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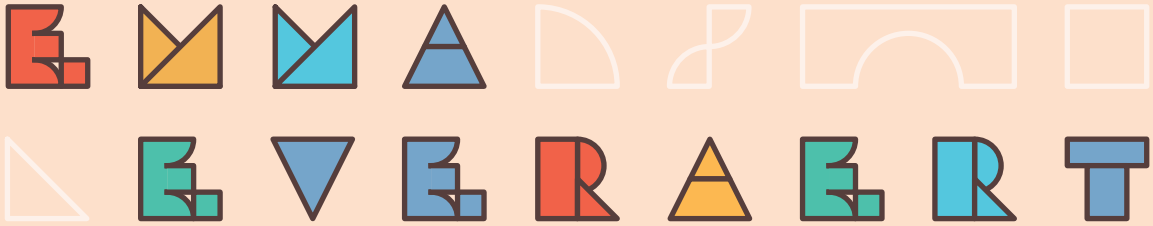

LANGUAGE IMPAIRMENT AND EXECUTIVE FUNCTIONING IN CHILDREN

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Taalstoornissen en executieve functies bij kinderen

Het 22q11.2 deletiesyndroom als etiologisch homogeen model voor taalontwikkelingsstoornis

(met een samenvatting in het Nederlands)

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Table of content

Abbreviations

List of frequently used abbreviations in this dissertation in alphabetical order.

22q11DS	22q11.2 deletion syndrome
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BW	Backward (condition of the Corsi block tapping)
CELF	Clinical Evaluation of Language Fundamentals
CHD	Congenital Heart Defect
CI	Confidence interval
CLI	Core Language Index (CELF index)
COMT	Catechol-O-methyltransferase
dB	Decibel
DLD	Developmental Language Disorder
EF	Executive Functioning
ELI	Expressive Language Index (CELF index)
EV	Expressive Vocabulary (CELF subtest)
FW	Forward (condition of the Corsi block tapping task)
HS-CHD	Hemodynamically Significant Congenital Heart Defect
HTKS	Head-Toes-Knees-Shoulders task
IQ	Intelligence Quotient
LBW	Low Birth Weight
MANOVA	Multivariate Analysis of Variance

METC	Medical Ethical Committee (Medisch-Ethische Toetstingscommissie)
MLU	Mean Length of Utterance
PFC	Prefrontal Cortex
PPVT	Peabody Picture Vocabulary Test
PRODH	Proline dehydrogenase
RLI	Receptive Language Index (CELF index)
RoB	Risk of Bias
RS	Recalling Sentences (CELF subset)
SA	Selective Attention
SD	Standard Deviation
SE	Standard Error
SES	Socioeconomic Status
SLP	Speech-Language Pathologist
SON	Snijders-Oomen Non-verbal IQ test
STM	Short-term Memory
TD	Typically Developing
WM	Working Memory
WNV	Wechsler Non-Verbal IQ test
WS	Word Structure (CELF subtest)

Chapter 1

General introduction.

Language acquisition is fundamental to the early development of children, as language abilities are important for outcomes later in life, such as academic achievement (e.g., Bleses et al., 2016). Language abilities also play a crucial role in the development of social competence (Longobardi et al., 2015; Longoria et al., 2009). In a large cohort study of more than 1,000 children, it was found that children with low language abilities had more social-emotional and behavioral difficulties and lower health-related quality of life (Le et al., 2021; McKean et al., 2017). In general, children rapidly acquire their native language(s), seemingly effortless and without explicit instruction from parents and caregivers. However, for some children the process of language acquisition is not as effortless, including a large group of children with Developmental Language Disorder (DLD [1]). Children with DLD have unexplained and persistent difficulties with primary language acquisition, which lead to functional impairment in their day-to-day lives.

In accordance with the findings that language skills play an important role in various areas of a child's life, children with DLD have poorer outcomes for academic achievement, socio-emotional development, and mental wellbeing than typically developing (TD) peers (Conti-Ramsden et al., 2013; Conti-Ramsden et al., 2018; Durkin et al., 2017; St. Clair et al., 2011; Van den Bedem, 2020). Furthermore, children with DLD have a lower quality of life than TD peers (Eadie et al., 2018) and rates of psychopathology are higher in children with DLD than in the general population (Clegg et al., 2005; Mouridsen & Hauschild, 2008; Snowling et al., 2006; Yew & O'Kearney, 2013).

Language interventions have been shown to be effective in children with DLD, but the systematic evaluation of the efficacy of interventions is still in progress (e.g., Frizelle et al., 2021). To improve interventions, it is crucial to understand the underlying mechanism of an impairment and the respective risk and protective factors that might influence it (Guralnick, 2011). This knowledge can also support prognostic information and early detection. This dissertation explores the effect of cognitive functioning, specifically executive functioning

1 Although different terminology has been used, in this dissertation the term DLD is used throughout, following Bishop et al. (2017), even for describing findings of studies that use a different term such as specific language impairment, primary language impairment, language impairment, and developmental language impairment.

(EF), on the language abilities of young children with DLD. While many studies have found EF deficits in children with DLD (e.g., Pauls & Archibald, 2016; Vissers et al., 2015), relationships between these deficits and children's language difficulties are poorly understood. This line of research is hampered by the large etiological and phenotypical [2] heterogeneity of the group of children with DLD (Newbury et al., 2005). This dissertation therefore also explores whether studying an etiologically homogeneous population – i.e., children with 22q11.2 deletion syndrome (22q11DS) – can reduce variability in the behavioral phenotype and provide a model to study atypical language development. Relative to a population with a heterogeneous etiology, such as children with DLD, the use of a selected population with a homogeneous etiology, such as children with 22q11DS, can reduce the amount of unexplained variance in both the language and EF phenotype. This method increases our ability to detect relationships in the presence of multiple causative factors. This dissertation focuses on children in the preschool and early school age (3-6 years old), as this is the time during which both language and EF both develop rapidly (Best & Miller, 2010; Hoff, 2015).

DEVELOPMENTAL LANGUAGE DISORDER

The diagnosis of DLD is not based merely on the *presence* of persistent language problems, but also on the *absence* of explanatory factors such as hearing loss, neurological damage, intellectual disability, and/or an associated biomedical condition (Bishop et al., 2017). The prevalence of DLD is estimated to be 2-7% in all children (Calder et al., 2022; Lindsay & Strand, 2016; Norbury et al., 2016) and it is more common in boys than in girls (Lindsay & Strand, 2016; Rudolph, 2017, but see Calder et al., 2022). There are no official reports of the number of children with DLD in the Netherlands, where the current study took place, as this diagnosis is not registered at a national level. With a prevalence of 2-7%, we estimate that there are between 17,700 and 62,100 children with DLD between the ages of 3 to 7 year in the Netherlands [3].

2 Phenotype refers to the observable characteristics of an individual that are determined by their genotype (i.e., genetic profile) and their environment.

3 There were about 886,700 children between the age of 3 and 7 years old in the Netherlands in 2020 (CBS, 2022).

We can distinguish between receptive language abilities (i.e., comprehension) and expressive language abilities (i.e., production). Impaired expressive morphosyntactic (i.e., grammatical) abilities are considered a hallmark deficit of DLD (Rice et al., 1996; Leonard, 2014). Problems with receptive language abilities are present in only a part of the group (Conti-Ramsden & Botting, 1999; Rapin, 1996). Previous research has reported that children with DLD have smaller vocabularies than their peers (McGregor et al. 2013; Rice & Hoffman, 2015), although others have noted that vocabulary is a relative strength within the language profile of children with DLD (Gray et al., 1999). Children with DLD can also experience difficulties with phonology [4] (Bortolini & Leonard, 2000) and narrative abilities [5] (Blom & Boerma, 2016; Fey et al., 2004). Pragmatic [6] skills may also be affected in some children with DLD (Bishop et al., 2000; Craig & Evans, 1993; Osman et al., 2011). Overall, children with DLD are very heterogeneous in terms of the severity and the type of language problems they experience (Leonard, 2014).

Previously, DLD was referred to as Specific Language Impairment (SLI), illustrating the idea that DLD was a disorder that exclusively affected language development (Van der Lely et al., 1998; Van der Lely, 2005; Stark & Tallal, 1981). However, a growing body of research shows that children with DLD also have deficits in other cognitive domains. This is in line with the idea that language phenotypes are the result of a complex interplay between domain-general cognitive mechanisms required for learning language, an environment that provides input, but also genetic variation (Onnis et al., 2018). Some have suggested that the language deficits of children with DLD may be the result of, or at least are exacerbated by, impairments in such domain-general learning mechanisms that are essential for acquiring language (Botting & Marshall, 2017; Karmiloff-Smith, 1998). For example, limited processing capacity (Kail, 1994; Im-Bolter et al., 2006) or impairments in verbal short-term memory (Gathercole & Baddeley, 1990), phonological working memory (WM)

4 Phonological abilities refer to the systematic organizational mechanisms underlying the ability to correctly utter and distinguish between speech sounds.

5 Narrative abilities encompass the skills to tell and understand stories with causality and inferences.

6 Pragmatics refers to the use of language in context and social situations.

(Gathercole & Baddeley, 1993), or procedural or sequence learning (Lukács & Kemény, 2014; Lum et al., 2014; Ullman & Pierpont, 2005) have been suggested as possible underlying deficits in children with DLD.

One cognitive domain that has been the focus of many studies in the field of DLD research is the domain of EF, as it has been argued that EF plays an important role in language learning (Ellis & Sinclair, 1996; Mazuka et al., 2009). EF is an umbrella term for cognitive resources that manage lower-level cognitive processes to plan and achieve goals (Friedman & Miyake, 2017; Baddeley & Hitch, 1974; Barkley, 2012; Diamond, 2013; Jurado & Rosselli, 2007). EF is commonly divided into sub-components that can include attention, short-term and working memory, inhibition, shifting, and planning. It is also often assumed that all these components can be both verbal and non-verbal in nature.

A relationship between EF and language has been shown in TD children (Blom & Boerma, 2019; Fuhs & Day, 2011; McClelland et al., 2007; Kaushanskaya et al., 2017; Kuhn et al., 2016; Romeo et al., 2022; Slot & Suchodoletz, 2018; Schmitt et al., 2019; Weiland et al., 2014; White et al., 2017). In line with theories that suggest domain-general deficits underlying language impairment, impaired EF has been frequently observed in children with DLD (Ebert & Kohnert, 2011; Henry & Botting, 2017; Kapa & Erikson, 2019; Kapa & Plante, 2015; Montgomery et al., 2010; Pauls & Archibald, 2016; Vissers et al., 2015; Vugs et al., 2013). EF may be implicated in language development in various ways. EF abilities may support the processing and storage of linguistic input but are likely also necessary for efficient retrieval and production of language. For example, selective attention abilities help infants attend to linguistic input and related referents, while ignoring other stimuli in the environment (D'Souza et al., 2017). Additionally, EF might support word-learning by inhibiting semantic competitors [7] (Yoshida et al., 2011), while deficits in WM could limit children's ability to process complex sentences (Archibald, 2017), which not only hampers comprehension but may also slow down the acquisition of

7 Semantic competitors are words or concepts that are related to the target word in meaning or form (phonologically). They can also become activated due to their similarity to the target word and need to be suppressed to allow for correct and efficient storage and encoding of new information.

certain syntactic constructions and patterns. Other research has shown that the correct use and conjugation of the past tense has been associated with inhibition abilities (Ibbotson & Kearvell-White, 2015).

The role of domain-general cognitive functions in atypical language development is currently not well understood. Mixed outcomes have been reported regarding whether all components or only specific components of EF are impaired, whether EF deficits are only verbal or also non-verbal in nature, and how these different (verbal and non-verbal) impairments relate to language abilities in children with DLD. These discrepant outcomes likely reflect the complex nature of this relationship and may be partly due to methodological differences between studies.

Etiological and phenotypical heterogeneity in DLD

Language development is affected by a myriad of biological and environmental factors that interact and can be present or absent in varying degrees (Newbury & Monaco, 2010; Onnis et al., 2018). As described above, children with DLD present with varying phenotypes. This is likely at least in part due to differences in underlying etiology (Bishop, 2001; Conti-Ramsden & Durkin, 2015; Rice, 2012). A recent study showed that when genetic screening was performed on children referred for suspected DLD, 28% of children were found to have genetic mutations or chromosomal abnormalities (Plug et al., 2021). This indicates that the DLD population likely contains multiple subgroups with differing etiologies. A wide variety of genetic mutations has been observed in children diagnosed with DLD (Mountford et al., 2022; Nudel et al., 2020; Reader et al., 2014; Rice et al., 2009; Simpson et al., 2015). Not all genetic mutations can be directly linked to the development of language impairment, but they contribute to the cumulative risk of developing DLD. In addition to genetic etiological factors, language abilities of children with DLD may further be negatively affected by cognitive and environmental factors, such as aberrant auditory processing (Ganga et al., *in preparation*), maternal smoking during pregnancy (Calder et al., 2022), maternal education (Rudolph, 2017), or parental distress (Horwitz et al., 2003). The complex interplay between endogenous

and environmental factors results in a heterogeneous group of children with language impairments without a clear and known underlying cause.

Irrespective of the exact etiology, children with DLD experience difficulties with language, predisposing them to poorer outcomes for school achievement, mental wellbeing, and societal participation (Conti-Ramsden et al., 2018; Durkin et al., 2017; St. Clair et al., 2011). To improve prognosis and intervention for children with DLD, researchers are exploring different avenues to better understand the role of specific factors, such as EF abilities, in atypical language development. One important challenge in this context is the etiological heterogeneity of DLD, as it increases the amount of unexplained variance, thereby hampering research efforts that aim to determine the contribution of various factors to the atypical language development of children with DLD. While it is difficult to limit variation in environmental factors, etiological variability can be reduced by studying a selected population with a clear etiology. Studying an etiologically homogeneous population with language impairment can reduce the amount of unexplained variance because individuals who share the same etiology are likely more similar than individuals with language difficulties stemming from diverse (unknown) etiologies. In summary, in an etiologically homogeneous population, the signal of a given phenotype and its association with other factors is likely stronger, as such a population is less variable than the general population (see Figure 1.1).

In other disciplines, the prospective study of specific, etiologically homogeneous, groups with a higher risk for certain disorders has been used to identify clinical markers and track the development of the disorders. Such groups can function as a model for the general population. In the case of neurodevelopmental disorders such as DLD, pathogenic Copy Number Variant (CNV) carriers, that is individuals with a 'disease-causing' deletion or duplication of one or more genes, may constitute such a population. Pathogenic CNVs are frequently associated with a clinically significant neurodevelopmental phenotype (Cook & Scherer, 2008; Gill, 2012; Girirajan et al., 2011; Takumi & Tamda, 2018). For DLD such an investigation could be done with a group of CNV carriers that shows

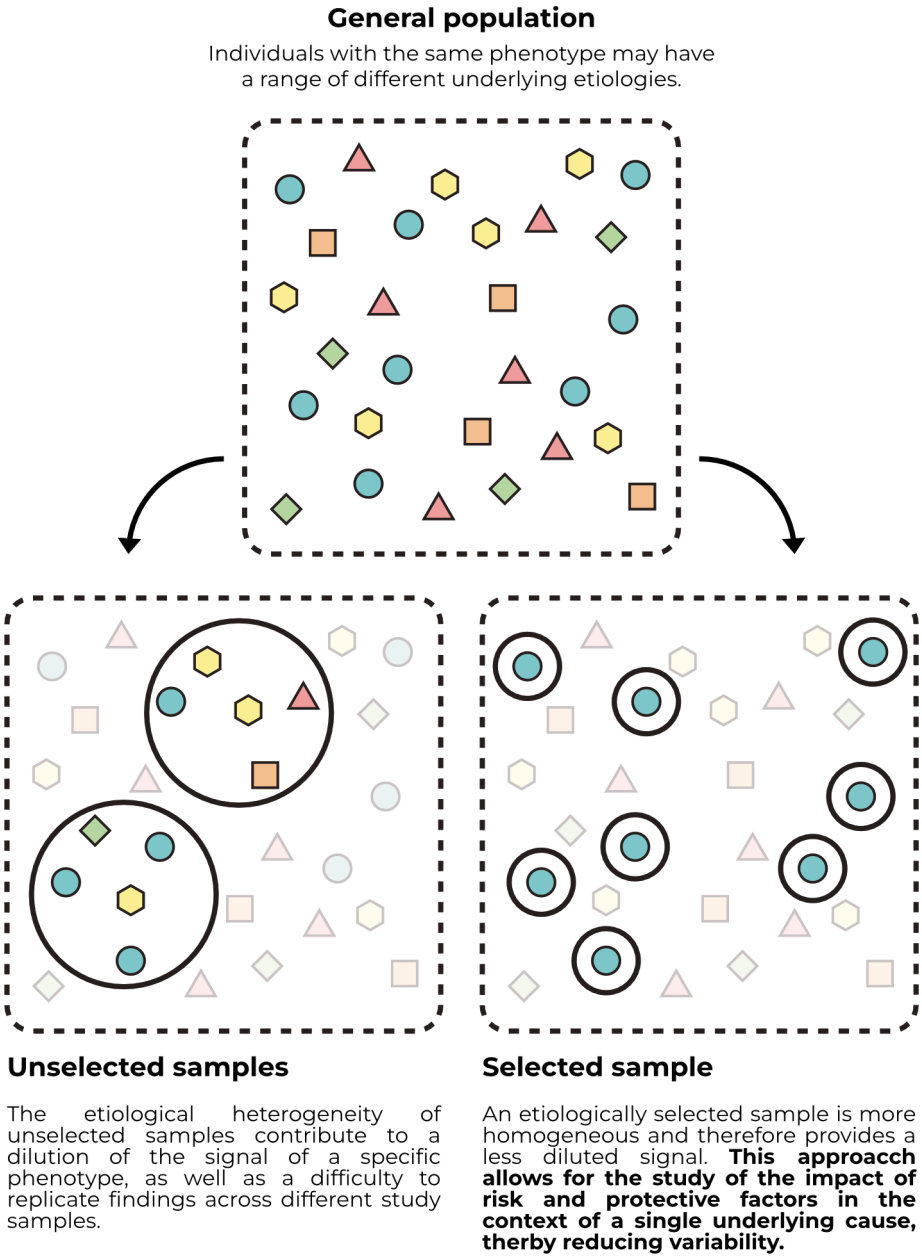

Figure 1.1. Graphic depiction of the benefit of studying etiologically homogeneous groups for a given phenotype (adapted from Figure 5.1 in **chapter 5** in this dissertation)

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phenotypical overlap with children with DLD. For the purpose of this dissertation, the phenotypic overlap should constitute impairments in both language and EF. One such group is the group of children with the 22q11.2 deletion syndrome.

22Q11.2 DELETION SYNDROME

The 22q11.2 deletion syndrome (22q11DS; OMIM #192430, #188400, #611867) is the most frequently occurring microdeletion syndrome in humans. It has also been called Velocardiofacial syndrome (VCFS) or DiGeorge syndrome (Shprintzen, 2005)[8]. In this dissertation, the term *22q11.2 deletion syndrome* is used throughout, as it is preferred by the International 22q11.2 Foundation Inc. and because it refers to the cause of the syndrome, which is a hemizygous (i.e., on one allele) deletion of band 11.2 on the long arm (q) of chromosome 22 (Edelmann et al., 1999; Morrow et al., 1995). In 85% of cases, it concerns a 'typical' deletion of around 3 million (Mb) base pairs, encompassing up to 60 genes (Edelmann et al., 1999; Morrow et al., 1995; Shaikh et al., 2000). The syndrome has an estimated prevalence of 1 per 2,148 live births (Blagojevic et al., 2021), which corresponds to either 0.05% of the 3- to 6-year-olds or 80 children born annually in the Netherlands, where the current study took place. 22q11DS equally affects males and females and has an autosomal inheritance pattern which entails that people affected by the syndrome have a 50% chance of passing it on to their children. However, 85-90% of cases are *de novo* mutations (McDonald-McGinn et al., 2001; Ryan et al., 1997), meaning that the deletion was not inherited from either parent, but a new variant.

Developmental delays and cognitive problems are common in children with 22q11DS. Notably, speech-language problems are reported in virtually all children with 22q11DS (Solot et al., 2019), making this one of the most prevalent symptoms in early childhood. Additionally, 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). The IQ scores of the 22q11DS population follow a normal distribution similar to the general population, with the mean at

8 Other previously used names include: Shprintzen Syndrome, Sedlačková syndrome, Cayler (cardiofacial) Syndrome, Conotruncal Anomaly Face Syndrome (CAFS), Takao Syndrome, and CATCH-22.

approximately 70 (Klaassen et al., 2016; Niklasson & Gillberg, 2010). Strikingly, it has been observed that the IQ scores of individuals with 22q11DS generally decline over time, starting around an average of 80 in early childhood and decreasing by almost 10 points during childhood and adolescence (Duijff, Klaassen, de Veye, et al., 2012; Vorstman et al., 2015). Additionally, 22q11DS is associated with an increased risk for neurodevelopmental disorders and psychiatric problems, such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and anxiety disorders (Bassett et al., 2005; Fiksinski et al., 2018; Schneider et al., 2014; Vorstman et al., 2006). Most prominently, individuals with 22q11DS have a twentyfold increased risk for developing schizophrenia (Karayiorgou et al., 2010).

The most common physical symptoms of 22q11DS include congenital heart defects (CHD), palatal abnormalities, thyroid disease, hypocalcemia as a result of hypoparathyroidism, thymic hypoplasia leading to T-cell lymphocytopenia, scoliosis, genitourinary abnormalities, typical facial features, and small stature (McDonald-McGinn et al., 2015). The most common palatal abnormality is velopharyngeal insufficiency (VPI), occurring in more than 55% of the children, and notably present in the absence of a palatal cleft in almost 33% of the children (Jackson et al., 2019). However, overall phenotypic expression varies greatly between patients, with some patients going undiagnosed into adulthood because of a lack of severe symptoms.

22q11DS: A (genetic) model for idiopathic disorders?

There are several reasons why, given the etiological homogeneity and the elevated prevalence of specific phenotypical characteristics, 22q11DS has been proposed to be a well-suited model for idiopathic (i.e., etiology unknown) disorders, such as scoliosis (Homans et al., 2019) and neuropsychiatric disorders like schizophrenia (Fiksinski et al., 2021; Gur et al., 2017; Zinkstok et al., 2019; Jonas et al., 2014). First, because the etiology of the disorder and its associated phenotype are known, it may be easier to study how different risk and protective factors impact a given phenotype, as their relations may vary as a function of underlying etiology (see Figure 1.1). Second, the higher prevalence of specific traits or conditions in 22q11DS allows

researchers to use smaller sample sizes for prospective studies (see Box 1.1). A third reason 22q11DS is well-suited as a model for studying idiopathic disorders, is that children with 22q11DS are often regularly seen for clinical follow-up. Clinical data can be used for research purposes, which lessens the burden of data collection for both the patients and the researchers, but also makes it more likely for early development to be well-documented, which is likely less detailed and less common for children in the general population. Lastly, another benefit is that with increasing accessibility and affordability of genetic testing, children with 22q11DS are frequently diagnosed at a young age, with 50-71% already diagnosed before the age of 2 years (Cancrini et al., 2014; Goodwin et al., 2014). The combination of early diagnosis and clinical follow-up are beneficial to prospective investigations of potential clinical markers and mechanistic factors (determinants of outcomes).

Box 1.1. Sample size in prospective studies of low-incidence disorders

To study whether certain factors contribute to an increased risk for a disorder or precede the onset of the disorder, one needs to obtain measurements before disease onset. However, if the incidence of a given disorder is low, this would require following up an exceedingly large cohort of individuals to eventually obtain a large enough sample size of individuals who develop the disorder. For example, the prevalence of schizophrenia is less than 1% in the general population (Moreno-Küstner et al., 2018). Of 100 individuals who are followed up, approximately one can be expected to develop the illness. Consequently, to see whether there are early indications of disease onset with a sample of 70 individuals who go on to develop schizophrenia, a follow-up study of a cohort of 7.000 individuals is needed. In contrast, in 22q11DS, the prevalence of schizophrenia is 20-25% (Fiksinski et al., 2018; Karayiorgou et al., 2010). Therefore, to obtain a sample of 70 individuals who develop schizophrenia, approximately 300 individuals will need to be followed.

2Q11DS AS A MODEL FOR DLD

Children with 22q11DS can technically not be diagnosed with DLD because an associated biomedical condition precludes a DLD diagnosis (Bishop et al., 2017). One could argue that these groups are therefore inherently different and cannot be compared. However, it has been argued that the presence of specific medical conditions or genetic variants should not preclude the diagnosis of neurodevelopmental disorder (Vorstman & Scherer, 2021). We argue the same should hold for DLD, and that as argued above, the clear etiology of 22q11DS can actually provide a benefit to researchers. Provided that children with 22q11DS and children with DLD show phenotypical overlap, we thus propose that these diagnostic criteria do not hamper the use of 22q11DS as a model for DLD. In this case, children with 22q11DS can be viewed as a select group of children with language disorders that is more homogeneous than the group of children with DLD (see Figure 1.2).

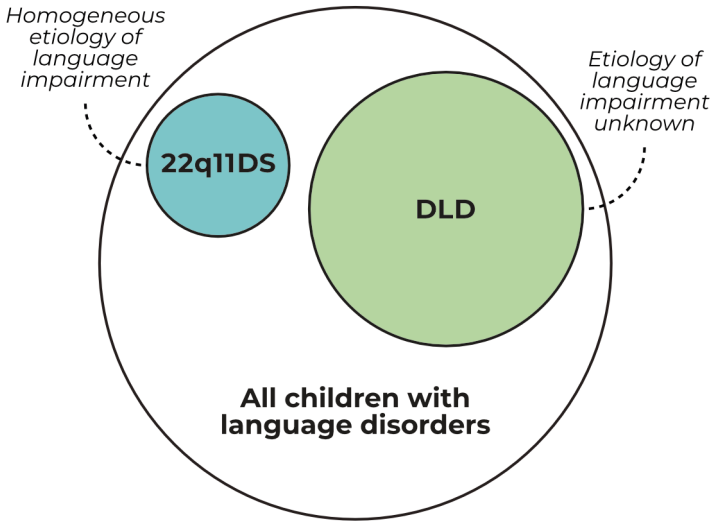

Figure 1.2. Subgroups of children with language impairments.

Descriptions of the 22q11DS phenotype in the literature point to substantial overlap with the phenotype of children with DLD. Firstly, language problems are observed in the majority of children with 22q11DS (Solot et al., 2019). Delays in the onset of expressive language

and the achievement of early language milestones are frequently reported in infants and toddlers with 22q11DS (Gerdes et al., 1999; Mills et al., 2006; Solot et al., 2000; Roizen et al., 2007). At preschool-age (1-6 years old) children with 22q11DS are reported to have impairments in both receptive and expressive language abilities (Gerdes et al., 1999; Gerdes et al., 2001; Solot et al., 2001). In school-aged children, a profile of relatively weak receptive semantic abilities and strong expressive syntactic abilities has been described (Glaser et al., 2002; Van den Heuvel et al., 2018), but such a profile is not available for preschool children with 22q11DS. Importantly, even though intellectual disabilities are present in some children with 22q11DS, their language difficulties appear to be disproportional to their level of intellectual functioning (Persson et al., 2006; Scherer et al., 1999; Selten et al., 2021; Van den Heuvel et al., 2018). Secondly, similar to children with DLD, EF deficits have also been reported in children with 22q11DS. A meta-analysis showed that cognitive deficits, including EF, are widespread in school-aged children, adolescents, and young adults with 22q11DS (Moberg et al., 2018). However, the cognitive profile of preschool age is not well-described.

Particularly for preschool-aged children, it cannot yet be determined whether phenotypical overlap between children with 22q11DS and children with DLD exists, as to date there are only a few studies on the early language and EF abilities of children with 22q11DS and these are hampered by various limitations. This dissertation addresses these limitations. Using a larger sample than most previous studies, this dissertation describes the language abilities of preschoolers with 22q11DS beyond global composite scores and describes EF performance on various tasks in an age range not previously studied. These studies will allow us to compare phenotypic profiles of children with 22q11DS and children with DLD as a first step to determine whether 22q11DS can function as a model for DLD. In 22q11DS it may be easier to prospectively investigate behavioral measures and potential clinical markers (see Figure 1.3). Although such clinical markers can likely not be directly generalized to DLD, they can provide directions for research into early clinical markers for DLD.

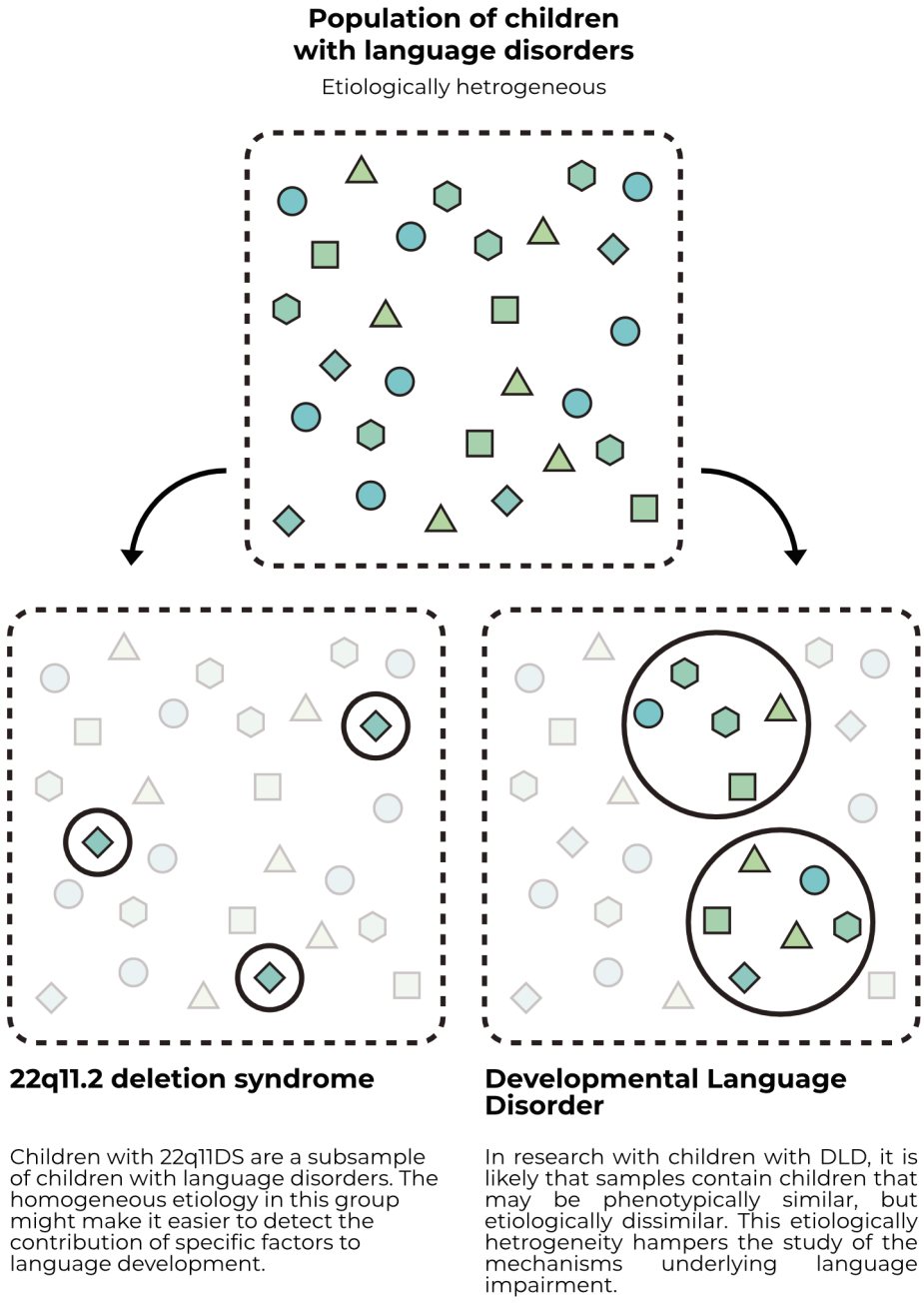

Figure 1.3. Graphic depiction of the benefit of studying 22q11DS for the investigation of specific factors and mechanisms in atypical language development as a way to reduce the variability present in children with DLD.

THE CURRENT DISSERTATION

Global context of the current dissertation

The current study took place within a larger research project 'Language impairment in the 22q11.2 deletion syndrome: a model for DLD?' (*3T project* [9]), which was funded by the Netherlands Organization for Scientific Research (NWO) [project number 360-89-080]. The two main objectives of the *3T project* were: 1) to provide a detailed psychological profile of preschoolers with 22q11DS. This includes a quantitative and qualitative description of early language development in children with 22q11DS, comprising expressive and receptive abilities in various language domains (semantics, morphology, syntax, pragmatics), early cognitive functioning and socio-emotional development; and 2) to determine if children with 22q11DS and children with DLD show similar impairments in various cognitive functions (e.g., executive functions) and in their socio-emotional abilities and, in turn, whether such impairments are similarly related to their language abilities. Given the rapid development of EF and language in early childhood and the possibility of early intervention, this project focused on children between 3 to 6.5 years old.

The studies in this dissertation report data collected in the first measurement wave of the *3T project*. Additionally, one chapter contains data from school-age children with 22q11DS or peers with DLD who participated in the EPISODE study, which focused on language processing and activation in the brain (CCMO registry nr. NL62366.041.17). This research was supported by a grant from Utrecht University's research theme Dynamics of Youth and conducted prior to the start of the *3T project*. See **chapter 4** for more details.

Research aims

The goal of this dissertation is to further our understanding of atypical language development and the factors that affect it. Results from studies investigating EF in children with DLD have been mixed (Kapa

9 3T refers to the abbreviation for the shortened Dutch project title Taal, Tweeëntwintig-q-elf (22q11), en TOS (Taalontwikkelingsstoornis) which translates to 'Language, Twenty-two-q-one-one (22q11), and DLD'.

& Erikson, 2019). Although particularly the presence of non-verbal EF deficits has been contended, evidence for such deficits is growing (Ebert & Kohnert, 2011; Pauls & Archibald, 2016; Vugs et al., 2013). If non-verbal EF impairments are present and are related to language abilities, this would provide support for the hypothesis that deficits in domain-general cognitive functions are part of the mechanism contributing to atypical language development (Kapa & Plante, 2015). Furthermore, non-verbal EF impairments may thus also be part of the clinical phenotype of DLD, which is important for assessment and prognostic information (e.g., Archibald, 2018). This dissertation aims to investigate the role of non-verbal EF in atypical language development (**aim 1**).

Investigations of non-verbal EF impairments in children with DLD and the relationship between EF and language have been hampered by the large etiological and phenotypical heterogeneity in children with DLD. To address the challenges brought on by the etiological heterogeneity of children with DLD, this dissertation also explores whether studying an etiologically homogenous population (i.e., children with 22q11DS) is a viable approach to reduce variability. 22q11DS has been successfully used to investigate pathogenic processes in other idiopathic conditions, such as schizophrenia (Fiksinski et al., 2021; Gur et al., 2017) and scoliosis (Homans et al., 2019). To investigate whether the same can be done for DLD, a comprehensive comparison of the language and cognitive phenotype of children with DLD and children with 22q11DS is needed. It has been tentatively suggested that children with 22q11DS may be similar to children with DLD with regards to language abilities (Goorhuis-Brouwer et al., 2003; Kambanaros & Grohmann, 2017; Swillen et al., 2001). However, in contrast to the large body of work on DLD, research on the early language and cognitive profile of children with 22q11DS is scarce. Therefore, we set out to obtain a detailed profile of both language and EF abilities of young children with 22q11DS, allowing us to determine whether the phenotype of children with 22q11DS is similar to that of children with DLD (**aim 2**). Summarizing, we formulate the following **research aims**:

1. Investigate how non-verbal EF relates to the language abilities of children with DLD.
2. Determine whether 22q11DS can function as an etiologically homogeneous model for DLD, which requires:
    a. A detailed language profile of preschool children with 22q11DS.
    b. A detailed EF profile of preschool with 22q11DS.
    c. A comparison between the language and EF abilities of preschoolers with 22q11DS or DLD.

The scope of **aim 1** is too broad to be completed within this dissertation alone. However, with **aim 2** we hope to provide a method that can support research concerning **aim 1**. In addition to these research objectives, this dissertation also contributes to clinical aims. Although children with 22q11DS can technically not be diagnosed with DLD because their language problems are associated with an underlying biomedical condition (Bishop et al., 2017), we see that in clinical settings, they frequently receive care from the same professionals and make use of the same services as children with DLD. For example, all but one child with 22q11DS who participated in the *3T project* received speech-language therapy. Additionally, in the cohort (*n* = 306) of the national multidisciplinary outpatient clinic for children with 22q11DS (Wilhelmina Children's Hospital, UMCU, the Netherlands), a retrospective review of medical records showed that at least 33% of children with 22q11DS was attending or had attended '*cluster-2 education*', a type of special education in the Netherlands for children who have communicative problems (i.e., speech and/or language problems, hard-of-hearing or deafness) (Boerma et al., 2022). Clinically, it is thus useful to investigate to what extent the language profiles of children with 22q11DS and children with DLD overlap to determine whether the children may benefit from the same interventions and therapies.

Moreover, 22q11DS is relatively unknown, even though it is thought to be the most common genetic disorder after Down syndrome (Umlauf, 2008; Blagojevic et al., 2021). Research into the origin of 22q11DS and its symptoms was scarce for years but has

gained momentum in the past decades. Due to the variability in phenotypic expression, studies investigating this syndrome remain vital to improve diagnostic criteria, characterize a more elaborate phenotype, raise awareness, and develop adequate therapies and interventions for those affected.

Participants and recruitment of the *3T project*

A total of 44 children with 22q11DS, 65 children with DLD, and 81 TD children participated in the *3T project*. The project was approved by the Medical Ethical review board of the University Medical Centre Utrecht (UMCU) (CCMO registry nr. NL63223.041.17). Written informed consent was provided by all parents and/or legal guardians of participating children.

Children were recruited between November 2018 and November 2019. Children with 22q11DS were recruited through the national multidisciplinary outpatient clinic for children with 22q11DS (Wilhelmina Children's Hospital, UMCU, the Netherlands) and the Dutch 22q11DS patient support group (Stichting Steun 22Q11). Four other medical centers (Amphia Ziekenhuis, Erasmus Medisch Centrum, Leids Universitair Medisch Centrum, and Máxima Medisch Centrum) in the Netherlands that regularly treat and refer 22q11DS patients were also approached to assist in recruitment. One center provided information about our study to the parents of one patient, but the other three centers indicated that there were no patients known that met the inclusion criteria who were not already known at the UMCU. Children with DLD were recruited through organizations that provide diagnostic assessment, care, and education for children with communicative impairment in the Netherlands (Royal Auris Group, Royal Kentalis, Viertaal, NSDSK) and through word of mouth. TD children were recruited through day-care centers and elementary schools throughout the Netherlands. In some cases, they were recruited from the same schools that were attended by children with 22q11DS who participated in this study. Other schools were approached separately by the research team. Children with 22q11DS attended different types of education or daycare, varying from regular education or daycare to different types of special education or specialized daycare facilities. All children with DLD were enrolled in

early intervention programs, attending special education or regular education with ambulatory care. All TD children attended regular day-care or primary schools.

Inclusion criteria of the *3T project*

Inclusion criteria were checked through a short parent-survey that was conducted over the phone before enrollment. Inclusion criteria for all children were:

1. Aged between 3.0 and 6.5 years;
2. Monolingual Dutch (more than 80% of Dutch spoken at home, checked with Questionnaire for Parents of Bilingual Children (PaBiQ, Tuller, 2015);
3. No bilateral permanent hearing loss (>35 dB) as reported by parents. In the Netherlands, children undergo multiple standardized hearing assessments as part of the routine clinical follow-up for all infants (otoacoustic emissions tests) and preschoolers (pure tone/tonal audiometry test). Parents were asked about these assessments.
4. Additional inclusion criteria were:
    a. For children with 22q11DS: a 22q11.2 deletion as confirmed by genetic testing (CNV/CGH/SNP array, MLPA, or WES [10]).
    b. For children with DLD: a diagnosis of DLD and eligibility for early intervention or special education following official criteria (Stichting Siméa, 2017, see below).
    c. For TD children: no history of developmental concerns and no family history of dyslexia or language impairment, as children with familial risk of dyslexia are at higher risk of developing DLD (Nash et al., 2013).

Inclusion criteria 4b is described is more detail below. In the Netherlands, where this study took place, a child can receive the diagnosis DLD if the child has persistent language difficulties that

10 CNV = Copy Number Variation; CGH = Comparative Genomic Hybridization; MLPA = Multiple Ligand-dependent Probe Amplification; SNP = Single Nucleotide Polymorphism; WES = Whole Exosome Sequencing.

cannot be attributed to hearing loss, general developmental delay, or insufficient input (Nederlandse Vereniging voor Logopedie en Foniatrie, 2015). Children with severe DLD can be eligible for intervention and support in the form of early intervention day-care, special education, or ambulatory care in regular education when they meet following official criteria (Stichting Siméa, 2017):

- A score of at least 2 standard deviations (SD) below the normed mean of a general standardized language assessment;
- Or scores of 2 *SD* below the normed mean in one domain (speech, pragmatics, grammar, semantics) on 2 subtests of a standardized language assessment;
- Or scores of 1.5 *SD* below the normed mean in two or more domains on two or more subtests of a standardized language assessment;
- Or scores of 1.3 *SD* below the normed mean in at least three language areas on two or more subtests of a standardized language assessment.

All children with DLD in the *3T project* met these criteria prior to study enrollment. These criteria are stricter than the criteria of 1.25 *SD* below the age-normed mean on at least two out of five composite language scores commonly used in academic research (Tomblin et al., 1997). Normal intellectual functioning has also been commonly used as a diagnostic criterium for DLD (Plante, 1998; Stark & Tallal, 1981). We decided not to use a minimum non-verbal IQ score as an inclusion criterium for our DLD group, because this practice has been criticized (Gerrits et al., 2017; Norbury et al., 2008) and because such a criterium was not used for the 22q11DS group either and would likely not affect the comparison between these groups as children with 22q11DS generally have lower IQ scores (De Smedt et al., 2007; Swillen et al., 2018).

Study design and procedures

The studies described in this dissertation always included the maximum number of children to maximize power. As not all children were able to complete all tasks, the demographic characteristics of

children with incomplete task data are discussed in the respective studies. The full datasets generated and/or analyzed in this dissertation are not publicly available due to GDPR compliance and legal and ethical limitations, but a limited amount of data can be shared upon reasonable request.

The project was initially set up with a prospective longitudinal design comprising three measurement waves (six months apart). For each measurement wave, assessment took place at the child's school or day-care center and consisted of two sessions of 45-minutes each, which were on average five days (*SD* = 3, range: 0-14) apart. Both sessions were always conducted by the same trained researcher. Language, EF, and other cognitive tasks were mixed and administered in a fixed order. Parents filled in online questionnaires at every measurement wave regarding demographic information and their child's language and socio-emotional development.

Due to the global COVID-19 pandemic, data collection had to be halted in March 2020. At that moment, the first measurement wave was completed, but waves two and three were still in progress. At that time, 32 children with 22q11DS, 42 children with DLD and 19 TD children had completed two measurement waves, and 6 children with 22q11DS, 0 children with DLD, and 6 TD children had completed all three waves. As measurement waves were only six months apart, and children develop rapidly at this age, the temporary halting of measurements had a large impact on the longitudinal nature of the project. Questionnaires were sent to parents electronically at the times of the original measurement waves, providing longitudinal data regarding socio-emotional development. In the summer of 2020, it was determined that the data collection of behavioral measures could not be fully resumed. It was decided to focus on the follow-up measurements of children with 22q11DS, as least is known in the literature about the developmental trajectory of their language abilities. In September 2020, a new follow-up wave was started for children with 22q11DS. To ensure the amount of time between the first measurement and the follow-up measurement (eighteen months) was the same for all children, new assessments were planned for all children with 22q11DS, irrespective of the number of measurement waves they had already completed. However, in December 2020,

schools were closed again due to the ongoing COVID-19 pandemic. At this time, 13 children with 22q11DS had been seen for follow-up. Unfortunately, schools remained closed until March 2021, which definitively concluded our efforts to collect longitudinal behavioral data.

Chapter overview

To achieve the aims described above, we undertook various steps. First, **chapter 2** investigates whether non-verbal EF is impaired in preschool-aged (3-6 years old) children with DLD and explores the relationship between the EF and language abilities of children with and without DLD (**aim 1**). To investigate whether 22q11DS can be used as a model for DLD, we needed to further characterize the pediatric cognitive phenotype of children with 22q11DS to see whether they are phenotypically similar to children with DLD (**aim 2**). In **chapter 3**, we describe the language abilities of the children with 22q11DS as assessed with standardized tests and investigate whether their language abilities are related to their speech intelligibility, as speech difficulties are common in young children with 22q11DS. In **chapter 4**, we use both standardized language assessment and spontaneous language analysis to compare the grammatical abilities of preschool-age and school-age children with 22q11DS and children with DLD. **Chapter 5** reviews the literature regarding executive functioning in children with 22q11DS and highlights the benefit of considering a specific genetic condition to study certain factors and processes underlying cognitive development. In **chapter 6**, we investigate the EF abilities of preschool children with 22q11DS compared to TD peers. This chapter furthermore studies the relationship between congenital heart defects and executive impairment. This investigation illustrates how the association between two conditions and their underlying mechanism can be studied using an etiologically homogeneous population. Lastly, **chapter 7** summarizes the findings from this dissertation and provides a general discussion. Additional analyses for considering the comparison between children with 22q11DS and children with DLD are presented. Finally, limitations, future directions, and both theoretical and clinical implications are discussed.

Chapter 2

Non-verbal executive functioning in relation to vocabulary and morphosyntax in preschool children with and without Developmental Language Disorder.

Everaert, E., Boerma, T., Selten, I., Gerrits, E., Houben, M., Vorstman, J., & Wijnen, F. (*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*.

Abstract

Purpose. Developmental Language Disorder (DLD) is characterized by persistent and unexplained difficulties in language development. Accumulating evidence shows that children with DLD also experience deficits in other cognitive domains, such as executive functioning (EF). There is ongoing debate on whether exclusively verbal EF abilities are impaired in children with DLD or whether non-verbal EF is also impaired, and whether these EF impairments are related to their language difficulties. The aims of the current study were: 1) to compare non-verbal performance of preschoolers with DLD and typically developing (TD) peers; 2) to examine how non-verbal EF and language abilities are related; 3) to investigate whether a diagnosis of DLD moderates the relationship between EF and language abilities.

Method. A total of 143 children (n_{DLD} = 65, n_{TD} = 78) participated. All children were between 3 and 6.5 years old and were monolingual Dutch. We assessed non-verbal EF with a visual selective attention task, a visuospatial short-term and working memory task, and a task gauging broad EF abilities. Vocabulary and morphosyntax were each measured with two standardized language tests. We created latent variables for EF, vocabulary, and morphosyntax.

Results. Analyses showed that children with DLD were outperformed by TD peers on all non-verbal EF tasks. Non-verbal EF abilities were related to morphosyntactic abilities in both groups, whereas a relationship between vocabulary and EF skills was found in the TD group only. These relationships were not significantly moderated by a diagnosis of DLD.

Conclusions. We found evidence for non-verbal EF impairments in preschool children with DLD. Moreover, non-verbal EF and morphosyntactic abilities were significantly related in these children. These findings may have implications for intervention and support the improvement of prognostic accuracy.

Key words: *Developmental Language Disorder; Executive functioning; Preschool*.

Introduction

Developmental Language Disorder (DLD) is characterized by persistent difficulties in language learning in the absence of hearing loss, neurological damage, intellectual disability, and/or an associated biomedical condition (Bishop et al., 2017). DLD occurs in 2-7% of all children (Calder et al., 2022; Norbury et al., 2017; Tomblin et al., 1997). Morphosyntactic deficits are a hallmark feature of DLD (Leonard, 2014; Rice & Wexler, 1996), but the population of children with DLD is very heterogeneous in terms of the severity of the problems and the language domains that are affected (Leonard, 2014). In addition to morphosyntax, children with DLD may also experience problems with other language domains, such as phonology, vocabulary, and pragmatics (Ellis Weismer et al., 2021; Graf Estes et al., 2007; Gray et al., 1999; Rice & Hoffman, 2015).

Previously, DLD [1] was referred to as Specific Language Impairment (SLI) reflecting the view that DLD was a disorder specific – and limited to – the domain of language (Rice & Wexler, 1996; Van der Lely, 2005). However, a growing body of research shows that children with DLD also have deficits in other cognitive domains, such as non-declarative learning (e.g., Mayor-Dubois et al., 2014) or motor functioning (e.g., Finlay & McPhillips, 2013). Deficits in executive functioning (EF) have also been frequently observed in children with DLD (e.g., Pauls & Archibald, 2016; Vissers et al., 2015). This has raised the question if and how EF impairments of children with DLD and their language problems are related. It is currently debated whether EF deficits should be considered to be part of DLD or, alternatively, as contributory factors leading up to the individual differences that affect language development in the general population (Lancaster & Camarata, 2019). A better understanding of the relationship between language and EF is important for intervention and clinical practice (e.g., Archibald, 2018; Delage et al., 2021).

In the current study, we investigate the performance of preschoolers (3-6.5 years old) with DLD on non-verbal EF tasks in comparison to typically developing (TD) peers and examine how their

1 We will use the term DLD throughout, even for describing findings of studies that use a different term for the disorder (e.g., specific language impairment, primary language impairment, language impairment, developmental language impairment).

EF and language abilities are related. By using three non-verbal EF tasks in a substantial sample of preschoolers, we add to the existing body of research that investigates EF impairments in children with DLD, which has revealed mixed outcomes. Furthermore, by examining the (concurrent) relationship between latent measures of both vocabulary and morphosyntax with EF abilities, we aim to further elucidate the mechanism underlying atypical language development.

Executive functioning

EF is a term that is used to describe a set of cognitive functions that manage lower-level cognitive functions to achieve goal-directed behavior and include working memory (WM), inhibitory and attentional control, and cognitive flexibility (Diamond, 2013; Miyake et al., 2000; Munakata, 2001; Zelazo & Müller, 2010). The most frequently cited model is that of Miyake et al. (2000), which includes three components: *updating*, *inhibition*, and *shifting*. Updating refers to the ability to store, update, and manipulate information in working memory; inhibition refers to the ability to ignore irrelevant stimuli (both internal and external) and suppress habitual responses; and attentional shifting refers to the ability to smoothly transition between internal states and tasks.

Updating in the model of Miyake et al. (2000) is often used synonymously with the concept of working memory. A more detailed model of WM specifically proposes that it consists of four components (Baddeley & Hitch, 1974; Baddeley, 2003). These components can be distinguished based on whether they are specific to verbal or non-verbal input and based on whether they merely store input (i.e., short-term memory (STM)) or also manipulate this input (i.e., executive components). Especially this executive component of WM has been suggested to be highly dependent on attentional abilities (Engle et al., 1999; Engle, 2002; Engle, 2010). Accordingly, Garon et al. (2008) have extended the model of Miyake et al. (2000) by including selective attention as a precursor of shifting, inhibition and updating (from here on referred to as working memory). Selective attention refers to the ability to direct attentional resources to a specific target to facilitate processing in the presence of distractors. Garon et al. (2008)

suggest a hierarchy of the EF components, in which attention provides the basis on which WM develops. This is followed by the development of inhibition and finally shifting. In this view, attention and WM are thus the most relevant components to study in early development.

EF and language in typical development: implications for DLD

In TD children, a relationship between EF and language abilities has been observed for various language domains, including vocabulary (Blom & Boerma, 2019; Kapa & Erikson, 2020; Kuhn et al., 2016; Majerus et al., 2009; McClelland et al., 2007; Schmitt et al., 2019; White et al., 2017) and morphosyntax (Delage & Frauenfelder, 2020; Finney et al., 2014; Kaushanskaya et al., 2017; White et al., 2017).

To explain these relations, it has been proposed that EF plays a role in language learning (Archibald, 2017; Ellis & Sinclair, 1996; Mazuka et al., 2009). EF might facilitate word-learning by regulating the inhibition of semantic competitors (Yoshida et al., 2011), and might allow children to monitor grammatical rules, inhibit incorrect words or sentences from being uttered, and inhibit incorrect interpretations of complex or ambiguous sentences (Choi & Trueswell, 2010; Ibbotson & Kearvell-White, 2015; Pomper et al., 2022; Woodard et a., 2016; Ye & Zhou, 2009). Accordingly, the observed impairment of EF in children with DLD has led researchers to propose various theories that suggest that these EF deficits might underly their language problems (e.g., Gathercole & Baddeley, 1993). The critical presumption of such theories is that certain domain-general cognitive skills are essential to acquiring and using language. Accordingly, some studies have shown that EF abilities are related to word-learning in children with DLD (Kapa & Erikson, 2020; Jackson et al., 2021).

However, it is also possible that language skills support EF development by allowing children to label internal representations, structure their thoughts, and form mental representations of problems and goals, which may facilitate monitoring and planning behaviors (Jacques & Zelazo, 2005; Kuhn et al., 2014; Zelazo & Frye, 1998). Indeed, research with TD children has shown that verbal labeling and inner speech increase performance on EF tasks (Alarcón-

Rubio et al., 2014; Kirkham et al., 2003). It has therefore also been suggested that the EF weaknesses observed in children with DLD could be the consequence of their language difficulties rather than the cause (Gooch et al., 2016). Difficulties with non-verbal EF especially may be the result of inefficient verbal encoding (Archibald & Gathercole, 2006; Botting et al., 2013; Gillam et al., 1998) or of limited self-directed speech in children with DLD (Abdul Aziz et al., 2016; Kapa & Mettler, 2021).

Research on the direction of the relation between language and EF abilities in TD children has resulted in mixed findings. Some studies have shown language abilities to be a stronger predictor of EF than vice versa (Blom & Boerma, 2019; Fuhs & Day, 2011; Kuhn et al., 2016; Romeo et al., 2022; Slot & Suchodoletz, 2018), whereas other studies observed the opposite (Schmitt et al., 2019; Weiland et al., 2014; White et al., 2017) or found the relation between EF and language abilities to be reciprocal (McClelland et al., 2007; Schmitt et al., 2019; Romeo et al., 2022; Slot & Suchodoletz, 2018). It has been suggested that these mixed outcomes reflect distinct relations throughout different developmental stages and between different language and EF domains (Kaushanskaya et al., 2017; Kuhn et al., 2016). Although the exact nature and direction of the relationship are not yet clear, it seems likely that language and EF develop, at least partly, in unison (Fischer & Bidell, 2006). Consequently, deficits in either language or EF may hamper development in the other.

