressive language, additionally, it is recommended to investigate the role of specific aspects of receptive or expressive language in the occurrence of neuropsychiatric symptoms. For instance, in this dissertation a composite measure of receptive language was used, but it may be that one specific component within this composite measure carried the association with the occurrence of ASD-related

problems in children with 22q11DS. Furthermore, future studies should aim to include the mechanisms that might mediate the association between language difficulties and neuropsychiatric symptoms. For instance, avoiding others and reduced opportunities to practice social skills are suggested as mechanisms through which weak receptive language impacts the development of ASD-related behaviors. If empirical evidence would support this suggestion, this could have implications for tailoring the intervention strategy for children with receptive language difficulties.

Looking beyond neuropsychiatric or DSM-based categories

The results of this dissertation do not only underscore the importance of differentiating between different types of language problems, but also highlight the need to differentiate between different core symptom domains that are a part of a larger neuropsychiatric category (e.g., between inattention- and hyperactivity-symptoms within the category ADHD). The results in *chapter 2* demonstrated that the distribution of neuropsychiatric symptoms varied between core symptom domains that belong to the same neuropsychiatric category. This may imply that different mechanisms are contributing to the development of these symptoms (Lilienfeld & Treadway, 2016). The results of *chapter 6* seem to confirm this suggestion, as only an association was detected between receptive language and one aspect of ASD-related behaviors in the children with 22q11DS (i.e., the problems in the domain of socio-communication and interaction). Furthermore, results of this dissertation complement existing reports in both the 22q11DS and DLD literatures: the children who did not meet the criteria for a clinical diagnosis of a neuropsychiatric disorder presented with a range of sub-threshold symptoms (see for instance *chapter 2* and *chapter 6*; Baker & Vorstman, 2012; Conti-Ramsden et al., 2006). Such subthreshold symptoms may warrant clinical attention, also in absence of a clinical diagnosis (Baker & Vorstman, 2012). Thus, to be of relevance to all individuals with 22q11DS or DLD, findings of this dissertation imply that future studies should not be limited to neuropsychiatric categories, including the DSM-based diagnostic categories, when studying the impact of different factors, including early language difficulties, on the occurrence of neuropsychiatric symptoms. Instead we recommend to adopt a dimensional approach, which allows to study factors that may explain inter-individual differences on a symptom-level.

Looking beyond language

The findings in this dissertation also indicated that there was much inter-individual variation in ASD-related behaviors, both among children with 22q11DS and among children with DLD, that was not explained by either receptive or expressive language difficulties. Notably, the level of intellectual functioning also did not (fully) explain inter-individual variation, neither in 22q11DS, nor in DLD. As suggested in *chapter 6*, factors such as motor functioning or sensory processing may play a role in explaining the observed variation in the domain of repetitive and restricted behaviors (Berry et al., 2018; Wigham et al., 2015). Another important factor that may contribute to inter-individual variation in the severity of neuropsychiatric symptom expression in a range of neuropsychiatric domains are deficiencies in executive functions. For instance, impairments in attention, working memory and shifting have been associated with symptoms in the domains of ADHD, anxiety and psychosis spectrum. Impairments in these cognitive domains have also been reported in children with DLD (Kapa & Erikson, 2019) and in children with 22q11DS (see Everaert et al., 2021 for a review). Future studies are needed to shed light on the impact of such factors on the inter-individual differences in the occurrence of neuropsychiatric symptoms in these groups of children.

Looking beyond 22q11DS and DLD

The abovementioned recommendations to improve the study of the association between early language difficulties and the occurrence of neuropsychiatric symptoms in children with 22q11DS and children with DLD are also relevant to other populations with similar characteristics. For instance, there are other genetic high-risk populations with increased prevalence of language problems and neuropsychiatric symptoms (e.g., 16p11.2 duplication or 7q11.23 deletion; see Barnett & van Bon, 2015). Moreover, 40-80% of children with a diagnosis of a neuropsychiatric disorder in the general population have language impairment that often goes unnoticed (see Njiokiktjien, 2006 for a literature review). As such, it would be highly relevant to further our understanding to what extent language difficulties in these populations influence the development of neuropsychiatric symptoms, as this ultimately may have implications for tailoring the intervention pathway.

Broader applications of a genetic model for DLD

Our findings suggest that 22q11DS could function as a genetic model for a subset of children with DLD, i.e., those children with receptive language problems. In other words, the study of 22q11DS might be relevant to

understand the behavioral consequences that are associated with language difficulties in this subset of children with DLD specifically. In addition to the behavioral consequences, the study of 22q11DS may also shed light on the cognitive mechanisms that are thought to underlie the language difficulties in DLD (Everaert, 2023), in particular in a specific subset. It has been suggested that deficits in working memory, attention and statistical learning contribute to the altered development of language skills in children with DLD (Blom & Boerma, 2019; Lammertink et al., 2020; Vissers et al., 2015). However, it may be difficult to study the role of these mechanisms in DLD, given that DLD is only identified when developmental language problems have been found to persist in a child (in the Netherlands, usually not before the age of 3 years). A genetic condition, such as 22q11DS, is often identified at an earlier age, most often because of the presence of physical symptoms, e.g., congenital heart defect. The early identification of 22q11DS facilitates the exploration of the early cognitive factors that may precede the developmental language difficulties, particularly because children with 22q11DS already present with such cognitive difficulties at an early age (Everaert et al., 2021, 2022). Subsequently, a next step would be to further explore whether similar mechanisms play a role in the specific subset of children with DLD who share most characteristics with 22q11DS.

The current knowledge about the genetic factors that are associated with developmental language difficulties, indicates that in a small proportion of children with language deficits, these difficulties are associated with a clear genetic cause, such as 22q11DS (Mountford et al., 2022). Given that genetic testing is not part of the standard diagnostic procedure for DLD, it may therefore be argued that there are participants in the sample of children with DLD that was used in this dissertation, who do have an, as of yet undetected, underlying genetic cause, that may even be 22q11DS. However, to receive a diagnosis of DLD in the Netherlands, and thus to be eligible for participation in this study, the diagnostic procedure includes an assessment to exclude any physical or neurological factors that can explain a child's developmental language difficulties. As 22q11DS, and many other pathogenic genetic conditions, are associated with such features, it may be expected that these would have been identified in the diagnostic process. Moreover, it has been shown that only a small number of children with different types of CNVs could be identified in a population of children who were initially diagnosed with DLD (Kalnak et al., 2018; Pettigrew et al., 2015), making it rather unlikely that there were many of such cases in the sample used for this dissertation Nevertheless, results of such studies may indicate that, besides 22q11DS, there could be

several other relevant subgroups with a homogeneous genetic etiology and a phenotype corresponding to (a subset of) children with DLD. A further comparison between such subgroups and children with DLD may thus potentially provide leads for future studies aiming to investigate relationships between different behavioral phenotypes in (a subset of) children with DLD.

