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“Investigating cerebral laterality for writing in healthy adults and children with dyslexia and dysgraphia with the use of functional transcranial Doppler ultrasound (fTCD)”

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Η έγκριση διδακτορικής διατριβής από το Παιδαγωγικό Τμήμα Δημοτικής Εκπαίδευσης του ΕΚΠΑ δεν υποδηλώνει αποδοχή των απόψεων του συγγραφέα εκ μέρους του Τμήματος και της επιτροπής εξέτασης.

Η συγγραφέας της παρούσας διδακτορικής διατριβής βεβαιώνει ότι:

α) κανένα τμήμα της δεν έχει χρησιμοποιηθεί για την σύνταξη και αξιολόγηση άλλης εργασίας ή πτυχίου της συγγραφέως,

β) αποτελεί πνευματικό προϊόν της συγγραφέα και κανένα τμήμα του ανά χείρας διατριβής δεν συνιστά αποτέλεσμα αναπαραγωγής (μερικώς ή ολικώς) κειμένου τρίτου προσώπου και

γ) έχει γίνει η κατάλληλη αναφορά στην εργασία τρίτων, όπου κάτι τέτοιο ήταν απαραίτητο, σύμφωνα με τους προβλεπόμενους κανόνες της ακαδημαϊκής δεοντολογίας.

Abstract

This thesis delves into the cerebral lateralization for *written* language, a domain overshadowed by the extensive research on *oral* language lateralization. While it is well-established that the left hemisphere is dominant for oral language in the majority of individuals, investigations into written language lateralization, particularly in left-handers, remain sparse. In parallel, individuals with conditions that are associated with writing difficulties, such as specific language disorder, and, of particular importance for this thesis, dyslexia, remain neglected in terms of studying their lateralization for written language. It has been shown that dyslexia is associated with a more symmetrical or right lateralized pattern for reading and oral language, which can be reorganized following an appropriate educational intervention. Writing involves both language and motor components, jointly contributing to cerebral activation, yet prior research has not effectively disentangled these elements.

The three studies in this thesis built upon one another and aimed to disentangle the language and motor components of writing lateralization by comparing cerebral activation during (i) written word generation and (ii) letter copying. Cerebral lateralization was measured using functional transcranial Doppler (fTCD) ultrasound and the strength of the evidence was assessed using the Bayesian approach. For the first study, an adult sample balanced for handedness was recruited (n = 60), and preregistered hypotheses anticipated (a) weaker cerebral lateralization for the linguistic component in left-handers compared to right-handers, and (b) a lack of correlation between oral language and the linguistic component of written language in terms of cerebral lateralization. However, the findings did not provide compelling evidence for either hypothesis, underscoring the intricate processes involved in both written and oral language. For the second study, 7- to 9-year-old children at risk for dyslexia (n = 12) were compared with age-matched typically developing peers (n = 24) in terms of the lateralization for the linguistic component of written language and it was hypothesized that the linguistic component of written language would be less left-lateralized in children at risk for dyslexia

than in controls, but there was inadequate evidence to support this hypothesis. Additionally, the study explored correlations between writing competence, handwriting quality, orthography, and cerebral lateralization, revealing a lack of evidence for such correlations. For the third study, which was a pilot study (n = 5 children at risk who were administered a phonological intervention compared to n = 5 age-matched, gender-matched, and intelligence-matched peers), the aim was to explore the impact of a phonological intervention on the cerebral lateralization of the linguistic component of written language in children at risk for dyslexia. A pragmatic intervention was also tested for feasibility. Although the phonological intervention was hypothesized to induce a leftward shift in cerebral lateralization, the findings did not decisively support or refute this hypothesis.

Collectively, these findings suggest that, despite a predominant left lateralization for written language among most participants, factors such as handedness, age, and proficiency in reading and writing moderate this pattern. Furthermore, this thesis confirmed that fTCD lends itself to measure cerebral lateralization in adults and also extended this practice to children as young as 7 years old, while emphasizing the difficulty in devising a control task that effectively isolates the motor component of writing. Overall, the outcomes derived from this series of studies carry potential implications for the importance of including written language in language lateralization studies when assessing the typical brain, as well as in the context of special learning difficulties, such as dyslexia. Finally, the present thesis underscores the impact of educational interventions on reading performance and how this is reflected in the cerebral lateralization for written language.

Περίληψη

Αυτή η διατριβή ασχολείται με την εγκεφαλική πλευρίωση της γραπτής γλώσσας, έναν τομέα που επισκιάστηκε από την εκτεταμένη έρευνα για την πλευρίωση της προφορικής γλώσσας. Ενώ έχει καταστεί σαφές ότι το αριστερό ημισφαίριο κυριαρχεί για την προφορική γλώσσα στην πλειονότητα των ατόμων, η γραπτή γλώσσα, ιδιαίτερα στους αριστερόχειρες, παραμένει υπομελετημένη. Παράλληλα, περιπτώσεις που σχετίζονται με δυσκολίες γραφής, όπως ειδικές γλωσσικές διαταραχές και, με ιδιαίτερη σημασία για αυτή τη διατριβή, η δυσλεξία, δεν έχουν εξεταστεί από την άποψη της πλευρίωσης για γραπτή γλώσσα. Έχει δειχθεί ότι η δυσλεξία συνδέεται με ένα πιο συμμετρικό ή δεξιόπλευρο πρότυπο πλευρίωσης για την ανάγνωση και την προφορική γλώσσα, το οποίο μπορεί να αναδιοργανωθεί μετά από ~~μια~~ κατάλληλη εκπαιδευτική παρέμβαση. Η γραφή αποτελείται τόσο από ~~ένα~~ γλωσσικές όσο κι από ~~ένα~~ κινητικές συνιστώσες, οι οποίες συμβάλλουν από κοινού στην εγκεφαλική ενεργοποίηση, ωστόσο οι πρότερες έρευνες δεν έχουν κατορθώσει να διαχωρίσουν αυτές τις συνιστώσες όσον αφορά στην πλευρίωση.

Οι τρεις μελέτες που περιλαμβάνονται στην παρούσα διατριβή δομήθηκαν η μία πάνω στην άλλη και αποσκοπούσαν στην απομόνωση της γλωσσικής και της κινητικής συνιστώσας της γραφής στο πλαίσιο της πλευρίωσης, συγκρίνοντας την εγκεφαλική ενεργοποίηση κατά τη διάρκεια (i) γραπτής παραγωγής λέξεων και (ii) αντιγραφής γραμμάτων. Η εγκεφαλική πλευρίωση μετρήθηκε χρησιμοποιώντας λειτουργικό διακρανιακό υπέρηχο Doppler (FTCD). Για την πρώτη μελέτη, στρατολογήθηκε ένα δείγμα ενηλίκων ισοκατανεμημένο ως προς την κυριοχειρία (n = 60) και οι προκαταχωρημένες υποθέσεις υπέθεταν (α) ασθενέστερη εγκεφαλική πλευρίωση της γλωσσικής συνιστώσας της γραφής στους αριστερόχειρες σε σύγκριση με τους δεξιόχειρες και (β) την έλλειψη συσχέτισης μεταξύ της προφορικής γλώσσας και της γλωσσικής συνιστώσας της γραπτής γλώσσας όσον αφορά στην εγκεφαλική πλευρίωση. Ωστόσο, τα ευρήματα δεν παρείχαν ισχυρές ενδείξεις για καμία από τις ανωτέρω υποθέσεις, υπογραμμίζοντας τις περίπλοκες διαδικασίες που εμπλέκονται τόσο στη γραπτή όσο

και στην προφορική γλώσσα. Για τη δεύτερη μελέτη, παιδιά 7 έως και 9 ετών με κίνδυνο εμφάνισης δυσλεξίας (n = 12) συγκρίθηκαν με τυπικά αναπτυσσόμενους συνομηλίκους (n = 24) όσον αφορά στην πλευρίωση της γλωσσικής συνιστώσας της γραπτής γλώσσας. Διαμορφώθηκε η υπόθεση ότι η γλωσσική συνιστώσα της γραπτής γλώσσας θα είναι λιγότερο αριστερά πλευριωμένη σε παιδιά με κίνδυνο εμφάνισης δυσλεξίας από ό,τι στο δείγμα ελέγχου, αλλά δεν υπήρχαν αρκετές ενδείξεις για να υποστηρίξουν αυτή την υπόθεση. Επιπλέον, η μελέτη διερεύνησε συσχετισμούς μεταξύ της ικανότητας γραφής, δηλαδή της ποιότητας του γραπτού λόγου ή της ορθογραφίας, και της εγκεφαλικής πλευρίωσης, αλλά δεν προέκυψαν ισχυρές συσχετίσεις. Τέλος, διενεργήθηκε πιλοτική μελέτη (5 παιδιά με κίνδυνο εμφάνισης δυσλεξίας στα οποία χορηγήθηκε φωνολογική παρέμβαση σε σύγκριση με παιδιά τυπικής ανάπτυξης αντιστοιχισμένα για την ηλικία, το φύλο, και το νοητικό δυναμικό), η οποία αποσκοπούσε στη διερεύνηση της επίδρασης μιας φωνολογικής παρέμβασης στην εγκεφαλική πλευρίωση της γλωσσικής συνιστώσας της γραπτής γλώσσας σε παιδιά με κίνδυνο εμφάνισης δυσλεξίας. Μια παρέμβαση πραγματολογίας δοκιμάστηκε επίσης για το ενδεχόμενο να εφαρμοστεί μελλοντικά. Παρόλο που είχε διαμορφωθεί η υπόθεση ότι η φωνολογική παρέμβαση θα επάγει μια μετατόπιση προς τα αριστερά στην εγκεφαλική πλευρίωση της γλωσσικής συνιστώσας του γραπτού λόγου, τα ευρήματα δεν υποστήριξαν επαρκώς ή αντέκρουσαν αυτήν την υπόθεση.

Στο σύνολό τους τα παρόντα ευρήματα είναι ενδεικτικά μίας αριστερής πλευρίωσης για τη γραπτή γλώσσα για την πλειονότητα των συμμετεχόντων, με την κυριοχειρία, την ηλικία, και τις αναγνωστικές και γραφικές ικανότητες να περιπλέκουν τη διαμόρφωση ενός εμφανούς προτύπου πλευρίωσης για το γραπτό λόγο. Επίσης, αυτή η διατριβή υπογραμμίζει τη δυσκολία ανάπτυξης μιας συνθήκης ελέγχου που να απομονώνει αμιγώς την κινητική συνιστώσα της γραφής. Εν κατακλείδι, τα αποτελέσματα που προκύπτουν από αυτή τη σειρά μελετών αναδεικνύουν τη σημασία της συμπερίληψης της γραφής στις μελέτες γλωσσικής πλευρίωσης όσον αφορά στη μελέτη του τυπικού εγκεφάλου, όπως και σε ειδικές μαθησιακές δυσκολίες όπως η δυσλεξία και υπογραμμίζουν τον αντίκτυπο μιας εκπαιδευτικής παρέμβασης στην εγκεφαλική πλευρίωση για τη γραπτή γλώσσα.

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Tickling the relationship of brain and behavior has been a dream for many years. So, here I am… Chasing that dream… It is, hence, my duty and my pleasure to thank the people who have helped throughout this hunt.

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Publications stemming from the PhD work

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Papadopoulou, A. K., Vlachos, F., & Papadatou-Pastou, M. (2022). Cerebral lateralization of language in children at risk for dyslexia: A review of neuroscientific evidence. Dialogues in Clinical Neuroscience & Mental Health, 5(2), 89-97. https://doi.org/10.26386/obrela.v5i2.228

Participation in conferences during the elaboration of this PhD

4th Brain and Mind Congress (15-17/12/2023)	"Risk for dyslexia and the lateralization for written language: Their relationship and the effect of a phonological intervention" (e-poster)
30th Meeting of the Hellenic Society for Neuroscience (24-26/11/2023)	"Investigating how written language is lateralized in children at risk for dyslexia and the effects of a phonological intervention on lateralization" (poster)
3rd Scientific Conference of the Hellenic Society of Developmental Pedetricians/12th Panhellenic Congress of Developmental and Behavioral Pediatrics (18-19/11/2023)	"Επίδραση φωνολογικής παρέμβασης στην εγκεφαλική πλευρίωση του γραπτού λόγου σε παιδιά με κίνδυνο εμφάνισης δυσλεξίας: Μελέτη με τη χρήση λειτουργικού διακρανιακού υπερήχου Doppler" (e-poster)
8th Scientific Meeting of the Federation of the European Societies of Neuropsychology/2nd Panhellenic Conference on Neuropsychology (27-29/09/2023)	"Exploring the cerebral laterality of writing and its relationship to handedness: A functional transcranial Doppler ultrasound study" (e-poster)
27th JURE 2023 Pre-conference (20-21/08/2023)	"Cerebral lateralization for writing in children at risk for dyslexia using fTCD ultrasonography: A Registered Report" (oral presentation)

18th Panhellenic Conference of Psychological Research (05-09/10/2022)	“Καταχωρημένες αναφορές (Registered Reports): Καταπολεμώντας τη μεροληψία στις επιστημονικές δημοσιεύσεις” (oral presentation)
8th North Sea Laterality Meeting (24-27/08/2022)	“Exploring the cerebral lateralization of writing in relationship to handedness and to risk for dyslexia using functional transcranial Doppler ultrasonography” (poster)
2nd Brain and Mind Congress (17-18/12/2021)	“Cerebral lateralization of written language in children at risk for dyslexia and the effects of a phonological intervention” (e-poster)
Society for the Improvement of Psychological Science (SIPS) Meeting 2021 (23-25/06/2021)	*“Lateralization shift: Can a phonological intervention shift the pattern of cerebral lateralization of written language in children at risk for dyslexia?” (e-poster)*

CONTENTS

LIST OF ABBREVIATIONS

ADHD: Attention-deficit/Hyperactivity Disorder

ASEBA: Achenbach's system of empirical based assessment

BF: Bayes Factor

CBCL: Children behaviour checklist

CPM: Coloured progressive matrices

CrI: Credibility interval

DSM-V: Diagnostic and statistical manual of mental disorders (5th Edition)

EHI: Edinburgh's handedness inventory

ERP: Event-related potentials

fMRI: Functional magnetic resonance imaging

fTCD: Functional transcranial Doppler ultrasonography

LH: Left hand

LI: Lateralization index

Max.: Maximum

MCA: Medial cerebral arteries

MEG: Magnetoencephalography

Min.: Minimum

MRI: Magnetic resonance imaging

PET: Positron emission tomography

POI: Period of interest

QHPT: Quantification of hand preference task

RH: Right hand

RSAT: Reading skills assessment test

SBF: Sequential Bayesian Factor

SD: Standard deviation

SLD: Specific language difficulties

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1 GENERAL INTRODUCTION

1.1 LATERALIZATION

"The universe is asymmetric and I am persuaded that life, as it is known to us, is a direct result of the asymmetry of the universe or of its indirect consequences"

(Louis Pasteur, 1822-1895).

There are multiple examples of asymmetry in nature, from a microscopic to an organismic level. Originated from the fundamental principles of chemistry and cellular biology (Opitz & Utkus, 2001; Spirito et al., 2024) and an evolutionary urge for left and right organ-intrinsic morphogenesis (Inaki et al., 2016; McDowell et al., 2016; Okumura et al., 2018), one of the most important instances of asymmetry for humankind (Dai et al., 2024; Francks, 2015; Gee et al., 2011; Gerrits et al., 2020; Gotts et al., 2013; Hugdahl, 2000), even though it is also apparent in other species (Davison et al., 2016; Gainotti, 2021; Inaki et al., 2016; Lebreton et al., 2018; McDowell et al., 2016; Pennisi, 2023), is hemispheric asymmetry. Hemispheric asymmetry or dominance, also known as cerebral laterality or lateralization, describes the differential function of the left and the right brain hemispheres (Corballis, 2014; Ocklenburg et al., 2017) drawn by differences in gene expression (Bishop & Bates, 2020; Kong et al., 2018; Ocklenburg et al., 2017), volume (Altarelli et al., 2014; Saygin et al., 2013), structure (Bishop & Bates, 2020; Ocklenburg et al., 2017), and connectivity (Bouhali et al., 2014; Caevenberghs & Leemans, 2014; Nielsen et al., 2013).

Employing predominantly one hemisphere for a function bears some advantages. From an evolutionary perspective, while the cortex is expanding phylogenetically, cerebral lateralization secures a more efficient brain activity and response with the minimum wiring costs (Crow et al., 1989). Neural capacity is increased by accelerating neuronal processing, whilst the overall energy consumption is decreased by reserving neural resources, disconnecting the two hemispheres, segregating networks, and restricting blood flow changes

(Joliot et al., 2016; Liu et al., 2009; McAvoy et al., 2016; Rogers, 2014; Vallortigara, 2006; Wu et al., 2022). An additional benefit of hemispheric asymmetry is a better social coordination at a population level (e.g., flying in swarms; Corballis, 2009; Ghirlanda & Vallortigara, 2004; Ocklenburg et al., 2017; Serrien & O'Regan, 2023). This leads to a lateralization pattern that is characteristic for each function of the individual.

Asymmetric development of brain hemispheres begins in embryogenesis, 5-8 weeks post-partum (de Kovel et al., 2017, 2019; Hepper et al., 1991), indicating that hemispheric asymmetry is in part genetically-determined (Güntürkün & Ocklenburg, 2017; Ocklenburg et al., 2013; Schmitz et al., 2018). In twin studies, heritability of asymmetries in brain structure reaches 80% (Hervé et al., 2013). In fact, mutations of a single gene might lead to the reversed left-right placement of the visceral organs of an individual, a monogenic disease called situs inversus totalis (Eitler et al., 2022; Fliegauf et al., 2007; Peeters & Devriendt, 2006). Taken together, these findings show that the direction of the hemispheric asymmetry is a trait-level characteristic of individuals (Gotts et al., 2013; Joliot et al., 2016; Liu et al., 2009; McAvoy et al., 2016; Wu et al., 2022), though it is prone to neuroplastic modifications by environmental factors (Renteria, 2012).

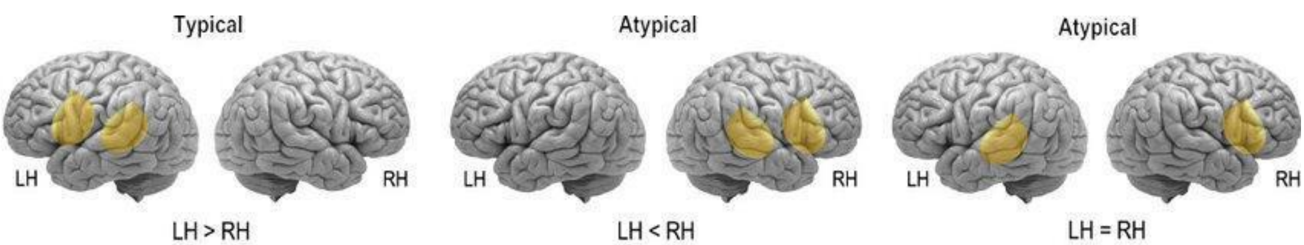
The observation of the French physicist, anatomist, and anthropologist Paul Broca in the 1860s that the common symptoms of patients with a left-hemisphere lesion were loss of speech and hemiplegia of the right side of the body was the first piece of evidence for the two most prominent manifestations of cerebral lateralization: language lateralization and handedness, the latter defined as the direction and/or the degree of the preference in using one hand for unimanual tasks or the relative skillfulness of hands (Brown et al., 2006; Kershner, 2020). Following this observation, language was hypothesized to be left lateralized for right-handers, a concept that has been established for the majority of right-handers across different studies from then on (Bartha et al., 2003; Corballis et al., 2012; Knecht et al., 2000; Main & Carey, 2014; Tzourio-Mazoyer et al., 2010). In fact, a postulation that has been derived from

Broca's findings was that language activation of left-handers mirrors that of right-handers ("Broca rule"), even though Broca did not explicitly claim this (Harris, 1993). Since then, not only neuroimaging studies, but also data-driven algorithms that classify the task-specific activation of brain regions, have established that oral language production is left-lateralized for the majority of individuals, not just right-handers (Bishop et al., 2021; Knecht et al., 1998; Labache et al., 2019, 2020, 2023; Nielsen et al., 2013; Price, 2012; Roger et al., 2022).

As distinct from typical lateralization, the term "atypical lateralization" is used to describe the less common asymmetry patterns, meaning a more rightward lateralization or a bilateral activation of brain hemispheres. For oral language, atypical lateralization, (Bradshaw et al., 2020; also see Figure 1) is frequent in cases of neurodevelopmental disorders, such as autism spectrum disorder (Fletcher et al., 2010; Herbert et al., 2002; Kleinhans et al., 2008; Lange et al., 2010), or specific learning disabilities, such as dyslexia (Beelen et al., 2019; Kershner, 2020; Richards et al., 2005; Robichon et al., 2000; Rumsey et al., 1992; van Setten et al., 2019; Vanderauwera et al., 2018; Zhao et al., 2016). However, for most individuals, atypical lateralization for oral language does not coincide with performance difficulties, but it seems to be correlated with atypical handedness, in other words left-handedness, mixed-handedness, or ambidexterity (Cai et al., 2013; Knecht et al., 2001; Labache et al., 2020, 2022; Nielsen et al., 2013; Szaflarski et al., 2002).

Figure 1

Typical and atypical patterns of language lateralization (Adapted from Baciu & Perrone-Bertolotti, 2015)



This evidence comes from studies assessing oral language production, while other modalities of language, such as writing, remain significantly understudied in terms of cerebral lateralization. Hence, the aim of the present thesis was to investigate the pattern of cerebral lateralization for writing across different handedness groups, but also in relationship with the risk for dyslexia, a specific learning disability that affects writing in addition to reading.

1.2 WRITING

"I write to find out what I am talking about"

(Edward Albee, 1928-2016)

There are at least three language forms; oral, written, and sign language. Clark (1997) characterized the relationship between oral language and writing as a virtual loop in which the two interact and modify each other. Infants initiate communication with their caregivers through gestures and unintelligible sounds. As they grow, they develop their oral language skills and they mainly express themselves with speech. During their early school years, they rely on oral language to learn how to read and write (Shanahan et al., 2006) and, consequently, educational achievement is related to students' performance in oral language tasks (Bishop & Snowling, 2004). Handwriting starts as shape and line drawing at the age of two and it develops into fine letter scribing (Dinehart, 2015; Feder & Majnemer, 2007). As people become literate, expressly capable of reading and writing, writing gradually becomes equally important to oral language for communication. Taking into account the results of a recent survey showing that 86% of the world's population are literate (Roser & Ortiz-Ospina, 2016), written language is part of many people's lives.

Written language is widely used in school and higher education and in a plethora of professions (Walsh et al., 2010). Moreover, a principal leverage of written over oral language production is that when one uses written language, they have the time to collect, preserve, and conduct information across different time periods, locations, and cultures (Graham et al., 2012). It is noteworthy that many people believe that they express more adequately by writing than by speech. Graham et al. (2012, p. 4) quoted that "people use writing to create imagined worlds, tell stories, share information, explore who they are, combat loneliness, and chronicle their experiences".

