1. Main applicant

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2. Title

Language impairment in the 22q11.2 deletion syndrome: a model for SLI?

3. Summary (max. 250 words)

Specific language impairment (SLI) in children is characterized by severe and persistent difficulties in acquiring a native language, unrelated to intellectual disability, physical limitations, or psychosocial deprivation. The etiology of SLI, in particular the role of neurocognitive processes such as learning and information processing, is poorly understood. Progress in this domain is difficult because of the large etiologic and phenotypic heterogeneity of the SLI population.
Here, we propose to address this challenge by examining a population with developmental language impairment resulting from a uniform etiology: the 22q11.2 deletion (22q11DS). Children with 22q11DS display delayed language development, and learning- and information processing deficits similar to SLI. The fact that all 22q11DS share the same genetic etiology provides us with a unique opportunity to identify the mechanisms underlying this language disorder.
Our program has three interrelated objectives: (1) to provide a detailed description of language development in 2-6-year old children with 22q11DS; (2) to examine neurocognitive mechanisms associated with language acquisition in children with 22q11DS, with special reference to implicit learning and executive functions; (3) to describe the language skills of adolescents with 22q11DS and investigate its possible relationship to psychopathology, in particular the elevated genetic predisposition (25-30%) for schizophrenia. The synthesis will investigate what the language profile of 22q11DS and its neurocognitive underpinnings tell us about developmental language disorders and general language acquisition. This program will provide further clues into the etiology of language impairment in both 22q11DS and SLI, and can be used to inform coaching and professional intervention. [249 wrds]

4. NWO Research fields

Main discipline:	Linguistics	
Subdiscipline:	30.40.00	Psycholinguistics and neurolinguistics
	30.55.00	Language acquisition
Main discipline:	Psychology	
Subdiscipline:	40.40.00	Experimental and cognitive psychology
Main discipline:	Medicine	
Subdiscipline:	23.30.00	Medical specialisms

5. Infrastructural component: yes/no

No.

6. Previous and Future Submissions

A previous version of this proposal was submitted to NWO–GW (open competition) in 2015; file number PR-15-061. Applicants are currently not considering submission of this proposal to other organizations.

7. Institutional Setting

Utrecht University, Utrecht Institute of Linguistics OTS (UIL OTS) & University Medical Center Utrecht, Wilhelmina Children's Hospital (WKZ/UMCU)

8. Period of funding

July 1, 2017 – June 30, 2022.

9. Composition of the Research Team

Main applicant	*Area of expertise*	*Institutional setting*	*Role*
Prof. dr. Frank Wijnen	Psycholinguistics, language acquisition & language disorders	UU, UIL OTS	PI; 1st promotor of PhDs in projects 1&2; supervisor of post-doc, project 3
Co-applicants			
Dr. Sasja Duijff	Pediatric psychology; developmental and cognitive psychology; 22q11DS	WKZ/UMCU & Brain Center Rudolph Magnus	Co-PI; responsible for synthesis; co-promotor of PhDs in projects 1&2; daily supervisor of project 1 PhD; co-supervisor post-doc (project 3)
Prof. dr. Ellen Gerrits	Speech and language pathology	UU, UIL OTS and University of Applied Sciences Utrecht	Adviser language disorders; 2nd promotor PhDs in projects 1&2
Dr. Jacob Vorstman, MD	Child psychiatry; genetics; 22q11DS	WKZ/UMCU & Brain Center Rudolph Magnus	Adviser genetics, medical aspects of 22q11DS; co-promotor of PhD's in projects 1&2
Advisers			
Dr. Rob Zwitserlood	Speech and language pathology	Koninklijke Aurisgroep, Gouda	Adviser language disorders / SLI; liaison with Auris
Dr. Marie-José van den Boogaard	Clinical genetics	WKZ/UMCU	Adviser 22q11DS and genetics
Dr. Elma Blom	Language development, cognitive development, SLI	UU	Adviser normal and disordered language development & cognitive function

Dr. Judith Rispens	Language development, SLI	UvA	Adviser normal and disordered language development & statistical learning
Dr. Rens van de Schoot	Methodology and statistics	UU	Statistics/methodology adviser
Dr. Aebele Mink van der Molen, MD	Pediatric plastic surgery, 22q11DS	WKZ/UMCU	Adviser orofacial symptoms of 22q11DS, and (surgical) interventions
Dr. Michiel Houben, MD	Pediatrics, 22q11DS	WKZ/UMCU	Adviser physical symptoms of 22q11DS: diagnosis and intervention
Researchers			
PhD candidate 1	Exp. psycholinguistics / language acquisition *promotors*: Wijnen & Gerrits *co-promotors*: Duijff & Vorstman	UU & UMCU	Researcher project 1
PhD candidate 2	Exp. psycholinguistics / language acquisition *promotors*: Wijnen & Gerrits *co-promotors*: Duijff & Vorstman	UU & UMCU	Researcher project 2
Post doc researcher	Developmental cognitive neuroscience; (behavioral) genetics	UU & UMCU	Researcher project 3; co-directing projects 1 & 2

10. Structure of the proposed research

Project	Researcher	Supervision	Location	Title
1	PhD	promotors: Wijnen / Gerrits co-promotors & daily supervision: Duijff, Vorstman	UMCU/WKZ	The language phenotype in young children with 22q11DS
2	PhD	promotors: Wijnen / Gerrits; co-promotors: Duijff, Vorstman daily supervision: Wijnen	UU/ UIL OTS	Language acquisition mechanisms and cognitive profile in 22q11DS
3	postdoc	Wijnen/Duijff/Vorstman/Gerrits	UMCU & UU	Language phenotype in adolescents with 22q11DS
synthesis	co-applicant / Co-PI (Duijff)	Wijnen/Gerrits/Vorstman	UMCU	Synthesis

11a. Description of the Proposed Research

Developmental language impairments have a profound impact on an individual's life; they are associated with academic failure, social disadvantage, and behavioral and psychiatric problems[1]. Apart from language delays due to unfavorable social or educational conditions, language impairments in children can arise from other conditions of a physical or psychological nature. In addition, severe and persistent delays in the development of primary language skills (speaking and/or understanding) can occur in the absence of any obvious neurological, psychological or social causes[2]. This condition, labeled *specific language impairment* (SLI) is seen in approximately 7% of children; it is one of the most frequently occurring developmental disorders (cf. prevalence of autism is ~1%).[3,4]