Implications for clinical practice

Assessment of language development in 22q11DS

Findings in this dissertation support existing recommendations (see recommended best practices by Solot et al., 2019). In short, it is recommended that language assessment is included in routine clinical care for all children with 22q11DS, from a young age onward and continuing into adolescence. Specifically, findings of the current dissertation add to this proposition that such assessment should go beyond the development of expressive vocabulary (i.e., spoken words), as most children with 22q11DS have impaired language development across multiple language domains, and in both the expressive and receptive language. In addition, results of this dissertation underscore that language assessment should be carried out in *all* children with 22q11DS, regardless of their speech intelligibility problems or degree of intellectual impairment, as language skills in 22q11DS develop, at least in part, independent from both these factors. In this context, it is important to note that a measure of verbal intellectual functioning (e.g., Verbal IQ) thus does not reflect a child's level of language development.

Furthermore, the existing evidence highlights the need for the assessment of receptive language skills in children with 22q11DS. In daily life interactions, receptive language difficulties go more easily unnoticed than expressive language difficulties (Im-Bolter & Cohen, 2007), and are therefore easily overlooked by caregivers or teachers, especially in context of the complex symptom presentation of children with 22q11DS. Findings in this dissertation confirm earlier studies (e.g., Van den Heuvel et al., 2018), indicating that receptive language is impaired in almost all children with 22q11DS. Moreover, the data presented here indicate that those children with the weakest receptive language skills may be at increased risk to develop neuropsychiatric symptoms that are associated with ASD. Together, this thus highlights the need to carefully assess and monitor receptive language development of all children with 22q11DS.

Assessment of neuropsychiatric symptoms in 22q11DS and DLD

While it has been known for some time that children with 22q11DS are at increased risk to develop a range of neuropsychiatric disorders, the present dissertation adds to the existing knowledge that there is a large group of those children who do not meet criteria for a formal diagnosis of a neurodevelopmental disorder, but nevertheless display a range of subthreshold symptoms (*chapter 2*). Likewise, the results of *chapter 6* indicate that approximately half of the preschool-aged children with 22q11DS or DLD had a level of ASD-related behaviors in the subclinical or clinical range, whereas none of these children had a clinical diagnosis of ASD. Even in the absence of a clinical categorical diagnosis, the presence of subthreshold symptoms may be associated with significant distress and impairment, particularly when these symptoms are expressed across several neuropsychiatric domains (Baker & Vorstman, 2012). Therefore, the results of this dissertation emphasize the need of repeated screening on a broad range of neuropsychiatric symptoms in all children with 22q11DS and DLD, regardless of having a clinical diagnosis, and from a young age onwards.

Multidisciplinary collaboration

In line with what has been reported about DLD and 22q11DS, results in multiple chapters of this dissertation indicate that both 22q11DS as well as DLD are characterized by a complex behavioral profile that comprises a variety of language difficulties and neuropsychiatric symptoms. Moreover, children in both groups may experience a range of problems in other developmental domains, such as disturbances in cognitive functions or, especially in case of 22q11DS, physical complaints. To optimally comprehend and support a child's functioning across different developmental domains, we therefore highlight the need for multidisciplinary care for these populations, implying collaboration of clinical professionals in different fields (Boerma, et al., 2023; Fiksinski et al., 2021).

For an individual child, such multidisciplinary collaboration will support their ability to maintain a balance between their individual profile of capabilities and vulnerabilities on the one hand, and the environmental or social demands on the other. This is a requirement for a healthy mental development (Swillen et al., 2018). Furthermore, a risk for both children with 22q11DS and children with DLD is that either language difficulties or neuropsychiatric symptoms are wrongly ascribed to other clinical features of the respective condition (e.g., "*social problems as a result of expressive language impairment in DLD"* or *"language problems as a result of intellectual*

disability in 22q11DS"). A side-effect of such diagnostic overshadowing (Fiksinski et al., 2021) is that some clinically relevant symptoms do not receive timely and adequate attention. As such, collaboration between clinicians from various discipline may enable a better understanding of a child's symptoms and problems, which in turn may provide leads for strategies to address these problems.

Another type of multidisciplinary collaboration, is the collaboration between researchers, clinicians and the 'stakeholders', that are for instance the patients themselves or their caregivers. Such collaborations will lead to establishing relevant research questions, while at the same times providing a platform for the results of research to be translated back into clinical practice. One example of this collaboration in the context of the present dissertation, is the organization of a workshop for Speech-Language Therapists (SLT), which resulted in the successful development of a hand-out for Dutch SLTs working with children with 22q11DS (Boerma et al., 2022).

Clinical genetic testing and professional education

Bishop and colleagues (2017) recommend to differentiate children with DLD from those children who have language problems in the presence of a known etiology, by referring to the latter group as having a '*language disorder associated with condition X'* (e.g., *with 22q11DS*; see also Vorstman & Scherer, 2021 for a similar approach in other neuropsychiatric conditions). The clinical value of integrating the genetic etiology into the diagnostic classification of language disorders, is that this information may have important clinical ramifications in terms of early screening and intervention, also in domains outside of language (Bishop et al., 2017; Pinzón-Espinosa et al., 2022; Vorstman & Scherer, 2021). For instance, the clinical guidelines for 22q11DS include recommendations to support an optimal development in many different developmental domains (Boot et al., 2023; Óskarsdóttir et al., 2023). In addition, a genetic diagnosis is increasingly made around birth or in the first year of life and this knowledge may be used to explore the benefit of primary prevention. For instance, in a child with 22q11DS, language development may be screened more intensively, even before developmental language difficulties emerge. These examples illustrate how clinical genetic testing may be of clinical relevance to adapt the intervention pathway for the subset of children that have developmental language difficulties which are associated with a biomedical condition.

However, it appears that professionals working with children with speech-language deficits are frequently not aware of the clinical advantages

of knowing a genetic diagnosis, and therefore are hesitant towards clinical genetic testing. Moreover, these professionals may withhold from referring their clients or patients for clinical genetic testing because they are not aware of the possibility that a language impairment may be due to a genetic cause (Pinzón-Espinosa et al., 2022), or because they are apprehensive about the ethical issues that come with clinical genetic testing, such as the potentially negative psychological effects (Appelbaum & Benston, 2017).