Writing has been termed the "pale imitation" of oral language (Klimova, 2012). Nevertheless, writing is much more complex than oral language. It comprises of four constituents: linguistic word generation (covert text production in one's mind), working memory (recollection of the orthography and organization of the text), which are also components of oral language, and additionally, executive functions (corresponding to converting text to script), and transcription (rough and fine manual movements; Berninger, 2000; Berninger & Amtmann, 2003; Berninger, 1998). The latter constitutes the motor component of writing and is encountered exclusively in written language. In fact, there is evidence that as students progress in their education, they ascribe more salience on semantics and orthography rules for transcription compared to oral language generation (Dockrell & Connely, 2009). Therefore, it is important to disentangle the components of writing and assess them separately. Having said that, throughout this project I aimed to dissociate the motor and the linguistic component of written language and examine the cerebral lateralization for the latter.

1.3 CEREBRAL LATERALIZATION FOR LANGUAGE

"Language helps develop life as surely as it reflects life. It is the most important part of our human condition"

(Yolen, 1981)

For decades since Broca's discovery, determining language lateralization has been considered to be critical, especially pre-operatively, to avoid impairing the patient's language ability during surgery and to secure a good post-operative quality of life (Chen, 2023; Petrella et al., 2006; Ruff et al., 2008). Even though direction and degree of language lateralization is specific for each individual (Habib et al., 1995), our species shows a population-level asymmetry for oral language functions. For most people, the left hemisphere is dominant for oral language production (Gazzaniga, 2000; Keller & Kell, 2016; Long et al., 2016), auditory perception (Hahn, 1987), and language comprehension (Dehaene-Lambertz et al., 2002; Schlaug et al., 1995, Steinmetz, 1996). More specifically, the regions of the left hemisphere that are more activated during oral language tasks are the inferior frontal gyrus, temporoparietal and temporooccipital regions, and the hippocampus together with the adjacent parahippocampal area (Aylward et al., 2003; Boets et al., 2013; Brambati et al., 2004; Brown et al., 2001; Dehaene et al., 2015; Démonet et al., 2004; Eckert, 2004; Eden & Moats, 2002; Eden et al., 2004; Franceschini et al., 2017; Gabrieli, 2009; Gebauer et al., 2012; Goswami, 2006, 2015; Hoeft et al., 2006, 2007; Holland et al., 2001, 2007; Horwitz & Braun, 2004; Johansson, 2006). The more anterior regions of this hub have been associated with language production, while the more posterior ones with language perception and comprehension (Ardila et al., 2016; DeWitt & Rauschecker, 2012; Schlaug et al., 1995; Steinmetz, 1996). Noteworthy, some manifestations of speech are predominantly associated with the activation of the right hemisphere. Instances of right-lateralized functions of speech are non-propositional language (e.g., counting, listing the days of week, complementing well-known phrases, repeating) and automatic responses (Blank et al., 2002; Chang & Lambon Ralph, 2020; Code, 1997; Mazoyer et al., 2014).

While the activation of speech muscles and the generation of words associated with limbs and movement, as well as abstract words, may lead to minimal motion-related activation in oral language (Carota et al., 2012; Pulvermüller, 2018; Zhang et al., 2018), the complexity of written language goes beyond, encompassing both a linguistic and a motor component that is not minimal in this case (Berninger et al., 2015; James & Atwood, 2009; James & Engelhardt, 2012; James & Gauthier, 2006; Longcamp et al., 2008). When it comes to the linguistic component of written language, this is related to the activation of the same areas of the left hemisphere that subserve oral language generation, in particular frontal, temporoparietal, and temporooccipital regions (Berninger, 2009; Haaland et al., 2004; Joseph et al., 2003). The remaining areas that are activated during writing are associated with different aspects of the motor component of written language. Specifically, the activation of the primary motor cortex is related to the hand movement required for drawing shapes or letters, while Exner's area, a region of the left ventral premotor cortex, is considered critical for written word generation specifically (Exner, 1881; James & Gauthier, 2006; Longcamp et al., 2003, 2014). Motor planning is controlled by the parietal cortex and the bilateral fusiform gyrus (Gauthier et al., 2000; James & Gauthier, 2006; Longcamp et al., 2003, 2011; Vinci-Bouher et al., 2019). Taken together, these observations converge to a leftward lateralization for written language, similarly to oral language. However, with nine out of 10 individuals being right-handed (Papadatou-Pastou et al., 2020; Pearson & Hodgetts, 2020), the vast majority of studies on the lateralization for written language have sampled only right-handed participants and, thus, these findings might not apply in other handedness groups.

1.4 HANDEDNESS

"*The hand is the tool of tools*"

Aristotle (384-322 BC)

Most of us preferentially choose one hand over the other for simple or for more demanding activities throughout the day. This preference is reflected both in trained activities, such as drawing and writing, but also in the spontaneous choice of one hand (e.g., when someone throws a ball towards us). For activities that can be practiced, one hand might turn out to be more skillful in comparison to the other. This characteristic is not encountered in our species exclusively. Asymmetrical patterns of limb preference are evident across the animal kingdom in invertebrates and vertebrates, bipeds and quadrupeds, humans and non-human primates (Boulinguez-Ambroise et al., 2022; Cui et al., 2024; Hopkins et al., 2013; Manns et al., 2021; Ocklenburg et al., 2019). American lobsters randomly develop one claw to be stronger than the other, while for most of the species of fiddler crabs a dominant left claw is considered a disadvantage in fights (Backwell et al., 2007; Govind, 1984, 1989). Non-human primates tend to show a bias towards using the one limb over the other, especially when they stand in a bipedal posture instead of a quadrupedal, for several activities, including cradling, gestures, grasping, manual communication, predation, and tool use (Blois-Heulin et al., 2006, 2007; Boulinguez-Ambroise et al., 2020, 2022; Giljov et al., 2012; Hopkins et al., 2013; Manning et al., 1994). In fact, the more positive emotional valence primates attribute to what they grasp, inanimate object or a conspecific, the more they prefer their right limb, and vice versa (Boulinguez-Ambroise et al., 2022). When it comes to humans, handedness is an early developmental trait phylogenetically, considering that according to the fossils and the tools found, a strong population bias for one (the right) hand was evident even in hominins and later on (Frayer et al., 2016; Groenen, 1988, 1997). As discussed above, an increased strength of manual lateralization was required for the evolutionary demands of the expanding brain while also the tool use and manufacture might have also driven humans to a certain direction of handedness at a population level (Caspar et al., 2022; Frost, 1980; Hecht et al., 2015).

Both the direction and the degree of handedness are bound by genetic and non-genetic factors (Brandler & Paracchini, 2014; de Kovel et al., 2019; Horstick et al., 2020; Hujoel, 2019; Leach et al., 2011; McManus, 1985; Papadatou-Pastou et al., 2020, 2021; Paracchini, 2021). Originally, it was thought that a single gene was responsible for the individual's handedness (Annett, 1975; Klar, 1999; McManus, 1985), but genome-wise analyses provided evidence for several loci (Armour et al., 2014; Cuellar-Pertida et al., 2021). However, heritability only accounts for 24% of handedness, which might indicate that external pressure could have a stronger effect on the determination of handedness (Medland et al., 2009; Schmitz et al., 2017). Non-genetic factors that affect handedness are the intra-uteral position of the fetus, birth conditions, nutrition, the preferred hand of parents as manifested during interactive social play, the hand used for cradling, and the psychological state of the mother during the cradling period (Boulinguez-Ambroise et al., 2020, 2022; Damerose & Vauclair, 2002; de Kovel et al., 2019; Fagard, 2013; Fleva & Khan, 2015; Hujoel, 2019; Malatesta et al., 2019, 2020a,b).

Both genetic and non-genetic factors have led to a strong (89.4%) population-level bias towards the right hand worldwide (Papadatou-Pastou et al., 2020). There are several interpretations for the supremacy of the right hand in this "left versus right" competition, such as that left-handed warriors fought with their left hand, leaving their heart unprotected and not surviving the battles (Van Biervleit, 1899). Nevertheless, it should be noted that in many cultures left-handers are urged to be converted to right-handers, leading to a single-digit prevalence of left-handedness in parts of the world such East Asia and sub-Saharan Africa (Kushner, 2013; Papadatou-Pastou et al., 2020). On the other hand, left-handers gain attention for competitive sports, as they are less often encountered during practice and they hold strategic advantages (Annett, 1985; Loffing et al., 2010; Wood & Aggleton, 1989). When it comes to neuropsychological research, attention should also be drawn to left-handers in terms of cerebral lateralization for writing and the reason will be discussed below.

1.5 CEREBRAL LATERALIZATION FOR ORAL AND WRITTEN LANGUAGE AND THE RELATIONSHIP WITH HANDEDNESS

“*The left-handed are precious; they take places which are inconvenient for the rest*.”

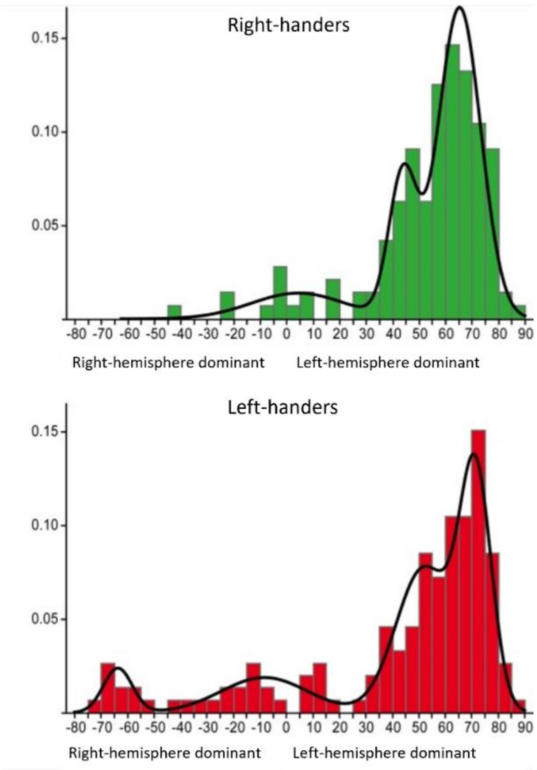
(Hugo, 1862)

There is still no consensus for the inclusion of participants of different handedness groups in language-related research. Nevertheless, the relationship of handedness with (oral) language lateralization is profound, yet complex (Finch et al., 2017; Oslejskova et al., 2007; Pearson & Hodgetts, 2020). The time course of the establishment of this relationship is debatable; which came first, the egg or the chicken? To begin with, given that handedness is already apparent at the fetal or neonatal phase, it is proposed that the cerebral lateralization for manual preference pushes the language lateralization network to a specific hemisphere (Archer et al., 1988; Bates et al., 1986; Gainotti, 2022; Johnston et al., 2009). On the contrary, some researchers suggest that when hemispheric specialization for language is reduced, right handedness turns out to be less probable (Botha et al., 2018). Due to the lack of clear evidence for any of the two hypotheses, an alternative approach is that the lateralization of language and of manual preference are established independently and by chance (Mazoyer et al., 2014; Rogers, 2020).

Irrespective of handedness, the majority of individuals are left-lateralized for oral language. However, the actual percentage differs between handedness groups: 83-96% of right-handed participants show left-hemispheric dominance, while the prevalence for left-handers ranges from 64% to 85% across studies that differ chronologically, geographically, and methodologically (Figure 2; Bartha et al., 2003; Bishop & Bates, 2020; Carey & Johnstone, 2014; Clarke et al., 2016; Johnstone et al., 2021; Knecht et al., 2000; Szaflarski et al., 2002). It remains debated whether these differences in language lateralization between left-handers and right-handers are attributed to a more diffused language lateralization within the group of left-handers or to the incidence of strongly atypical lateralization among left-handers (Johnstone et al., 2021; Mazoyer et al., 2014; Papadatou-Pastou et al., 2021). Notably, the degree of handedness is positively correlated with the degree of language lateralization regardless of their direction (Bartha-Doering et al., 2018; Berl et al., 2014; Papadatou-Pastou, 2008; Springer et al., 1999). The variability of the left-handers in terms of lateralization renders their inclusion crucial for this type of research (Bailey et al., 2020; Van Der Haegen & Brysbaert, 2018; Van der Haegen et al., 2012).

Figure 2

Prevalence of atypical language lateralization among left-handed and right-handed individuals (Adapted from Mazoyer et al., 2014)



However, in contrast to the richer literature on the lateralization for oral language, when it comes to written language lateralization, there were only four studies including left-handers in their sample before the start of this PhD work (Kondyli et al., 2017; Papadatou-Pastou et al., 2022; Siebner et al., 2002; Zaman et al., 2002; but also see Papadopoulou et al. 2023, which is part of this PhD work [Chapter 2 of this thesis] for a review). Siebner et al. (2002), using positron emission tomography (PET), compared (i) left-handers, (ii) right-handers, and (iii) natural left-handers, who had been obliged to become right-handers, while writing with their dominant and non-dominant hands. They showed that, while consistent left-handers and right-handers display a strong contralateral hemispheric activation during writing with their dominant hand, "converted" left-handers display bilateral activation when writing with the right hand. Furthermore, cerebral blood flow to the right premotor and parietal regions during right-hand writing was positively correlated with the degree of left-handedness. Siebner et al. also showed that functional activity in the primary sensorimotor cortex was unaffected by handedness. Zaman et al. (2002) applied functional magnetic resonance imaging (fMRI) to compare brain activation during normal and mirror writing using the dominant and the non-dominant hand. For normal writing, they demonstrated that switching hands did not alter hemispheric activation in left-handers, but, in right-handers, switching hands also activated the ipsilateral hemisphere. For mirror writing, bilateral activation was evident, independent of handedness.

Neither Siebner et al. (2002) nor Zaman et al. (2002) dissociated the motor and linguistic components of writing, as they used writing tasks with both components (namely, the repeated writing of the German verb "bellen" in Siebner et al., 2002; and writing the alphabet in Zaman et al., 2002). Moreover, in both studies, handedness was indexed by nominal writing hand. However, 13.5% of left-handers are mismatched when using writing as the handedness criterion, compared to using hand preference questionnaires as the handedness criterion: the mismatch is negligible for right-handers (0.4%) (Papadatou-Pastou et al., 2013). In addition, both studies had small samples, considering that they used frequentist statistical models, with six left-handers (n=28, Siebner et al., 2002) and 12 left-handers (n=24, Zaman et al., 2002) respectively, the small samples likely being due to the restrictive cost of the imaging techniques.

A technique that provides comparable results to fMRI when assessing laterality (Deppe et al., 2000; Knecht et al., 1998; Schmidt et al., 1999; Somers et al., 2011), while being relatively inexpensive and easy to use, is fTCD (for a detailed description of the method see 1.9).

Functional transcranial Doppler ultrasonography (fTCD) was used to study cerebral laterality for writing in Kondyli et al. (2017) and Papadatou-Pastou et al. (2022), allowing for considerably larger sample sizes compared to Siebner et al. (2002) and Zaman et al. (2002). Specifically, 30 left-handers (*n*=60, Kondyli et al., 2017) and 23 left-handers (*n*=54, Papadatou-Pastou et al., 2022) were included. Kondyli et al. compared language laterality during silent oral word generation and written word generation. They showed that right-handers had left lateralization for both oral and written word generation, while left-handers had left lateralization for oral word generation, but right lateralization when writing. An important limitation of this study was that the oral word generation was a language control task and not a motor control task, therefore only the motor and not the linguistic component of writing could be isolated (as also mentioned for Siebner et al., 2002; Zaman et al., 2002).

More recently, Papadatou-Pastou et al. (2022) addressed this limitation by comparing written word generation with symbol copying, which is a motor control task: symbol copying has similar motor demands to writing (fast and precise coordination of fingers, wrist, and arm movements, planning of sequential action, management of visual landmarks, eye-hand coordination, and hand placement in space), but removes the language component. Papadatou-Pastou et al. found that there was stronger left lateralization for writing than symbol copying in right-handers, implying that the linguistic component of writing is based on the left hemisphere. In left-handers, the activation patterns of writing and symbol copying were more varied across the sample compared to right-handers and were not clearly differentiated. These findings could be explained by a more dispersed language network in left-handers or by the fact that symbol copying is not precisely comparable to writing, because writing is more practiced. Moreover, symbols are novel stimuli compared to letters and, thus, could have increased attentional demands. Therefore, using the copying of letters rather than symbols as a control task, might better control both for the motor and attentional demands of handwriting.

When it comes to the measurement of handedness, it is usually assessed through questionnaires that request participants to declare the hand they prefer to perform everyday activities with, such as writing, using tools, perform more or less fine movements, and communicate through gestures (Prieur et al., 2017, 2018; Williams, 1991). In addition, the lack of consensus for the tasks employed to determine handedness has led to contradictory findings in literature (Fagard & Marks, 2000). To address this limitation, both Kondyli et al. (2017) and Papadatou-Pastou et al. (2022) employed three different continuous handedness measures - in addition to writing hand - in order to assess both (i) hand preference, namely the Edinburgh Handedness Inventory (EHI, Oldfield, 1971) and the Qualification of Hand Preference Task (QHPT, Bishop et al., 1996), and (ii) hand skill, namely Annett's Peg-Moving task (Annett et al., 1979). All handedness measures showed similar patterns of results, but the EHI was correlated more highly with written language (Kondyli et al., 2017) and with the difference between written language and symbol copying (Papadatou-Pastou et al., 2022), compared to the other two measures.

The use of different handedness measures by Kondyli et al. (2017) and Papadatou-Pastou et al. (2022) helps to clarify which measurement should be optimally used when studying handedness differences in cerebral laterality for the linguistic component of writing, namely the EHI; although more data coming from studies better isolating the linguistic component of writing are still needed. In addition, both of these projects showcase the good practice of using different handedness measures (and uploading raw data on osf.io). This practice not only addresses the issues surrounding writing hand use as the handedness criterion (i.e., the mismatch with preference questionnaires described above), but also provides handedness data in a format comparable to studies that might have used different handedness measures. Indeed, optimal handedness measurement remains a matter of debate within the literature (e.g., Brown et al., 2004), which is troubled by the noise introduced by the fact that different studies use different handedness measurements. To that respect, large studies (e.g., Annett, 1983; Cornish & McManus, 1996; DeLisi et al., 2002; Fernandes et al., 2023; Loffing et al., 2024; Gorynia & Müller, 2006; Groen et al., 2013) and meta-analyses (e.g., Papadatou-Pastou et al., 2020) have suggested that handedness researchers should consider measuring and sharing data on both hand preference and hand skill, as will also be the case in the present PhD work.

Given the profound complexities associated with the relationship between handedness and language lateralization, it becomes evident that a nuanced understanding of how these factors intersect is essential for advancing research in this area. As research progresses, it is crucial to employ robust methodologies and consider multiple measures of handedness to account for its multidimensional nature. This approach not only mitigates inconsistencies in findings but also lays the groundwork for exploring how these dynamics influence learning difficulties, such as dyslexia. Notably, understanding the interplay between handedness, language lateralization, and dyslexia can provide deeper insights into the etiology of these learning disorders that affect language skills and inform more effective diagnostic and intervention strategies.

1.6 DYSLEXIA

"I like to think I have a superpower called dyslexia."

(Lorin Morgan-Richards, 1975-).

The term "dyslexia", originating from the Greek words "dys" and "léxi", was originally introduced by William Berlin in 1887 to describe the reading problems faced by adult patients of a cerebral disease classified in the class of aphasias (Richardson, 1992). Since then, the characteristics of dyslexia, otherwise called psycholexia, strephosymbolia, visual agnosia for words, and specific reading disability, have been widely studied, and attempts for a more concrete definition have been made (Wolf & Ashby, 2007). The prevalence of dyslexia ranges between 3 to 17% globally, depending on the definition and the transparency of the orthographic system (Wagner et al., 2020). For Greece, the only official estimation is that 5.52% of adolescents have dyslexia (Vlachos et al., 2013).

According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), dyslexia is under the umbrella of specific learning disorders, affecting learning and/or using academic skills which are specific for each disorder (e.g., reading, arithmetic, writing; American Psychiatric Association, 2013; Petretto & Masala, 2017). The World Health Organization (2015) adds to the definition the fact that the observed difficulties in reading ability, but also in writing, cannot be explained by low intelligence, limited access to education, or by sensory problems. Previously, Lyon et al. (2003) pinpointed that the difficulty in spelling and reading in dyslexia can be traced back to a neurobiological impairment. Taken together, dyslexia is partially caused by a neurobiological impairment that leads to a special learning difficulty affecting spelling, reading fluency and comprehension, and writing skills, which cannot be explained by sensory deficiencies, mental age, and educational opportunity (American Psychiatric Association, 2013; Fletcher, 2009; Lyon et al., 2003; Margari et al., 2013; Miciak & Fletcher, 2020; National Institute of Neurological Disorders and Stroke, 2017; Tunmer & Greany, 2010; Vlachos, 2010; Vlachos & Avramidis, 2020; World Health Organization, 2015).

Heritability of dyslexia ranges between 40% and 70% in twin studies, while there is a 50% chance for a first-degree relative of an individual with dyslexia to also develop dyslexia (Grigorenko, 2009; Paracchini et al., 2007; Snowling & Melby-Lervag, 2016). Dyslexia is multifactorial, and there are many causal theories for its origin (Bishop, 2015; Blomert, 2011; Dresler et al., 2018; Goswami, 2000; Lallier & Valdois, 2012). The multiple potential causes for dyslexia reflect the perplexing genetic basis of the disorder (Krafnick & Evans, 2018).

Polymorphisms on, at least, 42 genetic loci have been associated with characteristics of dyslexia (Doust et al., 2022; Gialluisi et al., 2020; Kere, 2014; Konig et al., 2011; Scerri & Schulte-Korne, 2010). Additionally, mutations of specific genes have been associated with the risk for dyslexia (Carrion-Castillo et al., 2013; Poelmans et al., 2011; Scerri & Schulte-Korne, 2010).

Auditory and visual processing deficits, an interrupted connection between brain hemispheres, and impaired automaticity due to deficient cerebellar function have all been suggested to cause dyslexia (Badzakova-Trajkov et al., 2005; Facoetti et al., 2006; Fernandez et al., 2016; Iles et al., 2000; Lobier et al., 2012; McLean et al., 2011; Monaghan & Shillcock, 2008; Nicolson & Fawcett, 2019). However, the cause for dyslexia that has received the most support is the phonological deficit theory (Adlof & Hogan, 2018; Araújo et al., 2012; Beeson et al., 2018; Berninger et al., 2008; Boets et al., 2006, 2013; Cao et al., 2006; Catts et al., 2017; Dresler et al., 2018; Fletcher et al., 2018; Georgiewa et al., 2002; Hebert et al., 2018; Kovelman et al., 2012). This theory suggests that the major impairment in dyslexia is deficient phonological awareness, a deficiency in the ability to detect, recognize, represent, internally monitor, store, categorize, recall, and manipulate the sounds of spoken language (Adlof & Hogan, 2018; Beeson et al., 2018; Boets et al., 2006, 2013; Fletcher et al., 2018).