With regard to DLD, it is also possible that EF deficits are neither the cause nor the result, but possibly just co-occurring deficits stemming from the same unrelated underlying cause as the language deficits (Bishop et al., 2014). In that case, impaired EF does not give rise to the language problems of children with DLD, but is likely not beneficial to language development either (Kapa & Plante, 2015).

EF deficits in DLD and relations with language ability

There has been ongoing debate on whether only verbal or also non-verbal EF abilities are impaired in children with DLD. Some theories of DLD have proposed specific deficits in verbal or auditory cognitive functions (Gathercole & Baddeley, 1990; Gathercole & Baddeley, 1993),

while others have suggested that domain-general deficits, including non-verbal cognition, underlie the language problems of children with DLD (Im-Bolter et al., 2006; Kail, 1994; Lukács & Kemény, 2014; Lum et al., 2014; Ullman & Pierpont, 2005).

A meta-analysis focusing on sustained attention deficits in children with DLD showed the largest deficits in the linguistic-auditory domain, followed by the non-linguistic auditory domain, and the smallest deficit for the visual domain (Ebert & Kohnert, 2011). More recent studies have corroborated these outcomes for the auditory domain (Duinmeijer et al., 2012; Jongman et al., 2017; Kapa et al., 2017; Kapa & Erikson, 2020; Tonér et al., 2021), but also strengthened the finding that visual attention is impaired in children with DLD (Boerma, Leseman et al., 2017; Dispaldro et al., 2013; Jongman et al., 2017; Kapa et al., 2017; Plym et al., 2021; Smolak et al., 2020), although this may depend on the length of the task (Blom & Boerma, 2020; Boerma & Blom, 2020).

Deficits of verbal STM and WM have been widely reported in children with DLD (Duinmeijer et al., 2012; Henry et al., 2012; Hick et al., 2005; Kapa & Erikson, 2020; Lukács et al., 2016; Marini et al., 2020; Vugs et al., 2014). Although initially several studies reported no difference in performance between children with DLD and TD peers on non-verbal WM tasks (Archibald & Gathercole, 2006; Arslan et al., 2020; Hick et al., 2005; Lum et al., 2012; Petruccelli, et al., 2012), a meta-analysis on non-verbal WM showed significant impairments in children with DLD (Vugs et al., 2013). A few recent studies have provided more evidence for impaired non-verbal WM in young children with DLD (Boerma & Blom, 2020; Kapa et al., 2017; Larson & Ellis Weismer 2022; Vugs et al., 2014; but see Lukács et al., 2016), although this was found to be dependent on the severity and persistence of DLD (Blom & Boerma, 2020). A similar finding was presented by a study that investigated verbal and non-verbal STM in two subgroups of children with DLD (Nickish & von Kries, 2009). They showed that only the children with both receptive and expressive language difficulties had non-verbal STM impairments compared to TD controls, in contrast to children with only expressive language problems. Taken together, this supports the idea that non-verbal WM deficits may be related to language problems.

Studies directly investigating the relationship between language skills and EF in children with DLD are relatively scarce. Various measures of vocabulary have been found to be related to non-verbal attention (Finneran et al., 2009; but see Dispaldro et al., 2013), non-verbal STM (Vugs et al., 2016), and a latent EF factor containing non-verbal tasks measuring selective attention, WM, and inhibition (Blom & Boerma, 2019). The latter study used crossed-lagged analysis of longitudinal data to show that EF predicted lexical skills in school-aged children with DLD, while in their TD sample, lexical skills predicted EF. Syntax was unrelated to EF in both the TD and DLD group of this study. This contrasts with cross-sectional studies that found that morphosyntactic abilities were related to non-verbal attention (Dispaldro et al., 2013; but see Finneran et al., 2009), and verbal STM and verbal WM (Delage & Frauenfelder, 2020; Vugs et al., 2016) in children with DLD. There are also several studies on children with DLD that have reported no relation between various language and EF abilities (Yang & Gray, 2017), or between non-verbal WM and narrative abilities (Smolak et al., 2020), inflectional morphology (Calder et al., 2022), vocabulary and syntax (Vugs et al., 2016), or morphosyntactic abilities (Ellis Weismer et al., 2017).

In summary, a substantial number of studies have observed non-verbal deficits in children with DLD, although the findings are mixed. As such, the relationship between language abilities and non-verbal EF is currently unclear. These discrepant outcomes likely reflect the complex nature of this relationship and may in part be due to methodological differences between studies. Performance on verbal EF tasks may be affected by language problems, so it is essential to use non-verbal EF tasks to study the role of domain-general EF in language development (Kaushanskaya et al., 2017).

Current study

Given the mixed findings of previous studies, more research into non-verbal EF impairments with sufficiently large sample sizes is warranted. Additionally, both language and EF develop rapidly during early childhood (Best & Miller, 2010; Hoff, 2015) and early impairments may lead to cascading effects in other domains at a later age, making it highly relevant to study these abilities at the preschool age. In the

current study, we compared non-verbal EF performance of 65 preschoolers (3-6.5 years) with DLD with that of 78 age-matched TD peers. The aims of this study were threefold.

The first aim of this study was to compare non-verbal EF abilities of children with DLD and TD children. EF was measured with three tasks: a visual selective attention task, a visuospatial STM and WM task, and a broad EF task tapping various domains, including motoric inhibition. Based on the more recent studies that reported non-verbal impairments (Boerma & Blom, 2020; Dispaldro et al., 2013; Jongman et al., 2017; Kapa et al., 2017; Plym et al., 2021; Smolak et al., 2020; Vugs et al., 2013; Vugs et al., 2014), we hypothesized that the children with DLD would be outperformed by their TD peers on all EF measures.

The second aim was to investigate concurrent relations between EF and language abilities in the children with DLD and the TD controls. We differentiated between morphosyntactic abilities and lexical knowledge, using separate latent factors, as these domains may be differentially (Blom & Boerma, 2019) and uniquely (White et al., 2017) related to EF. Given that EF domains may not yet be differentiated in children, or at least may not be distinguishable from one another and might thus be best reflected by a single construct (e.g., Brydges et al., 2012; Wiebe et al., 2008), we also created a latent factor reflecting EF. The direction of the relationship between language and EF is currently unclear, but is likely reciprocal (Schmitt et al., 2019; Slot & Suchodoletz, 2018), possibly with varying degrees of interrelatedness between different domains at different developmental stages. In children with DLD, studies on the direction of the relationship are limited. Therefore, we did not have specific hypotheses about the outcomes for this aim. We could not complete longitudinal data collection due to the COVID-19 pandemic. However, we aimed to learn more about the direction of the relationship by an exploratory analysis, running separate regressions with EF as the predictor of language and vice versa. A similar strategy has previously been used to obtain information on the direction of the relationship in cross-sectional data (Botting et al., 2017) and these findings were later confirmed with longitudinal data from the same children (Jones et al., 2020), which attests to the validity of such an approach. We also

considered the effect of age, sex, intellectual abilities, and socioeconomic status.

The final aim was to determine whether the relationship between non-verbal EF and language are different for the DLD and the TD group, using a moderation analysis. Based on previous research, we expect that the relationship between EF and language abilities may differ between the two groups (Blom & Boerma, 2019; Ellis Weismer et al., 2017; Larson et al., 2019).

Methods

Participants

As part of a larger prospective study ('*3T project*') investigating children's language, cognitive, and behavioral development, 65 children with DLD and 81 TD controls participated in the current study. Children were recruited between November 2018 and November 2019. Children with DLD were recruited through organizations that provide care and education for children with DLD in the Netherlands (Royal Auris Group, Royal Kentalis, Viertaal, NSDSK) and via word of mouth. TD children were recruited through day-care centers and elementary schools throughout the Netherlands.

The study was approved by the Medical Ethical review board of the University Medical Centre Utrecht (CCMO registry nr. NL63223.041.17). Written informed consent was provided by all parents and/or legal guardians. Inclusion criteria were: 1) monolingual Dutch, 2) aged between 3.0 and 6.5 years, and 3) absence of bilateral permanent hearing loss (>35 dB). These criteria were checked through a short parent-survey that was conducted over the phone before inclusion. 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. For children with DLD, an additional inclusion criterion was: 4) a diagnosis of DLD and eligibility for early intervention or special education for children with DLD following the official national criteria (Stichting Siméa, 2017, see appendix 2-A) prior to study enrollment. For TD children, an additional

inclusion criterion was: 4) no history of developmental concerns and no family history of dyslexia or language impairment. Three TD children who met the inclusion criteria, were excluded for the current study because they had a score of more than 1 standard deviation (SD) below the normed mean on a standardized language screening measure (see footnote 3 of Table 2.1). Group characteristics and comparisons are presented in Table 2.1.

Table 2.1. Demographic characteristics of the children with DLD and the TD children.

	DLD (*n* = 65)	**TD** (*n* = 78)	
***n* female** (%)	13 (20%)	44 (56.4%)	$\chi^2(1) = 19.61$, $p < .001$, $V = .37$
Mean age (*SD*) Range (year;month)	4.8 (0.82) 3;1 – 6;2	4.7 (0.92) 3;0 – 6;6	$t(141) = -.72$, $p = .47$, $d = -.12$
Mean IQ [a] (*SD*) Range	97.7 (12.9) 69 – 124	106.4 (13.0) 81 – 139	$t(140) = 3.98$, $p < .001$, $d = .67$
Mean SES [b] (*SD*) Range	6.3 (1.6) 3.5 – 9	7.8 (1.3) 3.5 – 9	$t(119{,}871) = 6.07$, $p < .001$, $d = 1.05$
Mean CELF CLI [c] (*SD*) Range	76.9 (12.4) 55 – 107	106.4 (12.8) 85 – 133	$t(139) = 13.79$, $p < .001$, $d = 2.34$

Abbreviations: CELF CLI = Core Language Index of the Clinical Evaluations of Language Fundamentals, DLD = Developmental Language Disorder, IQ = Intelligence Quotient, SD = Standard Deviation, SES = Socio-Economic Status, TD = Typically Developing.

a. For children with DLD, IQ scores were obtained from school. These IQ tests were administered by a licensed psychologist in the context of formal cognitive assessments (SON-R, *n* = 44; WISC-V, *n* = 2; RAKIT, *n* = 1). For all TD children and the 18 children with DLD for whom there was no recent IQ score, the shortened version of the Wechsler Non-Verbal (WNV; Wechsler & Naglieri, 2008) was administered by one of the trained researchers from the current study. For one child with DLD, the full WNV was administered. A valid IQ score could not be obtained for one TD child after repeated non-compliance to the WNV task instructions.

b. Socioeconomic status was indexed by the average education level of both parents, ranked on a 9-point scale reflecting the Dutch educational system. The scale ranges from 1 'not completed primary education' to 9 'university degree'. The average of both parents was taken unless the child came from a single parent household (DLD n = 3, all single mothers; TD n = 0). SES is missing for two children with DLD and one TD child, as both parents declined to answer.

c. The CELF CLI is a normed composite score (*M* = 100, *SD* = 15) used to screen for language impairment. The CLI score of two children with DLD was missing (see Results).

Procedure

Assessments were performed by a trained researcher at the child's school or day-care center. The assessment consisted of two 45-minute

sessions conducted by the same researcher, which were on average 5 (*SD* = 3, range: 0-14) days apart. Researchers were graduate or postgraduate psychologists or linguists and were all trained using a standardized manual. During the assessment, language tests were mixed with cognitive tasks. The tasks were administered in a fixed order.

Children's responses to expressive language subtests of the Clinical Evaluations of Language Fundamentals (CELF) were recorded and were also scored by a second researcher. One of the EF tasks (HTKS; see below) was recorded on video and scored by a second researcher. In case of discrepancies, final scores were determined through a consensus procedure. Parents filled in online questionnaires regarding demographic information and their child's development.

Outcome measures

Language

We used the Dutch version of the Clinical Evaluation of Language Fundamentals Preschool (CELF Preschool-2-NL) (Wiig et al., 2012) and the Peabody Picture Vocabulary Test (PPVT-III-NL) (Schlichting, 2005) to assess language ability. The CELF is a standardized language test battery for children between ages 3;0 and 6;11 (years; months) and comprises six subtests. The CELF subtest scores for each task can be transformed into age-corrected norm scores (*M* = 10, *SD* = 3). The PPVT is a standardized vocabulary measure (*M* = 100, *SD* = 15) for children from 2;0 onward. Both the CELF and the PPVT were administered in accordance with the instruction manual.

Morphosyntax

The CELF subtest Recalling Sentences (RS) indexes expressive syntactic abilities. The child is asked to repeat sentences which increase in length and complexity. A maximum of 13 sentences is read by the experimenter. A score of up to 3 points per sentence can be obtained based on the number of mistakes made.

The CELF subtest Word Structure (WS) measures expressive morphosyntax. 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.

Vocabulary

The PPVT was used as a measure of receptive vocabulary. Children are asked to point to the picture that matches the target word read out by the experimenter. The test consists of 17 sets of 12 items. The exact number of items administered differs per child based on their age and the number of correct answers.

The CELF subtest Expressive Vocabulary (EV) measures expressive vocabulary. 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. Answers that are correct but are too general and/or are not the target answer(s) are awarded 1 point (e.g., 'baby cow' instead of 'calf').

Executive functioning

Selective attention

We used a task developed to measure selective attention (SA) in young children (Mulder & Verhagen, 2010; Mulder et al., 2014). Children had to search images of elephants among distractor images (donkeys and bears) in four displays, which differed in number and/or size of the images (see Figure 2.1). The search displays were presented on a 15.6-inch screen on a HP ProBook 450 G5 Notebook laptop using E-Prime 2.0 (Schneider et al., 2002). Children were instructed to point to the elephants they had found. To minimize working memory load, targets detected by the child were crossed with a blue line. Each display was presented for 40 seconds. The first two displays contained 40 distractors and 8 targets, the third contained 64 distractors and 8 targets, and the fourth contained 195 distractors and 9 targets. The task thus increased in complexity. The total number of targets found (Hits), with a maximum of 33, was taken as the outcome measure.

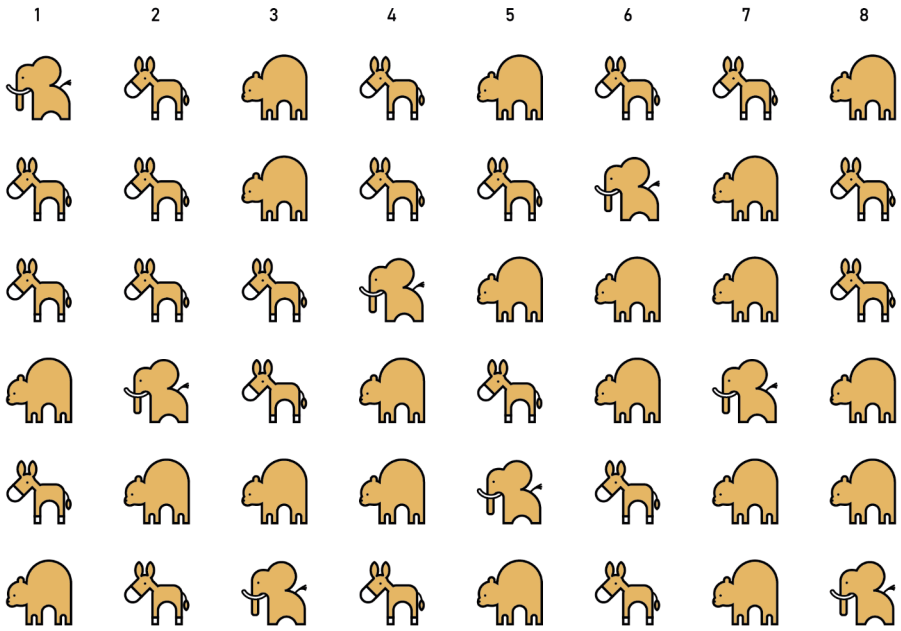

Figure 2.1. Search display 1 of the SA task (Mulder & Verhagen, 2010).

Working memory

The Corsi Block tapping task was administered to gauge visuospatial STM and WM skills (Milner, 1971; Corsi, 1973; Berch et al., 1998). Children were presented with a white board (25.5 x 20.5 cm) with nine blue blocks (3 x 3 cm), see Figure 2.2. We followed the procedure of the Mind Prekindergarten Curriculum (Farrell Pagulayan et al., 2006; Farran et al., 2015) as translated into Dutch by Wijnroks et al. (2017). This task has two conditions with two tests each.

In the Forward (FW) condition, gauging STM skills, the child was instructed to copy the experimenter, by tapping the blocks in the same order. The task started with a two-item sequence. If the child copied the sequence correctly, the experimenter moved on to the next sequence length. Otherwise, the experimenter showed a second trial with a different sequence of the same length. If the child failed to copy this second sequence, the test was terminated. The Backward (BW) condition, gauging WM abilities, was administered following a similar procedure, except that the child had to copy the sequences in reverse order.

The sequences in both conditions increased in length, with a maximum of nine blocks in the FW condition and six blocks in the BW condition. All sequences were predetermined and the same for all children. In each condition, the longest successfully copied sequence length of the two tests was taken as the outcome measure. In the FW condition, children who successfully completed the practice items but did not repeat any of the test items correctly were awarded a score of 1. Children who did not understand the BW condition instructions but who successfully completed at least one trial of the FW condition, thereby demonstrating comprehension of the task instructions, were awarded a score of 1 for the BW condition.

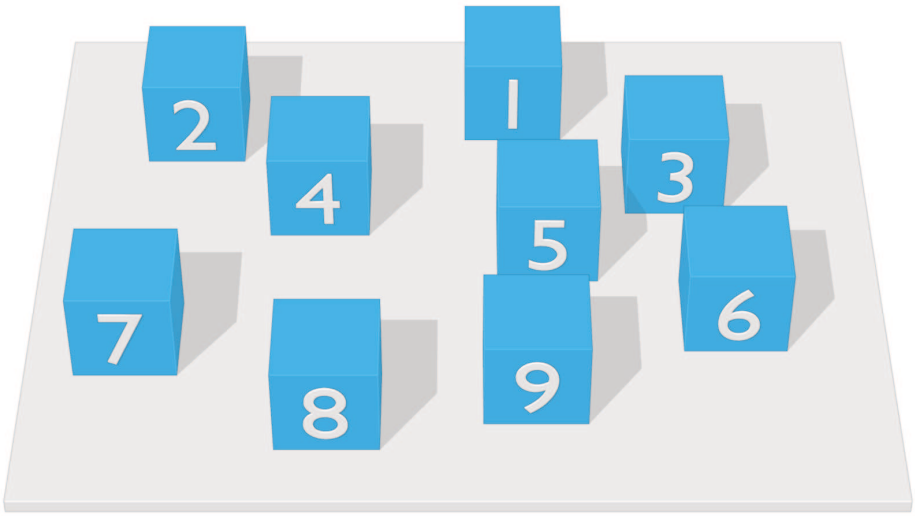

Figure 2.2. Corsi block task as seen from the perspective of the experimenter. Numbers on the blocks were not visible to the participant. Figure adapted from Kessels et al. (2008).

Broad EF

The Head-Toes-Knees-Shoulders task (HTKS; Ponitz et al., 2009; McClelland et al., 2007) is a task gauging a broad scope of EF abilities. The HTKS was developed as an ecologically valid measure of multiple aspects of EF for children aged 4 to 8 years old. The HTKS is considered a broad EF measure, as it requires the child to keep the rules of the game active in working memory during the task, use these rules to select correct responses and to inhibit a natural, but

incorrect response, while directing their attention to the experimenter. We followed the procedure of the Mind Prekindergarten Curriculum (Ponitz et al., 2008; Ponitz et al., 2009; Farran et al., 2015) as translated into Dutch by Wijnroks et al. (2017). The task consists of two parts.

In the first part, children were asked to point to their toes when the experimenter says: 'point to your head' and vice versa (HT condition). Experimenter instructions were supplemented with gestures. After four practice trials, ten test trials were administered. Head and Toe trials were administered in a fixed non-alternating order. The second part also included trials with knees and shoulders (KS condition). After four KS practice trials, HT trials were added. Following the same procedure as for the HT condition, ten test trials were administered and scored.

Final scores were only calculated for children who responded correctly to at least two practice trials. Otherwise, their score was marked as missing. Correct responses were awarded 2 points and self-corrections were awarded 1 point. The second part of the task was only administered if a child obtained more than 10 points in the first part of the task. The total number of points for both conditions taken together was used as the outcome measure with a maximum score of 40.

Data Analyses

Data was prepared and analyzed using R version 4.0.2 (R Core Team, 2020) and IBM SPSS 28.0 (2021). Analyses always included the maximum number of available participant scores. Parametric results are reported unless non-parametric tests were required and showed different outcomes than parametric tests. All significance tests were two-tailed with an α of 0.05. Effects sizes were interpreted following Cohen (1988). As not all children completed all tasks, we ran t-tests and χ^2-tests to compare the sample characteristics between children with incomplete data and children with complete data for both the DLD and the TD group.

First aim: Group comparisons of non-verbal EF abilities (ANCOVA)
The first aim of the current study was to investigate whether preschool children with DLD differed from TD peers on non-verbal EF tasks. We used ANCOVAs to compare the groups on the *SA task*, *Corsi FW* and *BW*, and the *HTKS*, while taking *Age*, *Sex*, *IQ*, and *SES* as covariates [2]. For the *SA task*, a repeated measures ANCOVA was used to investigate whether the groups differed on accuracy (*Hits*) for different levels of complexities (*Display*).

Second aim: Relationship language and non-verbal EF abilities in DLD and TD groups (regression)
The second aim of this study was to examine concurrent relations between EF and language abilities in children with DLD and TD controls, using linear regression. As explained in the introduction, we created latent factors for vocabulary, morphosyntax, and EF abilities.

Latent language factors. The CELF RS and WS subtests were combined into a latent factor reflecting morphosyntactic abilities. The CELF EV subtest and the PPVT were combined into a latent factor reflecting vocabulary knowledge. To derive these latent morphosyntax and vocabulary factors, principal components analyses were run with the raw scores of the respective language measures. The saved factor scores were used for regression analyses. ANCOVAs were used to compare groups on the latent factor prior to primary analysis. For a comparison of raw and norm scores of each language measure, see appendix 2-B.

Latent EF factor. Exploratory correlations showed that only *SA*, *Corsi BW*, and *HTKS* were significantly related to the language outcomes (see appendix 2-C). The *Corsi FW* did not correlate with any language measure in either group (see appendix 2-C) and was highly correlated to *Corsi BW* (see appendix 2-D). Therefore, it was not included in the latent factor. Furthermore, the *HTKS* was only completed by 57% of children with DLD and 82% of TD children. Including it in the latent factor thus resulted in a substantial loss of data. To include as many children as possible in the analyses, we

2 These variables have been related to language and EF development (Arffa, 2007; Gallinat & Spaulding, 2014; Lange et al., 2016; Lawson et al., 2018; Rice & Hoffman, 2015) and the groups differed on the demographic variables (see Table 2.1). Although the groups did not differ in age, it was used as a covariate, as it was strongly correlated with the outcome measures.

therefore decided not to include the *HTKS* in the latent EF factor. The saved factor scores from a principal components analysis were used for regression analyses.

After creating latent variables, correlations showed significant associations between the latent EF factor and both latent language factors (see appendix 2-D). Therefore, regression analyses were run with both language factors and the EF factor. *Age*, *Sex*, *IQ*, and *SES* were used as covariates. Correlations between the latent variables and *Age*, *IQ*, and *SES* can be found in appendix 2-E. As we also aimed to learn more about the direction of the relationship, we ran four exploratory regression analyses: two with *EF* as the predictor of either language factor and two with either language factor as a predictor of *EF*. We first ran baseline regression models with only the covariates predicting *Morphosyntax*, *Vocabulary*, or *EF* for each group separately. As a second step, *EF* was added to the models predicting either *Morphosyntax* or *Vocabulary*, and *Morphosyntax* or *Vocabulary* were added to the model predicting *EF*. By comparing the differences between the reversed models in change in variance explained (ΔR^2), we could explore whether EF explained more variance in language abilities or vice versa.

Third aim: Effect of DLD on relationship language and non-verbal EF abilities (moderation)

Finally, the last aim of the current study was to determine whether the relation between EF and language was moderated by impairment status (diagnosis of DLD), using moderation analysis (Hayes, 2013). Similar to the regression analyses, we ran four models with *Morphosyntax*, *Vocabulary*, or *EF* as either dependent or independent variable, *Group* as an additional independent variable, and *Age*, *Sex*, *IQ*, and *SES* as covariates. Subsequently, the interaction between *Group* and the other independent variable was added.

Results

Task completion data

All children completed the selective attention task. Ten children with DLD and four TD children did not complete one or both conditions of

the working memory task. For the broad EF task, 28 children with DLD and 14 TD children did not complete the task.

In the TD group, children missing one or both conditions from the working memory task were younger than children who completed the task ($t(8.96) = 7.85$, $p < .001$, $d = 1.42$). They did not differ in sex, IQ, SES, or Core Language Index (CLI). The same was observed for the children with DLD who did not complete the broad EF task. They were on average younger than those children with DLD who did complete the broad EF task ($t(63) = 7.26$, $p < .001$, $d = 1.82$), but did not differ in sex, IQ, SES, or CLI. In the TD group, only four children were missing one or both conditions from the working memory task. Given the small samples and unequal sample sizes, we did not run statistical analyses for these comparisons. They appear to be younger, but do not seem to differ in *Sex*, *IQ*, *SES*, or *CLI*. The same was observed for TD children who did not complete the broad EF task. They were on average younger than TD children who did complete the task ($t(71.40) = 13.78$, $p < .001$, $d = 2.19$), but did not differ in *Sex*, *IQ*, *SES*, or *CLI*. See appendix 2-F for a more detailed description of the HTKS task completion.

Additionally, three children had missing language scores. One child with DLD missed their second testing session due to repeated illness. Another child with DLD was suspected of having selective mutism and was thus unable to complete the expressive tasks. One TD child could not comply with the task instructions of the RS.

First aim: Group comparison of DLD and TD on non-verbal EF abilities (ANCOVA)

Outcomes of the EF tasks of both groups are reported in Table 2.2. Children with DLD obtained significantly lower scores than their TD peers on every EF task while taking *Age*, *Sex*, *IQ*, and *SES* into account as covariates.

For the selective attention task, a repeated measures ANCOVA with *Age*, *Sex*, *IQ*, and *SES* as covariates showed a main effect of Group ($F(1, 133) = 7.18$, $p = .008$, $\eta_p^2 = .05$) but not of Display ($V = .04$, $F(3, 131) = 1.57$, $p = .20$, $\eta_p^2 = .04$). There was also no interaction between *Group* and *Display* ($F(3, 131) = 0.48$, $p = .70$, $\eta_p^2 = .01$), indicating that the number of targets found decreased equally for both groups with

increased display difficulty. These results should be interpreted with caution as the assumption of homogeneity of covariance matrices was violated.

Table 2.2. Means, *SD* and ANCOVA statistics of the four non-verbal EF tasks for both the DLD and TD group.

	DLD			TD			
	n	*M*	*SD*	*n*	*M*	*SD*	*ANCOVA*
1. SA	63	20.8	4.7	76	22.9	3.8	$F(1, 133) = 7.18$, $p = .008$, $\eta_p^2 = .05$, CI(95%) [.43-2.85]
2. Corsi FW	56	3.1	0.9	74	3.5	0.9	$F(1, 124) = 7.13$, $p = .009$, $\eta_p^2 = .05$, CI(95%) [.11-.76]
3. Corsi BW	54	1.9	0.9	73	2.5	1.2	$F(1, 121) = 8.84$, $p = .004$, $\eta_p^2 = .07$, CI(95%) [.18-.90]
4. HTKS	37	18.5	11.4	64	27.0	10.1	$F(1, 93) = 4.17$, $p = .044$, $\eta_p^2 = .04$, CI(95%) [.13-9.47]

Abbreviations: BW = Backward, DLD = Developmental Language Disorder, FW = Forward, HTKS = Head-Toes-Knees-Shoulders Task, SA = Selective Attention, SD = Standard Deviation, TD = Typically Developing.

Note. The means and SDs presented here included one or two additional children, who could not be included in the ANCOVA due to missing IQ or SES scores. Effects of covariates per EF outcome were as follows: 1. SA: Age, $F(1, 133) = 123.74$, $p < .001$, $\eta p2 = .48$; IQ, $F(1, 133) = 28.71$, $p < .001$, $\eta p2 = .18$; Sex and SES were not significant. 2. Corsi FW: Age, $F(1, 124) = 55.34$, $p < .001$, $\eta p2 = .31$; Sex, IQ, and SES were not significant. 3. Corsi BW: Age, $F(1, 121) = 72.07$, $p < .001$, $\eta p2 = .37$; Sex, IQ, and SES were not significant. 4. HTKS: Age, $F(1, 93) = 22.49$, $p < .001$, $\eta p2 = .20$; IQ, $F(1, 93) = 9.64$, $p = .003$, $\eta p2 = .09$; SES $F(1, 93) = 6.27$, $p = .014$, $\eta p2 = .06$; Sex was not significant.

Second aim: Relationship language and EF abilities in DLD and TD (regression)

Children with DLD had lower scores on the latent *Morphosyntax* variable ($M = -0.8$, $SD = 0.6$) than TD children ($M = 0.7$, $SD = 0.8$; $F(1, 131) = 172.76$, $p < .001$, $\eta_p^2 = .57$). They also had lower scores on the latent *Vocabulary* variable ($M = -0.5$, $SD = 0.9$) than TD peers ($M = 0.4$, $SD = 1.0$; $F(1, 131) = 45.66$, $p < .001$, $\eta_p^2 = .26$). In both analyses, *Age*, *Sex*, *IQ*, and *SES* were included as covariates.

The baseline model included only the covariates *Age*, *Sex*, *IQ*, and *SES* as predictors. Significance of the covariates did not differ between the baseline models and the regression models including the independent variable, therefore only the models with the independent variable are presented here (see appendix 2-G for the baseline models). For the DLD group, adding *EF* as an independent

variable to the baseline model with *Morphosyntax* as the dependent variable, lead to a significant increase of explained variance ($\Delta F(1, 47) = 5.63$, $p = .022$, $\Delta R^2 = .06$). This regression model was significant ($F(5, 47) = 9.54$, $p < .001$, $R^2 = .50$), see Table 2.3. Adding *EF* as independent variable to the model with *Vocabulary* as the dependent variable did not lead to a significant increase of explained variance ($\Delta F(1, 47) = 3.17$, $p = .082$, $\Delta R^2 = .02$), but the final model was significant ($F(5, 47) = 19.49$, $p < .001$, $R^2 = .68$), see Table 2.3.

In the TD group, adding *EF* as an independent variable to the baseline model with *Morphosyntax* as the dependent variable, lead to a significant increase of explained variance ($\Delta F(1, 67) = 7.14$, $p = .009$, $\Delta R^2 = .04$). The regression model was significant ($F(5, 67) = 24.52$, $p < .001$, $R^2 = .65$), see Table 2.3. Adding *EF* as independent variable to the model with *Vocabulary* as the dependent variable lead to a significant increase of explained variance ($\Delta F(1, 67) = 4.81$, $p = .032$, $\Delta R^2 = .02$). The regression model was significant ($F(5, 67) = 41.17$, $p < .001$, $R^2 = .75$), see Table 2.3.

For the DLD group, adding *Morphosyntax* as an independent variable to the regression model with *EF* as the dependent variable, and *Age*, *Sex*, *IQ*, and *SES* as covariates, lead to a significant increase of explained variance ($\Delta F(1, 47) = 5.63$, $p = .022$, $\Delta R^2 = .04$). This regression model was significant ($F(5, 47) = 17.79$, $p < .001$, $R^2 = .65$), see Table 2.4. Adding *Vocabulary* (instead of *Morphosyntax*) as independent variable to the model with *EF* as the dependent variable did not lead to a significant increase of explained variance ($\Delta F(1, 47) = 3.17$, $p = .082$, $\Delta R^2 = .02$), but the final model was significant ($F(5, 47) = 16.52$, $p < .001$, $R^2 = .64$), see Table 2.4.

In the TD group, adding *Morphosyntax* as an independent variable to the regression model with *EF* as the dependent variable, and *Age*, *Sex*, *IQ*, and *SES* as covariates, lead to a significant increase of explained variance ($\Delta F(1, 67) = 7.14$, $p = .009$, $\Delta R^2 = .03$). The regression model was significant ($F(5, 67) = 30.17$, $p < .001$, $R^2 = .69$), see Table 2.4. Adding *Vocabulary* (instead of *Morphosyntax*) as the independent variable to the model with *EF* as the dependent variable lead to a significant increase of explained variance ($\Delta F(1, 67) = 4.81$, $p = .032$, $\Delta R^2 = .02$). The regression model was significant ($F(5, 67) = 28.80$, $p < .001$, $R^2 = .68$), see Table 2.4.

Table 2.3. Regression models for the DLD and TD group with EF as a predictor for both latent language variables while taking *Age*, *Sex*, *IQ*, and *SES* into consideration as covariates.

		DLD				TD		
	B	*SE B*	*β*	*p*	*B*	*SE B*	*β*	*p*
Morphosyntax	***Step 2***							
Constant	-2.218	.950		.024	-2.184	.766		.006
Age	.282	.120	.382	**.023***	.386	.104	.454	**<.001***
Sex	-.227	.137	-.184	.103	-.167	.114	-.109	.148
IQ	.002	.005	.057	.624	.003	.005	.044	.584
SES	.053	.035	.159	.141	.125	.043	.218	**.006***
EF	.229	.097	.392	**.022***	.251	.094	.333	**.009***
Vocabulary	***Step 2***							
Constant	-4.164	1.114		.001	-4.449	.787		.000
Age	.686	.140	.643	**<.001***	.648	.107	.618	**<.001***
Sex	-.088	.160	-.049	.585	-.137	.117	-.073	.245
IQ	.004	.006	.068	.468	.011	.005	.152	**.025***
SES	.043	.041	.090	.303	.103	.045	.146	**.024***
EF	.201	.113	.238	.082	.212	.097	.228	**.032***

Abbreviations: B = unstandardized regression coefficient, β = standardized regression coefficient, DLD = Developmental Language Disorder, EF = Executive functioning (latent factor), IQ = Intelligence Quotient, SE = Standard Error, SES = Socioeconomic Status, TD = Typically Developing.

Note. Significant outcomes in bold and * $p < .05$. Step 1, the regression model only containing the covariates, can be found in appendix 2-G.

Third aim: Group comparison relationship language and EF abilities (moderation)

Moderation analyses were run on the combined DLD and TD samples to investigate whether impairment status moderated the relation between EF and language abilities.

The moderation analysis with *EF* as the independent variable, *Group* as the moderator, and *Age*, *Sex*, *IQ*, and *SES* as covariates, was significant with either *Morphosyntax* ($F(6, 119) = 84.00$, $p < .001$, $R^2 = .81$) or *Vocabulary* as the dependent variable ($F(6, 119) = 64.38$, $p < .001$, $R^2 = .76$). Adding the interaction term (*Group*EF*) did not lead to a significant increase of explained variance in the model with

Table 2.4. Regression models for the DLD and TD group in which the two latent language variables are used as predictors for EF while taking *Age*, *Sex*, *IQ*, and *SES* into consideration as covariates.

		DLD				TD			
		B	*SE B*	*β*	*p*	*B*	*SE B*	*β*	*p*
EF	***Step 2a***								
	Constant	-5.629	1.175		.000	-4.084	.867		.000
	Age	.680	.151	.539	**<.001***	.644	.117	.572	**<.001***
	Sex	.214	.198	.102	.287	-.009	.143	-.005	.948
	IQ	.018	.006	.245	**.009***	.016	.005	.205	**.005***
	SES	.031	.051	.054	.550	-.084	.056	-.111	.137
	Morphosyntax	.467	.197	.273	**.022***	.383	.143	.290	**.009***
EF	***Step 2b***								
	Constant	-5.685	1.349		.000	-3.675	1.077		.001
	Age	.636	.194	.504	**.002***	.613	.144	.545	**<.001***
	Sex	.141	.199	.067	.484	-.032	.144	-.016	.824
	IQ	.018	.007	.255	**.008***	.014	.006	.180	**.020***
	SES	.045	.052	.079	.392	-.070	.056	-.093	.215
	Vocabulary	.314	.176	.265	.082	.316	.144	.294	**.032***

Abbreviations: B = unstandardized regression coefficient, β = standardized regression coefficient, DLD = Developmental Language Disorder, EF = Executive functioning (latent factor), IQ = Intelligence Quotient, SE = Standard Error, SES = Socioeconomic Status, TD = Typically Developing.

Note. Significant outcomes in bold and * $p < .05$. Step 1, the regression model only containing the covariates, can be found in appendix 2-G.

Morphosyntax ($\Delta F(1, 118) = 1.54$, $p = .22$, $\Delta R^2 = .00$), nor in the model with *Vocabulary* ($\Delta F(1, 118) = .03$, $p = .87$, $\Delta R^2 = .00$), indicating that *Group* did not moderate the relationship between *EF* and either *Morphosyntax* or *Vocabulary*.

The moderation analysis with *Morphosyntax* or *Vocabulary* as the independent variable, *Group* as the moderator, and *Age*, *Sex*, *IQ*, and *SES* as covariates, was significant with *EF* as the dependent variable (*Morphosyntax*: $F(6, 119) = 44.10$, $p < .001$, $R^2 = .69$; *Vocabulary*: $F(6, 119) = 42.26$, $p < .001$, $R^2 = .68$). Adding the interaction term *(Group*Morphosyntax/Vocabulary)* did not lead to a significant increase of explained variance in either the model with *Morphosyntax*

($\Delta F(1, 118) = 1.30$, $p = .26$, $\Delta R^2 = .00$), nor in the model with *Vocabulary* ($\Delta F(1, 118) = .41$, $p = .53$, $\Delta R^2 = .00$), indicating that *Group* did not moderate the relationship between either *Morphosyntax* or *Vocabulary* and *EF*.

Discussion

The first aim of this study was to determine whether preschool children with Developmental Language Disorder (DLD) have impaired non-verbal executive functioning (EF) compared to typically developing (TD) peers, as research so far has presented mixed findings. The second aim was to investigate concurrent relationships between EF and separate latent factors for morphosyntax and vocabulary in both groups. The final aim was to determine whether these relationships differed between the groups.

Non-verbal EF impairments in DLD

We found that children with DLD were outperformed by their TD peers on four different non-verbal EF tasks. Overall, effect sizes were small to medium, in line with previous research. When looking at the amount of variance explained by a DLD diagnosis on the separate non-verbal EF tasks, the largest effect size was observed for visuospatial working memory (WM; Corsi BW).

Visual selective attention

Children with DLD had poorer non-verbal selective attention than their TD peers. On average, they found fewer targets amidst distractors. These results are in line with previous studies showing impaired non-verbal selective attention in DLD (Dispaldro et al., 2013; Ebert & Kohnert, 2011; Plym et al., 2021), although there are also studies that found no differences between DLD and TD groups on measures of non-verbal attention (Finneran et al., 2009; Spaulding et al., 2008). Two other studies, that used a comparable search-type task (i.e., the Visual Sky Search) as in the current study in older (6-9y) children, also found no difference in selective attention between children with and without DLD (Blom & Boerma, 2020; Boerma & Blom, 2020). However, the same authors have observed a difference in sustained attention in their participant sample using a Continuous Performance Task

(Boerma, Leseman et al., 2017). They propose that especially sustained attention might be impaired in children with DLD. Indeed, multiple studies that report impaired non-verbal attention in children with DLD use sustained attention tasks (Jongman et al., 2017; Kapa & Erikson, 2020; Kapa et al., 2017) or a selective attention task similar to the one used in the current study with younger (4-7y) children (Smolak et al., 2020). Arguably, the selective attention task used in the current study can also be considered to measure sustained attention, as substantial effort might be required from such young children to maintain attentional control throughout the task. This illustrates that participant age and task type could explain the mixed results in the literature and highlights the need for more studies with children of different ages using different types of tasks.

Additionally, we showed that children with DLD and TD children respond similarly to an increase in task difficulty, that is a higher target-to-distractor ratio. This was in line with research with older (8-13y) children with DLD on various visual EF tasks (Windsor et al., 2006). This result, however, contrasts with a previous study that found that differences between TD children and children with DLD (4-6y) on sustained selective attention only appeared in high-load conditions (Spaulding et al., 2008). However, the group difference in this study only emerged in the linguistic and non-verbal auditory conditions. In the visual condition, there was no difference between the TD and DLD groups. The fact that Spaulding et al. (2008) observed an interaction between group and complexity while we did not may be explained by the fact that in the current study the display with the highest difficulty may have shown a floor effect as it was also challenging for the TD group. More research is needed to determine under which conditions EF deficits appear in children with DLD.

Visuospatial short-term and working memory

We observed impaired non-verbal short-term memory (STM) and working memory (WM) performance in our DLD group. This is in line with the outcomes of the meta-analysis of Vugs et al. (2013) and several experimental studies (Bavin et al., 2005; Boerma & Blom, 2020; Kapa et al., 2017; Nickisch & von Kries, 2009; Vugs et al., 2014; Yang & Gray, 2017), but contrasts with others (Arslan et al., 2020; Blom &

Boerma, 2020; Botting et al., 2013; Ellis Weismer et al., 2017; Lukács et al., 2016; Petruccelli et al., 2012). Notably, the previous studies that observed non-verbal WM impairments, studied younger children (4-8y), while the studies that reported no impairments mostly looked at older children (6-10y). It may be that non-verbal STM and WM deficits are only present early on but resolve as children get older. These early STM and WM impairments may have cascading effects on other, more complex EF domains, like inhibition and planning, that build upon WM skills (Garon et al., 2008). The meta-analysis of Vugs et al (2013), however, found no effect of age on working memory abilities. This does not preclude such a developmental account of EF impairment, but it suggests there are also other factors at play.

An alternative explanation for the impaired non-verbal STM and WM of our participants with DLD is that such impairments stem from limited *verbal* STM abilities (Lukács et al., 2016). Limited verbal STM abilities could lead to inefficient verbal strategies that support task performance or could lead to difficulties retaining (verbal) instructions. In the current study, we could not control for verbal STM. However, a previous study showed that non-verbal WM differences between TD and DLD groups remained significant even after verbal STM was controlled for (Boerma & Blom, 2020). Moreover, the set-up of the Corsi Block tapping task makes it difficult, especially for young children, to use verbal strategies to support performance. The blocks are the same color and are distributed non-linearly across a board, hindering the labeling of blocks or movements between them. Therefore, we argue that verbal STM impairments are unlikely to fully explain our findings and that our findings strengthen the hypothesis that non-verbal STM and WM deficits are part of the clinical profile of young children with DLD.

Complex non-verbal EF

We used the HTKS as a measure of complex non-verbal EF. Children need to inhibit gross motor responses, retain the rules in their WM, and pay attention to the instructions of the experimenter (McClelland et al., 2014; Ponitz et al., 2009). The DLD group in the current study performed significantly poorer than their TD peers on this task.

However, only 57% of the children with DLD completed this task. Results should therefore be interpreted with caution.

The use of the HTKS had several limitations that could explain the poorer performance and task completion of the DLD group. First, although the responses required from children are non-verbal (i.e., motoric), the instructions of the HTKS are verbal and complex. Children with DLD, particularly young children, may struggle more with the instructions than their TD peers due to their lower language level and limited verbal working memory abilities. Second, TD children may be better able than children with DLD at using (internal) verbal strategies to aid their performance on this task (e.g., Eichon et al., 2014). Third, the HTKS was recently revised, as it was suggested that the planning of gross motor movements may be challenging and disobeying the experimenter goes against the social expectations that children have (Gonzales et al., 2021). Children with DLD may especially struggle with these aspects, as they frequently also have motor problems (e.g., Finlay & McPhillips, 2013) and difficulties with social cognition and pragmatic abilities (St. Clair et al., 2011; Nilsson & Jensen de López, 2016). Despite these limitations, it would be interesting to further investigate why this task poses a challenge to children with DLD.

Relationship non-verbal EF and language

The second aim of the current study was to study the relationship between non-verbal EF ability and morphosyntax or vocabulary skills, respectively, in children with DLD and TD children. The third aim was to investigate whether these relationships differed between the groups. Research regarding the relationship between EF and language abilities has presented conflicting results in both children with DLD and TD children. Here, we focus on comparing our results to a few studies that are similar in set-up and methodology.

Relationship non-verbal EF with morphosyntax and vocabulary

Our results provide evidence that EF and morphosyntax were related in both the DLD and TD group, which is in line with previous studies on children with DLD (Dispaldro et al., 2013; Ellis Weismer et al., 2017; Delage & Frauenfelder, 2020) and findings in TD children (Blom &

Boerma, 2019; Kaushanskaya et al., 2017; White et al., 2017). However, Blom and Boerma (2019) reported that there was no relation between EF and syntax in children with DLD. This discrepancy between their findings and ours may be explained by the age range of our participants (3-6y) versus theirs (5-8y). Deficits in WM could limit children's ability to process complex sentences, hampering their syntactic development (Archibald, 2017). As morphosyntactic development is rapidly progressing in the preschool period (Hoff, 2015), the effect of such EF deficits may be more prominent at this age.

In line with previous research (e.g., Blom & Boerma, 2019; Schmitt et al., 2019; White et al., 2017), we found a relationship between non-verbal EF and vocabulary in our TD sample. However, we did not observe this relationship in the children with DLD. One explanation for the absence of this relationship in the DLD group may be that children with DLD have smaller vocabulary sizes (current study, see appendix 2-B; Gray et al., 1999; Rice et al., 2010; Rice & Hoffman, 2015). A smaller vocabulary size limits children's ability to label stimuli, which may be particularly disadvantageous for young children. This hypothesis has been supported by other studies that observed no significant relationship between EF and vocabulary in children with DLD (Dispaldro et al., 2013; Yang & Gray, 2017). Notably, Blom and Boerma (2019) found that in their DLD sample EF predicted vocabulary. This discrepancy with our findings may be partly explained by the fact that their latent EF factor also included an interference control (inhibition) task, which may have driven their observed predictive relation, and that they studied slightly older (5-8y) children. We speculate that, especially in young children with DLD, EF may contribute relatively less to vocabulary acquisition. For example, the number of lexical competitors is smaller in young children, who still have limited vocabulary sizes. Thus, fewer competitors have to be inhibited thereby imposing lower demands on EF abilities (Yoshida et al., 2011). Nevertheless, the outcomes of the moderation analysis showed that DLD diagnosis did not moderate the relations between language and EF, which suggest that the absence of evidence for a relationship between vocabulary and EF in the DLD group could also be due to a lack of power.

Effect of impairment status on relationship EF and language

Although the relationship between EF and vocabulary seemed to differ between the children with DLD and the TD children, as a significant relationship was only found in the latter, there was no significant effect of impairment status on the relationship between either language factor and EF in a moderation analysis. This means that, contrary to our expectations, there is no evidence that the relationship between EF and either morphosyntax or vocabulary differs between the groups.

We hypothesize that even though language abilities are impaired in children with DLD, the relationship with other factors, such as EF, is comparable to that in TD children (Lancaster & Camarata, 2019). However, previous studies with slightly older children with DLD and TD children observed differences in the relationship of language abilities with EF between the groups (Blom & Boerma, 2019; Ellis Weismer et al., 2017; Larson et al., 2019). Given these diverging outcomes from studies with older children, it may be that a difference between TD children and children with DLD in how language and EF develop and support one another arises during the course of development. More longitudinal research is needed to determine the reciprocal relationship between language and EF during development.

Direction of the relationship

Elucidation of the direction of the relationship between EF and language abilities was limited by the lack of longitudinal data, due to the COVID-19 pandemic. Using a similar strategy as Botting et al. (2017), we nevertheless attempted to gain insight into the direction of the relationship by using both language and EF as predictors in regression models. For example, we ran one regression model with EF as the predictor for morphosyntactic abilities, and in a second model we used morphosyntactic abilities as the predictor for EF. This allowed us to compare the change in explained variance from both regression models.

Non-verbal EF explained more variance in morphosyntactic abilities than vice versa in both the DLD and TD group. This was because adding EF to the model predicting morphosyntax resulted in

a larger change in R^2 and a larger β than when morphosyntax was added as a predictor to the model for EF. This finding can be interpreted in two ways. On the one hand, it suggests that it is unlikely that non-verbal EF deficits of children with DLD can be fully attributed to their language impairment. However, on the other hand, these findings can be taken as an indication that the language tasks used to measure morphosyntax require a substantial amount of attention and WM abilities, which is likely the case (e.g., Fortunato-Tavares et al., 2015). The CELF subtest Recalling Sentences indeed requires children to retain information in WM, but, as this concerns verbal information, this would presumably call primarily on verbal WM (Baddeley & Hitch, 1974; Baddeley, 2003). Given the fact that our WM task was visuospatial, this would not directly explain this link. It is possible that our finding of impaired visuospatial WM reflects a limited amount of processing resources that may be shared by verbal and non-verbal EF. This underlying processing deficit would then explain impairments in both verbal and non-verbal domains (e.g., Hoffman & Gillam, 2004; Kail, 1994; Im-Bolter et al., 2006), and, in turn, could impact children's morphosyntactic task performance.

In the TD children, vocabulary explained more variance in EF than vice versa, in line with the direction of the effect observed in older children (Blom & Boerma, 2019). For the DLD children, vocabulary was not related to EF, although a marginal trend was observed in the same direction as for the TD children. The absence of evidence for an effect in the DLD group is discussed above.

Taken together, these findings provide tentative support for the idea that non-verbal EF deficits either stem from the same underlying cause that leads to language impairment or may even causally be related to language impairment. The individual variability seen in the EF abilities of children with DLD, however, precludes the proposal that these EF deficits are a causal factor in language impairment of all children with DLD (Kapa & Erikson, 2019). Rather, it is likely that the co-occurrence of language and EF deficits stem from a shared underlying etiology (Bishop et al., 2014), although it is not unlikely that EF deficits hamper language development (Kapa & Plante, 2015).

Implications, strengths, limitations, and future directions

The presence of non-verbal EF impairments in DLD may have important clinical implications. If EF deficits, both verbal and non-verbal, are in fact part of the clinical profile of many children with DLD, clinicians should be aware of these deficits and the effect these might have on assessment and intervention (Archibald, 2018). Non-verbal EF impairments may also be indicative of a poorer prognosis, that is a more severe and persistent DLD (Blom & Boerma, 2020; Nickish & von Kries, 2009).

This study had a relatively large sample size and focused on preschool children in whom both EF and language are still rapidly developing, making this the optimal age range for early intervention. Furthermore, we used tests gauging multiple EF domains, especially those relevant in early development (Garon et al., 2008). An important limitation of this study, however, is the lack of longitudinal data. By comparing the change in explained variance in regression models in both directions, we tried to gain insight into the direction of the relationship. However, longitudinal data is needed to draw solid conclusions about the direction of this relationship during various stages of development (Bishop, 1997).

Despite the lack of longitudinal data, we tried to gain insight into the direction of the relationship between EF and language by comparing the change in explained variance in regression models in both directions. Our finding showing that EF explained more variance in morphosyntax than vice versa support the idea that EF may play a role in supporting language development. This could imply that language abilities may be improved by targeting EF abilities in intervention. Indeed, there is tentative evidence to suggest that specifically WM may be a promising target for intervention programs for children with DLD (Delage et al., 2021; Henry et al., 2022; Maleki Shahmahmood et al., 2018; Stanford et al., 2019). However, it should be noted that two of these studies targeted only verbal WM (Henry et al., 2022; Maleki Shahmahmood et al., 2018) and the other two targeted both verbal and non-verbal elements (Delage et al., 2021; Stanford et al., 2019). In addition to the fact that these intervention effects need to be corroborated in larger samples, it remains unclear whether specifically targeting non-verbal EF would also benefit language

outcomes and more research is needed to be able to draw any conclusions about the possibility of strengthening language skills through non-verbal EF training.

Looking at the relationship between EF and language, the current study used latent factors in the analyses, while making a distinction between vocabulary and morphosyntax, as these language domains may rely on different learning mechanisms (e.g., Bates & Goodman, 1997; Gleitman, 1990) and may differ in how they are related to EF (Blom & Boerma, 2019; Kaushanskaya et al., 2017). In contrast to some previous studies, we used two tasks for both vocabulary and morphosyntax, thereby reducing measurement error. However, it should be noted that we used one expressive and one receptive task for the vocabulary factor, whereas both tasks for the morphosyntax factor were expressive tasks. Future research should preferably use an even larger number of tasks covering both receptive and expressive abilities across different domains.

In contrast to language, we did not make a distinction between EF domains, but used one latent variable including two EF domains that have been argued to be particularly relevant to language development (Montgomery et al., 2021). We opted for a latent EF factor, because EF has been shown to be undifferentiated in early childhood (Brydges et al., 2012; Wiebe et al., 2008), although not unequivocally (Miller et al., 2012; Usai et al., 2014; Van der Ven et al., 2013). Moreover, the use of latent factors limits the number of predictors in the regression models, in turn increasing power. Our latent factor approach, however, does not allow us to draw conclusions about differential relations between specific EF and language domains. Future research using separate latent factors for the various EF domains can provide more insight into the exact nature of the processes underlying EF and language development.

The mixed outcomes in the literature with regard to non-verbal EF impairments and their relationship with language abilities of children with DLD may in part be the result of methodological differences between studies, such as the tasks used (e.g., Blom & Boerma, 2020; Boerma & Blom, 2020), but are likely also due to the large etiological and phenotypical variability seen in children with DLD (Bishop, 2001; Conti-Ramsden & Durkin, 2015; Leonard, 2014; Rice,

2012). Recent studies have shown that a wide variety of genetic variants may be implicated in the etiology of DLD (Plug et al., 2021; Reader et al., 2014; Simpson et al., 2015). This supports the idea that the population of children with DLD consists of many smaller etiological subgroups. More research into the underlying genetic and neurobiological etiology of DLD will be crucial to better understand language impairment, the factors that are implicated in it, and to support adequate intervention strategies (Newbury & Monaco, 2010).

Conclusion

There is ample evidence for verbal EF deficits in children with DLD, but whether non-verbal EF is also impaired in children with DLD is still under debate. Here, we report impaired non-verbal EF in preschool children with DLD as compared to TD peers. Non-verbal EF was significantly related to morphosyntax in both children with DLD and TD children, but to vocabulary only in the TD group. Moderation analysis, however, revealed no significant differences in these relationships between the groups. This study provides evidence for non-verbal EF impairments and a relationship between language and non-verbal EF abilities in preschool children with DLD. This has clinical implications with regard to intervention and prognosis.