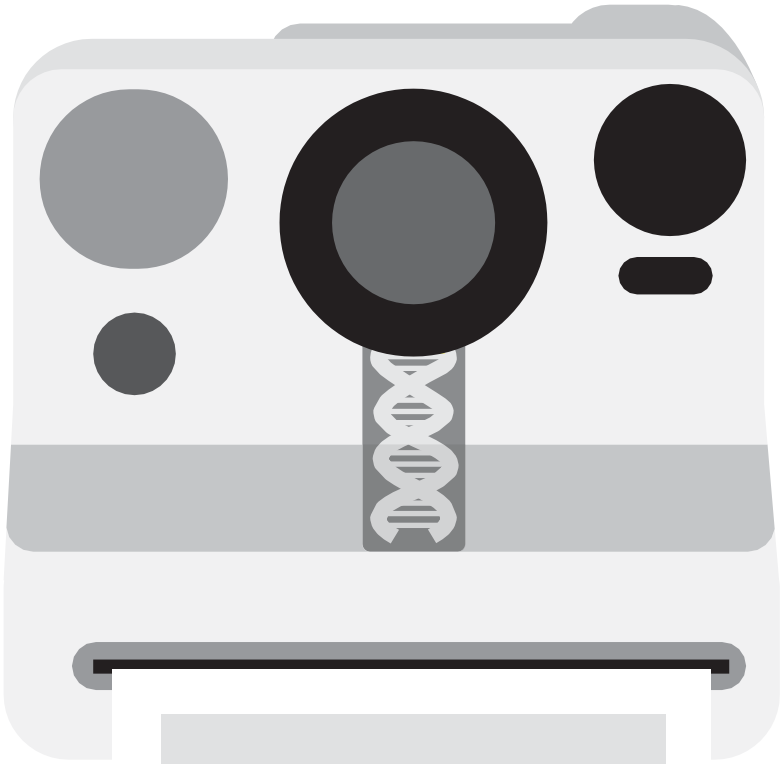
Professional education could be a useful tool to provide more insight into the benefits and pitfalls of genetic testing. Such education will benefit from the fact that genetic analysis techniques are improving quickly (Savatt & Myers, 2021; Vorstman & Scherer, 2021), furthering progress in the discovery of genetic factors that may cause a language disorder in children who are currently being diagnosed as having DLD (Mountford et al., 2022; Savatt & Myers, 2021). In addition, future studies aiming to discover the clinical characteristics that are associated with a positive genetic test, would provide relevant information to educate clinical professionals. This might help clinicians to make informed decisions as to which children with DLD would benefit from clinical genetic testing (Plug et al., 2021). Ultimately, this would contribute to the best care for those children with language disorders that are associated with a biomedical condition.

General Conclusion

The current dissertation contributed to the understanding of the inter-individual differences in the occurrence of neuropsychiatric symptoms in children with Developmental Language Disorder (DLD), by specifically focusing on the association between early language difficulties and the occurrence of neuropsychiatric symptoms. Previously, advancement in this field may have been hampered by the etiological heterogeneity characterizing DLD. Therefore, the approach in this dissertation was to study whether a genetically homogeneous group of children, children with the 22q11.2 Deletion Syndrome (22q11DS), could function as a genetic model to promote a better understanding of the association between language difficulties and co-occurring neuropsychiatric symptoms in DLD. This required to (1) provide more detailed descriptions of the language and neuropsychiatric phenotype of children with 22q11DS, (2) make direct comparisons between 22q11DS and DLD in these domains, and (3) compare the strength of the association between language skills and neuropsychiatric symptoms between a group of children with 22q11DS and a group of children with DLD.

Throughout this dissertation, mostly a dimensional approach was used to describe the occurrence of neuropsychiatric symptoms and the language difficulties in 22q11DS and DLD, which allowed for a fine-grained comparison between these populations on a symptom level, looking beyond group-level averages. The results showed that children in both populations are characterized by having a range of subclinical symptoms that might need clinical attention. In children with 22q11DS, receptive language difficulties contributed to the occurrence of symptoms associated with autism spectrum disorder. A comparison between 22q11DS and DLD, including the strength of the association between early language difficulties and the occurrence of behaviors associated with autism spectrum disorder, revealed that 22q11DS cannot function as a genetic model for the population of DLD as whole. Nevertheless, the study of 22q11DS could be of relevance to understand a subset of children with DLD, being those with below-average receptive language skills.

Future research is needed to investigate how variation in early language difficulties might explain the variable occurrence in neuropsychiatric symptoms in both 22q11DS and DLD. The results of the current dissertation underscore the relevance of including dimensional measures, as well as the important of differentiating between receptive and expressive language and between different core symptom domains that are part of the traditional neuropsychiatric categories. Furthermore, future studies are needed to explore the relevance of differentiating between subgroups of children with DLD, specifically within the context of understanding the association between language difficulties and co-occurring neuropsychiatric symptoms. Ultimately, a better insight in the role of language difficulties in the development of neuropsychiatric symptoms has implications for clinical care for children with 22q11DS as well as children with DLD, but may also be relevant to children with similar clinical characteristics in the general population.



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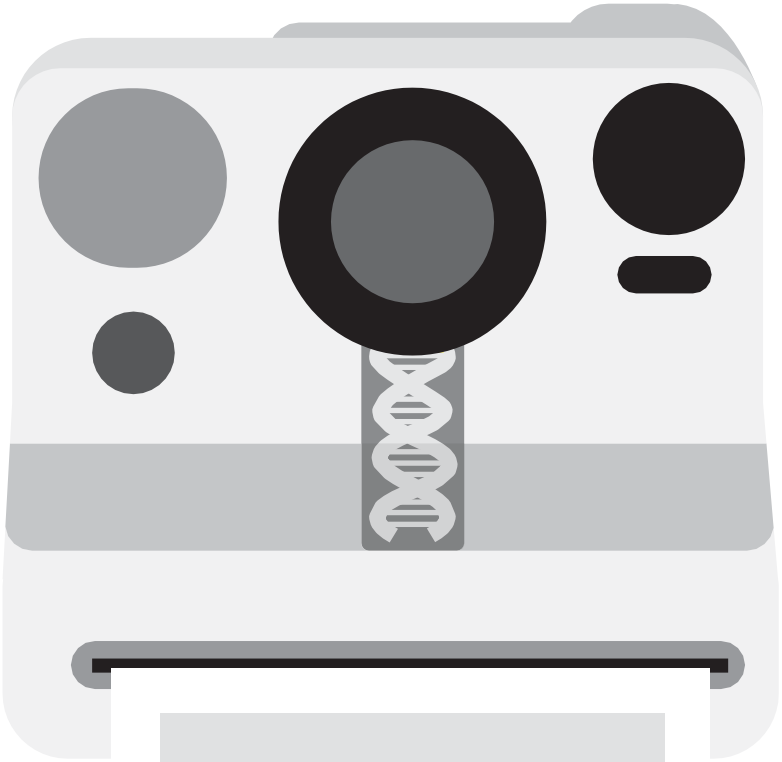


