Neuropsychological and Neuroimaging Investigations of Developmental Language Disorder (DLD)



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"*Des beautés spécifiques naissent dans le langage, par le langage, pour le langage*" [A special kind of beauty exists which is born in language, of language, and for language]

— GASTON BACHELARD, *Fragments d'une Poétique du Feu*

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Abstract

Developmental language disorder (DLD) affects approximately 7% of children, leading to persistent difficulties in learning language without a known cause. Previous studies have used neuroimaging to understand the brain basis of DLD, but these studies are limited by their small sample sizes. In addition, to the best of our knowledge, no longitudinal neuroimaging studies of DLD exist, which are needed to determine patterns of brain change in this population. To address these issues, extensive neuropsychological and neuroimaging data were collected from 156 children and adolescents aged 10 to 15 years with a range of language learning abilities, including 54 who met our criteria for DLD, 74 who were typically developing, and 28 with a history of speech-language difficulties who otherwise did not meet the DLD criteria. Fifty-three of these participants were followed up four to five years later in a longitudinal investigation.

At initial assessment, participants with DLD performed poorer than their typically developing peers on all behavioural measures of language, memory, reading, nonverbal reasoning, and motor control. At follow up, the gap in performance between participants with DLD (n = 20) and typically developing controls (n = 22) persisted, despite similar rates of gain in both groups on most tests. The performance of participants with a history of speech-language difficulties (n = 11) typically lay between the two other groups.

Analysis of the structural scans in the cross-sectional cohort using FreeSurfer-derived cortical metrics revealed reduced surface area in participants with DLD compared with controls in several brain regions, including symmetric portions of the anterior inferior frontal gyrus. Analysis of the whole cohort using a language proficiency factor revealed a positive correlation between language ability and surface area in similar cortical regions. Longitudinal analyses in the subsample showed significant cortical changes over time across the cortex, but following whole-brain correction for multiple comparisons, the DLD and typically developing groups did not differ significantly in any of the cortical metrics, nor did they differ significantly in the rate of change in cortical metrics over time. Exploratory analyses at lower statistical thresholds, however, indicated a pattern of change in surface area in participants with DLD consistent with prolonged and delayed neuromaturation.

Lastly, functional MRI was used to investigate differences in brain activity associated with learning to repeat pseudowords in DLD. Pseudoword repetition evoked activity in a left-lateralised network of fronto-temporal cortical areas and in the cerebellum bilaterally. Differences in patterns of activity in participants with DLD (n = 46) were seen in parts of the dorsal motor cortex that were not activated above baseline in controls (n = 71). There was also less pronounced attenuation of neural activity in DLD in cortical regions that are typically considered parts of the default-mode network. These regions were robustly task-negative in controls. The neural activity associated with learning to articulate pseudowords did not differ between groups. Examining activity in the fronto-striatal network using region-of-interest analyses revealed a difference in participants with DLD in the pattern of lateralised activity during pseudoword repetitions in the inferior frontal gyrus.

In summary, the work presented in this thesis provides new information regarding neural differences in individuals with DLD in terms of brain structure and function, and how behaviour and brain structure change over the late adolescent period. The relevance of these behavioural, structural, and functional findings is discussed in relation to current theories of DLD and clinical practice.

Table of Contents

Acknowledgements ... 3

Abstract ... 5

Aims and Structure of Thesis ... 14

Declaration ... 16

Ethics Statement ... 18

Data and Code Availability ... 19

1 Framing Developmental Language Disorder ... 20

1.1 Developmental Language Disorder ... 21

1.2 Language and Literacy Deficits in DLD ... 24

1.2.1 Semantics and the Lexicon ... 24

1.2.2 Phonology and Words ... 24

1.2.3 Morphosyntax and Sentences ... 26

1.2.4 Narrative and Discourse ... 27

1.2.5 Literacy ... 27

1.2.6 Pragmatics ... 30

1.3 Deficits Beyond Language ... 30

1.3.1 Nonverbal Reasoning ... 31

1.3.2 Executive Functioning ... 32

1.3.3 Motor Skills and Praxis ... 33

1.4 Diagnostic Criteria for DLD ... 34

1.4.1 Advantages of Diagnostic Labels ... 34

1.4.2 Diagnostic Guidelines ... 34

1.4.3 The Role of Nonverbal Intelligence in Diagnosis ... 37

1.5 Theories of DLD ... 37

1.6 Genetics of DLD ... 39

1.6.1 Family Aggregation Studies ... 39

1.6.2 Twin Studies ... 40

1.6.3 Pedigree Studies ... 40

1.6.4 Molecular Genetics 41
1.7 Neurobiology of DLD 41
1.7.1 Structural Imaging Studies 43
1.7.2 Functional Imaging Studies 48
2 Behavioural and Cognitive Profiles in the OxBOLD Cohort 54
2.1 Introduction 55
2.2 Methods 56
2.2.1 Participant Recruitment and Screening 56
2.2.2 Behavioural Measures 57
2.2.3 Study Sample 59
2.2.4 Longitudinal Procedure and Sample 60
2.2.5 Statistical Analysis 62
2.3 Results 62
2.3.1 Cross-sectional Sample Characteristics 62
2.3.2 Longitudinal Sample Characteristics 67
2.3.3 Neuropsychological Test Results Over Time 68
2.3.4 Parent Questionnaires 77
2.4 Discussion 80
2.4.1 Language Skills and Their Longitudinal Trajectories in DLD 80
2.4.2 Longitudinal Trajectories of Nonverbal Skills in DLD 84
2.4.3 Parent Questionnaires 86
2.4.4 Limitations and Future Directions 87
3 Differences in Cortical Surface Area in Developmental Language Disorder 89
3.1 Introduction 90
3.2 Methods 91
3.2.1 Study Sample 91
3.2.2 MRI Acquisition 91
3.2.3 MRI Processing 92
3.2.4 Cortical Metrics 92
3.2.5 Whole-brain Cortical Morphometry 92
3.2.6 Surface-based Structural Asymmetry Analysis 94

3.3 Results 94
3.3.1 Brain Morphometric Data 94
3.3.2 Whole-brain Analysis of Cortical Morphology in DLD vs. TD 95
3.3.3 Analyses of Cortical Morphometry and Language Proficiency in the Whole Cohort 97
3.3.4 Analysis of Structural Asymmetry in DLD vs. TD 100
3.4 Discussion 101
3.4.1 Inferior Frontal Cortex Anomalies in DLD 102
3.4.2 Ventral Occipito-temporal Anomalies in DLD 103
3.4.3 No Differences in Cortical Asymmetry Associated with DLD 104
3.4.4 Surface Area and Cortical Thickness Development 105
3.4.5 Limitations and Future Directions 106
4 Longitudinal Changes in Grey Matter in Developmental Language Disorder 108
4.1 Introduction 109
4.2 Methods 111
4.2.1 Study Sample 111
4.2.2 MRI Acquisition 111
4.2.3 MRI Processing 112
4.2.4 Whole-brain Cortical Morphometry 112
4.3 Results 113
4.3.1 Sample Characteristics 113
4.3.2 Whole-brain Morphometric Data 114
4.3.3 Group Differences in Cortical Metrics (Main Effect of Group) 114
4.3.4 Changes in Cortical Metrics Over Time (Main Effect of Time) 116
4.3.5 Group Differences in the Changes in Cortical Metrics Over Time (Group and Time Interaction) 118
4.4 Discussion 123
4.4.1 Group Differences in Cortical Metrics and Their Developmental Trajectories 125
4.4.2 Factors Driving Grey Matter Volume Change During Adolescence 127
4.4.3 Limitations and Future Directions 129
5 Neural Activity for Learning Novel Word Forms in Developmental Language Disorder 131

5.1 Introduction 132
5.2 Methods 134
5.2.1 Study Sample 134
5.2.2 In-scanner Pseudoword Learning Task 135
5.2.3 MRI Acquisition 137
5.2.4 MRI Analysis 137
5.2.5 Behavioural Analysis 140
5.3 Results 140
5.3.1 Neuroimaging Results 140
5.3.2 Post-scan Behavioural Results 147
5.4 Discussion 149
5.4.1 No Significant Group Differences in Neural Activity During Pseudoword Learning 150
5.4.2 Greater Motor Cortex Activity in DLD During Pseudoword Repetition 152
5.4.3 Weaker Task-related Deactivation in DLD During Pseudoword Repetition 153
5.4.4 Limitations and Future Directions 154
6 General Discussion 155
6.1 Summary 155
6.2 Sentence Recall as a Powerful Assessment Test 156
6.3 The Case for a Neuromaturational Lag in DLD 157
6.4 Deficits in the Frontostriatal Circuitry in DLD 159
6.5 Towards a Neurocognitive Model of DLD 161
6.6 Concluding Remarks and Broader Outlook 164
7 References 166
8 Supplementary Material and Appendices 206
8.1 Chapter 2 208
8.2 Chapter 3 216
8.3 Chapter 5 221

List of Figures

Fig. 1.1 *Relationship between DLD and dyslexia as proposed by Bishop and Snowling (2004) and later revised by Catts and colleagues (2005).* 29
Fig. 1.2 *Overview of statements from CATALISE.* 35
Fig. 2.1 *Time gap between the two testing sessions per group.* 68
Fig. 2.2 *Longitudinal trajectories for vocabulary tests per group.* 69
Fig. 2.3 *Longitudinal trajectories for grammar tests per group.* 70
Fig. 2.4 *Longitudinal trajectories for narrative subtests per group.* 71
Fig. 2.5 *Time I NNWR data per group.* 72
Fig. 2.6 *Time II CNRep data per group.* 73
Fig. 2.7 *Longitudinal trajectories for memory subtests per group.* 73
Fig. 2.8 *Longitudinal trajectories for reading subtests per group.* 74
Fig. 2.9 *Longitudinal trajectories for nonverbal intelligence subtests per group.* 76
Fig. 2.10 *Longitudinal trajectories for motor subtests per group..* 77
Fig. 2.11 *Longitudinal trajectories for parent questionnaires per group.* 78
Fig. 3.1 *Cortical regions showing smaller surface area in the DLD group.* 96
Fig. 3.2 *Relationship between language and memory proficiency scores in the whole cohort.* 98
Fig. 3.3 *Continuous analysis of surface area and language proficiency in the whole cohort.* 99
Fig. 3.4 *Cortical asymmetries for surface area and cortical thickness in TD vs. DLD* 101
Fig. 4.1 *Differences in surface area between TD and DLD groups.* 115
Fig. 4.2 *Differences in cortical thickness between TD and DLD groups..* 115
Fig. 4.3 *Differences in grey matter volume between TD and DLD groups..* 116
Fig. 4.4 *Changes in cortical metrics over time in the whole cohort (n = 42)..* 117
Fig. 4.5 *Group-by-time interaction for the rate of change in surface area between groups.* 119
Fig. 4.6 *Changes in surface area over time per group..* 120
Fig. 4.7 *Group-by-time interaction for rate of change in cortical thickness between groups.* ... 121
Fig. 4.8 *Changes in cortical thickness over time per group.* 121
Fig. 4.9 *Group-by-time interaction for rate of change in grey matter volume between groups* 122
Fig. 4.10 *Changes in grey matter volume over time per group..* 123

Fig. 5.1 *Schematic of experimental design.* 136
Fig. 5.2 *fMRI activity for pseudoword repetition per group*..... 141
Fig. 5.3 *Brain areas engaged during pseudoword repetition in DLD>TD contrast.* 142
Fig. 5.4 *Probabilistic overlap maps for pseudoword repetition vs. rest in TD and DLD groups*144
Fig. 5.5 *Brain regions showing learning-related activity decreases in TD and DLD groups.*..... 145
Fig. 5.6 *Brain activity associated with pseudoword learning in the inferior frontal gyrus in TD vs. DLD.*..... 146
Fig. 5.7 *Percent correct form-referent recognition scores per group for non-repeated vs. repeated stimuli, by syllable length*..... 148
Fig. 5.8 *Percent accurate pseudoword repetition scores per group for non-repeated vs. repeated stimuli, by syllable length*..... 149

List of Tables

Table 1.1 *Summary of studies investigating structural grey matter correlates of DLD.* 44

Table 1.2 *Summary of studies investigating neural correlates of DLD using task-based fMRI.*. 49

Table 2.1 *Examples from TROG-2 assessing embedded relative clauses.*..... 61

Table 2.2 *Demographic information of groups in the cross-sectional analysis.*..... 63

Table 2.3 *Results from the neuropsychological test battery for TD, DLD, and HSL groups*.....64

Table 3.1 *Brain regions showing lower surface area and grey matter volume in DLD relative to TD group*.....97

Table 3.2 *Brain regions showing positive correlation between surface area and language proficiency factors.*.....100

Table 5.1 *Sample characteristics for TD and DLD groups*..... 135

Table 5.2 *Group differences in brain activity during pseudoword repetition in DLD>TD contrast*. 143

Aims and Structure of Thesis

This thesis is structured into a general introduction, neuropsychological studies, neuroimaging investigations, and a general discussion.

Chapter 1 provides an overview of key topics in the study of developmental language disorder (DLD), previously known as specific language impairment (SLI). The aim of this chapter is to provide the reader with the essential background knowledge on DLD before introducing the cohort I studied in the experimental chapters that follow. This cohort participated in the Oxford Brain Organisation in Language Development (OxBOLD) project, funded by a Medical Research Council grant awarded to Professors Kate Watkins and Dorothy Bishop. Extensive behavioural and brain imaging data were collected between autumn 2018 and winter 2020 from 160 children aged 10 to 15 years with a range of language abilities, including 55 with DLD, 77 with typical language development, and 28 with a history of speech and language difficulties. The OxBOLD project is currently the largest neuroimaging project on DLD, providing a unique opportunity to investigate the neurobiological underpinnings of this condition in depth.

Chapter 2 reports the neuropsychological profiles of the OxBOLD participants, with the aim of characterising the functional deficits common to DLD. I first summarise the cohort's performance on tests of language, memory, reading, nonverbal intelligence, and motor control. Since this behavioural data was previously published, I focus my attention on the new longitudinal data obtained during my thesis. Here, I present changes in the behavioural profiles of 53 of the original OxBOLD participants who were followed up approximately four to five years after the initial session, when aged 14 to 20 years. Most research on DLD has been cross-sectional and conducted in younger populations, limiting our understanding of how language and other cognitive skills develop beyond childhood in this population. As such, the aim of the follow-up study was to investigate developmental gains in a range of cognitive skills in DLD during adolescence and young adulthood.

Chapter 3 presents results of our investigation of the structural brain differences, including cortical asymmetry, associated with DLD in the cross-sectional cohort. One limitation of the existing neuroanatomical studies of DLD is the sole focus on grey matter

volume, leaving uncertainty about whether previously found group differences relate to surface area or cortical thickness, two subcomponents of volume that are genetically and ontologically distinct. The aim of this chapter was to fill in this gap using imaging data from a relatively large sample. Language proficiency factor scores based on an exploratory-confirmatory factor analysis of the behavioural data further allowed us to explore the relationship between brain structures and language ability in more depth using a continuous measure across the whole cohort of participants.

Chapter 4 presents the longitudinal structural imaging results from the subset of the OxBOLD cohort in whom longitudinal neuropsychological and brain imaging data were obtained. This study represents the first longitudinal neuroimaging investigation of DLD, aiming to provide insights into neuroanatomical changes during adolescence and young adulthood. Some theories of DLD suggest prolonged or delayed maturation of neural pathways in this population. We aimed to test the maturational lag versus delay hypothesis across the cortex. Recognising that most research on DLD focuses on children and preadolescents, our follow-up study extended the investigation to older individuals to explore long-term outcomes beyond childhood.

Chapter 5 shifts focus to a functional MRI study exploring the neural correlates of novel word form learning in DLD. Some theoretical frameworks suggest that individuals with DLD have specific deficits in brain networks underlying implicit learning of sequences. To examine this type of learning in DLD, we employed a paradigm in which participants from the larger cross-sectional cohort were repeatedly exposed to a set of pseudowords and were asked to overtly repeat these pseudowords while being scanned. The results have implications for current theoretical frameworks of DLD, which are discussed in this chapter.

Chapter 6 synthesises the findings from the neuropsychological and neuroimaging studies and proposes directions for future research.

Declaration

This thesis comprises work conducted by Nilgoun Bahar in fulfilment of the degree of Doctor of Philosophy in Experimental Psychology at University of Oxford. The contributions of Nilgoun Bahar and collaborators are as follows: For the cross-sectional studies presented in Chapters 3 and 5, conceptualisations were co-led by Nilgoun Bahar and Prof. Kate Watkins. Nilgoun Bahar led the formal analysis, visualisation, and writing. Prof. Saloni Krishnan led the investigation and project administration. Prof. Gabriel Cler and Dr. Salomi Asaridou supported with investigation and project administration. Drs. Harriet Smith, Hanna Willis, and Máiréad Healy supported with investigation. For the longitudinal studies presented in Chapters 2 and 4, conceptualisations were co-led by Nilgoun Bahar and Prof. Kate Watkins. Nilgoun Bahar led the investigation, project administration, formal analysis, visualisation, and writing. Dr. Salomi Asaridou supported with project administration. Prof. Kate Watkins led the funding acquisition, and supported with project administration, formal analysis, review of writing, and supervised all work across all chapters.

The study in Chapter 3 was presented at the 14th Annual Meeting of the Society for the Neurobiology of Language, held in Philadelphia, USA (October 6-8, 2022). It was published in 2024 as:

Bahar, N., Cler, G. J., Krishnan S., Asaridou, S. S., Smith, H. J., Willis, H. E., Healy, M. P., & Watkins, K. E. (2024). Differences in cortical surface area in developmental language disorder. *Neurobiology of Language*, *5*(2): 288–314.
doi: https://doi.org/10.1162/nol_a_00127

The study in Chapter 5 was presented at the 15th Annual Meeting of the Society for the Neurobiology of Language, held in Marseille, France (October 24-26, 2023). This study along with the ones presented in Chapters 2 and 4 will be submitted for publication upon completion. The list of other relevant publications for the OxBOLD project as listed below:

Cler, G. J., Asaridou, S. S., Bahar, N., Krishnan, S., Smith, H. J., Willis, H. E., Healy, M. P., & Watkins, K. E. Subcortical macro- and microstructural differences in children with developmental language disorder (*in prep*).

Asaridou, S. S., Cler, G. J., Wiedemann, A., Krishnan, S., Smith, H. J., Willis, H. E., Healy, M. P., & Watkins, K. E. (2024). Microstructural properties of the cerebellar peduncles in children with developmental language disorder. *Neurobiology of Language*, *5*(3): 774-794. doi: https://doi.org/10.1162/nol_a_00142

Krishnan, S., Cler, G. J., Smith, H. J., Willis, H. E., Asaridou, S. S., Healy, M. P., & Watkins, K. E. (2022). Quantitative MRI reveals differences in striatal myelin in children with DLD. *eLife*, *11*(e74242). doi: https://doi.org/10.7554/eLife.74242

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Ethics Statement

Ethical approval for the studies presented in the following chapters was granted by the Medical Sciences Interdivisional Research Ethics Committee at the University of Oxford (R55835/RE002). We obtained written informed consent from the parents or guardians of the participants (aged 11-15 years) and written assent from all participants. Ethical approval for the longitudinal study was granted by the University of Oxford's Medical Sciences Interdivisional Research Ethics Committee (R84342/RE001). Written informed consent was obtained from participants aged 18 years and older, and from the parents or guardians of participants younger than 18. Participants under 18 provided written assent.

Data and Code Availability

The statistical analyses presented in the following chapters were conducted using either Matlab R2022b (TheMathWorks, Inc) or the R programming language (R Core Team, 2022). The anonymised neuropsychological scores and codes supporting the findings presented in Chapter 3 are openly available on the Open Science Framework (https://osf.io/wmkrq/), and the whole-brain significance maps of group differences can be viewed on NeuroVault (https://identifiers.org/neurovault.collection:13977). The anonymised neuropsychological scores, statistical neuroimaging maps, and codes from the studies presented in Chapters 2, 4 and 5 will be openly available upon their publication.

1

Framing Developmental Language Disorder

ABSTRACT

Approximately 7% of children, or potentially two in every classroom of 30, persistently struggle to learn their native language without an obvious reason. In this chapter, I provide an overview of this neurodevelopmental condition, known as developmental language disorder (DLD). I explore the reasons behind the lack of widespread awareness of DLD despite its high prevalence and significant functional impacts. The behavioural phenotype associated with DLD is summarised, encompassing both linguistic and non-linguistic features. Current diagnostic guidelines are discussed, followed by an overview of some of the prominent theoretical accounts of DLD. Finally, I review evidence on the biological foundations of DLD, beginning with a brief summary of its genetic architecture, then focusing primarily on structural and functional brain imaging findings to date.

1.1 Developmental Language Disorder

Approximately 7% of children persistently struggle to learn language from an early age, resulting in a failure to develop age-appropriate receptive and expressive language skills (Calder et al., 2022; Norbury et al., 2016; Tomblin et al., 1997). The language deficits associated with this neurodevelopmental condition, called developmental language disorder (DLD), are lifelong and cannot be attributed to known biomedical or environmental factors, such as an acquired brain injury, frank neurological disorder, childhood hearing loss, or social disadvantage (Bishop et al., 2016). Early intensive intervention is essential, and therapy gains can be maintained in the medium term depending on the specific domain of language (Rinaldi et al., 2021). Children do not outgrow their language difficulties, however, and it was concluded in a recent meta-analysis that the long-term effects of intervention alone are unclear (Fan et al., 2022).

DLD has a complex genetic and multifactorial aetiology, and the gene-environment interactions result in considerable variability in the phenotypic manifestations of this condition (Mountford et al., 2022). As such, children's language deficit profiles often vary significantly from individual to individual. This heterogeneity becomes even more pronounced within the dynamic course of development, with the interaction between language and other cognitive mechanisms resulting in a variety of profiles of language disorder (Botting, 2005). Acknowledging this wide variability in language abilities, recent research supports characterising DLD as a spectrum or continuum, like other neurodevelopmental conditions such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) (Lancaster & Camarata, 2019).

DLD can negatively affect multiple areas of life (see review by Dubois et al., 2020). Early oral language deficits impede the development of reading and writing skills, which hinder academic performance and career prospects (Conti-Ramsden et al., 2018; Ziegenfusz et al., 2022). Adults with DLD often experience prolonged periods of unemployment (Law et al., 2009; Schoon et al., 2010), earn lower incomes (Beitchman et al., 2014), and tend to occupy less skilled jobs that require lower levels of education (Johnson et al., 2010). Young adults with DLD exhibit lower rates of financial literacy, leading to increased reliance on family support (Winstanley et al., 2018), and many report living at home with parents or without a partner (Schoon et al., 2010). Additionally, mothers of children with language difficulties are less likely to be employed, substituting paid work for unpaid caregiving (Cronin et al., 2017). These factors contribute to DLD imposing a significant burden on health and welfare systems, impacting human capital

and economic success. The overall societal cost of childhood language disorders is estimated to range in the billions per annum, with productivity losses making up the largest proportion (Cronin et al., 2017; Ruben, 2000).

Another body of research has underscored the increased risk of poor mental health and adverse life experiences associated with DLD (Goh et al., 2021). Adolescents with DLD are more likely to experience elevated levels of depression and social stress (Conti-Ramsden & Botting, 2008; Forrest et al., 2021; Wadman et al., 2011). Females with DLD face a threefold higher risk of sexual assault (Brownlie et al., 2007) and report higher incidences of teen pregnancy (Schoon et al., 2010). Males with DLD show significantly higher rates of arrests and convictions (Brownlie et al., 2004). A disproportionate number of incarcerated juveniles have language impairment profiles consistent with a diagnosis of DLD (Anderson et al., 2016; Sowerbutts et al., 2021).

Despite its high prevalence and unfavourable outcomes, the public's awareness of DLD remains markedly limited compared with other neurodevelopmental conditions. The estimated prevalence of DLD is comparable to that of developmental dyslexia (3-7%, Wagner et al., 2020) and exceeds that of ADHD (5%, Posner et al., 2020). Notably, DLD is seven times more prevalent than ASD (1.1%, Brugha et al., 2011) and 46 times more common than childhood hearing loss (0.16%, Fortnum et al., 2001). Yet, the public tends to be far more familiar with these other conditions than with DLD. Even within the scientific community, research output related to DLD remains comparatively low when measured against other neurodevelopmental disorders (Bishop, 2010; McGregor, 2020).

The lack of mainstream awareness of DLD has direct consequences on healthcare services, resulting in children with DLD being underserved (McGregor, 2020). The percentage of children accessing clinical services for DLD is significantly lower than the disorder's prevalence in community samples. For instance, in their American population cohort, Tomblin and colleagues (1997) found that only 29% of the 216 kindergarteners identified with DLD were flagged for support. Twenty-five years later, Calder and colleagues (2022) observed a similar situation in their Australian cohort, where only two out of 104 10-year-olds with DLD had been identified by a health professional. This trend was also evident in the cohort studied by Norbury and colleagues (2016) in England, where less than half of the identified children with language disorder were receiving extra support during the first years of school, and only 3% had a statement of special educational need. Outdated policies further exacerbate this issue. For

example, in the United States, children with DLD receive limited insurance coverage because the disorder is often viewed either as a delay–implying that the child will eventually "catch up" –or as an educational issue, with the assumption that some form of support will be provided at school (McGregor, 2020).

The reasons for the lack of mainstream awareness of DLD are complex and plenty, but one major factor is that DLD is largely a hidden disorder (McGregor, 2020). Unlike conditions such as dyslexia or stuttering, where the reading difficulties or speech dysfluency become immediately apparent when a child is asked to read aloud in the classroom, DLD is not easily observed. Children with DLD do not sound or behave much differently from their peers and often manage well in basic conversations by extracting meaning from context. Consequently, DLD can be easily overlooked at home or at school. Worse still, the inconspicuous nature of DLD can result in it being misinterpreted as laziness, inattentiveness, or a lack of intelligence. The issue is further exacerbated by camouflaging, where children mask their language difficulties with socially acceptable behaviours (Hobson & Lee, 2023). DLD is more readily identifiable when the language difficulties are accompanied by more "visible" co-occurring difficulties, such as poor self-regulation or a speech sound disorder (Lindsay & Strand, 2016; Morgan et al., 2017; Zhang & Tomblin, 2000).

Another factor hindering awareness of DLD is the inconsistent terminology used over the decades; historically, more than 30 different terms have been applied to DLD, with labels changing as our understanding of the phenotype advances (Bishop, 2014). This inconsistency is compounded by the inherent heterogeneity of DLD as a neurodevelopmental condition. Children with DLD do not form a homogeneous group. The condition that is now understood as DLD encompasses a wide range of difficulties that manifest at various developmental stages, affecting all aspects of language and, to some extent, other cognitive and motor domains. The high degree of interactivity between cognitive processes during development (Botting, 2005), coupled with the overlap between children's learning difficulties and processing limitations, make it challenging to draw clear boundaries between language and other cognitive domains. In the following three sections, I have categorised these into language and literacy deficits versus deficits beyond language.

1.2 Language and Literacy Deficits in DLD

1.2.1 Semantics and the Lexicon

Children with DLD are typically late in learning their first words as toddlers, with many not speaking until around 23 months of age (Trauner et al., 2000). When words emerge, the lexical type and diversity are similar to those of typically developing children, with a predominance of nominals, followed by action words and properties (Thordardottir & Weismer, 2001). Specific difficulties with learning verbs are common, as verbs are generally more abstract and require more complex linguistic processing (Oetting et al., 1995; Rice et al., 1994). The extent of these difficulties, however, can vary based on the type of action words. For example, children with DLD tend to use common verbs at similar rates to their typically developing peers (Watkins et al., 1993). The rate of vocabulary growth in children with DLD initially aligns with that of younger, unaffected children (Rice, 2004), but the vocabulary gap may widen over time (Stothard et al., 1998).

Children with DLD often start with a weak vocabulary foundation, resulting in smaller lexical storage (vocabulary breadth) and shallower word knowledge (vocabulary depth), both of which tend to persist into adolescence (McGregor et al., 2013). Pre-schoolers with DLD recognise fewer semantic features and lexical labels (Alt et al., 2004). School-age children with DLD are slower in making lexical decisions, exhibit weaker semantic priming, and make more errors in lexical-semantic associations (Girbau, 2014). They also struggle to provide accurate definitions, especially for action words (Mainela-Arnold et al., 2010; Marinellie & Johnson, 2002). In one study, 6-year-olds with DLD were asked to draw objects they had mislabelled; their drawings revealed limited conceptual understanding, indicating that their semantic knowledge limitations extended beyond retrieval issues (McGregor et al., 2002).

1.2.2 Phonology and Words

Broadly speaking, phonology can be broken down into two distinct but interrelated domains of phonological representations and phonological skills (Ramus et al., 2013). The former encompasses speech sound discrimination, categorisation, and articulation, which are crucial for oral language development. Phonological skills refer to abilities such as phonological awareness and verbal working memory, which are fundamental for word learning and literacy. In terms of phonological representations, the difficulties of children with DLD were early on

proposed to derive in part from low-level auditory perception deficits affecting downstream language processes. A classic series of experiments showed that children with DLD were significantly impaired in the ability to discriminate and sequence speech stimuli at rapid presentation rates (Stark & Tallal, 1981; Tallal & Piercy, 1973, 1974). A primary temporal processing deficit was suggested to have a cascading effect on higher level phonological processes. These findings have not always been replicated, however, and the pattern of impaired speech perception is not seen in all children with DLD (e.g., see Bishop & McArthur, 2005; Rosen, 2003).

Others have argued that poor performance on speech perception tasks may result from task demands and stimulus properties rather than perceptual deficits *per se* (Coady et al., 2007; Cohen et al., 2005). Investigations into this topic are ongoing. More recently, it was found that children with DLD exhibited greater trial-to-trial variability in speech sound categorisation, which had a unique impact on language ability even after controlling for phonological processing skills (Kim et al., 2024). The variability in responses suggested that children with DLD exhibited more inconsistency in reaching the same interpretation of identical speech stimuli, even though their categorisations generally aligned with proper speech category structures.

Most children with DLD exhibit deficits in both phonological representations and phonological skills. This is perhaps best reflected in their poor performance on pseudoword (nonword) repetition, a widely recognised clinical marker of DLD (Bishop et al., 1996; Dollaghan & Campbell, 1998; Graf Estes et al., 2007). Accurate pseudoword repetition requires maintaining a heard phonological sequence in short-term memory while transforming it into precisely timed and coordinated oromotor movements (Krishnan et al., 2013). Pseudoword repetition is therefore a multifaceted task that probes the memory and motor systems underlying vocabulary acquisition and fluent speech. Numerous studies have found significant associations between children's pseudoword repetition ability, word learning, and vocabulary size (e.g., Adlof & Patten, 2017; Hoff et al., 2008). While children with DLD often perform similarly to their typically developing peers on short pseudowords, their accuracy declines dramatically with longer stimuli, indicating limitations in phonological working memory beyond general perceptual or encoding deficits (Archibald & Gathercole, 2007; Coady & Evans, 2008). Similarly, a recent meta-analysis reported that children with DLD perform significantly worse on all measures of verbal working memory used in the field, including digit span tests,

listening and counting recall, and word or pseudoword list recall (Niu et al., 2024). I will return to the contribution of motor control to pseudoword repetition in Section 1.3.3, and in Chapters 2 and 5.

1.2.3 Morphosyntax and Sentences

Children with DLD exhibit noticeable difficulties in using and understanding many morphosyntactic constructs. Grammatical deficits in this population are documented in all languages studied so far, but the difficulties manifest differently based on the structure of the language examined (see Leonard, 2014). I focus on English here, but the key point is that an underlying cognitive computation drives morphosyntactic deficits, and how these deficits manifest depends on the grammatical properties of each language (Goffman & Gerken, 2023). Common deficits in English-speaking children with DLD include the omission or inconsistent use of function morphemes like articles, copulas, and auxiliary verbs (Fey et al., 1997; Leonard, 2014). Pronoun substitution, over-regularisation of irregular verbs (e.g., "he eated"), and inconsistent use of irregular third person forms (e.g., "he have") are also frequent. Another significant area of difficulty is in understanding and using complex grammatical constructs (Marinis & Van Der Lely, 2007). These constructs involve sentences with non-adjacent relationships within hierarchical structures, requiring the ability to compute dependencies between non-local linguistic units. The challenges for children with DLD in this domain often lead to issues with assigning syntactic roles to nouns and pronouns, subject-verb agreement, and processing passive and embedded constructions (Van Der Lely, 2005).

Classic accounts of DLD identify difficulties with inflectional morphology, such as inconsistent marking of verb finiteness, as hallmarks of the disorder (Leonard, 2014; Rice et al., 1995; Van Der Lely et al., 1998). Extensive longitudinal studies have indeed shown that these morphosyntactic constructs are less developed in children with DLD than in younger children matched for language levels, supporting the Extended Optional Infinitive (EOI) account of DLD (Rice et al., 1995). This theory posits that children with DLD treat verb finiteness as optional for a longer period than typically developing children, often persisting well beyond the early years (Van Der Lely et al., 1998). Aside from pronounced difficulties in inflectional morphology, most grammatical errors in DLD resemble those of younger, typically developing children, reflecting partial knowledge applied inconsistently (Gopnik, 1994; Rice et al., 1998, 1999; Van Der Lely & Stollwerck, 1997). Overall then, the pattern of grammatical errors in DLD

appears to align with a delayed maturation profile rather indicating an absence or atypical development of syntax.

1.2.4 Narrative and Discourse

Generating stories requires sophisticated linguistic and social-cognitive skills to create a story structure and use context-appropriate language concurrently. As such, storytelling provides an excellent impression of a child's overall linguistic and communicative competence. In one study, subjective ratings of children's narratives by laypersons and teachers successfully differentiated children with typical language from those with DLD with 70% non-overlap, with raters describing the narratives of children with DLD as lacking "sparkle" or charm (Newman & McGregor, 2006).

A systematic review identified narrative coherence and cohesion as areas of difficulty for children with DLD (Petersen, 2011). When given a book, children with DLD are more likely to describe the pictures without alluding to the story episodes under a united framework (Kraljević et al., 2020). The narratives are on average shorter and less fluent (Fichman & Altman, 2024), lexically impoverished, and contain more grammatical errors (Govindarajan & Paradis, 2019; Norbury & Bishop, 2003; Reilly, 2004). Deficits in grammatical accuracy (story microstructure) and overall story grammar (macrostructure) were the most significant contributors to narrative disparities in DLD in a recent meta-analysis (Winters et al., 2022).

Difficulties with narrative in children with DLD can sometimes improve (Guo & Schneider, 2016), but more often persist into adolescence (Reed et al., 2007). Factors such as story format (e.g., storytelling vs. retelling), genre (e.g., personal vs. fictional), and the type of support provided (e.g., pictorial aids, conversation prompts, etc.) all influence the quality of narrations in these children (Rezzonico et al., 2015; Schneider & Dubé, 2005; Tsimpli et al., 2016). For instance, both children and adolescents with DLD made fewer linguistic errors and generated more well-formed stories when narrating personal experiences as opposed to telling stories based on a picture book (McCabe et al., 2008; Wetherell et al., 2007).

1.2.5 Literacy

Strong oral language skills in early years are the building blocks of literacy development (Hulme et al., 2015; Snowling et al., 2000). Children who start out with a weak foundation in language may not fully develop the skills that are required for fast and fluent reading (Botting

et al., 2006; Snowling & Melby-Lervåg, 2016). For example, phonological deficits directly impact children's phonological awareness, or the ability to manipulate syllables and sounds, which is critical for decoding the sound structure of written words (Bishop & Clarkson, 2003; Bortolini & Leonard, 2000). Sparse lexical and semantic knowledge, coupled with phonological and morphosyntactic deficits interrupt word recognition, decoding efficiency, and reading comprehension ability in children with DLD (Buil-Legaz et al., 2015; McGregor et al., 2013).

Interestingly, many children who meet the diagnostic criteria for DLD are not identified until they reach school age, when reading difficulties become evident (Botting et al., 2006; Catts et al., 2005). That is, language deficits only come to light during literacy assessment, again underscoring the hidden nature of DLD. The frequent overlap between language and reading difficulties raises questions about the relationship between DLD and dyslexia, and the extent to which the two constitute separable conditions. Like DLD, dyslexia is a persistent neurodevelopmental disorder with a strong genetic basis (Bishop & Snowling, 2004). Both conditions are dimensional, varying in severity, with no clear boundaries distinguishing one from the other. DLD and dyslexia are currently understood as distinct but closely related conditions that commonly co-occur (Bishop et al., 2009; Catts et al., 2005; Ramus et al., 2013; Snowling et al., 2019).

Drawing on the Simple View of Reading (Gough & Tunmer, 1986), which posits that phonological decoding and linguistic comprehension are two core aspects of reading comprehension, Bishop and Snowling (2004) proposed a two-dimensional framework to differentiate between DLD and dyslexia (Fig. 1.1A). According to this model, language and reading can be understood along two axes comprising phonological and oral language skills. Dyslexia primarily involves deficits in phonology, which hamper the ability to decode written text (with the assumption of sufficient language to understand the material). On the other hand, children with DLD exhibit broader language deficits in addition to poor phonological skills, which impede their ability to decode and understand written text (Bishop et al., 2009; Nation et al., 2004; Snowling & Hulme, 2012). DLD and dyslexia are therefore only partially distinct in this model, separable mainly through language skills. A third group of children are "poor comprehenders" who struggle with reading comprehension and tend to have associated difficulties with semantics and syntax, despite intact phonological processing abilities (Nation et al., 2004).

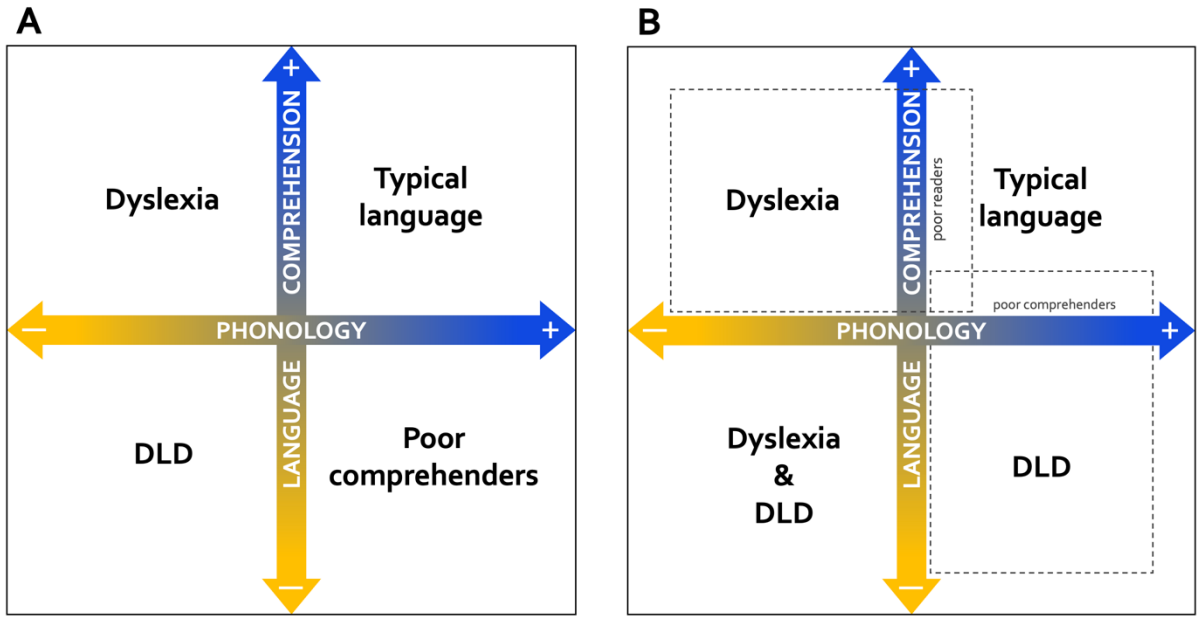


Fig. 1.1 ***Relationship between DLD and dyslexia as proposed by Bishop and Snowling (2004) and later revised by Catts and colleagues (2005).*** Panel A depicts the partial distinction hypothesis, which predicts that children with dyslexia and children with DLD both exhibit phonological deficits, but the latter also have poor language skills. As Catts and colleagues (2005) argued, however, not all children with DLD have poor phonology. Panel B depicts the fully distinct hypothesis, viewing dyslexia and DLD as two separate conditions that frequently overlap, in which case those children have the most severe reading and language deficits. Both panels are adapted from Adlof and Hogan (2018).

The model proposed by Bishop and Snowling (2004) has some limitations. As the researchers themselves pointed out, clinical groups tend to be defined by arbitrary cut-offs, leading to overlap between DLD and dyslexia. Moreover, many children with dyslexia also exhibit language weaknesses ranging from mild to severe (Snowling & Melby-Lervåg, 2016). To address this continuum of impairment, Catts and colleagues (2005) refined the framework drawing from a large, longitudinal population-based sample, which showed that, first, not all children who meet the criteria for DLD have poor phonological skills (Fig. 1.1B). They argued that clinically ascertained samples do not consistently capture this group due to a bias to overrepresent children with co-occuring DLD and dyslexia, as these children are more likely to be referred to clinicians (Adlof & Hogan, 2018). In this regard, DLD and dyslexia are distinct conditions that frequently co-occur. Children in the co-occuring dyslexia and DLD group will be at risk of difficulties with decoding as well as understanding the text. These children are likely to show the most severe reading comprehension problems (Snowling et al., 2019).

1.2.6 Pragmatics

Children with DLD exhibit difficulties across various pragmatic domains, primarily due to linguistic challenges rather than deficits in social cognition (Lapadat, 1991; Troia et al., 2023). For example, they struggle with figurative language such as idioms and metaphors because of difficulties in the semantic coding of nonliteral language (Cardillo et al., 2018; Ferrara et al., 2020; Mashal & Kasirer, 2012; Norbury, 2005). Like in other domains, children with DLD exhibit immature rather than absent or atypical pragmatic abilities. For instance, they struggle with making inferences based on presuppositions compared with age-matched peers but perform similarly to language-matched controls (Botting & Adams, 2005). Similarly, while they find it challenging to understand emotional states and solve false-belief tasks (Andrés-Roqueta et al., 2013, 2016; Brinton et al., 2019), their performance on theory of mind tasks is comparable to that of their language-matched peers (Andrés-Roqueta & Katsos, 2020; Bakopoulou & Dockrell, 2016). Importantly, when structural language abilities are accounted for, children with DLD exhibit better social communication skills than those with ASD, indicating that their pragmatic deficits align more closely with their linguistic development (Adams et al., 2009, 2018; Reed et al., 2007). These pragmatic difficulties negatively impact their daily interactions, leading to emotional distress and social incompetence (Mok et al., 2014; St Clair et al., 2011).

1.3 Deficits Beyond Language

Mounting evidence suggests that the cognitive deficits in DLD extend beyond the realm of language (e.g., Ullman & Pierpont, 2005). Understanding the nature and severity of these impairments has been challenging in part due to the complex and bidirectional relationship between language and cognition (e.g., see Just & Carpenter, 1992). In the context of executive functioning this complexity results in "task impurity," where cognitive processes cannot easily be scrutinised as isolated components (Pauls & Archibald, 2016). Many tasks that are ostensibly "non-linguistic" still engage verbal processing either implicitly or explicitly. Verbal mediation is indeed shown to facilitate problem-solving across a range of cognitive functions, even when verbalisation is unnecessary (Perrone-Bertolotti et al., 2014). For example, self-directed or inner speech facilitates self-regulation (Alarcón-Rubio et al., 2014), problem solving (Lidstone et al., 2010), and the maintenance of information in working memory (Fatzer & Roebers, 2012). Inner speech can also serve as a self-cuing mechanism to initiate new tasks during executive functioning (Emerson & Miyake, 2003). Children with DLD often exhibit significant delays in

using inner speech, which places them at a disadvantage when their presumably nonverbal cognitive skills are put to test (Baron & Arbel, 2022).

Beyond the conceptual challenges, methodological constraints further complicate the investigation of non-linguistic cognitive deficits in DLD. A simple yet often overlooked issue is that language may be explicitly required to fully understand the instructions provided by examiners. A meta-analysis found that 81% of cognitive flexibility and 52% of inhibitory control tasks used to assess executive functioning in children with DLD imposed extra verbal demands (Pauls & Archibald, 2016). Consequently, children with DLD may perform poorly not just due to cognitive deficits but also because of difficulties understanding the instructions (Gallinat & Spaulding, 2014). These points underscore some of the challenges of assessing nonverbal cognition in the language-impaired population, and the need to exercise caution to not inadvertently confound language ability with nonverbal cognitive performance.

1.3.1 Nonverbal Reasoning

Below-average performance on tests of nonverbal intelligence quotient (NVIQ) in children with DLD is among the most consistent findings in the field (Botting, 2005; Gallinat & Spaulding, 2014). Children with DLD score on average more than 10 points lower than their typically developing peers on standardised NVIQ tests, with a significant effect size even after controlling for variables such as age range, task variability, and statistical cut-offs (Gallinat & Spaulding, 2014). Conceptually, the relationship between language and NVIQ is complex and there is considerable debate on whether and how the two affect each other (e.g., Griffiths et al., 2022; Ivanova et al., 2021). There are accounts of sufficient linguistic performance in children with low NVIQ, challenging the notion that nonverbal ability limits language development (e.g., Rice, 2020). On the other hand, lower NVIQ scores among children with DLD may be due to the strong correlation between their verbal and nonverbal skills (Liao et al., 2015; Plym et al., 2021). In general, children with DLD and those with below-average language development have significantly lower NVIQ scores compared with typically developing children (Liao et al., 2015). Longitudinal studies show that NVIQ scores in DLD can decline significantly over time (Botting, 2005; Conti-Ramsden et al., 2012). These findings suggest that poor language may impede the development of nonverbal reasoning skills, in turn creating a negative feedback loop that further hinders language acquisition. I discuss the role of NVIQ in diagnosing DLD in Section 1.4.3.

1.3.2 Executive Functioning

Children with DLD exhibit difficulties in several executive functioning domains, with deficits in verbal working memory being well-documented (see Section 1.2.2). There is also growing evidence of visuospatial working memory deficits in this population (Vugs et al., 2014). For example, pre-schoolers with DLD perform poorly on tasks like Block Recall and Dot Matrix, which test the short-term storage of visuospatial information (Niu et al., 2024). Children with DLD also struggle with tasks such as Backward Block Tapping and Odd-One-Out, which probe the ability to mentally reverse visual sequences or identify unique items. There is some evidence that group differences diminish in school-aged children with DLD, suggesting improvements in visual recoding abilities in this population over time (Niu et al., 2024).

Children with language impairments are more likely to have concurrent attention difficulties, and likewise, several children with ADHD exhibit difficulties with language (Cohen et al., 2000). There are various hypotheses regarding the relationship between language and attention deficits; some suggest they stem from a common underlying disorder, while others argue that deficits in one domain may exacerbate difficulties in the other (Redmond, 2005). Attentional deficits in children with DLD are particularly prominent in selective and sustained attention (Finneran et al., 2009; Noterdaeme et al., 2001; Spaulding et al., 2008; Stevens et al., 2008). The former refers to the ability to focus on specific targets while excluding distractors, and the latter refers to maintaining focus over time. Deficits in sustained attention in DLD are most pronounced in auditory linguistic tasks, followed by auditory non-linguistic, and visual tasks (Ebert & Kohnert, 2011). The extent to which auditory attention deficits can be attributed to impaired auditory processing or domain-general deficits in attention is unclear. Regardless, difficulties with sustained auditory attention are closely linked to poor performance on a broad range of working memory and language tasks in this population (see Smolak et al., 2020). Attentional shifting, or the ability to disengage from one focus and shift to another, is another area of difficulty in DLD (Aljahlan & Spaulding, 2021). Overall, attentional deficits appear to remain consistent across age groups, suggesting that the difficulties do not diminish with age.

Underperformance on inhibitory control and cognitive flexibility tasks have also been documented in children and adolescents with DLD (Pauls & Archibald, 2016). Notably, task performance can be influenced by linguistic load; in one study group differences disappeared on tasks with low linguistic demands, like the flanker task (Arbel & Donchin, 2014) or visual search (Das & Äystö, 1994). In contrast, children with DLD exhibited greater interference from

non-target stimuli in tasks with higher linguistic demands, such as sentence recall (Marton et al., 2007) and naming with linguistic distractors (Seiger-Gardner & Brooks, 2008). Furthermore, these children can perform comparably to their typically developing peers in simple task-switching scenarios, but performance declines in DLD on tasks involving complex or multivalent stimuli (Dibbets et al., 2006; Henry et al., 2012; Im-Bolter et al., 2006). Deficits in inhibitory control have been proposed to drive poor performance on complex tasks in this population (Cragg & Chevalier, 2012).

1.3.3 Motor Skills and Praxis

General weaknesses in gross and fine motor skills, as well as speech motor patterns are well documented in DLD (Brumbach & Goffman, 2014; Hill, 2001; Sanjeevan & Mainela-Arnold, 2019; Vuolo et al., 2017; Zelaznik & Goffman, 2010). In 6- to 12-year-olds with DLD, these weaknesses are evident in tasks like hopping and line walking, with balance issues being particularly prominent (Johnston et al., 1981; Powell & Bishop, 1992). Early fine and gross motor deficits have been found to predict persistent language impairment, explaining up to 40% of the variance in language outcomes among children with DLD (Sack et al., 2022).

Deficits in praxis–the ability to coordinate purposeful, skilled movements–are also prominent in DLD, especially in tasks requiring the imitation of representational or non-symbolic gestures (Dewey et al., 1988; Hill, 1998; Hill et al., 1998). Recent research suggests that the core difficulty in DLD lies in the ability to coordinate temporally organised sequences with dependency relations, be it in motor, language, or other cognitive domains (Goffman & Gerken, 2023). This is supported by impaired performance on tasks like nonverbal serial reaction time, bimanual clapping, and drumming musical sequences (Hsu & Bishop, 2014; Kreidler et al., 2023; Lum et al., 2014; Tomblin et al., 2007).

Children with DLD also exhibit speech motor deficits that mirror those observed in manual tasks. Their accuracy and stability in speech motor movements decrease, particularly when sequential dependencies are involved (Sack et al., 2022; Saletta et al., 2018). This is evident in both perceptual and kinematic studies showing difficulties in coordinating precise lip and jaw movements (Goffman, 1999; Smith et al., 1995). Network science studies have also shown that speech sound sequences in children with DLD are less efficiently organised, leading to suboptimal phonological network structures (Benham et al., 2018). In a similar vein, researchers have found that non-linguistic oromotor skills predict children's pseudoword repetition ability,

challenging the long-standing assumption that phonological storage or working memory alone contribute to these children's poor performance on pseudoword repetition tasks (Krishnan et al., 2013).

1.4 Diagnostic Criteria for DLD

1.4.1 Advantages of Diagnostic Labels

Diagnostic labels serve different purposes depending on the contexts in which they are used (Werkhoven et al., 2022). A diagnosis of DLD is essential for accessing clinical and educational support. Receiving a diagnosis can foster connections among the affected individuals and families for resource sharing and support. Moreover, the labels SLI and DLD have been pivotal in establishing international advocacy platforms such as Raising Awareness of Developmental Language Disorder (RADLD) or DLD and Me. The current best practice guidelines for identifying and diagnosing DLD were established less than a decade ago by the multinational Criteria and Terminology Applied to Language Impairments consortium (CATALISE; Bishop et al., 2016). This interdisciplinary effort led to the inclusion of updated diagnostic criteria for DLD in two major diagnostic manuals: the International Classification of Diseases-11th Revision (ICD-11) and the Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5), although the DSM-5 uses the term "Language Disorder."

1.4.2 Diagnostic Guidelines

DLD is traditionally diagnosed based on exclusionary criteria, implying a significant deficit in language that is not explained by perceptual, cognitive, or motor factors (Leonard, 2014). In the context of research, recruiting cases of DLD without co-occurring diagnoses like ASD or ADHD is often preferred to isolate language-specific findings from confounding factors. In clinical settings, strict exclusionary criteria are not required, as the goal is to support the child's language skills regardless of other diagnoses. Cases of DLD with co-occurring diagnoses are however the norm rather than the exception, creating a trade-off between the precision of scientific conclusions and their generalisability to the broader population. A transdiagnostic approach to research and practice, i.e., focusing on a few set of broader phenotypic traits that are shared across different conditions, could be valuable to study and provide services for children with DLD (e.g., Astle et al., 2022; Bishop et al., 2016).

DLD is usually diagnosed around ages 4 to 6, shortly before and after children enter formal schooling (Fig. 1.2). A referral is advised if caregivers express concerns about a child's speech, language, or communication abilities; if the child fails to meet language milestones or academic standards; or if they exhibit behavioural issues, listening difficulties, or poor reading comprehension. A comprehensive clinical assessment includes caregiver interviews, naturalistic observation, and administering standardised or criterion-based tests. The child's perspective on areas of challenge should also be considered. A test battery that covers a broad range of expressive and receptive language skills is employed when administering standardised assessments. Statistical cut-offs in these assessments are usually arbitrary (but clinically agreed upon), and there is no definitive line that separates language impairment from the lower end of normal language ability. For clinical purposes, children who are identified as having DLD tend to score > 1SD below the normative mean on several standardised language tests (Spaulding, 2012; Spaulding et al., 2006).