When it comes to the writing difficulties present in cases of dyslexia, these difficulties are considered to be a projection of reading difficulties that persist even if reading difficulties are overcome (Caravolas et al., 2020; Döhla & Heim, 2016; Ehri, 1997; Habib, 2000). The writing of individuals with dyslexia is often characterized by poor spelling, handwriting that is difficult to read, limited vocabulary, lack of organization, and insufficient development of ideas (Hebert et al., 2018). While good writers adopt strategies, such as re-reading their text to detect errors in spelling, grammar, and organization and to improve their writing, the reading difficulties and the hesitation in corresponding letters (graphemes) to sounds (phonemes) found in people with dyslexia impede this self-feedback (Hayes, 1996; Hebert et al., 2018). It is unclear whether handwriting problems correlate with dyslexia, considering handwriting quality varies equally among children of the same age regardless of the incidence of dyslexia (Badian, 1999; Barnett et al., 2006; Graham & Weintraub, 1996). One possible explanation for the little attention that writing difficulties have received, both in terms of research and for remediation, is that learning to write postdates reading instruction. Therefore, by that time, reading difficulties would have developed, reading problems would be considered more important to address than writing problems. However, the persistence of writing difficulties might imply additional impairments that should be taken into consideration, and together all these difficulties in language use can affect the social life and personality of individuals (Adams & Bishop, 1989; Botting, 2002; Cappelli et al., 2022; Lam & Ho, 2014).

Reading and writing difficulties might lead to low academic performance. This could result in children being mistakenly considered as lazy or “stupid”, which could in turn lead to low self-esteem, anxiety and depressive behaviors (Feder & Majnemer, 2007; Francis et al., 2019; McArthur et al., 2020; Mugnaini et al., 2009). This emotional condition could lead children to decreased socialization and a high risk for negative behaviors and psychotic episodes, even for suicide attempts (Huang et al., 2020; Karande & Venkataraman, 2013). This psychological burden could become even worse, taking into consideration the dyslexia paradox, which describes the delay between the earliest time that signs of dyslexia are apparent (in preliteracy or early elementary school years) and the time point at which dyslexia is actually diagnosed and begins to be managed (Gallagher et al., 2000; Lyytinen et al., 2006; McBride-Chang et al., 2008; Ozernov-Palchik & Gaab, 2016; Torgesen, 2002). In fact, the earlier the induction into a management program, the better the results for children with or at risk for dyslexia (Snowling, 2013). Keeping these in mind, it is important to recognize and manage the difficulties of children at risk for dyslexia as early as possible.

1.7 Cerebral Lateralization for Language and Its Relationship with Dyslexia

"Dyslexia is a neurological issue, not a character flaw."

James Redford (1962-2020)

A large number of studies have assessed the relationship of the direction and the degree of language lateralization with individuals' performance in language tasks. There are some findings showing that the performance in listening comprehension tasks is related to the degree of lateralization and independent of the direction of lateralization (Hirnstein et al., 2014), or that better academic performance is achieved when language functions are less lateralized and both hemispheres are involved (Bartha-Doering et al., 2018; Lidzba et al., 2011; Yeatman et al., 2010). However, most of the evidence suggests that a leftward pattern of lateralization is positively correlated with performance in language tasks (Berl et al., 2010, 2014; Groen et al., 2012; Lillywhite et al., 2009). In fact, this left lateralization is task and region specific. The preferential activation of frontal regions of the left hemisphere is observed for reading comprehension tasks, while the relative increase in activation of left temporal regions is associated with object naming skills (Berl et al., 2010, 2014).

Reading can be considered as a dual-route path process depending on how recognition of a single word is proceeded in the brain (Hautala et al., 2022). The correspondence of each phoneme with the equivalent letter (grapheme) is tracked in the sublexical route, and people with dyslexia might encounter barriers in this route (Figure 3; Miciak & Fletcher, 2020). The sublexical route includes frontal, temporoparietal, and occipitotemporal regions of the left hemisphere that are less developed, wired, or activated in children with dyslexia compared to typically developing children (Altarelli et al., 2014; Banfi et al., 2019; Bishop, 2013; Boets et al., 2013; Chen et al., 2014; de Moura et al., 2016; de Smet et al., 2013; Dehaene et al., 2015; Eckert et al., 2016, 2017; Franceschini et al., 2017; Goswami, 2015; Kershner, 2020; Martin et al., 2016; Munzer et al., 2020; Nora et al., 2021; Paulesu et al., 2014; Quin-Conroy et al., 2024; Richards et al., 2015; Richlan, 2020; Richlan et al., 2013; Sturm et al., 2021; Tomasino et al., 2020; Vanderauwera et al., 2018; Vandermosten et al., 2013; Vlachos & Avramidis, 2020). Typically, following adequate experience in reading, the left hemisphere adapts to word processing, while the right hemisphere retains its specialization for other functions, such as face processing (Gerlach et al., 2022; Rossion & Lochy, 2022). However, in children with dyslexia, potentially for compensation, the activation of homologous regions of the right hemisphere increases (Figure 4; Altarelli et al., 2014; Hoeft et al., 2011; Kershner, 2020; Maisog et al., 2008; Richlan et al., 2009; Saban-Bezalel et al., 2019). Therefore, phonological decoding and coding during reading and oral word generation are less left-lateralized and more symmetrically represented in the brain hemispheres of children with dyslexia, and it has been suggested that this pattern is negatively correlated with their performance in language tasks (Eckert et al., 2022; Habib & Robichon, 1996; Horowitz-Kraus et al., 2024; Waldie & Hausmann, 2010) and that it can act as a symptom biomarker (Ocklenburg et al., under review). Yet, the above evidence has been collected using oral language tasks; the lateralization for written language has not yet been assessed in children, whether with dyslexia or not.

Figure 3

Representation of the dual-route for reading (Adapted from Friederici, 2011)

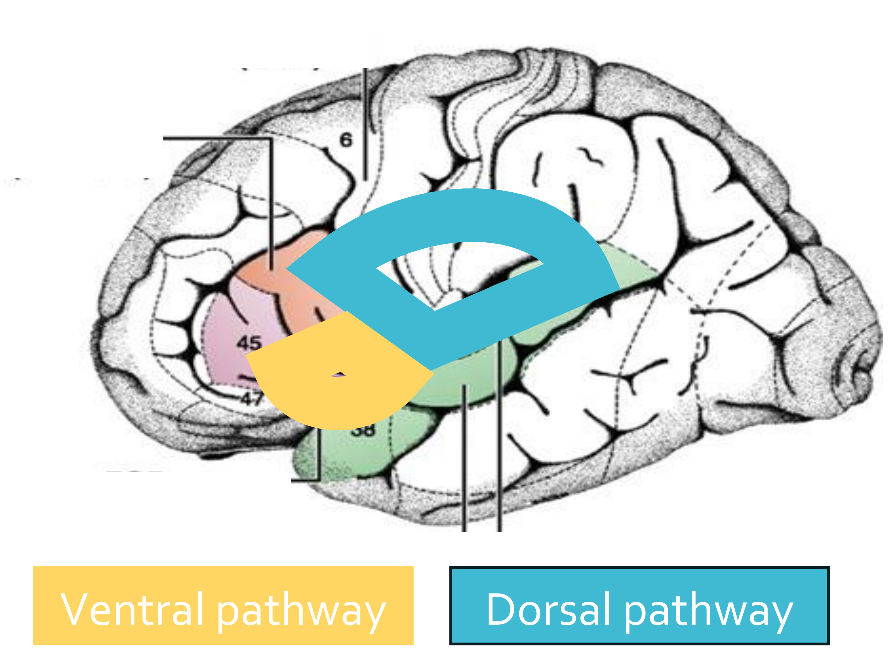
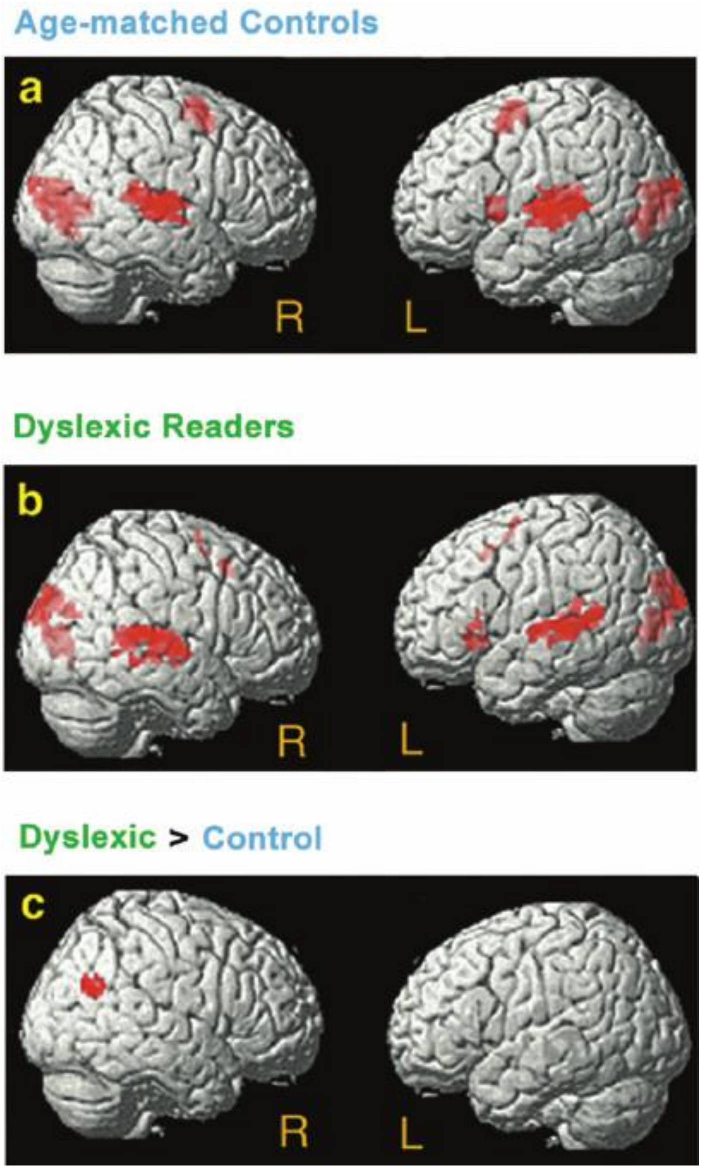


Figure 4

Cerebral lateralization for oral language in children with and without dyslexia (Kovelman et al., 2012)



Examining the patterns of language lateralization in children, whether oral or written, gains heightened significance, particularly concerning dyslexia. This becomes even more important considering the timing of the establishment of a language lateralization pattern and the effect of an intervention administered as early as possible on neuroplasticity. Although it is generally agreed that a clear language lateralization pattern is formed by the age of six or seven (Groen et al., 2012), there are contradictory findings regarding language lateralization in infancy and in early childhood (Bishop et al., 2014; Blasi et al., 2015; Bosseler et al., 2021; Gurunandan et al., 2020; Hodgson et al., 2016; Kohler et al., 2015; Lawrence et al., 2021; Mushtaq et al., 2019; Obrig et al., 2017); most of them suggest that brain activation is bilateral during language comprehension for the first three years of age and it progressively becomes more left-lateralized. However, there are also studies showing that left lateralization for language is apparent in neonates (Lawrence et al., 2021) and that there is no change in the degree of lateralization between ages one and five (Kohler et al., 2015). Taking into consideration that children develop oral language generation and comprehension earlier than written language generation, the establishment of the lateralization for written language might delay. Thus, the lack of knowledge about the milestones of written language lateralization underscores the importance of including different age groups to better understand the development of lateralization patterns.

Structural and functional deviations of the typical pattern of lateralization related to dyslexia are observed prior to the onset of formal reading instruction, showing a predisposition of these children for learning difficulties that can be identified early (Im et al., 2016; Langer et al., 2017; Leppänen et al., 2012). For example, Dębska et al. (2016) found that the same regions shown to be atypically lateralized in individuals diagnosed with dyslexia, particularly the temporo-parietal region, the occipito-temporal cortex, and the inferior frontal gyrus, are less left-lateralized during phonological processing in Polish kindergarten children at familial risk for dyslexia compared to typically developing children of their age group, despite the absence of behavioral indicators. In fact, the activation of the left ventral occipito-temporal cortex in phonology-related tasks has been positively correlated with the ability of kindergarten children at varying risk for dyslexia to respond to short educational training (Pleisch et al., 2019). An increasing number of studies include children at risk for dyslexia in their sample, marking that indications of dyslexia are apparent in preschool or early school years, long before the diagnosis of dyslexia (Bishop, 2013; Cantiani et al., 2016, 2019; Choudhury & Benasich, 2011; Davis et al., 2011; Dębska et al., 2016; Hämäläinen et al., 2013; Kuuluvainen et al., 2016; Langer et al., 2017; Mittag et al., 2021; Nora et al., 2021; Pleisch et al., 2019). Therefore, assessing the pattern of lateralization for different language tasks lends itself to the recognition of signs of dyslexia and for an early intervention.

1.8 EFFECTS OF EDUCATIONAL INTERVENTIONS ON THE LANGUAGE LATERALIZATION IN CHILDREN WITH OR AT RISK FOR DYSLEXIA

"*Expecting all children, the same age to learn from the same materials is like expecting all children the same age to wear the same size clothing*"

(Madeline Hunter, 1916-1994).

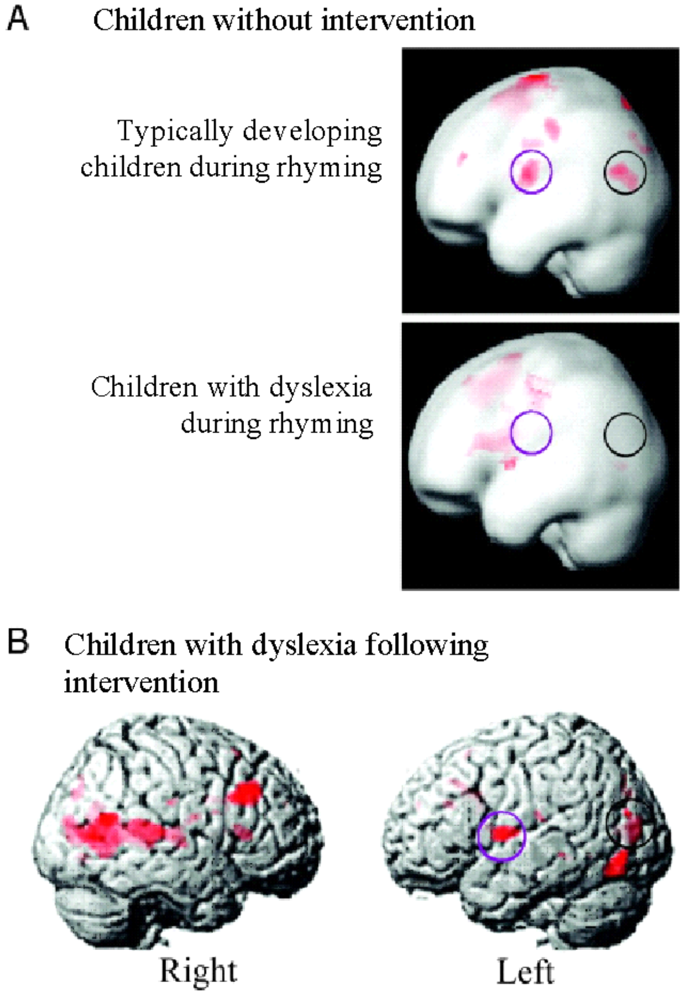
A valuable point for teachers and guardians of children with dyslexia to take into consideration is that these children do not differ from their peers except for requiring a reading instruction more oriented to their needs and difficulties (Manilla & de Braga, 2017). Several types of intervention have been suggested and administered not only to children with dyslexia, but also to younger children showing signs of developing dyslexia in the future, including instructional or remediation auditory and reading programs, brain stimulation treatment, or a combination thereof (Aylward et al., 2003; Constanzo et al., 2019; Eden & Moats, 2002; Eden et al., 2004; Frey et al., 2019; Hamilton et al., 2021; Heth & Lavidor, 2015; Horowitz-Kraus et al., 2015; Keller & Just, 2009; Krafnick et al., 2011; Loo et al., 2016; Lovett et al., 2017; Meyler et al., 2008; Nugiel et al., 2019; Odegard et al., 2008). Of note, the younger the children and the more targeted to phonological awareness the instruction, the more efficient the intervention is in the amelioration of the symptoms of dyslexia (Connor et al., 2013; Démonet et al., 2004; Hatcher & Hulme, 1999; Lovett et al., 2017). Therefore, an early screening of children at risk for dyslexia can ensure a well-timed inclusion in intervention and potentially a better response.

As long as dyslexia is associated with a decreased left lateralization during speech perception even long before diagnosis in children at familial risk for dyslexia (Guttorm et al., 2010; Hämäläinen et al., 2013; Leppänen et al., 2010; Lyytinen et al., 2005; Nora et al., 2021), this could add to the recognition of the signs for the risk for dyslexia in general.

The functional reorganization of the brain could not only mirror the academic performance of children, but also provide additional evidence indicating the effectiveness of an intervention for children with dyslexia or those at risk. Educational interventions and especially the ones with a phonological component are shown to shift the atypical language lateralization that is related to dyslexia leftwards so that it can simulate that of typically developing children (Figure 5; Berninger & Richards, 2010; Eckert et al., 2017; Eden et al., 2004; Elbro & Jensen, 2005; Gabrieli, 2009; Kraft et al., 2015; Manilla & de Braga, 2017). For most of these studies, the atypical lateralization (decreased activation of the left hemisphere and increased activation of right homologous regions) found in children with or at risk for dyslexia compared to controls prior to intervention, was weaker following intervention (Gaab et al., 2007; Shaywitz et al., 2004; Simos et al., 2002, 2007a,b; Spironelli et al., 2010). For example, Spironelli et al. provided evidence for a redirection of the early response to written words from the right hemisphere to the left in children with dyslexia following phonological intervention. Shaywitz et al. compared the effect of different interventions, one with a phonological component and a community one (i.e., a variety of remedial trainings commonly provided at school facilities), on the reorganization of the brain of children at familial risk for dyslexia and they showed that only the phonological intervention led to the increase in activation of left regions and the decrease in activation of right regions, while the community intervention could not provide any benefit to the children. Nonetheless, what remains unclear is whether the phonological component per se led to these moderations in lateralization, suggesting the study of the effects of an exclusively phonological intervention on language lateralization.

Figure 5

The effect of an intervention including a phonological component on the language lateralization of children with dyslexia (Adapted from Temple et al., 2003)



With writing and reading being opposite sides of the same coin in terms of dyslexia, writing quality is among the language skills that are improved through interventions with a phonological component. In particular, studies examining the effect of phonological interventions in preschool (e.g., Manrique, 1997; Silva & Alves-Martins, 2002) and school-aged children (e.g., Patterson, 2015; for a meta-analysis, see Graham et al., 2017) have shown that children improved in generating written text by adhering more to conventional rules for writing following the intervention rather than prior to it (but also see Patterson, 2015, for the effect of the socioeconomic background of children's families). Notably, Erdoğan (2011), by evaluating the phonological awareness of first-grade students at the beginning of the school year and comparing it to the writing skills that students developed by the end of the school year, emphasized the importance of phonological awareness for predicting children's performance in learning how to write. Despite the evidence for the dependence of writing skills on phonological awareness, none of the studies assessing the effect of phonological interventions on language lateralization has involved lateralization for written language, potentially due to the limitations of neuroimaging techniques in terms of the age of the children or their unpredictable movement during writing.

1.9 The use of functional Transcranial Doppler ultrasonography for studying language lateralization

"*The aim defines the method*"

(Wiker & Hahn, 2006).

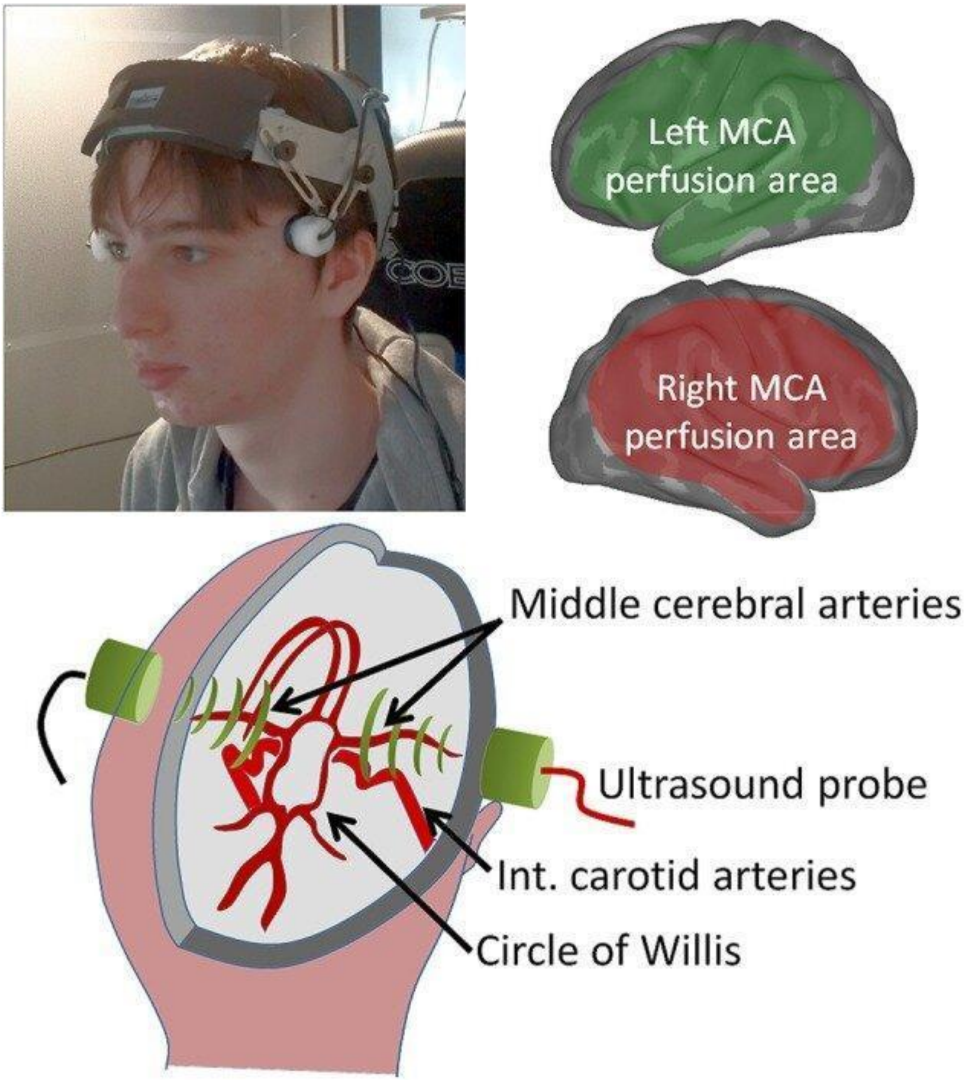
For many years, studies on language lateralization focused on structural differences between brain hemispheres including the observation of patients with hemispheric lesions, neurobiological assessment of post-mortem specimens, and the investigation of brain morphometry (Broca, 1861; Filipek, 1996; Galaburda et al., 1985; Hynd et al., 1990; Pennington et al., 1999; Richlan et al., 2013; Sharma & Kadis, 2024). Technological achievement has more recently allowed scientists to examine functional differences between brain hemispheres that are evident while the individual performs a linguistic task. The widely used, gold-standard technique to measure cerebral language lateralization pre-operatively is the Wada test, during which an anaesthetic, sodium amytal, is infused in one internal carotid artery at a time to transiently inhibit the ipsilateral brain hemisphere and to assess the performance of the other hemisphere in language tasks (Curot et al., 2014; Dym et al., 2011; Labache et al., 2020; Wada, 1949; Wada & Rasmussen, 1960). However, important limitations of Wada testing are that it is invasive, carrying health risks, and that there is a narrow time window for language assessment (Binder et al., 1996; Kundu et al., 2019). Therefore, non-invasive techniques have started replacing Wada testing, with the most popular for clinical use being fMRI. Functional magnetic resonance imaging allows for high spatial resolution of the whole brain and the results are in agreement with that of Wada testing (Dym et al., 2011; Glover, 2011; Labache et al., 2020). Nevertheless, this technique also has some drawbacks for research use, including being expensive, immobile, unserviceable for several groups, such as pacemaker users, and prone to statistical analysis difficulties and misinterpretations (Bishop et al., 2009; Johnstone et al., 2021; Loring et al., 2002; Pelletier et al., 2007; Whitehouse et al., 2009). When it comes to acquiring a brain image during writing, fMRI measurements are sensitive to any other than minor body movements, such as limb movements in the case of writing, while the equipment does not allow the participant to write in a natural sitting position (Bishop et al., 2009; Papadatou-Pastou et al., 2022; Woodhead et al., 2018). The neurophysiological technique that outcompetes fMRI in these aspects is the fTCD.