9

Nederlandse Samenvatting

Het leren van taal is één van de belangrijkste stappen in de vroege ontwikkeling van een kind. Kinderen hebben immers taal nodig om contact te maken met hun ouders, leeftijdsgenoten en leerkrachten. Bij sommige kinderen gaat het leren van taal echter niet vanzelf. Dit proefschrift gaat over twee groepen kinderen die vanaf jonge leeftijd problemen ondervinden met het leren van hun moedertaal of -talen. Dit zijn kinderen met een taalontwikkelingsstoornis (TOS) en kinderen met het 22q11.2 deletiesyndroom (22q11DS). Naast taalproblemen hebben relatief veel kinderen met een TOS en kinderen met 22q11DS een diagnose van een ontwikkelingsstoornis of psychiatrische stoornis. In dit proefschrift noem ik deze stoornissen samen neuropsychiatrische stoornissen. Voorbeelden van neuropsychiatrische stoornissen zijn ADHD, autisme, een angststoornis of psychotische stoornis. Elke neuropsychiatrische stoornis wordt weer getypeerd door verschillende kenmerken. Die noem ik hier neuropsychiatrische symptomen. Voorbeelden van deze symptomen zijn: concentratieproblemen, woede-aanvallen, somberheid, teruggetrokken gedrag, of moeite met het inschatten van emoties van anderen. Dergelijke neuropsychiatrische symptomen kunnen een kind ernstig belemmeren in het dagelijks functioneren, en zijn dan ook een zorg voor ouders en leerkrachten.

Zowel binnen de groep kinderen met TOS als binnen de groep kinderen met 22q11DS zien we echter dat sommige kinderen veel neuropsychiatrische symptomen hebben en andere kinderen vrijwel geen. Ook zijn er verschillen in het soort neuropsychiatrische symptomen die kinderen ontwikkelen. Als we deze onderlinge verschillen beter begrijpen, kunnen we de kinderen die een hoog risico hebben op het ontwikkelen van neuropsychiatrische symptomen mogelijk op jongere leeftijd identificeren. Zulke kennis kan bijdragen aan het verbeteren van de zorg voor kinderen met TOS of 22q11DS, bijvoorbeeld als het gaat om het inzetten van gerichte preventie of ondersteuning. Het doel van dit proefschrift is om inzicht te krijgen in het ontstaan van onderlinge verschillen in neuropsychiatrische symptomen van kinderen met TOS en kinderen met 22q11DS. In deze samenvatting introduceer ik de context en de werkwijze van mijn onderzoek, en bespreek ik de belangrijkste resultaten en aanbevelingen.

Wat is een taalontwikkelingsstoornis (TOS)?

Een TOS komt voor bij ongeveer 3-7% van de kinderen in de algemene bevolking. TOS wordt bij een kind gediagnosticeerd als er problemen zijn in de taalontwikkeling, zonder dat hier een aanwijsbare oorzaak voor gevonden wordt. Kinderen met TOS hebben bijvoorbeeld geen aantoonbare hersenbeschadiging, geen gehoorproblemen en meestal geen verstandelijke beperking. Ook groeien zij op in een omgeving waarin zij voldoende in aanraking komen met gesproken taal. Momenteel begrijpen we dus niet precies hoe TOS ontstaat. Eerder onderzoek heeft wel inzicht gegeven in mogelijke factoren die bijdragen aan het ontwikkelen van TOS. Zulke factoren zijn bijvoorbeeld kleine genetische afwijkingen of complicaties bij de geboorte. Er wordt gedacht dat verschillende combinaties van zulke factoren TOS kunnen veroorzaken. Dit betekent dan ook dat de oorzaak van TOS per kind sterk kan verschillen.

Zulke verschillen tussen kinderen met TOS zien we ook terug in de taalproblemen van kinderen met TOS. Taal bestaat uit verschillende domeinen, zoals klankontwikkeling, grammatica, woordenschat en pragmatiek (taalgebruik in een sociale context). Vrijwel alle kinderen met TOS hebben moeite met grammatica, zoals het correct opbouwen van zinnen of het vervoegen van werkwoorden. Een deel van de kinderen heeft daarnaast problemen in de woordenschatontwikkeling, maar bij een ander deel van de kinderen met TOS is dit geen probleem. Een ander, en opvallend, voorbeeld van verschillen tussen kinderen met TOS is dat vrijwel alle kinderen met TOS moeite hebben met het produceren van taal, terwijl ongeveer de helft van de kinderen daarbij ook moeite heeft met taalbegrip.

Het is bekend dat verschillende neuropsychiatrische stoornissen vaker voorkomen bij kinderen met TOS dan bij hun leeftijdsgenoten in de algemene bevolking (zie tabel 1 in hoofdstuk 1). Tegelijkertijd is ook bekend er grote verschillen zijn tussen kinderen met TOS in de mate waarin zij neuropsychiatrische symptomen ontwikkelen. Het is mogelijk dat deze variatie in neuropsychiatrische symptomen samenhangt met de variatie in taalproblemen van kinderen met TOS. Zo is eerder gesuggereerd dat kinderen met de ernstigste taalproblemen ook de kinderen waren met de meeste neuropsychiatrische symptomen. Ook het soort taalproblemen kan van belang zijn. Zo zouden de kinderen die meer moeite hebben met taalproductie

veel frustratie kunnen ervaren, omdat zij hun gedachten en wensen niet kunnen verwoorden. Als gevolg hiervan zouden deze kinderen vaker opstandig of agressief gedrag vertonen. Taalbegripsproblemen zouden juist kunnen samengaan met moeite om instructies te volgen op school. Dit kan zich weer uiten als concentratieproblemen in de klas. Het lijkt dus aannemelijk dat de ernst van de taalproblemen, of het soort taalproblemen, samenhangt met het ontwikkelen van neuropsychiatrische symptomen bij kinderen met TOS.