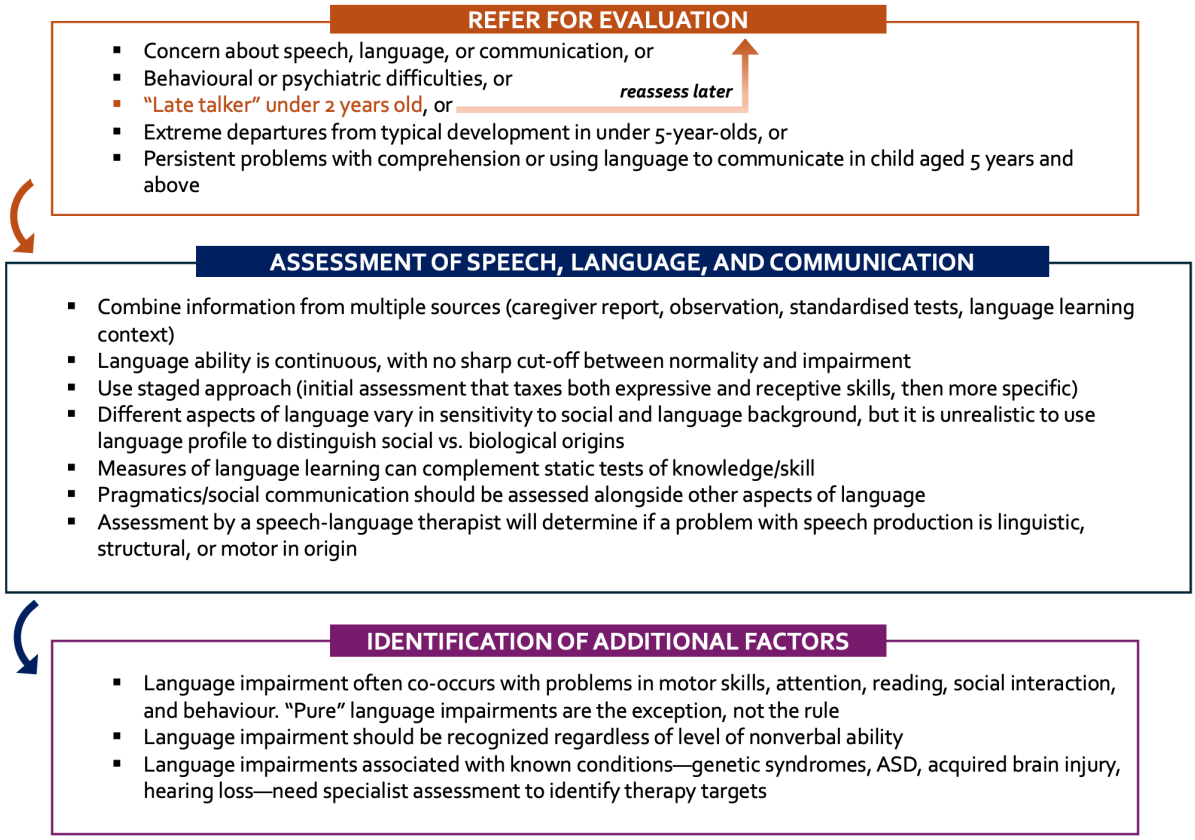


Fig. 1.2 ***Overview of statements from CATALISE.*** The figure (adapted from Bishop and colleagues (2016) with slight modifications) summarises the referral and diagnosis route for children who show early speech, language, and/or communication difficulties.

Predicting which children will experience long-term language problems is challenging. For example, many late talkers (i.e., toddlers with limited expressive vocabulary at 18-24 months of age) who are referred for assessment often catch up without intervention. Factors that can help expect a poor prognosis include being male, exposure to nicotine in utero, weak language comprehension, poor use of gestures, difficulty in multiple language areas, a family history of language impairments, and poor response to intervention (Bishop et al., 2016; Calder et al., 2022). The more risk factors present, the higher the likelihood that the child's language difficulties will persist. Despite these indicators, predicting individual outcomes remains unreliable, especially when issues are not severe. Reassessment after six months is therefore recommended. This is because many pre-schoolers who meet minimum language ability levels still present with language problems, and some children with language difficulties in pre-school years were not late talking toddlers (Reilly et al., 2010; Snowling et al., 2016; Zambrana et al., 2014). The term "language delay" is often avoided as it is subject to misinterpretation. If language difficulties are associated with a biomedical condition, the term "language disorder associated with x" is used. Otherwise, the diagnosis of DLD is given. Conditions with known genetic bases, acquired brain injury, sensorineural hearing loss, intellectual disability, or ASD fall under biomedical conditions.

The distinctions between ASD and other developmental language difficulties are less clear-cut at the moment (Bishop et al., 2016). On the one hand, many children with ASD present with structural language deficits that are like those seen in DLD (Kjelgaard & Tager-Flusberg, 2001; Loucas et al., 2008). On the other hand, some individuals with DLD present with social communication difficulties which superficially overlap with core features of ASD (Andreou et al., 2022). There are important differences, however. According to the DSM-5, difficulties with structural language are not necessary for an ASD diagnosis (despite being strongly associated with ASD), but such language impairments are the primary markers of DLD (Andreou et al., 2022; Tager-Flusberg et al., 2011). In case of language disorder associated with ASD, severe problems with receptive language and functional communication are expected (Loucas et al., 2008). Furthermore, receptive and expressive language are thought to be equally impaired ASD, whereas in DLD receptive language is commonly stronger than expressive. It remains a matter of debate the extent to which ASD and DLD overlap. Similar to the characterisation of DLD and dyslexia discussed in Section 1.2.5, they are perhaps best viewed as distinct dimensional conditions that can co-occur.

1.4.3 The Role of Nonverbal Intelligence in Diagnosis

A diagnosis of DLD does not exclude children with low-average nonverbal intelligence quotient (NVIQ) scores (defined as a score between 70-85 on most standardised tests). Historically, the diagnosis of DLD/SLI required nonverbal intelligence to be within the "normal" range, that is a statistical cut-off of not lower than 1SD below the normative mean (i.e., > 85 on most standardised tests). This criterion often restricted access to clinical services for children whose NVIQ scores fell within the low-average 70-85 range, in which case the deficit was no longer considered "specific" to language. A pivotal study demonstrated that the severity of language deficits, educational attainment, and psychosocial needs did not differ significantly between children with DLD who had average versus low-average NVIQ scores (Norbury et al., 2016). Additionally, nonverbal intelligence is not a reliable predictor of a child's potential, response to intervention, or long-term outcomes (Bishop et al., 2016; Norbury et al., 2016). Low nonverbal ability is currently best viewed as a correlate of, not an explanation for DLD, and the key factor in identifying language impairment is whether the child is likely to benefit from intervention, regardless of performance on NVIQ tests.

1.5 Theories of DLD

Two main theoretical frameworks have traditionally been used to explain the nature of deficits in DLD: linguistic-based theories and cognitive-based accounts (see Bishop, 2006). Linguistic-based theories, which gained prominence just before the turn of the century, suggest that the deficits in DLD are confined to language abilities, particularly within the grammatical domain (e.g., Clahsen, 1989; Crago & Gopnik, 1994; Rice et al., 1995; Van Der Lely et al., 1998). Proponents of this framework argue that DLD provides evidence for a domain-specific linguistic system that is either atypical or underdeveloped (e.g., Clahsen, 1991; Rice et al., 1995). It was further proposed that the heritable nature of DLD (see Section 1.6) and the selective impairment of syntactic abilities in this population support the existence of an innate language acquisition device (Van Der Lely, 1997).

Language-based theories soon encountered criticism as evidence accumulated showing that children with DLD exhibit deficits in broader cognitive and motor domains that cannot be solely attributed to language impairment. These observations led to the development of cognitive-based accounts, which propose that the language impairments in DLD are secondary to more general perceptual or cognitive deficits, such as limitations in auditory processing

(Tallal & Piercy, 1973, 1974), short-term memory (Gathercole & Baddeley, 1990), or general processing capacity (Bishop, 1992).

Research has indeed demonstrated a strong link between DLD and reduced processing speed (Leonard et al., 2007; Miller et al., 2001; Park et al., 2015), which is a key component of cognitive functioning and closely tied to nonverbal intelligence (Dehn, 2014; Engle et al., 1999; Gillam et al., 2021). Children with DLD often score lowest on timed nonverbal reasoning tasks, such as Block Design, Object Assembly, and Picture Completion, indicating general cognitive slowness. These observations led to the theory that children with DLD have a reduced processing capacity, which further diminishes as the computational complexity of tasks increases (Bishop, 1994; Hayiou-Thomas et al., 2004). Although the processing limitation hypothesis accounts for many of the difficulties observed in DLD, it has been criticised for lacking specificity and being difficult to test empirically (Ullman & Pierpont, 2005).

Within the cognitive framework, the Procedural Deficit Hypothesis (PDH; Ullman & Pierpoint, 2005) and its more recent extension, the Procedural Circuits Deficit Hypothesis (Ullman et al., 2020), have gained significant attention. Drawing on the distinction between the declarative and procedural learning mechanisms from classic memory theories (e.g., see Squire, 2009), the domain-general deficits in DLD are proposed to stem from neurobiological abnormalities in the brain's procedural learning systems, specifically the cortico-basal ganglia-thalamo-cortical circuits (see Krishnan et al., 2016). The procedural learning system possibly contributes to many functions, including statistical learning (Evans et al., 2009), tacit learning of morphophonological and morphosyntactic rules (Ullman et al., 2020), and serial reaction time tasks (Lum et al., 2014). The PDH predicts that children with DLD exhibit impairments in these implicit learning tasks, both verbal and nonverbal, and that their language difficulties arise from an inability to extract the underlying structures from the statistical features of input. Additionally, the theory suggests that unlike the procedural system, the declarative memory system, which underlies explicit knowledge acquisition, remains relatively unaffected in DLD and may even compensate for procedural learning deficits. Neurobiologically, this compensatory role is thought to be represented in the structure and function of the medial temporal lobes.

The main strength of the PDH is its ability to offer a unifying explanation for domain-general deficits in DLD, and the delineated neurobiological circuitries enables the generation of testable hypotheses. In support of the PDH, individuals with DLD often underperform on tasks

involving statistical and artificial grammar learning (Krishnan et al., 2016). This poor performance nonetheless appears to be more limited to the ability to encode and learn sequences (e.g., see Krishnan et al., 2016), with some authors further suggesting impairment in a very specific type of sequence rather than all aspects of sequential learning (Gerken et al., 2021). Goffman and Gerken (2023) recently proposed a theory inspired by the PDH but focused on developmental changes in learning constructs that specifically contain 2nd-order sequence dependencies. In these constructs, the appearance of a segment in one position depends on a segment occurring in another position, creating a contextual dependency characterised by an "if and only if" relationship between units. Children and adults with DLD reportedly struggle most with learning such dependencies.

1.6 Genetics of DLD

The idea of a hereditary basis for language impairments in children can be traced back to as early as 1929, when neurologist Jacques Ley studied monozygotic twins with congenital aphasia, which was the term then used for DLD (Ley, 1929). Mounting evidence since then has underscored the contribution of genes to typical and atypical language learning patterns (Mountford & Newbury, 2019). Various methodologies have classically been employed in this domain, from family aggregation to pedigree studies. The recent technological advancements in molecular genetics coupled with large-scale population studies are rapidly enhancing our understanding of the underlying genetic architecture of DLD, though much remains to be explored.

1.6.1 Family Aggregation Studies

Speech and language impairments often cluster within families (e.g., Hurst et al., 1990). Family aggregation studies consistently report a higher number of affected first-degree relatives in individuals with DLD compared with matched controls (Chilosi et al., 2021). The prevalence of affected relatives in DLD varies considerably, ranging from 20% (Neils & Aram, 1986) to 40% (Stromswold, 1998; Tallal et al., 1989). This variation likely reflects differences in sample sizes, types of kinship studied, methods of language assessment, and criteria for defining "affected" individuals. Nonetheless, these studies cannot conclusively establish genetic causation, as families share environmental factors alongside their genes (Bishop et al., 2003). Twin studies

can offer a more precise approach to disentangling genetic and environmental contributions to DLD.

1.6.2 Twin Studies

Twin studies are particularly helpful in distinguishing genetic influences from environmental effects. This was illustrated in an early study where twins with DLD were assessed on pseudoword repetition and auditory processing tasks (Bishop, 2002). While both abilities were impaired, pseudoword repetition showed strong genetic influence, whereas auditory processing did not. An early review reported concordance rates of 75% for monozygotic twins and 43% for dizygotic twins in language disorder (Stromswold, 2001). A large-scale longitudinal study found a higher-than-expected proportion of twins lagging in language during pre-school years (a phenomenon called the "twinning effect"), which was more pronounced in monozygotic twins but tended to resolve by age 6 (Rice et al., 2014). Some argue that twin studies may overestimate heritability due to unaccounted differences in shared environments. Therefore, pedigree studies tracing inheritance patterns across generations can provide more compelling genetic evidence.

1.6.3 Pedigree Studies

A significant breakthrough in the genetics of language disorders occurred with the discovery of the KE family, a large multigenerational family where speech and language deficits were linked to a mutation in the *FOXP2* gene (Fisher et al., 1998; Hurst et al., 1990; Lai et al., 2001). Affected family members exhibited what is arguably a severe form of DLD, with significant deficits in tasks involving sequencing (Liégeois et al., 2003; Watkins et al., 2002). The inheritance pattern suggested a 50% likelihood of passing the disorder to offspring, affecting males and females equally. Subsequent pedigree studies did not however replicate this clear inheritance pattern in other families with DLD (Stromswold, 1998; Tomblin et al., 1996). Moreover, the equal sex distribution in the KE family contrasted with the male bias commonly observed in DLD. Nonetheless, a note of caution here is that the predominance of DLD in males may reflect a referral bias, since boys are more frequently referred for assessment (Flax et al., 2003).

1.6.4 Molecular Genetics

Monogenic variants like the one in *FOXP2* in the KE family are rare causes of language disorders (Mountford et al., 2022). In fact, *FOXP2* is not a major candidate gene for DLD, and its variants do not contribute to most cases of DLD (Eising et al., 2019; Newbury et al., 2002). However, as a transcription factor, *FOXP2* regulates other genes, including *CNTNAP2*, which plays a crucial role in neuronal development and synapse formation (George-Hyslop et al., 2022). *CNTNAP2* has been found to influence brain connectivity in regions implicated in language and other cognitive functions. Associations between *CNTNAP2* and performance on pseudoword repetition tasks are reported in families with DLD (Vernes et al., 2008). Other genes, such as *ATP2C2* and *CMIP*, have also been implicated in DLD and associated with pseudoword repetition ability (Andres et al., 2021; Chen et al., 2017).

To date, over 30 genes have been identified, providing molecular evidence for genetic involvement in DLD. The prevailing view is that similar to other neurodevelopmental disorders, DLD has a complex genetic aetiology, but it can be monogenic in some cases. For instance, in a study of 43 individuals with severe DLD, variations in just three genes fully accounted for their language difficulties (Chen et al., 2017). Notably though, such cases represent only a minority; most individuals with DLD exhibit a complex genetic model where variants in multiple genes collectively increase the risk for a language impairment (Graham et al., 2015; Mountford et al., 2022). Currently, the field is increasingly utilising imaging transcriptomic analyses to identify genes whose expression patterns correlate with neuroimaging phenotypes, offering deeper insights into the relationship between genetics and neurobiology during neurodevelopmental (Arnatkeviciute et al., 2021; Whitaker et al., 2016).

In summary, heritability studies and genome screening suggest that DLD is linked to subtle genetic disruptions, likely impacting the development of neural circuits involved in language acquisition during pre- and post-natal stages (Den Hoed & Fisher, 2020; Mountford et al., 2022; Newbury & Monaco, 2010). Advances in brain imaging can help detect these structural and functional neural differences, with the ultimate goal of identifying potential endophenotypes that link genetic, neural, and behavioural variations in DLD.

1.7 Neurobiology of DLD

Studying the brain basis of DLD has practical and theoretical implications. Clinically, advancing our understanding of the biological mechanisms underlying DLD can lead to

designing more reliable assessment methods and advanced treatments (e.g., see Cancer et al., 2021 for the use of neurofeedback for dyslexia). Moreover, pinpointing the neural differences in DLD can help combat the prevailing myths that attribute DLD to poor parenting or environmental factors (Matić et al., 2021).

From a scientific standpoint, understanding the neurobiological basis of DLD is crucial for insights into language development. Current prominent theories of how language is processed in the brain are largely based on adult literature, which do not adequately address how the brain learns language in childhood. Interestingly, children with DLD can perform worse on language tasks than children who miss an entire left hemisphere due to congenital defects or hemispherectomy (Asaridou et al., 2020; Curtiss & Schaeffer, 2005; Liégeois et al., 2008; Newport et al., 2017), prompting questions about the distinction between how the brain processes and represents language in its fully developed state versus how it acquires language in development. A comprehensive theory of language must therefore consider the learnability question both in typically developing children and in those who struggle to learn language.

Since the 1980s there have been fewer than 60 brain imaging studies of individuals with DLD. These studies have investigated brain structure and function using methods such as voxel-based morphometry, task-based functional MRI, and diffusion imaging. Most structural studies have focussed on grey matter volume, comparing individuals with DLD with typically developing controls or those with related conditions like ASD. A handful of studies have explored white matter tract integrity or functional brain differences using task fMRI. To date, no published studies have used resting-state imaging, likely due to the challenges of obtaining such scans in younger populations.

Despite clear indications of neuroanatomical, and to a lesser extent, functional differences in DLD, findings across studies are inconsistent (Asaridou & Watkins, 2022). This inconsistency is partly due to evolving definitions and diagnostic criteria for DLD, its inherent heterogeneity, and frequent co-occurrence with other neurodevelopmental conditions. There are also methodological challenges, including the wide age ranges of participants (spanning the age range 4-27 years), which complicate comparisons between studies given the brain's prolonged and non-uniform maturational trajectory. Other sources of inconsistency involve small sample sizes, and variations in analysis techniques and statistical approaches.

With these limitations in mind, I provide an overview of the neuroimaging landscape in this section, highlighting the most consistent findings. Interpretations of these findings are

presented in Chapters 3 through 5. I have confined this summary to findings of grey matter since that is the focus of my structural imaging chapters. For a summary of studies on white matter in DLD refer to the review by Asaridou and Watkins (2022). Similarly, because Chapter 5 presents a functional MRI investigation, the summary of functional results is limited to studies using this method. Other functional imaging techniques used for studying DLD, including single-photon emission computed tomography (SPECT), positron emission tomography (PET), and transcranial Doppler ultrasound (TCD) were comprehensively reviewed by Abbott and Love (2023).

1.7.1 Structural Imaging Studies

Manual tracing, semi-automated, and quantitative methods have been used to examine the size, shape, or asymmetry of grey matter structures in DLD (Table 1.1). These studies have also explored whether variations in neuroanatomical structures correlate with performance on neuropsychological assessments (e.g., Badcock et al., 2012; Kurth et al., 2018; Soriano-Mas et al., 2009). The cumulative evidence suggests a distributed, bilateral pattern of subtle morphological abnormalities, primarily focused on perisylvian cortical regions involved in speech and language, and subcortical structures implicated in habit formation and implicit/procedural learning (Krishnan et al., 2022; Mayes et al., 2015). There is a lack of agreement on the precise location and direction of these differences, i.e., whether affected regions are smaller or larger in those with DLD.

In terms of cortical anomalies in the frontal lobes, both smaller (Gauger et al., 1997) and larger (Badcock et al., 2012) volume of the left inferior frontal gyrus in DLD were reported. Greater volume in DLD was also found in perisylvian regions in the right hemisphere (Pigdon et al., 2019; Plante, 1991a; Soriano-Mas et al., 2009) including in the pars orbitalis (Lee et al., 2020), pars triangularis (Kurth et al., 2018), and insula (Badcock et al., 2012). Posteriorly, there were reports of lower volume in DLD in the left (Jernigan et al., 1991) and the right hemisphere, comprising the planum temporale (Preis et al., 1998), other portions of the superior and middle temporal gyri, and parietal regions (Badcock et al., 2012; Girbau-Massana et al., 2014).

Table 1.1 ***Summary of studies investigating structural grey matter correlates of DLD.***

Study	Participants		Method	Results
	Group (*n*)	Mean age		
Krishnan et al. (2022)	DLD (33) TD (56) HSL (28)	12.48y 12.41y 12.4y	Semi-quantitative MRI (multi-parameter mapping)	➢ TD > DLD – MTsat values in L/R caudate nucleus bilaterally, L ventral sensorimotor cortex, Heschl's gyrus, L insula. ➢ DLD – Globally lower R1 values. ➢ MTsat and R1 values in the above-mentioned areas positively correlated with language proficiency. ➢ No group differences in R2* maps.
Lee et al. (2020)	Cohort 1 DLD (14) TD (12) Cohort 2 DLD (19) TD (61)	 22.42y 22.1y 16.96y 16.62y	FreeSurfer ROI	➢ TD > DLD – Intracranial volume. ➢ DLD > TD – L transverse temporal gyrus, L/R temporal poles, R pars orbitalis.
Pigdon et al. (2019)	DLD (17) TD (40)	9–11y	Whole-brain and ROI VBM	➢ DLD > TD – R inferior frontal gyrus, posterior superior temporal gyrus, and putamen but did not survive Bonferroni correction. R cerebellum. ➢ DLD – Uncorrected comparisons at $p < 0.001$ showed larger peak volume in transverse temporal gyrus, pars triangularis, parahippocampal gyrus, and caudate tail on the R side, less peak volume in R cuneus and inferior occipital lobe.
Kurth et al. (2018)	DLD (13) TD (18)	10.21y 10.2y	ROI VBM using cytoarchitectonic atlas	➢ DLD > TD – R pars triangularis. ➢ DLD – Greater R > L asymmetry in pars triangularis at trend level.
Girbau-Massana et al. (2014)	SLI (10) TD (14)	8.5–10.9y 8.2–11.8y	Whole-brain VBM	➢ TD > SLI – L/R medial occipital gyri, R postcentral gyrus. ➢ SLI > TD – R superior occipital gyrus, CSF volume. ➢ GM/WM ratio not significantly different between groups.
Lee et al. (2013)	DLI (12) TD (12)	21.99y 22.06y	ROI analysis with AutoWorkup	➢ TD > DLI – L/R caudate nucleus, globus pallidus, thalamus. Cerebral lobes including the occipital lobe and frontal lobe. ➢ DLI > TD – Hippocampus, putamen, R globus pallidus, nucleus accumbens.
Badcock et al. (2012)	SLI (10) TD (16) SIB (6)	13.5y 12.5y 18y	Whole-brain VBM	➢ SLI > TD – L inferior frontal gyrus, L intraparietal sulcus, R insula.

				➢ TD > SLI – L/R posterior superior temporal sulcus, R superior temporal gyrus, R caudate nucleus, R substantia nigra, medial frontal polar cortex, R medial superior parietal cortex, L occipital pole. ➢ SLI > SIB – L anterior intraparietal. ➢ SIB > SLI – R parietal opercular, L occipital cortex.
Hodge et al. (2010)	Whole sample (6–13y) SLI (9) NC (11) ALN (6) ALI (16)	 9.9y 10.4y 8.3y 9.8y	MRI cerebellar volumetric segmentation and parcellation	➢ Reversed asymmetry in language-impaired (SLI and ALI) relative to unimpaired (NC and ALN) in posterior-lateral cerebellar lobule VIIIA (R larger in language-unimpaired group, L larger in language-impaired). Decreased size of anterior vermis in SLI and ALI. ➢ ALI > SLI – Lobule VIIA Crus I. ➢ Positive correlation between language scores and lobule VIIIA asymmetry and anterior vermis.
Soriano-Mas et al. (2009)	Whole sample (5–17y) SLI (36) TD (36)	 10.58y 10.88y	Whole-brain VBM	➢ SLI > TD – Mean global volume, R posterior superior temporal gyrus, L middle occipital gyrus. ➢ Positive correlation (age and GM volume) in TD but not SLI.
	Younger cohort SLI (19) TD (14)	 <11y		➢ SLI > TD – Mean global volume, L/R entorhinal area, L temporopolar cortex, L caudate nucleus, L motor cortex, L precuneus. ➢ SLI > TD – Juxtacortical WM of R medial frontal cortex, L/R middle temporal gyrus. ➢ Increase with age in several of these regions in TD but not SLI.
	Older cohort SLI (17) TD (22)	 >11y		➢ No group differences in GM or WM volume.
Jäncke et al. (2007)	DLD (21) TD (21)	8.33 (4-10y) 9.26 (4–10y)	Whole-brain VBM	➢ No group differences in GM volume. ➢ TD > DLD – WM volume in a network of L hemisphere regions comprising the motor cortex, dorsal and ventral premotor cortex, and planum polare on superior temporal gyrus.
Herbert et al. (2005)	DLD (15) TD (15) ASD (16)	5.7–11.3y	Whole-brain manual and semi-automated analysis	➢ Similar cerebral asymmetry patterns in DLD and ASD, different from TD. ➢ Higher aggregate cortical parcellation unit R > L asymmetry in DLD and ASD. ➢ Group differences in unimodal and higher-order association cortex in DLD but not in primary sensory-motor cortex.
De Fossé et al. (2004)	SLI (9) TD (11) ALI (16) ALN (6)	9.9y 10.4y 9.8y 8.3y	ROI manual and semi-automated analysis	➢ SLI – Atypical asymmetry in language-related brain regions in SLI. Reduced L > R volumetric asymmetry of Broca's area. Positive correlation between verbal IQ and greater L asymmetry of pars triangularis. ➢ Typical size of planum temporale in language-normal TD and ALN but larger in L in language-impaired SLI and ALI groups.

Herbert et al. (2003)	DLD (24) TD (30)	8.24y 9.13y	Whole-brain manual and semi-automated analysis	➢ DLD > TD in total brain size, driven by increase in cerebral WM volume. ➢ Cerebral cortex and caudate nucleus relatively but not absolutely smaller in DLD.
Watkins et al. (2002b)	KE family members Affected (10) Unaffected (7) TD (17)	 9-75y 9-27y ---	VBM	➢ No differences between unaffected and TD. ➢ Unaffected, TD > affected – R/L caudate nucleus. ➢ Positive correlation between size of caudate and nonword repetition abilities. ➢ No differences in structural asymmetry of cortical or subcortical regions.
Preis et al. (1998)	DLD (21) TD (21)	8.33y 8.25y	ROI manual parcellation	➢ No group difference in planum temporale and planum parietale asymmetry. ➢ Planum temporale bilaterally smaller in DLD, accounted for by smaller forebrain sizes.
Gauger et al. (1997)	SLI (11) TD (19)	9.1y 8.9y	Manual ROI morphometry	➢ TD > SLI – L pars triangularis. ➢ Correlation between a smaller L pars triangularis and lower language outcomes. ➢ SLI – Reduced L > R asymmetry in pars triangularis, planum temporale, posterior ascending ramus.
Plante et al. (1991)	SLI (8) TD (8)	5y2m 4y2m–9y6m	Manual ROI morphometry	➢ SLI – Atypical (R = L and R > L) asymmetry of perisylvian areas. ➢ No significant group differences in extra-perisylvian regions.
Jernigan et al. (1991)	LI (20) TD (12)	8.9y 9.0y	Whole-brain semi-automated and manual morphometry	➢ TD > LI – L posterior perisylvian region. ➢ LI – Less L/R ratio in prefrontal cortex, including orbitofrontal, dorsolateral, and medial frontal cortex. More L/R ratio in superior parietal lobe and superior occipital lobe. Increased R > L asymmetries in perisylvian region but weak statistical evidence.

Note: The second column provides information of the sample sizes and mean age in years. The age range is provided in parentheses when available. Studies are ordered based on publication date (most recent first). *Abbreviations*: DLD – developmental language disorder; TD – typically developing; HSL – history of speech-language impairment; MTsat – magnetisation transfer saturation; L – left; R – right; R1 – longitudinal relaxation rate; R2* – effective transverse relaxation rate; ROI – region of interest; VBM – voxel-based morphometry; DSD – developmental speech disorder; DSLD – developmental speech and language disorder; SLI – specific language impairment; LI – language impairment; ASD – autism spectrum disorder; ALI – autism and language impairment; ANL – autism with no language impairment; DLI – developmental language impairment; T-SLI – twin specific language impairment; ASD-LI – autism with language impairment; SIB – siblings of children with DLD; NC – normally developing controls; ALN– autism with normal language.

Greater volume in DLD was seen in the transverse temporal gyrus, temporopolar cortex (Lee et al., 2020; Soriano-Mas et al., 2009), medial parietal cortex (Soriano-Mas et al., 2009), and intraparietal sulcus (Badcock et al., 2012). Smaller volume of the right perisylvian region and the occipital petalia were associated with higher verbal intelligence and receptive vocabulary in DLD, respectively (Soriano-Mas et al., 2009). Some studies did not find grey matter differences between typically developing children and those with DLD (Jancke et al., 2007).

A quantitative MRI study from the OxBOLD cohort, using multi-parametric mapping, found lower levels of myelin, indexed through lower magnetisation transfer saturation values, in DLD in several regions of the left hemisphere's speech and language network, including in pars opercularis, insula, and several parts of the temporal lobe. In addition, lower mean global values in longitudinal relaxation rate (R1, another myelin marker) were found in DLD, reflecting widespread differences in myelin across cortical and subcortical grey matter bilaterally, and notably in the caudate nucleus (Krishnan et al., 2022). Moreover, the MTsat values in the left caudate nucleus positively correlated with language proficiency scores.

Subcortically, smaller size of the caudate nucleus in DLD has been reported, especially in the right hemisphere (Badcock et al., 2012; Herbert et al., 2003; Jernigan et al., 1991; Lee et al., 2013). Smaller caudate nucleus bilaterally was also found in the affected KE family members, which positively correlated with nonword repetition scores (Watkins et al., 2002). A recent quantitative synthesis and meta-analysis of data from the neuroanatomical studies of DLD, totalling 577 participants (250 DLD, 327 typically developing), found strong evidence of structural anomalies specifically clustering in the anterior neostriatum (the caudate head and anterior putamen), with almost 100% of participants with DLD showing abnormalities in this region (Ullman et al., 2024). The frontal cortex yielded the second highest rate of neuroanatomical anomalies with a weighted proportion of 82.6% likelihood. Most recent results from the OxBOLD cohort also revealed smaller caudate nucleus bilaterally, though the same was true of all other subcortical structures studied, including the putamen, globus pallidus, thalamus, and hippocampus, all bilaterally (Cler et al., *in prep*).

Another focus of brain imaging in DLD is whether atypical structural asymmetries could provide clues to the neuroanatomical basis of functional lateralisation in this population. Research in this domain remains mixed. There were some reports of atypical structural asymmetry in perisylvian areas in DLD, especially less leftward asymmetry of the inferior

frontal gyrus (see Mayes et al., 2015 for a review). More pronounced rightward (right-greater-than-left) asymmetry of pars triangularis was also reported, and a positive correlation between verbal intelligence and more leftward asymmetry of pars triangularis (De Fossé et al., 2004; Kurth et al., 2018). The atypical pars triangularis asymmetry was specifically associated with language difficulties; boys with DLD or with ASD and concurrent language impairment showed atypical asymmetry, whereas those with ASD but no language impairment did not (De Fossé et al., 2004).

In a whole brain analysis, children with DLD showed greater rightward asymmetry in the aggregate amount of cortical parcellation units and smaller volume of left-asymmetrical cortex, with significant differences in language-related cortical parcellations, including the posterior supramarginal gyrus and planum polare (Herbert, 2005). An older study found atypical (right-greater-than-left) asymmetry in the prefrontal region and left-greater-than-right asymmetry in the parietal region in language impaired children, but no group differences in the posterior perisylvian regions (Jernigan et al., 1991). A study of a small sample of boys with DLD found atypical perisylvian asymmetries due to larger right hemisphere structures, while the left structures were of typical size (Plante, 1991a). In contrast, typical asymmetry of the planum temporale and planum parietale was reported for a cohort of children with DLD and their age-matched controls (Preis et al., 1998).

In sum, studies of grey matter in DLD reveal subtle morphological differences in both hemispheres, most commonly in the frontal cortex and subcortically in the head of the caudate nucleus and anterior putamen. Findings are inconsistent regarding the exact locations and whether these regions are smaller or larger in DLD. Some studies report atypical structural asymmetries in perisylvian regions, but results are mixed.

1.7.2 Functional Imaging Studies

Around 12 task-based fMRI studies, mainly with small sample sizes, have been conducted with individuals with DLD, with inconsistent results that mirror the findings on brain structure (Table 1.2). There are reports of underactivity, overactivity, or a combination of both depending on the brain region, type of task employed, and severity of language impairment in the studied cohorts. The study with the largest sample size, from the OxBOLD cohort, did not find significant group differences in neural activity between children with DLD and those with typical language during an overt verb generation task (Krishnan et al., 2021). In

Table 1.2 ***Summary of studies investigating neural correlates of DLD using task-based fMRI.***

Study	Participants		fMRI task	Results
	Group (*n*)	Mean age		
Krishnan al. (2021)	Whole sample (10y-15y11m) DLD (50) TD (67) HSL (26)	 12y 12.1y 11.9y	Overt verb generation	➢ No group differences in task-related activity or lateralisation. ➢ Group differences at sub-threshold level in L inferior frontal gyrus, L/R caudate nucleus in a subgroup of DLD with lowest performance. ➢ Language ability positively correlated with task-related activity in L pars orbitalis and L supramarginal gyrus at sub-threshold level.
Vansteensel et al. (2021)	DLD (16) 22q11DS (14) TD (25)	10-16y	Spoken narrative processing	➢ Very similar activation pattern between all groups. ➢ No lateralisation differences. ➢ Lower level of language task-related activation in language network in DLD and 22q11DS compared with TD. ➢ DLD and 22q11DS showed an opposite relationship between activation in L-Broca and language performance scores on PPVT.
			Hand movement	➢ TD > DLD – L sensorimotor hand area. ➢ No lateralisation differences.
Pigdon et al. (2020)	Whole sample (9y3m-11y2m) DLD (18) TD (42) DSD (5)	 10.33y 10.25y 10.25y	Overt pseudoword repetition	➢ No group differences despite lower behavioural performance in DLD, though the two clinical groups engaged slightly different brain area when compared at identical thresholds. ➢ DLD and DSD mainly showed activity in subcortical regions (thalamus and globus pallidus), and TD mainly in cortical regions similar to adult activation patterns for pseudoword repetition.
Plante et al. (2017)	DLD (16) TD (16)	20y 20y	Implicit word learning	➢ Roughly similar brain networks of learning activated by DLD and TD. ➢ Hyperactivity in DLD in L inferior frontal gyrus; L supramarginal and angular gyrus; L superior temporal gyrus/sulcus. ➢ All participants showed L hemisphere lateralisation on task.
Liégeois et al. (2016)	Case A-II (1) TD (24)	8y 8-11y	Overt pseudoword repetition	➢ Little fMRI activation in case A-II and de-activation (negative response) in pars opercularis + activity in L posterior superior temporal gyrus. ➢ Extensive brain activity in TD group in L/R sensorimotor and superior temporal cortices; L supplementary motor area, anterior cingulate cortex, pars opercularis; L/R globus pallidus. ➢ Difference between A-II and TD group did not survive correction for multiple comparisons.
Badcock et al. (2012)	SLI (10) TD (16) SIB (6)	13.5y 12.5y 18y	Overt word generation and passive listening	➢ Similar activity in TD and SIB; no activation in L inferior frontal gyrus and lower activation in L/R superior temporal gyrus in DLD.

				➢ less L lateralised activation in frontal and temporal regions during speech in DLD, but not TD and SIB.
De Guibert et al. (2011)	SLI (21) TD (18)	11.4y 12.7y	Covert word generation from categories	➢ Significant lack of left lateralisation in pars opercularis in SLI.
			Covert responsive naming (providing definitions)	➢ Under-activity in SLI in L posterior superior temporal and supramarginal junction. ➢ Significant lack of L lateralisation in Broca's area, supramarginal gyrus in SLI.
			Covert naming of phonological minimal pairs (e.g., *poule*, *boule*, moule)	➢ Under-activity in SLI in R anterior insula, R Broca's area, head of caudate nucleus. ➢ Significant lack of left lateralisation in pars opercularis in SLI.
			Covert naming of phonological segmentations (e.g., *car*, *carte*, *carton*)	➢ Significant lack of left lateralisation in pars opercularis in SLI.
Liégeois et al. (2011)	KE family Affected (4) TD (4)	 > 20y age-matched	Over pseudoword repetition	➢ Under-activity in affected members in R anterior cingulate and supplementary motor; L precentral gyrus and rolandic operculum; L/R putamen; L cerebellum.
Dibbets et al. (2006)	SLI (6) TD (7)	6.10y 6.10y	Switch task	➢ Increased activation in SLI in L superior and medial temporal gyrus; R angular gyrus.
			Non-switch task	➢ Increased activation in L/R frontal cortex, superior parietal and occipital lobes.
Weismer et al. (2005)	SLI (8) TD (8)	13.10y 14y	Listening span measure including sentence encoding and recognition of final words in prior sets of sentences	➢ Overall similar patterns between groups, similar to adult language processing and working memory literature. ➢ No laterality differences, L hemisphere bias for verbal stimuli. ➢ Encoding phase = significant under-activity in SLI in precentral sulcus and parietal regions. Less coactivation between inferior frontal gyrus and superior temporal gyrus during task. Significant correlations in DLD between activity in parietal and frontal regions and parietal and superior temporal gyrus during encoding. DLD showed more activity in inferior frontal gyrus during encoding, but this effect did not survive alpha correction. ➢ Recognition phase = underactivity in insular portion of inferior frontal gyrus in DLD + weak association between superior temporal gyrus and frontal regions + superior temporal gyrus and parietal regions.
Hugdahl et al. (2004)	Family members SLI (5) TD (6)	 11-70y 15-61y	Passive listening to vowels, pseudowords, and real words	➢ Hypoactivity in DLD in L middle temporal gyrus/superior temporal sulcus. ➢ DLD also showed activity R inferior frontal lobe, unlike TD. ➢ No laterality differences.
	KE family			➢ No activation in affected members in L/R inferior frontal cortex.

			Covert verb generation	➢ Overall higher, more diffuse activity in R hemisphere compared to L and posterior compared with anterior regions bilaterally. ➢ Interaction analysis = under-activation in affected members in L pars opercularis; R pars triangularis; L precentral gyrus; L supramarginal gyrus; R putamen/globus pallidus. Over-activation in L precentral gyrus; R temporal pole; L/R posterior superior temporal gyrus; a number of parietal regions.
Liégeois et al. (2003)	Affected (5) Unaffected (5) TD (10)	19-56y6m 25.3y Age-matched	Overt verb generation	➢ Activation in L inferior frontal gyrus and L/R putamen but significantly less than unaffected members. ➢ Overall mainly bilateral activation in affected members. ➢ No significant overactive regions.
			Overt word repetition	➢ Pattern similar to covert verb generation task in affected members, with extensive bilateral and posterior activation and no detectable activation in L/R inferior frontal gyrus. ➢ Significant under-activation in affected members compared with unaffected in L pars triangularis. ➢ Significant overactivation in L anterior insular cortex in affected members.

Note: The second column provides information of the sample sizes and mean age in years. The age range is provided in parentheses when available. Studies are ordered based on publication date. *Abbreviations:* DLD – developmental language disorder; TD – typically developing; HSL – history of speech-language impairment; L – left; R – right; PPVT – Peabody picture vocabulary test; DSD – developmental speech disorder; SLI – specific language impairment; SIB – siblings of children with DLD.

contrast, using a similar paradigm, Liégeois and colleagues (2003) found brain activity differences between the affected KE family members versus unaffected members and typically developing controls. The authors reported more bilateral activation patterns in the affected members, in addition to hypoactivity in the left inferior frontal gyrus and putamen bilaterally. Several other group differences also emerged during covert verb generation and an overt word repetition task, which are summarised in Table 1.2.

Studies that matched children on task performance found highly similar activation pattern between DLD and typically developing groups. In the study from the OxBOLD cohort, sub-threshold group differences emerged only when a subset of DLD children with weakest performance were compared against typical developing children with highest performance (Krishnan et al., 2021). These differences clustered around the left inferior frontal cortex, right motor cortex, and caudate nucleus bilaterally. Probabilistic activation maps also revealed a high degree of overlap between groups, indicating that at least in cases when children were matched on performance, the network of activated regions in DLD was similar to typically developing children (Krishnan et al., 2021; Pigdon et al., 2020).

The lack of consistent functional results between studies is probably in part due to the variety of tasks that have been employed, tapping different underlying cognitive processes. Moreover, most studies have used covert tasks, i.e. requiring passive participation (e.g., De Guibert et al., 2011; Hugdahl et al., 2004; Plante et al., 2017; Vansteensel et al., 2021; Weismer et al., 2005). It is difficult to disentangle whether neural activity differences reported in these studies are specific to the task or secondary to factors such as reduced engagement in children with DLD, especially given their known difficulties with sustained attention and executive functioning (see Section 1.3.2). Echoing these observations, a systematic synthesis of fMRI studies totalling 414 unique scans (176 DLD, 238 typically developing) yielded limited evidence for group differences in neural activity patterns (Ullman et al., 2024). In cases where anomalies were detected in the meta-analysis, these centred in the basal ganglia, similar to the structural results.

The idea of atypical functional lateralisation has long been proposed to explain speech and language difficulties in neurodevelopmental disorders, including in DLD. This theory attributes language difficulties to a failure to establish typical patterns of lateralisation for speech and language processing in the brain (see Bishop, 1990, 2013, for review). Similar to structural asymmetry studies, the evidence from the task-based imaging to support this theory remains

mixed. Two earlier studies provided tentative support the idea of atypical functional lateralisation in DLD (Badcock et al., 2012; De Guibert et al., 2011), while other findings do not support this hypothesis (Hugdahl et al., 2004; Krishnan et al., 2021; Plante et al., 2017; Vansteensel et al., 2021; Weismer et al., 2005). In the study by Badcock and colleagues (2012), brain activity during covert naming was less left-lateralised in children with DLD compared with their siblings and typically developing peers. Similarly, De Guibert and colleagues (2011) reported reduced left hemisphere activity in DLD in the posterior superior temporal and inferior parietal cortex during a definition task, and increased activity in the right inferior frontal cortex, anterior insula and caudate nucleus during a covert visual naming task. Furthermore, the affected KE family members had more extensively bilateral brain activity pattern during verb generation and word repetition tasks (Liégeois et al., 2003). Despite these findings, a well-powered investigation of a sample of twin children with over 100 cases of DLD using transcranial Doppler ultrasonography (fTCD) showed that there were no differences between school-age DLD and typically developing children on language lateralisation (Wilson & Bishop, 2018). The authors even found a greater incidence of right laterality for language in children with typical language, suggesting that an "atypical" pattern of language lateralisation is not necessarily at odds with developing typical language skills (Wilson & Bishop, 2018).

2

Behavioural and Cognitive Profiles in the OxBOLD Cohort

ABSTRACT

Numerous cross-sectional studies have investigated language deficits in children with developmental language disorder (DLD). Although DLD is characterised primarily as a disorder of language, it can co-occur with deficits in other cognitive and motor domains. A full characterisation of DLD requires studying these other skills and how they change over time, especially beyond childhood. In this chapter, we compared the performance of the OxBOLD cohort, including 54 participants with DLD and 74 age-matched typically developing controls (age range 10-15 years), on a comprehensive neuropsychological test battery. A subset of these participants (n = 53) was reassessed about four to five years later to examine changes in their neuropsychological profiles. At time I, participants with DLD had weaker performance than controls on all measures of language, memory, reading, nonverbal reasoning, and motor control. At time II, participants with DLD, now aged 14-20 years, showed similar rates of progress to controls across most measures, but a persistent performance gap remained, especially notable on a test of sentence recall. Additionally, the poorest longitudinal outcomes were on timed nonverbal tasks with a motor component. Our results indicated that individuals with DLD have qualitatively similar but quantitatively lower performance on a range of skills.

2.1 Introduction

Developmental language disorder (DLD) was primarily referred to as specific language impairment (SLI) prior to the CATALISE (Criteria and Terminology Applied to Language Impairments) consensus study (Bishop et al., 2016, 2017). The label SLI by definition implied poor language in the context of intact ability in other cognitive domains. Extensive research and clinical observations have shown, however, that DLD can be and commonly is accompanied by deficits in several domains beyond language (e.g., Sanjeevan & Mainela-Arnold, 2019; Smolak et al., 2020). In the first part of this chapter, I describe the behavioural profiles of 156 participants aged 10 to 15 years who took part in the OxBOLD project. I compare the performance of 54 children and adolescents who met the criteria for DLD with 74 who had typical development, and another 28 who had a history of speech and language difficulties. Neuropsychological data on measures of language, memory, reading, nonverbal reasoning, and motor skills was available.

Cross-sectional studies have been instrumental in advancing our understanding of the phenotype associated with DLD, but they offer limited insight into the developmental trajectories of cognitive skills in this population. A comprehensive characterisation of DLD requires investigating patterns of change in verbal and nonverbal abilities over time. At the moment, there is a dearth of research on longitudinal changes in cognitive development in DLD, and this is especially the case in adolescents and adults with DLD. Longitudinal research can determine whether children with DLD retain their relative positions among their age-matched peers and how their cognitive abilities develop as they transition into adulthood. Some evidence suggests that language abilities may plateau if sufficient growth does not occur by pre-adolescence, making it crucial to test this hypothesis (Rice et al., 2023).

In the second part of this chapter, I present longitudinal behavioral results from 53 of the OxBOLD participants, including 20 with DLD, 22 typically developing, and 11 with a history of speech-language difficulties. These participants were reassessed with behavioural testing and brain imaging after a mean gap of four years and six months. We investigated whether the behavioural deficits in DLD documented prior to age of 16 years (i.e., at time I) persisted into later adolescent years and early adulthood, and whether the direction and rate of change in the measures differed compared with age-matched controls. The group with a history of speech-language difficulties offered an interesting opportunity to explore behavioural profiles in individuals whose speech and language skills could be considered as resolved cases

of earlier challenges in these areas (i.e., cases of transient language problems in contrast to the persisting problems seen in the DLD group).

2.2 Methods

2.2.1 Participant Recruitment and Screening

One hundred and seventy-five children took part in the OxBOLD project. Children older than 10 years and younger than 16 who had grown up in the UK speaking English were included. Children were recruited through a range of venues, including those who took part in previous studies: the SCALES study (Norbury et al., 2016), the Wellcome Reading and Language Project (Snowling et al., 2016), and the OSCCI Twins study (Wilson & Bishop, 2018). We also recruited from schools for children with language learning difficulties and organisations conducting outreach with those with language impairments (ICAN, Afasic, RADLD), and dyslexia (British Dyslexia Association). Typically developing controls were recruited mainly from local schools and schools participating in university outreach programs.

Children were not recruited if they (1) had a diagnosis of another developmental disorder (e.g., Down syndrome, ASD, or ADHD); (2) indicated a history of neurological disorders such as epilepsy; (3) scored above seven on the Hyperactivity subscale of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997), which was filled out by parents; (4) scored above 15 on the Social Communication Questionnaire (SCQ; Rutter et al., 2003), also completed by parents; or (5) had any contraindication to MRI. We did not exclude children based on handedness or speaking multiple languages. Children who passed the initial screening underwent a comprehensive neuropsychological test battery (lasting approximately two hours) to evaluate their hearing, language, memory, reading, nonverbal reasoning, and motor skills. They were included in the sample if they passed the bilateral pure tone audiometric screening test and scored no more than 2 SDs below the normative mean on a composite nonverbal intelligence test.

Children's parents completed a background questionnaire on general demographic information. Socioeconomic status was estimated based on maternal education levels, which were categorised into eight subgroups based on the UK's Regulated Qualifications Framework (https://www.gov.uk/what-different-qualification-levels-mean/list-of-qualification-levels). We subsequently collapsed the eight categories into five ranks (1-2 [left education aged ~16 yrs] = 1; 3-5 [stayed in education to age ~18 yrs] = 2; 6 [bachelor's degree or equivalent] = 3; 7

[master's degree] = 4; 8 [doctorate level] = 5). Parents also completed the Children's Communication Checklist-Version 2 (CCC-2; Bishop, 2003), a screening questionnaire used to facilitate the identification of social communication difficulties and their potential impact on daily life in children with language disorder.

2.2.2 Behavioural Measures

Language

Vocabulary was assessed using (1) Receptive One-Word Picture Vocabulary-4th Edition (ROWPVT-4; Martin & Brownell, 2011b) and (2) Expressive One-Word Picture Vocabulary-4th Edition (EOWPVT-4; Martin & Brownell, 2011a). Norms are available in both tests for ages 2-80+. In ROWPVT-4 the participant hears a word and picks the picture matching it out of four options. The test consists of 190 developmentally sequenced words. EOWPVT-4 requires the participant to use one word to name the concept or object pictured, for a total of 190 items.

For receptive grammar we used the (3) Test for Reception of Grammar-2nd Edition (TROG-2; Bishop, 2003). Participants heard a sentence and picked one of four pictures that matched the sentence. The test consists of 80 sentences, presented over 20 blocks, with each block testing a different syntactic construct through four sentences. Blocks are failed if one of the four sentences in the block is incorrectly matched with a picture. Standard scores are obtained based on the number of blocks passed. The test is normed on the age range 4-16y11m but is often used in older populations too.

The (4) Recalling Sentences subtest of the Clinical Evaluation of Language Fundamentals-4th Edition (CELF-IV; Semel et al., 2003) was used as a proxy for expressive grammar. The rationale was that children do not repeat grammatical constructs that they do not yet use in their own language. To use syntax correctly at the sentence level, children need to use their auditory processing and immediate recall skills to formulate and repeat syntactically correct sentences. Performance on this subtest is a complex measure of auditory processing, immediate recall, and expressive grammar. Scaled scores are available for ages 5-16 years.

Narrative skills were assessed using the (5) Expression, Reception, and Recall of Narrative Instrument (ERRNI; Bishop, 2004). The children were presented with a short picture book used to elicit a narrative that was recorded and transcribed. After completion, they were evaluated on how well they understood the story's context. This test provides measures of

discourse comprehension, and storytelling both immediately upon seeing the story and after a short delay of 10-20 minutes (story retell). Standard scores are available from 4 years of age.

Participants were categorised into groups based on six scores from these five language tests: one each from expressive and receptive vocabulary and grammar, the comprehension score from the narrative test and one of the initial or the delay recall score but not both.

We also administered a new nonword repetition test (NNWR) used in the SCALES (Norbury et al., 2016) and the Wellcome Language and Reading projects (Snowling et al., 2016). NNWR consists of 30 nonwords of two to four syllables in length (10 per syllable length). Only raw scores are reported as this test is not norm-referenced.

Memory

Short-term and working memory were assessed using the Digit Span Forwards and Digit Span Backwards subtests from Children's Memory Scale (CMS; Cohen, 2011). We also administered the Word Lists subtest from the CMS to assess long-term memory for words. Raw scores from all CMS subtests were converted into age-scaled scores using published norms. Norms are available for ages 5-16 years.

Reading

Word decoding skills were assessed using the Test of Word Reading Efficiency-2nd Edition (TOWRE-2; Torgesen et al., 2012). Children had to read aloud a list of printed words (Sight Word Efficiency) and then phonemically regular nonwords (Phonemic Decoding Efficiency). The number of words read accurately and fluently in 45 sec was recorded. Norms are available for the age range 6-25 years.

Nonverbal Reasoning

The Block Design, Matrix Reasoning, and Coding subtests of the Wechsler Intelligence Scale for Children-4th Edition (WISC-IV; Wechsler, 2004) were administered to estimate nonverbal reasoning skills. The results obtained from the Block Design and Matrix Reasoning were used to calculate a mean composite nonverbal intelligence score. For the Coding subtest the participants were asked to copy geometric shapes that were paired with numbers. The task was to draw each symbol in its corresponding box by using a key in a 2-min period. This subtest

provides a measurement of processing speed, visuomotor coordination, visual short-term memory, and implicit learning. Norms were available for age range 6-16 years.

Motor

We recorded handedness based on self-reported preferred hand for writing. Manual dexterity was assessed through two subtests of the Purdue Pegboard Test (Tiffin, 1968; Tiffin & Asher, 1948). The scores were age- and gender-scaled based on published norms (age range 5-80+). We administered the Oromotor Sequences subtest of the NEuroPSYchology test (NEPSY; Korkman et al., 2001) to assess oromotor coordination. Notably, the other tests with a motor component were the Block Design and Coding subtests of WISC-IV, and nonword repetition.

2.2.3 Study Sample

Consistent with previous studies (Hsu & Bishop, 2014; Tomblin et al., 1996; see Bishop et al., 2016, for discussion), children were categorised as having DLD if they (1) had previously reported a history of speech-language difficulties, and (2) scored ≥ 1 SDs below the normative mean on two or more of the six scores from the standardised language tests. They were categorised as having typical language (TD) if they had no history of speech-language problems and received no more than one language test score of ≥ 1 SDs below the mean. Participants who had a history of speech-language problems but did not score ≥ 1 SDs below the mean on more than one language test formed the history of speech and language difficulties group (HSL).

All children passed audiometric screening at 25 dB at 500 Hz, 1000 Hz, and 2000 Hz. After testing, we excluded data from 15 children for the following reasons: three obtained a mean nonverbal IQ below 70 (more than 2 SDs below the mean); three were later discovered to have not grown up in the UK speaking English; one had scores on two or more tests of language that were more than one SD below the mean but no history of speech and language difficulties; two did not complete behavioural assessment; three did not have MRI; three were excluded due to incidental findings of unknown clinical significance on the MRI.