Functional transcranial Doppler ultrasonography measures the changes in the velocity of cerebral blood flow in the middle cerebral arteries in each brain hemisphere, with the application of two ultrasound probes on the left and the right temple (Figure 6; Aaslid et al., 1982; Bishop et al., 2021; Hage et al., 2021; Newell & Aaslid, 1992). These arteries supply the temporal and parietal regions with blood (Oo et al., 2021). These regions are related to language generation in the left hemisphere and the homologous regions of the right hemisphere. Even though the spatial resolution of this technique is low, as it assesses blood flow at the level of the whole territory that the middle cerebral arteries supply, its high temporal resolution allows to assess the fluctuations in activation of brain hemispheres in real-time (Deppe et al., 2000). Next to being non-invasive, portable, and inexpensive, fTCD findings are positively correlated with the results of studies using Wada testing and fMRI (Bishop et al., 2009, 2024; Deppe et al., 2000; Knecht et al., 1998). Functional transcranial Doppler ultrasonography is also characterized by strong internal reliability (r = 0.61 to 0.83; Stroobant & Vingerhoets, 2001). An important development that rendered fTCD measurements more useful and reliable is the analysis package that Deppe et al. (1997) developed, named “Average”. This package included an automatic analysis plan for the removal of variations due to the heart rate cycle of the participant and of any existing differences of the left and the right hemisphere in terms of blood flow. Badcock et al. (2012) incorporated the “Average” package in a larger analytic tool that serves for an easy manipulation of fTCD data and is upgraded over the years, with the most updated version currently used being “dopStep” (Badcock et al., 2012, 2018).

Functional transcranial Doppler ultrasonography can be applied to the majority of individuals regardless of condition or age, as it has been used for even 1-year-olds (Badcock et al., 2018). Nonetheless, in 5-20% of participants, the ultrasound beam may encounter difficulty penetrating the skull, and this percentage tends to rise from childhood to adulthood (Knake et al., 2003; Kondyli et al., 2017; Lohmann et al., 2006; Papadatou-Pastou et al., 2022). Of importance, there is evidence that fTCD measurements are robust to speech-related head and face-muscle movements and to more energy-demanding manual activities, such as tool use, driving, or, to what concerns our studies, writing (Bishop et al., 2009; Guttierez-Sigut et al., 2015; Heimann et al., 2022; Kondyli et al., 2017; Lust et al., 2011; Papadatou-Pastou et al., 2022). Therefore, fTCD lends itself for studies like those that are part of the present PhD thesis, assessing the cerebral lateralization for written language across different age groups.

Figure 6

Functional transcranial Doppler ultrasonography technology and application (Adapted from Meyer et al., 2014)



1.10 SUMMARY OF AIMS

The necessity of this thesis arises from the gaps in the current literature regarding cerebral lateralization for written language, particularly in diverse populations and under varying conditions. The three studies comprising the present thesis aim to address these gaps by exploring several critical and unanswered questions: how the linguistic component of written language is lateralized across handedness groups (Study 1), how written language is lateralized in children with and without risk for dyslexia (Study 2), and what is the effect of an exclusively phonological intervention in the lateralization pattern of written language in children at risk for dyslexia (Study 3).

Cerebral lateralization was assessed during three conditions: (a) oral generation of words (Study 1), (b) written generation of words (all Studies), and (c) copying a letter multiple times, which was employed as a motor control task (all Studies). The lateralization for the linguistic component of written language was calculated by subtracting the measurement for the letter-copying condition from the measurement for the written word generation condition. Three measures of handedness were used throughout this project to assess both hand preference and relative hand skill of participants: a questionnaire (EHI; Oldfield, 1971), an active preference task (QHPT; Bishop et al., 1996, 2005), and a task estimating the relative skill in rapidly and accurately moving pegs (Peg-moving task; Annett et al., 1979).

By assessing cerebral lateralization during oral and written word generation and a motor control task, and utilizing comprehensive measures of handedness, this research seeks to elucidate the relationship between oral and written language lateralization, the impact of dyslexia risk on these patterns, and the effectiveness of targeted interventions. This work is crucial for advancing theoretical knowledge and developing practical strategies to support individuals with dyslexia.

1.10.1 Study 1: Exploring cerebral laterality of writing and the relationship to handedness

For Study 1, the lateralization for the linguistic component of written language was compared between left-handed and right-handed adults. Thirty participants of each handedness group performed all of the three conditions.

This study had two aims/research questions:

(i) to investigate the potential differences in the lateralization for the linguistic component of writing between left-handers and right-handers and

(ii) to assess the relationship of oral language and the linguistic component of written language in terms of lateralization.

Of note, in this study a novel motor control task was used as an attempt to address the drawbacks of the symbol copying task used in Papadatou-Pastou et al. (2022). For the purposes of the present PhD, cerebral lateralization during letter copying occurred as a difference between the cerebral lateralization for written word generation and the cerebral lateralization for letter copying. This motor control task has participants mimic the exact same movement that they do when writing a word, using the same stimuli (letters instead of symbols), without the linguistic component of word generation.

1.10.2 Study 2: Cerebral lateralization of writing in students at risk for dyslexia

Considering the time-intensive nature of Study 1, which includes three conditions, and the interest in examining the potential developmental trajectory of lateralization patterns, adults were only included in Study 1 and the remaining two studies focused on children. For Study 2, the lateralization for the linguistic component of written language was assessed in children at risk for dyslexia and typically developing controls. Thirty-six children formed two groups (12 at-risk and 24 typically developing) according to their performance on reading skill tests. They performed the Space Portal fTCD task, during which they were requested to copy as many times as possible the letter that appeared on a screen or to write as many words as possible that were depicted as images on a screen within a given time.

The aims of this study were:

i) To compare the cerebral lateralization for the linguistic component of written language in children at risk for dyslexia in comparison to typically developing children and

ii) To investigate the relationship between the lateralization for the linguistic component of written language and the writing competence of children of the whole sample.

For the second aim, writing competence, manifested as handwriting quality and orthography, was assessed according to the number of errors that children made when they wrote dictated, copied, and spontaneous text.

1.10.3 Study 3: The effects of a phonological intervention in the cerebral lateralization for written language in children at risk for dyslexia

Finally, Study 3 was a pilot study comparing the lateralization for the linguistic component of written language of children at risk for dyslexia prior and after the administration of a phonological intervention. An exclusively phonological intervention was administered to five of the participants of Study 2 and both their reading performance and their fTCD data following intervention were juxtaposed to their results prior intervention, but also the results of typically developing peers.

The aims of this study were the following:

i) To investigate whether the exclusively phonological intervention could shift the lateralization pattern of children at risk for dyslexia towards the lateralization pattern of typically developing children and

ii) To examine a non-phonological intervention for feasibility as an active control intervention in future, larger studies.

In this vein, a pragmatic intervention, aiming to enhance communication skills, was administered to one girl at risk for dyslexia and her lateralization for the linguistic component of written language was measured prior and after the intervention.

2 Exploring cerebral laterality of writing and the relationship to handedness[1]

Abstract

Cerebral lateralization for oral language has been investigated in a plethora of studies and it is well established that the left hemisphere is dominant for production tasks in the majority of individuals. However, few studies have focused on written language and even fewer have sampled left-handers. Writing comprises language and motor components, both of which contribute to cerebral activation, yet previous research has not disentangled. The aim of this study was to disentangle the language and motor components of writing lateralization. This was achieved through the comparison of cerebral activation during (i) written word generation and (ii) letter copying, as assessed by functional Transcranial Doppler (fTCD) ultrasound. I further assessed cerebral laterality of oral language. The sample was balanced for handedness. I preregistered the hypotheses that (i) cerebral lateralization for the linguistic component of writing would be weaker in left-handers compared to right-handers and (ii) oral language and the linguistic component of written language would not be correlated in terms of cerebral lateralization. No compelling evidence for either of our hypotheses was found. Findings highlight the complexity of the processes subserving written and oral language.

[1] This study was published in the journal Laterality: Papadopoulou, A.K., Samsouris, C., Vlachos, F., Badcock, N., Phylactou, P., & Papadatou-Pastou, M. (2024). Exploring cerebral laterality of writing and the relationship to handedness: A functional transcranial Doppler ultrasound investigation, *Laterality*, *29*(1), 117-150, https://doi.org/10.1080/1357650X.2023.2284407

Keywords: cerebral lateralization, writing, functional transcranial Doppler ultrasound, handedness

2.1 Introduction

Cerebral language lateralization is largely studied using oral language production and comprehension tasks, through overt or covert speech (Bruckert et al., 2021; Groen et al., 2012; Kondyli et al., 2017). Writing is another important manifestation of language used for social, educational, and work purposes by the majority of the population (Roser & Ortiz-Ospina, 2016). It requires cognitive, motor, and other sensory skills (Haertl & Ero-Phillips, 2019; Julius et al., 2016). However, the neurophysiology of the writing process and, particularly, the cerebral laterality of writing, is a relatively recent enquiry (Dufor & Rapp, 2013; Kondyli et al., 2017; Planton et al., 2017, 2013; Potgieser et al., 2015; Segal & Petrides, 2012; Yang et al., 2020). Moreover, while handedness is linked to the cerebral laterality of oral language, only four studies have compared cerebral lateralization for written language in left-handers and right-handers (Kondyli et al., 2017; Papadatou-Pastou et al., 2022; Siebner et al., 2002; Zaman et al., 2002). In the present preregistration, I aim to further explore the cerebral laterality of written language in left-handers and right-handers.

Laterality is a fundamental feature of brain organization (Corballis, 2014; Ocklenburg et al., 2017). Cerebral language lateralization and handedness are the two most prominent examples of laterality. Language functions and most prominently language production are left lateralized in the majority of the population (e.g., Manilla & de Braga, 2017; Nielsen et al., 2013; Potgieser et al., 2015; van Setten et al., 2016). However, there are also cases of atypical laterality (i.e., bilateral or right-dominant activation) in individuals with neurodevelopmental disorders (e.g., Chance et al., 2008; Fletcher et al., 2010; Herbert et al., 2002; Kleinhans et al., 2008; Lange et al., 2010; Vanderauwera et al., 2018), but also in neurotypical individuals, especially in left-handed and ambidextrous individuals (e.g., Szaflarski et al., 2002); overall, about 6.5% of the population show right-hemispheric language lateralization and 10-15% display bilateral language lateralization (Bishop & Bates, 2019; Nielsen et al., 2013; Vingerhoets, 2019).

The aforementioned population statistics for language lateralization refer to oral language. However, language is also expressed in writing. Writing is a multidimensional skill combining motor, linguistic, and other cognitive skills, but also sensory properties (Berninger et al., 2015; Feder & Majnemer, 2007; Limbu et al., 2019). It is performed by refined movements for complex manipulation of tools, response to visual or auditory stimuli, cooperation of sensory systems and attentional networks as well as proprioception: comprehending the position of one's own body parts and coordinating their movements (Cornish & McManus, 1996; Feder & Majnemer, 2007; Potgieser et al., 2015). In 2016, 86% of the world's population was capable of reading and writing (Roser & Ortiz-Ospina, 2016). Thus, written language is a multi-faceted, widely used expression of language, yet little is known about its neural underpinnings.

When it comes to the cerebral laterality of writing, neuroimaging studies show that the linguistic properties of writing mainly activate the left hemisphere (Potgieser et al., 2015; Yang et al., 2020), similarly to oral language. Exner's area, located in the left middle frontal gyrus, has been characterized as a region specialized for writing (Anderson et al., 1990; Matsuo et al., 2003; Roux et al., 2009; Yang et al., 2020). Other left-lateralized language-related regions activated during writing are: the middle frontal gyrus, associated with written phonemic fluency (Kircher et al., 2011); the anterior superior temporal gyrus, activated during writing with either hand compared to tapping (Potgieser et al., 2015); and parietal regions, activated independently of which hand is used for writing (Sugihara et al., 2006). Regarding the motor dimension of writing, this employs the primary motor cortex, which controls spinal cord efferents to upper limbs. Feed-forward and feedback regulation are performed mainly by the ventral premotor cortex that modulates distal upper limb movements, to support the primary motor cortex (Potgieser et al., 2015).

These findings on the neural underpinnings of writing are based on right-handers, even though one out of 10 individuals is left-handed (Papadatou-Pastou et al., 2020). Only two neuroimaging studies (reviewed below) on writing sampled left-handers to the best of our knowledge (Siebner et al., 2002; Zaman et al., 2002; of note, Golestanirad et al., 2015, also sampled three left-handers in their study on the neural underpinnings of phonemic fluency in writing, but their data were merged with the data of the right-handed participants). This is not an exception for the neuroimaging literature as a whole, whereby left-handers are typically under-represented (Bailey et al., 2020). Thus, information on a large portion of the neurotypical population remains untapped. This is particularly worrisome when it comes to the study of cerebral lateralization for writing, taking into account the relationship between cerebral lateralization for oral language and handedness, and the fact that the motor component of writing activates different hemispheres in left-handers and right-handers. Recently, two neurophysiological studies (also reviewed below) focused on the cerebral lateralization for writing and the handedness differences thereof, using fTCD (Kondyli et al., 2017; Papadatou-Pastou et al., 2022). Overall, findings on the cerebral lateralization for writing heavily rely on right-handers, making our understanding incomplete.

Functional transcranial Doppler ultrasonography is a non-invasive technique that measures the changes in blood flow velocity in the middle cerebral arteries (MCA) representing changes in regional metabolic activity in brain areas during cognitive tasks (Deppe et al., 2000; Meyer et al., 2014; Woodhead et al., 2018). Measurements with fTCD are in agreement not only with fMRI data, but also with intra-carotid amobarbital procedure (Wada test) measurements (Deppe et al., 2000; Deppe et al., 2004). Moreover, fTCD lends itself better to the study of cerebral laterality of writing compared to fMRI, as it is unaffected by body movements (Bishop et al., 2009; Kondyli et al., 2017; Lust et al., 2011; Salinet et al., 2012) and does not require special equipment, while allowing participants to write in a natural position (e.g., fMRI-compatible tablets, see Golestanirad et al., 2015). Furthermore, it can be applied to participant groups that cannot undergo fMRI, such as very young children or those anxious about the scanning environment (Badcock et al., 2018; Deppe et al., 2004; Gutierrez-Sigut et al., 2015; Kohler et al., 2015; Meyer et al., 2014; Rey et al., 2011; Rosch et al., 2012; Whitehouse & Bishop, 2009; Woodhead et al., 2018). In addition, due to its low cost, fTCD may be preferable for large cohort studies and in longitudinal and follow-up analyses (Lohmann et al., 2006). Limitations include poor spatial resolution, limited to the comparison of left-activation vs. right-activation, and the fact that the required temporal window cannot be obtained in around 5%-20% of the population (Knake et al., 2003; Kondyli et al., 2017; Lohmann et al., 2006; Woodhead et al., 2018).

As mentioned in Chapter 1, the four studies on writing lateralization that included left-handers showed a more consistent leftward lateralization during different writing tasks for right-handed compared to left-handed participants, for whom there are only indications of a more scattered activation pattern depending on the task performed and the sample size. A crucial difference between these studies was that for the older ones (Siebner et al., 2002; Zaman et al., 2002), handedness was only nominally declared according to the writing hand, while the more recent studies (Kondyli et al., 2017; Papadatou-Pastou et al., 2022) described handedness through both hand preference questionnaires and hand skill tasks, which is very important to assess mismatches and it is also adopted in this study (for details, see Papadatou-Pastou et al., 2013). Moreover, an important limitation of these studies was that the absence of an appropriate motor control task, in order to disentangle the linguistic from the motor component of writing. Papadatou-Pastou et al. (2022) attempted to use symbol copying as a motor control task for written word generation, howbeit symbols might have been more attentionally demanding as novel stimuli compared to the letters comprising the words, thus activating other brain regions alongside the ones related to motor functions. For this study, I hypothesized that copying of letters of the native language would be a more suitable motor control task.

The aim of the present study was to further investigate handedness differences in the cerebral laterality of writing by using a motor control to writing. In order to accomplish this, I aimed to compare two conditions: (1) Written Word Generation, a generative language and motor condition, and (2) Letter Copying, a task that lacks the generative language component but is comparable in terms of its motor component and familiarity. The linguistic component of writing was isolated from the motor component of writing by using the Letter Copying condition as an active baseline for the Written Word Generation condition. I am also interested in examining the correlation between the cerebral lateralisation for oral language and the linguistic component of writing. In this vein, I included a third condition, Oral Word Generation, which entailed a generative linguistic component, but lacked the hand motion. I employed fTCD to assess cerebral lateralization.

I had two hypotheses:

Hypothesis 1: Left-handers will have weaker left-sided lateralization for the linguistic component of the written word generation compared to right-handers.

Hypothesis 2: Oral language and the linguistic component of written language will not be correlated in terms of cerebral lateralization.

2.2 Methods

2.2.1 Sampling plan

A total of 48 healthy adult (18-50 years old) volunteers would be initially recruited to participate in the study, a sample size which ensured adequate counterbalancing (there were 6 versions of the order of tasks). Participants were balanced for handedness, according to their

EHI scores. Using a Sequential Bayesian Factor (SBF) with Maximal *n* design (Schönbrodt & Wagenmakers, 2018), two extra participants were added in each handedness group until BF_{10} would exceed 6 (or BF_{10} is smaller than 1/6), corresponding to “moderate evidence” (Lee & Wagenmakers, 2013), for both Hypotheses 1 and 2 (which was not accomplished for either Hypothesis), or until an upper limit of 60 participants in total (30 participants per group) was reached, given time and resources restraints. The initial sample was also in line with Schönbrodt et al. (2017) according to which, 24 participants per group for the SBF Design is an average sample size without wrong inference related to false-negative evidence. Participants were monolingual (i.e., not having been systematically exposed to a second language until the age of 6 yrs.), native Greek speakers, and their vision was normal or corrected-to-normal. No monetary reimbursement was made for participation, but university students were awarded with course credits. Participants were only included if they (1) were free from neurological and hand-mobility difficulties, (2) had never been diagnosed with dysgraphia or dyslexia, (3) had not been treated with medication affecting the central nervous system in the last six months, and (4) were not under illicit drug or other substance abuse.

2.2.2 Participants’ characteristics after recruitment

Sixty participants comprised our final sample, in accordance with our sampling plan. More specifically, two handedness groups of equal size based on their score in the EHI (for left handers, mean score = 18.5, SD = 14.8; for right-handers, mean score = 88.3, SD = 12.6) completed all the tasks and provided acceptable fTCD data. The left-handers’ group (mean age = 30.6 years, SD = 9.3) consisted of seven male participants and 23 female participants, while the right-handers’ group (mean age = 30.6 years, SD = 9.2) consisted of three male participants and 27 female participants. Three rounds of data analysis were performed before recruiting the maximum number of participants. Following our SBF design, data collection was discontinued after reaching our upper limit of 60 participants, as the BF for each round failed to reach our predetermined threshold (⅙ < BF < 6). The outcomes for each round for the *t*-test and correlation are provided in Supplementary Tables 1 and 2 respectively. Additionally, an SBF analysis for each individual comparison is presented in Supplementary Figures 1 and 2.

One hundred and forty-eight people declared interest to participate in the study, out of whom, 81 agreed to participate. Eleven volunteers (13.6%) were dismissed after a failure to detect the temporal window for one of their medial cerebral arteries, an exclusion rate lower compared to previous studies (e.g., 15% in Knake et al., 2003, 18.9% in Kondyli et al., 2017, 19% in Papadatou-Pastou et al., 2022), possibly due to the use of robotic probes. Data were collected from 70 of the remaining participants and 10 more participants were excluded (14.3%), having less than 10 epochs accepted in at least one of the three conditions (an exclusion rate similar to Kondyli et al., 2017 and Papadatou-Pastou et al., 2022; 16.7% and 14.8%, respectively).