Linguistics is interested in SLI because it may help in answering the question how language development relates to other components of human neurocognition. Early studies argued that the existence of SLI implied that language is neurologically and genetically dissociated from other components of the neurocognitive system[5,6]. We now know, however, that SLI is associated with impairments beyond language. Reduced working memory (WM), attention deficits, difficulties in motor coordination and motor learning, and deficient social cognition[7–11] are often attested, and can even be clinically significant; SLI is frequently comorbid with attention deficit (hyperactivity) disorder (AD(H)D), developmental coordination disorder (DCD) and/or autism spectrum disorder (ASD)[12]. The cause of these comorbidities is unclear, but the observed patterns suggest that SLI is a phenotypic expression of atypical brain development. SLI, in other words, is not just a disorder of the 'language module'. Rather, it likely results from complex interactions between the language system and various domain-general capacities: memory, learning, executive function, Theory of Mind. Genetic research[2,13,14] supports this idea. SLI probably has a complex and non-homogeneous genetic architecture, involving interactions of genes that play a critical role in brain maturation[15]. Strikingly, several of these genes are also implicated in other developmental disorders, notably AD(H)D, ASD and schizophrenia[15]. This suggests that these disorders are all multifactorial in nature, and that their high co-morbidity is due to shared genetic risk factors[13].

Clarifying the complex (causal) connections between genes, development and functioning of the neurocognitive system, and impaired language is of great value for clinicians, and will also contribute to our understanding of the genetic and neurocognitive underpinnings of language. The route via SLI is notoriously difficult, however, as the SLI phenotype is heterogeneous, and diagnosis is based on *exclusion* of potential causal factors, rather than inclusion based on clinical markers. Genetic studies suggest that SLI does not have a uniform genetic etiology either. The literature furthermore suggests that associations between SLI and impairments in neurocognitive for information processing, learning, and memory are variable[16].

The etiological heterogeneity of SLI hampers our ability to advance the understanding of the trajectory from cause to the neurocognitive deficits that ultimately lead to the abnormalities of language (acquisition) that warrant a diagnosis of SLI. To overcome this obstacle, one would have to study a developmental language disorder that overlaps phenotypically with SLI but has a uniform genetic etiology. In fact, such a disorder exists. The **22q11.2 deletion syndrome** (22q11DS; a.k.a. Velocardiofacial-, DiGeorge-, or Shprintzen syndrome) is identified in an estimated 1 out of every 2000-4000 births[17]. Individuals with 22q11DS have a micro-deletion in the long arm of chromosome 22, band 11.2, causing them to carry only one copy of the genes in this genomic region, instead of two. Affected children can have various physical symptoms, notably velopharyngeal insufficiency (with or without cleft palate), immune deficiency and cardiac defects. Intellectual impairments and psychopathology are frequently seen[18–20]. Some children

show a cognitive decline with age (mostly after age 6). A striking 25-30% of all patients develop schizophrenia in adolescence or early adulthood.

Virtually all individuals diagnosed with 22q11DS display severe language delays in early childhood[21–23], which is not related to intellectual disability. This makes 22q11DS an ideal model for studying the development of SLI, from a shared etiology to the expression of SLI and its underlying neurocognitive processes.

Although language delays are a core symptom of 22q11DS, and a major concern for affected children's parents/caretakers, detailed, linguistically informed descriptions of language development in 22q11DS are scarce, in particular in the age range of 2 to 6 years, the main formative period of (typical) primary language acquisition. Available observations also strongly indicate that studying language impairment in 22q11DS may provide relevant insights into the underlying neurocognitive deficits, as studies consistently report compromised memory functions, information processing and learning, similar to those found in the general SLI population. However, to date no study has been undertaken on the possible (and probable) connection of these deficits with the language phenotype in 22q11DS. In addition, there is virtually no information on language skills in people with 22q11DS at a mature age. It appears that some overcome their language difficulties, while others, according to clinicians, have persistent difficulties. However, objective studies on the prevalence and nature of language deficiencies in adolescents and young adults with 22q11DS are lacking. An important additional motivation for including adolescents is that an estimated 25-30% of them will develop schizophrenia, a devastating condition that has recently been associated with (deviant) patterns in language prior to its onset[24,25].

The objectives of the present research program, therefore, are the following:

(A) To provide a precise description of early language development in the 22q11DS population, comprising expressive and receptive abilities, covering all levels of linguistic structure, as well as pragmatics. (*project 1)*

(B) To determine if, and to what extent, domain-general neurocognitive mechanisms for information processing, memory and learning are deficient in 22q11DS, and to relate them to language difficulty. (*project 2*)

(C) To describe the language profile of adolescents with 22q11DS, and to associate language difficulties with their cognitive and mental health status. This is intended to set a basis for future studies in relation to the onset of schizophrenia. (*project 3*)

(D) To synthesize the results obtained by addressing the following points:
   a) the developmental interrelations of various linguistic domains in 22q11DS and SLI (project 1);
   b) the developmental relation between (deficient) neurocognitive mechanisms and language outcome (projects 1 and 2);
   c) the relationship between the language profile of adolescents with 22q11DS and early language development (projects 1, 2 & 3);
   d) informing clinicians and supporting diagnosis and intervention for children and adolescents with 22q11DS, on the basis of the obtained results.

Importantly, although 22q11DS is a specific genetic disorder, examining the developmental language trajectory and associated neurocognitive deficits in this restricted population may provide novel insights that are relevant to SLI in the general population.

Methods

Participants & recruitment

To attain *objectives A and B* (projects 1 & 2; see below), we will investigate children diagnosed with 22q11DS in the age range 2;6 - 6;0 (yrs; months). In order to acquire sufficient data for the full age range, we will use a sequential cohort design[26], and include children whose age falls within one of a series of successive age brackets. All children will take part in three measurement waves, separated by intervals of either 6 months (for the age range 2;6-4;6), or 1 year (after age 4;6; see project 1).

The children with 22q11DS will be compared with typically developing (TD) controls and children with SLI. Since cleft palate and velopharyngeal insufficiency (VPI) are frequently occurring symptoms in 22q11DS, and these orofacial deficiencies lead to speech impediments, which in turn can impact language acquisition, we will also include a control group of children with a cleft palate (CP) without a syndromic origin. The age stratification of the three control groups (TD, SLI, CP) will be identical to that in the 22q11DS group. The four groups will be matched on chronological age and gender.

