# CHILDHOOD STUTTERING

From clinical practice to population-based research and vice versa

Simone P.C. Koenraads

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Simone Petronella Christina Koenraads

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# Childhood Stuttering
# From Clinical Practice to Population-Based Research and Vice Versa

Stotteren bij kinderen
Van dagelijkse klinische praktijk tot populatie gebaseerd onderzoek en vice versa

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*"Vergeet niet om tijdens de reis ook eens achterom te kijken."*
Mama en Papa

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# 1

General introduction
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# 1. Background of childhood stuttering

## 1.1 Prevalence of stuttering

Stuttering is a speech fluency disorder characterized by repeated, blocked or prolonged sounds, and repeated syllables and words that disrupt the normal fluent rhythm. A distinction is generally made between childhood stuttering (i.e. develomental stuttering) and late/adult onset stuttering. The former typically begins between the ages of 2 and 4, while the latter is often the result of stroke or brain injury (neurogenic stuttering), emotional trauma later in life (psychogenic stuttering), or a side effect of medication (pharmacogenic or drug-induced stuttering). The focus of this work of research is on childhood stuttering. The incidence of stuttering is 5-11%, with onset typically occurring during the preschool-age years (Yairi & Seery, 2015). Although the majority of children recover within 2 to 3 years of onset (Yairi & Ambrose, 1999; Yairi & Ambrose, 2005), approximately 20-35% continue to stutter beyond this period (Ambrose, Yairi, Loucks, Seery, & Throneburg, 2015; Kefalianos, Onslow, Packman, et al., 2017). Given the high recovery in childhood, the proportion of stuttering is higher in younger than in older age groups. In the general population, the prevalence of stuttering has been estimated at 0.7-1% worldwide (NVLF, 2020; Yairi & Seery, 2015). Persistent stuttering can negatively impact communication and social skills, as well as overall quality of life in adolescents and adults (Chun, Mendes, Yaruss, & Quesal, 2010; Craig, Blumgart, & Tran, 2009; Koedoot, Bouwmans, Franken, & Stolk, 2011; Nang, Hersh, Milton, & Lau, 2018).

## 1.2 Theories of stuttering

Most researchers investigating stuttering agree that childhood stuttering is explained by a multi-factor theory, which incorporate a range of factors (Bloodstein, Bernstein Ratner, & Brundage, 2021; Smith & Weber, 2017; Yairi & Ambrose, 2005). Smith and Weber (2017) introduce the Multifactorial Dynamic Pathways (DMP-)model, which suggests that the origins and mechanisms of stuttering may be shaped by the combination of environmental, neurological (e.g., structural and functional differences in brain regions involved in speech motor control that impair the timing and coordination of speech muscle), and genetic factors, which influence speech development over time. These factors influence speech in a non-linear way. As a result, the severity of stuttering can fluctuate across time. Such fluctuations depend on the individual's experiences, developmental stage, and the demands placed on their speech system. While neurological and genetic

predispositions influence stuttering, environmental factors, such as high demands on speech or stressful communication situations, can exacerbate the fluency condition. Early life experiences, such as caregiver communication situations, may either promote fluency or contribute to dysfluency. Furthermore, the model suggests that recovery from stuttering is possible when environmental factors become more supportive, allowing the brain's neuroplasticity to improve speech patterns over time.

## 1.3 Classification of stuttering recovery and persistence

Classifying children as recovered from or persisting in stuttering is not as straightforward as it may seem. Stuttering is likely to be episodic in nature; it may vary from day to day, appear for a few months, disappear for a few days and reappear again; it can wax and wane (Bloodstein et al., 2021; Constantino, Leslie, Quesal, & Yaruss, 2016; Guitar, 2016). Classification is therefore a challenging task. Recovery from stuttering can occur as early as the first year after onset (6-11%) (Reilly et al., 2013; Yairi & Ambrose, 1992), although the majority of children tend to recover in the second and third years after onset (Yairi & Ambrose, 1999; Yairi & Ambrose, 2005). Some studies have classified stuttering based on the expert judgement of stuttering frequency and severity in a single speech sample (Jones et al., 2008), while others have been exclusively based on the parental judgement of their child's speech fluency (Dworzynski, Remington, Rijsdijk, Howell, & Plomin, 2007; Kloth, Kraaimaat, Janssen, & Brutten, 1999). The traditional criteria are based on a combination of both judgements (Conture, 2001; Yairi & Ambrose, 1999; Yairi & Ambrose, 2005). To date, children's self-reports of fluency have not been part of any assessment to define the stuttering status in childhood. When children are old enough to report on this (de Sonneville-Koedoot, Stolk, Rietveld, & Franken, 2015), these self-reports can contribute to expert and parental judgements to determine the actual stuttering status (Perkins, 1983). The emphasis on Patient Reported Outcome Measures (PROMs) had introduced self-reports on speaking experience, providing insight into recovery from stuttering and refining stuttering phenotypes (Ambrose & Yairi, 1994; Yaruss, Coleman, & Quesal, 2010). In this thesis, we therefore included children's self-reports, focusing on their subjective experiences with speech fluency and dysfluency, and their satisfaction with communication.

## 1.4 Etiology of childhood stuttering

The exact etiology of childhood stuttering is unclear. However, there is general consensus that multiple intrinsic and extrinsic factors, including genetic predisposition as well

as linguistic, speech motor, temperamental, psychological, socioenvironmental and neurobiological factors, contribute to the onset and developmental course of stuttering in childhood (Ambrose et al., 2015; Bloodstein et al., 2021; Franken, Oonk, Bast, Bouwen, & De Nil, 2024; Smith & Weber, 2017; Walden et al., 2012; Yairi, Ambrose, Paden, & Throneburg, 1996). At the onset of stuttering, it is important for Speech-Language Pathologists (SLPs) to identify distinguishing characteristics and (risk) factors associated with recovery or persistent stuttering in order to utilize resources to those most likely to persist in stuttering (Usler & Weber-Fox, 2015). It is known that persistent stuttering affects more boys than girls (Frigerio-Domingues & Drayna, 2017; Reilly et al., 2009; Yairi et al., 1996), that stuttering tends to run in families and in twins, and that stuttering has been associated with some genetic mutations (Ambrose, Cox, & Yairi, 1997; Dworzynski et al., 2007; Felsenfeld et al., 2000; Frigerio-Domingues & Drayna, 2017; Kang et al., 2010; Kazemi, Estiar, Fazilaty, & Sakhinia, 2018; Rautakoski, Hannus, Simberg, Sandnabba, & Santtila, 2012; Raza et al., 2015). In addition, although limited research exists, a few environmental factors (e.g., socioeconomic status, parenting practices, experiences at school, and occurrence of life events) have been suggested to be associated with both stuttering and persistent stuttering (Conture et al., 2006; Richels, Johnson, Walden, & Conture, 2013). These heritable and environmental factors, as well as a range of linguistic, behavioral, and neurobiological factors as described above, have been considered as causal or risk factors for the onset of stuttering and its developmental course over time (Arenas, 2016; Conture et al., 2006; Smith & Weber, 2017). In the following sections, perspectives on these factors associated with childhood stuttering are further specified to provide an overview of the possible causes and consequences of childhood stuttering. Genetic research is not included in the scope of this thesis.

# 2. Current perspectives

## 2.1 Perspectives on language skills

The role of language skills and linguistic factors in the onset and development of stuttering is still a matter of debate, and these factors can be considered as potential risks for childhood stuttering. One common assumption for the occurrence of stuttering in general, as suggested by Reilly et al. (2013), is that a child needs to speak. The onset of stuttering usually occurs during a dynamic period in children's speech and language development, characterized by a substantial growth in speech sounds, and in lexical, morphological, syntactic and pragmatic skills, in both receptive (e.g., comprehension) and expressive

(e.g., production) language skills (Bloodstein et al., 2021; Brundage & Bernstein Ratner, 2022; Packman & Attanasio, 2004). For over a century, researchers have investigated the language skills of children who stutter, in an effort to clarify the relationship. Some studies have reported that children who stutter exhibit lower language skills compared to fluent speaking controls, while other studies have reported higher language skills in children who stutter (Anderson, Pellowski, & Conture, 2005; Choo, Burnham, Hicks, & Chang, 2016; Nippold, 2018; Ntourou, Conture, & Lipsey, 2011; Reilly et al., 2013; Watts, Eadie, Block, Mensah, & Reilly, 2017). The interpretation of these findings remains inconclusive due to the diversity of study designs, including different age ranges, sample sizes, methodologies, and outcomes. Therefore, it has become a focus of scientific interest in stuttering research, reflecting psycholinguistic perspectives. Children with lower language skills can be expected to have immature or limited speech motor skills due to less practice, or neuro-physiological limitations, and, therefore, a higher probability of (persistent) stuttering. On the other hand, language development may trigger stuttering if the language skills are too demanding for the child's speech motor skill development at that moment in time. Parents often report that their child had a spurt of language growth at the time of stuttering (e.g., "his brain seemed to be working faster than his mouth"). In summary, although language skills and linguistic factors at all levels have been considered relevant to the onset and development of stuttering in childhood, the relationship between language skills before and at the time of the onset of stuttering and its developmental course remains unclear.

## 2.2 Perspectives on behavior and temperament

Literature suggests that behavioral and temperamental characteristics and difficulties, rather than psychiatric disorders in particular, may be associated with the onset and development of stuttering (Yairi & Ambrose, 2013). Temperament is defined as constitutionally based individual differences in emotional reactivity and self-regulation (Rothbart, 1991). In behavior, a distinction is made between internalizing and externalizing. Internalizing behaviors are directed inwards and focus on negative problem behaviors (e.g., anxious or depressed behavior, social withdrawn behavior, physical complaints), whereas externalizing behaviors are directed outwards (e.g., oppositional and aggressive behavior, hyperactive) (Achenbach & Rescorla, 2000; Eisenberg, Hernández, & L. Spinrad, 2017). Both types of behaviors are associated with poor self-regulation (Eisenberg, Spinrad, & Eggum, 2010). A bidirectionality in the relationship between internalizing, externalizing, and temperamental traits and stuttering is suggested. The first hypothesis (i.e. first direction)

in literature is that behavioral and temperamental factors cause or contribute to the onset and persistence of stuttering. Researchers have observed behavioral difficulties among preschool-age children, in the period they started stuttering. A slightly higher tendency towards internalizing difficulties, especially shyness and sadness (but not social anxiety), has been found in preschool-age children who stutter (Eggers, De Nil, & Van den Bergh, 2010; Embrechts, Ebben, Franke, & van de Poel, 2000; Kefalianos, Onslow, Ukoumunne, Block, & Reilly, 2017). Few studies have found evidence of externalizing difficulties such as inattention, hyperactivity-impulsivity, and poorer self-regulation in children who stutter during the preschool-age period (Anderson, Pellowski, Conture, & Kelly, 2003; Eggers, De Nil, & Van den Bergh, 2009; Embrechts et al., 2000; Karrass et al., 2006). The second hypothesis (i.e. second direction) in the literature is that stuttering may contribute to behavioral difficulties and shape temperamental traits. Researchers have investigated the association between stuttering and children's later behavioral difficulties and temperament traits at school-age. Limited studies have found that school-age children who stutter experience greater emotional reactivity in later life, such as frustration or hyperactivity-impulsivity, and more regulation problems than their fluently speaking peers (Ambrose et al., 2015; Blomgren, 2013). Furthermore, stuttering appeared to be associated with a risk of developing internalizing problems with increasing age (McAllister, 2016). School-age children who stutter have been shown to exhibit internalizing problems of increased sensitivity, vulnerability, and negative attitudes towards speech (De Nil & Brutten, 1991; Fowlie & Cooper, 1978). These issues may be linked to the occurrence of stuttering moments. As children grow older, they often develop a negative attitude toward speech, which can continue even when stuttering moments are no longer present. These attitudes often impact their communication skills and social activities (e.g. speaking in a group). However, the cross-sectional design of several studies with measurements at only one point in time, did not allow for conclusions to be drawn about the (first or second) directionality of the relationship (Donaher & Richels, 2012; Iverach et al., 2017). Thus, behavior and temperament may be associated with the onset and development of stuttering, while stuttering may in turn (also) contribute to or exacerbate psychosocial problems. Identifying the bidirectionally of this relationship in childhood may contribute to knowledge of risk factors for stuttering, and may help to optimize early intervention strategies for children who stutter. To date, only limited large population-based research has examined the association between behavior and temperament and childhood stuttering (Kefalianos, Onslow, Packman, et al., 2017; Kefalianos, Onslow, Ukoumunne, et al., 2017; Reilly et al., 2013). This thesis addresses this gap.

## 2.3 Perspectives on brain development

The exact neural mechanisms underlying childhood stuttering remain unclear. Gaining insight into the neurological processes involved in speech production is essential for clarifying the mechanisms that support fluent and dysfluent speech.

### 2.3.1 Development of speech production

The development of speech production is a complex process involving physiological and neurological mechanisms. Beginning in the first year of life, babbling forms the foundation for spoken language. Sound waves enter the ear, stimulating hair cells in the cochlea, which convert them into electrical impulses. These impulses travel via the auditory nerve to the brainstem and auditory motor cortex (i.e. the central nervous system) for sound perception. Hearing speech triggers a verbal response, activating cranial nerves that control the vocal tract, including mouth, tongue, lips, and facial muscles (i.e. the peripheral nervous system). By age one, a child can intentionally produce speech sounds, which, alongside sufficient hearing and cognitive ability, leads to the development of communication. Producing speech requires precise coordination in rhythm and time of numerous muscles, and depends on a widely distributed neural network (see Guenther (2016) for an overview of functions of these regions of speech). Cortical regions such as the primary motor cortex, premotor cortex, and inferior frontal gyrus (Broca's area) are essential for planning and executing speech movements (Chang & Zhu, 2013). The superior temporal gyrus and auditory cortex support speech perception and feedback (Chow & Chang, 2017). Subcortical structures, including the basal ganglia and thalamus, play important roles in regulating smooth speech motor control and contribute to the timing and rhythm of speech (Bohland & Guenther, 2006; Grahn, 2012). The cerebellum plays a role in fine-tuning coordination (Garnett et al., 2018). Achieving speech fluency involves both auditory and somatosensory feedback (e.g., detect and correct errors) and feedforward control (e.g., memory and sound reproduction) (Levelt, 1993; Tourville & Guenther, 2011). These feedback and feedforward control loops continuously compare produced speech with the intended target sound. Given this complex process, it is surprising that speech is usually fluent, and dysfluency remains relatively rare.

### 2.3.2 Pediatric neuroimaging studies

Over the past two decades, neuroimaging studies have significantly advanced pediatric neuroscience, particularly with the increased use of child-friendly Magnetic Resonance

Imaging (MRI). With regard to speech, research has shown that brain regions involved in speech production develop rapidly during childhood due to learning, growth, and auditory feedback (Guenther, 2016; Lenroot & Giedd, 2006). While both hemispheres contribute, the left hemisphere is typically dominant in speech processing in most cases (Dorsaint-Pierre et al., 2006). In relation to stuttering, limited structural and functional neuroimaging studies have focused on children, as scanning was long considered too intrusive due to anxiety, movement, noise, and scan duration (Etchell, Civier, Ballard, & Sowman, 2018). More recently, child-friendly procedures, such as mock sessions (simulating the scan), shorter scans, and audiovisual distractions, have enabled more reliable assessments of pediatric populations. These improvements, together with enhanced imaging techniques and quality control (e.g. MRI artefacts, subject movement) have contributed to better results (White et al., 2013).

Evidence suggests a neurobiological component in childhood stuttering, highlighting (micro-)structural abnormalities (e.g. cortical and subcortical gray matter morphometry, white matter tracts, diffusivity) and reduced functional connectivity (e.g. activity patterns, connectivity between regions) in brain regions associated with speech (Etchell et al., 2018). A common finding across structural studies is differences in the left hemisphere speech network. In cortical gray matter structures, smaller volume and thinner cortex were reported in children who stutter compared to fluent peers (Beal, Gracco, Brettschneider, Kroll, & De Nil, 2013; Garnett et al., 2018). Smaller gray matter volumes and thinner cortex in the right frontal lobe have also been previously reported (Beal et al., 2013). In subcortical structures, smaller volumes in the basal ganglia were observed in children who stutter (Beal et al., 2013; Foundas, Mock, Cindass, & Corey, 2013). Focusing on white matter microstructures measured with Diffusion Tensor Imaging (DTI), differences in neurodevelopmental trajectories were observed between children who recovered from stuttering and those who persisted (Chow & Chang, 2017). Children who recovered showed normalized white matter growth with age, whereas those who persisted showed a reduction in growth rate.

Overall, most literature on childhood stuttering has examined brain (micro-)structures years after the onset, covering broad age ranges (3-10 years or 6-13 years) with small sample sizes (only one study included more than 30 participants per group). Few studies have stratified children into persistent and recovered stuttering groups (Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008). Most studies used cross-sectional designs and recruited children from clinical settings, often focusing on the

most severely affected children. This highlights the need for larger longitudinal studies to investigate the neuroanatomical origins of childhood stuttering, especially in pediatric population. Identifying brain structures involved in stuttering may lead to opportunities for neuroscience-informed therapies.

# 3. Treatment in childhood stuttering

## 3.1 Early intervention

In the Netherlands, the barrier to seeking help for a stuttering in childhood is low due to the widespread availability of SLPs specialized in stuttering and coverage under basic health insurance. The evaluation of speech (dys)fluency in preschool-age children includes, among others, an analysis of the stuttering severity and the impact of stuttering on child and parent. For children under 4.5 years of age who have begun stuttering within the last 6 months, the SLP should monitor the potential of natural recovery (NVLF, 2020). It is generally recommended to start treatment within 9 to 12 months after parents and their child first notice stuttering, if there are no signs of significant improvement in speech fluency. However, when the child's stuttering causes a serious burden in parents or child, or in case of serious risk factors for persistent stuttering, treatment should not be delayed. The Dutch guideline recommends two treatment strategies: either indirect treatment (Demands and Capacities Model) or direct treatment (Lidcombe Program, LP) (de Sonneville-Koedoot et al., 2015; Donaghy & Smith, 2016; NVLF, 2020; Onslow & O'Brian, 2013).

In the eighties and nineties of the previous century, DCM-based treatment was the standard treatment for young children who stuttered in Europe and the United States. DCM-based treatment does not target fluent and dysfluent speech directly, but this treatment approach aims to achieve a favorable balance by lowering environmental and internal demands, and strengthening the child's capacities to speak fluently (e.g., the child's speech motor skills, word finding capacity, emotional self-regulation skills) (Franken, Laroes, van Ormondt, de Smit, & Stipdonk, 2025). Demands can come from the child him- or herself (e.g., advanced language, emotional reactive and slow self-regulatory capacity), and from the environment (e.g., little opportunity for the child to initiate a speaking turn, high cognitive-linguistic level of questioning, conflicting temperaments in the family, "demand" speech), mostly unconsciously. In the early 2000s, LP was introduced in Europa, were it had already been the standard treatment for preschool-age children who stutter in Australia. It is a behavioral treatment for the child, based on the assumption that

verbal contingencies provided by parents (or teachers) for fluent and dysfluent speech are the mechanisms that increase fluent speech and decreasing stuttering (Onslow, Menzies, & Packman, 2001; Onslow, Packman, & Harrison, 2003). LP has demonstrated efficacy, however, the specific components in this treatment responsible for reducing stuttering in childhood are not fully understood (Donaghy et al., 2015).

In daily practice, SLPs participate in shared decision-making with parents to determine whether a child should receive treatment and which method to apply. They also decide, based on their observations and experiences, how long treatment may be delayed to monitor the possibility of natural recovery. Early intervention is important because moderate or severe stuttering can lead to avoidance and compensatory behavior. The longer the stuttering persists, the stronger the neural pathways for these speech patterns, reducing the likelihood of recovery. Although treatment can start later, it is less effective in older individuals, with a higher change of relapse (Kohmascher et al., 2023; Laiho et al., 2022). Stuttering treatment for children aged 7 years and older, as well as young adolescents, is primarily based on the International Classification of Functioning Disability and Health (ICF)-model (NVLF, 2020). This model assesses how stuttering affects a child's daily activities and participation. If such impacts are identified, the focus shifts to addressing the emotional, cognitive, social, and speech motor aspects of stuttering.

### 3.2 Effect of intervention

Although most children recover from stuttering before the age of 9, it remains unclear whether early intervention facilitates recovery or accelerates the 'natural' or 'spontaneous' recovery process. When early intervention was introduced, experimental research comparing its effect with the natural course of childhood stuttering over a 2 to 3 year period was not conducted. Such a study is now considered unethical because treatment has been shown to be effective when compared with a (9 months) no treatment condition (Jones et al., 2005).

## 4. Aim and objectives of this thesis

This thesis aims to improve knowledge of the origin and development of childhood stuttering. More specifically, the objectives of this thesis are:

1. To examine the recovery rate and explore the speaking experiences of children who recovered from stuttering compared to those who persisted, in a clinical sample.

2. To examine the association between language skills and behavioral development with childhood stuttering and its developmental course, and to define the direction of these associations in a population-based study.
3. To explore (micro-)structural brain differences among children who stutter, comparing those who recovered, those who persisted, and fluently speaking peers.

## 5. Study design

The research presented in this thesis aims to provide insights into childhood stuttering, spanning from daily clinical practice to population-based research, and vice versa. It was conducted within four contexts; two clinical studies and one population-based birth cohort in the Netherlands, and one longitudinal neuroimaging study in the United States of America (USA).

The first clinical study was embedded in a prospective clinical cohort study with collaboration from several general practitioners and SLPs in and around Rotterdam. This study included 18 children whose parents consulted a SLP for the first time for reasons of stuttering. The children were followed for 9 years. The second clinical multicenter study was performed with 5 or more years post-treatment data of the RESTART randomized trial (the Rotterdam Evaluation study of Stuttering Therapy in preschool-age children: A Randomized Trial) (de Sonneville-Koedoot et al., 2015). This study originally included 199 preschool-age children who stutter who received indirect (DCM-based) or direct (Lidcombe Program) treatment.

Population-based research within this thesis was embedded in The Generation R (Rotterdam) Study, a prospective population-based birth cohort from fetal life onwards, situated in Rotterdam (Kooijman et al., 2016). The Generation R Study was designed to identify early environmental and genetic causes of children's growth, development, and health. Pregnant women living in Rotterdam with expected delivery were invited to participate. After birth, 9901 parents reported repeatedly on several aspects of their children's development by postal questionnaires. From ages 5 years onwards, parents and children visited the research center where a range of physical and behavioral examinations, and brain imaging were collected. This study included 145 children with stuttering and more than 3200 children without stuttering.

Finally, a pediatric longitudinal neuroimaging study was performed using data from the Speech Neurophysiology Lab, situated in Ann Arbor and East Lansing, Michigan

USA. This is the largest research institute on neural bases of childhood stuttering, in a pediatric combined clinical- and population-based neuroimaging study of fluent and dysfluent speech. This study originally included 190 children aged 3 to 12 years old with and without stuttering and was focused on their brain development (Garnett et al., 2018).

## 6. Outline of this thesis

This thesis is divided into three parts.

### Part I. Childhood stuttering in clinical practice

In **Chapter 2**, children aged 4-5 years were followed for 9 years. Children's recovery rates were assessed based on parental and expert judgements, as well as children's self-reports, which were considered for the first time in the literature. Additionally, children's subjective experience with speech fluency and dysfluency were observed. **Chapter 3** presents the first outcomes of longitudinal parental ratings of speech fluency 5 or more years post-treatment in a randomized trial comparing LP and DCM-based treatments for stuttering. It also examines long-term speech fluency by children, SLPs and teachers, communication satisfaction, and children's overall assessment of speech (dys)fluency experiences (OASES).

### Part II. Childhood stuttering in population-based research

The Generation R Study offers a unique opportunity to explore early and late factors associated with childhood stuttering. **Chapter 4** examines early (expressive and receptive) language skills between 1.5 and 4 years of age as predictors of stuttering onset and its developmental course. **Chapter 5** explores the bidirectional relationship between behavior difficulties and temperament traits in childhood stuttering. It examines whether early behavioral and temperamental characteristics (between 0.5 and 4 years) may contribute to the onset and persistence of stuttering, while also considering how stuttering may influence the development of behavior and temperament in later years (between 5 and 9 years).

### Part III. Childhood stuttering and brain development

The Generation R neuroimaging subset study allowed us to explore the association between childhood stuttering and speech motor and auditory brain structures. **Chapter**

**6** examines cortical and subcortical gray matter structures in children with and those without stuttering, aged 5 to 9 years. **Chapter 7** focuses on gray matter and white matter microstructure brain differences among children who persisted in stuttering, those who recovered, and fluently speaking peers, aged 9 to 12 years. Finally, **Chapter 8** uses longitudinal neuroimaging data from the Speech Neurophysiology Lab in Michigan to examine both gray and white matter volume and trajectories over time. This relates and extents to earlier chapters, as it explores differences in brain development trajectory in children (aged 3 to 12 years) who recovered or persisted in stuttering, compared to fluent speaking peers.

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*“Your self-worth is determined by you.*
*You don’t have to depend on someone telling you who you are.”*
Beyoncé

# PART I

Childhood stuttering in clinical practice


White matter
Persistent
Fluency
Speech
Research
Recov
Brain
Gray matter
Neuroimaging
Cortical
Girls
Children
Stutter
Explore
Population
Temperament
Dysfluency
Fluency
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Outcome
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Long-term
Behavior
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Satisfaction
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Subcortical
Girls
Rotterdam
Self-report
Persistent
Stutter
Boys
Cortical
Speech-motor


# 2

# Recovery from stuttering in preschool-age children: 9 year outcomes in a clinical population

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*Equal contribution

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## Abstract

**Purpose:** The first purpose was to define the recovery rate in children who stutter in a clinical sample, adding self-report to validate recovery status. The second purpose was to explore whether children who were judged to be recovered showed subjective experiences that might be interpreted as coping behaviors used to control speech fluency.

**Methods:** In this longitudinal study, preschool-age children whose parents consulted a speech-language pathologist about stuttering were followed for 9 years. At follow-up, children's self-reports on stuttering were reported, as well as traditional criteria on recovery (parental and expert judgement). The Overall Assessment of the Speaker's Experience of Stuttering (OASES) was used to collect children's experiences with speaking.

**Results:** Eleven of the 15 children (73%) were judged by parents and clinicians to have recovered from stuttering. However, when considering children's self-reports, 9 children (60%) might be considered to have recovered. In addition, 3 children who were judged to be recovered reported experiences with speaking that were uncommon, even compared to children who continued to stutter.

**Conclusion:** In this exploratory study of a clinical population, the recovery rate in children that received treatment for stuttering appeared to be comparable to a non-clinical population. Considering self-reports can improve validity of assessing the "recovery rate". Moreover, recovery in children may not be effortless; instead, it may be the result of conscious or unconscious coping behavior. Future studies are recommended to consider self-reports to improve validity of recovery, and to document experiences with speaking to explore effortless, spontaneous fluency versus controlled fluency.

# 1. Introduction

Approximately 74-80% of children who start to stutter recover "naturally" or "spontaneously", that is, unassisted by treatment. These high percentages are based on longitudinal population studies and community studies with assessments of children identified and followed for 1 to 5 years without receiving therapy for stuttering (Andrews & Harris, 1964; Panelli, McFarlane, & Shipley, 1978; Yairi & Ambrose, 1999; Yairi & Ambrose, 2005). Interestingly, comparable recovery percentages (65-82%) are reported in studies where children did receive stuttering therapy, irrespective of treatment intensity (Dworzynski, Remington, Rijsdijk, Howell, & Plomin, 2007; Kefalianos et al., 2017; Kloth, Kraaimaat, Janssen, & Brutten, 1999; Månsson, 2000; Rommel, Häge, Kalehne, & Johannsen, 1999; Yairi & Ambrose, 1992).

However, due to case selection, a lower percentage of recovery from stuttering might be suspected in a clinical population compared to a non-clinical population. Among other reasons, time since onset may have surpassed a certain term, stuttering may have worsened, or stuttering may appear abnormally severe (Ingham & Cordes, 1999). There are only a few clinical longitudinal studies investigating the outcomes of children who stutter (Jones et al., 2008; Ramig, 1993; Ryan, 2001); these studies reported notably large variations in reported baseline characteristics, treatment modality, time since onset, follow-up time and outcome measures.

Classifying children as persistent or recovered is not as straightforward as it might seem. One might seriously question whether the expert rating percentage of syllables stuttered (%SS) based on one single telephone call interview, as in the study by Jones et al. (2008) can be considered a valid outcome measure to assess recovery from stuttering. Other studies have classified children who stutter as persistent or recovered based only on the judgement of parents (Dworzynski et al., 2007; Kloth et al., 1999). A recognized and common flaw to parental reporting is underestimating stuttering behaviors because parents grow accustomed to it. At the same time, parental judgement of disfluencies has been recognized as important because stuttering is likely to be episodic in nature; it may appear for a few months, disappear for a few days and reappear (Bloodstein & Bernstein Ratner, 2008; Guitar, 2016; Kloth et al., 1999). Judgements made by an examiner at a single time point cannot account for these variations. Other studies used a combination of a parental judgement and expert judgement (e.g. based on the percentage stuttering-like disfluencies; %SLD; see Yairi and Ambrose (2005)). Again, however, the severity of

stuttering may vary on a day-to-day basis (Constantino, Leslie, Quesal, & Yaruss, 2016) and be associated with the speaking situation at hand (Yaruss, 1997), for example talking to an unfamiliar person. Even 3 speech samples of 15 minutes may not be sufficient to capture stuttering given the fact that its high variable.

Traditionally, studies on recovery from stuttering and persistency of stuttering in young children do not include self-reports (Dworzynski et al., 2007; Howell, Davis, & Williams, 2008; Kloth et al., 1999; Månsson, 2000; Yairi & Ambrose, 2005). Including children's self-report on the fluency of their speaking may contribute to the validity of this outcome measure, if children are old enough to report on this (de Sonneville-Koedoot, Stolk, Rietveld, & Franken, 2015). To the knowledge of the authors of the current study, so far, children's self-reports have not been included in the criteria to decide about recovery or persistency status in childhood stuttering.

Children who were diagnosed as stuttering while in the preschool years who later self-reported that they no longer stuttered may have different subjective experiences with speaking than other children who also feel they recovered from stuttering. They may also have different experiences compared to children who never stuttered. Moreover, recent writing has highlighted the importance of assessing children's reaction to speaking and the impact their speaking ability has on their daily living (Finn, Howard, & Kubala, 2005; Guntupalli, Kalinowski, & Saltuklaroglu, 2006; Ingham & Cordes, 1997). It has been found that stuttering in children and adults can lead to negative emotional or cognitive reactions and interfere with daily communication. Stuttering can also negatively impact quality of life (QOL) domains in vitality, social functioning, emotional functioning and mental health (Chun, Mendes, Yaruss, & Quesal, 2010; Craig, 2010; Craig, Blumgart, & Tran, 2009; Davis, Howell, & Cooke, 2002; Klompas & Ross, 2004; Koedoot, Bouwmans, Franken, & Stolk, 2011).

In this study, we present clinical data for children whose parents first consulted a speech-language pathologist for reasons of stuttering while the children were in the preschool years. These children, who received treatment for stuttering, were followed for 9 years. We aimed to explore and document: (1) the recovery rate of stuttering in children in a clinical population based on traditional outcome measures (parental and expert judgement); (2) the recovery rate of stuttering considering children's self-report; and (3) the subjective experiences of the children judged to be recovered, specifically, whether they report experiences that might be interpreted as coping behavior to control speech fluency.

# 2. Material and methods

## 2.1 Participants

A prospective clinical study was organized by the Speech and Hearing department of the Erasmus University Medical Center in Rotterdam, the Netherlands. This department asked speech centers and speech-language pathologists in and around the city Rotterdam to invite parents on their caseload to participate in this study. Preschool-age children were included if their parents were concerned that the child was stuttering and, for that reason, consulted a speech-language pathologist for the first time. All children were native speakers of the Dutch language. None of the children had received any treatment for stuttering prior to participation. Also, children had no known or reported neurological, intellectual, or psychosomatic problems. All parents provided written informed consent.

## 2.2 Study design

Data were collected at three time points: at baseline (t=0) in 2004-2005; at the first follow-up 5-6 years after inclusion (t=1) in 2010; and at the second follow-up, 9 years after inclusion (t=2) in 2014 (Table 1 and Figure 1). The follow-up time periods were to longitudinally assess the trajectories of the children's stuttering.

Table 1. Timetable of measurements

| | **First visit in 2004 or 2005 (t=0)** | **1st follow up in 2010 (t=1)*** | **2nd follow up in 2014 (t=2)** |
|---|---|---|---|
| Parental questionnaire | ● | ● | ● |
| Speech sample | ● | ● | ○ |
| Reading sample | ○ | ● | ○ |
| Children's self-rating | ○ | ● | ● |
| OASES questionnaire | ○ | ○ | ● |

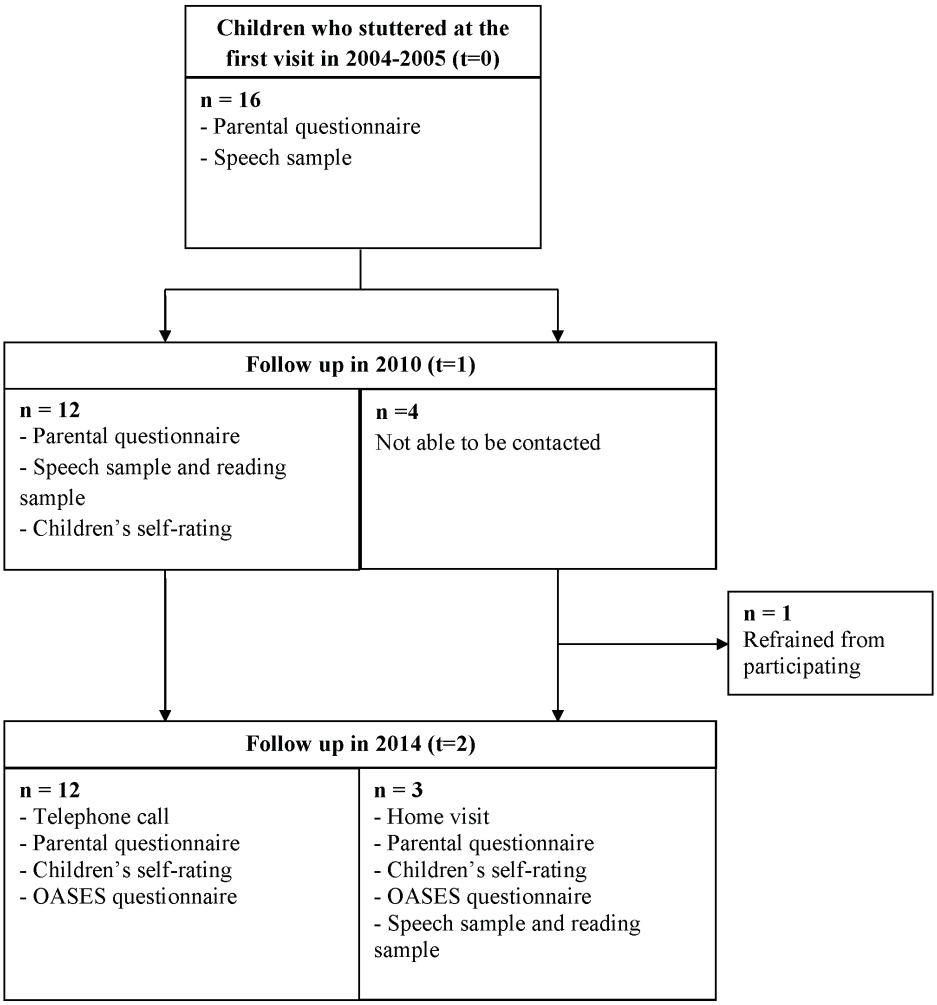
t = time period; OASES = Overall Assessment of the Speaker's Experience of Stuttering.
* Cases 3, 5 and 15 had the first follow-up in 2014 (t=2)

At baseline (t=0), children and their parents visited a speech-language-researcher at the Erasmus Medical Center two times, with visits scheduled two weeks apart from one another. The visits consisted of questionnaires, to clarify the characteristics of the stuttering, onset conditions, medical history, and to elicit detailed family history of stuttering, and two parent-child interaction sessions. After the children were judged to meet inclusion criteria for the study, the referring speech-language pathologist provided

treatment based on the needs of the individual child. Hence, the children were treated in different speech centers with varying methods, duration and intensity in speech therapy.

At the first follow-up (t=1), researchers collected parental and child questionnaires and video-recorded conversational interactions between the parent and child and between the speech-language researcher and child, as well as a reading a passage. Speech samples obtained from these interactions were used for the expert fluency evaluation. All children and their parents were approached by telephone and were asked to complete these follow-up reports.

Figure 1. Flowchart of the study design




n = number; OASES = Overall Assessment of the Speaker's Experience of Stuttering.

The second follow-up (t=2) followed the same procedure as for t=1 and consisted of telephone calls and questionnaires. Three children (participants 3, 5, and 15) could not be contacted at t=1, so their first follow-up visit was conducted at t=2. For these children, home visits were completed to record speech samples. All visits and follow-up data were administered by an independent speech-language-researcher from the Erasmus Medical Center.

## 2.3 Fluency evaluation

### 2.3.1 Speech samples

At baseline, two parent-child interaction sessions were video-recorded in the Erasmus Medical Center in an acoustic treatment room with a one-way screen. These recordings were considered most likely to elicit spontaneous speech of the children. This interaction situation lasted approximately 60 minutes in total (2 samples of 30 minutes per sample). The follow-up speech recordings included a conversational session between parent and child, an interview of the child by the researcher, and a reading passage by the child. Twelve children were assessed in the Erasmus Medical Center at t=1, and three children in their home environment at t=2.

### 2.3.2 Expert ratings

The first 500 syllables of each recorded sample (2 samples per child) were transcribed orthographically (Yairi & Ambrose, 2005). Speech samples were coded and identified by a trained speech-language pathologist. For these samples, the following rates were computed: the percentage of syllables stuttered (SS), the Stuttering Severity Instrument, 4$^{th}$ Edition (SSI-4) (Riley, 2009), the percentage of stuttering like disfluencies (SLD), the weighted SLD score (Yairi & Ambrose, 2005), and the sound prolongation index (SPI) (Schwartz & Conture, 1988). The SSI-4 score is a widely used assessment of stuttering severity based on stuttering frequency, duration, and physical concomitant behaviors. The weighted SLD represents the severity of SLD. SPI is the proportion of the total number of stuttered disruptions that are judged to be sound prolongations. A higher SPI relates to judgements of more severe stuttering (Yaruss, LaSalle, & Conture, 1998).

All children were confirmed as stuttering at the baseline visit (t=0) by speech-language pathologists. A child was scored as "a child who stutters" if they exhibited 3 or more SLDs per 100 syllables (SLD≥3.0%) (Yairi & Ambrose, 1999) or if their SSI-4 score was 9 or higher (SSI≥9).

### 2.3.3 Parental judgement

Parents judged their child's speech fluency using a qualitative rating scale of stuttering severity (Yairi & Ambrose, 1999), ranging from 0 ("normally fluent, no stuttering"), 1 ("borderline stuttering") to 7 ("very severe stuttering"). This outcome measure was scored by the parents at baseline and at long-term follow-up. A child was scored as "stuttering" if the parent rating score was 2 or higher (2= "mild stuttering").

### 2.3.4 Children's self-report

Children were asked to classify their fluency of speaking at the first (t=1) and second follow-up (t=2) visits. A categorical 4-point stuttering scale was used: 0 ("I do not stutter (any more)"), 1 ("I (still) stutter a bit"), 2 ("I (still) stutter moderately"), and 3 ("I (still) stutter a lot") (de Sonneville-Koedoot et al., 2015). A participant was scored as "stuttering" if the rating was 1 or higher.

## 2.4 Overall Assessment of the Speaker's Experience of Stuttering (OASES)

The speakers' experiences with speaking were collected at the second follow-up (t=2) using the Overall Assessment of the Speaker's Experience of Stuttering (OASES) questionnaire. This self-reported outcome measure was designed to provide an assessment of the experience of stuttering and the impact of stuttering from the perception of the individual who stutters (Yaruss & Quesal, 2006, 2010/2016). Two age-specific versions of the questionnaire have been developed for children: one for school-aged children (OASES-S for ages 7-12; 60 questions) (Lankman, Yaruss, & Franken, 2015; Yaruss, Coleman, & Quesal, 2010); and one for teenagers (OASES-T for ages 13-17; 80 questions). Unlike the OASES-S version, the OASES-T was not validated in Dutch, but it has been validated in English (Yaruss & Quesal, 2010/2016) and was translated according to the same validated procedure. The OASES consists of 4 sections: Section I (General information) measures the speaker's self-assessment of their impairment and knowledge of stuttering disorders. Section II (Reactions to stuttering) measures the speaker's affective, behavioral, and cognitive reactions to stuttering. Section III (Communication in daily situations) measures the difficulties experienced by speaker in communicative situations. Section IV (QOL) measures the overall impact of stuttering. Questions are scored on a Likert-type scale from 1-5 and are used to calculate the impact rating per section. Impact ratings provide an indication of the severity by dividing the scores into 5 severity groups; mild

(score 1.00–1.49), mild-to-moderate (score 1.50–2.24), moderate (score 2.25–2.99), moderate-to-severe (score 3.00–3.74), and severe (score 3.75–5.00). Higher score on the OASES questionnaire indicates a higher negative impact. All outcomes are scored as at least mild, because the minimum score is 1 for every question. Because we compared all children using the same rating, however, this did not influence the results.

If children considered themselves to be stuttering based on their self-report, they received the OASES-S or OASES-T, depending on their age. If they considered themselves to not be stuttering, they received a non-validated, slightly adapted version of the OASES for speakers who do not stutter. This adaptation replaced the word "stuttering" with "speaking ability" and omitted certain ambiguous items (e.g. "How do you feel about being a person who stutters" and "I do not want people to know that I stutter"). Similar adaptations have been used in other studies to provide an indication of the experiences of people who do not stutter (Lankman et al., 2015; Mulcahy, Hennessey, Beilby, & Byrnes, 2008); using the scoring procedure outlined by Yaruss and Quesal (2006). The mean of scores for each section was calculated by total sum divided by the number of items answered.

## 2.5 Criteria on recovery from stuttering

### 2.5.1 Traditional criteria

Consistent with criteria described by Yairi & Ambrose (1999) and Conture (2001), children were classified as still stuttering at follow-up (t=1, t=2) if they met at least one of the following criteria: (1) the number of SLD was 3 or more per 100 syllables (SLD≥3.0%), (2) the SSI-4 score was 9 or higher (SSI≥9), or (3) the parental rating was higher than 1. As can be seen, this classification combines parents' reports with expert judgements (Conture, 2001; Jones et al., 2008; Yairi & Ambrose, 1999).

### 2.5.2 Extended criteria

In addition to the traditional criteria, self-reports about stuttering or recovery were also collected from the children themselves. Children were classified as still stuttering at follow-up (t=1, t=2) if they met any of the traditional criteria or if their own self-rating of stuttering was higher than 0. We assumed that children between the ages of 12 and 15 years were able to use the rating and that they had knowledge about their own experiences of speech fluency.

## 2.6 Statistics

Descriptive statistics are reported in Tables as absolute numbers and proportions. Because of the small sample size, no inferential statistical analyses were completed.

# 3. Results

## 3.1 Participants

At baseline (t=0), 16 preschool-age children were enrolled in the study (median age = 3 years and 9 months; range 2;9 to 5;0 years) (see Table 2). The parents of these 16 children had consulted a speech-language pathologist for the first time because they were concerned that their child was stuttering. As can be seen in Table 3, all children were confirmed as stuttering by speech-language researcher.

Table 2 displays all 16 participants' characteristics including age at onset of stuttering, sex, handedness, and family history of stuttering. The median age of stuttering onset was 3;1 years (range: 2;0 to 4;5 years); 10 children (63%) were boys and 10 children (63%) were right-handed. Eleven of the 16 children (69%) had a positive family history of stuttering: 8 children (50%) had at least one person of recovered stuttering in their family, and 3 children (19%) had at least one person with persistent stuttering in their family. The median time for the first visit since onset of stuttering was 7 months (range: 3 to 15 months). Fourteen children (88%) received treatment for stuttering after the first visit. The period of treatment for children ranged between 1 month and 6 years. The median time period of stuttering after onset of stuttering in children who recovered was 15 months (range: 6 to 36 months), and the median age that parents reported that their children had recovered was 4 years and 5 months (range: 3;1 to 6;6 years).

Fifteen of the 16 included children could be followed up for the full 9 years covered in this study. One child dropped out of the study, but at t=2, the child's mother reported by phone that the child was generally speaking fluently, but stuttered "sometimes, in periods of more stress." Figure 1 and Table 1 display a summary of the 15 children who participated in the full study, including a list of the measurements per time period.

Table 2. Baseline characteristics per participant

| Child | Gender | Handedness | Age at onset of stuttering[1] | Age at baseline[1] (t=0) | Age at 1st follow up[1] (t=1) | Time period from onset to 1st visit[2] | Speech therapy | Age at start therapy[1] | Time period of speech therapy[2] | Duration of speech therapy[3] | Duration of stuttering[2] | Family history of stuttering | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | Recovered | Persistent |
| **1** | boy | both | 4;5 | 5;0 | 11;1 | 7 | yes | ± 6 | few | - | - | brother, mother | no |
| **2** | boy | right | 2;3 | 3;1 | 9;5 | 11 | yes | - | 1 | 60 | 21 | no | no |
| **3** | boy | right | 2;3 | 3;0 | 13;3 | 3 | yes | ± 3 | 36 | 60 | 36 | mother, brother of mother | no |
| **4** | girl | right | 4;0 | 4;9 | 10;8 | 9 | yes | ± 4 | 12 | - | 6 | no | father |
| **5** | girl | right | 3;7 | 4;8 | 14;9 | 12 | yes | ± 3 | 30 | 30 | 15 | father | no |
| **6** | girl | right | 3;0 | 3;6 | 9;4 | 6 | yes | ± 3;6 | 6 | 60 | 12 | cousin of mother | no |
| **7** | girl | both | 3;2 | 3;8 | 9;3 | 6 | yes | - | 12 | 15 | 15 | no | no |
| **8** | boy | right | 2;7 | 3;9 | 9;0 | 14 | yes | ± 4 | 6 | - | 6 | no | no |
| **9** | boy | right | 3;3 | 4;5 | 9;8 | 15 | yes | ± 2;6 | 72 | 60 | - | sister | no |
| **10** | boy | both | 3;11 | 4;5 | 9;8 | 6 | yes | - | 12 | 20 | - | aunt of father | no |
| **11** | boy | right | 2;0 | 3;7 | 8;7 | 7 | yes | ± 4 | 45 | 30 | - | aunt of mother, uncle of father | no |
| **12** | girl | right | 2;6 | 2;9 | 7;8 | 3 | yes | ± 2 | 12 | 30 | 12 | brother, mother, mother of mother, brother of mother | no |
| **13** | boy | right | 3;6 | 3;10 | 8;7 | 4 | no | - | 0 | - | 36 | no | father |
| **14** | boy | left | 3;2 | 3;10 | 8;4 | 8 | yes | - | 0.5 | 60 | - | no | sister of mother |
| **15** | boy | both | 2;10 | 3;5 | 11;10 | 7 | yes | - | 1.5 | 60 | - | - | no |
| **16** | girl | - | 2;6 | 4;6 | - | 12 | - | - | - | - | - | no | no |

[1] age in years;months, [2] duration in months, [3] minutes per week

## 3.2 Expert ratings of fluency

Descriptive statistics of the expert outcomes for the 15 children are shown in Table 3. At baseline, the median percentage of SLD was 5.6 (range: 1.1 to 11.9), and the median weighted SLD score was 10.8 (range: 1.1 to 41.7). The median total SSI-4 was 17 (range: 6 to 27).

At follow-up (t=1), the median percentage of SLD was 0.8 (range from 0.2 to 4.4) and the median SSI-4 score was 4 (range: 2 to 16). Regarding to the expert ratings, including the SLD and SSI-4 criterion, only three participants were considered to have continued stuttering (children 1, 9 and 14). In all children, the SSI-4 scores were lower in the follow-up condition than at baseline.

## 3.3 Judgement of recovery or persistency of stuttering

Table 4 shows each child's recovery status based on the traditional criteria and on the extended criteria. Four of the 15 parents (27%) rated their child to still be stuttering: one parent gave a rating of "moderate to severe" (score=5); two parents gave a rating of "mild to moderate" (score=3), and one gave a rating of "mild" (score=2). In addition, one parent gave a rating of "normally fluent to borderline stuttering" (score=0 to 1). Ten of the 15 parents (67%) judged their child's fluency of speech to be "normally fluent, no stuttering" (score=0). Six of the 15 children (40%) rated themselves as still stuttering. Five children reported "I (still) stutter a bit" (score=1), one child reported "I (still) stutter a lot" (score=3), and nine children reported "I do not stutter (anymore)" (score=0).

According to traditional criteria of recovery, 11 children (73%) were judged to have recovered from stuttering. Using the extended criteria, which adds children's self-report, 9 children (60%) were judged to have recovered from stuttering.

Table 3. Descriptives on speech samples

| Child | Baseline | | | | | | Follow up | | |
|---|---|---|---|---|---|---|---|---|---|
| | Parental judgement (score 0-7) | Frequency of dysfluency (% SLD) | Severity of dysfluency (weighted SLD) | Severity of stuttering (SSI-3, score) | Percentage SS (%) | Risk factor SPI (%) | Parental judgement (score 0-7) | Frequency of dysfluency (% SLD) | Severity of stuttering (SSI-3, score) |
| **1** | 5 | 4.1 | 6.4 | 14 | 3.4 | 46.3 | 5 | 0.8 | 9 |
| **2** | 5 | 11.5 | 41.7 | 25 | 10.3 | 9.6 | 0 | 1.2 | 6 |
| **3** | 3 | 11.9 | 17.3 | 26 | 8.5 | 22.2 | 0 | 0.2 | 4 |
| **4** | 5 | 10.9 | 17.8 | 23 | 9.3 | 9.2 | 0 | 0.4 | 4 |
| **5** | 5 | 1.1 | 1.1 | 6 | 0.5 | 0 | 0 | 0.8 | 4 |
| **6** | 6 | 5 | 6.9 | 14 | 3.0 | 10 | 0-1 | 0.7 | 2 |
| **7** | 3 | 3 | 4.8 | n/a | n/a | 16.7 | 0 | 0.8 | 4 |
| **8** | 4 | 6.7 | 14 | 18 | 5.4 | 6 | 0 | 0.7 | 4 |
| **9** | 4 | 6.9 | 10.8 | 20 | 5.6 | 27.5 | 3 | 4.4 | 16 |
| **10** | 2 | 2.9 | 3.7 | 10 | 2.2 | 13.8 | 3 | 1.6 | 7 |
| **11** | 5 | 10.2 | 20.7 | 27 | 9.6 | 70.8 | 2 | 2.1 | 6 |
| **12** | 3 | 1.7 | 2.7 | 8 | 1.4 | 41.2 | 0 | 0.3 | 2 |
| **13** | 4 | 5.6 | 11.2 | 16 | 4.8 | 14.3 | 0 | 0.5 | 2 |
| **14** | 5 | 9.3 | 16 | 18 | 7.3 | 31.2 | 0 | 2.8 | 9 |
| **15** | 4 | 2.1 | 3.3 | 10 | 1.7 | 42.9 | 0 | 0.3 | 2 |

SLD = stuttering-like disfluencies; SSI = stuttering severity instrument; SS = syllables stuttered; SPI = sound prolongation index; N/A = not applicable

Table 4. Recovery of stuttering

| Participant | Child self-assessment | | Parental judgement | | Expert judgement | | Recovered stuttering | |
|---|---|---|---|---|---|---|---|---|
| | Stuttering (yes/no) | Stuttering scale (score 0-3) | Stuttering (yes/no) | Stuttering scale (score 0-7) | SLD (%) | SSI-3 (score) | Traditional criteria | Extended criteria |
| **1** | yes | 1 | yes | 5 | 0.8 | 9 | **Stuttering** | **Stuttering** |
| **2** | no | 0 | no | 0 | 1.2 | 6 | Recovered | Recovered |
| **3** | no | 0 | no | 0 | 0.2 | 4 | Recovered | Recovered |
| **4** | no | 0 | no | 0 | 0.4 | 4 | Recovered | Recovered |
| **5** | no | 0 | no | 0 | 0.8 | 4 | Recovered | Recovered |
| **6** | no | 0 | no | 0-1* | 0.7 | 2 | Recovered | Recovered |
| **7** | no | 0 | no | 0 | 0.8 | 4 | Recovered | Recovered |
| **8** | no | 0 | no | 0 | 0.7 | 4 | Recovered | Recovered |
| **9** | yes | 1 | yes | 3 | 4.4 | 16 | **Stuttering** | **Stuttering** |
| **10** | yes | 3 | yes | 3 | 1.6 | 7 | **Stuttering** | **Stuttering** |
| **11** | yes | 1 | yes | 2 | 2.1 | 6 | **Stuttering** | **Stuttering** |
| **12** | no | 0 | no | 0 | 0.3 | 2 | Recovered | Recovered |
| **13** | no | 0 | no | 0 | 0.5 | 2 | Recovered | Recovered |
| **14** | yes | 1 | no | 0 | 2.8 | 9 | Recovered | **Stuttering** |
| **15** | yes | 1 | no | 0 | 0.3 | 2 | Recovered | **Stuttering** |

SLD = stuttering-like disfluencies; SSI = stuttering severity instrument.
* 0 - 1 is normally fluent (no stuttering) to borderline stuttering

## 3.4 OASES

Table 5 presents an overview of the OASES scores. Five of the 15 children (33%) completed the OASES-S: 2 of these 5 children considered themselves to be still stuttering and completed the original version; 1 child who considered himself to be still stuttering erroneously filled in the adapted version for nonstuttering children (child 14); 2 children who considered themselves to be recovered from stuttering completed the adapted version. Ten children (67%) completed the OASES-T: 3 of these 10 completed the original version; and 7 completed the adapted version for non-stuttering speakers.

As noted above, 6 of the 15 children reported that they were still stuttering. These children had a median overall OASES score of 1.93 (range: 1.60 to 2.67). Nine children who did not report themselves as stuttering on the children's self-report, had a median overall OASES score of 1.58 (range: 1.32 to 2.93). Both groups had an overall impact rating of "mild-to-moderate." The OASES contains 4 sub-sections. Children in both the persistent and recovered groups had an impact rating of "moderate" (score = 2.83 and 2.62) in section I. In section II, children who considered themselves to still be stuttering reported a slightly higher median impact rating ("mild-to-moderate", score = 1.94) than children who considered themselves to no longer be stuttering ("mild", score = 1.35). Likewise, in section III, children who considered themselves to still be stuttering had a higher impact rating ("mild-to-moderate", score = 2.01) than children who considered themselves to no longer be stuttering ("mild", score = 1.18). In section IV, the median impact rates were "mild" in both groups (score = 1.27 and 1.00, respectively). Looking at the overall scores on the OASES for individual children, only two of the six children who considered themselves as still stuttering experienced a "mild-to-moderate" impact of stuttering (child 10 and 15). Two of the nine children who considered themselves to be recovered reported a "moderate" to "moderate-to-severe" impact of speaking (child 4 and 5).

Figure 2 shows the subjective experiences of speaking for each section of the OASES of the 15 children who had been diagnosed as stuttering as a preschooler and years later considered themselves to be still stuttering or recovered. The impact scores of three children (child 4, 5 and 6) who considered themselves to be recovered were clearly higher in sections II, III and IV as compared to the rest of the children who had recovered. Even in comparison to the children who considered themselves to still be stuttering, their scores are relatively high. These three children experienced moderate and moderate-to-severe impact on reactions to stuttering and on communication in daily situations.

Table 5. OASES per participant

| Child | OASES Version | Recovery status (extended criteria) | Impact score per section (median impact score (range)) | | | | |
|---|---|---|---|---|---|---|---|
| | | | I | II | III | IV | Total score |
| **1** | OASES-T | **Stuttering** | 2.92^ | 1.95+ | 1.80+ | 1.32 | 1.90+ |
| **2** | OASES-T* | Recovered | 3.08# | 1.25 | 1.05 | 1.00 | 1.46 |
| **3** | OASES-T* | Recovered | 2.00+ | 1.30 | 1.15 | 1.00 | 1.32 |
| **4** | OASES-T* | Recovered | 2.77^ | 2.15+ | 3.55# | 3.25# | 2.93^ |
| **5** | OASES-T* | Recovered | 1.00 | 1.95+ | 1.58+ | 2.94^ | 1.90+ |
| **6** | OASES-T* | Recovered | 2.58^ | 2.21+ | 2.00+ | 1.25 | 1.99+ |
| **7** | OASES-T* | Recovered | 2.62^ | 1.15 | 1.18 | 1.00 | 1.41 |
| **8** | OASES-T* | Recovered | 2.36^ | 1.42 | 1.00 | 1.00 | 1.35 |
| **9** | OASES-T | **Stuttering** | 3.07# | 1.92+ | 1.95+ | 1.25 | 1.96+ |
| **10** | OASES-T | **Stuttering** | 2.73^ | 3.36# | 2.63^ | 1.74+ | 2.67^ |
| **11** | OASES-S | **Stuttering** | 3.00^ | 2.15+ | 2.47^ | 1.22 | 2.28^ |
| **12** | OASES-S* | Recovered | 3.08# | 1.29 | 1.00 | 1.00 | 1.59+ |
| **13** | OASES-S* | Recovered | 2.92^ | 1.35 | 1.36 | 1.14 | 1.73+ |
| **14** | OASES-S* | **Stuttering** | 2.55^ | 1.53+ | 1.27 | 1.00 | 1.60+ |
| **15** | OASES-S | **Stuttering** | 2.46^ | 1.40 | 2.07 | 1.56+ | 1.84+ |
| | **Overall impact score** | Recovered (n = 9) | 2.62^ (1.00-3.08) | 1.35 (1.15-2.21) | 1.18 (1.00-3.55) | 1.00 (1.00-3.25) | 1.58+ (1.32 - 2.93) |
| | | **Stuttering** (n = 6) | 2.83^ (2.46-3.07) | 1.94+ (1.40-3.36) | 2.01+ (1.27-2.63) | 1.27 (1.00-1.74) | 1.93+ (1.60 - 2.67) |

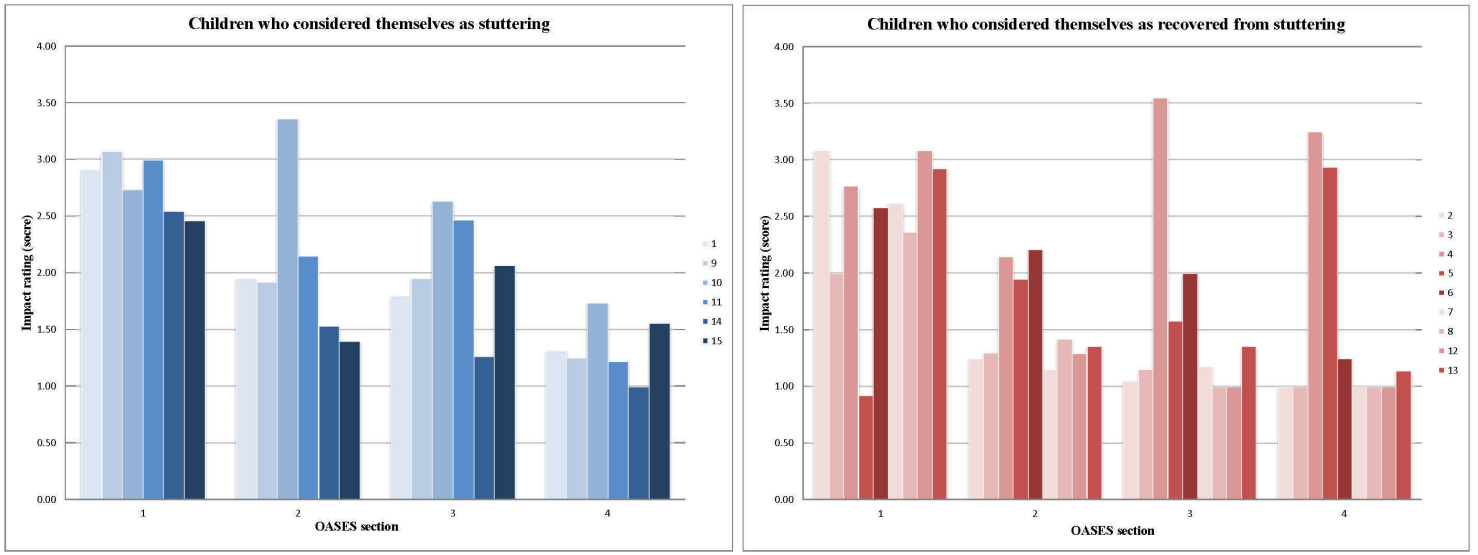
Recovered status on stuttering is following the extended criteria. OASES-S, OASES-T = Overall

Assessment of the Speaker's Experience of Stuttering for school-age children (S) or for teenagers (T); Impact ratings: mild (score 1.00–1.49), + = mild-to-moderate (score 1.50–2.24), ^ = moderate (score 2.25–2.99)^, # = moderate-to-severe (score 3.00–3.74), and severe (score 3.75–5.00).