2.2.3 Assessment of cerebral lateralization

Cerebral lateralization was assessed during three tasks: (1) Written Word Generation, (2) Letter Copying, and (3) Oral Word Generation. Participants completed 60 trials: 20 of each task, with blocks of 10 sequential trials interleaved for each condition (e.g., 10 Written Word Generation, then 10 Letter Copying, and finally 10 Oral Word Generation, which were then repeated in the same order after a break). Task order was counterbalanced for handedness. Each trial included the following (Figure 7):

1. Thirty-five seconds of rest, starting when a visual cue (reading “try to clear your mind”) was displayed on grey background

2. A preparatory cueing tone of 440 Hz for 500 milliseconds. At that time point, a marker was sent from the PC to the fTCD device for synchronization purposes

3. A five-second pause (not including the preparatory cueing tone)

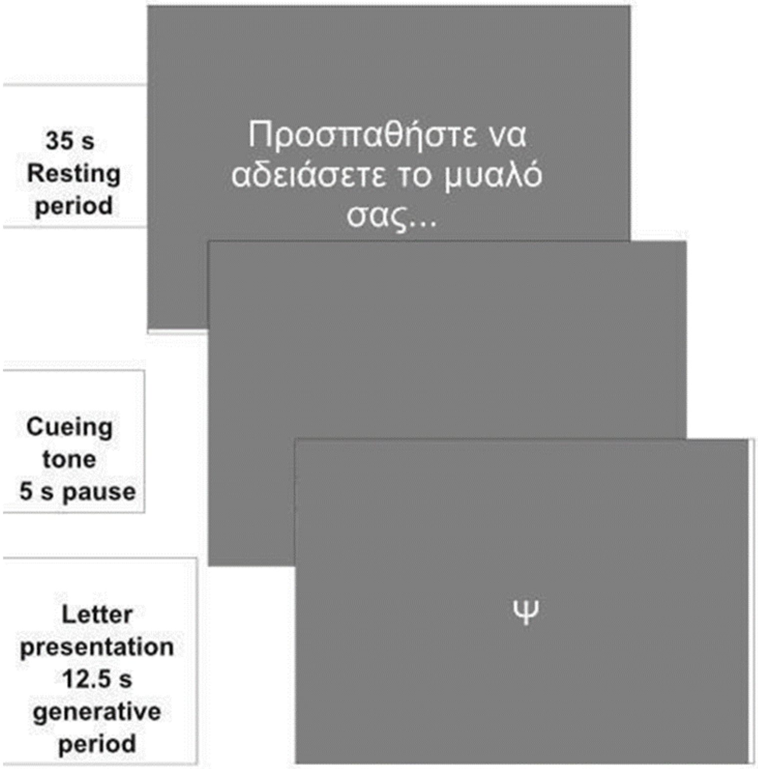
4. The appearance of a letter of the Greek alphabet (in white Arial font) in the middle of the screen (grey background) for 2.5 seconds

5. A generating period of 12.5 seconds

For the Written Word Generation condition, participants were asked to write down as many words as possible starting with the presented letter. For the Letter Copying condition, they were asked to copy as many times as possible the presented letter. Finally, for the Oral Word Generation condition, participants were asked to orally produce as many words as possible starting with the presented letter. The words were whispered to avoid adding memory demands to the test, which is the case when participants are asked to silently generate the words and then report them afterwards (e.g., as in Kondyli et al., 2017). Of note, muscle movements during speech did not affect fTCD results (Gutierrez-Sigut et al., 2015; Woodhead et al., 2018). Twenty out of the 24 letters of the Greek alphabet were chosen, selected based on the highest levels of word generation (Kondyli et al., 2017).

Figure 7

Example of an fTCD task trial



2.2.4 Assessment of handedness

Edinburgh Handedness Inventory (EHI, Oldfield, 1971): Twelve questions based on the Greek translation of EHI (Papadatou-Pastou et al., 2022) were administered to assess hand, foot, and eye preference (the latter two collected for completion, to be uploaded with the rest of data, but not to be here analyzed). In order to assess hand preference, participants were asked which hand they used for writing, drawing, sweeping (the upper hand on a broom), holding a knife to carve meat, holding a spoon, opening the lid of a box, striking a match, throwing a ball, using scissors, and brushing their teeth. Moreover, the participants' preferred foot for kicking a ball indicated foot preference and the preferred eye for looking with one eye indicated eye preference. Participants were provided with five response options: "Always left" (= 0 points), "Usually left" (= 1 point), "No preference" (= 2 points), "Usually right" (= 3 points), and

"Always right" (= 4 points). A laterality index (LI) was calculated for each participant by dividing their total score by 40 (i.e., the maximum score for consistent "Always right" responses) and multiplying by 100. Zero % represented extreme left-handedness, while 100% represented extreme right-handedness. Participants with scores lower or equal to 50% were classified as left-handers and participants with scores higher than 50%, as right-handers, a cut-off point typically used in the literature (Kondyli et al., 2017; Papadatou-Pastou et al., 2022).

Annett's Peg-moving task (J. Annett et al., 1979): Participants were standing in front of a desk upon which a 38x18 cm wooden pegboard was placed (see Figure 8). The long sides of the pegboard house 20 x 1,2 cm (diameter) holes, 10 on each side, separated by 1,5 cm (from the centre of the holes on each side). The ten pegs were 7 cm long and 1 cm in diameter. Participants were asked to move all pegs from the full side to the empty side as quickly as possible, starting with the peg that was placed ipsilaterally to the hand used to move the pegs. Participants began with the right hand and alternated between hands, until they successfully performed three trials with each hand. In case a peg fell, the trial was repeated. Participants were asked to remain silent to avoid delays. A stopwatch was used to time each trial, starting when the first peg was touched and finishing when the last peg was released. The starting hand was positioned on top of the to-be-moved peg. An LI was calculated: LI = (LH - RH)/(LH + RH)*100, where LH was the mean completion time using the left hand and RH was the mean completion time using the right hand. A negative score indicated left-hand superiority and a positive score, right-hand superiority.

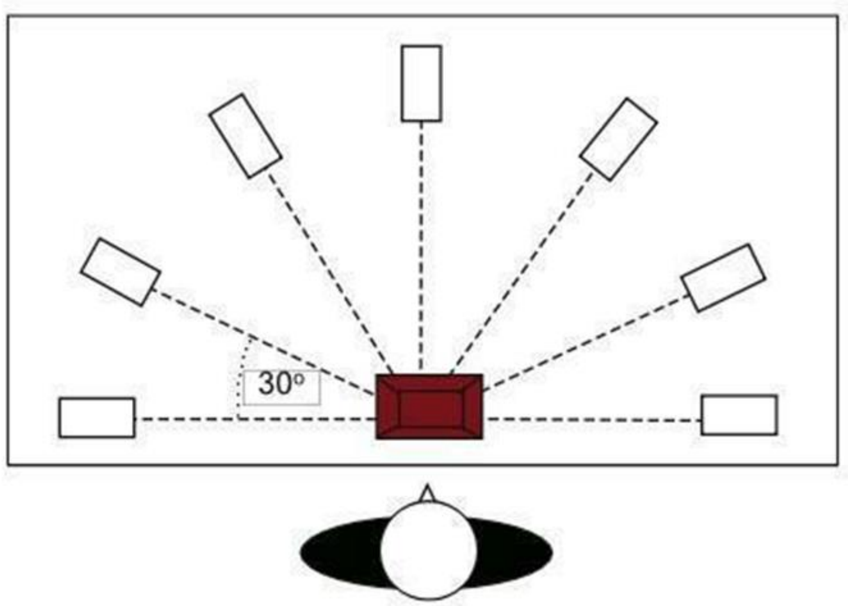
Figure 8

Wooden platform with wooden pegs, designed according to J. Annett et al. (1979)

Quantification of Hand Preference Test (QHPT, Bishop et al., 1996): Participants stood in front of a table with their hands resting on their sides. Seven positions were marked on the table, 40 cm from the midpoint of a baseline, at successive 30^{o} intervals (i.e., at the end of the arms in Figure 9). Three playing cards were stacked at each marked point. Participants were asked to pick up a named card and put it in a box in front of them. Cards were collected in a pseudo-random order (the same hand was not used more than two times in a row), identical for all participants. The hand used to pick up the card was recorded and 0 points were given for the use of the left hand, 1 point for changing hands (picking up with one hand and passing to the other for placement), and 2 points for the use of the right hand. For the LI, the total score was divided by 42 (i.e., the maximum score for consistent right-hand usage) and the fraction was multiplied by 100. Similarly to the LI for the EHI, 0% corresponded to extreme left-handedness, 100% corresponded to extreme right-handedness.

Figure 9

Representation of the spatial planning of the Quantification of Hand Preference Task (QHPT)



2.2.5 FTCD data collection and analysis

Two 2-MHz robotic transducer probes of a commercially available Doppler ultrasonography device (Delica EMS-9F) were fitted to an agile headset and situated on the left and the right temporal windows of the participant. The ultrasonography was performed at a depth optimal for each participant (45-56 mm) and at angles that provided the optimal signal density per participant. I used the PsychoPy open software (Peirce et al., 2019) to present visual and auditory stimuli (i.e., the letters and the cueing tone), and to send marker pulses to the Delica system to annotate the preparatory cueing tone. The spectral envelope of the Doppler signal was extracted at a frequency of 100 Hz and was saved for offline analysis. Participants were excluded in cases where ultrasonography was not technically possible due to insufficient penetration of the skull by the ultrasound beam or due to poor recordings, when there were fewer than ten accepted epochs per condition.

Data analysis was carried out using the MATLAB-based toolbox DopStep (https://github.com/nicalbee/dopStep). The data were trimmed to remove unnecessary data from the start and end of the data file based on the epoch: 18 seconds prior to the cueing tone and 36 seconds after its appearance. Variability caused by heartbeat was removed (Deppe et al., 1997; Knecht et al., 1998; Meyer et al., 2014) using a linear correction (see Badcock et al., 2018). Extreme values, beyond -3 to 4 SD from the mean (following Bishop et al., 2014) affecting less than 5% of the data (assumed due to minor signal dropout) were corrected using a linear interpolation from 1.5 s either side of the extreme value. The blood flow velocity of each channel, left and right, was normalized to a mean of 100 at an epoch-by-epoch basis. Epochs containing cerebral blood flow velocity values outside the range of 70% to 130% of the mean or an absolute left-minus-right channel difference of 20% multiplied by each individual's inter-quartile range, affecting more than 1% of the data, were rejected. The remaining data were corrected for the baseline activation during the control period, prior to the cueing tone, on an epoch-by-epoch basis. The final data were then averaged and the laterality index (LI) was calculated as the average left-minus-right channel difference within the period of interest (POI). The POI included the time period 7 to 24 seconds after the cueing tone, when maximum activation was taking place. I calculated an LI for each condition: LI_{words} for the Written Word Generation condition, $LI_{letters}$ for the Letter Copying condition and LI_{oral} for the Oral Word generation. A fourth LI was also calculated, representing the difference between the Written Word Generation condition and the Letter Copying condition ($LI_{difference} = LI_{words} - LI_{letters}$). The split-half reliability for the consistency of mean LI across trials for each task was correlated between odd and even trials (Bishop et al., 2021). Analysis proceeded only for those tasks that provided a split-half reliability coefficient greater than or equal to 0.5 ("moderate reliability"; Koo and Li, 2016; Parsons et al., 2019).

2.2.6 Procedure

Participants received an online questionnaire including items on native language and quality of vision, for screening purposes. For those who met the inclusion criteria, I sent an online information sheet 72 hours prior to their participation, allowing adequate time to make their final decision. On the day of participation, the experimenters described the process and the aims of the study to the participants, inviting them to express any concerns and they also reminded participants that they were free to leave the study at any time without justification. After providing written informed consent, participants were led to a quiet room and requested to sit in front of a computer screen, while given the choice of watching the beginning of a movie while the probes were being placed. The collection of fTCD data then took place. During the fTCD break, the participants' handedness was assessed. After completion, participants were debriefed.

2.2.7 Analysis plan

Analyses were performed using R [Version 4.1.2; R Core Team (2021)]. For the editing of the manuscript I used the package *papaja* [Version 0.1.0.9997; Aust and Barth (2020)], and for the Bayesian analyses I used the packages: BayesFactor (Morey & Rouder, 2022), Bolstad (Curran & Bolstad, 2020), correlation (Makowski et al., 2019), devtools (Wickham et al., 2022), dplyr (Wickham et al., 2022), readxl (Wickham & Bryan, 2022), remotes (Csárdi et al., 2021), stats (R Core Team, 2022), tidyverse (Wickham et al., 2019), utils (R Core Team, 2022; specific analysis packages were not preregistered). I adopted a Bayesian approach to hypothesis testing. Bayesian inference is becoming increasingly popular (van Doorn et al., 2021), as it allows the monitoring of evidence as the data accumulate (Rouder, 2014). Moreover, in contrast to the frequentist approach, the Bayesian approach can discriminate between "absence of evidence" and "evidence of absence," by providing evidence in favor of the null hypothesis (Dienes, 2014; Keysers et al., 2020), which was particularly important in the case of Hypothesis 2 (*"Oral* *language and the linguistic component of written language will not be correlated in terms of cerebral lateralization"*).

Hypothesis 1: Our first hypothesis (*"Left-handers will have weaker left-sided lateralization for the linguistic component of the written word generation"*) was tested using the Bayesian *t*-test for independent groups (left-handers vs. right-handers; outcome variable: $LI_{difference}$). The linguistic component of writing was isolated from the motor component of writing by using the Letter Copying condition as an active baseline for the Written Word Generation condition. The Bayes Factor implied the likelihood of the alternative (difference between handedness groups in the linguistic components of writing) over the null hypothesis. The prior for the *t*-test was described by a half-Cauchy distribution (Rouder et al., 2009) and with a width parameter of 0.94 (Schmalz et al., 2021). The value of the width parameter was equal to Cohen's *d* for the difference in lateralization for the linguistic component of writing (using copying symbols as an active baseline to writing words) between left-handers and right-handers in Papadatou-Pastou et al. (2022).

Hypothesis 2: The second hypothesis (*"Oral language and the linguistic component of written language will not be correlated in terms of cerebral lateralization"*) was tested by performing a Bayesian Spearman correlation for the LI_{oral} and $LI_{difference}$. Assuming that our results were in favor of the null hypothesis (Kondyli et al., 2017), the prior of the correlation was expressed from a Beta distribution with a width of 1.

LI measurement reliability: The consistency of the measurement of the lateralization indices across trials was verified using Spearman correlation of the mean LI of each task type (LI_{oral}, LI_{words}, and $LI_{letters}$) between odd and even trials (Bishop et al., 2021). In order to ensure that I was able to estimate any level of reliability, I assigned equal probability to all possible correlations. Therefore, the priors for the Spearman correlations were described by Beta(1,1) distributions, which corresponded to uniform distributions with equal probabilities for all values between 0 and 1.

Exploratory (non-registered) analyses: The additional analyses that I conducted to further explore our data are the following:

(a) Bayesian one-sample *t*-tests against zero for each condition in each handedness group. For each of these *t*-tests priors were described by a half-Cauchy distribution (Rouder et al., 2009). For oral language, the width parameter was set to 1.47 (Kondyli et al., 2017), for written language, 0.55 and 1.28 for left-handers and right-handers respectively (Papadatou-Pastou et al., 2022), for letter copying, 0.6 and 0.5 for left-handers and right-handers respectively (Papadatou-Pastou et al., 2022), and for the linguistic component of written language, 0.94 (Papadatou-Pastou et al., 2022).

(b) Bayesian *t*-tests for the independent handedness groups for each condition except for the pre-registered analysis for the $LI_{difference}$. For each of these *t*-tests, priors were described by a half-Cauchy distribution (Rouder et al., 2009). For oral language, the width parameter was set to 1.47 (Kondyli et al., 2017), while for the remaining conditions the default width parameter of the R-based module was kept, which was equal to 0.707.

(c) Classification of participants according to the cerebral lateralization for oral language using jackknifed standard deviations both for the registered period of interest, but also for a shorter period of interest following observation of the results (Papadatou-Pastou et al., 2022; Robertson, 1991).

(d) Bayesian *t*-tests for the groups representing cerebral lateralization for oral language for $LI_{difference}$ (i.e., left-hemisphere dominant and right-hemisphere dominant participants). Priors were described by a half-Cauchy distribution (Rouder et al., 2009) and the width parameter had the default value of 0.707.

(e) Bayesian Spearman's correlations between LI_{oral} and $LI_{difference}$ for each handedness group. The priors were described by Beta(1,1) distributions.

(f) A Bayesian Spearman correlation between even and odd trials for the difference of the $LI_{letters}$ from LI_{words} on a case-wise basis (e.g., trial 1 for written word generation was matched with trial 1 for letter copying, trial 2 for written word generation was matched with trial 2 for letter copying). The priors were described by a Beta (1,1) distribution.

2.2.8 Ethical considerations

The study has received ethical approval from the National and Kapodistrian University, School of Education (Protocol Number: 1936/02.25.2020) and the Biomedical Research Foundation of the Academy of Athens' Ethics Committee (Protocol Number: 66/05.25.2020). The data collection started no sooner than the acceptance of Stage 1 submission.

2.2.9 Data availability

All materials, code and data have been uploaded in the Open Science Framework online repository (https://osf.io/56vnq/).

2.3 RESULTS

High split-half reliability was found for all tasks (for oral word generation: rho = 0.80, BF = 5.04×10^{12}; for written word generation: rho = 0.94, BF = 8.50×10^{24}; for copying letters: rho = 0.92, BF = 2.54×10^{23}; for the difference scores: rho = 0.63, BF = 6.26×10^{5}). Therefore, our preregistered LI measurement reliability criterion of rho > 0.5 was met and all tasks were entered into the analysis.

The average change in blood flow velocity in each condition is presented separately for the two handedness groups in Figure 10. The lateralization indices (LI) for the different handedness groups in each condition are plotted in Figure 11 and summarized in Table 1. In accordance with the literature, both oral and written word generation were left-lateralized for right-handed participants. When it comes to left-handers, the use of their dominant hand while writing led to a right-sided lateralization for written word generation, but the mean lateralization index for oral word generation was only slightly positive (left-sided). Cerebral lateralization for copying letters was also right-sided, as expected, for left-handers, even more to a higher degree compared to that for written word generation. Surprisingly, the lateralization index for copying letters was barely positive for left-handers. Moreover, using jackknifed standard deviations (following Papadatou-Pastou et al., 2022) to classify participants in terms of lateralization for copying letters, I showed that 19 right-handers (63%) and two left-handers were left-lateralized (7%). Considering that copying letters would only engage the motor component of writing and, hence, that typically participants would be lateralized contralaterally to their dominant hand, 37% of right-handers were atypically lateralized for copying letters as opposed to 7% for left-handers. Despite the differences in the lateralization for written language and letter copying between handedness groups, the lateralization for the linguistic component of written language, calculated by subtracting the LI for copying letters from the LI for written word generation, was left-sided for both left-handed and right-handed participants.

To confirm that the LI in each condition and each handedness group were different to zero, I conducted non-preregistered one-sample Bayesian *t*-tests against zero. I showed strong or extreme evidence in favor of the alternative hypothesis for the lateralization index for oral word generation in right-handers (BF =20.18, [95% Credible Interval] 95%CrI = [0.263, 1.034]), for written word generation in both handedness groups (right-handers: BF = 2337225, 95%CrI = [0.962, 2.031]; left-handers: BF = 6503.39, 95%CrI = [-1.479, -0.543]), for letter copying in left-handers (BF = 1.04×10^7, 95%CrI = [-2.098, -1.069]), and for the linguistic component of written language in both handedness groups (right-handers: BF = 2923149, 95%CrI = [0.888, 1.939] ; left-handers: BF = 80.48 , 95%CrI = [0.323, 1.111]). Noteworthily, our data provided moderate evidence that the lateralization index for oral word generation in left-handers was not different to zero (BF = 0.28, 95%CrI = [-0.092, 0.627]), while there was only anecdotal evidence that the lateralization index for letter copying in right-handers was not different than zero (BF = 0.43, 95%CrI = [-0.164, 0.502]).

Table 1

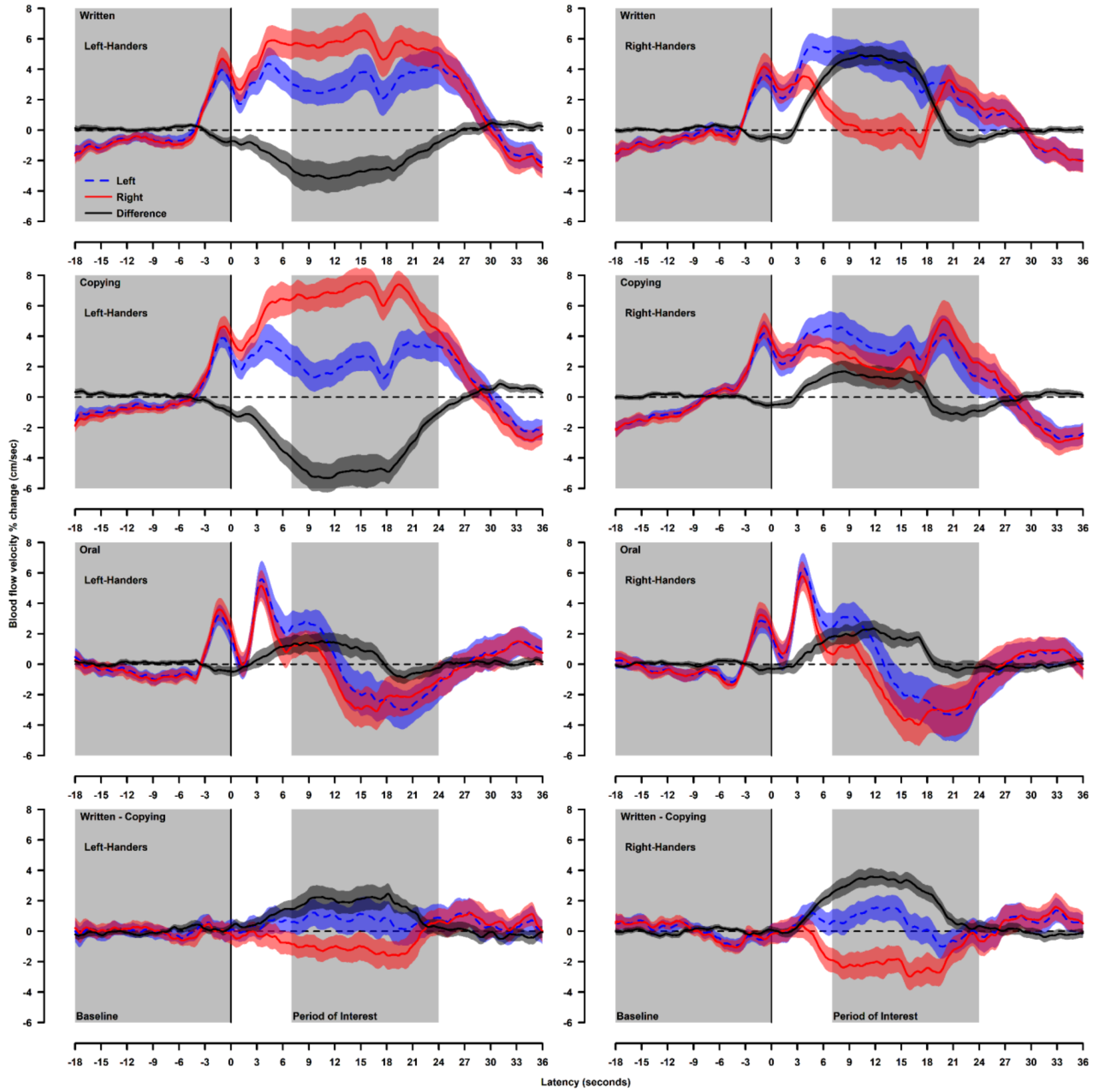
Descriptive statistics for cerebral lateralization in the different functional transcranial Doppler ultrasonography conditions.