We expect to be able to include ~80 children with 22q11DS, and comparable numbers for each of the three comparison groups. We have excellent access to all clinical populations:

- 22q11DS. WKZ/UMCU is the only NFU (Netherlands Federation of University Hospitals) recognized 22q11DS expertise center in the Netherlands, and is host to one of the largest cohorts of 22q11DS patients internationally (N ~350). Study participants will be recruited at WKZ/UMCU as well as with help from the national parental support group *Stichting Steun 22q11* (www.steun22q11.nl), which collaborates closely with WKZ/UMCU. There is also a standing collaboration with the Center for Human Genetics of the University Hospital Gasthuisberg in Leuven (Belgium), who are willing to collaborate in including Dutch-speaking children from Belgium, if needed to reach our recruitment target.
- Cleft. The WKZ/ UMCU is home to the largest cleft palate team within The Netherlands, annually treating ~75 out of 350 children born with clefts throughout The Netherlands. The WKZ/ UMCU Cleft team has expressed its dedication towards participating in this study.
- SLI. The standing collaboration of UIL OTS with *Auris* (www.auris.nl), an organization providing care and education for children with speech and language difficulties, will be instrumental in getting access to children with SLI.

To attain *Objective C* (project 3), we will collect data from a group (N=40) of 14-18 year olds with 22q11DS. As in the case of the 2-6 year olds, we will compare this group to groups of age and gender matched TD controls, individuals with SLI and individuals with CP.

All children and adolescents with 22q11DS will be seen at least once at the WKZ/UMCU 22q11DS outpatient clinic for a standard medical examination. Specifically relevant for this study is an assessment of the presence of a cleft palate and/or velopharyngeal insufficiency. Also, special attention will be paid to hearing, as hearing difficulties are common in children with 22q11DS[27]. All children will be tested at least twice with behavioral observational audiometry and oto-acoustic emission (age up to 3;6), or tone

audiometry combined with tympanometry (children older than 3;6). Tone audiometry will be used for adolescent participants. A severe and persistent hearing loss (>35 dB) will be a ground for exclusion. Medical records will be carefully inspected to record any physical condition, particularly of a neurological nature, that may have impacted the development of language and cognition (e.g. neonatal hypocalcemia and seizures). The standard diagnostic procedures at WKZ/UMCU also encompass psychological and psychiatric screening, targeting IQ and general mental health, both of which are critical in the light of our specific research questions (see below).

A similar procedure as above will be applied to all controls (children/ adolescents with SLI, cleft palate and typical development), where information is missing. In some cases this will not be necessary; for example, individuals with SLI (who will be recruited through Auris) have all been assessed on language, speech, and hearing as part of the admittance procedure to special education.

Innovation, feasibility and added value

We propose to study a unique population of young children and adolescents with 22q11DS as a model for SLI. SLI is etiological heterogeneous, and against this background, 22q11DS-language impairment (LI) can be considered as one specific, etiologically homogeneous type of SLI. While one could argue that observations in 22q11DS–LI may not necessarily hold true for SLI in general, the study of an etiological subpopulation is intrinsically innovative and valuable, as it represents the first attempt to elucidate a specific pathway from etiology to the expression of language impairment. Work in other developmental disorders (particularly autism) strongly indicates that observations obtained in one particular genetic subgroup can provide highly relevant insights for the broader group of individuals with ASD. Connecting neurocognitive mechanisms (working memory, executive function, implicit learning, etc.) to the language profile is both theoretically and clinically relevant. We will use the results obtained to determine if language impairment can be explained on the basis of deficient neurocognitive mechanisms, and if so, what specific mechanisms are at stake. Thus, our innovative approach of leveraging the genetic homogeneity of 22q11DS has a clear potential to shed new light on the complex pathway from genes via basic neurocognitive mechanisms to language.

We believe our research program has great clinical potential. The results we will obtain can and will be used as a basis for new and much desired practical guidelines for speech-language therapists who work with children with 22q11DS. A better, more detailed picture of the developmental language trajectories in children with 22q11DS will support formulating prognoses for individual children. This may, for example, assist pediatric plastic surgeons in assessing the extent to which a surgical intervention targeting orofacial abnormalities may be effective in improving a child's spoken language. Similarly, improving the quality of prognosis is of great value to speech-language therapists.

For children with 22q11DS and their parents, the early language impairment is a major source of frustration and concern. Increasing our knowledge on this aspect of 22q11DS and translating this into practical guidelines will therefore be an important contribution to the wellbeing of this population. In addition, the present program is expected to function as a stepping stone for investigations of the associations between early language development and mental health in later life. Twenty-five to 30% of individuals with 22q11DS develop schizophrenia during adolescence and there are indications that, in general, the emergence of schizophrenia is foreshadowed by language difficulties earlier in life[24,25].

The parent group *Stichting Steun 22q11* will assist in disseminating our findings, e.g. through their website, through lectures in parent/family meetings, and through the incorporation of our findings in future revisions of the Dutch clinical guidelines.

The objectives set out in this proposal can only be attained through a multidisciplinary collaboration of linguists, speech-language pathologists, psychologists and medical specialists. All of these disciplines are represented in the project team, and all team members have excellent track records and extensive experience with the methods and techniques that will be employed. The infrastructure is already in place. Assessments with standardized procedures (tests and profiling; project 1 & 3) will be carried out at WKZ/UMCU; the experimental work (project 2) will be done at the UIL OTS, which offers state of the art facilities for behavioral and neurocognitive research with young children.

Project 1: The language phenotype in young children with 22q11DS

The research questions of project 1 are:

1. What is the developmental language profile in 22q11DS, and
2. how does it compare to that of SLI?

Delayed language development is typical for children with 22q11DS[21–23,28–30]. However, the available studies are limited with regard to sample sizes and age range. The early stages of development are understudied; linguistically detailed analyses are lacking. Thus, a detailed picture of the language phenotype in 22q11DS is lacking; systematic comparisons with SLI are not yet possible.

The primary area of difficulty in SLI is grammar[31–33]. Phonology is often affected too, while vocabulary is an area of relative strength. Production is often affected more than comprehension. It is unclear if language profiles seen in SLI reflect a delayed or a deviant development, due to inconsistent results across studies[32], possibly related to the genetic heterogeneity of SLI. The language profile of 22q11DS, which is genetically homogeneous, may shed new light on this issue. In a pilot study we found that children with 22q11DS are delayed in vocabulary, phonology and grammar. The exact pattern of weaknesses and strengths still needs to be established and we need to determine if difficulties also occur in comprehension, as this will contribute to clarifying the underlying deficits. Furthermore, it is necessary to disentangle 'pure' language difficulties from those that may result from speaking impediments. For this reason, we will also include a comparison group of children with non-syndromic cleft palate (CP), next to a typically developing (TD) control group.

We will conduct detailed quantitative and qualitative analyses of productive and receptive language skills in children with 22q11DS, and the three comparison groups (SLI, CP, and TD), using normed tests, profiling instruments, and parent questionnaires, mostly identical to those used by Bruinsma in her project 'Effectiveness of speech and language therapy in preschool children with severe developmental language disorders' (NWO 023.003.101; supervised by Gerrits and Wijnen).