I General information
II Reactions to stuttering or speaking
III Communication in daily situations
IV Quality of life

* Received adapted version of OASES-S or OASES-T

Figure 2. OASES subjective experiences of speaking




Recovered status on stuttering is following the extended criteria. OASES = Overall Assessment of the Speaker's Experience of Stuttering.

# 4. Discussion

Based on outcomes using parental and expert judgement (the "traditional criteria"), the current study found a recovery rate from stuttering in a clinical population of 73%. This number is comparable to reported recovery rates of stuttering children in the general population. Adding children's self-reports to the parental and expert judgements, the recovery rate in this clinical population of stuttering children dropped to 60%. Published clinical and non-clinical studies might have also found a lower occurrence of recovery from stuttering if they had considered children's self-reports. Moreover, 3 of the 9 children (33%) children who considered themselves to be recovered from stuttering acknowledged experiences with speaking that appear to point to a lack of spontaneous fluency. Thus, adding children's self-report to the criteria for determining on recovery status may improve the definition of recovered stuttering in children.

## 4.1 Recovery rate based on parental and expert ratings, the traditional criteria

In this study, which used a clinical sample, the recovery rate from stuttering was comparable to that seen in larger general, non-clinical population samples. For example, the study of Yairi and Ambrose (2005), which included 89 children who stuttered aged between 2 to 4 years, reported a recovery percentage of 79% five years after stuttering onset, somewhat higher (even in a shorter follow up period) than the rate found in the present study. In contrast, two more recent population studies found lower recovery rates: (1) Kefalianos et al. (2017) reported a recovery rate of 65% by the age of 7 years in 103 children who had been confirmed to stutter by the age of 4 years; and (2) Ambrose, Yairi, Loucks, Seery, and Throneburg (2015) reported a recovery rate of 67% in a sample of 58 children 1 to 4 years following stuttering onset. This lower recovery rate may be due to the age of the children and the follow-up period. Ambrose et al. (2015) started with 81 children, aged 2 to 4 years, but 23 of them could not be classified as persistent or recovered because they dropped out of the study before their recovery status could be documented. These children were thus omitted from the analyses, which may have affected the recovery rate. Moreover, in both studies it remains unclear if children received speech therapy or not.

Two older studies also reported a lower recovery rate in clinical populations than the present study and are better comparable to the current study due to the number of participants. Ryan (2001) reported a recovery rate of 68% in 22 children (age ranging from 2 to 6 years) 2 years after the first visit, and Ramig (1993) reported a recovery rate of 9.5% in 17 children

(age ranging from 3 to 8 years) 6 to 8 years after the first visit. In these studies, the age range at baseline was higher than the age in children in the present study. In Ryan (2001), the follow-up time was substantially smaller, so a lower recovery rate can be expected, given that children may continue to recover up to 4 years after the onset of stuttering (Yairi & Ambrose, 1999). Overall, this might suggest that in a clinical population, the recovery from stuttering starts later and occurs less frequently than in a general population sample.

In the present study, all but one of the children received speech therapy. Still, the overall percentage of recovery was comparable to that found in previous population-based studies. In most population-based studies, it is unclear whether children had received speech therapy, and if so, for how long. In the present study, there was great variation between participants in the duration of treatment, the child's age at the start of treatment, and the intensity of the treatment. Every individual did have the option of regular, weekly therapy visits by a professional speech-language pathologist. This is because in the Netherlands, everyone can visit a speech-language pathologist within one hour travelling time, with costs covered by the obligatory healthcare insurance. In contrast, the population-based study of Yairi & Ambrose (2005) reported that some parents only received some general recommendations and educational advice. Nevertheless, Yairi & Ambrose (2005) reported a comparable recovery rate as in the present study. We assume, therefore, that therapy for stuttering in children from a clinical population, similar to our exploratory study, is positive; if it is not helpful to recover from stuttering, it has helped to maintain stuttering to a mild severity level. The children from a clinical population might have stuttered more severe without therapy for stuttering.

## 4.2 Adding children's self-rating of stuttering

Taking into account the children's self-reports in the extended criteria, the recovery rate in the clinical population was substantially lower (60%) than the rate according to the traditional criteria (73%). It is appropriate to interpret this result cautiously given the small sample size, but the findings clearly demonstrate that considering children's self-report can affect estimates of stuttering recovery rate. It is important to note that while our study focused on the recovery from stuttering in a clinical group of preschool-age children, a self-report of the child him- or herself enables to investigate a more valid recovery status. It is possible that other studies of recovery (e.g., Yairi and Ambrose, 2005) might have also found a lower recovery rate from stuttering if they had considered children's self-reports.

## 4.3 The importance of subjective experiences of speaking

Information regarding children's speaking experiences indicated that some children recover spontaneously from stuttering, while others do so less spontaneously. With "less spontaneous recovery," children continued to experience negative thoughts about speaking or used coping behavior for speaking fluently. It is possible that these children became adept at controlling their way of speaking in some situations (e.g. speaking a bit more slowly or inserting fillers to allow more planning time). In contrast, children who have spontaneously recovered (or, indeed, children who never stuttered at all) speak fluently without paying special attention to their way of speaking. Three of the 15 children who were judged to have recovered by experts, parents, and themselves (child 4, 5 and 6) reported experiences with speaking that were not common within the group of children who recovered or even compared to children who continued to stutter. For example, following results of the OASES, these children reported experiencing physical tension, facial movements (e.g. blinking eyes), and breaking eye contact when speaking (in section II). They also reported using filler words or starters to be more fluent (e.g. "ehm", clearing throat), letting someone else speak for them due to a fear of stuttering, and avoiding speaking in front of a large groups of people (e.g. asking a question in the classroom). Likewise, they reported difficulties in social situations, such as talking with friends outside the classroom, ordering food in a restaurant, telling stories or jokes; they particularly expressed difficulty in talking with unknown people (in section III). Finally, 2 of the 3 children reported difficulties in self-confidence and communication (e.g. dissatisfied with communication at school or with educational opportunities) (in section IV). Some of these behaviors might be interpreted as coping behavior to control speech fluency or reactions to underlying difficulty with producing speech fluency. It is also possible that they simply did not enjoy speaking or being social, had developed generalized social anxiety, or experienced a combination of speaking anxiety and covert stuttering. Either way, the findings support the idea mentioned above that recovery from stuttering is not always effortless, "just a matter of time", but the result of adaptations of the person who stutters.

## 4.4 Strengths and Limitations

The primary limitation in this study is the relatively small number of participants, which precluded the possibility of conducting inferential statistics to compare subgroups of children and limits generalizability of findings. Second, background information was

based on a parent questionnaire, completed soon after visiting the speech centers. The use of this questionnaire was essential for collecting information about the child and family history; however, such information may be confounded by parental perceptions, emotions and reactions to stuttering. Third, the child's self-report scale has not been validated, and it is possible that children may misinterpret descriptions such as, "stuttering a bit" as referring to disfluencies that might be judged by expert listeners to be typical disfluencies. Still, the scale has been used successfully in previous studies (de Sonneville-Koedoot et al., 2015), and it seems safe to assume that children ages 12 to 15 can rate whether they are experiencing difficulty with their own speech (particularly given that even very young children can express awareness and concern about stuttering; see cites by Ezrati-Vinacour, Platzky, and Yairi (2001); Langevin, Kleitman, Packman, and Onslow (2009); Vanryckeghem, Brutten, and Hernandez (2005)). Similarly, the Dutch OASES-T questionnaire has not been validated with a population of Dutch teenagers, though the translation process followed the same procedures as was done with the OASES-S (Lankman et al., 2015; Yaruss & Quesal, 2010/2016). We have no reason to doubt the accuracy of the OASES-T, as teenagers may better able to report their experience than younger children. Finally, the modified versions of the OASES assessing "speaking ability" have not been validated, though, again, similar scales have been used successfully in other studies to prevent substantial missing data when using the questionnaire for children who consider themselves as non-stuttering speakers (Lankman et al., 2015; Mulcahy et al., 2008).

Balancing these potential limitations of the study are a number of strengths. First, data collection commenced as soon as parents first consulted a speech-language pathologist due to concerns about their child's stuttering. Thus, the first visit for all participants was relatively close to the onset of stuttering (within 3 to 15 months) and conducted while the child was still young (less than 5 years of age), which is comparable to previous literature (Yaruss et al., 1998). Our study provided the opportunity for a prospective study of a clinical population, a study design that is relatively rare in the stuttering literature. Second, this is the first recovery study that considered children's self-report when determining recovery from stuttering. Uniquely, these self-reports included both children who had continued to stutter and children who had recovered. Finally, this study involved a long prospective tracking of participants (9 years). This term is sufficient to determine conclusively whether a child has recovered from stuttering; prior work has suggested minimum follow-up periods of 3.5 years (Ambrose et al., 2015) to 5 years (Conture, 2001; Yairi & Ambrose, 2005).

## 4.5 Future research directions

Future studies investigating recovery rates in childhood should further explore children's self-report (e.g. not limit the recovery rate to the judgement of the parents and experts) and OASES data to enable a maximally valid assessment of recovery. Further study should involve validation of these various scales with larger samples of participants to ensure the reliability and validity of the present findings.

## 4.6 Clinical implications

Results from this study suggest that it is important and appropriate for clinicians to consider children's experiences with speaking, as well as their own self-reports, when determining whether a child has recovered from stuttering. While clinicians may already collect longitudinal self-report data of children who persist in stuttering, it is unlikely that many clinicians also collect data about the speaking experiences of children who appear to have recovered from stuttering. The present study suggests that such information may be valuable, for even some "recovered" children may exhibit signs of controlled fluency or social anxiety; the need for additional treatment in such cases should be further explored.

## 4.7 Conclusion

This exploratory study demonstrated that recovery rates in a clinical population of children who stutter, are comparable to those previously reported in population-based studies. At the same time, the inclusion of children's self-reports regarding recovery and assessment of speaking experiences also reveal that earlier research on recovery rates may overestimate the actual occurrence of recovery. Therefore, self-reports and additional assessment of speaking experience should be considered to improve the field's understanding of recovery and refine definitions of the phenotype of stuttering.

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White matter
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Self-report
Persistent
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# 3

# Childhood stuttering outcomes in the RESTART trial: Long-term comparison of the Lidcombe Program and Restart-DCM

S.P.C. Koenraads, L.W. Stipdonk, T. Rietveld, M.C. Franken

*Submitted*

## Abstract

**Aim:** Stuttering is a common speech fluency condition that typically begins in early childhood. This study presents long-term (5+ years post-treatment) outcomes from the RESTART randomized trial, comparing Lidcombe Program (LP) and Demands and Capacities Model-based treatment (Restart-DCM) in preschool-aged children who stutter.

**Method:** Of the 199 children originally enrolled (all stuttering for at least 6 months), follow-up data were available for 149 children. Outcome measures included longitudinal parental ratings of speech fluency, assessments by children, teachers, and speech-language pathologists (SLPs), satisfaction with communication (SCESS), and children's self-reported speaking experiences (OASES).

**Results:** No significant long-term differences in speech fluency were found between treatment groups based on parent ratings. Both treatments were similarly effective in reducing stuttering among children at higher risk for persistent stuttering. Age at treatment onset and sex were significantly predicted recovery; family history did not. Self-reported recovery (72%) was slightly lower than ratings by parents (74%), teachers (82%), and SLPs (75%). SCESS scores were comparable across groups, though children who still stuttered reported higher satisfaction than their parents. Children who recovered reported slightly lower OASES scores.

**Conclusion:** Both the LP and Restart-DCM yielded sustained positive outcomes for preschool-aged children who stutter over a long-term follow-up period. Age at treatment and sex are stronger predictors of long-term outcomes than familial history or stuttering duration. These finding underscore the importance of starting intervention at an early age and continued monitoring.

*“Life without obstacles removes opportunity for growth.”*
Chad E. Foster

# PART II

Childhood stuttering in population-based research


White matter
Persistent
Fluency
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Subcort
Satisfaction
Gray matter
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# 4

# Risk of stuttering onset and persistence linked to early language skills: Results from the Generation R Study

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## Abstract

**Background:** Although linguistic factors are considered relevant to stuttering onset and its developmental course, the exact relationship between language and childhood stuttering remains unclear. Low, average and above-average expressive and receptive language skills have been associated with childhood stuttering. This study aimed to evaluate whether early language skills in children are associated with the risk of stuttering onset and persistence, using population-level data.

**Methods:** In a prospective, population-based cohort, we analyzed early-childhood language data from 123 nine-year-old with a history of stuttering (22 persistent, 101 recovered) and 2819 children without such a history. Expressive and receptive language skills were assessed at five time points using parental-reported questionnaires between 18 and 48 months of age. Multiple logistic regression analyses were performed.

**Results:** Higher expressive and receptive language skills at 24 months were significantly associated with a decreased risk of stuttering (Odds Ratio (OR) = 0.78, 95% Confidence Interval (CI) [0.65, 0.93], p-value <0.01). Language assessments at 18, 30, 36 and 48 months showed no evidence of any association with stuttering (persistence).

**Conclusion:** These findings support previous studies indicating that lower language skills in early childhood add to the risk of stuttering onset, but not with the persistence of stuttering. This association does not imply causality, it only demonstrates the association. Therefore, clinicians are advised to screen language skills in preschool children referred shortly after stuttering onset. Early language assessment may also reveal concomitant, clinically relevant language disorders, which are more prevalent in children already identified with one developmental concern.

# 1. Introduction

While many children with an onset of stuttering experience unassisted (natural) recovery/remittance, approximately 20–30% continue to stutter into later childhood and beyond (Franken, Koenraads, Holtmaat, & van der Schroeff, 2018; Yairi & Ambrose, 2005). Identifying factors that contribute to the onset and persistence of stuttering is crucial for early intervention and effective management, as it has been shown that starting stuttering treatment in the first fifteen months after onset increases the chance of full recovery (Ingham & Cordes, 1998).



Developmental stuttering typically starts during a dynamic period in children's language development when children's language is characterized by a substantial growth in speech sounds, and in lexical, morphological, syntactic and pragmatic skills, in both expressive (i.e. production) and receptive (i.e. comprehension) (Bloodstein, Bernstein Ratner, & Brundage, 2021; Brundage & Bernstein Ratner, 2022; Packman & Attanasio, 2004) language skills. Stuttering has been shown to be associated with longer and more complex utterances (Zackheim & Conture, 2003). However, whether the child's language abilities contribute to the cause and development of stuttering is still a matter of debate. Some researchers argue that stuttering results from motor coordination deficits that become apparent as speech demands increase with longer, more complex utterances (Namasivayam & van Lieshout, 2011; Nippold, 2018), while others propose that stuttering is not purely a speech disorder, and focus more on the interface of stuttering and language (Brundage & Bernstein Ratner, 2022). Among others (e.g., (Bloodstein, 2002; Packman & Attanasio, 2004; Smith & Weber, 2017), Brundage and Bernstein Ratner (2022) argue that linguistic factors influence the frequency and location of stuttering, that people who stutter appear to have underlying linguistic differences or impairments, and that language factors are associated with the course of stuttering (i.e. remission and persistence).

## 1.1 Research on language skills as a risk factor for childhood stuttering

Stuttering mostly emerges between 30 and 48 months, during a critical period of language development, when children begin using longer and more complex utterances (Watts, Eadie, Block, Mensah, & Reilly, 2017; Yairi & Ambrose, 1999; Yairi & Ambrose, 2005). While this may suggest that language plays a causal role in stuttering, it is more likely that multi-word utterances only reveal it. Specifically, stuttering may become apparent when linguistic demands, among others, exceed a child's capability for producing stable speech

motor movements (Nippold, 2018; Smith & Weber, 2017). For over a century, researchers have investigated the language skills of children who stutter, in an effort to clarify the relationship. Regardless of the discussion whether stuttering can be caused by language abilities, they may serve as indicators of an increased likelihood of stuttering. Identifying such indicators is essential for the timely recognition of children at elevated risk.

## 1.2 Language skills associated with stuttering onset

Only a limited number of studies have examined language skills prior to the onset of stuttering. Kloth, Kraaimaat, Janssen, and Brutten (1999) investigated preschool-age children with a family history of stuttering and found no difference in the linguistic abilities between children who later developed stuttering and those who remained fluent. Reilly et al. (2009) examined a large population cohort of young children, data from the Early Language in Victoria Study (ELVS), and found that those who began to stutter by 36 months of age demonstrated higher (parent rated) expressive vocabulary at 24 months, and a mother with a degree or post-graduate qualification, compared to children without stuttering onset. In the same cohort, Watts, Eadie, Block, Mensah, and Reilly (2015) adjusted for maternal education level and no longer found a significant association between expressive vocabulary at 24 months and stuttering onset. However, the authors did find a higher expressive vocabulary at 36 and 48 months of age for children who commenced to stutter, compared to children who did not. Additionally, Shimada, Toyomura, Fujii, and Minami (2018) investigated preschool-age children who stutter from a Japanese population and found an association between lower language skills at 18 months and the onset of stuttering. This study suggests that language delay at early age is indicative for a risk of stuttering. In summary, findings on the association between early language skills and stuttering onset are mixed. One study found no association with language (Kloth et al., 1999); another study initially reported higher language skills at 24 months in children who later stuttered (Reilly et al, 2009), but this association was no longer significant after adjustment (Watts et al, 2015), and a third study -despite methodological concerns- found lower language skills in children with a history of stuttering (Shimada et al., 2018). Overall, there is no consensus on the relationship between early language development (approximately 18-30 months) and the onset of stuttering.

## 1.3 Language skills associated with persistent stuttering

Several systematic literature reviews examined language skills associated with childhood stuttering (Nippold, 2012, 2018; Ntourou, Conture, & Lipsey, 2011; Singer, Hessling, Kelly, Singer, & Jones, 2020; Sugathan & Maruthy, 2021). These reviews indicated that only few studies have specifically investigated the relationship between language skills and the persistence of stuttering. Here, we summarize the findings regarding receptive and expressive language related to stuttering persistence from the recent meta-analysis (Singer, Hessling, et al., 2020) representing the most evidence currently available, and the most recent systematic review (Sugathan & Maruthy, 2021).

The meta-analysis conducted by Singer, Hessling, et al. (2020) included data from eleven studies and examined seven early language skills. Four measured using norm-referenced tests (receptive vocabulary, receptive language, expressive vocabulary, and expressive language), and three assessed through language sample analysis (Index of Productive Syntax (Scarborough, 1990), Developmental Sentence Scoring (Lee & Canter, 1971), and mean length of utterance (MLU)) (Ambrose, Yairi, Loucks, Seery, & Throneburg, 2015; Arenas, Walker, & Oleson, 2017; Buhr, 2007; Hollister, Van Horne, & Zebrowski, 2017; Kefalianos et al., 2017; Kloth et al., 1999; Leech, Bernstein Ratner, Brown, & Weber, 2017; Roehl, 2018; Singer, Walden, & Jones, 2020; Watkins, Yairi, & Ambrose, 1999; Yairi & Ambrose, 2005). The results of the meta-analysis showed that children who persist in stuttering, compared to those who eventually recover, demonstrated lower receptive language and lower expressive language near stuttering onset (Ambrose et al., 2015; Yairi & Ambrose, 2005). All other differences were non-significant. The modest effect sizes suggest that children who persist in stuttering may exhibit vulnerabilities underlying lower expressive and receptive language (and other clinical characteristics not discussed here) that increase their risk for persistent stuttering (Singer, Hessling, et al., 2020). The systematic review by Sugathan and Maruthy (2021) included six studies on receptive language, eight studies on expressive language ability and five studies on spontaneous language measures (MLU, number of different words, number of total words) (Ambrose et al., 2015; Kloth et al., 1999; Ryan, 2001; Shimada et al., 2018; Spencer & Weber-Fox, 2014; Watkins & Yairi, 1997; Watkins et al., 1999; Yairi, Ambrose, Paden, & Throneburg, 1996). The significant findings of several studies (Ambrose et al., 2015; Shimada et al., 2018; Yairi et al., 1996) suggest that, at the time of stuttering onset, children who later persisted in stuttering exhibited lower expressive language skills compared to those who

eventually recovered, whereas differences in receptive language skills and spontaneous language were not significant. One or two years post-onset, both expressive and receptive language abilities in children who persisted lag behind those observed in children who recovered. The authors identified mixed, contradictory findings on receptive and expressive language abilities, thus questioning the predictive power of these factors (Ambrose et al., 2015; Shimada et al., 2018; Yairi et al., 1996). In addition, almost all the studies that measured spontaneous language reported that these factors are not indicators of persistence or recovery of stuttering.

The contradictory conclusion between the two reviews may be attributed to the limited overlap in studies —only four studies (Ambrose et al., 2015; Kloth et al., 1999; Watkins et al., 1999; Yairi & Ambrose, 1999) of which only one reported significant findings, were included in both reviews. This divergence is likely due to differences in inclusion criteria. For example, the inclusion criteria of Singer, Hessling, et al. (2020) included studies involving young children up to 6 years of age at study entry, and a follow-up after study entry of at least 24 months. In contrast, Sugathan and Maruthy (2021) included children up to 12 years of age and did not specify a minimum length follow-up duration, requiring only that the studies included children who persisted in stuttering and children who recovered. Limitations of both reviews include the small number of studies, limited data from children prior to stuttering onset and the methodological variability across included studies (e.g., different designs, sample size, age ranges and follow up). Moreover, most included studies measured language at only one or two time points, thereby limiting insights into developmental trajectories of language.

## 1.4 What can this study contribute to the understanding of language as risk factor for (persistent) stuttering?

In sum, early language skills might be associated with childhood stuttering. The inclusion of extensive data from larger groups of participants can make a significant contribution to our understanding of language as a risk factor for (persistent) stuttering. More specifically, large population cohort studies with prospectively collected data prior to the onset of stuttering could contribute to clarifying this association. Therefore, one goal of this study was to investigate whether during early childhood, (parent rated) language skills are associated with stuttering onset - not implying causality but to clarify the relationship. Another goal was to investigate whether early language skills in children predict persistent (vs. recovered/remitted) stuttering. Based on prior literature described above, our first

hypothesis is that very early language abilities are not related to the onset of stuttering, and our second hypothesis is that lower language abilities (although not necessarily impaired or disordered) in early childhood are related to stuttering persistency. Investigating this association will contribute to the understanding of the role of language as a potential risk in the maintenance of stuttering. Moreover, it may underscore the importance of screening and monitoring early language skills in the diagnosis, treatment, and long-term follow-up of children who stutter.

Our study contributes to the existing literature on the potential association between language and stuttering because it extends these earlier studies in several important ways. First, we analyzed language data at different time points from a large prospective, longitudinal, population-based birth cohort, which allowed us to examine early vocabulary and language skill differences in (very) young children before and around the age at which stuttering usually begins. Second, because this longitudinal study followed up the participants over a period of several years, it is possible to compare early language skills in different fluency groups: children with a history of stuttering (those who persisted in stuttering and those who had recovered by 9 years of age), and peers without a history of stuttering.

In this article, which uses population-level data, the terms 'lower vocabulary' or 'lower language skills' refer to relatively lower performance on language measures, which serve as indirect indicators of general language ability. Conversely, the terms 'higher vocabulary' or 'higher language skills' refer to relatively advanced language performance. It is important to note that lower scores do not necessarily indicate a clinical language disorder or diagnosis, but rather represent a position on the continuum of language skills observed in the general population.

# 2. Material and methods

## 2.1 Study design and population

This study was embedded in the Generation R Study, a multi-ethnic population-based prospective cohort from fetal life onward (n=9901), in Rotterdam, the Netherlands (Kooijman et al., 2016). Women living in Rotterdam were enrolled during pregnancy. Children participating in this study were born between April 2002 and January 2006. The study was approved by the Medical Ethics Committee of Erasmus Medical Center and written informed consent was obtained from parents of all participating children.

In early childhood, at ages 18, 24, 30, 36 and 48 months, information on language skills was collected. When the children were nine years old, sending a questionnaire about hearing, language and stuttering to mothers who had provided consent for follow-up was approved of by the management team of the Generation R study for the first time (n = 6887). The questionnaire was returned for 4141 children (60%). After excluding subjects for whom the questions about stuttering had not been completed (n = 312 participants who did not answer the questionnaires about stuttering), (un)defined language disorder reported by parents (n = 398), or with missing parent-report language assessment data at all five time points (n = 489), valid information on stuttering and language skills was available for 2942 children (Figure 1). Based on the information from this questionnaire, 2819 children had no history of stuttering (fluent speakers) and 123 children (4%) were categorized as having a history of stuttering. Of these children with a history of stuttering, 22 children persisted (18%) and 101 children recovered (82%) from stuttering.

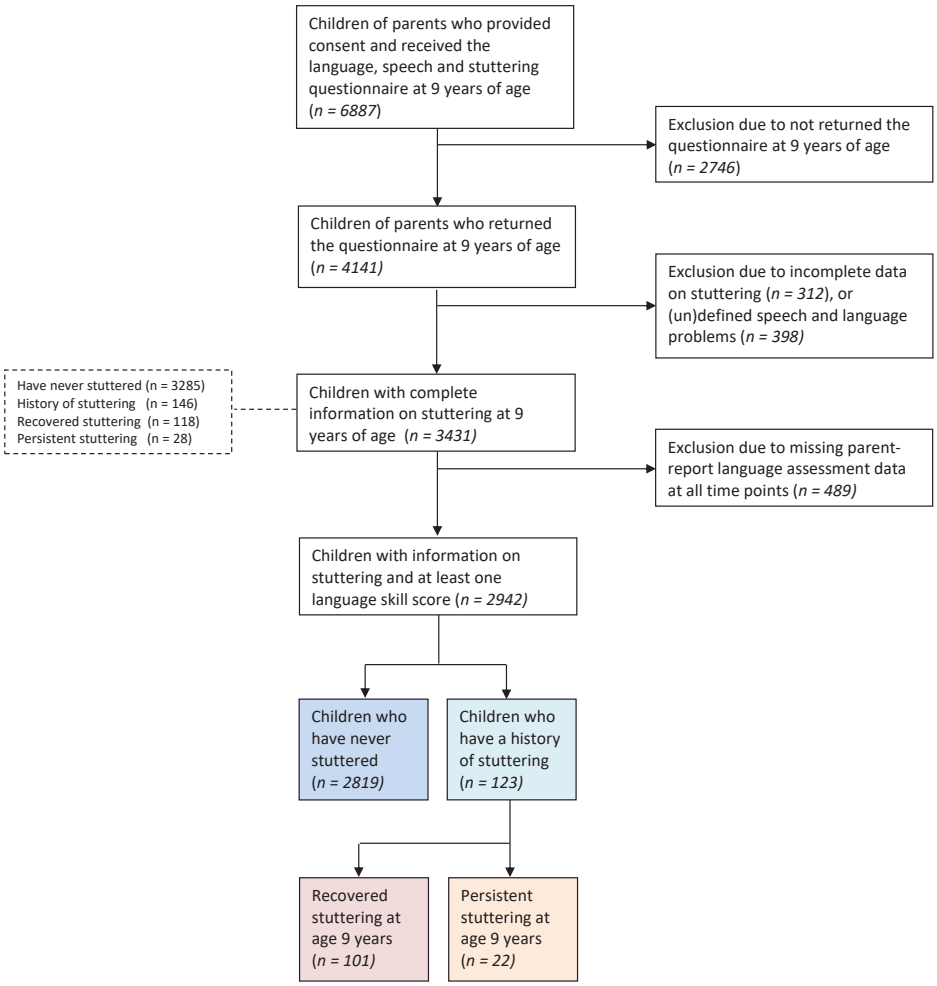
## 2.2 Stuttering

In this study, when the children were nine years old, parents completed a speech and language developmental questionnaire to obtain a measure of childhood stuttering. Parents were informed about the meaning of stuttering (i.e. "stuttering is not speaking fluently"). The questionnaire contained four questions specifically regarding stuttering and speech therapy: (1)"Does your child currently stutter?", (2)"Has your child ever stuttered in the past?", (3)"Is your child currently being treated for stuttering?", (4)"Has your child ever been treated for stuttering in the past?". Participants were classified as having a history of stuttering if a parent answered "yes" to any of these questions. Participants were classified as persisting in stuttering if "yes" was answered to any of the questions about the past (2 or 4) and any about the present (1 or 3). Participants were classified as recovered from stuttering if "yes" was answered to any of the questions about the past (2 or 4) and "no" was answered to both questions about the present (1 and 3). This categorization was thus based on parental reports. Parental reports have been used in several previous studies investigating persistence and recovery of stuttering in childhood (Dworzynski, Remington, Rijsdijk, Howell, & Plomin, 2007; Kloth et al., 1999; Koenraads et al., 2019; Månsson, 2000). Parents of children who stutter were shown to be accurate in recognizing stuttering in their child (Einarsdottir & Ingham, 2009). Relying solely on parental reports may result in missed cases of (very) mild stuttering. By the time children were nine years old, some parents may no longer recall early signs

of stuttering. The incidence of stuttering in the Generation R Study is in line with the historical incidence of stuttering among children between two and ten years as reported in other population-based samples (Boyle et al., 2011; Craig, Hancock, Tran, Craig, & Peters, 2002; Dworzynski et al., 2007; Månsson, 2000). Only Reilly et al. (2013) found higher incidence rates (up to 11%).



Figure 1. Flowchart of the participants included in the study



## 2.3 Language assessment

Information about language skills was obtained when the children were 18, 24, 30, 36 and 48 months of age. These skills were assessed by parent questionnaires selected by researchers of the Generation R population study based on (sufficient) validity and reliability. The questionnaires were sent out at these ages and thus included age appropriate assessments of language skills. Parents varied, however, in how promptly they filled in and returned the questionnaires; for that reason, we adjusted each analysis for the age at language assessment. Detailed information on the distribution of data collected at 18 and 30 months from the Generation R has been described (Henrichs et al., 2013; Henrichs et al., 2011). Language skills were assessed with the following questionnaires.

### 2.3.1 MacArthur Communicative Development Inventory-Netherlands (MCDI-N)

Expressive and receptive vocabulary at 18 months were assessed using the parental report on the MCDI-N composed of a 112 monomorphic root words checklist derived from the complete Dutch version of the MCDI (Fenson et al., 1993; Zink & Lejaegere, 2003). In the current study, the number of positive responses were calculated by summing the expressive ("says" column, the word production) and receptive language skills ("understands" column, the word comprehension) separately. As a sensitivity analysis, we also scored the MCDI-N using the common practice of crediting all "says" words as "understands", even if the parent did not check "understands" for that word (Henrichs et al., 2013). No substantive differences were found in this sensitivity analysis. The Dutch short form of the MCDI has demonstrated excellent internal consistency, test–retest reliability and strong concurrent validity (Zink & Lejaegere, 2002).

### 2.3.2 Child Development Inventory (CDI)

Combined receptive and expressive language skills at 24, 36 and 48 months were obtained using the maternal reports on the Dutch CDI. The CDI is a standardized assessment that provides an overall representative score of the development of language, letter and number skills of children correlating closely with age (Ireton & Glascoe, 1995). At its core, it can be considered a vocabulary inventory that also assesses whether the child combines words into utterances. For this study, at 24, 36 and 48 months we did not obtain scores for 'receptive and expressive language separately' (as is done at 18 months) because of the relatively small number of assessed items (11-17 questions). The CDI contains 11

questions to assess language skills at 24 months, 17 questions to assess language skills at 36 months, and 14 questions to assess language skills at 48 months. For example, parents were asked to indicate whether their child (at 36 and 48 months) had provided explanations or had begun combining words into simple phrases.

### 2.3.3 Language Development Survey (LDS)



Expressive vocabulary at 30 months was assessed using maternal reports in the Dutch version of the LDS (Rescorla, 1989). The LDS contains a checklist of 310 words arranged alphabetically covering various semantic categories (e.g., animals, foods, modifiers, vehicles) (Achenbach & Rescorla, 2000; van Batenburg-Eddes et al., 2013). Parents were asked to identify each word that their child uses spontaneously, yielding a total score for expressive vocabulary. The LDS has demonstrated excellent internal consistency, test-retest reliability and concurrent validity (Rescorla, 1989; Rescorla & Alley, 2001).

## 2.4 Covariates

General demographic characteristics including maternal age at intake, ethnicity and education level, as well as child birth factors, date of birth, sex, ethnicity, mono- or bilingualism, and handedness were prospectively obtained by postal questionnaires. Maternal ethnicity was defined according to the classification of the Statistics Netherlands institute, into Western (Dutch and Non-Dutch Western) and non-Western (Statistics Netherlands, 2004). Also following the definition of the Statistics Netherlands institute, maternal educational level was categorized into: low to medium education level and high education level (consisting of higher vocational education or university) (Statistics Netherlands, 2005). Birth predictions (e.g. gestational age at birth, and birth weight), date of birth, and sex were extracted from medical records. Child ethnicity was categorized as Western (Dutch and Non-Dutch Western) and non-Western (Kooijman et al., 2016; Statistics Netherlands, 2004). Native language was obtained by parental report at nine years of age. Mono- or multilingualism was defined as having acquired only one, or more than one languages by age six years from parents (Peng & Wang, 2011). Handedness was determined using the Edinburg Handedness Inventory and categorized into right- and left-handers (Oldfield, 1971). This test was administered by a research assistant at age six to nine years. In addition, in the Generation R study several variables (e.g., premature birth, twin birth, head circumference at birth, breastfeeding, hours attending day-care/preschool, number of children in household, net family monthly income) were obtained

to present general characteristics of all children with complete information on stuttering. These variables were analyzed across our four fluency groups (no stuttering, history of stuttering, recovered, persistent) revealing no significant differences. Therefore, they are acknowledged but not further incorporated into this article.

## 2.5 Data analysis

Differences in demographic and clinical variables between children who stutter and fluently speaking controls, and between those who recovered from and persisted in stuttering, were determined using Chi-squared or Fisher's Exact tests (for small sample sizes) for categorical variables and t-tests for continuous variables. Mann-Whitney U test (for two groups) or Kruskal-Wallis test (for two or more than two groups) were used for non-parametric continuous variables. All language skills scores were z-standardized across the study sample to enable comparability. Because not all language questionnaires were completed by all parents at each time point, the number of participants varied per analysis. For the main analysis, to reduce the effect of selective non-response, we used multiple imputation to replace missing values (at most 7% for maternal education) in the covariates. We generated five data sets that sampled these values from their predictive distribution based on the relations between all variables included in the present study (Sterne et al., 2009). All analyses were performed in SPSS (version 24.0).

To test our hypotheses, univariate logistic regression models were used to examine the association between language skills scores (dependent variable) and the risk of stuttering and its persistence (outcome). For multivariate models, covariates were retained in the model if they changed the main effect estimates by more than 5%. Retained covariates included child age at language assessment, child sex, and maternal education. Including maternal education in the model indirectly adjusts for health consciousness and knowledge about health care (Bicego & Boerma, 1993), which may relate to initiatives of families to deal with children's stuttering (e.g., obtaining therapy for children, working with their children on their own, using resources from internet). Covariates that remained below the 5% cut-off, and therefore not included in further analyses were ethnicity and mono- or multilingualism. In our study, these factors appeared not related to language development and/or stuttering and its persistence. Findings of the univariate and multivariate logistic regression models are presented as Odds Ratios (OR) with 95% Confidence Interval (CI).

# 3. Results

## 3.1 Descriptions of study sample

As summarized in Table 1, 123 (4%) of the 2942 children had a history of stuttering by nine years of age (SD=0.4 year) and boys (68%) more often have a history of stuttering than girls (32%, p-value <0.05). Of these 123 children, 22 (18%) persisted in stuttering at age nine, and 101 (82%) had recovered from stuttering. Also, children with a history of stuttering had a lower maternal age at inclusion in Generation R (31 years old) than those without a history of stuttering (32 years old, p-value <0.05). No statistically significant differences across the groups were demonstrated for other variables. Children were on average born at term (39.8 weeks, SD=1.7), were mostly right-handed (88%), and mostly had a Western ethnicity (80%). Non-response analyses showed that children who participated in the current study were more likely to have higher birth weight, have Western ethnicity, to be monolingual, have lower age at stuttering questionnaire, have higher maternal age and education at intake, than children who did not participate in the study (i.e. those with missing data (n=2746), incomplete data (n=312), undefined speech and language problems (n=398), or missing parent-report language assessment data at all timepoints (n=489), see Flowchart in Figure 1).

One or more language assessments were available in children included in the present study at the five different timepoints tested (n= 2924, Table 2). All six language assessments were available in 1894 children (64%), five assessments in 557 children (19%), four in 249 children (9%), three in 125 children (4%), two assessments in 67 children (2%), and one language assessment was available in 50 children (2%). The number of participants included at each time point varied. Specifically, the MCDI-N at 18 months included n=2591 for expressive vocabulary and n=2686 for receptive vocabulary, CDI at 24 months n=2649, LDS at 30 months n=2698, CDI at 36 months n=2528, and CDI at 48 months n=2649. Figure 2 and Supplementary Table 1. visually illustrate that lower language skills at 24, 30, 36 and 48 months were found in children with a history of stuttering compared to those without a history of stuttering. Furthermore, lower language skills at 30 months were observed in children who persisted in stuttering compared to those who recovered from stuttering.

Supplementary Table 2. presents mean raw language skills scores including low (cut-off percentile 20), moderate (> percentile 20 and < percentile 80) and high (cut-off percentile 80) scores for children with no history of stuttering, those who recovered from stuttering, and those who persisted.

Table 1. Participants characteristics

| Characteristics | All participants (n=2942) *Mean (SD) or n (%)* | | | Children with stuttering (n=123) *Mean (SD) or n (%)* | | |
|---|---|---|---|---|---|---|
| | **Children without a history of stuttering n=2819** (95.8%) | **Children with a history of stuttering n=123** (4.2%) | p-value | **Children who recovered from stuttering n=101** (82.1%) | **Children who persisted in stuttering n=22** (17.9%) | p-value |
| **General** | | | | | | |
| Gestational age at birth (weeks) | 39.8 (1.8) | 39.8 (1.5) | *0.58* | 39.8 (1.6) | 39.8 (1.1) | *0.98* |
| Birth weight (gram) | 3444 (578) | 3474 (530) | *0.92* | 3451 (535) | 3578 (501) | *0.31* |
| Sex (% boy) | 1343 (47.6%) | 84 (68.3%) | *<0.01** | 67 (66.3%) | 17 (77.3%) | *0.45* |
| Ethnicity (% Western) | 2280 (81.1%) | 94 (77.0%) | *0.29* | 79 (79.0%) | 15 (68.2%) | *0.28* |
| Handedness (% right- handed) | 1994 (89.3%) | 87 (86.1%) | *0.33* | 71 (86.6%) | 16 (84.2%) | *0.72* |
| Multilingualism (% yes) | 486 (17.5%) | 23 (18.9%) | *0.72* | 19 (18.8%) | 4 (19.0%) | *0.99* |
| Age at stuttering questionnaire (yrs) | 9.9 (0.4) | 9.8 (0.3) | *0.54* | 9.9 (0.3) | 9.7 (0.2) | *0.04** |
| **Family** | | | | | | |
| Maternal age at intake (yrs) | 32.1 (4.3) | 31.2 (4.2) | *0.02** | 31.0 (4.3) | 31.9 (3.8) | *0.35* |
| Maternal ethnicity (% Western) | 2230 (79.1%) | 92 (74.8%) | *0.41* | 78 (77.2%) | 14 (603.6%) | *0.32* |
| Maternal education level (% high) | 1873 (70.0%) | 80 (69.0%) | *0.84* | 69 (71.1%) | 11 (57.9%) | *0.28* |

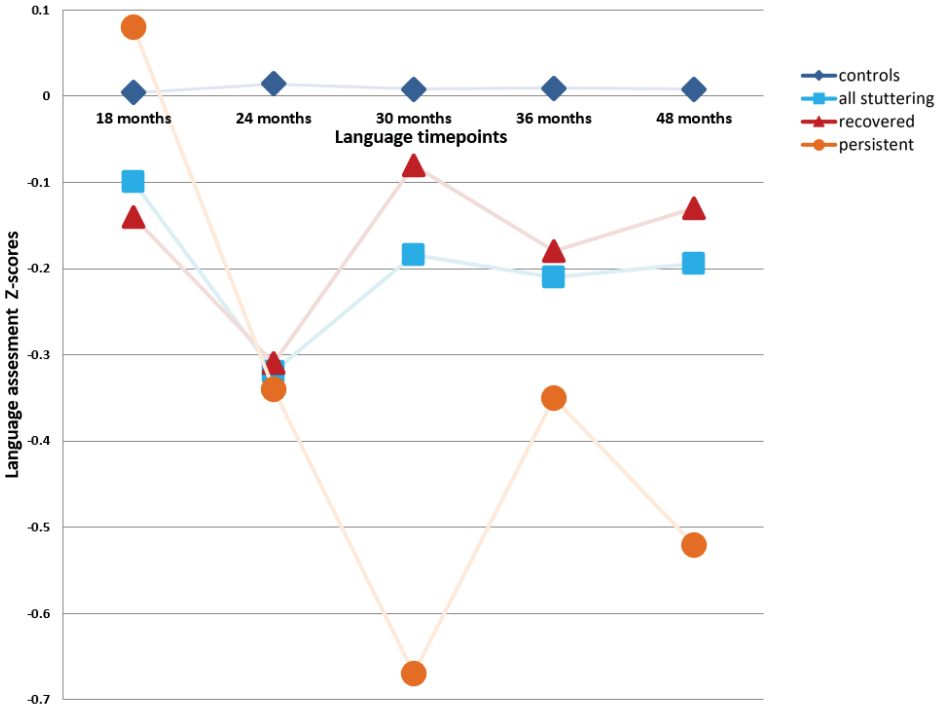
All categorical variables are presented with numbers (n) and percentages, and continuous variables are presented as mean with standard deviation (SD).
* p-value < 0.05
In the *total sample* (n=2942), data was based on birth weight (n=2934), ethnicity (n=2932), handedness (n=2335), multilingualism (n=2897), and maternal education (n=2931).
In the *children with a history of stuttering* sample (n=123), data was based on ethnicity (n=122), multilingualism (n=122), handedness (n=101), and maternal education (n=116).

Table 2. Association between language skills and stuttering

| | | All participants (n=2942)+ *OR for stuttering (95% CI)* | | | | | Children with stuttering (n=123)++ *OR for persistent stuttering (95% CI)* | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Language assessment** | **n** | **Univariate** | **p-value** | **Multivariate** | **p-value** | **n** | **Univariate** | **p-value** | **Multivariate** | **p-value** |
| **18 months** expressive vocabulary **(MCDI-N)** | 2588 | 0.89 (0.72;1.11) | *0.31* | 0.91 (0.73;1.14) | *0.41* | 97 | 1.21 (0.76;1.90) | *0.42* | 1.29 (0.79;2.10) | *0.31* |
| **18 months** receptive vocabulary **(MCDI-N)** | 2683 | 0.87 (0.72;1.06) | *0.16* | 0.88 (0.73;1.08) | *0.22* | 112 | 1.22(0.74;2.01) | *0.45* | 1.24 (0.74;2.08) | *0.41* |
| **24 months** expressive and receptive language skill **(CDI)** | 2648 | 0.74 (0.63 ;0.88) | *<0.01** | 0.78 (0.65;0.93) | *<0.01** | 113 | 0.98 (0.66;1.46) | *0.91* | 1.09 (0.72;1 .66) | *0.69* |
| **30 months** expressive vocabulary**(LDS)** | 2598 | 0.85 (0.71; 1.00) | *0.06* | 0.86 (0.72;1.03) | *0.11* | 110 | 0.63 (0.40;0.98) | *0.04** | 0.60 (0.36;0.99) | *0.05* |
| **36 months** expressive and receptive language skill **(CDI)** | 2528 | 0.83 (0.71;0.99) | *0.03** | 0.85 (0.72;1.02) | *0.07* | 109 | 0.91 (0.62;1.34) | *0.64* | 0.92 (0.61;1.38) | *0.68* |
| **48 months** expressive and receptive language skill **(CDI)** | 2649 | 0.84 (0.71;0.99) | *0.04** | 0.87 (0.73;1.04) | *0.12* | 107 | 0.69 (0.43;1.1) | *0.13* | 0.69 (0.41;1.15) | *0.16* |

Values represent are regression coefficients (Odds Ratios, OR) and 95% Confidence Intervals (95% CI) derived from multiple logistic regression analyses.
CDI = Child Development Inventory, CI = confidence interval, LDS = Language Development Survey, MCDI-N = MacArthur Communicative Development Inventory-Netherlands, n = number, OR = Odds Ratios
+ Reference = non stuttering group, ++ Reference = recovery from stuttering group
Univariate (unadjusted) model: logistic regression with stuttering as outcome, language Z-scores as dependent variable
Multivariate (adjusted) model: univariate model and adjusted for age, sex and education mother
* p-value < 0.05

Figure 2. Language skill scores



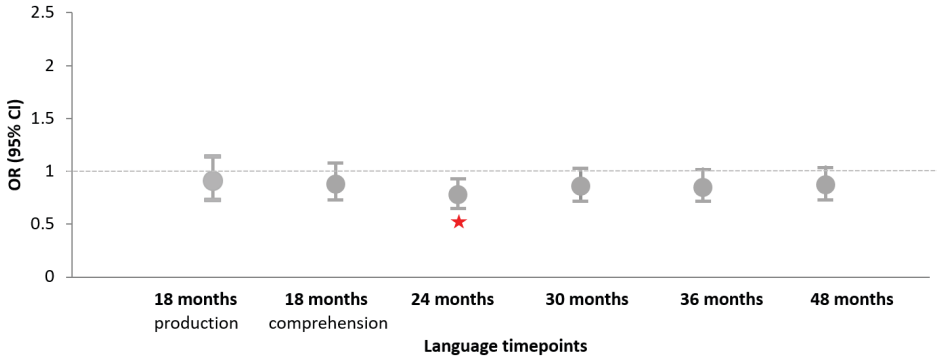

All languages skills scores were z-standardized across the study sample (n=2942), mean Z-scores per language time point per group are presented in this Figure in different colours.
The word production scores are showed at time point 18 months.

## 3.2 Association between language skills and stuttering

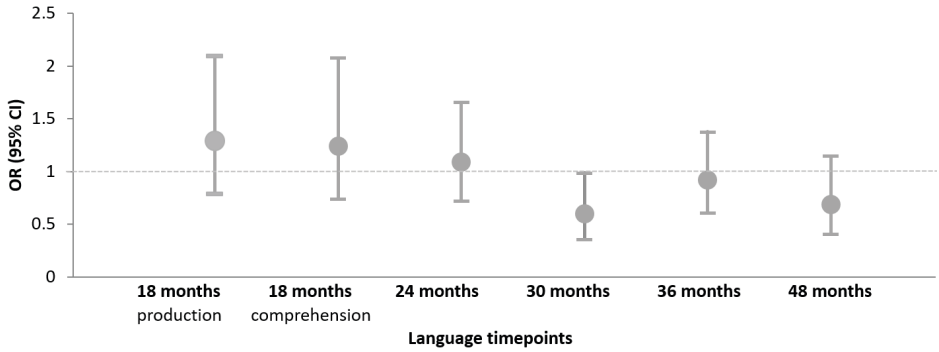
Table 2 and Figure 3 illustrate the relation between early language skills and stuttering. First, language skills and a history of stuttering. The univariate unadjusted analysis indicated that better (receptive and expressive) language skills at 24 months (e.g., per 1 SD higher score, OR=0.74, 95% CI [0.63, 0.88], p-value <0.01), 36 months (OR=0.83, 95% CI [0.71, 0.99], p-value 0.03), and 48 months (OR=0.84, 95% CI [0.71, 0.99], p-value 0.04) were associated with a decreased risk of stuttering, as reflected by ORs below 1 (Table 2). Table 2 also presents the results of the multivariate logistic regression analysis, which adjusted for age, sex, and maternal education, examining the six early language skills assessments. Among these, only language skills at 24 months was significantly associated with a history of stuttering, and the effect size was modest. Specifically, a 1 standard deviation (SD) increase in language skill score at 24 months was associated with a reduced risk of stuttering (OR = 0.78, 95% CI [0.65, 0.93], p-value < 0.01).

Figure 3. Associations between language skills and the risk of stuttering

**a) All participants** (n=2942) – ORs for stuttering




**b) Children with stuttering** (n=123) – ORs for persistent stuttering




Odds ratio estimates and confidence intervals of one standard deviation higher language scores on the risk of stuttering (Fig 3a) and on the risk of persistent stuttering (Fig 3b) from multivariable logistic regression model.

CI = confidence interval, n = number, OR = odds ratios, *p-value < 0.05

This suggests that better language skills are linked to a lower risk of stuttering, whereas poorer language skills (lower scores) are associated with an increased risk. Expressive and receptive vocabulary at 18 months, and language skills at 30, 36, and 48 months were not significantly related to stuttering incidence.

Then, language skills and stuttering persistence. The univariate unadjusted analysis indicated that better (expressive) language skills at 30 months (OR=0.63, 95% CI [0.40, 0.98], p-value 0.04) was significantly associated with a decreased risk of stuttering (Table 2). However, in the multivariate logistic regression analyses, higher expressive vocabulary

at 30 months was not statistically significantly associated with a lower risk of stuttering persistence (OR=0.60, 95% CI [0.36, 0.99], p-value = 0.05, Table 2). Expressive and receptive vocabulary at 18 months, and language skills at 24, 36, and 48 months were also not significantly related to stuttering persistence. This finding suggests that early language skills are not associated with an increased risk of persistent stuttering.

To see if the effect estimates were due to some age outliers (e.g. the hypothesis that older children have higher language development), we excluded the participants whose parents filled in the questionnaire with a delay more than six months and reran the analyses. These findings were highly similar.

# 4. Discussion

This prospective population-based study provided no support for our hypotheses regarding early language development and its relationship with childhood stuttering. Although observed effect sizes were modest, the findings showed that lower receptive and expressive language skills at 24 months were linked to a greater risk of stuttering. However, early language skills were not found to be associated with persistent stuttering. This study contributes to the growing body of evidence suggesting a relationship – without implying causality - between stuttering and language skills around the age at which children typically begin to combine words into early phrases.

## 4.1 Our findings compared to the literature

### 4.1.1 Language skills at 24 months of age and the risk of stuttering

Concerning children with and without a history of stuttering, stuttering incidence was found to be associated with lower receptive and expressive language skills at 24 months of age. At this age, a negligible proportion of children has commenced to stutter (Reilly et al., 2009). Lower language skills were not necessarily related to clinical language delay (late talking onset, language impairment, or language disorder) since clinical information was missing. Clinical language delay diagnoses are usually based on scores of a standardized language test of at least 1.5 SD, or even 2 SD. Although a language delay cannot be confirmed, it is worth considering whether the outcome may have clinical relevance -for instance, when scores fall below 20$^{th}$ or above 80$^{th}$ percentile.

Our association of lower language skills at 24 months of age and risk of stuttering is consistent with one population-based study about stuttering incidence at 3 years of age

(1.4%), that found that one third of the children who stuttered at 3 years of age had lower language skills at 18 months of age (Shimada et al., 2018). In contrast, other studies found that language skills before the onset of stuttering fell within the normal to advanced range in children with a later onset of stuttering, compared to children without an onset of stuttering (Kloth et al., 1999; Reilly et al., 2009; Watts et al., 2015). In addition, some clinical and population-based studies in preschool-age children who stutter have found that their language skills were lower (Shimada et al., 2018; Watkins et al., 1999; Zaretsky, Lange, Euler, Robinson, & Neumann, 2017). However, in cases where children showed either lower or normal to advanced language and communicative abilities, the effect of these differences was small (Ntourou et al., 2011; Zaretsky et al., 2017).



### 4.1.2 Language skills and the risk of stuttering persistency

We did not find that language skills in early childhood were associated with a risk of persistent stuttering. This finding contrasts with prior reviews of Singer, Hessling, et al. (2020) and Sugathan and Maruthy (2021), which reported lower early expressive and receptive language skills in children who persisted in stuttering. In our study, only an univariate association (unadjusted for age, sex, and maternal education) at 30 months was observed. This outcome did not hold in multivariate analyses and the effect estimate changed only slightly. Importantly, there is no consistent pattern in the association across different ages. Furthermore, even in studies showing differences (Ambrose et al., 2015; Watkins et al., 1999; Yairi & Ambrose, 2005; Yairi et al., 1996), children who persist in stuttering still scored within normal limits. Some population-based findings suggest early language skills may play a role in children whose stuttering persisted, but limitations in designs (e.g., a single time point, use of a non-standardized language test, and a very short follow-up period) and subgroup effects (e.g., finding did not hold for boys) call for cautious interpretation when comparing with ours (Kefalianos et al., 2017; Shimada et al., 2018).

## 4.2 Potential mechanisms of childhood stuttering

Several mechanisms may help explain our finding that lower language skills at 24 months of age are related to the onset of stuttering. First, following multifactorial theories (Smith & Weber, 2017), we speculate that some children as young as 24 months with lower language proficiency can be expected to have immature speech motor skills, because of less speaking experience. Furthermore, our speculation aligns with multiple theoretical

and empirical perspectives. These include the limited speech motor skills theory (Namasivayam & van Lieshout, 2011), the clinical model suggesting that an imbalance between developing language and speech motor skills can elicit stuttering (Starkweather, 1991), and evidence showing that children who persist in stuttering exhibit chronically immature speech motor coordination compared to those who recovered (Usler, Smith, & Weber, 2017). Together, these perspectives support the possibility that a sub-group of the children with lower early language skills may also have limited speech motor skills. This is further supported by research on typically developing children aged 9 to 21 months, which has demonstrated a correlation between speech motor control and language proficiency during early childhood years (Nip, Green, & Marx, 2011).

Another mechanism can be that temporary stuttering is associated with normal speech motor skills in combination with (very) rapidly growing language skills (e.g., to an advanced language skill level). More complex words (new or less familiar) and longer sentences put a relatively high demand on speech motor capacity. This appears to be in line with research showing that morphosyntactic complexity is related to dysfluency in non-stuttering children, and that sentence length and complexity are related to stuttering frequency (Bernstein Ratner & Sih, 1987; Brundage & Bernstein Ratner, 1988; Hollister et al., 2017; Rispoli & Hadley, 2001; Usler & Walsh, 2018; Watkins et al., 1999). These scenarios resonate with parents' reports that their child had a spurt of language growth (e.g., "his brain seemed to be working faster than his mouth"), spoke in relatively long sentences, and used new words prior to the onset of stuttering (Watkins, 2005). This can be especially true for children who start stuttering at 2 years of age (Ambrose et al., 2015; Reilly et al., 2009; Watkins et al., 1999).

Third, the finding that lower language skills at 24 months are associated with a higher probability of stuttering onset, may reflect the timing of early neural maturation in both language and speech motor control. At age 18 months, the variability in language scores may be relatively high, perhaps too high to allow an association. At ages 30 to 48 months, children who lagged behind in neural maturation initially, at 24 months, may have partially or fully caught up, potentially explaining the absence of the association at these later ages. Such slower linguistic development may signal atypical motor planning, programming, and execution, which are crucial for fluent speech.

Lastly, other important milestones related to the development of language and speech motor skills, such as the child's emotional, behavioral, sensorimotor, and cognitive capacities, will become more elaborate, and these may also interact with the development

of fluent and disfluent speech (Eggers, De Nil, & Van den Bergh, 2010; Sasisekaran, Basu, & Weathers, 2019; Smith & Weber, 2017).

## 4.3 Limitations and strengths

The limitations of this study must be discussed. First, our data on language skills and stuttering were based completely on parent-reported measures. We acknowledge that some parents might find it hard to differentiate between stuttering and normal dysfluencies. However previous studies have shown that parents can accurately and reliably identify the absence or presence of stuttering in their children (Bloodstein et al., 2021; Einarsdottir & Ingham, 2009). Additionally, although our study relies on parental reports rather than direct behavioral assessments, the language instruments are well validated. There is support for the validity of parental reports of expressive vocabulary. For example, van Noort-van der Spek, Franken, Swarte, and Weisglas-Kuperus (2021) reported a strong correlation between a parent-report questionnaire and a standardized expressive vocabulary tests in a 2 year old preterm children. This supports the use of parent-report instruments in early language research. However, over- or under-reporting of stuttering in our study is unlikely, as the incidence of stuttering in our study population is in line with the literature. Second, we should note that the far majority of children with stuttering in the current study had probably not yet started to stutter at 24 months of age (Reilly et al., 2009). Although we relied on validated language questionnaires, the parent reports on language at ages 30-36 months and up could have been affected by children who had already started stuttering, since developmental stuttering typically starts around 30 months of age (Bloodstein et al., 2021). That would mean that the associations between stuttering and language skills at 30 months and up could be somewhat inflated. A third limitation is that we assessed language skills on a general level rather than syntactic encoding, linguistic planning, and processing. Expressive and receptive vocabulary is an important indicator of language development, however, it is primarily limited to assessing language skills in children under the age of three. Moreover, detailed information such as the time of stuttering onset, its duration, and therapy (e.g., type, duration) were unfortunately not available. Fourth, although we were able to convert the language scores into age- and sex-specific percentile scores (e.g. 15$^{th}$ specific-percentile or 2 SD absolute distance to the mean) based on the Generation R sample and on previous literature (Achenbach & Rescorla, 2000; Henrichs et al., 2013), the relatively small sample sizes within the stuttering groups limited our ability to use these scores in additional regression analyses. To address this limitation, we adjusted for several relevant variables

in the logistic regression models. Finally, due to specific age-related language skills, the language questionnaires were not identical (e.g., receptive language skills, expressive language skills, or a combination of both). Therefore, we analyzed the time points separately rather than looking at developmental trajectories of language.