Chapter 2 – Supplementary material

Appendix 2-A – Diagnostic criteria for DLD

In the Netherlands, where this study took place, children are assessed during routine follow-up every few months the first few years of their life (accessible for everyone, free of charge). Children for whom there are concerns about hearing and/or language development are referred to a certified audiological center, where their hearing, non-verbal IQ, and language abilities are assessed. A child can receive the diagnosis DLD if the child has persistent language difficulties that cannot be attributed to hearing loss, general developmental delay, or insufficient input (Nederlandse Vereniging voor Logopedie en Foniatrie, 2015). Children with severe DLD can be eligible for intervention and support in the form of early intervention day-care, special education, or ambulatory care in regular education when they meet following official criteria (Stichting Siméa, 2017):

- A score of at least 2 *SD* below the normed mean of a general standardized language assessment (e.g., the Core language Index of CELF Preschool-2-NL or CELF 4-NL);
- Or scores of 2 *SD* below the normed mean in one domain (speech production or perception, pragmatics, grammar, semantics) on 2 subtests of a standardized language assessment;
- Or scores of 1.5 *SD* below the normed mean in two or more domains on two or more subtests of a standardized language assessment;

Or scores of 1.3 *SD* below the normed mean in at least three language areas on two or more subtests of a standardized language assessment.

If children meet these criteria, they receive an indication for intervention and support in the form of specialized day-care, special education, or speech-language therapy and extra assistance in regular education. All children with DLD in the current study had received such an indication and were enrolled in one of these forms of intervention and support at the time of participation.

Appendix 2-B – Group comparison on raw and norm scores of each language measure separately

Table 2.5. Group comparison on raw and norm scores of language tasks with ANCOVAs while controlling for *Age*, *Sex*, *IQ*, and *SES*.

	DLD			TD			
	n	*M*	*SD*	*n*	*M*	*SD*	
WS raw	62	8.8	4.2	76	16.6	4.2	$F(1, 132) = 104.97$, $p < .001$, $\eta_p^2 = .44$
RS raw	62	6.5	3.7	75	19.9	8.1	$F(1, 131) = 136.42$, $p < .001$, $\eta_p^2 = .51$
EV raw	61	18.8	7.5	76	26.9	6.9	$F(1, 131) = 49.43$, $p < .001$, $\eta_p^2 = .27$
PPVT raw	63	62.7	13.6	76	71.7	15.8	$F(1, 133) = 13.27$, $p < .001$, $\eta_p^2 = .09$
WS norm	62	4.4	2.5	76	10.9	2.9	$F(1, 132) = 88.08$, $p < .001$, $\eta_p^2 = .40$
RS norm	62	4.6	1.7	75	10.0	2.4	$F(1, 131) = 130.20$, $p < .001$, $\eta_p^2 = .50$
EV norm	61	6.2	2.4	76	10.6	2.4	$F(1, 132) = 52.70$, $p < .001$, $\eta_p^2 = .29$
PPVT norm	63	95.8	10.4	76	109.0	11.7	$F(1, 133) = 13.01$, $p < .001$, $\eta_p^2 = .09$

Abbreviations: DLD = Developmental Language Disorder, EV = Expressive Vocabulary, SD = Standard Deviation, PPVT = Peabody Picture Vocabulary Test, RS = Recalling Sentences, TD = Typically Developing, WS = Word Structure.

Note. Raw scores of the tests can range as follows: WS: 0-23, RS: 0-39, EV: 0-40, PPVT: 0-204. The norm scores of the CELF subtests (WS, RS, EV) can range from 1-19 with a mean of 10 and an *SD* of 3 and the PPVT norm scores can range from 55-145 with a mean of 100 and an *SD* of 15.

Appendix 2-C – Correlations between the latent language factors and the separate EF tasks and the latent EF factor.

Table 2.6. Partial correlations controlling for age between both latent language factors and each EF tasks per group.

		Morphosyntax			Vocabulary		
		n	*r*	*p*	*n*	*r*	*p*
SA	*DLD*	**61**	**.28**	**.024**	**60**	**.41**	**.001**
	TD	**74**	**.24**	**.040**	**75**	**.27**	**.020**
Corsi FW	*DLD*	53	.22	.10	53	.15	.28
	TD	71	.03	.81	72	.09	.43
Corsi BW	*DLD*	**51**	**.30**	**.032**	51	.17	.22
	TD	**71**	**.27**	**.021**	71	.23	.053
HTKS	*DLD*	**33**	**.48**	**.004**	**32**	**.40**	**.018**
	TD	61	.02	.89	61	.17	.18
Latent EF	*All*	128	**.52**	**<.001**	125	**.53**	**<.001**
	DLD	51	**.33**	**.017**	51	**.36**	**.008**
	TD	71	**.31**	**.007**	71	**.33**	**.004**

Abbreviations: BW = Backward, DLD = Developmental Language Disorder, FW = Forward, HTKS = Head-Toes-Knees-Shoulders Task, SA = Selective Attention, TD = Typically Developing.

Note. Significant results in bold.

Appendix 2-D – Correlations between the EF tasks

Table 2.7. Partial correlations controlling for age between the non-verbal EF tasks for both groups.

	1. SA	2. Corsi FW	3. Corsi BW	4. HTKS
1.	-	*r*(72) = .16, *p* = .18	*r*(71) = .04, *p* = .76	*r*(61) = .18, *p* = .28
2.	***r*(54) = .35, *p* = .009**	-	***r*(71) = .32, *p* = .006**	*r*(60) = .16, *p* = .23
3.	*r*(52) = .01, *p* = .96	***r*(52) = .35, *p* = .010**	-	*r*(60) = .06, *p* = .65
4.	*r*(34) = .22, *p* = .20	*r*(32) = .32, *p* = .064	*r*(31) = .34, *p* = .051	-

Abbreviations: BW = Backward, FW = Forward, HTKS = Head-Toes-Knees-Shoulders Task, SA = Selective Attention.

Note. DLD group below the diagonal, TD group above the diagonal. Significant correlations in bold. All Pearson correlations (without partialling out age) are significant in both groups.

Appendix 2-E – Correlations of the latent factors with demographic variables

Table 2.8. Correlations with demographic variables.

		Age			SES			IQ		
		n	*r*	*p*	*n*	*r*	*p*	*n*	*r*	*p*
Morphosyntax	*All*	141	**.45**	**<.001**	138	**.47**	**<.001**	140	**.35**	**<.001**
	TD	77	**.75**	**<.001**	76	**.27**	**.017***	76	.18	.12*
	DLD	64	**.65**	**<.001**	62	.15	.24	64	.17	.17
Vocabulary	*All*	141	**.72**	**<.001**	138	**.29**	**<.001**	140	**.32**	**<.001**
	TD	78	**.83**	**<.001**	77	**.25**	**.028***	77	**.25**	**.028**
	DLD	63	**.82**	**<.001**	61	-.00	.97	63	.17	.18
EF	*All*	129	**.68**	**<.001**	127	**.22**	**.01**	129	**.33**	**<.001**
	TD	74	**.78**	**<.001**	73	.11	.35	74	**.26**	**.024**
	DLD	55	**.68**	**<.001**	54	.11	.41	55	**.28**	**.038***

Abbreviations: DLD = Developmental Language Disorder, EF = Executive functioning, IQ = Intelligence Quotient, SES = Socio-Economic Status, TD = Typically Developing.

Note. * indicates Spearman's Rho as these non-parametric outcomes differed from the Pearson correlation. Pearson correlations were as follows: TD Morphosyntax-SES: *r*(76) = 0.19, *p* = .094; TD Vocabulary-SES: *r*(77) = 0.16, *p* = .18; TD Morphosyntax-IQ: *r*(76) = 0.24, *p* = .036; DLD EF-IQ: *r*(55) = 0.21, *p* = .13.

Appendix 2-F – Comparison of demographic variables of children who completed the HTKS and those who did not for both groups

Table 2.9. Group comparison of demographic variables between children with complete data and children with incomplete data for the Broad EF task for both the DLD and TD group.

		HTKS complete		**HTKS missing**		
		M	*SD*	*M*	*SD*	
Age	*DLD*	5.3	0.5	4.1	0.7	**$t(63) = 7.26$, $p < .001$, $d = 1.82$**
	TD	4.9	0.8	3.4	0.2	**$t(71.40) = 13.78$, $p < .001$, $d = 2.19$**
Sex	*DLD*	*n* f/m = 5/32		*n* f/m = 8/20		$\chi^2(1) = 2.26$, $p = .13$, $V = .19$
	TD	*n* f/m = 36/28		*n* f/m = 8/6		$\chi^2(1) = .00$, $p = .95$, $V = .01$
IQ	*DLD*	97.6	12.4	97.9	13.9	$t(63) = -.09$, $p = .93$, $d = -.02$
	TD	106.6	12.2	105.5	17	$t(75) = .27$, $p = .80$, $d = .08$
SES	*DLD*	6.3	1.6	6.3	1.6	$t(61) = -.07$, $p = .95$, $d = -.02$
	TD	7.9	1.3	7.6	1.6	$t(75) = .85$, $p = .40$, $d = .25$
CLI	*DLD*	76.9	13.2	76.8	11.6	$t(61) = .03$, $p = .98$, $d = .01$
	TD	106.3	12.9	106.6	12.8	$t(76) = -.10$, $p = .92$, $d = -.03$

Abbreviations: CLI = CELF Core Language Index, DLD = Developmental Language Disorder, IQ = Intelligence Quotient, SD = Standard Deviation, SES = Socioeconomic status, TD = Typically Developing.

Note. Significant outcomes in bold.

Appendix 2-G – Baseline regression models

Table 2.10. Baseline regression models, that is only including the covariates (*Age*, *Sex*, *IQ*, and *SES*), for the DLD and TD group for both latent language variables and the latent EF factor.

		DLD				TD		
	B	*SE B*	*β*	*p*	*B*	*SE B*	*β*	*p*
Morphosyntax	***Step 1***							
Constant	-3.926	.649		.000	-3.554	.594		.000
Age	.490	.085	.664	**<.001***	.607	.066	.713	**<.001***
Sex	-.199	.143	-.162	.169	-.187	.119	-.122	.119
IQ	.007	.005	.171	.125	.007	.004	.124	.113
SES	.067	.036	.202	.072	.114	.045	.200	**.014***
Vocabulary	***Step 1***							
Constant	-5.666	.743		.000	-5.604	.601		.000
Age	.869	.098	.814	**<.001***	.834	.067	.795	**<.001***
Sex	-.064	.163	-.036	.698	-.155	.120	-.082	.202
IQ	.008	.005	.138	.118	.015	.005	.207	**.002***
SES	.056	.042	.116	.188	.095	.046	.134	**.042***
EF	***Step 1***							
Constant	-7.462	.927		.000	-5.445	.733		.000
Age	.908	.122	.720	**<.001***	.877	.081	.779	**<.001***
Sex	.121	.204	.057	.556	-.081	.147	-.040	.582
IQ	.021	.007	.292	**.002***	.018	.006	.241	**.001***
SES	.062	.052	.109	.237	-.040	.056	-.053	.474

Abbreviations: B = unstandardized regression coefficient, β = standardized regression coefficient, DLD = Developmental Language Disorder, EF = Executive functioning (latent factor), IQ = Intelligence Quotient, SE = Standard Error, SES = Socioeconomic Status, TD = Typically Developing.

Note. Significant outcomes in bold and * $p < .05$.

Chapter 3

The language profile of preschool children with 22q11.2 deletion syndrome and the relationship with speech intelligibility.

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Abstract

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.

Key words: *22q11DS; DiGeorge syndrome; language disorder; standardized language assessment; speech intelligibility.*

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., 2019), 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; Persson et al., 2006; Moss et al., 1999; 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 et al., 1999; for an overview see 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 (Gerdes et al., 1999; Mills et al., 2006; 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; Gerdes et al., 2001; Solot et al., 2001). 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 assessments 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., 2019). 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; Jackson et al., 2019; Persson et al., 2003; Solot et al., 2019).

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; Gerdes et al., 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 3-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 3.1.

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.

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)

Table 3.1. 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		80		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	59	18	41	-	-
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. 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 (Wechsler & Naglieri, 2008). 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 3-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).

1 The Snijders-Oomen Non-verbal IQ test (SON-R) is a standardized non-verbal IQ test, which is often used in the Netherlands and has been objectively evaluated as valid and reliable with a high correlation with other IQ tests such as the WPPSI and WISC.

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: 0.71 with the verbal IQ component of the Wechsler Preschool and Primary Scale of Intelligence (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 3-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 3-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*, *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 comparisons 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 (Wiig et al., 2012). 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 and 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; $t(21.62) = -2.31$, $p = .031$, $d = .78$, 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; $U = 98.5$, $p = .036$, $r = -.42$, 95% CI [-1.0 – -6.46]). There was no difference between these groups in sex distribution ($\chi^2(1) = 0.01$, $p = .94$, $V = .06$), parental

education (t(20.95) = -1.14, p = .27, d = .39, 95% CI [-1.94 – 0.57]), or IQ scores (t(14.52) = -1.59, p = .13, d = .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 3.1 and appendix 3-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 = .58, 95% CI[1.97 –8.81]). Scores on the CELF RLI and ELI were strongly correlated (r(31) = .75, p < .001, 95% CI [0.55 – 0.88]).

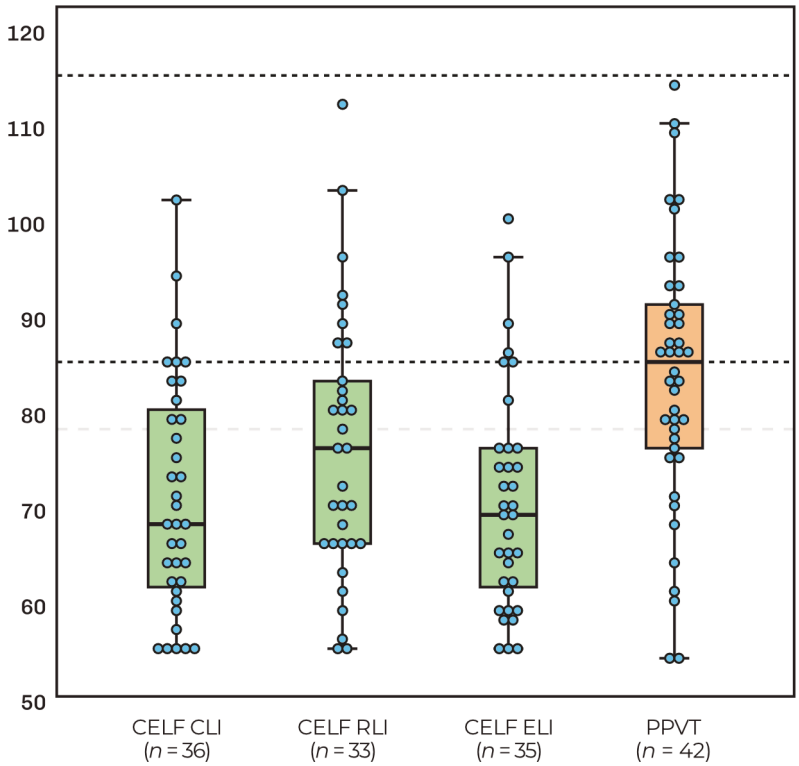

Figure 3.1. Box and whisker plot (boxplot with individual data points) for the three CELF index scores (green) and the PPVT (orange)[a].

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.

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 3.2). 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.

Table 3.2. 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

Lastly, parents reported a delayed production of the first word and sentence in 23 (52%) and 34 (78%) children, respectively (see Figure 3.2).

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 = -.03, *p* = .80).

Table 3.3. 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 R²***
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 3.3). 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.

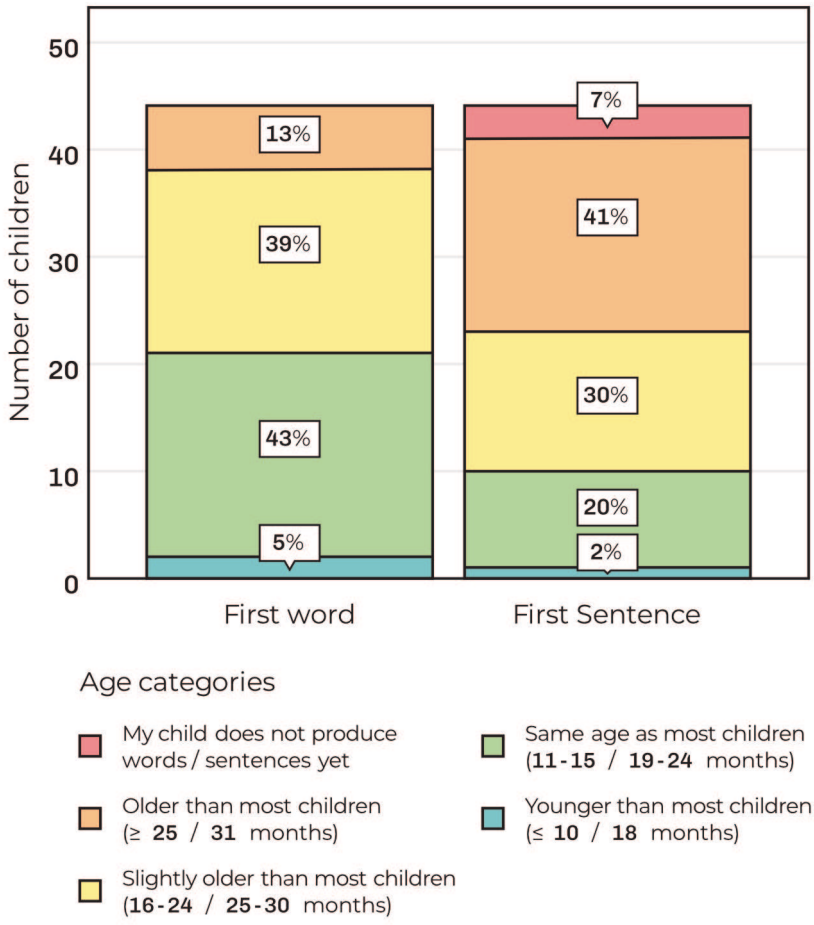

Figure 3.2. Stacked bar chart with percentages of children in a specific age category during which the first word or sentence was produced based on parental report[1].

1. Answer-categories were based on three parameters from the Van Wiechen-Developmental screening instrument (Laurent de Angulo et al., 2005; see appendix 3-D). The ages between the brackets indicate the cut-off for words before the slash and for sentences after the slash.

Intelligibility scores were weakly to moderately correlated with language outcomes (CELF CLI: τ_b = .35, p = .005; CELF RLI: τ_b = .33, p = .016; CELF ELI: τ_b = .32, p = .012; PPVT: τ_b = .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 3.3).

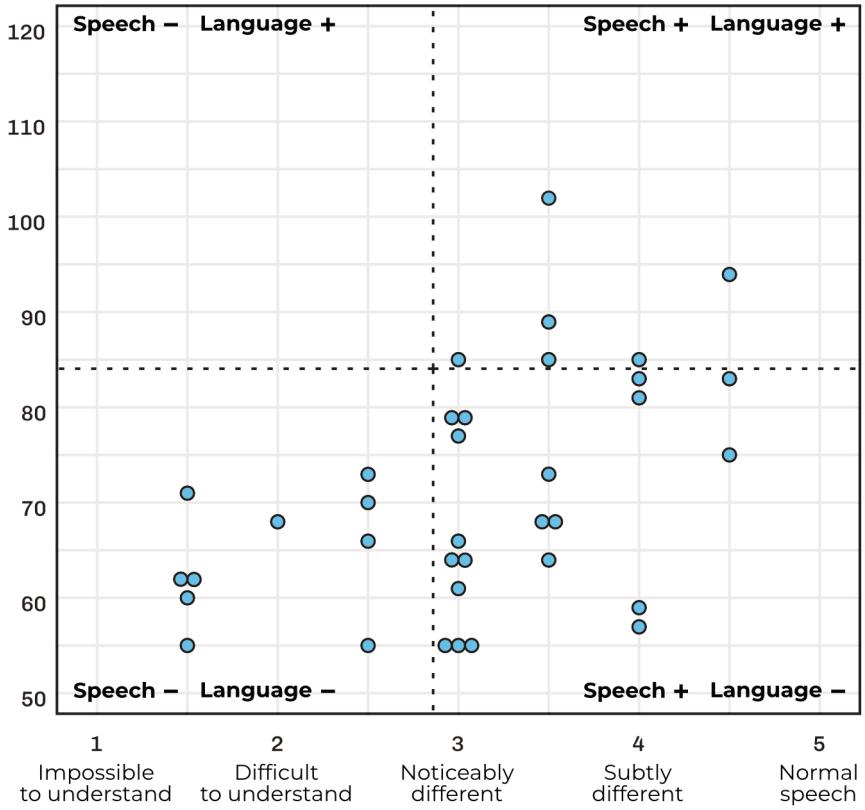

Figure 3.3. Core Language Index score[a] in relation to speech intelligibility scores[b] and classification of individuals based on these scores into different categories[c].

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. The quadrants represent 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; Gerdes et al., 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., 2000; Solot et al., 2001). 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; Gerdes et al., 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 (see recommended best practices by Solot et al., 2019) 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; Snijder 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., 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 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., 1999; 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., 2017).

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.

Chapter 3 – Supplementary material

Appendix 3-A.

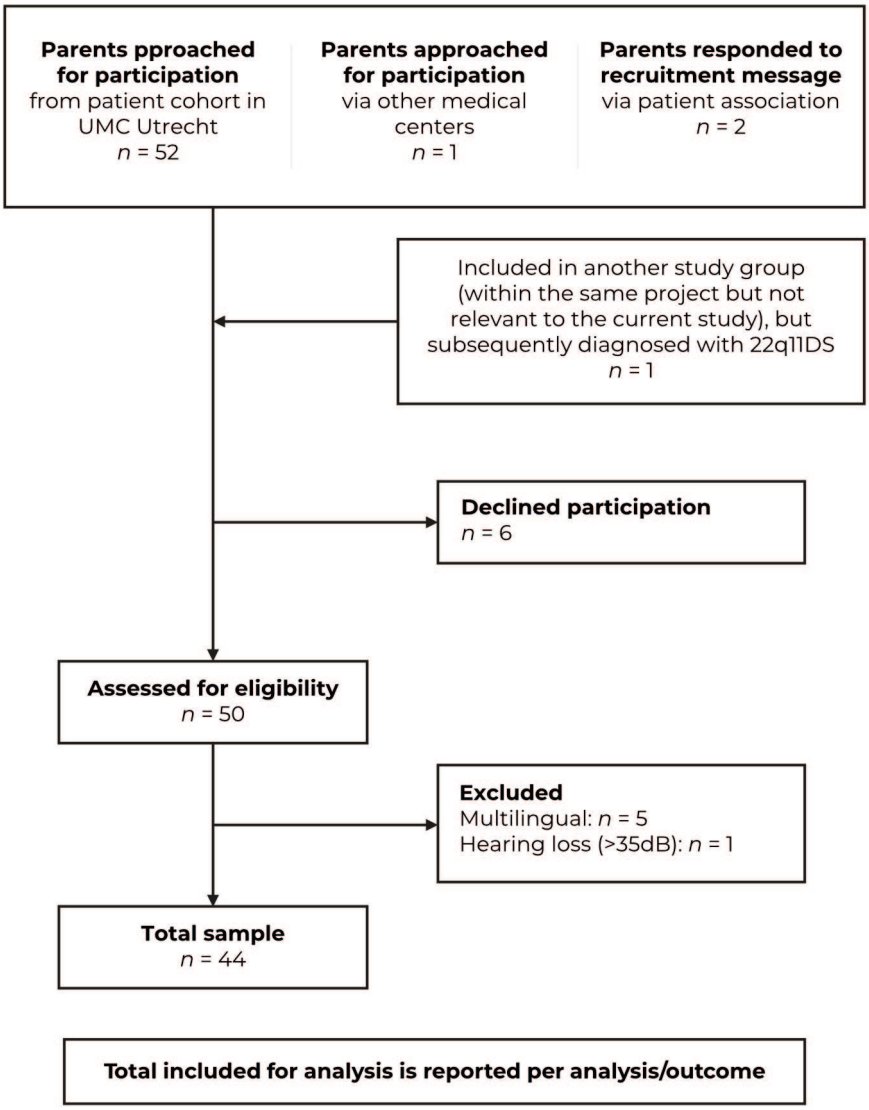

Figure 3.4. Flowchart of participant enrollment and inclusion.

Note. The patient cohort is based at the national multidisciplinary outpatient clinic for children with 22q11DS at the University Medical Utrecht, the Netherlands. 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 3-B.

Table 3.4. The highest attained educational level[a] for both mother and father as compared to the average Dutch population[b].

	Mother		Father		Dutch population
	n	%	*n*	%	%
Category *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 3-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 3.5.

- 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 3.5. 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 3-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, the 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 3-E.

Table 3.6. Task completion, mean scores, *SD*, 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, SD = Standard Deviation.

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.

Chapter 4

Grammatical skills of children with 22q11.2 deletion syndrome in comparison with children with Developmental Language Disorder: Evidence from spontaneous language and standardized assessment.

Boerma, T., Everaert, E., Vlieger, D., Steggink, M., Selten, I., Houben, M., Vorstman, J., Gerrits, E., & Wijnen, F. (2023). Grammatical skills of Dutch children with 22q11.2 Deletion Syndrome in comparison with children with Developmental Language Disorder: Evidence from spontaneous language and standardized assessment. *Frontiers in Communication*, 8:1111584. https://doi.org/10.3389/fcomm.2023.1111584

Abstract

Background. Virtually all children with 22q11.2 deletion syndrome (22q11DS) experience language difficulties, next to other physical and psychological problems. However, the grammatical skills of children with 22q11DS are relatively unexplored, particularly in naturalistic settings. The present research filled this gap, including two studies with different age groups in which standardized assessment was complemented with spontaneous language analysis. In both studies, we compared children with 22q11DS to children with Developmental Language Disorder (DLD), for whom the origin of language difficulties is unknown.

Methods. The first study included 187 preschool children (*n* = 44 with 22q11DS, *n* = 65 with DLD, *n* = 78 typically developing; TD). Standardized assessment consisted of grammar and vocabulary measures in both expressive and receptive modality. Spontaneous language during a play session was analyzed for a matched subsample (*n* = 27 per group). The second study included 29 school-aged children (*n* = 14 with 22q11DS, *n* = 15 with DLD). We administered standardized tests of receptive vocabulary and expressive grammar, and elicited spontaneous language with a conversation and narrative task. In both studies, spontaneous language measures indexed grammatical accuracy and complexity.

Results. Spontaneous language analysis in both studies did not reveal significant differences between the children with 22q11DS and peers with DLD. The preschool study showed that these groups produced less complex and more erroneous utterances than TD children, who also outperformed both groups on the standardized measures, with the largest differences in expressive grammar. The children with 22q11DS scored lower on the receptive language tests than the children with DLD, but no differences emerged on the expressive language tests.

Discussion. Expressive grammar is weak in both children with 22q11DS and children with DLD. Skills in this domain did not differ between the groups, despite clear differences in etiology and cognitive capacities. This was found irrespective of age and assessment method, and highlights the view that there are multiple routes to (impaired) grammar development. Future research should investigate if interventions targeting expressive grammar in DLD also benefit children with 22q11DS. Moreover, our findings indicate that the receptive language deficits in children with 22q11DS exceed those observed in DLD and warrant special attention.

Keywords: *22q11.2 deletion syndrome; Developmental Language Disorder; spontaneous language; standardized language assessment; grammar; school-age; preschool*.

Introduction

The 22q11.2 deletion syndrome (22q11DS) is a genetic condition, which leads to multiple physical and psychological problems, including congenital heart defect and low intellectual functioning (McDonald-McGinn et al., 2015). Although phenotypic expression is heterogeneous, speech and/or language problems are reported in 95% of the children with 22q11DS (Solot et al., 2019), making this one of the most common features of the syndrome. The language problems in children with 22q11DS have, however, almost exclusively been described with standardized tests. Very few studies have analyzed children's spontaneous language, even though this is a more ecologically valid way to evaluate language development and can be used to set therapy goals (Klatte et al., 2022). The current study aimed to fill this gap.

In addition, we compared the language abilities of children with 22q11DS to children with Developmental Language Disorder (DLD). Similar to children with 22q11DS, children with DLD have severe difficulties with learning language. However, their language difficulties exist in the absence of the challenging physical and cognitive conditions that we see in 22q11DS. As of yet, there are no direct, large-scale comparative studies of children with 22q11DS and children with DLD. Such comparisons are meaningful to determine whether interventions for children with DLD may also be suited for children with 22q11DS. Moreover, given the etiological differences between the groups, it can enhance our understanding of the mechanisms underlying language impairment. We therefore conducted two studies, comparing the spontaneous language of both preschool and school-aged children with 22q11DS to peers with DLD. Moreover, we analyzed the results of a number of standardized language tests. In the study with preschool children, we also included a typically developing (TD) control group. In both studies, we focused on the domain of grammar, as this is a hallmark deficit in DLD, while relatively unexplored in 22q11DS.

22q11.2 deletion syndrome

22q11DS is caused by a microdeletion on the long arm ('q') of chromosome 22, with the name thus referring to its genetic cause.

The syndrome was previously also called Velo-Cardio-Facial, DiGeorge or Shprintzen syndrome, but we now know that these conditions are all due to the same genetic deletion: 22q11DS (McDonald-McGinn et al., 2015). It is the most frequently occurring genetic syndrome after Down syndrome, with an incidence of 1 in 2,148 live births (Blagojevic et al., 2021). Despite the relatively uniform etiology, individuals with 22q11DS differ greatly in symptom expression. Over 180 manifestations have been associated with the syndrome (McDonald-McGinn et al., 2015). Congenital heart defects are the most common physical symptom, estimated to occur in up to 75% of the population. Palatal abnormalities, such as cleft palate and velopharyngeal insufficiency, are also frequently observed. In addition, cognitive and psychiatric problems are part of the syndrome. Many individuals with 22q11DS have borderline intellectual functioning or mild intellectual disability (Fiksinski et al., 2022). Moreover, 22q11DS is associated with elevated rates of psychopathology, including attention deficit hyperactivity disorder, autism spectrum disorder, anxiety disorder and psychotic disorder (Schneider et al., 2014).

Language impairment in children with 22q11DS

Next to the symptoms mentioned above, speech-language problems are observed in virtually all children with 22q11DS (Solot et al., 2019) and do not appear to be related to other manifestations of the syndrome, such as congenital heart defect and palatal abnormalities (Gerdes et al., 1999; Solot et al., 2001). In early childhood, it is reported that the first words and sentences emerge relatively late (e.g., Gerdes et al., 1999; Roizen et al., 2007; Solot et al., 2000), with some children even remaining non-verbal until the age of 4 years (Solot et al., 2001). During the preschool age, both expressive and receptive language abilities of children with 22q11DS are significantly weaker in comparison to TD children, as indicated by lower scores on standardized language tests (Everaert et al., 2023; Gerdes et al., 1999; Gerdes et al., 2001; Solot et al., 2001). A recent study (Everaert et al., 2023; **chapter 3** in this dissertation), using the same preschool sample as the current study, for example showed that Dutch children with 22q11DS between 3 and 6.5 years old scored, on average, 2 standard deviations (SD) below the normed mean on a composite measure of

expressive language. For receptive language, this was 1.5 *SD* below the normed mean. The significant difference in the severity of the expressive and receptive language impairment is in line with what is reported in other research with preschoolers (Gerdes et al., 1999; Solot et al., 2001). Next to composite measures, Everaert et al. (2023) also examined subtest outcomes of the standardized assessment and observed pervasive difficulties across language domains, with the lowest scores on expressive morphosyntactic skills. With the exception of Scherer et al. (1999), who showed low lexical diversity in the spontaneous language of 4 children with 22q11DS between 0;6 and 2;6 years old, an investigation of the spontaneous language of preschool children with 22q11DS has not yet been undertaken.

Research on school-age children with 22q11DS also used standardized language assessment and indicates that language impairment in 22q11DS is persistent, both in production and comprehension (Glaser et al., 2002; Moss et al., 1999; Rakonjac et al., 2016; Solot et al., 2001; Van den Heuvel et al., 2018). Language impairment even goes beyond what is expected based on children's level of intellectual functioning (Glaser et al., 2002; Persson et al., 2006; Van den Heuvel et al., 2018), in agreement with what is found for preschoolers (Gerdes et al., 1999; Scherer et al., 1999). However, in contrast to preschool children, school-age children with 22q11DS are reported to have weaker receptive than expressive language and relatively strong expressive morphosyntactic abilities (Glaser et al., 2002; Van den Heuvel et al., 2018). These contrasting findings may reflect unique developmental trends for different language modalities and domains, although more research is needed to confirm this.

Next to reporting standardized test scores, a number of studies with school-age children with 22q11DS have examined children's language profile in more detail. Van den Heuvel et al. (2018) conducted a fine-grained error analysis of two standardized tests of expressive syntax. Difficulties interpreting and using contextual cues were found to characterize the errors of their 6- to 13-year-old participants with 22q11DS on these tasks. In addition, three studies reported weak narrative abilities of children with 22q11DS at the macrolevel, gauging story structure and information transfer (Persson

et al., 2006; Selten et al., 2021; Van den Heuvel et al., 2017). Persson et al. (2006) also analyzed the microstructural narrative production abilities of their 19 participants between 5 and 8 years old. Grammatical errors were not highly prevalent in the narrative samples, but low grammatical complexity, as indicated by short sentences and few subordinate clauses, was found to be characteristic of the stories that these children told. Van den Heuvel et al. (2017) also reported a reduced sentence length of their 6- to 13-year-old participants with 22q11DS in comparison with TD peers.

22q11DS and Developmental Language Disorder

Given the severe language impairment of children with 22q11DS, which cannot be (fully) explained by cognitive or physical features of the syndrome, it is not surprising that parallels have been drawn with children with DLD. DLD is a neurodevelopmental disorder which primarily affects the ability to learn a native language (Bishop et al., 2017), estimated to occur in 3-7% of the child population (Calder et al., 2022; Norbury et al., 2016; Tomblin et al., 1997). The language difficulties of children with DLD cannot be explained by an obvious cause, such as a biomedical condition, hearing impairment, or intellectual disability. Instead, DLD is thought to arise from the interaction between multiple genetic and environmental risk factors (Bishop, 2009). These risk factors may differ from child to child, making the etiology of DLD heterogeneous. On the phenotypic level, diverse language problems in all language domains can be observed (for an overview, see Gerrits et al., 2017; Leonard, 2014). However, morphosyntactic difficulties, in Germanic languages particularly those related to verbs, are seen as a hallmark deficit and have been proposed as clinical markers that support the identification of DLD (see Leonard, 2014). Such difficulties can be observed in performance on standardized tests or other elicitation probes (e.g., Boerma, Wijnen et al., 2017; Krok & Leonard, 2015; Riches, 2012), but are also often shown in children's spontaneous language. Low grammatical accuracy and complexity in the spontaneous language of Dutch children with DLD is for example reflected by frequent tense and agreement errors, difficulties with argument structure, the over-use of root infinitives, a short sentence length, and the use of few complex

sentences (e.g., Bol & Kuiken, 1988; De Jong, 1999; Verhoeven et al., 2011; Wexler et al., 2004; Zwitserlood et al., 2015).

As DLD per definition precludes a known biomedical condition, children with 22q11DS cannot be diagnosed with DLD. Instead, they may have a so-called 'language disorder associated with X' (Bishop et al., 2017). Despite the different labels, there appears to be substantial clinical overlap between the groups. Children with 22q11DS are often seen and treated by the same professionals that provide treatment for children with DLD (Boerma et al., 2022). It is, however, unclear whether the two groups can be differentiated based on their language profile. Previous research comparing children with DLD and children with 22q11DS is scarce. In their discussion section, Persson et al. (2006) indirectly compared the results from their 22q11DS sample with the results from a different study including children with DLD. They observed similarities across the two groups with respect to sentence length and the production of subordinate clauses, but noticed differences in grammatical accuracy, with lower accuracy for the children with DLD compared to the children with 22q11DS. Three studies directly compared children in the two groups. Kambanaros and Grohmann (2017) conducted a longitudinal case study of a boy with 22q11DS, testing him at age 6 and age 10, and compared him to children with DLD. At the age of 6, the boy produced longer sentences relative to peers with DLD, but at age 10 he scored worse on the comprehension of subject relative clauses. Other measures, including a wide range of standardized tests and experimental tasks, did not differentiate the boy from the children with DLD, neither at age 6 nor at age 10. In addition, Selten et al. (2021), using the same school-aged sample as the current study, examined narrative comprehension and production at the macrolevel of 6- to 10-year-old children with 22q11DS and children with DLD. They did not find a significant difference on any of the narrative measures between the two groups. Using fMRI data from the same children, Vansteensel et al. (2021) even reported comparably reduced brain activation during language processing in both groups.

The current study

Previous research showed that language impairment is a common feature of 22q11DS. Children with 22q11DS experience severe language difficulties across all language domains and in both receptive as well as expressive modality. However, our knowledge of the language profile of children with 22q11DS is almost exclusively based on standardized test performance. While such tests give important information on whether language abilities are age-appropriate, they also have a number of limitations. For example, standardized language assessment does not provide insight into grammatical production skills in real-life situations, some aspects of grammar are difficult to reliably test in a standardized way, and some children may not comply with the necessary behavioral restrictions of standardized testing (Costanza-Smith, 2010; Doedens & Meteyard, 2022; Klatte et al., 2022). The latter may also hold for young children with 22q11DS, as indicated by the task completion rates reported in the study of Everaert et al. (2023). Ideally, standardized language assessment is complemented with the analysis of spontaneous language, which is ecologically valid, can be used with all children, and is considered to be the gold standard for setting therapy goals in the domain of grammar (Heilmann, 2010; Price et al., 2010).

The current study therefore investigated the spontaneous language of children with 22q11DS, aiming to further our knowledge on the syndrome's language profile. In view of the contrasting findings of previous work between preschool and school-age children, we conducted a study with each age group. We complemented spontaneous language analysis with standardized measures and, in the study with preschool children, included a TD control group. In addition, in both studies, we compared the children with 22q11DS to age-matched peers with DLD. This is the first large-scale comparison of a group of children with language problems associated with 22q11DS, a known biomedical condition accompanied by physical and cognitive challenges, and a group of children experiencing language difficulties that are not associated with such challenges. An open question is whether those two groups can be differentiated at the phenotypic level, which may have important implications for both our understanding of the required conditions for language acquisition as

well as for clinical care. We focused on grammar, as weaknesses in this domain are characteristic of DLD. At the same time, relatively little is known about the grammatical skills of children with 22q11DS, especially in naturalistic settings.

Based on previous research (Kambanaros & Grohmann, 2017; Persson et al., 2006), we expected that the grammatical complexity in the language of children with 22q11DS and children with DLD would be comparably low. Moreover, grammatical errors could be more prevalent in the group of children with DLD in comparison with the children with 22q11DS, although the evidence base for this prediction is very limited. For the preschool children, we predicted that both children with 22q11DS and children with DLD would perform below TD peers on all measures, although grammatical accuracy of the children with 22q11DS could be on par with the control group. Finally, although we expected roughly similar results in the preschool and school-age study, we reckoned with the possibility that school-age children with 22q11DS would have relatively stronger grammatical skills than preschoolers, given the previous contrasting findings on expressive morphosyntactic abilities in these age groups (preschool: Everaert et al., 2023; school-age: Glaser et al., 2002; Van den Heuvel et al., 2018).

Study 1: Preschool

Methods

Participants

The children in the preschool study participated in a prospective cohort study ('*3T project*') which examined development in the domains of behavior, cognition and language. Participants were recruited between November 2018 and November 2019. All children were between 3 and 6.5 years of age, grew up monolingually, and had no hearing impairment. The latter two criteria were verified through a telephone interview with parents. The first group, children with 22q11DS (see Everaert et al., 2023; chapter 3 in this dissertation), had a genetically confirmed diagnosis of 22q11DS. They were recruited via the 22q11DS expertise center at University Medical Center Utrecht in

the Netherlands and via the Dutch patient support association. The second group, children with DLD, had been diagnosed with DLD before and independent of the *3T project* by licensed professionals. In the Netherlands, this means that they obtained an overall score of 2 *SD* below the mean on a standardized language test battery or a score of 1.5 *SD* below the mean on two out of four language domains which were tested with at least two measures (for the full protocol, see Stichting Siméa, 2017). Moreover, next to the absence of hearing impairment, they had a non-verbal intelligence of 70 or above. The children with DLD were recruited via organizations that provide care and education services for children with communication difficulties, including Royal Kentalis, Royal Auris, VierTaal and NSDSK. At the time of the study, they all received speech-language therapy at day care or school. Finally, the third group, TD children, did not have documented developmental delays and no family history of language disorders or dyslexia. They were recruited via regular day care centers or elementary schools. Three TD children were excluded, because they obtained a score of more than 1 *SD* below the mean on standardized language assessment that was administered for the purpose of the *3T project*. The final sample included 44 children with 22q11DS, 65 children with DLD and 78 TD children. The demographic characteristics of this sample are presented in Table 4.1. For a description of the prevalence of physical symptoms in our 22q11DS sample and the percentage of children receiving speech-language therapy, we refer to Everaert et al. (2023).

The three groups of children did not differ in age in months ($F(2, 184) =. 97$, $p = .38$, $\eta_p^2 = .01$). However, there were significant differences in sex ($\chi^2(2, n = 187) = 19.6$, $p < .001$, $V = .32$), with relatively more boys in the group with DLD than in the other two groups (in line with what is known on DLD; Tomblin et al., 1997, but see Calder et al., 2022). Intellectual functioning, obtained from medical/school records or assessment by the current researchers, also differed significantly between the groups ($F(2, 181) = 58.04$, $p < .001$, $\eta_p^2 = .39$). The TD children obtained the highest scores, followed by the children with DLD and, finally, the children with 22q11DS (all $p < .001$). The average education level of both parents, measured with an online questionnaire, was also higher for the TD children in comparison with

the 22q11DS and DLD groups ($H(2) = 38.0$, $p < .001$, $\eta^2 = .20$), but did not differ significantly between the latter two groups. The same pattern was observed for global language ability ($F(2, 174) = 142.2$, $p < .001$, $\eta_p^2 = .62$), assessed with the Core Language Index Score of the CELF-Preschool-2-NL (Wiig et al., 2012).

Table 4.1. Demographic characteristics of the preschool participants.

	Sex		Age (months)		IQ [a]		SES [b]		CELF CLI [c]	
	n	*f/m*	*M (SD)*	*Range*	*M (SD)*	*Range*	*M (SD)*	*Range*	*M (SD)*	*Range*
Full sample										
22q11DS	44	19/25	58.4 (12.4)	37-77	80.0 (12.0)	50-103	6.4 (1.8)	2-9	70.8 (12.2)	55-102
DLD	65	13/52	56.7 (9.9)	36-74	97.7 (12.9)	69-124	6.3 (1.6)	3.5-9	76.9 (12.4)	55-107
TD	78	44/34	55.5 (11.0)	36-78	106.4 (13.0)	81-139	7.8 (1.3)	3.5-9	106.3 (12.8)	85-133
Subsample										
22q11DS	27	1-16	54.7 (11.3)	37-73	81.9 (11.4)	50-103	6.9 (1.9)	2-9	73.8 (12.8)	55-102
DLD	27	11-16	54.6 (11.5)	37-74	97.0 (13.8)	70-124	6.3 (1.6)	3.5-9	78.3 (10.3)	60-94
TD	27	11-16	54.4 (11.6)	37-75	104.6 (11.9)	84-131	7.7 (1.3)	5-9	101.3 (8.3)	87-120

Abbreviations: 22q11DS = 22q11.2 deletion syndrome, CELF CLI = Core Language Index of the Clinical Evaluation of Language Fundamentals, DLD = Developmental Language Disorder, IQ = Intelligence Quotient, SD = Standard Deviation, SES = Socioeconomic Status, TD = Typical Development.

a. This information is based on a wide variety of standardized, age-appropriate measures ($M = 100$, $SD = 15$). In the full sample, scores were missing for one TD child and two children with 22q11DS. In the subsample, this was the case for one child with 22q11DS.

b. Parental education is average education level of both parents, measured on a nine-point-scale (1 = no education, 9 = university degree). In the full sample, information was missing for one TD child and two children with DLD. In the subsample, this was the case for one child with DLD.

c. This score of global language ability is a standardized composite ($M = 100$, $SD = 15$) of three language tests from the CELF-Preschool-2-NL. In the full sample, scores were missing for eight children with 22q11DS and two children with DLD. In the subsample, this was the case for four children with 22q11DS.

As can be observed in Table 4.1, a subsample of 27 children in each of the three groups was selected to allow for individual matching on age in months and sex, making the groups as comparable as possible (age in months: $F(2, 78) = .01$, $p = 1.0$, $\eta_p^2 < .01$; sex: $\chi^2(2, n = 81) = .00$, $p = 1.0$, $V = .00$). Spontaneous language was analyzed for this subsample. A child with 22q11DS was matched to a child with DLD and a TD child

from the same sex who were at most 3 months older or younger. Moreover, only TD children were selected who scored in the average range (between 85 and 115) on the Core Language Index. For one matched TD child, the quality of the language sample recording appeared to be too poor. We therefore had to replace this child with another, who did have the right sex and age but who scored above average on global language ability (i.e., 120). Similar to the full sample, the TD children in the subsample obtained higher core language scores than children in the other two groups ($F(2,74) = 50.8$, $p < .001$, $\eta_p^2 = .58$), which, in turn, did not differ from each other. We did not match on intellectual functioning, as differences between the groups are inherent ($F(2, 77) = 22.8$, $p < .001$, $\eta_p^2 = .37$). In the subsample, intellectual functioning of the children with DLD and TD children was not significantly different anymore ($p = .082$), and was higher than the intellectual functioning of the children with 22q11DS (all $p < .001$). Finally, parental education differences between the three groups remained significant ($H(2) = 9.5$, $p = .009$, $\eta^2 = .10$). This effect was driven by differences between the DLD and TD groups ($p = .003$).

Instruments

Standardized language measures

Standardized language measures were used to assess children's abilities in the domains of expressive and receptive grammar. To determine whether grammatical skills are a relative strength or weakness, we also included measures of expressive and receptive vocabulary. Scores of the children with 22q11DS on these tests have been reported in Everaert et al. (2023).

Subtests of the Preschool version of the Clinical Evaluation of Language Fundamentals, CELF-Preschool-2-NL (Wiig et al., 2012), evaluated expressive grammar, receptive grammar and expressive vocabulary. All subtests were administered following the official manual and have a normed mean of 10 ($SD = 3$). Expressive grammar was measured with two subtests, on word level and on sentence level. During the subtest Word Structure, children saw one or two pictures and were asked to complete a sentence uttered by the researcher, thereby eliciting the production of verbs, adjectives, plurals, pronouns

and diminutives. The second subtest of expressive grammar was Recalling Sentences, which is a sentence repetition task with items that increase in length and complexity. This type of task is considered to test syntactic skills (Polišenská et al., 2015). Receptive grammar was measured with the subtest Sentence Structure. Children saw four pictures and were asked to point to the picture that best matched a sentence uttered by the researcher. The test assesses children's understanding of different grammatical structures, including passives, relative clauses, negation and prepositional phrases. Finally, expressive vocabulary was evaluated with the Expressive Vocabulary subtest. Children saw a picture of an object or action and had to label the picture.

Receptive vocabulary skills were assessed with the Peabody Picture Vocabulary Test (PPVT-III-NL; Schlichting, 2005). The test was administered in accordance with the official manual and quotient scores with a mean of 100 (*SD* = 15) are reported. Children saw four pictures and heard a target word. They were asked to point to the picture which corresponded to the target word.

Spontaneous language samples

Spontaneous language of children was collected during a play session of approximately 15 to 20 minutes. The play break followed a standardized protocol and was divided in three parts. In the first part, children played alone with a fixed set of toys, including the Playmobil city life petting zoo set and a number of plastic fruits/vegetables. After a few minutes, or sooner if the child did not speak during this part, the researcher brought a tractor and joined the child. In this second part, the child and researcher played together, but the child remained in charge of what was happening. The researcher was instructed to follow the child, only taking initiative when the child had clear difficulty playing with the toys. After around 10 minutes, the final part of the play break began, in which both the child and researcher colored with crayons. If the child did not speak much, the researcher would ask open-ended questions.

Procedure

The *3T project* was approved by the Medical Research Ethics review board of the University Medical Center Utrecht (CCMO registry nr. NL63223.041.17). Parents of participating children signed an informed consent form. The researchers who worked with the children had a background in linguistics or psychology and were trained using a standardized protocol. Children were individually tested in a quiet room at day care or school. Standardized language tests, cognitive tasks and the play break were administered in a fixed order during two sessions of approximately 45 minutes each. The two test sessions were on separate days and were always administered by the same researcher. The play break was in the second session. This was video-recorded with a GoPro HERO camera and, for adequate audio recordings, a Samson Go Mic portable USB microphone was used. The standardized tests for expressive language were recorded with the same USB microphone and also scored by a second researcher. Discrepancies were discussed and solved by consensus.

The language samples of the 27 children in each of the three groups were transcribed according to the Codes for the Human Analysis of Transcripts (CHAT) conventions (part of CHILDES; MacWhinney, 2000), by trained researchers with a background in linguistics. The T-unit was used as the basic unit of analysis, defined as a main clause with subordinate clauses attached to it (Hunt, 1965). Quality checks were done by the first and senior author to guarantee that the conventions were accurately followed. Moreover, the transcripts were annotated on a separate tier for grammatical accuracy and complexity (see Data analysis). For sake of reliability, the annotations of nine transcriptions (three of each group; 11%) were compared with annotations from a second researcher. Annotation agreement was reached in 94.6% of the T-units.

Data analysis

The analyses were performed in Computerized Language Analysis Software (CLAN, part of CHILDES; MacWhinney, 2000) and SPSS version 28 (IBM Corp., 2013). Univariate ANOVAs were done to compare the three groups on the five standardized language measures. As the groups significantly differed in SES and sex, while

these differences are not inherent to the groups, we also conducted univariate ANCOVA's. The inclusion of the covariates SES and sex did not change the results. Intellectual functioning differences are inherent to the groups and intellectual functioning was therefore not included as a covariate in the analyses (Dennis et al., 2009; Miller & Chapman, 2001). All analyses were done for the full sample as well as the subsample. Results for the subsample did not differ from the results of the full sample and are therefore not reported. As an additional analysis, we conducted paired samples t-tests in the DLD and 22q11DS groups to investigate whether there was a discrepancy between expressive grammar (measured with subtests 'word structure' and 'recalling sentences') and the other language domains. For this analysis, quotient scores of the receptive vocabulary task were transformed to CELF-scores.

The analyses of the spontaneous language samples focused on grammatical accuracy and grammatical complexity and were based on the work of Zwitserlood and colleagues (2015). The main outcome parameters of both categories are presented in Table 4.2 (see Appendix 4-A and 4-B for examples of errors and complex utterance categories). All outcome parameters exclude interjections and communicators (e.g., 'uh', 'yes', 'no'; on average 19% of the total number of a child's utterances), onomatopoeia (2%), unintelligible utterances (6%), as well as incomplete sentences due to trailing off and interruption (2%). Furthermore, the outcome parameters are corrected for length of the included language sample, as this differed per child. That is, all outcome parameters are calculated as proportions, taking into account the total number of T-units (or, in some specific cases, the total number of clauses). Sample length, calculated as the total number of T-units after exclusions, did not significantly differ between the three groups of children (22q11DS: M = 108, SD = 51; DLD: M = 130, SD = 61; TD: M = 122, SD = 61; $F(2,78) = 1.02$, $p = .37$, $\eta_p^2 = .025$).

Next to the outcome parameters presented in Table 4.2, we also report on a number of specific verb-related errors (part of the main parameter '% verb-related errors'), as these errors are known to occur frequently in the spontaneous language of Dutch children with DLD. These specific verb-related errors include (1) the number of subject-

verb agreement errors relative to the total subject-verb agreement attempts, (2) the number of past tense errors relative to the total number of T-units requiring a past tense, (3) the number of root infinitives relative to the number of T-units containing a verb, (4) the omission of an argument (subject, object or other) relative to the number of T-units containing a verb. Comparable to the analyses with the standardized language measures, univariate AN(C)OVA's were done to compare the three groups on all main outcome parameters for grammatical accuracy and grammatical complexity. The inclusion of SES as covariate did not change the results. For the specific verb-related errors and for the main outcome parameter '% complex utterances', we conducted non-parametric tests (Kruskall Wallis H test and, for post-hoc comparisons, Mann Whitney U test), as inspection of the data showed violations of the assumptions of normality and equality of error variances. Effect sizes were interpreted following Cohen (1988).

Results

Standardized language measures

The performance of the three groups of children (full sample) on the standardized tests of grammar and vocabulary is presented in Table 4.3. The results showed significant group effects on all five measures. For receptive grammar ($F(2, 180) = 68.6$, $p < .001$, $\eta_p^2 = .43$), all groups differed significantly from each other (all $p < .001$), with the highest scores for the TD children and the lowest scores for the children with 22q11DS. The TD children also obtained the highest scores on both subtests of expressive grammar (word level: $F(2, 175) = 116.9$, $p < .001$, $\eta_p^2 = .57$; sentence level: $F(2, 173) = 135.3$, $p < .001$, $\eta_p^2 = .61$), but there were no differences between the group of children with 22q11DS and the group of children with DLD on these measures (all $p = 1.00$). Receptive vocabulary showed similar results as receptive grammar ($F(2, 182) = 64.3$, $p < .001$, $\eta_p^2 = .41$), with significant differences between all groups (TD > DLD > 22q11DS; all $p < .001$). Finally, performance on expressive vocabulary ($F(2, 177) = 88.6$, $p < .001$, $\eta_p^2 = .50$) was best for the TD children in comparison to the other two groups. Scores of the children

with 22q11DS and the children with DLD did not differ significantly (p = .09).

Table 4.2. Main outcome parameters of the spontaneous language samples.

	Parameter	Description
Grammatical accuracy		
	% T-units correct	Number of error-free T-units divided by the total number of T-units.
	% Verb-related errors [a]	Number of verb-related errors divided by the total number of clauses.
	% Non-verb-related errors [b]	Number of non-verb-related errors divided by the total number of T-units.
Grammatical complexity		
	MLU	Number of words divided by the total number of T-units.
	MLU 5	Number of words divided by the total number of T-units in the 5 longest T-units.
	% Clauses with a verb	Number of utterances containing a verb divided by the total number of clauses.
	% Complex utterances [c]	Number of complex utterances divided by the total number of T-units.

Abbreviations: MLU = Mean Length of Utterance.

a. Verb-related errors include argument omissions, subject-verb agreement errors, tense errors, root infinitives, verb-second placement errors, overgeneralizations, past participle errors, verb omissions and other verb-related errors which could not be further categorized. Examples can be found in appendix 4-A.

b. Non-verb-related errors include determiner errors, errors with adjectival inflection, preposition errors, pronoun errors, errors with conjunction, plural errors, errors with the pronominal/adverbial 'er ('there/it'), word order errors (not related to verb-second placement), and other non-verb-related errors which could not be further categorized. Examples can be found in appendix 4-A.

c. Complex utterances include subordinate clauses, clauses with conjunction reduction, direct speech, and infinitival clauses. Examples can be found in appendix 4-B.