Instruments to be used:

- *CELF preschool*[34]: phonology, morphology, syntax, semantics, and pragmatics; expressive and receptive.

- *Peabody Picture Vocabulary Test* (PPVT)[35]: passive vocabulary.
- *Computer Articulation Instrument* (CAI)[36]: speech sound production.
- *Discrimination* subtest of the *Taaltoets Alle Kinderen* (TAKD)[37]: speech sound discrimination.
- Dutch LARSP[38,39] (2-4 yrs), and *STAP*[40] (4-6 years): profiling grammar on the basis of spoken language samples.
- *FAN*[41] (2-4 yrs): profiling phonology on the basis of a language sample.

We anticipate that some of youngest language-impaired children do not yet speak. In these cases, we will apply the *Communicatief Intentie Onderzoek* (CIO)[42] to assess language comprehension and (pre-) communicative behavior.

To complement normed test data on grammar and grammatical profiling, we will use the 'Coloring Book' test[43] to assess children's understanding of specific aspects of Dutch grammar: verbal tenses; coordination/subordination; passives; reflexives and pronouns.

Parents will be asked to complete an online questionnaire (developed by Bruinsma, Gerrits, Wijnen), addressing SES, parents' educational attainment, pedagogical style, and patterns of engagement in verbal activities (e.g. book reading, singing), which may affect children's language outcomes.

Intelligence quotients of all participants will be determined (using WPPSI-III-NL[44]) at the earliest possible age. In the Netherlands, an SLI diagnosis entails that the child's performal IQ (PIQ) is 70 or higher. This score will be the lower boundary for inclusion for all children. Our pilot data indicate that a majority of children with 22q11DS in the targeted age range have a PIQ of 70 or higher. Nonetheless, PIQs in the TD and CP (possibly also SLI) groups are likely higher than in 22q11DS; consequently, exact PIQ matching may be unattainable. If so, we will control for PIQ in our data analyses.

To implement our sequential cohort design[26], which will enable us to track development across the entire target age range within a limited period, children will be included at ages 2;6, 3;0, 3;6; 4;0 or 4;6 (all ±1 month), thus creating 5 cohorts. All children will take part in three successive assessment sessions separated by 6 month (up to age 5) or 12 month intervals (after age 5). In each session, as many of the instruments listed above as possible will be applied, limiting factors being the age range in which an instrument can be used, and the maximum duration of a session, which we set at 2 hours. Our goal is to minimally include a spontaneous language sample, PPVT, and CELF sentence repetition (with alternating sets of sentences) in every session for every child.

We will apply latent growth curve modeling to estimate developmental trajectories for all variables measured[26]. This approach also allows examination of inter-individual differences and the comparison of populations.

The outcome of project 1 will be a comprehensive overview of the progression of skills in different linguistic domains across both modalities as function of age in children with 22q11DS. This will allow an in-depth comparison with SLI, as well as TD children and children with non-syndromic CP.

Project 2: Acquisition mechanisms and cognitive profile in 22q11DS

The proximal cause of language impairment in SLI is unknown. There are indications that the ability to detect (sequential) statistical and distributional patterns in perceived language, most likely fundamental to language acquisition, is compromised in children with SLI[45–48]. On the other hand, SLI has also consistently been associated with deficiencies in neurocognitive mechanisms that are needed to attend to, store, and present the input to the learning mechanism, notably phonological short term memory (STM) and working memory (WM), and executive function (EF)[8,9,16].

Children with 22q11DS are reported to have learning problems, but also, more specifically, attention, EF, and STM/WM deficits[49,50]. However, the evidence is limited, and it is as yet unknown if these deficits can be related to their language impairment. Statistical learning in connection to language has not been studied at all in children with 22q11DS. The motor deficits observed in children with 22q11DS may reflect deficient implicit procedural learning, which has been argued to entail deficient linguistic statistical learning, as it is hypothesized that both types of learning share a neural substrate[12,47,51].

Project 2 seeks to relate the putative proximal neurocognitive causes to the language profile in 22q11DS, by addressing the following questions. Do children with 22q11DS:

1. show a deficiency in detecting statistical patterns in verbal material?
2. show deficiencies in their ability to process and store (auditory) verbal materials?
3. show a deficiency in non-linguistic procedural learning?
4. show deficiencies in attention or (other) executive functions?

The same questions will have to be addressed for children with SLI, so as to enable a comparison. To this end we will select ~40 children with 22q11DS from the sample taking part in project 1, as well as equally large samples of TD children, children with SLI, and children with CP, matched for age and gender, and who are as similar as possible to the 22q11DS children in terms of PIQ. These children will take part in two additional sessions comprising a series of experiments, at ages 4;6 and 6.

The ability to detect and employ statistical patterns in language will be studied in two different areas, representing crucial processes in language acquisition:

1. *Detecting word boundaries*. Eight-month-olds can detect word boundaries in continuous speech on the basis of differences in transitional probabilities (TPs) between syllables[52]. Evans et al. showed that school age children with SLI were unable to exploit TPs to find words[46]. Evans et al.'s task will be adapted in this project for use with Dutch speaking 4-6 year-olds.
2. *Non-adjacent dependency learning* (NADL). Infants can detect the systematic co-occurrence (dependency) of recurring words *a* and *b* in an artificial language consisting of *aXb* strings, where X represents a larger set of words[53]. Detection of the a-b co-occurrence hinges on the high predictability of *b* vs. the low predictability of *X*, given *a*. Children with language difficulties perform poorly on this and similar tasks[54–56].

Non-linguistic procedural learning will be assessed with a Serial Reaction Time Task[57], in which a series of simple stimuli presented in a fixed order are to be associated with motor responses.

To test children's phonological STM/WM, attention and executive functions, we will use the following tests:

- Phonological STM / WM: digit span task (forward and backward); non-word repetition[58].

- Continuous attention: Integrated Visual and Auditory Continuous Performance Test (IVA CPT) [59].
- Selective attention: Sky search tasks[60].
- Executive function/ inhibition: Flanker task[61].

The tests and experimental tasks will be adapted from those developed for previous research projects at UIL-OTS, as well as for experiments within the VIDI research projects of Elma Blom (Utrecht University; 'Cognitive development in the context of emerging bilingualism') and Judith Rispens (University of Amsterdam; 'Understanding the contribution of procedural learning to the development of grammatical and literacy skills'). The applicant is involved in both these research programs (as promotor) and drs. Blom and Rispens have consented to act as advisers for the present program.