Notwithstanding these limitations, our study has several advantages over previous studies. To our knowledge, this is one of the largest population-based studies to date focused on early language skill outcomes, enabling us to compare different fluency groups, specifically those who recovered and those who persisted in stuttering. Only a few studies have repeated language observations before stuttering onset (Reilly et al., 2013), or repeated observations to measure expressive language skill growth (Leech et al., 2017; Yairi & Ambrose, 1999). Our prospective study allowed us to examine differences in early language development in young children before and around the onset of stuttering, in comparison to children without this onset. In contrast to our study, most previous studies were conducted in clinically high-risk populations (e.g., one or both parents stuttered, risk of more severe stuttering, and comorbidity of speech or language problems), and used designs retrospectively assessing language. This might have generated information bias (e.g., parents who are aware of their infant's problems in dysfluency could have been more sensitive to lower language development). Besides, previous studies compared groups coming from appreciably higher social groups known to have higher language skills without controlling for it (Nippold, 2018; Ntourou et al., 2011; Watkins & Johnson, 2004). Furthermore, the short intervals (6 months) of the language reports follow-up between 18 and 48 months in our prospective study offers an advantage for specifically evaluating early childhood when language development may be related to stuttering incidence at preschool-age, or persistent stuttering at school-age.

## 4.4 Clinical implication and further research directions

Although our study did not find a relationship between language skills and stuttering persistence, previous research has observed such a connection. Our study underscores the importance of evaluating language skills as part of the diagnostic process for all young children who stutter. In line with others (Bernstein Ratner, 2018; Brundage & Bernstein Ratner, 2022; Brundage et al., 2021; Watkins & Yairi, 1997; Yairi & Seery, 2014), we recommend that screening children's language skills be included as part of an evaluation of early stuttering, as lower language skills were shown to add risk to childhood stuttering. If screening suggests low language skills, clinicians are recommended to formally test

expressive and receptive language skills. In combination with other risk factors, such as (persistent) stuttering in the family, male sex, and low socioeconomic status (SES, which may influence language development, access to services, and stuttering severity, potential predicting (persistence in) stuttering (Singer, Hessling, et al., 2020)), low language skills should motivate the clinician to start early stuttering intervention without any delay. This aligns with the recommendation in the German stuttering guideline stating that the simultaneous presence of developmental language problems should not lead to postponement of the indicated therapy for stuttering (Neumann et al., 2017).

Furthermore, additional clinical and epidemiological research is recommended to enable predicting the prognosis of children who stutter, and, in the end, to select the best clinical approach. Future research would benefit from collecting long-term language outcomes, including language outcomes that allow clinical classification to improve further understanding, from a large group of children who recovered or persisted in stuttering including language skills at similar time points as the stuttering assessments, stuttering severity and speech motor problems.

## 5. Conclusion

In conclusion, our study has contributed to the debate of the association between early language skills and stuttering by showing that lower language skills at 24 months of age add to the risk of stuttering history. However, we did not find a significant association between language skills and the risk of stuttering persistence. This contrasts with a meta-analysis by Singer et al. (2020), which found a relationship between lower language skills and stuttering persistence. Despite our study's focus on stuttering onset rather than persistence, it supports the broader view that lower language skills in early childhood, particularly around the time of stuttering onset, can be considered a risk factor for stuttering and its persistence. The level of language skills at stuttering onset can influence clinical decisions regarding whether to wait for natural recovery or to initiate treatment without delay. These findings underscore the value of early language assessments to investigate links with stuttering and identify co-occurring, clinically relevant language disorders, which may be more prevalent in children already presenting with one developmental concern. Therefore, clinicians are advised to screen the language skills of preschool-aged children referred within six months after stuttering onset. If screening indicates weak language skills, further formal language assessment is recommended.

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# Supplementary Materials

Supplementary Table 1. Language skill scores

| Language assessment | | All participants (n=2942) | | | Children with stuttering (n=123) | | |
|---|---|---|---|---|---|---|---|
| | | n | Children without a history of stuttering n=2819 (95.8%) | Children with a history of stuttering n=123 (4.2%) | n | Children who recovered from stuttering n=101 (82.1%) | Children who persisted in stuttering n=22 (17.9%) |
| **18 months** expressive vocabulary **(MCDI-N)** | | | | | | | |
| *Age* (months) | | | 18.1 (17.7-18.5) | 18.2 (17.8-18.6) | | 18.1 (17.8-18.5) | 18.4 (17.8-18.7) |
| *Score* | *median (IQR)* | 2591 | 14.0 (7.0-25.0) | 13.0 (5.0-21.0) | 103 | 13.0 (4.0-20.0) | 13.5 (6.8-31.3) |
| | *mean Z-score* | | 0.004 | -0.099 | | -0.14 | 0.08 |
| **18 months** receptive vocabulary **(MCDI-N)** | | | | | | | |
| *Age* (months) | | | 18.4 (17.8-18.5) | 18.5 (17.8-18.5) | | 18.1 (17.8-18.5) | 18.4 (17.8-18.7) |
| *Score* | *median (IQR)* | 2686 | 54.0 (37.0-73.0) | 50.0(33.0-66.0) | 109 | 49.0 (33.0-66.0) | 60.0 (33.8-72.8) |
| | *mean Z-score* | | 0.006 | -0.131 | | -0.16 | -0.03 |
| **24 months** expressive and receptive language skill **(CDI)** | | | | | | | |
| *Age* (months) | | | 24.2 (23.8-24.5) | 24.2 (23.8-24.6) | | 24.2 (23.8-24.6) | 24.4 (23.8-24.7) |
| *Score* | *median (IQR)* | 2649 | 9.0 (7.0-11.0 ) | 8.0 (6.0-10.5) | 113 | 9.0 (6.0-11.0) | 8.0 (6.3-10.0) |
| | *mean Z-score* | | 0.014 | -0.320 | | -0.31 | -0.34 |
| **30 months** expressive vocabulary **(LDS)** | | | | | | | |
| *Age* (months) | | | 30.7 (30.1-31.6) | 30.7 (30.1-32.5) | | 30.7 (30.1-32.9) | 30.8 (30.1-31.2) |
| *Score* | *median (IQR)* | 2698 | 260 (225-282) | 251 (204-280) | 104 | 256 (214-282) | 221 (180-254) |
| | *mean Z-score* | | 0.008 | -0.184 | | -0.08 | -0.67 |
| **36 months** expressive and receptive language skill **(CDI)** | | | | | | | |
| *Age* (months) | | | 36.1 (35.8-36.7) | 36.2 (35.8-36.7) | | 36.2 (35.8-36.7) | 36.0 (35.8-36.9) |
| *Score* | *median (IQR)* | 2528 | 16.0 (14.0-17.0) | 15.0 (14.0-16.0) | 100 | 16.0 (13.5-16.5) | 15.0 (14.3-16.0) |
| | *mean Z-score* | | 0.009 | -0.210 | | -0.18 | -0.35 |
| **48 months** expressive and receptive language skill **(CDI)** | | | | | | | |
| *Age* (months) | | | 48.2 (47.9-48.7) | 48.6 (47.9-49.0) | | 48.2 (47.9-49.0) | 48.4 (47.9-49.0) |
| *Score* | *median (IQR)* | 2946 | 12.0 (12.0-13.0) | 12.0 (11.0-13.0) | 109 | 12.0 (12.0-13.0) | 11.5 (10.8-12.3) |
| | *mean Z-score* | | 0.008 | -0.194 | | -0.13 | -0.52 |

All continuous variables are presented as median with interquartile range (IQR).
CDI = Child Development Inventory, LDS = Language Development Survey, MCDI-N = MacArthur Communicative Development Inventory-Netherlands, n = number

Supplementary Table 2. Proportion of children with low, moderate and high language assessment scores at 24 months (CDI) and 30 months LDS) in four fluency groups

| Language assessment | score range | Children without a history of stuttering | | Children with a history of stuttering | | Children who recovered from stuttering | | Children who persisted in stuttering | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | n | % |
| **24 months expressive and receptive language skill (CDI)** | 0-11 | 2539 | | 113 | | 93 | | 20 | |
| low | | 26 | 1% | 4 | 4% | 3 | 3% | 1 | 5% |
| moderate | | 625 | 25% | 41 | 36% | 35 | 38% | 6 | 30% |
| high | | 1888 | 74% | 68 | 60% | 55 | 59% | 13 | 65% |
| **30 months expressive vocabulary (LDS)** | 0-310 | 2494 | | 104 | | 86 | | 18 | |
| low | | 30 | 1% | 1 | 1% | 1 | 1% | 0 | 0% |
| moderate | | 945 | 38% | 49 | 47% | 38 | 44% | 11 | 61% |
| high | | 1519 | 61% | 54 | 52% | 47 | 55% | 7 | 39% |

CDI = Child Development Inventory, LDS = Language Development Survey, n = number
Low scores were defined as language assessment scores in the lowest 20th percentile, moderate scores were defined as language assessment scores in the 20th to 80th percentile, high scores were defined as language assessment scores in the highest 80th percentile


White matter
Persistent
Fluency
Speech
Research
Recov
Brain
Subcort
Satisfaction
Gray matter
Neuroimaging
Self-report
Explore
Cortical
Girls
Children
Stutter
Temperament
Population
Dysfluency
Fluency
Neuroplasticity
Boys
Outcome
Long-term
Brain
Speech
Behavior
Treat
Satisfaction
Development
Subcortical
Girls
Rotterdam
Self-report
Persistent
Stutter
Cortical
Boys
Population
Speech-motor


# 5

# Bidirectional associations of childhood stuttering with behavior and temperament

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## Abstract

**Purpose:** Behavior and temperament (e.g., emotional reactivity, self-regulation) have been considered relevant to stuttering and its developmental course, but the direction of this relation is still unknown. Knowledge of behavior difficulties and temperament in childhood stuttering can improve screening and intervention. The current study examined both directions of the relationship between stuttering and behavior difficulties and temperament, and between persistent stuttering and behavior difficulties and temperament across childhood.

**Method:** This study was embedded in the Generation R Study, a population-based cohort from fetal life onward in the Netherlands. We analyzed data from 145 children (4.2%) with a history of stuttering (118 recovered, 27 persistent) and 3276 children without such a history. Behavior and temperament were repeatedly assessed using parental questionnaires (Child Behavior Checklist (CBCL) and Infant/Child Behavior Questionnaire (IBQ/CBQ)) between 0.5 and 9 years of age. Multiple logistic and linear regression analyses were performed.

**Results:** Six-month-old children who were less able to "recover from distress," indicating poor self-regulation, were more likely to develop persistent stuttering later in childhood (odds ratio (OR) = 2.05, 95% confidence interval (CI) [1.03;4.05], $p$ = .04). In the opposite direction, children with a history of stuttering showed more negative affectivity (β = 0.19, 95% CI [0.02;0.37], $p$ = .03) at 6 years of age than children without such a history. Stuttering persistence was associated with increased internalizing behaviors (β = 0.38, 95% CI [0.03;0.74], $p$ = .04) and higher emotional reactivity (β = 0.53, 95% CI [0.09;0.89], $p$ = .02) at age 9.

**Conclusion:** Behavior and temperament were associated with stuttering persistency – seemingly both as predictor and consequence – but did not predict a history of stuttering. We suggest that children who persist in stuttering should be carefully monitored, and if behavioral or temperamental problems appear, treatment for these problems should be offered.

# 1. Introduction

## 1.1 Developmental stuttering

Developmental stuttering is a speech fluency disorder that originates in childhood between 2 and 5 years of age (Kefalianos et al., 2017a; Yairi & Ambrose, 2013). Stuttering occurs in 5-11% of preschool-age children (Boyle et al., 2011; Craig et al., 2002; Dworzynski et al., 2007; Månsson, 2000; Reilly et al., 2013). Three to nine years after onset, 65-80% will have recovered from stuttering, so that 20-35% children develop persistent stuttering (Ambrose et al., 2015; Andrews & Harris, 1964; Franken et al., 2018; Kefalianos et al., 2017; Månsson, 2000; Rommel et al., 1999; Yairi & Ambrose, 2013). Current views on the etiology and developmental course of stuttering emphasize multifactorial models combining genetic/epigenetic, neurobiological, speech motor control, linguistic, behavioral (temperament, executive functioning) and environmental (socioeconomic status) factors (Conture et al., 2013; Smith & Kelly, 1997; Smith & Weber, 2017). Of all these factors, temperament has most recently been considered as potentially relevant to stuttering incidence (i.e., having a history of stuttering) and its developmental course (Ambrose et al., 2015; Eggers et al., 2010; Rocha et al., 2019).



## 1.2 Behavior and temperament: Definition and characteristics

Rothbart and Derryberry (1981) define temperament as constitutionally based individual differences in emotional reactivity and self-regulation. A person with an emotionally reactive temperament has strong (intense and quick) emotional reactions, such as frustration, fear, excitement, joy or anger, to various situations. Reactivity also refers to a process or state determined by factors such as stimulus intensity, signal qualities, internal state and novelty (Rothbart, 1991). Self-regulation refers to processes that modulate (inhibit or stimulate) reactivity (Rothbart et al., 2011). There is a continuous interaction between emotional reactivity and self-regulation. With growth and development, self-regulation increases and comes under conscious control (Rothbart & Ahadi, 1994). Temperament is constitutional and is thought to be stable over time. However, comparable to personality, of which temperament is the predecessor, temperament can change slightly from early childhood onward. The child's ability to limit the impact of strong emotions, to self-regulate, may improve and is indicated by behaviors as for example, seeking comfort, self-talking, inhibiting approach, withdrawing, distracting, taking time-out from a situation, or shifting attention away from something that is emotionally arousing (Evans & Rothbart, 2007; Rothbart et al., 2001).

Problems with self-regulation can result in both externalizing and internalizing behaviors (Achenbach & Rescorla, 2000; Achenbach & Rescorla, 2001; Eisenberg et al., 2017). Externalizing behaviors are directed toward others and typically occur in interaction with others. They may include disruptive behavior that causes conflicts in relationships (e.g., attention problems, aggressive behavior). Internalizing behaviors are emotional symptoms turned toward oneself. They include fearfulness, social withdrawal, somatic complaints and negative affect as seen in anxiety disorders and depression. Those who internalize keep emotions to themselves.

## 1.3 Measurements of behavior and temperament

Researchers have examined behavior and temperament in preschool children near the timing of stuttering onset using several methods of measurement (Conture et al., 2013; Jones et al., 2014). First, using behavioral observations and experimental tests in home or clinical settings, researchers have found that preschool children who stutter show more emotional reactivity and poorer self-regulation skills than their nonstuttering peers (Choi et el., 2013; Eggers et al., 2012, 2013, 2018; Erdemir et al., 2018; Walden et al., 2012). Second, using psychophysiological methods - electroencephalograms, salivary cortisol, skin conductance level, respiratory sinus arrhythmia, or sympathetic activity - during video viewing or a stressful speaking task, some researchers have found that children who stutter show more emotional regulation (e.g., respiratory sinus arrhythmia or higher sympathetic arousal) during speaking or a stressful task (Arnold et al., 2011; Choi et al., 2016; Jones et al., 2014, 2017; Walsh et al., 2019; Zengin-Bolatkale et al., 2018). Third, parental reports have been widely used to study temperament and behavior in childhood (Putnam et al., 2006; Rothbart et al., 2001). Using a parental questionnaire, rating scale, performance test, or self-perception scale researchers have found a relationship between stuttering and temperament and behavior during early childhood. In the next two paragraphs, parent-report studies of temperament and behavior in preschool-age and school-age children who stutter are summarized in the following order: findings on temperament, externalizing behaviors, and internalizing behaviors.

## 1.4 Temperament, behavior and stuttering at preschool-ages

Parental reports reveal reactivity-related behaviors and poorer self-regulation in preschool children who stutter (Anderson, et al. 2003; Eggers et al., 2009; Embrechts et al., 2000; Karrass et al., 2006). Ambrose et al. (2015) found that an emotionally reactive

temperament and poorer self-regulating skills increase the risk that early childhood stuttering will persist (see Supplementary Table 1. for additional information about these and other studies). However, other researchers have failed to find differences in temperament between preschool children who do (persist) and do not stutter (Kefalianos et al., 2014, 2017).

Parental reports have been used to examine different types of comorbid problems in children who stutter. Studies among young children who stutter found that these children displayed more externalizing behaviors, more inattention (distractibility, perceptual sensitivity, and shifting attentional), hyperactivity-impulsivity (e.g., higher emotional reactivity), and poorer emotional regulation and inhibitory control than children who do not stutter (Anderson et al., 2003; Druker et al., 2019; Karrass et al., 2006). Some children who stutter are likely to exhibit these behaviors even though they might not have a clinical diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) (Lee et al., 2017; Tetnowski, 2004). Furthermore, Alm (2014) argued that hyperactivity might be a positive (i.e., advantageous) prognostic factor in the development of childhood stuttering, since children who stutter with a family history of recovering stuttering showed a higher occurrence of traits related to ADHD than children with a family history of only persistent stuttering (Donaher & Richels, 2012). Studies investigating internalizing behaviors in preschool-age children found that children who stutter show some more indication of negative affectivity and a slightly higher level of shyness and sadness, though was not statistically significant (Alm, 2014; Eggers et al., 2010; Smith et al., 2014). Stuttering was also not related to social or general anxiety during the preschool period (Kefalianos et al., 2014; van der Merwe et al., 2011).



## 1.5 Temperament, behavior and stuttering at school-age

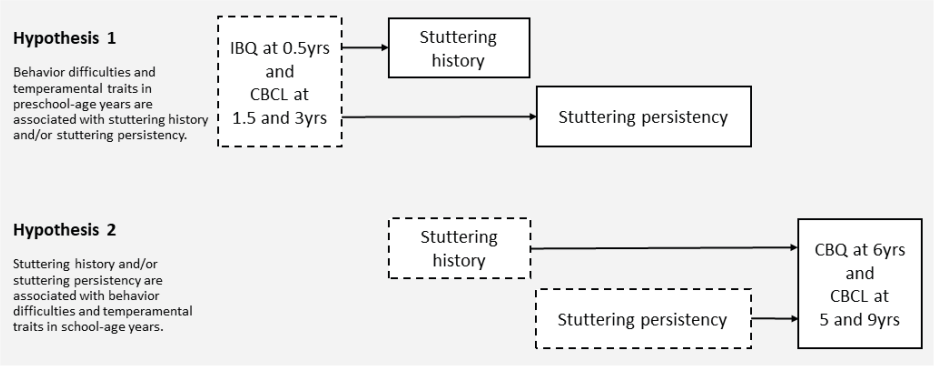
Research on the direction of the association between persistent stuttering and temperament, and persistent stuttering and behavior at later school-ages is limited. So far, only a few studies have explored the relationship between persistent stuttering and temperament during the school-age years, using a parent questionnaire, performance test or self-perception scale (Hollister & Zebrowski, 2015; Rocha et al., 2019). Both of these studies found that school-age children who stutter experienced greater emotional reactivity and more regulation problems than their nonstuttering peers. With regard to externalizing behaviors, Donaher and Richels (2012) found that children who recovered showed higher levels of ADHD than those who persisted in stuttering, and Iverach et

al. (2017) found that boys who stuttered showed more aggressive and rule-breaking behavior. However, the cross-sectional design of this study, with measurements at only one point in time, did not allow for conclusions about the direction of the relationship. With regard to internalizing behaviors, and in contrast to preschool children who stutter, school-aged children who stutter appear to have internalizing behaviors, although within normal variation and not directly indicating clinical disorders (De Nil & Brutten, 1991; McAllister, 2016). Specifically, school-age children who stutter were shown to exhibit higher sensitivity, vulnerability, and negative attitudes toward speech (De Nil & Brutten, 1991; Fowlie & Cooper, 1978). However, other studies did not find that stuttering persistence was related to internalizing behaviors at school-age (Rocha et al., 2019; Smith et al., 2017). Additionally, studies in (young) adolescents who stutter reported elevated social anxiety, compared to those who recovered and controls (Blood et al., 2007; Davis et al., 2007; Gunn et al., 2014; Iverach et al., 2016). A plausible explanation for internalizing and social problem behaviors in those who persist in stuttering is that they have to deal with issues such as bullying and negative evaluations, which might lead to social phobia (Beilby et al., 2013; Blood & Blood, 2016; Blood et al., 2011).

## 1.6 The current study (hypotheses)

Despite reported associations of behavior and temperament with childhood stuttering, the direction of these relations remains unknown because of the cross-sectional design of most studies. As others, we believe that behavior and temperament may be associated with the incidence and development of stuttering, and that stuttering may also cause or exacerbate psychosocial problems. Identifying the nature of this relationship in childhood can help us understand why stuttering develops and persists, and how we may improve early intervention strategies, for example, when to start intervention and how to determine the type, frequency, and duration of treatment. The present longitudinal study assessed bidirectionality in the relation of behavior and temperament with stuttering across childhood (Figure 1). We hypothesized that behavior difficulties such as internalizing and externalizing behavior and traits of temperamental such as fear, recovery from distress, or sadness at preschool-age are associated with stuttering and its persistence (hypothesis 1). Furthermore, we hypothesized that stuttering and its persistence may be associated with behavior difficulties and traits of temperament such as high reactivity and poor self-regulation, later during school-age years (hypothesis 2).

Figure 1. Hypotheses and timeline of data collection points




CBCL = Child Behavior Checklist, CBQ = Child Behavior Questionnaire, IBQ-R = Infant Behavior Questionnaire Revised

# 2. Method

## 2.1 Study design and population

This study was embedded in the Generation R Study, a multi-ethnic population-based prospective cohort from fetal life onward in Rotterdam, the Netherlands (Kooijman et al., 2016). The study enrolled pregnant woman living in Rotterdam between April 2002 and January 2006 (n = 9901), a sample that was largely representative of the Rotterdam female population. The parents of all participating children gave written informed consent and the study was approved by the Medical Ethics Committee of the Erasmus Medical Center. When the children were 9 years old, their parents were sent a questionnaire about speech and language development (n = 6887). The questionnaire was returned for 4141 children (60.1%). Children with incomplete information on stuttering (n = 312), with another (un) defined language disorder (n = 398), or with missing data on all assessments of behavior and temperament (n = 10) were excluded, resulting in a sample of 3421 children. Of these, 3276 children had no history of stuttering and 145 (4.2%) had a history of stuttering, of whom 27 (18.6%) persisted and 118 children (81.4%) recovered from stuttering by age 9. A flowchart of the subject selection process is in Supplementary Figure 1.

## 2.2 Measures

### 2.2.1 Stuttering

When children were 9 years of age, parents completed a speech and language development questionnaire that contained four yes/no questions about stuttering. Two questions

regarding present or past stuttering history ("Does your child currently stutter?" and "Has your child ever stuttered in the past?") and two questions about treatment for stuttering ("Is your child currently being treated for stuttering?" and "Has your child ever been treated for stuttering in the past?"). Participants were classified as children with a history of stuttering if a parent answered "yes" to one of these questions. Participants were classified as children with persistent stuttering if a parent answered "yes" to both questions. The classification of stuttering and persistent stuttering was not determined directly, by speech sample or expert assessment at any point in the Generation R Study, but was based only on parental reports of 9-year-old children. Parental reports have been used in several previous studies of persistence and recovery of stuttering in childhood (Dworzynski et al., 2007; Kloth et al., 1999; Koenraads et al., 2019; Månsson, 2000). Parents of children who stutter and parents of nonstuttering children can accurately and reliably identify the absence/presence of stuttering (Bloodstein & Bernstein-Ratner, 2008; Einarsdottir & Ingham, 2009; Onslow et al., 2018; Reilly et al., 2009; Tumanova et al., 2018). This last study retrospectively examined behavior and temperament from data collected when the children were younger (at ages 6 months and 18 months, and 3, 5 and 6 years), and currently (at 9 years).

### 2.2.2 Behavioral assessment

Behavior was assessed using the parent reported Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2000; Achenbach & Rescorla, 2001). The CBCL is a widely used inventory that is a reliable and valid screening tool for mental health problems in children (Achenbach & Ruffle, 2000), and it has been shown to predict Diagnostic and Statistical Manual of Mental Disorders (DSM) based psychiatric disorders (Hofstra et al., 2002). The CBCL is used as a screening instrument for behavior problems and not for examining the full range of a child's behavior. This checklist quantifies behavior problems across a broad spectrum of behaviors making it possible to compare the behavior problems of children who stutter. In the Generation R Study Achenbach and Rescorla (2000) administered the CBCL/1.5-5 (preschool version) at ages 1.5, 3 and 5 years and (see Figure 1) at age 9 years. The same researchers administered the CBCL/6-18 (school-age version) (Achenbach & Rescorla, 2001). Items were scored by parents on a three-point scale (0 = not true, 1 = somewhat or sometimes true, 2 = very or often true), based on behavior over the past two months in the preschool version and over the past six months in the school-age version. By using age-appropriate items, both of the two CBCL versions include two broadband

scales (i.e., externalizing and internalizing). These broadband scales are based on second-order factor analyses of factor-analytically derived syndromes, measuring behavioral problems on a continuous severity scale. Given the specific literature on stuttering and emotional reactivity, we also examined the DSM-oriented scale of emotional reactivity (Basten et al., 2013). This nine-item scale is a validated scale of the CBCL/1.5-5, while the CBCL/6-18 has no official emotional reactivity scale. Therefore, we created an emotional reactivity scale by summing five-items of the CBCL/1.5-5 emotional reactivity scale that were also assessed in the older version. The internal consistency of the scales in our sample was good with a Cronbach's alpha of 0.63 for emotional reactivity and more than 0.70 for all other scales (Achenbach & Edelbrock, 1983).



### 2.2.3 Assessment of temperament

Children's temperament was assessed by parental reports when the children were 0.5 and 6 years old (Figure 1), using an adapted version of the Infant and Child Behavior Questionnaires (IBQ-R) (Gartstein & Rothbart, 2003) and CBQ (Rothbart et al., 2001). These questionnaires consist of age-appropriate items to assess temperament in infancy and childhood. Details have previously been described (Gartstein & Rothbart, 2003; Jansen et al., 2009; Roza et al., 2008). Briefly, the IBQ-R at 6 months of age assesses different temperamental traits, of which we assessed activity level (e.g., movements of arms and legs, 12 items), distress to limitations (e.g., fussing or crying while in caretaking activities, 13 items), duration of orienting (e.g., attention to a single object for extended periods of time, 10 items), fear (e.g., startle or distress to novelty or sudden changes in stimulation, 15 items), recovery from distress (e.g., rate of recovery from general arousal, or ease of falling asleep, 12 items), and sadness (e.g., general low mood, 12 items). Parents were asked to indicate how often the infant engaged in the various behaviors during the last week. Items were scored by parents on a 3-point scale (0 = never, 1 = sometimes, 2 = often). Higher scale scores indicate more of a problem, but do not directly point to a disorder level.

The CBQ, assessed at 6 years of age, provides a highly differentiated assessment of temperament in children (Rothbart et al., 2001). The questionnaire clusters three broad dimensions, labeled as extraversion/surgency (or positive reactivity, 12 items), negative affectivity (or negative reactivity, 12 items), and effortful control (self-regulation, 12 items). Parents were asked to tell how the child reacted in various situations during the last six months. Parents scored the answer that was most applicable to their children's reaction

on an 8-point scale (from 1 = extremely untrue, 7 = extremely true, to 8 = not applicable) for each of the scales. In the CBQ, surgency comprises the subscales impulsivity, activity level, high intensity pleasure, motor activation, shyness, approach, and smiling/laughter. Negative affectivity comprises the scales anger/frustration, discomfort, sadness, fear, and decreasing reactivity/soothability. Finally, effortful control comprises the scales low intensity pleasure, inhibitory control, perceptual sensitivity, attentional focusing and shifting, and excitatory control. Due to developmental changes, items and subscales belonging to specific temperamental factors are slightly different between the IBQ-R and CBQ versions. Internal consistencies for the adapted IBQ-R (ranged from 0.70 to 0.83) and CBQ (ranged from 0.69 to 0.74) are comparable to the internal consistencies of the original questionnaires (Gartstein & Rothbart, 2003; Rothbart et al., 2001).

### 2.2.4 Covariates

Participants' characteristics, including maternal age at intake, ethnicity, education, and psychopathology, as well as childrens' characteristics derived from medical records, ethnicity, mono- or bilingualism, intelligence, and psychotherapy were obtained prospectively by questionnaires. Maternal age at intake was taken at the first visit of the study. The majority entered the study early in pregnancy. Maternal ethnicity was defined according to the categorization of Statistics Netherlands, into Western (Dutch and Non-Dutch Western) and non-Western (Statistics Netherlands, 2004). Maternal educational level was categorized into low to medium, and high education levels (consisting of higher vocational education or university) (Statistics Netherlands, 2005). Maternal psychopathology symptoms were assessed in a prenatal questionnaire, through the 53-item self-reported Brief Symptom Inventory (BSI) (Derogatis & Melisaratos, 1983). Birth predictions (gestational age and birth weight), date of birth, and sex were taken from medical records. Child ethnicity was defined as Western (Dutch and Non-Dutch Western) and non-Western (Kooijman et al., 2016; Statistics Netherlands, 2004). Child intelligence was measured at 6 years of age with the Snijders-Oomen nonverbal intelligence test (Tellegen et al., 2005). At children's age of 9 years, parents completed a questionnaire assessing information about Dutch native language, treatment for stuttering, and psychotherapy. Treatment for stuttering was categorized as either: never had treatment for stuttering, or ever had treatment for stuttering, speech and/or language problems. Finally, information about whether 9-year-old children had received psychosocial treatment in the last twelve months was assessed.

## 2.3 Statistical analyses

For the main analyses, we divided the total sample into two groups. First, we identified children with a history or incidence of stuttering (with no distinction between persistent and recovered stuttering), and children without such a history. Second, we divided the group of children with a history of stuttering into two subgroups: children in whom stuttering persisted, and children who recovered from stuttering. Differences in descriptive characteristics between the groups were determined using Chi-squared and Fisher's exact tests for categorical variables and t-tests for continuous variables. All behavior and temperament scores were transformed into standard deviation (SD) scores across the study sample to enable comparability. Data outliers and missing values were checked. Because of different data collection points for CBCL and IBQ-R/CBQ, the number of participants included in each analysis varied.



In logistic regression analyses (hypothesis 1), we retrospectively examined whether behavior (externalizing, internalizing, emotionally reactive) at the ages of 1.5 and 3 years predicted the incidence of stuttering (comparing children with and without a history of stuttering). We also retrospectively examined whether temperamental traits (fear, recovery from distress, sadness) of infants at 6 months of age predicted the incidence of stuttering. Both analyses were repeated to examine whether behavioral difficulties or temperamental traits in early childhood predicted stuttering persistency (comparing children who persisted in stuttering and those who recovered). The presented models were unadjusted and adjusted for covariates. For all logistic regression analyses, values are presented in odds ratios (OR) and 95% confidence interval (95% CI). Since there may be overlap in the behaviors and temperament across the CBCL at different ages and the IBQ-R and CBQ, correlations between the measurements were analyzed (Pearson correlations in Supplementary Table 2.).

In linear regression analyses (hypothesis 2), we examined the relationship between stuttering history and behavior (externalizing, internalizing, emotionally reactive) at ages 5 and 9 years. We also examined the relationship between stuttering history and temperamental traits (effortful control, negative affectivity, surgency) at 6 years of age. Both analyses were repeated to examine the relationship between stuttering persistency, and behavioral difficulties and temperamental traits. The presented models were unadjusted, adjusted for covariates, and additionally adjusted for baseline behavior scores (at 1.5 and 3 years). In all linear regression analyses, values are presented in beta coefficients (β) and 95% CI.

To reduce the effect of selective non-responding, multiple imputation techniques were used to account for missing values in covariates (maximum percentage: 22.4% for maternal psychopathology, Supplementary Table 3.) (Sterne et al., 2009). Multiple imputations were based on the relations between available information on all variables included in the current study. The reported effect estimates are the pooled results of five imputed datasets according to standard procedures (Rubin, 2004). All analyses were performed in SPSS (version 24.0).

# 3. Results

## 3.1 Descriptions of study sample

The baseline sample characteristics are shown in Table 1. Boys stuttered more often than girls (68.3% vs. 31.7%, respectively), and boys persisted more often than girls (77.8% vs 22.2%, respectively). In the study sample, mothers were relatively highly educated with 66.2% having a higher vocational education or university degree. Descriptive characteristics of behavior and temperament scores are shown in Table 2.

## 3.2 Associations of behavior and temperament in early childhood with stuttering history and its developmental course (hypothesis 1)

In the first set of logistic regression analyses, behavioral scores at 1.5 and 3 years were not statistically significantly associated with the risk of stuttering history, nor with the risk of stuttering persistence in later school-age years (Table 3, $p > .05$).

Likewise, temperamental trait scores at 6 months were also not associated with risk of stuttering history (Table 4, $p > .05$), except for the "recovery from distress" scale score, where higher scores were associated with persistent stuttering (OR = 2.05, 95% CI [1.03;4.05], $p = .04$). This OR means that poorer ability to recover from distress at 6 months, an indication of higher reactivity and poorer self-regulation, was associated with an increased risk of persistent stuttering.

Table 1. Participants' characteristics

| Participants' characteristics | All participants (n = 3421) Mean (SD) or n (%) | | | Children with a history of stuttering (n = 145) Mean (SD) or n (%) | | |
|---|---|---|---|---|---|---|
| | Children without a history of stuttering n = 3276 (95.8%) | Children with a history of stuttering n =145 (4.2%) | *p* | Children who recovered from stuttering n = 118 (81.4%) | Children who persisted in stuttering n = 27 (18.6%) | *p* |
| **Child characteristics** | | | | | | |
| Gestational age at birth (weeks) | 39.8 (1.9) | 39.8 (1.7) | .95 | 39.8 (1.8) | 39.9 (1.2) | .78 |
| Birth weight (gram) | 3434 (578) | 3454 (539) | .62 | 3443 (553) | 3527 (479) | .46 |
| Sex (% boy) | 1571 (48.0%) | 99 (68.3%) | < .01* | 78 (66.1%) | 21 (77.8%) | .36 |
| Ethnicity (% Western) | 2552 (78.3%) | 107 (74.3%) | .26 | 90 (76.9%) | 17 (63.0%) | .15 |
| Multilingualism (% yes) | 625 (19.4%) | 30 (20.8%) | .67 | 23 (19.5%) | 7 (26.9%%) | .43 |
| Intelligence Quotient at 6 years (score) | 104.3 (14.1) | 103.0 (15.6) | .31 | 103.3 (15.7) | 101.4 (15.4) | .57 |
| Age at stuttering questionnaire (years) | 9.8 (0.4) | 9.8 (0.3) | .89 | 9.9 (0.4) | 9.7 (0.2) | .06 |
| Ever had treatment for stuttering (% yes) | 0 | 65 (44.8%) | - | 46 (38.9%) | 19 (70.4%) | .01* |
| Ever had treatment for stuttering, speech and/or language problems (% yes) | 585 (17.9%) | 79 (54.5%) | < .01* | 60 (50.8%) | 19 (70.4%) | .05 |
| Psychosocial treatment at 9 years (% yes) | 247 (7.6%) | 14 (10.5%) | .26 | 10 (9.1%) | 4 (17.4%) | .26 |
| **Maternal characteristics** | | | | | | |
| Maternal age at intake (years) | 31.9 (4.50) | 31.1 (4.2) | .03* | 30.9 (4.3) | 31.5 (4.0) | .51 |
| Maternal ethnicity (% Western) | 2490 (76.5%) | 105 (72.9%) | .61 | 89 (76.1%) | 16 (59.3%) | .09 |
| Psychopathology score | 0.2 (0.3) | 0.2 (0.3) | .32 | 0.3 (0.3) | 0.2 (0.3) | .61 |
| Maternal education level (% high) | 2042 (66.3%) | 88 (64.2%) | .65 | 75 (66.4%) | 13 (54.2%) | .35 |

For all continuous variables the mean with standard deviation (SD) are presented; for categorical variables the n (%) is presented.
In the *total sample* (n = 3421), data was missing for some variables: gestational age (n = 3404), birth weight (n = 3418), child ethnicity (n = 3403), multilingualism (n = 3364), IQ (n = 2974), psychotherapy (n = 3240), maternal ethnicity (n = 3401), psychopathology score (n = 2655), and education (n = 3218).
In the *children with a history of stuttering* sample (n = 145), data was missing for some variables: child multilingualism (n = 144), IQ (n = 105), psychotherapy (n = 133), maternal ethnicity (n = 144), psychopathology score (n = 121), and education (n = 144).
* $p < .05$

Table 2. Descriptive behavioral and temperamental scores

| Outcomes questionnaires | All participants (n = 3421) Median (IQR) | | | Children with a history of stuttering (n = 145) Median (IQR) | | |
|---|---|---|---|---|---|---|
| | Children without a history of stuttering n = 3276 (95.8%) | Children with a history of stuttering n = 145 (4.2%) | *p* | Children who recovered from stuttering n = 118 (81.4%) | Children who persisted in stuttering n = 27 (18.6%) | *p* |
| **Behavior** | | | | | | |
| **CBCL at 1.5 years** | | | | | | |
| Age (months) | 18.4 (17.8-18.5) | 18.2 (17.8-18.6) | .11 | 18.1 (17.8-18.5) | 18.4 (17.8-18.7) | .49 |
| Externalizing score | 9.0 (5.0-14.0) | 9.0 (5.0-17.0) | .65 | 9.0 (5.0-16.0) | 9.0 (3.0-20.0) | .90 |
| mean Z-score | -0.005 | 0.111 | .24 | 0.096 | 0.186 | .77 |
| in normal range (n,%) | 2263 (88.9) | 86 (80.4) | .03* | 73 (82.0) | 13 (72.2) | .34 |
| Internalizing score | 4.0 (2.0-6.0) | 4.0 (2.0-7.0) | .20 | 4.0 (2.0-6.7) | 4.1 (1.0-11) | .93 |
| mean Z-score | -0.006 | 0.145 | .13 | 0.114 | 0.295 | .60 |
| in normal range (n,%) | 2402 (94.8) | 100 (93.5) | .56 | 84 (94.4) | 16 (88.9) | .39 |
| Emotionally reactive score | 1.0 (0.0-2.0) | 1.0 (0.0-3.0) | .25 | 1.0 (0.0-2.3) | 1.0 (0.0-3.3) | .85 |
| mean Z-score | -0.005 | 0.106 | .26 | 0.073 | 0.270 | .48 |
| in normal range (n,%) | 2485 (98.0) | 102 (95.3) | .21 | 86 (96.6) | 16 (88.9) | .34 |
| **CBCL at 3 years** | | | | | | |
| Age (months) | 36.1 (35.8-36.7) | 36.2 (35.8-36.7) | .85 | 36.6 (35.8-36.7) | 36.1 (35.8-37.0) | .90 |
| Externalizing score | 7.0 (3.0-11.0) | 7.0 (4.0-12.0) | .40 | 7.2 (4.0-12.0) | 4.0 (2.8-13.5) | .33 |
| mean Z-score | -0.004 | 0.104 | .27 | 0.123 | 0.007 | .68 |
| in normal range (n,%) | 2086 (80.6) | 83 (76.9) | .33 | 71 (78.9) | 12 (66.7) | .27 |
| Internalizing score | 4.0 (2.0-6.0) | 4.0 (2.0-7.8) | .30 | 4.0 (2.0-8.0) | 3.5 (1.0-7.3) | .47 |
| mean Z-score | -0.007 | 0.176 | .15 | 0.165 | 0.231 | .84 |
| in normal range (n,%) | 2097 (81.1) | 81 (75.0) | .16 | 67 (74.4) | 14 (77.8) | .77 |
| Emotionally reactive score | 1.0 (0.0-2.0) | 1.0 (0.0-2.0) | .29 | 1.0 (0.0-2.0) | 1.0 (0.0-2.3) | .30 |
| mean Z-score | -0.005 | 0.118 | .21 | 0.146 | -0.026 | .55 |
| in normal range (n,%) | 2054 (79.4) | 85 (78.7) | .86 | 71 (78.9) | 14 (77.8) | .92 |

| Outcomes questionnaires | All participants (n = 3421) Median (IQR) | | | Children with a history of stuttering (n = 145) Median (IQR) | | |
|---|---|---|---|---|---|---|
| | Children without a history of stuttering n = 3276 (95.8%) | Children with a history of stuttering n = 145 (4.2%) | *p* | Children who recovered from stuttering n = 118 (81.4%) | Children who persisted in stuttering n = 27 (18.6%) | *p* |
| **CBCL at 5 years** | | | | | | |
| Age (years) | 5.9 (5.8-6.1) | 5.9 (5.8-6.1) | .77 | 5.9 (5.8-6.1) | 5.9 (5.7-6.1) | .37 |
| Externalizing score | 5.0 (2.0-10.0) | 7.0 (3.0-11.0) | .02* | 6.0 (3.0-11.0) | 8.0 (2.0-16.8) | .30 |
| mean Z-score | -0.007 | 0.156 | .06 | 0.093 | 0.443 | .20 |
| Internalizing score | 4.0 (2.0-7.0) | 5.0 (2.0-8.0) | .10 | 5.0 (2.0-8.0) | 6.0 (1.0-11.5) | .52 |
| mean Z-score | -0.004 | 0.092 | .27 | 0.043 | 0.315 | .31 |
| Emotionally reactive score | 1.0 (0.0-2.0) | 1.0 (0.0-3.0) | .18 | 1.0 (0.0-2.0) | 1.0 (0.0-3.0) | .71 |
| mean Z-score | -0.001 | 0.027 | .75 | -0.000 | 0.149 | .43 |
| **CBCL at 9 years** | | | | | | |
| Age (year) | 9.7 (9.5-9.8) | 9.7 (9.6-9.8) | .76 | 9.7 (9.6-9.8) | 9.6 (6.5-9.8) | .07 |
| Externalizing score | 2.0 (0.0-5.0) | 3.0 (1.0-5.0) | .21 | 3.0 (0.3-5.0) | 3.0 (1.0-6.0) | .38 |
| mean Z-score | -0.002 | 0.046 | .57 | 0.006 | 0.219 | .31 |
| in normal range (n,%) | 2589 (81.8) | 118 (82.5) | .83 | 97 (83.6) | 21 (77.8) | .32 |
| Internalizing score | 3.0 (1.0-6.0) | 3.1 (2.0-6.0) | .12 | 3.0 (2.0-6.0) | 5.0 (2.1-9.0) | .08 |
| mean Z-score | -0.001 | 0.020 | .81 | -0.042 | 0.289 | .06 |
| in normal range (n,%) | 2547 (80.4) | 112 (78.3) | .53 | 93 (80.2) | 19 (70.4) | .48 |
| Emotionally reactive score | 1.0 (0.0-2.0) | 1.0 (0.0-2.0) | .11 | 1.0 (0.0-2.0) | 1.0 (1.0-3.0) | .04* |
| mean Z-score | -0.005 | 0.109 | .19 | 0.014 | 0.515 | .06 |
| **Temperament** | | | | | | |
| **IBQ at 0.5 years** | | | | | | |
| Age (months) | 6.4 (6.0-7.6) | 6.3 (6.0-7.4) | .56 | 6.4 (6.1-7.5) | 6.4 (5.8-7.5) | .70 |
| Activity level | 0.8 (0.5-1.0) | 0.8 (0.5-0.8) | .61 | 0.7 (0.5-0.9) | 0.8 (0.5-1.0) | .52 |
| mean Z-score | 0.001 | -0.034 | .76 | -0.086 | 0.163 | .35 |

| Outcomes questionnaires | All participants (n = 3421) Median (IQR) | | | Children with a history of stuttering (n = 145) Median (IQR) | | |
|---|---|---|---|---|---|---|
| | Children without a history of stuttering n = 3276 (95.8%) | Children with a history of stuttering n = 145 (4.2%) | *p* | Children who recovered from stuttering n = 118 (81.4%) | Children who persisted in stuttering n = 27 (18.6%) | *p* |
| Distress to limitations | 0.7 (0.5-0.8) | 0.7 (0.5-0.8) | .99 | 0.7 (0.5-0.8) | 0.7 (0.3-0.8) | .85 |
| mean Z-score | 0.002 | -0.044 | .68 | -0.005 | -0.193 | .46 |
| Fear | 0.3 (0.1-0.5) | 0.3 (0.1-0.5) | .82 | 0.3 (0.1-0.4) | 0.3 (0.1-0.7) | .59 |
| mean Z-score | -0.000 | 0.008 | .94 | -0.062 | 0.281 | .20 |
| Duration of orienting | 1.0 (0.7-1.2) | 1.0 (0.8-1.3) | .15 | 1.0 (0.8-1.3) | 1.1 (0.6-1.3) | .34 |
| mean Z-score | -0.006 | 0.159 | .15 | 0.176 | 0.090 | .77 |
| Recovery from distress | 1.6 (1.3-1.8) | 1.6 (1.3-1.8) | .70 | 1.5 (1.3-1.8) | 1.7 (1.5-1.9) | .13 |
| mean Z-score | -0.003 | 0.063 | .57 | -0.050 | 0.485 | .04* |
| Sadness | 0.7 (0.4-0.8) | 0.7 (0.5-0.9) | .14 | 0.8 (0.5-0.9) | 0.6 (0.4-0.8) | .07 |
| mean Z-score | -0.007 | 0.157 | .14 | 0.263 | -0.256 | .09 |
| **CBQ at 6 years** | | | | | | |
| Age (years) | 6.0 (5.8-6.2) | 6.0 (5.8-6.3) | .98 | 6.1 (5.8-6.3) | 6.0 5.8-6.3) | .56 |
| Effortful control | 5.3 (4.9-5.8) | 5.3 (4.7-5.8) | .31 | 5.3 (4.8-5.8) | 4.5 (3.6-5.2) | .29 |
| mean Z-score | 0.005 | -0.111 | .20 | -0.037 | -0.435 | .18 |
| Negative affectivity | 3.7 (3.1-4.3) | 3.8 (3.3-4.3) | .03* | 3.8 (3.3-4.3) | 3.8 (3.6-4.9) | .09 |
| mean Z-score | -0.008 | 0.191 | .03* | 0.162 | 0.318 | .46 |
| Surgency | 4.4 (3.9-5.0) | 4.5 (3.8-5.0) | .95 | 4.5 (3.8-5.0) | 4.5 (3.6-5.2) | .95 |
| mean Z-score | 0.001 | -0.026 | .77 | -0.031 | -0.001 | .89 |

CBCL = Child Behavior Checklist, CBQ = Child Behavior Questionnaire, IBQ = Infant Behavior Questionnaire
All continuous variables are presented as median with interquartile range (IQR).
In normal range means that children did not scored in the borderline or clinical behavioral range
In the *total sample* (n=3421), data was missing for some questionnaires: CBCL at 1,5 years (n=2653), CBCL at 3 years (n=2695), CBCL at 5 years (n=3218), CBCL at 9 years (n=3308), CBQ at 0,5 years (n=2081), and CBQ at 6 years (n=3029).
In the *children with a history of stuttering* sample (n=145), data was missing for some questionnaires: based on CBCL at 1,5 years (n=107), CBCL at 3 years (n=108), CBCL at 5 years (n=137), CBCL at 9 years (n=142), CBQ at 0,5 years (n=83), and CBQ at 6 years (n=129).
* $p < 0.05$

Table 3. Behaviors in preschool years and stuttering history and stuttering persistency

| CBCL score | Risk of stuttering history | | | | | Risk of stuttering persistency | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Unadjusted | | Confounder adjusted # | | | Unadjusted | | Confounder adjusted # | |
| | n | OR (95% CI) | *p* | OR (95% CI) | *p* | n | OR (95% CI) | *p* | OR (95% CI) | *p* |
| **at 1.5 years** | | | | | | | | | | |
| Externalizing | 26 | 1.12 | .24 | 1.04 | .68 | 107 | 1.06 | .77 | 1.04 | .87 |
| Internalizing | 26 | 1.14 | .13 | 1.07 | .49 | 107 | 1.15 | .52 | 1.25 | .48 |
| Emotionally reactive | 26 | 1.11 | .26 | 1.06 | .54 | 107 | 1.18 | .48 | 1.19 | .21 |
| **at 3 years** | | | | | | | | | | |
| Externalizing | 26 | 1.11 | .27 | 1.04 | .72 | 108 | 0.90 | .68 | 0.83 | .49 |
| Internalizing | 26 | 1.17 | .06 | 1.12 | .23 | 108 | 1.04 | .84 | 1.04 | .88 |
| Emotionally reactive | 26 | 1.12 | .21 | 1.07 | .47 | 108 | 0.86 | .55 | 0.79 | .42 |

CBCL = Child Behavior Checklist, CI = confidence interval, OR = odds ratio, SD = standard deviation
Values were derived from logistic regression analyses in children with and without a history of stuttering. CBCL scores were Z-standardized across the study sample.
Confounders included child sex, and maternal ethnicity, education, and psychopathology score
* $p < 0.05$

Table 4. Temperament at 6 months and stuttering history and stuttering persistency

| IBQ-R at 6 months | Risk of stuttering history | | | | | Risk of stuttering persistency | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Unadjusted | | Confounder adjusted # | | | Unadjusted | | Confounder adjusted # | |
| | n | OR (95% CI) | *p* | OR (95% CI) | *p* | n | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Activity level | 20 | 0.97 | .76 | 0.90 | .37 | 81 | 1.29 | .35 | 1.21 | .52 |
| Distress to limitation | 20 | 0.95 | .68 | 0.87 | .24 | 82 | 0.80 | .46 | 0.75 | .37 |
| Fear | 20 | 1.01 | .94 | 1.01 | .97 | 83 | 1.38 | .21 | 1.75 | .07 |
| Duration of orienting | 20 | 1.18 | .15 | 1.15 | .22 | 80 | 0.92 | .77 | 0.85 | .59 |
| Recovery from distress | 20 | 1.07 | .57 | 1.16 | .22 | 81 | 1.90 | .05* | 2.05 | .04* |
| Sadness | 20 | 1.18 | .14 | 1.10 | .41 | 83 | 0.64 | .09 | 0.62 | .14 |

CI = confidence interval, IBQ-R = Infant Behavior Questionnaire Revised, OR = odds ratio, SD = standard deviation
Values were derived from logistic regression analyses in children with and without a history of stuttering. IBQ-R scores were Z-standardized across the study sample.
Confounders included child sex, and maternal ethnicity, education, and psychopathology score
* $p < .05$

Table 5. Relation of stuttering history and stuttering persistency with later behaviors in school years

| | CBCL score | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | At 5 years | | | | | | | | | At 9 years | | | | | | | | |
| | Externalizing | | | Internalizing | | | Emotionally reactive | | | Externalizing | | | Internalizing | | | Emotionally reactive | | |
| | n | beta (95% CI) | *p* | n | beta (95% CI) | *p* | n | beta (95% CI) | *p* | n | beta (95% CI) | *p* | n | beta (95% CI) | *p* | n | beta (95% CI) | *p* |
| **Stuttering history** | | | | | | | | | | | | | | | | | | |
| Unadjusted | 3218 | 0.16 (-0.01-0.33) | .06 | 3207 | 0.10 (-0.07;0.27) | .27 | 3203 | 0.03 (-0.14-0.20) | .75 | 3306 | 0.05 (-0.12;0.22) | .57 | 3308 | 0.02 (-0.15;0.19) | .80 | 3301 | 0.11 (-0.05;0.28) | .18 |
| Confounder adjusted # | 3218 | 0.08 (-0.09;0.25) | .35 | 3207 | 0.05 (-0.12;0.21) | .59 | 3203 | -0.02 (-0.19;0.15) | .81 | 3306 | -0.02 (-0.18;0.15) | .84 | 3308 | 0.01 (-0.16;0.18) | .92 | 3301 | 0.09 (-0.07;0.26) | .28 |
| *Additionally adjusted for* | | | | | | | | | | | | | | | | | | |
| CBCL at 1.5 years | 2537 | 0.13 (-0.04;0.30) | .14 | 2521 | 0.07 (-0.11;0.24) | .45 | 2522 | 0.02 (-0.16;0.20) | .81 | 2577 | -0.01 (-0.19;0.17) | .91 | 2569 | 0.03 (-0.16;0.21) | .76 | 2564 | 0.14 (-0.05;0.33) | .14 |
| CBCL at 3 years | 2591 | 0.08 (-0.07;0.24) | .29 | 2585 | -0.01 (-0.17;0.15) | .91 | 2584 | -0.05 (-0.22;0.13) | .60 | 2625 | -0.09 (-0.26;0.08) | .32 | 2626 | -0.08 (-0.26;0.10) | .14 | 2620 | 0.06 (-0.13;0.24) | .53 |
| **Stuttering persistency** | | | | | | | | | | | | | | | | | | |
| Unadjusted | 137 | 0.35 (-0.07;0.78) | .11 | 137 | 0.27 (-0.15;0.69) | .21 | 137 | 0.15 (-0.22;0.52) | .43 | 142 | 0.21 (-0.17;0.18) | .30 | 142 | 0.33 (-0.19;0.11) | .06 | 142 | 0.50 (0.07;0.93) | .02* |
| Confounder adjusted # | 137 | 0.33 (-0.10;0.76) | .13 | 137 | 0.35 (-0.08;0.77) | .11 | 137 | 0.18 (-0.20;0.57) | .35 | 142 | 0.18 (-0.22;0.58) | .38 | 142 | 0.38 (0.03;0.74) | .04* | 142 | 0.53 (0.09;0.98) | .02* |
| *Additionally adjusted for* | | | | | | | | | | | | | | | | | | |
| CBCL at 1.5 years | 101 | 0.46 (-0.06;0.97) | .08 | 101 | 0.52 (0.04;0.99) | .04* | 101 | 0.37 (-0.10;0.83) | .12 | 105 | 0.28 (-0.23;0.79) | .29 | 105 | 0.47 (0.03;0.90) | .04* | 105 | 0.82 (0.25;1.40) | .01* |
| CBCL at 3 years | 103 | 0.51 (0.05;0.98) | .03* | 103 | 0.67 (0.21;1.14) | .01* | 103 | 0.51 (0.08;0.94) | .02* | 106 | 0.25 (-0.22;0.72) | .30 | 106 | 0.43 (0.05;0.81) | .03* | 106 | 0.83 (0.30;1.36) | .00* |

CI = confidence interval, SD = standard deviation
Values were derived from linear regression analyses. CBCL scores were Z-standardized across the study sample.
# Confounders included child sex, and maternal ethnicity, education, and psychopathology score
* $p < .05$

## 3.3 Associations of stuttering history and persistence with behavior and temperament at (pre-)school-age (hypothesis 2)

No significant association was found between stuttering history and later behavior (Table 5, $p > .05$). Persistence of stuttering (compared to those who recovered) was significantly associated with internalizing behavior scores at 5 years of age when additionally adjusted for baseline problem scores at 1.5 (β = 0.52, 95% CI [0.04;0.99], $p = .04$) and 3 years (β = 0.67, 95% CI [0.21;1.14], $p = .01$), and with externalizing behavior scores (β = 0.51, 95% CI [0.05;0.98], $p = .03$) and emotional reactivity (β = 0.51, 95% CI [0.08;0.94], $p = .02$) when adjusted for scores at 3 years. Persistence of stuttering was significantly associated with increased internalizing behavior scores at 9 years of age (β = 0.38, 95% CI [0.03;0.74], $p = .04$). A similar significant result was found for higher emotional reactivity at 9 years of age (β = 0.53, 95% CI [0.09;0.89], $p = .02$). For a final step, the analyses were adjusted for baseline behavior scores at 1.5 and 3 years. The effect estimate in internalizing and emotionally reactive scores at 9 years remained statistically significant, and if anything, even strengthened (e.g., at 9 years emotionally reactive β = 0.53 became β = 0.83 after adjustment for baseline scores).

The analyses with temperament (Table 6) showed that children with a history of stuttering had higher "negative affectivity" scores at 6 years of age (β = 0.19, 95% CI [0.02;0.37], $p = .03$) compared to those without a history of stuttering. No association was found between stuttering persistency and temperament at 6 years of age ($p > .05$).

Table 6. Stuttering history and stuttering persistency and temperament at 6 years

| | CBQ score at 6 years | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Effortful control | | | Negative affectivity | | | Surgency | | |
| | n | Beta (95% CI) | *p* | n | Beta (95% CI) | *p* | n | Beta (95% CI) | *p* |
| **Stuttering history** | | | | | | | | | |
| Unadjusted | 3024 | -0.12 (-0.29;0.06) | .20 | 3028 | 0.20 (0.02;0.38) | .03* | 3026 | -0.03 (-0.20;0.15) | .77 |
| Confounder adjusted # | 3024 | -0.03 (-0.20;0.14) | .74 | 3028 | 0.19 (0.02;0.37) | .03* | 3026 | -0.05 (-0.23;0.12) | .26 |
| **Stuttering persistency** | | | | | | | | | |
| Unadjusted | 128 | -0.40 (-0.87;0.07) | .10 | 128 | 0.16 (-0.25;0.57) | .46 | 128 | 0.03 (-0.42;0.48) | .89 |
| Confounder adjusted # | 128 | -0.24 (-0.71;0.24) | .33 | 128 | 0.17 (-0.26;0.59) | .44 | 128 | -0.02 (-0.48;0.44) | .94 |

CBQ = Child Behavior Questionnaire, OR = odds ratio
Values were derived from linear regression analyses. CBQ scores were Z-standardized across the study sample.
Confounders included child sex, and maternal ethnicity, education, and psychopathology score
* $p < .05$

# 4. Discussion

In the Generation R Study, a large group of children from the general population with stuttering (recovered and persistent) and another group without a history of stuttering were analyzed. We found hardly any evidence for our first hypothesis that either behavior or temperament at 6 months to 3 years of age was associated with a history of stuttering. However, we found that young children who were less able to recover from distress, because of high reactivity and poor self-regulation, were more likely to persist in stuttering. This result supports our second hypothesis that both stuttering history and stuttering persistence in early years are associated with behavior difficulties and temperament later on, at 5 to 9 years of age. These findings provide a first glimpse into processes contributing to the association of childhood stuttering with behavior difficulties and temperament.

## 4.1 The association of behavior and temperament in early childhood with stuttering history and persistence (hypothesis 1)

We first examined whether behavior and temperament at very early ages, up to 3 years, were associated with stuttering and its developmental course (hypothesis 1). Our finding of no significant associations with stuttering history agreed with the review of Alm (2014), which concluded that behavior and temperament were equally prevalent in preschool-age children who stutter and in those who do not stutter. It also agreed with Reilly et al. (2009) who found no significant differences in behavior (e.g., internalizing, shyness) between 0-3 year-old children who stutter and those who do not stutter. In addition, it agreed with Embrechts et al. (2000) who found that 3-8 year-old children who stutter were not more shy or fearful than children of the same age who do not stutter. We did find, however, that children who later persisted in stuttering were less able to "recover from distress" at 6 months, suggesting regulation problems in infancy. This has not been examined in studies of stuttering before. However, studies focusing on other outcomes also suggest that early life factors related to "recovery from distress" predict later functioning in children. One study reported that 15-month-old children who exhibited high levels of reactivity but low levels of regulation (linked to "recover from distress") had poorer executive function at preschool-age (Ursache et al., 2013). Another study reported that emotionality (i.e., a tendency to react even to low-intensity stimuli with negative emotions) in infancy predicted later behavior problems and less social competence (Mathiesen & Prior, 2006). It is clearly conceivable that young children with poorer self-regulation skills, such as difficulty in recovering from peak distress, or

from excitement or general arousal (Rothbart & Derryberry, 1981) are more likely to persist in stuttering (Conture et al., 2006; Eggers et al., 2010; Zengin-Bolatkale et al., 2015). However, the weak associations, and the small proportion of explained variation, in our study and the evidence from other studies suggest that these early temperamental traits are at most a secondary or minor risk factor for persistent stuttering. Several other genetic, neurodevelopmental, behavioral, and environmental factors are probably more influential in the developmental course of stuttering.