De resultaten van eerder onderzoek naar dit verband tussen taalproblemen en het ontwikkelen van neuropsychiatrische symptomen bij kinderen met TOS zijn echter erg wisselend. Hierdoor begrijpen we dit verband nog onvoldoende. Een mogelijke verklaring voor de wisselende resultaten is de grote variatie in oorzaken van TOS, zoals hierboven beschreven. Bij sommige oorzaken van TOS kan het zo zijn dat er een sterke samenhang is tussen taalproblemen en het ontstaan van neuropsychiatrische symptomen, terwijl dit niet zo is voor andere oorzaken van TOS. Een gevolg van deze variatie is dat het moeilijk is om de samenhang tussen taalproblemen en neuropsychiatrische symptomen bij kinderen met TOS vast te stellen – zelfs als deze (voor sommige kinderen) wel bestaat. Om meer inzicht te krijgen in het verband tussen taalproblemen en neuropsychiatrische problemen, stel ik daarom voor om dit te onderzoeken in een groep kinderen bij wie taalproblemen dezelfde oorzaak hebben. Dit is het geval bij de groep kinderen met het 22q11.2 deletiesyndroom.

Wat is het 22q11.2 deletie syndroom (22q11DS)?

Het 22q11.2 deletiesyndroom is een aangeboren genetische aandoening, die voorkomt bij ongeveer 1 op de 3000 levend geboren kinderen. Bij mensen met 22q11DS ontbreekt er een gedeelte van het DNA op het 22ste chromosoom. Hierdoor kunnen zij last hebben van verschillende fysieke en mentale problemen, maar de combinatie van aanwezige problemen verschilt van persoon tot persoon. Voorbeelden van veel voorkomende fysieke problemen zijn: een aangeboren hartafwijking, problemen met het gehemelte en scoliose. Daarnaast heeft de meerderheid van de mensen met 22q11DS een benedengemiddeld intelligentieniveau en heeft een kleiner deel een licht verstandelijke beperking. Ongeveer 95% van de kinderen met 22q11DS heeft

problemen in de taalontwikkeling. Op jonge leeftijd staan de problemen met de productie van taal op de voorgrond, terwijl problemen met taalbegrip gedurende de basisschoolleeftijd lijken toe te nemen. Neuropsychiatrische stoornissen komen relatief veel voor bij kinderen met 22q11DS, met name autisme, ADHD en angststoornissen in de kinderleeftijd en depressie en psychose in de jongvolwassenheid. Anders dan bij TOS, is er bij alle kinderen met 22q11DS een duidelijk verband tussen een genetische oorzaak (de deletie op chromosoom 22) en het ontstaan van taalproblemen en neuropsychiatrische symptomen. We zien echter ook een grote variatie in de ernst en het soort neuropsychiatrische symptomen die kinderen met 22q11DS ontwikkelen. Naast de 22q11.2 deletie spelen dus andere factoren een rol bij het ontstaan van deze symptomen. Eén van die factoren zouden taalproblemen kunnen zijn. Hier is echter nog weinig onderzoek naar gedaan bij kinderen met 22q11DS.

22q11DS als genetisch model voor TOS

Gegeven de gedeelde genetische oorzaak in de groep kinderen met 22q11DS, is de verwachting dat de samenhang tussen taalproblemen en neuropsychiatrische symptomen bij verschillende kinderen met 22q11DS meer overeenkomsten vertoont dan het geval is bij TOS. Hierdoor is dit verband, als dit bestaat, gemakkelijker aan te tonen in een groep kinderen met 22q11DS dan in een groep kinderen met TOS. Onderzoek naar kinderen met 22q11DS kan ons dus belangrijke inzichten opleveren voor het begrijpen van de samenhang tussen taalproblemen en neuropsychiatrische symptomen. Het is mogelijk dat de bevindingen uit het onderzoek naar kinderen met 22q11DS daarnaast relevant zijn om verschillen tussen kinderen met TOS te begrijpen. Dit wordt bedoeld met de ondertitel van dit proefschrift: "*22q11DS als genetisch model voor het begrijpen van variatie in neuropsychiatrische problemen van kinderen met TOS*".

Een voorwaarde voor het fungeren van 22q11DS als genetisch model voor TOS, is dat de kenmerken van deze groepen kinderen grotendeels overeen moeten komen. Op basis van de eerdere beschrijvingen van 22q11DS en TOS lijkt dit zo te zijn, maar de taalontwikkeling en neuropsychiatrische symptomen van kinderen met 22q11DS zijn nog onvoldoende beschreven om deze conclusie te kunnen trekken. Bovendien is er in eerder onderzoek geen

directe vergelijking gemaakt tussen kinderen met 22q11DS en kinderen met TOS. Ten slotte is de samenhang tussen taalproblemen en neuropsychiatrische symptomen in 22q11DS nog nauwelijks bestudeerd.

Doelen van dit proefschrift

De verschillende studies in dit proefschrift hebben daarom als doel om:

- Kennis te vergroten over de neuropsychiatrische problemen van kinderen met 22q11DS (hoofdstukken 2 en 6)
- Kennis te vergroten over het taalniveau van kinderen met 22q11DS (hoofdstukken 3 en 4)
- Het taalniveau, de hersenactiviteit en de neuropsychiatrische problemen van kinderen met 22q11DS te vergelijken met dat van kinderen met TOS (hoofdstukken 4, 5 en 6).
- Het verband tussen taalproblemen en neuropsychiatrische problemen te onderzoeken in een groep kinderen met 22q11DS en een groep kinderen met TOS (hoofdstuk 6).

Methode

Ten eerste werden gegevens van de 'psychiatrie-cohort studie' gebruikt (hoofdstuk 2). Dit is een langlopend onderzoeksproject op de afdeling psychiatrie van het Universitair Medisch Centrum in Utrecht. Voor dit project wordt een groep jongeren met 22q11DS gevolgd, en informatie verzameld over onder andere neuropsychiatrische symptomen en cognitief functioneren. Ten tweede werden gegevens van het 3T-onderzoek gebruikt (hoofdstukken 3 en 6). Dit is een longitudinaal onderzoek naar de taalontwikkeling, cognitieve ontwikkeling en neuropsychiatrische symptomen van peuters en kleuters met 22q11DS en leeftijdsgenoten met TOS. Ook werden in het 3T-onderzoek gegevens verzameld van een groep Typisch Ontwikkelende kinderen (TO groep). Ten derde werden gegevens gebruikt van de EPISODE-studie (hoofdstukken 4 en 5). In dit onderzoek werd door middel van functionele MRI scans de hersenactiviteit tijdens taalverwerking gemeten van basisschoolkinderen met 22q11DS en leeftijdsgenoten met TOS. Ook werd de taalvaardigheid van deze kinderen in kaart gebracht.