Performance of the four groups of participants will be compared for all tasks at two time points. We will also correlate outcomes across tasks within time points and within and across tasks across time points.

Thus, project 2 will result in a comprehensive overview of the relative weaknesses and strengths in neurocognitive mechanisms considered critical for language acquisition in language impaired and unimpaired children. The results will help us determine if language impairment is associated with a specific profile regarding memory (STM, WM), executive function, procedural learning and statistical learning, and if this association is the same, or not, for 22q11DS and SLI.

Project 3: Language phenotype in adolescents with 22q11DS

Objective studies on the mature language skills of people with 22q11DS are lacking, while it is our clinical impression that some adult patients still struggle, apparently having difficulties with word finding and sentence formulation. There is an additional strong potential clinical relevance in studying mature language skills in 22q11DS as an astounding 25-30% of individuals with 22q11DS develop schizophrenia during adolescence[62] (compared to about 1% in the general population) and there are indications that, in general, the emergence of schizophrenia is foreshadowed by language difficulties earlier in life [24]. Schizophrenia is one of the most catastrophic mental illnesses, with debilitating effects on both a personal and societal level. A recent study found that a combination of semantic and syntactic characteristics of spontaneous speech of young adults at high risk of developing schizophrenia predicted later occurrence of psychosis with 100% accuracy[25]. It is not yet known if characteristics of language acquisition in childhood can be used to predict later mental illness at an individual level.

The goal of project 3 is therefore twofold:

1. to determine the language profiles of adolescents and young adults (14-18 years) with 22q11DS in order to establish the 'mature language state' and specifically the degree of variability in this state, and
2. to relate the profile of 'mature language' in 22q11DS to psychological and psychiatric status. As the participants in this project will also be selected from the WKZ/UMCU database, we can avail of their childhood medical and psychological records and relate these to language outcomes in adolescence. We will therefore be in a position to relate early development to later language status and occurrence of psychiatric disorders.

A group of 40 youngsters in the age range 14-18 years will be included in the study. We will be able to draw on the WKZ/UMCU cohort. Comparison groups will be adolescents in the same age range with non-

syndromic cleft palate and adolescents with SLI. We will also include siblings of the participants with 22q11DS as a third control group.

To chart language, we will assess phonology, vocabulary, verbal-conceptual knowledge, morphology and grammar, discourse and pragmatic skills, as well as literacy skills, with both norm-referenced instruments and spontaneous language analysis. Specifically, we will use the PPVT[35], CELF-4-NL[63], a non-word repetition test[58] and a Cloze test[64,65]. In addition, to probe competence with respect to more advanced aspects of grammar, we will apply an age-adequate version of coloring book comprehension tests described under project 1. A (semi-)spontaneous language sample (comprising both monologue and dialogue) will be collected from every participant, transcribed according to CHAT guidelines (http://childes.psy.cmu.edu/), and analysed with respect to content, pragmatic adequacy, grammatical errors and complexity, lexical variability, and speech fluency.

The standard psychiatric assessment at the UMCU 22q11DS psychiatric outpatient clinic includes multidisciplinary clinical observation, a standardized interview (K-SADS, DSM-IV interview) and IQ testing by use of the Wechsler scales (WISC-III-NL or WAIS-IV). The psychiatric assessment will aid us in monitoring if adolescents are already experiencing psychotic symptoms which in turn could affect speech outcomes.

The study is a cross-sectional design for 4 groups of adolescents (22q11DS, SLI, CP, siblings). It will also involve retrospective data collection of the early language, general medical, physical and cognitive development of each participant.

Project 3 will result in a comprehensive overview of the mature language state of people with 22q11DS and discuss these findings in the light of psychiatric comorbidity. Although the duration of the project is not long enough to actually identify those transitioning into psychosis, the clinical relevance of the risk of schizophrenia is obviously very high. Given the important clinical potential we see it as our moral duty to include any analysis that may contribute to improving early prediction of schizophrenia in this population. In this case we are well positioned to lay the foundation of a future study (beyond the scope of the present proposal) that would entail further follow-up of the adolescents, to examine to what extent linguistic abnormalities in childhood and/ or adolescence may serve as a predictor for the onset of schizophrenia later in life (late adolescence, early adulthood). This hypothesis is grounded in a solid theoretical basis as many studies in the general population have demonstrated verbal abnormalities (e.g. abnormal verbal fluency) to be implicated in this disorder. As the children and youngsters with 22q11DS will remain in the care of UMCU/WKZ, the data collected in this program will allow us to explore this issue in the future.

Synthesis

We will relate the outcomes of the three projects to one another in addressing a number of overarching questions:

1. Project 1 will yield a detailed picture of the development in several linguistic subdomains (phonology, grammar, etc.) in 22q11DS, and will compare this to the developmental profile of SLI. In the synthesis we will take a closer look at the developmental interrelations between the linguistic subdomains, both synchronously (relating two or more domains at the same age) and developmentally (relating different domains across ages). This will allow us to explore the degree to which developmental profiles are harmonious or not, and to see if there are developmental dependencies between domains. The

spontaneous language data, which will be collected for all participants at all ages, and which will be used for grammatical and phonological profiling, as well as the vocabulary data, will be critical to this endeavor.

2. Project 2 will explore to what extent neurocognitive mechanisms involved in language acquisition are deficient in 22q11DS and SLI. In the synthesis, we will dig deeper into this. Our research design allows us to see if a language delay in a certain domain (phonology, grammar, etc.) at a certain age is associated with a neurocognitive deficit at an *earlier* age (or vice versa). This will help elucidating causal relations between linguistic competence and domain-general neurocognitive mechanisms, and thus further our knowledge of the cognitive underpinnings of language development in general and its genetic basis.

3. Project 3 charts the language skills of adolescents and relates these to mental status and emerging schizophrenia. The synthesis will begin to explore relations between early (language) development and later language status.

4. Finally, the synthesis will address the clinical implications of the results obtained in both children and adolescents. Clinicians who care for children with 22q11DS are in need of detailed and concrete information about language development in this population, and about the language *potential* of affected children. This will facilitate early diagnosis, early language interventions, and perhaps also prognosis of language outcomes later in life. The extensive and detailed data that this research program will yield will serve to fill this lacuna. The synthesis component will provide a detailed, clinically relevant description of the overall *staging* and *timing* of language development in 22q11DS, as well as the level of competence attained in adolescence.