## 4.2 Stuttering history and its association with behavior and temperament at preschool-ages and school-age (hypothesis 2)

We also hypothesized that stuttering history is associated with, or precedes, behavioral difficulties such as high reactivity and low self-regulation skills at preschool and school-ages, from 5 to 9 years of age. Indeed, the current study found more negative affect such as anger, frustration, or sadness among 6-year-old children with a history of stuttering. This small but significant association is consistent with Ambrose et al. (2015) who found higher negative affectivity in preschool-age children who persisted in stuttering, with Eggers et al. (2010) who reported higher temperament scores in children who stutter, and with Anderson et al. (2003) who found that children who stutter were less distractible and less adaptable to change. A negative perception of speaking may occur when the awareness of stuttering becomes more pronounced (Vanryckeghem et al., 2005, 2015; both using the KiddyCAT (Communication Attitude Test)), which can be expected to happen around 4 years of age (Ambrose & Yairi, 1994; De Nil & Brutten, 1991; Vanryckeghem & Brutten, 1997). Similarly, Ezrati-Vinacour et al. (2001) using a pair of puppets, one fluent and the other displaying disfluent speech, found that children from age 3 showed awareness of the disfluency, but most children reached full awareness at age 5. Also, negative self-evaluation of disfluent speech was observed from age 4.

Furthermore, previous findings on temperament (Anderson et al., 2003; Eggers et al., 2010) suggest that less adaptability to change, as well as increased emotional reactivity and decreased self-regulation might cause stuttering children to respond negatively to disruptions in their speech fluency (Guitar, 2016; Walden et al., 2012). These responses may in turn cause increased physical tension in the speech musculature after a fluency breakdown, which might exacerbate the stuttering.

## 4.3 Stuttering persistence and its association with behavior and temperament at preschool-age and school-age (hypothesis 2)

Finally, we also found that children who persisted in stuttering had increased internalizing behaviors and higher emotional reactivity at 5 and 9 years of age compared to children who recovered from stuttering (hypothesis 2). These results remained significant after adjusting for behavior scores at 1.5 and 3 years, which suggests that these behaviors had developed between ages 3 and 9 years. This finding agrees with studies suggesting that emotional reactivity, hyperactivity, and social anxiety are higher in children who persist in stuttering (Ambrose et al., 2015; Davis et al., 2007; Donaher & Richels, 2012; Hollister & Zebrowski, 2015; Rocha et al., 2019). We do acknowledge the small number (n=27) of children who persisted in stuttering in our study sample.

Our findings of both behavior and temperament traits may be explained by temperament studies reporting that school-age children with a high negative affectivity and low self-regulation are prone to externalizing behaviors, with the effect of lower regulation stronger for those with high negative emotionality (Eisenberg et al., 1996; Rothbart & Bates, 2006). For example, we suggest that if children with high negative affectivity and low self-regulation become anxious, get irritated or angry because of their stuttering, or if they receive negative reactions to their stuttering from others, these reactions may cause a longer lasting negative affectivity. Moreover, the effect of self-regulation can be strong for those with high positive emotionality. For example, we suggest that if these children become easily excited, or very enthusiastic about something new, or if they respond with high sensitivity to ordinary stimuli, this reaction may impair their ability to regulate these emotions, which may increase their speech dysfluencies. Furthermore, we speculate that the older the children are, the more likely it is that their behavior and emotional well-being has been affected or shaped by the experiences of stuttering. So, a vicious cycle may occur in which stuttering and behavior and temperament influence and exacerbate each other (Conture et al., 2013).

## 4.4 Clinical implications

Clinically, it is important to determine if behavior difficulties and temperament increase the probability of persistent stuttering, and at what age these predictors emerge, because they can indicate not only stuttering, but other serious problems later in life, such as social anxiety (Blumgart et al., 2010; Iverach et al., 2016; Stein et al., 1996). Our study suggests

that behavior and temperament asessments may help Speech-Language Pathologists and other clinicians in the treatment of stuttering. This knowledge, in combination with other risk factors for persistent stuttering, could contribute to planning interventions that integrate psychological issues for children and young adolescents who stutter and their parents (Messenger et al., 2015; Smith et al., 2014). Treatment that includes behavioral and temperament targets may be more successful than treatment for speech alone (Druker et al., 2020). This has been shown in adults, but it may also be true for children (Menzies et al., 2008). In general, we recommend that Speech-Language Pathologists and other clinicians screen behavior and temperament for internalizing behaviors, self-regulation problems, and reactive temperament as part of a comprehensive evaluation of stuttering, starting at preschool-age. Such screening may improve the caseload selection, and thereby prevent or reduce the psychological burden on school-age children who stutter, and simultaneously reduce the costs for society. An example of a recently developed screening tool is the Short Behavioral Inhibition Scale (SBIS), a valid and reliable parent-report scale of Behavioral Inhibition (Ntourou et al, 2020). Using this scale, the authors found that behavior inhibition in early childhood stuttering is presented with greater stuttering frequency, more severe stuttering, and more negative communication attitudes.



## 4.5 Limitations and strengths

One limitation of this study is that all data were parent-reported. Parental questionnaires have the important advantage of tapping into the vast knowledge base of parents who observe their child in many different, everyday situations over a long period of time. Parents may notice infrequently occurring or variable behaviors and speech dysfluencies that might be missed by a professional's single observation or test. On the other hand, parents may not remember mild or transient stuttering after several years. To this point, the female-male ratio is 1:1.5 at stuttering onset, but with increasing age it is estimated to be 1:3, suggesting the recovery rate in girls is higher (Yairi & Ambrose, 2013). Since we found a sex ratio of 1:2.2, it may be that the parents of girls in our study under reported a history of stuttering. Besides, parental questionnaires might be biased by subjective factors resulting in over- or under-estimation of their child's fluency, behavioral problems or temperamental traits, because the parents have a history of stuttering or psychopathology, or because other children in the family have speech or psychosocial problems. A second limitation is that because of uncertainty in some of the information about stuttering, such as the exact age of onset or the duration and severity of stuttering, or a family history of

stuttering, and the large time gaps between the behavioral measures, we could not perform a cross-lagged analysis to estimate which direction of the association between stuttering and behavior was stronger. Also, since our study is observational, conclusions concerning causality are limited. Conclusions about causality are also limited because we examined behavior and temperament data at ages 6 months, 3, 5, 6 and 9 years, and do not know exactly when the stuttering began. Specifically, we do not know if the stuttering began before, after or around the time a behavior or temperament measure was administered. Therefore, caution must be taken when interpreting the findings. A third limitation is that we emphasize that high or low scores on behavior and temperament tests are not the same as clinical disorders, but it rather reflect the distribution of scores on a continuum in the general population. Furthermore, we could not perform a dose-response analyses (from which causality might be inferred) to estimate the relationship between severity of stuttering and psychological issues. Fourth, though this is one of the largest population-based studies of the association between behavior and temperament and stuttering, the sample size of those who stuttered, and particularly those who persisted, are still limited. Finally, non-response analyses showed that children included in the current study were more likely to have more highly educated mothers and a Western ethnicity than children who were excluded from the study due to incomplete data (n = 3466, Supplemantary Table 4.). Therefore, our findings may not be generalized to a less advantaged population. However, since most other studies have recruited participants from clinical populations, our findings are more representative of the wider population of children who do and do not stutter. Additionally, the incidence of stuttering in the Generation R Study corresponds with the generally accepted incidence of stuttering in preschool-age children as reported in many other population-based samples (Boyle et al., 2011; Craig et al., 2002; Dworzynski et al., 2007; Månsson, 2000), suggesting a balanced reflection of our society.

These limitations are offset by various strengths of the study. First, a prospective population-based study design allows us to examine early behavior and temperament traits in young children roughly before (age 0.5, 1.5 and 3 years) and after (age 5, 6 and 9 years) the onset of stuttering. Second, this longitudinal study tracks participants over a period from infancy, through preschool and the school-age years. Therefore, we were able to compare very early behavioral outcomes in different fluency groups: children who persisted in stuttering, children who began to stutter but eventually recovered, and peers without a history of stuttering. Finally, our study is a rare longitudinal population-based study and is comparable so far to only one other study cohort that also investigated behavior development and stuttering in young children (Kefalianos et al., 2017).

### 4.6 Further directions

More future research on stuttering and its psychological correlates will add to our understanding of the relationship between stuttering, behavior and temperament. It may also determine how stuttering onset or persistency impacts, and is impacted by, behavior and temperament in early childhood. We still lack knowledge about how behavior and temperament are related to the specific time of stuttering onset, the severity of stuttering in different situations, the duration of stuttering, and treatment details (Kraft et al., 2019). Such studies should assess behavior more frequently, with smaller time gaps between ages, and at similar time points as the stuttering assessments. Research has shown that stuttering severity becomes a predictive sign one year after onset (Yairi & Ambrose, 1999), but the association of severity with behavior and temperament has not yet been investigated. Future longitudinal research would benefit from collecting long-term outcomes from a larger group of children who recovered or persisted in stuttering. Furthermore, studies are needed to improve current multifactorial models combining genetic, neurobiological, psychological and environmental factors. For example, genetic research may help clarify the relationship of persistent stuttering with behavior and temperament by identifying a common genetic or neurobiological cause. Also, linguistic and speech motor problems should be monitored since temperamental factors have been suggested to interact with both (Ambrose et al., 2015).



## 5. Conclusions

The current study supported bidirectionality in the relationship of behavior and temperament with stuttering and its persistence in childhood. Poorer recovery from distress because of higher reactivity and poorer self-regulation at 6 months, was associated with stuttering persistence. It is important to note this was the only significant finding in infancy. We can cautiously conclude that persistent stuttering puts children at risk for developing or increasing emotional reactivity and internalizing behaviors in the school-age years. Therefore screening for behavior difficulties and temperament in preschool-age children who stutter is highly recommended. In addition, children who persist in stuttering at school-age should be monitored for behavior problems and the development of temperamental traits, enabling timely targeted treatment that may help prevent disorders such as a social anxiety.

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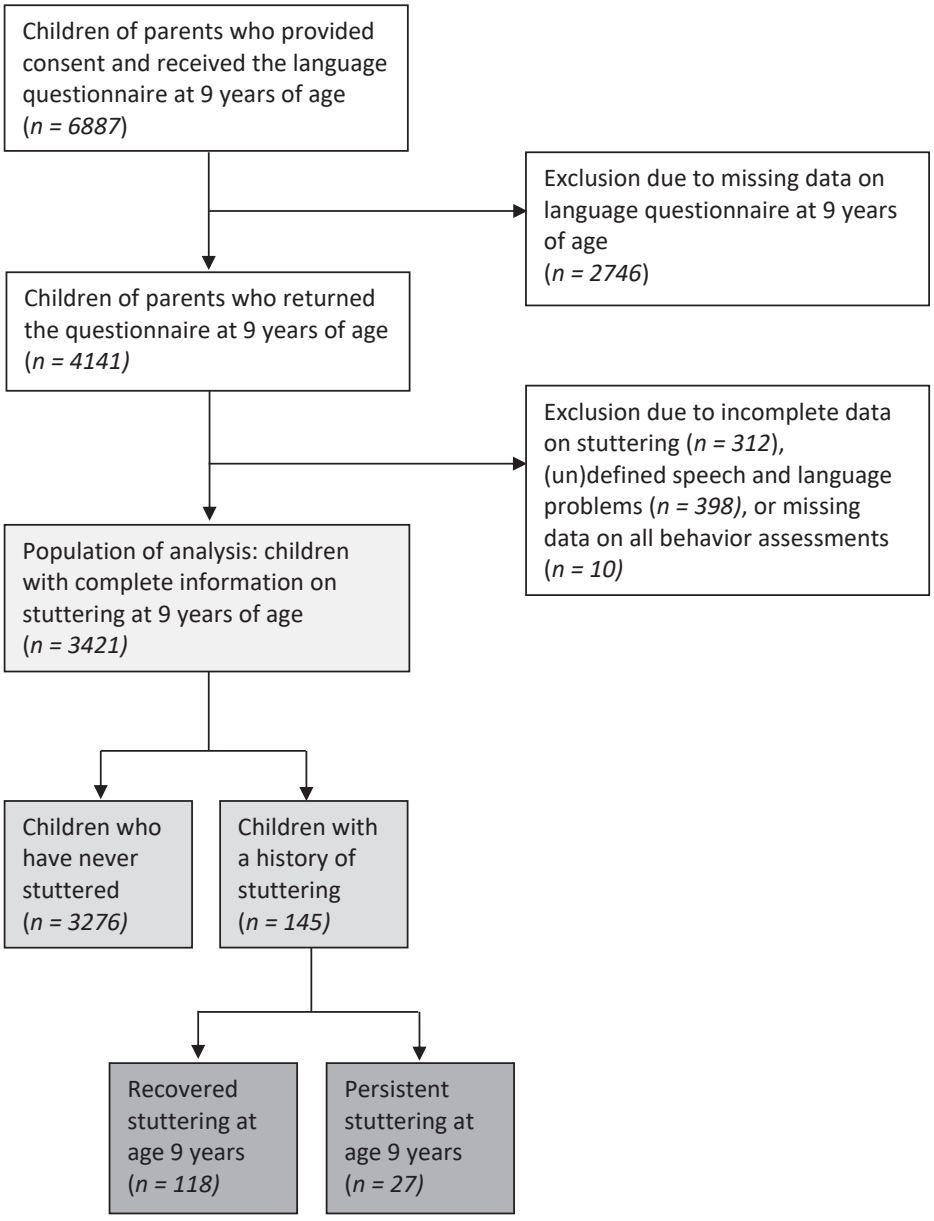
# Supplementary Materials

Supplementary Figure 1. Flowchart of subject selection



Supplementary Table 1. Detailed information about references from the introduction

| Author | Participants | Age | (pre)school-age | Groups | Measurement | Behavior |
|---|---|---|---|---|---|---|
| Ambrose et al. 2015 | n=98 | 2-9 year-old | preschool-age | pCWS, rCWS, CWNS | CBQ | Temperament |
| Anderson et al. 2003 | n=62 | 3-5 year-old | preschool-age | CWS, CWNS | BSQ | Temperament, and externalizing |
| Blood et al. 2007 | n=72 | 10-18 year-old | school-age | CWS, CWNS | RCMAS | Internalizing |
| Davis et al. 2007 | n=54 | 10-18 year-old | school-age | pCWS, rCWS, CWNS | STAI | Internalizing |
| De Nil and Brutten 1991 | n=341 | 7-14 year-old | school-age | CWS, CWNS | Communication attitude test | Internalizing |
| Donaher and Richels 2012 | n=36 | 3-17 year-old | preschool and school-age | CWS | ADHD rating scale | Externalizing |
| Druker et al. 2019 | n=185 | 2-6 year-old | preschool-age | CWS and completed stuttering therapy <3 months prior to study | ADHD rating scale | Externalizing |
| Eggers et al. 2010 | n=116 | 3-8 year-old | preschool-age | CWS, CWNS | CBQ | Temperament, externalizing and internalizing |
| Embrechts et al. 2000 | n=76 | 3-8 year-old | preschool-age | CWS, CWNS | CBQ | Temperament, externalizing and internalizing |
| Gunn et al. 2014 | n=37 | 12-17 year-old | school-age | PWS seeking stuttering treatment | Psychometric tests | Internalizing |
| Hollister et al. 2015 | n=92 | 8-15 year-old | school-age | CWS, CWNS | EATQ-R, HBQ | Temperament, externalizing and internalizing |
| Iverach et al. 2016 | n=225 | 7-12 year-old | school-age | CWS, CWNS | SCAS, SDQ, SMFQ, YODA | Internalizing |

| Author | Participants | Age | (pre)school-age | Groups | Measurement | Behavior |
|---|---|---|---|---|---|---|
| Iverach et al. 2017 | n=102 | 11-17 year-old | school-age | PWS seeking stuttering treatment | CBCL, CDI, RCMAS, YSR | Externalizing |
| Karrass et al. 2006 | n=121 | 3-7 year-old | preschool-age | CSW, CWNS | BSQ | Temperament, and externalizing |
| Kefalianos et al. 2014 | n=1444 | 2-4 year-old | preschool-age | CSW, CWNS | STS | Temperament and internalizing |
| Kefalianos et al. 2017 | n=141 | 1-7 year-old | preschool and school-age | pCWS, rCWS, CWNS | CSBS, SDQ, STS | Temperament and internalizing |
| McAllister 2016 | n=18878 | 3-11 year-old | preschool and school-age | CWS, CWNS | SDQ | Externalizing and internalizing |
| Reilly et al. 2009 | n=1619 | 2-3 year-old | preschool-age | CWS, CWNS | CSBS | Temperament, and internalizing |
| Reilly et al. 2013 | n=1619 | 2-5 year-old | | rCWS, pCWS, CWNS | CSBS | Temperament, and internalizing |
| Rocha et al. 2019 | n=100 | 7-12 year-old | school-age | CWS, CWNS | CBQ, MASC, TMCQ | Temperament, and internalizing |
| van der Merwe et al. 2011 | n=14 | 3-4 year-old | preschool-age | CWS, CWNS | PAS | Internalizing |

ADHD = Attention Deficit Hyperactivity Disorder, BSQ = Behavior Screening Questionnaire, CBQ = Child Behavior Questionnaire, CDI = Children's Depression Inventory, CSBS = Communication and Symbolic Behavior Scale, CWS = children who stutter, CWNS = children who do not stutter, EATQ-R = Early Adolescence Temperament Questionnaire-Revised, HBQ = Health and Behavioral Questionnaire, PWS = person who stutters, MASC = Multidimensional Anxiety Scale for Children, PAS = Preschool Anxiety Scale, RCMAS = Revised Children's Manifest Anxiety Scale, SCAS = Spence Children's Anxiety Scale, SDQ = Strengths and Difficulties Questionnaire, SMFQ = Short Mood and Feelings Questionnaire, STAI = State-Trait Anxiety Inventory, STS = Short Temperament Scale, TMCQ = Temperament in Middle Childhood Questionnaire, YODA = Youth Online Diagnostic Assessment, YSR = Youth Self Report

Supplementary Table 2. Correlation between CBCL and IBQ and CBQ

| | IBQ at 0.5 year | | | | | | CBQ at 6 years | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Activity level** | **Distress to limitations** | **Fear** | **Duration of orienting** | **Recovery from distress** | **Sadness** | **Effortful control** | **Negative affectivity** | **Surgency** |
| **CBCL at 1 year** | | | | | | | | | |
| Externalizing | .230** | .237** | .121** | -.035 | -.179** | .273** | -.094** | .253** | .128** |
| Internalizing | .226** | .202** | .272** | .039 | -.170** | .283** | -.014 | .252** | -.047* |
| Emotionally reactive | .230** | .199** | .220** | .041 | -.154** | .272** | .010 | .244** | .001 |
| **CBCL at 3 years** | | | | | | | | | |
| Externalizing | .191** | .175** | .079** | -.016 | -.156** | .205** | -.107** | .303** | .160** |
| Internalizing | .210** | .156** | .184** | .060** | -.161** | .221** | -.041* | .301** | -.110** |
| Emotionally reactive | .180** | .154** | .126** | .027 | -.148** | .202** | -.033 | .283** | -.012 |
| **CBCL at 5 years** | | | | | | | | | |
| Externalizing | .117** | .136** | .039 | -.047* | -.125** | .168** | -.183** | .386** | .172** |
| Internalizing | .106** | .102** | .115** | .024 | -.100** | .181** | -.047* | .443** | -.189** |
| Emotionally reactive | .096** | .085** | .053* | .005 | -.066** | .131** | -.050** | .422** | -.067** |
| **CBCL at 9 years** | | | | | | | | | |
| Externalizing | .091** | .128** | .002 | -.037 | -.118** | .132** | -.100** | .267** | .090** |
| Internalizing | .115** | .110** | .124** | -.003 | -.140** | .172** | -.012 | .302** | -.171** |
| Emotionally reactive | .091** | .112** | .039 | .004 | -.111** | .140** | -.028 | .291** | -.058** |

CBCL = Child Behavior Checklist, CBQ = Child Behavior Questionnaire, IBQ-R = Infant Behavior Questionnaire Revised
Pearson correlation values were derived from all children with complete information on stuttering at 9 years of age (n = 3421). * $p < .05$, ** $p < .01$

Supplementary Table 3. Missing values in covariates in total study sample

| | **All participants n = 3421** |
|---|---|
| **Participant's characteristics** | **n (%) missing values** |
| **Child characteristics** | |
| Gestational age at birth | 17 (0.5%) |
| Birth weight | 3 (0.1%) |
| Sex | na |
| Ethnicity | 18 (0.5%) |
| Multilingualism | 57 (1.7%) |
| Intelligence quotient at 6 years | 277 (8.1%) |
| Age at stuttering questionnaire | na |
| Ever had treatment for stuttering | na |
| Ever had treatment for stuttering, speech and/or language problems | na |
| Psychosocial treatment at 9 years | 172 (5.0) |
| **Maternal characteristics** | |
| Maternal age at intake | na |
| Maternal ethnicity | 20 (0.6%) |
| Psychopathology score | 766 (22.4%) |
| Maternal education level | 203 (5.9%) |

n = number, na = not applicable
Multiple imputation technique was performed in SPSS version 24.0.

Supplementary Table 4. Differences between included (n = 3421) and excluded (n = 3466) participants

| | Participants included n = 3421 | Participants excluded** n = 3466 | p-value of the difference |
|---|---|---|---|
| **Child characteristics** | | | |
| Gestational age at birth (weeks) | 39.8 (1.8) [n=3404] | 39.8 (1.8) [n=3433] | 0.52 |
| Birth weight (gram) | 3435 (577) [n=3418] | 3389 (571) [n=3448] | <0.05* |
| Sex (% boy) | 1670 (48.8%) | 1775 (51.2%) | 0.05 |
| Ethnicity (% Western) | 2659 (78.1%) [n=3403] | 1917 (58.4%) [n=3284] | <0.05* |
| Multilingualism (% yes) | 655 (19.5%) [n=3364] | 128 (31.7%) [n=404] | <0.05* |
| Intelligence quotient at 6 years (score) | 104.2(14.2) [n=2974] | 98.4 (15.3) [n=2441] | <0.05* |
| Age at stuttering questionnaire (years) | 9.8 (0.4) | 10.0 (0.4) [n=720] | <0.05* |
| **Maternal characteristics** | | | |
| Maternal age at intake (years) | 31.8 (4.5) | 29.8 (5.2) | <0.05* |
| Maternal ethnicity (% Western) | 2595 (75.9%) [n=3401] | 1791 (51.7%) [n=3275] | <0.05* |
| Psychopathology score | 0.2 (0.3) [n=2655] | 0.3 (0.3) [n=2347] | <0.05* |
| Maternal education level (% high) | 2130 (66.2%) [n=3218] | 1208 (50.7%) [n=2383] | <0.05* |

For all continuous variables the mean with standard deviation (SD) are presented; for categorical variables the n (%) is presented.
* p-value < .05
** children with missing data on language questionnaire (n=2746), incomplete data (n=312), undefined speech and language problems (n=398), or missing data on all behavior skill tests (n=10), see Figure 1.

*“Logic will get you from A to B, imagination will take you everywhere.”*
Albert Einstein

# PART III

Childhood stuttering and brain development


White matter
Persistent
Fluency
Speech
Research
Recov
Brain
Subcort
Satisfaction
Gray matter
Neuroimaging
Self-report
Explore
Cortical
Girls
Children
Stutter
Temperament
Population
Dysfluency
Fluency
Neuroplasticity
Boys
Outcome
Speech
Satisfaction
Brain
Behavior
Treat
Long-term
Development
Subcortical
Girls
Rotterdam
Self-report
Persistent
Stutter
Cortical
Boys
Population
Speech-motor


# 6

# Stuttering and gray matter morphometry: a population-based neuroimaging study in young children

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## Abstract

Stuttering is a developmental speech disorder originating in early childhood. We aimed to replicate the association of stuttering and structural morphometry using a large, population-based prospective cohort, the Generation R Study, and explore the neurobiological mechanism of stuttering in children. Twenty-six children with a history of stuttering and 489 fluent speaking peers (ages 6-9) were included in the MRI sub-study. Cortical and subcortical regions of interest were analyzed using linear regression models. Compared to fluent speakers, children with a history of stuttering had less gray matter volume in the left inferior frontal gyrus and supplementary motor area. Exploratory surface-based brain analysis showed thinner cortex in the left inferior frontal gyrus, and in bilateral frontal and parietal areas. These findings corroborate previous studies that reported aberrant brain morphometry in speech motor and auditory regions in children who stutter. Future research is needed to explore the causal nature of this association.

# 1. Introduction

Stuttering is a developmental speech production disorder that originates in early childhood with typical age of symptom onset between 2 to 5 years (Yairi & Ambrose, 1999). Stuttering occurs in 5-10% of preschool-age children (Andrews & Harris, 1964; Craig, Hancock, Tran, Craig, & Peters, 2002; Månsson, 2000, 2005; Reilly et al., 2013). Most affected children recover within 2-3 years after onset of stuttering (Yairi & Ambrose, 1999; Yairi & Ambrose, 2005). Stuttering is characterized by repeated, blocked or prolonged sounds, and repeated syllables and words, which cause disruptions in the normal, fluent rhythm of speech. In general, speech production is a complex human motor behavior involving the central nervous system. Although cortical and subcortical regions in both left and right hemisphere contribute to speech production, the left hemisphere is dominant in most cases (Dorsaint-Pierre et al., 2006). So far, the pathophysiology of childhood stuttering and its possible neuro-anatomical origins are still unclear.



Studying brain morphometry in relation to stuttering is highly important to increase our knowledge of the neurological architecture of stuttering. Moreover, identifying the structures involved may help with both neuroscience informed treatments and defining prognosis. Research updates in neuroimaging studies of stuttering have reported various differences in brain structure (e.g. gray and white matter volume, morphometry, white matter tracts, basal ganglia) in those who stutter as compared to fluent speakers (Chang, 2014; Chang, Horwitz, Ostuni, Reynolds, & Ludlow, 2011; Etchell, Civier, Ballard, & Sowman, 2018; Foundas, Mock, Cindass, & Corey, 2013). So far, most neuroimaging studies have focused on adult populations because assessment was considered to be too intrusive (e.g. movement artefacts, volume of noise) for children who stutter. Over the last years, some convergent as well as inconsistent results have been published. In cortical structures, on the one hand, larger gray matter volumes in the left inferior frontal gyrus as well as the bilateral precentral and postcentral gyri, regions involved in motor speech production, were shown in adults who stutter (Beal, Gracco, Lafaille, & De Nil, 2007; Kikuchi et al., 2011; Lu et al., 2010; Song et al., 2007). On the other hand, others reported smaller gray matter volume in similar regions (Kell et al., 2009; Lu et al., 2010) or found no differences (Kikuchi et al., 2011). Some neuroimaging studies have also investigated structural gray matter morphometry in children who stutter (Beal, Gracco, Brettschneider, Kroll, & De Nil, 2013; Beal et al., 2015; Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008; Foundas et al., 2013; Garnett et al., 2018; Mock et al.,

2012). Neuroanatomical differences were found in the left frontal brain region, specifically in the pars opercularis, triangularis and orbitalis, with less gray matter volume in children who stutter. These studies also reported less gray matter volume in the right frontal brain region, similarly in the pars opercularis and triangularis. In deeper subcortical structures, the basal ganglia (caudate, putamen, palladum) play an important role in smooth speech motor control and adequate timing and rhythm (Bohland & Guenther, 2006; Grahn, 2012). These regions have extensive and important connections with cortical structures. Multiple studies have reported abnormalities in the basal ganglia in childhood stuttering such as less gray matter volume in the left putamen and in the right caudate (Beal et al., 2013; Foundas et al., 2013).

These few studies on stuttering in children, in general examined gray matter morphometry years after the onset of stuttering as the age of participants in these studies varied from 6 to 13 years (Beal et al., 2013; Chang et al., 2008; Foundas et al., 2013; Mock et al., 2012). Only the study by Garnett et al. (2018) investigated brain morphometry including children that were at an age closer to the onset of stuttering (3 to 10 years) (Garnett et al., 2018). In addition, most previous studies recruited children via a clinical setting or children who were recruited for specific reasons. Only recently, published studies on children who stutter exceeded 30 participants per group (Chang et al., 2018; Chow & Chang, 2017; Garnett et al., 2018); most available literature dealt with much smaller sample sizes (Beal et al., 2013; Chang et al., 2008; Foundas et al., 2013; Mock et al., 2012).

Given this background, there is a need for more studies investigating the association between stuttering in early childhood and gray matter morphometry, especially within the general population. Therefore, we aimed to replicate previous pediatric structural neuroimaging studies on stuttering in a sample from a large population-based cohort of young children (aged 6-9 years). In birth cohort studies, children are recruited before the onset of stuttering. Furthermore, mild phenotypes who would probably not otherwise seek medical assistance, can be identified and studied. Importantly as well, a birth cohort offers plenty of matched controls, a feature most clinical studies lack. In summary, our design allows us, for the first time, to compare brain morphometry in children who stutter, or with a stuttering history, to a very large group of non-stuttering children from a general pediatric population. Secondly, the prospective study design with a vast amount of information of children's development and growth from birth onward enables us to adjust for several relevant confounding variables (e.g. sex, right-left handedness, mono- and bilingual children). This is relevant since these variables play a role in both

the development of speech as well as brain morphometry. Thirdly, the study design also enables us to explore brain morphometry closer to the onset of stuttering. Lastly, our study validates and extends the findings of prior research so that these are contributed toward understanding the brain morphometry of stuttering. Based on prior studies, we hypothesized that brain regions involved in speech production will be different in young children who stutter compared with fluently speaking children, primarily in the cortical auditory-motor network of the left hemisphere and in the subcortical basal ganglia nuclei.

# 2. Methods

## 2.1 Design and setting



This study is part of the Generation R Study, an ongoing population-based prospective birth cohort study investigating children's development from fetal life onwards (n=9901). An overview of the Generation R Study design and population has been described previously (Kooijman et al., 2016). In brief, pregnant women with an expected delivery date between April 2002 and January 2006 living in Rotterdam were eligible for participation. All participants provided written informed consent and were recruited. Mothers received extensive questionnaires at different time points, and from the age of the child of 5 years onwards, all participants were invited to the research center to undergo various physical examinations and measurements. In September 2009, 6 to 9-year-old children from the Generation R Study were invited to participate in an MRI component as part of a sub study (White et al., 2018). Children were scanned between September 2009 and July 2013. This neuroimaging study was initially directed at studying specific subpopulations within the Generation R cohort (White et al., 2013), and is different from other large neuroimaging studies in that it is a population-based prenatal cohort. There were no differences in the specific subpopulations between the groups in the current study (Table 1). Exclusion criteria for MRI-scan included having a significant motor or sensory disorder, moderate to severe head trauma with loss of consciousness, neurological disorders (including seizure disorder, neuro-motor disorder, or a history of brain tumors), claustrophobia, and contraindications to MRI (e.g. having a pacemaker). The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam.

Table 1. Descriptive statistics of the study population

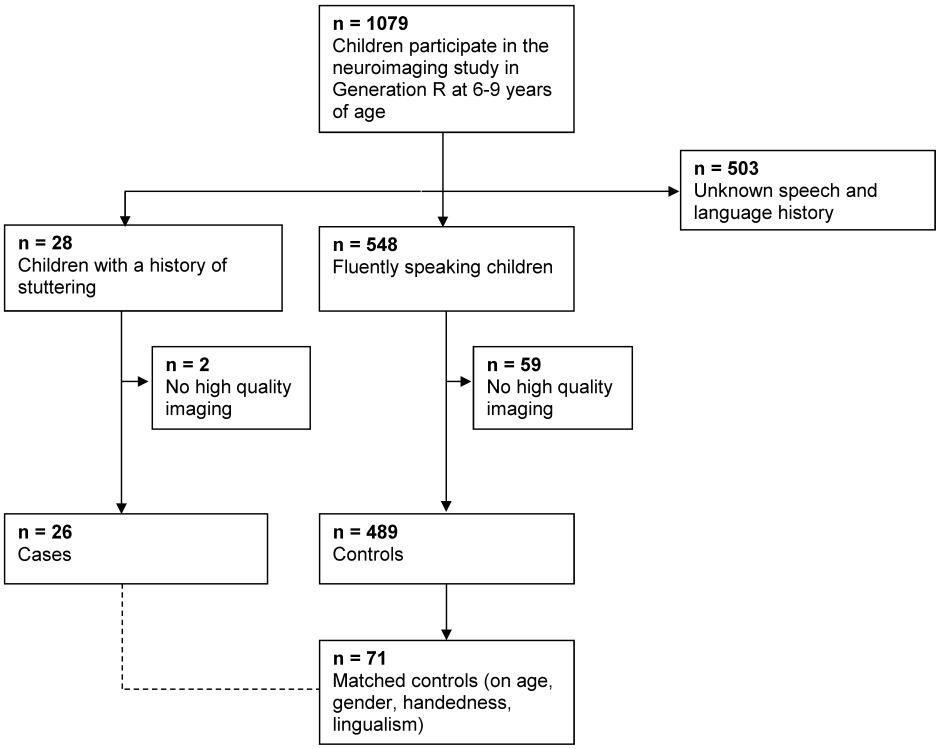
| | Children with a history of stuttering n = 26 | Fluently speaking children* n = 489 | Matched fluently speaking children n = 71 | Stuttering vs. fluent speakers p-value | Stuttering vs. matched fluent speakers p-value |
|---|---|---|---|---|---|
| **Child characteristics** | | | | | |
| Age at MRI in years | 8.18 (0.97) | 7.98 (1.02) | 8.33 (1.03) | 0.35 | 0.51 |
| Age at language questionnaire in years | 9.79 (0.24) | 9.83 (0.39) | 9.79 (0.44) | 0.62 | 0.95 |
| Sex (boy) | 19 (73.07) | 235 (48.06) | 50 (70.42) | 0.01 # | 0.80 |
| Ethnicity (Western) | 25 (96.15) | 417 (85.28) | 60 (84.51) | 0.15 | 0.17 |
| Handedness (right- handed) | 22 (84.62) | 448 (91.62) | 63 (88.73) | 0.27 | 0.73 |
| Lingualism (monolingual education) | 22 (84.62) | 434 (89.30) [n=486] | 61 (85.92) | 0.51 | 0.74 |
| Total problems (score) | 23.1 (12.6) [n=25] | 22.7 (18.3) [n=471] | 25.7 (18.0) [n=70] | 0.91 | 0.68 |
| Gestational age at birth in weeks | 39.70 (1.69) | 39.86 (1.98) | 40.02 (1.83) | 0.70 | 0.44 |
| Birth weight in gram | 3401 (639) | 3443 (587) | 3418 (570) | 0.72 | 0.90 |
| Head circumference at birth in cm | 33.63 (1.26) [n=12] | 34.05 (1.65) [n=261] | 34.02 (1.54) [n=32] | 0.38 | 0.44 |
| **Maternal characteristics** | | | | | |
| Maternal age at intake in years | 30.76 (4.68) | 31.32 (4.38) | 31.53 (4.32) | 0.52 | 0.44 |
| Maternal ethnicity (Western) | 24 (92.31) | 399 (81.60) | 58 (81.69) | 0.29 | 0.34 |
| High maternal education level | 16 (61.54) | 300 (63.69) | 45 (63.38) | 0.98 | 0.96 |
| Lower maternal education level | 10 (38.46) | 171 (36.31) [n=471] | 26 (36.62) | | |

MRI = magnetic resonance imaging, n = number
All categorical variables are presented with numbers (n) and percentages (%); all continuous variables are presented as mean with standard deviation (SD). Chi-squared and Fisher's Exact Tests were used for categorical variables and t Tests were used for continuous variables.
# p-value < 0.05
* including matched fluent speaking children

## 2.2 Participants

Neuroimaging data were available for 1079 children at age 6 to 9 years (White et al., 2013), of whom 576 completed the speech and language history parental questionnaire (see flowchart in Figure 1). Based on the information from this questionnaire, 28 children (4.9%) were categorized as children with stuttering history and 548 children without stuttering history (fluent speakers). Of these children, 26 children with a history of stuttering and 489 fluent speakers had a structural brain scan with good image quality.

Figure 1. Flowchart participants




In addition, and in line with previous studies (Chang et al., 2008; Chang & Zhu, 2013; El Marroun et al., 2016) children who stutter (n=26) were matched with children who had never stuttered (n=71) based on matching variables age, sex, handedness and bilingualism using a "fuzzy matching" procedure (Peck, 2011). The smaller matched control group is used to maximize comparison with cases and controls in previous literature. Matching is intended to eliminate confounding and increases the efficiency of the estimates if

the matching variables are associated with both stuttering and brain development. This procedure randomly searches for a case-control match that falls within a set of predefined matching criteria. We required an exact match for sex, handedness and bilingualism with a match for age at MRI scan with a maximum age difference of 1 year (a smaller age difference did not yield a match for each stuttering child).

## 2.3 Stuttering

Parents of children who stutter and parents of non-stuttering children can accurately and reliably identify stuttering (Bloodstein & Bernstein Ratner, 2008; Einarsdottir & Ingham, 2009). At the age of 9 to 12 years, parents completed a speech and language developmental questionnaire to obtain a measure of childhood stuttering. The questionnaire contained questions specifically regarding stuttering and had categorical items, for example "Does your child stutter at this moment?" and "Did your child ever stutter in the past?" Questions about speech therapy were assessed as well: "Does your child have treatment for stuttering at this moment?" and "Did your child ever have treatment for stuttering in the past?" Participants were classified as having a stuttering history if a parent answered "yes" to one of the above-mentioned questions. This categorization was based on parental reports only, and has been used in several previous publications investigating persistency and recovery of stuttering in childhood (Bloodstein & Bernstein Ratner, 2008; Dworzynski, Remington, Rijsdijk, Howell, & Plomin, 2007; Guitar, 2016; Kloth, Kraaimaat, Janssen, & Brutten, 1999). The results are related to stuttering – referring as children with a history of stuttering - but not necessarily persistent stuttering since most children were found to have recovered from stuttering at the time of parental report. The incidence of stuttering in the Generation R Study corresponded to incidence of stuttering among school-age children between 2 and 10 years reported in previous studies (Boyle et al., 2011; Craig et al., 2002; Dworzynski et al., 2007; Månsson, 2000).

## 2.4 Magnetic Resonance Imaging

All children were first familiarized to the MRI environment and procedures during a mock scanning session. All images were acquired using the same sequence on the same scanner, located at the Radiology department in the Erasmus University Medical Center. Images were acquired on a 3 Tesla scanner Discovery MR750, (General Electric, Milwaukee, Wisconsin) using an eight-channel head coil. A high-resolution 3D T1 inversion recovery fast spoiled gradient recalled sequence was acquired with the following

parameters: echo time = 4.24 ms, inversion time = 350 ms, repetition time = 10.26 ms, number of excitations = 1, flip angle = 16°, and 0.9 $mm^3$ isotropic voxel resolution.

## 2.5 Brain morphology

Images were processed using the FreeSurfer image analysis suite (version 5.1 http://surfer.nmr.mgh.harvard.edu/; Martinos Center for Biomedical Imaging, Charlestown, Massachusetts) to perform cortical reconstruction and volumetric segmentation of the brain images. Technical procedures have been extensively described previously (Fischl et al., 2002). Cortical thickness measurements of Freesurfer have been validated against histological (Rosas et al., 2002) and manual measures (Kuperberg et al., 2003; Salat et al., 2004). FreeSurfer morphometry has demonstrated good test-retest reliability across scanner manufacturers and field strengths (Han, 2006; Reuter, 2012). Numerous studies using FreeSurfer in typical and atypical developing school-aged children are available (Blanken et al., 2015; Derauf, Kekatpure, Neyzi, Lester, & Kosofsky, 2009; Ducharme et al., 2012; El Marroun et al., 2016; Ghosh et al., 2010; O'Donnell, Noseworthy, Levine, & Dennis, 2005). In this study, FreeSurfer output of each child was visually inspected for quality control. Brain measures of interest, auditory and speech motor regions, that were examined included subcortical volume, and cortical gray matter volume, thickness, and surface area.



## 2.6 Covariates

General demographic characteristics including maternal age at intake, ethnicity and education level, as well as the child's age, sex, ethnicity, and native language were prospectively obtained by postal questionnaires. Maternal ethnicity was defined according to the classification of Statistics Netherlands, into Western (Dutch and Non-Dutch Western) and non-Western (Statistics & Netherlands, 2004). Maternal educational level was categorized into low to intermediate (no or primary education, lower or intermediate vocational training) and high (higher vocational education or university) education level (Statistics & Netherlands, 2005). Child sex, gestational age at birth, birth weight and head circumference at birth were extracted from medical records. Child ethnicity was defined into Western and non-Western, and considered non-Western if the participants themselves or if one of their parents were born in a non-Western country (Kooijman et al., 2016; Statistics & Netherlands, 2004). Native language was obtained by parental reports at 9 years of age. Mono- or bilingualism education refers to acquiring one or more than one native language by age of 6 years through their parents (Peng & Wang, 2011). If languages are acquired

simultaneously by 6 years of age, these languages are considered to be native languages. Handedness was determined using the Edinburg Handedness Inventory and categorized into right- and left-handers (Oldfield, 1971). This test was assessed by a research assistant at the time of the MRI sub-study. Total problem score was quantified using parental reported Child Behavior Checklist (CBCL) at 5 years of age. The CBCL is a widely used reliable and valid measure for behavioral problems (Achenbach & Ruffle, 2000).

## 2.7 Data analysis

We included all children with available information on stuttering. For additional sensitivity analyses, we used a matched case-control approach as described above. Differences in demographic and clinical variables between children who stutter and fluent speaking controls were determined using Chi-squared and Fisher's Exact Tests for categorical variables and T-tests for continuous variables.

First, we selected specific brain regions of interest based on prior literature on children who stutter to assess regional structural brain differences (Beal et al., 2013; Beal et al., 2015; Chang et al., 2008). Specifically, the selected cortical regions included the perisylvian frontotemporal regions, the premotor and primary motor regions, the postcentral and supramarginal gyrus, and the Brodmann Areas (BA) 4, 6, 44, and 45. The subcortical regions included the basal ganglia including caudate nucleus, globus pallidum, and putamen. These regions of interests were separately tested for each hemisphere using general linear regression model analyses. The model was adjusted for child age, sex, handedness, native language, and total brain volume as well as education level of mother (Amunts et al., 1996; Lenroot & Giedd, 2006; Mechelli et al., 2004). The analyses were performed in SPSS (version 24.0). False Discovery Rate (FDR) corrected p-values ($< 0.05$) were used to correct for multiple testing using the R Statistical Software (version 3.4.4).

Second, the association between stuttering and cortical thickness, cortical volumes and surface area was examined using a surface-based whole brain approach using a vertex-based general linear model. This analysis was performed in both hemispheres using the Freesurfer linear model module QDEC (Query, Design, Estimate, Contrast). Because of limitations in the number of covariates in QDEC (Blanken et al., 2015; El Marroun et al., 2016), our module was adjusted for age and sex and expanded in the region of interest analysis. Cortical thickness and volume measures were smoothed with a 10 mm full width at half maximum (FWHM) Gaussian kernel. Cortical surface area was analyzed smoothed with a 5 mm FWHM Gaussian kernel. This procedure allows for generation of statistical parametric

maps with an uncorrected threshold of p-value < 0.01 for initial vertex-wise comparison (cluster-wise p- value). Thereafter, a cluster-wise correction for multiple comparisons (Monte Carlo correction) was performed using the built-in simulation procedure with 5000 iterations and a cluster-wise threshold of p-value < 0.05, which controls for false positive clusters (Hagler, Saygin, & Sereno, 2006). Cortical thickness, surface area and volumetric data were extracted from each cluster for each subject and ANOVA was used to identify the mean differences in these clusters for each hemisphere.

# 3. Results

## 3.1 Descriptive information



Demographic characteristics of the participants divided into three groups are displayed in Table 1. The average age at neuroimaging was similar across the groups (8.2 years of age) and can be considered comparable. Boys more often stuttered than girls (73% vs. 17%). Therefore, the stuttering and matched control group included more boys than the larger control group (50% boys, p<0.05). No differences across the groups were demonstrated on other variables.

## 3.2 Regions of interest analyses on stuttering

Table 2 demonstrates the results of the prespecified speech motor and auditory brain regions, for all 515 children: gray matter volume in the frontal lobe, parietal lobe, temporal lobe, different Brodmann Areas (BA), and subcortical structures in the left and right hemisphere respectively. The results show that stuttering is associated with lower gray matter volume in specific speech motor regions. In the left hemisphere, lower gray matter volumes were found in children with a history of stuttering in the frontal lobe in BA 6 (ß -1350mm3, 95%CI -2176;-523), and in BA 45 (ß -764mm3, 95%CI -1264;-263) compared to fluent children (p-value < 0.05 and survived Monte Carlo correction). Although most cortical volumes were not significantly different, they point toward a similar result: children with a history of stuttering mostly had less gray matter volume (negative unstandardized ß, corrected p-value > 0.05) in the speech motor and auditory brain regions than normally fluent controls.

Table 3 displays the results of cortical gray matter thickness and surface area, and subcortical basal ganglia nuclei in specific brain regions of interest. In these speech motor and auditory regions, the cortical thickness and surface areas were similar across the groups in both hemispheres (corrected p-values > 0.05).

Table 2. Region of interest analyses for cortical gray matter volume in children with stuttering (n=26) compared to fluently speaking children (n=489)

| | Gray matter volume | | | | | |
|---|---|---|---|---|---|---|
| | Left Hemisphere | | | Right Hemisphere | | |
| | ß * | 95% CI | P-value | ß * | 95% CI | P-value |
| **Cortical structures** | | | | | | |
| **Frontal lobe** | -3369.76 | -3417.89; -1295.04 | 0.00 # | -2429.24 | -4742.25; -136.23 | 0.04 + |
| Caudal anterior cingulate | 63.45 | -130.83; 257.72 | 0.52 | -0.98 | -215.29; 213.34 | 0.99 |
| Insula | -282.57 | -405.88; -159.26 | 0.02 + | -167.87 | -390.06; 54.32 | 0.14 |
| Lateral orbitofrontal | -391.42 | -588.78; -194.05 | 0.05 + | -6.53 | -368.07; 355.02 | 0.97 |
| Pars opercularis | -392.26 | -760.33; -24.19 | 0.04 + | -306.09 | -618.26; 6.08 | 0.06 |
| Pars orbitalis | -113.44 | -304.21; 77.32 | 0.24 | -10.99 | -230.51; 208.54 | 0.92 |
| Pars triangularis | -331.33 | -645.39; -17.27 | 0.04 + | 6.73 | -383.06; 396.52 | 0.97 |
| Precentral gyrus | -404.17 | -1029.22; -220.89 | 0.21 | -672.14 | -1316.17; -28.11 | 0.04 + |
| Rostral anterior cingulate | -136.19 | -342.45; 70.07 | 0.20 | -130.21 | -328.67; 68.27 | 0.20 |
| **Parietal lobe** | | | | | | |
| Postcentral gyrus | 109.37 | -569.32; 788.06 | 0.75 | -475.85 | -1035.27; 83.56 | 0.10 |
| Supramarginal gyrus | -378.64 | -1050.55; 293.27 | 0.27 | 14.04 | -648.02; 676.10 | 0.97 |
| **Temporal lobe** | -437.06 | -2197.38; 1323.26 | 0.63 | 214.23 | -1484.55; 1913.00 | 0.81 |
| Inferior temporal | 242.80 | -458.62; 944.22 | 0.50 | -109.17 | -770.25; 551.92 | 0.75 |
| Middle temporal | -77.65 | -724.73; 569.43 | 0.81 | 350.79 | -385.30; 1086.88 | 0.35 |
| Superior temporal | -425.07 | -999.24; 149.10 | 0.15 | 136.39 | -419.83; 692.60 | 0.63 |
| Temporal pole | -49.09 | -258.64; 160.47 | 0.66 | -130.86 | -336.78; -75.054 | 0.21 |
| Transverse temporal | -36.55 | -138.75; 65.66 | 0.48 | -48.33 | -126.89; 30.24 | 0.24 |
| **Brodmann Area** | | | | | | |
| BA 4 anterior | -129.94 | -297.07; 37.19 | 0.13 | -136.21 | -287.94; 15.53 | 0.08 |
| BA 4 posterior | -52.78 | -192.86; 414.86 | 0.47 | -68.04 | -221.72; 85.65 | 0.39 |
| BA 6 | -1350.03 | -2176.14; -523.92 | 0.00 # | -973.01 | -1772.00; -174.01 | 0.02 + |
| BA 44 | -176.33 | -460.99; 108.34 | 0.23 | -533.37 | -725.33; -341.41 | 0.01 + |
| BA 45 | -764.10 | -1264.34; -263.87 | 0.00 # | -82.62 | -618.26; 453.01 | 0.77 |
| **Subcortical structures** | | | | | | |
| Caudate | 73.24 | -113.03; 259.51 | 0.44 | 71.80 | -120.53; 264.14 | 0.47 |
| Pallidum | 3.04 | -66.28; 72.35 | 0.94 | 4.52 | -61.20; 70.23 | 0.89 |
| Putamen | -167.98 | -348.53; 74.58 | 0.17 | -101.01 | -334.55; 132.54 | 0.40 |

ß, unstandardized beta of stuttering; CI, confidence interval; BA, Brodmann Area
* Referent is fluently speaking children
+ $p < 0.05$ not survived correction for multiple testing
# $p < 0.05$ survived correction for multiple testing

Table 3. Region of interest analyses for cortical gray matter thickness and surface area in children with stuttering (n=26) compared to fluently speaking children (n=489)

| | Gray matter thickness | | | | | | Surface area | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Stuttering vs. fluent speakers (n=515) | | | | | | Stuttering vs. fluent speakers (n=515) | | | | | |
| | Left Hemisphere | | | Right Hemisphere | | | Left Hemisphere | | | Right Hemisphere | | |
| | ß * | 95% CI | P-value | ß * | 95% CI | P-value | ß * | 95% CI | P-value | ß * | 95% CI | P-value |
| **Cortical structures** | | | | | | | | | | | | |
| **Frontal lobe** | -0.04 | -0.10; 0.01 | 0.13 | -0.03 | -0.09; 0.03 | 0.27 | -299.91 | -869.07; 269.26 | 0.30 | -223.39 | -828.26; 381.49 | 0.47 |
| Caudal anterior cingulate | -0.15 | -0.26; -0.05 | 0.01 + | -0.02 | -0.13; 0.09 | 0.75 | 40.15 | -4.95; 85.24 | 0.08 | 21.97 | -30.31; 74.24 | 0.41 |
| Insula | 0.01 | -0.05; 0.07 | 0.69 | -0.04 | -0.10; 0.03 | 0.29 | -82.89 | -120.49; -45.29 | 0.03 + | -25.23 | -91.71; 41.26 | 0.46 |
| Lateral orbitofrontal | -0.02 | -0.11; 0.07 | 0.66 | -0.04 | -0.13; 0.05 | 0.42 | -101.40 | -199.09; -3.71 | 0.05 + | 34.60 | -76.81; 146.00 | 0.55 |
| Pars opercularis | -0.06 | -0.12; -0.01 | 0.03 + | -0.02 | -0.09; 0.05 | 0.60 | -53.41 | -145.62; 38.80 | 0.26 | -78.04 | -158.63; 2.55 | 0.06 |
| Pars orbitalis | -0.10 | -0.22; 0.03 | 0.12 | -0.03 | -0.16; 0.10 | 0.63 | -14.57 | -43.42; 14.29 | 0.35 | 17.24 | -18.49; 52.96 | 0.35 |
| Pars triangularis | -0.09 | -0.16; -0.01 | 0.03 + | -0.03 | -0.11; 0.05 | 0.46 | -48.69 | -120.87; 23.49 | 0.19 | 28.35 | -62.53; 119.23 | 0.54 |
| Precentral gyrus | -0.03 | -0.09; 0.03 | 0.26 | -0.02 | -0.08; 0.05 | 0.56 | -22.77 | -227.45; 181.91 | 0.83 | -175.47 | -377.86; 26.92 | 0.09 |
| Rostral anterior cingulate | -0.05 | -0.14; 0.05 | 0.37 | -0.10 | -0.19; 0.01 | 0.06 | -14.16 | -66.03; 37.72 | 0.59 | -8.32 | -49.44; 32.80 | 0.75 |
| **Parietal lobe** | | | | | | | | | | | | |
| Postcentral gyrus | -0.03 | -0.09; 0.03 | 0.30 | -0.02 | -0.09; 0.04 | 0.47 | 99.20 | -82.42; 280.83 | 0.29 | -112.07 | -280.09; 55.95 | 0.19 |
| Supramarginal gyrus | -0.02 | -0.09; 0.04 | 0.50 | -0.04 | -0.11; 0.03 | 0.27 | -5.89 | -189.90; 178.13 | 0.95 | 65.07 | -110.22; 240.36 | 0.47 |
| **Temporal lobe** | 0.00 | -0.06; 0.07 | 0.90 | -0.01 | -0.07; 0.06 | 0.85 | -12.43 | -371.30; 346.44 | 0.95 | 45.29 | -107.95; 198.52 | 0.79 |
| Inferior temporal | 0.02 | -0.07; 0.11 | 0.65 | -0.03 | -0.12; 0.06 | 0.49 | 53.22 | -97.09; 203.52 | 0.49 | 0.49 | -137.44; 138.42 | 0.99 |
| Middle temporal | 0.01 | -0.08; 0.11 | 0.77 | 0.01 | -0.08; 0.11 | 0.77 | 4.94 | -111.64; 121.52 | 0.94 | 43.98 | -76.30; 164.25 | 0.47 |
| Superior temporal | 0.01 | -0.06; 0.08 | 0.79 | 0.00 | -0.07; 0.08 | 0.97 | -99.65 | -226.11; 26.81 | 0.12 | 25.18 | -86.35; 136.70 | 0.66 |
| Temporal pole | -0.08 | -0.17; 0.00 | 0.34 | -0.11 | -0.20; 0.08 | 0.26 | 3.40 | -9.23; 16.02 | 0.79 | -13.79 | -38.80; 11.23 | 0.28 |
| Transverse temporal | 0.00 | -0.09; 0.10 | 0.95 | -0.01 | -0.06; 0.04 | 0.77 | -6.52 | -33.64; 20.60 | 0.64 | -13.64 | -33.52; 6.25 | 0.18 |

| | Gray matter thickness | | | | | | Surface area | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Stuttering vs. fluent speakers (n=515) | | | | | | Stuttering vs. fluent speakers (n=515) | | | | | |
| | Left Hemisphere | | | Right Hemisphere | | | Left Hemisphere | | | Right Hemisphere | | |
| | ß * | 95% CI | P-value | ß * | 95% CI | P-value | ß * | 95% CI | P-value | ß * | 95% CI | P-value |
| **Brodmann Area** | | | | | | | | | | | | |
| BA 4 anterior | 0.00 | -0.09; 0.08 | 0.93 | -0.05 | -0.14; 0.05 | 0.32 | -33.10 | -82.98; 16.78 | 0.19 | -25.54 | -74.30; 23.23 | 0.31 |
| BA 4 posterior | -0.03 | -0.09; 0.04 | 0.46 | -0.01 | -0.08; 0.06 | 0.82 | -10.95 | -59.34; 37.45 | 0.66 | -23.78 | -72.59; 25.03 | 0.34 |
| BA 6 | -0.06 | -0.13; 0.01 | 0.12 | -0.03 | -0.11; 0.05 | 0.48 | -175.38 | -414.36; 63.61 | 0.15 | -195.04 | -413.91; 25.83 | 0.08 |
| BA 44 | -0.05 | -0.11; 0.01 | 0.11 | -0.05 | -0.12; 0.02 | 0.16 | -18.08 | -97.78; 61.62 | 0.66 | -122.40 | -230.834; -13.96 | 0.03 + |
| BA 45 | -0.08 | -0.16; -0.01 | 0.02 + | -0.02 | -0.10; 0.06 | 0.61 | -109.31 | -248.80; 30.19 | 0.09 | 16.81 | -118.88; 152.49 | 0.81 |

ß, unstandardized beta of stuttering; CI, confidence interval; BA, Brodmann Area
* Referent is fluently speaking children
+ $p < 0.05$ not survived correction for multiple testing
# $p < 0.05$ survived correction for multiple testing

## 3.3 Exploratory whole-brain analyses

Table 4 demonstrates the relationship between childhood stuttering and gray matter structures on a vertex-based level. Whole brain exploratory analyses showed that cortical gray matter volume and surface area were not associated with stuttering history (cluster-wise p-value >0.01).

Table 4. Exploratory whole-brain analyses in cortical gray matter thickness

a) in children with stuttering (n=26) compared to fluently speaking children (n=489)

| Hemisphere | Lobe | Region | Cluster size (mm2) | Talairach coordinates (x, y, z) | Number of vertices within cluster (NVtxs) | Cluster-wise p-value* |
|---|---|---|---|---|---|---|
| **Left** (Figure 2) | **Frontal** | Frontotemporal | 697.24 | -36.4 7.9 33.4 | 1430 | 0.0007 |
| | | Caudal middle frontal | 585.44 | -25.4 15.7 36.6 | 938 | 0.0034 |
| | | Superior frontal | 634.27 | -16.1 45.0 33.1 | 1068 | 0.0021 |
| | **Parietal** | Superior parietal | 526.56 | 23.3 -68.6 28.9 | 965 | 0.0069 |
| **Right** (Figure 2) | **Frontal** | Rostral middle frontal | 833.95 | 15.5 58.6 -7.9 | 1087 | 0.0002 |
| | **Parietal** | Inferior parietal | 1002.43 | 39.3 -77.3 23.8 | 1692 | 0.0001 |
| | **Occipital** | Lateral occipital | 754.80 | 24.7 -85.9 -2.9 | 915 | 0.0004 |

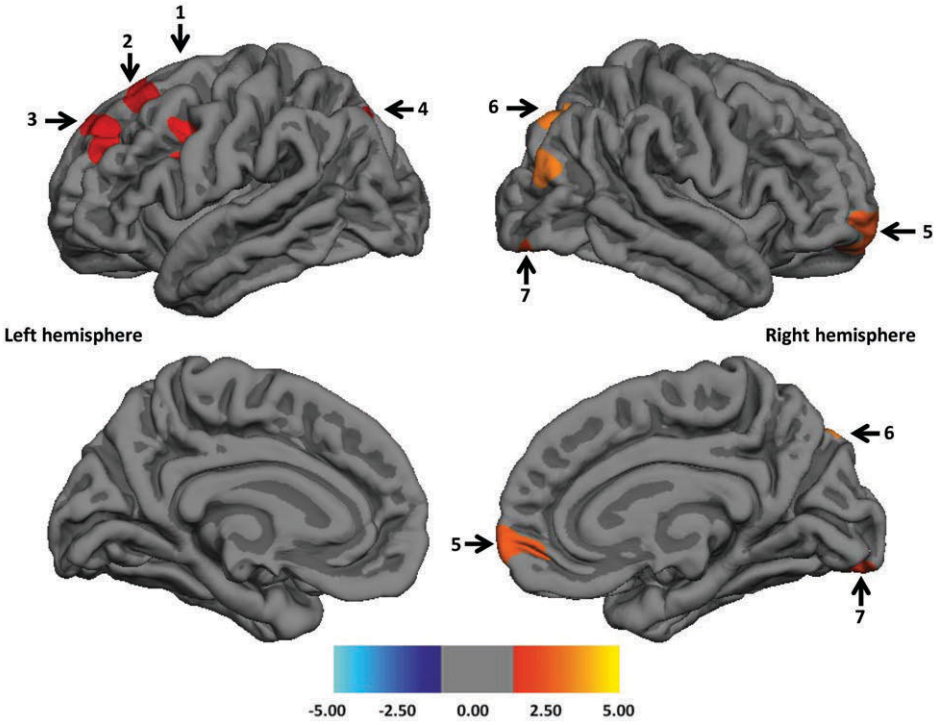
b) in children with stuttering (n=26) compared to matched fluently speaking children (n=71)

| Hemisphere | Lobe | Region | Cluster size (mm2) | Talairach coordinates (x, y, z) | Number of vertices within cluster (NVtxs) | Cluster-wise p-value* |
|---|---|---|---|---|---|---|
| **Left** (Figure 3) | **Frontal** | Frontotemporal | 583.32 | -37.0 8.8 34.1 | 1244 | 0.0034 |
| **Right** (Figure 3) | **Parietal** | Inferior parietal | 652.30 | 37.6 -77.2 17.5 | 1029 | 0.0018 |
| | | Superior parietal | 989.47 | 26.7 -63.4 29.3 | 1620 | 0.0001 |

* Cluster-wise p-value <0.01

Children with stuttering history had significantly thinner cortex than fluently speaking children in both hemispheres (table 4a). Figure 2 depicts the association in both hemispheres. In the left hemisphere, we found cluster-wise differences in the frontotemporal lobe in the pars opercularis (difference -0.140mm, 95%CI -0.213;-0.048), caudal middle frontal area (difference -0.147mm, 95%CI -0.284;-0.009), and superior frontal area (difference -0.112mm, 95%CI -0.232;-0.008), and in the parietal lobe in the superior parietal area (difference -0.094mm, 95%CI -0.185;-0.003). In the right hemisphere, children with a stuttering history had a thinner cortex in the rostral middle frontal area (difference -0.208mm, 95%CI -0.329;-0.088), inferior parietal area (difference -0.200mm, 95%CI -0.296;-0.104), and lateral occipital area (difference -0.077mm, 95%CI -0.188;-0.010). After accounting for handedness and native language results remained the same (not shown).