These exclusions resulted in an initial cohort of 160 children for whom both MRI and behavioural data were available. Another four (one DLD, three TD) were excluded after imaging quality control for the imaging analysis that is presented in the next chapter. The final cross-sectional cohort whose behavioural data are presented in this chapter consisted of 74 TD

participants (*m* = 12.6 yrs, SEM = 0.2; 33 female), 54 with DLD (*m* = 12.43 yrs, SEM = 0.3; 15 female), and 28 with HSL (*m* = 12.4 yrs, SEM = 0.3; five female).

2.2.4 Longitudinal Procedure and Sample

We invited back 85 of the 160 participants for follow-up testing. The participants were selected based on having complete behavioural and imaging data from time I, including quantitative multi-parameter maps to investigate brain microstructure (see Krishnan et al., 2022). A schematic of participant selection and inclusion is provided in Figure S2.1. The participants were aged between 10y1m-15y11m at time I, and 14y2m-20y5m at time II follow-up. The interval between the two visits was between 3y8m and 5y8m, with a mean gap of 4y6m.

Parents completed the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997), and the Social Communication Questionnaire (SCQ; Rutter et al., 2003) again. The SDQ is a brief behavioural screening questionnaire typically used for the age range 4-17 years. Parents provide answers to 25 attributes that are divided between five scales of conduct problems and hyperactivity/inattention (together forming externalising problems), emotional symptoms and peer problems (together forming internalising problems), and prosocial behaviour. Data from the first four scales are added together to yield a total difficulties score, that can range from zero to 40. Scores for each of the five scales can range from zero to 10.

The SCQ is typically used as a screening tool for signs of ASD and social communication difficulties in individuals who are at least 4 years old. The questionnaire has 40 items, all answered with either "Yes" or "No". Each item scores up to a single point, but the scores are different for each item. The maximum score is 25, with higher scores indicating higher social communication difficulties.

Parents also completed a shortened version of the background questionnaire. Socioeconomic status was estimated based on maternal education level and a newly added Index of Multiple Deprivation (IMD; Gill, 2015). The IMD is based on area measures of relative deprivation across the UK, ranking neighbourhoods from the most (rank of one) to the least deprived areas (rank of 10).

Participants retained their original group assignment from time I. Data from time I and time II were available in 20 with DLD (*m* = 17.02 yrs, SEM = 0.39; seven female), 22 TD (*m* = 17.56 yrs, SEM = 0.37; 11 female), and 11 with HSL (*m* = 16.93 yrs, SEM = 0.46; all male). Independent *t*-tests indicated no significant differences in time I test scores between those

selected for follow-up and those who were not, suggesting that score severity was comparable across groups.

We used the same neuropsychological test battery as time I with some minor changes; for receptive grammar using TROG-2 (Bishop, 2003), we calculated the scores as the number of correct sentences (rather than blocks). For a closer investigation, the scores for 16 sentences from blocks K, Q, S and T, which specifically examine embedded relative clauses (an area of known difficulty in DLD) were calculated as well. Examples of these grammatical constructs are provided in Table 2.1.

Table 2.1 ***Examples from TROG-2 assessing embedded relative clauses.***

Block	Syntactic construct	Sample sentence from block
K	Reversible passive	The cow is chased by the girl
Q	Postmodified subject	The elephant pushing the boy is big
S	Relative clause in subject	The girl chases the dog that is jumping
T	Centre-embedded sentence	The sheep the girl looks at is running

At time II we administered the Children's Nonword Repetition Test (CNRep; Gathercole et al., 1994) instead of the NNWR. The test consisted of 40 nonwords, ranging from two to five syllables (10 per syllable length). CNRep is normed on children aged 4-9 years. The raw data are presented as the number of nonwords repeated correctly.

Since longitudinal data using the same nonword repetition test was not available, we instead analysed each timepoint's data in more detail. Time I NNWR stimuli varied in "wordlikeness," or how closely their phoneme sequences and stress patterns followed the phonotactic rules of English (Chomsky & Halle, 1968). We compared group performance on this aspect as well as the length of the nonwords (number of syllables). Time II CNRep stimuli contained 20 nonwords with simple articulation, and 20 with consonant clusters that required complex articulation, so we assessed group differences on this dimension as well as nonword length.

For nonverbal reasoning, we used a mean composite score from the same Block Design and Matrix Reasoning subtests as before but from the Wechsler Abbreviated Scale of Intelligence-2nd Edition (WASI-II; Wechsler, 2011) as it contained normed scores for ages 6-90 years. We readministered the Coding subtest of WISC-IV (Wechsler, 2004). Lastly, we administered the same memory, reading, and motor tests, but excluded the Word Lists subtest from CMS (Cohen, 1997) and Oromotor Sequences from NEPSY (Korkman et al., 2001).

2.2.5 Statistical Analysis

Time I standard scores were compared between the TD, DLD, and HSL groups using one-way analysis of variance (ANOVA) tests. For time II, we used the raw scores in the statistical analyses to index the absolute amounts of change. Separate linear mixed models were built using restricted maximum likelihood estimation, modelling the fixed effects of interval between time I and II (in decimal years), Group (TD, DLD), and their interaction. The HSL group was excluded from these analyses for model simplicity and due to the group's small size, but their data are shown in the plots for visual comparison. Sex and baseline age were included as covariates of no interest. Random intercepts for participants were added to account for within-subject correlations. Missing data accounted for only 0.37% of the total dataset so we dropped subjects with missing values as required. Time I and TD group were set as the reference categories. In cases of substantial heteroscedasticity, a weighted least squares approach was implemented to account for unequal variances across groups and improve the robustness of models.

Because the results from the SCQ and SDQ were skewed, we treated the scores as ordinal variables for inference testing, using an ordinal mixed effects modelling approach (https://drizopoulos.github.io/GLMMadaptive/articles/Ordinal_Mixed_Models.html). Similar to previous analyses, we modelled the fixed effects of interval between time I and II, Group (TD, DLD), and their interaction, controlling for sex and baseline age, and accounting for non-independence of the longitudinal data. For these non-parametric models, adaptive Gauss-Hermite quadrature with ten quadrature points was employed to approximate the likelihood function. The logit link function was used to model the cumulative probabilities of the ordinal response. All the analyses were performed in R v4.3.2 (R Core Team, 2023).

2.3 Results

2.3.1 Cross-sectional Sample Characteristics

The cross-sectional cohort's demographic information is summarised in Table 2.2. A one-way ANOVA revealed no significant group differences in mean age ($F(2, 153) = 0.24$, $p = 0.785$). In contrast, a chi-square test of independence indicated that the distribution of sex differed significantly between groups ($\chi^2(2, N = 156) = 7.88$, $p = 0.019$, Cramer's $V = 0.12$). Although the TD group was nearly balanced (55.4% male), the DLD and HSL groups had higher

proportions of males (72.2% and 82.1%, respectively). Post hoc pairwise comparisons (Bonferroni corrected) showed a significant difference in sex ratio between the HSL and TD groups ($\chi^2 = 6.21$, 95% CI [0.09, 0.78], $p_{adj} = 0.039$, $\Phi = 0.24$), but no significant differences were observed between DLD and TD ($\chi^2 = 3.76$, $p_{adj} = 0.156$), or between HSL and DLD ($\chi^2 = 0.98$, $p_{adj} = 0.963$). There were no significant group differences in the distribution of handedness ($\chi^2(2, N = 156) = 0.01$, $p = 0.997$), or in the proportion of participants who spoke a language other than English at home ($\chi^2(2, N = 156) = 2.06$, $p = 0.356$). A Kruskal-Wallis test indicated that the groups did not differ significantly in median maternal education levels ($\chi^2(2, N = 156) = 5.43$, $p = 0.065$).

Table 2.2 ***Demographic information of groups in the cross-sectional analysis.***

Demographics	**TD (*n* = 74)**	**DLD (*n* = 54)**	**HSL (*n* = 28)**
Mean age in years ± SEM	12.6 ± 0.2	12.4 ± 0.3	12.4 ± 0.3
Age range (y;m)	10;0-15;7	10:0-15;11	10;5-15;7
Sex (M:F)	41:33	39:15	23:5
Handedness (R:L)	63:11	46:8	24:4
Language(s) spoken at home other than English (% Yes)	13.43% (*n* = 67)	5.55%	10.71%
Median maternal education level (range)	3 (1-5) (*n* = 69)	3 (1-5)	3 (2-4)

Note: See text for inferential statistics results. *Abbreviations*: y – years; m – months; M – Male; F – Female; R – Right; L – Left.

Results from the neuropsychological test battery for the TD, DLD, and HSL groups are presented in Table 2.3. Children in the DLD group performed significantly lower than their TD peers on all measures of language, memory, nonverbal reasoning, motor, and reading skills. Detailed statistical results, including post-hoc pairwise comparisons and effect sizes, are reported in Table 2.3. Additionally, scores on the CCC-2 (Bishop, 2003) indicated that the DLD group had significantly lower General Communication Composite (GCC) values than the TD group, reflecting reduced structural language skills. Although the HSL group's GCC scores were also significantly lower than TD, they remained significantly higher than those of the DLD group.

Table 2.3 ***Results from the neuropsychological test battery for TD, DLD, and HSL groups.***

Test battery	TD (n = 74)	DLD (n = 54)	HSL (n = 28)	F(2 ,153)	η^2	Pairwise comparisons	Mean difference (95% CI)	p_{adj}	Cohen's d
Language									
ROWPVT-4	128.4 ± 1.9	100.1 ± 2.1	122 ± 2.9	52.06***	0.40	DLD – TD	-28.27 (-34.92, -21.62)	**<0.001**	-1.80
						HSL – TD	-6.40 (-14.64, 1.841)	0.160	---
						HSL – DLD	21.87 (13.22, 30.52)	**<0.001**	1.39
EOWPVT-4	117.9 ± 1.7	92.4 ± 1.7	108.3 ± 2.5	55.32***	0.41	DLD – TD	-25.55 (-31.31, -19.80)	**<0.001**	-1.88
						HSL – TD	-9.66 (-16.79, -2.52)	**0.004**	-0.71
						HSL – DLD	15.89 (8.40, 23.38)	**<0.001**	1.17
TROG-2	105.2 ± 0.9 (n = 73)	80.9 ± 1.8 (n = 53)	98.9 ± 1.6	91.91***	0.54	DLD – TD	-24.32 (-28.60, -20.03)	**<0.001**	-2.42
						HSL – TD	-6.35 (-11.63, -1.07)	**0.013**	-0.63
						HSL – DLD	17.96 (12.41, 23.51)	**<0.001**	1.79
CELF-IV	11.6 ± 0.3 (n = 70)	4.9 ± 0.4	9 ± 0.6	112***	0.60	DLD – TD	-6.76 (-7.83, -5.69)	**<0.001**	-2.70
Recalling Sentences[1]						HSL – TD	-2.65 (-3.97, -1.32)	**<0.001**	-1.06
						HSL – DLD	4.11 (2.73, 5.48)	**<0.001**	1.64
ERRNI									
Initial Recall	100.1 ± 1.5	83.7 ± 1.7	96.3 ± 2.1	28.45***	0.27	DLD – TD	-16.40 (-21.62, -11.19)	**<0.001**	-1.33
						HSL – TD	-3.82 (-10.29, 2.63)	0.342	---
						HSL – DLD	12.58 (5.79, 19.36)	**<0.001**	1.02
Delayed Recall	104.4 ± 1.3	85.1 ± 1.7	99.1 ± 1.9	43.13***	0.36	DLD – TD	-19.33 (-24.29, -14.36)	**<0.001**	-1.64
						HSL – TD	-5.26 (-11.41, 0.89)	0.110	---
						HSL – DLD	14.06 (7.60, 20.53)	**<0.001**	1.19
Comprehension	106.7 ± 1.6	93.2 ± 2.1	101.9 ± 1.9	15.53***	0.16	DLD – TD	-13.53 (-19.29, -7.77)	**<0.001**	-0.99
						HSL – TD	-4.80 (-11.94, 2.32)	0.250	---
						HSL – DLD	8.72 (1.23, 16.21)	**0.017**	0.64
NNWR (max. 30)[2]	26.3 ± 0.3 (n = 71)	17.8 ± 0.8 (n = 53)	22.6 ± 0.7	71.06***	0.48	DLD – TD	-8.54 (-10.23, -6.84)	**<0.001**	-2.16
						HSL – TD	-3.65 (-5.73, -1.56)	**<0.001**	-0.92
						HSL – DLD	4.88 (2.70, 7.07)	**<0.001**	1.23
Memory									
CMS									
Digit Span Forwards[1]	11.5 ± 0.3	5.8 ± 0.4	7.5 ± 0.6	62.89***	0.45	DLD – TD	-5.66 (-6.89, -4.43)	**<0.001**	-1.94
						HSL – TD	-4.03 (-5.56, -2.50)	**<0.001**	-1.38
						HSL – DLD	1.63 (0.02, 3.23)	**0.045**	0.56
Digit Span Backwards[1]	11.8 ± 0.3	7.2 ± 0.5	8.5 ± 0.6	39.88***	0.34	DLD – TD	-4.54 (-5.79, -3.30)	**<0.001**	-1.54
						HSL – TD	-3.30 (-4.85, -1.76)	**<0.001**	-1.12

						HSL – DLD	1.24 (-0.37, 2.86)	0.168	---
Word List Immediate Recall[1]	10.1 ± 0.4	6.2 ± 0.4 (*n* = 52)	8.4 ± 0.5	25.92***	0.25	DLD – TD	-3.89 (-5.17, -2.61)	**<0.001**	-1.30
						HSL – TD	-1.75 (-3.32, -0.17)	**0.024**	-0.58
						HSL – DLD	2.14 (0.48, 3.80)	**0.007**	0.71
Word List Delayed Recall[1]	10.2 ± 0.4 (*n* = 73)	7.3 ± 0.5 (*n* = 51)	9.8 ± 0.6	13.13***	0.14	DLD – TD	-2.94 (-4.34, -1.54)	**<0.001**	-0.91
						HSL – TD	-0.43 (-2.13, 1.26)	0.818	---
						HSL – DLD	2.51 (0.71, 4.31)	**0.003**	0.77
Word List Delayed Recognition[1]	8.6 ± 0.4 (*n* = 73)	6.6 ± 0.5	7.4 ± 0.6	5.80**	0.07	DLD – TD	-2.04 (-3.47, -0.61)	**0.002**	-0.60
						HSL – TD	-1.18 (-2.96, 0.58)	0.254	---
						HSL – DLD	0.85 (-1.00, 2.71)	0.522	---
Reading									
TOWRE-2									
Sight Word Efficiency	106 ± 1.3	82.6 ± 1.9	89.1 ± 2.6	56.61***	0.42	DLD – TD	-23.36 (-28.73, -17.99)	**<0.001**	-1.84
						HSL – TD	-16.94 (-23.59, -10.28)	**<0.001**	-1.33
						HSL – DLD	6.42 (-0.56, 13.41)	0.078	---
Phonemic Decoding Efficiency	112.2 ± 1.6	81.3 ± 2.2	87.1 ± 2.5	79.84***	0.51	DLD – TD	-30.86 (-36.96, -24.77)	**<0.001**	-2.14
						HSL – TD	-25.09 (-32.65, -17.53)	**<0.001**	-1.74
						HSL – DLD	5.77 (-2.16, 13.70)	0.200	---
Nonverbal reasoning									
WISC-IV									
Composite score	12.3 ± 0.2	8.7 ± 0.4	11.3 ± 0.4	42.26***	0.35	DLD – TD	-3.60 (-4.54, -2.67)	**<0.001**	-1.63
						HSL – TD	-0.96 (-2.12, 0.19)	0.125	---
						HSL – DLD	2.64 (1.42, 3.86)	**<0.001**	1.19
Block Design[1]	13.3 ± 0.2	9.8 ± 0.4	12.8 ± 0.4	33.67***	0.30	DLD – TD	-3.54 (-4.58, -2.49)	**<0.001**	-1.43
						HSL – TD	-0.55 (-1.85, 0.74)	0.574	---
						HSL – DLD	2.98 (1.62, 4.35)	**<0.001**	1.20
Matrix Reasoning[1]	11.2 ± 0.3	7.6 ± 0.4	9.9 ± 0.5	25.12***	0.24	DLD – TD	-3.67 (-4.90, -2.44)	**<0.001**	-1.26
						HSL – TD	-1.37 (-2.89, 0.14)	0.086	---
						HSL – DLD	2.30 (0.70, 3.89)	**0.002**	0.79
Coding[1]	9.6 ± 0.3 (*n* = 71)	5.9 ± 0.4	6.5 ± 0.4	38.48***	0.33	DLD – TD	-3.72 (-4.79, -2.65)	**<0.001**	-1.48
						HSL – TD	-3.18 (-4.50, -1.86)	**<0.001**	-1.27
						HSL – DLD	0.53 (-0.84, 1.91)	0.625	---
Motor									
NEPSY									
Oromotor Sequencing (max. 70)[2]	60.5 ± 0.9	41.4 ± 1.5	53.4 ± 1.9	66.54***	0.46	DLD – TD	-19.09 (-23.01, -15.17)	**<0.001**	-2.06
						HSL – TD	-7.14 (-12.00, -2.28)	**0.001**	-0.77

						HSL – DLD	11.94 (6.84, 17.05)	**<0.001**	1.29
Purdue Pegboard									
Dominant hand (*z*)	-0.4 ± 0.1	-1.5 ± 0.2	-0.9 ± 0.2	18.66^{***}	0.19	DLD – TD	-1.09 (-1.52, -0.67)	**<0.001**	-1.09
						HSL – TD	-0.49 (-1.01, 0.03)	0.072	---
						HSL – DLD	0.60 (0.05, 1.15)	**0.028**	0.60
Non-dominant hand (*z*)	0.0 ± 0.1	-1.1 ± 0.2	-0.8 ± 0.2	16.18^{***}	0.17	DLD – TD	-1.04 (-1.49, -0.60)	**<0.001**	-0.99
						HSL – TD	-0.71 (-1.26, -0.16)	**0.007**	-0.67
						HSL – DLD	0.33 (-0.24, 0.91)	0.365	---
Children's Communication Checklist-2									
GCC[3]	85.3 ± 1.7	35.9 ± 2.7 (n = 53)	48.4 ± 4.4	123.7^{***}	0.61	DLD – TD	-49.41 (-57.14, -41.68)	**<0.001**	-2.72
						HSL – TD	-36.85 (-46.38, -27.32)	**<0.001**	-2.03
						HSL – DLD	12.56 (2.52, 22.59)	**0.009**	0.69

Note: Values are presented as means ± standard error of the mean (SEM). All variables were compared between groups using a one-way analysis of variance (ANOVA) with Tukey's post-hoc comparisons in case of a statistically significance result ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$). Effect sizes for significant effects are reported in columns 6 and 10. Significant pairwise differences are indicated in boldface. Scores are reported as follows: No superscript: Standard scores (M = 100, SD = 15); [1] Scaled scores (M = 10, SD = 3); [2] Raw scores; [3] Scaled scores (M = 80) based on the sum of the eight subtests.

2.3.2 Longitudinal Sample Characteristics

The demographic details of the longitudinal cohort are summarised in Table 2.4. A more detailed overview of individual behavioural profiles is provided in Figure S2.2. A one-way ANOVA revealed no significant group differences in mean age at time I ($F(2, 50) = 0.11$, $p = 0.898$) or at time II ($F(2, 50) = 0.72$, $p = 0.492$). The mean interval between sessions, however, differed significantly among groups ($F(2, 50) = 8.16$, $p < 0.001$, $\eta^2 = 0.24$). Tukey's post-hoc comparisons (Bonferroni corrected) showed a significantly longer interval for the TD group compared with the DLD group, with a mean difference of -0.53 years (95% CI [-0.86, -0.21], $p_{adj} < 0.001$, Cohen's $d = -1.22$). No significant differences were found in the interval between sessions for the HSL-TD ($m = -0.35$, $p_{adj} = 0.07$) or the HSL-DLD ($m = 0.17$, $p_{adj} = 0.52$) group comparisons.

Table 2.4 ***Demographic information for TD, DLD, and HSL groups seen at time II.***

Demographics	**TD (*n* = 22)**	**DLD (*n* = 20)**	**HSL (*n* = 11)**
Time I mean age in years ± SEM	12.67 ± 0.3	12.67 ± 0.4	12.4 ± 0.5
Time I age range (y;m)	10;1-15;6	10;4-15;11	10;9-15;5
Time II mean age in years ± SEM	17.56 ± 0.3	17.02 ± 0.4	16.93 ± 0.4
Time II age range (y;m)	14;4-20;4	14;2-20;5	15;3-20;0
Interval in years ± SEM	4.89 ± 0.1	4.35 ± 0.1	4.53 ± 0.1
Interval range (y;m)	4;0-5;11	3;9-4;8	4;1-5;0
Sex (M:F)	11:11	13:7	11:0
Handedness (R:L)	18:4	14:6	8:3
Language(s) spoken at home other than English (%Yes)	18.18%	5%	9.09%
Parental history of speech-language difficulties (%Yes)	9.09%	55%	45.45%
Median maternal education level (range)	3 (1-5)	2 (1-5)	2 (2-3)
Index of Multiple Deprivation	8 (2-10)	7.5 (4-10)	8 (1-10)

Note: See text for inferential statistics results. *Abbreviations*: y – years; m – months; M – Male; F – Female; R – Right; L – Left.

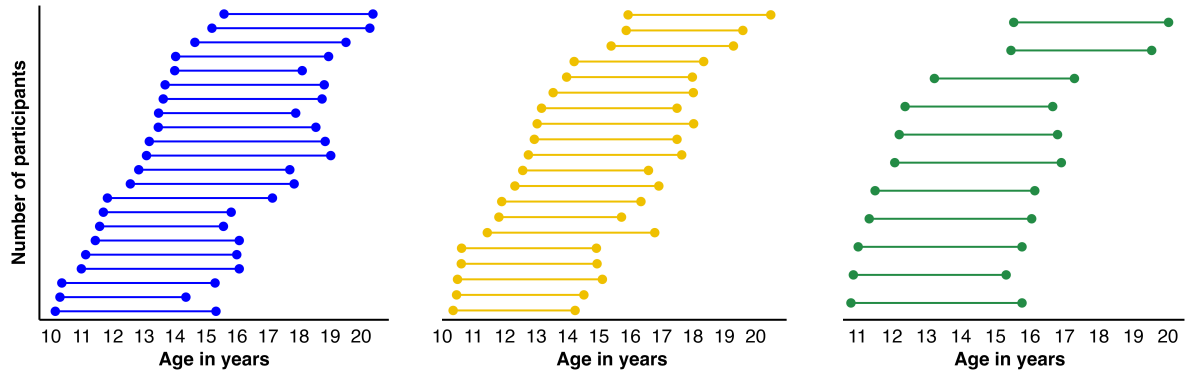


Fig. 2.1 ***Time gap between the two testing sessions per group.*** The mean interval between sessions was significantly longer in the TD group compared with the DLD group. Refer to text for statistical details. Blue = TD; yellow = DLD; green = HSL.

Five of the participants with DLD no longer met DLD criteria at time II. One performed within the typical range on all tests, and the other four had scores of ≥1 SDs below the mean only on the Recalling Sentences subtest of CELF-IV. Interestingly, none of these five participants had a parental history of speech-language difficulties. Two HSL participants now met criteria for DLD. Three in the DLD group and one in the HSL had a new diagnosis of ASD. All DLD and HSL participants seen at time II had Special Educational Needs and Disabilities (SEND) support, with the types of support ranging from small classrooms, extra exam time, and one-on-one reading aid. Eight of the participants with DLD seen at time II were receiving speech-language therapy services at different frequencies, ranging from once a month to several sessions per week.

2.3.3 Neuropsychological Test Results Over Time

Mixed models were built to assess the effect of time (in decimal years), group (TD, DLD), and their interaction on the raw test scores, controlling for sex and baseline age, and adding random intercepts for participants. Ninety-five percent confidence intervals are presented in cases of significant results. Results from the HSL group are shown only for visual comparison. An overview of the mean standard scores per group is presented in Table S2.1. Longitudinal plots of the standard scores are presented in Appendix A.

Language

Vocabulary

Raw receptive vocabulary scores increased over time across the participants (β = 2.35, SE = 0.67, CI [1.04, 3.7], p = 0.001), but remained significantly lower in the DLD group across both time points (β = -23.11, SE = 4.75, CI [-32.15, -14.06], p < 0.001; Fig. 2.2A). There was no group by time interaction (β = 0.21, SE = 1.04, p = 0.84). Likewise, there was a significant increase in expressive vocabulary scores (β = 2.66, SE = 0.5, CI [1.67, 3.66], p < 0.001), with lower scores in DLD over both time points (β = -28.4, SE = 3.74, CI [-35.52, -21.28], p < 0.001), and no group by time interaction (β = 0.83, SE = 0.78, p = 0.29; Fig. 2.2B). The performance of the HSL group was most similar to that of the TD group for both vocabulary tests.

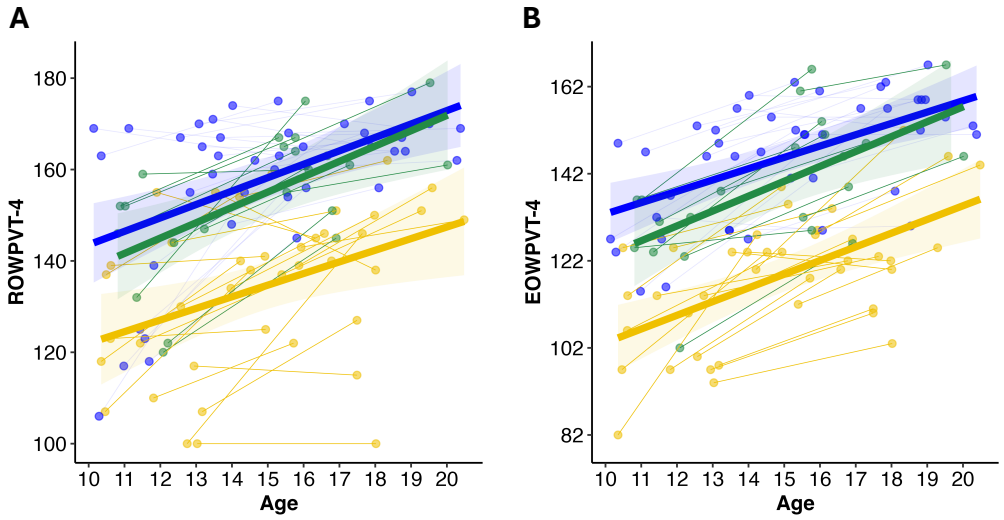


Fig. 2.2 ***Longitudinal trajectories for vocabulary tests per group.*** The plots depict raw scores as a function of age in years. The points and lines represent each participant's score. The bold lines are the regression lines with shaded areas showing standard error of mean per group. Blue = TD; yellow = DLD; green = HSL.

Grammar

The receptive grammar plots in Figure 2.3 showed that a lot of the TD participants scored at or close to the ceiling on TROG-2. Due to this skewness we did not perform group analysis and instead assessed changes in scores in the DLD group alone. Receptive grammar scores significantly increased over time in the DLD group (β = 1.25, SE = 0.37, CI [0.48, 2.01], p = 0.003; Fig. 2.3A). Scores on the TROG-2 subtests that specifically assessed embedded relative clauses also improved over time in the DLD group (β = 0.43, SE = 0.18, CI [0.05, 0.79], p = 0.03), but as it can be seen in Figure 2.3B, the scores remained on average lower than the

TD group, who reached ceiling. For expressive grammar, there was a gain in scores on sentence recall over time across the DLD and TD participants (β = 1.45, SE = 0.32, CI [0.82, 2.1], p < 0.001), with significantly lower performance in DLD across time points (β = -28.96, SE = 2.85, CI [-34.38, -23.53], p < 0.001), and no group by time interaction (β = 0.22, SE = 0.49, p = 0.65; Fig. 2.3C).

For receptive grammar, the HSL group performed most like the TD group, apart from one participant whose performance overlapped with that of the DLD participants (Fig. 2.3A). The same was true when looking at the subset of grammatical constructs with embedded relative clauses; most HSL participants performed similar to the TD group apart from two with rather lower performance more like the DLD group (Fig. 2.3B). For sentence recall, the pattern of performance in HSL followed a similar growth trajectory as for the other two groups and average performance lay between DLD and TD groups (Fig. 2.3C).

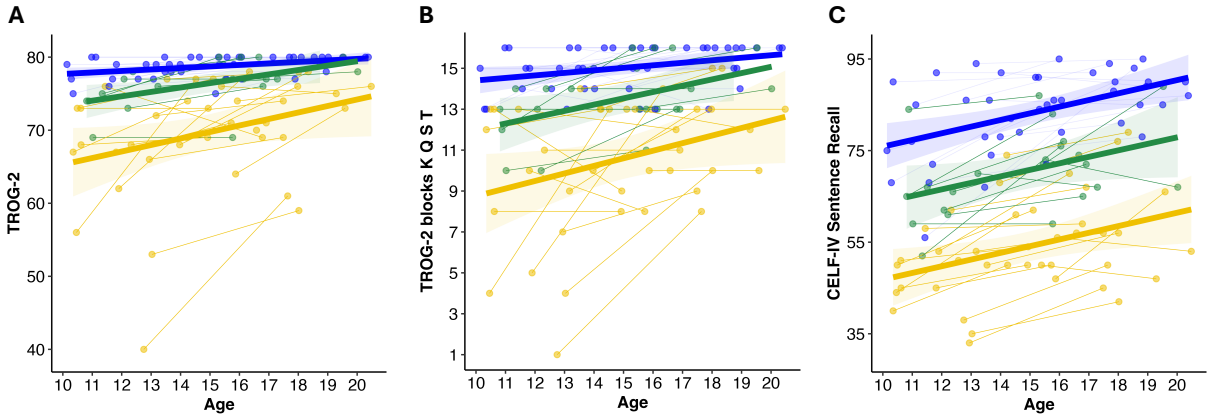


Fig. 2.3 ***Longitudinal trajectories for grammar tests per group.*** Blue = TD; yellow = DLD; green = HSL.

Narrative

Story comprehension scores increased over time across both groups (β = 0.44, SE = 0.12, CI [0.19, 0.68], p = 0.001), and the DLD group performed only marginally lower than the TD group (β = -1.36, SE = 0.059, CI [-2.72, -0.001], p = 0.08; Fig. 2.4A). There was no group by time interaction (β = 0.24, SE = 0.19, p = 0.22). For initial storytelling, the scores increased over time in both groups, but this was not a significant change (β =0.37, SE = 0.28, p = 0.19; Fig. 2.4B). The DLD group had lower scores across both time points relative to TD (β = -5.94, SE = 1.64, CI [-9.07,-2.81], p < 0.001). There was a trend towards a significant group by time interaction, suggesting more pronounced gain in scores in DLD across time (β = 0.73, SE = 0.39, p = 0.073). The pattern of results was similar for narrative retell, with no significant

change over time in scores (β = 0.41, SE = 0.33, p = 0.22), lower performance in DLD (β = -7.67, SE = 1.79, CI [-11.09, -4.25], p < 0.001), and a marginally significant group by time interaction showing accelerated growth in the DLD group (β = 0.82, SE = 0.47, CI [-0.12, 1.74], p = 0.092; Fig. 2.4C). The results in the HSL group were most similar to that of the TD group across all narrative scores, with even slightly better gains than the TD group on initial story telling.

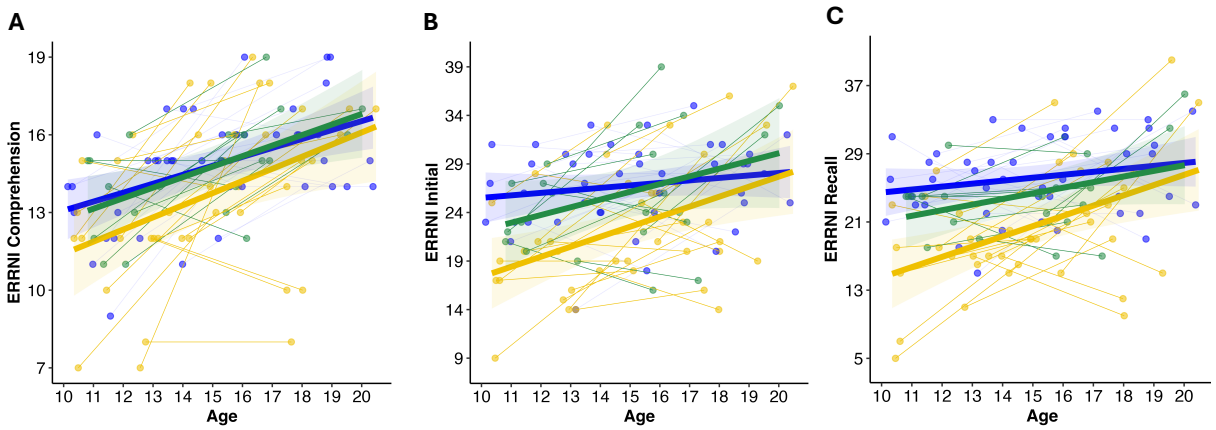


Fig. 2.4 ***Longitudinal trajectories for narrative subtests per group.*** Blue = TD; yellow = DLD; green = HSL.

Nonword repetition

For time I NNWR data, mixed models were built to examine the effect of group (TD, DLD), syllable length (2, 3, 4), wordlikeness (high, low), and their interaction on nonword repetition accuracy, controlling for sex and age, and with random intercepts for participants. TD group, 2-syllable nonwords, and high "wordlikeness" were set as reference categories. A similar model was built for time II CNRep data but with word complexity instead. TD group, 2-syllable, and simple nonwords were set as references.

Time I NNWR test showed that repetition accuracy was overall lower on 4-syllable nonwords in both groups (β = -21, SE = 5.46, CI [-31.82, -10.17], p < 0.001; Fig. 2.5). Wordlikeness did not affect repetition accuracy (β= -4, SE = 5.46, p = 0.47). Two interactions emerged: group by 3-syllable nonwords (β = -27.42, SE = 8.08, CI [-42.92, -11.91], p < 0.001), and group by 4-syllable nonwords (β = -31.63, SE = 8.08, CI [-47.13, -16.12], p < 0.001). Post-hoc tests showed that the DLD group's accuracy decreased on 3-syllable nonwords that were low in wordlikeness (β = -38.74, SE = 6.99, CI [-62.81, -14.65], p_{adj} < 0.001). Accuracy in the DLD group also decreased on 3-syllable nonwords that were high on wordlikeness, but group differences only approached significance (β = -23, SE = 6.99, p_{adj} = 0.08). For the 4-syllable

stimuli, the DLD group's accuracy was lower than TD on both nonwords that were low (β = -42.95, SE = 6.99, CI [-67.02, -18.86], $p_{adj} < 0.001$) and high in wordlikeness (β = -38.68, SE = 6.99, CI [-62.76, -14.61], $p_{adj} < 0.001$). Performance of the HSL group lay between that of the TD and DLD groups at time I.

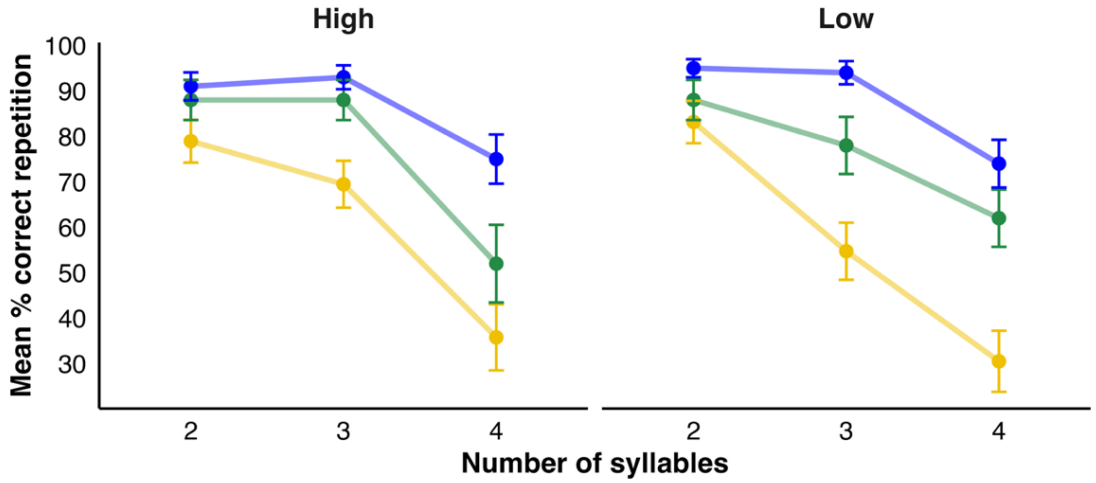


Fig. 2.5 ***Time I NNWR data per group.*** Repetition accuracy (calculated as mean percent correct repetition) is shown as a function of group, syllable length, and wordlikeness. Blue = TD; yellow = DLD; green = HSL.

At time II on the CNRep test, there was a significant three-way interaction between group, length, and complexity (β = -16.14, SE = 8.21, CI [-31.89, -0.38], $p = 0.05$; Fig. 2.6). Post-hoc tests showed that this effect was driven by poorer performance of the DLD group on longer nonwords, especially when the nonwords were complex (i.e. contained consonant clusters), including complex 3-syllable nonwords (β = -20.25, SE = 4.09, CI [-37.69, -2.81], $p_{adj} = 0.006$), complex 4-syllable nonwords (β = -39.58, SE = 4.95, CI [-57.03, -22.13], $p_{adj} < 0.001$), as well as complex 5-syllable nonwords (β = -27.91, SE = 4.95, CI [-45.36, -10.47], $p_{adj} < 0.001$). A significant two-way interaction between group and 4-syllable stimuli also emerged (β = -17.28, SE = 5.81, CI [-28.42, -6.14], $p = 0.003$), with post-hoc tests indicating lower repetition accuracy on 4-syllable stimuli in the DLD group on average, regardless of complexity (simple: β = -20.34, SE = 4.95, CI [-37.79, -2.89], $p_{adj} = 0.005$; complex: β = -39.58, SE = 4.95, CI [-57.03, -22.13], $p_{adj} < 0.001$). The performance of the HSL group most closely resembled that of the TD group at time II.

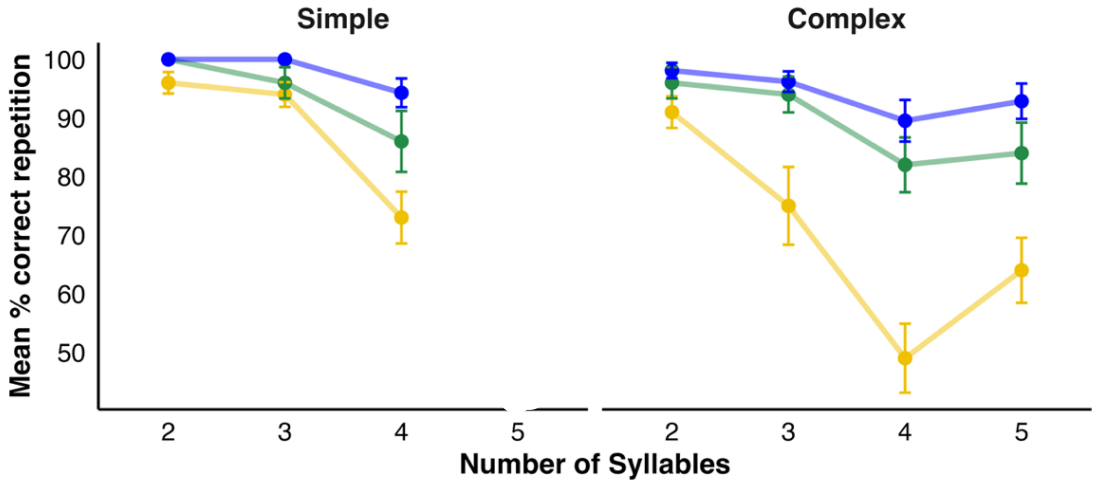


Fig. 2.6 ***Time II CNRep data per group.*** Repetition accuracy (calculated as mean percent correct repetition) is shown as a function of group, syllable length, and word complexity. Simple nonwords had a maximum of four syllables. Blue = TD; yellow = DLD; green = HSL.

Memory

Performance on digit span forwards remained stable with no significant effect of time (β = 0.007, SE = 0.03, p = 0.84), and the DLD group had lower scores across time points (β = -2.04, SE = 0.3, CI [-3.12, -0.87], p < 0.001; Fig. 2.7A). In contrast, the scores increased across time in both groups on digit span backwards (β = 0.3, SE = 0.6, CI [0.16, 0.43], p < 0.001), and again the DLD group's performance was lower than that of the TD group (β = -3.1, SE = 0.56, CI [-4.21, -2.04], p < 0.001; Fig. 2.7B). The was no group by time interaction (β = -0.11, SE = 0.11, p = 0.32). The performance of the HSL group was closer to the DLD group on these two tests.

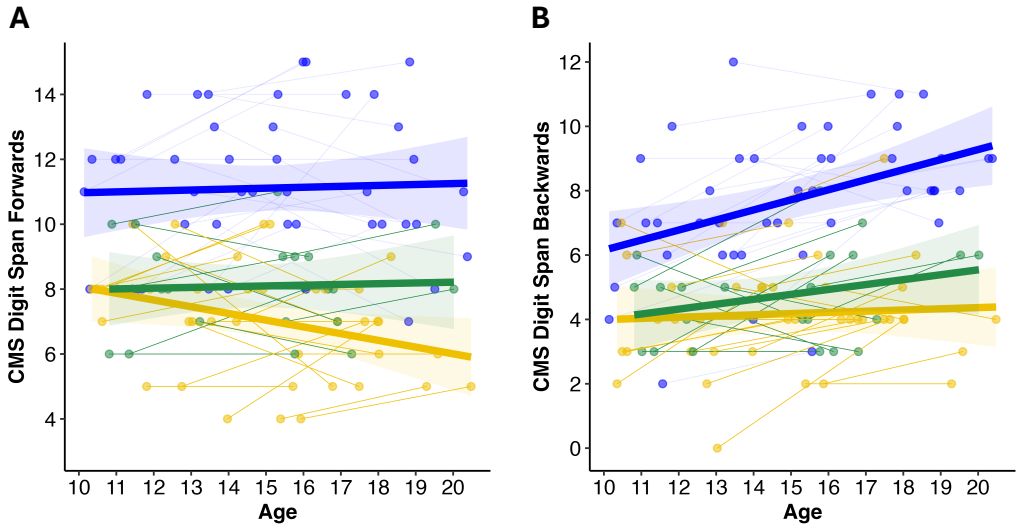


Fig. 2.7 ***Longitudinal trajectories for memory subtests per group.*** Blue = TD; yellow = DLD; green = HSL.

Reading

There was an increase on Sight Word Efficiency scores of TOWRE-2 across time (β = 1.86, SE = 0.34, CI [1.19, 2.53], $p < 0.001$) and the DLD group had significantly lower scores (β = -27, SE = 3.48, CI [-33.63, -20.37], $p < 0.001$; Fig. 2.8A). The group by time interaction approached significance, indicating greater gain in scores for TD relative to DLD (β = 0.92, SE = 0.52, $p = 0.08$). Phonemic Decoding Efficiency (nonword reading) scores also significantly increased across time in both groups (β = 1.44, SE = 0.23, CI [0.99, 1.91], $p < 0.001$) with lower performance in DLD (β =-25.6, SE = 3.61, CI [-32.49, -18.71], $p < 0.001$; Fig. 2.8B). Performance of the HSL group overlapped more closely with that of the DLD group particularly for the Phonemic Decoding scores.

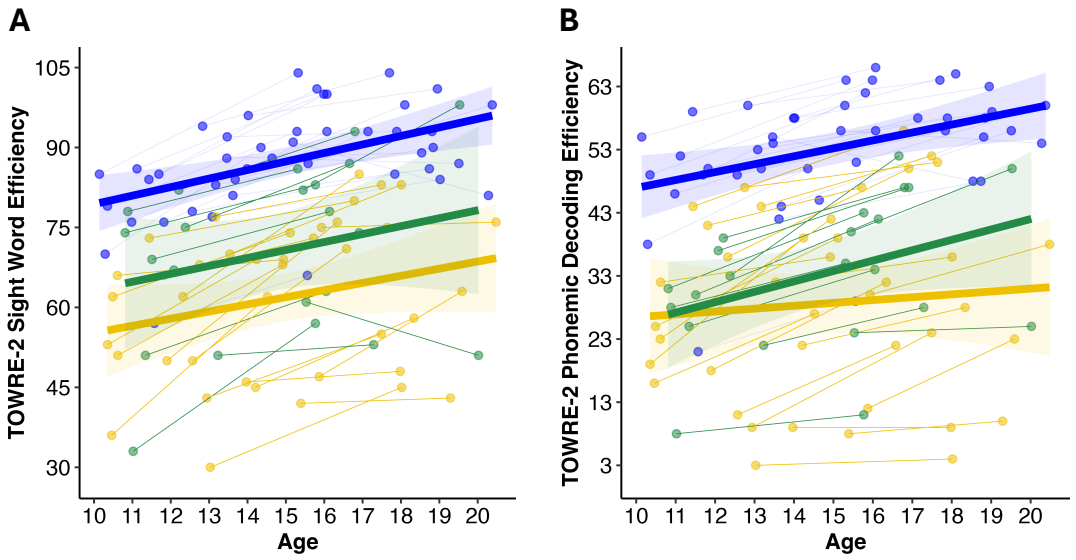


Fig. 2.8 ***Longitudinal trajectories for reading subtests per group.*** Blue = TD; yellow = DLD; green = HSL.

Nonverbal Reasoning

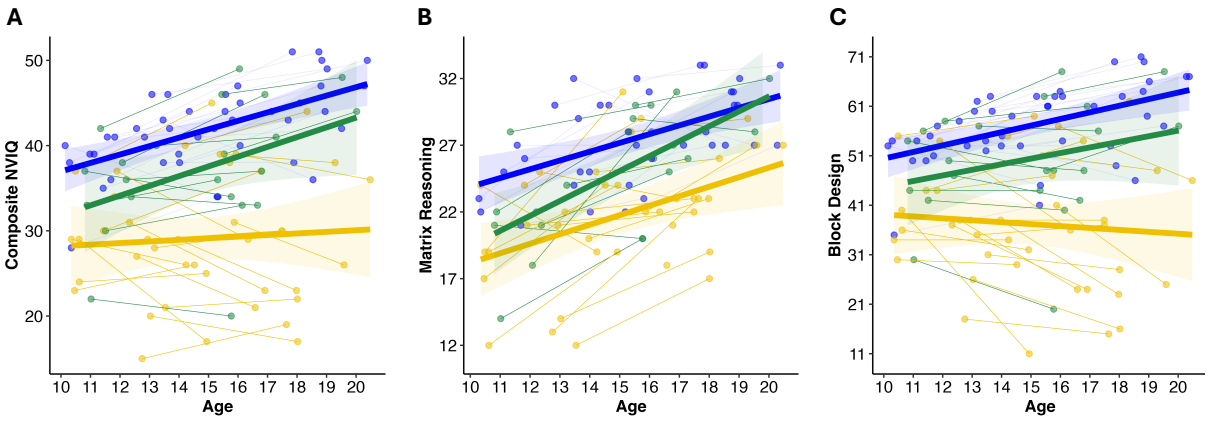
Nonverbal intelligence (NVIQ) was calculated as the composite score on Block Design and Matrix Reasoning subtests of WISC-IV at time I and WASI-II at time II. There was an increase in NVIQ scores in both groups across time (β = 0.74, SE = 0.21, CI [0.32, 1.16], $p = 0.001$), but with lower average scores in the DLD compared with the TD group (β = -10.98, SE = 1.89, CI [-14.59, -7.37], $p < 0.001$; Fig. 2.9A). A significant group by time interaction showed that the DLD group had a less pronounced gain in NVIQ scores over time compared with the TD group (β = -0.94, SE = 0.32, CI [-1.58, -0.31], $p = 0.005$). To better understand the nature of this effect we examined each subtest separately.

On Matrix Reasoning, scores increased over time on average for both groups (β = 0.55, SE = 0.16, CI [0.23, 0.88], p = 0.001), but remained lower in the DLD group (β = -6.18, SE = 1.44, CI [-8.36, -4], p < 0.001; Fig. 2.9B). No interaction emerged (β = 0.27, SE = 0.25, p = 0.28). On Block Design, there was a significant increase in raw scores over time averaged across both groups (β = 1.01, SE = 0.15, CI [0.64, 1.38], p < 0.001; Fig. 2.9C). The DLD group had lower scores than TD (β = -15.77, SE = 2.54, CI [-20.7, -11.05], p < 0.001). A significant group by time interaction showed a pronounced increase in scores in the TD group, unlike the DLD group who showed a drop in scores (β = -2.17, SE = 0.34, CI [-2.75, -1.62], p < 0.001).

Administration and scoring of the Block Design subtest assesses timing (speed of completion) and accuracy (correctness of the design). We reanalysed the Block Design scores this time with a focus on accuracy regardless of timing. There were 14 block design trials on time I WISC-IV and 13 trials on time II WASI-II. Scores were turned into percentages (percent accurate correct trials). Similar to performance on receptive grammar, the TD group's scores were at ceiling (Fig. 2.9D) so we analysed data in the DLD group alone for block design accuracy. As it can be seen in Figure 2.9D, the accuracy scores of the DLD participants did not change much over time (β = -0.96, SE = 0.87, p = 0.28) but were lower than their TD peers.

For Coding (which was not part of the composite NVIQ score), both TD and DLD participants improved their raw scores over time (β = 3.63, SE = 0.43, CI [2.77, 4.47], p < 0.001), but again performance was lower in DLD (β = -18.41, SE = 3.22, CI [-24.54, -12.27], p < 0.001; Fig. 2.9E). A significant group by time interaction showed that the gain in the TD group was significantly greater than in the DLD group (β = -1.79, SE = 0.66, CI [-3.08, -0.47], p = 0.01).

The pattern of performance of the HSL group resembled that of the TD group for the Block Design and Matrix Reasoning tests, including the composite NVIQ score, but was closer to that of the DLD group for the Coding subtest.



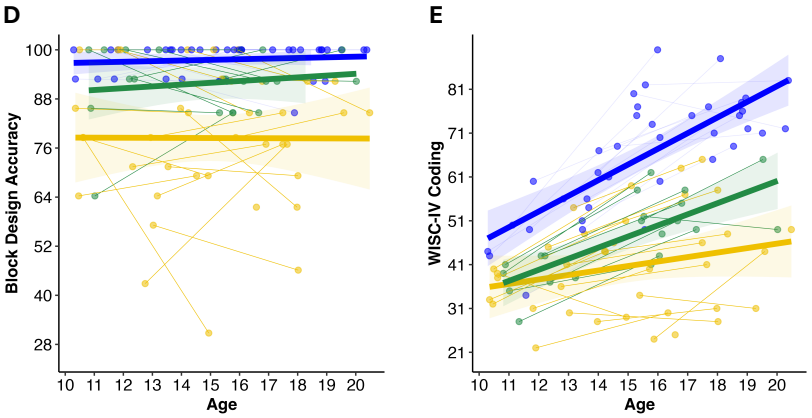


Fig. 2.9 ***Longitudinal trajectories for nonverbal intelligence subtests per group.*** Blue = TD; yellow = DLD; green = HSL.

Motor

For the Pegboard test there was an increase in manual dexterity across time in both dominant (β = 0.28, SE = 0.07, CI [0.14, 0.42], $p < 0.001$) and nondominant peg-moving trials (β = 0.35, SE = 0.07, CI [0.21, 0.49], $p < 0.001$; Fig. 2.10A-B). The DLD participants performed lower than TD on both measures (dominant: β = -2.59, SE = 0.43, CI [-3.42, -1.77], $p < 0.001$; nondominant: β = -2.21, SE = 0.48, CI [-3.12, -1.28], $p < 0.001$). The change with time (β = -0.04, SE = 0.25, $p = 0.88$) and group difference (β = -0.06, SE = 0.07, $p = 0.33$) for dominant minus nondominant scores were not significant despite the TD participants showing a steady decrease, which indicated gaining more manual dexterity in their nondominant hand (Fig. 2.10C). This last measure was very noisy when looking at the change in the raw date from time I to time II, perhaps reflecting poor reliability.

The pattern of change in the HSL group most closely resembled that of the TD group for the dominant hand. For the nondominant hand, the HSL group performed more similarly to the TD group at time I, but scores appeared to approach the DLD group over time. The HSL group showed more gain in dominant minus nondominant scores than the other two groups.

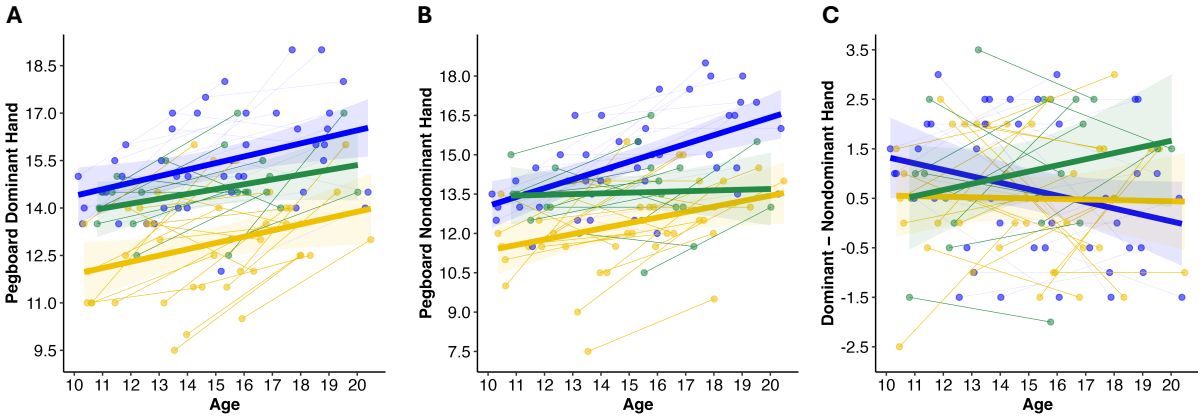


Fig. 2.10 ***Longitudinal trajectories for motor subtests per group.*** Blue = TD; yellow = DLD; green = HSL.