Condition	Handedness	n	Number of epochs	Mean	SD	Median	Min /Max
Oral word generation	R L	30 30	17.5 18.1	1.18 0.47	.79 .75	1.59 0.39	[-3.63, 3.74] [-2.79, 4.87]
Written word generation	R L	30 30	18.6 18	2.82 2.73	.91 .58	2.87 2.67	[-0.94, 6.91] [-8.47, 1.43]
Letter copying	R L	30 30	18.7 17.7	0.45 4.47	.26 .77	0.67 4.37	[-5.71, 3.43] [-9.38, 2.59]
Word - Letter	R L	30 30		2.37 1.73	.58 .34	2.13 1.94	[-0.54, 5.56] [-5, 6.94]

Note: SD: Standard Deviation, Max: The maximum score observed in the handedness group for the condition, Min: The minimum score observed in the handedness group for the condition.

Figure 10

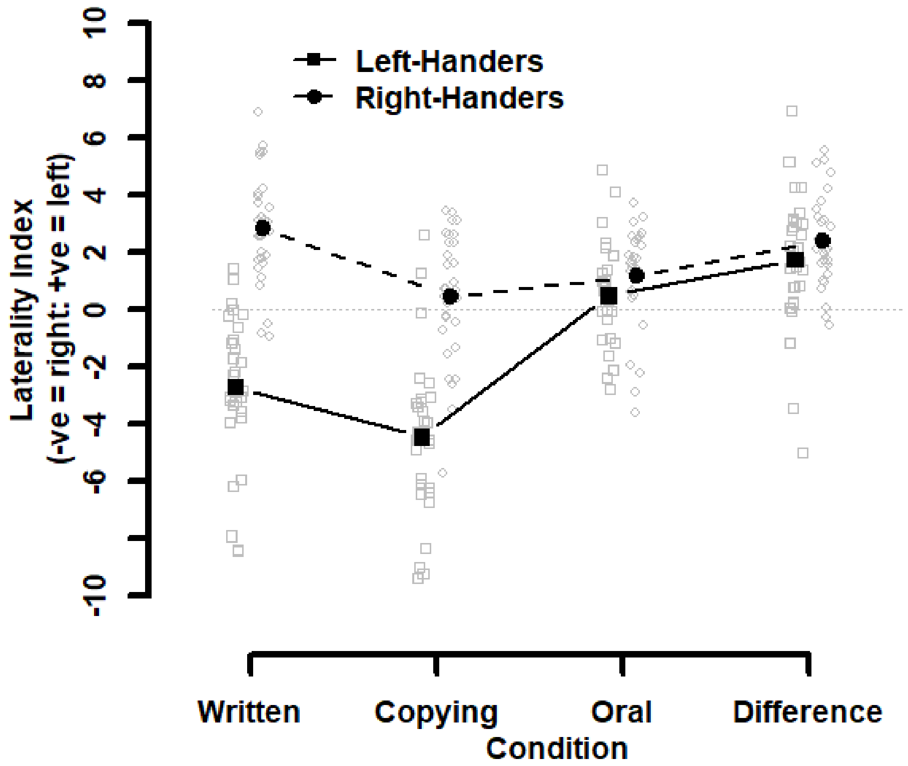
Event-related blood flow chart for each condition and each handedness group



Note: Different conditions are presented in separate rows (first row: written word generation, second row: copying letters, third row: oral word generation, fourth row: written word generation minus copying letters). Different handedness groups as determined by EHI are presented in separate columns (left column: left-handers, right-column: right-handers). The dashed blue line represents the average blood flow of the left channel, the red line represents the average blood flow of the right channel, and the black line represents the average blood flow when subtracting the blood flow of the right channel from the blood flow of the left channel. The colored shades around these lines depict the respective 95% confidence intervals. The baseline period and the period of interest are grey.

Figure 11

Lateralization indices per condition and handedness group



Note: Different conditions are presented in different columns (starting from the right, first column: written word generation, second column: copying letters, third column: oral word generation, and forth column: linguistic component of written language). The handedness of participants according to EHI is depicted as squares crossed by straight lines (left-handers) and circles crossed by dashed lines (right-handers). Grey symbols correspond to each participant's indices and black bold symbols correspond to the mean lateralization index of each handedness group in each condition.

2.3.1 Registered hypotheses

Hypothesis 1: *Left-handers will have weaker left-sided lateralization for the linguistic component of the written word generation compared to right-handers*

A Bayesian *t*-test for independent groups (left-handers vs. right-handers; outcome variable: $LI_{difference}$; prior described by a half-Cauchy distribution with a width parameter r = 0.94) provided anecdotal evidence that the $LI_{difference}$ does not differ between left-handers and right-handers (BF = 0.40, 95%CrI = [-0.786, 0.20]). Therefore, not enough evidence was found to support either hypothesis.

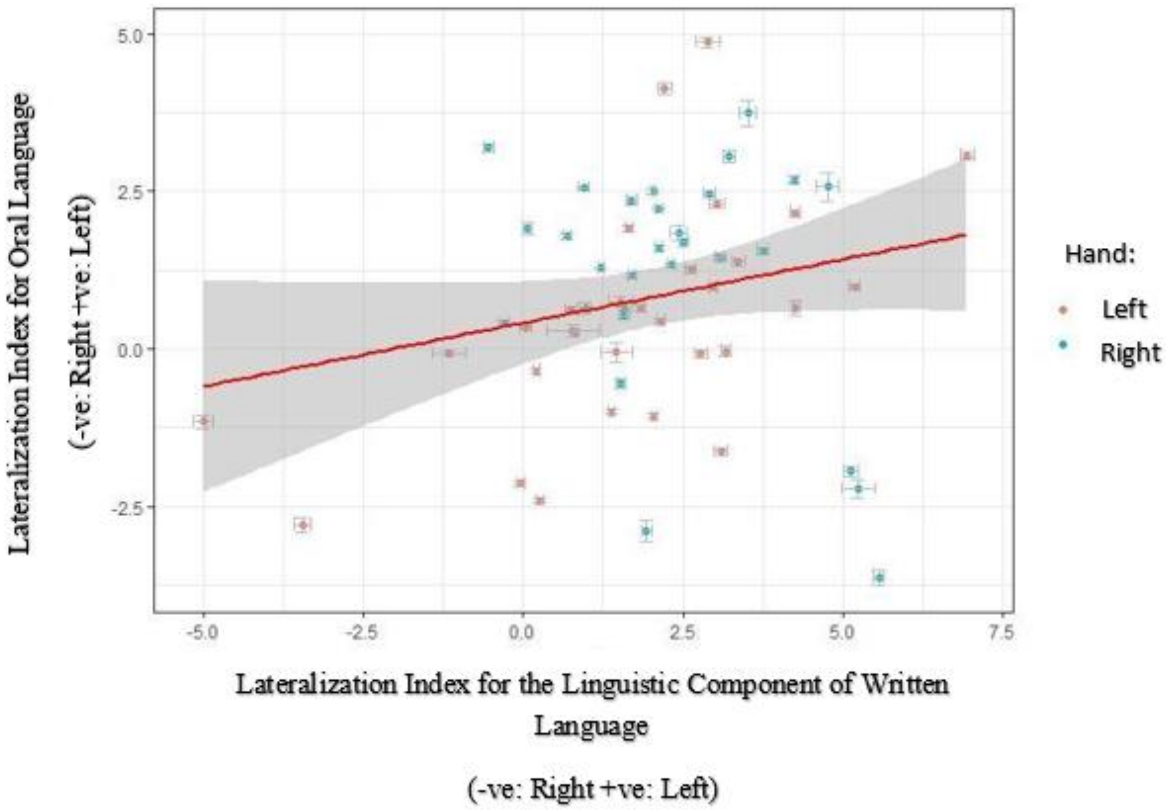
A robustness check was performed for a wide range of priors (0-1.5) and showed that only for Cauchy priors wider than 1.25 the Bayes factor stays between 1/10 and ⅓, corresponding to moderate evidence in favor of the null hypothesis, while smaller priors would still provide evidence in favor of the null hypothesis, however, that evidence is considered anecdotal. Therefore, for the given sample size, adequate evidence for the null hypothesis was only provided with very wide (r = 1.5) priors (Supplementary Figure 3).

Hypothesis 2: *Oral language and the linguistic component of written language will not be correlated in terms of cerebral lateralization*

The Bayesian approach for Spearman's correlation showed that there was only anecdotal evidence in favor of the alternative hypothesis for a weak correlation between the LI_{oral} and $LI_{difference}$ (rho = 0.27, BF = 1.75; Figure 6). For Hypothesis 2, the Beta prior distribution that was used creates a uniform distribution, which assumes equal probabilities for all values of rho. Thus, contrary to a Cauchy prior, any changes on the prior scale value changes the assumptions of the test. For example, for smaller priors (e.g., width > 1), the assumption could correspond to the alternative hypothesis that a correlation is not small (e.g., for a width of 0.1, the correlation is not -0.25 < rho < 0.25). Therefore, a robustness check was not conducted here, as it could have resulted in a misinterpretation of the results.

Figure 12

Scatter plot of the lateralization indices for the oral word generation condition and the linguistic component of written language.



Note: The bars correspond to the 95% confidence intervals for the LI of each participant (horizontal: $LI_{difference}$, vertical: LI_{oral}). The different handedness groups are depicted with different colours (red for left-handers and blue for right-handers), with handedness being determined according to Edinburgh Handedness Inventory. The red line shows the linear trend of the correlation surrounded by the standard deviation of the values (grey area).

2.3.2 Exploratory analyses

Different handedness criteria

The handedness of participants was determined according to the score in EHI for the preregistered analysis. Complementary data of handedness using another handedness task that assesses preference (Quantification of Hand Preference) and a handedness task that assesses hand skill (Peg-moving) are presented on Supplementary Table 3. The distribution of participants following the classification with the different handedness criteria is described in Supplementary Table 4. Correlations of the different handedness tasks with the LI corresponding to the three conditions as well as the LI corresponding to the linguistic component of writing are presented in Supplementary Table 5.

Differences between left-hemispheric and right-hemispheric dominant individuals

I further classified participants according to their lateralization for oral language using the jackknifed standard deviations (following Papadatou-Pastou et al. 2022). Twenty-five of the 30 right-handers (83%) and 18 out of the 30 left-handers (60%) were left-hemispheric dominant for oral language. Therefore, our sample consisted of 43 left-hemispheric dominant participants, 15 right-hemispheric dominant participants, and two bilateral left-handed participants (in total 17 participants of atypical lateralization), in terms of the lateralization for oral language.

A Bayesian *t*-test for independent groups (left-hemispheric dominant for oral language, right-hemispheric dominant for oral language; bilateral participants were excluded from this analysis) according to oral language hemispheric dominance with the $LI_{difference}$ as the dependent variable was conducted to assess the difference in the lateralization for the linguistic component of written language based on oral language lateralization. Similarly to the comparison between handedness groups, this analysis provided only anecdotal evidence in favor of the null hypothesis (BF = 0.90; 95% CrI = [-0.136, 0.987]), meaning that I cannot conclude a difference in lateralization for the linguistic component of written language even when I classify participants according to their lateralization for oral language instead of handedness.

Conducting this analysis separately for each group showed that there is moderate evidence that the lateralization index for the linguistic component of written language is greater for participants who are right-lateralized or bilateral in terms of oral language compared to participants typically lateralized for oral language in each handedness group (right-handers: BF = 3.37, 95%CrI = [0.023, 1.975]; left-handers: BF = 5.95; 95%CrI = [-1.673, -0.135]).

Shortening the period of interest (POI)

Upon observing the average blood flow for each group of participants in each condition (Figure 10), I noticed a change in the blood flow velocity 18 seconds after the presentation of the visual stimulus, irrespective of the task performed. For exploration and given that the literature on cerebral lateralization for oral language is more common, I was interested in classifying participants as left or right dominant for oral word generation using 7-18 seconds as an alternative POI, in addition to the preregistered 7-24 POI. For the 7-18 sec POI, 84% of right-handers and 70% of left-handers were left-dominant for oral language.

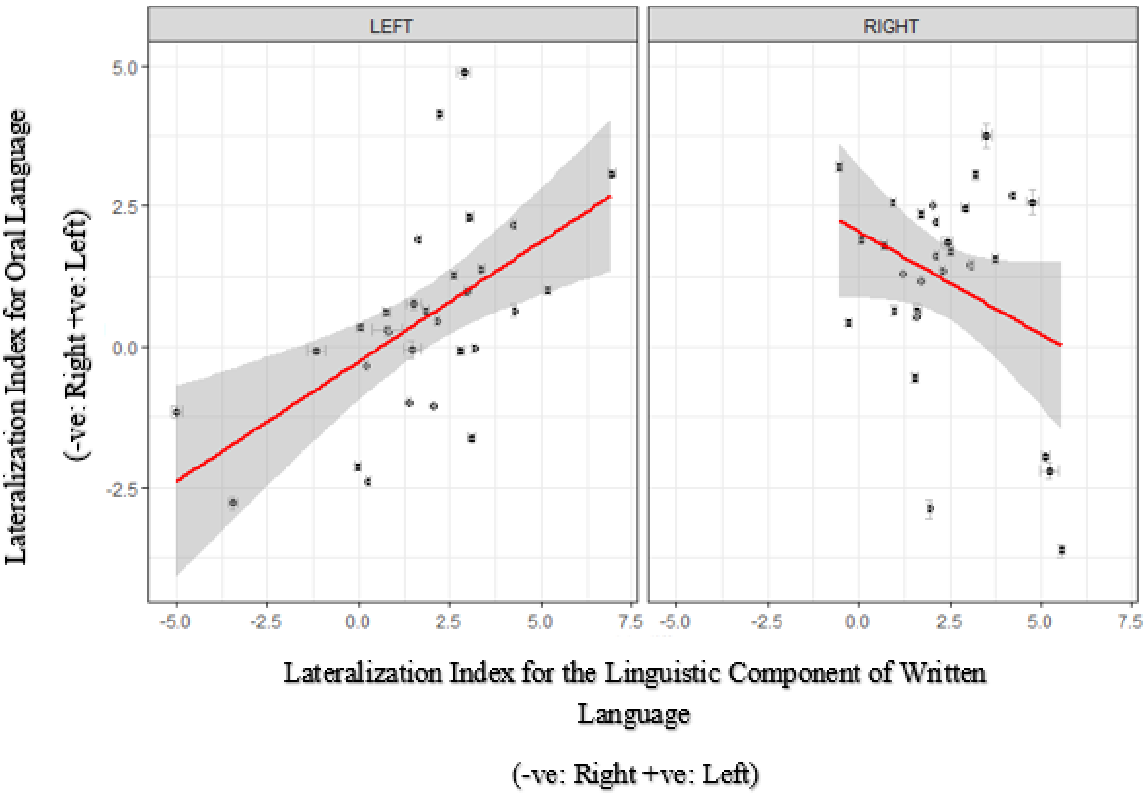
The most published approach, though now superseded, to assess cerebral lateralization is to focus on a 2-second period around the peak activation during the given POI (7-24 in our case). I conducted this approach for comparison purposes, which showed 84% of right-handers and 70% of left-handers were left dominant for oral language. Of note, there is evidence that the peak approach produces biased findings (Petit et al., 2020; Woodhead et al., 2020).

Correlations between the indices for the linguistic component of written language and the oral language in each handedness group

Visual inspection of Figure 12 suggested that some effects might be found within handedness groups, but without resulting in a correlation between these variables throughout the sample (as tested in Hypothesis 2). I therefore conducted Bayesian Spearman's correlation for each handedness group separately (Figure 13). Noteworthily, these analyses provided anecdotal evidence for a lack of correlation between the LI_{oral} and the $LI_{difference}$ for right-handers (rho = -0.16, BF = 0.351) and extreme evidence for a moderate positive correlation between these two variables in left-handers (rho = 0.58, BF = 114.37). Consequently, while in left-handers oral word generation and the linguistic component of written language tend to be lateralized in the same direction, for right-handers, the evidence is unclear.

Figure 13

Scatter plot of the lateralization indices for oral word generation condition and for the linguistic component of written language for each handedness group (left panel: left-handers, right panel: right-handers.



Note: The bars correspond to the 95% confidence intervals for the LI of each participant (horizontal: $LI_{difference}$, vertical: LI_{oral}). The different handedness groups have been determined according to the Edinburgh Handedness Inventory. The red line corresponds to the linear trend of the correlation coefficients surrounded by their standard deviation (grey area).

2.4 Discussion

The aim of the present registered study was (a) to compare the lateralization for the linguistic component of written language between left-handed and right-handed adults and (b) to explore the correlation between the lateralization indices corresponding to the linguistic component of written language and oral language. To achieve these goals, the relative hemispheric activation of 30 participants in each handedness group was recorded using fTCD while participants performed three different tasks: (a) oral word generation, (b) written word generation, and (c) letter copying. The lateralization index for the linguistic component of written language was computed by subtracting the lateralization index for copying letters (control task) from the lateralization index for writing words. Of note, this control task was chosen as an improvement upon the control task used by Papadatou-Pastou et al. (2022), who employed symbol copying as a control task, a task that was suggested to have higher attentional demands (as symbols are more novel stimuli compared to letters), which in turn could have resulted in right-hemispheric activation. The data for each of our variables were strongly reliable, with the split-half reliability for the lateralization for the linguistic component of written language being the lowest among them. This was potentially due to the reduction of the usable data related to the case-wise basis of our analysis. In other words, when a trial was excluded in either of the two tasks due to poor signal quality, then the trial was excluded for the other task too, even if the signal quality was good.

Our first hypothesis was that the linguistic component of written language would be less left-lateralized in left-handers compared to right-handers. This hypothesis was developed following the findings of Papadatou-Pastou et al. (2022) and under the rationale that oral language production is left-lateralized in the majority of neurotypical adults (e.g., Assaneo et al., 2019; Kell et al., 2011; for a review, see Hodgson & Hudson, 2018), though to a smaller degree in left-handers (Bruckert et al., 2021; Knecht et al., 2000; Kondyli et al., 2017; van der

Haegen & Brysbaert, 2018), and I expected the linguistic component of written language to share this property. Even though the linguistic component of written language was indeed left-lateralized for both handedness groups and the absolute mean for left-handers was smaller compared to right-handers, evidence was insufficient to support either hypothesis (BF = 0.40, 95% CrI = [-0.691, 0.281]). This null finding could be attributed to the fact that written and oral language production do not share the same neural underpinnings, therefore properties of oral language production (e.g., the weaker lateralization of left-handers) might not apply to written language. It is worth noting that within the modality of oral language there are properties, such as the affective aspects (Kreiner & Eviatar, 2014; Schirmer et al., 2001) and intonation (Behrens, 1989) that seem to be right-lateralized, and this could also be true for the linguistic component of written language production. However, I suggest that a more likely interpretation is the failure of the control task to isolate motor movement. More specifically, with respect to the lateralization for letter copying, one third of right-handers were not left lateralized, which is higher than expected. If letter copying solely engaged the motor component of writing, as assumed, the majority of left-handers should have been right dominant. Nevertheless, this is the case for only 7% of left-handers. This observation, together with the indication for the lack of difference between handedness groups in terms of the linguistic component of written language, might imply that the control task (letter copying) failed to isolate the motor component of written language that activated the two hemispheres. More specifically, letter copying seems to be associated with right hemisphere-related functions, as discussed below.

Letter copying and word generation require the retrieval of the individual's writing type for a grapheme (allograph) and for a sequence of words starting with the same grapheme, respectively. Moreover, they both require muscle movement and coordination for handwriting, as well as the involvement of working memory to repeat the same letter for several seconds (letter copying) or to write down the list of the retrieved words (written word generation; Palmis et al., 2017). Yet, there are several additional properties in written word generation compared to letter copying that predict a difference in hemispheric activation during these tasks. Higher linguistic processes, such as syntactic, orthographic, and semantic processes are necessary for the formation of actual words (Palmis et al., 2017) compared to the rather automatic and monotonous process of non-propositional repetitive letter copying (Chang, 2020). Non-propositional language generation of speech is attributed to the activation of the right hemisphere (Code, 2021; Lindell, 2006; Speedie et al., 1993; Wray, 1992). Additionally, unless participants were thinking of the letter phoneme (e.g., /o/) and not the letter name (e.g., “omicron”), they may have been repeating these names approximately as many times as they wrote the grapheme during the copying period. This process is like the letter-by-letter reading strategy performed by poor readers, which has been associated with increased right-hemispheric activation (Hellige et al., 1989; Lindell, 2006). Furthermore, although participants were familiar with the to-be-copied visual stimuli, copying the same letter multiple times is an unusual task for adults and, thus, they might have needed to suppress some reflexive actions, such as writing the following letter of the alphabet or thinking of a word starting with that letter. This inhibition of behavioral responses during working memory requiring tasks is shown to be mediated by the right hemisphere (Aron et al., 2004; Van Ettinger-Veenstra et al., 2011; Villar-Rodriguez et al., 2024; Völlm et al., 2006). To conclude, there are several parameters in the nature of the letter copying task that could be linked to the relatively high involvement of the right hemisphere in the letter copying task.

Having observed the performance of participants during data collection, one could also take into consideration the emotional state of the participants during letter copying. On the one hand, what discriminated letter-copying from the rest of the tasks was the absence of creative thinking, making it less cognitively demanding. This led to boredom in some participants. Bored, low sensation seekers intensely activated right hemisphere regions in Joseph et al.’s (2009) study. Other participants, while engaging in the letter-copying, had their visual attention completely focused on repeating the letters and writing as many letters as possible in a competitive rhythm and they were aroused to listen for the stop cue. This restlessness could have led to an increased representation of right hemispheric activation in their data (for a review, see Comer et al., 2015). In fact, boredom and restlessness might have also been the case for participants having to copy symbols for the Papadatou-Pastou et al. (2022) study. Thus, the right-hemispheric activation found in that study during symbol-copying might be also attributed to these factors, in addition to the novelty of the to-be-copied stimuli.

Our second hypothesis was that the linguistic component of written language would not correlate with oral language in terms of cerebral lateralization. There was only anecdotal evidence for a weak positive correlation between these two variables (rho = 0.27, BF = 1.75), not allowing us to draw conclusions for our whole sample. However, when I assessed this correlation within each handedness group (i.e., non-registered analyses), there was extreme evidence that in left-handers oral word generation and the linguistic component of written language were lateralized in the same direction (rho = 0.58, BF = 114.37), while for right-handers there was only anecdotal evidence for no correlation (rho = -0.16, BF = 0.351). Thus, it seems that oral word generation and the linguistic component of written language are differently correlated in each handedness group, which explains the little evidence (BF<3) for Hypothesis 2. There are at least two possible interpretations for this finding. Firstly, it could be an aftereffect of the unexpected incidence of atypical lateralization for copying in right-handers, which might add to the argument that our task lacked sensitivity to disentangle the motor from the linguistic component of language. Nevertheless, this approach would cancel out the result for left-handers, which is supported by extreme evidence. Alternatively, this observation could be interpreted by hemispheric functional crowding. This theory hypothesizes that functions compete for the neural resources within the cortex (Levy, 1969), leading to complementary hemispheric dominance for interrelated functions (Cai et al., 2013; Gerrits et al., 2020; Gotts et al., 2013). This could imply that oral language and the linguistic component of written language might not occupy different regions as a result of the limited access to cortical resources of the right hemisphere assumed mainly in left-handers due to the higher degree of atypical lateralization for oral language. On the contrary, right-handers show typical organization for both oral and written language generation without facing crowding effects. This provides a target for future research.