De belangrijkste bevindingen

Kennis over neuropsychiatrische problemen van jongeren met 22q11DS

Het doel van hoofdstuk 2 was om een compleet overzicht te creëren van de neuropsychiatrische symptomen die voorkomen onder jongeren met 22q11DS. De resultaten toonden aan dat er binnen iedere neuropsychiatrische stoornis jongeren zijn met veel en met weinig symptomen. Daarnaast zagen we dat bepaalde symptomen van een neuropsychiatrische stoornis vaker voorkwamen dan andere symptomen. Bij de stoornis ADHD hadden jongeren met 22q11DS bijvoorbeeld vaker aandachtsproblemen dan hyperactiviteit. Daarnaast was het een belangrijke bevinding dat er veel jongeren waren met klinisch relevante symptomen zonder dat bij hen een neuropsychiatrische stoornis was gediagnosticeerd Op basis van de resultaten van hoofdstuk 2 hebben we een completer beeld van de variatie in neuropsychiatrische problemen binnen de gehele groep jongeren met 22q11DS.

Kennis over het taalniveau van kinderen met 22q11DS

In eerdere onderzoeken werd de taalvaardigheid van basisschoolkinderen met 22q11DS omschreven. Er waren echter nog weinig uitgebreide beschrijvingen van de taalontwikkeling van jongere kinderen met 22q11DS. In hoofdstuk 3 wordt het onderzoek beschreven waarin de taalvaardigheid van peuters en kleuters met 22q11DS in kaart is gebracht. Uit de resultaten kwam naar voren dat vrijwel al deze kinderen problemen hadden in alle onderzochte taaldomeinen, waaronder woordenschat en grammatica. Er was wel variatie in de ernst van de taalproblemen, al was er maar een klein aantal kinderen met een taalniveau dat passend was voor hun leeftijd. Over het algemeen was de achterstand in taalproductie van de meeste kinderen groter dan hun achterstand in het taalbegrip. De productie van grammatica was relatief het minst goed ontwikkelde taaldomein. Het bleek dat de verschillen in taalvaardigheid tussen de kinderen met 22q11DS niet volledig kon worden verklaard door verschillen in de verstaanbaarheid van hun spraak.

In hoofdstuk 4 wordt het onderzoek naar de narratieve vaardigheden van basisschoolkinderen met 22q11DS beschreven. Narratieve vaardigheden zijn de vaardigheden die nodig zijn voor het vertellen en begrijpen van een verhaal. Kinderen met 22q11DS werden vergeleken met een groep jongere TO kinderen, die op eenzelfde cognitief niveau functioneerden als de kinderen

met 22q11DS. Uit de resultaten bleek dat de vertelvaardigheden van de kinderen met 22q11DS niet verschilden van de TO kinderen, maar dat kinderen met 22q11DS verhalen wel minder goed leken te begrijpen. Dit geeft aan dat de begripsvaardigheden van kinderen met 22q11DS dus achterbleven bij wat werd verwacht op basis van hun cognitieve niveau.

Vergelijking van kinderen met 22q11DS en kinderen met TOS

Uit de resultaten van dit proefschrift komen verschillen en overeenkomsten naar voren tussen kinderen met 22q11DS en kinderen met TOS. Wat betreft taalproductie zien we de grootste overeenkomsten. Zo blijkt uit de resultaten van hoofdstuk 4 dat kinderen met TOS en kinderen met 22q11DS een vergelijkbare achterstand hadden als het ging om het vertellen van verhalen. Uit de resultaten van hoofdstuk 6 bleek ook dat de taalproductiescores gebaseerd op een gestandaardiseerde taaltest niet tussen de groepen verschilden. In hoofdstuk 3 zagen we bovendien dat kinderen met 22q11DS de meeste moeite hadden met de productie van grammatica, wat overeenkomt met wat we weten uit de literatuur over TOS. In zowel hoofdstuk 4 als hoofdstuk 6 bleek dat het taalniveau van kinderen met 22q11DS achterblijft bij het niveau dat passend is bij hun intelligentie. Dit komt overeen met wat bekend is over kinderen met TOS.

Wat betreft taalbegrip zagen we in hoofdstuk 6 dat peuters en kleuters met 22q11DS over het algemeen een grotere achterstand hebben in taalbegrip dan hun leeftijdsgenoten met TOS. Binnen de groep kinderen met TOS was echter veel variatie in het niveau van taalbegrip. Dit betekent dat we zagen dat er kinderen met TOS zijn die, net als kinderen met 22q11DS, veel problemen met taalbegrip hebben. Maar ook dat er kinderen met TOS zijn zonder deze problemen. Uit hoofdstukken 2 en 6 bleek dat er veel variatie is, zowel binnen de groep kinderen met 22q11DS als binnen de groep met TOS, als het gaat om de aanwezigheid van autisme kenmerken en andere neuropsychiatrische symptomen. De resultaten van hoofdstuk 6 lieten zien dat dat zowel jonge kinderen met TOS als hun leeftijdsgenoten 22q11DS meer autisme kenmerken vertonen dan typisch ontwikkelende kinderen, maar dat er geen verschillen waren tussen kinderen met TOS en kinderen met 22q11DS.

In hoofdstuk 5 werd een onderzoek beschreven naar de hersenactiviteit van basisschoolkinderen met 22q11DS en kinderen met TOS

wanneer zij naar een voorgelezen verhaal luisteren. Deze hersenactiviteit werd vergeleken met een TO groep van kinderen met dezelfde leeftijd. De resultaten toonden aan dat kinderen met 22q11DS en kinderen met TOS dezelfde gebieden in hun hersenen lijken te gebruiken als ze naar een verhaal luisteren als TO kinderen. Dit zijn vooral gebieden in de linkerhersenhelft. Een aantal van deze hersengebieden werd echter minder actief bij kinderen met 22q11DS en kinderen met TOS dan bij TO kinderen. Daarom concludeerden we dat zowel kinderen met 22q11DS als kinderen met TOS taal deels op een andere manier verwerken dan kinderen zonder taalproblemen.

Samenvattend blijkt uit de resultaten van de verschillende hoofdstukken dat 22q11DS en TOS op veel punten gelijkenissen vertonen, zowel als het gaat om neuropsychiatrische symptomen als om taalproblemen. Een belangrijke observatie is dat vrijwel alle kinderen met 22q11DS problemen hebben met taalbegrip, terwijl dit slechts voor ongeveer de helft van de kinderen met TOS het geval is. Nu we meer weten over verschillen en overeenkomsten tussen 22q11DS en TOS, is het tijd om te onderzoeken in hoeverre de studie van 22q11DS relevant kan zijn om het verband tussen taalproblemen en neuropsychiatrische symptomen in TOS beter te begrijpen.