Comparing the average scores per group across language domains, we see low performance of children with 22q11DS on all measures. For both the children with 22q11DS and the children with DLD, the lowest mean scores are on the two subtests of expressive grammar (close to -2 *SD* below the mean). For the children with DLD, a larger discrepancy between expressive grammar and the other domains are observed than for the children with 22q11DS. Paired samples t-tests between the two expressive grammar subtests on the one hand and the other standardized measures on the other hand

showed significant differences across the board in the DLD group (all $p < .001$), with effect sizes ranging from .79 to 1.73. In the 22q11DS group, significant differences were also observed ($p < .05$), with the exception of 'recalling sentences' in comparison with 'active vocabulary' ($p = .20$) and 'recalling sentences' in comparison with 'sentence comprehension' ($p = .053$). Effect sizes ranged from .22 to .98.

Table 4.3. Performance of the three groups of preschool children on the standardized language measures[a].

	22q11DS			DLD			TD		
	n [b]	*M (SD)*	*Range*	*n*	*M (SD)*	*Range*	*n*	*M (SD)*	*Range*
Receptive grammar	40	5.7 (2.6)	1-10	65	8.1 (3.0)	1-14	78	11.5 (2.5)	7-18
Expressive grammar: word	36	4.3 (3.1)	1-12	64	4.4 (2.5)	1-11	78	10.8 (2.9)	4-17
Expressive grammar: sentence	35	4.8 (2.3)	1-11	64	4.5 (1.7)	1-9	77	10.0 (2.4)	5-15
Receptive vocabulary	42	83.7 (14.0)	55-114	65	96.0 (10.5)	72-120	78	108.9 (11.6)	82-144
Expressive vocabulary	39	5.2 (2.3)	1-10	63	6.3 (2.4)	1-11	78	10.6 (2.4)	6-16

Abbreviations: 22q11DS = 22q11.2 deletion syndrome, DLD = Developmental Language Disorder, TD = Typical Development.

a. Sentence Structure, Word Structure, Recalling Sentences and Expressive Vocabulary of the CELF-Preschool-2-NL ($M = 10$, $SD = 3$) were used to measure receptive grammar, expressive grammar: word, expressive grammar: sentence and expressive vocabulary, respectively. The PPVT-III-NL ($M = 100$, $SD = 15$) was used to test receptive vocabulary.

b. Not all children, particularly children with 22q11DS, were able to complete all tests due to poor task compliance and limited language production (for an elaborate discussion of the task completion rates of the group of children with 22q11DS, see Everaert et al., 2023).

Spontaneous language samples

For each of the three groups, the means and *SD* on all outcome measures for grammatical accuracy and grammatical complexity are presented in Table 4.4.

Table 4.4. Outcomes of the three groups of preschool children on the spontaneous language measures.

	22q11DS		DLD		TD	
	M (SD)	*Range*	*M (SD)*	*Range*	*M (SD)*	*Range*
Grammatical accuracy						
% T-units correct	70.9 (9.6)	52-95	69.3 (7.5)	52-83	82.1 (8.4)	60-100
% Verb-related errors	22.0 (9.7)	4-41	22.2 (8.0)	8-41	10.0 (6.7)	0-29
% Non-verb-related errors	16.8 (6.4)	2-29	20.1 (7.4)	8-34	11.1 (5.7)	0-23
Specific verb-related errors:						
% Subject-verb agreement [a]	8.0 (5.8)	0-23	8.3 (8.4)	0-29	3.6 (3.6)	0-12
% Past tense	6.3 (20.0)	0-100	6.2 (18.6)	0-67	3.6 (8.8)	0-33
% Root infinitives	1.9 (3.8)	0-16	1.9 (3.2)	0-15	.23 (.74)	0-3
% Argument omissions	17.5 (11.5)	0-47	19.3 (11.8)	2-46	5.8 (5.7)	0-25
Grammatical complexity						
MLU	3.0 (.94)	1-5	3.0 (.73)	2-5	3.9 (.62)	03-5
MLU 5	6.6 (2.5)	2-12	6.5 (1.8)	4-11	9.1 (2.6)	4-16
% Clauses with a verb [b]	54.8 (12.6)	25-76	53.6 (13.9)	21-78	65.6 (10.4)	42-78
% Complex utterances	1.2 (2.0)	0-8	1.5 (1.7)	0-6	4.1 (3.1)	0-10

Abbreviations: 22q11DS = 22q11.2 deletion syndrome, DLD = Developmental Language Disorder, TD = Typical Development.

a. One very extreme outlier in the 22q11DS group was excluded (see main text).

b. One very extreme outlier in the 22q11DS group was excluded (see main text).

Grammatical accuracy

Grammatical accuracy was subdivided into three main outcome parameters and four specific verb-related errors. The relative number of error-free T-units is a broad measure of grammatical accuracy, for which a significant effect of Group was observed ($F(2, 78) = 18.0$,

p < .001, η_p^2 = .32). TD children produced relatively more error-free T-units than children with 22q11DS and children with DLD (both p < .001). No significant differences emerged between the latter two groups (p = 1.0). The same pattern was found for the other two main outcome parameters. That is, there were significant effects of Group on both verb-related errors (F(2, 78) = 19.4, p < .001, η_p^2 =.33) and non-verb-related errors (F(2, 78) = 12.9, p < .001, η_p^2 = .25). In comparison with the other two groups, TD children produced relatively less verb-related (both p < .001) and non-verb-related (22q11DS: p = .007; DLD: p < .001) errors. The groups of children with 22q11DS and children with DLD did not differ significantly from each other on either parameter (verb-related: p = 1.0; non-verb-related: p = .20).

Results from the specific verb-related errors showed one very extreme outlier in the 22q11DS group on the proportion of subject-verb agreement errors (scoring 100%). This child was very young (3;1 year old) and produced a limited number of utterances. We excluded this outlier from the analyses, although results with and without the outlier remained the same. The analyses demonstrated significant group effects on the proportion of subject-verb agreement errors (H(2) = 9.3, p = .009, η^2 = .10), root infinitives (H(2) = 12.4, p = .002, η^2 =.13) and argument omissions (H(2) = 27.7, p < .001, η^2 = .33). On all three error categories, TD children scored lower, and thus produced less errors, than children with 22q11DS (subject-verb agreement errors: U = 183.0, z = -3.0, p = .003, r = .41; root infinitives: U = 266.0, z = -2.3, p = .02, r = .31; argument omissions: U = 118.5, z = -4.3, p < .001, r = .58) and children with DLD (subject-verb agreement errors: U = 243.0, z = -2.1, p =.035, r = .29; root infinitives: U = 187.0, z = -3.6, p = .02, r = .49; argument omissions: U = 87.0, z = -4.8, p <.001, r = .65). There were no significant differences between the children with 22q11DS and the children with DLD on these three specific verb-related errors (subject-verb agreement errors: p = .48); root infinitives: p = .22; argument omissions: p = .72). With respect to the number of past tense errors, no significant group effect emerged (p = .80), likely due to the relatively infrequent use of past tense contexts.

Grammatical complexity

Grammatical complexity was subdivided into four main outcome parameters. Results from the analyses on Mean Length of Utterance (MLU) showed significant group effects on both MLU ($F(2, 78) = 13.1$, $p < .001$, $\eta_p^2 = .25$) and MLU 5 ($F(2, 78) = 10.5$, $p < .001$, $\eta_p^2 = .21$). TD children produced longer sentences than children with 22q11DS and children with DLD (all $p < .001$), whereas the latter two groups did not differ in their MLU and MLU 5 (all $p = 1.0$). Another index of grammatical complexity was the proportion of utterances containing a verb. There was one very extreme outlier in the 22q11DS group from a young child (3;4 years old; scoring 1.8%) which was excluded from the analyses; results with and without the outlier remained the same. A significant effect of Group emerged on the proportion of utterances containing a verb ($F(2, 77) = 7.7$, $p < .001$, $\eta_p^2 = .17$), with TD children producing relatively more utterances with a verb than the groups of children with 22q11DS and children with DLD (all $p < .001$), who did not differ ($p = 1.0$). Finally, the same pattern appeared from the proportion of complex sentences ($H(2) = 18.2$, $p = .002$, $\eta^2 = .21$). There were no significant differences between the children with 22q11DS and the children with DLD ($p = .25$), who produced less complex sentences than their TD peers (22q11DS: $U = 147.5$, $z = -3.8$, $p < .001$, $r = .52$; DLD: $U = 174.5$, $z = -3.3$, $p < .001$, $r = .45$).

Study 2: School-age

Methods

Participants

The children in the school-age study participated in a project on language processing and activation in the brain (see Selten et al., 2021; Vansteensel et al., 2021). Participants were recruited between November 2017 and July 2018. The 6- to 10-year-old participants included 14 children with a genetically confirmed diagnosis of 22q11DS and 15 children with an official diagnosis of DLD (for a description of the DLD criteria and protocol used in the Netherlands, see Study 1). All children had either a verbal or non-verbal intellectual

functioning level of 70 or above. Moreover, they did not have hearing loss of more than 35 dB, as determined by pure tone audiometry, nor a diagnosis of autism spectrum disorder. Finally, due to an fMRI scan which was also part of the research protocol (Vansteensel et al., 2021), children were excluded if they had metal objects in their bodies or if they experienced severe anxiety in the scanner. Recruitment procedures were similar to the study with preschool children. Demographic characteristics of the two groups of children are presented in Table 4.5. The two groups did not differ on age in months ($t(27) = .79$, $p = .44$, $d = .29$) and sex ($\chi^2(1, n = 29) = .04$, $p = .84$, $V = .04$). As expected, significant differences in intellectual functioning were observed ($t(1, 20.2) = 6.57$, $p < .001$, $d = 2.48$), with higher levels of the children with DLD relative to the children with 22q11DS.

Table 4.5. Demographic characteristics of the school-aged participants.

	Sex		**Age** (months)		**IQ** [a]	
	n	*Girls/Boys*	*M (SD)*	*Range*	*M (SD)*	*Range*
22q11DS	14	6-8	104.2 (19.1)	80-131	74.0 (8.6)	64-94
DLD	15	7-8	98.4 (20.5)	74-131	105.4 (15.7)	86-136

Abbreviations: 22q11DS = 22q11.2 deletion syndrome, DLD = Developmental Language Disorder, SD = Standard Deviation.

a. This information is based on a wide variety of standardized, age-appropriate measures ($M = 100$, $SD = 15$), obtained from medical/school records or via own administration. Data for one child with DLD was missing.

Instruments

Standardized language measures

We included one standardized measure of expressive grammar and, as a reference, one standardized measure of receptive vocabulary, which were both administered in line with the official manuals. Results from these measures have been reported as background measures in the study of Selten et al. (2021). Similar to the study with preschool children, expressive grammar was tested with a sentence repetition task. The Recalling Sentences subtest of the school-aged version of the CELF, the CELF-IV-NL (Kort et al., 2010), required children to repeat sentences of increasing length and complexity. The

normed scores have a mean of 10 (*SD* = 3). Receptive vocabulary was assessed with the PPVT-III-NL (see Study 1).

Spontaneous language samples

Spontaneous language of children was collected with a narrative task which was preceded by a conversation between the researcher and the participating child. We used the Multilingual Assessment Instrument for Narratives (MAIN) (Gagarina et al., 2012; for the Dutch version, see Blom et al., 2020) to elicit semi-spontaneous language. The MAIN targets narrative abilities of 3- to 10-year-old children and consists of four comparable stories, all matched to six full-color picture sequences. In the current research, the stories 'Cat' and 'Baby Birds' were used. The children first saw the picture sequence belonging to 'Cat'. The researcher told the story and asked the child ten comprehension questions. Subsequently, children saw the picture sequence belonging to 'Baby Birds' and were asked to generate their own story, which was, again, followed by ten comprehension questions. The MAIN can be used to analyze children's understanding and production of story structure (i.e., narrative abilities at the macrolevel; see Selten et al., 2021), but can also be used to examine microstructural narrative skills, including grammatical accuracy and complexity. For the current study, we used the narrative generated by the children, thus excluding children's answers to the comprehension questions, and complemented this with spontaneous language from a preceding conversation. This allowed us to elicit more utterances and to more reliably investigate grammatical skills. The conversation between the researcher and child was about day-to-day topics, such as birthdays, vacations, and hobbies.

Procedure

Ethical approval was obtained from the Medical Research Ethics review board of the University Medical Center Utrecht (CCMO registry nr. NL62366.041.17). Parents of participants gave written informed consent. The researchers who worked with the children were the same as those who worked with the preschool children. The individual test session of approximately one hour took place in a quiet room at the University Medical Center Utrecht. Language tests were

administered in a fixed order. Spontaneous language as well as the standardized test for expressive grammar were recorded with a Samson Go Mic portable USB microphone. With respect to the transcriptions and annotations of the spontaneous language samples, procedures were similar to what has been previously described for the preschool children (see Study 1). A total of 10% of the annotations, randomly selected from three participants with 22q11DS and three participants with DLD, were compared with annotations from a second researcher. Annotation agreement was reached in 91.5% of T-units.

Data analysis

Similar to the preschool study, the analyses were performed in Computerized Language Analysis Software (CLAN; MacWhinney, 2000) and SPSS version 28 (IBM Corp., 2013). Independent samples t-tests were done to compare the children with 22q11DS and the children with DLD on the two standardized language measures. Moreover, a paired samples t-test was done to investigate whether there was a discrepancy between expressive grammar (measured with the subtest 'recalling sentences') and other language domains (in this case, receptive vocabulary). The data-analysis approach of the spontaneous language of the school-age children corresponded to the approach of the study with preschoolers (see Study 1). The mean percentage of excluded utterances was 17% for interjections/ communicators, 1% for onomatopoeia, 4% for unintelligible utterances, and 3% for incomplete sentences. Sample length, calculated as the total number of T-units after exclusions, did not significantly differ between the two groups of children (22q11DS: M = 69, SD = 28; DLD: M = 80, SD = 26; $t(27) = 1.09$, $p = .29$, $d = .41$). Independent samples t-tests compared scores of the two groups on the main outcome parameters for grammatical accuracy and complexity (Table 4.2), as well as on the four specific verb-related error categories. As the groups in the school-age study were small, we provided the full statistics for both significant and non-significant results. Effect sizes were interpreted following Cohen (1988).

Results

Standardized language measures

The mean scores of the children with 22q11DS and the children with DLD on the expressive grammar test were 5.1 (*SD* = 2.2, range = 1-8) and 3.9 (*SD* = 2.0, range = 1-7), respectively. These scores were not significantly different from each other ($t(27) = 1.6$, $p = .13$, $d = .58$). On the receptive vocabulary test, the children with 22q11DS scored, on average, 83.1 (*SD* = 13.7, range = 66-110). The children with DLD had a mean score of 93.2 (*SD* = 13.6, range = 72-117), which fell just short of significance relative to the children with 22q11DS ($t(26) = 2.0$, $p = .06$, $d = .74$). Comparable to the results from the preschool children, the weakest mean scores for both groups were found on expressive grammar. The discrepancy between the expressive grammar and receptive vocabulary scores was larger for the children with DLD than for the children with 22q11DS, as shown by the results of the paired samples t-tests. A significant difference emerged between expressive grammar and receptive vocabulary in the DLD group ($t(14) = 7.0$, $p < .001$, $d = 1.81$), whereas this difference did not reach significance in the 22q11DS group ($t(12) = 1.0$, $p = .08$, $d = .52$).

Spontaneous language samples

For each of the two groups, the means and *SD* on all outcome measures for grammatical accuracy and grammatical complexity are presented in Table 4.6.

Grammatical accuracy

Again, grammatical accuracy was subdivided into three main outcome parameters and four specific verb-related errors. On all three main outcome parameters, no significant differences emerged between the children with 22q11DS and the children with DLD (error-free T-units: $t(27) = .13$, $p = .90$, $d = .05$; verb-related errors: $t(27) = .28$, $p = .78$, $d = .10$; non-verb related errors: $t(27) = .06$, $p = .95$, $d = .02$). Effect sizes were all small. Results from the specific verb-related errors showed one very extreme outlier in the 22q11DS group on the proportion past tense errors (scoring 100% due to one incorrect past tense attempt). We excluded this outlier from the analyses, although

results with and without the outlier remained the same. The analyses demonstrated that the groups did not differ significantly on the proportion of subject-verb agreement errors ($t(27) = .58$, $p = .57$, $d = .22$), past tense errors ($t(26) = .54$, $p = .59$, $d = .21$), and argument omissions ($t(27) = 1.4$, $p = .17$, $d = .52$). The effect sizes were all small, except for the proportion of argument omissions for which a medium effect size was found. The proportion of root infinitives was very small in both groups, so no statistical analyses were performed for this category.

Grammatical complexity

Grammatical complexity was subdivided into four main outcome parameters. The same pattern was observed for all complexity parameters. The children with 22q11DS and the children with DLD did not differ on MLU ($t(22.7) = .55$, $p = .59$, $d = .20$), MLU 5 ($t(27) = .23$, $p = .82$, $d = .09$), the proportion of clauses containing a verb ($t(23.0) = .04$, $p = .99$, $d = .02$) and the proportion of complex sentences ($t(23.0) = .02$, $p = .99$, $d = .01$). Effect sizes were all small.

Discussion

Language impairment is characteristic of children with 22q11.2 deletion syndrome (22q11DS; Solot et al., 2019), next to other physical and psychological symptoms such as congenital heart defect and low intellectual functioning (McDonald-McGinn et al., 2015). However, the language difficulties of children with 22q11DS have almost exclusively been described with standardized language tests, while the analysis of spontaneous language is more ecologically valid and the preferred method for setting therapy goals in the domain of grammar (Klatte et al., 2022). We aimed to contribute to a more complete overview of the language profile of preschool and school-age children with 22q11DS, conducting two studies in which we complemented standardized language testing with the analysis of spontaneous language. In both studies, we compared children with 22q11DS to age-matched children with Developmental Language Disorder (DLD), who also experience severe language difficulties but for whom the cause is unknown. We focused on children's grammatical skills, as these are typically weak in children with DLD (Leonard, 2014) while relatively unexplored in children with 22q11DS.

Table 4.6. Outcomes of the two groups of school-aged children on the spontaneous language measures.

	22q11DS		DLD	
	M (SD)	*Range*	*M (SD)*	*Range*
Grammatical accuracy				
% T-units correct	71.0 (8.8)	58-87	71.4 (8.5)	60-84
% Verb-related errors	17.5 (8.7)	8-35	16.8 (5.8)	9-30
% Non-verb-related errors	19.8 (7.2)	9-33	20.0 (7.7)	8-37
Specific verb-related errors:				
% Subject-verb agreement	5.7 (5.1)	0-17	4.8 (3.3)	0-13
% Past tense [a]	9.1 (10.0)	0-33	11.7 (14.3)	0-43
% Root infinitives	.35 (.74)	0-2	.17 (.46)	0-2
% Argument omissions	4.9 (3.7)	0-12	7.1 (4.7)	2-17
Grammatical complexity				
MLU	5.3 (.67)	5-7	5.1 (1.2)	4-7
MLU 5	11.3 (2.1)	8-15	11.6 (3.3)	8-18
% Clauses with a verb	70.5 (8.0)	49-87	70.4 (11.2)	51-81
% Complex utterances	8.7 (4.9)	2-21	8.7 (8.3)	0-28

Abbreviations: 22q11DS = 22q11.2 deletion syndrome, DLD = Developmental Language Disorder, TD = Typical Development.

a. One very extreme outlier in the 22q11DS group was excluded (see main text).

The language profile of children with 22q11DS

The standardized test results from both the study with preschool children and school-age children confirm that language impairment is common in children with 22q11DS (e.g., Everaert et al., 2023; Solot et al., 2019; Van den Heuvel et al., 2018). Although there was substantial variation within our 22q11DS samples, the mean scores on the

standardized subtests were all more than 1 *SD* below what is expected based on chronological age. In both the preschool and school-age study, the lowest scores were found on the subtests for expressive grammar, with mean scores between 1.7 and nearly 2 *SD* below the mean. Although this contrasts with previous research on school-age children with 22q11DS (Glaser et al., 2002; Van den Heuvel et al., 2018), which reported a relative weakness in receptive grammar and semantics, differences between the mean subtest scores were small and strong conclusions about relative strengths and weaknesses in the language profile of children with 22q11DS can therefore not be drawn (see also Everaert et al., 2023; chapter 3 in this dissertation). In addition, the results from the two studies that we conducted with different age groups do not give reason to assume unique developmental trends for different language domains or modalities in 22q11DS, as was previously suggested (for a discussion, see Van den Heuvel et al., 2018). Although direct comparisons between the age groups should be interpreted with caution, mean norm scores on the two standardized tests that were included in both studies were comparable between the preschool and school-age children with 22q11DS and thus do not point to a developmental shift in the language profile.

The spontaneous language analysis in the preschool study, which included a typically developing (TD) control group, confirmed the findings from the standardized assessments. Hence, the current study shows that language impairment in 22q11DS is also characterized by weak language performance in real-life situations. During play, our 3- to 6-year-old participants with 22q11DS produced shorter and less complex utterances than their age-matched TD peers. They also made more grammatical errors in both verb- and non-verb-related categories. The low complexity of the spontaneous language that we observed in the children with 22q11DS corresponds to previous results from a narrative and a perspective-taking task (Persson et al., 2006; Van den Heuvel et al., 2017). However, the results from the current study diverge from Persson and colleagues (2006) with respect to grammatical accuracy. Their 5- to 8-year-old participants with 22q11DS produced substantially fewer utterances with grammatical errors than both the preschool and school-age

participants with 22q11DS of the current study. This could possibly be explained by a relatively short utterance length of the participants of Persson et al. (2006), which, in turn, could result in fewer grammatical errors. However, Persson et al. (2006) used a narrative task to elicit spontaneous language, which is associated with longer utterances and more errors than elicitation methods such as play or conversation that were used in the current study (e.g., Wetherell et al., 2007). A reverse pattern of findings would have therefore been easier to understand. Note that if we compare our findings to Zwitserlood et al. (2015), a Dutch study which also elicited spontaneous language with a narrative task, we do see differences in the expected direction. The participants of Zwitserlood et al. (2015) produced relatively longer/more complex utterances and made relatively more errors than the participants of the current study, in line with results from research comparing different elicitation methods (e.g., Wetherell et al., 2007).

Comparing children with 22q11DS to children with DLD

The comparisons of the children with 22q11DS to children with DLD pointed towards differences in their respective receptive language skills and similarities in their expressive language abilities. The preschool children with 22q11DS were outperformed by the children with DLD on the standardized receptive language tests of grammar and vocabulary. A trend in the same direction was observed in the school-age study, which only included one receptive language measure (i.e., receptive vocabulary). We did not find significant differences between the children with 22q11DS and children with DLD on the expressive language tests, in either age group. Like the children with 22q11DS, the children with DLD also scored lowest on the subtests measuring expressive grammar, which was to be expected based on what is known about DLD (e.g., Leonard, 2014). A clear discrepancy between the expressive grammar subtest scores and the scores on the other tested domains was only found in the children with DLD.

The analysis of spontaneous language also revealed that expressive grammar is vulnerable in both 22q11DS and DLD. We did not find evidence for a difference on any of the main outcome parameters gauging grammatical accuracy and complexity between

children with 22q11DS and peers with DLD, irrespective of age group. Moreover, the frequency of specific verb-related errors which are known to characterize the spontaneous language of Dutch children with DLD (e.g., De Jong, 1999; Zwitserlood et al., 2015) also did not differ between the groups. In fact, mean scores of the two groups were remarkably close together on many of the outcome variables. This largely confirms the findings from the three previous studies that directly compared children with 22q11DS to children with DLD and also reported substantial overlap between the groups (Kambanaros & Grohmann, 2017; Selten et al., 2021; Vansteensel et al., 2021). Of note, although we were not able to include a TD control group in the school-age study, the overlap in expressive language performance between 22q11DS and DLD suggests that school-aged children with 22q11DS are likely to struggle with language production in naturalistic settings. This confirms the findings in the preschool study.

Implications, limitations, and future directions

Our findings highlight the necessity to regularly assess and monitor the language development of children with 22q11DS as part of routine clinical care, as recommended by Solot and colleagues (2019). Given the broad linguistic weaknesses of children with 22q11DS, but also the large individual differences in the severity of these weaknesses, routine assessments from a young age onward are necessary to support early interventions, and, in turn, mitigate the ramifications of language impairment and improve outcomes. Research can contribute to these goals by providing more knowledge on these individual differences and the factors that are associated with those differences (e.g., intellectual functioning, SES, physical symptoms, etc.), which was beyond the scope of the current research. In addition, future research can provide more insight into the developmental trajectory of the language skills of children with 22q11DS. Although our results suggest comparably severe weaknesses in both preschool and school-age groups, a limitation of the current research is the lack of a TD control group in the school-age study as well as the small sample size in this age group. Moreover, the cross-sectional nature of our research does not allow us to draw conclusions about children's developmental trajectories. There is a strong need for longitudinal

research on the language impairment of children with 22q11DS in comparison to TD peers, particularly as previous work suggested an increasing severity of receptive language impairment with age (Van den Heuvel et al., 2018) and in light of the observation that intellectual functioning declines during childhood and adolescence in 22q11DS (e.g., Fiksinski et al., 2022).

The current study showed substantial overlap between children with 22q11DS and children with DLD in terms of expressive grammatical skills, as evidenced by both standardized language assessment and spontaneous language analysis. Given inherent differences between children with 22q11DS and children with DLD, this overlap has important theoretical implications. Neither the large differences in intellectual functioning and co-occurring physical symptoms, nor the presence or absence of a known genetic condition, seems to result in differences in the expressive grammatical skills of these two groups of children. Our findings thereby correspond to other studies that showed more commonalities than differences in the grammatical skills of etiologically diverse groups of children (e.g., Bloom & Lahey, 1978; Bol & Kasparian, 2009; Bol & Kuiken, 1990; Laws & Bishop, 2004), and support the consensus among professionals on this topic (Bishop et al., 2016). It appears that there are multiple routes toward impaired grammar development with similar, or even virtually identical, phenotypic characteristics. The shared phenotypic characteristics of children's expressive grammar could be hypothesized to reflect, at least in part, simplification processes that are typical for earlier stages of development. In other words, if acquiring or using grammatical rules is, for whatever reason, difficult, there are common ways to make it easier. The current study was, however, not set up to test this hypothesis and was limited by the use of standardized tests and spontaneous language samples. Comparative research on language impairment in etiologically diverse groups, preferably with experimental designs (see e.g., Perovic et al., 2013), is needed to understand the observed commonalities and differences in children's language profiles.

As mentioned, the current study did not only find similarities in the language profiles of children with 22q11DS and children with DLD.

Receptive language difficulties were more severe in children with 22q11DS, showing that, despite overlap, different disorders have their own profile of relative strengths and weaknesses (e.g., Fidler et al., 2007; Rice et al., 2005). Given the poor prognosis of children with receptive language problems (e.g., Snowling et al., 2006; Zambrana et al., 2014) and the uncertainty about the effectiveness of therapy in this group (Law et al., 2003), special attention to these problems in children with 22q11DS is warranted in both research and clinical care. A possible avenue for future research would be to compare children with 22q11DS to a subgroup of children with DLD who both have expressive and receptive language problems. This can provide further insight into the mechanisms underlying (impaired) language development, for example enhancing our knowledge on the relation between low intellectual functioning and receptive language problems. It is also of clinical relevance, as children with 22q11DS and children with DLD often get language support in similar services, such as speech-language therapy and special education (see Boerma et al., 2022). The overlap in expressive grammar of the two groups of children may offer professionals working with children with 22q11DS a starting point for setting therapy goals in the domain of grammar. Moreover, it may even suggest that expressive grammar interventions targeting children with DLD also benefit children with 22q11DS. Although studies directly investigating the effectiveness of interventions in 22q11DS are a crucial next step, a subgroup comparison with children with DLD who have both expressive and receptive language problems could furthermore inform professionals about the usefulness of receptive language interventions with children with 22q11DS.

Conclusion

The current study is the first to investigate grammatical accuracy and complexity in the spontaneous language of children with 22q11DS. Complementing spontaneous language analysis with standardized testing in preschool and school-aged children, we showed weak expressive grammar in both naturalistic as well as standardized test settings, thereby contributing to a more complete description of the language profile of children with 22q11DS. The expressive

grammatical skills of the children with 22q11DS did not differ from those of children with DLD, despite clear differences between the two groups in the presence or absence of known etiology and accompanying cognitive and physical challenges. This overlap indicates that expressive grammar may be a shared and significant vulnerability across different populations that can further our knowledge of the mechanisms underlying language acquisition and that can improve clinical care for children such as those with 22q11DS. The observed weaker receptive language skills of the children with 22q11DS compared to the children with DLD show that different disorders are associated with a unique language profile of strengths and weaknesses. It is an open question whether the differences in receptive language are related to factors which inherently differentiate the 22q11DS and DLD groups.

Chapter 4 – Supplementary material

Appendix 4-A

Examples of the error categories as coded in the spontaneous anguage analysis.

Parameter	Category [a]	Examples
% Verb-related errors	Argument omissions	**ik moet nog even wachten* [now have to wait] correct: nu moet je nog even wachten [now you have to wait]
	Subject-verb agreement errors	**ik komt* [I comes] correct: ik kom [I come]
	Tense errors	**toen krijg ik een verrekijker* [then I get a binocular] correct: toen kreeg ik een verrekijker [then I got a binocular]
	Root infinitives [b]	**jij varken tekenen* [you pig draw] correct: jij tekent (een/het) varken [you draw (a/the) pig]
	Verb-second placement errors	**waar deze moet?* [where this goes?] correct: waar moet deze? [where does this go?]
	Overgeneralizations	**hij vliegde weg* [he flied away] correct: hij vloog weg [he flew away]
	Past participle errors	**ik heb die voor mama maakt* [I have that for mama makes] correct: ik heb die voor mama gemaakt [I have made that for mama]
	Verb omissions	**deze niet rood* [this one not red] correct: deze is niet rood [this one is not red]
	Other verb-related errors	**hij moet deze dichtmaak* [he has to this one close] correct: hij moet deze dichtmaken [he has to close this one]

% Non-verb-related errors	Determiner errors	**mag ik naar traktor kijken?* [can I look at tractor?] correct: mag ik naar de traktor kijken? [can I look at the tractor?]
	Adjectival inflection errors	**een grote ding* [a big thing] correct: een groot ding [a big thing]
	Preposition errors	**ook één jou* [also one you] Correct: ook één voor jou [also one for you]
	Pronoun errors	**naar mij huis* [to me house] correct: naar mijn huis [to my house]
	Conjunction errors	**hij kan open dicht* [he can open close] correct: hij kan open en dicht [he can open and close]
	Plural errors	**ik heb drie bos* [I have three forest] correct: ik heb drie bossen [I have three forests]
	Errors with 'er' [there]	**de dieren passen niet in* [the animals do not fit in] correct: de dieren passen er niet in [the animals do not fit in there]
	Word order errors	**het lijkt een hond op* [it looks a dog like] correct: het lijkt op een hond [it looks like a dog]
	Other non-verb-related errors	**ik wil die als jij* [I want that as you] correct: ik wil diezelfde als jij [I want the same as you]

a. Categories may include different types of errors. For example, argument omissions include both subject and object omissions. With the exception of a number of categories that specify the type of error in the name (e.g., verb omissions), error categories can include omission and substitution errors (and in rare cases also addition errors). The given examples illustrate just one type of error within a specific error category.

b. Root infinitives are clauses in which an infinitive is used as main predicate, although a finite verb is expected. In Dutch, the latter can only be determined with certainty when an overt subject is expressed. Therefore, this category only includes non-finite clauses with an overt subject. Previous research may have used less stringent operationalizations of root infinitives.

Appendix 4-B

Examples of the complex utterance categories as coded in the spontaneous language analysis.

Parameter	Category	Examples
% Complex utterances	Subordinate clauses	*ik dacht dat ik een spelletje ging doen* [I thought I was going to play a game]
	Conjunction reduction	*de kat is bang en de hond boos* [the cat is afraid and the dog angry]
	Direct speech	*hij zegt: "ik wil slapen"* [he says: "I want to sleep"]
	Infinitival clauses	*kan je even helpen om dit aan elkaar te maken* [can you help to tie this together]

Chapter 5

Learning from atypical development: A systematic review of executive functioning in children and adolescents with 22q11.2 deletion syndrome.

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Abstract

In this systematic review, we investigate executive functioning (EF) in a selected population: children and adolescents with 22q11.2 deletion syndrome (22q11DS). Studying a selected subset of the population can inform our understanding of typical development by reducing the etiological variability associated with phenotypic expression of EF. In 22q11DS, EF deficits are, at least in part, the consequence of the deletion on chromosome 22. However, the expression of EF phenotype in 22q11DS varies and is possibly influenced by certain risk factors that occur at increased rates in this population. As such, 22q11DS allows us to study the impact of these factors on EF in the context of one underlying genetic etiology.

This review shows that inhibition and shifting are impaired in children with 22q11DS, while updating may be spared in childhood. Notably, EF deficits are found in this population after controlling for intellectual abilities, supporting the hypothesis that EF and intelligence do not reflect the same construct. Current evidence suggests that risk factors previously identified in the general population, such as congenital heart defects or low socioeconomic status, may not impact EF in a similar way in 22q11DS. In the process of demonstrating how studying the 22q11DS population can inform and advance our understanding of EF development, we identify gaps in the literature and highlight opportunities for future research.

Key words: *22q11.2 deletion syndrome; Executive functioning; Atypical development; Children; Velocardiofacial syndrome*.

Introduction

Executive functioning (EF) refers to the higher-level cognitive mechanisms that regulate lower-level cognitive processes to effectuate goal-oriented behavior (Friedman & Miyake, 2017). It is associated with many variables, including quality of life, mental and physical health (Diamond, 2013), and later outcomes, such as literacy and academic skills (Altemeier et al., 2008; Nayfeld et al., 2013; Shaul & Schwartz, 2014; St Clair-Thompson & Gathercole, 2006). Although EF is frequently studied, knowledge concerning its developmental trajectory and putative risk factors is hampered by the variability in the general population. This variability not only exists as inter-individual differences in EF, but also in the heterogeneity of both endogenous (internal) and exogenous (external) variables contributing to these differences. Indeed, many different putative risk and protective factors for impaired EF have been identified in the general population (e.g., Zysset et al., 2018). The complex interplay between some of these factors further impedes our ability to evaluate their individual contributions to EF development. The variability of underlying etiologies is a major challenge to studies in the general population and likely contributes to inconsistent findings in this field.

Research in individuals who share the same pathogenic genetic variant related to their EF deficits provides a unique opportunity to address this challenge. The expectation is that the reduced etiological heterogeneity may increase the strength of some of the associations that may be more difficult to observe in the general population where this signal is diluted due to a larger etiological heterogeneity (see Figure 5.1). The aim of this systematic review is to gain a better understanding of specific EF deficits, their developmental trajectory, and underlying contributing factors in a selected population: children and adolescents with the 22q11.2 deletion syndrome.

The 22q11.2 deletion syndrome (22q11DS) is the most frequently occurring chromosomal microdeletion syndrome, with an estimated incidence of approximately 1 per 3,000-6,000 (McDonald-McGinn et al., 2015). It is caused by a hemizygous microdeletion on the long arm of chromosome 22 (Edelmann et al., 1999; Morrow et al., 1995). Previously called velocardiofacial syndrome, the most common symptoms of 22q11DS include congenital heart disease and palatal

abnormalities, but also immunodeficiency, endocrine abnormalities, and cognitive impairments, such as intellectual disability. Phenotypic expression, however, varies greatly among patients (McDonald-McGinn et al., 2015). Developmental delays are common, both physically, e.g., small stature (Habel et al., 2012), and cognitive, e.g., delayed achievement of motor and language milestones (McDonald-McGinn et al., 2015; Roizen et al., 2007). Moreover, individuals with 22q11DS have an increased risk for developing psychiatric problems, most prominently Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder, and schizophrenia (Fiksinski et al., 2018; McDonald-McGinn et al., 2015). These psychiatric disorders are all associated with EF deficits (Corbett et al., 2009; Happé et al., 2006; Lai et al., 2017; Knowles et al., 2015).

We add to previous work (Moberg et al., 2018) by providing a detailed EF profile and by reviewing the role of several factors impacting developmental EF performance in 22q11DS. Moberg et al. (2018) have shown widespread cognitive impairments, including EF deficits, in 22q11DS. In this population, EF deficits are, at the very least, partly due to this genetic variant, and thus more homogeneous in their etiology than EF deficits of individuals that are randomly selected from the general population (Figure 5.1). Several putative risk factors for EF deficits occur at increased rates in this population. The unique characteristics of this specific population can advance theoretical debates, such as that on the division of EF domains and its developmental differentiation, or whether EF and general intelligence should be considered part of the same underlying (cognitive) construct.

Below, we first discuss theories on the division of EF and its development in the general population. Next, we describe the biological underpinnings of EF in the typical population, as well as in 22q11DS, followed by a discussion of both endogenous and exogenous risk factors for EF impairment. Lastly, we consider how studying selected populations can inform the debate on the relation between EF and intellectual abilities, before detailing the current study.

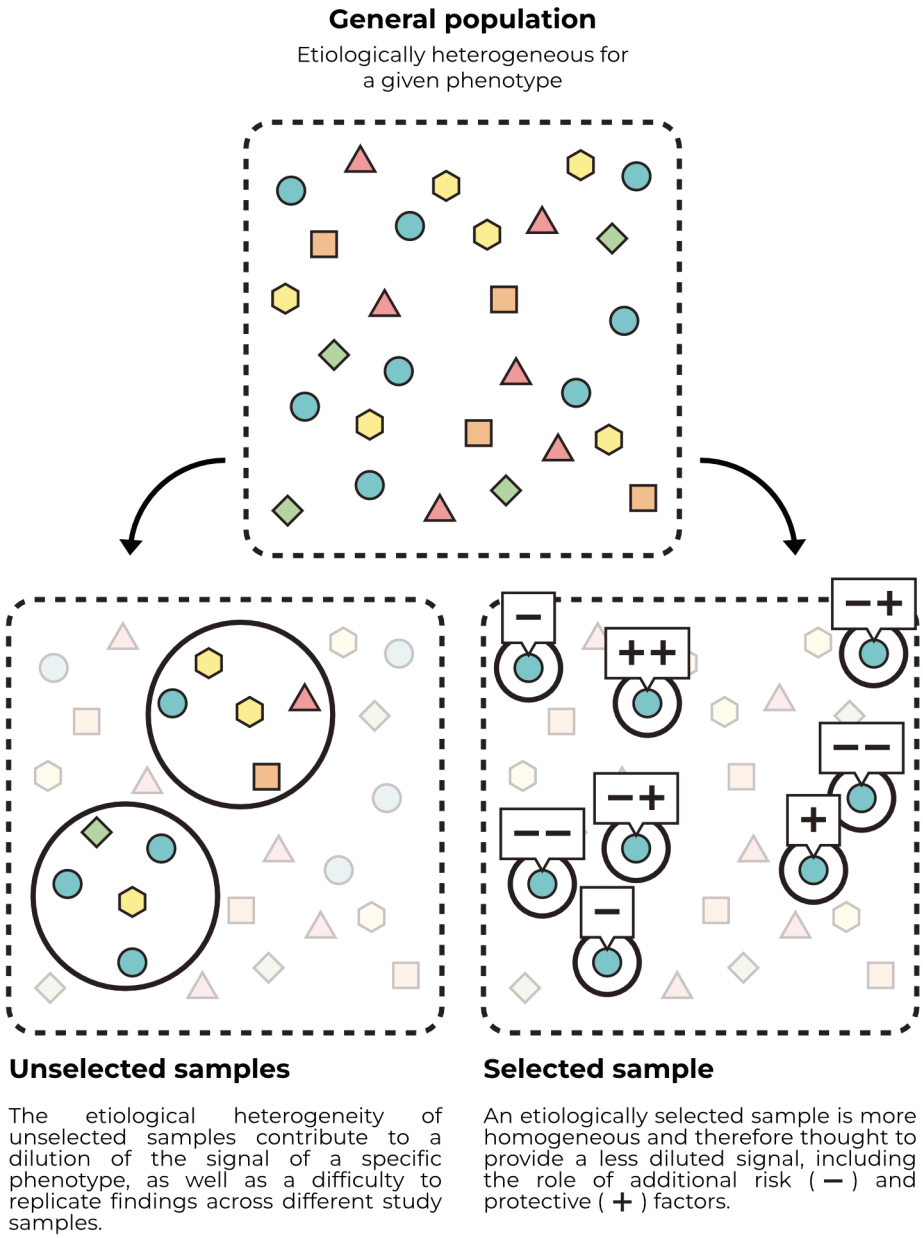


Figure 5.1. Graphic depiction of the contribution of studying etiologically homogeneous groups for a given phenotype.

Executive functioning

Various models of EF have been proposed (e.g., Barkley, 1998; Friedman & Miyake, 2017; Lezak, 1995), but generally the concept is adopted as an umbrella term for higher-level cognitive functions used to manage lower-level cognitive processes to effectuate goal-oriented behavior (Friedman & Miyake, 2017). In the present study, we follow Miyake et al.'s (2000) proposal to divide EF into *inhibition*, *shifting*, and *updating*. Inhibition refers to the ability to suppress responses and ignore irrelevant information. Shifting refers to the ability to switch smoothly between tasks and mental states. Updating refers to the ability to monitor and manipulate the information stored in the working memory.

The subdivision of EF by Miyake et al. (2000) has mostly been validated in adults. In contrast, some studies argue that children's EF is undifferentiated and reflects a general competence at top-down control of behavior and cognition (Brydges et al., 2012; Hughes et al., 2009; Wiebe et al., 2008; Wiebe et al., 2011; Willoughby et al., 2012). Other models of children's EF differentiate between two factors, including studies reporting an inhibition factor separate from an updating-shifting factor (Miller et al., 2012; Monette et al., 2015; Usai et al., 2014), but also a separate updating and an inhibition-shifting factor (Lee et al., 2013; Van der Ven et al., 2013). The differentiation of executive functions may happen as late as early adolescence, as Xu et al. (2013) showed that even up to the age of 12 years a unitary EF model is a better fit than a multiple-factor model (but see Lee et al., 2013). Differentiation can be gradually seen in the developmental patterns of the different executive functions. Best and Miller (2010) describe that inhibition shows more rapid growth in childhood with slower gains during adolescence, while shifting shows a more protracted development. Working memory improves linearly throughout both childhood and adolescence. During development, children also become increasingly better at tasks that require the integration of these different functions (Davidson et al., 2006). Considering these developmental changes, we will distinguish between children and adolescents where possible in this review.

Biological foundation of EF

EF is argued to be influenced substantially by genetic variation (Friedman et al., 2011; Lee et al., 2012). Some have even argued that EF abilities can almost entirely be explained by genetic variance (Engelhardt et al., 2016; Friedman et al., 2008). Nevertheless, little is known about the specific genes implicated. Genome-wide association studies and polygenic scores derived from these studies show that these genetic associations are likely driven by numerous genes (Hatoum et al., 2023; Schork et al., 2018). Associations of specific genetic variants with EF can strengthen research describing the full genetic architecture of EF, for example by contributing to polygenic scores (Wray et al., 2014). Polygenic scores reflect the cumulative estimated effect of many different genetic variants on specific phenotypic traits.

At a cellular level, the biological underpinnings of EF development include maturation of synaptic functioning and certain neurotransmitter systems (e.g., dopamine) (Logue & Gold, 2014). Furthermore, neuronal migration, myelination, and pruning (i.e., synaptic elimination), as well as mitochondrial functioning are regarded essential to early neural development and subsequent cognitive development (Frye & Rossignol, 2012; Geary, 2018; Perone et al., 2018). The neural substrates of EF are considered to be mostly located in the frontal cortex, specifically the prefrontal cortex (PFC), dorsolateral PFC, orbitofrontal cortex, and the anterior cingulate cortex (Alvarez & Emory, 2006). The PFC matures later than other cortical areas, developing up into late adolescence both structurally (Best et al., 2009; Gogtay et al., 2004; Sowell et al., 2003) and functionally (Casey et al., 2005; Satterthwaite et al., 2013). On a structural level, white matter in the PFC appears to increase linearly throughout childhood, likely as a result of synaptogenesis (i.e., synapse formation), neuronal proliferation, and myelination, whereas gray matter has been reported to similarly increase *before* the onset of puberty, but to decline thereafter (Giedd et al., 1999; Gogtay et al., 2004), presumably as the result of synaptic pruning, apoptosis (i.e., programmed cell death), or an increase in intra-cortical gray matter (Paus, 2005). This structural development of the PFC is consistent with

the protracted developmental trajectory reported for EF, as indicated by behavioral data.

Biological underpinnings of EF in 22q11DS

Evidently, children with 22q11DS differ from typically developing children in that they have a hemizygous (i.e., on one allele) deletion of 1.5- to 3-Mb encompassing up to 60 genes in band 11 of chromosome 22 (McDonald-McGinn et al., 2015; Edelmann et al., 1999; Morrow et al., 1995). Genes located in the 22q11.2 region, such as catechol-O-methyltransferase (*COMT*) and proline dehydrogenase (*PRODH*), contain different variants (i.e., polymorphisms). In the case of *COMT*, it primarily concerns the Val[158]Met (rs4680) variant, whereas for *PRODH* there are many different functional variants. These variants have been linked to cognitive performance in individuals without 22q11DS (e.g., Barnett et al., 2007; Li et al., 2008; Mier et al., 2010; Moriguchi & Shinohara, 2018; but see Barnett et al., 2008). Moreover, individuals with 22q11DS thus only have one copy of genes located in the deleted region, creating unique opportunities to study genotype-phenotype interactions. The hemizygous deletion of genes such as *COMT*, *RANBP1*, and *PRODH* may affect the dopaminergic, GABAergic, and glutamatergic systems, thereby impacting the development and regulation of subsequent neural pathways (Kempf et al., 2008; Paronett et al., 2015; Sobin et al., 2004). It is likely that multiple genes within the 22q11.2 region may contribute to the EF profile of these children, but these relations appear to be largely unexplored. Similarly, knowledge concerning the role of genes in this region during different developmental stages is limited due to our incomplete understanding of expression patterns in the brain, and changes thereof during development.

Nonetheless, research has suggested that the 22q11.2 deletion may impact cortical development throughout various stages of development, starting with altered neuronal identity, aberrant neurogenesis (i.e., neuron formation) and neural migration patterns, and finally alterations in connectivity as a result of deficient mitochondrial functioning (resulting in lower energy production) (Li et al., 2019; Meechan et al., 2011). Indeed, aberrant trajectories of cortical development have been observed in individuals with 22q11DS

(Nuninga et al., 2018; Ramanathan et al., 2017; Schaer et al., 2009), with increased cortical thinning during adolescence presumably due to disrupted synaptogenesis and pruning (Meechan et al., 2011; Schaer et al., 2009). This is corroborated by research showing reduced structural connectivity in networks associated with EF (Jonas et al., 2015; Padula et al., 2017; Scariati et al., 2016) and reduced activation of frontal areas in adults with 22q11DS during EF tasks (Harrell et al., 2017; Montojo et al., 2015).

Risk factors for EF impairment

EF development can be impacted by various factors throughout different phases of development. These factors can be both endogenous (child-internal) or exogenous (child-external) (e.g., Zysset et al., 2018) and with either protective or deleterious impacts on EF development. Many risk factors for EF impairment observed in the general population are more prevalent in the 22q11DS population, as will be detailed below. Investigating the effect of specific endogenous and exogenous factors on EF outcomes in 22q11DS provides an opportunity to reduce the variability caused by at least one of the many factors that might be at play: genetic variation. The specific genetic profile of these children can guide hypotheses on mechanisms crucial to EF development.

Endogenous risk factors for EF impairment

Endogenous risk factors for EF impairment are generally biological in origin and most likely impact EF by disrupting early cortical development. For example, variation of specific genes located in the 22q11.2 region have been associated with EF. Other endogenous factors that are frequently associated with EF impairment in the general population are premature birth, low birth weight, and congenital heart defects.

Meta-analyses have shown that children born preterm or with a very low birth weight (LBW) generally perform lower on measures of EF than children born term or with normal birthweight (Aarnoudse-Moens et al., 2009; Brydges et al., 2018; Mulder et al., 2009). On average, children born preterm or with LBW have smaller volumes of both gray and white matter (Davis, Buss, et al., 2011; De Kieviet et al., 2012).

Preterm birth or LBW may be the result of an underlying genetic cause, which may also separately affect early brain growth. Additionally, both pre- or postnatal factors, such as nutritional deficiencies in utero or spending the first weeks of life in a Neonatal Intensive Care Unit, may be adverse to neural development. In Western countries, preterm birth occurs in around 9% of all births (Blencowe et al., 2012; Purisch & Gyamfi-Bannerman, 2017) and LBW in 7% of all births (Blencowe et al., 2019). In 22q11DS, a small but significantly heightened incidence of preterm birth (13-17%) and LBW (9-20.3%) has been observed (Kufert et al., 2016; Lima et al., 2010; Van et al., 2015).

IIn the general population, children with Congenital Heart Defects (CHD) have poorer neurodevelopmental outcomes, including EF impairment (Mebius et al., 2017; Sterken et al., 2015). Their EF deficits may be the result of abnormal brain development. Infants with CHD are at risk for brain lesions, show delayed brain maturation, and have smaller total brain volumes (Khalil et al., 2014; Licht et al., 2009; Limperopoulos et al., 2010; Morton et al., 2017; Watanabe et al., 2009). In these children, brain lesions in, and delayed maturation of brain regions subserving EF, may result from a complex interaction of various factors, such as abnormal cerebral blood flow in utero, reduced oxygen supply, or surgery-related factors (Peyvandi et al., 2019; Wernovsky & Licht, 2016). In 22q11DS, CHD prevalence rates are estimated to be as high as 75% (McDonald-McGinn et al., 2015). One study reported reductions of cortical thickness in various brain regions in individuals with 22q11DS and CHD as compared to those with 22q11DS and without CHD (Fountain et al., 2014). While these findings indicate a relation between CHD and cortical thickness, conclusive evidence in support of causality is not yet available. Plausible causal mechanisms include reduced oxygen supply which may be most pronounced at the borders of blood supply regions (watershed areas) and may have the largest impact on regions with the highest energy demand. This is supported by the beneficial effect that physical activity, which increases cerebral blood flow and oxygen saturation, seems to have on EF as reported in the general population (see section *Exogenous risk factors for EF impairment* below). However, these findings cannot rule out the possibility that the

observed cortical abnormalities could also be the result of the deletion itself or be related to other medical issues common in 22q11DS (e.g., hypocalcemia or seizures). Indeed, a previous study by the same group reported a significant mean difference in total cerebral volume in 22q11DS (with and without CHD) compared to controls (without CHD) (Schaer et al., 2009). Furthermore, a meta-analysis has revealed widespread volumetric reductions in cortical matter in 22q11DS (Tan et al., 2009). Future studies are required to further elucidate the nature of the observed association. Research in 22q11DS can guide hypotheses on mechanisms crucial to EF development, such as the role of oxygen supply in mitochondrial functioning and subsequent neural development.

Exogenous risk factors for EF impairment

In addition to changes and disturbances of biological origin, exogenous factors can also impact EF. Some of the exogenous factors associated with EF impairment are stress, socioeconomic status, parenting behaviors, play, and exercise.

Early life stress has been argued to affect the development of the brain areas underlying EF (Pechtel & Pizzagalli, 2011). Excessive levels of cortisol (a hormone released in response to stress) can suppress physiological processes critical to early brain development, such as neuron and synaptogenesis, as well as lead to changes in neural development (atypical axon and dendrite development) (Conrad, 2008; Gould & Tanapat, 1999; Woolley et al., 1990). In the general population heightened cortisol has been linked to poorer EF outcomes in early childhood (Blair et al., 2011; Wagner et al., 2016). However, certain demographic or familial factors may mitigate the effects of early life stress (Lopez et al., 2021). Children with 22q11DS and their parents may experience more stress due to the presence of severe medical issues, insecurity about the future, and challenges in finding appropriate healthcare and education (Goodwin et al., 2017; Vo et al., 2018). This might be further exacerbated by a biological predisposition for disrupted cortisol levels (Van Duin et al., 2019; Sandini et al., 2020).

Demographic or familial factors, such as socioeconomic status (SES) or parenting style, are also suggested to impact the EF

development in children (Kao et al., 2018; Rhoades et al., 2011). A meta-analysis shows that during development there is a stable small to medium effect of SES on EF in children, with lower SES associated with poorer EF performance (Lawson et al., 2018). Factors such as parental scaffolding, stimulation, control, and responsiveness have been linked to better EF abilities in typically developing children (Blair, Raver, & Berry, 2014; Fay-Stammbach et al., 2014; Hughes & Devine, 2019; Hammond et al., 2012). Additionally, more unstructured play time has been linked to stronger EF, presumably because it allows children to practice self-directed choice and planning skills (Barker et al., 2014). Parenting styles and the amount of structured time may differ between typically developing children and clinical populations. Chronic illness in children with additional stressors, such as behavioral or communication problems, has been shown to incite a more protective parenting style (Pinquart, 2013). There is currently no evidence that children with 22q11DS differ in SES from typically developing children, and research on parenting behaviors in parents of these children is scarce (Swillen et al., 2018).

Additionally, physical activity may have a positive impact on EF during childhood, supposedly by supporting physiological processes beneficial to EF development. This includes processes likely also affected by congenital heart defects, such as cerebral blood flow and oxygen saturation. Physical activity might furthermore benefit EF development due to the cognitive demands that accompany complex and goal-directed motor movements and exercise (Best, 2010; Chaddock et al., 2012). A randomized controlled trial with typically developing children showed that an intervention boosting physical activity improved EF performance (Hillman et al., 2014). Little is known about the physical activity of children with 22q11DS, but adolescents with 22q11DS report increased rates of fatigue and reduced activity (Vergaelen et al., 2017). Reduced activity might be a consequence of the presence of certain medical conditions, like CHD, but it may also further exacerbate the negative impact of such conditions on EF development in this vulnerable population.

Similarly, the role of factors like stress, parenting style, and unstructured time may also be affected by the presence of medical problems, such as CHD. Furthermore, many of these exogenous

factors may also interact with endogenous factors (i.e., gene-environment interaction) (e.g., Chen et al., 2020). This underscores the complexity of the relation between such factors and EF outcomes.