11b. Description of the Proposed Investment Component (optional)

N/A

12. Word count

Aantal woorden 11a (Algemene beschrijving):	2306
Aantal woorden 11a (Beschrijving deelprojecten en synthese):	800 + 747 + 735 + 387
Aantal woorden 11b: (Investeringencomponent):	0
Totaal aantal woorden 11a + 11b:	4975

13. Summary in Key Words

22q11DS; language development; cognitive development; SLI

14. Work Program

The preliminary work program is outlined in the table below. The anticipated starting date is July 1, 2017. We expect to have obtained approval of the Ethical Review Board (METC) prior to the start of the research program.

		1st quarter	*2nd quarter*	*3rd quarter*	*4th quarter*
2017	P1*	/	/	- Recruitment participants (22q11DS, SLI , CP & control) - Set up test battery & test procedures - write literature review (paper 1.1)	
	P2	/	/	/	- Design, implement, & pilot experiments
	P3	/	/	- Coordinating/ assisting with design & implementation of projects 1 & 2 - Assist PhD1 (project 1) with literature review	
2018	P1	- 1st assessment wave (320 children; ~15 weeks)	- Complete 1st assessment wave - Data processing, transcribing, analyzing - Attend summerschool (LOT or other)	- Summer vacation - 2nd assessment wave (~15 weeks)	- Complete 2nd assessment wave - Data processing, transcribing, analyzing
	P2	- Design, implement & pilot experiments - Select participants (22q11DS, matching w/ SLI , CP & control)	- 1st exp test wave (160 children; ~ 8 weeks) - Initial data processing; - Summerschool (LOT or other)	-Summer vacation - Data analysis 1st exp test wave	- Data analysis (cont'd) - Paper 2.1: review, cognitive functions (memory, attention, learning) in 22q11DS and SLI.
	P3	- Contributions to projects 1 & 2; assist PhD2 (project 2) with literature review		- Recruitment participants (22q11DS, SLI, CP & control) - Set up test battery & test procedures - Prepare paper 3.1	
2019	P1	- Winterschool (LOT or other) - 3rd assessment wave (~15 weeks)	- Complete 3rd assessment wave - Data processing, transcribing, analyzing	- Summer vacation - Complete data processing waves 1, 2, 3	- Paper 1.2 (norm referenced test data; comparison of 4 groups): data analysis & writing
	P2	-Winterschool (LOT or other); -completing paper 2.1	2nd exp test wave (160 children; ~ 8 weeks) - Initial data processing - Summerschool	- Summer vacation - Data analysis 2nd exp test wave	- Paper 2.2: working memory and EF in 22q11ds, SLI, CP and TD
	P3	- Assessments of adolescents - Initial data processing	- Contributions to projects 1 & 2 - Prepare paper 3.2	- Summer vacation - Data processing - Organize international symposium (w/ co PI)	Prepare paper 3.3

2020	P1	- Complete paper 1.2 - Begin paper 1.3	- Paper 1.3 (development of grammar; focus on qualitative results): data analysis; writing - Summerschool	- Summer vacation - Attend biennial 22q11DS conference - Begin paper 1.4	- Paper 1.4 (development of phonology; focus on qualitative results): data analysis; writing
	P2	- Complete paper 2.2	- Paper 2.3: word segmentation (22q11, SLI, CP, TD)	- Summer vacation - Attend biennial 22q11DS conference - Paper 2.3 cont'd	- Paper 2.4: Non-adjacent dependency learning
	P3	- Organize biennial 22q11DS conference (with co-PI) - Paper 3.3 cont'd		/	
	S	- Paper S.1: synthesizing results from projects 1, 2, & 3 - Organize biennial 22q11DS conference (with post doc)		- Paper S.2: synthesizing results from projects 1, 2, & 3	
2021	P1	- Paper 1.5 (vocabulary development)	- Write dissertation: introduction and conclusion - paper 1.6: for professional audience	/	/
	P2	- Paper 2.5: procedural learning (Serial Reaction Time Task)	- Write concluding dissertation chapter – synthesis of results	- Finalize dissertation - paper 2.6: for professional audience	/
	P3	/	/	/	
	S	- Paper S.2 cont'd	Prepare book/ special issue (on 2020 conference materials)	- Summary of project results for clinicians; - Develop clinical guidelines wrt 22q11DS language/ speech	
2022	S	Winding up	/	/	/

*P1, 2, 3 = project 1, 2, 3; S = synthesis

15. Planned Deliverables

Project 1:

deliverable	topic	manuscript ready	outlet
paper 1.1	Literature review language & speech development in 22q11DS	January 2018	journal*
paper 1.2	Overview of language development in Utrecht 22q11DS sample based on norm referenced test results; comparison SLI (and other comparison groups)	January 2020	journal*
paper 1.3	Development of grammar in 22q11DS (focus on qualitative data)	June 2020	journal*
paper 1.4	Development of phonology in 22q11DS (focus on qualitative data)	December 2020	journal*
paper 1.5	Development of vocabulary in 22q11DS	March 2021	journal*
dissertation	Papers 1 – 5, + introduction and discussion chapters	June 2021	LOT dissertation series
paper 1.6	Summary of main findings for a professional audience	to be determined	*Ned Tijdschrift voor Logopedie*, or similar.

Project 2:

deliverable	topic	manuscript ready	outlet
paper 2.1	Literature review cognitive functions in 22q11DS	January 2019	journal*
paper 2.2	Working memory & EF	January 2020	journal*
paper 2.3	Word segmentation	July 2020	journal*
paper 2.4	Non-adjacent dependency learning	December 2020	journal*
paper 2.5	Procedural learning	February 2021	journal*
dissertation	Papers 2.1-2.5 + intro + conclusion / discussion chapters	September 2021	LOT dissertation series
paper 2.6	Summary of main findings for a professional audience	to be determined	*Ned Tijdschrift voor Logopedie*, or similar.

Project 3:

deliverable	topic	manuscript ready	outlet
paper 3.1	Overview of mature language in Utrecht 22q11DS adolescent sample based on norm referenced test results and controls	December 2018	journal*
paper 3.2	Mature language profile in 22q11DS and psychopathology	July 2019	journal*
paper 3.3	Spontaneous speech in 22q11DS and SLI	February 2020?	journal*

Synthesis

The synthesizing component (co-applicant Duijff) will yield *at least two theoretical reviews* in which results of the three projects are integrated. We intend to host the 12th Biennial International 22q11.2 deletion syndrome meeting (http://22qsociety.org) in 2020 in Utrecht with as subject the linguistic and cognitive aspects of 22q11DS in the final phase of the program. Contributions to this symposium will be assembled in a book or special issue of a journal. The co-applicant will also take responsibility for disseminating the results of the research program to the relevant professionals (pediatricians, speech-language therapists). Part of this is expected to take the form of a clinical guideline.