Figure 2. Differences in gray matter cortical thickness in children with stuttering compare to fluently speaking children



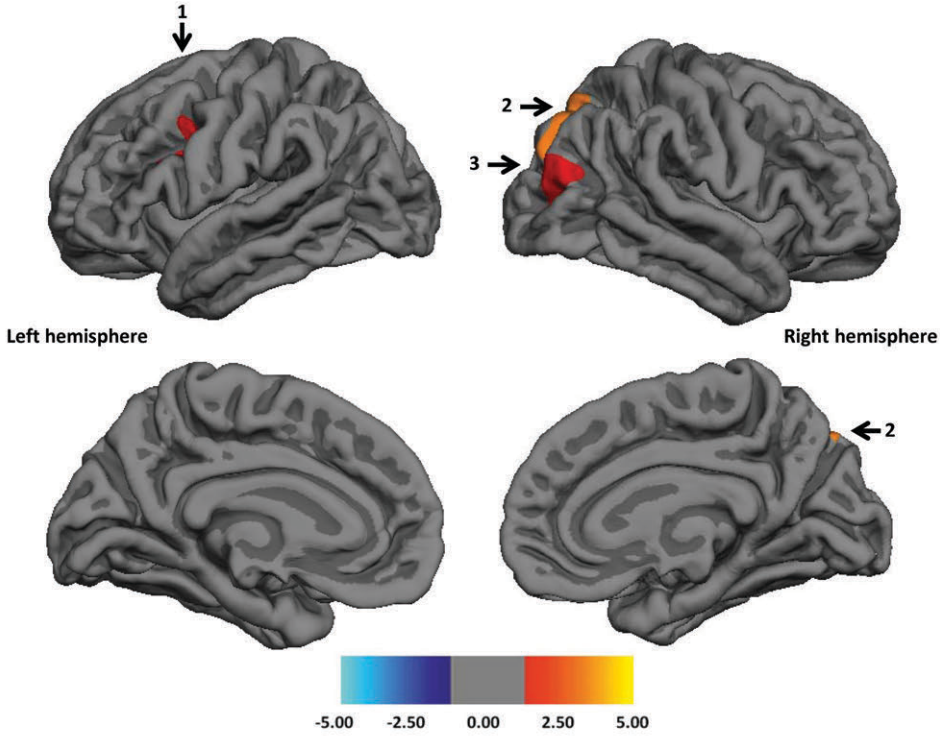

Significant brain regions: 1. Frontotemporal, 2. Caudal middle frontal, 3. Superior frontal, 4. Superior parietal, 5. Rostral middle frontal, 6. Inferior parietal, 7. Lateral occipital
Colorbar (indication of the statistical range) represent – log10
Lateral and medial view of both hemispheres. Values were thresholders at an uncorrected cluster-wise $p<0.01$, and a cluster-wise multiple correction (Monte Carlo) with threshold of $p<0.05$. Colored areas are thinner in children who stutter compare to controls.

## 3.4 Additional analyses with matched controls

Our findings remained consistent with separate sensitivity analysis in the matched control group. Supplementary Tables 1 and 2 show that in children with stuttering history, cortical gray matter volume was lower in left BA 45 (ß -938mm3, 95% CI -1486;-390) than in the fluent speakers (Monte Carlo corrected p-value < 0.05).

Furthermore, we found significantly thinner cortex in the left pars opercularis (cluster size 583mm, p-value 0.0034) and in the right inferior parietal area (cluster size 989mm, p-value <0.0001) (Table 4b, Figure 3). The association between childhood stuttering and the left frontal and the right parietal region remained significant across groups, even in this matched group comparison.

Figure 3. Differences in gray matter cortical thickness in children with stuttering compare to matched fluently speaking children




Significant brain regions: 1. Frontotemporal, 2. Inferior parietal, 3. Superior parietal
Colorbar (indication of the statistical range) represent – log10
Lateral and medial view of both hemispheres. Values were thresholders at an uncorrected cluster-wise $p<0.01$, and a cluster-wise multiple correction (Monte Carlo) with threshold of $p<0.05$. Colored areas are thinner in children who stutter compare to matched controls.

## 4. Discussion

We investigated the association between stuttering and brain morphometry in early childhood, within a population-based setting. In children with a history of stuttering (not necessarily associated with persistent stuttering) compared to fluent speaking controls in a large pediatric population, we found smaller gray matter volumes in the left BA6 and BA45 and thinner cortex in the left frontotemporal and right parietal region. These brain regions are known to be involved in speech production as they overlap with the speech motor and auditory regions.

We replicated the reduced gray matter volume findings in the left frontotemporal region in children previously described (Beal et al., 2013; Chang et al., 2008). In addition, we replicated the association between stuttering and reduced cortical thickness in both hemispheres. This is in line with Beal et al. (2015), who were the first to study cortical thickness and stuttering. They reported thinner cortex in children and adults (age 6 to 48 years) who stutter. Garnett et al. (2018) recently reported decreases in cortical thickness in the left premotor and motor areas specific to children with persistent stuttering. As we did not focus specifically on persistent stuttering, our study helps parse the mixed findings in the literature. The frontotemporal brain regions found to be different in gray matter morphometry in previous studies are those that contribute to speech motor control, including planning, adequate rhythm and timing of speech production. Altogether, our results suggest that the speech motor and auditory gray matter regions found to be smaller in young children who have a history of stuttering may be a consistent finding and, therefore, evidence is accumulating for aberrant brain morphometry in children who stutter.

In addition, our gray matter findings in the left BA6 and BA45 incorporate well with earlier white matter tract findings that indicate abnormality in the microstructural properties of the frontal aslant tract, which connects these two regions for speech production, in children and adults who stutter (Chow & Chang, 2017; Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier, & Ben-Shachar, 2016; Misaghi, Zhang, Gracco, De Nil, & Beal, 2018). While our study focused on structural gray matter differences, it may still be highly relevant for researchers who target the white matter, because there is accumulating evidence for an association of white and gray matter abnormalities in stuttering (Beal et al., 2013; Chang, Zhu, Choo, & Angstadt, 2015; Choo et al., 2011; Chow & Chang, 2017; Jancke, Hanggi, & Steinmetz, 2004).

Our results do not support earlier findings that show higher gray matter density and volumes in the right superior temporal gyrus of adults who stutter (Beal et al., 2013; Beal et al., 2007). The superior temporal gyrus seems to induce fluency in people who stutter (Craig-McQuaide, Akram, Zrinzo, & Tripoliti, 2014; De Nil et al., 2008). Given the fact that this study included children with a history of stuttering and not necessarily those with persistent stuttering, the developmental neuroanatomy might be different in this population relative to those found in earlier studies. For children with a history of stuttering, most regions of interest did not differ significantly from controls (Table 2 and 3), suggesting that for example superior temporal gyrus develops in a normalized manner

in children who recover from stuttering. Also, the present negative findings in the right superior temporal gyrus may suggest the involvement of this region in spontaneous recovery from stuttering.

Contrary to previous studies that have reported less volume in the left putamen in children who stutter (Beal et al., 2013; Chang et al., 2015) and greater putamen volume in adults who stutter (Beal et al., 2013; Lu et al., 2010) relative to controls, we did not find any significant group differences in the subcortical areas. This absence of differences involving subcortical areas suggests that subcortical structures is not associated with a history of stuttering. This may be indicative of an abnormal trajectory of neuroanatomic development in the putamen in persistent stuttering specifically.



Several potential mechanisms may underlie the relationship between stuttering and altered structural brain morphometry.

First, although caution must be taken when interpreting cross-sectional findings, our results suggest a delayed or aberrant neurodevelopment of motor speech regions. Cortical gray matter volume tends to follow an "inverted U shape" developmental pattern in childhood, which means that in early childhood brain size increases and thereafter decreases (Dekaban, 1978; Giedd et al., 1996; Lenroot & Giedd, 2006). Hence, interpretation of the smaller volume found in the stuttering group is not clear-cut and can be due to overall decreased volume throughout development, initially delayed maturation that is later normalized (e.g. this could relate to recovery of stuttering as thinner brain regions mature), or due to other mechanisms.

Second, frontal brain region findings may represent neurodevelopmental (e.g. in the domain of emotions, behavior, motor skills, or language) differences that contribute to the manifestation of stuttering (Blomgren, 2013; Smith & Weber, 2017). For example, children who stutter exhibited greater cortical responses (evoked response potentials (ERP) sensitive to emotional stimuli) to unpleasant pictures than children who do not stutter suggesting an association between temperamental characteristics, emotional reactivity and stuttering (Zengin-Bolatkale, Conture, Key, Walden, & Jones, 2018). Stuttering is a disorder of speech production, however stuttering has been hypothesized to be a multidimensional disorder (Bennett, 2006; Smith & Kelly, 1997). On the one hand, stuttering is often more pronounced when a child is in a rush, is very excited, or speaks in a stressful situation (e.g. asking a question in the classroom, talking on the telephone) (Kraft, Ambrose, & Chon, 2014; Yaruss, Coleman, & Quesal, 2010), while on the other hand, stuttering itself may trigger negative emotions such

as frustration, anger, and shame (Blomgren, 2013; Kefalianos, Onslow, Ukoumunne, Block, & Reilly, 2017). In young children, these emotions are mostly connected to the moment of stuttering, but in children aged 6 and up, these emotions often negatively impact their social activities. Neuroimaging studies which consider the interaction between stuttering and behavior aspects, and which evaluate the brain morphometry and behavior (e.g. Child Behavior Checklist, CBCL) prior to the onset of stuttering with repeated assessments are required to test these possible pathophysiological pathways.

Third, brain differences may represent alterations in response to motor control, training or mental activity. Adult studies have shown gray matter increases following a juggling motor training (Draganski et al., 2004), lifetime of practice in musicians (Gaser & Schlaug, 2003), and learning a second language (Mechelli et al., 2004). Stimulation and speech training may remodel the brain as there is neuroplasticity, which refers to the ability of gray matter to change their structure and change throughout an individual's life (Zatorre, Fields, & Johansen-Berg, 2012). Given the lack of similar findings in young children so far, because only adults who stutter have shown slightly *increased* gray matter volume in the right hemisphere (Beal et al., 2007; Beal et al., 2015; Foundas, Bollich, Corey, Hurley, & Heilman, 2001; Foundas et al., 2004; Lu et al., 2010; Song et al., 2007), the right cortical increase might develop after childhood as a result of persistent stuttering (Chang et al., 2008). Moreover, as well as behavior in children has related brain morphology (Wildeboer et al., 2018) persistent stuttering may also shape the morphology of the brain, and neuroplasticity seems to require intensive stimulation, because only intensive stuttering treatment resulted in different activation patterns (De Nil, Kroll, Lafaille, & Houle, 2003).

Finally, differences in the frontotemporal regions may be due to genetic vulnerability for stuttering. Twin studies have shown that stuttering tends to run in families. They found stuttering to be attributed to additive genetic effects (70-85% variance of liability) and moderate non-shared environmental effects in early childhood (Dworzynski et al., 2007; Felsenfeld et al., 2000; Rautakoski, Hannus, Simberg, Sandnabba, & Santtila, 2012). However, the genes that are involved in stuttering may also generate differences in the neurodevelopment in childhood and thus it is important to investigate whether stuttering is determined solely by neural influences or additive genetic effects (e.g. genes that affect both stuttering and brain differences which might be related to stuttering).

A strength of this study is the use of a large birth cohort, which is well suited to study neurodevelopmental disorders due to the fact that recruitment occurs prior to disorder

onset, from the community rather than from a clinical setting, and the presence of a large group of non-stuttering controls. Second, our study design provides a unique opportunity to explore brain morphometry in young children, similar to the recent publication of Garnett et al. (2018) where children closer to the onset of stuttering were examined. Finally, our results will be generalizable to the general population children who stutter, because, for the first time, we investigated both boys and girls with a history of stuttering, including both right and left handers, and with both mono- and bilingualism education. However, some limitations should be mentioned. First, due to the small sample size in children with a history of stuttering, we could not stratify children into persistent stuttering and recovered stuttering groups. Second, we used parental reports of stuttering at 9 to 12 years of age as it was not possible to examine stuttering by an expert in a large population-based cohort at the time of scanning, which occurred when the children were 6-9 years of age. These reports pointed to a history of stuttering, however detailed information such as the time of onset, and duration of the stuttering were not assessed. Inclusion based on parental reports could in theory lead to selection bias. However, over- or underreporting of stuttering is unlikely, as the incidence of stuttering in our study population is in line with the expected 5-10% (Bloodstein & Bernstein Ratner, 2008; Boyle et al., 2011; Craig et al., 2002; Dworzynski et al., 2007; Månsson, 2000; Reilly et al., 2013). Furthermore, we acknowledge that stuttering can occur with other speech and language disorders, intellectual disabilities, and behavior problems (Healey & Reid, 2003; Ntourou, Conture, & Lipsey, 2011; Wolk, Edwards, & Conture, 1993). Therefore, the speech and language developmental questionnaires contained questions specifically regarding stuttering, speech, and language problems. As we focused on stuttering in a general pediatric population, we did not exclude children with speech and language problems. Fourth, non-responsitive analyses showed, in line with White et al. (2013), that children who participated in the current study were more likely to have higher educated mothers, Western ethnicity, monolingual education, and total problems than children who did not participate in the MRI sub study. Lastly, due to the cross-sectional design of this study, we cannot infer causality.

The brain regions found to be associated with stuttering in our study are those that rapidly develop in childhood and contribute to speech motor control (Guenther, 2016; Lenroot & Giedd, 2006). Future research should explore the causal nature of this association. A longitudinal neuroimaging study is needed to determine if abnormalities in the brain are present before and at stuttering onset, indicating a causal pathway, disappear in

later age, or if these abnormalities develop as a result of stuttering. Also, multi-modal neuroimaging studies investigating other characteristics of brain development using diffusion imaging to examine white matter integrity in addition to functional MRI to obtain information on brain connectivity are important to track neurodevelopment with childhood stuttering (Misaghi et al., 2018). Further, because stuttering affects more boys than girls (Guitar, 2016; Yairi, Ambrose, Paden, & Throneburg, 1996), and boys and girls exhibit different coping styles when facing potentially stressful events (Freud, Kichin-Brin, Ezrati-Vinacour, Roziner, & Amir, 2017; Matud, 2004), it is important to examine sex differences. Overall, it is highly interesting to find out which internal and external factors contribute to stuttering and how these are related to brain development in children who stutter.

In conclusion, our findings based on a population-based cohort replicated previous findings from clinical groups that there is an association between stuttering in early childhood and structural brain morphometry. The brain regions found to be associated with stuttering play an important role in speech motor control regions, and appear indispensable for achieving fluent speech.

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# Supplementary Materials

Supplementary Table 1. Region of interest analyses in cortical gray matter volume in children with stuttering (n=26) compared to matched fluently speaking children (n=71)

| | Gray matter volume | | | | | |
|---|---|---|---|---|---|---|
| | Left Hemisphere | | | Right Hemisphere | | |
| | ß * | 95% CI | P-value+ | ß * | 95% CI | P-value |
| **Cortical structures** | | | | | | |
| **Frontal lobe** | -3700.07 | -6125.77; -1274.37 | 0.00 # | -1367.60 | -3850.35;1115.15 | 0.35 |
| Caudal anterior cingulate | 53.74 | -197.67; 305.15 | 0.68 | 36.29 | -213.02;285.61 | 0.78 |
| Insula | -271.00 | -527.76; -14.23 | 0.044 + | -294.93 | -538.26; -51.59 | 0.02 + |
| Lateral orbitofrontal | -494.12 | -993.34; 5.11 | 0.05 | 73.589- | 341.61;488.79 | 0.73 |
| Pars opercularis | -4.62.278 | -869.19; -55.36 | 0.03 + | -467.43 | -650.69; -284.17 | 0.01 + |
| Pars orbitalis | 123.64 | -351.90; 104.61 | 0.29 | 69.91 | -183.44;323.26 | 0.59 |
| Pars triangularis | -486.80 | -847.70; -125.90 | 0.01 + | -43.52 | -469.00;381.96 | 0.84 |
| Precentral gyrus | -427.17 | -1309.49; 455.16 | 0.34 | -442.29 | -1085.30;200.72 | 0.23 |
| Rostral anterior cingulate | 16.35 | -249.31; 282.01 | 0.90 | -156.17 | -388.99;76.66 | 0.19 |
| **Parietal lobe** | | | | | | |
| Postcentral gyrus | -41.61 | -708.96; 625.74 | 0.90 | -568.34 | -1154.92;18.23 | 0.06 |
| Supramarginal gyrus | -494.54 | -1324.35; 335.26 | 0.24 | -271.18 | -975.85;433.49 | 0.45 |
| **Temporal lobe** | -859.61 | -1781.34; 62.11 | 0.35 | 311.02 | -1635.67;2257.71 | 0.75 |
| Inferior temporal | 533.97 | -179.10; 1247.04 | 0.14 | 128.63 | -557.25;814.51 | 0.71 |
| Middle temporal | -91.46 | -792.46; 609.55 | 0.80 | 593.89 | -174.53;1362.31 | 0.13 |
| Superior temporal | -493.03 | -1193.26; 207.20 | 0.17 | 63.06 | -628.50;754.62 | 0.86 |
| Temporal pole | -111.76 | -377.05; 153.53 | 0.41 | -118.86 | -364.92;127.21 | 0.34 |
| Transverse temporal | -48.20 | -152.98; 56.68 | 0.37 | -78.90 | -173.94;16.14 | 0.10 |
| **Brodmann Area** | | | | | | |
| BA 4 anterior | -95.92 | -314.45; 122.61 | 0.39 | -212.56 | -412.43; -12.96 | 0.04 + |
| BA 4 posterior | -59.59 | -201.17; 81.99 | 0.41 | -118.47 | 307.77; 70.83 | 0.22 |
| BA 6 | -1058.59 | -2045.27; -71.91 | 0.04 + | -653.89 | 1588.35; 280.57 | 0.17 |
| BA 44 | -157.27 | -448.85; 134.31 | 0.29 | -449.79 | -905.88; 6.30 | 0.06 |
| BA 45 | -938.58 | -1486.36; -390.80 | 0.00 # | -207.13 | 864.58; 450.33 | 0.54 |
| **Subcortical structures** | | | | | | |
| Caudate | 71.37 | -145.54; 288.27 | 0.52 | 17.09 | -211.03;245.21 | 0.88 |
| Pallidum | -15.99 | -100.01; 68.04 | 0.71 | -13.92 | -91.18;63.34 | 0.72 |
| Putamen | -243.20 | -549.44; 63.04 | 0.12 | -169.93 | -441.03;101.17 | 0.22 |

ß, unstandardized beta of stuttering; CI, confidence interval; BA, Brodmann Area
* Referent is fluently speaking children
+ $p < 0.05$ not survived correction for multiple testing
# $p < 0.05$ survived correction for multiple testing

Supplementary Table 2. Region of interest analyses in cortical gray matter thickness and surface area in children with stuttering (n=26) compared to matched fluently speaking children (n=71)

| | Gray matter thickness | | | | | | Surface area | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Left Hemisphere | | | Right Hemisphere | | | Left Hemisphere | | | Right Hemisphere | | |
| | ß * | 95% CI | P-value | ß * | 95% CI | P-value | ß * | 95% CI | P-value | ß * | 95% CI | P-value |
| **Cortical structures** | | | | | | | | | | | | |
| **Frontal lobe** | -0.05 | -0.12; 0.02 | 0.13 | -0.02 | -0.05; 0.02 | 0.68 | -213.26 | -882.63; 456.12 | 0.53 | 14.22 | -673.53; 701.98 | 0.97 |
| Caudal anterior cingulate | -0.13 | -0.27; -0.01 | 0.04 + | 0.01 | -0.12; 0.15 | 0.85 | 43.35 | -15.90; 102.59 | 0.15 | 24.87 | -36.86; 86.60 | 0.43 |
| Insula | 0.01 | -0.05; 0.08 | 0.70 | -0.04 | -0.11; 0.04 | 0.33 | -66.66 | -149.15; 15.82 | 0.14 | -42.23 | -114.15; 29.69 | 0.25 |
| Lateral orbitofrontal | -0.05 | -0.16; 0.06 | 0.36 | -0.04 | -0.15; 0.06 | 0.41 | -95.34 | -217.27; 26.59 | 0.01 | 74.75 | -55.06; 204.56 | 0.26 |
| Pars opercularis | -0.07 | -0.14; -0.01 | 0.03 + | -0.01 | -0.09; 0.08 | 0.88 | -63.34 | -169.48; 42.80 | 0.25 | -106.93 | -200.43; -13.44 | 0.03 + |
| Pars orbitalis | -0.11 | -0.30; 0.08 | 0.27 | 0.03 | -0.10; 0.17 | 0.64 | -16.69 | -54.00; 20.62 | 0.38 | 21.42 | -22.87; 65.72 | 0.34 |
| Pars triangularis | -0.09 | -0.18; 0.01 | 0.07 | 0.00 | -0.10; 0.09 | 0.97 | -88.54 | -170.03; -7.05 | 0.03 + | 7.59 | -95.54; 110.71 | 0.89 |
| Precentral gyrus | -0.04 | -0.11; 0.03 | 0.28 | -0.01 | -0.09; 0.07 | 0.78 | 24.88 | -234.07; 283.84 | 0.85 | -88.67 | -299.80; 122.47 | 0.41 |
| Rostral anterior cingulate | -0.03 | -0.15; 0.09 | 0.60 | -0.08 | -0.15; -0.06 | 0.24 | 13.19 | -58.11; 84.49 | 0.71 | -18.09 | -78.85; 42.68 | 0.56 |
| **Parietal lobe** | | | | | | | | | | | | |
| Postcentral gyrus | -0.07 | -0.13; -0.01 | 0.03 + | -0.04 | -0.11; 0.03 | 0.27 | 113.16 | -83.75; 310.06 | 0.26 | -118.39 | -284.34; 47.56 | 0.16 |
| Supramarginal gyrus | -0.05 | -0.12; 0.02 | 0.16 | -0.05 | -0.14; 0.03 | 0.21 | -6.03 | -229.88; 217.82 | 0.96 | -2.79 | -200.46; 194.89 | 0.98 |
| **Temporal lobe** | -0.02 | -0.08; 0.05 | 0.60 | 0.00 | -0.07; 0.07 | 0.99 | -19.73 | -423.04; 383.59 | 0.93 | 61.26 | -319.01; 441.53 | 0.75 |
| Inferior temporal | 0.02 | -0.07; 0.10 | 0.74 | -0.01 | -0.10; 0.08 | 0.79 | 126.79 | -43.95; 297.53 | 0.15 | 50.03 | -105.06; 205.12 | 0.54 |
| Middle temporal | 0.01 | -0.09; 0.11 | 0.85 | 0.02 | -0.08; 0.12 | 0.68 | 8.63 | -143.23; 160.50 | 0.91 | 97.81 | -37.83; 233.44 | 0.16 |
| Superior temporal | -0.01 | -0.09; 0.08 | 0.89 | 0.00 | -0.09; 0.09 | 0.94 | -93.13 | -240.45; 54.19 | 0.22 | 7.24 | -121.76; 136.23 | 0.91 |
| Temporal pole | -0.10 | -0.30; 0.11 | 0.36 | -0.03 | -0.27; 0.20 | 0.78 | -14.63 | -43.38; 14.12 | 0.32 | -21.41 | -47.62; 4.80 | 0.11 |
| Transverse temporal | -0.02 | -0.09; 0.12 | 0.78 | -0.01 | -0.13; 0.11 | 0.87 | -5.82 | -32.69; 21.05 | 0.67 | -20.72 | -31.99; 1.68 | 0.07 |

| | Gray matter thickness | | | | | | Surface area | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Left Hemisphere | | | Right Hemisphere | | | Left Hemisphere | | | Right Hemisphere | | |
| | ß * | 95% CI | P-value | ß * | 95% CI | P-value | ß * | 95% CI | P-value | ß * | 95% CI | P-value |
| **Brodmann Area** | | | | | | | | | | | | |
| BA 4 anterior | 0.01 | -0.04; 0.07 | 0.79 | -0.05 | -0.15; 0.06 | 0.38 | -25.00 | -82.85; 32.86 | 0.40 | -40.86 | -105.29; 23.56 | 0.21 |
| BA 4 posterior | -0.03 | -0.11; 0.43 | 0.40 | -0.01 | -0.08; 0.06 | 0.79 | -3.00 | -48.45; 42.44 | 0.90 | -36.57 | -99.63; 26.49 | 0.26 |
| BA 6 | -0.05 | -0.13; 0.03 | 0.21 | -0.02 | -0.11; 0.07 | 0.70 | -68.70 | -349.31; 211.92 | 0.63 | -83.58 | -293.06; 125.91 | 0.44 |
| BA 44 | -0.05 | -0.13; 0.03 | 0.21 | -0.02 | -0.10; 0.06 | 0.64 | -5.49 | -88.03; 77.05 | 0.90 | -106.46 | -241.42; 28.51 | 0.13 |
| BA 45 | -0.10 | -0.19; -0.01 | 0.03 + | 0.02 | -0.06; 0.09 | 0.72 | 143.86 | -284.01; -3.70 | 0.04 + | -35.09 | -197.49; 127.30 | 0.67 |

ß, unstandardized beta of stuttering; CI, confidence interval; BA, Brodmann Area
* Referent is fluently speaking children
+ $p < 0.05$ not survived correction for multiple testing
# $p < 0.05$ survived correction for multiple testing


White matter
Persistent
Fluency
Speech
Research
Recov
Brain
Gray matter
Neuroimaging
Self-report
Explore
Satisfaction
Cortical
Girls
Children
Stutter
Population
Temperament
Dysfluency
Fluency
Neuroplasticity
Outcome
Boys
Long-term
Brain
Behavior
Speech
Satisfaction
Development
Subcortical
Girls
Rotterdam
Self-report
Persistent
Stutter
Cortical
Boys
Population
Speech-motor


# 7

## Structural brain differences in pre-adolescents who persist in and recover from stuttering

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S. Lamballais, H. Tiemeier, R.J. Baatenburg de Jong, T. White,
M.C. Franken, R.L. Muetzel

*NeuroImage: Clinical*, 2020: 27: 102334

## Abstract

**Background:** Stuttering is a complex speech fluency disorder occurring in childhood. In young children, stuttering has been associated with speech-related auditory and motor areas of the brain. During transition into adolescence, the majority of children who stutter (75-80%) will experience remission of their symptoms. The current study evaluated brain (micro-)structural differences between pre-adolescents who persisted in stuttering, those who recovered, and fluently speaking controls.

**Methods:** This study was embedded in the Generation R Study, a population-based cohort in the Netherlands of children followed from pregnancy onwards. Neuroimaging was performed in 2211 children (mean age: 10 years, range 8-12), of whom 20 persisted in and 77 recovered from stuttering. Brain structure (e.g., gray matter) and microstructure (e.g., diffusion tensor imaging) differences between groups were tested using multiple linear regression.

**Results:** Pre-adolescents who persisted in stuttering had marginally lower superior frontal gray matter volume compared to those with no history of stuttering (β -1344, 95%CI -2407;-280), and those who recovered (β -1825, 95%CI -2999;-650). Pre-adolescents who recovered, compared to those with no history of stuttering, had higher mean diffusivity in the forceps major (β 0.002, 95%CI 0.001;0.004), bilateral superior longitudinal fasciculi (β 0.001, 95%CI 0.000;0.001), left corticospinal tract (β 0.003, 95%CI 0.002;0.004), and right inferior longitudinal fasciculus (β 0.001, 95%CI 0.000;0.001).

**Conclusion:** Findings suggest that relatively small difference in prefrontal gray matter volume is associated with persistent stuttering, and alterations in white matter tracts are apparent in individuals who recovered. The findings further strengthen the potential relevance of brain (micro-)structure in persistence and recovery from stuttering in pre-adolescents.

# 1. Introduction

Childhood-onset fluency disorder, commonly referred to as stuttering, is a complex developmental speech production disorder that occurs in childhood between two and five years of age (American Psychiatric Association, 2013; Yairi & Ambrose, 1999). Stuttering occurs in 5-10% of preschool-age children (Boyle et al., 2011; Craig, Hancock, Tran, Craig, & Peters, 2002; Dworzynski, Remington, Rijsdijk, Howell, & Plomin, 2007; Månsson, 2000; Reilly et al., 2013). Most children who stutter recover spontaneously (75-80%) within 2-3 years after onset (Andrews & Harris, 1964; Kefalianos et al., 2017; Månsson, 2000; Reilly et al., 2013; Rommel, Häge, Kalehne, & Johannsen, 1999; Yairi & Ambrose, 2013). Persistent stuttering impacts social and professional communication in adults, as well as overall quality of life (Beilby, Byrnes, Meagher, & Yaruss, 2013; Craig, Blumgart, & Tran, 2009; Finn, 2003; Klompas & Ross, 2004; Koedoot, Bouwmans, Franken, & Stolk, 2011; Nang, Hersh, Milton, & Lau, 2018; Yaruss & Quesal, 2006). Current views on the etiology of developmental stuttering are multifactorial, combining genetic, neurobiological, psychological and environmental factors (Smith & Weber, 2017). Identifying the brain structures involved in stuttering and the accompanying developmental course may lead to new opportunities for neuroscience-informed therapies.



There is increasing evidence for differences in gray matter structure (Beal, Gracco, Brettschneider, Kroll, & De Nil, 2013; Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008; Foundas, Mock, Cindass, & Corey, 2013; Garnett et al., 2018; Koenraads et al., 2019) and white matter micro-structure (Beal et al., 2013; Chang, Zhu, Choo, & Angstadt, 2015; Chow & Chang, 2017) in the brains of children who stutter compared to their fluently speaking peers. Neuroimaging studies in adults whose stuttering persisted have also shown differences in brain (micro-)structure (Etchell, Civier, Ballard, & Sowman, 2018). The most common finding across morphometric studies in children and adults who stutter are differences in the left hemisphere speech network. In cortical gray matter structures, specifically, the pars- opercularis, triangularis and orbitalis, smaller volume and thinner cortex were reported in children who stutter compared to fluent peers (Beal et al., 2013; Garnett et al., 2018; Koenraads et al., 2019). Smaller gray matter volume and thinner cortex in the right frontal lobe have also been previously reported (Beal et al., 2013; Koenraads et al., 2019). In subcortical structures, smaller volumes in the basal ganglia were observed in children who stutter. The left putamen and right caudate have also been associated with stuttering, both of which play an important role

in smooth speech motor control and adequate timing and rhythm (Beal et al., 2013; Bohland & Guenther, 2006; Foundas et al., 2013; Grahn, 2012). Further, in adults with persistent stuttering, smaller gray matter volumes were shown in regions involved in the left inferior frontal gyrus (IFG) as well as the bilateral precentral and postcentral gyri, compared fluent controls (Kell et al., 2009; Lu et al., 2010). In contrast, larger gray matter volume in similar regions have also been reported in adults who stutter (Beal, Gracco, Lafaille, & De Nil, 2007; Lu et al., 2010; Song et al., 2007).

White matter microstructural metrics also differed in children who stutter compared to fluent peers along the left arcuate fasciculus, left superior longitudinal fasciculus (SLF), bilateral corticospinal tracts, and in the interhemispheric corpus callosum fibers (Chang et al., 2008; Chow & Chang, 2017). Chow and Chang (2017) found that children who recover from stuttering could be differentiated from those who persist by distinct neurodevelopmental trajectories; the recovered group showed normalized white matter growth with age, and the persistent group showed a reduction of growth rate. Similarly, in adults with persistent stuttering compared to fluent controls, lower fractional anisotropy (FA) was also reported in the left perisylvian region, left SLF, forceps minor, and body of the corpus callosum (Cykowski, Fox, Ingham, Ingham, & Robin, 2010; Sommer, Koch, Paulus, Weiller, & Buchel, 2002; Watkins, Smith, Davis, & Howell, 2008). Studies including both children and adults that identified brain areas with white matter microstructural properties, found lower FA in stuttering than in fluent speakers. The discrepancy in results among studies might reflect sampling differences in participants, including age differences, statistical significance thresholds (Cykowski et al., 2010; Sommer et al., 2002), or perhaps heterogeneity across individuals in the spatial location of affected brain areas.

Although (micro-)structural brain regions associated with auditory function and motor aspects of speech have been associated with stuttering, several gaps exist in the literature. First, with the exception of studies by Chang and colleagues investigating brain morphometry in (pre-)adolescents (ages 9-12 years), the examination of recovery from and persistence in stuttering has been limited (Chang et al., 2008; Chow & Chang, 2017; Garnett et al., 2018). Understanding the neurobiological determinants or consequences of recovery will be a crucial step towards personalized and targeted therapies in the future. Second, the vast majority of work focuses on case-control designs which is potentially biased by a.) recruitment of severely affected individuals who stutter and b.) reference samples (control groups) which are substantially different from cases in terms of, for example, certain demographic characteristics. Sampling cases and the reference sample

from the general population allows for more variability in the distribution in the case group (i.e., not only the most severely affected children are included) and a reference group which is better sampled on several factors (e.g., SES), thereby likely improving generalizability. Given this background, studying brain morphometry in relation to stuttering in pre-adolescents is essential to further increase our knowledge of the neural architecture of persistency in and recovery from stuttering.

This study aimed to build upon earlier work (Koenraads et al., 2019) and explored whether there were gray and white matter differences in a large population-based cohort of pre-adolescents ages 8-to-12 years amongst those who persisted in stuttering, those who recovered, and fluently speaking peers. Based on prior findings, we hypothesized that brain regions involved in speech production will show differences (e.g., smaller volume, thinner cortex, lower FA) in pre-adolescents who persisted in stuttering compared with those who had recovered and controls who have always spoken fluently. We further hypothesized these differences to be primarily concentrated in the cortical auditory-motor network of the left hemisphere, in the subcortical basal ganglia nuclei, and in white matter underlying those auditory-motor network areas. Finally, we hypothesized that, compared to those who never stuttered, differences in brain regions underlying stuttering in pre-adolescents who persist in stuttering will be larger than differences observed in the group of children who recovered from stuttering.



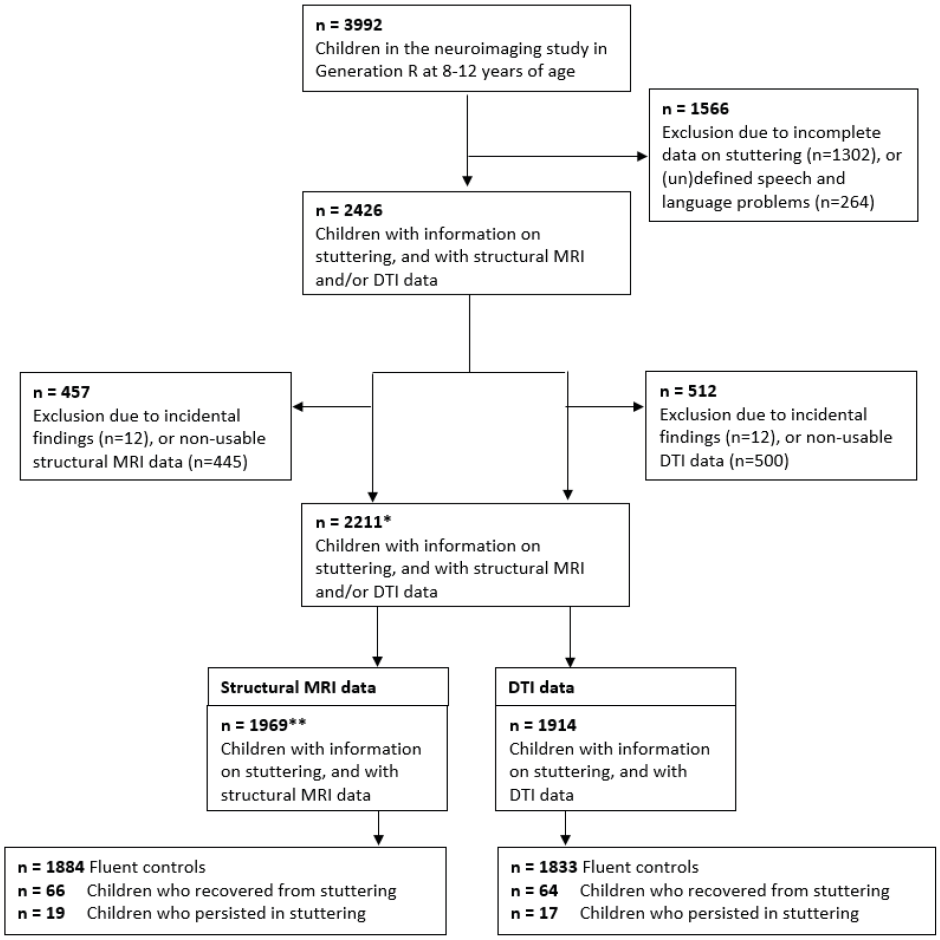
# 2. Methods

## 2.1 Study design and population

This study was embedded in the Generation R Study, a multi-ethnic population-based prospective cohort from fetal life onward in Rotterdam, the Netherlands (Kooijman et al., 2016). The Generation R Study follows children of mothers who were living in Rotterdam with a delivery date from April 2002 to January 2006. Parents of all participating children provided written informed consent and the study was approved by the Medical Ethics Committee of Erasmus Medical Center. Children underwent brain MRI scans when they were ten years old starting in March 2013 (White et al., 2018). Neuroimaging data was available for 3992 children (Figure 1). Children with incomplete information on stuttering or other (un)defined speech and language problems (e.g., based on speech and language history parental questionnaire) were excluded (n=1566). Additionally, children with poor MR image quality (n = 445 in structural MRI ($T_1$-weighted), n = 500 in DTI)

as well as children with major incidental findings (n = 12) were excluded from analyses. In total, 1969 datasets were available for $T_1$-weighted MRI analysis and n=1914 for DTI analysis).

Figure 1. Flowchart of sample selection




* this number of participants is used in Table 1 for participant demographics
** this number of participants is used in Supplementary Table 1 for participant demographics
DTI = Diffusion Tensor Imaging, MRI = Magnetic Resonance Imaging, n = number

## 2.2 Stuttering

When the children were around nine years old, their parents completed a speech and language developmental questionnaire to obtain a measure of childhood stuttering (Koenraads et al., 2019). The questionnaire contained two questions specifically regarding stuttering and had categorical items: "Does your child currently stutter?" and "Has your child ever stuttered in the past?" (yes/no). Two questions about speech therapy were assessed as well: "Is your child currently being treated for stuttering?" and "Has your child ever been treated for stuttering in the past?" (yes/no). Participants were classified as children who persisted in stuttering if both questionnaires, about the past and the present, were endorsed. Similarly, participants were classified as having recovered from stuttering if parents only endorsed previous stuttering and not current stuttering. Based on parent report, treatment for stuttering was retrospectively categorized as either: ever had treatment for stuttering, or ever had treatment for stuttering, speech and/or language problems. This categorization was based on parental reports only, and has been used in several previous studies investigating persistency in and recovery from stuttering in childhood (Dworzynski et al., 2007; Kloth, Kraaimaat, Janssen, & Brutten, 1999; Koenraads et al., 2019; Månsson, 2000). Parents of children who stutter and parents of fluently speaking children can accurately and reliably identify stuttering (Bloodstein & Bernstein Ratner, 2008; Einarsdottir & Ingham, 2009).



## 2.3 Magnetic resonance imaging

An overview of the imaging procedure, acquisition, sequences, and quality assessment in the Generation R neuroimaging Study has been described previously (White et al., 2018). All children were familiarized with the scanning environment in a mock scanning session prior to the actual MRI scanning session. Brain images were acquired on a 3 Tesla scanner (General Electric Discovery MR750w, Milwaukee, WI, USA) with an eight-channel head coil. High-resolution $T_1$-weighted images were obtained with a 3D inversion recovery fast-spoiled gradient recalled sequence (TR = 8.77 ms, TE = 3.4 ms, TI = 600 ms, Flip Angle = 10°, Field of View (FOV) = 220x220 mm, Acquisition Matrix = 220x220, slice thickness = 1 mm, number of slices = 230, Parallel Imaging Factor (ARC) = 2). The diffusion weighted images were collected with an axial spin echo, echo-planar imaging sequence with three volumes with b=0 s/mm$^2$ and 35 diffusion-weighted images (TR = 12,500 ms, TE = 72.8 ms, FOV = 240x240 mm, Acquisition Matrix = 120x120, slice thickness = 2 mm, number of slices = 65, Parallel Imaging Factor (ASSET) = 2, b = 900 s/mm$^2$).

## 2.4 Image Processing

Cortical reconstruction and volumetric segmentation were conducted with the FreeSurfer image suite version 6.0 (http://surfer.nmr.mgh.harvard.edu/) (Fischl, 2012). To summarize, removal of non-brain tissue (e.g., skull strip), voxel intensity normalization, initial tissue segmentation, cortical reconstruction and automated anatomical labeling were performed. The anatomical metrics we measured for this study were: gray matter volumes for subcortical and cortical structures, white matter volume of the corpus callosum and surface-based thickness and surface area of the cortex.

The diffusion tensor imaging (DTI) data was processed with the FMRIB Software Library (FSL) (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012), and the Camino diffusion MRI toolkit (Cook et al., 2006). Non-brain tissue was removed and images were corrected for motion and eddy-current artifacts. The resulting transformation matrices were used to rotate the gradient direction table to account for rotations applied to the data. The diffusion tensor was fitted at each voxel with FSL (BEDPOSTx package) (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/UserGuide#BEDPOSTX ), and the most common scalar metrics (e.g., FA and mean diffusivity (MD)) were computed. The full procedure is described previously (Muetzel et al., 2018). Fully-automated probabilistic tractography was performed to estimate connectivity distributions for a number of large fiber bundles using the FSL Probtrackx module with a set of predefined seed and target masks supplied by the FSL plugin, AutoPtx (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/AutoPtx ) (de Groot et al., 2015). The number of samples passing through a given voxel on a successful seed-to-target run were registered, and the resulting distributions were normalized (by the number of total successful seed-to-target attempts) and low-probability voxels were removed. In order to estimate a 'global' indicator of FA and MD, analogous to total brain volume in structural MRI, mean FA and MD were extracted from each tract, and confirmatory factor analysis was used to generate latent FA and MD measures across 12 tracts (forceps major and minor, and the left and right cingulum bundle, corticospinal tract, inferior and superior longitudinal fasciculus (ILF, SLF), and the uncinate fasciculus) which represent global white matter microstructure across the brain (Muetzel et al., 2018). The confirmatory factor analysis determines a linear combination of all tracts in order to estimate a single factor which maximally explains the variability of these tracts. This measure from now on is referred to as global FA and global MD.

FreeSurfer image reconstructions of the T1-weighted images were visually inspected for quality. All scans rated as unusable were excluded from statistical analyses (Muetzel et al., 2019). Diffusion image quality was assessed by manual inspection (visualization of residual error maps from the tensor fit and inter-subject registration) and automated methods (DTIprep toolkit, https://www.nitrc.org/projects/dtiprep) (Muetzel et al., 2018).

## 2.5 Covariates

In order to minimize the effect of confounding bias, all analyses were adjusted for several covariates. Child sex and age were calculated based on birth records. Child ethnicity was defined according to the classification of the Statistics Netherlands institute, into Western (i.e., Dutch and other non-Dutch Western) and Non-Western (Statistics Netherlands, 2004). Mono- or bilingualism was defined as acquiring one or more than one native language by age of six years through their parents in the home environment, and was assessed via questionnaires (Peng & Wang, 2011). Handedness (tendency to be right or left-handed) was determined using the Edinburg Handedness Inventory (Oldfield, 1971). Child non-verbal intelligence quotient (IQ) was assessed in the research center when children were five to seven years old, with a validated Dutch non-verbal intelligence test: Snijders-Oomen Niet-verbale intelligentie test, 2.5-7- revisie (SON-R 2.5-7) (Tellegen, Winkel, Wijnberg-Williams, & Laros, 2005). A total behavioral and emotional problem score was quantified using parental reported Child Behavior Checklist (CBCL for ages 6-18) when children were approximately nine years old. The CBCL is a widely used reliable and valid instrument that measures behavioral and emotional problems in children (Achenbach & Rescorla, 2000; Achenbach & Ruffle, 2000).

Maternal educational level was categorized following the definitions of Statistics Netherlands into two categories: medium or low (none, high school or some vocational training), and high educational attainment (higher vocational education or university) (Statistics Netherlands, 2005).

## 2.6 Data analysis

For main analyses, we divided the sample into three groups: children whose stuttering persisted, children who recovered from stuttering, and fluently speaking controls. We examined associations of the groups with brain morphology and white matter microstructure. First, the reference sample was compared with both children who

persisted in their stuttering over time, and those who recovered from stuttering over time. Second, in analyses where differences were observed with the reference sample, we also compared brain metrics of children who persisted in stuttering to those who recovered in order to ascertain whether those who persisted showed larger differences than those who recovered. Differences in demographic variables between the different stuttering groups were determined using Chi-squared and Fisher's exact tests for categorical variables and t-tests for continuous variables.

The a priori regions of interest in structural gray matter (i.e., cortical volume, thickness and surface area, and subcortical volume) and white matter (i.e., volume) were our primary outcomes. Specifically, based on prior literature on gray matter, we selected the left and right frontal and temporal lobe, the perisylvian frontotemporal regions (e.g., IFG, insula), the premotor and primary motor regions (e.g., post- and precentral gyrus), the parietal lobe with supramarginal gyrus (Chang et al., 2008; Garnett et al., 2018; Koenraads et al., 2019). We also tested whether stuttering was associated with total brain volume. Additionally, we selected the following subcortical structures: basal ganglia (caudate, putamen, pallidum) and thalamus. Further, for white matter structures, we chose to examine the five main components of the corpus callosum volume quantified in FreeSurfer (5mm thick midline section) separately (Beal et al., 2013). Our second set of outcomes were measures of white matter microstructure (FA and MD), derived from DTI. Specifically, we selected 14 different fiber bundles, including the forceps minor and major, and the left and right ILF and SLF, uncinate fasciculus, inferior fronto-occipital, corticospinal tract, and the posterior thalamic radiations (Chow & Chang, 2017). As different terms such as microstructure and integrity have been used to describe the constructs measured by DTI (Jones, Knosche, & Turner, 2013), we would like to clarify on the terminology used in this paper. We refer to DTI metrics as describing white matter microstructure, consistent with a substantial proportion of the DTI literature. However, confusion can arise in this terminology, as the resolution of DTI data are typically such that many hundreds of thousands of neurons are sampled within a single voxel, which is far from the micro-scale. The tissue sampled in this study is certainly at the macroscale, however, the signal underlying the diffusion metrics is the result of various microscale physiological processes.

We examined the association between stuttering groups and brain outcomes with multiple linear regression models. We adjusted models for the following confounders: child sex, age, handedness, bilingualism, ethnicity, and maternal education. We further

added intracranial brain volume (ICV) in models with volumetric outcomes. For all brain structural measures, regression beta coefficients (β) are presented the of millimeter scale (e.g., volume in $mm^3$, surface area in $mm^2$, thickness in mm, FA unitless with a value between 0-1, MD have been scaled by a factor of 1000 and are reported in $10^3$ mm2/sec).

Non-response analyses were conducted, contrasting the group of children who had missing data (n=1566), or non-usable data (n=215) to our study sample. Several supplemental analyses were also conducted. First, given the large number of covariates, we reran models only adjusting for age and sex in order to rule out overfitting. Second, given the complex relationship between stuttering and child's cognition and behavior, we adjusted our analyses in separate models for child's intelligence score and for total behavior problems to test the specificity of the effect. Third, analyses were performed in boys only, since stuttering is more common in boys, and to ascertain the robustness of findings without girls.



All analyses were performed in SPSS (version 24.0) and R statistical software (version 3.5.1). Missing values of covariates (maximum percentage: bilingualism = 6.1 %) were replaced by using multiple imputation to generate five data sets that sampled these values from their predictive distribution based on the relations between all variables included in the present study (Sterne et al., 2009). Results were pooled according to standard procedures (Rubin, 2004). False Discovery Rate (FDR) correction was applied to correct for the number of tests (Benjamini & Hochberg, 1995). Correction was applied separately for morphological (e.g., volume) and DTI (e.g., FA).

# 3. Results

## 3.1 Description of study sample

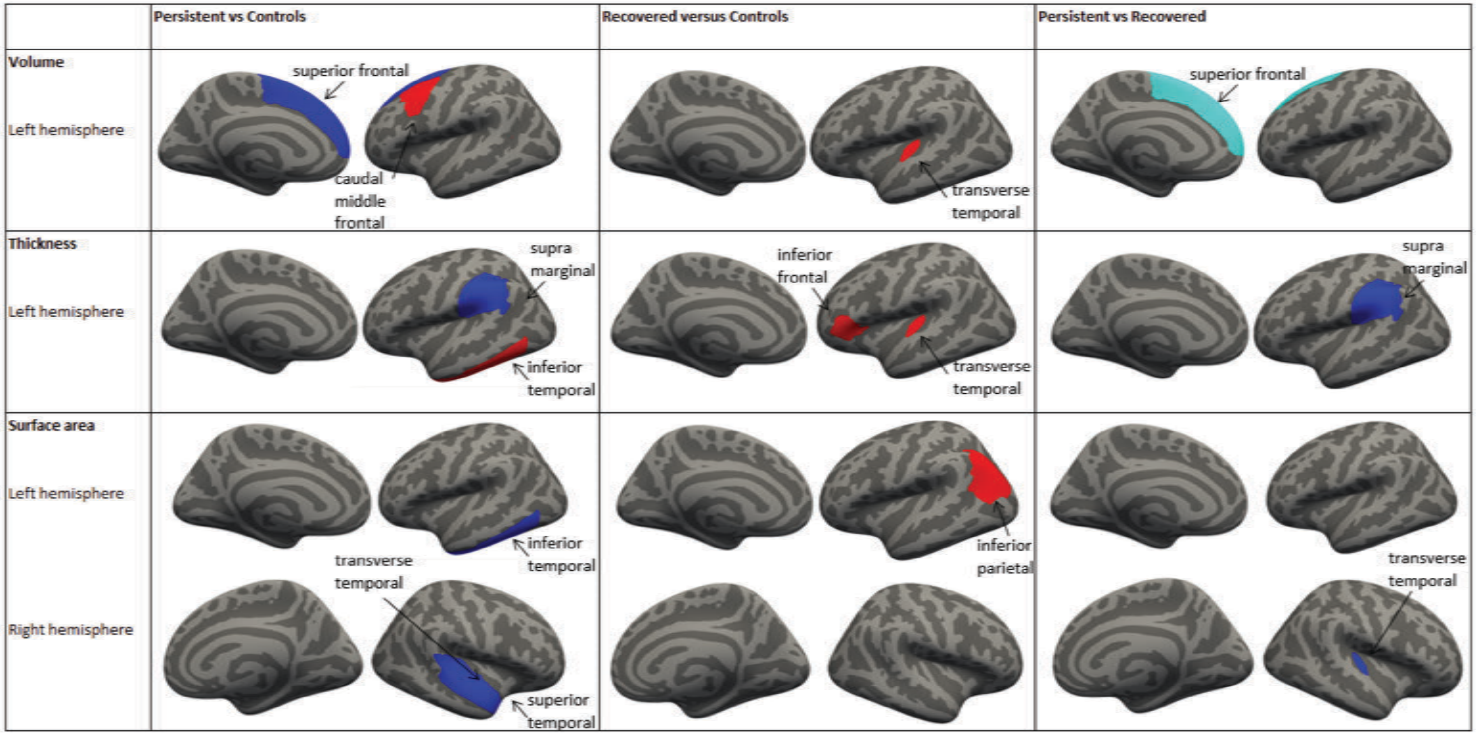
Summarized in Table 1, 20 children persisted in stuttering and 77 recovered from stuttering, which is 97 of the 2211 children (4%) were classified as having a history of stuttering by nine years old (SD= 0.3 year). Boys were more likely to persist in stuttering than girls (80% boys, p-value <0.05). Children in this study were mostly of Western ethnicity (77%), were monolingual (80%), and were right handed (89%). Seventy-five percent of children in the persistent group ever had treatment for stuttering, and 39% in the recovered group. Non-response analyses showed that children who participate in the current study were more likely to have Western ethnicity, and higher educated mothers than children who did not participate in the study. Demographics for all participants with $T_1$-weighted data are summarized in Supplementary Table 1.

Table 1. Demographics for all participants with structural and/or DTI MRI data (n=2211)

| | **Fluent controls** n = 2114 | **Children who recovered from stuttering** n = 77 | **Children who persisted in stuttering** n = 20 | **p-value** |
|---|---|---|---|---|
| **Child** | | | | |
| Age at questionnaire (years) | 9.8 (0.3) | 9.8 (0.2) | 9.8 (0.4) | > 0.05 |
| Age at MRI (years) | 10.1 (0.6) | 10.0 (0.5) | 9.9 (0.6) | 0.05 |
| Sex (% boy) | 1018 (48.2) | 53 (68.8) | 16 (80.0) | 0.01[a], 4E-4[b] |
| Ethnicity (% Western) | 1632 (77.7) [n=2100] | 54 (71.1) | 13 (65.0) | > 0.05 |
| Handedness (% right) | 1883 (89.4) [n=2106] | 70 (92.1) [n=76] | 16 (80.0) | > 0.05 |
| Lingualism (% monolingual) | 1667 (80.3) [n=2075] | 60 (77.9) | 15 (70.0) | > 0.05 |
| Ever had stutter therapy (% yes) | - | 29 (37.7) | 15 (75.0) | 0.01* |
| Ever had stutter, speech and/or language therapy (%yes) | 317 (17.5) | 34 (44.2) | 16 (80.0) | 2E-9[a], 1E-7[b], 0.01[c] |
| IQ (score) | 104.9 (14.3) [n=1871] | 102.6 (15.8) [n=67] | 103.8 (15.1) [n=18] | > 0.05 |
| Total behavior problem score (mean, SD) | 15.9 (14.1) [n=2024] | 16.3 (13.6) [n=76] | 25.6 (18.6) [n=19] | 3E-3[a],0.01[c] |
| Total behavior problem score (median, IQR) | 12.0 (6.0 – 22.0) | 13.5 (7.0 – 20.0) | 23.0 (10.1 – 36.3) | 4E-3[a],0.01[c] |
| **Maternal** | | | | |
| Ethnicity (%Western) | 1566 (74.6) [n=2098] | 54 (71.1) [n=76] | 12 (60.0) | > 0.05 |
| Education level (% high) | 1332 (67.1) [n=1984] | 51 (68.9) [n=74] | 8 (47.1) [n=17] | > 0.05 |

All categorical variables are presented with numbers (n) and percentages (%); all continuous variables are presented as mean with standard deviation (SD).
IQ = intelligence quotient, MRI = magnetic resonance imaging, n = number
[a] persistent stuttering > fluent controls (p-value < 0.05)
[b] recovered stuttering > fluent controls (p-value < 0.05)
[c] persistent stuttering > recovered stuttering (p-value < 0.05)

Figure. 2 Gray matter morphometry differences associated with stuttering




| | | | |
|---|---|---|---|
| Red | positive, did not survive FDR | Blue | negative, did not survive FDR |
| Yellow | positive, $p_{FDR} < 0.05$ | Light blue | negative, $p_{FDR} < 0.05$ |

## 3.2 Gray matter morphometry

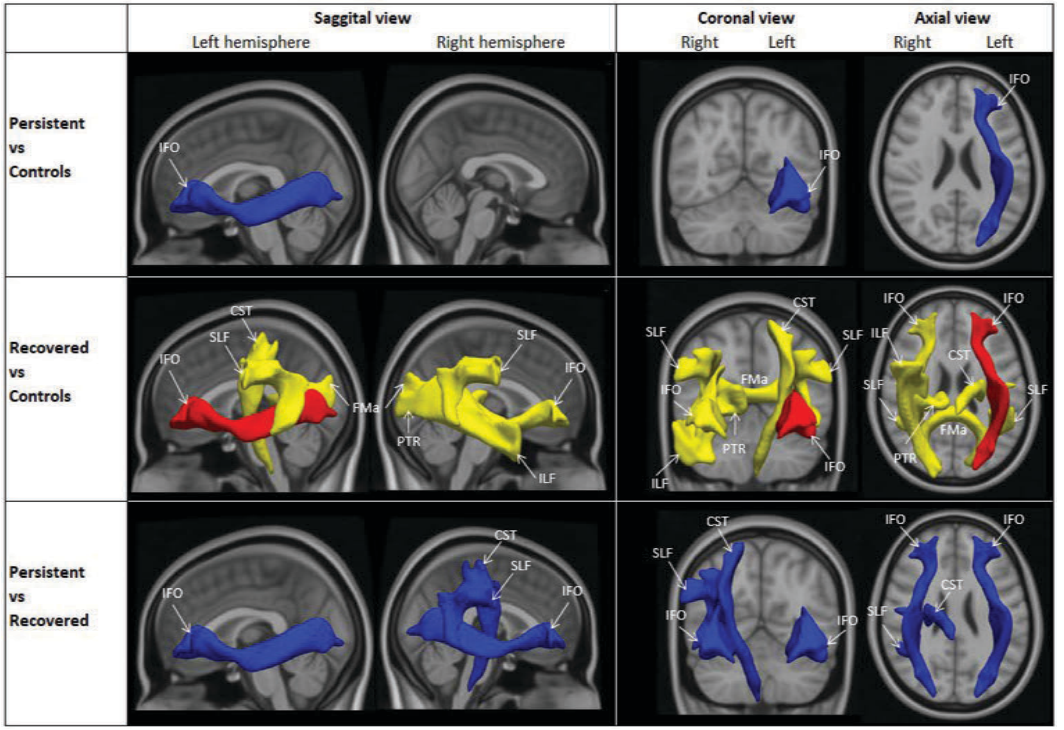
Stuttering was associated with structural morphology in pre-adolescents. Figure 2 demonstrates marginally smaller gray matter volume in the left superior frontal lobe in children who persisted in stuttering compared to those with no history of stuttering (β -1344, 95%CI -2407;-280, $p_{FDR}$ = 0.16) and also versus those who recovered (β -1825 95%CI -2999;-650, $p_{FDR}$ = 0.046). Note, this difference between children who persisted and those with no history of stuttering was non-significant after correction for multiple testing. Many other cortical brain regions of interest were also associated, but did not survive correction for multiple testing (Supplementary Table 2 t/m 5). No association was observed between stuttering and the global brain measure.