Summary: EF risk factors and 22q11DS

Various risk factors associated with EF impairment in the general population, such as CHD and stress, are clearly more prevalent in 22q11DS. Other risk factors, such as preterm birth, low birth weight, specific parenting styles, limited play and physical activity are likely to be more prevalent, but limited research so far precludes robust conclusions. In the case of the effects of endogenous risk factors, studying 22q11DS can help us determine whether a common underlying genetic origin is responsible for atypical neural development, or whether downstream effects of the genetic defect might cause additional damage. For instance, pleiotropic effects of genetic variation associated with CHD may separately impact neural development (McQuillen & Miller, 2010; Nattel et al., 2017). If an underlying genetic mutation is responsible for both CHD and atypical neural development (leading to EF impairment), the secondary effects of CHD on EF abilities may be negligible in populations such as individuals with 22q11DS (see *Results*).

Association EF with intellectual abilities

It has been argued that EF and intellectual abilities are two sides of the same coin (e.g., Duncan et al., 1996), with some studies showing that EF functions can be fully incorporated into theories of general intelligence (Frischkorn et al., 2019; Jewsbury et al., 2016). In contrast, others argue that EF and general intelligence are separate constructs (Ardila et al., 2000; Crinella & Yu, 1999). A correlation between Intelligence Quotient (IQ) and EF has been observed in typically developing children (Arffa, 2007; Ardila et al., 2000), although not unequivocally (Montoya-Arenas et al., 2018). Furthermore, while measures of intelligence and EF have been found to share some variance, EF also explains additional variance not captured by measures of intelligence (Davis, Pierson & Finch, 2011; Friedman et al., 2006). Likewise, Polderman et al. (2006) found that EF at age 5 appears to be a weak predictor for IQ at age 12. Thus, the constructs of

intelligence and EF are correlated but there are distinct components to each of them.

As the evidence from typically developing children is mixed, evidence from children with atypical development, specifically those associated with intellectual disability, can be informative. Studying such populations may either reveal a double dissociation between EF and intelligence, supporting the idea that they are separate entities, or it may show that EF and IQ share a common underlying factor. If the latter is true, EF deficits in populations with intellectual impairment should weaken when controlling for IQ. The 22q11DS population lends itself well to this end as intellectual disability (IQ <70) occurs in around ~50% of children, with most having an IQ-score in the borderline range between 55 to 85 (McDonald-McGinn et al., 2015; De Smedt et al., 2007). Crucially, the IQ-scores of the 22q11DS population follow a normal distribution similar to the general population (Klaassen et al., 2016; Niklasson & Gillberg, 2010). Similar debates, such as that of the division of EF domains, could also be informed by observing specific populations, such as 22q11DS.

Current study

In summary, EF is a critical component of cognitive development, as it is associated with concurrent development of other cognitive functions and later outcomes, such as academic and psychosocial functioning. Beyond a direct clinical relevance to the population of individuals with 22q11DS, we suggest that findings reported here also have a broader value. It has been widely argued that 22q11DS can be taken as a model for the study of schizophrenia and its risk mechanisms (Gur et al., 2017; Insel, 2010). We propose that the same holds for other phenotypes, such as EF profile. As there are indications that EF is impaired in individuals with 22q11DS (e.g., Campbell et al., 2010; Moberg et al., 2018), understanding which factors, in addition to the deletion itself, impact EF abilities in this group, can further our understanding of underlying mechanisms.

This systematic review aims to comprehensively describe what is currently known about the specific EF profile of children and adolescents with 22q11DS. We will consider longitudinal studies or studies regarding the effect of age to provide insight into the

developmental trajectory of EF in 22q11DS. Additionally, we focus on studies investigating the effect of various endogenous and exogenous risk factors, previously identified in the general population, on EF performance of children and adolescents with 22q11DS. This allows us to identify gaps in the literature and provide directions for future research. This can guide potential interventions for children with 22q11DS and support research in, and relevant to the general population.

Methods

This systematic review was conducted in adherence to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Moher et al., 2009).

Search strategy

Title, abstract and keyword searches were conducted in PubMed, PsychInfo, and EMBASE in February 2020 using the search terms presented in Table 5.1. Due to the variability in terms used for both 22q11DS and EF, final search terms were selected based on whether they increased the number of hits in exploratory searches in Pubmed. In these exploratory searches the 22q11DS and EF terms were not combined.

Table 5.1. Search terms used in the query combining terms for 22q11DS with terms for EF.

22q11.2 deletion syndrome	AND	**Executive functions**
22q11* OR *22q11 OR del22q11* OR VCFS OR Velo-cardiofacial syndrome OR Velo-cardio-facial syndrome OR VCF syndrome OR DiGeorge syndrome OR Di-George syndrome OR Shprintzen syndrome OR Velocardiofacial OR Velo-cardio-facial OR DiGeorge OR Di-George OR Shprintzen OR CATCH22 OR catch 22 OR Sedlackova syndrome OR Takao syndrome OR Cayler cardiofacial syndrome OR Conotruncal Anomaly Face Syndrome		Executive funct* OR Executive control OR Executive dysfunc* OR Working memory OR Inhibition OR Attention* OR Cognitive flexibility OR Shifting OR Switching OR Prefrontal cognition

Note. For the exact queries per search engine, see Appendix 5-A.

No limits were imposed on publication type, date, or language. The only limit imposed was the exclusion of articles published in PubMed in the EMBASE search to limit duplicates. In our search strings, the asterisk shortens the word to identify different endings, and MeSH terms (or equivalents) for 22q11DS were used when available.

Study selection

In the first screening, titles and abstracts were independently checked by two authors each (EE, IS and/or TB) for reporting original data of behavioral methods in human subjects with 22q11DS. Any discordance was resolved by consensus. In the second screening, the remaining articles were assessed for eligibility to be included. The full text of the articles was examined for:

1. mean age (≤ 18 years);
2. age range (≤ 10 years) or the standard deviation (SD) of the mean age (< 3.5) of the participants;

   A maximum age range of 10 years was chosen to limit heterogeneity due to developmental differences in the participant sample. The SD of the age of the participants was used as an indication of the age range only in studies that did not report the age range of their sample.

3. sample size ($n \geq 15$);

   A minimum sample size of 15 was taken to ensure some ability to generalize given the heterogeneity within the 22q11DS population.

4. reporting a genetically confirmed diagnosis of 22q11DS for all participants in the 22q11DS group;
5. which task was used and whether this task is generally recognized as a task that validly gauges EF;

   In order to be considered for this review, we required tasks to be commonly known for measuring EF. Alternatively, tasks were considered if the original authors of the study being screened, explained how the task they used measures one or more specific sub-components of EF and this explanation was in agreement with theories of EF. The current authors classified tasks into one of three EF domains, following the division by Miyake et al. (2000): inhibition, shifting, and updating (working memory; WM). Updating was further divided in verbal WM and visual(-spatial) WM (see Table 5.3).

This classification did not consider the domain intended by the original authors.

- Tasks taken to measure verbal and/or visual(-spatial) WM were defined as tasks that require participants to keep the information active during an interfering task or to manipulate the input rather than just reproducing it (Baddeley, 1992). This means that for some tasks (e.g., Digit Span) only the *backward* condition is considered in this review. *Forward* conditions are thought to gauge short-term memory rather than WM. In a similar vein, only Trail Making Test (TMT) B, but not TMT A was considered to represent shifting.
- Both the verbal and the visual condition of the Self-Ordered Pointing Task were considered to represent visual WM, because the verbal condition also uses pictures, but just ones that are easy to encode verbally. However, there is no way to check whether participants used a verbal strategy.
- Although frequently used to represent EF, verbal fluency and the Working Memory Index of the Wechsler Intelligence Scale for Children (WISC-WMI) are not discussed in the current review, because there is no consensus on what verbal fluency exactly measures (Shao et al., 2014; Stolwyk et al., 2015) and because the WISC-WMI is a composite score that combines both verbal and non-verbal WM measures in addition to short-term memory measures.

6. whether the EF outcomes (e.g., mean score) were reported explicitly and not just in relation to other outcomes, and;

7. whether there was a comparison with a control group, norm group, or a within-group comparison.

A comparison with a control group or norm scores, or a comparison between two groups of participants with 22q11DS, was deemed necessary in order to interpret the results, since many neurocognitive measures do not produce outcomes that can be interpreted without context.

Studies were only classified as longitudinal if they reported EF outcomes for at least two time points.

The authors of the current study reviewed and discussed the articles. To limit possible bias, all studies were reviewed for potential overlap in study groups. In case of uncertainty, authors were contacted to verify whether there was overlap in the data reported in the paper. In case of confirmed or suspected overlap of data, the study with the lowest risk of bias and/or largest sample size was included.

Assessment of risk of bias

The risk of bias (RoB) assessment for all individual studies was performed by one author (EE) using the checklist below, see Table 5.2. A second author (FW) performed a secondary RoB assessment for eight of the studies (27.5%). Agreement was deemed satisfactory and in case of differing assessments, agreement was reached by consensus.

We created a risk of bias assessment tool based on various other risk-of-bias assessment tools, such as the RoBANS (Kim et al., 2013) and the Newcastle-Ottawa scale for assessing the quality of nonrandomized studies (Wells et al., 2000), but tailored to the specific characteristics of this field of study and the studies identified with the search. The reason for doing this was that many RoB assessment tools include criteria irrelevant to the studies in this review. Since one of the inclusion criteria for studies in this review is that cases are required to have a confirmed genetic diagnosis of 22q11DS, assessment of cases was not considered in the risk of bias assessment. Some criteria frequently assessed in risk-of-bias assessments were not considered here, because they applied to all or virtually none of the studies. These criteria are discussed in the results section of the risk of bias assessment. The last three items on the list are considered only if a study is longitudinal.

The final category was either a (1) high, (2) medium, or (3) low RoB. These categories were based on sample size and the overall result of the criteria specified in the checklist, although items varied in the weight ascribed to them. While studies with high or medium RoB provide valuable data, their conclusions should be considered with more caution compared to studies with low RoB.

Table 5.2. Risk of bias assessment checklist.

Risk of bias assessment for individual studies			
Control group?	Yes		No
Cohort?	Longitudinal		Cross-sectional
Study			
1. A clear research question and hypotheses;	-	-/+	+
Participants			
2. Clearly stated in- and exclusion criteria;	-	-/+	+
3. Comprehensive demographic data of the sample;	-	-/+	+
4. Cases and controls are selected from comparable populations;	-	-/+	+
5. Recruitment procedure is described (period, consecutive recruitment, non-response, etc.);	-	-/+	+
Data collection and analysis			
6. The study uses well defined, frequently used, and/or standardized measures (with norms or controls);	-	-/+	+
7. Confounds are identified and controlled for;	-	-/+	+
8. Adequate statistical analysis (e.g., correction for multiple testing);	-	-/+	+
Outcomes			
9. Confidence interval and effect sizes are reported;	-	-/+	+
10. All expected/pre-determined outcomes are included in the study descriptions;	-	-/+	+
If longitudinal:			
11. Time between measurements is long enough to see development/changes;	-	-/+	+
12. Cases and controls were included during the same time period;	-	-/+	+
13. Drop-out described or no participants lost.	-	-/+	+

Note. When a study did not report certain elements or did not perform certain procedures: - ; if some information was reported but insufficiently: -/+ ; if adequately performed and/or reported: +.

Data collection and statistical analysis

Data was extracted based on a pre-developed extraction form (see Box 5.1). Note that some studies report both a comparison of their 22q11DS participants and controls/norms, and a comparison of groups

within their 22q11DS sample. Additionally, various studies report on more than one task or report one task that spans multiple domains. If a study reports multiple tasks, each task is reported in the respective domain, whereas if one task spans multiple domains the outcomes are reported in the primary domain. The primary domain is determined based on the task itself and the reported outcome measures. Some studies report mixed outcomes with respect to different tasks or different outcome variables within one task, in which case both outcomes are reported. Some studies have overlap with other studies but are included nonetheless because they contain an additional analysis, data relevant for development, or because they provide (more detailed) information on factors associated with EF. These studies are not described or discussed in the results of individual studies per domain.

Box 5.1. *Data collected for analysis.*

Data collected for analysis

22q11DS group
Sample size, genetic confirmation, age (mean, SD, range)

Executive functions
EF domain as stated by the original article, EF domain as classified by the current authors, name of test(s)

Control group
Yes/no, and if yes, sample size, type of control group, age (mean, SD)

Longitudinal
Yes/no and if yes, how many measurement points and time between them

Other factors
Genetic variants, CHD, SES, prematurity, LBW, stress, parenting, play, physical activity, or IQ

Results

Study selection

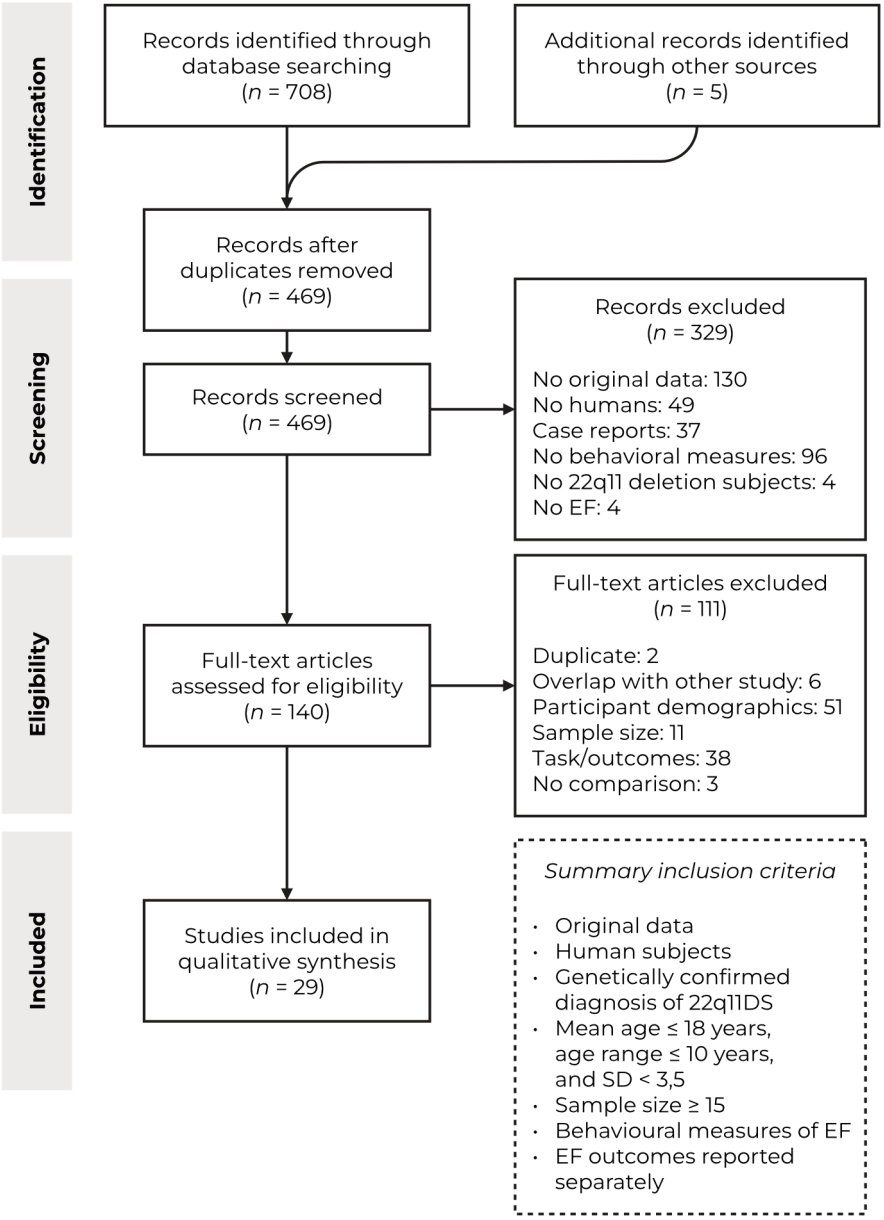
Our query returned 713 studies. After elimination of duplicates, the titles and abstracts of 469 studies were screened for original data of behavioral measures of cognition in human subjects with 22q11DS. A

total of 140 studies met these inclusion criteria. The full texts of all these articles were available and these were screened for the secondary inclusion criteria. A total of 29 studies met the criteria for inclusion in this systematic review (see Figure 5.2).

Study characteristics

The 29 studies included in this review reported on a total of 1274 participants with 22q11DS with a mean age of 11.3 (*SD* = 2.3) years (this excludes four studies that only reported age range). Overall, the average age range was 7.6 years as reported by 19 out of 29 studies (see Table 5.3). Following the age division of the World Health Organization (2017) guidelines, nine studies reported on children (mean age < 10), three reported on adolescents (mean age > 14), and 16 reported on a mix of children and adolescents (mean age > 10 and < 14). One study reported separately on a group of children and a group of adolescents. All included studies and an overview of their content is displayed in in Table 5.3.

Twenty-one studies had a typically developing (TD) control group; two of these studies had an additional control group consisting of a different clinical sample (Turner Syndrome and CHD without 22q11DS). Seven studies made comparisons between two groups within their 22q11DS sample which are relevant for the current review. Three studies were longitudinal, all of which had a control group.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. *PLoS Med*, 6(7): e1000097. doi:10.1371/journal.pmed1000097

Figure 5.2. Flow diagram of the systematic search and subsequent in- and exclusion (Moher et al., 2009).

Table 5.3. Overview of the characterstics of the studies included for analysis.

Author, Year	Sample size	Mean age (*SD*)	Age range	Task(s)	Domain	Control group? If so, *n*	Mean age (*SD*)	Outcome	RoB
1. Bearden et al. (2004)	44	11.1 (3.2)	N.R.	DS, TMT B, VF, WISC-3 Arithematic	Broad EF	-		Met > Val	High
2. Carmel et al. (2014)	32	8.1 (2.4)	N.R.	Flanker	Shifting	-		Met = Val Arg = Trp	Medium
	28	14.6 (1.7)	12 – 18	Flanker	Shifting	-		Met = Val Arg = Trp	
3. De Sonneville et al. (2018)	58	13.5 (2.6)	9 – 18.5	AmstNT SSV	Inhibition	-		22q < TD error 22q = TD speed	Medium
				AmstNT SSV	Shifting			22q < TD, 22q = TD 22q > TD	
				AmstNT MSL	Updating			22q < TD speed and error	
4. Niklasson et al. (2005)	30	N.R.	7 – 13	Becker Go/No-Go	Inhibition	-		22q < TD	High
5. Niklasson et al. (2010)	30	N.R.	6 – 13	ToL	Inhibition	-		22q = TD	Medium
	22	N.R.	7 – 15	TMT B	Shifting	-		22q < TD	

6. Shashi, Howard, et al. (2010)	40	9.5 (2.5)	7 – 16	CPT_IP, CPT_AX	Inhibition	-		Met = Val	High
				WCST	Shifting			Met > Val	
7. Sobin, Kiley-Brabeck, Daniels, et al. (2005)	40	7.7 (2.4)	5.2 – 12.9	NEPSY Tower	Inhibition	-		22q = TD	Medium
				NEPSY AARS	Shifting			22q < TD	
8. Stoddard et al. (2012)	53	N.R.	6 – 15	Flanker	Shifting	-		Met = Val	High
9. Albert et al. (2018)	63	12.2 (2.3)	N.R.	ToL, GDS, Stroop	Inhibition	43	11.8 (2)	22q < TD, 22q = TD	Low
				WCST	Shifting			22q < TD	
				DS, VSp	Updating			22q < TD	
10. Antshel et al. (2017)	78	11.9 (2.1)	N.R.	CPT	Inhibition	50	12 (2)	22q < TD	Medium
				WCST	Shifting			22q < TD	
				VSp	Updating			22q < TD	
11. Baker et al. (2005)	25	16.3 (2.1)	13.8 – 0.8	Sentence span task, Dot test	Updating	25	15.9 (3)	22q < TD, TD > 22qMet, TD > 22qVal, 22qMet = 22qVal	High

12. Bish et al. (2005)	18	9.2 (1.7)	7 – 14	Flanker	Shifting	16	9.6 (1.8)	22q < TD	High
13. Brankaer et al. (2017)	25	9.8 (1.9)	6 – 12	DS, LSp	Updating	48	9.4 (1.8)	22q = TD	Low
14. Campbell et al. (2015)	24	16.8 (3.1)	12 – 21	ToL	Inhibition	27	16.3 (3.7)	22q < TD	Medium
				2 experimental WM tasks	Updating			22q < TD	
15. Cunningham et al. (2018)	70	11.2 (2.2)	6.2 – 14.9	CANTAB SOC	Inhibition	32	11.5 (2.1)	22q < TD	Low
				WCST	Shifting			22q < TD, 22q = TD	
				CANTAB SWM	Updating			22q < TD	
16. De Smedt et al. (2008)	25	9.8 (1.9)	N.R.	DS, LSp, Counting span	Updating	25	9.3 (1.7)	22q = TD	Low
17. Kates et al. (2007)	17	N.R.	8 – 15	2-back non-spatial WM	Updating	20	N.R.	22q = TD	Medium
18. McCabe et al. (2014)	25	16.8 (2.9)	N.R.	ToL	Inhibition	30	16.5 (3.5)	22q < TD	Medium
19. Sanders et al. (2017)	20	12.2 (2.4)	7 – 16	Shapes WM computer task	Updating	32	10.9 (2.5)	22q < TD	Medium

20. Shapiro et al. (2014)	71	11.4 (2.5)	7 – 14	Stroop, Go/No-Go	Inhibition	52	10.6 (2.2)	22q < TD, Met = Val +, Met < Val	Medium
				WCST	Shifting			22q < TD, Met = Val	
				SOPT	Updating			22q < TD, Met = Val	
21. Shashi, Keshavan, et al. (2010)	65	10.2 (2.6)	N.R.	CPT_IP, CPT_AX	Inhibition	52	10.4 (2.3)	22q < TD	Medium
				WCST	Shifting			22q < TD	
22. Shashi et al. (2012)	66	10.5 (2.6)	N.R.	CPT_IP, CPT_AX	Inhibition	54	11 (2.3)	22q < TD	Medium
				WCST	Shifting			22q < TD	
23. Sobin et al. (2004)	32	7.6 (1.6)	5 – 11.5	Flanker	Shifting	20	8.3 (2)	22q < TD	Medium
24. Sobin, Kiley-Brabeck, & Karayiorgou (2005)	21	10.4 (2.6)	6 – 15.1	Flanker	Shifting	25	9.5 (2.0)	22q < TD	High
25. Stoddard et al. (2011)	53	10.7 (2.0)	7 – 14	Flanker	Shifting	46	10.0 (2.4)	22q < TD	Medium
26. Yi et al. (2014)	27	11.4 (2.2)	8 – 14	CNB	Broad EF	16 (CHD)	10.8 (1.3)	22q+CHD = 22q-CHD	Medium
						48 (TD)	N.R.	22q < TD	

27. Antshel, Shprintzen, et al. (2010)	80	11.9 (2.2)	N.R.	CPT, ToL	Inhibition	73	12.2 (1.9)	TD_2 > TD_1* 22q_2 = 22q_1 + 22q_2 > 22q_1	Medium
				WCST	Shifting			TD_2 = TD_1 22q_2 = 22q_1 + 22q_2 > 22q_1	
				VSp	Updating			TD_2 > TD_1 22q_2 > 22q_1	
28. Chawner et al. (2017)	75	9.9 (2.4)	6 – N.R.	CANTAB SOC	Inhibition	33	10.6 (2)	Growth: 22q = TD	Low
				WCST	Shifting			Growth: 22q = TD	
				CANTAB SWM	Updating			Growth: 22q = TD	
29. Hooper et al. (2013)	42	10.1 (2.5)	7 – 15.7	CPT_IP, CPT_AX	Inhibition	29	10.3 (1.7)	Growth: 22q > TD, 22q = TD	Medium
				WCST	Shifting			Growth: 22q = TD	

*Except for CPT commission errors for TD for which TD_2 = TD_1

Note. Studies are divided in studies without a control group (1-8), studies with a typically developing (TD) control group (9-26) and longitudinal studies (27-29). Within this division, studies are presented alphabetically. Outcomes are summarized per domain per study. Studies with outcome 22q < TD or 22q > TD found a significant difference between their 22q11DS group and the conrol group or norms on at least one task. Studies in the 22q = TD category did not report a significant difference between groups. Studies with mixed outcomes receive the labels of both outcomes. For studies that made a comparison within their 22q11DS sample based on genetic variants, abbreviations for these genetic variants were used (COMT $Val^{158}Met$: Val/Met and PRODH $Arg^{185}Trp$: Arg/Trp, see section Genetic variation in Results). For longitudinal studies, outcomes reflect the comparison between growth trajectories. An exception is the study by Antshel, Shprintzen, et al. (2010) which did not compare growth trajectories between groups. For that study the comparison between the first (_1) and the second (_2) timepoint is shown for the 22q11DS and TD group seperately.

Abbreviations: AmstNT = Amsterdam Neuropsychological Tasks, MSL = Memory Search Letters and SSV = Shifting Attentional Set Visual; ANT = Attention Network Task; CANTAB = Cambridge Neuropsychological Test Automated Battery, SOC = Stockings of Cambridge and SWM = Spatial Working Memory; CHD = Congenital Heart Defect; CNB = Penn Computerized Neurocognitive Battery; CPT = Continuous Performance Task, IP = Identical Pairs and AX = A before X; DS = Digit Span; GDS = Gordon Diagnostic System; LSp = Listening span tasks; NEPSY = A Developmental NEuroPSYchological Assessment, AARS = Auditory Attention Response Set; N.R. = Not reported; RoB = Risk of Bias; SOPT = Self Ordered Pointing Task; TD = Typically Developing; TMT B = Trail Making Task version B; ToL = Tower of London (/Hanoi, or similar tasks); VF = Verbal fluency; VSp = Visual span task; WCST = Wisconsin Card Sorting Task; WISC-3 = Wechsler Intelligence Scale for Children 3; WM = Working memory.

Methodological quality and/or risk of bias

Risk of bias in individual studies

We assessed seven studies as having a high risk of bias (RoB), thus providing more tentative evidence. Seventeen studies were assessed to have a medium risk of bias, and five studies were assessed to have a low risk of bias. None of the studies, except for one (Yi et al., 2014), actively checked contamination of their control group by inadvertently including cases as controls. However, given the low prevalence of the deletion and the high penetrance of associated phenotypes, the probability of contamination can be considered nearing null. Only two studies reported a post-hoc power analysis (Shashi, Howard, et al., 2010; Sobin et al., 2004). See Table 5.3 for the RoB outcomes and Table 5.4 (Appendix 5-B) for the full quality assessment.

Risk of bias across studies

The risk of bias of the cumulative evidence in the field may be affected by publication bias or selective reporting. In the case of studies reporting on clinical populations, such as 22q11DS, we would argue that publication bias is less likely, because null findings are typically also considered informative in these kinds of populations. Bias in the cumulative evidence presented here, most likely stems various ascertainment biases; for example, individuals recruited via clinical sites are more likely to have prominent phenotypical characteristics. Moreover, given that 22q11DS is a relatively rare disorder, studies may be recruiting participants from the same participant pool and/or reuse participants/data in different articles. Additionally, many studies do not report important demographic information, limiting our ability to confidently generalize these findings to the entire 22q11DS population.

Results of individual studies: EF performance per domain

None of the studies discussed here clearly differentiated between children and adolescents. Of the nine studies on children (mean age < 10), none had a maximum age below 11.5 years. Similarly, none of the four studies that reported on adolescents (mean age > 14) reported a

minimum age of 14 years or higher [1]. Therefore, we decided to not discuss outcomes for children and adolescents separately. This does not preclude a discussion of age effects, however. We address these in the section *EF Development* below.

Results for all EF domains are presented in Figure 5.3. To get a clear image of both the quantity and quality of evidence for a specific outcome, studies have been categorized by their respective risk of bias. As can be seen in Figure 5.3, in most instances the control group or norm group outperformed the 22q11DS group. Updating is the only EF domain for which there is a more mixed distribution of outcomes. None of the studies reported that their 22q11DS sample outperformed the TD group.

Inhibition

Twelve studies had outcome measures that represent inhibition, eight of these had a control group. The three studies that did not have a TD group used normed tasks. There was one additional study (Shashi, Howard, et al., 2010) reporting on inhibition measures, but this study only made a within 22q11DS comparison with different genetic variants (see section *Genetic variation* below).

Shifting

Thirteen studies reported outcomes classified as representing shifting; 10 of these had a control group. The three studies that did not have a TD group used normed tasks. Two additional studies (Carmel et al., 2014; Shashi, Howard, et al., 2010) reported on shifting measures by comparing different genetic variants within a 22q11DS population.

Updating

Eleven studies investigated updating, of which two looked at verbal WM, seven at visuospatial WM, and two looked at both verbal and visuospatial WM. All studies had a control group.

1 It should be noted that Baker et al. (2005) reported a mean age of 16.3 (SD: 2.1) and an age range from 13.8 to 20.8 years

Broad EF

Two studies looked at (composite) measures of broad EF. Both studies had a TD control group. Additionally, Bearden et al. (2004) compared two groups of 22q11DS with different genetic variants. The other study (Yi et al., 2014) had a control group of children with CHD without 22q11DS in addition to their TD group. This study also divided their 22q11DS sample into those with and those without CHD (see section *Congenital heart defects* below).

EF development

Longitudinal studies

All three longitudinal studies had two timepoints. The mean interval between time points was 3 years (range 2.7 – 3.5). A fourth longitudinal study (Antshel et al., 2017) only visualized longitudinal change graphically, without providing exact numbers, and was therefore not further considered in this section.

One study showed that the TD group demonstrated a larger increase in performance on a measure of shifting and one measure of inhibition, but not on another inhibition task (Hooper et al., 2013). Chawner et al. (2017) showed a developmental deficit for children with 22q11DS, meaning that they lag behind their peers, but appeared to develop at a similar rate. The difference between TD and 22q11DS (TD > 22q) remained stable over time on tasks spanning all EF domains. The third study compared the difference between their first and second measurements outcomes for the 22q11DS group and the TD group separately, but they did not compare the longitudinal trajectories of both groups (Antshel, Shprintzen, et al., 2010). They found that children with 22q11DS improved significantly in their performance on a task measuring updating and one task measuring inhibition. No growth was observed on a second inhibition task. The outcomes for shifting were mixed, with growth on one outcome measure, but not on another. The TD group showed significant growth on all outcomes except for the shifting task and one of the outcome measures of an inhibition task.

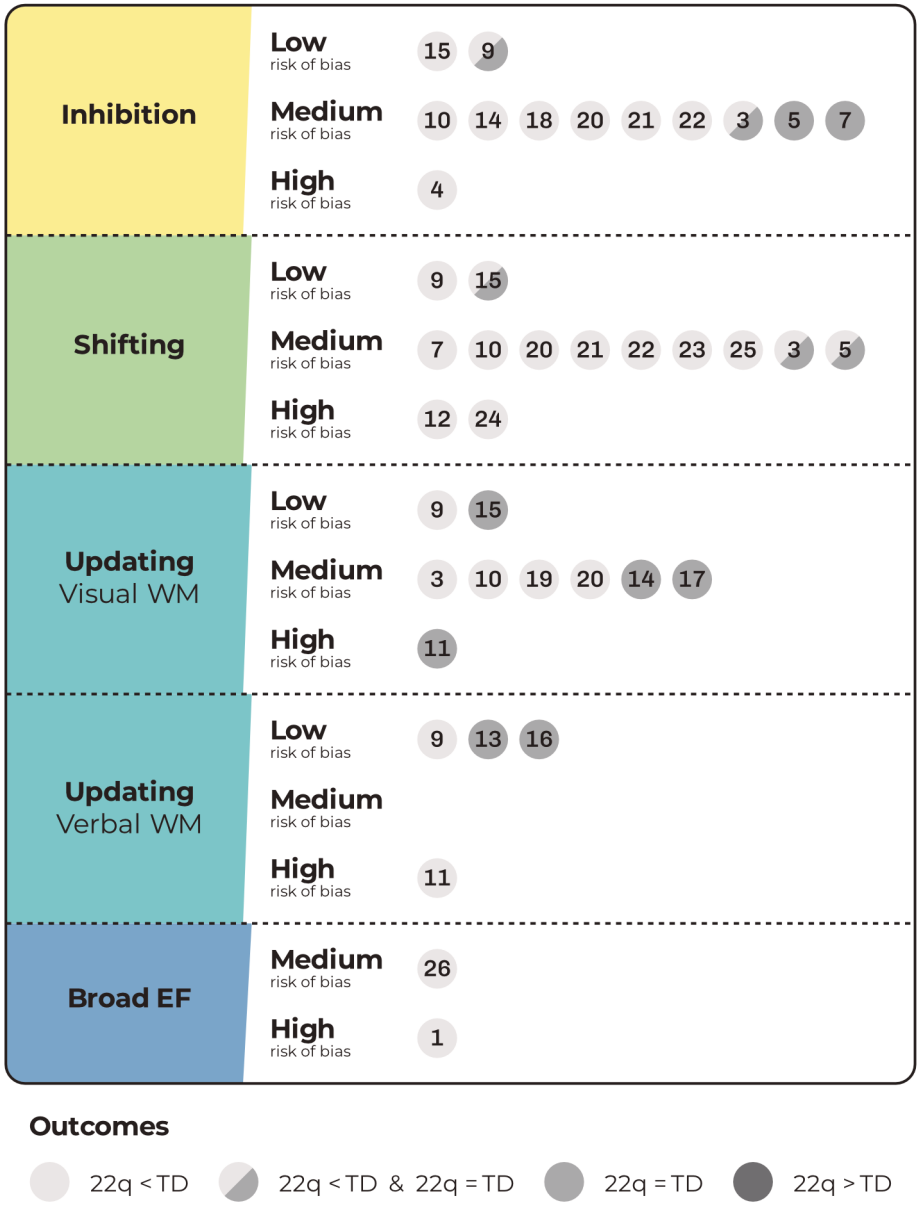


Figure 5.3. Number of studies with certain outcomes per EF domain presented according to their RoB category.

Note. Each circle represents one study (numbers correspond to those in Table 5.3) and the gray scale indicates the outcome. Circles with the two colors represent studies with mixed outcomes. Studies in the 22q < TD or 22q > TD category found a significant difference between groups on at least one task. Studies in the 22q = TD category did not report a significant difference between groups.

Cross-sectional studies with age as a covariate

Six studies took age as a covariate in their analyses. Three of these studies (De Smedt et al., 2008; De Sonneville et al., 2018; Shashi, Keshavan, et al., 2010) did not explicitly report the effect of age on the EF tasks within their 22q11DS sample. Of the remaining three studies, two studies showed that older children with 22q11DS do better than younger children with 22q11DS on a measure of shifting (Carmel et al., 2014; Stoddard et al., 2011). The third study by Shapiro et al. (2014) reported that older children with 22q11DS perform better on an updating task and had higher accuracy for a shifting task, but there was no effect of age on performance on either of the inhibition tasks. They did note that the absence of an effect of age for the inhibition tasks was caused by more variability in the older children with 22q11DS, where a subgroup of children performs similar to TD peers, but some do much worse. There was no clear difference in the mean age of participants between these three studies.

Summary EF development

In summary, the limited evidence from longitudinal studies suggests a developmental deficit: children with 22q11DS lag behind their peers, but appear to develop at a similar rate. The outcomes of cross-sectional studies were mixed, showing either positive correlations between EF and age, or no relation. This is consistent with a developmental deficit.

Results of individual studies considering protective and risk factors

Genetic variation

Six studies investigated the effect of a common *COMT* polymorphism, *COMT* Val^{158}Met, which has been linked to cognitive outcomes in the general population (see section *Biological underpinnings of EF in 22q11DS* above). Five of these made comparisons within their 22q11DS sample only, but one study also compared the 22q11DS groups with a TD group (Baker et al., 2005). The outcomes of the studies classified by their respective risk of bias are presented in Figure 5.4. Outcomes were mixed, but most evidence indicated there was no effect of this

COMT variant on EF performance in children with 22q11DS. Baker et al. (2005) showed that a TD group performed better on measures of verbal WM than the 22q11DS Val[158] carriers, but not the 22q11DS Met[158] carriers. There was no difference between the 22q11DS Val[158] carriers and 22q11DS Met[158] carriers.

One study looked at different *PRODH* variants in their 22q11DS sample. Carmel et al. (2014) looked at the effect of the *PRODH* Arg[185]Trp (rs4819756) polymorphism, reporting no differences on measures of inhibition between Arg[185] and Trp[185] carriers in 22q11DS. No other genotypic variation was investigated in any of the included studies.

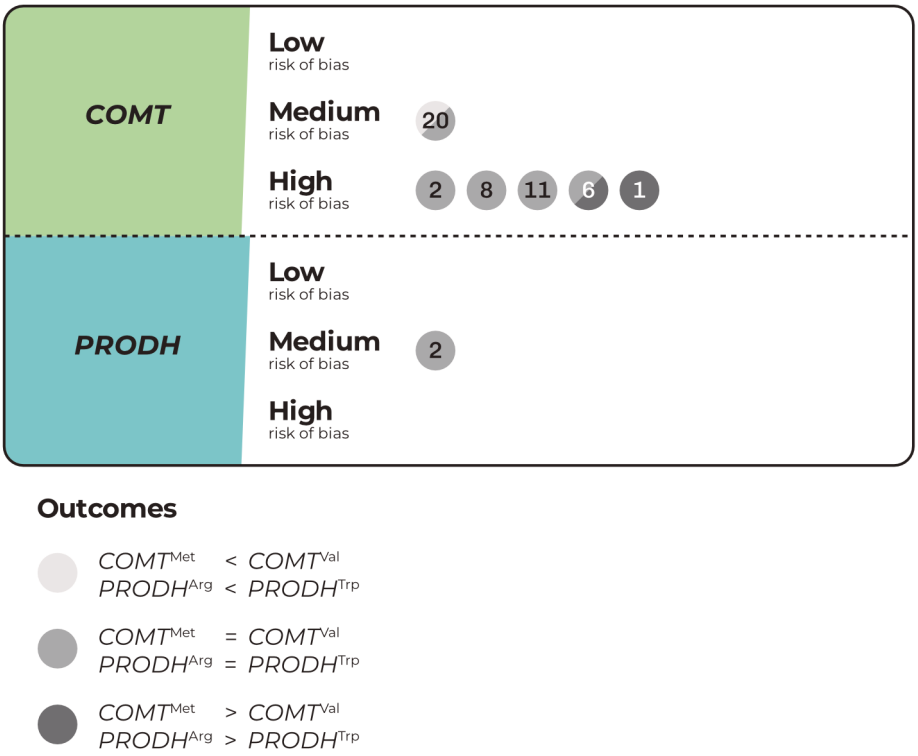


Figure 5.4. Number of studies with certain outcomes comparing genetic variants within their 22q11DS sample presented according to their RoB category.

Note. Each circle represents one study (numbers correspond to those in Table 5.3). The gray scale indicates the outcome. Studies with mixed outcomes are presented as circles with the colors of both outcomes. Studies in the *COMT* Met[158] < Val[158] / *PRODH* Arg[185] < Trp[185] or Met > Val / Arg > Trp category found a significant difference between groups on at least one outcome. Studies in the *COMT* Met[158] = Val[158] / *PRODH* Arg[185] = Trp[185] category did not report a significant difference between groups.

Congenital heart defects

A single study investigating CHD as a factor in EF performance compared children with 22q11DS with (22q+CHD) and without CHD (22q-CHD), children with CHD, but without 22q11DS (CHD-only) and TD children without CHD and 22q11DS (Yi et al., 2014: RoB medium). The 22q11DS groups did not differ from one another and had lower accuracy scores on measures of inhibition, shifting and updating than the TD and the CHD-only group. The latter two groups did not differ from each other. Authors noted that in the CHD-only group and 22q-CHD group factors such as type of CHD and surgery related factors could not be considered due to sample size.

Other potential moderators

Other risk factors as addressed in the introduction are preterm birth, low birth weight, stress, SES, parenting styles, limited unstructured time, play, and physical activity.

The only study investigating SES as a factor in EF performance (Shashi, Keshavan, et al., 2010: RoB medium) found that within their 22q11DS sample there was no relation between parental SES and shifting or inhibition outcomes. There was a relation between SES and EF outcomes in their TD group. They reported that children with 22q11DS and TD controls did not differ on parental SES.

The only study considering the effect of stress, as measured by salivary cortisol, in children with 22q11DS was not related to WM performance (Sanders et al., 2017: RoB medium). They did note that children with 22q11DS had heightened cortisol levels compared to peers.

The other risk factors appear to not yet have been systematically investigated in relation to EF in the 22q11DS population.

Relation EF and intellectual abilities

Although many studies reported both IQ and EF data in 22q11DS, correlation analyses between the two were scarce. In most studies, both IQ and EF were used as independent predictors of other outcomes, such as social skills or psychopathology. Three studies investigated the relation between IQ and EF directly. Kates et al. (2007: RoB medium) found that there was no significant correlation

between IQ scores and d-prime scores (representing accuracy) on their visual WM task (r = 0.2). De Sonneville et al. (2018: RoB medium) also reported no correlation between IQ scores and inhibition or shifting outcomes, however, contrary to Kates et al. (2007), they did observe a significant correlation between IQ and updating (r = 0.24). Shapiro et al. (2014: RoB medium) reported that IQ did not predict overall task performance, suggesting that the EF impairments they observed were not fully explained by intellectual abilities.

Four studies controlled for IQ in their analyses of EF data. Three of those reported that their EF results remained significant after controlling for IQ (Antshel et al., 2017: RoB medium; Bearden et al., 2004: RoB high; De Sonneville et al., 2018), but the fourth reported that results were no longer significant (De Smedt et al., 2008: RoB low). Two other studies appeared to have done some analyses while controlling for IQ, but the details of this were unclear (Brankaer et al., 2017: RoB low; Niklasson & Gillberg, 2010: RoB medium).

Discussion

In this systematic review, we investigated executive functioning (EF) in a selected population with a homogeneous etiology: children and adolescents with 22q11.2 deletion syndrome (22q11DS). Next to advancing knowledge of the cognitive phenotype associated with this syndrome, our review also informs our understanding of typical development by providing a focused context for the investigation of specific mechanisms and risk factors. In doing so, we identify gaps in the literature, highlight opportunities for future research, and discuss some clinical implications.

Our findings indicate frequent impairments in all domains of EF in individuals with 22q11DS, except for the subdomain updating. Evidence for updating is inconclusive but seems to suggest updating abilities might be a relative strength in (early) childhood. While in the general population EF is affected by congenital heart defects (CHD) and genetic variation, tentative evidence shows these relations might be absent in 22q11DS. This sheds light on the specific mechanisms underlying EF development and how they can be disrupted. Furthermore, EF abilities in 22q11DS seem to be independent of intellectual abilities, supporting the theory that in the general

population EF and intelligence are separate constructs. Below we will further discuss the implications of these results for our understanding of typical EF development.

EF profile and its developmental trajectory in 22q11DS

The current review yields substantial evidence that children and adolescents with 22q11DS have EF impairments in the domains of inhibition and shifting. On the other hand, evidence for deficits in updating, both visual and verbal working memory (WM), was mixed. The mixed evidence with respect to verbal WM impairment may be related to the reported IQ decline, including verbal IQ, during childhood and early adolescence in individuals with 22q11DS (Duijff et al., 2013; Vorstman et al., 2015). Notably, the two studies that observed impaired verbal WM studied groups with a higher mean age (Albert et al., 2018; Baker et al., 2005), whereas the two that found no verbal WM impairment studied younger children (Brankaer et al., 2017; De Smedt et al., 2008). Conceivably, verbal WM might follow a trajectory comparable to that of verbal IQ in a subset of individuals with 22q11DS. Moreover, a recent study reports that updating may be more impaired in older individuals with 22q11DS (Morrison et al., 2020), suggesting the different EF domains may follow differing developmental trajectories and result in different end states.

Regarding the developmental trajectory of EF, limited evidence suggests a developmental deficit. Children with 22q11DS generally perform less well than typically developing peers, but this deficit appears to remain stable over time, indicating that they develop at a rate similar to peers. We could not draw conclusions about the development of separate EF domains due to the small number of longitudinal studies and the differences in measures and analyses that were reported. However, Maeder et al. (2016, not included due to large age range) found that children, adolescents, and young adults with 22q11DS differ in their developmental trajectory on measures of verbal WM from controls, whereas the developmental trajectory of inhibition appears similar. This, taken together with the findings of Morrison et al. (2020) described above, would suggest a developmental deficit is not present for all domains throughout development.

Future studies should investigate whether verbal WM is indeed relatively spared during childhood as compared to other EF domains in 22q11DS, and to what extent verbal WM is related to the developmental trajectory of verbal IQ. Furthermore, more research is necessary to verify whether the separate EF domains in children with 22q11DS develop similarly to trajectories described in the typical population (Best & Miller, 2010). As suggested above, this may not be the case for inhibition and verbal WM. Differences in developmental trajectories between EF domains imply differentiation and might thus provide clues regarding the developmental progression of EF differentiation.

Risk factors for impaired EF in the context of 22q11DS

We considered endogenous and exogenous risk factors associated with EF in the general population, which are of particular relevance to, or are more prevalent in the 22q11DS population. Here we discuss some directions for future research based on the outcomes of this review.

Genetic variation.

A few studies considered the effect of specific genetic variants on EF outcomes. The most frequently investigated genetic variant (*COMT* Val^{158}Met) has been associated with EF in the general population (e.g., Barnett et al., 2007; Moriguchi & Shinohara, 2018), although not unequivocally (e.g., Barnett et al., 2008; but Mier et al., 2010). Similarly, the results of this review regarding the effect of this genetic variant on the EF performance of children with 22q11DS were mixed. Variants in another gene (*PRODH*) have been linked to changes in prefrontal-striatal brain circuits, impaired cognitive performance, and schizophrenia (Jacquet et al., 2003; Kempf et al., 2008; Raux et al., 2007). One study considered a single variant of this gene (*PRODH* Arg^{185}Trp) but observed no effect on EF in children with 22q11DS. These inconclusive findings so far mirror the observations of such genotype-phenotype associations in the general population (e.g., Mier et al., 2010), reflecting the complexity of the pathway from genes to behavioral expression. Future investigations can further elucidate this, amongst others by investigating the effects of other functional

variants of genes in the 22q11.2 region and their interactions with other genes (Bender et al., 2005; Jonas et al., 2014; Paterlini et al., 2005; Vorstman et al., 2009; De Koning et al., 2015). Although the effect of a single genetic variant on EF might be difficult to observe, these studies can elucidate which mechanisms and pathways are crucial to EF development. For example, 22q11DS also impacts genes implicated in mitochondrial functioning (Li et al., 2019; Meechan et al., 2011; Warren & Morrow, 2019), which has been linked to developmental disorders and cognitive impairments (El-Ansary, 2012; Fernandez et al., 2019). Future research can further our understanding of the exact role of mitochondrial functioning in cognitive outcomes. Furthermore, recently the cumulative effect of common genetic variants has been shown to modulate cognitive outcome (IQ) in the presence of the 22q11.2 deletion (Davies et al., 2020). Future studies could expand this approach to examine the polygenic contribution to the EF phenotype as well. Lastly, while it has been suggested that smaller deletions that are located at the end of the region may lead to milder phenotypes (Rump et al., 2014; McDonald-McGinn et al., 2015), none of the included studies considered possible effects of types of 22q11.2 deletions. Such studies could contribute to our knowledge of which genes should be in included in studies looking at the polygenic contributions to EF phenotype.

Congenital heart defects.

The only study that considered CHD, found no effect on EF abilities in either the participants with or without 22q11DS, nor in those with or without CHD (Yi et al., 2014). The findings in their sample without 22q11DS differed from other studies in the general population, which have so far broadly supported an association between CHD and poorer cognitive outcomes, such as decreased EF performance or a lower IQ (Sterken et al., 2015). However, Yi et al.'s findings do appear to be in line with other research in individuals with 22q11DS that observed no effect of CHD on EF (Fountain et al., 2014, not included due to age range). Likewise, Zhao et al. (2018) found no effect of CHD on IQ in a sample of more than 1,000 individuals with 22q11DS. This apparent absence of an effect of CHD in the 22q11DS population is further supported by previous studies that detected no effect on a

variety of cognitive outcomes (Duijff, Klaassen, Beemer et al., 2012; De Smedt et al., 2007; Gerdes et al., 1999; Niklasson & Gillberg, 2010; Swillen et al., 2005). The above seems to indicate that, at least for certain high impact genetic variants, the direct impact of this genetic variant on the brain and cognitive functioning exceeds the hypothesized impact of CHD. The potential relevance of these findings is that it should prompt a re-examination of the observed adverse neurodevelopmental trajectories in children with CHD. Possibly, in addition to the hypothesized assault of CHD on the developing brain, the genetic variant underlying the CHD could also directly impact neurodevelopment (McQuillen & Miller, 2010; Nattel et al., 2017). Indeed, a substantial proportion of genes associated with CHD in the general population are also associated with an increased risk of neurodevelopmental outcomes (e.g., Homsy et al., 2015). More specifically for 22q11DS, the gene *TBX1* in 22q11DS, which is thought to be one of the main contributors to CHD but has also been linked to psychiatric phenotypes (Paylor et al., 2006). This would help to explain the observed concurrence of both phenotypes in some of these children.

Other risk factors: Socioeconomic status and stress

Only one study considered socioeconomic status (SES) but reported no effect of it on EF (Shashi, Keshavan, et al., 2010). This corresponds with other work showing no correlation between SES and EF measures in children with 22q11DS (Allen et al., 2014, not included due to age range). This contrasts with findings in the general population, which suggests that the effect of SES on EF might be mediated by other factors in this population. Future research can elucidate the exact mechanisms underlying the relation between EF and SES.

Tentative evidence from a single study (Sanders et al., 2017) showed heightened cortisol levels, as an indicator for stress, but this did not correlate with EF performance. Again, this raises the question whether the impact of the deletion exceeds the impact of other factors. Jacobson et al. (2016, not included due to task type) also reported heightened cortisol in children with 22q11DS, but in their study there was a significant relation with memory and attention. However, in adults with 22q11DS reduced levels cortisol have been

reported, likely as the result of chronic overactivation of the hypothalamic–pituitary–adrenal axis (Van Duin et al., 2019). More research into the effect of stress on EF in 22q11DS is warranted, especially as this population is suggested to be more vulnerable to consequences of stress due to pituitary dysmaturation (Sandini et al., 2020). Such investigations can also further guide theories on the effect of stress on neural pathways subserving (early) cognitive development.

Relation EF and intellectual abilities

Most evidence suggests that EF deficits in children with 22q11DS are not (fully) explained by their intellectual abilities. This is further supported by studies in individuals with 22q11DS reporting that their EF results remained significant after controlling for IQ (Lewandowski et al., 2007, not included due to overlap; Maeder et al., 2016). Studies in other clinical populations also show a dissociation between EF and intellectual abilities. For example, despite an average to high IQ, EF impairments have been reported in individuals with Attention Deficit Hyperactivity Disorder (Antshel, Faraone, et al., 2010; Brown et al., 2009; Schuck & Crinella, 2005). Similar observations have been made in children with high-functioning Autism Spectrum Disorder (Lai et al., 2017). Our results are in line with these findings showing that executive dysfunction can occur irrespective of level of intellectual abilities.

These results support the hypothesis that EF and IQ are separate cognitive constructs, as has been previously argued for typically developing children (Ardila et al., 2000; Crinella & Yu, 1999). Nonetheless, in typically developing children, IQ and EF are not completely independent, and are in fact correlated with one another (Arffa, 2007; Ardila et al., 2000). The current findings seem to indicate this correlation is weak in children with 22q11DS, although this may in part be due to little power. Future research should address this and is required to draw robust conclusions.

Clinical implications

This systematic review shows that EF impairments are commonly found in children and adolescents with 22q11DS. The knowledge that

WM might be relatively preserved during childhood may be important to clinical practice. Relatively stronger verbal WM during childhood may cause children with 22q11DS to appear more competent than they are, increasing the likelihood of creating an imbalance between environmental demands and the child's abilities, heightening the risk for psychiatric problems (Fiksinski et al., 2018). Additionally, relatively preserved (verbal) WM in childhood, might provide an entry for interventions that can help improve later outcomes. Similar to the general population, EF abilities in 22q11DS have been shown to predict later outcomes, such as adaptive functioning and psychopathology (Albert et al., 2018; Fiksinski et al., 2019; Hamsho et al., 2017). Future research should investigate the development and effectiveness of interventions aimed at strengthening EF (e.g., Kirk et al., 2015) and explore whether such interventions could be beneficial to both children with 22q11DS, but also to other children predisposed to psychiatric illness.

Additionally, clinicians might benefit from the identification of other risk factors for EF impairment in the 22q11DS population, as risk factors previously identified in the general population, such as CHD and low SES, do not appear to have the same impact in this population.

Gaps in the literature and opportunities for future research

Our review identified several gaps in the current literature, thereby revealing opportunities for future studies. Firstly, studies considering various potential risk factors, both endogenous and exogenous, for EF impairment in 22q11DS are scarce. Risk factors associated with EF deficits, like CHD, stress, and SES, have been investigated, but only by a small number of studies. Factors such as preterm birth, low birth weight, parenting styles, limited unstructured time, play, and physical activity have not at all been investigated in any of the included studies, even though many of these factors are or may be more prevalent in 22q11DS (see section *Endogenous* - and *Exogenous risk factors for EF impairment* in *Introduction*). As we argued in the introduction, the 22q11DS population thus provides an opportunity to reduce variability in the study of these factors. Similarly, studies investigating the developmental differentiation of EF in 22q11DS are

scarce. Therefore, it is currently unclear if and how developmental EF differentiation differs from typical development. Studies looking at this could help validate models of EF development.

Secondly, while 22q11DS studies are likely hampered by various ascertainment biases, many currently available studies frequently do not report important characteristics of their study cohort (e.g., IQ, CHD, SES, etc.), making it difficult to assess whether they report on representative subsamples. Considering that sample sizes in some studies of the 22q11DS population are understandably small, the reliability of outcomes would benefit from further reduced heterogeneity within these samples (e.g., age range, phenotypic characteristics, etc.). Large cohort or population studies reporting the prevalence and severity of various symptoms should provide an unbiased characterization of the 22q11DS population. Conclusions concerning EF development in 22q11DS, and the effect of age were limited by the relatively high mean age at inclusion and the wide age ranges characterizing most study samples. Studies investigating EF in early childhood (<6 years) were absent precluding any insight into early cognitive development. More longitudinal studies covering the entire developmental period are essential for describing developmental trajectories. Longitudinal studies starting at preschool age could show whether EF impairments are present from an early age on and whether similar associations with an increased risk for psychiatric disorders can be observed (Vorstman et al., 2015). This could further support research on predictors of schizophrenia in the general population, for which the 22q11DS population can be taken as a model (Fiksinski et al., 2019; Gur et al., 2017; Insel, 2010).