2.3.4 Parent Questionnaires

Longitudinal analyses of mean SCQ and SDQ scores from parent questionnaires were conducted to examine behavioral, emotional, and social difficulties over time. Ordinal mixed effects models were built to assess the effects of time (in decimal years), Group (TD, DLD), and their interaction, controlling for sex and baseline age, with random intercepts for participants. At time II, 30% of participants with DLD (six out of 20) received a score of 15 or higher on the SCQ and a score of seven or higher on the hyperactivity subscale of the SDQ. Note that none had scores in this range at time I as these were exclusionary criteria for recruitment.

Social Communication Questionnaire

Parent-reported social communication difficulty scores increased over time across both groups (β = 0.58, SE = 0.21, CI [0.18, 0.99], p = 0.004), and the DLD group had consistently higher average scores across both time points (β = 6.44, SE = 1.41, CI [3.67, 9.21], p < 0.001; Fig. 2.11A). The time-by-group interaction was not significant (β = -0.01, SE = 0.23, p = 0.94).

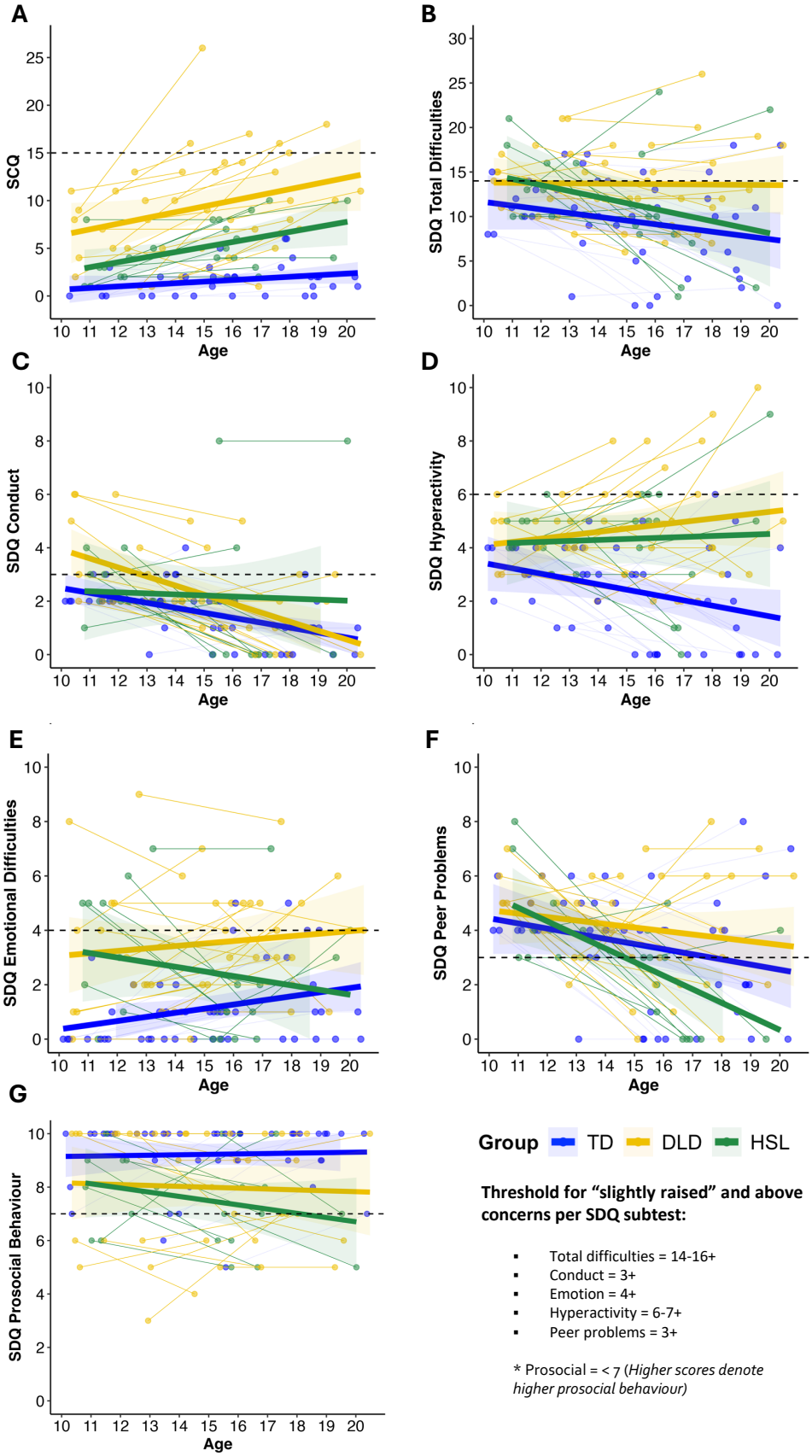


Fig. 2.11 ***Longitudinal trajectories for parent questionnaires per group.*** The points and lines represent each participant's score at time I and time II. The regression lines are shown in bold with shaded areas denoting standard error of mean. The dashed black line shows the clinical cut-offs per test.

Strengths and Difficulties Questionnaire

The total difficulty scores from the SDQ decreased from time I to II across both groups (β = -0.41, SE = 0.13, CI [-0.67, -0.16], p = 0.001), but scores were on average higher in the DLD group across time (β = 2.08, SE = 0.96, CI [0.21, 3.96], p = 0.029) and there was no group-by-time interaction (β = 0.19, SE = 0.18, p = 0.29; Fig. 2.11B).

Externalising Problems

For the conduct problems subtest, scores for all participants decreased over time (β = -0.61, SE = 0.15, CI [-0.91, -0.29], p < 0.001; Fig. 2.11C). The DLD group had higher average conduct problems across both time points, but this difference only approached significance (β = 1.59, SE = 0.91, p = 0.08). The group-by-time interaction was not significant (β = -0.27, SE = 0.21, p = 0.18). On the other hand, a significant group-by-time interaction on the hyperactivity subtest showed that scores increased in DLD group despite decreasing in the TD group (β = 0.71, SE = 0.21, CI [0.31, 1.11], p < 0.001; Fig. 2.11D). The main effect of time was significant, showing an overall reduction in hyperactivity scores across both groups over time (β = -0.41, SE = 0.13, CI [-0.67, -0.15], p = 0.001). There was no main effect of group (β = 1.01, SE = 0.65, p = 0.12).

Internalising Problems

Parents reported an increase in emotional difficulties scores across both groups over time (β = 0.71, SE = 0.19, CI [0.32, 1.11], p < 0.001), with higher average scores in DLD (β = 8.08, SE = 2.12, CI [3.91, 12.25], p < 0.001; Fig. 2.11E). The group-by-time interaction approached significance, indicating more pronounced increase in emotional issues in the TD cohort (β = -0.41, SE = 0.23, p = 0.076). In contrast, parents reported fewer peer problems at time II relative to time I across both groups (β = -0.41, SE = 0.12, CI [-0.65,-0.16], p = 0.001), with no group differences (β = 0.27, SE = 0.61, p = 0.65) or interaction effect (β = 0.05, SE = 0.17, p = 0.73; Fig. 2.11F). Scores on the prosocial scale remained stable, with no significant changes over time (β = 0.15, SE = 0.15, p = 0.31) or differences between DLD and TD groups (β = -1.33, SE = 1.16, p = 0.25; Fig. 2.11G).

The HSL group started with lower SCQ scores than the DLD group but increased over time, and average scores lay between the TD and DLD groups. Their SDQ total difficulties were also in between the other two groups and decreased similarly to the TD group. Unlike the TD

and DLD groups, conduct problems in the HSL group remained stable, appearing higher by time II, and hyperactivity/inattention slightly increased, aligning more with the DLD group. Emotional difficulties and peer problems decreased in the HSL group, Together, these observations indicate fewer internalising problems over time in the HSL group, while externalising problems stayed stable or slightly increased. Lastly, prosocial behaviour scores decreased in the HSL group.

2.4 Discussion

In this chapter I presented neuropsychological data from 156 children and adolescents with a range of language abilities. We reassessed 53 of these participants after approximately four to five years when they were aged 14 to 20 years to explore longitudinal changes in their behavioural profiles. At time I, the participants with DLD performed significantly below their TD peers on all neuropsychological measures administered. Over time, they showed steady gains in parallel to the TD group on most of those measures but with a constant gap in performance that remained throughout. An exception to these gains was seen on performance on the Block Design test, in which the raw scores dropped over time in the DLD group.

Parent-reported social communication difficulties increased in both TD and DLD groups but remained higher in DLD. Mean total SDQ scores remained the same in the DLD group across time and were higher than the TD group. The most notable pattern in SDQ subtests was in the hyperactivity/inattention subtest where scores accelerated in the DLD participants but decreased in the TD group. Peer interactions and prosocial behaviour were relative strengths for both groups, with no significant group differences and a decrease in peer problems over time. Below I discuss these findings with respect to previous literature and outline our plans for future analyses of the data. Results from the cross-sectional data have been previously published for different subsets of the OxBOLD cohort and will not be further discussed here (see Asaridou et al., 2024; Bahar et al., 2024; Krishnan et al., 2021).

2.4.1 Language Skills and Their Longitudinal Trajectories in DLD

Vocabulary

Raw vocabulary scores improved in both TD and DLD groups over time, following similar trajectories despite being consistently lower in the DLD group. Previous research on vocabulary development in DLD has been mixed; some studies reported a decline in standard

scores from childhood to adolescence (Mawhood et al., 2000; Rice et al., 2006; Stothard et al., 1998), while others observed steady gains up to age 12 (Beitchman et al., 1996). In a major study, Rice and Hoffman (2015) found parallel growth trajectories for receptive vocabulary in DLD and TD children from ages 2 to 21 years, though at lower proficiency levels in DLD, which is consistent with our findings. Unlike our results however, the authors further reported a widening gap in receptive vocabulary between groups. This may reflect methodological differences, such as vocabulary measures or DLD criteria, and likely varying proportions of children with reading difficulties in our groups. Reading and book exposure are crucial sources of new vocabulary from middle childhood to adulthood (Cunningham & Stanovich, 1991), and it would be hard to compare results across groups without careful consideration of these other factors.

Grammar

Previous longitudinal studies on grammar development in DLD indicate that, despite delays, these children often follow developmental trajectories similar to their TD peers, with both groups experiencing periods of accelerated growth (Rice, 2004, Rice et al., 2009; Rice & Hoffman, 2015). While we could not compare our groups directly due to a ceiling effect in the TD participants, receptive grammar scores improved in the DLD participants over time even though average performance remained below TD. The growth in the DLD group was also evident on subtests that specifically assessed comprehension of complex grammatical constructs, which is a particularly challenging area for this population (Marinis & Van Der Lely, 2007; also see Section 1.2.3).

In contrast to receptive grammar, sentence recall, our measure of expressive grammar, revealed the largest impairment in DLD relative to TD despite steady gains and similar rate of growth in both groups. Sentence recall is a reliable clinical marker for DLD (Archibald & Joanisse, 2009). A recent meta-analysis found that TD children outperform those with DLD by an average of 2.08 SDs on sentence recall tasks, with the test's utility consistent across a broad age range, and regardless of task variations or languages examined (Ward et al., 2024). Accurately repeating a sentence requires the ability to process and temporarily store linguistic information in short-term memory, and regenerating a grammatically correct sentence necessitates a strong prior language foundation and an ability to maintain a conceptual representation in mind (Klem et al., 2015; Potter, 2012). Sentence recall therefore taxes several

cognitive processes simultaneously, which might explain why we found the most striking group difference on this test. Despite this, steady gains were seen in our participants with DLD, and it would be interesting to explore whether they continue to improve on this test as they enter later adult years.

Narrative

An area of strength in our DLD group was on the three measures of narrative, with accelerated growth over time compared with changes in other language domains. This aligns with findings from another study, where children with DLD (who had typical literacy skills) demonstrated steady gains in listening comprehension and storytelling from preschool to grade three, ultimately reaching the level of their TD peers despite lower scores in vocabulary and morphology (Vandewalle et al., 2012). It should be noted, however, that our data are from a significantly later part of development (late adolescence) and the narrative test used in our study is designed for use in younger children. Other age-appropriate narrative tests are required to capture true performance in this older age range.

Pseudoword Repetition

Our DLD participants performed lower than their TD peers on both pseudoword repetition tasks we administered. Though the same test was not used longitudinally, separate analyses at each time point showed that repetition accuracy in the DLD group significantly declined as syllable count increased. At time I, stimuli wordlikeness did not affect accuracy significantly. At time II, pseudoword complexity negatively affected accuracy in DLD, with a significant interaction showing that the DLD participants struggled most with pseudowords that were both long and complex.

Pseudoword repetition is a recognised marker of DLD (Bishop et al., 1996; Conti-Ramsden et al., 2001; Dollaghan & Campbell, 1998) but like sentence recall, poor performance can stem from various factors. Repeating pseudoword accurately requires transforming newly encoded speech sound sequences into precisely timed and coordinated oromotor movements (Krishnan et al., 2013). While children with DLD often match their TD peers on producing short pseudowords, accuracy declines dramatically on longer stimuli. This pattern indicates limitations in phonological working memory beyond general perceptual or encoding deficits (Archibald & Gathercole, 2007). Our findings provide further support for this notion, that the

performance gap between groups widened as pseudowords got longer. The same observation held at time II in older adolescents and young adults with DLD. Lower scores of our DLD group on the digit span memory tests further highlights these limitations in short-term and working memory. The added influence of stimulus complexity suggests that deficits in pseudoword repetition in DLD are related not only to limitations in verbal storage but also difficulties in articulating phonological sequences, which are independent of memory. Together, these findings suggest that pseudoword repetition deficits in DLD have multiple underlying factors and can persist into young adulthood.

In typical development, accuracy improves when producing pseudowords that are more "wordlike," since familiar phonological and speech-motor patterns reduce memory demands (Gathercole et al., 1991). Despite this, wordlikeness did not significantly influence repetition accuracy in our cohort. We were unable to fully assess this effect in the TD group due to a ceiling effect, but the DLD group also did not appear to benefit much from wordlikeness. Our findings align with observations from affected members of the KE family, who also did not benefit from lexicality on word and pseudoword repetition tasks (Vargha-Khadem et al., 1995). A likely explanation is that smaller vocabularies and less developed phonological and speech-motor skills in individuals with DLD prevented them from leveraging their vocabulary knowledge to support memory for pseudowords.

Reading

Our DLD group initially scored lower than TD on both word and nonword reading tests. Over time, raw scores increased at a similar rate in both groups, but the gap in performance persisted between groups. Difficulties in accurate and fluent reading are well-documented in DLD, including in adolescents (Adlof, 2017; Bishop & Adams, 1990; Snowling et al., 2000). Snowling and colleagues (2000) reported a decline in reading accuracy standard scores in participants with DLD between ages 8-15 years. Variations in reading tests might have however impacted the findings since reading was assessed with different measures at each time point. In a later study, Catts and colleagues (2008) reported that language-impaired participants struggled with reading decoding over a decade between ages 7-16 years, yet their developmental patterns were similar to TD peers, which aligns with our findings. Similarly, another study found comparable developmental trajectories in reading decoding between 7 and

16 years in DLD and TD groups (Clair et al., 2010). Our data suggest that word recognition and phonological decoding skills continue to grow into early adulthood in individuals with DLD.

2.4.2 Longitudinal Trajectories of Nonverbal Skills in DLD

Nonverbal Reasoning

Examination of the NVIQ subtests revealed that participants with DLD experienced an average decline in raw Block Design scores, while the scores in the TD group continued to increase. In contrast, Matrix Reasoning scores improved in both groups, though the DLD group remained lower than the TD group. This indicates that the less pronounced gain in composite NVIQ scores among the DLD participants was due to the drop in Block Design performance. Declines in nonverbal intelligence scores, sometimes up to 10 standard points from childhood to early adulthood, are robust findings in this population (e.g., Botting, 2005; Johnson et al., 1999; Mawhood et al., 2000; Tallal, 1991). Similarly, affected members of the KE family showed significant decreases in NVIQ over time (Watkins et al., 2002). Research suggests that these declines may correlate with the severity of the language disorder; more persistent language impairments are linked to steeper declines in nonverbal intelligence (Stothard et al., 1998). Conversely, higher language abilities have been associated with stable or improving nonverbal intelligence in other studies (Conti-Ramsden et al., 2012; Rice et al., 2023).

The reasons for such decline in NVIQ scores are debated. Methodological factors like measurement issues may play a role. To accommodate the increasing age range, some studies used different measures across testing sessions based on the availability of normed scores, which can affect accuracy if the same test is not consistently used. This limitation applies to our study as well, as we transitioned from the WISC-IV to the WASI-II, although note that the two tests are nearly identical. On the other hand, some argue that the magnitude of this decline likely indicates a real change (e.g., Botting, 2005). In cases of a true decrease in scores, one potential explanation is that individuals with poorer language encounter fewer opportunities to develop the problem-solving abilities required for good performance on nonverbal reasoning tasks, leading to a gradual decline in scores.

Another plausible explanation relates the role of processing speed. A recent meta-analysis reported that DLD was associated with significantly longer reaction times across all timed tasks examined, indicating a domain-general deficit in processing speed that might

contribute to language, motor, and executive functioning difficulties (Zapparrata et al., 2023). Considering this, we re-analysed the Block Design scores this time with a focus on design accuracy regardless of timing. In this analysis, the average scores in the DLD group remained lower than TD (who reached ceiling levels) but performance did not decline either.

Processing speed is particularly relevant when considering motor dexterity. In our study, the performance gap between the DLD and TD groups widened only on two measures: Block Design and Coding. Both tasks involve not only timing but also motor components. The Coding subtest of the WISC-IV requires rapid inspection of visual numbers and abstract symbols, which must be converted into a series of written elements within two minutes. This test demands strong visual-motor integration and fine motor dexterity, among other skills. As reviewed in Chapter 1 (see Section 1.3.3), individuals with DLD often exhibit deficits in motor control, including manual dexterity. Therefore, their lower performance on Block Design and Coding may reflect the added challenge of motor control.

Motor Skills

Our DLD cohort began with lower scores on the pegboard test compared with the TD cohort but exhibited parallel rates of improvement over time; the gap between the two groups remained. Performance on neuromotor tests have been deemed as reliable and independent measures of developmental age in younger children, accounting for substantial percentage of variance in language skills (Wolff et al., 1985). Our results provide support for the "persistent developmental lag" account of DLD, initially proposed by Bishop and Edmundson (1987) who observed similar results in their longitudinal study of younger children with DLD. The authors proposed that both motor and language delays may stem from an underlying neurological immaturity in DLD (Gillberg, 1985; Wolff et al., 1985). Considering our results and numerous other reports of immature motor performance in individuals with DLD, we believe that the persistent developmental lag hypothesis merits further investigation. We will revisit this topic in Chapter 4 in relation to our longitudinal structural brain imaging results of this cohort. As a next step we plan to explore the predictive power of initial motor scores on later language outcomes for more insight into the interplay between motor and language scores in older adolescents and young adults with DLD.

2.4.3 Parent Questionnaires

In our study, hyperactivity scores in the DLD group increased over time, contrasting with a steady decline in the TD group. This finding aligns with self-reported data from adolescents with a history of DLD (Conti-Ramsden et al., 2013), indicating that hyperactivity may persist or escalate with age. Notably, lower receptive language ability was associated with increased reports of hyperactivity in that study, suggesting that deficits in language comprehension may contribute to hyperactivity and inattention in teens with DLD (Conti-Ramsden et al., 2013). Another study however reported a decline in hyperactivity from age 7 to 16 in this population (St Clair et al., 2011). Parents of both TD and DLD groups reported a decline in conduct problems in our study, aligning with other reports of conduct-related issues diminishing steadily as children enter adolescence (St Clair et al., 2011).

Regarding internalising problems, emotional difficulties increased across both groups, with DLD participants consistently scoring higher. Adolescents with DLD also reported higher emotional symptoms in the study by Conti-Ramsden et al. (2013). In contrast, St Clair et al. (2011) found a decrease in emotional problems between ages 7-16 but acknowledged ongoing difficulties during adolescence. Unlike their findings of increasing peer problems in DLD, our results showed a decrease in this domain, with no group differences and stable prosocial behaviour in both groups. Collectively, these results highlight substantial variability in emotional, behavioural, and social trajectories among individuals with DLD.

Echoing this variability, a study by Mok et al. (2014) identified four distinct longitudinal trajectories of peer relations among individuals with DLD: low or no peer problems, problems limited to childhood, childhood-onset persistent problems, and adolescent-onset problems. Positive peer trajectories were associated with stronger prosocial skills and pragmatic language abilities. Specifically, individuals in the low or no peer problems and childhood-limited problems groups experienced fewer peer issues over time, suggesting that early strengths in these areas can act as protective factors against persistent peer difficulties, findings that are consistent with our observations. In contrast, higher social communication difficulties were linked to elevated emotional difficulties, with both increasing over time. Together, these findings highlight the importance of addressing social communication and emotional difficulties early on to support peer outcomes in individuals with DLD.

2.4.4 Limitations and Future Directions

Investigating developmental trajectories of cognitive skills in DLD requires data from multiple time points with larger cohorts. The current two-time point study limits our ability to model growth patterns over time. We note however that the main aim of this longitudinal investigation was comprehensive phenotypic characterisation of our cohort to accompany their brain imaging data, beyond any goals to map out developmental trajectories *per se*. Regardless, future longitudinal studies with large cohorts are required to identify periods of acceleration or deceleration in cognitive skills beyond childhood in DLD. Notwithstanding the small sample size here, a clear message emerged in our study: that children and adolescents who started out with lower scores remained low performing compared with their typically developing peers, with participants retaining their relative positions as they transitioned into adulthood. Importantly, language skills continued growing in those with DLD and did not plateau.

Performance on nonverbal tests require further investigation in the future. For example, several other variables have been examined in relation to Block Design (e.g., Joy, 2001; McKee et al., 2024), including types of design (perceptual coherence), block placement strategies (cell ordering, starting position), errors (rotation errors, broken configurations), gaze patterns (frequency of consulting the pattern, gaze location), and motor dexterity (block rotations in hand, within-test practice effects). Comparing the performance of individuals with DLD on these variables could shed light on more specific aspects of problem-solving in this population, which can be particularly helpful in designing interventions that focus on learning strategies. Likewise, the Coding test has an interesting learning component embedded within in, such that through associative learning of the number-symbol pairs, performance should supposedly speed up. Future studies should examine the learning strategies that individuals with DLD use on Coding and similar tests.

As the next step, we aim to analyse the relationship and predictive power of several variables, including NVIQ and motor scores, on longitudinal outcomes. Previous research indicates that factors such as sex or maternal education can have small but significant impacts on vocabulary growth (Rice & Hoffman, 2015). Moreover, initial mean length of utterance predicted the rate of grammatical acquisition in one study, whereas non-syntactic measures such as NVIQ, vocabulary size, and maternal education did not (Rice et al., 1995, 1998, 2023). Examining the effect of such predictors may enhance our understanding of patterns of

cognitive development over time and help identify factors contributing to individual differences in outcomes among individuals with DLD.

3

Differences in Cortical Surface Area in Developmental Language Disorder

ABSTRACT

Previous studies of cortical grey matter in DLD have focused mainly on volume, leaving uncertainty as to whether cortical morphological differences reported in individuals with DLD reflect differences in cortical thickness or surface area, which are genetically and ontologically distinct components of grey matter volume. In this chapter we used FreeSurfer to investigate these cortical metrics in the OxBOLD cohort which included 54 individuals with DLD, 74 typical developing controls, and 28 with a history of speech-language difficulties. We also examined cortical asymmetries in those with DLD compared with controls using an automated surface-based technique. Relative to the control group, the DLD group showed smaller surface area bilaterally in the inferior frontal gyrus extending to the anterior insula, in the posterior temporal and ventral occipito-temporal cortex, and in portions of the anterior cingulate and superior frontal cortex. Analysis of the whole cohort using a language proficiency factor revealed that language ability correlated positively with surface area in similar regions. There were no differences in cortical thickness, nor in asymmetry of these cortical metrics between typically developing and DLD groups. Our study highlights the importance of distinguishing between surface area and cortical thickness in investigating the brain basis of neurodevelopmental disorders and suggests the development of surface area to be of importance to DLD.

3.1 Introduction

Previous structural imaging studies of DLD have found grey matter differences in perisylvian cortical regions involved in speech and language, and subcortical structures implicated in habit formation and learning (see Chapter 1, Section 1.7.1). One limitation of these studies is that almost all findings pertain to measures of grey matter volume, which in the cortex depends on both surface area and cortical thickness. As such it remains unclear whether the reported cortical morphological abnormalities in individuals with DLD reflect differences in surface area, cortical thickness, or a combination of both. Surface area and cortical thickness are heritable anatomical features that are under separate genetic influences and have independent developmental trajectories, suggesting that their changes during childhood reflect different developmental processes (Panizzon et al., 2009; Winkler et al., 2010).

Early in brain development, surface area and cortical thickness are thought to depend on pre- and early post-natal processes of neurogenesis, including the number of radial units, cell proliferation, neuronal migration, programmed cell death, and the density of the columns themselves (Rakic, 2009; Tamnes et al., 2017). In addition, surface area is closely linked to cortical folding, which in turn depends on the division of progenitor cells during early embryonic stages (Chenn & Walsh, 2002; Rakic, 2009). Surface area expansion during childhood is most likely driven by increases in dendritic complexity, spine and synaptic density, and glial cell numbers, along with axonal growth and intracortical myelination of these axons. Cortical thickness reductions (or "thinning") may be due to a decrease in synaptic density that arises from experience-dependent plasticity (Rakic, 2009; Sowell et al., 2004), and increased intracortical myelin potentially "whitening" the cortex (Paus, 2010). Investigating surface area and cortical thickness as distinct grey matter volume components may therefore enhance our understanding of the neurogenetic pathways underlying language learning difficulties in individuals with DLD.

In this study, we addressed the shortcomings of previous investigations by examining differences in surface area and cortical thickness in the OxBOLD cohort of children and adolescents with DLD compared with typically developing controls. FreeSurfer (Fischl, 2012) was used to generate mesh models of the cerebral cortex from MRI scans. We also investigated asymmetries in these measures using a reproducible and automated surface-based interhemispheric registration method (see Greve et al., 2013; Sha et al., 2021). Based on the previous literature, we predicted that relative to the controls, those with DLD would exhibit (1)

differences in the morphology of perisylvian regions relevant for language, specifically the inferior frontal gyrus; and (2) atypical cortical asymmetry between the same left hemisphere regions and their right hemisphere homologues. We expected morphological differences to include right hemisphere homologues of language regions due to accounts of children with typical language acquisition following focal unilateral brain injury (e.g., Liegeois, 2004; Newport et al., 2017) or even without a left hemisphere (Asaridou et al., 2020; Curtiss et al., 2001), indicating the potential of the intact right hemisphere to support language. Accordingly, in DLD where there are no obvious lesions to explain the language impairment, we expect that causal abnormalities in the cortex would occur bilaterally, else the high degree of plasticity available during development would support reorganisation of function to the unaffected hemisphere. Furthermore, given DLD's genetic component (Bishop, 2014), it is likely that genetic disruptions will affect neural development of pathways in both hemispheres rather than only one (e.g., Belton et al., 2003), though the latter possibility cannot be ruled out.

3.2 Methods

3.2.1 Study Sample

The cohort consisted of 156 children including 54 who met the criteria for DLD (*m* = 12.43 yrs, SEM = 0.3; 15 female), 74 typically developing (TD; *m* = 12.6 yrs, SEM = 0.2; 33 female), and 28 who did not meet the criteria for DLD at the time of testing but had a history of speech and language problems (*m* = 12.4 yrs, SEM = 0.3; five female). The demographic and neuropsychological data of these participants were presented in Chapter 2.

3.2.2 MRI Acquisition

Brain scans were acquired on a 3T Siemens Prisma scanner with a 32-channel radiofrequency head coil. The anatomical images were obtained in the sagittal plane using a T_1-weighted 3D magnetisation prepared rapid gradient echo (MPRAGE) sequence with the following pulse sequence parameters: repetition time = 1900 msec, echo time = 3.97 msec, flip angle = 8°, inversion time = 904 msec, with 192 × 192 sagittal field of view, 174 slices, with 1-mm in-plane resolution and 1-mm slice thickness. Participants wore earplugs and noise-cancelling headphones held in place by inflatable air pads. The total image acquisition time was 5 min and 30 sec.

3.2.3 MRI Processing

Prior to processing, an experienced rater carefully checked the structural scans for artefacts. We used FreeSurfer v7.2.0 (http://surfer.nmr.mgh.harvard.edu) to automatically parcellate the T_1-weighted images and generate 3D reconstructions of each child's cortex via the "recon-all" command (Dale et al., 1999; Fischl et al., 1999a). The reconstructed surfaces were then registered to the *fsaverage* template and assigned a neuroanatomical label (Fischl et al., 1999). To label the sulci and gyri, the Desikan-Killiany atlas was employed, which consists of 33 regions of interest (ROIs) per hemisphere, for a total of 66 ROIs (Desikan et al., 2006; Fischl, 2004).

We used the Qoala-T supervised-learning tool to assess the quality of cortical segmentations and parcellations post-processing (Klapwijk et al., 2019). This automated approach provided several advantages over manual correction, including reduced time and variability associated with manual quality control (e.g., inter-rater bias). Out of an initial sample of 160, four children were excluded after running Qoala-T on the T_1-weighted images (final n = 156). Qoala-T evaluates scan quality on a 0–100 scale. Nine scans with an average scan quality score below 50 were recommended for exclusion (the mean Qoala–T score of our entire dataset was 71.5). We retained five of these scans after visually inspecting the parcellation qualities. We additionally inspected the quality of image segmentations and cortical reconstructions in 51 scans with average quality above 50, as recommended by Qoala-T. We retained all 51 scans.

3.2.4 Cortical Metrics

Our morphometric measures of interest were surface area, cortical thickness, and grey matter volume. Surface area is defined as the average area of the triangles (on the tessellated surface) of which each vertex is a member, while cortical thickness is the distance between the white and pial surfaces at each vertex (Fischl & Dale, 2000). Grey matter volume is the product of surface area multiplied by cortical thickness at each vertex.

3.2.5 Whole-brain Cortical Morphometry

The surface area, cortical thickness, and grey matter volume maps were spatially smoothed in each hemisphere using a Gaussian smoothing kernel with a full width at half maximum (FWHM) of 10 mm. A two-group general linear model (GLM) was performed to investigate cortical differences between DLD and TD in vertex-wise whole-brain analyses.

Surface area, cortical thickness, and grey matter volume were separately entered as outcome variables with the participants' age and sex as covariates of no interest. Clusters were defined as groups of contiguous vertices using a vertex-wise threshold of $p < 0.001$ (two-tailed). We corrected for multiple comparisons by using a cluster-wise correction with a Monte Carlo simulation of 10,000 iterations and a threshold of $p < 0.05$ (two-tailed).

Participants in the HSL group were excluded from the whole-brain DLD-TD comparisons. Instead, we included them in two continuous analyses; first, to examine the effects of age and sex and their interaction on surface area, thickness, and volume at each vertex across all participants; and second to investigate the relationship between language ability and the cortical metrics across the whole cohort. For the latter, we created factor scores to increase the reliability of our measures and minimise the number of multiple comparisons in the statistical analysis. We entered the participants' standardised language and memory test scores from the neuropsychological test battery (described in Chapter 2, Section 2.2.2) into a factor analysis to identify the best weighted combination of measures that would yield a language factor score, and a memory factor score.

Following Brown (2006), we implemented an exploratory-confirmatory factor analysis (E-CFA), a hybrid approach where a model is specified with either one or two 'anchor' measures with no specification of cross-loadings per factor. This approach allows test scores to load on both factors, with paths being dropped if they do not improve the model fit. As anchor measures, we used the participants' scores from Word Lists subtest of Children's Memory Scale (CMS; Cohen, 2011) for the memory factor, and the Expressive One-Word Picture Vocabulary-4th Edition (EOWPVT-4; Martin & Brownell, 2011a) scores for the language factor. We tested the model with these two factors against a single factor model; if the latter provided an equally good fit (assessed through Bayesian Information Criteria [BIC]), we decided to proceed with one rather than two outcome measures.

The factor analysis was performed in R (R Core Team, 2020) using the `lavaan` package (Rosseel, 2012). The language and memory factor scores derived from this analysis were then entered into two separate GLM analyses, controlling for age and sex, implemented in FreeSurfer. The same smoothing kernel and correction for multiple comparisons method described above was used in these analyses.

3.2.6 Surface-based Structural Asymmetry Analysis

Following the steps proposed by Greve and colleagues (2013) we first registered the participants' surface area, cortical thickness, and grey matter volume maps of both hemispheres to FreeSurfer's symmetric standard template (*fsaverage_sym*). This step aimed to achieve vertex-wise correspondence between the two hemispheres through precise alignment of the cortical folding patterns between- and within-participants. For each participant, we calculated the asymmetry quotient (AQ) separately for each pair of vertices matched across the left (L) and right (R) hemispheres using the equation:

$$AQ = [L - R] / [(L + R)/2]$$

with negative values indicating right- and positive values indicating left-lateralisation. We masked out a region around the boundary between cortical and subcortical structures which had extreme AQ values in many participants, likely due to a warping artefact. We excluded any vertices from all individuals with asymmetry values of $|AQ| > 1$ in at least 25% ($n = 31$) of our cohort (see Fig. S3.1). Vertices with extreme AQ values were subsequently excluded from the thickness and volume analyses.

We used the vertex-wise AQ values between the DLD-TD groups as the dependent variable in a GLM with age and sex as covariates of no interest. Given previous reports of sex differences in grey matter in Broca's area (Kurth et al., 2018), we also assessed the interaction between group and sex. AQ values from surface area, thickness, and volume were each entered into the model above. Significant clusters were determined using SurfStat (https://www.math.mcgill.ca/keith/surfstat/) with a cluster-forming threshold of $p < 0.05$ (vertex-wise $p < 0.001$) and assessed against a random field with the same spatial correlation as the real map to minimise the likelihood of false positives. Clusters identified in this way had a peak vertex and contiguous vertices, with cluster-wise significance determined.

3.3 Results

3.3.1 Brain Morphometric Data

The TD, DLD, and HSL groups did not differ in the estimated total intracranial volume (eTIV), extracted with FreeSurfer's "aparcstats2table" command (in mm^3: DLD $m = 1{,}323{,}593$, SEM = 22,398; TD $m = 1{,}339{,}592$, SEM = 15,868; HSL $m = 1{,}409{,}468$, SEM = 34,784) or mean cortical thickness (in mm: DLD $m = 2.7$, SEM = 0.012; TD $m = 2.7$, SEM = 0.008; HSL $m = 2.7$,

SEM = 0.015). Participants in the HSL group had significantly larger mean surface area values (in mm^2: *m* =193,688, SEM = 4240) than those in the DLD group (*m* = 182,028, SEM = 2,805), $F(2, 156) = 3.31$, $p = 0.039$. There were no differences between these groups and the TD group (*m* = 186,051, SEM = 2,004).

We examined the influence of age and sex on our three cortical metrics (area, thickness, and volume) using the whole cohort (*n* =156; i.e. including the HSL group). For surface area, there was no relationship with age and no effect of sex in any brain region. Regarding cortical thickness, a small number of regions exhibited a decrease in thickness with increasing age, including portions of the medial parietal and occipital cortex, left ventral occipital cortex, and right orbitofrontal cortex. Conversely, increases in thickness with age were detected in the posterior ventro-medial frontal cortex and temporal poles (Fig. S3.2 and Table S3.1). We found that female participants had greater cortical thickness than male participants in a small portion of the left fusiform cortex only (Fig. S3.3 and Table S3.2). For grey matter volume, there was a significant negative correlation with age in a portion of the medial occipital cortex, with no effect of sex. We included age and sex as covariates in the analyses that compared DLD and TD participants below as well as in the continuous analyses with the language factor.

3.3.2 Whole-brain Analysis of Cortical Morphology in DLD vs. TD

The vertex-wise surface maps of brain regions where the DLD group had lower surface area than TD is depicted in Figure 3.1. The participants with DLD had significantly smaller surface areas in symmetric portions of the anterior inferior frontal gyrus (pars triangularis and pars orbitalis) in both the left and right hemispheres. This difference extended posteriorly to pars opercularis in the left hemisphere and ventrally into the anterior insula bilaterally. Additionally, smaller surface areas were observed in the lateral orbitofrontal cortex on the ventral surface of the left hemisphere. On the medial surface, smaller surface area in DLD was observed in the rostral anterior cingulate cortex bilaterally, anterior medial superior frontal cortex on the right, and posterior cingulate cortex at the boundary with the corpus callosum on the left. Smaller surface area was also seen in DLD in the posterior temporal cortex and ventral occipito-temporal cortex at the level of the mid-fusiform gyrus bilaterally.

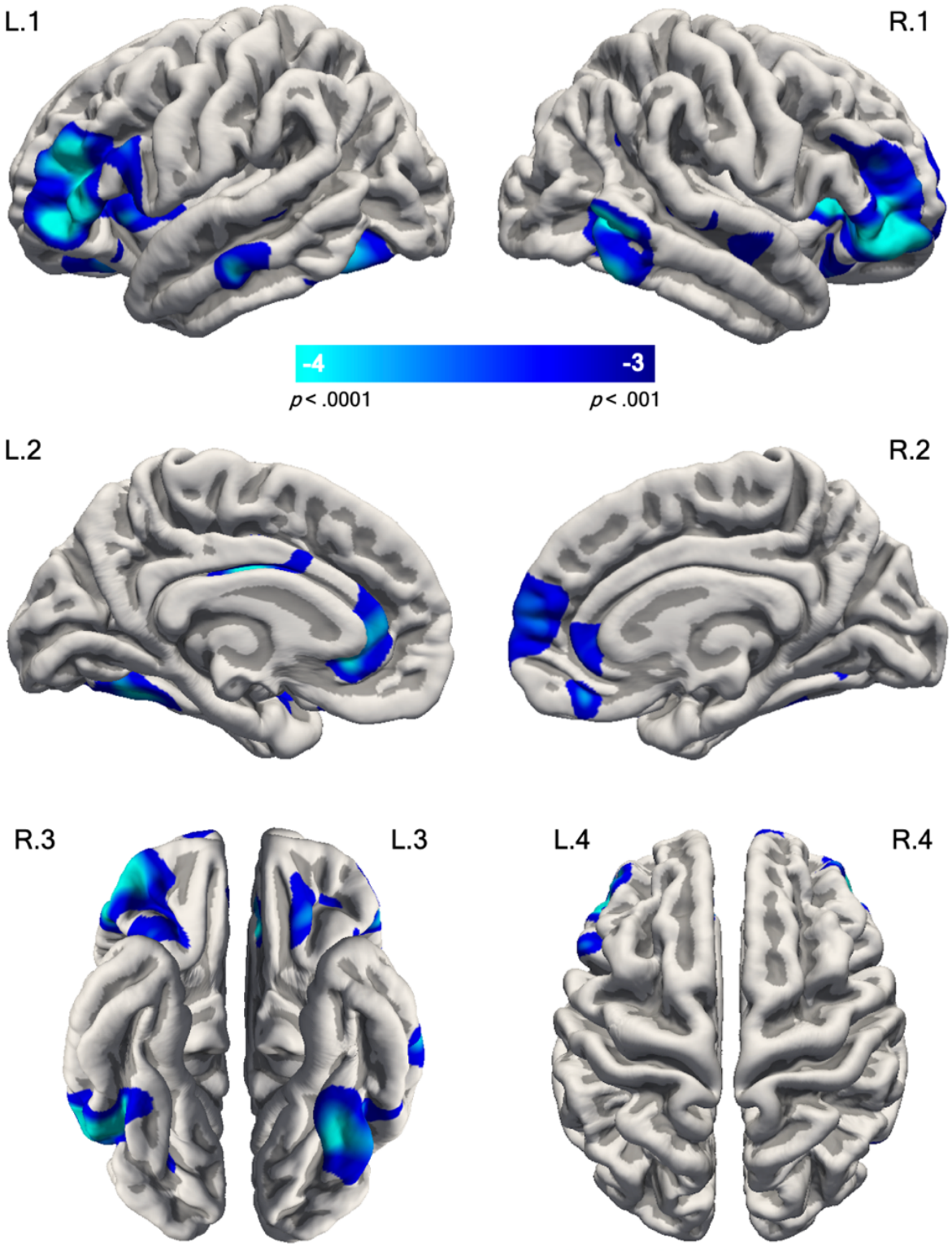


Fig. 3.1 ***Cortical regions showing smaller surface area in DLD.*** Whole-brain statistical map illustrating group differences in surface area between DLD and TD participants. The left and right hemispheres are shown on the left and right sides of the figure, respectively. The statistical map is overlaid on the pial surface of *fsaverage* and is displayed using an uncorrected vertex-wise threshold of $p < 0.001$ for visualisation purposes. The numbers inside the colour bar display the -log10(p), where p is the significance. The blue/cyan hues indicate the DLD < TD contrast. Cluster-corrected results are reported in the text. L.1/R.1 = lateral view; L.2/R.2 = medial view; L.3/R.3 = ventral view; L.4/R.4 = dorsal view.

The participants with DLD also had lower grey matter volume in similar regions to those showing smaller surface area but only small clusters survived thresholding. These were in pars triangularis and the inferior temporal gyrus in the right hemisphere, and the middle temporal gyrus on the left. The anatomical location of statistical peaks using MNI305-space coordinates, along their corresponding *p*-values and the extents of the cluster of voxels (in mm^2) for surface area and grey matter volume are presented in Table 3.1. There were no group differences in cortical thickness.

Table 3.1 ***Brain regions with lower surface area and grey matter volume in DLD relative to TD.***

Cluster (peak)	Cluster-wise *p*-value	Size	Centroid MNI305 coordinates		
			X	Y	Z
(A) Surface area					
R superior frontal	0.0012	6170	11	57	10
L pars orbitalis	0.0002	2269	-40	41	-06
R lateral orbitofrontal	0.0002	2212	29	25	03
L rostral anterior cingulate	0.0187	4020	-61	25	-02
L pars opercularis	0.0077	4710	-40	11	09
R posterior temporal	0.0002	1509	56	-53	-01
L fusiform	0.0002	1050	-33	-56	-16
(B) Grey matter volume					
R pars triangularis	0.0002	4520	47	36	-05
L middle temporal gyrus	0.0093	2450	-59	-20	-22
R posterior temporal gyrus	0.0002	4210	49	-57	-09

Note: Summary of significant clusters ($p < 0.05$, corrected) in the DLD < TD comparison for (A) surface area and (B) grey matter volume. The size of each cluster is reported in mm^2 for surface area and mm^3 for volume, along with the centroid MNI305 coordinates for Y (coronal), X (sagittal), and Z (axial) planes. Decimal values for the coordinates and cluster size were rounded to the nearest integer. Labels of peak location provided by FreeSurfer.

3.3.3 Analyses of Cortical Morphometry and Language Proficiency in the Whole Cohort

We used cut-offs on norm-referenced tests of language to categorise participants into TD and DLD groups. This resulted in a group of 28 with a history of speech and language problems (HSL) who did not meet criteria for DLD due to performance above the cut-off. To test the relationship between language and memory proficiency and our cortical metrics in the whole cohort, we used the language and memory factors derived from our exploratory-confirmatory factor analysis as predictors of our three parameter values across the whole sample ($n = 156$), controlling for age and sex (Fig. 3.2).

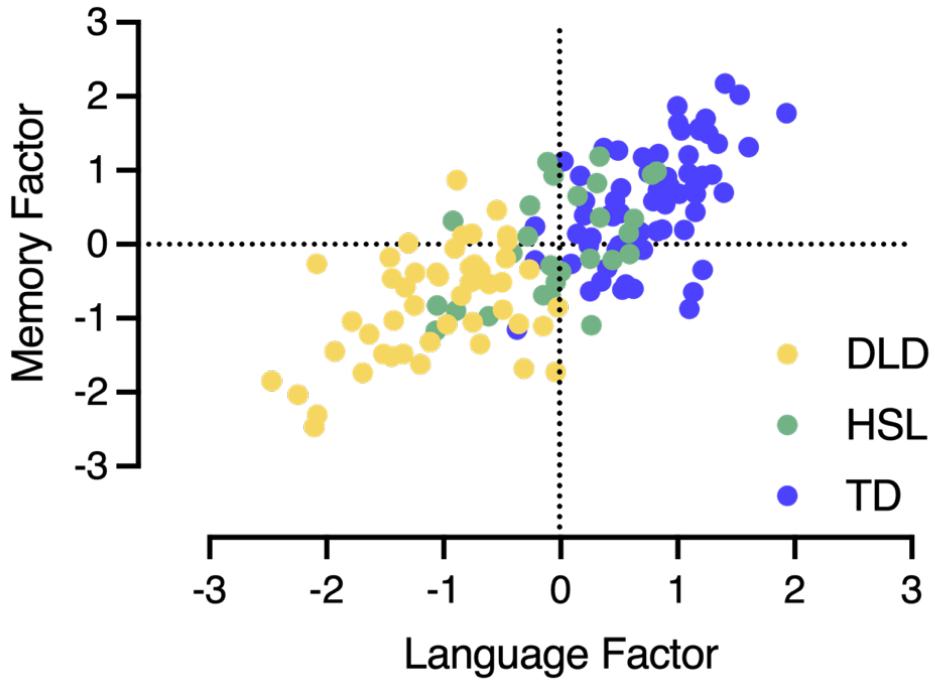


Fig. 3.2 ***The relationship between language and memory proficiency scores in the whole cohort.*** Language and memory factor scores are plotted on the X and Y axes, respectively Colours depict group membership. For details of factor analysis see Krishnan et al. (2021).

We found significant relationships between the language factor and surface area (Fig. 3.3 and Table 3.2) in similar regions to those seen in our whole-brain group analysis; lower language ability was associated with smaller surface area. Significant positive correlations were observed in the pars triangularis of the inferior frontal gyri bilaterally, and this effect was stronger and more extensive on the left. Significant positive correlations were also observed in the ventral occipito-temporal cortex at the level of the mid-fusiform gyrus also bilaterally but stronger on the left. The same pattern was observed in the continuous analysis of language factors and cortical volume, but results were less extensive and not as statistically robust as those seen in the analysis of surface area. There were no significant relationships between cortical thickness values and language proficiency. There were also no significant relationships between the memory factor scores and the surface area or cortical thickness values.

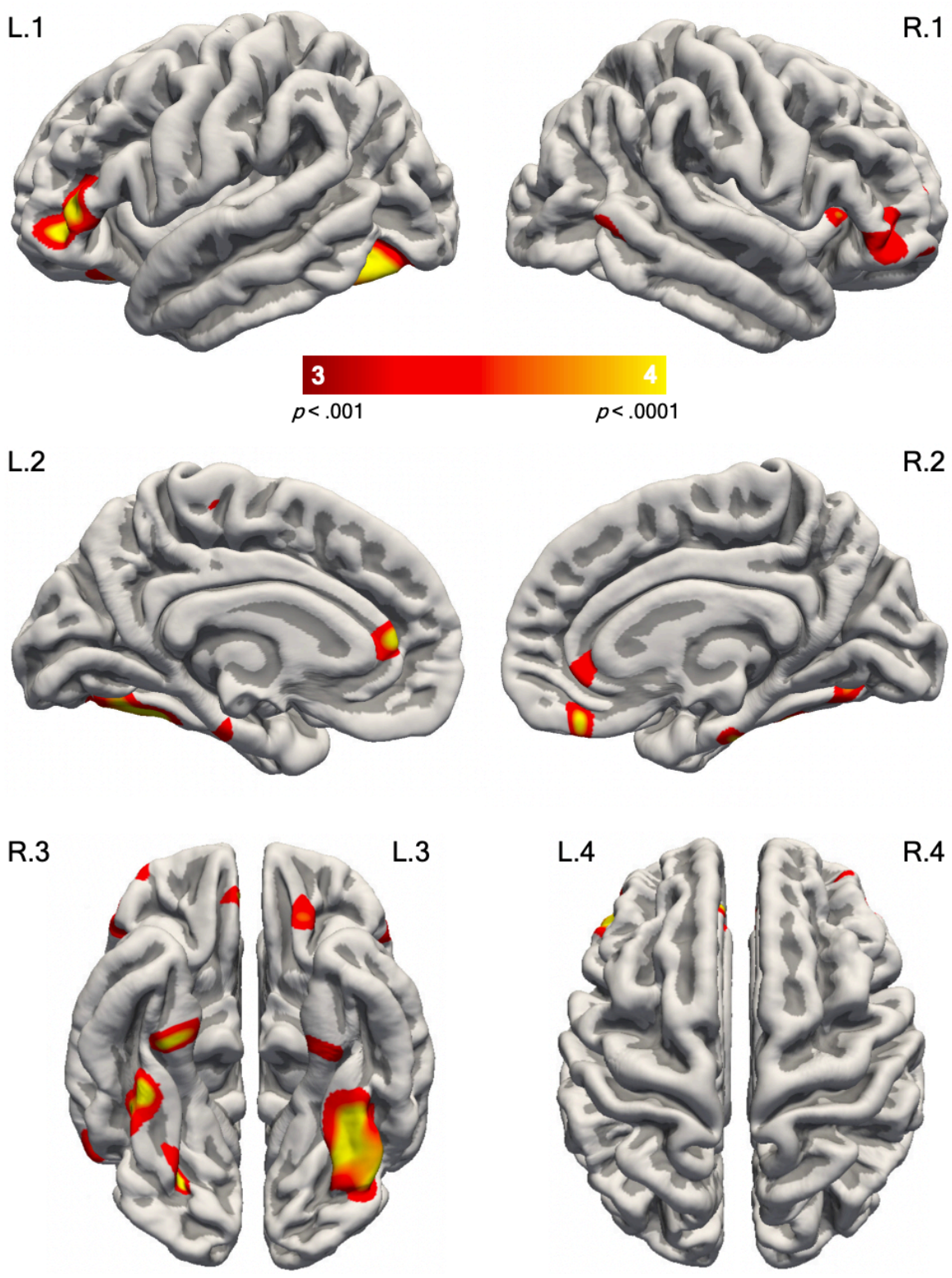


Fig. 3.3 ***Continuous analysis of surface area and language proficiency in the whole cohort.*** The red/yellow hues indicate the positive correlation between surface area and language factors after removing the effects of age and sex. See legend to Figure 3.1 for more details. Cluster-corrected results are reported in the text. L.1/R.1 = lateral view; L.2/R.2 = medial view; L.3/R.3 = ventral view; L.4/R.4 = dorsal view.

Table 3.2 *Brain regions showing positive correlation between surface area and language proficiency factors.*

Cluster (peak) – Surface area	Cluster-wise *p*-value	Size	Centroid MNI305 coordinates		
			X	Y	Z
L pars triangularis	0.0004	2212	-44	34	06
R pars triangularis	0.0183	4190	41	40	02
L fusiform	0.0002	1385	-41	-61	-13
R fusiform	0.0360	3570	39	-40	-22

Note: Summary of significant clusters ($p < 0.05$, corrected) in the continuous analysis of surface area values and language factors. Labels of peak location provided by FreeSurfer

3.3.4 Analysis of Structural Asymmetry in DLD vs. TD

For each of our 54 DLD and 74 TD participants, we generated surface area, cortical thickness, and grey matter volume asymmetry maps in which vertex-wise AQ values across the entire cortex were entered into a GLM with age and sex as nuisance variables. There were no differences between DLD and TD in the degree of structural asymmetry across the cortex in any of these three metrics. We re-ran the above analyses after excluding 19 participants (eight DLD, 11 TD) who reported being left-handed (using their left hand to write) and observed the same pattern of results for all three metrics (i.e., no significant group differences).

Figure 3.4 shows the mean AQ values indicating the degree of left- and right-ward structural asymmetry in surface area and cortical thickness, superimposed onto the left and right pial surfaces for DLD and TD participants. The patterns in both groups were very similar. In terms of surface area, both groups had a leftwards asymmetry (i.e., left-greater-than-right) in the frontal cortex and a rightwards asymmetry in the occipital lobe. The strongest leftward asymmetries in surface area were in the supramarginal and post central gyri in both groups. For cortical thickness, there was a leftwards asymmetry in the frontal cortex, which extended posteriorly and dorsally to the parietal cortex. Frontally, the strongest left asymmetries in cortical thickness were seen in rostral middle frontal gyrus, extending posteriorly to pars triangularis and precentral gyrus. The middle to posterior portions of superior and middle temporal gyri showed a rightwards asymmetry in thickness.