Taalproblemen en neuropsychiatrische symptomen in 22q11DS en TOS

In hoofdstuk 6 werd het verband tussen taalproblemen en kenmerken van autisme onderzocht bij peuters en kleuters met 22q11DS, leeftijdsgenoten met TOS en een TO groep van kinderen met dezelfde leeftijd. Alleen in de groep kinderen met 22q11DS vonden we een significant verband tussen taalproblemen en autismekenmerken. Specifiek bleek dat de kinderen met een zwakker taalbegrip meer problemen hadden met sociale communicatie. Ook in de groep kinderen met TOS leken ernstigere taalbegripsproblemen samen te hangen met ernstigere sociale communicatieproblemen. Dit verband was in deze groep echter niet statistisch significant.

We hebben ook de sterkte van het verband tussen taalbegrip en sociale communicatie vergeleken tussen kinderen met 22q11DS, kinderen met TOS en TO kinderen. Het bleek dat dit verband sterker was in de groep kinderen met 22q11DS dan in de groep met TO kinderen. Er was echter geen significant verschil in de sterkte van het verband tussen kinderen met 22q11DS en kinderen met TOS. De kinderen met TOS verschilden ook niet van de TO

kinderen. Deze bevinding bevestigde onze hypothese dat het bestuderen van een groep kinderen met een gedeelde oorzaak van taalproblemen het aantonen van zulke verbanden vergemakkelijkt. Op basis van deze bevinding suggereerden we dat zwakkere receptieve taalproblemen geassocieerd zouden kunnen zijn met verhoogde autismekenmerken bij kinderen met TOS, maar alleen in een specifieke subgroep van kinderen die de meeste kenmerken deelt met de groep kinderen met 22q11DS.

Conclusie en aanbevelingen

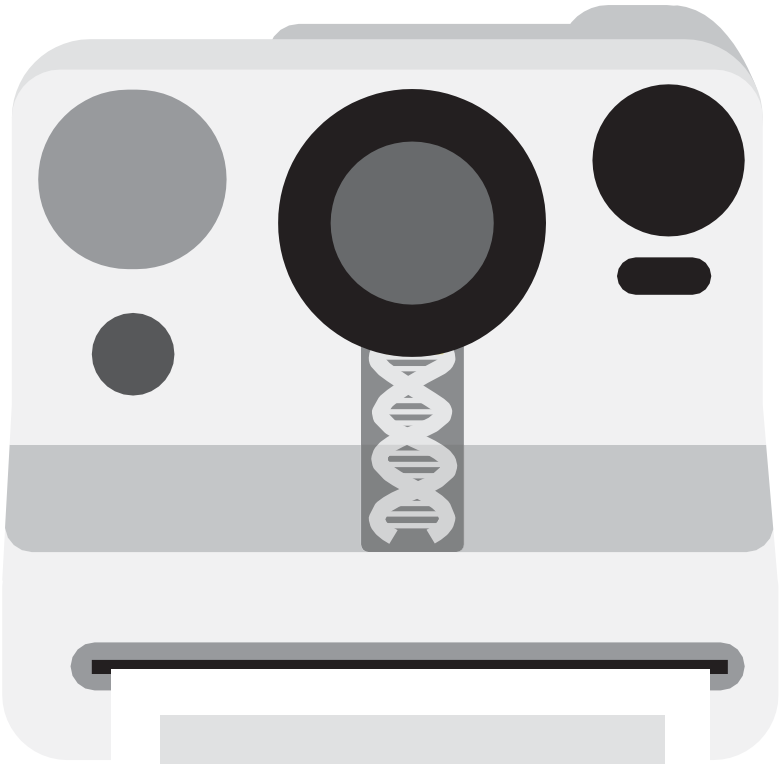
In dit proefschrift is onderzocht in hoeverre het onderzoek naar kinderen met 22q11DS relevant is om de onderlinge verschillen in neuropsychiatrische symptomen van kinderen met TOS te begrijpen. We probeerden de vraag te beantwoorden: kan 22q11DS fungeren als genetisch model voor TOS?

Een uitgebreide vergelijking tussen kinderen met 22q11DS en kinderen met TOS toonde zowel overeenkomsten als verschillen aan tussen beide groepen. Dit geeft aan dat 22q11DS niet kan fungeren als model voor alle kinderen met TOS. Niettemin zou de studie van 22q11DS van belang kunnen zijn om het verband tussen taalproblemen en neuropsychiatrische symptomen *in een subgroep van kinderen met TOS* te begrijpen, die het meest overeenkomt met de groep kinderen met 22q11DS. De resultaten van dit proefschrift, in combinatie met bestaande literatuur, suggereren dat dit de subgroep is met zowel problemen in taalproductie als taalbegrip. Toekomstig onderzoek is nodig om deze hypothese verder te onderzoeken, om zo meer inzicht te krijgen in hoeverre de studie van 22q11DS relevant is voor het begrijpen van TOS en om de onderlinge verschillen tussen kinderen met TOS beter te kunnen begrijpen.

De resultaten van dit proefschrift geven aan dat de kinderen met 22q11DS die de grootste taalbegripsproblemen hadden vaker autisme-gerelateerde kenmerken ontwikkelden. Dit verband bestond niet tussen taalproductieproblemen en kenmerken van autisme. Daarnaast zagen we dat taalbegripsproblemen alleen samenhingen met het ontwikkelen van een bepaald type autisme kenmerken (communicatieproblemen), maar niet met een ander type autisme kenmerken (repetitief gedrag). Hiermee benadrukken de resultaten van dit proefschrift het belang van het maken van een onderscheid tussen verschillende typen taalproblemen en neuropsychiatrische

symptomen. Meer onderzoek is nodig om de samenhang tussen taalproblemen en kenmerken van andere neuropsychiatrische stoornissen te onderzoeken, in zowel 22q11DS als TOS.

Resultaten van dit proefschrift bieden ook aanknopingspunten voor de ondersteuning en zorg van kinderen met TOS en kinderen met 22q11DS. Ten eerste is uitgebreide screening en monitoring van het taalniveau van kinderen met 22q11DS van belang, al vanaf jonge leeftijd en ongeacht de aanwezigheid van spraakproblemen. Aangezien vrijwel alle kinderen met 22q11DS problemen ondervinden in taalbegrip, en deze problemen kunnen samenhangen met autismekenmerken, is aandacht voor taalbegrip extra belangrijk. Zeker omdat problemen in taalbegrip, vergeleken met problemen in taalproductie, makkelijk over het hoofd worden gezien. De resultaten van dit proefschrift geven meer inzicht in de manier waarop taalproblemen kunnen samenhangen met neuropsychiatrische problemen bij kinderen met 22q11DS en met TOS. Veel blijft echter nog onduidelijk. Daarom benadrukken we het belang van een multidisciplinaire samenwerking van zorgprofessionals, zoals logopedisten, psychologen, kinderartsen en klinisch genetici. Kennisuitwisseling tussen deze professionals, en samenspraak met ouders en leerkrachten, zorgt voor het beste begrip van het gedrag van een kind, wat weer handvatten kan bieden voor het inzetten van de meest passende ondersteuning.