Strengths and limitations

We used predefined criteria for classifying which EF task measured which EF domain, independent of the classification in the original study. This reduces variability in our results by eliminating differences due to terminology and provides a clear image of what is being compared. The intricate nature of EF complicates assessment in a consistent and reliable way. As for all cognitive functions, behavioral indices of EF are indirect and require interpretation by researchers (Paap & Sawi, 2016). Moreover, tasks meant to measure EF are

frequently unable to measure only one single EF domain without interference of the other domains. This, in addition to the large variety of tasks used, makes it difficult to draw reliable and generalizable conclusions about the different EF domains in any population, including 22q11DS. By broadly grouping tasks and only including studies using tasks that are widely considered to measure EF, we have tried to diminish the effect of this to the best of our abilities.

This review focused on children and adolescents for which we used inclusionary restrictions with regard to mean age, age range, and sample size. Although the specifics of these restrictions are based on a reasonable rationale (see section *Study selection*), other choices could also be justified. However, given the variability in this population, we argue that the selected criteria ensure generalizability to the entire 22q11DS population and strengthen conclusions by reducing variability. Nonetheless, the selected upper age limit did limit our ability to review the full developmental trajectory into adulthood. With more data becoming available in the older age groups, this is important to examine in future work. The findings and outcomes discussed here could be further supplemented with biomarkers such as brain imaging or gene expression studies, which were not considered in this review.

Despite the limitations described above, the current review identifies relative strengths (verbal WM) and weaknesses in EF for children with 22q11DS. This review also finds tentative evidence in this population for a decreased or absent effect of certain risk factors for impaired EF, like congenital heart defect and low socioeconomic status. Our findings suggest the developmental trajectory of updating may differ to some extent from that of inhibition and switching. More research is needed to confirm this and to determine whether this is due to differences in the mechanisms underlying these EF domains. Lastly, our findings support studies in typically developing children that suggest that EF and intelligence are correlated but distinct cognitive constructs.

Chapter 5 – Supplementary Material

Appendix 5-A. Exact search queries per search engine

Pubmed

((22q11 deletion syndrome[mh]) OR (22q11*[Title/Abstract] OR *22q11[Title/Abstract] OR del22q11*[Title/Abstract] OR VCFS[Title/Abstract] OR Velocardiofacial syndrome[Title/Abstract] OR Velo-cardio-facial syndrome[Title/Abstract] OR VCF syndrome[Title/Abstract] OR DiGeorge syndrome[Title/Abstract] OR Di-George syndrome[Title/Abstract] OR Shprintzen syndrome[Title/Abstract] OR Velocardiofacial[Title/Abstract] OR Velo-cardio-facial[Title/Abstract] OR DiGeorge[Title/Abstract] OR Di-George[Title/Abstract] OR Shprintzen[Title/Abstract] OR CATCH22[Title/Abstract] OR catch 22[Title/Abstract] OR Sedlackova syndrome[Title/Abstract] OR Takao syndrome[Title/Abstract] OR Cayler cardiofacial syndrome[Title/Abstract] OR Conotruncal Anomaly Face Syndrome[Title/Abstract])) AND (Executive funct* [Title/Abstract] OR Executive control[Title/Abstract] OR Executive dysfunc*[Title/Abstract] OR Working memory[Title/Abstract] OR Inhibition[Title/Abstract] OR Attention*[Title/Abstract] OR Cognitive flexibility[Title/Abstract] OR Shifting[Title/Abstract] OR Switching[Title/Abstract] OR Prefrontal cognition[Title/Abstract])

OVID Psychinfo

((22q11* or *22q11 or del22q11* or VCFS or Velocardiofacial syndrome or Velo-cardio-facial syndrome or VCF syndrome or DiGeorge syndrome or Di-George syndrome or Shprintzen syndrome or Velocardiofacial or Velo-cardio-facial or DiGeorge or Di-George or Shprintzen or CATCH22 or catch 22 or Sedlackova syndrome or Takao syndrome or Cayler cardiofacial syndrome or Conotruncal Anomaly Face Syndrome) and (Executive funct* or Executive control or Executive dysfunc* or Working memory or Inhibition or Attention* or Cognitive flexibility or Shifting or Switching or Prefrontal cognition)).ab

EMBASE

([article]/lim OR [article in press]/lim) AND ('22q11*':ti,ab,kw OR 'del22q11*':ti,ab,kw OR 'vcfs':ti,ab,kw OR 'velocardiofacial syndrome':ti,ab,kw OR 'velo-cardio-facial syndrome':ti,ab,kw OR 'vcf syndrome':ti,ab,kw OR 'digeorge syndrome':ti,ab,kw OR 'di-george syndrome':ti,ab,kw OR 'shprintzen syndrome':ti,ab,kw OR 'velocardiofacial':ti,ab,kw OR 'velo-cardio-facial':ti,ab,kw OR 'digeorge':ti,ab,kw OR 'di-george':ti,ab,kw OR 'shprintzen':ti,ab,kw OR 'catch22':ti,ab,kw OR 'catch 22':ti,ab,kw OR 'sedlackova syndrome':ti,ab,kw OR 'takao syndrome':ti,ab,kw OR 'cayler cardiofacial syndrome':ti,ab,kw OR 'conotruncal anomaly face syndrome':ti,ab,kw OR 'chromosome deletion 22q11'/exp) AND ('executive funct*':ti,ab,kw OR 'executive control':ti,ab,kw OR 'executive dysfunc*':ti,ab,kw OR 'working memory':ti,ab,kw OR 'inhibition':ti,ab,kw OR 'attention*':ti,ab,kw OR 'cognitive flexibility':ti,ab,kw OR 'shifting':ti,ab,kw OR 'switching':ti,ab,kw OR 'prefrontal cognition':ti,ab,kw) NOT ([medline]/lim AND [embase]/lim)

Appendix 5-B. Full risk of bias assessment.

Table 5.4. Full risk of bias assessment of studies included in the analysis.

Study				*Aim*	*Participants*				*Data collection and analysis*			*Out-comes*		*If longitudinal:*			
	Controls?	*Longitudinal?*	*n 22q11DS*	1	2	3	4	5	6	7	8	9	10	11	12	13	Risk of Bias
Albert et al. (2018)	Yes	No	63	+	+	-/+	+	-/+	+	-/+	-/+	-/+	+	n.a.	n.a.	n.a.	**Low**
Antshel et al. (2010) [a]	Yes	Yes	80	-/+	-	-	+	-	+	-/+	-/+	-/+	-/+	+	-	+	**Medium**
Antshel et al. (2017)	Yes	No	78	+	-/+	-	-/+	-/+	+	-	-/+	-	-/+	n.a.	n.a.	n.a.	**Medium**
Baker et al. (2005)	Yes	No	25	+	-/+	-	-	-/+	-/+	-/+	-/+	-/+	-/+	n.a.	n.a.	n.a.	**High**
Bearden et al. (2004)	No	No	44	-/+	-	-	n.a.	-	+	+	-/+	-	+	n.a.	n.a.	n.a.	**High**
Bish et al. (2005)	Yes	No	18	+	-	-	-	-	+	-	-	-	+	n.a.	n.a.	n.a.	**High**
Brankaer et al. (2017)	Yes	No	25	+	+	+	+	-/+	+	+	-/+	-/+	+	n.a.	n.a.	n.a.	**Low**
Campbell et al. (2015)	Yes	No	24	+	+	-/+	+	-	-/+	-/+	-/+	-	+	n.a.	n.a.	n.a.	**Medium**

Carmel et al. (2014)	No	No	60	+	-	-/+	n.a.	-	+	-/+	-/+	-	+	n.a.	n.a.	n.a.	**Medium**
Chawner et al. (2017)	Yes	Yes	75	+	+	-	+	+	+	-/+	+	-/+	+	-/+	+	+	**Low**
Cunningham et al. (2018)	Yes	No	70	+	+	+	+	-/+	+	+	-/+	-/+	+	n.a.	n.a.	n.a.	**Low**
De Smedt et al. (2008)	Yes	No	25	+	+	-/+	+	-/+	+	+	-/+	-/+	+	n.a.	n.a.	n.a.	**Low**
de Sonneville et al. (2018)	No	No	58	+	-	-/+	n.a.	-/+	+	+	-/+	-/+	+	n.a.	n.a.	n.a.	**Medium**
Hooper et al. (2013)	Yes	Yes	42	-/+	-/+	+	+	-/+	+	-/+	+	-/+	+	+	-	-	**Medium**
Kates et al. (2007)	Yes	No	17	+	+	-	-/+	-/+	-/+	+	-/+	-/+	+	n.a.	n.a.	n.a.	**Medium**
McCabe et al. (2014)	Yes	No	25	+	+	-	-/+	-/+	-/+	-/+	-/+	-	+	n.a.	n.a.	n.a.	**Medium**
Niklasson et al. (2005)	No	No	30*	-/+	+	-/+	n.a.	-	+	-	-	-	+	n.a.	n.a.	n.a.	**High**
Niklasson et al. (2010)	No	No	30	-/+	-	-/+	n.a.	-/+	+	+	+	+	-/+	n.a.	n.a.	n.a.	**Medium**
Sanders et al. (2017)	Yes	No	20	+	+	-/+	-/+	-/+	-	-/+	+	-/+	+	n.a.	n.a.	n.a.	**Medium**
Shapiro et al. (2014)	Yes	No	71	+	+	-/+	-	-	-/+	+	-/+	-	+	n.a.	n.a.	n.a.	**Medium**

Shashi et al. (2010a)	No	No	40	-/+	-	-	-/+	-	+	-	-	-	-	n.a.	n.a.	n.a.	**High**
Shashi et al. (2010b)	Yes	No	65	+	-	-/+	+	-/+	+	+	+	-/+	+	n.a.	n.a.	n.a.	**Medium**
Shashi et al. (2012)	Yes	No	66	+	-/+	-/+	+	-	+	-	-	-/+	+	n.a.	n.a.	n.a.	**Medium**
Sobin et al. (2004)	Yes	No	32	+	-/+	-	+	-	+	-/+	-/+	-	+	n.a.	n.a.	n.a.	**Medium**
Sobin et al. (2005) [b]	Yes	No	21	+	-/+	-	+	-	+	-	-/+	-	+	n.a.	n.a.	n.a.	**High**
Sobin et al. (2005) [c]	No	No	40	+	-/+	+	n.a.	-/+	+	-	-/+	n.a.	+	n.a.	n.a.	n.a.	**Medium**
Stoddard et al. (2011)	Yes	No	60	+	-	-	-	-	+	-/+	+	-/+	+	n.a.	n.a.	n.a.	**Medium**
Stoddard et al. (2012)	No	No**	53	-/+	-	-	-/+	-	+	-	-/+	-	+	n.a.	n.a.	n.a.	**High**
Yi et al. (2014)	Yes	No	54	+	+	+	+	-/+	+	+	-/+	-/+	+	n.a.	n.a.	n.a.	**Medium**

Note. Numbers or RoB items correspond to assessment criteria described in Table 5.2. Legend: - = no or very limited information; -/+ = some information, but incomplete/not sufficiently detailed; + = information present and sufficiently detailed/qualitatively good; n.a. = not applicable.

* for Tower of London; *n* = 22 for Trail Making Test B

** There are controls, but they have not been genotyped for COMT and this paper is only considered for its outcomes regarding genetic variance.

a. Antshel. Shprintzen, et al. (2010)

b. Sobin Kiley-Brabeck, Daniels, et al. (2005)

c. Sobin, Kiley-Brabeck, & Karayiorgou (2005)

Chapter 6

Executive functioning in preschoolers with 22q11.2 deletion syndrome and the impact of congenital heart defects.

Everaert, E., Vorstman, J., Selten, I., Slieker, M., Wijnen, F., Boerma, T.*, & Houben, M.* (*under review*). Executive functioning in preschoolers with 22q11DS and the impact of congenital heart defects. *Under review with Journal of Neurodevelopmental Disorders*.
*Contributed equally as last authors

Abstract

Background. Executive functioning (EF) is an umbrella term for various cognitive functions that play a role in monitoring and planning to effectuate goal-directed behavior. The 22q11.2 deletion syndrome (22q11DS), the most common microdeletion syndrome, is associated with a multitude of both somatic and cognitive symptoms, including EF impairments in school-age and adolescence. However, results vary across different EF domains and studies with preschool children are scarce. As EF is critically associated with later psychopathology and adaptive functioning, our first aim was to study EF in preschool children with 22q11DS. Our second aim was to explore the effect of congenital heart defects (CHD) on EF abilities, as CHD are common in 22q11DS and have been implicated in EF impairment in individuals with CHD without a syndromic origin.

Methods. All children with 22q11DS (*n* = 44) and typically developing (TD) children (*n* = 81) were 3.0 to 6.5 years old and participated in a larger prospective study. We administered tasks measuring visual selective attention, visual working memory, and a task gauging broad EF abilities. The presence of CHD was determined by a pediatric cardiologist based on medical records.

Results. Analyses showed that children with 22q11DS were outperformed by TD peers on the selective attention task and the working memory task. As many children were unable to complete the broad EF task, we did not run statistical analyses, but provide a qualitative description of the results. There were no differences in EF abilities between children with 22q11DS with and without CHDs.

Conclusion. To our knowledge, this is the first study measuring EF in a relatively large sample of young children with 22q11DS. Our results show that EF impairments are already present in early childhood in children with 22q11DS. In line with previous studies in older children with 22q11DS, CHDs do not appear to have an effect on EF performance. These findings might have important implications for early intervention and support the improvement of prognostic accuracy.

Key words: *22q11.2 deletion syndrome; 22q11DS; Executive functioning; Congenital Heart Defect; Selective Attention; Working Memory; Velocardiofacial syndrome; DiGeorge syndrome*.

Introduction

The 22q11.2 deletion syndrome (22q11DS; OMIM #192430, #188400, #611867), previously also referred to as DiGeorge or Velo-Cardio-Facial Syndrome, is the most common chromosomal microdeletion syndrome in humans and has an estimated incidence of 1 per 2,148 (Blagojevic et al., 2021). It results from a hemizygous microdeletion on the long arm of chromosome 22 (Edelmann et al., 1999; Morrow et al., 1995; Saitta et al., 2004). The syndrome has a widely variable phenotype and symptoms can include, but are not limited to, congenital heart defects (CHD), palatal abnormalities, immunodeficiency, endocrine abnormalities, intellectual disability, and an increased risk for psychiatric disorders (McDonald-McGinn et al., 2015). In addition, impairments have been reported in various cognitive domains, including executive functioning (EF; Moberg et al., 2018).

A recent systematic review of EF abilities in children and adolescents with 22q11DS showed a relative paucity of research on the EF abilities of preschool-aged children with 22q11DS (Everaert et al., 2021). As EF is related to functional outcomes later in life (see section *Clinical importance of EF*), an accurate description of early EF abilities in children with 22q11DS can have important clinical implications for prognosis and early intervention. Here, we compare EF performance of 3.0- to 6.5-year-old children with 22q11DS to typically developing (TD) peers. Furthermore, we investigate whether the presence of CHD is associated with EF skills in children with 22q11DS, as CHD are common in the 22q11DS population and are associated with EF deficits in the general population (Mebius et al., 2017; Sterken et al., 2015).

The organization and development of executive functioning

EF refers to higher-level cognitive functions that regulate lower-level cognitive processes to achieve goal-directed behavior (Baddeley & Hitch, 1974; Barkley, 2012; Diamond, 2013; Friedman & Miyake, 2017; Jurado & Rosselli, 2007). The most commonly proposed EF components are *updating*, *inhibition*, and *shifting* (Miyake et al., 2000). *Updating* refers to the ability to store, update, and manipulate

information in working memory (referred to as working memory (WM) in the remainder of this paper); *inhibition* refers to the ability to ignore irrelevant stimuli and suppress habitual responses; and *shifting* refers to the ability to smoothly transition between internal states and tasks. In early childhood, these components are undifferentiated (Hughes et al., 2009; Wiebe et al., 2008; Wiebe et al., 2011; Willoughby et al., 2012); subsequent differentiation is gradual with distinct developmental trajectories (Best & Miller, 2010; Brydges et al., 2014; Huizinga et al., 2006). This is in line with the structural and functional development of the prefrontal cortex (Best et al., 2009; Fiske & Holmboe, 2019; Satterthwaite et al., 2013), which is the primary brain region associated with EF (Alvarez & Emory, 2006).

Expanding on the model of Miyake et al. (2000), Garon et al. (2008) proposed a hierarchical view of EF with selective attention as a basic cognitive function essential for the development of EF (see Figure 6.1). Selective attention refers to the ability to direct attentional resources to a specific target, highlighting its features while diminishing target-irrelevant features (Gazzaley, 2011). Attentional processes rapidly develop during early childhood, with selective attention emerging from 9 months onwards (Hendry et al., 2016). Indeed, measures of attention during infancy predict EF abilities in toddlerhood (Holmboe et al., 2008; Johansson et al., 2015). At the age of 2,5 years, selective attention, specifically, has been shown to predict working memory and inhibition skills at 3 years of age (Veer et al., 2017). Thus, given its importance for the development of other EF components, selective attention can be considered a highly relevant function in describing children's EF profile at the preschool age.

EF in 22q11DS

A recent systematic review reported impairments in the subdomains of inhibition and shifting in school-aged children and adolescents with 22q11DS (Everaert et al., 2021). Findings for working memory (WM), however, were inconclusive. For verbal WM, the mixed outcomes may be explained by developmental changes. Studies with younger children with 22q11DS have not found differences in verbal WM skills in comparison to TD peers (Brankaer et al., 2017; De Smedt et al., 2008), whereas studies with older children have (Albert et al.,

2018; Baker et al., 2005). Verbal WM may thus be a relative strength in early childhood. Several studies on visuospatial WM report weaker performance of children with 22q11DS (Albert et al., 2018; Antshel et al., 2017; De Sonneville et al., 2018; Sanders et al., 2017; Shapiro et al., 2014), although others observed no difference with TD peers (Baker et al., 2005; Campbell et al., 2015; Cunningham et al., 2018; Kates et al., 2007). However, most studies report age ranges that span more than 7 years and cover late childhood to adolescence (≥8 to ≤18 years old), making it difficult to determine whether visuospatial WM is already impaired in early childhood (≤7 years old).

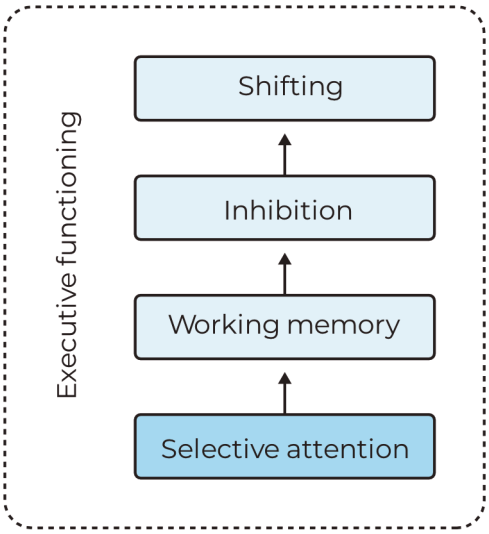


Figure 6.1. Simplified schematic illustration of EF structure according to the models of Miyake et al. (2000) and Garon et al. (2008).

Attentional deficits have also been reported in individuals with 22q11DS (e.g., Cabaral et al., 2012; Cunningham et al., 2018; Howley et al., 2012; Maeder et al., 2021; Sobin et al., 2005). However, selective attention specifically has not yet been studied in detail. One study examined selective attention as a predictor of social cognition and reported that children with 22q11DS (5-13 years) made more errors than TD controls on the selective attention task (Peyroux et al., 2020). To our knowledge, however, there are no studies that have investigated selective attention as a primary outcome in children with 22q11DS.

Clinical importance of EF

EF has been implicated in many domains of functioning, as well as quality of life, and mental and physical health (Diamond, 2013). For example, EF skills are known to predict later academic achievement and language outcomes for both TD children (Slot & von Suchodoletz, 2018; Spiegel et al., 2021; Valcan et al., 2020) and children with 22q11DS (Albert et al., 2018; Hamsho et al., 2017, but see Maeder et al., 2016). Moreover, in the general population, EF is associated with later physical and mental health outcomes (Snyder et al., 2015; Trossman et al., 2021). In 22q11DS, EF has been shown to relate to adaptive functioning and daily living skills (Albert et al., 2018; Fiksinski et al., 2019). Accordingly, in the general population, EF impairments have been associated with increased levels of psychopathology (McGrath et al., 2016) and developmental disorders, such as attention deficit hyperactivity disorder and autism spectrum disorder (Corbett et al., 2009; Happé et al., 2006; Lai et al., 2017), all of which occur at increased rates in children with 22q11DS (Albert et al., 2018; Antshel et al., 2017; Biswas & Furniss, 2016; Fiksinski et al., 2018; McDonald-McGinn et al., 2015). Deficits in EF have furthermore been suggested to precede the onset of schizophrenia (Erlenmeyer-Kimling et al., 2000; Fusar-Poli et al., 2012; Knowles et al., 2015; Morey et al., 2005; Simon et al., 2007). As 22q11DS is the strongest single genetic variant associated with schizophrenia (Marshall et al., 2017; McDonald-McGinn et al., 2015), an accurate description of early EF abilities in children with 22q11DS can have important clinical implications for prognosis and early intervention (e.g., Johann & Karbach, 2019; Wass et al., 2012).

Congenital Heart Defects

In the general population, the presence of CHDs is associated with poorer EF outcomes (Mebius et al., 2017; Sterken et al., 2015). CHDs are common in 22q11DS, with prevalence rates estimated from 31% to as high as 75% (Digilio et al., 2005; McDonald-McGinn et al., 2015; McDonald-McGinn et al., 1999; Ryan et al., 1997; Vogels et al., 2014). Types of CHDs in 22q11DS mostly consist of conotruncal abnormalities and atrioventricular septal defects, including tetralogy of Fallot, ventricular septal defects, interrupted aortic arch, and truncus arteriosus (McDonald-McGinn et al., 2015; Mlynarski et al., 2015; Unolt

et al., 2018). The association between CHDs and EF is thought to be the result of a complex interplay between various endogenous or exogenous factors, such as low oxygen saturation, abnormal cerebral blood flow, and the use of cardiopulmonary bypass during surgery, which in turn affect early brain development (Bragg, 2019; Claessens et al., 2019; Morton et al., 2017; Peyvandi et al., 2019; Volpe, 2014; Wernovsky & Licht, 2016). The various factors differ between different types of CHD as their hemodynamic impact varies, and as the type and magnitude of intervention depends on the nature and severity of the CHD. Alternatively – or additionally –, the concurrent presence of a CHD and neurodevelopmental impairments may be explained by pleiotropy; that is, the same pathogenic genetic variant underlying the CHD may also affect brain development (Homsy et al., 2015; McQuillen & Miller, 2010; Morton et al., 2022; Nattel et al., 2017). Figure 6.2 shows a simplified illustration of the various potential causal pathways between CHD and EF impairment.

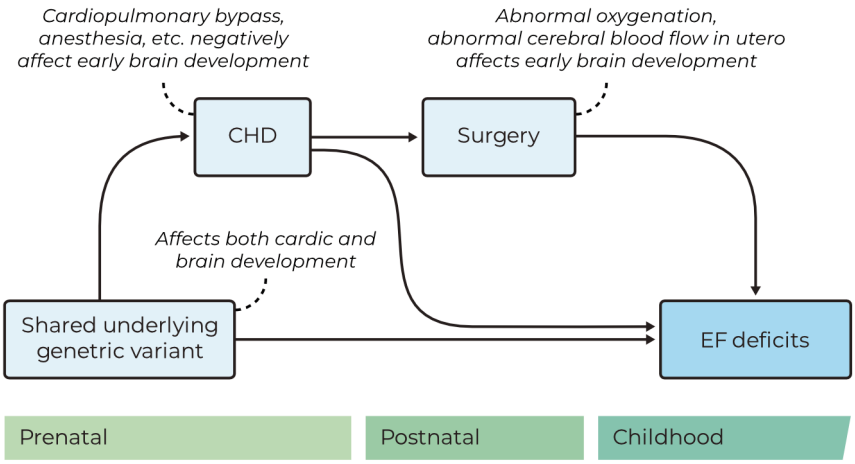


Figure 6.2. Schematic illustration of the potential causal pathways between CHD and EF deficits.

In line with the hypothesis that pleiotropy explains the concurrent presence of a CHD and neurodevelopmental impairments, studies with individuals with 22q11DS have reported that although differences in cortical thickness were related to CHDs (Fountain et al., 2014; Schaer et al., 2009), no effect of CHDs on the developmental trajectory of EF was observed (Fountain et al., 2014).

Additionally, several studies have reported an absence of evidence for an effect of CHDs on various components of cognitive functioning in 22q11DS (e.g., Atallah et al., 2007; Cheung et al., 2014; De Smedt et al., 2008; Duijff, Klaassen, Beemer et al., 2012; Gerdes et al., 1999; Maharasingam et al., 2003; Niklasson & Gillberg, 2010; Swillen et al., 2005). For example, Zhao et al. (2018) found an effect of deletion size, but not of CHD, on IQ in a sample of more than 1,000 individuals with 22q11DS. For EF specifically, one study investigated whether the presence of CHDs was associated with EF performance in four groups of 8- to 14-year-old children: children with 22q11DS with and without CHD, children with a CHD without a syndromic origin (CHD-only), and TD children (Yi et al., 2014). The 22q11DS groups did not differ from one another and both performed worse than the TD and the CHD-only group on all EF measures. Notably, in contrast to previous findings in non-syndromic CHD samples, the latter two groups did not differ from each other.

Taken together, these findings suggest that the impact of the 22q11.2 deletion exceeds the hypothesized impact of CHD. This is further supported by findings in another pathogenic variant, Down syndrome (trisomy 21), in which CHDs are also common. In this population, CHDs were largely unrelated to EF performance (Gandy et al., 2020), although a small impact of CHDs on neurodevelopmental outcomes may be present during the preschool age (Alsaied et al., 2016; Visootsak et al., 2011). In 22q11DS, it is yet unknown whether CHD are related to EF skills at such a young age.

Current Study

In the current study, we compared EF performance of 44 preschoolers with 22q11DS (3.0-6.5 years) to 81 TD peers. The first aim of this study was to provide an overview of EF abilities of preschool-aged children with 22q11DS. We administered measures of visual selective attention, visuospatial WM, and broad EF. Based on the literature discussed above, we hypothesized lower performance of the children with 22q11DS in comparison with TD controls. Given the mixed findings on WM in the literature and the scarcity of studies on selective attention, we had no specific hypotheses, although WM skills may be a relative strength of children with 22q11DS. Additionally, we investigated the

relations between the different EF tasks as a first step in exploring the overall EF profile in this young age-group. As selective attention has been proposed to be a prerequisite for further EF development (Garon et al., 2008), we expected it to be significantly correlated with both the working memory and the broad EF task. We also considered the effect of age, IQ, and socioeconomic status.

The second aim of this study was to explore the effect of a hemodynamically significant CHD (HS-CHD) on EF performance in preschoolers with 22q11DS. Based on studies in older children or adults with 22q11DS (e.g., Fountain et al., 2014; Yi et al., 2014), we hypothesized that the impact of a CHD on EF as observed in the general population (Mebius et al., 2017; Sterken et al., 2015), is overshadowed by the impact of the genetic deletion (Morton et al., 2017; Nattel et al., 2017). We also considered the possibility that a CHD would explain some variance in the EF performance of our participants with 22q11DS, as previous work in a different pathogenic variant (trisomy 21) suggests that the impact of CHDs may be particularly meaningful in the preschool age (Gandy et al., 2020).

Methods

Participants

A total of 125 children, of which 44 children with 22q11DS and 81 TD controls, participated in a larger prospective study ('*3T project*') investigating children's language, cognitive, and behavioral development. The study was approved by the Medical Research Ethics Committee of the University Medical Centre Utrecht, the Netherlands (CCMO registry nr. NL63223.041.17). All parents of the participating children provided written informed consent. Children were recruited between November 2018 and November 2019. Inclusion criteria were: 1) monolingual Dutch, 2) aged between 3.0 and 6.5 years, and 3) no documented hearing loss (>35 dB).

For children with 22q11DS, an additional inclusion criterium was: 4) a 22q11DS deletion confirmed by genetic testing (see appendix 6-A). Children with 22q11DS were recruited through the national multidisciplinary outpatient clinic for children with 22q11DS (University Medical Centre Utrecht) and the Dutch 22q11DS patient

support group (Stichting Steun 22Q11). One participant was recruited via a different medical center in the Netherlands. For TD children, an additional inclusion criterium was: 4) no history of developmental concerns and no family history of language impairment [1]. TD children were recruited through day-care centers and elementary schools throughout the Netherlands. In some cases, they were recruited from the same schools that were attended by children with 22q11DS who participated in this study. Other schools were approached separately by the research team. Sample characteristics are presented in Table 6.1.

Table 6.1. Sample characteristics of the children with 22q11DS (*n* = 44) and the TD children (*n* = 81).

	22q11DS	**TD**	
***n* female** (%)	19 (43%)	45 (56%)	$\chi^2(1) = 1.29$, $p = .26$, $V = 0.12$
Mean age (*SD*) Range (year;month)	4.9 (1.0) 3;1 – 6;5	4.7 (0.9) 3;0 – 6;6	$t(79.229) = 1.63$, $p = .21$, $g = 0.21$
Mean IQ [a] (*SD*) Range	80.2 (11.7) 50 – 103	105.6 (13.4) 78 – 139	$t(93.989) = 117.07$, $p < .001$, $g = 1.98$
Mean SES [b] (*SD*) Range	6.4 (1.8) 2 – 9	7.8 (1.3) 3.5 – 9	$t(69.007) = 20.96$, $p < .001$, $g = 0.94$

Abbreviations: 22q11DS = 22q11.2 deletion syndrome, IQ = Intelligence Quotient, SD = Standard Deviation, SES = Socio-Economic Status, TD = Typically Developing.

a. For children with 22q11DS, IQ scores were obtained from medical records or school. These IQ tests were administered by a licensed psychologist in the context of formal cognitive assessments. 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 (WNV; Wechsler & Naglieri, 2008). For TD children, the shortened version of the WNV was administered by one of the trained researchers from the current study. A valid IQ score could not be obtained for one TD child after repeated non-compliance to the task instructions.

b. Socioeconomic status was indexed by the average education level of both parents, ranked on a 9-point scale reflecting the Dutch educational system, ranging from 1 'not completed primary education' to 9 'university degree'. The average both parents was taken unless the child came from a single parent household (22q11DS *n* = 5; TD *n* = 0). SES is missing for one TD child, as parents declined to answer.

Cardiac phenotype

For the children with 22q11DS, the presence of any type of CHD, hemodynamic significance of the CHD, and surgical intervention

1 This was a criterium in the context of the larger project ('*3T project*').

were assessed by a pediatric cardiologist based on review of medical records (n = 42) and parental report (n = 2)[2]. Twenty-five children with 22q11DS had some type of CHD. There were 13 children with only a single CHD diagnosis, while 12 children had multiple cardiac diagnoses. The most common CHD was ventricular septal defect (n = 16). Children with hemodynamically significant CHD (HS-CHD; n = 16) were compared with all other children (n = 28) for the purpose of our analysis, as these types of CHD likely have the largest impact on early brain development (see Figure 6.2). All children in the HS-CHD group had undergone surgery, all but one with cardiac pulmonary bypass. See appendix 6-B for a more detailed description of the cardiac phenotypes of the sample.

Parents of TD children were asked if their child had CHD, but none of the parents reported that this was the case.

Procedure

Behavioral assessment of the EF tasks took place at the child's school or day-care center and consisted of two sessions of 45-minutes each, which were on average 5 (SD = 3, range: 0-14) days apart. Both sessions were always conducted by the same trained researcher. EF tasks were mixed with other cognitive and language tasks and administered in a fixed order. Parents filled in online questionnaires regarding demographic information and their child's development.

Outcome measures

Selective attention

We used a task developed by Mulder et al. (2014) to measure selective attention (SA). Children were instructed to search elephants among distractors (donkeys and bears) in four displays, which differed in the number and/or size of the animals. The search displays were presented on a 15.6-inch screen on a HP ProBook 450 G5 Notebook laptop using E-Prime 2.0 (Schneider et al., 2002). Children were

2 Medical records could not be obtained due to privacy regulations. For one of these children, parents reported they had regularly visited a multidisciplinary team in an academic hospital and that no CHD was detected. The parents of the other child provided a detailed report of their child's HS-CHD in a telephone interview with the researcher.

instructed to point to the elephants they had found. To minimize working memory load, targets detected by the child were crossed with a blue line. Each display was presented for 40 seconds. The first two displays contained 40 distractors and 8 targets (6 rows, 8 columns; see Figure 6.3). The third display contained 64 distractors and 8 targets (9 rows, 8 columns), and the fourth display contained 195 distractors and 9 targets (12 rows, 17 columns). SA outcome measures were: 1) the number of targets found (Hits), 2) the number of incorrect responses (i.e., pointing to distractors; Errors), and 3) the number of repeated responses (i.e., targets already marked as found; Repetitions). These were computed per display, as well as in total for all displays together.

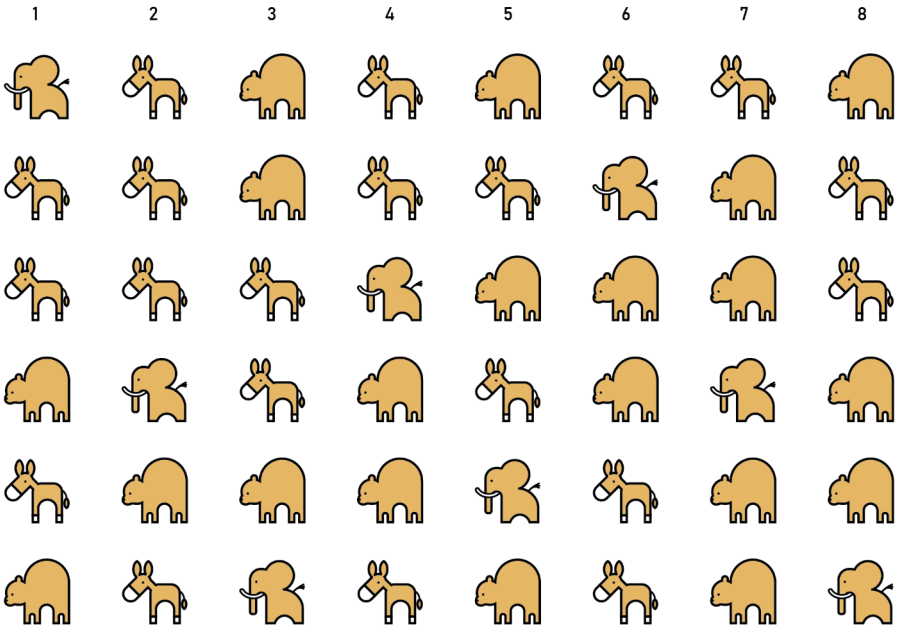


Figure 6.3. Search display 1 of the SA task Mulder & Verhagen (2010).

Working memory

The Corsi Block tapping task was administered to gauge visuo-spatial WM skills (Berch et al., 1998; Corsi, 1973; Milner, 1971). Children were presented with a white board with nine blue blocks, following the set-up of Kessels et al. (2000) (see Figure 6.4). We followed the procedure of the Mind Prekindergarten Curriculum (Farran et al., 2015; Farrell

Pagulayan et al., 2006), as translated into Dutch by Wijnroks et al. (2017). This task has two conditions with two tests each.

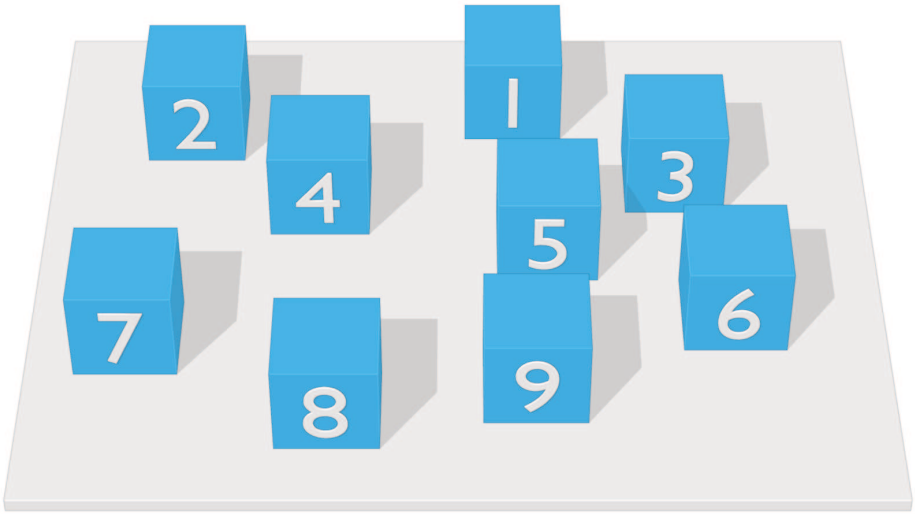


Figure 6.4. Corsi block task as seen from the perspective of the experimenter. Numbers on the blocks were not visible to the participant. Figure adapted from Kessels et al. (2008).

In the Forward (FW) condition, the child was instructed to tap the blocks in the same order as the experimenter. After four practice trials, the first test started with a sequence of two blocks. If the child copied the sequence correctly, the experimenter moved on to the next sequence length. If the response was incorrect, the experimenter showed a second trial with a different sequence of the same length. If the child failed to copy this sequence, the test was terminated. The Backward (BW) condition was administered in the same way, except that the child had to tap the sequences in reverse order. The BW condition requires the information stored to be manipulated (i.e., the sequence of the items must be reversed by the participant) and is therefore considered a more valid measure of working memory than the FW condition, for which information merely has to be reproduced (Baddeley, 1992). The sequences increased in length with one block each time with a maximum of nine blocks in the FW condition and six blocks in the BW condition. All sequences were predetermined and the same for all children. Of the two tests, the longest successfully copied sequence length was taken as the outcome measure. In the

FW condition, children who successfully completed the practice items but did not repeat any of the test items correctly were awarded a score of 1. Children who did not understand the BW condition, but who successfully completed at least one trial of the FW condition, thereby demonstrating comprehension of the task instructions, were awarded a score of 1 for the BW condition.

Broad EF

The Head-Toes-Knees-Shoulders (HTKS; Ponitz et al., 2008; Ponitz et al., 2009) is a task gauging a broad scope of EF abilities. The HTKS was developed as an ecologically valid measure of multiple aspects of EF. The HTKS is considered a broad EF measure, as it requires the child to keep the rules of the game active in working memory during the task, to use these rules to select correct responses, and to inhibit a natural, but incorrect response, while directing their attention to the experimenter. We followed the procedure of the Mind Prekindergarten Curriculum (Farran et al., 2015; Ponitz et al., 2008; Ponitz et al., 2009) as translated into Dutch by Wijnroks et al. (2017). The task consists of two parts.

In the first part, children were asked to point to their head and to their toes (HT condition). Children were told that they were going to play a 'weird' game and were instructed to do the opposite of what the experimenter told them to do. So, if the experimenter told them to point to their toes, they had to point to their head and vice versa. After four practice trials, ten test trials were administered. *Head* and *toe* trials were administered in a fixed non-alternating order. For a correct response, children were awarded 2 points. If a child made a clear self-correction, but eventually responded correctly, they were awarded 1 point. For incorrect responses, they were awarded 0 points. Thus, for the first part, a total of 20 points could be obtained. Scores were only considered valid if children responded correctly to at least two practice trials. Otherwise, their score was marked as missing as it could not be reliably established whether children either did not understand the task instructions or could not perform the task.

If a child obtained more than 10 points in the first part of the task, the second part of the task was administered. Children were asked to point to their knees and to their shoulders (KS condition).

Children were again instructed to do the opposite of what the experimenter told them to do. After four KS practice trials, HT trials were added. Following the same procedure as for the HT condition, ten test trials were administered and scored.0

The task was filmed and also scored by a second researcher. In case of discrepancies between the scores by the experimenter and the second researcher, final scores were determined through a consensus procedure (22q11DS: n = 1; TD: n = 4). In addition to the accuracy score, the number of self-corrections was also registered.

Data Analyses

Data was prepared and analyzed using R version 4.0.2 (R Core Team, 2020) and IBM SPSS 27.0 (2020). As not all participants were able to complete all tasks, analyses always included the maximum number of available participant scores. Parametric results are reported unless non-parametric tests were required and showed different outcomes than parametric tests. Comparison of demographic variables between the groups and between children with and without complete task data was done using Welch's t-test (Declare et al., 2017). All significance tests were two-tailed with an α of 0.05. No formal statistical analysis was performed when the majority of children had incomplete task data, as the outcomes would likely be biased and not give an accurate reflection of the capabilities of the respective populations.

The first aim of the current study was to provide an EF profile of young children with 22q11DS as compared to a TD control group. Incomplete task data was considered informative, as it is indicative of a child's level of functioning. χ^2-tests were used to compare the distributions of children with and without complete task data between the groups. Prior to the primary analysis, correlations were used to determine the relationship of different outcomes of the same task. As each task has multiple outcome measures, we report Pillai's trace values from Multivariate Analysis of Variance (MANOVA) which corrects for multiple testing. Greenhouse-Geisser corrections were used when Sphericity could not be assumed. For the MANOVAs, *Group* was taken as the independent variable. For the SA task, the dependent variables were *Hits*, *Errors*, and *Repetitions*; for the WM

task the dependent variables were longest *span* in the *Forward* (*FW span*) and in the *Backward* condition (*BW span*); and for the broad EF task, it was the accuracy *Score* and *Self-corrections (SC)* for both part I (HT) and part II (KS). Additionally, for the SA task, a repeated measures MANOVA was used to investigate whether the groups differed on performance (*Hits*, *Errors*, *Repetitions*) with increasing complexity (*Display*). Finally, to gain more insight into the overall EF profile of both groups of children, Pearson bivariate correlations were used to investigate the relations between the various EF outcomes.

The second aim of the current study was to explore the effect of CHD on EF performance in children with 22q11DS. Using the same analyses for the comparison with TD children, children with 22q11DS with HS-CHD were compared to children with 22q11DS without HS-CHD. As many factors related to CHD may impact early cognitive development (see section *Congenital Heart Defects*), we ran sensitivity analyses (Thabane et al., 2013). In these sensitivity analyses, we used different CHD grouping criteria: 1) the presence of any type of cardiac anomaly (n = 25), and 2) having undergone cardiac surgery[3] (n = 18). Sensitivity analyses were the same as the main analyses with regard to models and tests used.

In all analyses, *Age* was used as a covariate, as age is correlated with the outcome measures but unrelated to the independent variable *Group* (see Table 6.1 and appendix 6-C). Socioeconomic status (SES) was also considered as a covariate, as there was a significant difference in SES between the groups (see Table 6.1) and because previous research has suggested that SES might affect EF outcomes in TD children (Lawson et al., 2018; but see Allen et al., 2014 and Shashi et al., 2010 for 22q11DS). As differences in IQ are inherent to the groups, IQ was not considered as a covariate in the group comparisons with the TD controls (Dennis et al., 2009; Miller & Chapman, 2001). It was, however, used as a covariate in the CHD analyses and considered in relation to the EF measures in the exploratory correlation analyses. These correlations between the EF tasks and age, SES, and IQ can be found in appendix 6-C. Only covariates that had a significant effect on the outcome are reported.

3 There were two cases of children with aberrant subclavian arteries that were surgically corrected (because of esophageal compression), but who did not have HS-CHD.

Results

Selective attention

Descriptives and task completion data

Selective attention outcomes are reported in Table 6.2. Two children with 22q11DS of 4.6 and 3.3 years old could not complete the SA task due to low mental age and high levels of inattention, respectively. All TD children completed the SA task.

Table 6.2. Results of the SA task for the children with 22q11DS (*n* = 42) and the TD children (*n* = 81).

		Hits		Errors		Repetitions	
		M (SD)	*Range*	*M (SD)*	*Range*	*M (SD)*	*Range*
Total	*22q11DS*	19.95 (4.44)	10-28	1.88 (2.09)	0-9	0.48 (1.04)	0-5
	TD	22.73 (3.96)	13-31	0.57 (1.14)	0-6	0.31 (0.58)	0-2

Abbreviations: 22q11DS = 22q11.2. deletion syndrome, SD = Standard Deviation, TD = Typically Developing.

Note. The maximum number of Hits is 33. There was no maximum number of Errors and Repetitions. For outcomes per Display, see appendix 6-D.

Within task correlations SA outcome measures

Hits and *Errors* were negatively correlated in both the 22q11DS group ($r(42) = -.36$, $p = .018$, 95% CI [-0.60 – -0.07]) and the TD group ($r(81) = -.24$, $p = .029$, 95% CI [-0.44 – -0.03]), indicating that children who found more targets made fewer errors. In the 22q11DS group, *Repetitions* were not correlated with *Hits* ($r(42) = .06$, $p = .69$, 95% CI [-0.25 – 0.36]) or *Errors* ($r(42) = .18$, $p = .24$, 95% CI [-0.13 – 0.46]). *Repetitions* were also not correlated with *Hits* ($r(81) = -.06$, $p = .59$, 95% CI [-0.28 – 0.16]) or *Errors* ($r(81) = .05$, $p = .64$, 95% CI [-0.17 – 0.27]) in the TD group.

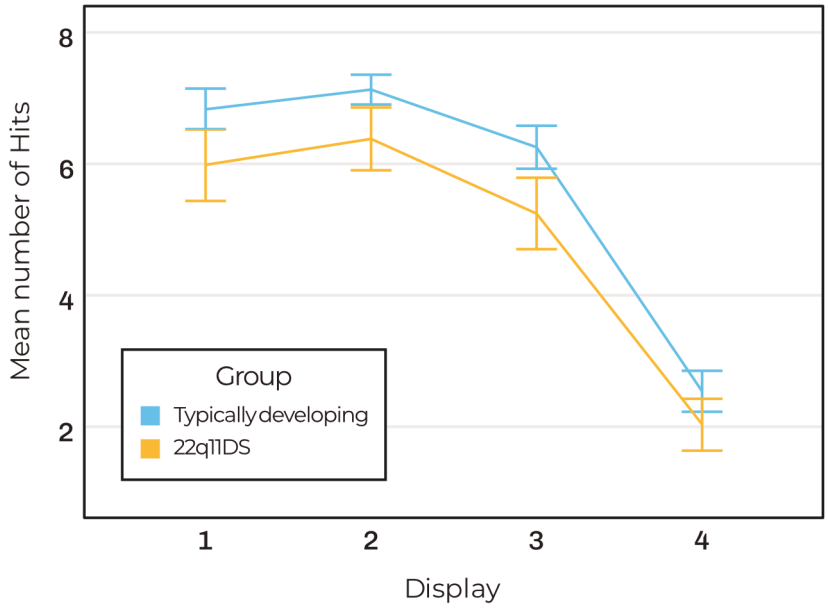


Figure 6.5. SA task for the children with 22q11DS (*n* = 42) and the TD children (*n* = 81); line chart of the mean number of Hits per display for each group. Errors bars indicate 95% CI.

Group comparisons between the children with 22q11DS and the TD children

A repeated measures MANOVA showed that there was an effect of *Group* on the SA task (V = 0.18, $F(3, 119) = 8.57$, $p < .001$, $\eta_p^2 = .18$). Children with 22q11DS had a lower total number of *Hits* ($F(1, 121) = 12.51$, $p < .001$, $\eta_p^2 = .09$) and made more *Errors* ($F(1, 121) = 20.44$, $p < .001$, $\eta_p^2 = .15$) than TD children. There was no difference in the total number of *Repetitions* between the groups ($F(1, 121) = 1.31$, $p = .26$, $\eta_p^2 = .01$). There was also a main effect of *Display* (V = 0.90, $F(9, 113) = 111.22$, $p < .001$, $\eta_p^2 = .90$). This effect of *Display* was only significant on *Hits* (after Greenhouse-Geisser correction) ($F(2.753, 333.143) = 424.09$, $p < .001$, $\eta_p^2 = .78$), but not on *Errors* ($F(2.908, 351.863) = 1.52$, $p = .21$, $\eta_p^2 = .01$) or *Repetitions* ($F(2.549, 308.382) = 1.44$, $p = .24$, $\eta_p^2 = .01$). This shows that the number of *Hits* decreased with increasing *Display* complexity. There was no interaction between *Group* and *Display* (V = 0.06, $F(9, 113) = .85$, $p = .57$, $\eta_p^2 = .06$), indicating that this effect of *Display* was similar across both groups (see Figure 6.5). These findings did not

change when *Age* and *SES* were entered as covariates. Only *Age* was a significant covariate (V = 0.32, $F(3, 118)$ = 18.52, p < .001, η_p^2 = .32), resulting in a larger effect size for *Group* (η_p^2 = .27). These results should be interpreted with caution as the assumption of homogeneity of covariance matrices was violated.

Working memory

Descriptives and task completion data

Working memory outcomes per group are reported in Table 6.3. In the 22q11DS group, eight children were unable to complete the FW and BW condition. In the TD group, three children were unable to complete the FW and BW condition, and one additional child was unable to complete the BW condition. Given the small samples and unequal sample sizes, we only describe the differences on demographic variables between children with complete and incomplete task data per group, but we did not carry out statistical analyses for these comparisons.

Table 6.3. Results of the WM task of the children with 22q11DS and the TD children.

		n	*M*	*Median*	*SD*	*Range*
FW span	*22q11DS*	36	2.86	3	0.83	1-5
	TD	78	3.51	4	0.94	1-6
BW span	*22q11DS*	36	1.81	2	0.82	1-3
	TD	77	2.43	2	1.14	1-7

Abbreviations: 22q11DS = 22q11.2 deletion syndrome, BW = Backward, FW = Forward, M = Mean, SD = Standard Deviation, TD = Typically Developing.

Note. The maximum span for the Forward condition is 9, and 6 for the Backward condition.

The children with 22q11DS who did not complete one or both conditions from the WM task included five boys and three girls. They were younger (n = 8; M_{age} = 3.6, SD = 0.5) than children with 22q11DS with complete task data (n = 36; M_{age} = 5.2, SD = 0.9). Their IQ score (M = 71.7, SD = 11.4, range 50 to 81) appeared lower than that of the total group, while their SES (range: 2-8.5) appeared similar. The TD children who did not complete one or both conditions from the WM task

included two boys and two girls. They were younger (n = 4; M_{age} = 3.5, SD = 0.2) than TD children with complete task data (n = 77; M_{age} = 4.7, SD = 0.9). They had average IQ scores (range: 96-109) and did not appear to differ in SES (range: 8-9) from the rest of the group.

Within task correlations WM outcome measures

The *FW span* and *BW span* were strongly correlated in the TD children ($r(77)$ = .58, p < .001, 95% CI [0.41 – 0.71]). In children with 22q11DS, *FW span* and *BW span* showed a trend towards a moderate correlation, but this did not reach statistical significance ($r(36)$ = .29, p = .083, 95% CI [-0.04 – 0.57]).

Group comparisons between the children with 22q11DS and the TD children

There was a significant effect of *Group* on the WM task (V = 0.13, $F(2, 110)$ = 6.77, p < .001, η_p^2 = .13). Children with 22q11DS had a shorter *FW span* ($F(1, 111)$ = 14.93, p < .001, η_p^2 = .12) and shorter *BW span* ($F(1, 111)$ = 8.63, p = .004, η_p^2 = .07) than TD children. These findings did not change when *Age* and *SES* were entered as covariates. Only *Age* was a significant covariate (V = 0.41, $F(2, 109)$ = 37.61, p < .001, η_p^2 = .41), resulting a larger effect size for the effect of *Group* (η_p^2 = .31).

Broad EF

Descriptives and task completion data

Broad EF outcomes per group are reported in Table 6.4. However, data of the broad EF task was incomplete for a substantial number of participants. There were relatively more children with incomplete task data in the 22q11DS group (n = 35/44, 80%) than in the TD group (n = 23/81, 28%; $\chi^2(1)$ = 30.0, p < .001, V = .49).

In the 22q11DS group, 31 children were unable to complete the HT part and one child had missing data due to a task administration error. The latter child did have data for the KS part. Three additional children were unable to complete the KS part of the task. Children with 22q11DS missing one or both conditions from the HTKS task were younger (M = 4.7, SD = 1.0) than children with 22q11DS who completed the task (M = 5.8, SD = 0.3; p < .001). There was no difference between

these groups in sex distribution (p = .40), SES (p = 1.0), or IQ scores (p = .55). In the TD group, 16 children were unable to complete the HT condition of the task, and 7 additional children were unable to complete the KS condition. TD children missing one or both conditions from the HTKS task were younger (M = 3.7, SD = 0.6) than TD children who completed the task (M = 5.0, SD = 0.7; p < .001). There was no difference between these groups in sex distribution (p = .912), SES (p = .19), or IQ scores (p = .081). See appendix 6-E for a detailed description and the complete statistics.

Since a substantial number of participants had incomplete task data for the HTKS, no formal statistical analyses were performed. Visual inspection of the data suggests that children with 22q11DS who were able to complete the task do not perform as well as the TD children in the HT condition. The mean score of the children with 22q11DS is lower, although the difference in median score is less substantial. The potential difference appears to be even less clear in the KS condition of the task.

Table 6.4. Results of the broad EF task of the children with 22q11DS and the TD children.

			n	*M*	*Median*	*SD*	*Range*
Part 1 – HT	*Score*	22q11DS	12	11.8	16	7.7	0 – 20
		TD	65	16.6	18	4.5	0 – 20
	SC	22q11DS	12	2.0	2.5	1.6	0 – 4
		TD	65	1.2	1	1.1	0 – 4
Part 2 – KS	*Score*	22q11DS	10	10	11	6	0 – 18
		TD	58	11.7	13.5	6	0 – 19
	SC	22q11DS	10	1.8	1	1.7	0 – 5
		TD	58	1.8	2	1.7	0 – 4

Abbreviations: 22q11DS = 22q11.2 deletion syndrome, HT = Head-Toes, KS = Knees-Shoulders, M = Mean, SC = Self-correction, SD = Standard Deviation, TD = Typically Developing.

Note. The maximum for Score is 20 and for SC is 10.

Exploratory correlations – EF profile

To explore the EF profile of the childen with 22q11DS as compared to that of TD children, we examined the correlations between the SA and

WM outcomes per group. The HTKS was excluded from these analyses due to the large amount of missing data.

There were several significant correlations between the SA task and the WM task (see Table 6.5). In the TD group, SA Hits was positively correlated with both the Corsi FW and BW scores, indicating that TD children who found more targets in the SA task also had longer WM span scores. These correlations were not significant in the 22q11DS group. SA Errors was negatively correlated with the Corsi FW in the children with 22q11DS and with the Corsi BW in the TD children.