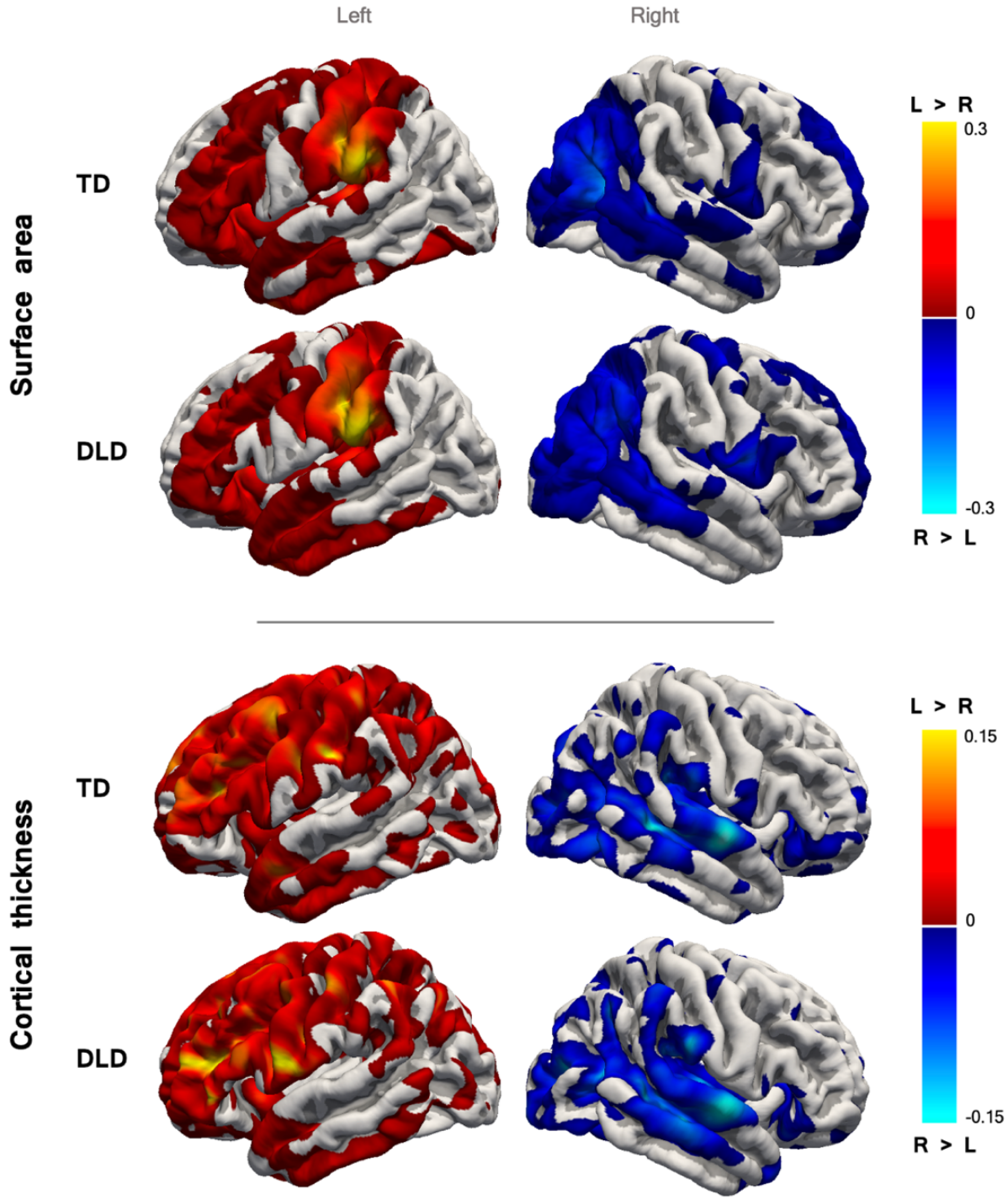


Fig. 3.4 ***Cortical asymmetries for surface area and cortical thickness in TD vs. DLD.*** Whole-brain map of DLD and TD participants' mean asymmetry quotient (AQ) values for surface area and cortical thickness. Red/yellow hues indicate left-greater-than-right asymmetry (L > R), and the blue/cyan hues indicate right-greater-than-left (R > L). See legend to Figure 3.1 for more details. L – left; R – right.

3.4 Discussion

We investigated cortical morphology in a large, well-characterised sample of 156 children and adolescents aged 10-15 years with a range of language abilities. The DLD group (n = 54) had smaller surface area relative to the TD group (n = 74) in the inferior frontal gyrus

extending to the anterior insula, in the posterior temporal cortex and the ventral occipito-temporal cortex, all bilaterally. Medially, portions of the anterior cingulate and superior frontal cortex also had smaller surface area in DLD. There were no group differences in cortical thickness. A similar pattern was observed when using a continuous variable of language proficiency based on a factor analysis of scores on tests of language. This analysis included the participants in the HSL group (n = 28) in addition to the DLD and TD groups. Lower scores on the language factor were associated with smaller surface areas in the inferior frontal gyrus and ventral occipito-temporal cortex again bilaterally but with more extensive effects in the left hemisphere. As for the group analysis, there was no significant relationship between cortical thickness and language proficiency in any region.

Overall, in terms of anatomical location, these results are consistent with many of the previous findings of cortical differences in DLD reported using other methods and confirm our prediction that children with DLD would show differences in the inferior frontal gyrus. Our second prediction that these regions would also show atypical cortical asymmetry in DLD was not upheld; we found no significant differences in asymmetry between groups. The finding that surface area but not cortical thickness is affected in DLD provides new insights into the underlying processes of brain development in this condition. To our knowledge, this is the first study in the DLD literature to focus on these separate morphological traits of the cortex. Below we discuss the implications of these findings with relevance to the relationship between cortical structure and function in the context of a developing brain.

3.4.1 Inferior Frontal Cortex Anomalies in DLD

The left inferior frontal gyrus consists of a mosaic of subregions implicated in phonological, semantic, and syntactic processing (e.g., see Vigneau et al., 2006). We found smaller surface area in our DLD cohort in all three subregions of this structure, namely pars orbitalis, triangularis and opercularis, bilaterally. The results of the continuous analysis with the language factor showed differences focused on the pars triangularis extending anteriorly to the orbitalis and these effects were more extensive on the left than the right. There is only one other study which reported structural abnormality in pars orbitalis in DLD (Lee et al., 2020), but this difference was a volumetric enlargement in the right hemisphere and the DLD groups were older on average, and with fewer participants than ours (m = 22.42 and 16.96 yrs, n = 14 and 19 in cohorts 1 and 2, respectively). Two other studies reported volume enlargement in the left

inferior frontal gyrus in DLD in a roughly similar age range to ours (Badcock et al., 2012; *m* = 13.5 yrs; *n* = 10) and more specifically, in pars triangularis (Kurth et al., 2018, *m* = 10.21 yrs; *n* = 13); but again the sample sizes were much smaller than ours. The only study that reported lower surface area in pars triangularis (measured through manual tracing with a mouse-operated cursor) was by Gauger and colleagues (1997) in a slightly younger and much smaller sample (*m* = 9.1 yrs; *n* = 11).

Pars orbitalis has been associated with an executive function role in semantic cognition tasks in adults (Krieger-Redwood et al., 2015) as well as narrative comprehension (Babajani-Feremi, 2017; Mar, 2011). In children, left pars orbitalis and triangularis are especially implicated in semantic processing (Skeide & Friederici, 2016). It has been argued that children rely more on these regions to process meaning from syntactically complicated sentences while their grammatical skills are still developing (Enge et al., 2021). Pars opercularis plays a critical role in syntactic ability as children's grammatical abilities become more mature towards adulthood (Friederici & Chomsky, 2017; Hagoort, 2014; Skeide & Friederici, 2016). In adults, non-invasive brain stimulation over pars triangularis and pars opercularis selectively impairs semantic and phonological judgements respectively (Gough et al., 2005). Furthermore, the strong connections between pars opercularis and the motor representations for the articulators are consistent with the known role of this region in spoken word production (Flinker et al., 2015). Given the functional significance of these cortical regions for language and their substantial connectivity to other brain areas (Bulut, 2022), the anomalous morphology of the inferior frontal cortex in our participants with DLD is therefore consistent with the behavioural profile of impaired language processing that characterises this population.

3.4.2 Ventral Occipito-temporal Anomalies in DLD

The region showing smaller surface area in the left hemisphere in the DLD group analysis was very much centred on the mid-fusiform gyrus. The same region showed significant correlation between surface area and language proficiency when the whole cohort was analysed. This portion of cortex is considered a hub for grapho-phonological word processing (Cohen & Dehaene, 2004). Several studies have provided evidence for the involvement of this region in long-term memory representations of visual word forms. In addition, functional and structural abnormalities in this region are reported in children with dyslexia (Kronbichler & Kronbichler, 2018; Paulesu et al., 2014). As discussed in Chapter 1 (see Section 1.2.5), DLD and dyslexia are

neurodevelopmental disorders that frequently co-occur and possibly have a shared aetiology (Bishop & Snowling, 2004). It is therefore not surprising to see overlapping structural abnormalities in both conditions. In fact, prior surface-based morphometric studies have found smaller area in both the inferior frontal gyrus and fusiform gyrus in individuals with dyslexia (Frye et al., 2010).

The lack of a strong foundation in oral language in early life hinders the development of essential literacy skills (Botting et al., 2006). This is supported by studies that found higher risk of reading problems in children with a history of oral language impairments (Snowling et al., 2000). Deficit in spoken language comprehension is a predictor of later reading difficulties in children with DLD (Tallal et al., 1988), likely reflecting the influence of early phonological skills on the development of literacy (Hulme et al., 2015). Cortical differences in the mid-fusiform gyrus in DLD could therefore be attributed to an underdeveloped neural network of skilful reading, perhaps due to lower print exposure.

3.4.3 No Differences in Cortical Asymmetry Associated with DLD

Previous structural asymmetry studies linked structural deviation in hemispheric dominance to language impairments (Jernigan et al., 1991; Plante et al., 1989; Plante, 1991a, 1991b), a finding which we failed to replicate. In accordance with a lack of difference in cortical asymmetry, previous work in DLD has also failed to find evidence to support for altered lateralisation of function. A well-powered functional MRI investigation from the same children and adolescents with DLD from our OxBOLD cohort found no difference in language lateralisation compared with TD during a verb generation task (Krishnan et al., 2021). Likewise, a large functional transcranial Doppler ultrasonography (fTCD) study of twin children with over 100 cases of DLD did not find evidence of altered language lateralisation in DLD (Wilson & Bishop, 2018). On the basis of both our structural findings reported here and previous functional results, we conclude that there is no evidence for consistently altered language lateralisation or cerebral asymmetry in DLD. The inconsistency in current results compared with past findings might either reflect a lack of sufficient statistical power due to the small number of participants, or that previous findings are false positives

3.4.4 Surface Area and Cortical Thickness Development

The differences found in DLD in this study were limited to cortical surface area and grey matter volume, with differences in the latter being neither extensive nor as statistically robust as those seen in the analysis of surface area. There were no group differences in cortical thickness. Since volume is the product of surface area and cortical thickness, the volume differences were most likely driven by the differences in surface area. As I will discuss in more detail in Chapter 4, surface area and cortical thickness follow distinct developmental trajectories. Post-natally, surface area increases over the first decade of life before reaching its plateau in late childhood, followed by areal decrease during adolescence (Raznahan et al., 2011; Tamnes et al., 2017). In contrast, there are major changes in cortical thickness in the first two years of life, followed by slow linear decreases with age that continue across the second decade (Amlien et al., 2016; Lyall et al., 2015). It is worth noting that in our study of children and adolescents aged 10-15 years, we found no relationship between age and surface area and only a handful of brain areas showed a reduction in cortical thickness across this age range.

Areal expansion of the cortex during development might be related to the myelination of cortico-cortical fibres (Cafiero et al., 2019). Notably, the recent quantitative MRI study from the OxBOLD cohort provides a clue to differences in the underlying microstructure of the cortex in DLD (Krishnan et al., 2022). Using multi-parametric mapping, these authors found lower levels of myelin, indexed through lower magnetisation transfer saturation values, in DLD in several regions of the left hemisphere's speech and language network, including in pars opercularis, insula, and several portions of the temporal lobe. In addition, lower mean global values in longitudinal relaxation rate (R1, another myelin marker) were reported for participants with DLD relative to their TD peers, reflecting potentially widespread differences in myelin across cortical and subcortical grey matter bilaterally (Krishnan et al., 2022).

Depending on whether cortical differences in DLD are viewed as atypical, delayed, or prolonged in maturation, lower surface area might be related to any number of the neurodevelopmental processes discussed in the introduction. It might be the case that the affected regions in DLD have not undergone typical processes of neurogenesis pre-natally. Surface area differences between DLD and TD could indeed be driven by genetic risk factors. Human genome-wide association studies have identified many loci for common genetic variants that explain variance in regional surface area and cortical thickness (Grasby et al., 2020). The genetic influences seen were stronger for surface area than for cortical thickness. In

the same vein, surface area anomalies in the temporal cortex of a cohort of pre-readers were associated with a family risk for dyslexia, regardless of children's later reading ability (Beelen et al., 2019). Relatedly, in a large genome-wide association study, shared genetic factors were identified as contributing to surface area of the superior temporal sulcus and performance on measures of reading and language, indicating links at the molecular level to variation in these traits (Eising et al., 2022).

While surface area differences in DLD might reflect a causal link to as yet unknown genetic disruptions, it cannot be ruled out whether the observed cortical differences are a consequence of language learning difficulties. In other words, plastic changes in the cortical areas involved in typical language processing may not have occurred at the same time or rate in the participants with DLD, due to their different language-learning experience. The latter argument could explain the strongly left-lateralised pattern of lower cortical myelin indexed by magnetisation transfer saturation in DLD in the study by Krishnan and colleagues (2022), compared with the lower R1 myelin marker that affected the brain globally. The language learning impairment seen in our study in DLD might have delayed the typical pattern of maturation of cortical areas, through a failure in specialisation of function in circuits involving these regions. Teasing apart the contributions of genetic risk factors and experience-dependent plasticity is an important next step in DLD neuroimaging work, which will require detailed longitudinal investigation.

3.4.5 Limitations and Future Directions

This study is limited by its cross-sectional nature, which prevents us from discerning whether the observed cortical differences are the cause of DLD or a consequence of having a language disorder. Longitudinal studies of large DLD cohorts in which children are followed over time could shed light on this question, while also having sufficient power to identify statistically robust differences in cortical metrics. Longitudinal investigations could also enhance our understanding of how these structural differences might affect specific aspects of function. Pursuing this question is especially important for guiding clinically oriented studies that attempt to answer whether cortical abnormalities could be targeted through behavioural interventions early on, while also gaining insight on the underlying mechanisms of cortical plasticity. A longitudinal comparison could also help to understand whether the trajectories of cortical development are atypical (i.e., different from typically developing children at all time

points) or prolonged/delayed (i.e., resemble those of typically developing children at a younger age) in DLD. This point is elaborated on further in the next chapter.

Lastly, it is worth noting that puberty is another important factor associated with brain development during adolescence which complicates attempts to find answers to the questions posed throughout this section. Measuring puberty through self-report can be unreliable and hormonal testing brings practical challenges (see Herting & Sowell, 2017 for a review). Even though we acknowledge the importance of pubertal influences on both behavioural and brain changes in this period, accounting for these effects was beyond the scope of this study. Longitudinal studies with several time points starting earlier in development and with even larger sample sizes would be required to capture the cortical maturation trajectories in relation to language and explore their interactions with physical and hormonal markers of puberty. Such studies could also shed light on whether the findings presented here are unique to the age period studied or are present earlier in development.

4

Longitudinal Changes in Grey Matter in Developmental Language Disorder

ABSTRACT

Previous studies on brain structure in developmental language disorder (DLD) have identified morphological differences in grey matter volume across both hemispheres, particularly in peri-sylvian regions involved in speech and language processing. However, these investigations have been exclusively cross-sectional, limiting our understanding of age-related effects in this population. It remains unclear whether these group differences reflect lagged or delayed brain maturation, or whether DLD is associated with a deviation from typical neuroanatomical development. Using FreeSurfer-derived cortical metrics, we estimated changes in cortical surface area, thickness, and volume in 84 structural scans collected at two time points from 20 individuals with DLD and 22 typically developing controls. The scans were acquired four to five years apart, with average ages of 12 and 17 years at each time-point. After applying stringent correction for multiple comparisons, we found no significant group differences or differences in the rate of change in any cortical metrics. However, exploratory analyses at more lenient thresholds revealed region-dependent group differences in surface area, characterised by lagged maturation in the frontal cortex in the DLD group. Evidence for delayed maturation was also observed, with accelerated growth in the DLD group in parts of the left anterior insula and pars opercularis, while the ventral postcentral gyrus exhibited stable patterns in DLD compared with reductions in controls. These findings suggest dynamic and region-specific patterns of cortical maturation in DLD, likely reflecting complex interactions between synaptic pruning, myelination, and experience-dependent plasticity.

4.1 Introduction

Previous cross-sectional studies of developmental language disorder (DLD) have identified morphological differences in grey matter volume across both hemispheres, particularly in peri-sylvian regions implicated in speech and language processing (Asaridou & Watkins, 2023; also see Chapter 1, Section 1.7). While these studies provide valuable insights into the neural correlates of DLD at specific developmental stages, their cross-sectional nature limits our understanding of how these neuroanatomical differences change over time. To the best of our knowledge, no study has yet investigated the neural correlates of DLD longitudinally. Longitudinal studies are crucial for mapping the developmental trajectories of neuroanatomical differences in individuals with DLD and have important clinical and theoretical implications. For example, tracking neuroanatomical changes during adolescence–a period of rapid biological and social changes–could shed light on mechanisms of cortical plasticity and help identify critical windows for targeted interventions beyond childhood (Knoll et al., 2016). From a theoretical perspective, longitudinal studies can determine whether neuroanatomical patterns in DLD stem from prolonged (i.e., lagged), delayed, or atypical maturation of neural pathways (see Bishop & Edmundson, 1987 for discussion).

A recent meta-analysis of structural imaging studies found that cortical anomalies in DLD are most frequently clustered in the frontal lobe (Ullman et al., 2024). Our own cross-sectional study of brain structure in the OxBOLD cohort provided further support for this (see Chapter 3, Section 3.3.2). We demonstrated that children and adolescents with DLD (n = 54) exhibited significantly smaller surface areas in several cortical regions, including in symmetric portions of the anterior inferior frontal gyrus (pars triangularis and pars orbitalis) in both hemispheres. In the left hemisphere, these differences extended posteriorly to the pars opercularis and ventrally to the lateral orbitofrontal cortex. Investigating whether these neuroanatomical differences persist or change over time can help better characterise the developmental trajectories in our DLD cohort. It will also be important to understand how neuroanatomical changes over time map onto changes in behaviour and cognitive measures we presented in Chapter 2.

Behaviourally, the developmental trajectories of many language and cognitive functions in DLD exhibit a pattern of persistent developmental lag (Bishop & Edmundson, 1987). That is, compared with their typically developing peers, children with DLD start out with significantly poorer performance in many domains but follow a growth trajectory that mirrors

that of their peers despite never "catching up," resulting in a consistent performance gap that remains between groups. This pattern is seen for example in the development of vocabulary (Rice & Hoffman, 2015), grammatical skills (Rice et al., 2023), and motor control (Goffman, 1999, 2004; Hill et al., 1998), where children with DLD perform similarly to younger, language-matched controls but significantly below their age-matched peers. In Chapter 2, we also observed a similar pattern in our longitudinal study of language and other cognitive skills in DLD; the neuropsychological profiles of adolescents and young adults with DLD continued to lag those of controls despite gains in performance.

In this chapter, we examine group differences in cortical structural changes in a subset of the OxBOLD cohort whose neuropsychological profiles were presented in Chapter 2. This subset includes 20 adolescents with DLD and 22 age-matched typically developing controls. These participants were followed up some four to five years after the initial assessment at an average age of 17 years. We propose two hypotheses regarding neurodevelopmental changes in DLD. First, if DLD is characterised by lagged or prolonged development, we would expect slower cortical maturation in these individuals, potentially never reaching the fully developed state of their typically developing peers. This pattern could have cascading effects on the development of multiple linguistic and other cognitive functions. Under this hypothesis, where neurodevelopmental changes occur in parallel but with a constant lag, we expect that the group differences will be maintained over time. In statistical terms, this would translate to significant main effects of group and time, but no significant interaction between group and time. Applying this scenario to our cohort, we predicted that group differences in surface area in the inferior frontal gyrus, anterior insula, and other regions that were statistically smaller in the DLD group at initial assessment will remain over time.

Alternatively, if DLD involves delayed development of neural pathways that ultimately reach full maturity at a later stage, the neuroanatomical differences between typically developing and DLD groups are expected to have diminished or disappeared over time. In our case, cortical regions that were smaller in individuals with DLD at time I may have "caught up" by time II. Statistically, this implies a significant interaction effect where the group differences in surface area decrease or disappear over time. In this scenario, we expected a different longitudinal trajectory in the DLD group (i.e., accelerated change) in regions that were different at time I, including the inferior frontal cortex. A significant interaction might also emerge in the case of atypical neuromaturation, i.e., if surface area growth plateaus and ceases to change

beyond a certain point in DLD. We could also find a combination of both of the mentioned scenarios in DLD depending on the cortical region, given the dynamic interplay between regionally distinct growth trajectories and experience-dependent plasticity in the brain (Giedd et al., 2015).

4.2 Methods

4.2.1 Study Sample

A total of 53 participants who at time I were between 10y1m-15y11m (*m* = 12.61 yrs, SEM = 0.22) and at time II between 14y2m-20y5m (*m* = 17.22 yrs, SEM = 0.23) took part in the longitudinal study. The time gap between the two visits was between 3y8m and 5y8m, with a mean gap of 4y6m. Of these 53 participants, 20 had previously met our DLD criteria (17.02 yrs, SEM = 0.39; seven female), and 22 were typically developing (TD; *m* = 17.56 yrs, SEM = 0.37; 11 female). In addition, there were 11 participants who had a history of speech and language difficulties but did not meet the DLD criteria at time of testing (HSL; *m* = 16.93 yrs, SEM = 0.46; all male). A detailed description of the follow-up recruitment process, exclusion and diagnostic criteria, as well as the neuropsychological test battery is provided in Chapter 2 (Section 2.2.4). For the analyses presented in this chapter, we excluded data from the HSL participants to focus on DLD-TD group comparisons.

4.2.2 MRI Acquisition

Participants completed a single MRI session during each visit. Imaging data were collected on the same 3T Siemens Prisma scanner with a 32-channel head coil at both visits. Participants wore Optoacoustics OptoActive II Active noise cancelling headphones and foam padding was used around their heads for comfort and movement minimisation. Anatomical images were obtained using a T_1-weighted MPRAGE sequence with the same pulse sequence parameters as time I: TR = 1900 msec, TE = 3.97 msec, flip angle = 8°, TI = 904 msec, with 192 × 192 sagittal FOV, 174 slices, with 1-mm in-plane resolution and 1-mm slice thickness. The acquisition time for the T_1-weighted scan was 5 min and 31 sec.

4.2.3 MRI Processing

Time I and time II structural scans were visually inspected by two raters for quality control before processing. All scans were deemed usable. We used FreeSurfer v7.4.0 (Fischl, 2012) to parcellate the structural images and generate 3D cortex reconstructions using the semi-automated "recon-all" command (Dale et al., 1999; Fischl et al., 1999b). The processing stream includes motion and intensity correction, surface-based registration, spatial smoothing, subcortical segmentation, and parcellation of cortical white and grey matter boundaries. Qoala-T was used to assess the quality of segmentations and parcellations post-processing (Klapwijk et al., 2019). Three scans from time I (two TD, one DLD) and one TD scan from time II were recommended for exclusion but were retained after careful visual inspection. Additionally, 14 scans at time I and 17 at time II were recommended for manual checking; all were retained after visual inspection.

The 84 scans used in the current group analysis were entered into FreeSurfer's longitudinal pipeline (Reuter et al., 2012). Two pre-processing steps were required for the longitudinal analysis. First, an unbiased subject-specific base template was created per person using data from both timepoints via a robust, inverse consistent registration (Reuter et al., 2010; Reuter & Fischl, 2011). Creating a within-subject template per participant minimises bias with respect to any time point, increases statistical power, and can better separate groups based on neuroanatomical changes over time (Reuter et al., 2012). We manually checked these templates and ran them through Qoala-T again as we did for the previous step. All base templates were retained. Data from each timepoint was processed again using the newly created base templates to standardise individual data across timepoints and calculate longitudinal changes per participant (Reuter et al., 2012). Our cortical measures of interest were surface area, cortical thickness, and grey matter volume. The final maps of these morphometric measures were spatially smoothed using a Gaussian smoothing kernel with a full width at half maximum (FWHM) of 10 mm.

4.2.4 Whole-brain Cortical Morphometry

Neuroanatomical changes over time in DLD and TD groups were compared across the whole cortex. We implemented a spatiotemporal linear mixed modelling method which considers the spatial and temporal dependencies in the data, thereby increasing the precision of parameter estimates that directly translates into a boost in statistical power. This method uses

the spatial structure of the anatomical images and pools the temporal covariance across neighbouring locations to estimate the model parameters (Bernal-Rusiel, Greve, et al., 2013; Bernal-Rusiel, Reuter, et al., 2013). The spatial covariance structure is modelled by using the dependency between the error terms associated with each voxel in the space as a function of the distance between the voxels.

With only two time points, we could only capture simple linear changes for each of our three cortical metrics (surface area, cortical thickness, grey matter volume). The statistical model included the following independent variables as fixed effects: the interval between scans at time I and II (in decimal years), group (TD, DLD), and the interaction between group and time interval. Baseline age and sex, and the estimated total intracranial volume (eTIV) extracted from the longitudinal data (from the base templates) were added as nuisance variables. Random intercepts for participants were included to account for within-subject variability.

We computed the initial vertex-wise estimates of temporal covariance components to use as features in the parcellations. FreeSurfer's spherical surfaces (~150,000 vertices) were used to parcellate the brain into homogeneous regions of vertices with similar covariance parameters, with the parameter value set to $k = 2$. The spatiotemporal model was then fitted together with these parcellations and the initial covariance estimates. A separate hypothesis test was conducted at each vertex. Whole-brain maps were corrected for multiple comparisons (also accounting for analyses of two hemispheres) using False Discovery Rate (FDR) at $q = 0.05$ (Benjamini & Hochberg, 1995). We repeated this procedure separately for each of the three cortical metrics in the left and right hemispheres. The statistical analyses were conducted in R v4.3.2 using the `fslmer` package (available at https://github.com/Deep-MI/fslmer).

4.3 Results

4.3.1 Sample Characteristics

The participant demographics and neuropsychological test results for time I and time II per group are presented in Chapter 2 (Section 2.3.2). The groups were not significantly different in age, sex, maternal education levels, or socioeconomic status. However, independent samples *t*-test showed that the interval between time I and time II was significantly longer in the TD group ($m = 4.89$ yrs, SEM = 0.11) than the DLD group ($m = 4.35$ yrs, SEM = 0.09), $t(39.64) = -3.77$, $p < 0.001$.

4.3.2 Whole-brain Morphometric Data

The TD and DLD groups did not differ in the estimated total intracranial volume (eTIV) at either time point (Table 4.1). There were no group differences in the mean global cortical thickness, surface area, or cortical grey matter volume values (averaged across both hemispheres), at either time point.

Table 4.1 ***Whole brain morphometric values per group.***

	TD (n = 22)		DLD (n = 20)		t(40)		Group differences
	I	II	I	II	I	II	
eTIV	1,297 ± 26	1,235 ± 28	1,293 ± 38	1,298 ± 53	0.75	0.75	---
Surface area	925 ± 21	893 ± 20	931± 22	908 ± 21	0.20	0.36	---
Cortical thickness	2.64 ± 0.04	2.54 ± 0.03	2.68 ± 0.01	2.58 ± 0.02	-0.63	1.09	---
Cortical volume	409 ± 32	380 ± 29	426 ± 33	403 ± 32	0.98	0.14	---

Note: Mean values and standard errors (± SEM) are provided. The values were compared between groups at each time point separately, using unpaired t-tests ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$). eTIV and cortical volume values are in cubic centimetres ($mm^3/1000$). Surface area values are in square centimetres ($mm^2/100$). Cortical thickness values are in millimetres (mm).

4.3.3 Group Differences in Cortical Metrics (Main Effect of Group)

Surface Area

Following FDR correction, there were no statistically significant group differences in any of the three cortical metrics. Exploring the data at an uncorrected threshold of $p < 0.05$, we found that the DLD group had smaller surface area relative to the TD group in several cortical regions (Fig. 4.1). The differences were most pronounced in the anterior middle frontal gyrus and anterior insular cortex bilaterally, and the left pars opercularis and temporopolar cortex. On the ventral surface, there was smaller surface area in DLD in mid occipitotemporal cortex bilaterally but more extensively on the right. There were also regions where the DLD group had larger surface area relative to the TD group, an effect that we did not observe in the larger cross-sectional sample at time I, even at lower statistical thresholds. These increased areas in DLD included the posterior superior frontal gyri at the junction with the precentral sulcus and extended to the dorsal primary motor cortex in the right hemisphere.

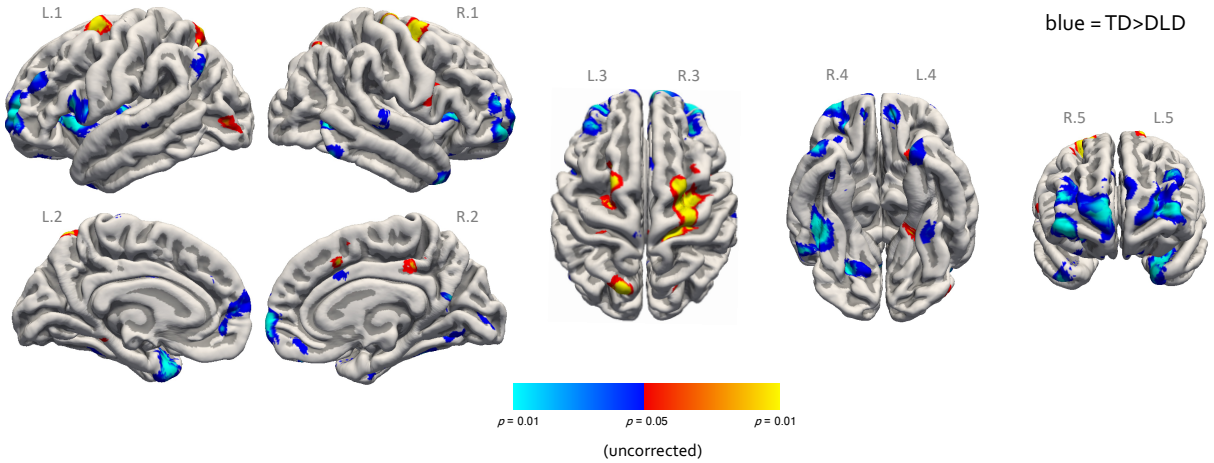


Fig. 4.1 ***Differences in surface area between TD and DLD groups.*** Whole-brain significance maps are overlaid on the pial surface of *fsaverage* and displayed with an uncorrected threshold of $p < 0.05$. L.1/R.1 = lateral view; L.2/R.2 = medial view; L.3/R.3 = dorsal view; L.4/R.4 = ventral view; L.5/R.5 = anterior view. L – left; R – right.

Cortical Thickness

For cortical thickness, at an uncorrected threshold of $p < 0.05$, group differences were evident in small portions of the frontal, parietal, and occipital cortex but these differences were not as extensive as those seen for surface area (Fig. 4.2).

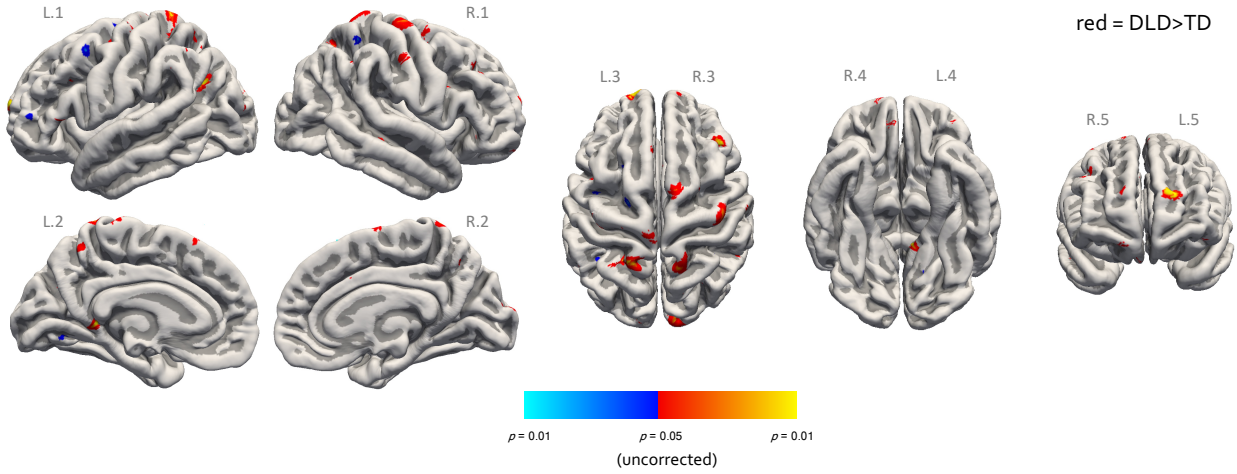


Fig. 4.2 ***Differences in cortical thickness between TD and DLD groups.*** See legend to Figure 4.1 for details.

Grey Matter Volume

For grey matter volume (which is a product of surface area and cortical thickness), at an uncorrected threshold of $p < 0.05$, there was a similar pattern of group difference to that seen for surface area, but these differences were less extensive (Fig. 4.3).

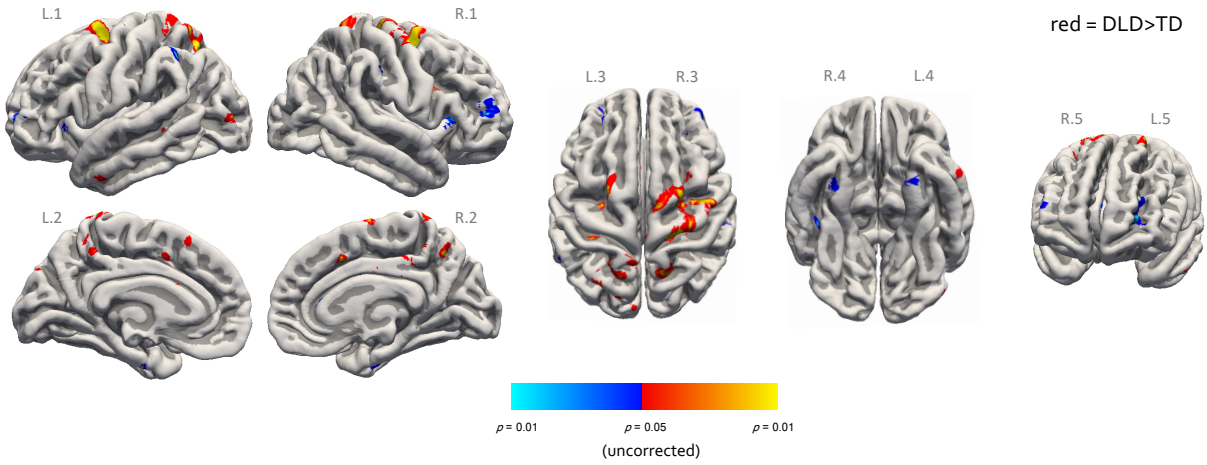


Fig. 4.3 Differences in grey matter volume between TD and DLD groups. See legend to Figure 4.1 for details.

In sum, using conservative statistical thresholding to compare cortical surface area, thickness, and volume between DLD and TD groups across both time points, we found no significant differences between these smaller subgroups. Exploratory analyses at a lower statistical threshold indicated that the pattern of lower surface area observed in DLD at time I in the larger cross-sectional study was similar to the pattern of subthreshold differences present in this smaller subsample. However, there were also regions where the DLD group showed significantly larger surface area than TD in the longitudinal sample, and these differences were not evident even subthreshold in the larger cross-sectional sample.

4.3.4 Changes in Cortical Metrics Over Time (Main Effect of Time)

Surface Area

Across both groups there were significant (FDR-corrected) widespread reductions in surface area from time I to time II (Fig. 4.4, left panel). Areal reductions were most prominent in the left and right temporal sulci and the middle portions of the inferior temporal cortex, the sensorimotor cortex, extending anteriorly to include parts of the premotor cortex, and posteriorly parts of the lateral parietal lobules. Other regions with surface area reductions included the medial and lateral orbitofrontal cortex, the callosal sulci medially, the posterior insular cortex, and ventral occipitotemporal and lateral occipital cortex. There were also regions that showed surface area expansion over time, including a small part of the left pars opercularis, the anterior superior temporal gyri near the temporal poles, and the left and right anterior insula.

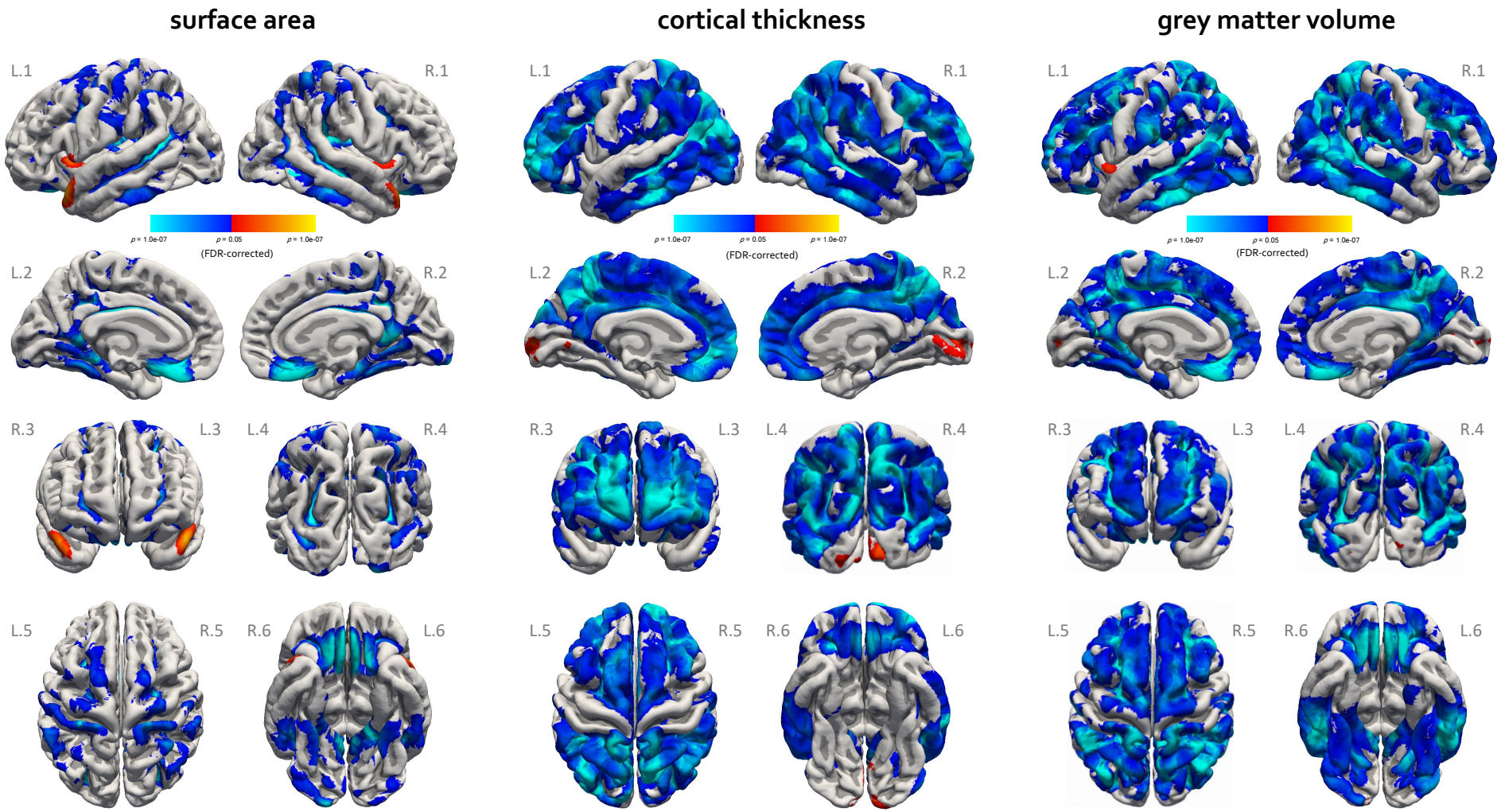


Fig. 4.4 ***Changes in cortical metrics over time in the whole cohort (n = 42)***. The whole-brain significance maps are overlaid on the pial surface of *fsaverage* and displayed after FDR-correction ($p < 0.05$). The blue/cyan hues indicate reductions over time. L.1/R.1 = lateral view; L.2/R.2 = medial view; L.3/R.3 = anterior view; L.4/R.4 = posterior view; L.5/R.5 = dorsal view; L.6/R.6 = ventral view. L – left; R – right.

Cortical Thickness

The main effect of time (FDR-corrected) for changes in cortical thickness showed widespread thinning across the entire cortex (Fig. 4.4, middle panel), most prominently in the dorsolateral and medial surfaces of the prefrontal cortex, lateral and medial parietal cortex, and the middle and inferior temporal regions. Cortical thickness reduction was more prominent in the right superior temporal regions than the left. In contrast, cortical thickness increased in the medial occipito-temporal regions and the occipital poles.

Grey Matter Volume

As expected in this age range, we observed an overall loss of grey matter across the entire cortex, with the notable exception of volume gains ventrally in the anterior insula and the occipital cortex, and less notable longitudinal changes in the primary motor regions (Fig. 4.4, right panel).

4.3.5 Group Differences in the Changes in Cortical Metrics Over Time (Group and Time Interaction)

Surface Area

When comparing the changes from time I to time II in the TD and DLD groups, there were no regions that showed a significant group-by-time interaction following FDR correction. Exploratory analyses at the uncorrected threshold of $p < 0.05$ revealed certain trends, however. The DLD group exhibited greater surface area expansion relative to the TD group in the left inferior frontal, anterior insular, and ventral sensorimotor cortex, the right temporal pole and anterior superior frontal cortex on the medial surface (Fig. 4.5).

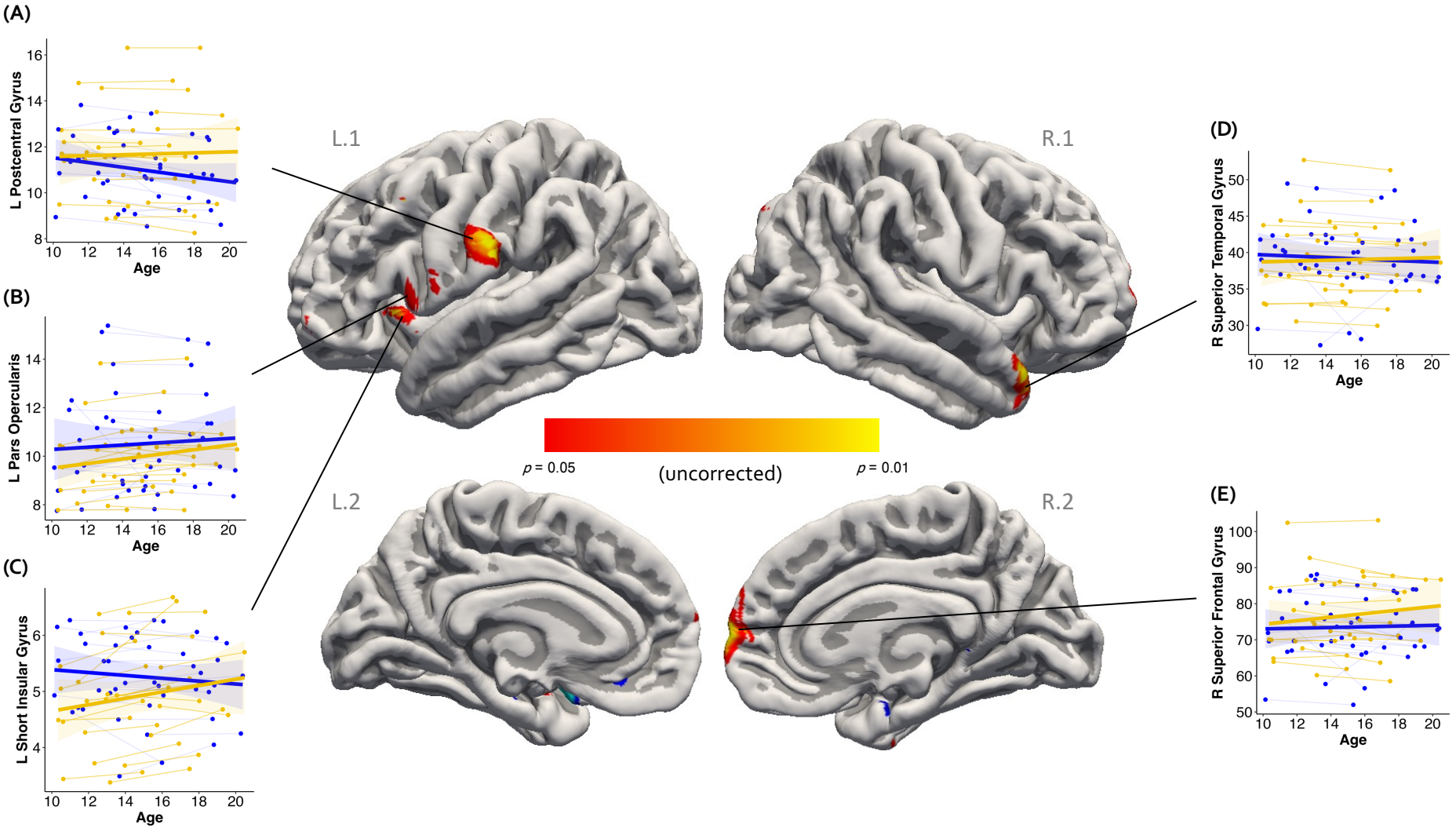


Fig. 4.5 ***Group-by-time interaction for the rate of change in surface area between groups.*** The whole-brain significance maps are thresholded at $p < 0.05$ (uncorrected) and overlaid on the pial surface of the *fsaverage* template. Coloured regions indicate greater change in surface area over time in the DLD group compared with the TD group. The spaghetti plots depict individual participants' surface area values across time points in square centimetres ($mm^2/100$), with regression lines in bold and shaded regions representing standard error of the mean. TD – blue; DLD – yellow; L – left; R – right.

To better understand these interaction patterns, we extracted the corresponding values from longitudinally processed parcellations, which are displayed in Figure 4.5 plots. The largest region showing a group-by-time interaction was the lateral postcentral gyrus in the left hemisphere. Here, the DLD group showed minimal changes in surface area despite areal reductions in the TD group (plot A). Both groups showed surface area expansions in the left pars opercularis (plot B) and the right superior frontal gyrus (plot E), but the expansion was more pronounced in the DLD group. In contrast, while the DLD group showed areal expansions in the anterior insula, the values in the TD group on average decreased in this region (plot C). Lastly, in the right anterior superior temporal gyrus, the DLD group exhibited a slight increase in surface area over time, while the TD group's values remained largely stable, with a slight negative trend (plot D).

We also analysed surface area changes in each group separately for a clearer view of the interactions. Both groups demonstrated significant reductions (FDR-corrected) in the superior temporal sulcus bilaterally and in the right posterior superior temporal gyrus (Fig. 4.6). Additionally, the DLD group exhibited significant increases in surface area in the left pars opercularis and anterior insula, and bilaterally in the temporopolar cortex. In contrast, the TD group showed a significant reduction over time in the ventral portion of the left postcentral gyrus.

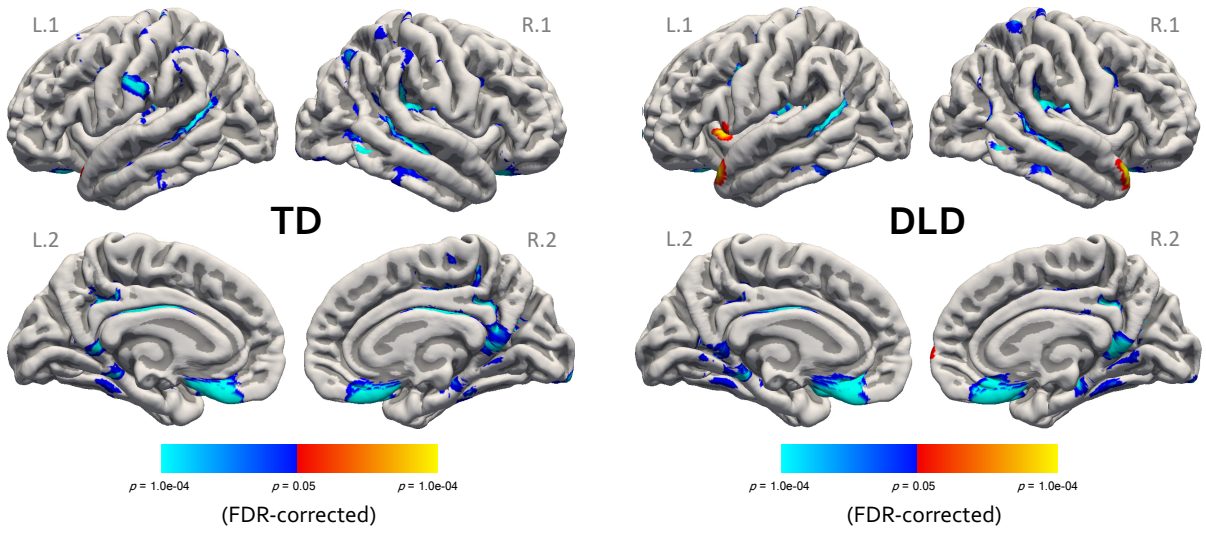


Fig. 4.6 ***Changes in surface area over time per group.*** Post-hoc whole-brain significance maps are displayed on the pial surface of *fsaverage* after FDR-correction. The blue/cyan hues indicate areal reductions over time. L.1/R.1 = lateral view; L.2/R.2 = medial view. L – left; R – right.

Cortical Thickness

The group-by-time interaction maps for cortical thickness did not show any significant patterns that survived FDR-correction. Exploratory analyses at the uncorrected threshold of $p < 0.05$ revealed very minor differences between groups in the rates of change in cortical thickness over time (Fig. 4.7).

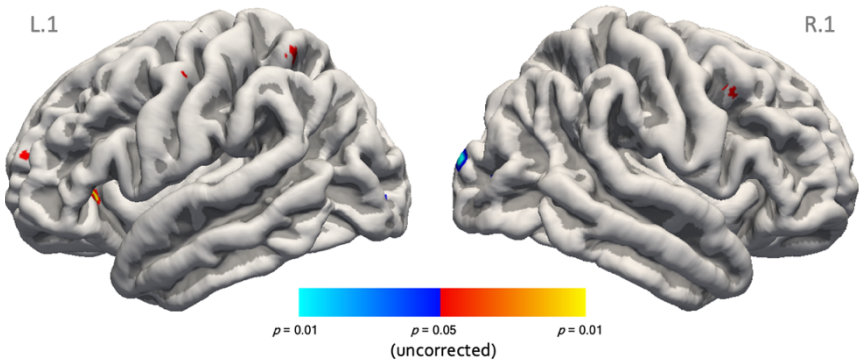


Fig. 4.7 ***Group-by-time interaction for the rate of change in cortical thickness between groups.*** Coloured regions indicate greater change in cortical thickness over time in the DLD group compared with TD. See legend to Figure 4.5 for more details.

Examination of cortical thickness changes for each group separately revealed very similar cortical thickness reduction patterns in both groups (Fig. 4.8). The changes in thickness in the left frontal cortex (dorsomedial prefrontal region), the left cingulate cortex, and the right inferior frontal gyrus were more pronounced in the TD group. In contrast, the DLD group showed cortical thickening in the right peri-calcarine cortex.

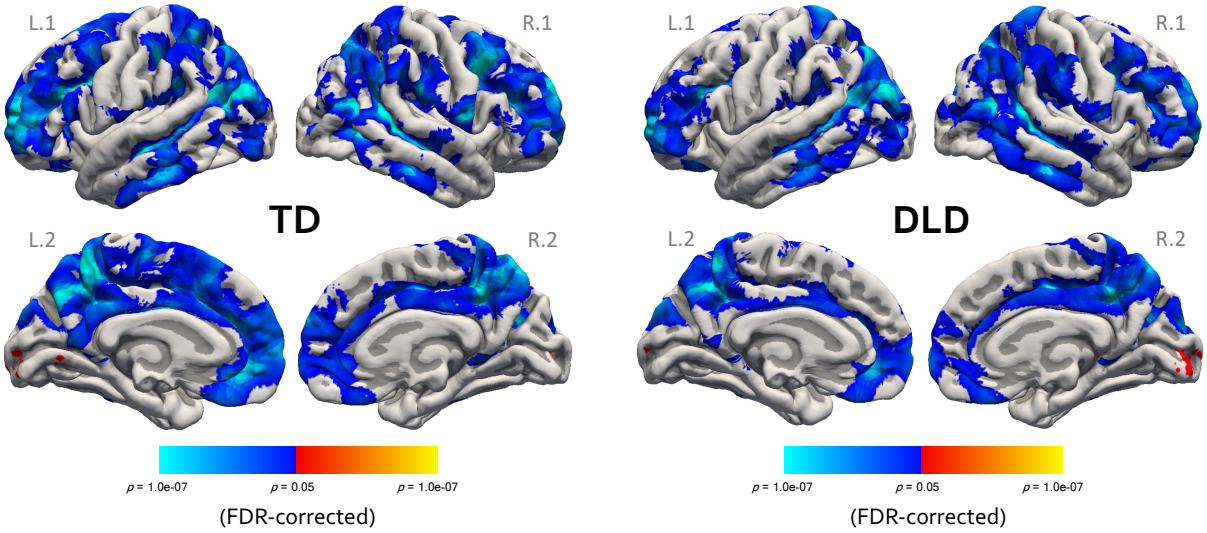


Fig. 4.8 ***Changes in cortical thickness over time per group.*** The blue/cyan hues indicate cortical thickness reductions over time. See legend to Figure 4.6 for more details.