Another explanation that could apply to the findings for both hypotheses is a decreased reliability of difference scores (e.g., $LI_{difference}$ in our case). However, this is true only when the original indices themselves have low reliability, leading to an even lower reliability for the difference score (Castro-Schillo & Grimm, 2017). Alternatively, the low reliability of difference scores could be caused by a low variance between participants (Hedge et al., 2018). In our case, the reliability for each of the constituent conditions is above 0.9, which is very high, while participants across our sample do not show low variance. Therefore, the possible low reliability of difference scores does not fit our data.

This study is characterized by several strengths and limitations. It is the first study to attempt to disentangle the linguistic component of written language from its motor complementary component using letter copying as a control task rather than the less ecologically equivalent task of symbol copying used in Papadatou-Pastou et al. (2022). Moreover, by adopting the Bayesian approach, I was able to distinguish between "absence of evidence" and "evidence of absence", which was crucial when dealing with the null hypothesis both in our registered and in our exploratory and supplementary analyses. One of the limitations of the study was that I might have underestimated the motor and/or linguistic activation required for letter copying compared to written word generation, which could have led to an insensitive measurement of the linguistic component of written language. Finally, fTCD measurements are limited by poor spatial resolution and, therefore, techniques that are designed to overcome this limitation, such as fMRI and Positron Emission Tomography could complement our findings.

In conclusion, while I showed that the linguistic component of written language is left-lateralized for both handedness groups, there is only anecdotal evidence that the linguistic component of writing does not differ in terms of lateralization between left-handers and right-handers. Moreover, there was anecdotal evidence for a positive relationship between the lateralization for the linguistic component of written language and the lateralization for oral word generation across our sample. Yet, when each handedness group was assessed separately, there was extreme evidence that oral word generation and the linguistic component of written language are positively correlated regarding lateralization. It seems that language, either oral or written, is complex and multifaceted with higher linguistic properties that remain to be unveiled and that handedness interplays with this complexity and should always be taken into consideration when it comes to cerebral lateralization.

Supplementary Table 1

Analyses results for the different lateralization indices for each round of data analysis prior to the collection of the final number of participants.

	LI_{oral}		LI_{words}		$LI_{letters}$		$LI_{difference}$	
Number of participants	95% CrI	BF_{10}	95% CrI	BF_{10}	95% CrI	BF_{10}	95% CrI	BF_{10}
48 (24 left- and 24 right-handers)	**[-0.891, 0.208]**	0.49	[-3.680, -1.994]	.31 x 10^{09}	[-3.171, -1.512]	1.48 x 10^{08}	[-0.814, 0.253]	0.38
52 (26 left- and 26 right-handers)	**[-0.897, 0.164]**	0.6	[-3.343, -1.800]	.47 x 10^{10}	[-3.103, -1.318]	.16 x 10^{08}	[-0.740, 0.285]	00.32
56 (28 left- and 28 right-handers)	**[-0.868, 0.138]**	0.6	[-3.155, -1.702]	.97 x 10^{10}	[-2.650, -1.349]	.79 x 10^{07}	[-0.749, 0.255]	0.33
60 (30 left- and 30 right-handers)	**[-0.879, 0.123]**	0.41	[-3.035, -1.762]	2.29 x 10^{10}	[-2.481, -1.190]	.02 x 10^{07}	[-0.786, 0.2]	0.40

Note: The *t*-scores for the first Hypothesis accompanied by the corresponding Bayes Factors are presented for the three rounds of data collection including 24, 26, 28, and 30 participants per handedness group respectively.

Supplementary Table 2

Analyses results for hypothesis 2 for each round of data analysis prior to the collection of the final number of participants

	Correlation	
Number of participants	Rho	BF_{10}
48 (24 left- and 24 right-handers)	0.26	0.956
52 (26 left- and 26 right-handers)	0.26	1.12
56 (28 left- and 28 right-handers)	0.2	0.521
60 (30 left- and 30 right-handers)	0.27	1.75

Note: The correlation coefficients for the second Hypothesis (lower table) accompanied by the corresponding Bayes Factors are presented for the three rounds of data collection including 24, 26, and 28 participants per handedness group respectively.

Supplementary Table 3

Descriptive statistics for handedness assessment measures.

Test	Handedness	n	Mean	SD	Median	Min/Max
Edinburgh Handedness Inventory	R	30	88.3	12.614.8	92.5	[55, 100]
	L	30	18.5		17.5	[0, 45]
Quantification of Hand Preference	R	30	65.9	1623.6	61.9	[42.9, 100]
	L	30	31.1		31	[0, 85.7]
Peg-moving task	R	30	4.5	3.8	4.4	[-3.6, 13]
	L	30	-5.3	4.4	-5.4	[-12.4, 5.2]

Note: SD: Standard Deviation, Max: The maximum score observed in the handedness group for the task, Min: The minimum score observed in the handedness group for the task.

Supplementary Table 4

Distribution of left- and right-handers following different handedness measures

		Writing hand	EHI	QHPT	Peg-Moving
Writing hand	28 R		28 R (100%)	24 R & 4 L (85.7%)	26 R & 2 L (92.9%)
	32 L		2 R & 30 L (93.8%)	6 R & 26 L (81.3%)	5 R & 27 L (84.4%)
EHI	30 R	28 R & 2 L (93.3%)		25 R & 5 L (83.3%)	27 R & 3 L (90%)
	30 L	30 L (100%)		5 R & 25 L (83.3%)	4 R & 26 L (86.7%)
QHPT	30 R	24 R & 6 L (80%)	25 R & 5 L (83.3%)		26 R & 4 L (86.7%)
	30 L	4 R & 26 L (86.7%)	5 R & 25 L (83.3%)		5 R & 25 L (83.3%)
Peg-Moving	31 R	26 R & 5 L (83.9%)	27 R & 4 L (87.1%)	26 R & 5 L (83.9%)	
	29 L	2 R & 27 L (93.1%)	3 R & 26 L (89.7%)	4 R & 25 L (86.2%)	

Note: The percentage value in italics in the parentheses indicates the agreement between the corresponding handedness measures for each handedness direction. EHI: Edinburgh Handedness Inventory, QHPT: Quantification of Hand Preference task, R: Right-handed, L: Left-handed.

Supplementary Table 5

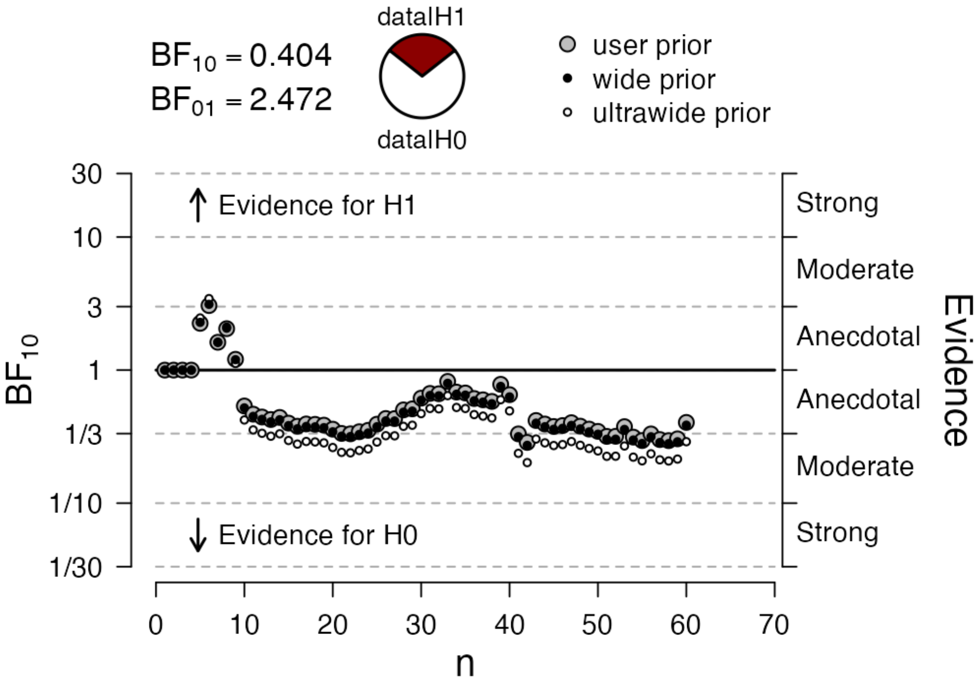
Correlation matrix for the different lateralization indices and handedness measures across the whole sample

	$LI_{difference}$	LI_{word}	LI_{letter}	LI_{oral}	EHI	QHPT
LI_{word}	*0.25 (1.17)*					
LI_{letter}	*-0.22 (0.726)*	*0.85 (1.13 x 10^{15})****				
LI_{oral}	*0.28 (1.75)*	*0.3 (2.82)*	*0.22 (0.721)*			
EHI	***0.06** (0.19)**	*0.75 (2.54 x 10^{07})****	*0.65 (4.82 x 10^{05})****	*0.27 (1.4)*		
QHPT	*0.1 (0.224)*	*0.52 (728.15)****	*0.46 (101.48)****	*0.24 (0.856)*	*0.63 (4.22 x 10^{04})****	
PEG	*0.38 (21.09)***	*0.7 (4.05 x 10^{07})****	*0.5 (1.06 x 10^{03})****	*0.29 (2.07)*	*0.75 (6.12 x 10^{08})****	*0.64 (2.84 x 10^{05})****

Note: The values represent the rho correlation coefficients and the numbers in parentheses correspond to the BF_{10} for each correlation. The asterisks show the level of evidence in favor of the alternative hypothesis (correlation between the assessed variables) with two asterisks corresponding to very strong evidence and three asterisks corresponding to extreme evidence. $LI_{difference}$: Lateralization index for the linguistic component of written language, LI_{word}: Lateralization index for written word generation, LI_{letter}: Lateralization index for letter copying, LI_{oral}: Lateralization index for oral word generation, EHI: Edinburgh Handedness Inventory, QHPT: Quantification of Hand Preference task, PEG: Peg-moving task.

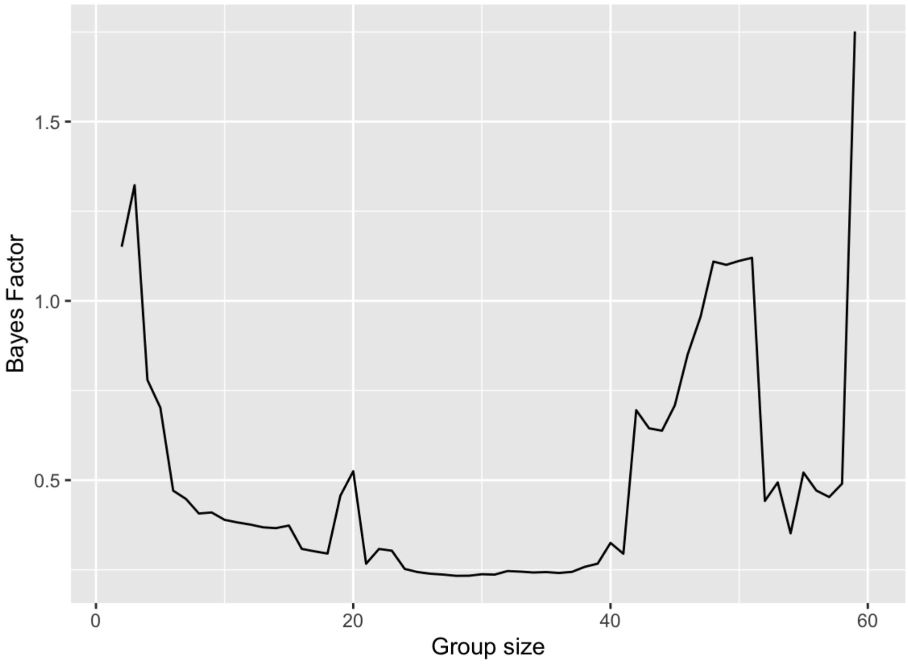
Supplementary Figure 1

Sequential analysis for Hypothesis 1.



Supplementary Figure 2

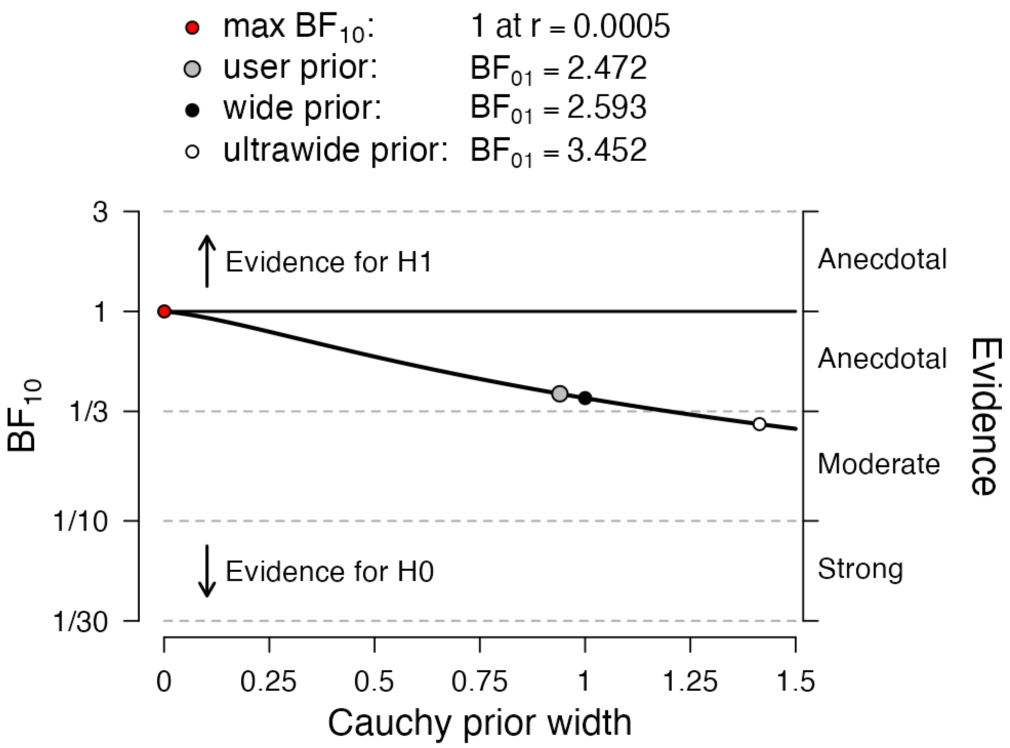
Sequential analysis for Hypothesis 2



Note: The x-axis represents the number of participants regardless of the handedness group in the order in which they were recruited in the study.

Supplementary Figure 3

Robustness check for priors for Hypothesis 1



3 CEREBRAL LATERALIZATION OF WRITING IN STUDENTS AT RISK FOR DYSLEXIA [2]

Abstract

It is well established that the left hemisphere is dominant for oral language in the majority of neurotypical individuals, while a more symmetrical pattern of activation is shown in cases of language disorders, such as dyslexia. Cerebral lateralization for written language, however, despite the critical role of writing in education and everyday communication, and the fact that children with dyslexia present with writing difficulties, has been investigated by only a few studies, none of which has sampled children, neurotypical or not. In this study, I aimed to investigate the cerebral lateralization for written language in 12 children at risk for dyslexia compared to 24 neurotypical children using functional transcranial Doppler ultrasonography. Although I hypothesized that the linguistic component of writing would be less lateralized in children at risk for dyslexia compared to controls, the data did not provide enough evidence either in favor or against this hypothesis. Additionally, I explored the correlation between writing competence, handwriting quality and orthography, and the cerebral lateralization for the linguistic component of written language and results indicated a lack of correlation.The inconclusive nature of the findings do not allow for a clear picture to be drawn. Future directions that this research could take to arrive at more robust conclusions are discussed..

[2] This study has received in principle acceptance as a Registered Report Stage 1: Papadopoulou, A.-K., Vlachos, F., Pervanidou, P., Anesiadou, S., Antoniou, F., Phylactou, P., Badcock, N.A. & Papadatou-Pastou, M. (2022). Cerebral lateralization of writing in students at risk for dyslexia using functional Transcranial Doppler ultrasonography, in principle acceptance of Version 2 by Peer Community in Registered Reports. https://osf.io/u54tk (under temporary private embargo)

Keywords: Writing, at-risk for dyslexia, functional Transcranial Doppler ultrasound, laterality

3.1 INTRODUCTION

An increasing number of students encounter difficulties keeping up with their peers in terms of reading and writing development as well as adjusting to the school curriculum (Karabulut, 2013; Morken et al., 2017; Seidenberg, 2017). Some of these children and adolescents might struggle with Specific Learning Disorders (SLD), such as dyslexia or dysgraphia. SLD are characterized by neurodevelopmental impairments (e.g., Altarelli et al., 2014; Bradshaw et al., 2020; Wilson & Bishop, 2018). A common trait of individuals with dyslexia or dysgraphia is an atypical pattern of cerebral lateralization for oral language, which corresponds to the relative degree of activation of brain hemispheres during oral language tasks (Araújo et al., 2012; Démonet et al., 2004; Filipek, 1996; Richards & Berninger, 2008; Vlachos & Avramidis, 2020; Wilson & Bishop, 2018). In fact, atypical lateralization for the perception of oral language is also observed in children at risk for familial dyslexia, even in infancy (Cantiani et al., 2019; Langer et al., 2017). Oddly, despite the importance of written language for educational and communication purposes (Graham & Hebert, 2010) and the presence of writing difficulties in individuals with dyslexia (Berninger et al., 2008; Berninger, 2007; Berninger & Richards, 2010; Morken et al., 2014), cerebral lateralization for written language is yet to be studied in individuals with dyslexia. The aim of the present pre-registration is to explore cerebral lateralization for written language in early primary school students at risk for dyslexia.

Dyslexia is a word of Greek origin standing for an impairment at the word level. Estimates of the worldwide prevalence of dyslexia vary between 3% to 10% (Miles, 2004; van Setten et al., 2016), while a 5.52% prevalence was shown in a sample of Greek adolescents

(Vlachos et al., 2013). This wide range of prevalence is mainly explained by the different orthographic complexity of languages and by the different diagnostic criteria used (Galliussi et al., 2020; Landerl et al., 2013; Richlan, 2020). For example, discrepancies in reading performance are less pronounced in regular orthographies (e.g., Italian) or semi-transparent spelling systems (e.g., Greek), for which a speech sound typically corresponds to a single written representation, compared to more complex orthographies, such as English or Hungarian (Landerl et al., 2013; Morken et al., 2017; Psaltou-Joycey et al., 2015). When it comes to the diagnostic criteria, according to the International Dyslexia Association, dyslexia is an unexpected -in relation to intelligence or access to education- neurobiological impairment reflecting difficulties in spelling, accuracy, and fluency in the process of oral reading (Lyon et al., 2003), while the fifth edition of the DSM-V (American Psychiatric Association, 2013) presents dyslexia as a manifestation of SLD, also including reading comprehension in the affected skills (Miciak & Fletcher, 2020; Richards & Berninger, 2008). In the definition of the tenth edition of the International Classification of Diseases, it is emphasized that dyslexia cannot be explained by the mental age, vision problems or inadequate education, and an addition of consequence for the current study is that writing difficulties often remain throughout life even after progress has been made in reading (World Health Organization, 2015).

The core deficit that characterizes the majority of individuals with dyslexia is a phonological impairment (de Jong et al., 1999; Gabrieli, 2009; Goswami, 2003; Morris et al., 1998; Peterson & Pennington, 2012; Shaywitz et al., 2004; Snowling, 2001; Snowling & Hulme, 2012; Vellutino et al., 2004; although also see Dickie et al., 2013; Kohnen et al., 2012; Werth, 2021, for subtypes of dyslexia without phonological impairment). This phonological impairment describes the difficulty in (i) the representation, that is the coding, of spoken syllables and phonemes (Archer et al., 2020; Goswami, 2011), (ii) in the storage, the categorization, and the conscious recollection of speech sounds and words (Araújo et al., 2012; Ramus & Szenkovits, 2008), and (iii) the difficulty in naming written letters and words (Boets et al., 2006, 2013; Démonet et al., 2004; Lieder et al., 2019; Manilla & de Braga, 2017; Marchesotti et al., 2020; Swan & Goswami, 1997; Vellutino et al., 2004; Vieira et al., 2013). In addition to the phonological impairment, individuals with dyslexia may have comorbid problems in aspects of their executive functions (Berninger et al., 2006, 2008; Guadalupe et al., 2017; Smith-Spark et al., 2003; Swanson, 1993; Swanson & Ashbaker, 2000), and of visual stimuli, such as written text (Archer et al., 2020; for a review see Elliott & Grigorenko, 2014). These difficulties manifest as early as the kindergarten years, when children may experience problems with pre-reading tasks (e.g., learning names), short-term memory tasks (e.g., memorizing a string of letters or digits for a short period of time), and phonological awareness tasks (e.g., matching letters to sounds) (Kujala & Näätänen, 2001; Ozernov-Palchik et al., 2017; Rouse & Fantuzzo, 2006; Temple et al., 2003; Vieira et al., 2013; Zakopoulou et al., 2011).

As mentioned, individuals with dyslexia often have persisting spelling and writing difficulties, which are significantly harder to overcome compared to reading difficulties (Berninger et al., 2008; Berninger, 2007; Lefly & Pennington, 1991; Richards et al., 2017). Coordination of fine hand movements and orthographic writing are key skills commonly impaired in these individuals (Berninger et al., 2002; Caravolas et al., 2020; Fawcett et al., 1996; Gross-Tsur et al., 1996; Kim et al., 2013; Nachshon & Horowitz-Kraus, 2019; Shanahan et al., 2006). These difficulties are probably related to an attenuated loop between phonological and orthographic memory (Chung et al., 2020). Moreover, 30% to 47% of individuals with dyslexia are also diagnosed with dysgraphia (Ashraf & Najam, 2020; Berninger et al., 2008), an SLD related to impairments in the handwriting component of written language in spite of typical motor function (Berninger, 2009, 2004). Both SLD share the feature of compromised phonological awareness (Döhla & Heim, 2016; Vlachos & Avramidis, 2020). They differ in that dysgraphia specifically affects handwriting skills, while dyslexia has an impact on all aspects of writing (Chung et al., 2020; Döhla & Heim, 2016; Vlachos & Avramidis, 2020). Given the fact that handwriting is a skill acquired in early school years, the emergence of difficulties in written language may be delayed (Chung et al., 2020). This delay might explain why studies investigating the neurophysiological basis of dyslexia have focused on oral, rather than written language difficulties.