In the subcortical structures, the volumes of the basal ganglia and the thalamus were similar across all groups in both hemispheres (Supplementary Table 2 and 3, $p_{FDR}$ >0.05).

## 3.3 White matter volume and microstructure

Corpus callosum volumes were not associated with stuttering (Supplementary Table 2 and 3, $p_{FDR}$ >0.05). DTI results showed that stuttering was associated with white matter microstructure in pre-adolescents (Figure 3 and Table 2). An association was observed between stuttering and the global MD, and not between stuttering and global FA measure. Children who recovered from stuttering had higher MD in the forceps major (β2.119, 95%CI 0.505;3.732, $p_{FDR}$ = 0.02), bilateral SLF (left β 0.848, 95%CI 0.292;1.404, $p_{FDR}$ = 0.01; right β 1.018, 95%CI 0.375;1.660, $p_{FDR}$ = 2E-3), left corticospinal tract (β 3.175, 95%CI 1.854;4.495, $p_{FDR}$ = 3E-5), right ILF (β 1.307, 95%CI 0.538;2.076, $p_{FDR}$ = 0.01), right inferior frontal-occipital (β 0.783, 95%CI 0.164;1.401, $p_{FDR}$ = 0.04), and right posterior thalamic radiation (β1.369, 95%CI0.374;2.364, $p_{FDR}$ = 0.02) compared to controls (Supplementary Table 6). Other a priori white matter tracts showed significance before, but not after, adjusting for multiple comparisons ($p_{FDR}$ >0.05, in Figure 3 and Table 2). Children who persisted in stuttering had similar MD compared to controls, and to those who had recovered. FA in pre-specified tracts were similar across all groups in both hemispheres ($p_{FDR}$ >0.05).

Figure. 3 White matter tracts differences associated with stuttering, in mean diffusivity (MD)




| | | | |
|---|---|---|---|
| Red | positive, did not survive FDR | Blue | negative, did not survive FDR |
| Yellow | positive, $p_{FDR} < 0.05$ | Light blue | negative, $p_{FDR} < 0.05$ |

CST = corticospinal tract, FMa = forceps major, IFO = inferior fronto-occipital, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, PTR = posterior thalamic radiation

Table 2. Overview of DTI differences associated with stuttering, mean diffusivity (MD)

| Regions # | Left hemisphere | Right hemisphere |
|---|---|---|
| Superior longitudinal fasciculus | R > C* | R > C*, P < R+ |
| Inferior longitudinal fasciculus | - | R > C* |
| Forceps minor º | - | |
| Forceps major º | R > C* | |
| Uncinate fasciculus | - | - |
| Inferior fronto-occipital | P < C+, R > C+, P < R+ | R > C*, P < R+ |
| Corticospinal tract | R > C* | P < R+ |
| Posterior thalamic radiation | - | R > C* |

P = persistent, R = recovered, C = fluent controls
Linear regression model: brain tract of interest = stuttering + age + gender + handedness + bilingualism + ethnicity + maternal education
The number of participants varied in each analysis: P vs R (n=1850), P vs R (n= 81), R vs C (n=1897).
# regions are selected based on previous literature
º forceps minor and major: one brain region of interest, not left and right separately
* $p_{FDR} < 0.05$
+ significant p-value < 0.05 and did not survive FDR correction

## 3.4 Sensitivity analysis

In sensitivity analyses, results remained highly similar in the model when only adjusting for age and sex as covariates, suggesting overfitting is not an issue in the fully adjusted model. Second, the effect estimates (referring to standardized regression coefficients) of the association of stuttering with gray and white matter structures remained highly consistent when adjusting for IQ and behavioral problems, suggesting that these factors are not explaining the results. Third, brain (micro-)structural associations in analyses of boys only were similar to the original analyses with boys and girls, suggesting that results were not driven by the relatively small number of girls in the stuttering group.

# 4. Discussion

The goal of this study was to determine whether pre-adolescents who stutter show distinct neuroanatomical features when compared to peers who do not stutter and to those who recovered from stuttering. Results indicate that volume of the left superior frontal lobe is smaller with persistent stuttering, though the effect size (standardized regression coefficient) is very small. Recovery was associated with higher MD in white matter microstructure interconnecting frontotemporal regions and sensorimotor areas of the cortex compared to fluently speaking peers. These results improve our insight into neural underpinnings of speech that are relevant for stuttering persistence and recovery in pre-adolescence.

After correcting for multiple testing, there were no significant differences in cortical gray matter structures in pre-adolescents with a history of stuttering compared to those with no history of stuttering. However, our data suggest the potential for some very subtle gray matter structural differences, for example smaller left superior frontal volume in children who persist in stuttering. This is consistent with earlier published studies in children with stuttering who reported smaller gray matter volume and thinner left frontotemporal cortex (Garnett et al., 2018; Koenraads et al., 2019) and with studies in adults with persistent stuttering who reported smaller gray matter volumes in the left IFG (Kell et al., 2009; Lu et al., 2010). Our subtle finding is in contrast with studies which reported smaller gray matter volume and thinner cortex in the right frontal lobe in children who stutter (Beal et al., 2013; Koenraads et al., 2019), or larger gray matter volume in left frontotemporal regions in adults who persist in stuttering (Beal et al., 2007; Song et al., 2007). Interestingly, the frontal lobes are known for neurodevelopmental differences that might contribute to the manifestation of stuttering in pre-adolescents (e.g., in the domain of emotions, behavior, motor skills, or language) (Blomgren, 2013; Smith & Weber, 2017). A potential mechanism that may underlie the smaller frontal gray matter findings is related to the general spatio-temporal development of brain macrostructure, where frontal areas mature later in adolescence (Giedd et al., 1996). Children with persistent stuttering may have a delay in growth in these frontal regions (e.g., slow maturation) (Thapar & Rutter, 2015). Those who spontaneously recover could experience a form of 'catch up' growth compared to those who persist. However, as these speculations were based on cross-sectional findings, as well as our findings, directionality between stuttering and brain development cannot be distinguished without longitudinal data. Further, the medial aspect of the frontal region is innervated by the left frontal aslant tract (FAT), which interconnects the left IFG with the pre-supplementary and supplementary motor area, and the cingulate gyrus, and is shown to support language production (Dick, Garic, Graziano, & Tremblay, 2019). More specific to stuttering, recent studies have found altered microstructure of the FAT in children and adults who stutter (Chow & Chang, 2017; Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier, & Ben-Shachar, 2016b; Misaghi, Zhang, Gracco, De Nil, & Beal, 2018; Neef et al., 2018), suggesting abnormal connectivity amongst these interconnected regions could explain the macrostructural frontal lobe differences.

Other a priori defined subcortical gray matter structures were not associated with stuttering after adjusting for multiple testing. This is in contrast with studies which found

the subcortical left putamen and right caudate to be associated with stuttering in right-handed boys who stutter (Beal et al., 2013; Foundas et al., 2013). We did not find any related subcortical regions (e.g., those involved voluntary movement) to stuttering in our previous study of young children (Koenraads et al., 2019) or in the current pre-adolescent study. This suggests that subcortical structures are not related to a history of stuttering in a general population.

We observed differences in white matter structures in MD but not FA. Previous literature in children and adults with stuttering reported mostly on FA differences rather than MD (Chow & Chang, 2017; Cykowski et al., 2010; Sommer et al., 2002; Watkins et al., 2008). MD has only been reported in a few studies (Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier, & Ben-Shachar, 2016a; Kronfeld-Duenias et al., 2016b; Neef et al., 2018). Kronfeld-Duenias et al. (2016b) found significantly increased MD in the left corticospinal tract and no FA differences along any of the tracts in adults who persist in stuttering compared to fluent controls. We found similar results in pre-adolescents who recovered from stuttering. They additionally found higher MD in the bilateral FAT, which partly overlaps with our bilateral SLF findings. This study speculated that increased MD and reduced FA values could stem from noisy communication (i.e., reduced synchrony) in the tract between one region to another region which could have led to excessive pruning of axons, as well as a more coherent fiber organization within the tract, which would elevate FA back to its typical range. Neef et al. (2018) also found increased MD, however not tested statistically, in all clusters with a reduced FA (e.g., tract between left SLF and IFG) in adults who persist in stuttering compared to fluent controls. This study speculated that adults who stutter exhibit a weakened connectivity of tracts along the major fiber direction, and therefore, atypical structures are insufficiently myelinated or axonal packing is reduced. This could have been the case for both recovered and persistent pre-adolescents in our study, however, we did not find this in our persistent group. Contrasting to our study, another study by Kronfeld-Duenias et al. (2016a) reported no MD difference in the language stream, which includes dorsal (SLF and FAT) and ventral tracts (ILF and uncinated fasciculus), and lower FA in the right dorsal tract in adults with stuttering. While FA quantifies the fraction of diffusion that is anisotropic, MD quantifies the total diffusion within a voxel (i.e., average of the three eigenvalues). A difference in MD without a difference in FA suggests an overall difference in diffusion which is not specific to one direction of diffusivity, and thus does not translate into a difference in anisotropy (Kronfeld-Duenias et al., 2016b). Based on previous work, we expected to

find higher FA in brain regions involved in speech production in pre-adolescents who recovered, but rather found higher MD. We speculate that pre-adolescents who recovered from stuttering in our study may have developed weaker microstructure (i.e., reduced connection) interconnecting frontotemporal regions and sensorimotor areas of the cortex. As this study was cross-sectional, directionality cannot be implied and these differences could have been a cause or a consequence of stuttering. These regions are known for involvement in speech motor control and auditory feedback, and could have played a role in the dysfluency of speech in pre-adolescents who eventually recovered from stuttering. Information about assisted or spontaneous recovery would be interesting for better interpretation of findings in the recovered group. Unfortunately, our study does not have suitable information on stuttering severity or the type of stuttering therapy, intensity of therapy, or outcome. Future research investigating the effectiveness of stuttering intervention should consider to include neuroimaging. This would useful in severe confounding by indication since the most severe stuttering cases get treated which would introduce bias. Therefore, randomized clinical trials which evaluate a stuttering therapy should include neuroimaging to evaluate any treatment effect on the brain. Based on our findings, persistent stuttering may be associated with gray matter deficit only, and contrary to our hypothesis, it may be not associated with white matter microstructures. However, of important note, the group of children who persisted in stuttering was relatively small, and it is possible we were underpowered to detect a difference. Furthermore, we may have been unable to find an association if the stuttering problems in the persistent stuttering group were relatively mild, however stuttering severity was not assessed in the study and could not be examined further.



Further, in contrast to our hypothesis, it is possible that recovery from stuttering is associated with only alterations in white matter structure and not in gray matter structures. Another possibility is that recovery from stuttering in childhood could be accompanied by a dynamic neural processes. For example, structural abnormalities related to stuttering may disappear along with stuttering around the time a child experiences remission. Several examples exist of the plastic nature of the brain, including after learning, music training and motor skill practice (Bengtsson et al., 2005; Scholz, Klein, Behrens, & Johansen-Berg, 2009; Zatorre, Fields, & Johansen-Berg, 2012). Importantly, a child could also experience remission of stuttering which is accompanied by functional, but not structural, reorganization in the brain. This could then manifest as a stable morphological difference in the brain. Finally, given the fact that this study included pre-adolescents

only, the (micro-)structural neuroanatomy might be different in this general population relative to those found in earlier studies.

Several strengths and limitations of our study should be mentioned. Though this is the largest neuroimaging study of stuttering in pre-adolescents to date, the sample size of those who stuttered are still comparable to previous studies of stuttering (Chow & Chang, 2017; Garnett et al., 2018). Second, we used parental reports of stuttering at eight to twelve years of age, as it was not possible to assess stuttering through an in-person assessment. While a combination of parent's reports with expert judgements remain the traditional criteria for classifying stuttering, over- or underreporting of stuttering is unlikely, as the incidence of stuttering in our study population is in line with the expected 5–10% prevalence rate (Boyle et al., 2011; Craig et al., 2002; Dworzynski et al., 2007; Månsson, 2000; Reilly et al., 2013). Third, the current study restricted analyses to a set of a priori areas based on previous literature (Beal et al., 2013; Chang et al., 2008; Garnett et al., 2018; Koenraads et al., 2019) and a widely-used neuroanatomical atlas (Desikan et al., 2006). Furthermore, these areas were relatively coarse compared to more fine-grained segmentation in these studies. However, impressive advances in the field now allow for more fine-grained characterization of brain features in stuttering and can be explored, potentially focusing on areas already identified to be related to stuttering. For example, the multimodal parcellation atlas which incorporates data from several modalities with over 300 parcellations, will be a priority in the future for studying stuttering (Glasser et al., 2016). Finally, previous studies have mostly focused on right-handed boys and the few that examined recovery and persistency in childhood stuttering used participants from predominantly small, clinic-based settings or were recruited for specific reasons (Chow & Chang, 2017; Garnett et al., 2018). In our study, the stuttering groups and the fluently speaking reference sample were both recruited from the general population. Thus, the results of this work have the potential to be more generalizable to the general population of pre-adolescents who stutter, as the sample better represents the general population in the context of both the reference sample and the stuttering phenotypes (e.g., severe stuttering phenotypes who seek medical care as well as mild stuttering phenotypes which would do not seek medical care).

However, this study is cross-sectional in nature and more work is needed to examine how stuttering is related to changes in structural cortical and subcortical brain regions over time in a longitudinal study design. Tracking the association of brain growth differences in these structures in relation to childhood stuttering over a period of time will improve

insight in long term outcomes in stuttering. In addition, the etiological origins of the neurobiological features of stuttering are still unknown. It will be critical to study whether other potential etiological factors, such as genetic, psychological, and environmental in combination with neurobiological markers can predict the developmental course of stuttering alongside brain image data. Lastly, the current study only observed differences between the children who recovered from stuttering and the reference group, and no significant (though trend) differences were observed in the group who persisted in stuttering. The group of children who persisted was relatively small, was potentially underpowered, and the stuttering severity was not assessed. The group of children who recovered was also not further stratified into assisted or spontaneous recovery since proper medical information about treatment for stuttering (e.g., type, frequency, outcome) is missing. In the future, studies should aim to assess whether treatment has effect on the brains of children who develop stuttering.



In conclusion, the our findings provide evidence for structural differences in speech-relevant brain areas of pre-adolescents with persistent and recovered stuttering from a population-based study. Relatively small differences in size of effect in prefrontal gray matter are associated with persistent stuttering, and alterations in white matter tracts are apparent in those who recovered. Although comparison of the current findings with previous reports is challenging due to methodological differences, these results further strengthen the potential relevance of brain structure in developmental stuttering.

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# Supplementary Tables

Supplementary Table 1. Demographics for all participants with structural data (n=1969)

| | **Fluent controls** n = 1884 | **Children who recovered from stuttering** n = 66 | **Children who persisted in stuttering** n = 19 | **p-value** |
|---|---|---|---|---|
| **Child** | | | | |
| Age at questionnaire (years) | 9.8 (0.3) | 9.8 (0.2) | 9.8 (0.4) | > 0.05 |
| Age at MRI (years) (mean, SD) | 10.1 (0.6) | 10.03 (0.5) | 9.9 (0.6) | > 0.05 |
| Sex (boy) | 912 (48.4) | 46 (69.7) | 15 (78.9) | 0.01[a], 1E-3[b] |
| Ethnicity (western) | 1454 (77.8) [n=1870] | 50 (75.8) | 13 (68.4) | > 0.05 |
| Handedness (right) | 1677 (89.3) [n=1877] | 60 (92.3) [n=65] | 15 (78.9) | > 0.05 |
| Lingualism (monolingual) | 1493 (80.5) [n=1855] | 52 (78.8) | 14 (73.7) | > 0.05 |
| Ever had treatment for stuttering (% yes) | - | 25 (37.9) | 14 (73.7) | 0.01[c] |
| Ever had stutter, speech and/or language therapy (%yes) | 322 (17.1) | 30 (45.5) | 15 (78.9) | 8E-4[a], 2E-7[b], 0.02[c] |
| IQ at 5 years (score) | 105.0 (14.4) [n=1677] | 102.9(15.3) [n=58] | 104.8 (14.8) [n=17] | > 0.05 |
| Total behavior problem score (mean, SD) | 15.9 (14.1) [n=1805] | 15.9 (13.9) [n=66] | 25.9 (17.9) [n=18] | 3E-3[a], 0.01[c] |
| Total behaviour problem score (median, IQR) | 12.0 (6.0 – 21.7) | 13.5 (7.0 – 20.0) | 24.0 (10.1 – 37.2) | 4E-3[a], 0.01[c] |
| **Maternal** | | | | |
| Ethnicity (Western) | 1394 (74.6) [n=1869] | 48 (72.7) | 12 (63.2) | > 0.05 |
| Education level (high) | 1198 (67.6) [n=1772] | 45 (70.3) [n=64] | 8 (50.0) | > 0.05 |

All categorical variables are presented with numbers (n) and percentages (%); all continuous variables are presented as mean with standard deviation (SD).
[a] persistent stuttering > fluent controls (p-value < 0.05)
[b] recovered from stuttering > fluent controls (p-value < 0.05)
[c] persistent stuttering > recovered stuttering (p-value < 0.05)

Supplementary Table 2. Overview of gray and white matter morphometry differences associated with stuttering

| Regions# | Left hemisphere | | | Right hemisphere | | |
|---|---|---|---|---|---|---|
| | Volume | Thickness | Surface area | Volume | Thickness | Surface area |
| **Gray matter** | | | | | | |
| ***Cortical structures*** | | | | | | |
| Frontal | | | | | | |
| Superior frontal | P < C+, P < R* | - | - | | | |
| Caudal anterior cingulate | - | - | | - | - | - |
| Caudal middle frontal | P > C+ | - | - | - | - | - |
| Inferior frontal gyrus | | | | | | |
| - Pars opercularis | - | - | - | - | - | - |
| - Pars triangularis | - | R > C+ | - | - | - | - |
| Lateral orbitofrontal | - | - | - | | | |
| Insula | - | - | - | | | |
| Postcentral | - | - | - | | | |
| Precentral | - | - | - | | | |
| Temporal | | | | | | |
| Transverse temporal | R > C+ | R > C+ | - | - | - | P < C+, P < R+ |
| Superior temporal | - | - | - | - | - | P < C+ |
| Middle temporal | - | - | - | | | |
| Inferior temporal | - | P > C+ | | | | |
| Parietal | | | | | | |
| Supramarginal | - | P < C+, P < R+ | - | - | - | - |
| Superior parietal | - | - | - | - | - | - |
| Inferior parietal | - | - | R > C+ | | | |
| ***Subcortical structures*** | | | | | | |
| Caudate | - | | | - | | |
| Putamen | - | | | - | | |
| Pallidum | - | | | - | | |
| Thalamus | - | | | - | | |
| **White matter** | | | | | | |
| Corpus callosum | | | | | | |
| Anterior | - | | | | | |
| Mid anterior | R > C+ | | | | | |
| Central | - | | | | | |
| Mid posterior | - | | | | | |
| Posterior | - | | | | | |

P = persistent, R = recovered, C = fluent controls
Linear regression with model: brain region of interest = stuttering + age + gender + handedness + bilingualism + ethnicity + maternal education + intracranial volume (in volumetric outcomes only)
The number of participants varied in each analysis: P vs R (n=1902), P vs R (n= 84), R vs C (n=1949).
# regions are selected based on previous literature
* $p_{FDR}$ <0.05
+ significant p-value <0.05 and did not survive FDR correction

Supplementary Table 3. Linear regression analysis in gray and white matter volume, left hemisphere

| | Persistent vs Controls | | | | Recovered vs Controls | | | | Persistent vs Recovered | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | P | $P_{FDR}$ | β | 95% CI | P | $P_{FDR}$ | β | 95% CI | P | $P_{FDR}$ |
| **Gray matter** | | | | | | | | | | | | |
| ***Cortical structures*** | | | | | | | | | | | | |
| Frontal | | | | | | | | | | | | |
| Superior frontal | -1344 | -2407;-280 | 0.01 | 0.16 | 116 | -455;689 | 0.69 | 0.84 | -1825 | -2999;-650 | 3E-3 | 0.05* |
| Caudal anterior cingulate | 89 | -24;203 | 0.43 | 0.92 | -5 | -67;56 | 0.93 | 0.93 | 65 | -193;325 | 0.62 | 0.83 |
| Caudal middle frontal | 563 | 22;1104 | 0.04 | 0.32 | -52 | -264;159 | 0.73 | 0.84 | 522 | -138;1183 | 0.12 | 0.48 |
| Inferior frontal gyrus | | | | | | | | | | | | |
| - Pars opercularis | -303 | -700;94 | 0.14 | 0.48 | -48 | -251;154 | 0.66 | 0.84 | -396 | -920;128 | 0.14 | 0.48 |
| - Pars triangularis | -6 | -347;333 | 0.97 | 0.97 | 26 | -119;171 | 0.78 | 0.84 | -70 | -547;407 | 0.77 | 0.87 |
| Lateral orbitofrontal | -27 | -395;339 | 0.88 | 0.97 | 38 | -167;245 | 0.71 | 0.84 | -27 | -474;419 | 0.91 | 0.91 |
| Insula | 242 | -87;572 | 0.15 | 0.48 | 71 | -102;245 | 0.43 | 0.84 | 165 | -221;552 | 0.40 | 0.83 |
| Postcentral | 81 | -488;651 | 0.78 | 0.97 | -43 | -352;265 | 0.78 | 0.84 | 173 | -507;854 | 0.62 | 0.83 |
| Precentral | 218 | -358;796 | 0.46 | 0.92 | -43 | -338;251 | 0.79 | 0.84 | 133 | -557;824 | 0.71 | 0.87 |
| Temporal | | | | | | | | | | | | |
| Transverse temporal | -8 | -104;86 | 0.85 | 0.97 | 50 | -1;102 | 0.05 | 0.80 | -59 | -175;56 | 0.31 | 0.83 |
| Superior temporal | 72 | -600;745 | 0.83 | 0.97 | 100 | -2.69;470 | 0.59 | 0.84 | 101 | -788;992 | 0.82 | 0.87 |
| Middle temporal | -29 | -730;671 | 0.93 | 0.97 | 200 | -176;577 | 0.29 | 0.84 | -287 | -1088;513 | 0.48 | 0.83 |
| Inferior temporal | -175 | -927;576 | 0.65 | 0.97 | -74 | -498;349 | 0.72 | 0.84 | -303 | -1192;586 | 0.50 | 0.83 |
| ***Subcortical structures*** | | | | | | | | | | | | |
| Parietal | | | | | | | | | | | | |
| Supramarginal | 341 | -534;1217 | 0.45 | 0.92 | -298 | -771;173 | 0.22 | 0.84 | 814 | -241;1869 | 0.13 | 0.48 |
| Superior parietal | 591 | -198;1382 | 0.14 | 0.48 | -301 | -710;128 | 0.17 | 0.84 | 828 | -298;1955 | 0.15 | 0.48 |
| Inferior parietal | 61 | -818;940 | 0.89 | 0.97 | 247 | -261;725 | 0.31 | 0.84 | -284 | -1370;800 | 0.61 | 0.83 |
| Caudate | 38 | -147;224 | 0.69 | 0.85 | -14 | -115;85 | 0.77 | 0.88 | 35 | -195;266 | 0.13 | 0.55 |

| | Persistent vs Controls | | | | Recovered vs Controls | | | | Persistent vs Recovered | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | P | $P_{FDR}$ | β | 95% CI | P | $P_{FDR}$ | β | 95% CI | P | $P_{FDR}$ |
| Putamen | 94 | -22;212 | 0.42 | 0.65 | -94 | -212;24 | 0.14 | 0.55 | 229 | -58;518 | 0.12 | 0.55 |
| Pallidum | 51 | -34;137 | 0.24 | 0.55 | 1 | -45;48 | 0.96 | 0.96 | 44 | -71.5;160 | 0.45 | 0.65 |
| Thalamus | 136 | -81;355 | 0.22 | 0.55 | -101 | -221;18 | 0.09 | 0.55 | 186 | -108;481 | 0.22 | 0.55 |
| **White matter** | | | | | | | | | | | | |
| Corpus callosum | | | | | | | | | | | | |
| Anterior | -15 | -71;41 | 0.60 | 0.98 | 27 | -2;58 | 0.08 | 0.53 | -44 | -121;-9 | 0.19 | 0.53 |
| Mid anterior | 24 | -40;90 | 0.45 | 0.82 | -37 | -72;-2 | 0.04+ | 0.53 | 51 | -29;131 | 0.21 | 0.53 |
| Central | 29 | -30;88 | 0.33 | 0.73 | -22 | -54;9 | 0.18 | 0.53 | 52 | -16;121 | 0.14 | 0.53 |
| Mid posterior | -6 | -44;31 | 0.72 | 0.98 | -1 | -22;21 | 0.98 | 0.98 | 3 | -41;48 | 0.87 | 0.98 |
| Posterior | 12 | -42;67 | 0.64 | 0.98 | 1 | -13;17 | 0.92 | 0.98 | 1 | -74;78 | 0.96 | 0.53 |

Linear regression with model: brain region of interest = stuttering + age + sex + handedness + bilingualism + ethnicity + maternal education + total intracranial volume (ICV, for volumetric outcomes only)
Beta coefficients are presented in volume in $mm^3$
The number of participants varied in each analysis: P vs R (n=1902), P vs R (n= 84), R vs C (n=1949).
* $p_{FDR} < 0.05$

Supplementary Table 4. Linear regression analysis in gray matter thickness, left hemisphere

| | Persistent vs Controls | | | | Recovered vs Controls | | | | Persistent vs Recovered | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | P | $P_{FDR}$ | β | 95% CI | P | $P_{FDR}$ | β | 95% CI | P | $P_{FDR}$ |
| **Gray matter** | | | | | | | | | | | | |
| ***Cortical structures*** | | | | | | | | | | | | |
| Frontal | | | | | | | | | | | | |
| Superior frontal | -0.02 | -0.08;0.04 | 0.50 | 0.80 | 0.01 | -0.01;0.04 | 0.57 | 0.87 | -0.04 | -0.11;0.03 | 0.27 | 0.60 |
| Caudal anterior cingulate | -0.03 | -0.13;0.08 | 0.66 | 0.81 | -0.02 | -0.07;-0.04 | 0.59 | 0.87 | -0.01 | -0.13;0.12 | 0.91 | 0.97 |
| Caudal middle frontal | 0.04 | -0.02;0.10 | 0.32 | 0.75 | -0.01 | -0.04;0.03 | 0.64 | 0.87 | 0.03 | -0.05;0.11 | 0.42 | 0.60 |
| Inferior frontal gyrus | | | | | | | | | | | | |
| - Pars opercularis | -0.04 | -0.10;0.02 | 0.19 | 0.70 | 0.01 | -0.01;0.02 | 0.65 | 0.87 | -0.06 | -0.13;0.00 | 0.05 | 0.40 |
| - Pars triangularis | 0.00 | -0.06;0.06 | 0.92 | 0.92 | 0.04 | 0.00;0.07 | 0.04 | 0.32 | -0.04 | -0.11;0.03 | 0.31 | 0.60 |
| Lateral orbitofrontal | 0.02 | -0.05;0.08 | 0.62 | 0.81 | 0.01 | -0.02;0.05 | 0.43 | 0.87 | -0.01 | -0.09;0.07 | 0.82 | 0.94 |
| Insula | -0.03 | -0.10;0.05 | 0.49 | 0.80 | 0.00 | -0.03;0.04 | 0.82 | 0.87 | -0.05 | -0.14;0.05 | 0.35 | 0.60 |
| Postcentral | -0.01 | -0.06;0.05 | 0.85 | 0.92 | 0.02 | -0.01;0.05 | 0.21 | 0.87 | -0.03 | -0.09;0.04 | 0.43 | 0.60 |
| Precentral | 0.01 | -0.04;0.07 | 0.62 | 0.81 | 0.01 | -0.02;0.04 | 0.49 | 0.87 | 0.00 | -0.07;0.07 | 0.99 | 0.99 |
| Temporal | | | | | | | | | | | | |
| Transverse temporal | 0.01 | -0.08;0.09 | 0.92 | 0.92 | 0.05 | 0.00;0.11 | 0.04 | 0.32 | -0.06 | -0.19;0.07 | 0.38 | 0.60 |
| Superior temporal | 0.03 | -0.04;0.09 | 0.43 | 0.80 | 0.01 | -0.02;0.05 | 0.55 | 0.87 | 0.02 | -0.06;0.10 | 0.65 | 0.80 |
| Middle temporal | 0.04 | -0.03;0.11 | 0.33 | 0.75 | 0.00 | -0.04;0.04 | 0.90 | 0.90 | 0.03 | -0.05;0.11 | 0.45 | 0.60 |
| Inferior temporal | 0.07 | 0.00;0.13 | 0.05 | 0.40 | 0.01 | -0.03;0.04 | 0.77 | 0.87 | 0.06 | -0.02;0.14 | 0.15 | 0.60 |
| Parietal | | | | | | | | | | | | |
| Supramarginal | -0.06 | -0.11;-0.00 | 0.05 | 0.40 | -0.01 | -0.04;0.03 | 0.74 | 0.87 | -0.06 | -0.11;0.00 | 0.05 | 0.40 |
| Superior parietal | 0.03 | -0.02;0.08 | 0.22 | 0.70 | -0.01 | 0.03;0.02 | 0.75 | 0.87 | 0.04 | -0.03;0.10 | 0.25 | 0.60 |
| Inferior parietal | 0.04 | -0.02;0.11 | 0.20 | 0.70 | -0.01 | -0.05;0.02 | 0.54 | 0.87 | 0.04 | -0.04;0.11 | 0.33 | 0.60 |

Supplementary Table 5. Linear regression analysis in gray matter surface area, left hemisphere

| | Persistent vs Controls | | | | Recovered vs Controls | | | | Persistent vs Recovered | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | P | $P_{FDR}$ | β | 95% CI | P | $P_{FDR}$ | β | 95% CI | P | $P_{FDR}$ |
| **Gray matter** | | | | | | | | | | | | |
| ***Cortical structures*** | | | | | | | | | | | | |
| Frontal | | | | | | | | | | | | |
| Superior frontal | -343.5 | -758;71 | 0.11 | 0.55 | 153.7 | -72;379 | 0.18 | 0.48 | -438.9 | -955;77 | 0.10 | 0.52 |
| Caudal anterior cingulate | 36.5 | -23;96 | 0.23 | 0.55 | 20.8 | -11;52 | 0.21 | 0.48 | 13.1 | -66;92 | 0.75 | 0.88 |
| Caudal middle frontal | 82.3 | -96;260 | 0.37 | 0.68 | 39.9 | -56;136 | 0.42 | 0.74 | 38.3 | -221;297 | 0.77 | 0.88 |
| Inferior frontal gyrus | | | | | | | | | | | | |
| - Pars opercularis | -88.5 | -211;34 | 0.16 | 0.55 | 9.6 | -57;76 | 0.87 | 0.98 | -109.9 | -275;55 | 0.19 | 0.61 |
| - Pars triangularis | -33.2 | -130;64 | 0.51 | 0.68 | 2.8 | 49;55 | 0.92 | 0.98 | -26.7 | -148;95 | 0.67 | 0.88 |
| Lateral orbitofrontal | -47.5 | -190;95 | 0.52 | 0.68 | 29.3 | 49;107 | 0.46 | 0.74 | -37.7 | -217;142 | 0.68 | 0.88 |
| Insula | 80.0 | -45;205 | 0.21 | 0.55 | 47.2 | -20;115 | 0.17 | 0.48 | 64.8 | -93;223 | 0.42 | 0.84 |
| Postcentral | -27.3 | -246;192 | 0.81 | 0.91 | -7.2 | -126;112 | 0.91 | 0.98 | 20.8 | -268;309 | 0.89 | 0.95 |
| Precentral | -8.6 | -233;216 | 0.94 | 0.94 | 48 | 74;171 | 0.44 | 0.74 | -66.4 | -33;250 | 0.68 | 0.88 |
| Temporal | | | | | | | | | | | | |
| Transverse temporal | -10.2 | -41;21 | 0.53 | 0.68 | 12.3 | -4;29 | 0.16 | 0.48 | -17.6 | -52;17 | 0.33 | 0.84 |
| Superior temporal | -62.9 | -266;140 | 0.55 | 0.68 | 86.3 | -25;197 | 0.13 | 0.48 | -102.2 | -381;176 | 0.47 | 0.84 |
| Middle temporal | -118.1 | -309;73 | 0.23 | 0.55 | 95.7 | -8;199 | 0.07 | 0.48 | -208.2 | -452;36 | 0.09 | 0.52 |
| Inferior temporal | -239.1 | -462;-16 | 0.04 | 0.55 | 25.4 | -95;146 | 0.69 | 0.98 | -256.8 | -518;4.6 | 0.05 | 0.52 |
| Parietal | | | | | | | | | | | | |
| Supramarginal | 116.6 | -201;434 | 0.46 | 0.68 | 0.05 | -172;172 | 0.99 | 0.99 | 192.2 | -235;619 | 0.39 | 0.84 |
| Superior parietal | -33.2 | -376;309 | 0.85 | 0.91 | 14.4 | -173;201 | 0.88 | 0.98 | -8.4 | -500;484 | 0.97 | 0.97 |
| Inferior parietal | -200.2 | -531;131 | 0.24 | 0.55 | 193.4 | -13;373 | 0.04 | 0.48 | -342.3 | -746;101 | 0.13 | 0.52 |

Linear regression with model: brain region of interest = stuttering + age + sex + handedness + bilingualism + ethnicity + maternal education
Beta coefficients are presented in thickness in mm, and in surface area in $mm^2$
The number of participants varied in each analysis: P vs R (n=1902), P vs R (n= 84), R vs C (n=1949).

Supplementary Table 6. White matter tracts differences associated with stuttering, in mean diffusivity (MD)

| Regions | Persistent vs Fluent controls | | | | Recovered vs Fluent controls | | | | Persistent vs Recovered | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | P | $P_{FDR}$ | β | 95% CI | P | $P_{FDR}$ | β | 95% CI | P | $P_{FDR}$ |
| **Left hemisphere** | | | | | | | | | | | | |
| Superior longitudinal fasciculus | -0.371 | -1.440;0.699 | 0.50 | 0.71 | 0.848 | 0.292;1.404 | 3E-3 | 0.01* | -1.437 | -2.904; 0.030 | 0.06 | 0.15 |
| Inferior longitudinal fasciculus | -0.526 | -1.694;0.643 | 0.41 | 0.71 | 0.613 | -0.039;1.264 | 0.07 | 0.10 | -1.270 | -2.885; 0.345 | 0.12 | 0.27 |
| **Forceps minor** ° | -0.407 | -1.907;1.092 | 0.60 | 0.71 | 0.248 | -0.536;1.032 | 0.54 | 0.54 | -1.027 | -2.698; 0.644 | 0.23 | 0.29 |
| Forceps major ° | 1.120 | -1.963;4.202 | 0.48 | 0.71 | 2.119 | 0.505;3.732 | 0.01 | 0.02* | -1.275 | -4.844; 2.295 | 0.48 | 0.48 |
| Uncinate fasciculus | -0.437 | -1.414;0.539 | 0.38 | 0.71 | 0.288 | -0.223;0.799 | 0.27 | 0.32 | -0.862 | -2.126; 0.403 | 0.18 | 0.28 |
| Inferior fronto-occipital | -1.093 | -2.204;0.018 | 0.05 | 0.71 | 0.645 | 0.062;1.228 | 0.03 | 0.05 | -1.845 | -3.256;-0.435 | 0.01 | 0.13 |
| Corticospinal tract | -0.618 | -2.081;0.845 | 0.41 | 0.71 | 3.175 | 1.854;4.495 | 2E-6 | 3E-5* | -6.478 | -18.496;5.540 | 0.29 | 0.34 |
| Posterior thalamic radiation | -0.507 | -2.260;1.245 | 0.57 | 0.71 | 0.711 | -0.217;1.640 | 0.13 | 0.17 | -1.407 | -4.221; 1.408 | 0.33 | 0.35 |
| **Right hemisphere** | | | | | | | | | | | | |
| Superior longitudinal fasciculus | -0.530 | -1.762;0.701 | 0.40 | 0.71 | 1.018 | 0.375;1.660 | 2E-3 | 0.01* | -1.946 | -3.572;-0.320 | 0.02 | 0.13 |
| Inferior longitudinal fasciculus | -0.197 | -1.680;1.285 | 0.80 | 0.79 | 1.307 | 0.538;2.076 | 1E-3 | 0.01* | -1.636 | -3.925; 0.652 | 0.16 | 0.28 |
| **Forceps minor** ° | - | - | - | - | - | - | - | - | - | - | - | - |
| Forceps major ° | - | - | - | - | - | - | - | - | - | - | - | - |
| Uncinate fasciculus | -0.362 | -1.396;0.673 | 0.49 | 0.71 | 0.419 | -0.121;0.960 | 0.13 | 0.17 | -0.794 | -2.058; 0.470 | 0.22 | 0.29 |
| Inferior fronto-occipital | -0.714 | -1.949;0.521 | 0.26 | 0.71 | 0.783 | 0.164;1.401 | 0.02 | 0.04* | -1.612 | -3.075;-0.149 | 0.03 | 0.14 |
| Corticospinal tract | -0.647 | -3.222;1.928 | 0.62 | 0.71 | 0.537 | -0.791;1.865 | 0.43 | 0.46 | -1.291 | -2.524;-0.059 | 0.04 | 0.14 |
| Posterior thalamic radiation | -0.425 | -2.322;1.472 | 0.66 | 0.71 | 1.369 | 0.374;2.364 | 0.01 | 0.02* | -2.137 | -4.934; 0.661 | 0.13 | 0.27 |

Linear regression with model: brain tract of interest = stuttering + age + sex + handedness + bilingualism + ethnicity + maternal education
Beta coefficients (β) are presented in mean diffusivity (MD) and have been scaled by a factor of 1000 and are reported in $10^3$ $mm^2/s$
The number of participants varied in each analysis: P vs R (n=1850), P vs R (n= 81), R vs C (n=1897).
° forceps minor and major: one brain region of interest, not left and right separately
* $p_{FDR} < 0.05$


White matter
Persistent
Fluency
Speech
Research
Recov
Brain
Gray matter
Neuroimaging
Self-report
Explore
Satisfaction
Cortical
Girls
Children
Stutter
Population
Temperament
Dysfluency
Fluency
Neuroplasticity
Outcome
Boys
Long-term
Brain
Behavior
Speech
Satisfaction
Development
Subcortical
Girls
Rotterdam
Self-report
Persistent
Stutter
Cortical
Boys
Population
Speech-motor


# 8

# Brain developmental trajectories associated with childhood stuttering persistence and recovery

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*Equal contribution

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## Abstract

Stuttering is a neurodevelopmental disorder affecting 5-8% of preschool-age children, continuing into adulthood in 1% of the population. The neural mechanisms underlying persistence and recovery from stuttering remain unclear and little information exists on neurodevelopmental anomalies in children who stutter (CWS) during preschool-age, when stuttering symptoms typically first emerge. Here we present findings from the largest longitudinal study of childhood stuttering to date, comparing children with persistent stuttering (pCWS) and those who later recovered from stuttering (rCWS) with age-matched fluent peers, to examine the developmental trajectories of both gray matter volume (GMV) and white matter volume (WMV) using voxel-based morphometry. A total of 470 MRI scans were analyzed from 95 CWS (72 pCWS and 23 rCWS) and 95 fluent peers between 3-12 years of age. We examined overall group and group by age interactions in GMV and WMV in preschool-age (3-5 years old) and school-age (6-12 years old) CWS and controls, controlling for sex, IQ, intracranial volume, and socioeconomic status. The results provide broad support for a possible basal ganglia-thalamocortical (BGTC) network deficit starting in the earliest phases of the disorder and point to normalization or compensation of earlier occurring structural changes associated with stuttering recovery.

# 1. Introduction

Developmental stuttering is a complex neurodevelopmental disorder (Smith & Weber, 2017) that disrupts the fluent flow of speech production. It is characterized by frequently occurring involuntary repetitions and prolongations in speech sounds, in addition to prolonged articulatory posture, and/or avoidance and struggle behaviors (Van Riper, 1971). Stuttering affects 5-8% of preschool-age children (Yairi & Ambrose, 2013) and remains as a chronic speech disorder in 1% of the general population. Typical onset of stuttering is reported to occur at 30-48 months (Bloodstein & Bernstein Ratner, 2008; Reilly et al., 2013; Yairi & Ambrose, 2005) with approximately 80% of children naturally recovering 24-36 months after the onset of stuttering (Yairi & Ambrose, 1999; Yairi & Ambrose, 2005; Yairi & Ambrose, 2013). Around this same developmental period, the neural systems supporting executive function, language, and speech-motor control undergo rapid and vigorous development (Almli, Rivkin, McKinstry, & Brain Development Cooperative, 2007; Chang, Garnett, Etchell, & Chow, 2019; Friederici & Gierhan, 2013; Gilmore, Knickmeyer, & Gao, 2018; Smith & Weber, 2017).



In the past 20 years, an increasing number of neuroimaging studies have been conducted to understand the possible neural bases of stuttering. Convergent findings from systematic reviews and meta-analyses have highlighted several neuroanatomical differences in children and adults who stutter (AWS) compared to fluent speakers (Belyk, Kraft, & Brown, 2015; Budde, Barron, & Fox, 2014; Chang et al., 2019; Ingham, Finn, & Bothe, 2005; Neef, Anwander, & Friederici, 2015; Smith & Weber, 2017). Structural and functional anomalies in the left speech motor neural system, including the inferior frontal gyrus (IFG), posterior superior temporal gyrus (STG), basal ganglia-thalamo-cortical (BGTC) loop and the cerebellum have been associated with stuttering (see Chang et al. (2019) for review). In addition to gray matter anomalies, children who stutter (CWS) were found to have less white matter volume (WMV) bilaterally in the forceps minor of the corpus callosum (Beal, Gracco, Brettschneider, Kroll, & De Nil, 2013) while another study found no significant differences (Choo, Chang, Zengin-Bolatkale, Ambrose, & Loucks, 2012). Several diffusion tensor imaging (DTI) studies have repeatedly reported that the anisotropic diffusivity in the corpus callosum and the left superior longitudinal / arcuate fasciculi (SLF / AF) is lower in children and AWS than controls who do not stutter (Chow & Chang, 2017; Neef et al., 2015) suggesting that sensorimotor integration and inter-hemispheric connections may be affected in stuttering. Putting these results

in the context of a recent theoretical perspective (Guenther, 2016), three distinct but not mutually exclusive loci of impaired neural processing along the BGTC network was proposed to occur to lead to stuttering, reviewed in Chang and Guenther (Chang & Guenther, 2019): first is the impairment in the BG proper (PDS-1); second, impairment of axonal projections between cortex, BG, and thalamus (PDS-2); and impairment in cortical processing among cortical areas supporting cognitive processing, sensory areas, and motor regions including the primary motor, premotor, and supplementary motor areas (PDS-3).

Many of these past studies, however, only examined AWS with small sample sizes (e.g., $N < 12$ per group), limiting the ability to characterize neurodevelopmental differences associated with stuttering persistence and recovery in children who stutter. Moreover, to date few studies have investigated neuroanatomical differences in children at or near the onset of stuttering (before 6 years of age). Examining children close to symptom onset is necessary to better understand the neural mechanisms that lead to the emergence of developmental stuttering (Packman et al., 2022). That is, neuroanatomical differences that are present near stuttering onset could help clarify what differences may be attributed to trait-linked differences associated with the disorder, compared to later occurring, adaptive changes that are more likely to be present in those who have been stuttering for many years. Furthermore, because stuttering becomes a chronic condition or resolves itself within a few years of onset in most CWS, it is important to examine the developmental trajectories of the brain during this critical period.

Children who go on to develop chronic, persistent stuttering may be those with neuroanatomical differences relative to their non-stuttering peers at stuttering onset that are not resolved as they become older and continue to stutter. Maladaptive changes may occur in additional brain areas as stuttering becomes chronic. In children who recover from stuttering (rCWS), on the other hand, normalization and/or successful compensations for prior deficits associated with stuttering onset may occur. In Chow and Chang (Chow & Chang, 2017) for example, anisotropic diffusion measures that reflect white matter coherence pointed to decreased structural connectivity in several major tracts including the left AF and the corpus callosum in CWS regardless of eventual persistence or recovery. What differentiated the recovered and persistent groups, however, was that the recovered group exhibited age-related increases in these tracts (e.g., the corpus collosum), while the persistent group showed plateaued, or even decreasing white matter integrity with age. The Chow and Chang (Chow & Chang, 2017) study is the only longitudinal study to date

that examined neuroanatomical differences occurring across development in persistent and recovered groups of CWS. This study was limited to examining white matter; thus, it is currently unknown what gray matter anomalies may be present near symptom onset, and further, whether age related gray matter changes differentiate children who persist versus recover from stuttering. Results from previous studies have pointed to deficiencies involving the BGTC loop, including function of the basal ganglia proper, cortical-subcortical connectivity, and cortico-cortical connectivity including auditory-motor regions (Chang & Guenther, 2019). It is unclear at this time whether these deficits occur near onset of the disorder, and whether recovery of stuttering is associated with normalization of the deficits in the BGTC loop, or perhaps compensations by other structures such as the cerebellum, an area that has been theorized to play a compensatory role in response to possible core deficits in the basal ganglia (Alm, 2004; Kotz, Schwartze, & Schmidt-Kassow, 2009; Petacchi, Laird, Fox, & Bower, 2005).

Therefore, in this study we sought to examine developmental changes in gray and white matter volume in the largest pediatric sample of developmental stuttering collected to date. These children were evaluated and scanned yearly for up to 4 years, a study design that allowed us to determine the eventual persistence or recovery of stuttering in each child and track developmental trajectories of their brain measures. For children in the persistent stuttering group (pCWS), we analyzed their structural magnetic resonance imaging (MRI) scans separately in two age groups based on the participant's age at each scan, one comprising those from 3-5 years of age (N=42, 64 scans) and another, comprising those who fell within 6-12 years of age (N=54, 112 scans). Our rationale for the separation of 3–5-year-olds (preschool-age) and 6-12-year-olds (school-age) was that they capture two critical stages of developmental stuttering. First, symptoms of stuttering typically start to appear during the preschool-age, and spontaneous recovery of stuttering in this age range is still relatively high. On the other hand, children who continue to stutter during school-age are less likely to recover and this is the period when the transition to a chronic form of stuttering occurs in most children. The CWS were compared with age- and sex-matched controls who do not stutter, who reported no personal or family history of stuttering (N=60, 91 scans for 3-5 years and N=63, 139 scans for 6-12 years). We expected that examining the subset of children closest to the onset of stuttering (3-5 years) would provide the clearest clues to neural trait deficits associated with the onset of stuttering. Examining the subset of children in the older age range (6-12 years) would, on the other hand, provide information on later occurring changes that are linked to

continued chronic stuttering. For the recovered group (rCWS), because the sample size was relatively small (N=23, 64 scans), we analyzed all children in one group to examine morphology changes linked to neuroplasticity associated with natural recovery from stuttering during childhood.

Given previous studies of gray matter (Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008; Garnett et al., 2018; Koenraads et al., 2019) and white matter structure (Beal et al., 2013; Chang, Zhu, Choo, & Angstadt, 2015; Chow & Chang, 2017), and theoretical perspectives on neural deficits associated with persistent developmental stuttering (Chang & Guenther, 2019), we hypothesized that: a) early in development (preschool-age), children who eventually become persistent stutterers (pCWS) would exhibit gray and white matter morphometric differences from controls in structures comprising the BGTC network; b) later in development, pCWS exhibit both original and compensatory/adaptive additional changes compared to controls and rCWS; c) stuttering severity would be correlated with morphometric deficits associated with early stuttering and compensatory changes occurring in later stuttering; d) those rCWS would show normalization of morphometric differences found in pCWS, as well as possible compensatory signs in the regions supporting speech planning and timing (i.e., BGTC motor loop and the cerebellum).

# 2. Materials and methods

## 2.1 Study design and population

A total of 485 children between the ages of 3 and 10 were screened through an initial phone screening to assess whether they met basic inclusion criteria to participate in an ongoing longitudinal neuroimaging study to be followed for a period up to 4 years (see flowchart Supplementary Fig. 1 for details). Of those screened, a total of 278 children (150 CWS and 128 controls) were determined eligible and successfully completed the initial speech and language testing visit. Of those 278 children, 199 children (102 CWS and 97 controls) participated in at least one MRI scan session (Suppl Fig. 1). Each participant was scanned up to four times, with an inter-scan interval of approximately 1 year. The age range for all visits was 3 to 12 years (12;11). The Institutional Review Board at Michigan State University approved of all procedures in the study. Subjects' consent was obtained according to the Declaration of Helsinki. All parents signed a written informed consent, and all children either provided verbal assent (non-readers; typically, 3–5-year-olds) or signed a written assent form (readers; typically, 6 years and older).

For this study, 470 high quality scans from 190 participants (95 CWS, 56 boys; 95 controls, 50 boys) were included in the final analyses, after excluding children whose MRI data was not useable due to excessive movement or incidental findings of abnormal brain structure. Incidental findings can range from normal variations in neuroanatomy to benign tumors, asymptomatic infarcts, and subclinical neurovascular pathology (Vernooij et al., 2007). Because these incidental findings were easily detected based on visual inspection, the abnormalities tended to cover a relatively large anatomical location and hence could have had the potential to influence the spatial normalization step of the VBM pipeline. Age at scan for each participant, showing the number of scans entered for each participant across groups for the 470 scans entered into the analysis are shown in Supplementary Fig. 2. Number of datapoints entered for data analysis (1-4 longitudinal scans) for each group are shown in Supplementary Table 2. Demographic information for the final group of participants can be found in Table 1. All participants were monolingual speakers of English who exhibited normal language and cognitive development as confirmed by detailed parent interviews that included review of speech-language developmental milestones and through a battery of speech, language and cognitive testing (see (Chang et al., 2015; Chow & Chang, 2017) for more details; see also Suppl Table 1). Handedness was assessed using a modified Edinburgh handedness battery (Oldfield, 1971) and was similar between CWS (right: n=76, left: n=8, mixed: n=9) and control groups (right: n=80, left: n=8, mixed: n=9).



Within the stuttering group, stuttering severity was assessed using samples of spontaneous speech, elicited through storytelling and conversational tasks (and reading for children typically six and older who could read) with a parent and a certified speech-language pathologist (SLP). These samples were video-recorded and analyzed according to the procedure from the Stuttering Severity Instrument (SSI-4; (Riley, 2009)). The SSI-4 provides a composite stuttering severity rating based on frequency and duration of disfluencies occurring in the speech sample, as well as physical concomitants associated with moments of stuttering. To determine measurement reliability of the SSI-4 score ratings, an intraclass correlation coefficient (ICC = 0.97) was calculated based on two independent judges' ratings of SSI-4 from a subset of children's speech sample, indicating high reliability.

Table 1. Participant characteristics in each age group (all subjects, 3–5-year-olds, and 6-12-year-olds).

| Measure | Control | Persistent | Recovered |
|---|---|---|---|
| ***3:0-12:11 (all subjects)*** | | | |
| # Subjects | 95 | 72 | 23 |
| # Scans | 230 | 176 | 64 |
| Boy to girl ratio | 50:45 | 44:28 | 12:11 |
| Age at initial scan (month) | 68.4 (21.1) | 69.2 (20.6) | 60.8 (20.7) |
| Age of stuttering onset (month) | N/A | 34.3 (11.9) | 32.9 (10.2) |
| SES[1] | 6.22 (0.74) | 6.11 (0.78) | 6.04 (0.74) |
| IQ[2] | 110.9 (13.1) | 106.5 (13.6)[a] | 108.7 (15.1) |
| SSI at initial visit | N/A | 19.7 (6.5) | 16.7 (5.9) |
| SSI at final visit | N/A | 18.63 (7.0) | 8.13 (3.1)[b] |
| ***3:0-5:11 (3-5 years old)*** | | | |
| # Subjects | 60 | 42 | 18 |
| # Scans | 91 | 64 | 34 |
| Boy to girl ratio | 34:26 | 27:15 | 10:8 |
| Age at initial scan (month) | 55.2 (9.2) | 54.4 (8.7) | 51.1 (6.8) |
| Age of stuttering onset (month) | N/A | 31.9 (9.9) | 31.4 (8.3) |
| SES | 6.22 (0.76) | 6.20 (0.76) | 5.92 (0.75) |
| IQ | 110.1 (12.6) | 108.3 (12.0) | 111.3 (15.3) |
| SSI at initial visit | N/A | 18.5 (5.5) | 17.3 (5.2) |
| SSI at final visit | N/A | 18.6 (5.8) | 8.9 (2.9)[b] |
| ***6:0-12:11 (6-12 years old)*** | | | |
| # Subjects | 63 | 54 | 14 |
| # Scans | 139 | 112 | 30 |
| Boy to girl ratio | 30:33 | 31:23 | 9:5 |
| Age at initial scan (month) | 84.6 (13.9) | 84.9 (11.7) | 83.5 (13.5) |
| Age of stuttering onset (month) | N/A | 36.0 (12.5) | 36.2 (11.2) |
| SES | 6.23 (0.69) | 6.10 (0.80) | 6.3 (0.49) |
| IQ | 113.7 (12.7) | 106.5 (14.2)[a] | 104.3 (14.1)[c] |
| SSI at initial visit | N/A | 20.6 (6.7) | 16.9 (7.1) |
| SSI at final visit | N/A | 19.4 (7.4) | 7.9 (3.2)[b] |

[1]SES (Socioeconomic status) was calculated based on the Hollingshead Four Factor Index of Socioeconomic Status (Hollinghead (1975)). In this study, a child's SES was measured based on the parent's (mother's) educational attainment, rated on a 7-point scale, e.g., a score of 6 indicates standard college or university graduation.

[2] WASI (Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999); ages 6+) or WPPSI (Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 2012); ages 3-5) was administered depending on the age of the child.

[a] Scores significantly lower in persistent than control group.

[b] Scores significantly lower in recovered than persistent group.

[c] Scores significantly lower in recovered than control group.

All CWS were diagnosed with stuttering during their initial visit by considering their composite SSI scores (=>10), %SLD (>3%), expressed concern of the parent and clinician confirmation. In a few instances, some children exhibited SSI and SLD scores below the cut-off used to determine stuttering status (SSI<10 and/or %SLD<=3%), however if their stuttering instances were qualitatively consistent with stuttering and both parent and clinician reports pointed to stuttering, the child was entered into the study as a child who stutters. On the other hand, a handful of control participants showed %SLD exceeding 3%, but the SLDs were qualitatively inconsistent with stuttering (e.g., easy repetitions of words rather than sound/syllable repetitions and no prolongations/blocks). If neither the parent nor SLP expressed concern and no family history of stuttering reported, such a child was entered as a control participant.

The CWS were later categorized as recovered or persistent through a combination of measures acquired in subsequent visits. Specifically, a child was categorized as persistent if the SSI0-4 score was equal or greater than 10 (corresponding to 'very mild' in SSI-4 severity classification) at the second visit or thereafter, and the onset of stuttering had been at least 36 months prior to his most recent visit. A child was considered recovered if the composite SSI-4 score was below 10 at the second visit or thereafter. Determination of recovery status also required the consideration of percent occurrence of stuttering-like disfluencies (%SLD) in the speech sample (>3 for persistent) as well as clinician and parental reports. Parents were interviewed each year to report on their children's stuttering status as observed in the home setting and other environments. Similar criteria were used to determine persistence versus recovery in stuttering children in previous studies (Yairi & Ambrose, 1999; Yairi, Ambrose, Paden, & Throneburg, 1996).

In cases where persistence versus recovery status remained unclear during the final visit, the stuttering participants' speech status was checked via parent phone interview 1-2 years post final visit to track and document any changes in the child's recovery or persistent status. Using these criteria, we identified 72 pCWS and 23 rCWS in the final analyses.

## 2.2 MRI data acquisition

Anatomical images were acquired on a GE 3T Signa scanner (GE Healthcare) with an 8-channel head coil at Michigan State University. In each scan session, a whole brain 3D inversion recovery fast spoiled gradient-recalled T1-weighted images with cerebrospinal

fluid suppressed was obtained using the following parameters: echo time = 3.8 ms, repetition time = 8.6 ms, inversion time = 831 ms, inversion repetition time = 2,332 ms, flip angle = 8°, and receiver bandwidth = 620.8 kHz. As part of the longitudinal imaging study, DTI and resting state functional MRI data were also collected but they are not reported in the current article. Previous studies have reported results from datasets collected from subsets of participants in the current study (shown in Suppl Table 3). DTI datasets from a subset of participants have been reported in three previous papers (Chang & Zhu, 2013; Chang et al., 2015; Johnson, Liu, Waller, & Chang, 2022; Neef, Angstadt, Koenraads, & Chang, 2023). Resting state fMRI datasets from a subset of participants were also reported in previous studies (Chang et al., 2018; Chang, Chow, Wieland, & McAuley, 2016; Chang & Zhu, 2013). These previous studies reported imaging findings from a different imaging modality than what is reported in the current study. With regard to studies that used T1 datasets as is reported in the current study, one previously published study reported cortical thickness (Garnett et al., 2018) and another reported on the relationship between gray matter volume and expression patterns of stuttering-related genes (Chow et al., 2019). All these previous studies only included approximately half the number of subjects that are reported in the current study (Suppl Table 3).

All children were trained with a mock MRI scanner to familiarize them with the MRI environment and procedures, and to practice keeping still while lying down inside the bore. Recordings of MRI scanning noises were played during this session, so that children were aware of the loud MRI sounds during scanning. During the MRI-scan visit, children viewed a movie to help them stay still, and a research staff member sat next to the child if needed to ensure comfort and compliance throughout the scanning procedure.

## 2.3 Voxel-based morphometry (VBM)

Voxel-Based Morphometry (VBM) analysis was conducted using the CAT12 toolbox (http://www.neuro.uni-jena.de/cat/). CerebroMatic Toolbox was used to create the study-specific templates based on an large publicly available data set and the demographic features (age and sex) of the participants in the current study (Wilke, 2018). Volume of each voxel were obtained by multiplying (or modulating) tissue probability by the deformation field derived from the DARTEL normalization procedure (Ashburner, 2007). Individual, modulated images were resampled to 1.5 mm isotropic voxels and spatially smoothed with a Gaussian kernel with FWHM of 6 mm. To account for the dependence of participants' multiple scans in the current study, gray matter volume (GMV) and white

matter volume (WMV) images were analyzed separately using Sandwich Estimator, which was designed for analyzing longitudinal and repeated measures data and has been shown to be robust to missing data and unbalanced designs (Guillaume et al., 2014; Ibrahim & Molenberghs, 2009). Because the sample sizes of the previous VBM studies of children who stutter (CWS) were relatively small, and this is the first time preschool-aged CWS were studied, we did not make assumptions that the structural differences were in specific areas or limit our analyses to certain regions of interest. For each age group, the model included group (pCWS, rCWS and controls) and sex as factors, group by age interaction, and quadratic age, IQ, intracranial volume, socioeconomic status (SES) and stuttering severity as covariates to control potential sources of variations. We included quadratic age as a covariate and do not report it separately (however, we show in Suppl Fig. 4 non-linear age effects found in our data, which complement the main linear age effects findings) as our main interest was to examine linear age effects. Examining linear age effects was a focus given our previously reported finding of linear (but not non-linear) effects in white matter structural data and given previous longitudinal studies of gray matter development encompassing large age ranges across the lifespan that have reported primarily linear age effects found within the age range of our participants (3-12 years) (Gogtay & Thompson, 2010; Mills et al., 2016). Voxel-wise *t*-statistics of the group differences were calculated. Voxel-wise height threshold $p<0.005$ and cluster-size threshold $k>457$ voxels in GMV analysis, and $k>318$ voxels in WMV analysis were used to control for false positives. This set of thresholds resulted in a corrected $p<0.05$. The cluster-size threshold was determined by AFNI 3dClustSim (version 17.2.13) with non-Gaussian auto-correlation function (-acf option) (Cox, Chen, Glen, Reynolds, & Taylor, 2017).