Grey Matter Volume

There were no significant group differences in the rate of change over time in grey matter volume, following FDR-correction. The exploratory analysis at an uncorrected threshold $p < 0.05$ revealed portions of left anterior middle frontal cortex (extending to the medial surface), anterior insula and pars opercularis where the groups differed in the change over time (Fig. 4.9).

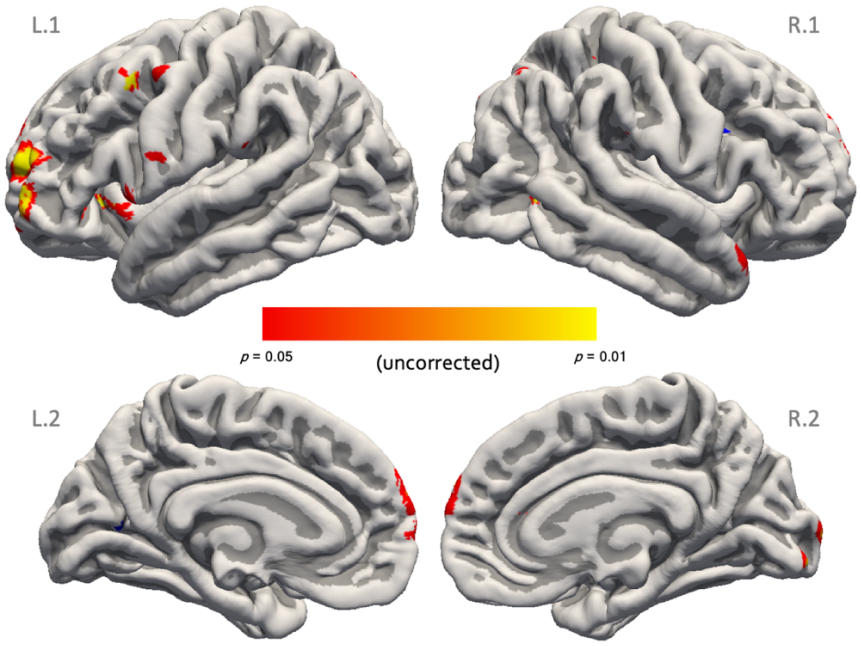


Fig. 4.9 ***Group-by-time interaction for the rate of change in grey matter volume between groups.*** Coloured regions indicate greater volumetric change over time in the DLD group compared with the TD group. See legend to Figure 4.5 for more details.

Assessing volumetric changes for each group separately showed significant reductions in both groups after FDR-correction (Fig. 4.10). Volume reduction was more extensive in the TD group. Moreover, the DLD group showed significant gains in volume in the left anterior insula that were not observed in the TD group.

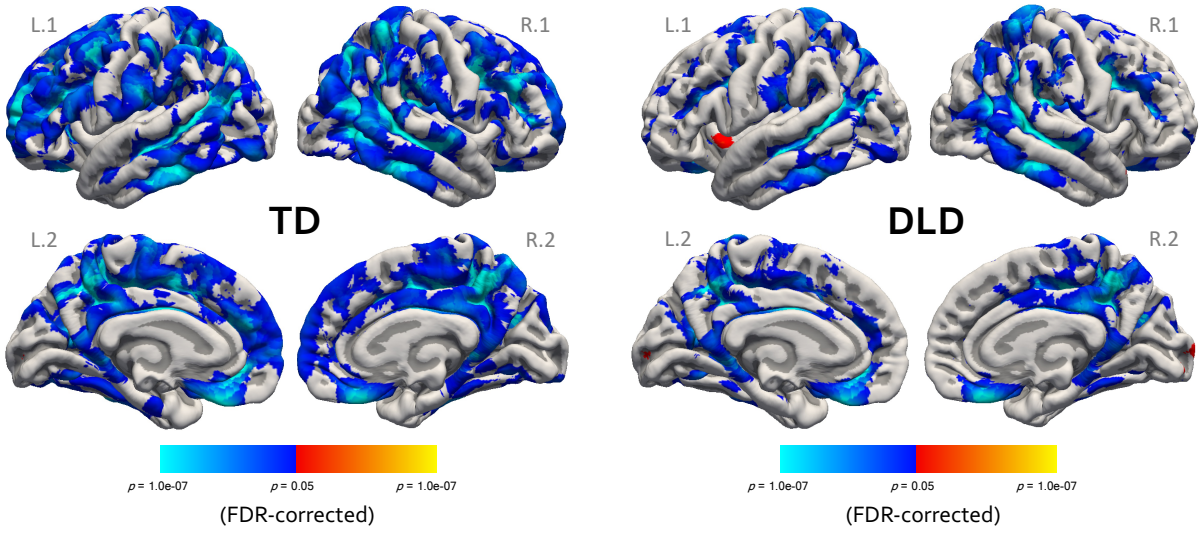


Fig. 4.10 ***Changes in grey matter volume over time per group.*** The blue/cyan hues indicate volume reductions over time. See legend to Figure 4.6 for more details.

In sum, the longitudinal changes in surface area seen in the exploratory analysis of the interaction between time and group was supported by the post-hoc analyses of each group separately. The groups differed in patterns of maturation in the left inferior frontal cortex and temporopolar cortex, which increased with time in the DLD group but not in TD, and in the left ventral postcentral cortex, which decreased in surface area over time in the TD group but not in DLD. There were fairly widespread and similar changes in cortical thickness and grey matter volume in both groups, and the group differences between these changes were small.

4.4 Discussion

In this study, we compared neuroanatomical changes over time in 20 adolescents and young adults with DLD and 22 age-matched typically developing (TD) controls. Our main questions related to differences between the two groups in the changes in surface area, cortical thickness, and grey matter volume. We hypothesised that if the DLD group followed a lagged or prolonged neuromaturational trajectory, we would expect the group differences seen at time I to be maintained at time II (i.e. a significant main effect of group but no interaction with time); the pattern of maturation across both groups would not differ (i.e. a significant main effect of time but no interaction with group). In contrast, if the DLD group followed a different, presumably delayed, neuromaturational trajectory, then statistically we would expect a significant group-by-time interaction indicating differential rates of change in cortical metrics between groups. Our analyses revealed that even though there were significant changes in the

metrics over time in several cortical regions, there were no regions, following stringent statistical correction, where the TD and DLD groups differed significantly or where the rate of changes in the metrics differed between the two groups.

In terms of group differences, exploratory analyses at a lower statistical threshold indicated that a subset of the DLD-TD differences in surface area observed at time I in the larger cross-sectional cohort were also present in this smaller subsample. These regions included parts of the left pars opercularis, anterior insula bilaterally, and to a lesser degree the anterior middle frontal gyrus bilaterally, the right anterior superior frontal gyrus medially, and the right ventral occipito-temporal cortex posteriorly. There were also regions in dorsal posterior prefrontal, sensorimotor and parietal cortex where surface area was greater in DLD relative to TD, which were not observed in the larger cohort at time I.

In terms of changes over time, there were highly significant reductions in cortical thickness and volume across nearly all of the cortical mantle laterally and medially. As expected in this age range, these changes were in association cortex in the frontal, parietal, temporal and occipital lobes bilaterally. There were no changes in the precentral gyrus (the primary motor cortex) and there was a significant increase in peri-calcarine cortex corresponding to the location of striate and extrastriate visual areas. The pattern of surface area reductions from time I to II was less extensive than that seen for the other two measures. There were however significant expansions in surface area in the temporal poles and the anterior insular cortex.

In terms of differences between the groups in the rate of change in the cortical metrics, we saw more accelerated surface area expansion in the left pars opercularis and anterior insula in the DLD group relative to TD. The group difference in areal changes was most pronounced in the ventral portion of the left postcentral gyrus, where surface area decreased over time in the TD group but remained unchanged in DLD. Two regions in the right hemisphere–the anterior superior frontal gyrus and the temporopolar cortex–also showed different rates of areal changes between groups. The group differences in the changes in cortical thickness were minor. The small differences in the changes in grey matter volume were a subset of the changes in surface area, reflecting the relationship between cortical surface area and volume. Below, I discuss these findings with respect to previous literature, some of the limitations of the dataset, and I outline our plans for future analyses of the data.

4.4.1 Group Differences in Cortical Metrics and Their Developmental Trajectories

Group differences in surface area between our DLD and TD participants in this smaller sample were not wholly consistent with those reported in the larger OxBOLD cohort (see Chapter 3) when collapsed across the two time points. There were some similarities, however. Smaller surface areas in DLD were most prominent in the anterior insula, the left pars opercularis, and extensive regions of the anterior middle frontal cortex. There are only two previous studies involving participants roughly in the same age range as ours; one of these also reported smaller frontal lobes in a cohort of 12 individuals with DLD, with a mean age of 21.99 years (Lee et al., 2013). More recently, Lee and colleagues (2020) found larger temporal poles in 31 individuals with DLD (age range = 14-27 years), 12 of whom were the same participants as in their previous study (Lee et al., 2013). Although not directly related to our group differences, these temporal lobe findings overlap with the temporopolar regions where our DLD participants showed surface area expansions over time.

In the longitudinal cohort, we further found larger surface area values in the DLD group relative to the TD group. These increases were observed in portions of the posterior superior frontal gryi, extending to the primary sensorimotor cortex in the right hemisphere, and in the medial parietal regions bilaterally. In our time I cross-sectional cohort, we did not find larger surface areas in any cortical regions, even at an uncorrected threshold. Notably, we found these larger values in the DLD group in an age range that is primarily characterised by widespread areal reductions in typical development (Tamnes et al., 2017). Previous studies have shown that posterior cortical regions undergo accelerated maturation trajectories during childhood, while accelerated maturation in frontal cortical regions does not occur until adolescence (Jernigan et al., 2011). This pattern was shown in studies where cortical reductions emerged first in the primary sensorimotor cortex, followed by secondary areas, and lastly in higher-order association areas (Gogtay et al., 2004; Shaw et al., 2008). These observations have led some researchers to suggest that cortical maturation advances in a posterior-to-anterior manner (Tamnes et al., 2013).

Under the prolonged neuromaturation hypothesis, if the DLD participants reach peak cortical surface area values at an older age, we would expect to see a pattern of enlarged surface areas more posteriorly, coupled with smaller values more anteriorly, when compared with TD participants. Using the same logic, if TD participants have undergone a normal course of cortical maturation characterised by maturation of the primary sensorimotor areas at a

younger age, then they have already entered the phase of surface area reduction in these regions that dominates adolescence. If cortical development lags behind in the DLD group, we can expect group differences to emerge, showing a pattern of prolonged posterior-to-anterior maturation. Specifically, the primary sensorimotor regions would attain peak values in DLD later than in TD, therefore appearing larger in group comparisons; conversely, for the frontal cortex, the DLD group have not attained peak maturation, thereby showing smaller values in this region. Taken together, these observations provide preliminary evidence of prolonged neuroanatomical maturation in the DLD group.

The lagged or prolonged neuromaturation hypothesis may also account for the observed clustering of structural group differences between TD and DLD cohorts most commonly in the frontal lobe, as reported in the meta-analysis by Ullman et al. (2024). In our study, these differences are particularly evident in the anterior middle frontal gyrus and the inferior frontal cortex. Supporting this, task-based fMRI studies have found atypical activation patterns in the frontal cortex, most notably in the inferior frontal gyrus, across various language tasks in individuals with DLD. For example, significant DLD-TD differences in the inferior frontal gyrus activation was reported for passive listening (Badcock et al., 2012) and implicit word learning tasks (Plante et al., 2017). Furthermore, in a subsample of the OxBOLD DLD group (n = 14) with the lowest task performance, sub-threshold group differences emerged in the left inferior frontal gyrus during a verb generation task (Krishnan et al., 2021). Studies involving executive functioning (Dibbets et al., 2006) and working memory tasks (Weismer et al., 2005) also found inefficient or compensatory activation patterns in children with DLD in this region. In short, group differences in brain activity in the inferior frontal cortex in DLD are consistent with the pattern of structural differences found in this region.

On the other hand, and more aligned with a delayed neuromaturation hypothesis, the surface area gains in the DLD group might be partly attributed to differences in experience-dependent plasticity. The uncorrected group-by-time interaction maps revealed steeper areal expansion in DLD in a primarily left-lateralised pattern, encompassing the anterior insula and pars opercularis. The insula is a complex, heterogeneous region that is implicated in a wide range of functions, from autonomic regulation to higher-level social cognition (Augustine, 1996; Craig, 2009). Importantly, the left anterior insula is also implicated in speech and language, especially in relation to speech motor coordination and control (Dronkers, 1996). Functional and structural differences in the insula were previously documented in individuals

with DLD (Badcock et al., 2012; De Guibert et al., 2011; Krishnan et al., 2022; Weismer et al., 2005), including in the affected members of the KE family (Liégeois et al., 2003). Similar observations apply to pars opercularis, with reports of functional differences in DLD during semantic and phonological tasks (De Guibert et al., 2011), or covert verb generation in the affected KE family members (Liégeois et al., 2003). More accelerated surface area expansion in DLD in the left pars opercularis and anterior insula might be related to late gains in speech and language skills over time. Given that the observation is limited to the left hemisphere, this might reflect a gradual late functional specialisation of the left hemisphere for language.

The uncorrected group-by-time interaction maps for surface area further showed group differences in a portion of the left postcentral gyrus, with very minimal changes in the DLD group in contrast to reductions in the TD group over time. Structural differences in this region were previously reported in closely related neurodevelopmental conditions. For example, lower grey matter volume in the same region was reported in a cohort of 29 children and adolescents with ADHD (Lim et al., 2013). In a more recent study, children and preadolescents with combined diagnoses of ASD and ADHD had smaller grey matter volume in the left postcentral gyrus compared with controls, but group differences disappeared in adolescents (Mizuno et al., 2019). The authors interpreted the findings as delayed sensorimotor maturation that improved over time in those with ASD + ADHD. Difficulties in sensory processing and motor function are indeed common in individuals with DLD (Armstrong-Gallegos & Nicolson, 2024; Simpson et al., 2022; also see Chapter 1, 1.3.3), and more pronounced growth in this region might reflect improved sensorimotor processing and control over time. Studies with larger cohorts and appropriate corrections are however required to confirm these speculations.

4.4.2 Factors Driving Grey Matter Volume Change During Adolescence

Grey matter volume markedly decreases during adolescence (Mills & Tamnes, 2014). From mid-childhood to adulthood, there is a monotonic decline in cortical thickness, while reductions in surface area are less extensive (Mills et al., 2014; Tamnes et al., 2017; Vijayakumar et al., 2016; Wierenga et al., 2014). The dominant contributor to volume decreases between late childhood and early adulthood is cortical thinning (Tamnes et al., 2017). We observed both of these patterns in our participants: a widespread decline in cortical thickness and comparatively less extensive decrease in surface area in both DLD and TD groups. The exact neurobiological mechanisms underlying these changes in structural MRI measures and their implications at a

cellular level remain debated (e.g., see Paus, 2010). Reductions in surface area and cortical thickness together may reflect a combination of selective pruning of synapses, reduction in the number of cortical glial cells, and intracortical myelination . There are three main hypotheses for the relationship between surface area and cortical thickness changes during development.

Experience-dependent synaptic elimination might explain some of the patterns of surface area reduction in teenagers (Giedd et al., 1999; Whitford et al., 2007). From this perspective, surface area gains in our DLD cohort might be attributed to prolonged synaptic proliferation, perhaps due to some late-blooming genetic mechanisms. DLD has a strong genetic component (Mountford et al., 2022). It is possible that variations or modulations in genes that regulate the duration and rate of neurogenesis may contribute to the surface area patterns observed in our study (Rakic, 1995, 2009b). Alternatively, regions like the ventral postcentral gyrus, which showed a stable surface area pattern in the DLD group but a decrease over time in the TD group, might suggest group differences in rates of synaptic pruning; the stable longitudinal trajectory in DLD could indicate reduced synaptic pruning, leading to minimal changes in synapses over time, while the TD group undergoes synaptic elimination. Nonetheless, synaptic proliferation and elimination account for only a minor portion of the observed volume changes, as the small size of synaptic boutons means they contribute minimally to the overall structure of grey matter volume (Bourgeois & Rakic, 1993).

Regarding the potential experience-dependent increases in DLD in areas such as the left anterior insula and pars opercularis, a second hypothesis suggests that the observed changes are not due to an actual gain in synapses *per se*, but rather areal expansion as a by-product of cortical stretching (Seldon, 2005). Increased myelination and changes in fibre density can cause the surface area to stretch tangentially, leading to its increase (Yakovlev & Lecours, 1967). In other words, this expansion might be due to mechanical pressure on the cortex rather than neurobiological processes involving grey matter and synapses (Högström et al., 2013).

Lastly, the time course of myelination coincides with synaptogenesis and pruning, with later and protracted myelination of frontal regions (Sowell et al., 2004; Yakovlev & Lecours, 1967). Studies have shown region-specific, age-related increases in cortical myelination during adolescence, which may be associated with increased cognitive efficiency (Baum et al., 2022; Whitaker et al., 2016). Reductions in cortical thickness during adolescence may partly result from myelin proliferation in the neuropil, which alters the grey–white matter boundary in image reconstruction. As myelination progresses, changes in signal intensity cause the

boundary to shift outwards, reclassifying voxels at the interface (Paus, 2010). This might explain the pattern of widespread "thinning" in our cortical thickness maps, which was especially prominent in the dorsomedial prefrontal and parietal regions. Examining the developmental trajectories of myelin alongside these changes can provide further insights into the relationship between myelination and surface-based cortical metrics in our cohort. We have collected longitudinal quantitative MRI maps in these participants, with planned future analyses to investigate the changes in microstructural properties, including myelin and iron, alongside the surface-based measures discussed throughout this chapter.

4.4.3 Limitations and Future Directions

To our knowledge, this study represents the first longitudinal investigation of brain structure in individuals with DLD. However, it has several limitations. First, the small sample size restricts the generalisability of our findings. Second, with only two measurement time points, we could only model linear changes in cortical metrics, even though changes during this age range are likely nonlinear. Additionally, discrepancies in scan interval lengths between the TD and DLD groups may have introduced bias; longer intervals in the TD group could have resulted in more pronounced cortical metric changes, complicating direct group comparisons. Despite these limitations, this study offers valuable insights and lays the groundwork for future hypothesis-driven research with larger samples.

More broadly, we acknowledge that using only (calendar) age as a measure to judge brain development may not fully capture the underlying physiological mechanisms or account for individual variations in neurodevelopment (Parent et al., 2003). Previous studies have shown that while the developmental trajectory of some brain regions are best captured using age, regions such as the precentral and paracentral cortex are best modelled using pubertal status (Ando et al., 2021). Relatedly, sex differences in cortical metric peaks have been linked to differences in pubertal timing, which can vary by as much as four to five years across adolescents (Parent et al., 2003; Giedd et al., 1999; Lenroot et al., 2007). These challenges highlight the need to consider other factors such as hormonal and sex-specific changes both between and within groups. Studies with larger cohorts could help examine such inter-individual and sex-related variabilities.

Future studies should also follow individuals with DLD from a younger age, when cortical development proceeds at a higher pace and the proportion of cortical variability

stemming from early neurogenesis may be greater (Rakic, 2009b). Such an approach, with the addition of multiple time points, could enable researchers to detect both linear and nonlinear patterns of neuromaturation and to define the age of peak cortical metrics in DLD. Lastly, if replicated, our results point to the commonality of neuroanatomical substrates in related neurodevelopmental disorders. There is at the moment a need for studies with participants with a range of distinct as well as co-occuring neurodevelopmental disorders to assess whether more specific brain markers emerge per clinical phenotype (Berg et al., 2023; Krishnan et al., 2016). Relatedly, a transdiagnostic approach might yield better insights on the associations between cortical metrics and clinically defined neurodevelopmental disorders (Astle et al., 2022).

Our next step is to analyse the current cortical patterns with respect to the neuropsychological results presented in Chapter 2 to firstly, include the data collected from the 11 participants with a history of speech-language difficulties, and secondly to determine the utility of the time I neuroanatomical results in predicting later language outcomes and vice versa. We will also analyse longitudinal changes in microstructure in this cohort, for which we have collected quantitative MRI maps. Analysing neurobiological data from a range of imaging modalities in tandem could help strengthen the validity of the observations.

In conclusion, we provided preliminary support for both hypotheses we put forward on neuroanatomical maturation in individuals with DLD. Our first prediction was that if DLD is characterised by lagged (prolonged) neuromaturation, then the group differences we detected at time I shall persist over time. This hypothesis was supported by continued group differences in some brain regions, most notably in the frontal cortex. The other prediction was that if DLD is marked by delayed neuromaturation, then group differences should diminish or disappear over time, as cortical metrics "catch up" in development. The group-by-time interaction analysis for surface area supported this hypothesis; we found accelerated growth in the DLD group in parts of the left anterior insula and pars opercularis, while the ventral postcentral gyrus demonstrated stable patterns in the DLD group despite reductions in typically developing participants. These findings highlight the dynamic and region-specific patterns of cortical maturation, likely reflecting a complex interplay between synaptic pruning, myelination, and experience-dependent plasticity working in tandem.

5

Neural Activity for Learning Novel Word Forms in Developmental Language Disorder

ABSTRACT

Individuals with DLD perform poorly on tasks that require implicit learning of sequences, such as pseudoword repetition, which is a crucial skill for vocabulary acquisition and fluent speech. The neural correlates of novel word form repetition and learning are not well understood in this population. In this study, we used a functional MRI paradigm involving pseudoword repetition to investigate patterns of learning in the whole brain and in the frontostriatal network. We compared 46 individuals with DLD, aged 10 to 15 years, with 71 age-matched typically developing controls. Participants listened to and overtly repeated a set of pseudowords corresponding to "alien" names they viewed while being scanned. Participants with DLD exhibited significantly greater activity in parts of the dorsal motor cortex that were not activated above baseline in the control group. In addition, the DLD group showed less pronounced attenuation of activity in cortical regions that were robustly task-negative in controls. These regions encompassed the medial and lateral portions of parietal cortex, which are often considered as parts of the default-mode network. There were no significant group differences in neural activity related to novel word form learning; both groups exhibited significant decreases in task-evoked activity over the course of unguided pseudoword learning. Region-of-interest analyses of the frontostriatal network showed that the DLD participants exhibited a different pattern of lateralised activity in the inferior frontal gyrus during pseudoword repetition trials.

5.1 Introduction

The ability to learn new words is a key component of language acquisition, enabling us to communicate thoughts, emotions, and ideas using a rich vocabulary. Word learning occurs fast and effortlessly, with young children displaying an impressive ability to map concepts onto novel word forms after just a few exposures (Carey & Bartlett, 1978). For the approximately 7% of children who meet the criteria for developmental language disorder (DLD), however, learning words can be quite challenging (e.g., Haebig et al., 2017; Jackson et al., 2019; Kan & Windsor, 2010). Word learning deficits in DLD are perhaps best reflected in these children's markedly poor performance on nonword (pseudoword) repetition tasks (Bishop et al., 1996; Schwob et al., 2021). To repeat a pseudoword accurately, children need robust phonological short-term memory and sensorimotor skills to encode novel phonological sequences and transform them into precisely coordinated speech-motor patterns (Gathercole et al., 2006; Konishi, 2004; Krishnan et al., 2013). Consequently, strong associations have been found between pseudoword repetition ability, word learning, and vocabulary size in children (Adlof & Patten, 2017; Gathercole et al., 1999; Hoff et al., 2008).

Analyses of word learning errors in children with DLD suggest that their main difficulty is in learning new word *forms*, while the ability to link words with meanings is fairly intact (Bishop & Hsu, 2015; Kan & Windsor, 2010; Leonard et al., 2021). For example, Bishop and Hsu (2015) found that 7- to 11-year-olds with DLD performed poorly on a verbal paired-associate word learning task but just as well as their typically developing peers on nonverbal auditory-visual paired learning. Moreover, both children and adults with DLD were found to struggle with learning novel words immediately after training, highlighting an encoding deficit, but their long-term retention was comparable to controls (McGregor et al., 2013, 2017, 2017). These observations have led to hypotheses regarding the differential involvement of the procedural and declarative learning systems in DLD. The Procedural Deficit Hypothesis (PDH; Ullman & Pierpont, 2005) or its more recent extension the Procedural Circuits Deficit Hypothesis (Ullman et al., 2020), propose neurobiological abnormalities in the anatomical structures and networks involved in procedural learning in DLD, specifically the cortico-basal ganglia-thalamo-cortical circuits. Neuroimaging studies testing this hypothesis in individuals with DLD are currently limited.

In typically developing adults, functional MRI studies of pseudoword repetition have shown significant activity across a network of "language" and "motor" areas, including the

posterior superior temporal gyrus, supramarginal gyrus, and medial and lateral frontal cortex (Rauschecker et al., 2008). Activity in these regions aligns with their involvement in perceptual processing, phonological working memory, and speech-motor planning/articulation (Guenther, 2016). Subcortically, activity has been detected in the basal ganglia and thalamus, regions implicated in phonological processing and enhancing speech production efficiency during learning (Simmonds et al., 2014; Tettamanti et al., 2005). The cerebellum also plays a role, particularly in mapping speech sequences into motor gestures (Blakemore et al., 1998; 2001; Rauschecker et al., 2008). Repeated exposure to pseudowords is thought to enhance their representations, thereby reducing dependence on initial striatal learning systems. This process is associated with decreased neural activity across several cortical motor, cerebellar, and left-lateralised temporal and frontal regions linked to language processing (Rauschecker et al., 2008).

The neural correlates of pseudoword repetition are less studied in DLD, and even less so in children with DLD. Recent fMRI studies, including one of overt verb generation in the OxBOLD cohort, found limited differences in the speech production networks in 10- to 15-year-olds with DLD (n = 50, Krishnan et al., 2021). Similarly, an fMRI study of overt pseudoword repetition in 9- to 11-year-olds with DLD (n = 18) did not detect significantly different neural activity patterns compared with controls (Pigdon et al., 2020). In fact, there was considerable overlap in activation patterns between the two groups despite the DLD group's poorer pseudoword repetition ability.

In contrast to these studies, significant group differences in brain activity were observed during overt pseudoword repetition in four affected members of the KE family (Liégeois et al., 2011), whose speech and language difficulties could be considered as severe cases of DLD. Specifically, the affected members showed reduced activity relative to age-matched typically developing controls in regions implicated in planning and executing speech motor sequences, including the supplementary motor area, precentral gyrus, and the ventral motor/premotor areas. Subcortically, hypoactivity was seen in the putamen and the left cerebellum. Liégeois and colleagues (2016) also studied pseudoword repetition in an eight-year-old male with a de novo *FOXP2* deletion and a phenotype consistent with DLD. Like the adult KE family members, this boy exhibited a reduced pattern of robust neural activity that correlated with task performance and atypical activity in the pars opercularis. Variability in the severity of language disorder may explain why some studies detected group differences while others did not. For instance, Pigdon

and colleagues (2020) noted that children with DLD in their study exhibited, on average, milder deficits compared with those reported in other studies.

There is only one fMRI study investigating language *learning* in individuals with DLD. Plante and colleagues (2017) assessed implicit learning of syllable sequences representing novel word forms in 16 young adults with DLD. In this statistical learning paradigm, the participants were exposed to novel word forms embedded in continuous speech in an unfamiliar language. They had to extract syllable order information and encode sequences with higher-order dependencies. Compared with controls, those with DLD exhibited more widespread activity in the inferior frontal cortex, superior temporal cortex, and the supramarginal gyrus, regions previously implicated in tracking word order information (Clark & Wagner, 2003; Kalm & Norris, 2014).

No studies have directly examined pseudoword learning in children and adolescents with DLD to date. Here, we used fMRI to compare brain activity during pseudoword repetition and changes in brain activity during pseudoword learning in 10- to 15-year-olds with DLD (n = 46) and age-matched typically developing controls (n = 71). We distinguished between participants' initial production of pseudowords (first-time repetitions), serving as a proxy for phonological short-term memory and speech-motor skills, and improvements over three subsequent repetitions, considered a measure of implicit learning without feedback. Post-scan, we assessed pseudoword productions and word-referent recognition after a short interval as measures of retention. Based on previous findings in typically developing adult learners (Rauschecker et al., 2008), we anticipated decreased activity in cortical regions involved in speech and language, and subcortical regions implicated in implicit learning. We expected to see differences between typically developing and DLD participants during this learning process.

5.2 Methods

5.2.1 Study Sample

The initial cohort consisted of the 160 children and adolescents from the OxBOLD cohort. Imaging data from 15 participants was excluded due to excessive movement during the functional scan. Excessive movement was defined as an average absolute motion greater than 2.4 mm (the size of one imaging voxel) after motion correction was applied to each volume for registration with the reference volume. These exclusions resulted in a final cohort of 145 participants with both imaging and behavioural data available for analysis. Of these, 46 met the

criteria for DLD, and 71 were classified as typically developing (TD) (see Chapter 2, Section 2.2.3 for diagnostic criteria). The 28 HSL participants–who did not meet the criteria for DLD at the time of testing but reported a history of speech-language problems–were excluded from the analyses in this chapter. The final sample characteristics are provided in Table 5.1. There was no significant group difference in mean age between the TD and DLD groups, $t(115) = 0.18$, $p = 0.896$. The sex distribution did not differ significantly between the two groups, $\chi^2(1, N = 117) = 2.06$, $p = 0.151$. Likewise, there were no significant group differences in the distribution of handedness, $\chi^2(1, N = 117) = 0.23$, $p = 0.631$. The groups' performance on the neuropsychological test battery is summarised in Table S5.1.

Table 5.1 ***Sample characteristics for TD and DLD groups.***

	TD (*n* = 71)	**DLD (*n* = 46)**
Demographics		
Mean age in years	12.6 ± 0.2	12.4 ± 0.3
Age range (y;m)	10;0-15;7	10;0-15;11
Sex (M:F)	40:31	32:14
Handedness (R:L)	61:10	38:8

Note: The means and standard errors (± SEM) are presented for age. See text for inferential statistics results. *Abbreviations*: y – years; m – months; M – Male; F – Female; R – Right; L – Left.

5.2.2 In-scanner Pseudoword Learning Task

During the scan, the participants were instructed to overtly repeat a set of pseudowords that were played through noise-cancelling headphones while they viewed the corresponding image of an "alien" (see Figure 5.1 for a schematic of the experiment). Participants were not told that some of the stimuli would be repeated, and they were not instructed to learn the names of the aliens.

Stimuli

We generated 32 pseudowords (i.e., phonotactically plausible English nonwords; see Appendix A) using Wuggy Pseudoword Generator (Keuleers & Brysbaert, 2010). Half of the pseudowords ($n = 16$) had two syllables (e.g., "Samper"), and the other half ($n = 16$) had four syllables (e.g., "Riscuplio"). A native British-English female speaker was recorded saying these pseudowords. We deterministically paired pseudowords with an image of an "alien" during the in-scanner repetition task to assess learning of form-referent associations (Fig. 5.1B). The alien

images, curated from the Shutterstock repository, were carefully selected to be novel and easily distinguishable from one another.

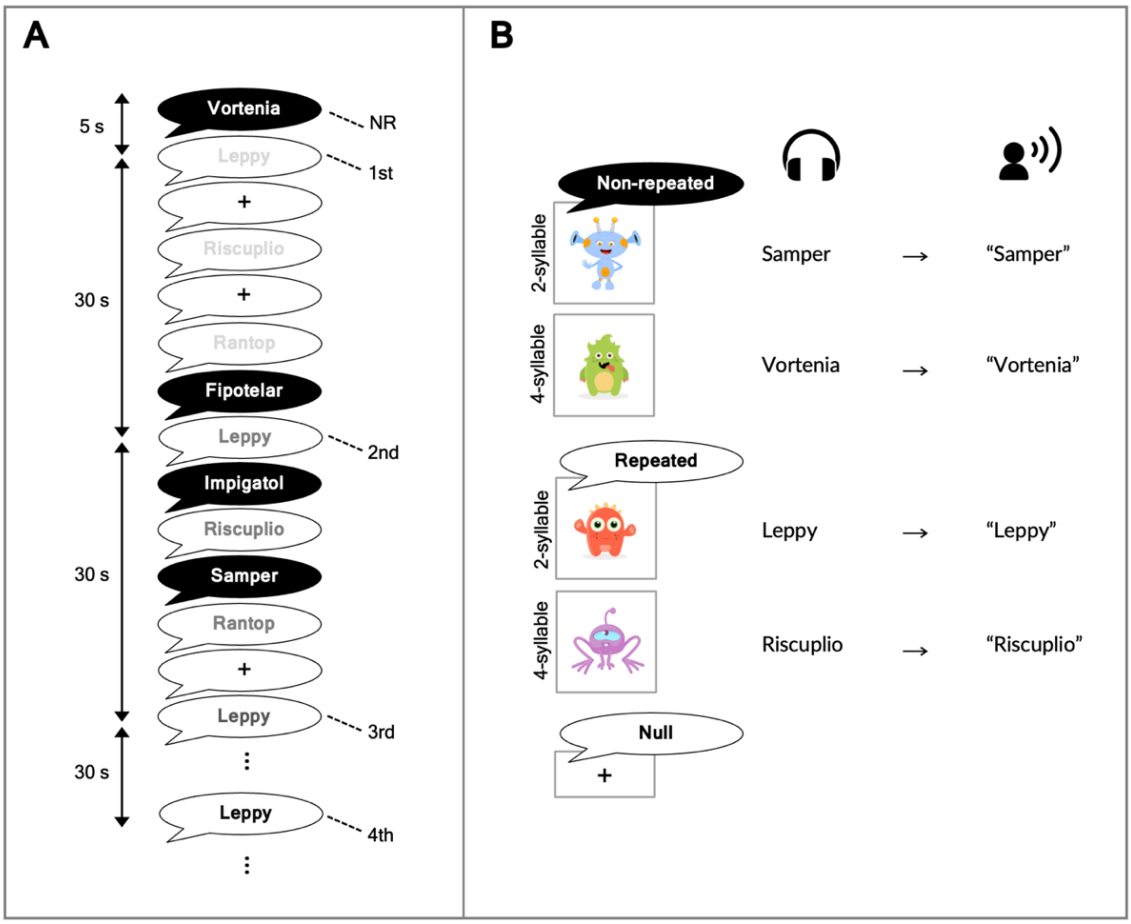


Fig. 5.1 ***Schematic of experimental design.*** **A.** Half of the stimuli were presented only once (black background), the other half (1st, 2nd, 3rd, 4th) were presented four times (grey font, lightest shade representing the 1st presentation, and darker shades corresponding to the 2nd, 3rd, and 4th presentations, respectively). Blank background with a fixation cross indicates null trials with no stimulus presented. **B.** Participants heard the pseudoword over noise-cancelling headphones and were instructed to produce each stimulus while a corresponding image of an alien appeared on the screen. The non-repeated and repeated conditions each had 16 stimuli, half of which had two syllables and the other half four syllables.

In-scanner Task Design

Half of the pseudowords (eight of each syllable length) were repeated four times at 30 sec intervals in a fixed pseudorandom order. These repeated pseudowords were intermixed with the remaining 16 pseudowords (also eight of each syllable length), which were presented only once to each participant (Fig. 5.1A). This resulted in a total of 80 stimulus presentations (16 × four repeated + 16 non-repeated). The repeated and non-repeated pseudowords were presented every 5 sec, either as a stimulus or during a null event (blank screen with a fixation cross). The onsets of repeated stimuli were separated by 30 sec intervals. To ensure task

compliance, researchers monitored the participants' overt responses in real time during the scan.

5.2.3 MRI Acquisition

Participants completed functional and structural scans as part of an hour-long scan session (see Krishnan et al., 2021). The pseudoword repetition task was completed after a verb generation task in the first 15 minutes. Data were collected using a 3T Siemens Prisma scanner with a 32-channel head coil. Participants wore Optoacoustics OptoActive II active noise-cancelling headphones (estimated to attenuate background noise by up to 30 dB), with foam padding placed around their heads for comfort and to minimise movement. The headphones were secured with inflatable pads. Auditory stimuli were presented at a comfortable listening level and were clearly audible above the background scanner noise due to active noise cancelling. Overt verbal repetitions of the stimuli were recorded using an Optoacoustics FOMRI-III noise-cancelling microphone.

We closely replicated functional scan parameters from the ABCD study (Casey et al., 2018). We collected 625 volumes of 60 T_2*-weighted echo-planar image (EPI) axial slices (TR = 800 msec, TE = 30 msec, flip angle = 52°, FOV = 216 mm, with multiband acceleration factor of six), with in-plane resolution was 2.4 × 2.4 mm, and 2.4 mm slice thickness yielding 1-mm isotropic voxels. Total acquisition time for the functional task was 8 min and 20 sec. The first 25 volumes were discarded as these were acquired when the noise cancelling algorithm was learning the scan sequence. Noise cancellation was applied while acquiring the following 600 volumes. We also collected B0 field maps.

For registration purposes, we obtained anatomical images using a T_1-weighted 3D magnetisation prepared rapid gradient echo (MP-RAGE) sequence (TR = 1900 msec, TE = 3.97 msec, flip angle = 8°, TI = 904 msec) with 208 × 256 × 256 sagittal field of view, 1-mm in-plane resolution, and 1-mm slice thickness. The total image acquisition time for the structural scan was 5 min and 30 sec.

5.2.4 MRI Analysis

Pre-processing

The imaging data were analysed using the General Linear Model (GLM) in the FMRI Expert Analysis Tool (FEAT) v6.0.0, part of FMRIB's Software Library (Smith et al., 2004). Pre-

processing steps included motion correction of each 3D volume in the time series using the Linear Image Registration Tool (MCFLIRT; Jenkinson, 2002), skull stripping with the Brain Extraction Tool (BET; Smith, 2002), and spatial smoothing with a 6 mm full-width half-maximum Gaussian kernel. Mean-based intensity normalisation of the 4D dataset was performed using a single multiplicative factor, followed by high-pass temporal filtering with a 90 sec cut-off to remove low-frequency drift. To enhance image registration to T_1-weighted scans, phase maps were unwrapped, and a field map was generated. FEAT applied this field map to correct for susceptibility-induced distortions in the functional scans. Each participant's distortion-corrected functional images were registered to their anatomical images using boundary-based registration (Greve & Fischl, 2009) and subsequently to MNI-152 standard space using the Non-linear Image Registration Tool (FNIRT; Andersson et al., 2008).

First-level Analysis

The statistical model included four explanatory variables (EVs) and their temporal derivatives: the first presentation of both repeated (R) and non-repeated (NR) pseudowords (1st = R and NR), the second presentation of stimuli in the repeated condition (2nd), the third presentation (3rd), and the fourth presentation (4th). The onset of each stimulus was modelled with a 5 sec duration to capture both auditory perception and overt production. To control for movement artefacts, six participant-specific motion correction parameters (translations and rotations in X, Y, and Z) were included as covariates of no interest. The evoked hemodynamic responses were modelled using double-gamma functions convolved with the stimulus. The contrast to capture mean activity associated with pseudoword repetition involved modelling 1st (R and NR)–the 1st presentation of repeated and non-repeated stimuli–against baseline. We also contrasted signal change related to the other three EVs (2nd, 3rd, 4th) against the baseline. We fitted a linear decrease and a linear increase contrast across the four presentations of repeated stimuli (1st, 2nd, 3rd, 4th) to capture learning-related changes in the whole-brain analysis. We modelled both the repeated (R) and non-repeated (NR) stimuli in the 1st EV for the best estimation of effect size.

Group Analysis

We performed a between-group comparison of TD and DLD groups in a higher-level analysis using FMRIB's Local Analysis of Mixed Effects (FLAME; Beckmann et al., 2003;

Woolrich et al., 2004). Statistical images were cluster thresholded at Z > 3.1 and clusters with extent significant at $p < 0.05$ (corrected using the Gaussian Random Field Theory and family-wise error rate) were identified.

We additionally created probabilistic overlap maps to evaluate the consistency of BOLD activity across each group. For each participant, we determined voxel-wise significance thresholds based on data smoothness and calculated the number of resolution elements (RESELs) by dividing the whole-brain volume by RESEL size. Using Gaussian Random Field maximum height theory and the number of RESELs, we calculated the corrected voxel-wise Z score significant at $p = 0.05$. Each individual's map was thresholded at this Z value, binarised and registered to MNI space. These binarised maps were summed and normalised by group size, resulting in overlap maps showing the percentage of participants with significant activity at each voxel.

ROI Analysis

In a separate analysis, percent signal change from baseline during the first presentation of the pseudowords as well as during each subsequent repetition was extracted for nine regions of interest (ROIs). The ROIs were nine masks extracted from the Harvard-Oxford Cortical and Jülich Histological atlases. Masks included pars triangularis, pars opercularis, caudate nucleus, and putamen all bilaterally, and one mask for the left and right supplementary motor area. These masks were selected as they are part of the corticostriatal circuitry, connecting cortical-subcortical networks involved in implicit learning and skill acquisition.

All masks were thresholded at 30% and applied to each participant's functional data to extract the median signal change for the voxels in these regions for each presentation of the repeated stimuli. Linear mixed effects models were built to investigate pattern of neural activity for learning pseudowords in DLD relative to TD participants. The models included fixed effects of repetition trial (1st, 2nd, 3rd, 4th), Group (TD, DLD), hemisphere (left, right), and their interactions. Random intercepts were used for the repetition trials and participants. The 1st trial, TD group, and the left hemisphere were set as reference categories. The alpha level was adjusted for multiple comparisons using a Bonferroni correction for five tests, setting the significance threshold to $p = 0.01$. Analyses were performed using the `lme4` package (Bates et al., 2015) in R v4.3.2 (R Core Team, 2023).

5.2.5 Behavioural Analysis

Post-scan Tasks

After completing the in-scanner task, participants remained in the scanner for an additional 30 min of scanning (see Krishnan et al., 2021). They were then moved to another room for post-scan testing. First, they were asked to overtly repeat the 32 pseudowords, with responses audio recorded for offline analysis. They were then tested on the recognition of associations between pseudowords and alien pictures in a three alternative forced choice task (3AFC) in which they heard each pseudoword and had to select the correct alien in an array of three alien pictures.

Due to technical failure, repetition accuracy data was not available in two TD and two DLD participants, and recognition scores were unavailable in one TD and one DLD participant. Accuracy of pseudoword repetitions were independently scored by two experimenters, who calculated the percentage of trials correct and the number of correct syllables for the 2- and 4-syllable stimuli. In cases of disagreement (8.68% from a total of 4,158 trials), the experimenters conferred to reach a consensus. If consensus was not achieved, input from a third experimenter was sought.

Statistical Analysis

A mixed effects logistic regression was used to assess pseudoword repetition accuracy (correct vs. incorrect production), modelling for pseudoword presentation (non-repeated vs. repeated), syllable length (2 vs. 4), and group (TD vs. DLD) as predictor variables. Random intercepts were included to allow variation across participants. Non-repeated stimuli, 2-syllable stimuli, and TD group were set as references. The same model was applied to examine the influence of these three predictors on pseudoword recognition scores.

5.3 Results

5.3.1 Neuroimaging Results

Pseudoword Repetition

In both TD and DLD groups, pseudoword repetition evoked significant activity in a bilateral, symmetric network of regions associated with speech perception, production, and visual processing (Fig. 5.2). These regions encompassed the posterior inferior frontal cortex,

lateral premotor cortex, sensorimotor cortex, supplementary motor area extending medially into the anterior cingulate gyrus, superior temporal gyrus, extending to mid- to posterior lateral parts, superior temporal sulcus, and large portions of occipital and inferior temporal cortex when listening to and overtly repeating pseudowords compared with baseline. We also observed activity in the medial temporal lobe and the anterior lobe of the cerebellum.

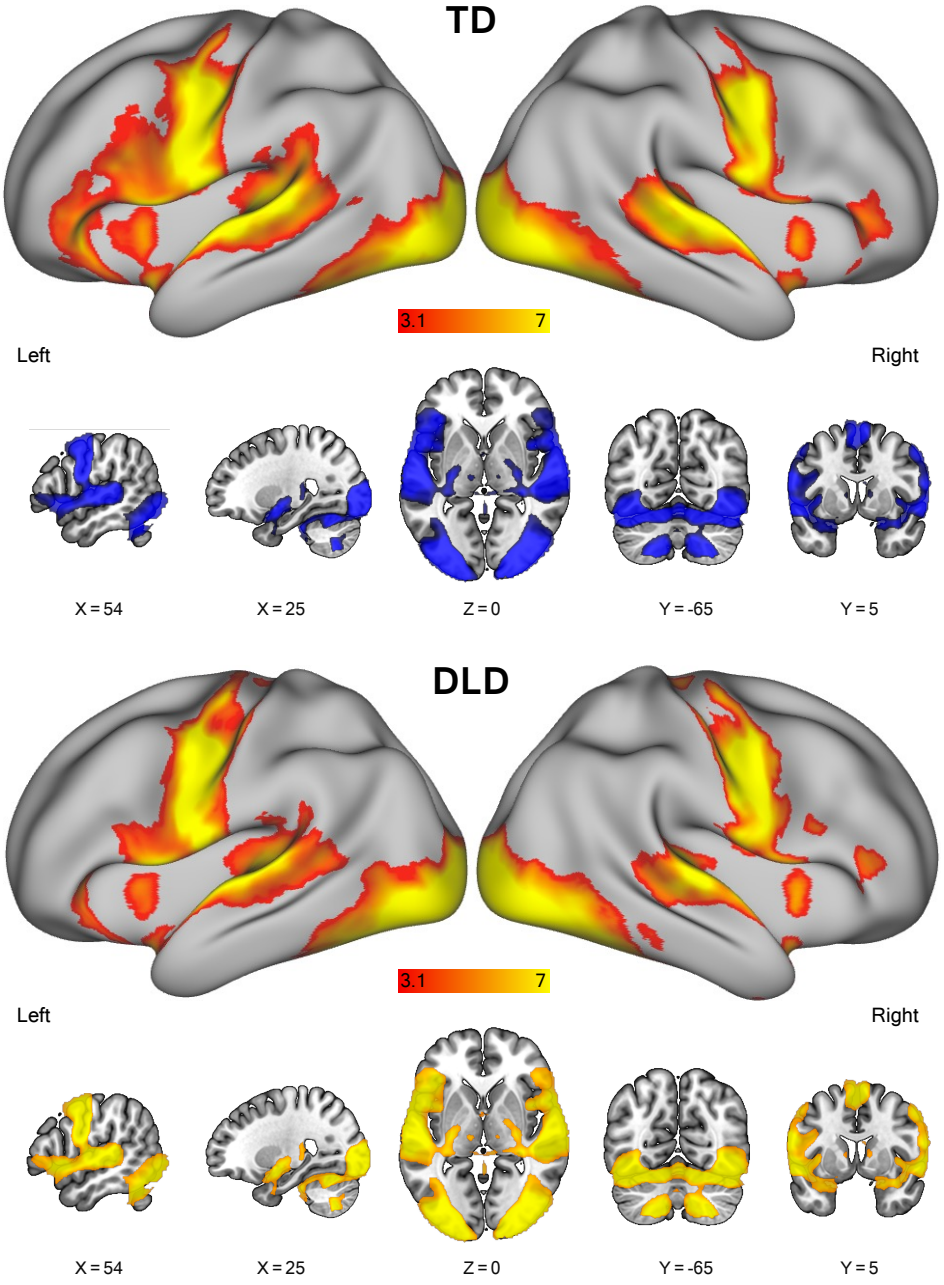


Fig. 5.2 ***fMRI activity for pseudoword repetition per group.*** Statistical maps of mean BOLD activity are overlaid on the lateral views of inflated left and right hemispheres (top row) and the sagittal, axial, and coronal slices (bottom row). Coloured areas indicate significant clusters thresholded at $Z > 3.1$, $p < 0.05$ (corrected). Numbers below each slice indicate its position in mm relative to the horizontal and vertical planes through the anterior commissure.

The comparison between DLD and TD groups revealed significantly different levels of activity in the superior and middle frontal gyri, precentral gyrus at the level of hand representation, medially in the posterior segment of the cingulate gyrus, and in the posterior part of the angular gyrus bilaterally (Fig. 5.3 and Table 5.2). Notably, this region included the retrosplenial cortex. None of these areas had task-evoked activity that was higher than baseline in the TD group. Most of the differences were due to considerably greater deactivation (lower than baseline) in the TD than in the DLD group.

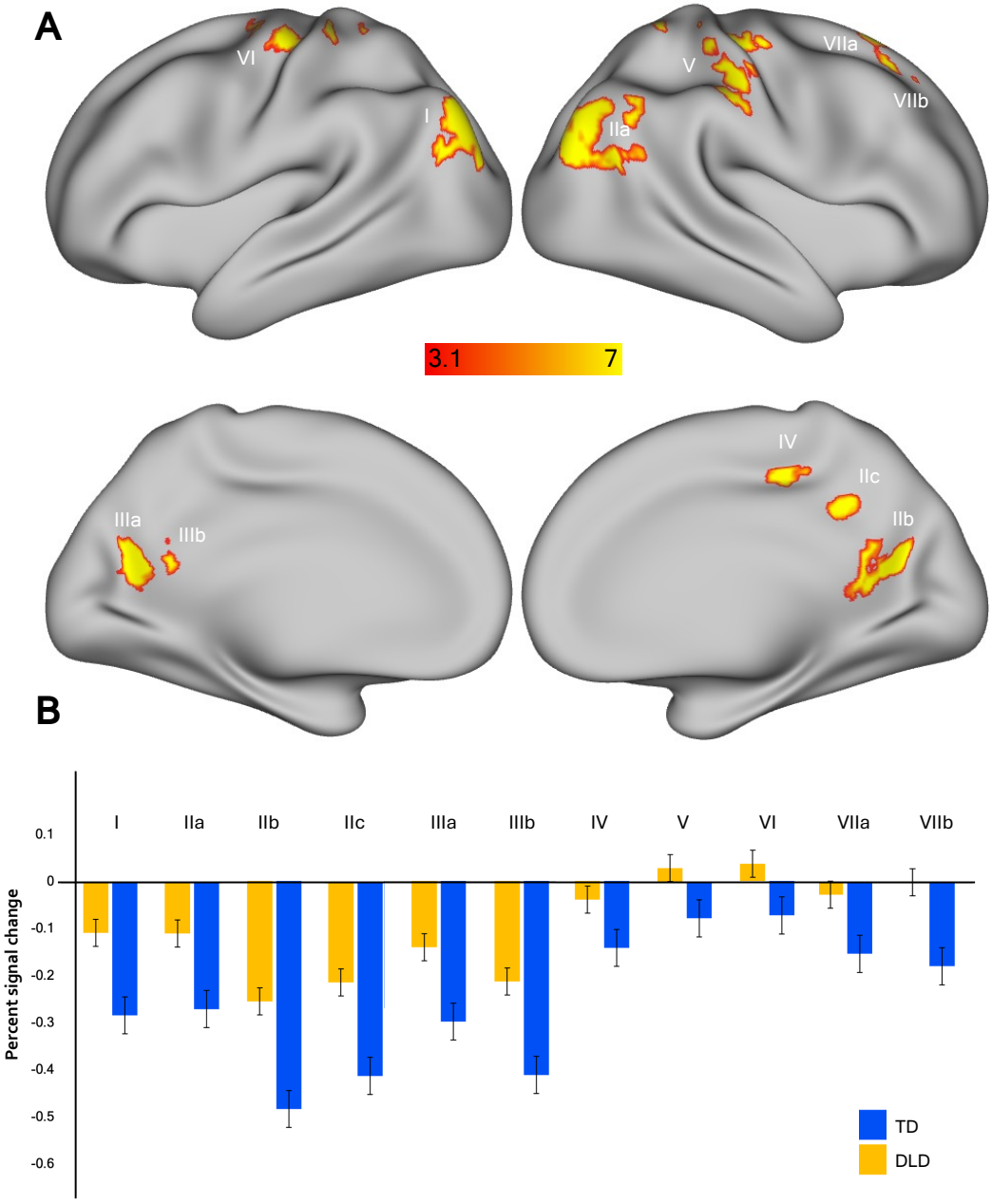


Fig. 5.3 ***Brain areas engaged during pseudoword repetition in DLD > TD contrast.*** **A.** Statistical maps of mean BOLD activity overlaid on the lateral and medial views of inflated left and right hemispheres. Coloured areas indicate masks of significant clusters thresholded at $Z > 3.1$, $p < 0.05$ (corrected). **B.** The bar plots of percent signal

change in each thresholded cluster from the DLD > TD contrast in 11 regions presented for TD (blue) and DLD (yellow). Error bars represent 95% confidence intervals. I, II = L and R lateral occipito-parietal cortex; III = L retrosplenial cortex; IV = R posterior cingulate cortex; V, VI = R and L sensorimotor cortex; VII = R superior frontal cortex. See Table 5.2 and text for details.