*We expect to submit papers to the following peer-reviewed journals: *Journal of Speech, Language, and Hearing Research, Journal of Child Psychology and Psychiatry*, *Journal of Communication Disorders, American Journal of Medical Genetics*.

16. Short Curriculum Vitae Applicants

Frank Wijnen (PhD 1990, Nijmegen; www.uu.nl/hum/staff/FNKWijnen) is full professor of psycholinguistics at Utrecht University and director of the Utrecht institute of Linguistics OTS. He is PI in a research group that studies the earliest phases of language acquisition in babies and toddlers, with a special focus on distributional and statistical learning (see www.let.uu.nl/babylab). He also works on language acquisition and processing in children and adults with (a familial risk of) dyslexia, SLI, and on sentence processing in first and second languages. He has published extensively and is/was supervisor of 16 completed PhD dissertations and 9 more ongoing PhD projects.

Sasja Duijff (PhD 2012, Utrecht) is a pediatric psychologist within UMC Utrecht/Wilhelmina Children's Hospital and is also employed as a researcher within the 22q11DS lab at the UMCU department of Psychiatry. She has gained a strong expertise in the diagnostic assessment of a broad range of psychopathology in children, adolescents and young adults. Moreover, since 2003, the focus has been on the early development of patients (1½ - 15½ years) with the 22q11.2 deletion syndrome. The focus of her thesis was on the cognitive development of children with 22q11DS. She was the first – on an international level - to report an absolute decline in IQ in this group. In the coming years she intends to continue her clinical work with children and adolescents with developmental disorders as well as her research in the area of early (psychological) interventions for this group of children and adolescents.

Ellen Gerrits (PhD 2001, Utrecht) is professor of Clinical Language, Speech and Hearing Sciences (hoogleraar Logopediewetenschap) at Utrecht University and chair of the research group Speech and Language Therapy (lector Logopedie) of HU University of Applied Sciences Utrecht. Her research program focuses on effectiveness of intervention for children and adults with language disorders.
Main topics of her expertise are clinical epidemiology, intervention studies, professional and research ethics, speech and language therapy in children with language disorders, dyslexia, deaf children and cochlear implantation. She currently supervises four PhD students.

Jacob Vorstman (PhD 2008, Utrecht) is a child and adolescent psychiatrist at the Department of Psychiatry, UMC Utrecht. He divides his time between clinical work with children with genetic disorders and/or (suspected) developmental disorders and research. Starting in 2001, his research focused on the psychiatric and genetic aspects of the 22q11.2 deletion. Between 2004 and 2006 he worked in the Children's Hospital

of Philadelphia, where he learned the basics of molecular genetics under the direct supervision of Professor Emanuel. He published several papers on genetic and phenotypic aspects of the 22q11.2 deletion syndrome, using data from his Utrecht cohort. Gradually he broadened the scope from 22q11DS to the study of genotype-phenotype relations in autism and schizophrenia. His ambition is to further insights into the genetic architecture underlying these disorders as well as to improve methods to measure the associated phenotypes.

17. Key publications applicants (max 5 per [co-]applicant)

Principal applicant, Prof. F. Wijnen

1. Boerma, T.D., Leseman, P.P.M., Timmermeister, M., **Wijnen, F.**, & Blom, W.B.T. (2016). Narrative abilities of monolingual and bilingual children with and without language impairment: implications for clinical practice. *International Journal of Language & Communication Disorders*. DOI: 10.1111/1460-6984.12234.
2. Kerkhoff, A., de Bree, E., de Klerk, M., & **Wijnen, F.** (2013). Non-adjacent dependency learning in infants at familial risk of dyslexia. *Journal of Child Language*, 40, 11-28.
3. **Wijnen, F.** (2013). Acquisition of linguistic categories: cross-domain convergences. In: Bolhuis, J. & Everaert, M. (Eds.), *Birdsong, Speech and Language: Converging Mechanisms*. Cambridge, MA: MIT press (pp. 157-178).
4. **Wijnen, F**., de Bree, E., van Alphen, P., de Jong, J., & van der Leij, A. (2015). Comparing SLI and dyslexia: developmental language profiles and reading outcomes. In: S. Stavrakaki (Ed.), *Specific language impairment: Current trends in research*. Amsterdam: John Benjamins.
5. Zwitserlood, R., van Weerdenburg, M., Verhoeven, L., & **Wijnen, F.** (2015). Development of grammatical complexity and accuracy in Dutch school-age children with SLI. *Journal of Speech, Language and Hearing Research*, 58, 891-305.

Co-applicant S. Duijff, PhD

1. Vorstman JA, Breetvelt EJ, **Duijff SN**, et al. Cognitive decline preceding the onset of psychosis in patients with 22q11.2 deletion syndrome. *JAMA psychiatry.* 2015;72(4):377-385.
2. **Duijff SN,** Klaassen PW, de Veye HF, Beemer FA, Sinnema G, Vorstman JA. Cognitive development in children with 22q11.2 deletion syndrome. *The British journal of psychiatry : the journal of mental science.* 2012;200(6):462-468.
3. **Duijff SN**, Klaassen PW, Swanenburg de Veye HF, Beemer FA, Sinnema G, Vorstman JA. Cognitive and behavioral trajectories in 22q11DS from childhood into adolescence: a prospective 6-year follow-up study. *Research in developmental disabilities.* 2013;34(9):2937-2945.
4. Klaassen P, **Duijff SN**, Swanenburg de Veye H, Vorstman J, Beemer F, Sinnema G. Behavior in preschool children with the 22q11.2 deletion syndrome. *American journal of medical genetics. Part A.* 2013;161A(1):94-101.
5. **Duijff SN**, Klaassen PWJ, Beemer FA, Swanenburg de Veye, HFN, Vorstman JAS, Sinnema G. Intelligence and visual motor integration in 5-year-old children with 22q11-deletion syndrome. *Res Dev Disabil* 2012; 33: 334-40

Co-applicant Prof. E. Gerrits

1. Visser-Bochane MI, **Gerrits, E**, van der Schans CP, Reijneveld SA, Luinge MR. (2016). Atypical speech and language development: a consensus study on clinical signs in the Netherlands. *International*

Journal of Language and Communication Disorders. DOI: 10.1111/1460-6984.12251
2. Zumach, A., **Gerrits, E**, Chenault, M. & Anteunis, L. (2010). Long-term effects of early-life otitis media on language development. *Journal of Speech, Language and Hearing Research,* 53, 34-43.
3. **Gerrits, E.** (2010). Acquisition of /s/-clusters in Dutch-speaking children with phonological disorders. *Clinical Linguistics & Phonetics*, 24, 199-209.
4. **Gerrits, E.** & Bree de, E. (2009). Speech perception and production in dyslexia and SLI: evidence from 3-4 year olds. *Journal of Communication Disorders, 42*, 180-194.
5. Alphen, P. van, Bree, E. de, **Gerrits, E.**, Jong, J. de, Wilsenach, C. & Wijnen, F. (2004). Early language development in children with a genetic risk of dyslexia. *Dyslexia, 10,* 265-288.