### 2.4. Data availability

The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request.

## 3. Results

### 3.1 Participant characteristics

The pCWS, rCWS and fluent controls did not differ significantly in sex ratios, age at the initial scan, or SES (Table 1). There were no significant differences between pCWS and rCWS in onset age of stuttering or stuttering severity at the initial visit. As expected,

stuttering severity was significantly lower in rCWS than pCWS at the final visit. Compared to controls, pCWS scored significantly lower on IQ than controls based on the combined age groups (total) and school-age subjects, while rCWS only scored significantly lower on IQ in the analyses of school-age subjects. It is important to note that the mean IQ scores in both pCWS and rCWS were well within the normal range. The differences in IQ were driven by above-average IQ in the control group. Given these differences, we entered IQ as a covariate in our statistical analyses.

## 3.2 Morphometric anomalies associated with persistent stuttering in preschool-age children

The key neuroimaging findings are shown in figures and described in the text below; results of all contrasts are listed in Supplementary Table 3.

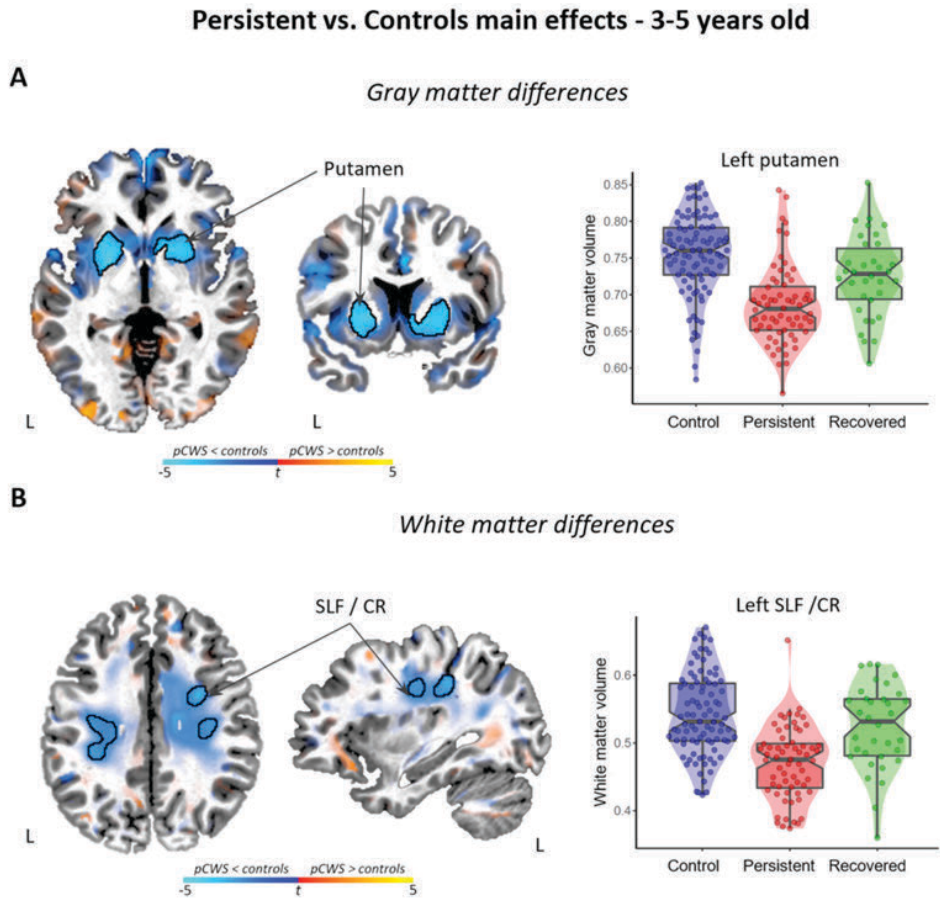
## 3.3 Overall differences (group effects) between pCWS and controls

Significant differences between pCWS and controls were found in gray (Fig. 1A) and white matter volume (Fig. 1B). In this preschool-age range (3-5 years), pCWS exhibited reduced GMV compared to controls in the putamen and the nucleus accumbens. In terms of white matter, decreased WMV was observed in white matter tracts encompassing the bilateral corona radiata, superior longitudinal fasciculi (SLF) and the corpus callosum for pCWS relative to controls (Fig. 1B).

## 3.4 Developmental trajectory differences (age effects) between pCWS and controls

In addition to group effects, we investigated whether there were significant group by age interactions, reflecting differences in developmental trajectories between groups. In the preschool-age group, differences were only observed in the development of WMV but not GMV when comparing pCWS with controls (Fig. 2). Decreasing WMV was observed in white matter tracts encompassing the bilateral corona radiata and SLF, including the white matter near the left ventral premotor area for pCWS, while WMV in these areas were increasing for controls. In addition, lower WMV growth rates were found for pCWS in the corpus callosum and the inferior longitudinal fasciculus (ILF).

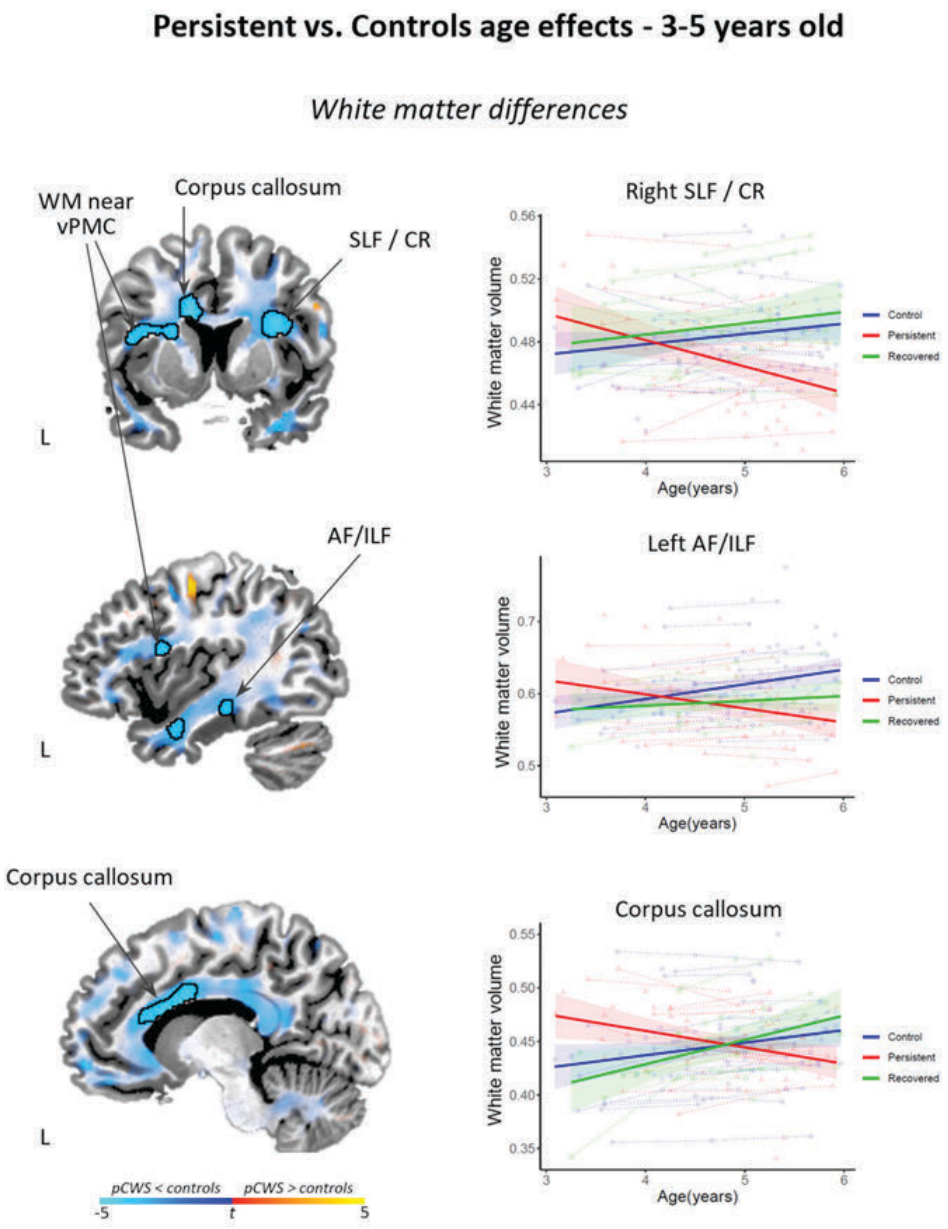
Figure 1. Differences between preschool-age children with persistent stuttering and controls (3-5 years old) in gray matter volume (A) and white matter volume (B).




In the left panel, between-group differences are overlaid on a single subject anatomical image. Orange and blue indicate increased and decreased volume at uncorrected $p<0.05$, respectively. Clusters exhibiting a significant difference at corrected $p<0.05$ are outlined by black lines.
In right panel, violin plots illustrate the group differences around the peak of a significant cluster.

*Notes for Figure 1-6:*
SLF: superior longitudinal fasciculus, CR: corona radiata, AF; arcuate fasciculus, ILF: inferior longitudinal fasciculus, vPMC: Ventral premotor cortex.
Each marker represents the modulated volume values averaged across voxels around the peak location in each scan. The values were adjusted for the effects of sex, age, IQ, intracranial volume and socioeconomic status. Longitudinal volume measures of a participant are connected using dotted lines. Solid lines represent the best-fit linear trend lines in each group and the shaded areas represent the standard errors of the trend lines.

Figure 2. Differences between school-age children with persistent stuttering and controls (3-5 years old) in growth rate of white matter volume.



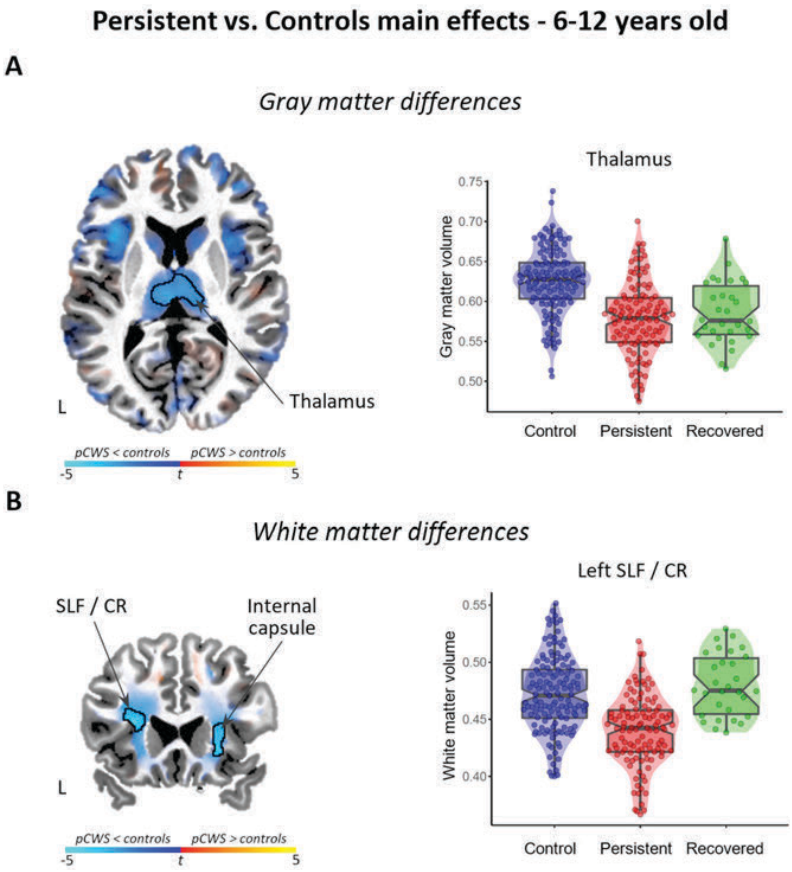

In the left panel, between-group differences in growth rate are overlaid on a single subject anatomical image. Orange and blue indicate increased and decreased growth rate at uncorrected $p<0.05$, respectively. Clusters exhibiting a significant difference at corrected $p<0.05$ are outlined by black lines. In the right panel, individual volume measures are plotted against age to illustrate the age-related changes in each group around the peak of a significant cluster.

## 3.5 Morphometric anomalies associated with persistent stuttering in school-age children

### 3.5.1 Overall differences (group effects) between pCWS and controls

Figure 3 shows results from the group contrast between pCWS and controls in the school-age range. In this older age group, GMV in the thalamus was significantly reduced in pCWS compared to controls (Fig. 3A). Regarding WM, pCWS exhibited smaller volume in white matter tracts encompassing the corona radiata, SLF and the internal capsule relative to controls (Fig. 3B).

Figure 3. Differences between older children with persistent stuttering and controls (6-12 years old) in gray matter volume (A) and white matter volume (B).

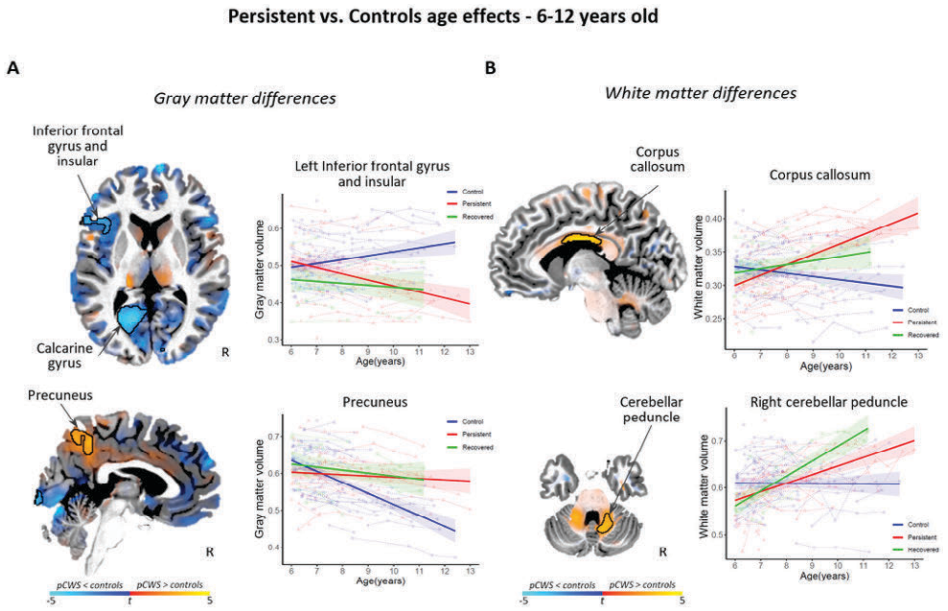



In the left panel, between-group differences are overlaid on a single subject anatomical image. Orange and blue indicate increased and decreased volume at uncorrected $p<0.05$, respectively. Clusters exhibiting a significant difference at corrected $p<0.05$ are outlined by black lines.
In right panel, the violin plots illustrate the group differences around the peak of a significant cluster.

### 3.5.2 Developmental trajectory differences (age effects) between pCWS and controls

For pCWS relative to controls in the school-age range, the GMV growth rate was lower in the left IFG and the insula as well as the calcarine gyrus in the visual cortex, whereas GMV growth rate was higher in the precuneus (Fig. 4A). PCWS also showed greater growth rates compared to controls in white matter areas including the body and isthmus of the corpus callosum and the WM near the right dentate nucleus (Fig. 4B).

Figure 4. Differences between older children with persistent stuttering and controls (6-12 years old) in growth rate of gray matter volume (A) and white matter volume (B).



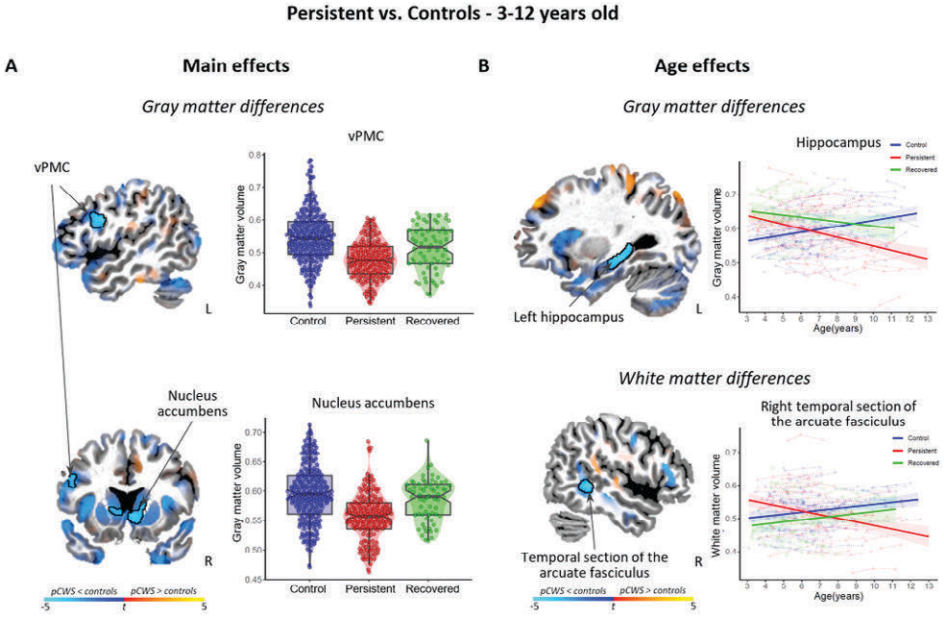

Between-group differences in growth rate are overlaid on a single subject anatomical image. Orange and blue indicate increased and decreased growth rate at uncorrected $p<0.05$, respectively. Clusters exhibiting a significant difference at corrected $p<0.05$ are outlined by black lines. In the scatter plots, individual volume measures are plotted against age to illustrate the age-related changes around the peak of a significant cluster in each group.

## 3.6 Morphometric anomalies associated with persistent stuttering from the entire sample of children

The comparison between pCWS and controls including all children (ranging from preschool-age to school-age children) showed significant decreases in GMV for pCWS in the left ventral premotor cortex (vPMC) and the nucleus accumbens (Fig. 5A). In addition, pCWS showed decreased GMV with age in the hippocampus and GMV in the

right posterior middle temporal lobe; in contrast, controls showed increased volume with age in both areas (Fig. 5B).

Figure 5. Differences between children with persistent stuttering and controls when scans from all subjects from age 3-12 years old were analyzed together in a single model.

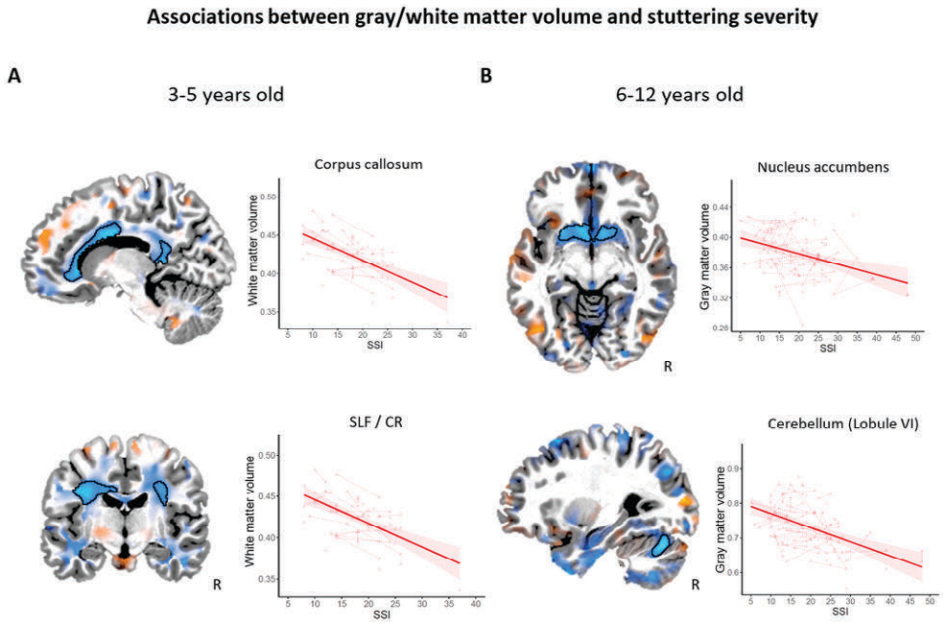



(A) Between group differences in gray matter volume are overlaid on a single subject anatomical image. Orange and blue indicate increased and decreased volume at uncorrected $p<0.05$, respectively. Clusters exhibiting a significant difference at corrected $p<0.05$ are outlined by black lines. The violin plots illustrate the group differences around the peak of a significant cluster.
(B) Between group differences in growth rate of gray matter are overlaid on a single subject anatomical image. The scatter plots illustrate the growth rate differences around the peak of a significant cluster in each group.

## 3.7 Association between brain volume and stuttering severity in children with persistent stuttering

In the preschool-age group, WMV in the bilateral corona radiata, corpus callosum (genu, mid body and splenium), and the right AF in the temporal lobe (not shown) was negatively associated with stuttering severity, but no significant association between stuttering severity and GMV was found. By contrast, in the school-age group, significant association with stuttering severity was only found in gray matter areas, including in the bilateral nucleus accumbens and the right cerebellar lobule VI (Fig. 6). Apart from stuttering severity, we did not find significant association between gray or white matter and other covariates (IQ and SES) nor sex by group interaction.

Figure 6. Associations between gray/white matter volume and stuttering severity scores in children who stutter from age 3-5 years old (A) and 6-12 years old (B).

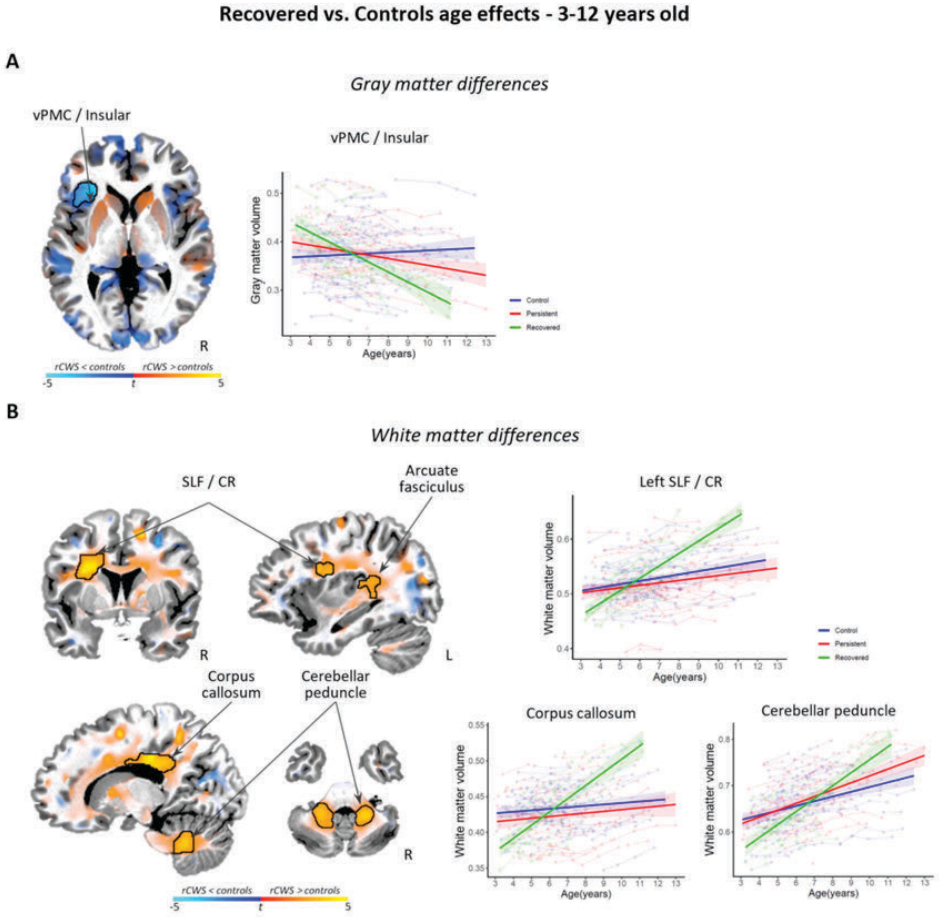



Estimated association between stuttering severity and volume measures in each voxel is overlaid on a single subject anatomical image. Orange and blue indicate positive and negative association at uncorrected $p<0.05$, respectively. Clusters exhibiting a significant association at corrected $p<0.05$ are outlined by black lines. In the scatter plots, individual volume measures around the peak of a significant cluster are plotted against stuttering severity scores.

## 3.8 Morphometric findings associated with recovery from stuttering

Compared to controls, rCWS exhibited a lower growth rate in the left insula/inferior frontal area (Fig. 7A). On the other hand, a higher growth rate in rCWS relative to controls were observed in extensive white matter areas including the bilateral corona radiata, SLF, corpus callosum, left AF, and bilateral cerebellar peduncles around the dentate nuclei (Fig. 7B).

Figure 7. Differences between children who recovered from stuttering and controls when scans from all participants from age 3-12 years old were analyzed together in a single model.




Between group differences in growth rate of gray matter volume (A) and white matter volume (B) are overlaid on a single subject anatomical image. Orange and blue indicate increased and decreased volume at uncorrected $p<0.05$, respectively. Clusters exhibiting a significant difference at corrected $p<0.05$ are outlined by black lines. The scatter plots illustrate the growth rate differences around the peak of a significant cluster in each group. The values were adjusted for the effects of sex, IQ, intracranial volume and socioeconomic status.

# 4. Discussion

The current study is the first longitudinal study that examined brain development trajectories associated with persistence and recovery of stuttering during childhood, encompassing both preschool-age (3-5 years of age) and school-age (6-12 years of age) children. The preschool-age group is particularly important for understanding the etiology of stuttering because it coincides with the typical onset time of stuttering. The results indicate that stuttering persistence is associated with wide-ranging structural anomalies, including in major structures of the BGTC loop, the left perisylvian speech language networks, the cerebellum and white matter tracts that interconnect these regions. Some of these morphometric variations across subjects were associated with stuttering severity, which further supports the pivotal role of the speech motor system in stuttering persistence. However, the patterns of structural anomalies appear to differ between preschool- and school- age pCWS. In preschool-age children, the most significant morphometric difference in pCWS relative to controls were in the bilateral putamen and nucleus accumbens, and in the white matter tracts that interconnect speech-language and motor areas such as the SLF and motor projection fibers. On the other hand, in school-age children, the main difference between pCWS and controls become evident in the thalamus and the white matter in the internal capsule, corona radiata and the SLF. The most prominent gray matter anomalies appeared to transition from regions receiving cortical projections in the BG (i.e., the putamen) at younger ages, to the region receiving output from the BG (i.e., the thalamus) at older ages. However, this dynamic developmental change could be the result of the interaction between stuttering-related anomalies and normal brain developmental processes such as the observation that GMV in many regions decreases with age in school-age children. It has been shown that GMV in many parts of the brain decrease with age, especially after the age of seven (Gogtay et al., 2004; Sowell et al., 2003; Tamnes et al., 2017).

While stuttering persistence was mainly associated with decreased gray and WMV or an attenuated growth rate in the speech-motor structures, recovery from stuttering was primarily associated with increased growth rate of white matter volume in tracts connecting these structures, suggesting that these increases reflect a process of compensation for the neural deficits in stuttering. These main findings are elaborated and discussed below.

## 4.1 Early involvement of BGTC structures associated with persistent stuttering

One strength of the current investigation was that, due to the relatively large sample size analyzed, we were able to examine children close to typical stuttering onset (3-5 years) and those who had been stuttering for longer periods (6-12 years) separately. In the preschool-age group, we found that compared to controls, CWS who eventually develop persistent stuttering (pCWS) had significant GMV decreases relative to controls in the bilateral putamen and nucleus accumbens (Fig. 1A). This GMV decrease in preschool-age pCWS was accompanied by reduced overall volume and growth rate in major white matter structures including the corpus callosum, corona radiata, SLF and ILF (Fig. 1B and Fig. 2). While the corona radiata and corpus callosum are known to be associated with motor projection fibers and interhemispheric connections respectively, ipsi- and contralateral corticostriatal projection fibers also pass through these structures (Shepherd, 2013). Given the gray matter anomalies in the striatum, the white matter anomalies in preschool-age CWS may also reflect connectivity deficits involving the BG. In addition, reduced WMV growth rate was found in the bilateral SLF near the vPMC and the ILF (Fig. 2). These white matter tracts are involved in transmitting speech sound representations, providing inputs to the BGTC loop (Hickok, 2012). Taken together, GMV and WM anomalies observed in preschool-age pCWS suggest that deficits in the BGTC motor loop plays an important role in the onset and persistence of stuttering behaviors. This notion is also supported by the negative association between stuttering severity and WMV in the corpus collosum, SLF and corona radiata in preschool-age pCWS (i.e., lower the volume, higher the severity, Fig. 6A). While the negative association between putamen and nucleus accumbens volume and stuttering severity was not significant in preschool-age CWS, it was significant in school-age pCWS (Fig. 6B).

Previous studies reported reduced volume in the putamen in school-age CWS (Beal et al., 2013; Foundas, Mock, Cindass, & Corey, 2013). Moreover, white matter anomalies in the corpus collosum, SLF, corona radiata and AF/ILF observed in the current study are consistent with the previous DTI studies of school-age pCWS, which reported decreased fractional anisotropy in those white matter areas (Chang et al., 2015; Chow & Chang, 2017). These structural anomalies may be associated with weaker connectivity between the putamen and several cortical regions, including the left insula, IFG and middle frontal gyrus and supplementary motor area (SMA) in pCWS, perhaps reflecting either decreased efficiency, or under-utilization of these connections (Chang et al., 2016;

Chang & Zhu, 2013; Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier, & Ben-Shachar, 2016). The current results provide empirical support for possible deficits in cortical-BG connections in stuttering, and that these deficits seem to be present early, near onset of stuttering. If connectivity within the BGTC circuit is not well developed, timing of motor sequences could be disrupted, which results in a mismatch between sensory targets and motor representations (Guenther, 2006, 2016).

In previous structural MRI studies of stuttering, the left IFG/vPMC region has been repeatedly reported to differentiate stuttering speakers from controls (Beal et al., 2013; Chang et al., 2008; Chang et al., 2015; Civier, Kronfeld-Duenias, Amir, Ezrati-Vinacour, & Ben-Shachar, 2015; Connally, Ward, Howell, & Watkins, 2014; Kell et al., 2009; Sommer, Koch, Paulus, Weiller, & Buchel, 2002; Watkins, Smith, Davis, & Howell, 2008). The left IFG/vPMC corresponds to the speech sound map area in the DIVA model (Directions into Velocities of Articulators) (Guenther, 2006), a critical area that is part of both feedforward and feedback pathways within the model that interconnects with several cortical and subcortical regions. The DIVA model provides a neurocomputational modeling framework to mechanistically interpret the neuroimaging findings from this study. Structurally, the inferior frontal/vPMC region has major connections with motor cortices and the sensory cortical areas via the SLF, language areas via the arcuate fasciculus and the SMA via the frontal aslant tract (Catani, Jones, & ffytche, 2005; Dick, Garic, Graziano, & Tremblay, 2019; Kronfeld-Duenias et al., 2016). The left vPMC is thus an important hub area within the BGTC loop in speech production that is linked to two of the three main loci within the BGTC loop that are posited to be affected in stuttering (i.e., impairment of axonal projections between cortex, BG, and thalamus; PDS2 and corticocortical connections; PDS3) (Chang & Guenther, 2019).

Specifically, we found evidence of reduced left vPMC volume based on the group contrasts of pCWS and controls across the whole age range tested (Fig. 5A). When examining within the separate younger and older groups, however, this decreased left vPMC volume did not reach significance for group effects (see Fig 3A). Significant age effects were nevertheless found in this region, whether it was in the preschool-age group in terms of white matter encroaching on the left vPMC region (Fig. 2) or in terms of GMV in this area for the school-age groups (Fig. 4). These results suggest that the reduced vPMC GMV found in school-age may be associated with reduced connections to the region during younger ages. We further discuss how our findings can be interpreted in the context of the DIVA model under the neuroanatomical accounts section below.

## 4.2 Emergence of thalamus anomalies in school-age children with persistent stuttering

While reduced volume of the structures supporting the corticostriatal projections as well as the input regions of the BG such as the putamen appear to be the hallmark of preschool-age pCWS, the most prominent structural anomalies associated with school-age pCWS were in the thalamus. In the BGTC loop, the thalamus receives projections from the BG and projects to the cortical motor areas. It also has bidirectional direct connections with the cerebellum and modulates functions of the BG and the cerebellum (Bostan & Strick, 2018; Chen, Fremont, Arteaga-Bracho, & Khodakhah, 2014). The decreased GMV in the thalamus may affect both the BGTC and cerebellar processes important for speech-motor control (Kotz, Brown, & Schwartze, 2016; Kotz & Schwartze, 2010). The thalamus anomalies could arise due to deficits occurring earlier in the putamen where structural anomalies were observed in preschool-age pCWS (Wu & Hallett, 2013). It also indicates that structural anomalies associated with persistent stuttering are not static; they may develop in tandem with the progression of the disorder. On the other hand, reversing this anomalous brain development or enhancing compensatory process may reduce stuttering severity or even facilitate recovery.



Interestingly, reduced putamen volume observed in the younger pCWS was not observed in the older age group. However, we believe that this negative result does not imply that the anomaly in the putamen is normalized, for two reasons. First, in the school-age pCWS, putamen and nucleus accumbens volume was negatively correlated with stuttering severity (Fig. 6B), indicating the functional importance of these structures in stuttering behaviors. Second, the reduction of volume in the putamen and possibly many other regions may become less evident due to normal development of gray and white matter. It has been shown that GMV in many parts of the brain decrease with age, especially after the age of seven (Gogtay et al., 2004; Sowell et al., 2003; Tamnes et al., 2017). Our data also showed that GMV of controls decreased in most of the cortical and subcortical areas including the putamen. If the GMV reduction in normal development is delayed in pCWS, that is, GMV reduction occurs at a lower rate relative to controls, the effect of lower GMV in the putamen in preschool-age pCWS will be diminished in the older age range, as illustrated in Supplementary Fig. 3. If these trends continue, this may also explain why several studies reported that adults with persistent stuttering showed greater GMV in the left putamen compared to adults who do not stutter (Lu et al., 2010; Montag et al., 2019; Neef et al., 2018). This interplay between stuttering-related anomalies and normal brain development shows the importance of studying finer-grained age groups to reveal the complexity of the neural development in pCWS.

## 4.3 White matter volume increases are associated with stuttering recovery

Similar to pCWS vs controls (Fig. 5), rCWS showed decreased GMV in the ventral premotor area and insula relative to controls when we included all the scans in the whole age range in the analysis (Fig. 7A). Different from pCWS vs controls, decreased volume in the BG and the thalamus was not found in rCWS vs controls. This qualitative difference may indicate that the causes of stuttering in pCWS and rCWS have different neuroanatomical origins. However, direct comparison between pCWS and rCWS did not show any significant group differences in these subcortical areas (Suppl Table 3). RCWS may have more confined deficits associated with corticostriatal connections while pCWS may have more widespread anomalies throughout the BGTC network. However, it is also possible that the deficits associated with the BG and the thalamus had resolved in preschool-age CWS or we did not have sufficient statistical power to detect the deficit due to the small number of rCWS in the current study.

A marked difference between pCWS and rCWS is that the growth rate was significantly higher for rCWS in several WM areas (Fig. 7B) where decreased volume or growth rate was observed in preschool- and school-age pCWS, including in the left corona radiata, the corpus callosum, SLF and the left AF (Figs. 1B, 2 & 3B). This observation was supported by direct comparison between pCWS and rCWS in age effects, which showed a significant group by age interaction in those areas (Suppl Table 3). This divergent development in pCWS and rCWS has also been reported in a longitudinal DTI study (Chow & Chang, 2017) that examined a subset of the same participants included in the current study and strongly suggests that the WMV increases underlie a possible normalization or compensatory process associated with natural recovery from stuttering.

Increased growth rate in the bilateral cerebellar peduncle around the dentate nucleus was also observed in rCWS (Fig. 7B). This is an interesting result because, different from other WM areas showing increased WM growth rate in rCWS, decreased volume or growth rate in the bilateral cerebellar peduncle around the dentate nucleus was not observed in pCWS. Instead, increased growth rate in the right cerebellar peduncle around the dentate nucleus as well as the corpus callosum was found in school-age pCWS, but the spatial extent is less than that observed in rCWS. This may indicate that increased growth rate in the cerebellar peduncle is associated with an incomplete compensatory process associated with stuttering regardless of persistence or recovery. The growing volume of the cerebellar peduncle also indicates the involvement of the cerebellum in compensatory process. This notion is further supported by the observation of negative association between the right

cerebellum lobule VI and stuttering severity in school-age pCWS (Fig. 6B). Overall, our results indicate that the cerebellum may support increased fluency, but it is insufficient to support complete recovery from stuttering. Rather, as discussed in an earlier section, recovery from stuttering may require compensation involving the BGTC loop.

## 4.4 An updated neuroanatomical account of childhood stuttering persistence and recovery

The current results corroborate many predictions of a neuroanatomical model of speech motor control, the DIVA model (Guenther, 2006, 2016). In theorizing of potential impairments in persistent developmental stuttering (PDS), Guenther (2016) proposes three possible locations of impairments in the BGTC loop (also described in Chang and Guenther (2019)). The first is in the basal ganglia proper (PDS-1), the second is the corticostriatal projections from cerebral cortex to the basal ganglia (PDS-2), and the third is the network of cortical regions that process cognitive and sensorimotor aspects of speech (PDS-3). The current finding of early presence of decreased GMV in the putamen and nucleus accumbens in pCWS supports PDS-1, and the decreased WMV that appear to intersect with the corticostriatal tracts within the motor projection fibers and the corpus callosum supports PDS-2. In addition, evidence for PDS-3 was also found, specifically relating to WMV decreases observed in the inferior frontal areas, SLF and AF/ILF in the left hemisphere. These WMV reductions may reflect either decreased efficiency, or under-utilization of left frontotemporal connections that enable auditory-motor integration needed for fluid speech motor control. Overall, our results support all three possibilities hypothesized in Guenther (2016). However, further research is needed to understand the contribution of these three structures to the onset and persistence of stuttering and their specific effects on stuttering behaviors.

Guenther (2016) questioned whether the weakened corticostriatal connectivity reported in CWS was a secondary consequence of impairment elsewhere rather than the root cause of stuttering, given that this finding had not been consistently found in adult speakers who stutter. The current findings in young children including those in preschool-age point to differences in corticostriatal connectivity as critical loci of impairment associated with stuttering. The lack of consistent findings of BGTC anomalies reported in older children and adults who stutter from previous studies may have been influenced by the effects of later occurring structural development that obscure earlier group differences (e.g., normal decreases in GMV in controls that occur later in development that could

then become similar to the level of low GMV in stuttering speakers; see Suppl Fig. 3 for example), as well as possibly the compensatory processes developed later in life. More longitudinal studies involving younger children close to stuttering onset will be needed to address this question further.

The current observation of significantly reduced GMV in the putamen and nucleus accumbens (NAcc) in the earliest stages of stuttering (in preschool-age CWS) is a novel finding that lends support for the crucial role of the basal ganglia and the dopamine system in speech and stuttering (reviewed in Alm (2021)). The dopamine system underlies our ability to learn and execute rapid, automatized movement sequences (Goerendt et al., 2003; Tremblay et al., 2010) and has been linked to stuttering due to related pharmacological effects in stuttering (Maguire, Riley, & Yu, 2002; Wu et al., 1997). The striatum, comprising the basal ganglia structures caudate, putamen, and NAcc, receives input from most parts of the cerebrum, is a major target for dopamine. Relevant to the findings of the current study, dopaminergic neurons from the substantia nigra pars compacta (SNc) project to the putamen (sensorimotor striatal region), whereas those from primarily ventral tegmental area (VTA) project to the NAcc, a ventral striatal region (Morales & Margolis, 2017). The dopamine signal from the SNc to putamen encodes timing and initiation (i.e., if and when) of planned movements (Howe & Dombeck, 2016; Klaus, Alves da Silva, & Costa, 2019), while dopamine signal from VTA to NAcc encodes the force or vigor of motivated movements (Hughes et al., 2020); Reviewed in Alm (2021). In one study, Neef et al. (2018) reported that among the BG areas, only the right NAcc differed in the volumetric comparisons between 33 AWS and controls, suggesting that NAcc function of interfacing cognition, emotion, and action might be affected in speakers who stutter. Though the NAcc has not been a focus of investigation in stuttering to date, it is an area that may be of relevance to stuttering neurophysiology given its role in interfacing limbic and motor areas and is relevant to encoding the motivation to move (Floresco, 2015; Goto & Grace, 2008), that is, it plays a central role in emotional evaluation, reward, and motivation.

The motivational value of movement as encoded by NAcc may have a particular relevance to speech occurring in a goal directed, social setting, as opposed to speech occurring in solo. The situational variability of stuttering, and in particular, the observation of little to no stuttering when speaking to oneself, is of relevance here as it may relate to the difference in dopaminergic activity that affects striatal function and the connectivity to cerebral areas these striatal structures interface during speech in social settings versus

speech that is not goal directed. The dopaminergic neurons have also been reported to have greater energy demands (Pacelli et al., 2015; Pissadaki & Bolam, 2013). It has been reported that brain areas with high energy demands coincide with those areas that are significantly different in brain anatomy in stuttering (Boley et al., 2021; Chow et al., 2019) (see review in Alm (2021)) and these undergo rapid growth during early childhood. The high metabolic demands in the dopamine system during dynamic periods of neurodevelopment, combined with possible deficits in connections among circuits that enable learning and execution of automatized motor sequences such as is the case in speech, may be affected in stuttering starting close to stuttering onset.

Kotz and colleagues have argued for the role of additional subcortical structures, including the basal ganglia (putamen), thalamus, and cerebellum, in temporal processing relevant to speech processing (Kotz et al., 2016; Kotz & Schwartze, 2010). Specifically, the basal ganglia and cerebellum are engaged in detecting and predicting temporal regularities, which is critical during speech acquisition, as they facilitate establishing basic routines that can lead to more complex behavior. Acquiring these routines requires the integration of auditory and sensorimotor information. Animal tracing and unit recording studies have shown that the cerebellum has direct inputs from the cochlear nuclei that enables rapid auditory transmission for temporal processing. The cerebellar dentate outputs to the thalamus, which projects to cortical motor areas that connects to the basal ganglia. This forms a network that links together cerebellar, auditory, and frontal-striatal circuitries, supporting the acquisition of basic motor routines (Akkal, Dum, & Strick, 2007; Dum & Strick, 2003).

In the case of stuttering, we speculate that earlier occurring structural deficits in the striatal putamen could negatively affect the acquisition of basic speech routines that are efficiently encoded through their temporal structure. Inefficient acquisition of these speech motor routines could lead to increased demand for constant sensory monitoring and corrective action that involves the cerebellar networks in children who stutter. In the present study, greater WMV around the dentate nucleus into the cerebellar peduncles was observed in both persistent and recovered CWS, but this was particularly greater in rCWS and this pattern increased with age. The greater WMV in this area may indicate a compensatory development of efferent fibers along the cerebellar dentato-thalamocortical loop. This development appears to be insufficient on its own to lead to recovery but may support an important functional increase to compensate for the deficit in the BGTC. These findings highlight the importance of considering the role of temporal processing in the pathophysiology of stuttering.

### 4.5 Strengths and limitations

To the best of our knowledge, this study involved the largest sample of MRI scans collected from a group of preschool- and school-age CWS and fluent age-matched peers, which allowed us to examine CWS close to the stuttering onset and later childhood when the chance of recovery diminishes. Our longitudinal experimental design allowed us to determine the clinical trajectories of each subject (persistent, recovered, and control). Even though we followed our participants for up to 4 years, it is possible that some of the pCWS included in our study may recover in later childhood or adolescence. However, chances of late recovery should be a minority (Yairi and Ambrose, 1999) and are not expected to significantly alter the present findings.

The results related to rCWS need to be interpreted with caution because the sample size for rCWS was relatively small (N=23). Due to the small sample size in rCWS, preschool- and school-age children who recovered from stuttering were not analyzed separately as was done in pCWS. Studies employing small sample sizes are more prone to sampling error and at a greater chance of both type I and II errors (Button et al., 2013). The findings related to stuttering recovery therefore will need to be replicated and confirmed in future larger studies.

It is likely that there are several biological, cognitive and environmental factors that influence the anomalous development of gray and white matter in children who stutter. We used sex, IQ and SES as proxies to controls for the potential effects of these factors. However, it is impossible to control for all the potential effects such as handedness and speech-language measures in our statistical models. These effects warrant further analyses in the future, in light of previous studies that have linked behavioral and demographic factors as potential predictors of stuttering persistence, such as speech sound accuracy, expressive/receptive language scores, and stuttering frequency (Singer, Hessling, Kelly, Singer, & Jones, 2020; Singer, Otieno, Chang, & Jones, 2022), the level of performance on nonword repetition (Spencer & Weber-Fox, 2014), time since onset (Yairi & Ambrose, 1999), and family history of persistent stuttering (Singer et al., 2020; Walsh et al., 2018).

## 5. Conclusion

Regional gray and white matter volume differences across the whole brain were examined in preschool- and school-age CWS (both persistent and recovered) compared to age matched peers in the largest MRI dataset collected for this clinical population to date.

Longitudinally collected scans that spanned up to 4 years per participant allowed tracking of developmental trajectories that differentiated among the groups. The results provide broad support for a possible BGTC network deficit starting at the early phase (preschool-age) of the disorder, involving the putamen, nucleus accumbens, left IFG/vPMC, and corticostriatal tracts. The deficits in input regions of the BGTC network appear to affect the output regions of the network including the thalamus in later phases of stuttering (school-age). The current data also provide insights into neural bases of natural recovery from stuttering during childhood. Children who recover from stuttering showed increased WMV in motor projection fibers, left AF, corpus callosum, and cerebellar peduncle around the dentate nuclei, suggesting that normalization or successful compensation of stuttering-linked neural deficits. Similar volume increases in corpus callosum, and cerebellar peduncle were also observed in pCWS, indicating an incomplete compensation. These results provide substantial new insights into possible neural bases of stuttering onset, persistence, and recovery during childhood.

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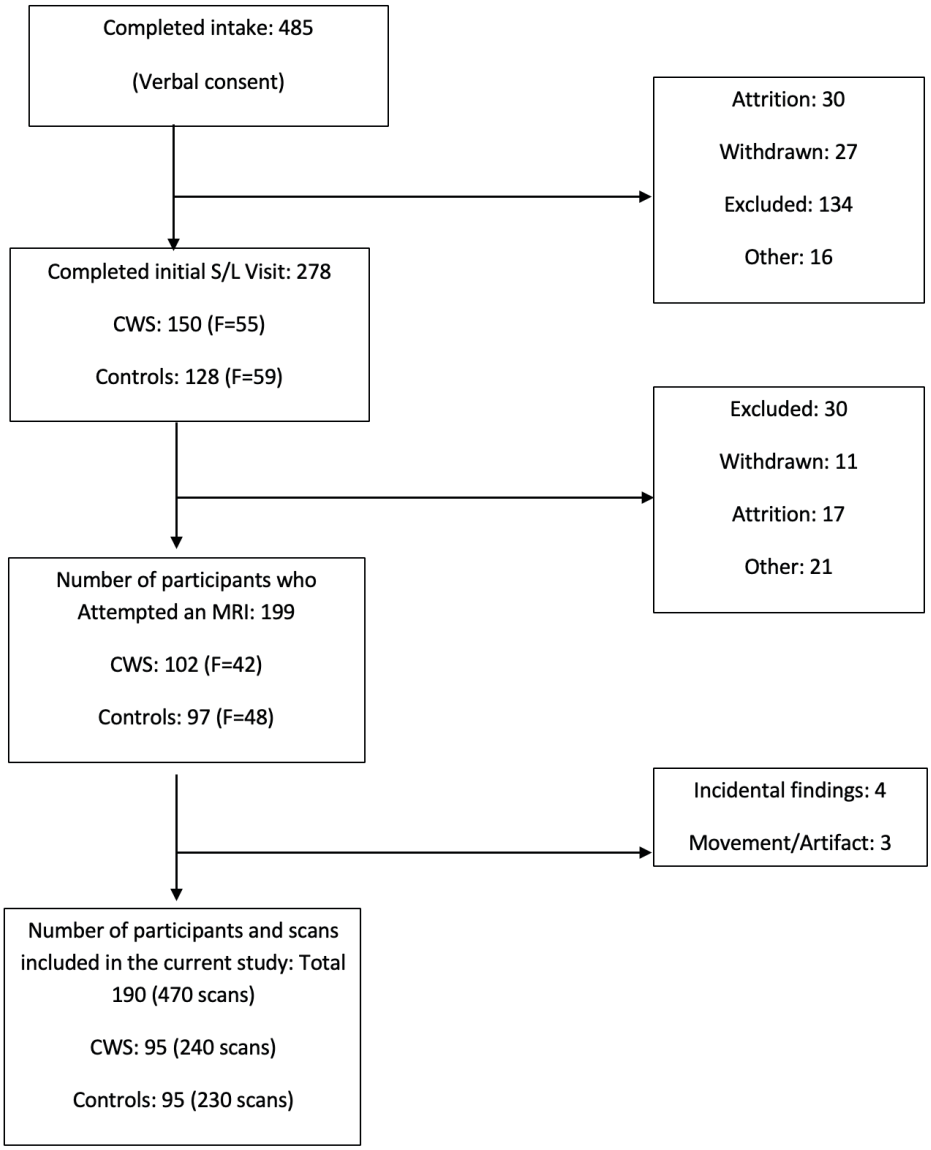
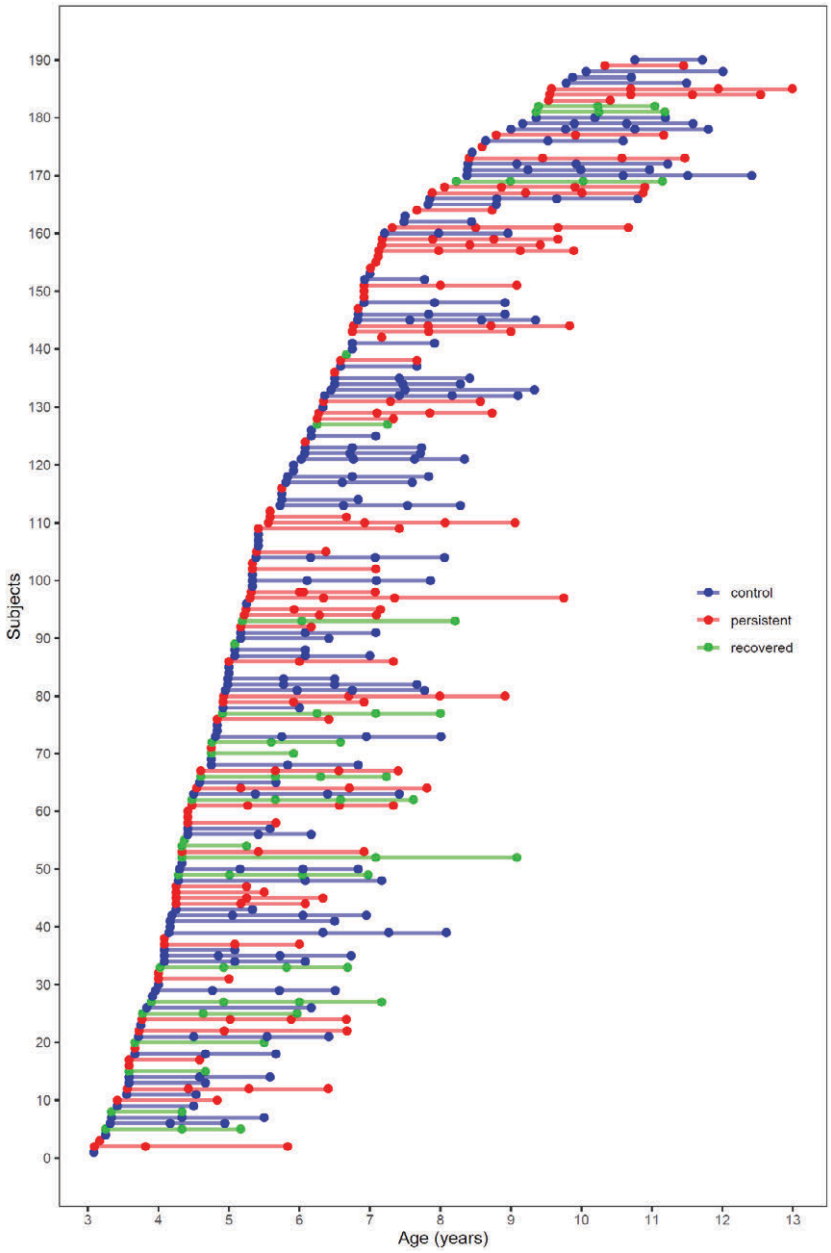
# Supplementary Materials

Supplementary Figure 1. Flowchart showing path leading to final number of participants and total number of scans that were included in the study.



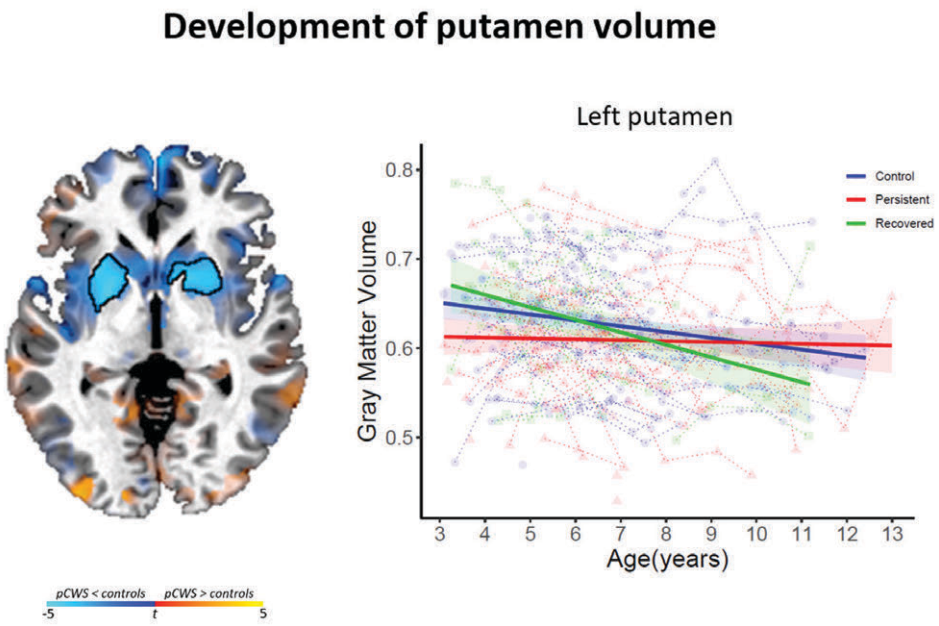

CWS: children who stutter

Supplementary Figure 2. Age at scan for all 190 participants across three groups (controls, persistent, recovered).




Each of the 470 scans is shown as a dot. Each participant is shown in a different row (y-axis), with their scans connected by a line. Note that at least a quarter of all participants in each group had all four useable data points entered, with similar distribution across groups in the relative number of data points entered into analysis as well as age representation.

Supplementary Figure 3. Differences between school-age children with persistent stuttering and controls (3-5 years old) in gray matter volume.

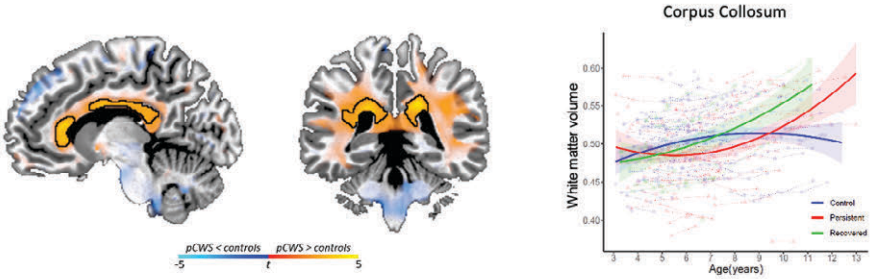



This figure illustrates how significant group differences (in this case, controls > pCWS) found during early stages of development may not be present when examining older groups of children (or in adults). In the left panel, between-group differences are overlaid on a single subject anatomical image. Orange and blue indicate increased and decreased volume at uncorrected $p<0.05$, respectively. Clusters exhibiting a significant difference at corrected $p<0.05$ are outlined by black lines. In right panel, the scatter plot illustrates the growth rate differences around the peak at the left putamen in each group.

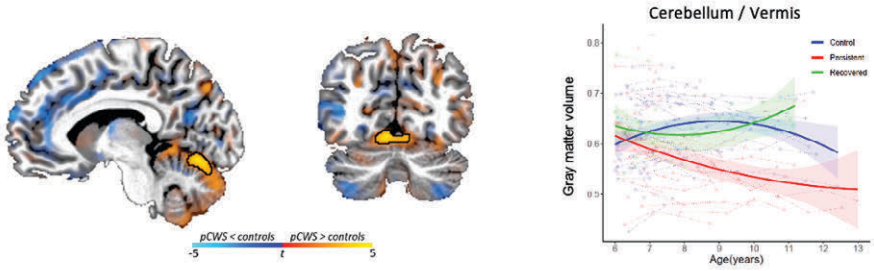
*Note for Supp Fig 3 and 4:*
Each marker represents the modulated volume values averaged across voxels around the peak location in each scan. The values were adjusted for the effects of sex, IQ, intracranial volume and socioeconomic status. Longitudinal volume measures of a participant are connected using dotted lines. Solid lines represent the best-fit linear trend lines in each group and the shaded areas represent the standard errors of the trend lines.

Supplementary Figure 4. Between group differences in non-linear (quadratic age) effects.

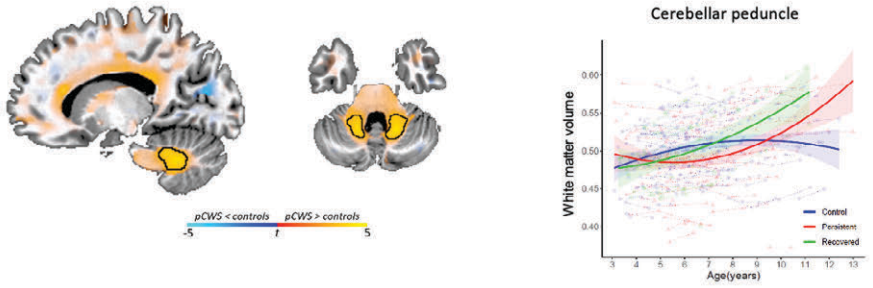
**A. Persistent vs. Controls quadratic age effects - 3-5 years old**



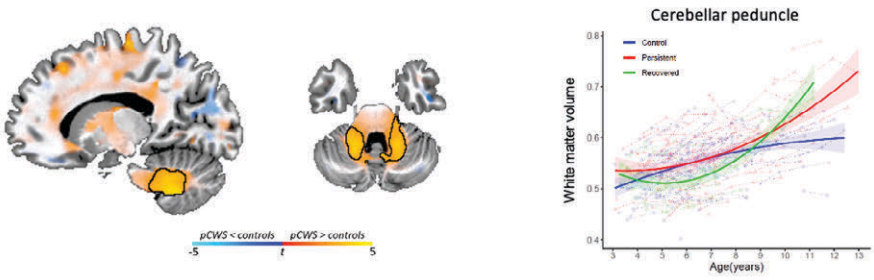

**B. Persistent vs. Controls quadratic age effects - 6-12 years old**




**C. Persistent vs. Controls quadratic age effects - 3-12 years old**




**D. Recovered vs. Controls quadratic age effects - 3-12 years old**



(A) Non-linear between-group white matter volume (WMV) differences between preschool-age children with persistent stuttering and controls. (B). Non-linear between-group gray matter volume (GMV) differences between school-age children with persistent stuttering and controls. (C) Non-linear between-group WMV differences between children with persistent stuttering and controls from 3 to 12 years old. (D) Non-linear between-group WMV differences between children who recovered from stuttering and controls from 3 to 12 years old.