Table 6.5. Correlations between the SA task and WM task for the children with 22q11DS and the TD children.

	WM Forward				WM Backward			
	n	*r*	*p*	*95% CI*	*n*	*r*	*p*	*95% CI*
SA Hits								
22q11DS	36	.29	.082	-0.04 – 0.57	36	.17	.32	-0.17 – 0.47
TD	78	**.59**	**<.001**	0.36 – 0.68	77	**.47**	**<.001**	0.27 – 0.63
SA Errors								
22q11DS	36	**-.50**	**.002**	-0.71 – -0.21	36	.11	.53	-0.23 – 0.42
TD	78	-.04	.71	-0.26 – 0.18	77	**-.23**	**.042***	-0.44 – -0.00
SA Repetitions								
22q11DS	36	-.08	.63	-0.40 – 0.25	36	.18	.29	-0.48 – 0.16
TD	78	.07	.51	-0.15 – 0.29	77	.05	.68	-0.27 – 0.18

Abbreviations: 22q11DS = 22q11.2 deletion syndrome, CI = Confidence Interval, M = Mean, SA = Selective Attention, SD = Standard Deviation, TD = Typically Developing, WM = Working Memory.

Note. Significant correlations are in bold. * Spearman's Rho, as these non-parametric outcomes differed from the Pearson correlation ($r(77) = -.22$, $p = .056$).

The impact of hemodynamically significant CHD on EF in 22q11DS

Task completion, age, SES, and sex distribution were not significantly different between the children with and without hemodynamically significant CHD (HS-CHD) ($p = .94$, $p = .76$, $p = .39$, and $p = .57$, respectively). However, there was a trend towards a lower IQ for the children with HS-CHD ($M = 75.4$, $SD = 12.2$) as compared to those without HS-CHD ($M = 82.9$, $SD = 10.7$; $p = .056$). See appendix 6-F for a

detailed description and the complete statistics. Outcomes per EF task of both groups are displayed in Table 6.6.

Table 6.6. EF results of the children with 22q11DS with and without HS-CHD.

	HS-CHD	*n*	*M*	*Median*	*SD*	*Range*
SA Hits	*Yes*	15	19.5	21	4.3	13-25
	No	27	20.2	21	4.6	8-28
SA Errors	*Yes*	15	2.8	3	2.4	0-9
	No	27	1.4	1	1.7	0-5
SA Repetitions	*Yes*	15	0.9	0	1.6	0-5
	No	27	0.3	0	0.5	0-2
WM Forward	*Yes*	13	2.8	3	0.9	1-4
	No	23	2.9	3	0.8	1-5
WM Backward	*Yes*	13	1.6	2	0.7	1-3
	No	23	1.9	2	0.9	1-3

Abbreviations: HS-CHD = Hemodynamically Significant Congenital Heart Defects, M = Mean, SA = Selective Attention, SD = Standard Deviation, WM = Working Memory.

Note. The maximum of SA Hits is 33, that of WM Forward is 9, and that of WM Backward is 6. SA Errors and SA Repetitions have no maximum.

Group comparisons between the children with 22q11DS with and without HS-CHD

There was no effect of *HS-CHD* on the SA task (V = 0.16, $F(3, 38)$ = 2.45, p = .079, η_p^2 = .16). Covariates *Age*, *SES*, and *IQ* were not significant and did not change these findings. Results should be interpreted with caution as the assumption of homogeneity of covariance matrices was violated.

There was no effect of *HS-CHD* on the WM task (V = 0.03, $F(2, 33)$ = .55, p = .58, η_p^2 = .03). These findings did not change when *Age*, *SES*, and *IQ* were entered as covariates. *Age* was a significant covariate (V = 0.26, $F(2, 29)$ = 6.36, p = .005, η_p^2 = .31), but did not change the effect of *HS-CHD*.

All sensitivity analyses showed similar results (see appendix 6-G). The only effect was observed in the comparison between children with any type of cardiac anomaly (CA) and those without.

Children with CA made more SA errors, but the distribution of errors was skewed and should be interpreted with caution.

Discussion

The aim of the current study was twofold. The first aim was to describe the executive functioning (EF) profile of 3.0- to 6.5-year-old children with the 22q11.2 deletion syndrome (22q11DS) and to compare this to that of typically developing (TD) peers. The second aim was to examine the relation between EF abilities and the presence of a hemodynamically significant congenital heart defect (HS-CHD) in children with 22q11DS. EF was assessed with behavioral tasks measuring visual selective attention (SA), working memory (WM), and a task gauging broad EF abilities.

Selective attention

To our knowledge, this is the first study to investigate SA in young children with 22q11DS. Our results show that visual SA is impaired in children with 22q11DS, as indicated by the fact they found 14% fewer targets and made more than three times as many errors as their TD peers. The finding of impaired SA is in line with outcomes in older children with 22q11DS (Peyroux et al., 2020), and with more general findings of impaired attentional functioning in these children (e.g., Cabaral et al., 2012; Cunningham et al., 2018; Maeder et al., 2021; Mannarelli et al., 2018; Sobin et al., 2005). A previous study looking at the domain of visual attention showed that children with 22q11DS were more sensitive to task load than TD peers as shown by an increase in errors with increasing task load (Cabaral et al., 2012). However, in our study, there was no evidence for a difference in response to increased task complexity between the children with 22q11DS and the TD children. That is, when the number of distractors in the display increased, the number of targets found decreased and the number of mistakes made increased roughly equally for both groups. It should be noted that the number of errors as well as repetitions were skewed due to their low occurrence and limited variance, so the results of the analyses with these outcomes should be interpreted with caution.

As SA is considered an important precursor of later EF abilities (Garon et al., 2008; Veer et al., 2017), this apparent impairment in SA suggests that EF impairment likely emerges already very early on in children with 22q11DS. Pending replication in other studies, this finding provides a rationale for early intervention aimed at strengthening SA in young children with 22q11DS as a possible means to support further EF development (Keilow et al. 2019; Neville et al., 2013; Rueda et al., 2005).

Working memory

Based on a recent review of previous studies that showed mixed outcomes regarding working memory abilities in school-aged children and adolescents with 22q11DS (Everaert et al., 2021), we reckoned with the possibility that WM could be relatively spared. Our results, however, show that visual WM abilities of preschoolers with 22q11DS are weaker than those of TD peers. Children with 22q11DS had a Forward span that was 23% and a Backward span that was 34% shorter than TD children on the Corsi block tapping task. Another group conducted two studies with the same sample of children with 22q11DS in which they administered the Forward condition of the Corsi task. The Backward condition of the Corsi was not administered. These studies, however, showed diverging outcomes. One study reported that the sample of 6- to 12-year-old children with 22q11DS (n = 25) performed worse than TD controls (De Smedt et al., 2008), while the other study reported that there was no difference on the Corsi Forward span between the groups (Brankaer et al., 2017). This difference is likely due to the inclusion of additional groups in the statistical analyses performed in the latter study. A study using a task similar to the Corsi Forward condition showed that children with 22q11DS (6-15 years old) made more mistakes than the TD controls (Wong et al., 2014). Our results support the outcomes of Wong et al. (2014) and De Smedt et al. (2008), and are in line with studies using different tasks to gauge WM skills (Albert et al., 2018; Antshel et al., 2017; De Sonneville et al., 2018; Sanders et al., 2017; Shapiro et al., 2014) and imaging studies that showed aberrant functional activity in brain areas associated with WM (Azuma et al., 2009; Harrel et al., 2017; O'Hanlon et al., 2016). This strengthens the hypothesis that

visuospatial WM is impaired in children with 22q11DS. The current study is the first to provide evidence that these impairments are probably already present at a young age. More research with young children with 22q11DS is necessary to corroborate our results.

Additionally, the Corsi Forward span and Backward span were significantly correlated in the TD children, in line with previous research (Berch et al., 1998; Lehmann et al., 2014), but notably this was not the case in the children with 22q11DS. This may be partly due a lack of power, or, alternatively, represents an aberrant developmental trajectory of WM in 22q11DS.

The outcomes of the current study regarding WM are limited to the visual domain. Future research should also investigate whether verbal WM is impaired at this young age, as research in primary school-aged children with 22q11DS found that verbal WM may be a relative strength (Brankaer et al., 2017; De Smedt et al., 2008). This may, however, be challenging as many of verbal WM tasks, such as the Digit Span, are not well suited for young children.

Broad EF

Results from the broad EF task were limited by the fact that a substantial number of children was not able to complete this task. This task might have been too difficult as it requires children to understand complex instructions, retain these instructions in their working memory, inhibit automatic responses and maintain attention to listen to the experimenter (McClelland & Cameron, 2012; McClelland et al., 2014; Ponitz et al., 2009; Wanless et al., 2011). Visual inspection of the data from children who could complete the task suggests that the children with 22q11DS did not perform as well as the TD children.

A majority of TD children, but only a small group of children with 22q11DS, were able to complete the task. There was no difference in chronological age between the two groups and in both groups, children missing one or both conditions from the HTKS task were significantly younger than children who completed the task. The fact that children who could not complete the task are significantly younger, could hint at either a 'developmental deficit' or a 'developmental lag' (Chawner et al., 2017), but longitudinal data is

needed to investigate this. The fact that there was no difference in intelligence quotient (IQ) scores between children with 22q11DS with and without complete task data suggests that chronological age and other factors play an equally significant or more important role in performing this task than intellectual level. This could be verified by research administering this task to older children with 22q11DS in comparison to both younger mental-age matched TD children and chronologically age-matched TD peers.

EF profile

Our results suggest that the different components of EF may be less strongly interrelated in 22q11DS compared to TD peers. Our findings in TD children support the model of Garon et al. (2008) and are in line with previous research showing that selective attention is related to WM skills (Veer et al., 2017). In contrast to the TD group, selective attention in children with 22q11DS was not related to either WM outcome. A moderate correlation between the SA task and the Corsi Forward emerged in the 22q11DS group, but this did not reach statistical significance. This may be explained by the small 22q11DS sample and therefore insufficient power to identify these correlations. Additionally, the number of errors in the selective attention task was negatively correlated with only the Forward condition of the Corsi task in children with 22q11DS, but negatively correlated with the Corsi Backward in TD children. This indicates that children with 22q11DS who made more errors in the selective attention task had lower Corsi Forward scores, while TD children who made fewer errors had lower Corsi Backward scores. A possible explanation for this difference is that the ability to perform well on the Backward condition builds upon the ability to perform well on the Forward condition, creating a developmental shift in the relation between these abilities. Hypothetically, it could be that children with 22q11DS are lagging behind in their development, resulting in an association between selective attention and the less complex WM task condition but, in contrast to TD children, not on the more advanced condition.

Our results are in line with findings in older children and adults with 22q11DS. A recent longitudinal study with older children and adults with 22q11DS (8-35y) found that all measures of attention and

WM were correlated, but that, compared to the TD group, there were fewer correlations between various EF components in the 22q11DS group (Maeder et al., 2021). Additionally, studies with older children and adults have suggested atypical development of various, but not all EF components (Maeder et al., 2016; Morrison et al., 2020). We had planned to collect longitudinal data but were unable to do so due to the COVID-19 pandemic. Future longitudinal research including preschoolers are needed to provide insight in the development and interrelatedness of the early EF profile of children with 22q11DS.

Congenital heart defects

Previous research has related the presence of congenital heart defect (CHD) to impaired EF in children with non-syndromic CHD (Mebius et al., 2017; Sterken et al., 2015). However, this negative impact of CHD on EF abilities may be less clear or even absent in children with 22q11DS (Fountain et al., 2014; Yi et al., 2014). Our results are in agreement with the latter, as we observed no differences in EF abilities between children with 22q11DS and hemodynamically significant CHD (HS-CHD) and children with 22q11DS without HS-CHD in this study. This supports the hypothesis that EF impairments are not (solely) the result of CHD-related procedures. The absence of an effect of HS-CHD on EF in our sample could be explained by the hypothesis that the observed concurrence of CHD and impaired EF is caused by the underlying genetic defect, which leads to CHD but also directly impacts neurodevelopment (Homsy et al., 2015; McQuillen & Miller, 2010; Nattel et al., 2017). It is also possible that there is in fact an effect of surgery and anesthesia or altered oxygenation, but that the direct impact of the 22q11.2 deletion on the brain and cognitive functioning exceeds the hypothesized impact of CHD-related factors.

Sensitivity analyses using different grouping criteria for CHD showed similar results. Overall, sensitivity analyses confirm the lack of evidence for a difference in EF abilities between children with 22q11DS with and without CHD.

Strengths and limitations

This study is the first to focus on EF abilities in young children with 22q11DS. We used different instruments to assess EF, yielding more

robust results and the possibility to study the interrelatedness of different findings (Carlson, 2005; Willoughby et al., 2012).

The conclusions of this study and the generalizability of the results are mainly limited by the number of children with 22q11DS who could not complete the WM and broad EF tasks. The variety in developmental level in this group and the rapid development of EF at this age made it difficult to select tasks that were suitable to capture the abilities of all children in this study, including the TD controls. We therefore consider reporting on task incompletion informative and important for transparency. The SA task was completed by 95% of children with 22q11DS and all TD children, thereby allowing us to confidently conclude that SA is impaired in young children with 22q11DS. Nevertheless, task performance may have been influenced by visuo-motor impairments, which have been reported in children with 22q11DS (Duijff, Klaassen, Beemer et al., 2012; McCabe et al., 2016; Sobin et al., 2006; Van Aken et al., 2009; but see Howley et al., 2012). Future studies looking at EF should account for impairments in visuo-motor processing and speed.

A strength of this study is our relatively large sample of children with 22q11DS within a narrow age range, allowing us to draw more robust conclusions, given the rapid development at this age. Our 22q11DS sample seems to be representative of the 22q11DS population when looking at phenotypical presentation (McDonald-McGinn et al., 2015). Nevertheless, our generalizability may be limited by the fact that children were recruited through medical centers, increasing the chance that our sample consists of children with relatively severe clinical phenotypes.

Although our sample was not large enough to consider the effect of various CHD types and CHD-related factors, we did consider the effect of CHD in various ways, such as grouping based on surgical intervention or hemodynamic significance. This is very important, as CHD is a major somatic symptom associated with the syndrome (Digilio et al., 2005; McDonald-McGinn et al., 1999; McDonald-McGinn et al., 2015; Ryan et al., 1997) and has also been related to EF abilities in populations with CHD of non-syndromic origin (Mebius et al., 2017; Sterken et al., 2015). Large scale studies, similar to Zhao et al. (2018), are needed to further investigate the effect of CHD on EF development in

22q11DS, thereby furthering our understanding of the mechanisms through which CHD affects cognitive functioning. Future studies with both syndromic and non-syndromic populations should look at the additive effects of both genetic variants and CHD related factors, like surgical intervention, to disentangle their respective impact on early cognitive development.

Implications

Our results suggest that EF impairments are already present at the preschool age in children with 22q11DS. EF has been shown to be an effective target for intervention (Johann & Karbach, 2019; Neville et al., 2013; Rueda et al., 2005; Traverso et al., 2015; Wass et al., 2012), but more research is needed to further characterize the early EF profile of young children with 22q11DS and to identify targets for intervention. Early intervention may be crucial, as strengthening EF abilities may be able to mitigate the development of psychopathology or the severity of associated problems (Cavalli et al., 2021; Kenworthy et al., 2014; Kluwe-Schiavon et al., 2013; Zelazo, 2020). This is highly relevant for children with 22q11DS who have a substantially increased risk for psychopathology, including schizophrenia, and developmental disorders such as Attenion Deficit Hyperactivity Disorder or Autism Spectrum Disorder (Albert et al., 2018; Antshel et al., 2017; Fiksinski et al., 2018; Biswas & Furniss, 2016; McDonald-McGinn et al., 2015).

Additionally, our results show that CHD does not appear to increase the risk for EF impairment in early childhood in children with 22q11DS. Although future research is needed to corroborate these findings, this information is useful for parents and clinicians regarding prognosis. More research is needed to determine whether other somatic symptoms experienced by children with 22q11DS, such as hypocalcemia (Grand et al., 2018; Sardella et al., 2021), or child-internal or child-external factors (Everaert et al., 2021) pose an additional risk for developing EF problems.

Conclusion

The present study showed that EF impairments are present at an early age in children with 22q11DS. Both selective attention and working memory abilities are impaired as compared to typically

developing peers. Furthermore, different EF components appear to be less interrelated in children with 22q11DS as compared to TD children. Our results do not provide evidence for an effect of congenital heart defects on EF abilities in children with 22q11DS.

Chapter 6 – Supplementary Material

Appendix 6-A – Genotype 22q11DS sample

All children with 22q11DS were tested with either Copy Number Variation (CNV), Comparative Genomic Hybridization (CGH), or Single Nucleotide Polymorphism (SNP) arrays, Multiple Ligand-dependent Probe Amplification (MLPA), or Whole Exosome Sequencing (WES).

Twenty-eight (64%) children had typical (LCR22A – LCR22D) deletions of ~3 Mb. Eight (18%) children had smaller proximal deletions, five of ~2 Mb (LCR22A – LCR22C), three of ~1.5 Mb (LCR22A – LCR22B), and two children with ~0.5 Mb (LCR22B) deletions. One (2%) child had a 2.7 Mb deletion with a start preceding LCR22A extending to LCR22B. One child (2%) had a ~4 Mb (LCR22B – LCR22F/G) deletion. Three children (7%) had smaller distal deletions: two children with ~0.4 Mb (LCR22C – LCR22D) deletions, and one child had a ~1.1 Mb (LCR22D – LCR22E) deletion. For two children (5%) a 22q11.2 deletion was confirmed by genetic testing, but the exact deletion size could not be obtained from medical records.

There were three (7%) confirmed familial deletions (1 maternal, 2 paternal) of which one was a typical A-D deletion, and the two others were both distal C-D deletions. For 21 children (48%), the deletion was confirmed de *novo*. For the other 20 children (45%), deletion origin was unknown.

Appendix 6-B – Detailed overview CHD characteristics of the 22q11DS sample.

Table 6.7. Frequency of CHD, CHD types, and surgical intervention for the children with 22q11DS.

		n	%	*n single CHD*	*n* multiple CHD	*n* surgical intervention
CHD	*No*	19	43	-	-	-
	Yes	25 [a]	56	13	12	18
CHD diagnosis						
Ventricular septal defect		16	64	8	8	10 [b]
Aberrant subclavian artery [c]		5	20	1	4	5
Right-sided aortic arch		4	16	1	3	2
Patent ductus arteriosus		4	16	0	4	3
Stenosis of pulmonary artery		3	12	0	3	2
Interrupted aortic arch		3	12	3	0	3
Tetralogy of Fallot		3	12	2	1	3
Pulmonary valve stenosis		2	8	0	2	2
Atrial septal defect		2	8	0	2	2
Truncus arteriosus		1	4	1	0	1
Double aortic arch		1	4	0	1	1

Abbreviations: CHD = Congenital Heart Defect.

Note. Multiple diagnoses occurred in 12 children, explaining a sum that is higher than the total. There were no children in the sample who had cardiac defects corrected by means of catheterization only. Four children had catheterization procedures, but these were additional to surgical intervention.

a. Of these, 16 (64%) were hemodynamically significant and 9 (36%) were not.

b. Of these, 4 were isolated cases of VSD.

c. The isolated case concerned the right subclavian artery, while the 4 cases that were accompanied by other cardiac anomalies all concerned the left subclavian artery.

Appendix 6-C – Correlations demographic variables and EF taks

There were significant correlations between the EF tasks and demographic variables (see Table 6.8). *Age* was significantly correlated with all outcomes in the TD group, except for *SA Repetitions*. In the group of children with 22q11DS, *Age* was only significantly correlated with *SA Hits* and *Corsi FW*. Overall, this indicates that older children did better on these EF outcomes as reflected by a positive correlation for all measures except for *SA Errors*, for which a negative correlation was found as lower scores on this outcome indicate better performance. In a non-parametric correlation analysis, *SA Hits* and *Age* were no longer significantly correlated in the 22q11DS group. Assumptions for a parametric analysis are met, but given the small sample size, the results of the Pearson correlation should be interpreted with caution. There were no significant correlations between *SES* and any outcome measure in either group. *IQ* was significantly correlated with SA Hits in TD children but not children with 22q11DS. This positive correlation in TD children indicates that children with higher IQ scores found more targets in the SA task. No other outcome measure was correlated to *IQ* in either group.

Table 6.8. Correlations between EF outcomes and age, SES and IQ for children with 22q11DS and TD children.

		Age				SES				IQ			
		n	*r*	*p*	*95% CI*	*n*	*r*	*p*	*95% CI*	*n*	*r*	*p*	*95% CI*
SA Hits	*22q11DS*	42	.28	.077*	-0.04 – 0.54	42	.04	.804	-0.27 – 0.34	41	.28	.072	-0.03 – 0.54
	TD	81	**.70**	**<.001**	0.57 – 0.80	80	.02	.867	-0.20 – 0.24	80	**.31**	**.005**	0.10 – 0.50
SA Errors	*22q11DS*	42	-.17	.280	-0.45 – 0.14	42	-.16	.314	-0.44 – 0.15	41	-.19	.231	-0.47 – 0.12
	TD	81	-.32	**.003**	-0.51 – -0.11	80	.01	.905	-0.21 – 0.23	80	-.003	.981	-0.22 – 0.22
SA Repetitions	*22q11DS*	42	.14	.368	-0.17 – 0.42	42	.04	.815	-0.27 – 0.34	41	-.11	.494	-0.40 – 0.21
	TD	81	-.17	.123	-0.38 – 0.05	80	-.08	.483	-0.29 – 0.14	80	.08	.496	-0.15 – 0.29
WM FW	*22q11DS*	36	**.44**	**.007**	0.13 – 0.67	36	.01	.958	0.32 – 0.34	35	.07	.678	-0.27 – 0.40
	TD	78	**.63**	**.001**	0.47 – 0.74	77	.05	.674	-0.18 – 0.27	78	.12	.295	-0.11 – 0.33
WM BW	*22q11DS*	36	.32	.058	-0.11 – 0.59	36	-.07	.701	-0.39 – 0.27	35	.31	.067	-0.02 – 0.59
	TD	77	**.63**	**<.001**	0.47 – 0.75	76	.16	.169	-0.07 – 0.37	77	.17	.141	-0.06 – 0.38

Abbreviations: BW = Backward, CI = Confidence Interval, FW = Forward, IQ = Intelligence Quotient, SA = Selective Attention, SES = Socioeconomic status, TD = Typically Developing, WM = Working Memory.

Note. Pearson bivariate correlations, significant correlations are in bold.

* = This is Spearman's Rho as these non-parametric outcomes differed from the Pearson correlation ($r(42) = 0.349$, $p = .023$, CI 95% [0.05 – 0.59])).

Appendix 6-D – SA outcomes per display

Table 6.9. Results of the SA task for children with 22q11DS (*n* = 42) and TD children (*n* = 81) per display.

		Hits		Errors		Repetitions	
		M (SD)	*Range*	*M (SD)*	*Range*	*M (SD)*	*Range*
Display 1	*22q11DS*	6.10 (1.59)	2-8	0.55 (0.83)	0-3	0.17 (0.58)	0-3
	TD	6.83 (1.40)	2-8	0.21 (0.49)	0-2	0.07 (0.31)	0-2
Display 2	*22q11DS*	6.50 (1.31)	4-8	0.36 (0.58)	0-2	0.1 (0.48)	0-3
	TD	7.12 (1.02)	5-8	0.16 (0.43)	0-2	0.12 (0.33)	0-1
Display 3	*22q11DS*	5.33 (1.66)	1-8	0.52 (0.89)	0-4	0.14 (0.35)	0-1
	TD	6.25 (1.47)	3-8	0.11 (0.35)	0-2	0.1 (0.34)	0-2
Display 4	*22q11DS*	2.02 (1.26)	0-5	0.45 (0.74)	0-3	0.07 (0.26)	0-1
	TD	2.53 (1.41)	0-7	0.09 (0.32)	0-2	0.01 (0.11)	0-1

Abbreviations: SD = Standard Deviation, TD = Typically Developing.

Note. For display 1-3 the maximum number of Hits is 8, for display 4 max. Hits is 9, and the max. is 33 for the total number of Hits. There was no maximum to the number of Errors and Repetitions.

Appendix 6-E – HTKS task completion comparison

Table 6.10. Comparison of demographic variables between children with and without complete HTKS data for both groups.

		HTKS complete		HTKS missing		
	22q11DS	*n* = 9		*n* = 35		
	TD	*n* = 58		*n* = 23		
		M	*SD*	*M*	*SD*	
Age	*22q11DS*	5.8	0.3	4.7	1.0	$t(39.060) = -5.49$, $p < .001$, $g = 1.21$, 95% CI [-1.55 – -0.72]
	TD	5	0.7	3.7	0.6	$t(45.004) = -8.02$, $p < .001$, $g = 1.93$, 95% CI [-1.63 – -0.98]
Sex	*22q11DS*	*n* f/m = 5/4		*n* f/m = 14/21		$\chi^2(1) = .71$, $p = .40$, $V = .13$
	TD	*n* f/m = 32/26		*n* f/m = 13/10		$\chi^2(1) = .01$, $p = .91$, $V = .01$
IQ	*22q11DS*	82.3	11.4	79.7	11.9	$t(13.128) = -0.62$, $p = .55$, $g = .22$, 95% CI [-12.02 – 6.69]
	TD	107.5	12.1	100.8	15.7	$t(30.848) = -1.81$, $p = .081$, $g = .51$, 95% CI [-14.28 – 0.86]*
SES	*22q11DS*	6.4	1.5	6.4	1.9	$t(15.312) = -0.00$, $p = 1.00$, $g = .00$, 95% CI [-1.24 – 1.23]
	TD	8	1.2	7.5	1.5	$t(34.237) = -1.34$, $p = .19$, $g = .39$, 95% CI [-1.17 – 0.24]

Abbreviations: IQ = Intelligence Quotient, SD = Standard Deviation, SES = Socioeconomic status, TD = Typically Developing.

Note. * Different from parametric: $t(78) = -2.04$, $p = .045$, $d = 0.51$, 95% CI [-13.27 – -0.15] and Mann-Whitney U ($U = 400.5$, p = .010).

Appendix 6-F – Task completion CHD group comparison

Table 6.11. Comparison of task completion and demographic variables between children with 22q11DS with and without HS-CHD.

	CHD		No HS-CHD		
Task completion	*Not complete*	*Complete*	*Not complete*	*Complete*	
n =	3	13	5	23	$\chi^2(1) = .01$, $p = .94$, $V = .01$
	M	*SD*	*M*	*SD*	
Age	4.96	1.06	4.86	1.04	$t(30.759) = .10$, $p = .76$, $g = .10$, 95% CI [-0.77 – 0.57]
Sex	*n* f/m = 6/10		*n* f/m = 13/15		$\chi^2(1) = .33$, $p = .57$, $V = .09$
IQ	75.4	12.2	82.9	10.7	$t(25.963) = 4.00$, $p = .056$, $g = .67$, 95% CI [-0.21 – 15.27]*
SES	6.75	1.33	6.27	1.97	$t(40.713) = .93$, $p = .34$, $g = .27$, 95% CI [-1.49 – 0.53]

Abbreviations: HS-CHD = Hemodynamically Significant Congenital Heart Defect, IQ = Intelligence Quotient, SD = Standard Deviation, SES = Socioeconomic status, TD = Typically Developing.

Note. *Different from parametric: $t(40) = 2.08$, $p = .044$, $d = .65$, 95% CI [0.20 – 14.85] and Mann-Whitney U ($U = 111.5$, $p = .017$).

Appendix 6-G – Sensitivity analyses CHD comparison

In the primary analysis, we used the contrast presence of hemodynamically significant CHD (HS-CHD) versus absence of HS-CHD (being the sum of hemodynamically insignificant CHD and no CHD). These sensitivity analyses used different grouping criteria for the CHD classification in the children with 22q11DS. In the first analysis, children with any type of cardiac anomaly (CA) were compared to children without cardiac anomalies. In the second analysis, children who had undergone cardiac surgery were compared to children who had not undergone surgery for cardiac corrections. There were two cases of children with aberrant subclavian arteries that were surgically corrected due esophageal compression, but who did not have hemodynamically significant CHD. See table 6.12 for EF outcomes for the respective groups.

Table 6.12. EF results of children with 22q11DS with and without cardiac anomalies and/or cardiac surgery.

		CA	No CA	Surgery	No surgery
SA Hits	*n*	24	18	17	25
	M	20.54	19.17	20.06	19.88
	SD	4.05	4.91	4.31	4.61
SA Errors	*n*	24	18	17	25
	M	2.38	1.22	2.53	1.44
	SD	2.34	1.52	2.40	1.76
SA Repetitions	*n*	24	18	17	25
	M	0.67	0.22	0.82	0.24
	SD	1.27	0.55	1.47	0.52
WM Forward	*n*	22	14	15	21
	M	2.68	3.14	2.8	2.9
	SD	0.78	0.86	0.86	0.83
WM Backward	*n*	22	14	15	21
	M	1.73	1.93	1.67	1.9
	SD	0.70	1.0	0.72	0.89

Abbreviations: CA = Cardiovascular Anomaly, SA = Selective Attention, SD = Standard Deviation, WM = Working Memory.

Note. The maximum of SA Hits is 33, that of WM Forward is 9, and that of WM Backward is 6. SA Errors and SA Repetitions have no maximum.

Sensitivity analysis 1: Group comparisons between children with 22q11DS with and without any Cardiac Anomaly (CA)

There was no effect of *CA* on the SA task (V = 0.17, $F(3, 38) = 2.57$, p = .069, η_p^2 = .17). These findings change when *Age*, *SES*, and *IQ* were entered as covariates (V = 0.21, $F(3, 34) = 3.07$, p = .041, η_p^2 = .21), although none of the covariates were significant. In the model with covariates, children with *CA* had more *Errors* ($F(1, 40) = 4.49$, p = .041, η_p^2 = .11) than children without any *CA* (see Table 6.12). There was no difference on the total number of *Hits* ($F(1, 40) = 1.60$, p = .21, η_p^2 = .04) and *Repetitions* between the groups ($F(1, 40) = .61$, p = .44, η_p^2 = .02). Results should be interpreted with caution as the assumption of homogeneity of covariance matrices was violated.

There was no effect of *CA* on the WM task (V = 0.077, F(2, 33) = 1.37, p = .27, η_p^2 = .08). These findings did not change when *Age*, *SES*, and *IQ* were entered as covariates. *Age* was a significant covariate (V = 0.31, F(2, 29) = 6.56, p = .004, η_p^2 = .31) but did not change the effect of *CA*.

Sensitivity analysis 2: Group comparisons between children with 22q11DS with and without cardiac surgery

There was no effect of *Cardiac Surgery* on the SA task (V = 0.13, F(3, 38) = 1.90, p = .15, η_p^2 = .13). These findings did not change when *Age*, *SES*, and *IQ* were entered as a covariate, nor were they significant covariates. Results should be interpreted with caution as the assumption of homogeneity of covariance matrices was violated.

There was no effect of *Cardiac Surgery* on the WM task (V = 0.02, F(2, 33) = .36, p = .70, η_p^2 = .02). These findings did not change when *Age*, *SES*, and *IQ* were entered as covariates. *Age* was a significant covariate (V = 0.30, F(2, 29) = 6.06, p = .006, η_p^2 = .30) but did not change the effect of *Cardiac Surgery*.

Chapter 7

General discussion.

Children with Developmental Language Disorder (DLD) experience severe and persistent difficulties with language acquisition in the absence of a clear cause (Bishop et al., 2017; Leonard, 2014). Their language difficulties are a source of concern for parents, a source of frustration for children themselves, and may predispose children to mental health problems and affect their academic and professional attainment (Clegg et al., 2005; Conti-Ramsden et al., 2013; Conti-Ramsden et al., 2018; Durkin et al., 2017; Snowling et al., 2006; St. Clair et al., 2011; Yew & O'Kearny, 2013). To improve interventions and prognosis, it is essential to better understand the factors that affect the atypical language development of children with DLD.

Amongst such factors may be domain-general [1] cognitive deficits, that could negatively affect language development (Botting & Marshall, 2017; Kail, 1994; Ullman & Pierpont, 2005). In children with DLD, impairments in domain-general cognitive functions have been observed in addition to their language problems (Ebert & Kohnert, 2011; Pauls & Archibald, 2016; Vissers et al., 2015). These broader cognitive deficits may not only provide insight into the underlying mechanisms of atypical language development but may also provide fruitful targets for intervention (e.g., Scionti et al., 2020). Executive functioning (EF) is one such cognitive function that may play a role in language learning and appears to be impaired in children with DLD. In the past decades, researchers have attempted to understand how EF is related to the language difficulties of children with DLD. Some have argued that only verbal EF (e.g., verbal working memory – the ability to store and manipulate auditory verbal information) is impaired in children with DLD and that this may be at the core of their language problems. Others, however, have also observed impaired non-verbal EF in children with DLD. This could suggest that the mechanism underlying DLD may not be specific to language. Findings have been inconsistent, especially with regard to non-verbal EF impairments, and the exact role of EF deficits in atypical language development is still not well understood (Kapa & Plante, 2015). This dissertation sets out to better understand the role of domain-general

1 Domain-general refers to the view that there are cognitive functions which do not process one specific type of information or are not important for a single process. Domain-general cognitive functions are thought to be used in the processing of various kinds of information and support learning in different domains.

cognitive abilities, specifically non-verbal EF, in atypical language development (**aim 1**).

The mixed outcomes regarding the EF abilities of children with DLD can at least in part be attributed to the phenotypical and etiological heterogeneity seen in children with DLD. Despite the robust impairments in morphosyntactic abilities, children with DLD show variability in the severity of their language impairment and the language domains that are affected (Leonard, 2014). For a long time, the etiology of DLD has been unknown – to the point that the identification of a specific cause is currently considered as an exclusion criterion for the diagnosis in (Bishop et al., 2017). However, recent studies provide evidence that genetic variants and chromosomal abnormalities contribute to the DLD phenotype (Mountford et al., 2022; Nudel et al., 2020; Reader et al., 2014; Rice et al., 2009; Simpson et al., 2015). In a recent study, 25% of children with DLD who were referred for genetic testing were found to have pathogenic genetic mutations or chromosomal abnormalities (Plug et al., 2021), for which evidence exists that they are causal to language impairment. This varied from known pathogenic variants, such as 22q11DS, to variants that have been previously identified in children with developmental delay. Of the 30 different diagnoses uncovered, 22 out of 26 had a single occurrence rate, and the other four diagnoses occurred in no more than two children. Although the sample of children with DLD in this study was highly specific and the results cannot be generalized to the population of DLD as a whole, these results do show that there likely is a lot of etiological variety in children with DLD. Etiological heterogeneity dilutes the association signal of any specific causal factor, thereby decreasing the observable effect (i.e., explained variance) on the behavioral outcome (i.e., phenotype; see Figure 1.1, p. 19). Hence, etiological heterogeneity hampers research efforts that focus on various factors impacting the atypical language development of children with DLD. In other disciplines, the prospective study of groups who share a specific risk factor for a certain disorder have been used to identify clinical markers and track the development of the disorders (e.g., Staps et al., 2017). The underlying principle of this approach is that by decreasing etiological

heterogeneity, such groups can function as a model for the general population.

This dissertation investigates whether children with 22q11.2 deletion syndrome (22q11DS) can function as a model for DLD (**aim 2**). 22q11DS has been successfully used as a model for other conditions, such as schizophrenia and scoliosis (Fiksinski et al., 2021; Homans et al., 2019; Gur et al., 2017). This has allowed researchers to identify specific risk factors and describe developmental trajectories (e.g., Vorstman et al., 2015). 22q11DS is etiologically homogeneous and may therefore decrease the amount of unexplained variance in outcomes, such as language and EF. This may allow researchers to detect relationships between such outcomes more easily, if such relationships actually exist. A prerequisite for 22q11DS to function as a model for DLD is that there is substantial phenotypical overlap between the groups. However, literature regarding the early cognitive profile of children with 22q11DS is scarce and had several limitations. To be able to compare the phenotypes of both groups, we thus first needed to further characterize the early language and EF profile of children with 22q11DS (**aim 2a** and **2b**). Subsequently, this dissertation investigated whether there is sufficient phenotypical overlap to justify the use of 22q11DS as a model for DLD (**aim 2c**). Summarizing, this resulted in the following **research aims**:

1. Investigate how non-verbal EF relates to language abilities of children with DLD.
2. Determine whether 22q11DS can function as an etiologically homogeneous model for DLD, which requires:
    - **a.** A detailed language profile of preschool children with 22q11DS.
    - **b.** A detailed EF profile of preschool with 22q11DS.
    - **c.** A comparison between the language and EF abilities of preschoolers with 22q11DS and peers with DLD.

In the following section, the results from this dissertation are summarized and for each aim implications, limitations and future directions are discussed. Clearly, the issues pertaining to **aim 1** cannot

be fully addressed by this dissertation alone. The role of **aim 2** was to investigate a potential method to support the research serving **aim 1**.

THE ROLE OF EXECUTIVE FUNCTIONING IN THE ATYPICAL LANGUAGE DEVELOPMENT OF CHILDREN WITH DLD (1)

Summary of results in the current dissertation

Our first research goal (**aim 1**) was to investigate how non-verbal EF relates to the language abilities of children with atypical language development, specifically children with DLD. In **chapter 2**, we found that preschoolers with DLD were outperformed by their typically developing (TD) peers on all four non-verbal EF tasks, with the largest effect observed for visuospatial working memory (WM). This confirms the presence of non-verbal EF deficits in children with DLD. Furthermore, using latent variables, we related their non-verbal EF abilities to both their morphosyntactic abilities and vocabulary skills. Non-verbal EF was significantly related to morphosyntax in both children with DLD and TD children. Vocabulary and non-verbal EF were, however, only related in the TD group, although a marginal trend was observed for the children with DLD. Moderation analysis showed that these relationships did not differ between the groups.

Our ability to determine the direction of the relationship between EF and language abilities was limited by the lack of longitudinal data. Due to the COVID-19 pandemic these data could not be collected. Making use of a similar strategy as Botting et al. (2017), we nevertheless attempted to gain insight into the direction of the relationship by using both language and EF as predictors in regression models. For example, we ran one regression model with EF as the predictor for morphosyntactic abilities, but in a second model morphosyntactic abilities were used as the predictor for EF. We could then compare the change in explained variance from both regression models. Non-verbal EF explained more variance in morphosyntactic abilities than vice versa in both groups. In the TD children, for whom EF was also significantly related to vocabulary, vocabulary explained more variance in EF than vice versa. For the EF tasks used in this dissertation, it is likely that it is difficult for children to support

performance by means of verbal labeling (see **chapter 2**). The fact that non-verbal EF was related to morphosyntactic abilities in children with DLD therefore provides tentative support for the hypothesis that non-verbal EF deficits either stem from the same underlying cause that leads to language impairment or that they may even be causally related to language impairment (Kapa & Plante, 2015). However, only longitudinal data can provide substantive evidence for the direction of the relationship between EF and language during various stages of development (Bishop, 1997).

Implications, limitations, and future directions

Addressing the role that EF may play in atypical language development is challenging. Language development is a complex process that involves a myriad of factors (D'Souza et al., 2017). As noted above, one prominent question regarding the association between EF deficits and language impairment is the direction of the relationship (Kapa & Plante, 2015). Currently, the presence of non-verbal EF deficits in children with DLD cannot tell us:

i. whether these deficits precede and play a causal role in the language problems of these children,
ii. whether they are a result of the language problems, or,
iii. whether both language and EF impairments stem from a shared underlying cause.

Kapa and Erikson (2019) note that the individual variability seen in the EF abilities of children with DLD weakens the support for the first proposition. Nevertheless, the variability in EF outcomes in children with DLD does not preclude a causal mechanism, albeit possibly only in a subgroup of children. The second proposition has been supported by findings from another clinical population. Research with school-age deaf children suggests that language ability mediates the relationship between hearing impairment status and non-verbal EF, but that non-verbal EF does not mediate language outcomes (Botting et al., 2017; Hall et al., 2017; Merchán et al., 2022). A subsequent study using longitudinal data from the same sample as Botting et al. (2017), confirmed this by showing vocabulary significantly predicted

EF abilities 2 years later (Jones et al., 2020). A study with hearing school-age children with and without DLD has shown the same pattern for the TD children but the opposite pattern for children with DLD (Blom & Boerma, 2019). This suggest the development of reciprocal relationships between language and EF in children with DLD may not be comparable to that of either deaf children or TD children. However, the third proposition, that the co-occurrence of language and EF deficits in children with DLD stems from a shared underlying etiology, could also explain the difference between children with DLD and deaf children. Another explanation for the difference between the groups may be the age of the participants in these studies. As mentioned in the discussion of **chapter 2**, relationships between EF and language may differ between preschoolers and school-age children. Indeed, EF predicted language ability in a longitudinal study with deaf preschoolers with a cochlear implant (Kroneberger et al., 2020), showing a reverse pattern than that from abovementioned research on school-age deaf children (Jones et al., 2020). More research, especially with longitudinal designs, is needed to determine whether EF deficits are a cause, a consequence, or a co-occurring phenotype in children with DLD. Studying different clinical populations might aid our ability to discern the different mechanisms underlying the causes of atypical language development.

Interestingly, one potential clinical implication for a (causal) relationship between EF and language, if established, would be that targeting EF in therapy may also benefit language outcomes. As mentioned in **chapter 2**, there is tentative evidence that language abilities of children with DLD may benefit from interventions aimed at improving EF abilities (e.g., Delage et al., 2021; Stanford et al., 2019), but this needs to be corroborated by larger studies.

Although the results reported in **chapter 2** are in line with some previous findings, there are others that reported divergent outcomes. These differences in results may in part be caused by methodological differences between studies, such as age of participants or tasks used (e.g., Blom & Boerma, 2020; Boerma & Blom, 2020). Additionally, the large etiological and phenotypical variability seen in children with DLD likely impedes our ability to detect relationships between

children's language deficits and other factors. Relationships may not emerge in group analyses as various etiological subgroups are grouped together, thereby diluting the signal of relationships that are strongly present in specific etiological subgroups but not (or to a lesser extent) in others. As discussed in **chapter 1**, one way to limit this variability is to use an etiologically homogeneous population that shares phenotypical characteristics with DLD. We hypothesized that 22q11DS might constitute such a population. Therefore, the second research goal (**aim 2**) of this dissertation was to determine whether 22q11DS could function as an etiologically homogeneous model for DLD, ultimately supporting our understanding of the underlying mechanisms of atypical language development.

22Q11DS AS A MODEL FOR UNDERSTANDING THE ROLE OF EF IMPAIRMENT IN DLD (2)

A prerequisite for using 22q11DS as a model for DLD is that there is sufficient phenotypical overlap between these two groups. As there is a paucity of research on the early cognitive abilities of children with 22q11DS, we first needed to further characterize the early language and EF profile of children with 22q11DS (**aim 2a** and **2b**). We then compared the phenotypes of both groups (**aim 2c**).

The language profile of children with 22q11DS (2a)

Language impairment is a frequently mentioned symptom in the 22q11DS literature, but a detailed description of the specific language profile was lacking for preschool children. All previous studies using standardized assessments only reported global composite language scores and no study with a substantial sample size had analyzed spontaneous language. In **chapter 3**, we studied the language profile of preschoolers with 22q11DS in more detail than has been done to date. In this chapter, we focused on standardized assessment, as such outcomes are often the main criteria for diagnostic labels and therefore frequently used by speech-language pathologists. In addition, the results of a standardized test provide a first and broad overview of the language profile, covering various language domains. We observed impairment across all tested language domains, with the weakest performance for expressive morphology, while receptive

vocabulary was a relative strength. In line with previous research in younger children with 22q11DS (Gerdes et al., 1999; Gerdes et al., 2001; Solot et al., 2001), our results showed a relatively larger impairment in expressive than in receptive language skills. Interestingly, for school-age children the opposite profile has been reported (Glaser et al., 2002; Van den Heuvel et al., 2018).

Standardized test performance provides important clinical information on whether language abilities are age-adequate. Spontaneous language analysis, however, is more ecologically valid and can also be used with children who cannot yet comply with the behavioral requirements for standardized testing (Costanza-Smith, 2010; Doedens & Meteyard, 2022). Furthermore, this type of assessment can be used by professionals to determine therapy goals (Heilmann, 2010; Klatte et al., 2022; Price et al., 2010). In **chapter 4**, we used spontaneous language analysis in addition to standardized tests to compare the language abilities of preschool children with 22q11DS to age- and sex-matched TD peers. The outcomes of the spontaneous language analysis showed that preschoolers with 22q11DS produced shorter and less complex utterances than their TD peers. We also found that children with 22q11DS made more verb- and non-verb-related grammatical errors. In addition to the preschool children from the *3T project*, the study in **chapter 4** also included a sample of school-age (6-10y) children with 22q11DS. Given the previous contrasting findings on expressive morphosyntactic abilities (cf. **chapter 3** for preschool; Glaser et al., 2002; Van den Heuvel et al., 2018 for school-age), we considered the possibility that school-age children would have relatively stronger grammatical skills than the preschoolers. In contrast to this hypothesis, the school-age children with 22q11DS showed a profile similar to that of the preschool children, with the most severe impairment in expressive morphosyntactic abilities and relatively less impaired receptive vocabulary skills. Standard scores for receptive vocabulary were similar for school-age and preschool children, while standard scores for the expressive grammar subtest on sentence level, showed a larger deficit in the preschool children than in the school-age children. This may indicate that the severity of impairment differentially varies across language domains during childhood. The only study that tracked the trajectory

of language development longitudinally seems to suggest that language abilities of children with 22q11DS decline with age (Solot et al., 2020). This study, however, did not differentiate between different language domains, like morphosyntax and vocabulary. Furthermore, it is unclear whether this decline in language abilities reflects an absolute decline (i.e., deterioration of language skills as reflected by a decrease in raw scores) or just a smaller increase in abilities than would be expected based on chronological age (i.e., a stagnation or small increase in raw scores reflecting growth in abilities but resulting in lower norm scores when growth is less than that of TD peers). Again, more research is needed to investigate the developmental trajectories of the language abilities of children with 22q11DS and to determine whether these language impairments persist into adolescence and adulthood.

Lastly, in **chapter 3**, we observed considerable inter-individual variation in children's language abilities on standardized tests, with a small number of children showing age-adequate performance, while most children had scores ranging from mildly to severely impaired. We hypothesized that one source that could explain this variability in language scores may be speech intelligibility. Young children with 22q11DS frequently have poor speech intelligibility (Persson et al., 2003; Solot et al., 2000), which may be the result of a combination of anatomical and/or neurological abnormalities (Baylis & Shriberg, 2019; Jackson et al., 2019; Solot et al., 2019). Speech intelligibility was indeed related to both expressive and receptive language abilities. This provides support for the hypothesis that speech intelligibility influences language development, for example by affecting the frequency and content of children's socio-communicative interactions. However, we found that many children with intelligible speech still had below-average language scores. This indicates that language impairment in children with 22q11DS cannot be fully attributed to their speech problems and highlights the importance of language assessment as part of routine clinical care for children with 22q11DS.

The EF profile of children with 22q11DS (2b)

To gain more insight into the EF abilities of children with 22q11DS, in **chapter 5** we systematically reviewed what is currently known about EF in 22q11DS. In this systematic review, we delineated how studying 22q11DS could inform our understanding of typical and atypical development in the general population. We did so by showing that a homogeneous population like 22q11DS provides a focused context for the investigation of specific mechanisms and relationships with both endogenous and exogenous (i.e., child-internal and child-external) factors. EF impairments in children with 22q11DS are, at least in part, the consequence of the deletion on chromosome 22. However, variability in their EF phenotype has been observed and EF deficits are likely affected by several risk factors, some of which occur at increased rates in this population. As such, we delineated how 22q11DS provides an opportunity to investigate the impact of such factors in the context of a single underlying genetic etiology. We distinguished EF domains as proposed in the model by Miyake et al. (2000), which includes updating (i.e., WM), inhibition, and shifting. Additionally, we differentiated children from adolescents, as developmental trajectories may differ between EF domains. However, most studies used samples with large age ranges, thereby prohibiting us from reporting findings for children and adolescents separately.

We found that previous research provided strong evidence for inhibition and shifting impairments in children with 22q11DS. Evidence for updating was mixed and thus inconclusive, although the literature so far seems to suggest that updating abilities, especially verbal WM, might be a relative strength in childhood. Findings were hampered by the relatively high participant age and the wide age ranges of most studies included in the review. Additionally, we showed that risk factors previously identified in the general population, such as congenital heart defects (CHD) (Mebius et al., 2017; Sterken et al., 2015) or low socioeconomic status (Lawson et al., 2018), may not impact EF abilities of children with 22q11DS in a similar way (Allen et al., 2014; Shashi et al., 2010; Yi et al., 2014). Such knowledge can help shed light on the mechanisms underlying EF development and how they can be disrupted.

In this systematic review (**chapter 5**), we observed that there were no studies with children under 6 years of age, precluding any conclusions about the early EF phenotype of children with 22q11DS. To compare the EF phenotype of young children with DLD and children with 22q11DS, more research was needed. Therefore, in **chapter 6,** we investigated the EF abilities of preschoolers with 22q11DS – using the same four tasks used in **chapter 2** – compared to the EF abilities of a TD group. Children with 22q11DS had substantially poorer performance on the non-verbal EF tasks as compared to the TD group. This shows that EF deficits are already present at a young age in children with 22q11DS. Our findings also suggest that the different components of EF may be less strongly interrelated in children with 22q11DS than in TD children. That is, in contrast to the theoretical model of Garon et al. (2008) and the outcomes of the TD group, visual selective attention was not related to visuospatial WM in children with 22q11DS.

In **chapter 5**, we also noted that the presence of CHD has been strongly related to EF deficits in children with non-syndromic CHD (Mebius et al., 2017; Sterken et al., 2015), although we found no evidence to support such an effect in 22q11DS. As CHD is common in 22q11DS (McDonald-McGinn et al., 2015; Unolt et al., 2018), in **chapter 6**, we also compared the EF abilities of preschoolers with 22q11DS with and without hemodynamically significant CHD. In line with two previous studies (Fountain et al., 2014; Yi et al., 2014), we observed no differences in EF abilities between children with and without CHD. This prompts us to reconsider the proposed pathway through which CHD supposedly affects EF abilities. Our findings support the hypothesis that the presence of CHD and concurrent EF impairments both stem from an underlying genetic defect and that EF deficits cannot (solely) be explained by CHD-related procedures (Homsy et al., 2015; McQuillen & Miller, 2010; Morton et al., 2022).

Comparing cognitive phenotypes of preschoolers with 22q11DS or DLD (2c)

To determine whether 22q11DS could function as a model for DLD, we needed to compare the phenotypic overlap between the two groups with regard to language and EF abilities. In the following section, we

summarize our findings and provide some additional analyses and take a first step in exploring the use of 22q11DS as a model for DLD.

Overlap in the language profile of children with 22q11DS and children with DLD

Previous research has tentatively suggested that children with 22q11DS may be similar to children with DLD with regard to language abilities (Goorhuis-Brouwer et al., 2003; Kambanaros & Grohmann, 2017; Swillen et al., 2001). Only one of these studies directly compared behavioral language data, using outcomes from a group of children with DLD in comparison to those of a single child with 22q11DS (Kambanaros & Grohmann, 2017). However, no such comparisons have been made using larger samples and using both broad standardized language assessment and spontaneous language analysis. Therefore, in **chapter 4** we compared the grammatical abilities of preschool- and school-age children with 22q11DS, children with DLD, and TD children using both standardized language measures and spontaneous language. As deficits in morphosyntax (i.e., grammar) are a hallmark characteristic of DLD (Rice et al., 1996; Leonard, 2014) and relatively little is known about the grammatical skills of children with 22q11DS, we focused on these grammatical abilities.

Outcomes of the standardized language assessment showed that preschool children with 22q11DS and preschool children with DLD performed similarly on expressive morphosyntax, which was significantly weaker than the performance of the TD children. For receptive morphosyntax, both clinical groups were also outperformed by the TD children, but the children with 22q11DS also showed poorer abilities than the children with DLD. A similar pattern between the groups was observed for vocabulary, with the TD children performing better on both receptive and expressive measures than the children with 22q11DS and the children with DLD, while the children with 22q11DS performed similar to the DLD group on the expressive vocabulary measure, but poorer on the receptive measure. A larger discrepancy between expressive morphosyntax and the other domains was observed for the children with DLD than for the children with 22q11DS. Next to the standardized tests, we also analyzed

spontaneous language samples of smaller age- and sex-matched subsamples. The preschool-age children with 22q11DS and children with DLD did not differ on any of the outcome measures indexing grammatical accuracy and complexity; and both groups made more errors and produced shorter and less complex utterances as compared to the TD children.

In addition to the three groups of preschool children from the *3T project*, in the study in **chapter 4** we also included two smaller samples of school-age (6-10y) children with 22q11DS and children with DLD, who participated in another study which focused on language processing and activation in the brain (Selten et al., 2021; Vansteensel et al., 2021). Standardized language outcomes showed that there was no difference between the children with 22q11DS and children with DLD on expressive morphosyntax. A marginal difference on receptive vocabulary was found, with the DLD group obtaining a higher mean score than the 22q11DS group. The children with DLD had a bigger discrepancy between expressive morphosyntax and receptive vocabulary skills than children with 22q11DS, similar to the results of the preschoolers. Moreover, the analysis of spontaneous language also showed no differences between the groups on grammatical complexity and accuracy.

In a Dutch article for professionals (Boerma et al., 2022), we also compared the global outcomes of the standardized language assessment between preschool children with 22q11DS and children with DLD. Here, we again showed that there was a discrepancy between receptive and expressive language abilities in both children with 22q11DS and children with DLD, but that this discrepancy was larger for children with DLD. The expressive language abilities of children with DLD are below-average, while on a group-level their receptive language abilities are within the average range, albeit with large interindividual differences. Children with 22q11DS, on the other hand, have both severe expressive and receptive language problems.

Overlap in the EF profile of children with 22q11DS and children with DLD

In **chapter 2**, we showed that children with DLD have lower non-verbal EF performance compared to TD peers. The same was

observed for children with 22q11DS in **chapter 6**. However, so far we have not compared the EF abilities of children with 22q11DS and children with DLD, and this has also not been done by others. Below, we present some additional analyses that address this matter. As the EF tasks are not standardized, we also included the TD group in these analyses. An ANCOVA with age as a covariate was used to compare the groups. The group means and comparisons with the TD group can be found in Table 2.2 in **chapter 2** for the children with DLD and Tables 6.2, 6.3, and 6.4 in **chapter 6** for the children with 22q11DS. Results from the additional analyses showed that the three groups differed significantly in their performance on the selective attention task ($F(2, 184) = 15.36$, $p < .001$, $\eta_p^2 = .14$), the Corsi forward span ($F(2, 167) = 19.45$, $p < .001$, $\eta_p^2 = .19$), the Corsi backward span ($F(2, 164) = 18.78$, $p < .001$, $\eta_p^2 = .19$), and the Head-Toes-Knees-Shoulders task ($F(2, 88) = 10.34$, $p < .001$, $\eta_p^2 = .19$). Post-hoc outcomes are presented in Table 7.1.