Table 5.2 ***Group differences in brain activity during pseudoword repetition in DLD > TD contrast.***

Anatomical area	Coordinates			Z-statistic	Voxels
	X	Y	Z		
L Lateral occipital cortex, superior division (I)	-42	-82	22	3.91	443
R Lateral occipital cortex, superior division (II)	44	-78	30	4.71	997
L Retrosplenial cortex (III)	-16	-62	18	4.09	346
R Posterior cingulate cortex (IV)	16	-40	32	4.71	203
R Postcentral gyrus (V)	30	-32	58	4.05	556
L Precentral gyrus (VI)	-34	-16	58	4.33	431
R Superior frontal cortex (VII)	18	18	58	4.00	224

Note: Contrast images for groups were thresholded at Z > 3.1. Peak coordinates for clusters with a minimum of 50 voxels are reported. Peak locations are presented for X (sagittal), Y (coronal) and Z (axial) coordinates in mm relative to the orthogonal planes through the anterior commissure, together with peak z-statistic and cluster extent in voxels. L – left; R – right.

The probabilistic overlap map for participants with DLD was largely like that for the TD group, but the proportion of each group showing consistent activation of the same voxels was on average less in DLD, especially in the superior temporal cortex bilaterally. Participants with DLD were less consistent therefore in activating these regions due to greater spatial variability in the regions activated, lower levels of reliable task-evoked activity, or some combination of both of these effects (Fig. 5.4).

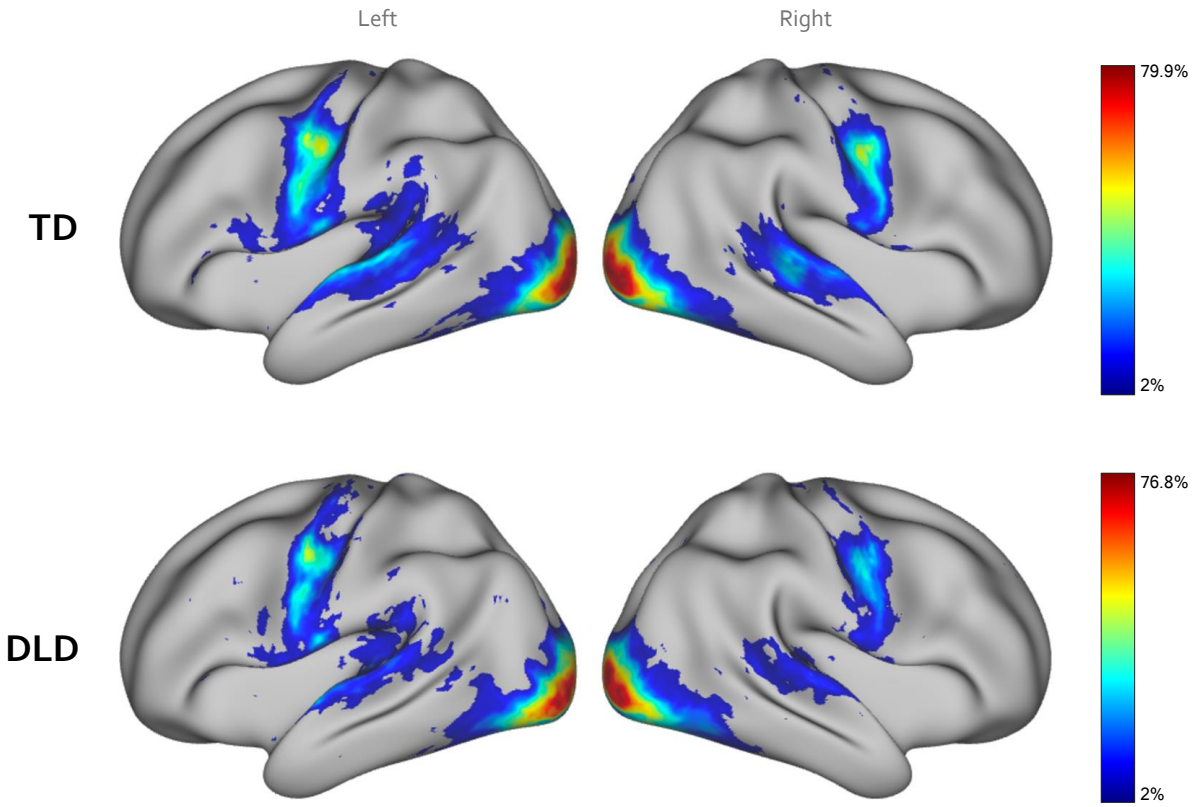


Fig. 5.4 ***Probabilistic overlap maps for pseudoword repetition vs. rest contrast in TD and DLD groups.*** The maps depict the percentage of participants in each group (71 TD and 46 DLD) with significant activation in each voxel. Warmer colours illustrate areas of higher overlap.

Learning Pseudowords

Brain activity in the TD group showed a linear decrease across the three repetitions in regions encompassing the inferior frontal cortex, anterior insular, superior temporal and occipital cortex bilaterally (Fig. 5.5). Medially, decreases in activity were visible in the supplementary motor area and anterior cingulate cortex. Decreases in activity were also seen in the left and right cerebellar lobules VIIb/VIIIa. The DLD group also showed linear decreases in the left inferior frontal cortex and the superior temporal and occipital cortex bilaterally. Statistical comparison of the two groups did not reveal any significant differences. At a lower statistical threshold of $Z > 2.3$, the TD > DLD contrast revealed group differences that were largely consistent with each group's mean activation patterns shown in Figure 5.5; TD participants had greater activity in the left frontal operculum. Higher activity in TD was also seen in portions of the temporal cortex bilaterally, including the superior and middle temporal gyri, extending posteriorly to the planum temporale. Subcortically, the TD group exhibited increased neural activity in the cerebellar lobule VI.

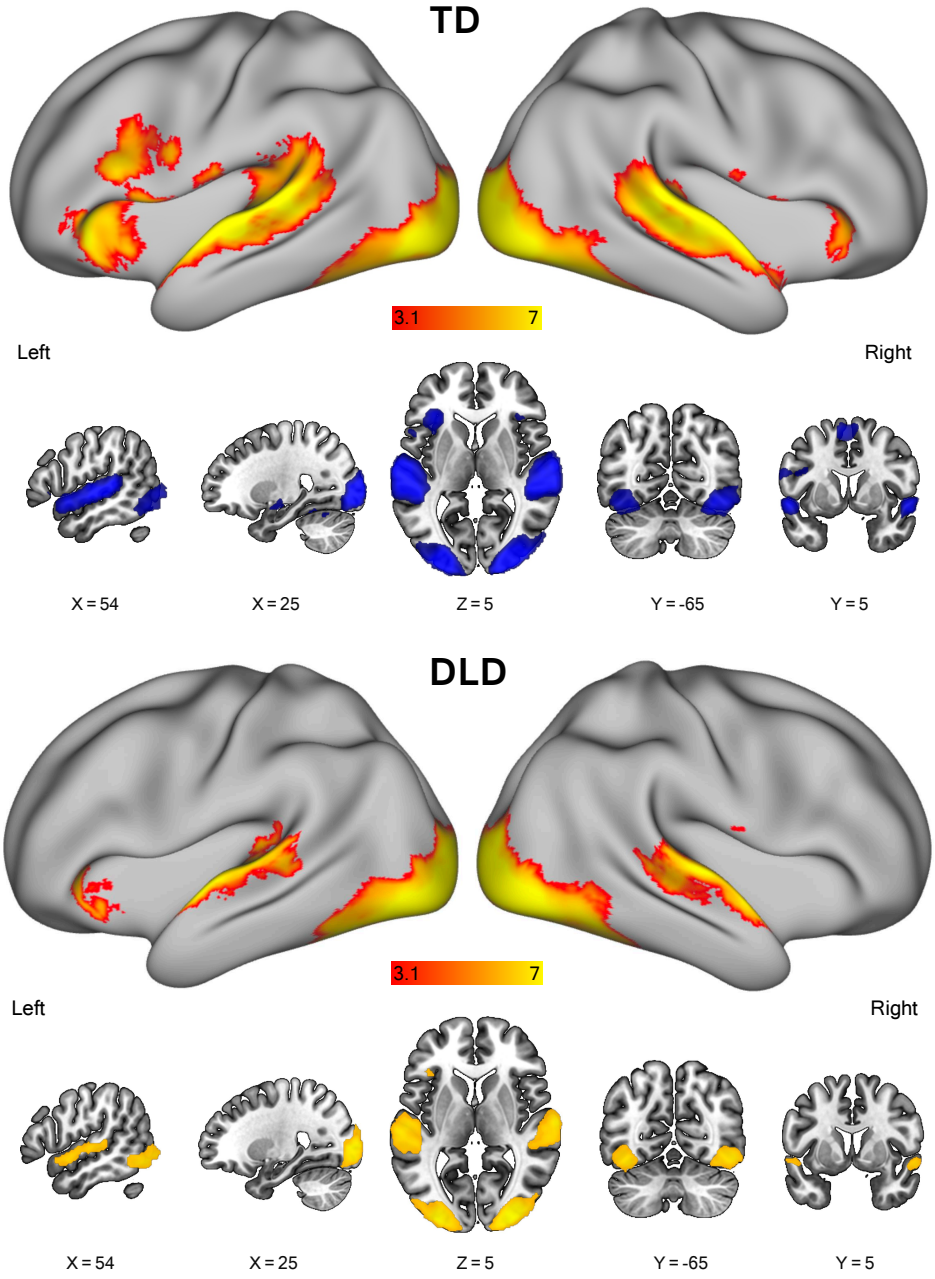


Fig. 5.5 ***Brain regions showing learning-related activity decreases in TD and DLD groups.*** See legend to Figure 5.2 for details.

Conversely, the DLD > TD contrast at the same lower threshold indicated elevated neural activity in the DLD group in some frontal, temporal, and lateral occipital regions, encompassing the middle frontal gyrus and precentral gyrus (at the hand representation area) in the left hemisphere, right superior frontal gyrus, the medial frontal pole, and a small portion of the right parahippocampal gyrus. The DLD group also showed greater subcortical activity in a small region of the right cerebellar lobules I-IV.

ROI Analysis

We used anatomical masks to extract the average percent signal change in a network of frontal cortical and striatal areas involved in learning. We compared the levels of activity in these ROIs between groups, hemispheres and across learning (repetition) trials.

In the pars triangularis, the pattern of left-greater-than-right activity averaged across both groups and all repetitions was significant (main effect of hemisphere: β = -0.05, SE = 0.02, CI [0.03, 0.11], p = 0.007; Fig. 5.6). There was no evidence of significant learning-related decrease in activity across the repetitions (main effect of repetition: 2nd, p = 0.228; 3rd, p = 0.141; 4th, p = 0.081). The group difference averaged across hemispheres was not significant either (main effect of group, p = 0.06). However, a significant group-by-hemisphere interaction indicated that the DLD and TD groups differed in the amount of activity in pars triangularis in the left and right hemispheres (β = 0.09, SE = 0.03, CI [0.03, 0.11], p = 0.006). For the TD group, there was greater activity in the left than the right pars triangularis (post-hoc testing, main effect of side: β = 0.05, SE = 0.01, CI [1.47, 5.34], $p_{adj} < 0.001$), whereas the DLD group showed no difference between hemispheres (post-hoc test, main effect of side: $p_{adj} = 1$).

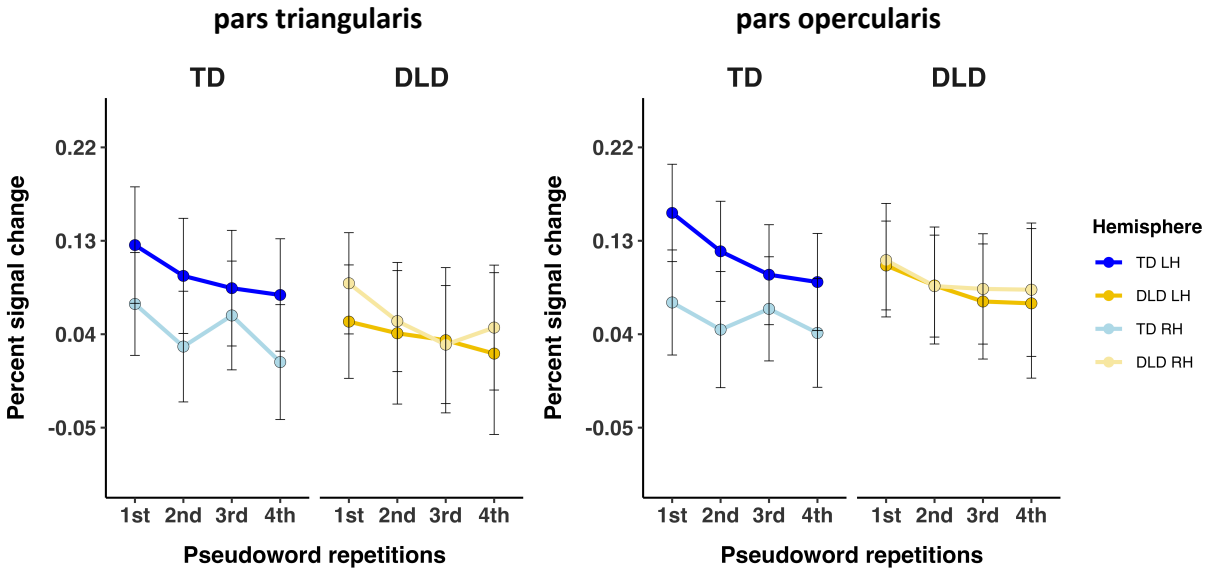


Fig. 5.6 ***Brain activity associated with pseudoword learning in the inferior frontal gyrus in TD vs. DLD groups.*** The pattern of BOLD signal changes in pars triangularis (left panel) and pars opercularis (right panel) across the four pseudoword repetition trials in TD (blue) and DLD (yellow) groups. Darker and paler shades correspond to the left and right hemispheres, respectively. Error bars represent 95% confidence intervals. LH – left hemisphere; RH – right hemisphere.

In the pars opercularis, the pattern of left-greater-than-right activity averaged across both groups and all repetitions was significant (main effect of hemisphere: β = -0.08, SE = 0.01, CI [-0.12, -0.05], $p < 0.006$; Fig. 5.6). For both groups combined, there was evidence of learning in terms of a decrease in activity over repetition trials. This was significant by the 4th repetition trial (β = -0.06, SE = 0.02, CI [-0.11, -0.02], $p = 0.006$), and at a trend level following Bonferroni correction ($p < 0.01$ required) for the 3rd repetition ($p = 0.012$). Learning-related activity decrease was not significant for the 2nd repetition ($p = 0.092$). The group difference averaged across hemispheres and repetitions was not significant ($p = 0.15$). A significant group-by-time interaction indicated a group difference in the pattern of lateralised activity (β = 0.09, SE = 0.02, CI [0.02, 0.19], $p = 0.001$), with left-greater-than-right hemisphere activity in the TD group (post-hoc testing, main effect of group: β = 0.06, SE = 0.009, CI [0.03, 0.08], $p_{adj} < 0.001$), but no difference between hemispheres in the DLD group (post-hoc testing, main effect of group: $p_{adj} = 1$).

There were no hemisphere, repetition, or group related differences in neural activity in the models for caudate nucleus, putamen, or supplementary motor area. Statistical results for these analyses are provided in Table S5.3-5.

5.3.2 Post-scan Behavioural Results

Form-referent 3-AFC Recognition Test

We assessed the effect of pseudoword presentation (non-repeated vs. repeated), syllable length (2 vs. 4), and group (TD vs. DLD) on the participants' ability to map pseudowords onto the corresponding alien images. Form-referent recognition scores were not significantly different between groups ($p = 0.58$; Fig. 5.7). As expected, recognition scores were higher for the repeated versus non-repeated pseudowords across all participants (β = 0.91, *SE* = 0.12, CI [0.66, 1.15], $p < 0.001$). Additionally, scores significantly decreased as the number of syllables increased (β = -0.61, *SE* = 0.12, CI [-0.85, -0.36], $p < 0.001$). There were no significant interactions involving group, indicating both TD and DLD participants showed equivalent form-referent learning.

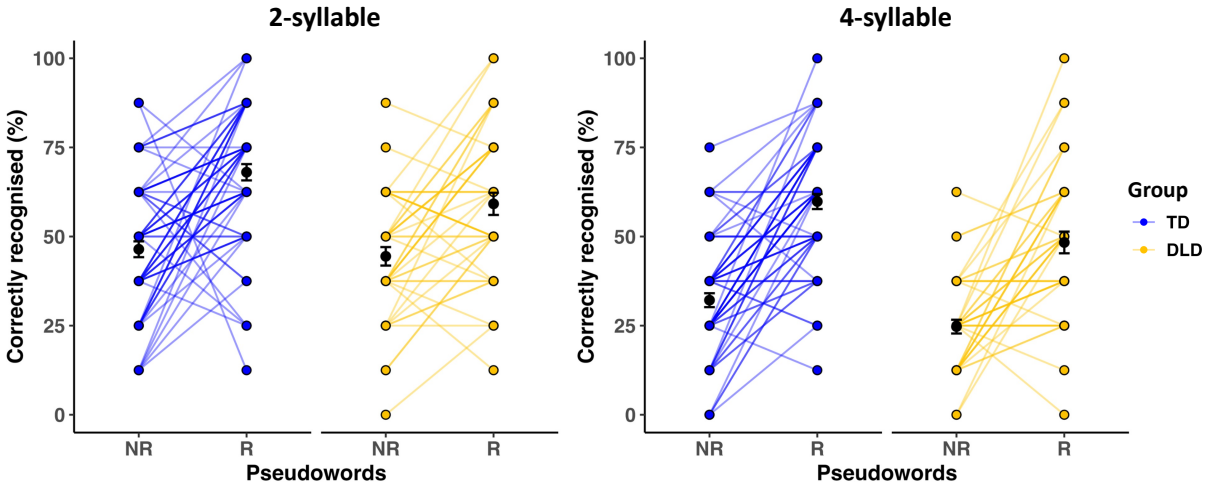


Fig. 5.7 ***Percent correct form-referent recognition scores per group for non-repeated vs. repeated stimuli, by syllable length***. The black points represent group means for each condition, with error bars indicating the standard error of the mean. The coloured lines connect each participant's performance across conditions, showing changes between non-repeated (NR) and repeated (R) pseudowords. Note that more than one participant's score may have contributed to some of the circles.

Pseudoword Repetition Test

The mains effects of presentation, syllable length, and group were all significant for the pseudoword repetition test (Fig. 5.8). Pseudoword productions in the DLD group were on average less accurate across both modes of pseudoword presentation and syllable lengths (β = -0.93, SE = 0.27, CI [-1.48, -0.38], $p < 0.001$). Producing *repeated* pseudowords was less accurate than non-repeated pseudowords averaged across all participants and syllables lengths (β = -0.76, SE = 0.23, CI [-1.23, -0.29], $p = 0.001$). Producing 4-syllable pseudowords was less accurate than 2-syllable pseudowords averaged across groups and pseudoword presentation modes (β = -1.07, SE = 0.22, CI [-1.53, -0.62], $p < 0.001$). A significant three-way interaction emerged between pseudoword presentation, length, and group (β = -0.85, SE = 0.4, CI [-1.64, -0.07], $p = 0.03$), with post-hoc tests revealing the following: There were no significant group differences in repeated 2-syllable stimuli ($p_{adj} = 1$), but productions were on average less accurate in the DLD group on non-repeated 2-syllable stimuli (β = 0.93, SE = 0.27, CI [0.09, 1.77], $p_{adj} = 0.022$). For the 4-syllable stimuli, production accuracy in the DLD group was lower for both repeated (β = 1.32, SE = 0.2, CI [0.72, 1.93], $p_{adj} < 0.001$) and non-repeated stimuli (β = 0.95, SE = 0.21, CI [0.31, 1.58], $p_{adj} = 0.001$). Taken together, these results indicate that the impact of pseudoword presentation and syllable length were more pronounced in the DLD group, with lowest scores on the repeated pseudowords that were four syllables long.

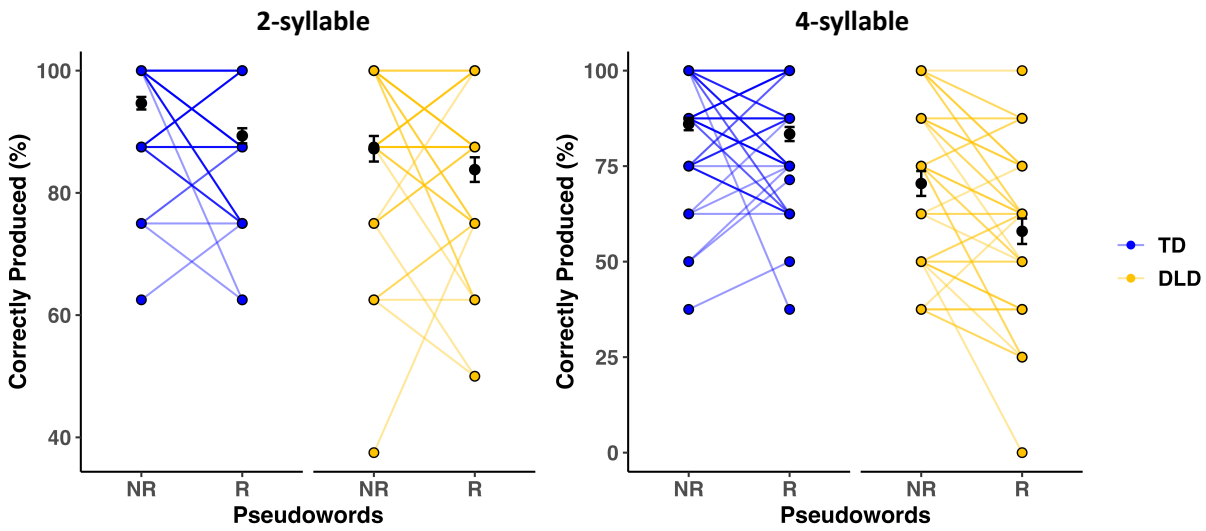


Fig. 5.8 ***Percent accurate pseudoword repetition scores per group for non-repeated vs. repeated stimuli, by syllable length.*** See legend to Figure 5.7 for details.

5.4 Discussion

Individuals with DLD perform poorly on tasks requiring implicit learning of sequences, such as pseudoword repetition, which is a crucial skill for vocabulary acquisition and fluent speech (Hsu & Bishop, 2014; Krishnan et al., 2016). The neural correlates of pseudoword repetition and learning in DLD are not well understood. In neurotypical adults, repeated production of pseudowords is linked to decreased activity in a primarily left-lateralised frontostriatal network (Rauschecker et al., 2008). Here, we used a functional MRI paradigm involving pseudoword repetition to investigate patterns of learning in the whole brain and in the frontostriatal network in 46 children and adolescents with DLD compared with 71 controls, spanning the age range 10 to 15 years. The DLD participants were able to perform the task of producing pseudowords in the scanner. We anticipated that learning related differences in the DLD group would be evident in the pattern of change in brain activity seen across repeated presentations of the stimuli.

When producing pseudowords, we found that the participants with DLD activated parts of the dorsal motor cortex that were not activated above baseline in the TD group. In addition, there was a pattern of reduced deactivation (i.e., below baseline) in some regions that were robustly task-negative in the TD group. These task-negative regions were typically medial and lateral portions of parietal cortex, which are considered as parts of the default-mode network (e.g., Alves et al., 2019). Across the repeated presentations of the pseudowords, both DLD and TD groups showed linear decreases in brain activity, but these learning-related

activity patterns did not differ between groups. Examining the fronto-striatal network using region-of-interest analyses, we again found no differences in learning-related activity between the groups. There was, however, a difference in the DLD group in the pattern of lateralised activity during pseudoword repetitions in the inferior frontal cortex. Specifically, in both pars triangularis and pars opercularis, DLD participants failed to exhibit the left-greater-than-right hemispheric difference that was observed in the TD group.

Behaviourally, the pattern of results was unexpected. On the one hand, the TD and DLD groups did not differ in form-referent learning (alien picture-name association), showing equivalent levels of recognition accuracy and the benefit of the repeated over the non-repeated stimuli. On the other hand, and to our surprise, both groups found producing repeated stimuli more difficult than the non-repeated stimuli in our post-scan pseudoword repetition test. The DLD group showed this effect more strongly for the repeated 4-syllable pseudowords. Below we discuss each of these points.

5.4.1 No Significant Group Differences in Neural Activity During Pseudoword Learning

Children with DLD have specific difficulties with the implicit learning of phonological and speech-motor sequences (Krishnan et al., 2016). Such impairment is in accord with predictions from the Procedural (Circuits) Deficit Hypothesis (Ullman & Pierpont, 2005; Ullman et al., 2020), which suggests that these difficulties are related to the structure and function of the fronto-striatal learning systems that support procedural and implicit learning. Accordingly, we previously reported evidence for structural differences in these regions in the same OxBOLD cohort of DLD participants, including in the inferior frontal cortex (Bahar et al., 2024) and the dorsal striatum (Krishnan et al., 2022; Cler et al., in *prep*). Yet, contrary to our expectations, we found no differences in learning related patterns of brain activity in the DLD group. There were however sub-threshold differences indicating higher activation in the TD group in the left frontal operculum as well as the superior and medial temporal cortex bilaterally.

One argument for the absence of compelling group differences in pseudoword learning relates to the task itself, in that not all types of sequences appear to pose a learning difficulty in individuals with DLD. Recent theories suggest that a computation specifically related to learning sequences of the "2nd-order dependency" type is the core challenge in DLD, while

other types of sequences are spared (Goffman & Gerken, 2023). These dependencies occur when a segment in one position depends on a segment in another position, creating a contextual dependency characterised by an "if and only if" relationship between units. From this perspective, our DLD group may have found learning our pseudowords relatively easy since the stimuli did not contain the types of phonologic and motoric sequencies that present challenges for this group. A further possibility relates to the incorporation of visual referents into our learning task. Studies have shown that speech motor learning accelerates in children with learning impairments (including DLD) when a visual referent is added to a novel word form (Gladfelter & Goffman, 2018; Heisler et al., 2010). Pairing pseudowords with visual referents might have aided in "crystallising" the novel word forms. Considering this, we note that probing implicit learning through repeated exposure to auditory stimuli that are paired with visual referents is only one way of evaluating learning in DLD. Lastly, a failure to demonstrate impairment on our task might further be related to our cohort's age range. The overwhelming majority of the literature on pseudoword learning in individuals with DLD have focused on younger populations. It is possible that the nature of learning deficits in this domain change over time.

On a different note, the DLD participants failed to exhibit left-lateralised activity in the pars triangularis and opercularis during learning trials. The TD participants showed the typical left-greater-than-right activity in these regions. This atypical functional laterality in DLD aligns with similar observations in various neurodevelopmental disorders (including DLD) suggesting that speech and language difficulties may partly stem from a failure to establish left-hemisphere specialisation for linguistic functions (e.g., see Bishop, 1990, 2013; Xu et al., 2015). Previous functional results in DLD have been inconsistent on this topic (see Chapter 1, Section 1.7) Nonetheless, most of the previous studies have probed language processing as opposed to language learning *per se*. One possible interpretation is that higher language efficiency in the TD group is linked to a more left-lateralised neural recruitment, suggesting a less efficient left hemisphere specialisation in the DLD cohort. Alternatively, the DLD group might be over-recruiting the right hemisphere to compensate.

In sum, we did not find compelling evidence of a group difference in brain activity during implicit learning of pseudowords in our study. However, the significant group differences found during pseudoword *repetition* when the participants encountered the stimuli

for the first time could provide evidence for an encoding deficit in DLD, a point we discuss in the next two sections.

5.4.2 Greater Motor Cortex Activity in DLD During Pseudoword Repetition

Behaviourally, pseudoword repetitions were on average less accurate in the DLD group compared with the TD group. Unexpectedly, however, all participants produced *non-repeated* pseudowords more accurately than the repeated ones. To investigate this result, we examined the characteristics of the stimuli in each condition and found that the repeated pseudowords inadvertently included more within-syllable-boundary consonant clusters than the non-repeated set–specifically, one in the two-syllable set and three in the four-syllable set. These pseudowords are highlighted in bold in Table S5.2. The increased phonological and speech-motor complexity may have made the repeated pseudowords more difficult to produce. The increased difficulty in producing the repeated pseudowords may also be reflected in the neural activity patterns observed, suggesting a link between stimulus complexity and neural processing demands.

In the pseudoword repetition versus rest condition, participants with DLD exhibited significantly greater activity in the motor cortex, particularly in the dorsal portions of precentral gyrus bilaterally (at the level close to the hand and dorsal laryngeal representations), and in the right dorsomedial frontal cortex. Interestingly, we did not see group differences in neural activity when the same participants performed a simple verb generation task (Krishnan et al., 2021). This discrepancy may be due to the nature of the tasks; pseudoword repetition requires producing unfamiliar and often more complex speech-motor sequences, which pose a greater challenge for individuals with DLD, whereas verb generation involves producing familiar and well-rehearsed sequences. Supporting this notion, behavioural studies have noted speech motor deficits in individuals with DLD when producing novel pseudowords (Goffman, 1999; Heisler et al., 2010), but less so with familiar words (Goffman & Westover, 2013).

These observations suggest that the greater activity of motor cortex representations in participants with DLD reflect their comparatively smaller repertoire of well-rehearsed speech-motor sequences, in contrast to their TD peers with efficient speech-motor systems and more focal neural representations. Motor skill acquisition is known to result in more focal neural activity in professional musicians and athletes (e.g., Bernardi et al., 2013; Petrini et al., 2011). Similarly, in motor speech literature, producing novel phonological syllables leads to more

extensive engagement of the entire motor speech system compared with the engagement seen during production of familiar syllables (Moser et al., 2009). Taken together, deficits in pseudoword repetition in individuals with DLD are partly linked to less efficient control over novel speech-motor sequences, reflected at a functional level in more effortful neural recruitment in the motor cortex.

5.4.3 Weaker Task-related Deactivation in DLD During Pseudoword Repetition

Significant differences in the BOLD signal were observed between the DLD and TD groups in cortical regions not activated by pseudoword repetition. These group differences were due to variations in the amount of deactivation below baseline, which was consistently less attenuated in the DLD group compared with the TD group. In other words, TD participants showed more robust task-negative activity in certain brain regions. Specifically, the right medial prefrontal cortex, retrosplenial cortex, posteromedial cortex, and the angular gyrus bilaterally were involved. These regions are thought to constitute key nodes of the default mode network (DMN), a constellation that shows robust synchronisation of low-frequency fluctuations in activity at rest (Smith et al., 2009). The DMN decreases its activity during cognitively demanding, goal-directed tasks (Raichle, 2015; Smallwood et al., 2021) and is arguably implicated in sustained attention (Buckner et al., 2013; Danckert & Merrifield, 2018). Inefficient suppression of activity in regions like the posterior cingulate cortex has been associated with reduced cognitive efficiency (Sonuga-Barke & Castellanos, 2007).

Attention to incoming stimuli is key for the successful encoding of information into memory (Erickson & Thiessen, 2015). The reduced task-induced deactivation in our DLD cohort may indicate less efficient suppression of baseline cognitive processes when engaging in demanding linguistic tasks. This interpretation aligns with findings from Dibbets et al. (2006), where children with DLD exhibited increased frontal and cingulate activations during a task-switching paradigm, and even in non-switch condition requiring minimal executive control, suggesting that these children found the task more challenging. Behavioural data further supports this notion; as I reviewed in Chapter 1 (see Section 1.3.2), children with DLD perform poorer on measures of sustained attention across both auditory and visuospatial domains (Ebert & Kohnert, 2011). Notably, performance on auditory sustained attention tasks is associated with vocabulary size in this population (e.g., see Smolak et al., 2020).

5.4.4 Limitations and Future Directions

One limitation of our study relates to the phonological structure of the pseudowords we employed, which might have limited our ability to fully assess learning-related differences. Future studies should systematically explore the specific challenges of children with DLD in learning stimuli that contain different types of phonological sequences and sequential dependencies. Research using alternative learning tasks from a wider age range, and in individuals with DLD with a range of language learning severities, may also be helpful to reveal more specific learning related deficits in the DLD population. One example of such research is to probe the learning of 2nd-order sequential dependencies using a statistical learning paradigm in children and adults with DLD. Such paradigms should also consider factors like prosodic variation and semantic cues, which have been shown to influence the learning of sequences (Goffman & Gerken, 2023). Systematically varying the types of sequences presented to individuals with DLD may help determine whether specific deficits appear at the neural level.

6

General Discussion

6.1 Summary

The studies presented in this thesis investigated the behavioural and neural correlates of developmental language disorder (DLD) cross-sectionally and longitudinally. The Oxford Brain Organisation in Language Development (OxBOLD) cohort comprised 160 children and adolescents aged 10 to 15 years with a range of language abilities. Of these, 55 met our DLD criteria, 77 were typically developing (TD group), and 28 had a history of speech and language difficulties but did not meet our DLD criteria (HSL group). Fifty-three participants from this cross-sectional cohort were followed up using similar behavioural and neuroimaging protocols some four to five years later.

This thesis had three main aims. The first was to characterise the language and cognitive deficits common to DLD by using a comprehensive neuropsychological test battery to compare the performances of the three groups on tests of language, memory, reading, nonverbal reasoning, and motor control. The second aim was to identify the cortical differences associated with DLD and to explore longitudinal changes in cortical metrics in a subset of the OxBOLD cohort approximately four to five years after the initial assessment, when participants were between 14 and 20 years old. To achieve this, FreeSurfer-derived cortical measures of surface area, cortical thickness, and grey matter volume were analysed using semi-automated cross-sectional and longitudinal pipelines to examine group differences and track changes over time. The third aim was to investigate the functional neural correlates of learning to articulate novel words in DLD, given the known difficulties this population has in this domain. We employed a functional MRI paradigm to investigate novel word form repetition and learning in the whole brain and in the frontostriatal network in DLD and TD groups in the initial cross-sectional cohort.

Our neuropsychological and neuroimaging results have clinical and theoretical implications for DLD. In the following sections, I will review some of our key behavioural and neurobiological findings, provide my thoughts on the current neurocognitive model of DLD based primarily on evidence from the OxBOLD cohort, and propose suggestions for future research. In the last section I underscore the advantages and potential pitfalls of employing transdiagnostic approaches to theory and practice moving forward.

6.2 Sentence Recall as a Powerful Assessment Test

The most notable performance gap between our DLD and TD participants emerged on the sentence recall test, which we used as a proxy for expressive grammar. Sentence recall is a valuable assessment tool because it simultaneously engages memory and language skills at various levels (Klem et al., 2015; Vinther, 2002). Poor performance on sentence recall is well-documented in children with DLD (Archibald & Joanisse, 2009; Ward et al., 2024), and was in fact found as the single best tool for identifying DLD, with higher sensitivity and specificity than other tests traditionally associated with DLD (Conti-Ramsden et al., 2001). Our own exploratory analysis using discriminant functional analysis (not reported in the thesis), identified sentence recall as the best test to differentiate the DLD and TD groups. A close look at the groups' neuropsychological profiles in Figure S2.2 is helpful. Firstly, 19 out of the 20 participants with DLD in the longitudinal cohort performed ≥ 1 SDs below the normative mean on sentence recall. At time II, 18 still had low performance, and the one DLD participant who did not meet the DLD criteria at time II had sentence recall scores within the typical range at both time points.

There is currently a clinical need for more reliable and efficient screening tools to identify language impairment in educational settings (Bao et al., 2024). Sentence recall presents as a promising candidate due to its broad sensitivity to capture a wide range of underlying cognitive weaknesses, and because it is quick and straightforward to administer. Moreover, this test appears to be reliable in differentiating between monolingual TD and DLD groups across several languages with diverse grammatical structures (e.g., see Taha et al., 2021; Ward et al., 2024). One important research area that merits further attention is the utility of this task in identifying bilingual children with DLD, which pose a particular challenge due to superficial overlaps between features of impaired language versus bilingualism or second language learning (Hemsley et al., 2014).

Addressing bilingualism in DLD was beyond the scope of this thesis, but it was identified as one of the 11 areas requiring further research in this population (Kulkarni et al., 2022). Efforts are already under way, and an example of this is the Language Impairment Testing in Multilingual Settings (LITMUS) Sentence Repetition tools which were created as part of the European Cooperation in Science and technology (COST) Action IS0804 to address DLD in a multilingual society (Armon-Lotem & Marinis, 2015). The main goal of COST Action is to profile bilingual children with DLD by establishing a network to coordinate research on language and other cognitive skills across migrant communities. Future studies could expand the scope to include testing in diverse language pairs, which requires careful consideration of morphosyntactic differences between languages and language-pairs. Work in this domain should also extend beyond focusing on school-age children to adolescents and adults with DLD.

6.3 The Case for a Neuromaturational Lag in DLD

In our behavioural analyses, participants with DLD had weaker performance on all neuropsychological measures at the initial assessment. Longitudinal analysis showed that their poorer performance relative to controls persisted over the years despite developing in parallel, suggesting that participants maintained their relative "rankings." These behavioural profiles, coupled with the neuroimaging evidence that I review below, re-emphasised a key question: how do we best explain the poorer performance of the DLD group across *all* other domains?

The complex relationship between verbal and nonverbal cognition makes it challenging to determine whether poor performance in other cognitive domains stems from language difficulties or if other factors, like executive functioning deficits, affect language. It is likely that a combination of both is at play. Regardless, one way out of this circular loop was by considering our participants' performance on a task of motor control. Interestingly, performance on the peg-moving task of manual dexterity mirrored other test results: lower performance at time I, similar growth trajectory, and no sign of closing the performance gap over time. Motor measures have historically been indicators of children's neurodevelopmental stage (Gillberg, 1985; Wolff et al., 1985), and the literature on motor weaknesses in the DLD population, reported as imprecise or a generally slower execution of a range of motion related tasks (e.g., balance, bilateral coordination, gross and fine motor skills, movement imitation)

have implications for neuromaturational accounts of this disorder (Bishop & Edmundson, 1987; Hill et al., 2001; Zelaznik & Goffman, 2010; Sanjeevan & Mainela-Arnold, 2019).

Neurobiologically, two lines of evidence from the OxBOLD cohort prompted us to consider the case for a lag in neurodevelopment in DLD. Firstly, in the quantitative MRI study by Krishnan and colleagues (2022), while magnetisation transfer saturation (MTsat) values revealed focal, primarily left-lateralised myelin reductions in DLD, the longitudinal relaxation rate (R1) index showed global reductions across the whole brain, which indicated that in addition to myelin reductions there are likely to be fewer neurites (axons and dendrites) in those with DLD. The affected regions included the lateral convexities of the frontal and parietal lobes bilaterally, the medial frontal cortex extending to the paracentral lobule, and the left posterior temporal cortex. Subcortically, differences appeared in the dorsal striatum, thalamus bilaterally, and anterior medial temporal lobe. These global, bilateral differences in neurites and myelination patterns are consistent with theoretical views postulating that DLD is associated with a generalised weakness in processing speed (Kail, 1994; Miller et al., 2001). They might also stem from less mature neural pathways more broadly.

Secondly, our analysis of subcortical volume (Cler et al., *in prep*) revealed that the DLD cohort had smaller globus pallidus, thalamus, and hippocampus in addition to smaller anterior neostriatum. Combined with the smaller surface area patterns presented in Chapter 3, these findings prompted us to consider neural maturation patterns longitudinally. In Chapter 4, we distinguished between lag, delay, and disorder in neuromaturation. A neuromaturational lag would correspond to the lower tail of the normal distribution of maturation, in which a specific factor (perhaps genetic) interferes with the timely maturation of the neural pathways, leading to persistent group differences. In contrast, a delay suggests a slower start but catch-up at a later point. In the case of delayed neuromaturation we expected that the interval between milestones will show rapid acceleration in maturation appearing as an interaction between time and group, with group differences diminishing over time. Our exploratory results provided preliminary support for both hypotheses, indicating region-dependent group differences in surface area (but not cortical thickness), with patterns consistent with both neuromaturational lag and delay accounts.

Evidence for lagged maturation was seen through lingering group differences, notably in the frontal cortex. Interestingly, when averaging scans from both time points, the DLD group further showed larger surface area in the sensorimotor cortex, which was a new observation

that we did not detect at time I. Studies from typical neurodevelopment suggest that cortical maturation advances in a posterior-to-anterior manner (Tamnes et al., 2013). Under the lagged neuromaturation hypothesis, children with DLD reach peak cortical surface area values later than their typically developing peers. In group comparison, this can emerge as larger posterior (sensorimotor) regions and smaller anterior (frontal) regions in individuals with DLD, which would be consistent with a prolonged posterior-to-anterior maturation pattern.

Evidence for delayed neuromaturation was also present, with accelerated growth in the DLD group in parts of the left anterior insula and pars opercularis. Interestingly, similar to the left-lateralised reductions in MTsat values (Krishnan et al., 2022), the group-by-time interaction maps of surface area, indicating accelerated areal expansion in DLD, were limited to pars opercularis and anterior insula in the left hemisphere, possibly suggesting a delayed use-dependent functional specialisation in DLD. Evidence for a neuromaturational lag in development has been provided in other closely related neurodevelopmental disorders like ADHD (e.g., see Rubia, 2007; Shaw et al., 2008; Sripada et al., 2014; Sudre et al., 2017). Future investigations with larger cohorts and several time points can help pinpoint the time of peak maturation in different cortical metrics in the DLD population to fully test this hypothesis.

6.4 Deficits in the Frontostriatal Circuitry in DLD

A domain-general deficit in procedural learning in DLD was first proposed by Ullman and Pierpont (2005) to describe the nature of cognitive difficulties in these children. Subsequent behavioural evidence for specific deficits in the implicit learning of sequences (which fall under the umbrella of procedural learning) called for a growing need to examine frontostriatal learning circuits in these children (Krishnan et al., 2016). Our results from a range of neuroimaging modalities in the OxBOLD cohort provided neuroanatomical evidence for abnormalities in these corticostriatal structures in 10- to 15-year-olds with DLD. I summarise these findings below.

Firstly, Krishnan and colleagues (2022) found lower levels of myelin, indicated by lower MTsat values, in participants with DLD compared with typically developing controls, specifically in the left pars opercularis and in the caudate nucleus bilaterally. MTsat values in the left caudate nucleus positively correlated with language proficiency scores across the whole cohort (n = 117). Secondly, our surface-based cortical analysis presented in Chapter 3 revealed smaller surface areas in participants with DLD relative to controls in several brain regions,

including symmetric portions of the inferior frontal gyrus bilaterally and the lateral orbitofrontal cortex on the ventral surface of the left hemisphere. Language proficiency factor scores (but not memory factor scores) again positively correlated with surface area in these regions across the whole cohort (n = 156). Lastly, our analyses of subcortical structures showed significantly smaller volumes of the caudate nucleus and putamen in participants with DLD, with diffusion analysis further revealing lower fractional anisotropy in the left and right caudate nucleus in these participants (Cler et al., *in prep*).

Results from OxBOLD functional imaging studies were less conclusive in detecting abnormalities in frontostriatal circuits in our DLD group. In two task-based fMRI paradigms–overt verb generation (Krishnan et al., 2021) and pseudoword repetition and learning (Chapter 5)–we did not find evidence of abnormal function in the left inferior frontal gyrus or dorsal striatum in the DLD group. In the verb generation study, subthreshold group differences in the left inferior frontal gyrus and caudate nuclei emerged only when the analysis was limited to a subset of DLD participants with the poorest task performance (n = 14). The authors suggested that the differences in task-evoked activity in the striatum reported in previous studies may reflect differences in task performance rather than inherent neural abnormalities in DLD.

Importantly, our participants with DLD used the same brain networks as their typically developing peers in both tasks, providing no evidence for a compensatory functional role of medial temporal lobe structures in DLD, as originally hypothesised by Ullman and colleagues (Ullman & Pierpont, 2005; Ullman et al., 2020). Similarly, our analysis of subcortical structures revealed smaller hippocampal volumes in the DLD group (Cler et al., *in prep*). If the medial temporal lobe structures were in any way compensating for basal ganglia abnormalities, we would expect to see larger hippocampi or increased functional activity in this region; neither was observed, however.

In the fMRI study presented in Chapter 5, group differences in brain activity for pseudoword learning emerged only at subthreshold levels, with the DLD group showing lower levels of activation in the left frontal operculum and parts of the temporal cortex bilaterally. In contrast, significant group differences emerged during the encoding stage of word learning, when the participants with DLD encountered the novel word forms for the first time. In the pseudoword repetition versus rest condition, participants with DLD exhibited increased motor cortex activity, which may reflect less focal and more extensive neural recruitment to execute novel speech-motor sequences. Moreover, our region-of-interest analysis of the frontostriatal

network showed that the DLD participants exhibited a different pattern of lateralised activity in the inferior frontal gyrus throughout the course of learning the pseudowords.

The other core finding emerging from this study was independent from the frontostriatal circuity that was of primary interest to us. Participants with DLD exhibited less pronounced attenuation of neural activity below baseline levels, i.e. had less robust task-negative activity than controls in regions that overlapped with key nodes of the default mode network. We proposed that this reduced deactivation may reflect difficulties with sustained attention and lower cognitive efficiency when individuals with DLD engage in demanding language tasks. Our results highlight the importance of considering other cognitive and motor factors, in addition to cortico-striatal learning loops, when examining the mechanisms of learning in individuals with DLD.

6.5 Towards a Neurocognitive Model of DLD

The emerging neuroimaging studies of DLD, including several findings from our OxBOLD project, necessitate a reassessment of current theories of this condition from a biologically grounded perspective. The culmination of our cross-sectional and longitudinal data suggests that DLD may be characterised by a lagged neuromaturational profile, co-occuring with a pronounced domain-general deficit in learning and processing complex sequential relationships. I propose that an immature neural system is a more parsimonious explanation that could account for the perceptual, motor, and cognitive deficits documented in the literature on DLD, including limitations in auditory processing (Tallal & Piercy, 1973, 1974), short-term memory (Gathercole & Baddeley, 1990), and general processing capacity (Bishop, 1992).

A particularly pronounced impairment in learning and processing hierarchical sequences may stem from specific, yet-to-be-characterised genetic mechanisms or represent an extension of neural immaturity. The latter hypothesis is supported by the fact that the neurocomputational mechanism underpinning hierarchical sequential processing is not only late-maturing in neurotypical children but also involves phylogenetically younger neocortical regions (e.g., see Friederici et al., 2006; Lind et al., 2023). In theoretical linguistics, this computation is referred to as “merge” (Chomsky, 1957, 1959) and is crucial for the comprehension and generation of non-canonical sentences or sequences with embedded constructs. Typically developing children do not reliably employ merge to process hierarchical

sequences until around 7.3 years of age (Dittmar et al., 2008). In contrast, individuals with DLD consistently perform poorly on tasks requiring this late-maturing cognitive computation, often well into adolescence or adulthood (Delage et al., 2021; Marinis & Saddy, 2013; Van Der Lely, 1996; Van Der Lely et al., 1998). This pattern aligns with our DLD cohort's poor longitudinal performance on a grammatical comprehension task probing hierarchical constructs (see Chapter 2, Section 2.3.3). Notably, however, performance on this task was not static; our participants with DLD demonstrated improvements over time, albeit lagging behind their neurotypical peers.

Extensive neuroimaging research in neurotypical adults has demonstrated the selective involvement of the pars opercularis in the inferior frontal gyrus (Brodmann's area 44) in processing hierarchically organised sequences, independent of modality, working memory demands, or cognitive effort (Friederici et al., 2006; Kaan & Swaab, 2002; Koelsch et al., 2002; Maess et al., 2001; Zaccarella & Friederici, 2015). Furthermore, the maturation of the arcuate fasciculus, i.e., the white matter tract connecting the pars opercularis to the posterior superior temporal gyrus, predicts both accuracy and processing speed for hierarchical structures as children develop (Brauer et al., 2011; Skeide et al., 2016). In our OxBOLD experiments, the pars opercularis consistently emerged as a region exhibiting significant differences in group analyses. In children with DLD, it was less myelinated than in controls (Krishnan et al., 2022), had lower surface area values (Chapter 3), and showed increased areal expansion over time, likely reflecting delayed maturation (Chapter 4). Additionally, functional imaging revealed reduced lateralisation of activity in DLD during pseudoword learning (Chapter 5). Future longitudinal studies focusing on the role of the pars opercularis and its associated white matter pathways in hierarchical sequencing in DLD will be essential in determining whether these deficits reflect a general neurodevelopmental lag or a specific neurobiological impairment. Such research will also contribute to our understanding of frontostriatal circuitries in DLD, as the basal ganglia interact with the frontal cortex, particularly the pars opercularis, in executing several speech and language-related functions.

Recent theoretical accounts suggest that DLD involves deficits in learning specific types of sequences rather than difficulties with all hierarchical sequential dependencies (Goffman & Gerken, 2023). If this hypothesis holds, future task-based fMRI studies will be needed to assess implicit learning of stimuli incorporating different sequential dependencies. Moreover, as I discussed in Chapter 5, the mode of probing learning in an experimental paradigm may

influence outcomes (e.g., statistical learning versus repeated exposure). Therefore, future paradigms should assess the performance of individuals with DLD across a wide age range using diverse stimuli and alternative methods for testing sequential learning.

Investigating neuronal function and connectivity in DLD without reliance on tasks may be another promising avenue for neuroimaging research. Resting-state fMRI could be particularly useful in this context, as it allows a shift from one-to-one brain region–behaviour mapping towards understanding whole-brain network organisation (Bassett & Sporns, 2017; Siugzdaite et al., 2020). Additionally, longitudinal resting-state fMRI studies could provide crucial insights into patterns of recovery versus persistent impairments, providing clues as to why some children with DLD do not outgrow their language impairments while others improve. For instance, the 28 participants in our HSL group exemplify cases where language deficits may be transient rather than persistent. Such studies may also clarify the impact of prolonged language impairment (or lagged neuromaturation) on the brain's functional connectivity patterns

The notion that DLD reflects a neuromaturational lag is not novel; Bishop and Edmundson (1987) explored this possibility, noting that "direct evidence of immaturity of brain development has never been demonstrated. Techniques such as NMR scanning do have the potential for demonstrating delayed myelination in children whose brains appear normal on CT scan … but such procedures are time-consuming and expensive and have not yet been widely applied to children with specific developmental disorder" (p. 442). Some 35 years later, our cross-sectional structural findings (Chapters 3 and 4) and quantitative MRI results (Krishnan et al., 2022) provide empirical support for these early speculations. Furthermore, our longitudinal analysis offers preliminary evidence of a lagged posterior-to-anterior cortical development. Our functional studies, though less conclusive, suggest that group differences are primarily quantitative (manifesting as variations in BOLD response magnitude associated with language deficit severity and linguistic competency) rather than qualitative, with no clear compensatory mechanisms observed in the tasks we tested.

Conceptualising DLD as a case of immature neurodevelopment carries significant clinical implications, which necessitates an interdisciplinary approach to care. Gaines and Missiuna (2007) noted that motor coordination deficits in young children with DLD may only become apparent in early school years when they begin to impact self-care and educational tasks. Accordingly, assessments should adopt a holistic view of a child's development,

particularly regarding early motor skills, and ideally involve close collaboration with occupational therapists. Recent studies have explored the role of primitive reflexes (PRs), the fundamental motor responses present from the prenatal stage, in the context of DLD (Matuszkiewicz & Gałkowski, 2021). In typical development, PR inhibition improves with age, reflecting central nervous system maturation and cerebellar functions that may later influence speech and language development (Highnam & Bleile, 2011). Research has shown that children with DLD exhibit a significantly higher frequency of uninhibited PRs, with reductions in these reflexes correlating with improvements in non-word repetition and literacy skills (e.g., see Grzywniak, 2017; McClelland et al., 2015). Future research should explore these relationships further by examining PRs in neonates with and without a family history of speech and language difficulties, investigating causal links between reflex inhibition and linguistic skills over time, and assessing the efficacy of integrative physical exercises in improving language and literacy outcomes.

6.6 Concluding Remarks and Broader Outlook

There is currently no evidence supporting a single major cause of developmental language disorder (DLD). Like other neurodevelopmental disorders, the aetiology of DLD appears to be heterogeneous, with multiple factors acting in combination, such as specific deficits in fronto-striatal learning circuits alongside a more global lag in neuromaturation. This heterogeneity has become increasingly evident in other neurodevelopmental conditions as well, and the common overlaps among these conditions have made it clear that neurodevelopmental disorders are not entirely independent entities. The absence of clear-cut boundaries between neurodevelopmental disorders has long been known in the clinical community; the caseloads of clinicians are often full of children with a range of overlapping diagnoses, which requires a multidisciplinary approach to clinical care. In the research community, this realisation is now prompting a shift away from rigid diagnostic categories and clear-cut boundaries towards a transdiagnostic approach to research. In practice, this translates to relaxing recruitment criteria to include participants with a range of overlapping conditions and applying novel data-driven analysis methods to a combination of behavioural, neurobiological, and genetic markers. The goal of such approaches is to uncover meaningful dimensions of behaviour, brain, and cognition that transcend traditional diagnostic categories.