In the brain images on the left panel, orange and blue indicate positive (inverted U-shape) and negative (U-shape) non-linear effects at uncorrected $p<0.05$, respectively. Clusters exhibiting a significant difference at corrected $p<0.05$ are outlined by black lines. In the scatter plots on the right panel, individual volume measures are plotted against age to illustrate the non-linear effect related to changes around the peak of a significant cluster in each group.

Supplementary Table 1. Average standardized test scores (standard deviations) and history of stuttering therapy

| | Controls | CWS (all) | Persistent | Recovered |
|---|---|---|---|---|
| GFTA | 102.65 (11.33) | 102.42 (11.92) | 101.93 (10.44) | 103.96 (15.58) |
| EVT (Cohort 1) | 116.81 (13.97) | 106.81 (12.29) | 105.91 (11.73) [b] | 108.80 (13.23) |
| PPVT (Cohort 1) | 118.30 (13.01) | 109.19 (13.55) | 108.18 (12.64) [b] | 111.40 (15.14) |
| CELF-5 (Cohort 2) | 107.98 (12.42) | 108.38 (12.68) | 108.26 (12.81) | 109.00 (11.97) |
| VIQ | 113.21 (14.32) | 108.40 (13.62) [a] | 108.00 (13.31) | 109.65 (14.50) |
| PIQ | 107.86 (15.25) | 105.55 (15.15) | 105.24 (15.02) [b] | 106.52 (15.49) |
| Full IQ | 110.95 (13.09) | 107.05 (13.99) [a] | 106.51 (13.56) [b] | 108.74 (15.13) |
| Stuttering therapy [c] | 0 | 31 (33%) | 27 (37.5%) | 4 (17.4%) |

a = significantly lower in CWS vs control
b = significantly lower in persistent vs. control
c = # children who received intervention for stuttering at any time during or prior to study enrollment
VIQ = Verbal Intelligence Quotient
PIQ = Performance Intelligence Quotient
Full IQ = Full-scale Intelligence Quotient.

GFTA = Goldman Fristoe Test of Articulation: R. Goldman, M. Fristoe Goldman–Fristoe Test of articulation-2 (2nd ed.), American Guidance Services, Inc., Circle Pines, MN (2000).
EVT = Expressive Vocabulary Test: Williams, K. T., & Williams, K. T. (2007). EVT-2: Expressive vocabulary test. Pearson Assessments.
PPVT: Peabody Picture Vocabulary Test: Dunn, L. M., & Dunn, L. M. (1997). Examiner's manual for the PPVT-III: Peabody Picture Vocabulary Test Third Edition. Circle Pines, MN: American Guidance Service.
CELF-5 = Clinical Evaluation of Language Fundamentals: Wiig, E. H., Semel, E., Secord, W. A. (2013). Clinical Evaluation of Language Fundamentals–Fifth Edition (CELF-5). Bloomington, MN: NCS Pearson.

Supplementary Table 2. Number of participants in each group with 1-4 scans entered into analysis.

| | # Controls | # Persistent | # Recovered |
|---|---|---|---|
| One scan | 27 (28%) | 21 (29%) | 3 (13%) |
| Two scans | 23 (24%) | 17 (24%) | 6 (26%) |
| Three scans | 23 (24%) | 15 (21%) | 7 (30%) |
| Four scans | 22 (23%) | 19 (26%) | 7 (30%) |

Supplementary Table 3. Significant clusters identified in VBM analyses

| Cluster | Side | Peak x , y , z | *t* | # voxels |
|---|---|---|---|---|
| ***pCWS vs controls, 3-5 year old (Fig. 1)*** | | | | |
| Putamen | R | 16.5 , 9 , -1.5 | -4.22 | 1131 |
| Putamen | L | -22.5, 0 , -6 | -4.59 | 1125 |
| SLF/CR | L | -34.5 , -34.5 , 36 | -4.07 | 581 |
| Internal capsule | R | 25.5 , -1.5 , 15 | -4.15 | 392 |
| SLF/CR | R | 37.5 , -13.5 , 34.5 | -3.74 | 376 |
| ***Age by group (pCWS vs controls) interactions, 3-5 years old (Fig. 2)*** | | | | |
| Corpus collosum (genu and midbody) | L | -13.5 , 1.5 , 27 | -4.36 | 1988 |
| ILF | L | -57 , -16.5 , -18 | -4.20 | 724 |
| Corpus collosum (genu) | R | 12 , 24 , -4.5 | -3.39 | 518 |
| SLF/CR | R | 33 , 6 , 22.5 | -3.82 | 478 |
| ***pCWS vs controls, 6-12 year old (Fig. 3)*** | | | | |
| Thalamus | L/R | -3 , -18 , 1.5 | -3.86 | 938 |
| ***Age by group (pCWS vs controls) interactions, 6-12 years old (Fig. 4)*** | | | | |
| Calcarine gyrus | L | -21 , -64.5 , 10.5 | -5.46 | 1079 |
| Precuneus | L/R | 1.5 , -48 , 46.5 | 3.96 | 739 |
| Calcarine gyrus | R | 15 , -97.5 , -3 | -5.26 | 561 |
| Inferior frontal gyrus / insular | L | -55.5 , 22.5 , 10.5 | -3.98 | 548 |
| Corpus collosum (midbody and isthmus) | L | -10.5 , -19.5 , 27 | 4.81 | 921 |
| Cerebellar peduncle | R | 13.5 , -60 , -34.5 | 4.01 | 526 |
| ***pCWS vs controls*, 3-12 year old (Fig. 5A)** | | | | |
| Thalamus / nucleus accumbens | L/R | -4.5 , -19.5 , 1.5 | -4.10 | 1925 |
| Ventral premotor cortex | L | -48 , 1.5 , 27 | -2.95 | 461 |
| ***Age by group (pCWS vs controls) interactions, 3-12 years old (Fig. 5B)*** | | | | |
| Precuneus | L/R | 1.5 , -48 , 45 | 4.42 | 1066 |
| Calcarine gyrus | L | -13.5 , -60 , 4.5 | -4.54 | 966 |
| Hippocampus | L | -33 , -27 , -12 | -5.25 | 617 |
| Cingulate cortex | R | 9 , -17 , 43 | -4.62 | 531 |
| Vermis | L/R | 0 , -73.5 , -15 | -4.54 | 509 |

| Cluster | Side | Peak x , y , z | *t* | # voxels |
|---|---|---|---|---|
| ***Association between SSI and gray/white matter volume in pCWS, 3-5 years old (Fig. 6A)*** | | | | |
| Corpus collosum / Corona radiata / Superior longitudinal fasciculus | L/R | 15 , -4.5 , 28.5 | -5.75 | 5817 |
| Corpus collosum / Corona radiata / Superior longitudinal fasciculus | R | 21 , -28.5 , 36 | -4.79 | 2347 |
| Arcuate fasciculus in temporal lobe | R | 36 , -36 , -2 | -5.92 | 628 |
| ***Association between SSI and gray/white matter volume in pCWS, 6-12 years old (Fig. 6B)*** | | | | |
| Putamen / nucleus accumbens | L/R | 6 , 3 , -1.5 | -4.35 | 1014 |
| Cerebellum (lobule VI) | R | 28.5 , -69 , -25.5 | -5.03 | 626 |
| ***rCWS vs controls, 3-12 year old*** | | | | |
| No significant difference was found | | | | |
| ***Age by group (rCWS vs controls) interactions, 3-12 years old (Fig. 7)*** | | | | |
| Inferior frontal gyrus / insular | L | -27 , 28.5 , 1.5 | -5.26 | 766 |
| Corpus collosum / Corona radiata / Superior longitudinal fasciculus | R | 31.5 , -24 , 42 | 5.01 | 2000 |
| Corona radiata / Superior longitudinal fasciculus | L | -28.5 , 1.5 , 27 | 5.29 | 1376 |
| Cerebellar peduncle | R | 21 , 49.5 , -37.5 | 4.29 | 900 |
| Cerebellar peduncle | L | -21 , -43.5 , -42 | 3.89 | 801 |
| ***rCWS vs controls, 3-12 year old*** | | | | |
| Corona radiata / Superior longitudinal fasciculus | R | 19.5 , 6 , 22.5 | -3.50 | 749 |
| Corona radiata / Superior longitudinal fasciculus | L | -33 , 16.5 , 22.5 | -4.97 | 706 |
| ***Age by group (pCWS vs rCWS) interactions, 3-12 years old*** | | | | |
| Cerebellum (lobule VI) | R | 21 , -57 , -22.5 | -4.60 | 932 |
| Cerebellum (lobule VI) | L | -13 , -65 , -20 | -4.35 | 674 |
| Corona radiata / Superior longitudinal fasciculus | L | -28.5 , 1.5 , 27 | -6.61 | 3381 |
| Corpus collosum / Corona radiata / Superior longitudinal fasciculus | R | 13.5 , -25.5 , 36 | -5.35 | 1556 |

*“Grote dingen gebeuren niet alleen door een impuls,*
*maar als een opeenvolging van kleine dingen die met elkaar verbonden zijn.”*
Vincent van Gogh

# GENERAL DISCUSSION AND SUMMARY


White matter
Persistent
Fluency
Speech
Research
Recov
Brain
Subcort
Satisfaction
Gray matter
Neuroimaging
Self-report
Explore
Cortical
Girls
Children
Stutter
Population
Temperament
Dysfluency
Fluency
Neuroplasticity
Boys
Outcome
Speech
Satisfaction
Brain
Behavior
Treat
Long-term
Development
Subcortical
Girls
Rotterdam
Self-report
Persistent
Stutter
Cortical
Boys
Population
Speech-motor


# 9

General discussion
and future perspectives

## 1. A multi-prospective approach

In the context of childhood stuttering research, this thesis aimed to deepen our understanding of its onset and developmental course, moving from clinical practice to population-based research and vice versa. Specifically, to examine which factors contribute to recovery or persistence to inform appropriate treatment. Stuttering is a multifaceted and dynamic phenomenon that typically emerges during a crucial phase in early development (age 2-4 years), when children begin and refine their spoken language, behavior, and social communication skills. Despite longstanding research efforts all over the world, whether investigated and explored by researchers, speech-language pathologists (SLPs), people who stutter, and others seeking answers through clinical or personal reflection, its etiology and developmental pathways remain only partially understood (Walsh et al., 2018). Rather than focusing on a single domain of influence or adhering to a theoretical model about moments of stuttering (Namasivayam & van Lieshout, 2011; Packman, 2012), this thesis examined multiple factors that may contribute to the onset and developmental course of childhood stuttering (**Chapter 4**-**7**). None of these factors offers a definitive cause on its own; rather, each represents a component within the broader framework of understanding developmental stuttering. While these factors were not studied in direct interaction, the overall combined findings suggest that no single factor alone accounts for the onset, recovery or persistence. Instead, the pattern of results supports the idea that stuttering is shaped by the accumulation or combined effects of characteristics (e.g. vulnerabilities, rapid maturation, or overactivity) across systems. This interpretation aligns with multifactorial and developmental models, such as the Multifactorial Dynamic Pathways (MDP) model by Smith and Weber (2017), which propose that stuttering arises from the non-linear interaction of multiple influences over time. It also aligns with recent theoretical integrations of multifactorial models of stuttering that emphasize developmental complexity and interdependence between domains (Franken, Oonk, Bast, Bouwen, & De Nil, 2024).

## 2. Understanding recovery and persistency

A central insight emerging from this thesis is that stuttering is variable in its manifestation and perception. We found that some children recover entirely, some may no longer be identified as stuttering but appear to rely on coping strategies to manage fluency, others continue to stutter intermittently or only in specific context, and others persist

in stuttering (**Chapter 2-3**). Despite this variability, current studies often conceptualize children who stutter as a bimodal heterogeneous group, typically classified in dichotomous terms, either stuttering or not. As a result, they overlook the variability within the population, including borderline and intermittent cases (SheikhBahaei, Millwater, & Maguire, 2023). By including patient-reported outcome measures (PROMs), specifically children's self-reports, which were introduced in the field by us (**Chapter 2)** and more recently applied by Einarsdottir, Hermannsdottir, and Crowe (2024), this thesis offers a more nuanced understanding of recovery. This approach highlights the importance of the child's subjective experience, in addition to the perspectives of parents and SLPs, in clinical evaluation. Thus, this thesis supports the view that stuttering is a multimodal heterogeneous developmental condition with multiple possible outcomes and varying impacts on quality of life.

# 3. Interpretation of main findings

## Part I. Clinical perspectives on recovery and treatment

In the two clinical population studies (**Chapter 2 and 3**) with follow-up periods ranging from 5 to 9 years, recovery rates were substantially higher when assessed by 'traditional observers' (i.e. parents, experts and teachers (74-82%)) than when assessed solely by 'additional observers' (i.e. children's self-reports (60-72%)). These differences suggest that other observers and children define recovery differently. Some children who appear recovered to adults may still experience subtle fluency difficulties or an emotional burden related to speaking. Children may also use compensatory strategies that are not observable to others (chapter 2). Instruments such as Overall Assessment of the Speaker's Experience of Stuttering (OASES) and Satisfaction with Communication in Everyday Speaking Situations (SCESS) capture this internal experience, adding valuable insight into the development of stuttering (Karimi et al., 2018). These findings align with broader shifts in stuttering research moving from a 'medical model', which treats stuttering as a disorder to be cured, toward a 'social model' that frames stuttering as a neurodiversity condition situated along a continuum of communicative experiences (Constantino, Campbell, & Simpson, 2022). Within this framework, fluency is not simply the absence of dysfluencies but also includes how speaking is experienced and managed in everyday life. This reconceptualization has implications for terminology, as well as for clinical practice and research. Rather than using binary labels such as 'recovered from stuttering', terms such as 'remitted', 'transient', and 'resolved' may better reflect the dynamic and individualized

nature of recovery, while also underscoring that stuttering is not a disorder in need of a cure. Recognizing stuttering as a spectrum disorder acknowledges its inherent variability and supports a more nuanced understanding of its diverse underlying mechanisms (SheikhBahaei et al., 2023).

In addition to these insights on recovery, **Chapter 3** compared the long-term effects of two early treatment approaches: the Lidcombe Program (LP) and the Demands and Capacities model (DCM) based treatment. After five years, no significant differences in longitudinal fluency outcomes were found, indicating that both treatments appeared equally effective. These findings suggest that individual responsiveness and contextual factors may be more important than the specific method itself. For instance, LP focuses on modifying speech behavior directly, while DCM aims to achieve an optimum balance between environmental demands and the child's capacities for fluent speech. A child's behavioral profile, such as high emotional reactivity and poor self-regulation (**Chapter 5**), may interact differently with each approach. According to the findings of Berani, Franken, and Stipdonk (2025), children with reduced self-regulation and attention control tend to benefit more from the LP approach. Its structured, operant framework, in which parents provide consistent feedback on fluent and dysfluent speech, offers external support that potentially compensates for limited regulatory skills. By contrast, the indirect, communicative adjustment of Restart-DCM provides less immediate structure, which may limit its effectiveness for these children. These findings highlight the importance of shared decision-making between SLPs and parents, and the need to match treatment to the individual child and environment.

## Part II. Language, behavior and temperament in a population-based context

The Generation R Study allowed for a comprehensive analysis of risk factors in a general population. Regarding early development factors, this thesis demonstrates that expressive and receptive language skills at age 2 are significantly associated with an increased risk of stuttering onset (**Chapter 4**). This suggests a potential sensitive period in which immature neural systems for speech motor planning may be particularly vulnerable. However, this association does not imply causality; it demonstrates a relationship. At the same time, early temperamental traits reflecting heightened reactivity and limited self-regulation in infants at age of 6 months (**Chapter 5**) were associated with persistent stuttering. This suggests that children with limited self-regulation may have fewer internal resources to develop fluent speech over time. As a result, their vulnerability may increase due to a

reduced ability to manage communicative demands. Interestingly, similar associations were not observed at other ages in this longitudinal study or in the existing literature, with the exception of Ambrose, Yairi, Loucks, Seery, and Throneburg (2015). This may be due to rapid neurodevelopmental changes and the emergence of compensatory mechanisms (Johnson, Onslow, Horton, & Kefalianos, 2023; Singer, Hessling, Kelly, Singer, & Jones, 2020; Sugathan & Maruthy, 2021). From the perspective in this thesis, early onset stuttering may reflect a temporary mismatch between rapid language growth (e.g., motor skill maturation), emotional reactivity and self-regulation capacities.

With regard to late development factors, childhood stuttering may contribute to or exacerbate psychosocial difficulties in children, adolescents, and adults (Messenger, Packman, Onslow, Menzies, & O'Brian, 2015; Smith, Iverach, O'Brian, Kefalianos, & Reilly, 2014). In line with these findings, we observed that stuttering in middle childhood (aged 6-9 years) was associated with increased emotional reactivity, as indicated by higher levels of negative affectivity, internalizing behaviors, and emotional reactivity. These traits may signal a reduced ability to regulate negative emotions (**Chapter 5**). This points to a possible bidirectional cycle in which temperament contribute to persistent fluency problems, which in turn later reinforce emotional difficulties.



Together, these outcomes support the Multifactor Dynamic Pathways model, which conceptualizes stuttering as the result of interacting developmental domains (Smith & Weber, 2017). Risk for onset may be shaped by early vulnerabilities across systems, while persistence may result from these systems' failure to resolve or adapt over time. These findings underscore the importance of monitoring the combined development of language, behavioral characteristics, and emotional traits in young children on a general longitudinal scale.

## Part III. The brain underlying childhood stuttering

The above findings suggest that developmental factors associated with stuttering should not be considered as isolated phenomena. Rather, they are best understood as expressions of underlying neural processes. Given that speaking is organized and regulated by the brain, it is plausible that stuttering, particularly when it persists at a moderate to severe level, contributes to atypical patterns of neurobiological development. Neuroimaging findings from two cohorts provide further support for this view, which occurs during a critical period of brain maturation when children begin to speak. Young children aged

6-9 years who stutter exhibited reduced gray matter volume in speech-related brain regions, such as the left inferior frontal gyrus and supplementary motor area (**Chapter 6**). Children who persisted in stuttering, aged 8-12 years, showed structural differences that extended to white matter tracts (**Chapter 7**). This supports the idea that stuttering may be associated with both early developmental deviations and later maladaptive plasticity. A critical question that remains is whether these neuroanatomical differences serve primarily as underlying factors in the development of stuttering, potentially rooted in genetic predisposition, or whether they develop as a consequence of prolonged stuttering experience (Neef & Chang, 2024). Recent research has increasingly focused on longitudinal studies to better understand the development of childhood stuttering (Chang, Garnett, Etchell, & Chow, 2019; Chow & Chang, 2017). The longitudinal imaging study (**Chapter 8**) further revealed that white structural tracts were associated with both persistent and recovered children at young ages. The observation that both children who persisted in stuttering and those who recovered showed structural abnormalities in early childhood suggests that these differences may be associated with the onset of stuttering. Recovery was associated with signs of normalization or compensation in brain structures over time, as deficits in the basal ganglia-thalamocortical (BGTC) network (Chang & Guenther, 2019). These findings support the idea that neuroplasticity may underlie spontaneous or treatment-facilitated recovery.

# 4. Methodological considerations

Though each study in this thesis applies a different methodological approach, they are unified by a developmental perspective. This thesis illustrates how these domains interact and influence developmental stuttering in diverse ways.

## 4.1 Selection of participants in this thesis

The clinical studies in this thesis include children whose parents initially sought the assistance of a SLP due to concerns about stuttering. This likely results in a sample with more persistent cases or severe symptoms, because parents tend to seek help when they feel the impact is high. Consequently, recovery may occur later and less frequently in clinical samples than in population-based ones. By contrast, population-based cohorts include children regardless of whether care was sought, and typically lack information on whether treatment was received and, if so, its type and duration. These cohorts capture a broad range of severity, including mild cases that were never referred to a clinic. While

this may lower the mean severity, it improves generalizability and offers insight into developmental stuttering. However, population-based studies are also vulnerable to bias. Selection bias may occur when the associations between developmental factors and outcomes differ between included and non-included participants. In the Generation R Study, for example, only 61% of eligible children participated, with underrepresentation of families with lower socio-economic status and non-European backgrounds (Kooijman et al., 2016). This could potentially skew the results toward lower-risk profiles (Jaddoe et al., 2006). Information bias may also occur due to reliance on parental questionnaires, which are vulnerable to recall bias by parents' levels of concern, awareness, or expectations.

## Part I. Considerations in clinical treatment studies

A key methodological issue in clinical stuttering research is the variability introduced by the timing and selection of treatment approaches and the duration of follow-up. These factors can influence outcomes and comparability between clinical studies. In the Netherlands, young children were commonly treated with the Restart-DCM approach (Franken, Laroes, van Ormondt, de Smit, & Stipdonk, 2025). The findings of this thesis, in line with earlier research, indicate that both treatment groups have comparable long-term fluency outcomes, suggesting that LP is a suitable alternative (de Sonneville-Koedoot, Stolk, Rietveld, & Franken, 2015). However, challenges arise when comparing these approaches across clinical studies because (dys)fluency is assessed using different measures, ranging from parental reports only, to combinations that include SLP evaluations, teacher input, and children's self-reports.



A further methodological consideration involves the use of untreated control groups. In theory, these groups could provide valuable insights into the natural course of early childhood stuttering and strengthen the interpretation of treatment effects. However, withholding potentially beneficial interventions from children raises ethical concerns. For this reason, although the inclusion of an untreated control group was considered, it was ultimately considered unsuitable.

## Part II and III. Interpretation of association and limitations of causal inference

In part II and III, we examined associations within an observational study design. Much of the data were cross-sectional, capturing measurements at a single point in time. This

limits our ability to draw causal or directional inferences. While the findings highlight associations between stuttering onset or persistence and language, behavior, or brain morphometry, they do not clarify whether these factors precede or result from stuttering. Still, these indicators may help identify children at risk of persistent stuttering. Some associations are supported by plausible underlying mechanisms, while others remain unclear. Establishing causality would require longitudinal or experimental designs. Only the longitudinal experimental design used in the University of Michigan's neuroimaging study (**Chapter 8**) enabled the tracking of developmental trajectories across different fluency groups: persistent, recovered, and control (Chow & Chang, 2017). However, because the design conducted after the onset of stuttering, it does not allow for conclusions regarding the origins of stuttering.

## Part III. Repeated measures in neuroimaging

The University of Michigan's neuroimaging study described in this thesis is the first in the literature to adopt a longitudinal design with repeated structural MRI scans of young children who stutter (**Chapter 8**). This design enables tracking neural maturation over time in specific regions, providing more reliable insight into developmental timing than exploratory cross-sectional approaches (**Chapter 6-7**). Longitudinal data are particularly valuable for identifying when neural differences emerge and whether compensatory changes occur during critical periods of speech and language development.

However, interpreting brain measures and their changes in early childhood presents specific methodological challenges (White et al., 2018). Brain development estimates depend strongly on structural metrics used (such as cortical volume, thickness, or surface area), which follow distinct developmental trajectories and are derived from different analytical methods. Because these metrics change differently across early childhood and show complex, region-specific relationships, each must be selected and interpreted with care (Tamnes et al., 2017). For instance, cortical gray matter volume follows a non-linear developmental trajectory in childhood, increasing in early childhood and decreasing as the brain matures and becomes more efficiently organized in young adolescence (Lenroot & Giedd, 2006; Sowell et al., 2004). Similarly, during childhood, white matter undergoes progressive maturation characterized by increasing myelination and structural organization, which enhances the efficiency of neural transmission. This developmental trajectory is particularly relevant for networks supporting speech motor control (Misaghi, Zhang, Gracco, De Nil, & Beal, 2018), and evidence suggests that both cortical gray matter

and the underlying white matter pathways may show atypical trajectories in persons with persistent stuttering (Beal, Gracco, Brettschneider, Kroll, & De Nil, 2013; Beal et al., 2015; Theys et al., 2024). When studying white matter in children, it is important to consider the indirect nature of diffusion measures, such as fractional anisotropy (FA) and mean diffusivity (MD), as well as age-related variability, in order to obtain reliable and interpretable results (Goddings, Roalf, Lebel, & Tamnes, 2021). Given that both brain development and speech fluency development occur simultaneously, differentiating normal maturation from stuttering-related changes is complex. This highlights the need for age-specific brain analyses and replication across independent samples (Corrigan et al., 2021). Moreover, it is unclear whether the observed brain differences reflect mechanisms specific to stuttering, or to more general neurodevelopmental characteristics, such as in language skills, speech motor coordination, emotional regulation, and behavior, that contribute to its manifestation. Clarifying this distinction is essential for the true representation of neuroanatomical findings in the context of childhood stuttering.

Finally, longitudinal neuroimaging studies in young children present practical challenges. Small sample sizes, variability in scan settings, long follow-up periods, and high costs reduce statistical power and complicate replication, particularly when effect sizes are modest (Button et al., 2013). Despite these limitations, longitudinal imaging, starting before the typical onset of stuttering, remains a critical method for advancing our understanding of the dynamic neural processes associated with stuttering.



## 5. Clinical implications

Based on the findings of this thesis, it is advisable to start stuttering treatment as early as possible in childhood, rather than waiting for spontaneous recovery during the first year. In the long term, both LP and DCM-based interventions are equally effective. However, there is no universal approach that fits all cases, and the variability in children's profiles underscores the need for a personalized approach. Screening for and taking into account risk factors can help guide clinical decision-making. Recently, a clinical practice model has become more widely applied as research has revealed that neurobiological factors and genetics play a primary role (Franken et al., 2024). Using such a model, SLPs can more easily discuss the onset and development of stuttering with the child and their parents, and together determine the initial focus of treatment (Bast et al., 2022; De Nil, 2012; Oonk et al., 2022).

Beyond early intervention, it is important to assess speech fluency from multiple perspectives, including the child's self-report. Evaluations should occur at multiple time points before and during treatment, and at follow-up. Rather than relying on binary questions, such as whether the individual has recovered or persisted in stuttering, it is recommended to use rating scales that assess fluency along a continuum. Tools such as SCESS and OASES can aid in monitoring progress and modifying support. The focus should be on minimizing the impact of stuttering on the child's communication and well-being. While fluency techniques can be helpful for older children, (pre-)adolescents, and adults, meaningful outcomes are defined by confidence, participation, and satisfaction with communication.

# 6. Directions for future research

The inclusion of self-reported experiences (i.e. PROMs) in future research on childhood stuttering may increase the validity of speech fluency assessments by providing a more complete understanding of recovery and persistency from the child's perspective. Further studies should validate different tools (e.g. OASES, SCESS) using larger samples to ensure the reliability and validity of the current findings.

## 6.1 Further clinical studies

The RESTART study includes valuable additional longitudinal data that allow for the analysis of language profiles, behavioral characteristics, and temperament as potential risk factors for persistent stuttering. Building on both these data and the findings presented in this thesis, it would be of particular interest to examine whether children who stutter and present with a high-risk language or behavior profile benefit more from LP or DCM-based treatment. While this thesis has made first explorations (e.g. age and sex), future treatment-effect studies could more systematically examine which child and family characteristics (such as parent-child interaction, child behavior, and parent temperament) predict better outcomes with each approach, in order to better match treatment to the individual child. Another direction would be to examine long-term effects of early stuttering intervention on broader developmental domains, such as socio-emotional functioning, quality of life, and aspects of family functioning. This would provide insight into secondary outcomes that are highly relevant across the child's life course.

## 6.2 Further population-based studies

To better understand the onset and development of stuttering, longitudinal population-based research starting at infant age is needed. This should investigate how stuttering relates to language development, behavior, and brain, and how these domains together may influence the onset, persistence, or recovery from stuttering. A multilayered data integration approach, investigating demographic, socioenvironmental, (epi)genetic, and genetic factors from preconception onwards, may help identify childhood stuttering risk factors.

This thesis points to an unknown factor, potentially genetic, that may help explain the unresolved variability in developmental stuttering. While not the focus of this thesis, large population-based genetic analyses are necessary to identify genes contributing to stuttering (Eising et al., 2025; Eising et al., 2024; Kazemi, Estiar, Fazilaty, & Sakhinia, 2018; Martin et al., 2018). Regarding stuttering genetics, future research should address sex-specific features, family-based patterns, and demographic influences across the lifespan. Future directions include identifying genetic variants associated with stuttering and linking them to neurobiological mechanism underlying speech motor control as well as recovery and persistence (Chang et al., 2025; Neef & Chang, 2024). Bridging genetic insights with neuroimaging and behavioral data will be important for clarifying how multiple risk factors contribute to developmental stuttering. As demonstrated in adjacent fields (i.e. ADHD, autism), meaningful progress in this area will require the formation of large-scale research consortia (Demontis et al., 2023; Warrier et al., 2022).



## 6.3 Further neuroimaging studies

In scientific research, replication across different speech fluency groups (including persistent, borderline, intermittent, recovered, and fluent speakers) is a crucial step in evaluating the robustness of results. Due to the potential impact of various neurobiological, cognitive and environmental factors on the abnormal development of gray and white matter in children who stutter, it is essential that these variables are considered in future analyses. To achieve this, large study populations are required to ensure statistical power and to capture the heterogeneity nature of the stuttering population. Future research should move beyond broad exploratory approaches and further build on targeted investigations of specific, well-characterized neural pathways that have consistently emerged across prior studies. Another direction would be to incorporate speech or singing tasks during

neuroimaging, similar to paradigms used in electroencephalography (EEG) research, to capture valid brain activity related to fluency (Liu et al., 2024). Additionally, there are emerging plans to explore neuromodulation as a treatment approach (Chang et al., 2025). Neuromodulation refers to the therapeutic modification of nervous system activity and its electrophysiological signals. It may offer a novel bridge between combined clinical and population-based research findings and exploratory clinical applications. This type of translational research could improve our understanding of both the mechanisms and the treatment of developmental stuttering.

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White matter
Persistent
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Speech
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Brain
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Satisfaction
Gray matter
Neuroimaging
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Explore
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Children
Stutter
Population
Temperament
Dysfluency
Fluency
Neuroplasticity
Boys
Outcome
Speech
Satisfaction
Brain
Behavior
Treat
Long-term
Development
Subcortical
Girls
Rotterdam
Self-report
Persistent
Stutter
Cortical
Boys
Population
Speech-motor


# 10

Summary

Samenvatting

## Summary

Developmental stuttering is affecting many children worldwide and persistency may negatively impact communication and social skills, as well as overall quality of life. Approximately 5-11% of preschool-age children are affected. Most of them recover within 2 to 3 years after onset, whereas approximately 20-35% of children have persistent stuttering. The exact etiology of stuttering and its developmental course is unclear, although there is a general consensus that multiple (risk)factors are involved, including genetic predisposition, linguistic, emotional, speech motor, and neuroanatomy. Therefore, a better definition of recovery and persistency in stuttering is needed, as well as the understanding whether underlying linguistic, behavior, and neuroanatomy components are associated with childhood stuttering. In this thesis, we investigated the origins of childhood stuttering, drawing on insights from clinical practice to enrich population-based research, and vice versa. We examined recovery rate and children's experiences of speaking, and explored how language, behavioral and neurobiological factors relate to the onset, persistence, and recovery of stuttering. Data were drawn from two clinical and two large prospective population-based cohorts.

**Part I** of this thesis focused on recovery rate in childhood stuttering and on children's subjective experiences with speaking using two clinical population samples.

In **Chapter 2**, we explored children's recovery rate and the Overall Assessment of Speaker's Experience of Stuttering (OASES) 9 years after their first visit to a Speech-Language Pathologist (SLP). Following parental and expert judgements (i.e. traditional criteria) the recovery rate is 73% and is comparable to those previously reported in non-clinical population-based populations. We applied an alternative approach to investigate children's self-report (i.e. extended criteria). Looking into these children's self-reports, the recovery rate in this clinical population decreased to 63%. This suggests that parents and children define recovery differently, and that earlier research may have overestimated the occurrence of recovery. The experience with (dys)fluency of speech suggest that recovery in children may not be effortless. Rather, it may result from conscious or unconscious coping mechanisms, which others may not necessarily notice. Therefore, the analysis of self-reports (Patient-Reported Outcome Measures, PROMs) is essential for a clear understanding of recovery and for gaining insight into individuals' speaking experiences.

In **Chapter 3**, we examined long-term outcomes, including those 5 or more years post-treatment, of preschool-age children who participate in the RESTART randomized trial (the Rotterdam Evaluation study of Stuttering Therapy in preschool-age children: A Randomized Trial). This trial compared two early stuttering interventions: the Lidcombe Program (LP) and the Demands and Capacities Model (DCM). The longitudinal parental speech fluency evaluation revealed no differences between both treatments. Both treatments were similarly effective in reducing stuttering among children at risk for persistent stuttering. Younger age at treatment onset and female sex significantly predicted recovery; family history did not. Self-reported recovery (72%) was slightly lower than ratings by parents (74%), SLPs (75%), and teachers (82%). Children who stutter reported more positive Satisfaction of Communication with Everyday Speaking Situations (SCESS) (82%) scores than their parents did (79%).

**Part II** of this thesis focused on the association between early and late (risk)factors and childhood stuttering. These studies were performed in the Generation R Study, a multi-ethnic population-based prospective cohort from fetal life onward.

In **Chapter 4**, improved insight in early language skills in children associated with childhood stuttering. Lower expressive and receptive language skills at 24 months were significantly associated with stuttering incidence. However, language assessments at other timepoints did not reveal any significant association with stuttering. This findings does not imply a causal relationship, it demonstrates that early language skills may add to the risk of childhood stuttering, but not with the persistence of stuttering. Therefore, clinicians are advised to screen language skills in preschool-age children referred shortly after stuttering onset.



**Chapter 5** investigated a bidirectional relationship between behavior and temperament, and childhood stuttering. Behavior difficulties and temperamental traits were associated with stuttering persistency, seemly both as predictor and consequence, but did not predict stuttering at a very young age. Such as (1) poorer recovery from distress because of higher reactivity and poorer self-regulation at 6 months was associated with stuttering persistence. (2) Children with a history of stuttering showed more negative affectivity at 6 years of age, than those without a history of stuttering. Also, (3) persistent stuttering was associated with higher emotional reactivity and increasing internalizing behaviors at the age of 9 years. Therefore, screening for behavior difficulties and temperament in preschool-age children who stutter is highly recommended, as well as providing treatment and follow-up.

**Part III** of this thesis explored the neurobiological mechanism of stuttering in children and pre-adolescents in a population-based sample. A neuroimaging subset study of the Generation R study included structural MRI scans, to examine structural morphometry. The Speech Neurophysiology Laboratory at the University of Michigan included longitudinal structural MRI scans, among other methods, to examine developmental gray and white matter volumes.

**Chapter 6** included a sample of young children aged 6 to 9 years, with or without a history of stuttering. Children with a history of stuttering had less gray matter volume in the left inferior frontal gyrus and supplementary motor area compared to fluent speakers. Exploratory surface-based brain analysis showed thinner cortex in the left inferior frontal gyrus, and in bilateral frontal and parietal areas. This may imply that children with persistent stuttering may have a delay in growth in these frontal regions, while those who (spontaneously) recover could undergo a form of catch up growth compared to those who persist. These brain regions play an important role in speech motor control, and appear indispensable for achieving fluent speech.

**Chapter 7** expanded on this, using a sample of pre-adolescents aged 8 to 12 years to study persistent versus recovered stuttering. Relatively small differences in size of effect in the left prefrontal gray matter are associated with persistent stuttering, and alterations in white matter tracts are apparent in those who recovered. Our findings provide evidence for structural differences in speech-relevant brain areas of pre-adolescents with persistent and recovered stuttering from a population-based study.

**Chapter 8** utilized a longitudinal neuroimaging study in preschool-age (3 to 5 years) and school-age (8 to 12 years) children, who either recovered from or persisted in stuttering, compared to fluent peers. Both gray and white matter volume and trajectories were assessed. Both those who persisted and recovered from stuttering exhibited reduced gray and white matter volume in regions associated with the basal ganglia-thalamocortical (BGTC) network during the preschool-age years, compared to fluent peers. As the children aged, those who recovered demonstrated normalization in these brain volumes. Whereas those who persisted continued to show reduced volumes in these critical areas. These results suggest that early anomalies in the BGTC network may contribute to stuttering, and that recovery is associated with neurodevelopmental changes and neuroplasticity, which lead to the compensation of these structures.

Finally, in **Chapter 9**, a general discussion of all studies included in this thesis is provided. We discussed the main findings of these studies in the context of the literature. We also discussed methodological considerations, as well as implications of these studies for clinical practice and further research directions of the study of childhood stuttering.

# Samenvatting

De meest voorkomende vorm van stotteren ontstaat op jonge leeftijd tijdens de vroege ontwikkeling. Circa 5–11% van de kinderen op peuter- en kleuterleeftijd stottert. De meeste kinderen herstellen binnen 2 tot 3 jaar na het ontstaan van stotteren, terwijl ongeveer 20–35% blijven stotteren (persisteren in stotteren). Het persisteren in stotteren kan een negatieve invloed hebben op communicatie en sociale vaardigheden. De exacte etiologie (oorsprong) en de ontwikkeling van stotteren zijn nog onduidelijk, hoewel er brede consensus bestaat dat meerdere factoren een rol spelen, waaronder genetische predispositie, linguïstische-, emotionele, spraakmotorische en neuro-anatomische factoren. Een beter begrip van deze onderliggende componenten is van belang. Tevens is het belangrijk om beter te begrijpen waarom sommige kinderen herstellen van stotteren en anderen persisteren in stotteren. In dit proefschrift werd het ontstaan van stotteren bij kinderen onderzocht, waarbij inzichten uit de klinische praktijk werden gebruikt om populatieonderzoek te verrijken en omgekeerd. Herstelpercentages en de ervaringen van kinderen met vloeiend en niet-vloeiend spreken werden onderzocht. Tevens werd geanalyseerd of taal, gedrag en neuro-anatomische factoren een associatie hebben met het ontstaan, het herstel en het persisteren in stotteren. De data van deze onderzoeken zijn afkomstig uit twee klinische en twee grootschalige prospectieve populatiecohorten.

**Deel I** van dit proefschrift richt zich op de herstelpercentages van stotteren en de subjectieve spreekervaringen van kinderen, onderzocht in twee klinische populaties.

In **Hoofdstuk 2** onderzochten wij het herstelpercentage en de Overall Assessment of Speaker's Experience of Stuttering (OASES) 9 jaar na het eerste bezoek aan een stottertherapeut. Volgens ouder- en expertbeoordelingen (traditionele criteria) was het herstelpercentage 73%, vergelijkbaar met eerdere studies in niet-klinische populatiecohorten. Bij gebruik van zelfrapportages van kinderen (uitgebreide criteria) daalde het herstelpercentage naar 63%. Dit suggereert dat ouders en kinderen een andere definitie van herstel van stotteren hebben en dat het herstel van kinderen in de literatuur mogelijk wordt overschat. De ervaringen van kinderen met vloeiend en niet-vloeiend spreken, wijzen erop dat herstel en spreken vaak niet vanzelf gaat. Dit spreken kan het resultaat zijn van zowel bewuste als onbewuste coping mechanismen, die anderen niet altijd opmerken. Het analyseren van zelfrapportages (Patient-Reported Outcome Measures, PROMs) is daarom essentieel voor een heldere betekenis van herstel en voor het beter begrijpen van individuele spreekervaringen.

In **Hoofdstuk 3** onderzochten wij de lange termijn uitkomsten (5 jaar en langer na de behandeling van stotteren) van kleuters die deelnamen aan de RESTART-randomized trial (the Rotterdam Evaluation study of Stuttering Therapy in preschool-age children: A Randomized Trial), waarin twee vroege stotterinterventies werden vergeleken: het Lidcombe Program (LP) en het Demands and Capacities Model (DCM). De longitudinale ouderbeoordeling van spraak(on)vloeiendheid liet geen verschil zien tussen de behandelingen. Beide interventies waren even effectief in het reduceren van stotteren bij kinderen met risico op het peristeren van stotteren. Jonge leeftijd bij aanvang van behandeling en vrouwelijk geslacht bleken significante voorspellers van herstel; familiegeschiedenis niet. Het zelfgerapporteerd herstel (72%) lag iets lager dan de beoordelingen van ouders (74%), logopedisten (75%) en leerkrachten (82%). Kinderen die stotterden rapporteerden bovendien hogere tevredenheidsscores (82% was tevreden) in de Satisfaction of Communication with Everyday Speaking Situations (SCESS) dan hun ouders (76% was tevreden).

**Deel II** van dit proefschrift richt zich op de samenhang tussen potentiële vroege en latere risicofactoren en stotteren bij kinderen. Deze studies werden uitgevoerd binnen de Generation R Study, een multi-etnisch, prospectief bevolkingscohort vanaf de prenatale fase.

In **Hoofdstuk 4** onderzochten wij de vroege taalvaardigheden van kinderen in relatie tot stotteren. Lagere expressieve en receptieve taalvaardigheden op de leeftijd van 24 maanden waren significant geassocieerd met het optreden van stotteren. Op andere meetmomenten werd echter geen significant verband gevonden. Hoewel dit geen causaal verband impliceert, kunnen beperkte taalvaardigheden bijdragen aan het risico op stotteren, maar niet aan het persisteren in stotteren. Daarom is aan te bevelen om de taalvaardigheden te screenen bij kinderen die stotteren kort nadat ze zijn verwezen naar een stottertherapeut.

**Hoofdstuk 5** onderzocht de bi-directionele relatie tussen gedrag, temperament en stotteren. Gedrags- en temperamentkenmerken bleken zowel voorspellers als gevolgen van persisterend stotteren, maar voorspelden niet het ontstaan ervan. Zo was een moeizaam herstel na stress op de leeftijd van 6 maanden (bijvoorbeeld door hoge reactiviteit en beperkte zelfregulatie) geassocieerd met persisterend stotteren. Daarnaast vertoonden kinderen die op 6-jarige leeftijd stotteren meer negatieve affectiviteit dan kinderen zonder stotteren. Ten slotte verhoogde persisterend stotteren het risico op meer

emotionele reactiviteit en internaliserend gedrag op 9-jarige leeftijd. Daarom is screening op gedragsproblemen en temperament bij kinderen die stotteren sterk aan te bevelen, evenals het bieden van behandeling en follow-up.

**Deel III** van dit proefschrift onderzocht de neuro-anatomische mechanismen van stotteren bij kinderen en jong-adolescenten in twee populatiecohorten.

In **Hoofdstuk 6** werden structurele MRI-scans van kinderen van 6 tot 9 jaar met en zonder stotteren onderzocht. Minder grijze-stofvolume in de linker inferieure frontale gyrus en de supplementaire motorische cortex werden significant meer gezien in kinderen die stotteren in vergelijking met kinderen die vloeiend spreken. Exploratieve analyses toonden een dunnere cortex in de linker inferieure frontale gyrus en bilateraal in frontale en pariëtale gebieden bij kinderen die stotteren. Deze hersengebieden spelen een belangrijke rol in spraakmotorische controle en zijn cruciaal voor vloeiende spraak.

In **Hoofdstuk 7** werden MRI-scans van pre-adolescenten van 8 tot 12 jaar met persisterend of hersteld stotteren geanalyseerd. Relatief laag grijze-stofvolume in de linker prefrontale cortex zijn geassocieerd met persisterend stotteren, terwijl veranderingen in witte-stofbanen zichtbaar zijn bij kinderen die herstelden. Dit zou kunnen impliceren dat kinderen met persisterend stotteren vertraging in de groei van deze frontale gebieden hebben, terwijl de kinderen die (spontaan) herstellen een vorm van inhaalgroei vertonen in vergelijking met kinderen die persisteren. Deze bevindingen ondersteunen de relatie met structurele verschillen in spraakrelevante hersengebieden bij pre-adolescenten met hersteld of persisterend stotteren.

In **Hoofdstuk 8** werden longitudinale MRI-scans geanalyseerd bij jonge kinderen van 3 tot 5 jaar en bij oudere kinderen van 8 tot 12 jaar, verdeeld en vergeleken in drie groepen: kinderen die herstelden van stotteren, kinderen die persisteerden in stotteren en kinderen die vloeiend spraken. Zowel kinderen die persisteerden als de kinderen die herstelden, hadden op de peuterleeftijd significant verminderde grijze- en witte-stofvolume in gebieden van het basale ganglia–thalamus–corticale (BGTC) netwerk. Naarmate de kinderen ouder werden, hadden de kinderen die herstelden gemiddelde hersenvolumes. Terwijl de kinderen die persisteerden in stotteren verminderde volumes in deze cruciale gebieden hadden. Dit suggereert dat vroege afwijkingen in het BGTC-netwerk mogelijk verband houden met stotteren. Daarnaast is het herstel geassocieerd met neuro-anatomische veranderingen en neuroplasticiteit, die compensatie van deze structuren mogelijk maken.

Tot slot bevat **Hoofdstuk 9** de algemene discussie van dit proefschrift. Hierin worden de belangrijkste bevindingen geplaatst in de context van bestaande literatuur. Er worden methodologische overwegingen, klinische implicaties en richtingen voor toekomstig onderzoek besproken.

*“It always seems impossible until it’s done.”*
Nelson Mandela

# ADDENDUM


White matter
Persistent
Fluency
Speech
Research
Recov
Brain
Subcort
Satisfaction
Gray matter
Neuroimaging
Self-report
Explore
Cortical
Girls
Children
Stutter
Population
Temperament
Dysfluency
Fluency
Neuroplasticity
Boys
Outcome
Speech
Satisfaction
Brain
Behavior
Treat
Long-term
Development
Subcortical
Girls
Rotterdam
Self-report
Persistent
Stutter
Cortical
Boys
Population
Speech-motor

# List of abbreviations

| | |
|---|---|
| ADHD | Attention Deficit Hyperactivity Disorder |
| AF | Arcuate Fasciculus |
| AWS | Adults Who Stutter |
| BA | Brodmann Area |
| BGTC | Basal Ganglia-Thalamo-Cortical |
| CBCL | Child Behavior Checklist |
| CBQ | Child Behavior Questionnaire |
| CDI | Child Development Inventory |
| CWS | Children Who Stutter |
| DCM | Demands and Capacities Model |
| DIVA | Directions Into Velocities of Articulators |
| DTI | Diffusion Tensor Imaging |
| FA | Fractional Anisotropy |
| FAT | Frontal Aslant Tract |
| FDR | False Discovery Rate |
| GMV | Gray Matter Volume |
| IBQ-R | Infant Behavior Questionnaire Revised |
| ICF | International Classification of Functioning Disability and Health |
| ICV | Intracranial Brain Volume |
| IFG | Inferior Frontal Gyrus |
| ILF | Inferior Longitudinal Fasciculus |
| IQ | Intelligence Quotient |
| LDS | Language Development Survey |
| LP | Lidcombe Program |
| MCDI-N | MacArthur Communicative Development Inventory-Netherlands |
| MD | Mean Diffusivity |
| MDP | Multifactorial Dynamic Pathways |
| MRI | Magnetic Resonance Imaging |
| OASES | Overall Assessment of the Speaker's Experience of Stuttering |
| pCWS | Children Who Persist in Stuttering |
| PROMs | Patient-Reported Outcome Measures |
| RCT | Randomized Controlled Trial |

| | |
|---|---|
| rCWS | Children Who Recovered from Stuttering |
| RESTART | Rotterdam Evaluation Study of Stuttering Therapy in children: A Randomized Trail |
| SCESS | Satisfaction with Communication in Everyday Speaking Situations |
| SLD | Stuttering-Like Disfluencies |
| SLF | Superior Longitudinal Fasciculus |
| SLP | Speech-Language Pathologist |
| SMA | Supplementary Motor Area |
| SPI | Sound Prolongation Index |
| SS | Syllables Stuttered |
| SSI | Stuttering Severity Instrument |
| STG | Superior Temporal Gyrus |
| VBM | Voxel-Based Morphometry |
| vPMC | Ventral Premotor Cortex |
| WMV | White Matter Volume |

# List of publications

## This thesis

Chow, H.M., Garnett, E.O.*, **Koenraads S.P.C.***, Chang, S.E. (2023) Brain developmental trajectories associated with childhood stuttering persistence and recovery. *Development Cognitive Neuroscience*, Apr; 60:101224.

Franken, M.J.P.*, **Koenraads, S.P.C.***, Holtmaat, C.E.M., van der Schroeff, M.P. (2018) Recovery from stuttering in preschool-age children: 9 year outcomes in a clinical population. *Journal of Fluency Disorders*, Dec;58:35-46.

**Koenraads, S.P.C.**, El Marroun, H., Muetzel, R.L., Chang, S.E., Vernooij, M.W., Baatenburg de Jong, R.J., White, T., Franken, M.C., van der Schroeff, M.P. (2019) Stuttering and gray matter morphometry: A population-based neuroimaging study in young children. *Brain and Language*, Jul;194:121-131.

**Koenraads, S.P.C.,** Jansen, P.W., Baatenburg de Jong, R.J., van der Schroeff, MP, Franken, M.C. (2021) Bidirectional Associations of Childhood Stuttering With Behavior and Temperament. *Journal of Speech Language and Hearing Research*, Dec;13;64(12):4563-4579.

**Koenraads S.P.C.**, Jansen P.W., Labuschagne J.E., van der Schroeff M.P., Franken M.C. (2025) Risk of stuttering onset and persistence linked to early language skills: Results from the Generation R Study. *Journal of Fluency Disorders*, Sep;85:106145.

**Koenraads, S.P.C.**, van der Schroeff, M.P., van Ingen, G., Lamballais S., Tiemeier H., Baatenburg de Jong R.J., White T., Franken M.C., Muetzel R.L. (2020) Structural brain differences in pre-adolescents who persist in and recover from stuttering. *Neuroimage Clinical*, Jun;27:102334.

**Koenraads, S.P.C.,** Stipdonk L.W., Rietveld T., Franken M.C., Childhood stuttering outcomes in the RESTART trial: Long-term comparison of the Lidcombe Program and Restart-DCM. *Submitted*.

## Not part of this thesis

Bast, B.J.E.G., Oonk, L.C., De Nil, L., Eising, E., **Koenraads, S.P.C.**, Bouwen, J., Franken, M.C. (2022). Ontwikkeling van stotteren: Inleiding tot een praktijkmodel. *Stem-, Spraak- en Taalpathologie*, 27, 1-27.

**Koenraads, S.P.**, Aarts, M.C., van der Veen, E.L., Grolman, W., Stegeman, I. (2016) Quality of life questionnaires in otorhinolaryngology: a systematic overview. *Clin Otolaryngol*, Dec;41(6):681-688.

**Koenraads, S.P.C.**, de Boorder, T., Grolman, W., Kamalski, D.M.A. (2017). A 1,470 nm diode laser in stapedotomy: Mechanical, thermal, and acoustic effects. *Lasers Surg Med*, Aug;49(6):619-624.

**Koenraads S.P.C.**, Franken M.C. De hersenontwikkeling bij kinderen die stotteren: een seminar van onderzoeker Soo-Eun Chang (2018). *Stem-, Spraak- en Taalpathologie*. Vol. 23, pp. 1-8

**Koenraads S.P.C.**, van Zanten G.A., Zonneveld B.J.G.L., Bleys R.L.A.W., Buwalda J. (2016) Unilaterale absentie van de nervus cochlearis, een case report. *NTvKNO*.

**Koenraads S.P.C.**, Vroegop J.L, van der Lugt J., van der Schroeff M.P (2017). Een kind met beiderzijds acuut gehoorverlies gedurende de behandeling van een medulloblastoom. *NTvKNO*.

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Neef, N.E., Angstadt, M., **Koenraads, S.P.C.**, Chang, S.E. (2022)Dissecting structural connectivity of the left and right inferior frontal cortex in children who stutter. *Cerebral Cortex*, 1–16.

Paping, D.E., Vroegop J.L., Geleijnse G., le Clercq, C.M.P, **Koenraads, S.P.C.**, van der Schroeff, M.P. (2022) Objective Measurement of Listening Device Use and Its Relation to Hearing Acuity. *Otolaryngology Head Neck Surgery*, Mar;166(3):515-522.

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van Zon, A., Smulders, Y.E., Stegeman, I., Ramakers, G.G., Kraaijenga, V.J., **Koenraads, S.P.**, Zanten, G.A., Rinia, A.B., Stokroos, R.J., Free, R.H., Frijns, J.H., Huinck, W.J., Mylanus, E.A., Tange, R.A., Smit, A.L., Thomeer, H.G., Topsakal, V., Grolman, W. (2017) Stable benefits of bilateral over unilateral cochlear implantation after two years: A randomized controlled trial. *Laryngoscope*, May;127(5):1161-1168.

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# PhD Portfolio

| | |
|---|---|
| Name PhD candidate: | Simone P.C. Koenraads |
| Erasmus MC department: | Otorhinolaryngology and Head and Neck Surgery |
| Research school: | Netherlands Institute for Health Science (NIHES) |
| PhD period: | April 2016 – August 2020 |
| Promotor(s): | Prof. dr. R.J. Baatenburg de Jong |
| Copromotor(s): | dr. M.P. van der Schroeff, dr, M.C.J.P Franken |

| | Year | Workload (ECTS) |
|---|---|---|
| **PhD Training** | | |
| **Master of Science in Clinical Epidemiology, NIHES, Erasmus University Rotterdam, the Netherlands** | 2016-2018 | |
| *Core courses* | | |
| Study Design | | 4.3 |
| Biostatistical Methods I: Basic Principles | | 5.7 |
| Biostatistical Methods II: Classical Regression Models | | 4.3 |
| English Language | | 1.4 |
| Introduction to Medical Writing | | 2.0 |
| Master Research | | 32.6 |
| *Required courses* | | |
| Principles in Causal Inference | | 1.4 |
| Principles of Research in Medicine and Epidemiology | | 0.7 |
| Methods of Clinical Research | | 0.7 |
| Clinical Trials | | 0.7 |
| Health Economics | | 0.7 |
| The Practice of Epidemiologic Analysis | | 0.7 |
| Fundamentals of Medical Decision Making | | 0.7 |
| Clinical Translation of Epidemiology | | 2.0 |
| Clinical Epidemiology | | 3.7 |

| | Year | Workload (ECTS) |
|---|---|---|
| *Elective courses* | | |
| Missing Values in Clinical Research | | 1.4 |
| Repeated Measurements in Clinical Studies | | 1.4 |
| Topics in Meta-analysis | | 0.7 |
| Psychiatric Epidemiology | | 1.1 |
| Psychopharmacology | | 1.4 |
| Women's Health | | 0.9 |
| Principles of Genetic Epidemiology | | 0.7 |
| Genomics in Molecular Medicine | | 1.4 |
| Genome Wide Association Studies | | 0.7 |
| **General academic courses** | | |
| Endnote course | 2016 | 0.3 |
| Research Integrity, Erasmus MC, the Netherlands | 2017 | 0.3 |
| MRI safety training, Erasmus MC, the Netherlands | 2017 | 0.3 |
| MRI incidental finding training, Erasmus MC, the Netherlands | 2018 | 0.3 |
| **Seminars and workshops** | | |
| Generation R research meetings, Erasmus MC, the Netherlands | 2016-2020 | 1.0 |
| Generation R Maternal and Child Health meetings, Erasmus MC, the Netherlands | 2016-2020 | 1.0 |
| Otolaryngology Research meetings, Erasmus MC, the Netherlands | 2018-2020 | 1.0 |
| Otolaryngology Science Day, Erasmus MC, the Netherlands | 2016-2020 | 0.3 |
| National ENT meeting of NVvKNO | 2016-2020 | 1.0 |
| **(Inter)national conferences and research visits** | | |
| Oxford Dysfluency Conference, Oxford, England (oral presentation) | 2017, 2020 | 1.0 |
| European Society Pediatric Otolaryngology (ESPO) Stockholm, Sweden (poster) | 2018 | 1.0 |
| Radiology on the move, Rotterdam, the Netherlands (poster) | 2018 | 1.0 |
| Sophia Research day, Rotterdam, the Netherlands (oral presentation) | 2018 | 0.3 |

| | Year | Workload (ECTS) |
|---|---|---|
| America Speech-Language-Hearing Association (ASHA), Boston, USA (oral and poster presentation) | 2018 | 1.0 |
| Lab meetings and Journal clubs, University of Michigan, Ann Arbor, USA | 2018, 2019 | 1.0 |
| Michigan Speech Language Hearing Association (MSHA), East Lansing, Michigan, USA (poster) | 2019 | 1.0 |
| Society for the Neurobiology of Language (SNL) Meeting, Helsinki, Finland (oral presentation) | 2019 | 1.0 |
| **Awards** | | |
| Junior poster Award ESPO 2018 – 1st Price | 2018 | |
| **Grants** | | |
| Erasmus Trustfonds Conference Participations Grant | 2017 | |
| KNAW Ter Meulen Beurs | 2018 | |
| Damsté-Terpstra Fonds | 2018 | |
| **Teaching activities** | | |
| Coaching bachelor medicine students | 2016-2020 | 1.0 |
| Supervising pracitcal's 3rd and 5th year medical students | 2016-2020 | 1.0 |
| Supervising various workgroups for ER and OR nurses in training | 2016-2020 | 1.0 |

1 ECTS (European Credit Transfer System) is equal to a workload of 28 hours

# About the author

Simone Koenraads was born on February 10 1988 in Breda, the Netherlands, where she also grew up. In 2006, she graduated from high school at Newman College in Breda. Simone first obtained a Propaedeutic degree in Pharmacy before studying Medicine at the University of Groningen (RUG).

During her medical studies and clinical internships in Groningen, Deventer and Utrecht, she developed a strong interest in Ear, Nose, and Throat (ENT) diseases. After graduating in 2015, she continued research at the University Medical Center Utrecht (UMCU) and soon began her clinical career as a General Surgery resident at Maasstad Hospital, in Rotterdam.

In 2016, she started her doctoral research at the Department of Otorhinolaryngology and Head and Neck Surgery, in the Erasmus MC, where she contributed to the Generation R Study, a longitudinal peadiatric cohort investigating child development. Her research focused on childhood stuttering and brain development. In 2018, she obtained a Master of Science degree in Clinical Epidemiology from the Netherlands Institute of Health Sciences (NIHES), in Rotterdam. The following year, she joined the Speech Neurophysiology Lab at the University of Michigan, in the United States, to work on research projects. The results of all research on childhood stuttering are presented in this thesis.

Since 2020, Simone has been a resident in Otorhinolaryngology at Erasmus MC. During this specialty training, she has also focused on healthcare management and organization. Simone currently lives in Rotterdam with her partner Tim. Together they have a daughter, Kiki, and son, Loet.

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*"At the end of the day, we can endure much more than we think we can."*
Frida Kahlo


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