There was no difference on WM span (Corsi backward) between children with 22q11DS and the children with DLD. Although they did not differ on the selective attention task and the forward condition of the Corsi block tapping task, a marginal trend emerged which points towards better performance for the DLD group. Results of the broad EF task should be interpreted with caution due to the limitations described in **chapter 2** and **chapter 6**.

Table 7.1. Post-hoc comparisons between the 22q11DS group, the DLD group, and the TD group on the four non-verbal EF tasks.

	SA	*Corsi FW*	*Corsi BW*	*HTKS*
22q11DS – DLD	$p = .087$	$p = .055$	$p = .64$	$p = 1.0$
TD – 22q11DS	***p* < .001**	***p* < .001**	***p* < .001**	$p = .083$
TD – DLD	***p* = .002**	***p* < .001**	***p* < .001**	***p* < .001**

Abbreviations: 22q11DS = 22q11.2 deletion syndrome, BW = Backward, DLD = Developmental Language Disorder, FW = Forward, HTKS = Head-Toes-Knees-Shoulders Task, SA = Selective Attention, TD = Typically Developing.
Note. Bonferroni correction applied

Phenotypical overlap: Relationship language abilities and intellectual functioning

The behavioral research reported in **chapter 4** and the analyses above show overlap in the language and EF phenotype of preschool children

with 22q11DS and children with DLD. Before summarizing the findings and drawing a conclusion, we provide some additional analyses to substantiate the phenotypical overlap between the groups, given the differences in intellectual functioning between children with 22q11DS and children with DLD.

Children with 22q11DS often have borderline intellectual abilities (De Smedt et al., 2007; Swillen et al., 2018). Children with DLD have Intelligence Quotient (IQ) scores in the normal range, although on average lower than TD peers (Gallinat & Spaulding, 2014). There is a difference in intellectual functioning between the two groups, and it could thus be argued that they cannot be compared. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5-TR; American Psychiatric Association, 2020) specifies that a language disorder may be diagnosed when "The difficulties [...] are not better explained by intellectual developmental disorder (intellectual disability) or global developmental delay" (F80.2). It has been suggested that children with 22q11DS experience language difficulties that exceed what would be expected based on their level of intellectual functioning (Persson et al., 2006; Scherer et al., 1999; Selten et al., 2021; Van den Heuvel et al., 2018). However, previous studies have not directly investigated the relationship between language abilities and intellectual functioning in children with 22q11DS.

To investigate if children with 22q11DS and children with DLD are comparable with respect to language and cognitive abilities, we explored the relationship between language abilities and intellectual functioning. The Core Language Index (CLI) of the Clinical Evaluation of Language Fundamentals Preschool (CELF Preschool-2-NL) is a measure of overall language ability (Wiig et al., 2012). The CLI and IQ scores are both standardized in reference to chronological age on a scale with a mean of 100 and an *SD* of 15 and can be therefore easily compared. Correlations were used to investigate the relationship between IQ and CLI, and paired samples t-tests were performed to investigate whether they differed from each other in each of the three groups of children. As can be seen in Table 7.2, the CLI and IQ scores are positively correlated in the 22q11DS and TD group. For the DLD group, a similar trend was observed but this was not significant. On

average, both children with 22q11DS and children with DLD have CLI scores that are significantly below their IQ score, which is not the case for the TD children.

Table 7.2. Mean (SD) for CLI and IQ scores with statistical analyses for the 22q11DS, DLD, and TD group.

	CLI	***IQ***	***Correlation***	***t-test***
	M (SD)	*M (SD)*		
22q11DS (*n* = 35)	71.1 (12.2)	82.1 (10.9)	***r*(35) = .64, *p* < .001**	***t*(34) = 6.59, *p* < .001, *d* = 1.11**
DLD (*n* = 63)	76.9 (12.4)	97.4 (13.0)	*r*(63) = .24, *p* = .057	***t*(62) = 10.39, *p* < .001, *d* = 1.31**
TD (*n* = 77)	106.4 (13.0)	106.3 (12.9)	***r*(77) = .25, *p* = .013**	*t*(76) = .07, *p* = .94, *d* = .01

Abbreviations: 22q11DS = 22q11.2 deletion syndrome, CLI = Core Language Index (from the CELF Preschool-2-NL), DLD = Developmental Language Disorder, IQ = Intelligence Quotient, SD = Standard Deviation, TD = Typically Developing.

Note. Significant outcomes are printed in bold. Some children could not be included in analyses due to missing CLI scores (22q11DS, *n* = 7; DLD, *n* = 2), missing IQ score (22q11DS, *n* = 1; TD, *n* = 1), or both (22q11DS, *n* = 1). TD children with a CLI more than 1 *SD* below the normed mean (*n* = 3) were not included in analyses.

Additionally, we calculated a difference score by subtracting the CLI score from the IQ score, see Figure 7.1. In an ANOVA with this 'IQ-CLI difference score', there was a significant effect of Group ($F(2, 172) = 33.10$, $p < .001$, $\eta_p^2 = .28$). Post-hoc analyses showed that the TD children had a smaller IQ-CLI discrepancy ($M = 0.1$, $SD = 15.8$) than the children with 22q11DS ($M = 11.0$, $SD = 9.9$, $p = .001$) and the children with DLD ($M = 20.5$, $SD = 15.7$, $p < .001$). The 22q11DS group, in turn, had a smaller IQ-CLI discrepancy than the DLD group ($p = .008$).

These results show that intellectual functioning and language abilities are more strongly related in children with 22q11DS than in children with DLD, but that both children with 22q11DS and children with DLD have language abilities that are significantly below their intellectual level. The correlation results also support our hypothesis that the homogeneous etiology of 22q11DS may provide a more focused context for the investigation of specific relationships where the signal for a given relationship is stronger than that in a more heterogeneous sample (**chapter 1** and **5**). However, an important limitation that should be taken into account when interpreting these

results, is that it is common to use non-verbal IQ tests in assessments for children with DLD, while this is not standard practice for children with 22q11DS. In our sample 62 of the 65 children with DLD were tested with a non-verbal IQ test as opposed to 19 out of 42 children with 22q11DS (see table 2.1 and 3.1). The fact that IQ strongly correlates with CLI in the children with 22q11DS may thus also be the result of the use of verbal subtests in the IQ assessment of the remaining 23 participants with 22q11DS. Furthermore, the larger discrepancy between language abilities and IQ in the DLD group than in the 22q11DS group may thus also partially reflect the use of different IQ tests in these groups. Future research should ideally use similar IQ assessments in both groups.

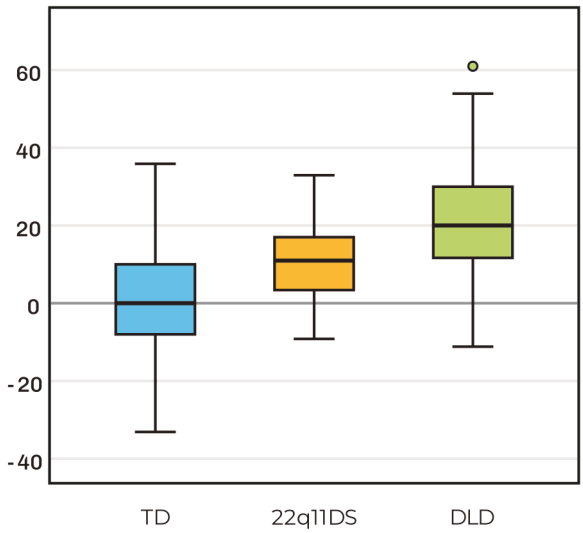


Figure 7.1. Boxplots of the difference scores between IQ minus CLI for all three groups.

SUMMARY AND TAKING A FIRST STEP IN USING 22Q11DS AS A MODEL FOR DLD

Summarizing, the work in this dissertation shows that children with DLD and children with 22q11DS both have impaired language and EF abilities in early childhood as compared to TD peers. At preschool age and school-age, both groups have below-average scores on standardized tests and show similar spontaneous language profiles

(**chapter 4**). At preschool-age both groups also have significantly better receptive than expressive language skills, but this discrepancy is larger for children with DLD than for children with 22q11DS (**chapter 4** and Boerma et al., 2022). Children with 22q11DS on average have more severe receptive language problems. In children with 22q11DS, intellectual functioning is more strongly related to language level than in children with DLD, but in both groups language abilities are significantly below their level of intellectual functioning (**chapter 7**). Additionally, the similarities in language difficulties between the two groups are also supported by a recent study with the school-age sample as used in **chapter 4**. This study showed that narrative production and comprehension (i.e., the ability to tell and understand stories, respectively) of children with 22q11DS did not differ from that of children with DLD (Selten et al., 2021). Regarding EF, both children with 22q11DS and children with DLD were outperformed by TD peers on non-verbal EF tasks (**chapter 2** and **6**), but they do not differ from one another (**chapter 7**). Overall, it thus seems there is sufficient phenotypical overlap to suggest that 22q11DS could be used as an etiological homogeneous model for DLD, similar to what is current practice in schizophrenia research (Fiksinski et al., 2021; Gur et al., 2017). However, it should be noted that we only included children with DLD that were eligible for special education (**chapter 1**), which constitutes the group of children with the most severe language problems. This means that these findings may not be generalizable to the broader group of children with DLD.

Below, we therefore make a first exploratory comparison of the relationship between EF and language abilities in children with 22q11DS compared to children with DLD or TD children, similar to the analyses in **chapter 2**. We created latent variables for EF, vocabulary, and morphosyntactic abilities using the same outcomes and procedures as in **chapter 2**. Correlations were used to explore whether *EF* was related to *Vocabulary* and *Morphosyntax* in children with 22q11DS. A significant correlation was found between *EF* and *Morphosyntax* ($r(34) = .44$, $p = .009$). For *EF* and *Vocabulary*, a medium correlation emerged, but this fell just short of statistical significance ($r(34) = .32$, $p = .066$). Regression analyses were then used to investigate whether *EF* predicted *Morphosyntax* and *Vocabulary* in

the children with 22q11DS [2]. The baseline model included only the covariates *Age*, *Sex*, *IQ*, and *SES* as predictors (step 1). Adding *EF* as an independent variable to the baseline model (step 2) with *Morphosyntax* as the dependent variable, did not lead to a significant increase of explained variance ($\Delta F(1, 27) = 2.32$, $p = .14$, $\Delta R^2 = .04$), but the final model was significant ($F(5, 27) = 5.17$, $p = .002$, $R^2 = .49$). Adding *EF* as independent variable to the model with *Vocabulary* as the dependent variable also did not lead to a significant increase of explained variance ($\Delta F(1, 27) = 1.61$, $p = .22$, $\Delta R^2 = .03$), but again the final model was significant ($F(5, 27) = 6.27$, $p = .001$, $R^2 = .54$), see Table 7.3.

We then used moderation analysis to determine whether the relationship between EF and language in children with 22q11DS differed from that of children with DLD or TD children. Moderation analysis with *EF* as the independent variable, *Group* as the moderator, and *Age*, *Sex*, *IQ*, and *SES* as covariates, was significant in both the model with *Morphosyntax* ($F(6, 152) = 80.40$, $p < .001$, $R^2 = .76$) and the model with *Vocabulary* as the dependent variable ($F(6, 150) = 15.09$, $p < .001$, $R^2 = .61$). Adding the interaction term (*Group*EF*) did not lead to a significant increase of explained variance in the model with *Morphosyntax* ($\Delta F(1, 151) = 2.45$, $p = .12$, $\Delta R^2 = .00$), nor in the model with *Vocabulary* ($\Delta F(1, 149) = .33$, $p = .57$, $\Delta R^2 = .00$), indicating that *Group* did not moderate the relationship between *EF* and either *Morphosyntax* or *Vocabulary*.

These outcomes are similar to the outcomes described in **chapter 2** with respect to the fact that the moderation analysis showed no difference between the groups in the relationship between language and non-verbal EF. However, the regression analyses did not show a significant relationship between the two in the 22q11DS group. Given the outcomes from the moderation analysis, the absence of evidence for a relationship in the 22q11DS group in the regression could be the result of a lack of power. This is further supported by the correlation outcomes that showed a significant relationship between EF and morphosyntax and a trend towards a medium effect for EF and vocabulary. However, these findings

2 To minimize the number of analyses we decided to only look at EF as a predictor for language, in contrast to **chapter 2** where these analyses were also run reversely. We deem it more likely that EF predicts language than vice versa at this age, see discussion **chapter 2** (p. 58-67).

currently do not provide support for the hypothesis presented in **chapter 1** and **5** that relationships may be easier to detect in an etiological homogeneous population.

Table 7.3. Regression models with EF as a predictor for both latent language variables while taking *Age*, *Sex*, *IQ*, and *SES* into consideration as covariates for the group of children with 22q11DS.

		22q11DS		
	B	*SE B*	*β*	*p*
Morphosyntax	***Step 2***			
Constant	-4.806	1.173		<.001
Age	.374	.116	.518	**.003***
Sex	-.138	.190	-.105	.475
IQ	.028	.009	.477	**.004***
SES	.055	.058	.139	.350
EF	.205	.134	.228	.139
Vocabulary	***Step 2***			
Constant	-4.865	1.608		.005
Age	.615	.158	.596	**.001***
Sex	.162	.262	.086	.543
IQ	.026	.013	.298	.052
SES	-.132	.082	-.223	.122
EF	.231	.182	.181	.215

Abbreviations: B = unstandardized regression coefficient, β = standardized regression coefficient, EF = Executive functioning (latent factor), IQ = Intelligence Quotient, SE = Standard Error, SES = Socioeconomic Status.

Note. Significance of the covariates did not differ between the baseline models (step 1) and the regression models including the independent variable (step 2), except for IQ in the model with Vocabulary as the dependent variable, which was significant in the baseline model (p = .025) while it fell just short of significance in step 2.

One explanation for the observation that relationships are not stronger in the 22q11DS group than in the DLD group could be that, despite phenotypical overlap, the nature of the relationship between EF and language differs between the groups. The work in this dissertation only considered non-verbal EF. There is ample evidence that verbal WM is impaired in children with DLD (e.g., Henry et al., 2012; Hick et al., 2005; Kapa & Erikson, 2020; Lukács et al., 2016; Marini

et al., 2020; Vugs et al., 2014), while this may be a relative strength in children with 22q11DS (**chapter 5**). For children with DLD, it has been shown that their verbal WM skills are related to their language abilities (Duinmeijer et al., 2012; Delage & Frauenfelder, 2020; Jackson et al., 2021; Montogomery & Evans, 2009; Vugs et al., 2016). More research is needed to describe the verbal WM abilities of preschool children with 22q11DS and to determine how these relate to their language abilities. If verbal WM is indeed relatively strong in children with 22q11DS, this would pose a serious limitation for the use of 22q11DS as a model for DLD, at least with regards to the role of EF deficits in the language abilities of children with DLD. It would, however, be interesting to further investigate this relationship in children with 22q11DS. If children with 22q11DS present with language impairment in the context of relatively intact verbal WM, this would show that verbal WM deficits are not necessary for the impaired development of language. This could enhance our understanding of the mechanisms underlying (a)typical language development and prompt investigations into the factors hindering language development in children with 22q11DS.

Another factor that could have contributed to the observation that the relationship between language and EF is not stronger in the 22q11DS group than in the DLD group, is the difference between the groups in other aspects than those considered in this dissertation. Firstly, the more severe receptive problems of children with 22q11DS should be considered when comparing them to children with DLD. Not all children with DLD have receptive language problems (Conti-Ramsden et al., 1999; Rapin, 1996). Children with 22q11DS may be more similar to the subgroup of children with DLD who have both receptive and expressive language problems. Secondly, although children with 22q11DS generally have lower IQ scores (De Smedt et al., 2007; Swillen et al., 2018) than children with DLD (Gallinat & Spaulding, 2014), we found a significant discrepancy between the standardized language composite scores and IQ scores for both groups. This difference was, however, smaller for children with 22q11DS than for children with DLD. The language profiles of these groups overlap despite the difference in intellectual functioning (**chapter 4**). Combined with the outcomes of Selten et al. (2021), this suggests that IQ is not the primary

determinant of language problems. Lastly, children with 22q11DS may be homogeneous in etiology but they are heterogeneous in phenotype. As can be seen in the variability of the outcomes in **chapter 3**, **4**, **6**, and **7**, the etiological homogeneity of 22q11DS does not necessarily lead to less variability in the behavioral phenotype. The same variability we observed in standardized language outcomes has also been observed for intellectual functioning (Zhao et al., 2018). Furthermore, children with 22q11DS are also heterogeneous with regard to the presence of somatic symptoms (McDonald-McGinn et al., 2015). Conditions such as CHD, hypothyroidism, and hypocalcemia can affect early brain development (e.g., Fountain et al., 2014; Muldoon et al., 2015), thereby possibly impacting EF and language development. These conditions are not present in children with DLD, which may hamper comparison. However, **chapter 6** shows that the presence of CHD did not seem to exacerbate EF impairments in children with 22q11DS. Furthermore, a quick explorative analysis of our data shows the same for language abilities. There was no evidence for a difference between children with 22q11DS with and without CHD on the CLI ($t(34) = 1.48$, $p = .15$, $d = .51$) or PPVT ($t(40) = 1.50$, $p = .14$, $d = .48$), keeping the limitation of a small sample in mind (see **chapter 6**). Despite previous review studies reporting poorer EF and language outcomes for children with CHD (Hicks et al., 2016; Huisenga et al., 2020; Mebius et al., 2017; Sterken et al., 2015), this dissertation finds no evidence that suggests CHD impacts EF and language outcomes of the children with 22q11DS. So, with regard to **aim 2**, we tentatively conclude that the presence of such somatic symptoms may not immediately hamper the comparison of children with 22q11DS and children with DLD. However, we cannot definitively determine the effect of CHD, and especially not the effect that other conditions may have had on the language and EF abilities of children with 22q11DS, warranting more research.

Nevertheless, work within the *3T project* has yielded promising results. Selten et al. (*in preparation*) investigated whether language abilities predicted autism spectrum disorder (ASD) related behaviors one year after language assessment in children with 22q11DS and children with DLD. Using the same participant samples as the studies in this dissertation, Selten et al. show that receptive language abilities

significantly predicted ASD behaviors in children with 22q11DS but not children with DLD. The absence of a relationship in the DLD group but not in the 22q11DS group suggests that the homogeneous etiology of the latter group can be used to reduce variability, allowing us to pick up relationships that may not emerge when collapsing data from children with differing etiologies.

Future opportunities for using 22q11DS as a model for DLD

The study of 22q11DS provides more opportunities to learn more about the causal chain from genes to brain development to behavior in atypical language development. A recent study using fMRI in the same school-age sample of children with 22q11DS and children with DLD as **chapter 4** found that both groups showed comparable hypoactivation in brain areas associated with language processing compared to healthy controls (Vansteensel et al., 2021). This may tentatively suggest that neural processes that underlie the atypical language processing in both groups may be comparable. However, imaging studies in DLD are scarce and no other studies have used imaging techniques to compare children with DLD and children with 22q11DS. More work is needed before any conclusions about neural processes can be drawn.

Although it is currently uncertain whether 22q11DS is suitable as a model for DLD with regards to the role of EF in atypical language development, 22q11DS may provide a model for DLD in other respects. For example, one could study other co-morbidities or factors that may co-occur with language impairment. Both children with 22q11DS and children with DLD show a heightened incidence of socio-emotional problems and psychiatric problems (Bassett et al., 2005; Beitchman et al., 1986; Clegg et al., 2005; Fiksinski et al., 2018; Murphy et al., 1999; Schneider et al., 2014; Snowling et al., 2006; Vorstman et al., 2006; Yew & O'Kearny, 2013). Children with 22q11DS have a clear genetic predisposition for psychiatric problems, while in children with DLD there is no clear etiological predisposition for such problems, although their language problems are thought to play a role in this (e.g., Conti-Ramsden et al., 2013; Snowling et al., 2006). The extent to which language difficulties further predispose children to psychosocial problems or whether they merely co-occur, could be

studied in these two groups. For instance, another study from the *3T project* shows that receptive language problems were related to ASD-related behaviors one year later in children with 22q11DS but not in children with DLD (Selten et al., *in preparation*). Of particular interest is the role of language in the development of psychotic disorders. In idiopathic schizophrenia, characteristics from spontaneous language, such as semantic incoherence, low syntactic complexity, and phonetic parameters, may provide a good predictive marker for conversion to psychosis (Bedi et al., 2015; Compton et al., 2018; Corcoran et al., 2018). Individuals with 22q11DS have a 20% risk of developing schizophrenia (Karayiorgou et al., 2010) and one study has already shown that in children and young adults with 22q11DS weaker language abilities were associated with later psychotic symptoms (Solot et al., 2020). Future research could investigate the use of language as a clinical marker for the development of psychotic symptoms. This may also have clinical relevance for children with DLD, as tentative evidence suggests that they may also be at greater risk for developing psychosis than the general population (Clegg et al., 2005; Mouridsen & Hauschild, 2008).

The presence of specific somatic symptoms may also provide opportunities for future research. Some somatic symptoms that are frequently present in children with 22q11DS, are also more common in children with DLD. For example, ear infections (i.e., otitis media with effusion) are common in both children with 22q11DS (Verheij et al., 2017), and children with DLD (Bishop & Edmundsen, 1985). It has been debated whether the presence of otitis media contributes is related to language problems in children with or without DLD (Casby, 2001; Lonigan et al., 1992; Shriberg et al., 2000; Zumach et al., 2010). Individuals with 22q11DS may also more frequently suffer from conductive and sensorineural hearing loss (Van Eynde et al., 2016). The effect of intermittent and/or chronic hearing loss on their speech and language development is currently unknown. In **chapter 1,** we delineate that the early diagnosis and regular clinical assessment of children with 22q11DS allows for the prospective study of such factors, which is difficult in DLD given its incidence and age of diagnosis (see **chapter 1**, **box 1**). Future prospective research with children with 22q11DS combined with research in children with DLD, both with and

without a history of otitis media, might contribute to elucidating the effect of temporary (mild) hearing loss on language development.

Children with 22q11DS also frequently have palatal abnormalities, which combined with neurological problems can lead to poor intelligibility (Baylis & Shriberg, 2019; Jackson et al., 2019; Persson et al., 2003; Solot et al., 2019). Some children with DLD also have speech-sound disorders (Tyler, 2002; Waring & Knight, 2013), which affect their speech intelligibility (Lousada et al., 2014). The relationship between intelligibility and the receptive and expressive language abilities of children in both groups can provide insight into factors affecting language development. In **chapter 3**, we hypothesized that speech intelligibility may negatively impact social interactions thereby affecting the quantity and quality of language input. If true, both children with 22q11DS and children with DLD with poor intelligibility should show weaker language abilities than those with good intelligibility. Future research could investigate to what extent intelligibility and speech disorders affect language development in both groups, ideally also taking into account the possibly mediating effect of social interactions (e.g., Pennington & McConachie, 2001).

CLINICAL IMPLICATIONS

Even though 22q11DS is more prevalent than many other syndromes and most children with 22q11DS receive speech-language therapy, the syndrome is not well-known amongst professionals. To raise awareness in the field of speech-language pathology and provide them with information, we wrote an article in Dutch for a professional journal (Boerma et al., 2022) and developed an information brochure for speech-language therapists. In **chapter 3**, we described that many of the children with 22q11DS who had intelligible speech obtained scores of more than 1 *SD* below the normed mean. This suggests that the language difficulties of these children are not secondary to their speech problems. Clinically, this is important, because it reiterates the message that language assessment should be part of the routine clinical care for all children with 22q11DS (Solot et al., 2019). Children with 22q11DS have been frequently labeled with non-verbal learning disorder (Schoch et al., 2012), suggesting that their language abilities

may not be a prominent source of concern. Professionals in medical or educational contexts who work with children with 22q11DS should be aware that the absence of speech problems or palatal abnormalities does not preclude language problems and that the threshold for referral for language assessment or therapy should be low. This also requires more knowledge among medical professionals, such as general practitioners, genetic counselors, child neurologists, and pediatricians, about language development and its importance for later academic and societal success, social competence, mental health, and quality of life (e.g., Eadie et al., 2018). This can likewise be beneficial to children with DLD, as it might help raise awareness about language problems and its early indicators.

As mentioned throughout this dissertation, children with 22q11DS and children with DLD may have similar needs with regard to the types of education or support they require. As discussed, there seems to be substantial overlap in their language profiles, but there are also some differences with respect to the severity of their receptive language impairments and their level of intellectual functioning. As they are frequently seen and treated by the same professionals (Boerma et al., 2022), this raises the question whether they benefit from the same interventions and treatment strategies. Future research is warranted to study the efficacy of interventions for children with DLD in children with 22q11DS. This may furthermore help answer questions regarding the effectiveness of such interventions for children with lower intellectual functioning or other co-morbid impairments, including behavioral problems. Currently, there are promising results from research showing tentative evidence that language interventions are equally effective in children with lower non-verbal abilities or IQ scores in the below average range (Bruinsma et al., 2022; Fey et al., 1994; Holmes et al., 2015; Kapa et al., 2020).

Finally, in **chapter 1** we argue that the fact that diagnostic criteria do not allow for a DLD diagnosis in children with 22q11DS does not hamper the use of 22q11DS as a theoretical model for DLD as long as they show phenotypical overlap. Recent findings that show a substantial number of pathogenic genetic variants in children with DLD challenge the existing exclusionary criterion for the diagnosis of

DLD, stipulating the absence of an associated biomedical condition (Bishop et al., 2017). The distinction made by Bishop et al. (2017) between 'DLD' and 'Language Disorder associated with biomedical condition X' suggests that these two groups are inherently different, while it is likely that the DLD group contains children who have an associated biomedical condition that has not (yet) been diagnosed. Furthermore, there is currently little evidence that the language problems of children with biomedical conditions are fundamentally different from children with DLD, nor that they do not benefit from the same interventions as children with DLD. In fact, **chapter 4** shows that spontaneous language profiles can be remarkably similar between children with DLD and children with a language disorder associated with a biomedical condition. Recently, the notion that the presence of a specific biomedical etiology should preclude the diagnosis of a neurodevelopmental disorder has been challenged (Vorstman & Scherer, 2021). In line with earlier suggestions (Tager-Flusberg & Cooper, 1999), we propose the same should be considered for the diagnosis of DLD. Both children with 22q11DS and DLD have language problems that have a negative impact on their daily life and that may predispose them to other difficulties later in life. As such, both groups of children have a need for intervention and support, which they can often only access with the 'right' diagnosis. After all, the primary function of a diagnosis should not be the categorization of 'pure' etiological groups but should provide parents and children with a means to obtain the help that they need.

CONCLUSION

This dissertation aimed to add to our understanding of the role of non-verbal EF impairments in atypical language development, specifically in children with DLD. This was done in two steps: (1) by directly investigating the relationship between non-verbal EF and language in young children with DLD, and (2) by exploring whether studying an etiologically homogeneous group of children, that is children with 22q11DS, could help reduce the large phenotypical variability that is seen in children with DLD. We conclude that a comparison between these groups is clinically relevant and provides interesting opportunities for fundamental research. However, this

dissertation does not present definitive proof that 22q11DS can function as a model for DLD regarding the role of EF in language impairment. Despite substantial phenotypical overlap in language and non-verbal EF abilities, preliminary analyses showed that the relationship between non-verbal EF and language abilities was not more pronounced in children with 22q11DS. More research is needed to address the questions and challenges raised in the foregoing paragraphs.

Furthermore, this dissertation shows that a multidisciplinary project that combines insights from different fields can both advance theory and support clinical practice. The causal pathway from genetics to neurological development to behavior (i.e., language and cognitive abilities) and the environmental factors that influence it are not yet well understood. The phenotypical similarity seen in conditions with differing etiologies highlight that 'many roads lead to Rome'. Comparison of different groups with known and unknown etiologies, while taking other child-internal and child-external factors into account, will step by step reveal the building blocks of the various mechanisms that are fundamental to language acquisition and cognitive development. Understanding the roots of human development and behavior requires a multidisciplinary approach. This is essential to improve the ways in which researchers and professionals can support those children whose development differs from that of most children and whose abilities are not accommodated by the current systems and structures of our society.

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Nederlandse samenvatting

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De meeste kinderen leren taal zonder problemen. Baby's beginnen met brabbelen, dan komen de eerste woordjes en als kinderen naar school gaan kunnen ze lange zinnen maken en verhalen vertellen. Dit is best bijzonder als je je bedenkt dat de meeste volwassenen die een nieuwe taal willen leren daar lang over doen en de taal vaak niet helemaal vloeiend leren spreken. Maar voor sommige kinderen gaat het leren van taal helemaal niet zo makkelijk. Kinderen met een taalontwikkelingsstoornis (TOS) hebben veel moeite met taal, maar het is niet duidelijk waarom. Zo kunnen de taalproblemen van kinderen met TOS bijvoorbeeld niet verklaard worden door problemen met hun gehoor. Ook ontwikkelen ze zich op andere vlakken net zoals andere kinderen van dezelfde leeftijd. Als kinderen meertalig zijn en nog niet zo veel Nederlands hebben gehoord, spreken we ook niet van TOS. Kinderen met TOS hebben moeite met het leren van taal in het algemeen, ook hun moedertaal. Dit heeft dus niet te maken met hoeveel ze een bepaalde taal hebben gehoord.

Ongeveer 5% van alle kinderen heeft TOS. Dat is meer dan het aantal kinderen met bijvoorbeeld autisme. Toch kennen veel mensen TOS niet. Kinderen met TOS kunnen verschillende problemen hebben. Sommige kinderen hebben vooral moeite met het produceren van taal. Ze kunnen sommige klanken niet goed zeggen of ze maken zinnen die niet kloppen. Andere kinderen vinden het ook lastig om de taal te begrijpen. Ook vinden ze het moeilijk om lange en ingewikkelde zinnen te begrijpen of meerdere opdrachtjes uit te voeren. Kinderen met TOS hebben vaak een kleinere woordenschat. De meeste kinderen met TOS hebben vooral moeite met grammatica. Een aantal jaren geleden werd nog gesproken over een specifieke TOS, omdat kinderen alleen moeite leken te hebben met taal. Maar er zijn steeds meer onderzoeken die laten zien dat kinderen met TOS ook andere problemen ervaren. Veel kinderen met TOS hebben bijvoorbeeld ook problemen met 'executief functioneren' (EF). EF is een verzamelnaam voor verschillende hersenfuncties die we gebruiken om ons gedrag aan te sturen en te plannen. Zo kunnen we onze aandacht focussen op één ding en prikkels in onze omgeving

negeren als ze niet relevant zijn (bv. luisteren naar de juf terwijl er buiten iets wordt geroepen door een ander kind). Ook kunnen we automatische reacties onderdrukken (bv. je hand opsteken en niet zo maar roepen in de klas), en informatie onthouden die we op dat moment nodig hebben (bv. het onthouden van de regels van een nieuw spelletje). Onderzoekers denken dat EF ook belangrijk is voor het leren van taal. De problemen met EF zouden kunnen verklaren waarom veel kinderen met TOS ook EF-problemen hebben. Maar niet alle kinderen met TOS hebben EF-problemen. Het is nog niet duidelijk wat de relatie tussen taalontwikkeling en EF precies is. Dit is lastig te onderzoeken, omdat kinderen met TOS heel erg van elkaar verschillen.

We weten nog niet wat de oorzaak van TOS is, maar waarschijnlijk zijn er verschillende factoren die ervoor kunnen zorgen dat deze kinderen taalproblemen hebben. Bij ieder kind kan er een andere oorzaak zijn. Een kind kan bijvoorbeeld een genetisch risico hebben. Er zijn dan vaak meer familieleden met taalproblemen. De oorzaak kan ook een combinatie van verschillende factoren zijn. Bijvoorbeeld een genetisch risico en te vroeg geboren worden. We weten namelijk dat kinderen die te vroeg geboren worden ook een hoger risico op TOS hebben. Net zoals dat jongetjes een hoger risico hebben op TOS dan meisjes. Deze variatie in oorzaken zorgt ervoor dat het voor onderzoekers moeilijk is om kinderen met TOS met elkaar te vergelijken. Voor het ene kind met TOS zou het kunnen zijn EF en taalproblemen wel met elkaar te maken hebben, terwijl dit voor een ander kind met TOS misschien niet het geval is.

Een groep kinderen die ook taalproblemen heeft, maar bij wie de oorzaak hiervan minder verschilt dan bij kinderen met TOS, is de groep kinderen met het 22q11.2 deletiesyndroom (22q11DS, zeg tweeëntwintig-Q-elf). 22q11DS is een genetische afwijking. Er mist een stukje DNA. De naam van het syndroom verwijst naar het stukje DNA dat ontbreekt bij deze mensen. In Nederland worden per jaar zo'n 50-70 kinderen geboren met 22q11DS. Kinderen met 22q11DS kunnen allerlei problemen hebben, zoals een aangeboren hartafwijking, problemen met het immuunsysteem, en een gehemeltespleet. Ook hebben kinderen met 22q11DS soms een intellectuele beperking en kunnen ze meer moeite hebben het eerdergenoemde executief

functioneren. Er komen ook meer mentale gezondheidsproblemen voor bij kinderen met 22q11DS, zoals autismespectrumstoornissen, ADHD, angststoornissen, en een hoger risico op het ontwikkelen van psychotische stoornissen. Daarnaast hebben deze kinderen dus ook vaak spraak- en taalproblemen. Ouders van kinderen met 22q11DS geven bijvoorbeeld aan dat hun kind laat begon met praten. Hoewel kinderen met 22q11DS ook erg van elkaar kunnen verschillen, is de oorzaak van hun taalproblemen wel hetzelfde: hun genetische afwijking. Dit kan onderzoekers misschien helpen bij het ontdekken van bijvoorbeeld relaties tussen EF en taal.

In dit proefschrift willen we meer leren over de relatie tussen EF en taal bij kinderen met taalproblemen. Het eerste onderzoeksdoel was om de relatie tussen non-verbale EF en taal te onderzoeken bij kinderen met TOS. Daarnaast kijken we of het vergelijken van kinderen met 22q11DS en kinderen met TOS ons kan helpen om meer te leren over de rol van EF bij taalproblemen. Voor dit tweede doel moeten we eerst onderzoeken of kinderen met 22q11DS en kinderen met TOS voldoende op elkaar lijken. Er is alleen nog niet zo heel veel onderzoek gedaan naar taal en EF bij jonge kinderen met 22q11DS. Daarom hebben we het tweede onderzoeksdoel opgedeeld in drie losse doelen:

a. Het beschrijven van de taalvaardigheden van kinderen met 22q11DS
b. Het beschrijven van de EF-vaardigheden van kinderen met 22q11DS
c. Het vergelijken van taal- en EF-vaardigheden van kinderen met 22q11DS en kinderen met TOS.

Dit is niet alleen interessant voor wetenschappelijk onderzoek, maar is mogelijk ook belangrijk voor professionals die werken met kinderen met 22q11DS of kinderen met TOS. We zien namelijk dat beide groepen kinderen bijna altijd hulp krijgen van een logopedist en soms ook ondersteuning vanuit het speciaal onderwijs (cluster-2). Voor logopedisten is het bijvoorbeeld nuttig om te weten of de taalproblemen van kinderen met 22q11DS lijken op die van kinderen met TOS. Dat zou namelijk kunnen betekenen dat logopedisten

dezelfde behandeling kunnen gebruiken voor kinderen met 22q11DS en kinderen met TOS.

In dit proefschrift beschrijven we de resultaten van het *Taal, 22q11 en TOS* (3T) onderzoek. Dit onderzoek werd gefinancierd door de Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO). In het 3T onderzoek hebben we drie groepen kinderen onderzocht: 1) kinderen met 22q11DS, 2) kinderen met TOS, en 3) kinderen zonder 22q11DS of TOS. De kinderen waren allemaal tussen de 3 en 6,5 jaar oud. Dit is de leeftijd waarop zowel taal als EF zich in hoog tempo ontwikkelen. Er deden 44 kinderen met 22q11DS, 65 kinderen met TOS en 81 kinderen zonder 22q11DS of TOS mee aan het onderzoek. De kinderen kwamen uit heel Nederland. Onderzoekers van het 3T onderzoek kwamen langs op school en deden verschillende opdrachten met de kinderen om onder andere grammatica, woordenschat, en EF te meten. Ouders vulden ook nog vragenlijsten in. Eigenlijk was het ook de bedoeling om drie keer op bezoek te gaan bij alle kinderen met steeds zes maanden tussen ieder bezoek. Maar door de COVID-lockdown is dat helaas niet gelukt. De hoofdstukken in dit proefschrift gaan dus alleen over de uitkomsten van de eerste bezoeken.

De resultaten van de studies die hieronder besproken worden gaan over gemiddelden van een groep, als je alle kinderen samenneemt. Dat betekent dus dat er ook kinderen zijn die het beter of juist minder goed doen dan dit gemiddelde. Er is namelijk veel variatie in de groepen kinderen die we hebben onderzocht. Dit geldt zowel voor kinderen met 22q11DS, kinderen met TOS, maar ook voor de kinderen zonder taalproblemen. Deze uitkomsten kunnen ons alleen iets vertellen over patronen die we zien bij de hele groep, maar zeggen niet direct iets over individuele kinderen. Ieder kind is uniek.

In **hoofdstuk 2** keken we naar *non-verbaal* EF bij kinderen met en zonder TOS. Non-verbaal betekent zonder taal. Bij non-verbaal EF kun je denken aan het onthouden van de volgorde waarop blokjes aangewezen worden of het zoeken van een bepaald diertje in een zoekplaat. Bij *verbaal* EF moeten kinderen bijvoorbeeld een lijst woorden onthouden of ze moeten aandachtig luisteren naar een verhaal en op een knop drukken als ze een bepaald woord horen. Het verschil tussen verbaal en non-verbaal EF heeft dus te maken met de

soort informatie die een kind tijdens een opdracht moet gebruiken. Er is al veel onderzoek dat heeft laten zien dat kinderen met TOS meer moeite hebben met verbale EF. Naar non-verbale EF is minder onderzoek gedaan en de uitkomsten van eerdere studies verschillen. In **hoofdstuk 2** laten we zien dat kinderen met TOS meer moeite hadden met non-verbaal taken dan leeftijdsgenootjes zonder TOS. De EF-vaardigheden van beide groepen kinderen hingen samen met hun grammaticale vaardigheden. Kinderen die hoger scoorden op taken die grammatica testen, scoorden ook beter op EF-taken. Bij de kinderen zonder TOS hing EF ook samen met woordenschat. Bij de kinderen met TOS lijken we hetzelfde patroon te zien, maar kunnen we het niet met zekerheid zeggen. Onze resultaten bevestigen de aanwezigheid van non-verbale EF-problemen bij kinderen met TOS en laten zien dat deze problemen samenhangen met ten minste een deel van hun taalproblemen.

In **hoofdstuk 3** onderzochten we de taalvaardigheid van kinderen met 22q11DS. Kinderen met 22q11DS hebben gemiddeld lagere scores op taaltesten dan leeftijdsgenoten zonder 22q11DS of taalproblemen. Kinderen met 22q11DS hebben meer problemen met taalproductie dan met taalbegrip. Het is bekend dat jonge kinderen met 22q11DS ook vaak problemen hebben met spraak en soms moeilijk te verstaan zijn. We zagen dat kinderen die minder goed verstaanbaar waren lager scoorden op de taaltesten. De kinderen die goed te verstaan zijn, verschilden erg van elkaar. Sommigen hadden erg veel moeite met taal, terwijl anderen scores hadden die hetzelfde waren als leeftijdsgenootjes. Maar de meeste kinderen die goed te verstaan waren hadden taalscores die lager zijn dan die van leeftijdsgenootjes. Het is dus belangrijk dat de taalontwikkeling van alle kinderen met 22q11DS goed in de gaten wordt gehouden, ook als hun spraak goed is.

In **hoofdstuk 4** hebben we onderzocht of de taalvaardigheid van kinderen met 22q11DS en kinderen met TOS van elkaar verschillen. Ook hebben we ze vergeleken met leeftijdgenootjes zonder taalproblemen. Hiervoor gebruikten we niet alleen taaltesten, maar keken we ook naar wat kinderen uit zichzelf zeggen terwijl ze met de onderzoeker aan het spelen waren. Kinderen met 22q11DS en kinderen met TOS hadden allebei meer moeite met grammatica dan

leeftijdsgenootjes zonder taalproblemen. Ze spraken in kortere en simpelere zinnen dan leeftijdsgenootjes zonder 22q11DS of TOS, en maakten ook meer fouten. Kinderen met 22q11DS verschilden hierin niet van kinderen met TOS. Beide groepen kinderen hadden evenveel moeite met het produceren van taal. Kinderen met 22q11DS behaalden echter gemiddeld lagere scores op taalbegrip dan kinderen met TOS.

Hoofdstuk 5 is een literatuurstudie. Dat betekent dat we alle onderzoeken over een bepaald onderwerp hebben gelezen en samengevat. In dit hoofdstuk hebben we alle onderzoeken over EF bij kinderen met 22q11DS beoordeeld, vergeleken en gekeken welke factoren invloed hebben op de EF-vaardigheden van kinderen met 22q11DS. De meeste onderzoeken lieten zien dat kinderen met 22q11DS EF-problemen hebben, maar sommige studies vonden geen verschil tussen kinderen met en zonder 22q11DS. Dit was vooral het geval voor verbaal geheugen. Bij kinderen zonder 22q11DS heeft onderzoek laten zien dat er allerlei factoren invloed hebben op de ontwikkeling van EF, zoals de aanwezigheid van een aangeboren hartafwijking. Kinderen met een aangeboren hartafwijking hebben vaak meer moeite met EF dan leeftijdgenootjes zonder hartafwijking. Bij kinderen met 22q11DS komen ook vaak aangeboren hartafwijkingen voor. In onze literatuurstudie hebben we twee onderzoeken gevonden die keken naar de invloed van een hartafwijking op EF bij kinderen met 22q11DS. Maar deze onderzoeken vonden allebei geen verschil tussen kinderen met en zonder hartafwijking. Dit is dus anders dan bij kinderen zonder 22q11DS. Verder kwamen we erachter dat er nog geen onderzoek was gedaan naar EF bij kinderen met 22q11DS die jonger waren dan 6 jaar.

Daarom hebben we in **hoofdstuk 6** onderzoek gedaan naar EF bij kinderen met 22q11DS uit het 3T onderzoek. Kinderen met 22q11DS scoorden lager dan leeftijdsgenootjes. Dit was hetzelfde als wat we zagen bij de kinderen met TOS in **hoofdstuk 2**, en laat zien dat EF-problemen bij kinderen met 22q11DS al op jonge leeftijd aanwezig zijn. Ook zagen we dat kinderen met 22q11DS die geboren zijn met een hartafwijking hetzelfde scoorden als kinderen met 22q11DS zonder hartafwijking. Dit sluit aan bij eerder onderzoek met kinderen met 22q11DS dat we hebben besproken in **hoofdstuk 5**.

Samenvattend laat dit proefschrift zien dat jonge kinderen met TOS en kinderen met 22q11DS allebei meer moeite hebben met taal en EF dan leeftijdsgenoten zonder 22q11DS of TOS. Kinderen met 22q11DS en kinderen met TOS lijken daarnaast ongeveer dezelfde taalproductieproblemen te hebben. Dit betekent dat we denken dat onderzoekers misschien meer kunnen leren over de relatie tussen taal en andere factoren bij kinderen met TOS door onderzoek te doen bij kinderen met 22q11DS. Maar er is meer onderzoek nodig om dit verder uit te zoeken. Er zijn namelijk ook belangrijke verschillen tussen de groepen. De vergelijking van deze twee groepen kinderen is mogelijk belangrijk voor professionals, zoals logopedisten en leerkrachten, omdat het op de lange termijn hopelijk kan helpen om de behandeling van kinderen met 22q11DS en kinderen met TOS te verbeteren. Een deel van de resultaten van het 3T onderzoek worden beschreven in een Nederlandstalig artikel met de titel 'Onbekend maakt onbegrepen: meer weten over het 22q11.2 deletiesyndroom' op https://vhz-online.nl. Ook hebben de onderzoekers van het 3T onderzoek een folder gemaakt voor logopedisten met meer informatie over de spraak- en taalontwikkeling van kinderen met 22q11DS. Deze is te vinden op https://3tonderzoek.sites.uu.nl/.

Dankwoord

Dankwoord

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About the author

Emma was born in 1994 in Utrecht, the Netherlands. She graduated from her high school, St. Bonifatiuscollege, in 2012. That same year, she started a bachelor Psychology at Utrecht University, where she specialized in neurobiological and cognitive psychology. In her second year, she joined the interdisciplinary honors program, the Von Humboldt college. She graduated in 2015 and then enrolled in the master program Neuroscience and Cognition at Utrecht University. During her master her interest in early cognitive and linguistic development was sparked by two internships. The first was with prof. Elma Blom and dr. Tessel Boerma in the CoDEmBi project at the department of Pedagogical Sciences at Utrecht University and focused on executive functioning in bilingual children. The second internship was at the Babylab of the Institute for Language Sciences at Utrecht University with dr. Brigitta Keij and dr. Caroline Junge (department of Psychology), focusing on eye-tracking and speech segmentation in infants. She graduated in 2017 and shortly worked as a Research and Education assistant at the Institute for Language Sciences (Utrecht University). In 2018 she started her PhD in the 'Language impairment in the 22q11.2 deletion syndrome: a model for SLI?' project, a collaborative project of Institute for Language Sciences (Utrecht University) and the department of Pediatrics at the Wilhelmina Kinderziekenhuis (UMC Utrecht). The project was funded by NWO and supervised by prof. Frank Wijnen, prof. Ellen Gerrits, dr. Michiel Houben, dr. Jacob Vorstman, and dr. Tessel Boerma. Together with another PhD, Iris Selten, Emma worked on this large longitudinal research program until 2022. During her PhD she helped organize the EMLAR conference, gave guest lectures in several Master programs in Utrecht and Amsterdam, co-taught a Psychology of Language course in the BA Linguistics program of Utrecht University, and supervised Master students during their internship or thesis writing. Furthermore, she presented her work at several national and international conferences and obtained her Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK) certificate. In the final year of her PhD, she visited the SickKids hospital in Toronto, supported by a UMCU Strategic Network Grant. Emma continues her career as a senior researcher at Royal Auris group, an organization providing care and education for children with speech, language, and hearing difficulties in the Netherlands.

List of publications

International peer-reviewed publications

Boerma, T., Everaert, E., Vlieger, D., Steggink, M., Selten, I., Houben, M., Vorstman, J., Gerrits, E., & Wijnen, F. (2023). Grammatical skills of Dutch children with 22q11.2 Deletion Syndrome in comparison with children with Developmental Language Disorder: Evidence from spontaneous language and standardized assessment. *Frontiers in Communication*, 8:1111584. https://doi.org/10.3389/fcomm.2023.1111584

Everaert, E.*, Selten, I. S.*, Boerma, T. D., Houben M. L., Vorstman, J. A. S., de Wilde, H., Derksen, D. A. M., Haverkamp, S. J., Wijnen, F. N. K., & Gerrits, E. (2022). The language profile of preschool children with 22q11.2 deletion syndrome and the relation with speech problems. *The American Journal of Speech-Language Pathology*. https://doi.org/10.1044/2022_AJSLP-21-00328
*These authors contributed equally

Everaert, E., Boerma, T. D., Selten, I. S., Vorstman, J. A. S., & Wijnen, F. N. K. (2021). Learning from atypical development: A systematic review of executive functioning in children and adolescents with the 22q11.2 deletion syndrome. *Developmental Review*, *60*, 100962. https://doi.org/10.1016/j.dr.2021.100962

Selten, I. S., Boerma, T. D., Everaert, E., Vansteensel, M.J., Vorstman, J. A. S., & Wijnen, F. N. K. (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

Junge, C., Everaert, E., Porto, L., Fikkert, P., de Klerk, M., Keij, B. & Benders, T. (2020). Contrasting behavioral looking procedures: a case study on infant speech segmentation. *Infant Behavior and Development*, *60*, 101448. https://doi.org/10.1016/j.infbeh.2020.101448

Janssen, C. P., Everaert, E., Hendriksen, H., Mensing, G., Tigchelaar, L. & Nunner, H. (2019). The influence of rewards on (sub-)optimal interleaving. *PLoS One*, *14*(3): e0214027. https://doi.org/10.1371/journal.pone.0214027

Blom, E., Boerma, T., Bosma, E., Cornips, L., & Everaert, E. (2017). Cognitive advantages of bilingual children in different sociolinguistic contexts. *Frontiers in Psychology*, 8:522. https://doi.org/10.3389/fpsyg.2017.00552

Papers in progress

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

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*.

Selten, I., Boerma, T., Everaert, E., Gerrits, E., Houben M., Wijnen, F., & Vorstman, J. (*submitted*). Behaviors related to Autism Spectrum Disorder in children with Developmental Language Disorder and children with 22q11.2 Deletion Syndrome. Submitted to *Autism & Developmental Language Impairments*.

Selected talks and posters

Talks

Everaert, E., Selten, I., Houben M., Vorstman, J., Wijnen, F., & Boerma, T. (July 2022). *Executive functioning in preschool children with 22q11.2 deletion syndrome and the impact of congenital heart defects*. The 12th Biennial International 22q11.2 Conference, Split, Croatia. Oral presentation.

Everaert, E. & Selten I. (March 2022). *Language abilities in 3-to 6-year-old children with 22q11.2 deletion syndrome and their relationship to cognitive abilities and psycho-social functioning*. Genetics Grand Rounds, Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, Canada. Invited oral presentation [online].

Everaert, E., Selten, I., Boerma, T., Houben M., Vorstman, J., de Wilde, H., Derksen, D., Haverkamp, S., Wijnen, F., & Gerrits, E. (October 2021). *The language profile of preschool children with 22q11.2 Deletion Syndrome*. The 4th European 22q11DS Conference, Berlin, Germany [online]. Oral presentation.

Everaert, E., Selten, I., Boerma, T., Huls, M., Gerrits, E., Houben, M., Vorstman, J., & Wijnen, F. (January 2021). *Same or Different? Language skills of children with 22q11.2 deletion syndrome and*

children with Developmental Language Disorder. Grote Taaldag/ Dutch Annual Linguistics Day, Utrecht, the Netherlands [online]. Oral presentation.

Boerma, T., Duijff, S., Vorstman, J., Gerrits, E., Everaert, E., Selten, I., Houben, M., Mink van der Molen, A., & Wijnen, F. (July 2018). *Language impairment in the 22q11DS*. The 11th Biennial International 22q11.2 Conference, Whistler, Canada. Oral presentation.

Posters

Everaert, E., Boerma, T., Selten, I., Huls, M., Houben, M., Vorstman, J., Gerrits, E. & Wijnen, F. (June 2021). *Same or different? Language skills of children with 22q11.2 Deletion Syndrome and children with Developmental Language Disorder*. Symposium on Research in Child Language Disorders (SRCLD), Madison, U.S.A. [online]. Poster presentation.

Selten, I., Everaert, E., Boerma, T., Huls, M., Houben, M., Vorstman, J., Gerrits, E. & Wijnen, F. (June 2021). Autism-like behaviors in children with language problems: A comparison of children with Developmental Language Disorder and Children with 22q11.2 Deletion Syndrome. Symposium on Research in Child Language Disorders, Madison, United States of America [online]. Poster presentation.

Everaert, E., Boerma, T., Selten, I., Huls, M., Gerrits, E., Houben, M., Vorstman, J., & Wijnen, F. (July 2021). *The relation between executive functioning and language abilities in preschoolers with Developmental Language Disorder and preschoolers with 22q11.2 deletion syndrome*. The 15th Congress of the International Association for the Study of Child Language (IASCL), Philadelphia, U.S.A. [online]. Poster presentation.

Boerma, T., Steggink, M., Everaert, E., Selten, I., Huls, M., Gerrits, E., Houben, M., Vorstman, J., & Wijnen, F. (July 2021). *Grammatical skills of Dutch children with 22q11.2 Deletion Syndrome in comparison with children with Developmental Language Disorder*. The 15th Congress of the International Association for the Study of Child Language (IASCL), Philadelphia, U.S.A. [online]. Poster presentation.

Junge, C., Everaert, E., Porto, L., Benders, T., Keij, B., de Klerk, M., & Fikkert, P. (June 2019). *Contrasting two behavioural methods to index infant perception ability*. The 4th Workshop on Infant Language Development (WILD 2019), Berlin, Germany. Poster presentation.

Everaert, E., Boerma, T., Duijff, S., Duijnkerke, F., Gerrits, E., Selten, I., Vorstman, J., & Wijnen, F. (February 2019). *Language impairment in the 22q11.2 deletion syndrome: a comparison with Developmental Language Disorder*. EUCLDIS, Tel Aviv, Israel. Poster presentation.

Selected non-scientific talks and publications

Everaert, E., Selten, I., Boerma, T., Gerrits, E., Vorstman, J., Houben, M., & Wijnen, F. (November 2022). *Taalonderzoek bij kinderen met 22q11DS*. Studiedag Stichting Steun 22Q11, Utrecht, the Netherlands. Oral presentation.

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/onbekend-maakt-onbegrepen-meer-weten-over-het-22q11-2-deletiesyndroom

Everaert, E., Fiksinski, A. & Houben, M. (2022). Verschillende types 22q11.2 deleties. *Jaarmagazine Overleven met 22Q11* (pp. 14-15).

Everaert, E., Boerma, T., Houben, M., Selten, I., & Wijnen, F. (2021). Presentatie Berlijn: Taalontwikkeling van jonge kinderen met 22q11. *Jaarmagazine Overleven met 22Q11* (p. 24-25).

Boerma, T., Everaert, E., Fiksinski, A., Houben, M., Selten, I.., Smeets, K., Wijnen, F., & Zinkstok, J. (2022). Onderzoek naar taal & Lopend taalonderzoek met jongeren met 22q11: MenTAAL. *Jaarmagazine Overleven met 22Q11* (p. 22-23).

Boerma, T., Selten, I., Everaert, E., Duinkerke, F., Wijnen, F., Gerrits, E., Houben, M., & Vorstman, J. (March 2020). *Het taalprofiel van kinderen met het 22q11.2 deletiesyndroom in vergelijking met kinderen met TOS*. TaalStaal, Nieuwegein, the Netherlands. Poster presentation.

Boerma, T., Selten, I., Everaert, E., Duijnkerke, F., Duijff, S., & Wijnen, F. (2019). Taal bij kinderen met 22q11. *Jaarmagazine Overleven met 22Q11* (p. 23).