While transdiagnostic approaches offer promising avenues for the future, they are not without limitations. Most notably, it is not immediately clear whether moving away from diagnostic labels is an entirely beneficial decision. After all, diagnostic labels have facilitated the formation of international advocacy organisations for DLD, supporting affected individuals and their families, creating communities for resource sharing, and, importantly, securing intervention funds. Challenging clinical boundaries might have unintended consequences, such as complicating access to therapy and support services that rely on receiving specific diagnoses. Moreover, from a methodological standpoint, data reduction methods common to transdiagnostic approaches may not be suitable for achieving a precise, mechanistic understanding of neurodevelopmental processes, particularly in conditions like DLD, which have only recently garnered sufficient attention to secure larger research funds to investigate its biological basis. Thus, while imposing discrete categories onto highly complex and multifaceted biological mechanisms can hinder scientific progress, the same categorisations have raised awareness of neurodevelopmental conditions and facilitated access to care. Balancing the move towards transdiagnostic research with the realities of clinical practice is a challenge that must be navigated carefully.

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Supplementary Material and Appendices

Chapter 2

Figures S2.1-2 (pp. 208-210)

Table S2.1 (pp. 211-212)

Appendix A (pp. 213-215)

Chapter 3

Figures S3.1-3 (pp. 216-218)

Table S3.1-2 (pp. 219-220)

Chapter 5

Tables S5.1-3 (pp. 221-224)

Appendix A (pp. 225)

Chapter 2

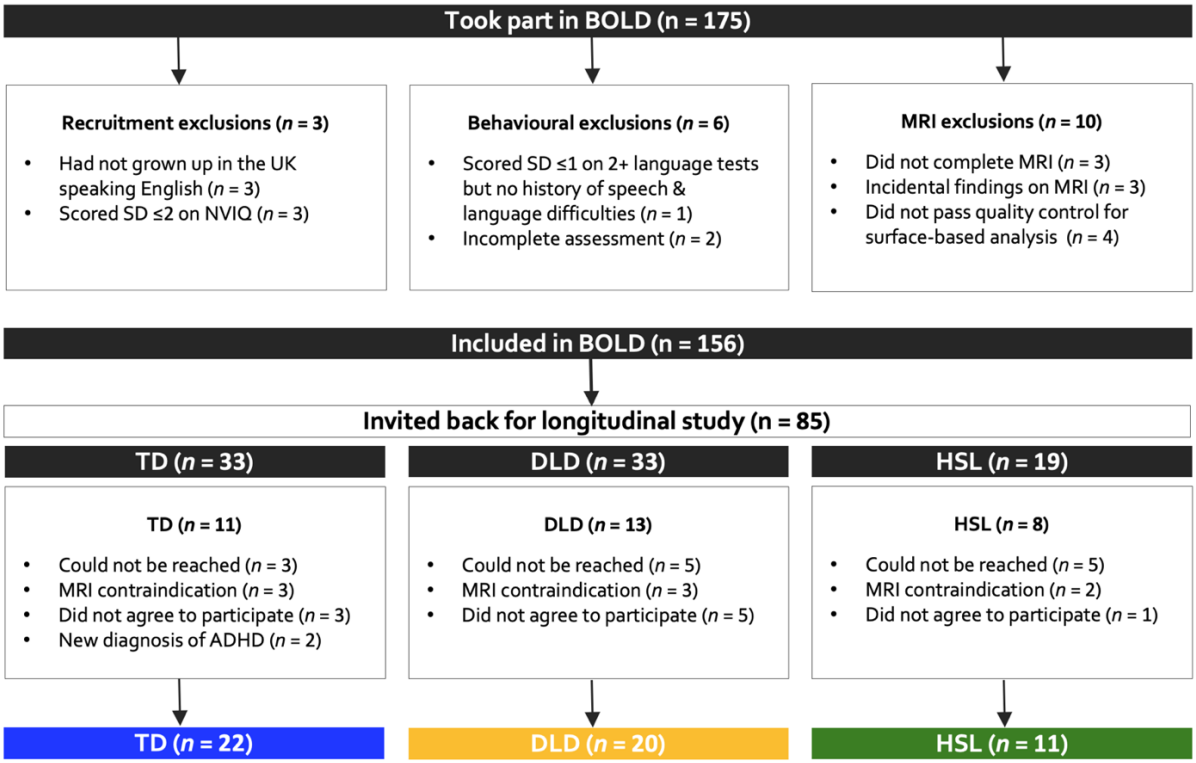


Fig. S2.1 ***Schematic overview of participant selection and inclusion criteria for the OxBOLD cohort***. Out of 175 initial participants, exclusions were made based on recruitment criteria, behavioral assessments, and MRI quality controls, resulting in 156 eligible participants for the surface-based analysis. Of these, 85 were invited back for longitudinal investigation. Following additional criteria and exclusions for each group, 22 TD, 20 DLD, and 11 HSL participants were included in the final longitudinal sample.

		Group	TD 1	TD 2	TD 3	TD 4	TD 5	TD 6	TD 7	TD 8	TD 9	TD 10	TD 11	TD 12	TD 13	TD 14	TD 15	TD 16	TD 17	TD 18	TD 19	TD 20	TD 21	TD 22
		Gender	M	M	F	F	F	F	F	F	F	F	M	F	F	F	M	M	M	M	M	M	M	M
Time Point I	RECEPTIVE	ROWPVT-4																						
		ERRNI (Comprehension)																						
		TROG-2																						
	EXPRESSIVE	EOWPVT-4																						
		ERRNI (Initial)																						
		ERRNI (Recall)																						
		CELF-4 (Recalling Sentences)																						
Time Point II	RECEPTIVE	ROWPVT-4																						
		ERRNI (Comprehension)																						
		TROG-2																						
	EXPRESSIVE	EOWPVT-4																						
		ERRNI (Initial)																						
		ERRNI (Recall)																						
		CELF-4 (Recalling Sentences)																						

		Group	DLD 1	DLD 2	DLD 3	DLD 4	DLD 5	DLD 6	DLD 7	DLD 8	DLD 9	DLD 10	DLD 11	DLD 12	DLD 13	DLD 14	DLD 15	DLD 16	DLD 17	DLD 18	DLD 19	DLD 20
		Gender	M	M	F	M	M	M	F	M	F	M	M	F	F	F	F	M	M	M	M	M
Time Point I	RECEPTIVE	ROWPVT-4																				
		ERRNI (Comprehension)																				
		TROG-2																				
	EXPRESSIVE	EOWPVT-4																				
		ERRNI (Initial)																				
		ERRNI (Recall)																				
		CELF-4 (Recalling Sentences)																				
Time Point II	RECEPTIVE	ROWPVT-4																				
		ERRNI (Comprehension)																				
		TROG-2																				
	EXPRESSIVE	EOWPVT-4																				
		ERRNI (Initial)																				
		ERRNI (Recall)																				
		CELF-4 (Recalling Sentences)																				

		Group	HSL 1	HSL 2	HSL 3	HSL 4	HSL 5	HSL 6	HSL 7	HSL 8	HSL 9	HSL 10	HSL 11
		Gender	M	M	M	M	M	M	M	M	M	M	M
Time Point I	RECEPTIVE	ROWPVT-4											
		ERRNI (Comprehension)											
		TROG-2											
	EXPRESSIVE	EOWPVT-4											
		ERRNI (Initial)											
		ERRNI (Recall)											
		CELF-4 (Recalling Sentences)											
Time Point II	RECEPTIVE	ROWPVT-4											
		ERRNI (Comprehension)											
		TROG-2											
	EXPRESSIVE	EOWPVT-4											
		ERRNI (Initial)											
		ERRNI (Recall)											
		CELF-4 (Recalling Sentences)											

Fig. S2.2 ***Schematic overview of the participants' performance on the language tests for time I and II in each group.*** Red boxes indicate scores that fell ≥ 1 SDs below the normative mean on each test. Grey boxes indicate data was not available. The HSL group is on the next page.

Table S2.1 ***Standard test scores for TD, DLD, and HSL groups per timepoint*****.**

	Time I									Time II								
	TD	**DLD**	**HSL**	***F*(2,50)**	**η^2**	**Pairwise comparisons**	**Mean difference (95% CI)**	**p_{adj}**	**Cohen's *d***	**TD**	**DLD**	**HSL**	***F*(2,50)**	**η^2**	**Pairwise comparisons**	**Mean difference (95% CI)**	**p_{adj}**	**Cohen's *d***
Language																		
ROWPVT-4	127.4 ± 4.01	102.2 ± 3.67	119.7 ± 4.43	11.62***	0.32	DLD – TD	-25.16 (-37.92, -12.40)	**<0.001**	-1.47	119.1 ± 2.35	94.8 ± 3.04	119.8 ± 4.25	23.44***	0.48	DLD – TD	-24.34 (-33.79, -14.88)	**<0.001**	-1.92
						HSL – TD	-7.63 (-22.88, 7.61)	0.453	-0.44						HSL – TD	0.72 (-10.57, 12.03)	0.986	0.05
						HSL – DLD	17.52 (2.02, 33.03)	**0.023**	1.02						HSL – DLD	25.06 (13.57, 36.55)	**<0.001**	1.97
	0%	15%	0%							0%	20%	0%						
EOWPVT-4	118.9 ± 2.92	90.4 ± 2.39	110.4 ± 3.95	27.68***	0.53	DLD – TD	-28.46 (-37.82, -19.10)	**<0.001**	-2.26	112.5 ± 3.11	86.3 ± 2.57	106.7 ± 4.28	20.80***	0.45	DLD – TD	-26.10 (-36.14, -16.06)	**<0.001**	-1.94
						HSL – TD	-8.50 (-19.68, 2.68)	0.168	-0.67						HSL – TD	-5.72 (-17.72, 6.27)	0.486	---
						HSL – DLD	19.96 (8.58, 31.33)	**<0.001**	1.59						HSL – DLD	20.37 (8.17, 32.57)	**<0.001**	1.51
	0%	35%	9%							4.55%	50%	0%						
TROG-2	108 ± 1.60	80 ± 2.66	99.9 ± 2.32	47.44***	0.65	DLD – TD	-28.00 (-35.04, -20.95)	**<0.001**	-2.96	107 ± 0.64	102 ± 2.92	87.4 ± 2.41	31.06***	0.55	DLD – TD	-19.51 (-25.60, -13.41)	**<0.001**	-2.38
						HSL – TD	-8.09 (-16.51, 0.32)	0.061	---						HSL – TD	-4.95 (-12.24, 2.33)	0.237	-0.61
						HSL – DLD	19.91 (11.35, 28.46)	**<0.001**	2.11						HSL – DLD	14.55 (7.13, 21.96)	**<0.001**	1.78
	0%	65%	9%							0%	45%	9%						
CELF-IV																		
Sentence Recall[1]	11.8 ± 0.60	4.7 ± 0.51	8.5 ± 0.66	42.35***	0.64	DLD – TD	-7.10 (-8.96, -5.23)	**<0.001**	-2.91	11.7 ± 0.38	4 ± 0.56	8.2 ± 0.75	61.74***	0.71	DLD – TD	-7.68 (-9.35, -6.01)	**<0.001**	-3.43
						HSL – TD	-3.25 (-5.47, -1.03)	**0.002**	-1.33						HSL – TD	-3.50 (-5.49, -1.51)	**<0.001**	-1.56
						HSL – DLD	3.84 (1.62, 6.06)	**<0.001**	1.57						HSL – DLD	4.18 (2.15, 6.21)	**<0.001**	1.86
	4.55%	90%	27.27%							0%	90%	45.45%						
ERRNI																		
Initial recall	100.5 ± 2.71	84 ± 3.06	93.6 ± 2.65	9.29***	0.27	DLD – TD	-16.54 (-25.82, -7.26)	**<0.001**	-1.32	104.1 ± 2.35	96.4 ± 4.27	105.7 ± 6.06	1.57	---	---	---	---	---
						HSL – TD	-6.91 (-18.01, 4.18)	0.297	-0.55						---	---	---	---
						HSL – DLD	9.63 (-1.64, 20.91)	0.107	0.77						---	---	---	---	---
	4.55%	55%	18.18%							9.09%	40%	18.18%						
Delayed recall	105.3 ± 2.43	85.5 ± 2.95	98 ± 2.53	15.34***	0.38	DLD – TD	-19.77 (-28.43,-11.11)	**<0.001**	-1.70	108.8 ± 2.67	98.3 ± 4.41	102.7 ± 5.10	2.14	---	---	---	---	---
						HSL – TD	-7.27 (-17.62, 3.08)	0.216	-0.62						---	---	---	---
						HSL – DLD	12.50 (1.97, 23.02)	**0.016**	1.07						---	---	---	---	---
	4.55%	55%	0%							0%	20%	27.27%						
Comprehension	104.8 ± 2.88	94.1 ± 3.53	103.2 ± 3.50	3.25*	0.12	DLD – TD	-10.67 (-21.21, -0.13)	**0.046**	-0.75	118.5 ± 2.13	114.5 ± 4.56	118 ± 3.77	0.39	---	---	---	---	---
						HSL – TD	-1.59 (-14.18, 11.01)	0.950	---						---	---	---	---
						HSL – DLD	9.08 (-3.72, 21.88)	0.210	---						---	---	---	---	---
	4.55%	20%	0%							0%	15%	0%						
Memory																		
CMS Digit Span																		
Forward[1]	11.8 ± 0.53	6.50 ± 0.76	7.80 ± 0.81	18.41***	0.42	DLD – TD	-5.31 (-7.50, -3.13)	**<0.001**	-1.81	11.2 ± 0.58	5.6 ± 0.65	7.1 ± 0.78	23.05***	0.48	DLD – TD	-5.67 (-7.75, -3.60)	**<0.001**	-2.04
						HSL – TD	-4.00 (-6.61, -1.39)	**0.001**	-1.36						HSL – TD	-4.13 (-6.61, -1.65)	**0.001**	-1.48
						HSL – DLD	1.31 (-1.33, 3.97)	0.458	0.45						HSL – DLD	1.54 (-0.97, 4.05)	0.310	0.55
	0%	55%	36.36%							13.64%	70%	63.64%						
Backward[1]	12.3 ± 0.66	7.2 ± 0.85	8.5 ± 0.69	13.51***	0.35	DLD – TD	-5.12 (-7.56, -2.68)	**<0.001**	-1.56	12.3 ± 0.51	7.1 ± 0.56	7.5 ± 0.84	25.45***	0.50	DLD – TD	-5.17 (-7.06, -3.27)	**<0.001**	-2.03
						HSL – TD	-3.72 (-6.64, -0.81)	**0.009**	-1.13						HSL – TD	-4.81 (-7.08, -2.55)	**0.001**	-1.89
						HSL – DLD	1.39 (-1.57, 4.36)	0.496	---						HSL – DLD	0.35 (-1.94, 2.65)	0.926	0.13
	9.09%	50%	36.36%							4.55%	65%	45.45%						
Nonverbal IQ																		
WISC-IV																		
Composite	12.7 ± 0.30	8.7 ± 0.60	11 ± 0.80	21.42***	0.47	DLD – TD	-4.08 (-5.59, -2.57)	**<0.001**	-2.04									-
						HSL – TD	-1.78 (-3.58, 0.01)	0.052	---									
						HSL – DLD	2.30 (0.48, 4.11)	**0.009**	1.15									
Block Design[1]	13.9 ± 0.30	9.9 ± 0.60	12.6 ± 0.66	17.62***	0.41	DLD – TD	-3.96 (-5.59, -2.33)	**<0.001**	-1.81									
						HSL – TD	-1.22 (-3.17, 0.72)	0.290	---									

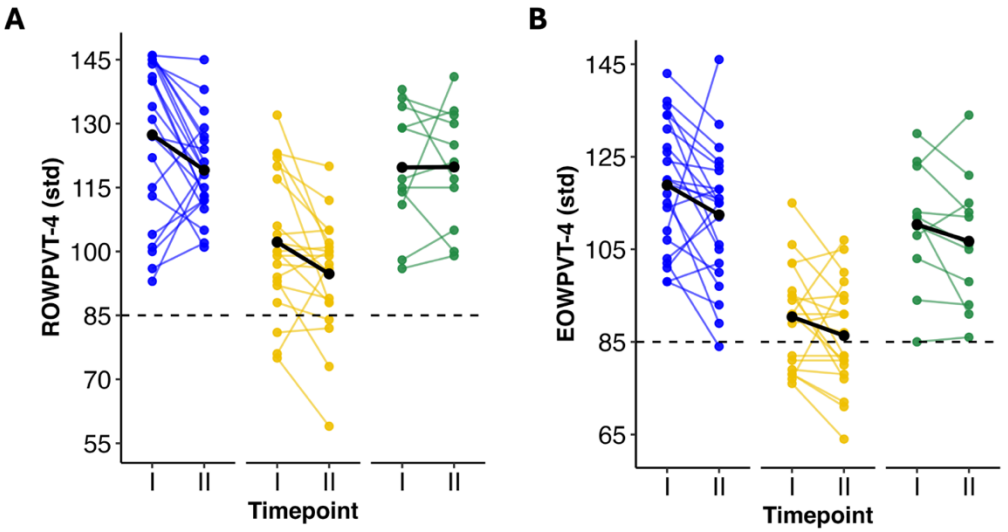
						HSL – DLD	2.73 (0.75, 4.71)	**0.004**	1.25											
	0%	15%	0%																	
Matrix Reasoning[1]	11.6 ± 0.62	7.5 ± 0.56	9.3 ± 0.90	12***	0.32	DLD – TD	-4.13 (-6.18, -2.08)	**<0.001**	-1.50											
						HSL – TD	-2.36 (-4.81, 0.08)	0.061	---											
						HSL – DLD	1.77 (-0.71, 4.26)	0.207	---											
	0%	40%	27.27%																	
Coding[1]	9.8 ± 0.41	5.3 ± 0.60	6.2 ± 0.39	24.6***	0.50	DLD – TD	-4.51 (-6.12, -2.89)	**<0.001**	-2.10	10.4 ± 0.45	4.3 ± 0.60	5.9 ± 0.48	39.69***	0.61	DLD – TD	-6.01 (-7.69, -4.33)	**<0.001**	-2.67		
						HSL – TD	-3.62 (-5.55, -1.69)	**<0.001**	-1.69						HSL – TD	-4.45 (-6.45, -2.44)	**<0.001**	-1.98		
						HSL – DLD	0.88 (-1.06, 2.82)	0.521	---						HSL – DLD	1.55 (-0.47, 3.59)	0.164	---		
	9.09%	75%	81.82%							4.55%	85%	72.73%								
WASI-II																				
Composite										12.3 ± 0.30	8.3 ± 0.60	10.6 ± 0.80	18.54***	0.43	DLD – TD	-3.96 (-5.54, -2.39)	**<0.001**	-1.88		
															HSL – TD	-1.72 (-3.61, 0.15)	0.078	---		
															HSL – DLD	2.24 (0.32, 4.15)	**0.018**	1.06		
Block Design[1]										13.2 ± 0.34	8.6 ± 0.74	11.2 ± 0.87	16.12***	0.39	DLD – TD	-4.62 (-6.59, -2.65)	**<0.001**	-1.75		
															HSL – TD	-2.04 (-4.39, 0.31)	0.100	---		
															HSL – DLD	2.58 (0.18, 4.97)	**0.031**	0.97		
										0%	40%	9.09%								
Matrix Reasoning[1]										11.4 ± 0.38	8.1 ± 0.58	10 ± 0.72	11.01***	0.31	DLD – TD	-3.31 (-5.01, -1.61)	**<0.001**	-1.44		
															HSL – TD	-1.41 (-3.44, 0.62)	0.226	---		
															HSL – DLD	1.90 (-0.17, 3.97)	0.078	---		
										0%	45%	18%								
Reading																				
TOWRE-2																				
Sight Word	106.2 ± 2.00	81.9 ± 2.66	91.6 ± 4.46	23.22***	0.48	DLD – TD	-24.28 (-32.94, -15.62)	**<0.001**	-2.09	98.0 ± 2.45	78.0 ± 2.21	84.0 ± 4.01	17.12***	0.41	DLD – TD	-20.04 (-28.49, -11.59)	**<0.001**	-1.77		
						HSL – TD	-14.54 (-24.89, -4.19)	**0.003**	-1.25						HSL – TD	-14.04 (-24.14, -3.95)	**0.004**	-1.24		
						HSL – DLD	9.73 (-0.78, 20.25)	0.075	---						HSL – DLD	6.00 (-4.26, 16.26)	0.342	0.53		
	0%	50%	36.36%							13.64%	80%	54.55%								
Phonemic Decoding	110.8 ± 3.20	82.3 ± 3.80	87.1 ± 2.83	21.14***	0.46	DLD – TD	-28.46 (-39.59, -17.34)	**<0.001**	-1.91	107.4 ± 2.60	80.7 ± 3.29	83.5 ± 3.71	24.58***	0.50	DLD – TD	-26.71 (-36.56, -16.85)	**<0.001**	-2.02		
						HSL – TD	-23.72 (-37.02, -10.43)	**0.001**	-1.59						HSL – TD	-23.95 (-35.73, -12.17)	**0.001**	-1.81		
						HSL – DLD	4.74 (-8.77, 18.25)	0.675	---						HSL – DLD	2.75 (-9.21, 14.72)	0.844	0.21		
	9.09%	55%	27.27%							4.55%	60%	45.45%								
Motor																				
Purdue Pegboard																				
Dominant	-0.3 ± 0.15	-1.9 ± 0.25	-0.7 ± 0.21	18.73***	0.43	DLD – TD	-1.63 (-2.30, -0.97)	**<0.001**	-1.84	0.0 ± 0.17	-1.3 ± 0.18	-0.2 ± 0.21	14.85***	0.37	DLD – TD	-1.24 (-1.81, -0.67)	**<0.001**	-1.62		
						HSL – TD	-0.38 (-1.17, 0.40)	0.471	---						HSL – TD	-0.22 (-0.91, 0.45)	0.704	---		
						HSL – DLD	1.25 (0.44, 2.05)	**0.001**	1.41						HSL – DLD	1.01 (0.32, 1.71)	**0.002**	1.33		
Non-dominant	0.0 ± 0.15	-1.4 ± 0.27	-0.6 ± 0.27	10.86***	0.30	DLD – TD	-1.39 (-2.11, -0.66)	**<0.001**	-1.43	0.2 ± 0.21	-1.4 ± 0.22	-0.7 ± 0.36	12.45***	0.33	DLD – TD	-1.60 (-2.38, -0.82)	**<0.001**	-1.53		
						HSL – TD	-0.54 (-1.41, 0.32)	0.291	---						HSL – TD	-0.85 (-1.78, 0.07)	0.075	---		
						HSL – DLD	0.84 (-0.03, 1.72)	0.061	---						HSL – DLD	0.74 (-0.19, 1.69)	0.147	---		
Dom – Nondom	-0.2 ± 0.15	-0.5 ± 0.18	-0.1 ± 0.24	1.02	---	---	---	---	---	-0.2 ± 0.17	0.7 ± 0.29	0.4 ± 0.30	2.15	---	---	---	---	---		
						---	---	---	---						---	---	---	---		
						---	---	---	---						---	---	---	---		

Note: Means along with the standard error of the mean (± SEM) are provided. The standard scores available for the oldest age per test were assigned to the raw scores of participants who were older than each test's normed ranges. The percentages below each score indicate the percentage of participants who performed ≥ 1 SDs below the normative mean at each timepoint. All variables were compared between groups using a one-way analysis of variance (ANOVA) with Tukey's post-hoc comparisons in case of a statistically significance result ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$). If the variables violated tests of normality and equal variance, the Welch test was used instead. Significant pairwise differences are indicated in boldface.

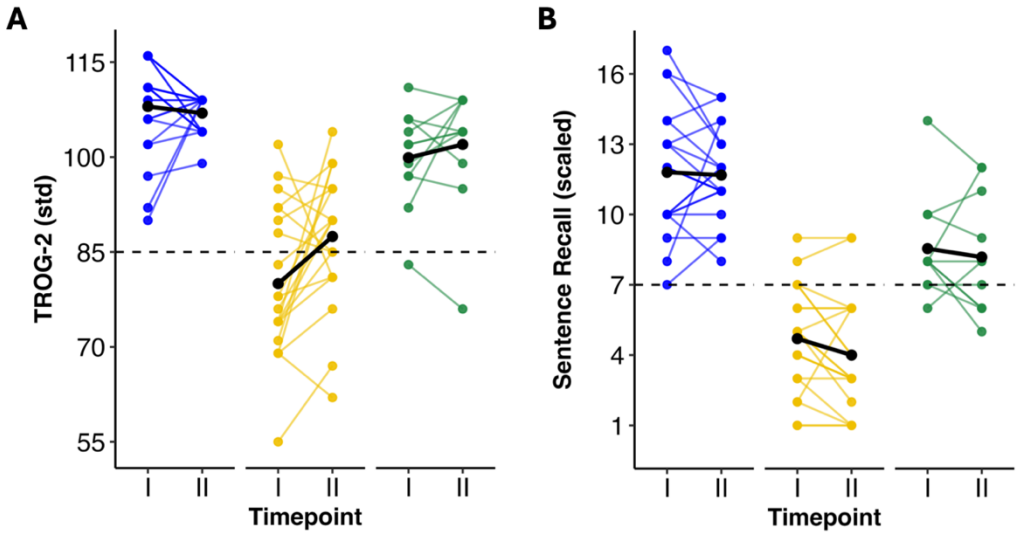
Appendix A

The figures below depict the longitudinal trajectories of participants' standard scores on the neuropsychological test battery per group**.** The plots show either the standard or scaled scores with the black points depicting the mean for each group at each time point categorically. The dashed black lines show the cut-offs for 1SD below the normative mean for each test. Blue = TD; yellow = DLD; green = HSL.

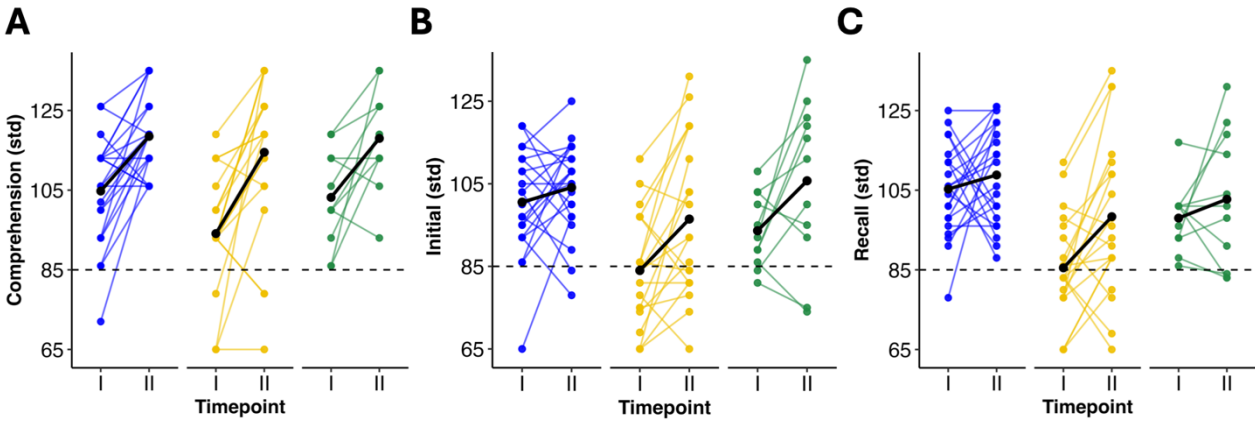
Vocabulary tests



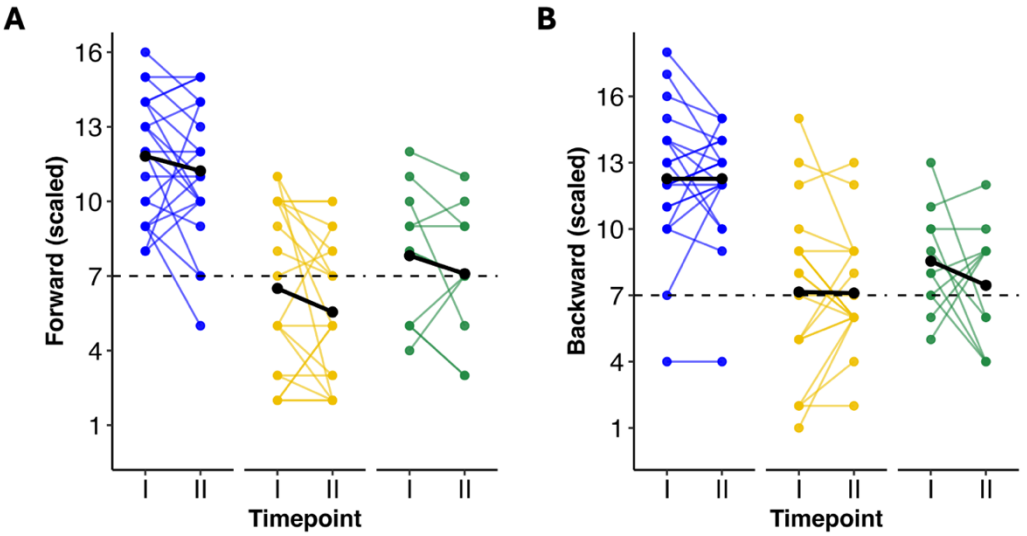
Grammar tests



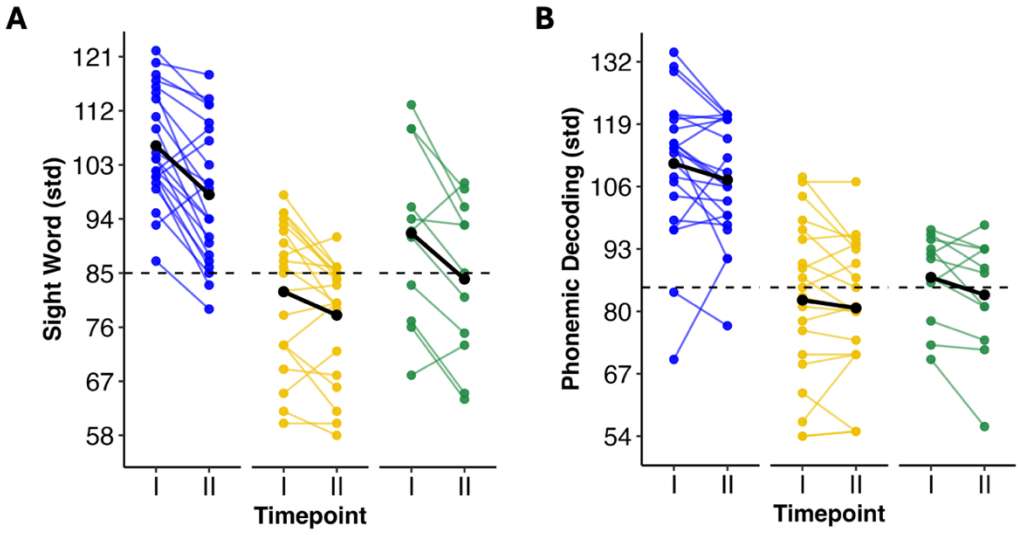
Narrative tests



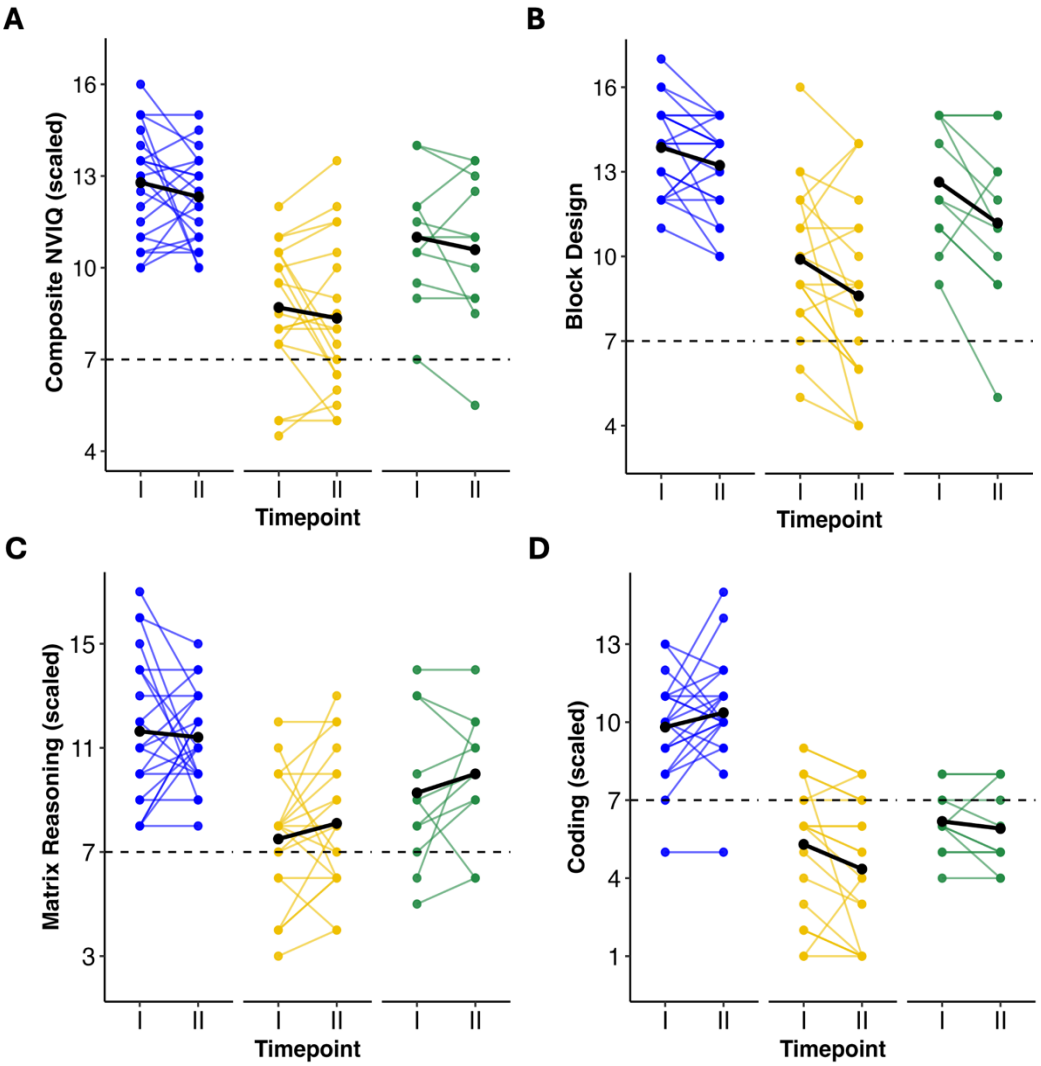
Memory digit span



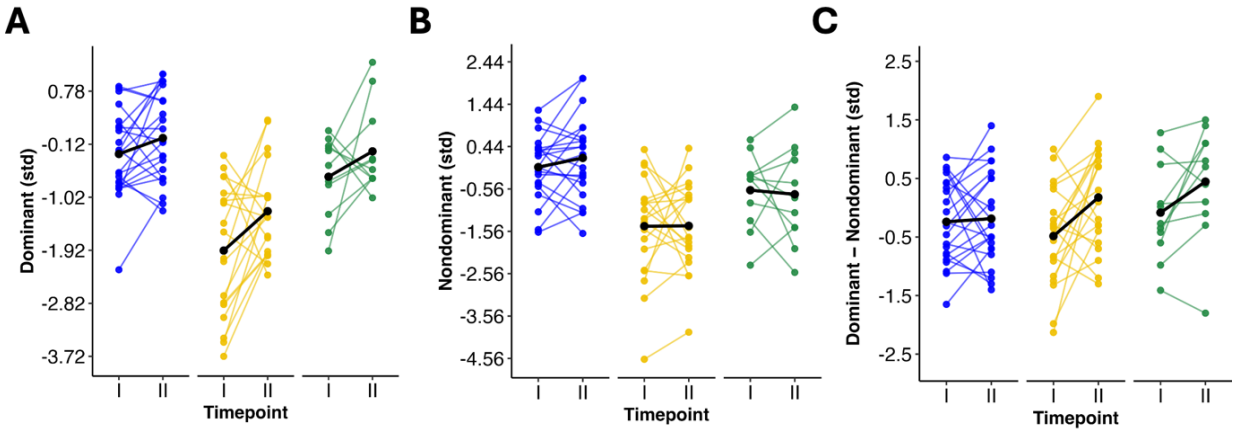
Reading efficiency



Nonverbal reasoning



Motor skills



Chapter 3



Fig. S3.1 ***The exclusion mask used in the structural asymmetry analysis***. The mask comprised vertices at the boundary between cortical and subcortical structures with extreme |AQ| values > 1 in at least one quarter of our participants. This left 157,992 vertex-wise asymmetry measures per individual spanning the rest of the cortex. |AQ| > 1 values possibly indicate a resampling artifact to the *fsaverage_sym* template.

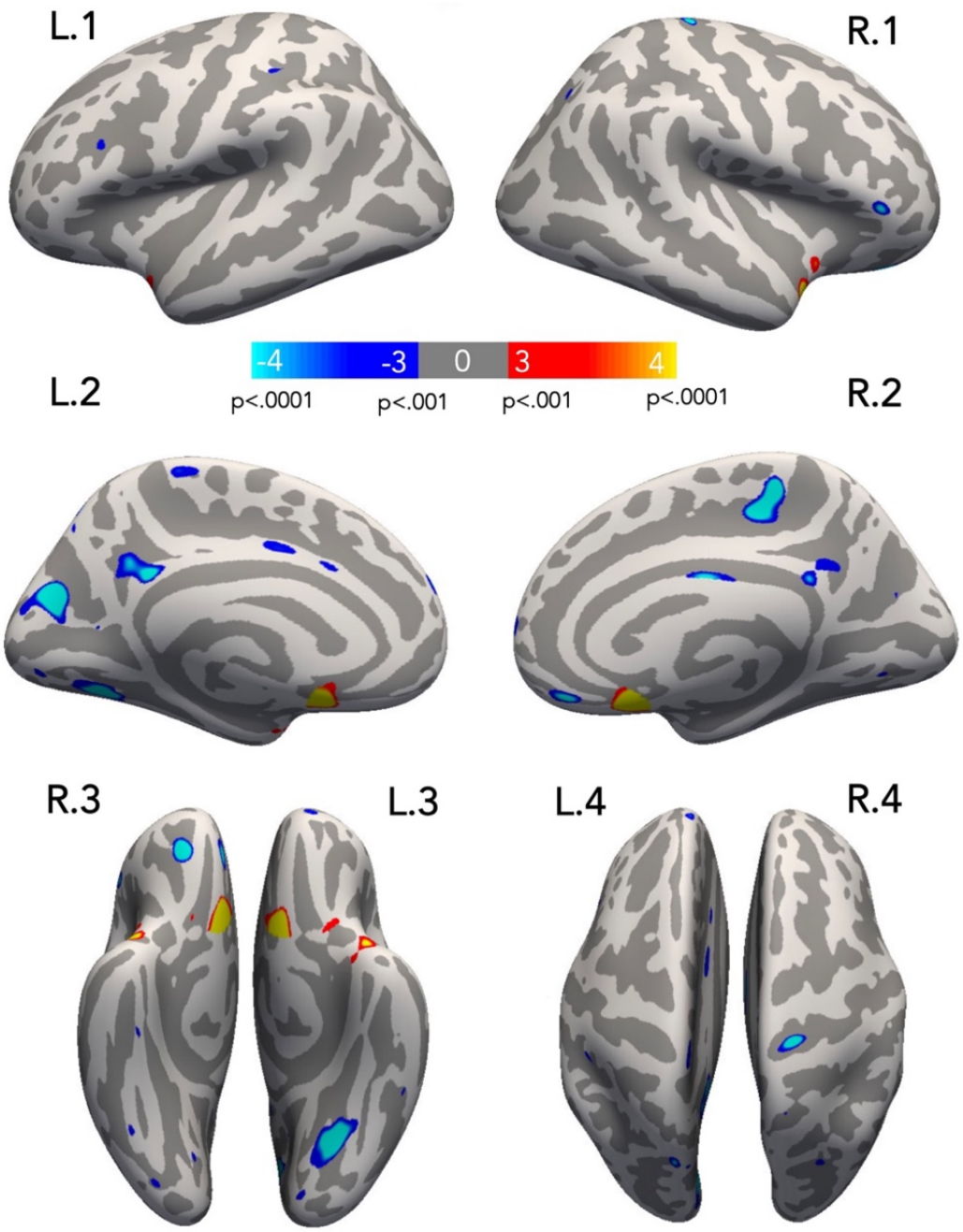


Fig. S3.2 Whole-brain significance map of age effects on cortical thickness across all participants. Results are depicted on the inflated surface with an uncorrected vertex-wise threshold $p < 0.001$. Positive correlations are shown in red/yellow and negative ones in blue/cyan. Refer to Table S3.1 for cluster-corrected values. L.1/R.1 = lateral view; L.2/R.2 = medial view; L.3/R.3 = ventral view; L.4/R.4 = dorsal view.

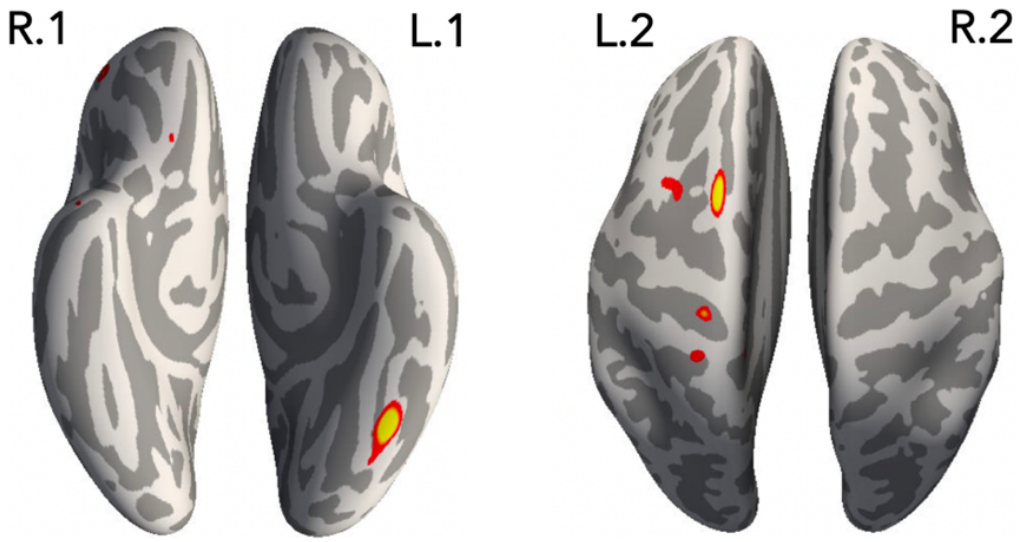


Fig. S3.3 ***Whole-brain significance map of sex effects on cortical thickness across all participants.*** Results are depicted on the inflated surfaces with an uncorrected vertex-wise threshold $p < 0.001$. This is a *t*-test with Males < Females being positive (red/yellow). Refer to Table S3.2 for cluster-corrected values. L.1/R.1 = lateral view; L.2/R.2 = medial view; L.1/R.1 = ventral view; L.2/R.2 = dorsal view.

Table S3.1 ***Summary of significant clusters for the change in (A) cortical thickness and (B) grey matter volume with age across all participants***.

Cluster (peak)	Cluster-wise *p*-value	Size	Centroid MNI305 Coordinates		
			X	Y	Z
(A) Cortical thickness					
Positive correlations					
L temporal pole	0.0431	169	-34	05	-31
R medial orbitofrontal	0.0286	186	06	19	-17
R superior temporal	0.0476	164	41	04	-25
Negative correlations					
L isthmus cingulate	0.0201	197	-05	-45	30
L fusiform	0.0002	452	-30	-64	-06
L cuneus	0.0002	486	-12	-75	19
R paracentral	0.0084	227	09	-33	52
(B) Grey matter volume					
L cuneus (negative correlation)	0.0008	362	-10	-68	10

Note: The size in mm^2 and centroid MNI305 coordinates are reported for significant clusters ($p < 0.05$, corrected). The coordinate decimals and cluster sizes were rounded to integer values. The extent of each cluster is provided in voxels. Labels of peak location provided by FreeSurfer.

Table S3.2 ***Summary of significant clusters in the Females > Males comparison for cortical thickness across all participants***.

Cluster (peak)	Cluster-wise *p*-value	Size	Centroid MNI305 Coordinates		
			X	Y	Z
Cortical thickness					
L fusiform	0.0074	234	-42	-59	-20

Note: The size in mm^2 and centroid MNI305 coordinates are reported for significant clusters ($p < 0.05$, corrected). The coordinate decimals and cluster sizes were rounded to integer values. The extent of each cluster is provided in voxels. Labels of peak location provided by FreeSurfer.

Chapter 5

Table S5.1 Demographic and behavioural data for the TD and DLD groups.

Demographics	**TD (*n* = 71)**	**DLD (*n* = 46)**	***t*(115)**	**Mean difference (95% CI)**	**Cohen's *d***
Mean age in years	12.6 ± 0.2	12.7 ± 0.3	-0.13	---	---
Age range (y;m)	10;0-15;7	10:0-15;11	---	---	---
			χ^2(1, *N* = 117)	**χ^2(95% CI)**	**Φ**
Sex (M:F)	40:31	32:14	1.54	---	---
Handedness (R:L)	61:10	38:8	0.05	---	---
Language(s) spoken at home other than English (%Yes)	13.84% (n = 65)	4.34%	1.76	---	---
			χ^2(1, *N* = 117)	**χ^2(95% CI)**	**Cliff's Δ**
Median maternal education level (range)	3 (1-5) (n = 66)	2 (1-5)	4.44*	1.17 (1.00, 1.37)	0.53
Neuropsychological test battery				**Mean difference (95% CI)**	**Cohen's *d***
Language					
ROWPVT-4	128.7 ± 1.9	99.1 ± 2.3	10.06***	-29.62 (-35.40, -23.85)	-1.90
EOWPVT-4	118.2 ± 1.8	91.1 ± 1.7	11.00***	-27.12 (-31.96, -22.29)	-2.03
TROG-2	105.5 ± 1	81.3 ± 2	11.02***	-24.16 (-28.46, -19.86)	-2.18
CELF-IV	11.8 ± 0.3	4.7 ± 0.4	15.29***	-7.11 (-8.03, -6.20)	-2.95
Recalling Sentences[1]					
ERRNI					
Initial Recall	100.4 ± 1.5	85.7 ± 1.8	6.30***	-14.75 (-19.33, -10.16)	-1.19
Delayed Recall	104.6 ± 1.3	86.6 ± 1.8	8.04***	-18.05 (-22.44, -13.65)	-1.54
Comprehension	107 ± 1.6	94.3 ± 2.2	4.71***	-12.70 (-17.98, -7.41)	-0.90
NNWR (max. 30)[2]	26.3 ± 0.3	17.4 ± 0.8	10.53***	-8.91 (-10.57, -7.25)	-2.14
Memory					
CMS					
Digit Span Forwards[1]	11.6 ± 0.3	5.5 ± 0.4	11.18***	-6.11 (-7.18, -5.04)	-2.15
Digit Span Backwards[1]	11.8 ± 0.3	6.9 ± 0.5	8.87***	-4.93 (-6.02, -3.84)	-1.71

Word List Immediate Recall[1]	10.2 ± 0.4	6.1 ± 0.4	7.13***	-4.05 (-5.17, -2.94)	-1.34
Word List Delayed Recall[1]	10.3 ± 0.4	7.3 ± 0.5	4.75***	-2.96 (-4.19, -1.74)	-0.90
Word List Delayed Recognition[1]	8.6 ± 0.4	6.7 ± 0.5	2.88**	-1.92 (-3.22, -0.61)	-0.55
Reading					
TOWRE-2					
Sight Word Efficiency	106 ± 1.3	81.8 ± 2	10.14***	-24.20 (-28.88, -19.52)	-1.95
Phonemic Decoding Efficiency	111.6 ± 1.6	80.8 ± 2.4	10.89***	-30.74 (-36.27, -25.21)	-2.11
Nonverbal reasoning					
WISC-IV					
Composite score	12.3 ± 0.2	8.6 ± 0.4	8.05***	-3.70 (-4.60, -2.80)	-1.58
Block Design[1]	13.3 ± 0.2	9.8 ± 0.4	6.90***	-3.48 (-4.47, -2.49)	-1.36
Matrix Reasoning[1]	11.3 ± 0.3	7.3 ± 0.5	6.76***	-3.69 (-5.11, -2.81)	-1.30
Coding[1]	9.6 ± 0.3 (n = 71)	5.7 ± 0.4	8.47***	-3.95 (-4.86, -3.03)	-1.60
Motor					
NEPSY					
Oromotor Sequencing (max. 70)[2]	60.5 ± 0.9	42.1 ± 1.6	10.01***	-18.43 (-22.04, -14.83)	-1.97
Purdue Pegboard					
Dominant hand (*z*)	-0.4 ± 0.1	-1.5 ± 0.2	5.68***	-1.12 (-1.50, -0.73)	-1.10
Nondominant hand (*z*)	-0.1 ± 0.1	-1.1 ± 0.2	5.00***	-1.03 (-1.43, -0.62)	-0.97
Children's Communication Checklist-2					
GCC[3]	84.7 ± 1.7	36.8 ± 3.1 (n = 45)	13.53***	-47.88 (-54.81, -40.94)	-2.68

Note: Values are presented as means ± standard error of the mean (SEM) unless otherwise indicated. Group comparisons for sex, handedness, and language background questionnaire responses were conducted using a chi-square test. Maternal education level was analysed with the Kruskal-Wallis test and the medians (with ranges) are provided for each group (ranked 1-5; 3 = degree-level education). All other variables were compared across groups using independent samples t-tests ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$). Effect sizes for significant effects are reported in the last column. Scores are reported as follows: No superscript: Standard scores ($M = 100$, $SD = 15$); [1] Scaled scores ($M = 10$, $SD = 3$); [2] Raw scores; [3] Scaled scores ($M = 80$) based on the sum of the eight subtests. *Abbreviations*: M – male; F – female; R – right; L – left.

***Table S5.2 ROI analysis of neural activity during pseudoword learning in the caudate nucleus and putamen*.**

Predictor	Caudate nucleus			Putamen		
	β	SE	*p*-value	β	SE	*p*-value
Repetition (1st)						
2nd	0.030	0.02	0.121	0.008	0.02	0.664
3rd	-0.007	0.02	0.753	-0.020	0.02	0.154
4th	-0.010	0.02	0.525	-0.020	0.02	0.223
Group (TD)						
DLD	-0.003	0.03	0.915	0.030	0.03	0.339
Hemisphere (left)						
Right	0.010	0.01	0.302	0.010	0.009	0.132
Repetition trial × Group						
2nd × Group	-0.050	0.03	0.093	-0.030	0.03	0.235
3rd × Group	-0.030	0.03	0.336	-0.020	0.03	0.489
4th × Group	-0.004	0.03	0.899	-0.009	0.03	0.764
Repetition trial × Hemi						
2nd × Hemisphere	-0.004	0.01	0.742	0.001	0.01	0.900
3rd × Hemisphere	0.010	0.01	0.435	0.010	0.01	0.306
4th × Hemisphere	-0.010	0.01	0.296	-0.002	0.01	0.830
Group × Hemisphere	0.008	0.01	0.609	-0.020	0.01	0.192
2nd × Group × Hemisphere	0.001	0.02	0.965	0.009	0.02	0.665
3rd × Group × Hemisphere	-0.010	0.02	0.571	0.002	0.02	0.905
4th × Group × Hemisphere	0.010	0.02	0.539	0.020	0.02	0.258

Statistical results from linear mixed-effects models predicting neural activity for pseudoword learning based on repetition trial (1st, 2nd, 3rd, 4th), group (TD, DLD), hemisphere (left, right), and their interactions. Random intercepts were included for repetition trials and participants. The 1st trial, TD group, and left hemisphere were set as reference categories.

Table S5.3 ROI analysis of neural activity during pseudoword learning in the supplementary motor area.

	Supplementary motor area		
Predictor	**β**	**SE**	***p*-value**
Repetition (1st)			
2nd	-0.02	0.01	0.225
3rd	-0.03	0.01	0.043
4th	-0.02	0.01	0.248
Group (TD)			
DLD	0.020	0.03	0.514
Repetition trial × Group			
2nd × Group	0.005	0.03	0.855
3rd × Group	0.005	0.03	0.861
4th × Group	0.008	0.03	0.787

Statistical results from linear mixed-effects models predicting neural activity for pseudoword learning based on repetition trial (1st, 2nd, 3rd, 4th), group (TD, DLD), hemisphere (left, right), and their interactions. Random intercepts were included for repetition trials and participants. The 1st trial, TD group, and left hemisphere were set as reference categories.

Appendix A

List of 32 pseudowords used in the fMRI study paradigm. The stimuli were created by the Wuggy Pseudoword Generator (Keuleers & Brysbaert, 2010). Half of the pseudowords were two syllables long and the other half contained four syllables. Each pseudoword was paired with the image of an alien during the in-scanner repetition task to assess children's learning of form-referent associations. Pseudowords with within-syllable-boundary consonant clusters are marked in bold.

Non-repeated (NR)		**Repeated (R)**	
2-syllable	**4-syllable**	**2-syllable**	**4-syllable**
Sa**mp**er	Belo**sp**ofic	Leppy	Barmicory
Pargo	Mittedatic	Ra**nt**op	**Fr**ipacerus
Ruker	Ba**ns**enica	Ba**np**et	Penicova
Demell	Matacolo	Meffon	Ri**sc**u**pl**io
Fe**nt**er	Jaterbadon	Do**mbr**in	Tosicotter
Henem	I**mp**igatol	**Tr**agle	Bodissary
Po**yr**on	Vortenia	Zellop	Sycarery
Ho**mb**id	Fipotelar	Boosin	Cadesogi**st**