Co-applicant J. Vorstman, MD, PhD

1. Sommer IE, Bearden CE, van Dellen E, Breetvelt EJ, Duijff SN, Maijer K, van Amelsvoort T, de Haan L, Gur RE, Arango C, Díaz-Caneja CM, Vinkers CH, **Vorstman JA**. Early interventions in risk groups for schizophrenia: what are we waiting for? NPJ Schizophr. 2016 Mar 9;2:16003.
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3. **Vorstman JA**, Breetvelt EJ, Duijff SN, Eliez S, Schneider M, Jalbrzikowski M, Armando M, Vicari S, Shashi V, Hooper SR, Chow EW, Fung WL, Butcher NJ, Young DA, McDonald-McGinn DM, Vogels A, van Amelsvoort T, Gothelf D, Weinberger R, Weizman A, Klaassen PW, Koops S, Kates WR, Antshel KM, Simon TJ, Ousley OY, Swillen A, Gur RE, Bearden CE, Kahn RS, Bassett AS; International Consortium on Brain andBehavior in 22q11.2 Deletion Syndrome. Cognitive decline preceding the onset of psychosis in patients with 22q11.2 deletion syndrome. JAMA Psychiatry. 2015 Apr;72(4):377-85.
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18. Public summary and title

'Taalontwikkeling in de problemen'

Prof. dr. F.N.K (Frank) Wijnen (m), UU – Utrecht Institute of Linguistics OTS

Dat kinderen gaan praten vinden we heel normaal. Maar wat als het niet vanzelf gaat, als je bijvoorbeeld een ontwikkelingsstoornis hebt? Door de vertraagde taalontwikkeling van kinderen met het 22q11-deletiesyndroom te onderzoeken hopen de onderzoekers beter te begrijpen wat taalontwikkeling mogelijk maakt, waar problemen kunnen ontstaan en hoe we kunnen helpen.

19. Summary for non-specialists

De ontwikkeling van taal bij jonge kinderen wordt doorgaans als iets normaals en vanzelfsprekends ervaren. De meeste kinderen beginnen met brabbelen en spreken doorgaans rond hun 1e levensjaar hun eerste woordje. Maar toch gaat bij vrij veel kinderen de taalontwikkeling niet gemakkelijk en vanzelf. Wetenschappelijk onderzoek naar taalontwikkelingsproblemen dient twee doelen. Enerzijds willen we proberen het falend proces te begrijpen, om zo tot betere zorg voor kinderen (en hun ouders) te komen. Anderzijds bestuderen we taalontwikkelingsproblemen om meer te begrijpen van de psychologische processen die aan normale taalontwikkeling ten grondslag liggen, hoe die processen in de hersenen vorm krijgen en wat daarvan de genetische basis is. Het meeste onderzoek is tot nu toe gedaan over kinderen met *specific language impairment (SLI)*, een taalontwikkelingsprobleem zonder duidelijk aanwijsbare neurologische of psychologische oorzaak. Dat is een nogal moeilijk af te bakenen stoornis, waarvan we ook het genetisch profiel nog niet goed kennen. Het 22q11.2 deletiesyndroom (22q11DS) daarentegen is een relatief frequent voorkomende ontwikkelingsstoornis (ong. 1 op de 2000-4000 geboorten), die tot diverse fysieke en psychologische problemen leidt. Een daarvan is een ernstige taalontwikkelingsachterstand. Er is tot nu toe erg weinig exacte kennis over de taalproblemen van kinderen met 22q11DS.

In dit onderzoeksprogramma willen we daarom de taalontwikkeling van kinderen (tussen 2 en 6 jaar) met 22q11DS nauwkeurig in kaart brengen. Dit is voor ouders en behandelaars (kinderartsen, logopedisten) belangrijk, maar er is ook een belangrijk theoretisch doel. Wat namelijk bijzonder is aan 22q11DS, is dat we precies weten waar het vandaan komt: een specifiek stukje van het genetisch materiaal ontbreekt en dat is bij vrijwel alle mensen met dit syndroom hetzelfde. Wanneer we nu de taalproblemen in kaart brengen, kunnen we hopelijk iets beter gaan begrijpen hoe het menselijk vermogen om spontaan een moedertaal te leren genetisch verankerd is.

Wat we verder willen doen, is bij deze kinderen een aantal cognitieve vaardigheden testen waarvan vermoed wordt dat ze met de taalontwikkeling in verband staan. Het gaat om kortetermijngeheugen en werkgeheugen, aandacht, executieve functies en procedureel leren. Bij kinderen met SLI zien we vaak beperkingen in deze vaardigheden. Er zijn aanwijzingen dat kinderen met 22q11DS met deze vaardigheden ook moeilijkheden hebben. Als we dat kunnen bevestigen en we bovendien zien dat zulke moeilijkheden (in vóórkomen en ernst) samenhangen met de taalmoeilijkheden, dan komen we iets meer te weten over de fundamentele processen van de taalontwikkeling. Mogelijk kan de zo verworven kennis ook helpen om betere interventies voor alle kinderen met taalontwikkelingsmoeilijkheden te ontwikkelen.

We kijken in dit programma ook naar het 'eindpunt' van de taalontwikkeling bij pubers/adolescenten met 22q11DS. Mensen met 22q11DS hebben een sterk verhoogd risico voor het ontwikkelen van schizofrenie (±25-30%, vergeleken met 1% in de algemene bevolking) en er aanwijzingen zijn dat het ontwikkelen van schizofrenie vooraf wordt gegaan door taalproblemen op jongere leeftijd. Door het scherper in beeld krijgen van de taal bij kinderen en jongeren kunnen we hopelijk een bijdrage leveren aan de tijdige behandeling van deze ernstige ziekte.

20. Research Budget

See appended document.

Wetenschappelijke Integriteit

Door het indienen van dit document verklaart de aanvrager te voldoen aan de nationaal en internationaal aanvaarde normen van wetenschappelijk handelen zoals neergelegd in de *Nederlandse Gedragscode Wetenschapschapsbeoefening 2014* (VSNU).

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