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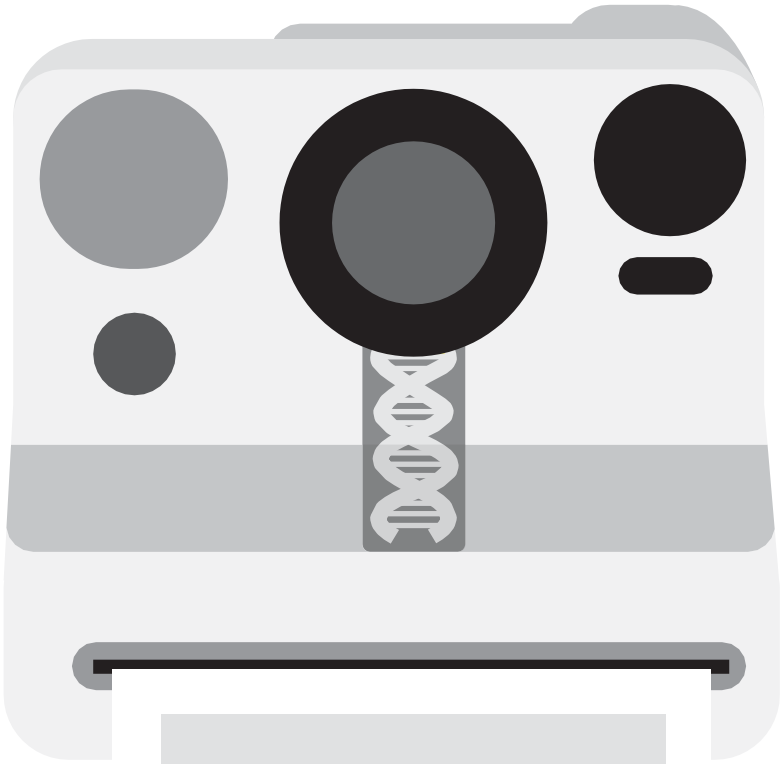

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About the author & Publications

Iris Selten was born on March 9, 1992 in Nieuwegein, the Netherlands. She completed her bachelor degree in child, family and education studies (pedagogische wetenschappen) in 2013 at Utrecht University, which she combined with a semester at Lund University in Sweden. In 2016, Iris completed both the research master Development and Socialization in Childhood and Adolescence and the clinical master in Child, Family and Education Studies (orthopedagogiek). After her studies she worked at the NICHE-lab in Utrecht as a research assistant, on the project *European Autism Interventions - A Multicentre Study for Developing New Medications (EU-AIMS).* In 2018 she started her PhD project at the Utrecht Institute for Language Sciences at Utrecht University, in close collaboration with the department of pediatrics of the Wilhelmina Children's Hospital in Utrecht (WKZ) and the department of psychiatry of the University Medical Center in Utrecht (UMCU). Besides her work directly related to the research project, she performed various other tasks, including seeing children, youth and young adults with 22q11DS and their families at the outpatient clinics at the UMCU and WKZ, teaching a statistics course at Utrecht University, and taking part in various summer and winter schools. She spent three months in Toronto, Canada, as a visiting researcher at the SickKids hospital. Currently, Iris is working as post-doctoral researcher within the Dutch Autism and ADHD research group (d'Arc) at the University of Amsterdam.

Scientific Publications - first author

Selten, I., Boerma, T., Everaert, E., Vansteensel, M. J., Vorstman, J., & Wijnen, F. (2021). Narrative comprehension and production abilities of children with 22q11.2 deletion syndrome. *Research in Developmental Disabilities*, *119*, 104109. https://doi.org/10.1016/j.ridd.2021.104109

Everaert, E*., Selten, I*., Boerma, T., Houben, M., Vorstman, J., de Wilde, H., Derksen, D., Haverkamp, S., Wijnen, F., & Gerrits, E. (2023). The Language Profile of Preschool Children With 22q11.2 Deletion Syndrome and the Relationship With Speech Intelligibility. *American Journal of Speech-Language Pathology*, *32*(1), 128–144. https://doi.org/10.1044/2022_AJSLP-21-00328 *contributed equally as first authors

Selten, I., Boerma, T., Everaert, E., Gerrit, E., Houben, M., Wijnen, F., & Vorstman, J. (under review). The impact of early language difficulties on the development of Autism symptomatology: A comparison between children with developmental language disorder and children with 22q11.2 deletion syndrome. *Under review with the journal of autism and developmental language impairment.*

Selten, I.,Blok, J., Boerma, T., Djelantik, A. A. A. M., Houben, M., Wijnen, F., Zinkstok, J., Vorstman, J.* & Fiksinski, A*. (submitted). A comprehensive and dimensional profile neurodevelopmental symptom expression of adolescents with 22q11.2 deletion syndrome. *contributed equally as last authors

Scientific Publications - co-author

Vansteensel, M. J., Selten, I. S., Charbonnier, L., Berezutskaya, J., Raemaekers, M. A. H., Ramsey, N. F., & Wijnen, F. (2021). Reduced brain activation during spoken language processing in children with developmental language disorder and children with 22q11.2 deletion syndrome. *Neuropsychologia*, *158*, 107907. https://doi.org/10.1016/j.neuropsychologia.2021.107907

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Everaert, E., Boerma, T. D., Selten, I. S., Gerrits, E., Houben M. L., Vorstman, J. A. S., & Wijnen, F. N. K. (*under review*). Non-verbal executive functioning in relation to vocabulary and morphosyntax in preschool children with and without Developmental Language Disorder. Under review with *Journal of Speech-Language and Hearing Research*.

Everaert, E., Vorstman, J. A. S., Selten, I., Slieker, M., Wijnen, F., Boerma, T., & Houben, M. (under review). Executive functioning in preschoolers with 22q11.2 deletion syndrome and the impact of congenital heart defects. Under review with *Journal of Neurodevelopmental Disorders*.

Other publications

Boerma, T., Selten, I., Everaert, E., Gerrits, E., & Wijnen, F. (2022) Onbekend maakt onbegrepen: meer weten over het 22q11.2 deletiesyndroom. *VHZ Online. https://vhz-online.nl/*

Boerma, T., Everaert, E., Selten, I., de Wilde, H., Derksen, D., Haverkamp, S., Houben, M., Gerrits, E., & Wijnen, F. (2022). *Spraak en taal bij kinderen met het 22q11.2 deletiesyndroom: Handreiking voor logopedisten.*

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