Such a neurophysiological inquiry is that of cerebral lateralization for language (see Ashburn et al., 2020; Munzer et al., 2020; Richlan, 2020). In terms of oral language, it has been established that, for the majority of neurotypical individuals, the network of brain regions implicated in oral language production and comprehension is located in the left hemisphere. This network is divided into two anatomical domains: (1) the anterior system, surrounding the left inferior frontal gyrus, associated with phonology and articulation (Barker et al., 2019; Braun et al., 2001; Richards et al., 2006; Richards & Berninger, 2008) and (2) the posterior system, a hub around the left superior temporal gyrus involved in speech planning and comprehension (Ardila et al., 2016; Barker et al., 2019; Braun et al., 2001; Lidzba et al., 2011). In terms of written language, research is more limited. However, findings show that the linguistic component of writing is also left-lateralized for most neurotypical individuals and associated with the activation of regions included in the above-mentioned network and adjacent brain areas (e.g., Nakamura et al., 2012; Potgieser et al., 2015; Yang et al., 2020). Regarding the motor component of language, while oral speech-related muscle movements are lateralized to the left motor cortex (Geranmayeh et al., 2012), motor demands of writing are more complex and are thus represented more broadly in the brain. They activate the primary motor and the premotor cortex of the hemisphere contralateral to the writing hand, which controls the execution of writing (Diwadkar et al., 2017; Longcamp et al., 2003; Potgieser et al., 2015; Richards et al., 2011), as well as the cerebellum, that is associated with the coordination of the movement and the automaticity of corresponding letters and sounds (Chung et al., 2020; Démonet et al., 2004; Planton et al., 2013; Purcell et al., 2011; Yang et al., 2020). Hence, the typical language lateralization is leftward for oral language and potentially less left-shifted for written language.

On the contrary, in individuals with dyslexia, language lateralization tends to be more atypical (i.e., less left lateralized or more symmetrically distributed) compared to that of neurotypical individuals (e.g., Altarelli et al., 2014; Araújo et al., 2012; Ashburn et al., 2020; Banfi et al., 2019; Illingworth & Bishop, 2009; Vlachos & Avramidis, 2020; Waldie & Hausmann, 2010). The decreased asymmetry for language in dyslexia could be attributed to the underactivation of regions of the network associated with oral language generation and processing (Araújo et al., 2012; Ashburn et al., 2020; Chen et al., 2014; Gabrieli, 2009; Hoeft et al., 2007; Kershner, 2019; Manilla & de Braga, 2017; Miciak & Fletcher, 2020; Munzer et al., 2020; Richards & Berninger, 2008; Richlan et al., 2011, 2009; Richlan, 2020; Scerri et al., 2011; Siok et al., 2008; van der Mark et al., 2011; Waldie & Hausmann, 2010) and to the hyperactivation of analogous regions of the right hemisphere, potentially to compensate for the atypical activation of regions of the left hemisphere (Jagger-Rickels et al., 2018; Richards et al., 2006; Richards & Berninger, 2008; Simos et al., 2002). Of note, phonological difficulties, similar to those found in individuals with dyslexia, are apparent in patients with agenesis of the corpus callosum (Banich & Brown, 2000). Therefore, the disruption in communication between the brain hemispheres, but also between regions of the reading network within the left hemisphere (Banfi et al., 2019; de Moura et al., 2016), could be associated with the atypical lateralization profile of individuals with dyslexia (Badzakova-Trajkov et al., 2005; Bradshaw et al., 2020; Kershner, 2019; Monaghan & Shillcock, 2008; Munzer et al., 2020). Eminently, many of the above-mentioned regions that show different activation during language tasks leading to a different cerebral lateralization pattern for individuals with dyslexia, are involved in the writing hub (Ashburn et al., 2020; Richlan et al., 2011; Scerri et al., 2011; Wang et al., 2020). Nevertheless, to our knowledge, no studies have assessed cerebral lateralization for written language per se, while only two studies have assessed differences in hemispheric functionality during writing in individuals with dyslexia (Richards et al., 2015; Richards et al., 2017).

In both studies (Richards et al., 2015; Richards et al., 2017), Richards and colleagues recruited 4th- to 9th- grade students with dyslexia or dysgraphia and typically developing controls in order to assess their white matter integrity, using diffusion tensor imaging, and their functional connectivity during single-letter writing, using fMRI. In Richards et al. (2015), they showed that (a) white matter integrity in left hemisphere seed regions (i.e., a collection of brain voxel points derived from previous brain imaging studies; Wu et al., 2018), associated with spelling, was decreased in both SLD groups compared to controls and (b) the functional connectivity of regions of the left hemisphere associated with writing was increased during the writing task in the dysgraphia group and at resting state in the dyslexia group, compared to the control group. In the 2017 study, Richards et al. (2017) showed that writing instruction affects white matter integrity in the left hemisphere in both SLD groups, with a difference in the affected regions of the left hemisphere between groups. The results for the functional connectivity of the left hemisphere regions did not meet the significance criterion for any diagnostic group. In both studies, Richards et al. assessed children that had already developed the full spectrum of SLD, and not children at risk for these SLD. This is important, as early detection and intervention for children at risk for dyslexia has been associated with greater efficiency in the reorganization of the language network compared to older children (Démonet et al., 2004; Munzer et al., 2020). Moreover, the writing task was a single letter writing task and not a word generation task, which would more closely replicate the actual writing procedure and its linguistic demands.

In this novel investigation, our pre-registration aims to compare the cerebral lateralization for written language between children at risk for dyslexia and typically developing children. I did so using a word generation task (Space Portal) based on the Magic Hat task described by (Quin-Conroy et al., 2022). For this task, children were: (a) presented with scenes containing items that start with the same letter of the Greek alphabet and asked to write down the names of the items or (b) presented with a letter and asked to write the letter multiple times, within a fixed time period. In this manner, I compared efficiency in recalling and naming items as well as speed and fluency in writing between children at risk for dyslexia and controls after subtracting the motor component of writing. Given that the motor component of written language results in the activation of the hemisphere contralateral to the writing hand, I plan to sample right-handers only, in order to minimize the potential parameters affecting cerebral lateralization. Moreover, I am interested in exploring whether there is a correlation between the cerebral lateralization for the linguistic component of writing and the (i) writing quality and (ii) orthographic skills of children in our sample. The latter is negatively correlated with the volume of left-hemispheric regions in adults with dyslexia (Tamboer et al., 2015). However, neither writing quality nor orthographic skills have been studied in relation to cerebral lateralization for written language. In order to assess writing competence I used the writing scale of the Greek adaptation of Luria-Nebraska's neuropsychological test (Golden, 1978; Vlachos & Bonoti, 2006), which evaluates how much a child's performance is influenced by atypical functions of the brain and nervous system (Geary & Gilger, 1984; Golden, 1987).

When studying cerebral lateralization during writing tasks, it is important to consider the influence of body movements on measurements. Our knowledge of cerebral lateralization for oral language in dyslexia comes from studies that leveraged behavioral data (see Berninger & Richards, 2010), histology (e.g., Galaburda et al., 1985), electroencephalography (e.g., Arns et al., 2007), and magnetoencephalography (Dresler et al., 2018; Fraga González et al., 2016), diffusion weighted imaging (Saygin et al., 2013), as well as MRI (Gori et al., 2016) and, substantially, either resting-state or task-based fMRI (Centanni et al., 2016; Fernandez et al., 2016; Kondyli et al., 2017; Morken et al., 2017; Richlan, 2020; Wang et al., 2020). Amongst these techniques, only behavioral assessment and fMRI lend themselves to the investigation of differential hemispheric activation during writing tasks. However, behavioral data are an indirect measure of lateralization, while fMRI is expensive, its basic equipment is immobile, and the assessment of brain activation during writing can be achieved only with the use of fMRI-compatible devices, which do not allow participants to engage in the natural body position for writing (Richards et al., 2015; Richards et al., 2017; but also see Baumann et al., 2022 for evidence on the independence of position on writing performance), and/or in combination with another technique, such as combined fMRI and electroencephalography (Lehongre et al., 2013). I used an alternative technique that is well suited for studying cerebral lateralization: fTCD (Aaslid et al., 1982; for further details on characteristics and advantages of fTCD, see Section 1.9 of this thesis). The main hypothesis is the following:

Hypothesis 1: The linguistic component of written language will be less lateralized in children at risk for dyslexia compared to the control group.

As a secondary aim, I also want to explore the relationship of writing competence with cerebral lateralization for written language. Given that this will be the first study to investigate this correlation, there is no evidence that could allow us to support an alternative hypothesis, meaning the existence of a correlation between writing competence and the lateralization for the linguistic component of written language. Therefore, we put forward the null hypothesis:

Hypothesis 2: Writing competence, as assessed by (a) writing quality and (b) orthographic skills, will not be correlated with the cerebral lateralization for the linguistic component of written language over the whole sample (children at risk for dyslexia and typically developing children).

3.2 METHODS

3.2.1 Participants

A total of 36 7- to 9-year-old participants were recruited for this study. They formed the following two groups: (a) 12 children characterized as at risk for dyslexia and (b) 24 typically developing children. A control group that is larger than the target group enhances statistical power, increasing the likelihood of detecting true effects and reducing the risk of Type II errors, while it allows to more safely extrapolate findings to a population level (Helmenstine, 2020; Oldfield, 2016; Riniolo, 1999).

3.2.2 Inclusion/exclusion criteria

All participants that were included in this study were:

(i) Language: Monolingual native speakers of Greek, who have not been systematically exposed to a foreign language prior to the 6th year of age,

(ii) Handedness: Determined according to the Edinburgh Handedness Inventory (EHI; Oldfield, 1971),

(iii) Vision: With normal or corrected-to-normal vision,

(iv) Intelligence: Of at least average intelligence, as indicated by a score higher than the 85th percentile in Raven's Coloured Progressive Matrices (Raven & Court, 1938; Sideridis et al., 2015, see below),

(v) Intervention: Not having received any type of educational intervention prior to the initiation of the study,

(vi) Comorbidity: Not fulfilling the clinical diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) and Internalizing and Externalizing problems, according to Achenbach's Child Behavior Checklist for school age (CBCL/6-18; Achenbach and Rescorla, 2001; Roussos et al., 1999, see below), and

(vii) Group membership:

(1) In order for children to be included in the "at risk for dyslexia" group, the following procedure took place:

(a) Children were considered at risk for dyslexia and were recruited by experienced special educators and pediatricians.

(b) The risk for dyslexia was confirmed by the *Reading Skills Assessment Test* (Panteliadou et al., 2019), in which scores ranking lower than the 10th percentile were required.

(2) In order for children to be included in the control group, the following procedure took place:

(a) Typically developing children were recruited through contact with local schools and online call for participation.

(b) Children needed to have scored higher than 25% in the *Reading Skills Assessment Test* (Panteliadou et al., 2019).

3.2.3 Participants' characteristics

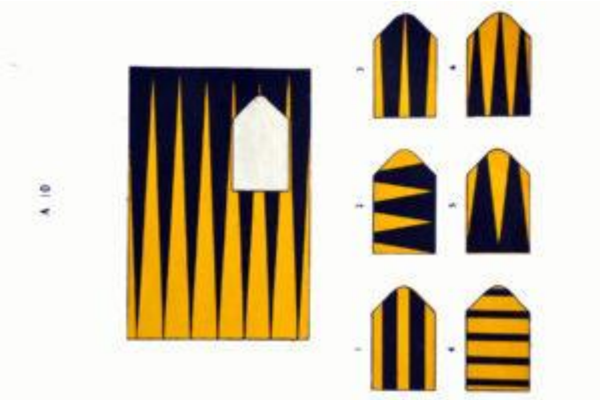
One hundred and sixty guardians of children were reached, eighty-six out of them provided their written consent for the participation of their children in the study, and seventy-one children assented to engage in all the tasks. The temporal windows of two out of the 71 children that assented could not be penetrated by the ultrasound beam and fTCD measurement was unapplicable for them. For 18 children, the usable data did not reach the limit of 10 acceptable epochs for each condition, while for 15 children the scores in the Reading Skills Assessment Test fell between 10% and 25%, therefore, these children could not be included in any of the two groups. Of the 36 participants that formed the final sample, 15 were girls (4 at-risk and 11 typically developing) and 21 boys (8 at-risk and 13 typically developing). Four participants were left-handed (3 at-risk boys and 1 typically developing girl) and 32 right-handed (9 at-risk and 23 typically developing). The mean age of the sample was 8.5 years and groups did not differ in terms of age (8.5 for typically developing, 8.2 for children at-risk). Six children were of average non-verbal intelligence (6 at-risk, 1 control), for eight children intelligence was above average (5 at-risk, 5 control), eight children were highly intelligent (1 at-risk, 7 control), while 11 typically developing children with scores higher than 143, can be characterized as gifted in terms of non-verbal intelligence.

3.2.4 Assessment of non-verbal IQ

Raven's Coloured Progressive Matrices (CPM): The Greek version of Raven's CPM (Raven & Court, 1938; Sideridis et al., 2015) was used to assess non-verbal intelligence of all participants. Intelligence testing allowed us to ascertain normal intelligence, which is a prerequisite for the diagnosis of dyslexia (Paracchini et al., 2007), and to match the two groups in terms of intelligence. I only assessed non-verbal intelligence, due to time restrictions and because the language difficulties of children at risk for dyslexia might not allow them to adequately perform in the language scales of full IQ tests. This tool tested how children were able to identify the missing piece of a large shape among six choices of similar pattern (e.g., Figure 14). Raven's CPM comprises three sets of 12 items each. The raw score was transformed to their non-verbal IQ score using standardized norms. Children with scores lower than 85 were excluded.

Figure 14

An example of Raven's Coloured Progressive Matrices (http://neuronpsychiatrichospital.com/tests)



3.2.5 Assessment of comorbidity

Child Behavior Checklist for school age (CBCL/6-18; Achenbach and Rescorla, 2001; Roussos et al., 1999): The Greek edition of CBCL for school age children from the Achenbach System of Empirical Based Assessment (ASEBA) was administered to the guardians of all the participants. Guardians were asked to answer 113 questions regarding their children's behavior and social competence. These questions are categorized in eight syndrome scale groups: (i) anxiety, (ii) depression/withdrawal, (iii) somatic complaints without profound physical cause, (iv) aggressive behavior, (v) rule-breaking behavior, (vi) ADHD, (vii) social/conduct problems, and (viii) oppositional defiant problems. There is an additional classification of Internalizing problems [including (i), (ii), and (iii)] and Externalizing problems [composed by (iv) and (v)]. For the purposes of this study, children assigned to the clinical range for ADHD scale and Internalizing and Externalizing problems category were excluded.

3.2.6 Identification of signs of dyslexia

Reading Skills Assessment Test (*RSAT; Panteliadou et al., 2019)*: The reading performance of all participants was evaluated using two tasks:

(i) Word decoding: Children were asked to read aloud a vertically printed series of 57 words (adjectives, nouns, passive particles, and verbs) with gradually increasing syllable numbers (two- to seven-syllable words) and semantic complexity and with a lowering frequency of occurrence. The number of words that each participant read correctly was noted. The task was discontinued in case of five consecutive errors

(ii) Pseudoword decoding: Children were asked to read aloud a vertically printed series of 40 non-words with gradually increasing syllable numbers (two- to six-syllable pseudowords) and phonological complexity. The number of non-words that each participant read correctly was noted, while the task was discontinued in case of five consecutive errors.

3.2.7 Assessment of writing competence

Luria-Nebraska neuropsychological test (Golden, 1978; Vlachos & Bonoti, 2006): The writing quality of participants was evaluated using three tasks: (a) spontaneous writing: writing their full name and the full name of their guardian (an adaptation compared to the original test that asks for their mother’s name in order to make sure that the test is relevant for all the children), (b) copying: writing down the small letters, the syllables, and the four-word sentence presented to them on a plastic card placed on the desk in front of them, and (c) dictated writing: writing down the capital letters, the words, and the 10-word sentence that the experimenter orated. Children were asked to write their answers on lined textbooks and were not allowed to erase. Each writing task was scored individually, according to the following criteria:

(a) Spontaneous writing: For each of the tasks included in this condition children received the following scores according to the number of errors: (i) 0 points for no error, (ii) 1 point for one or two errors, and (iii) 2 points for three to four errors. This scale was followed for both the child's own name and their guardian's name. Children were given 30 seconds to write down each name. [Minimum score for the condition (a): 0 points; Maximum score for the condition (a): 4 points]

(b) Copying: For each of the tasks included in this condition (copying letters or syllables and copying a phrase), children received the following scores according to the number of errors: (i) 0 points for no error, (ii) 1 point for one to two errors, and (iii) 2 points for three or more errors. Children were given 60 seconds to copy letters and syllables and 40 seconds to copy the phrase. [Minimum score for the condition (b): 0 points; Maximum score for the condition (b): 4 points]

(c) Dictated writing: For each of the tasks included in this condition (writing capital letters and writing words or a phrase) children received the following scores according to the number of errors: (i) 0 points for no error, (ii) 1 point for one or two errors, and (iii) 2 points for 3 to four errors. Children were given 40 seconds to write the capital letters and 100 seconds in total to write the words and the phrase. [Minimum score for the condition (c): 0 points; Maximum score for the condition (c): 4 points]

For each condition, any aberration in the written letters from the typically taught manner, regarding their position on textbook lines (e.g., leaned towards the lines, written above or below the lines) and their correct order in the words, their size, their form (differences compared to the typical form of letters or confusion of capital and small case letters), and their understandability, was accounted as an error and was taken into consideration for scoring. In case children do not successfully complete all the subtasks of each condition within the given time, the number of letters of the words missing was assigned to an equivalent number of errors and this number of errors was added to the total score of this condition. The total score for this test ranged from 0 to 12 points.

Orthography test (Vlachos & Papadimitriou, 2003): Orthographic skills were evaluated by writing a dictated text derived from the school book. The written text was examined for the presence of grammar (e.g., confusion regarding the orthography of different parts of speech) and/or thematic (related to words' etymology) errors in orthography, for reversing, omitting or misplacing letters (phonological errors) and for the omission of words. The score was: (a) zero, for a flawless text, (b) one, for one or two mistakes, (c) two, for three or four mistakes, or (d) three points, for at least five mistakes.

3.2.8 Assessment of handedness

Behavioural laterality was assessed in terms of handedness. Three handedness measures were used to estimate both hand preference and hand skill for completion reasons, in order to include these measurements in our online database of handedness data.

Hand preference was measured through a child-friendly version of EHI (Bishop, 2005; Oldfield, 1971), following Tomprou (2013) and the Picnic Packer task, a modification of Quantifying of Hand Preference task originally developed by Bishop et al. (1996). The material for the Picnic Packer task is freely available in https://osf.io/xjd9m/.

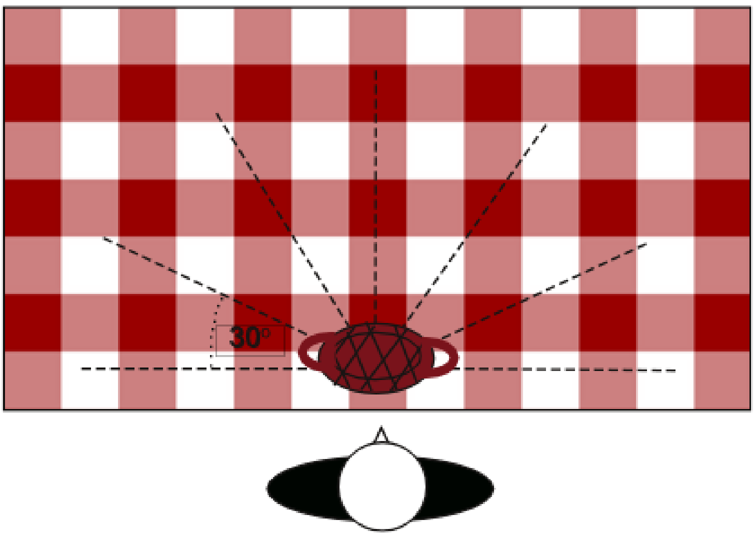
For the child-friendly version of EHI, participants were asked to perform 10 tasks (writing, brushing teeth, using scissors, drawing, throwing the ball, holding a spoon or a knife to carve, sweeping, opening the lid of a box, and reaching a card; Bishop, 2005; Oldfield, 1971). The experimenters noted the hand (or hands) that each child opted to perform each task and each hand use was scored as following: (a) 0 points for using the left hand, (b) 1 point for alternating hands during the task, and (c) 2 points for using the right hand. The Laterality Index

(LI) of each participant was calculated by dividing their total score with 20 (the maximum total score) and then multiplying it with 100%.

For the Picnic Packer task, children stood in front of a picnic table where 21 picnic-related items (e.g., cups, plates) were placed in groups of three in seven positions. Each of the seven positions was at 15 cm distance from the midpoint of the baseline with 30° intervals between them (Figure 15). Participants were asked to pick up and put in a picnic box the items in a pseudo-random order (identical for all participants). The starting position of the hands was at the edge of the desk, in front of children and participants returned in that position after placing each item in the box. Each use of the left hand was scored with 0 points, alternating hands was scored with 1 point, and each use of the right hand was scored with 2 points. The total score was divided by 42 (the maximum possible rating) and multiplied by 100%, resulting in a Lateralization Index (LI). For both the hand preference methods, a participant with an LI of 0% was considered as extremely left-handed, while a participant with an LI of 100%, as extremely right-handed.

Figure 15

Arrangement for the Picnic Packer Task (Adapted from Bishop et al., 1996)



Hand skill was assessed using Annett's Peg-Moving task (J. Annett et al., 1979; Brandler et al., 2013), that M. Annett (1985) proposed that it can also be applied to studies with children. For the present study, the original 32x18 wooden platform was used, with each one of its long sides housing 10 holes of 1.3cm diameter, 1.5cm distant from each other (measured from the centre of the holes on each side). Children were asked to move 10 wooden cylinders (pegs) from one long side (full) to the other (empty) as quickly as possible. The length of the pegs was 7cm and the diameter of the pegs was 1cm, in order to fit in the holes. Children began with the right hand by removing the pegs that were placed ipsilaterally to this hand and they alternated hands across trials. The task was completed when the participant had successfully performed three trials with each hand. The trial was repeated, if one peg falls down. Silence was requested in order to avoid delays. The speed of each participant's performance was measured using a stopwatch, starting when the child touched the first peg and stopping when the child released the last one. At the beginning of each trial, children placed the hand that they used on top of the first peg for consistency purposes. The LI for this task was calculated using the following equation: LI=100%(RH-LH)/(RH+LH), where RH corresponded to the mean time needed to complete right-hand trials and LH to the mean time needed to complete left-hand trials.

3.2.9 Assessment of cerebral lateralization

Space Portal task (Cerebral language lateralization): For the assessment of cerebral lateralization for written language, a modification of the Doppler experimental paradigm reported in Kohler et al. (2015) was employed. Children were requested to write down the names of items presented on screen (written language trials), or to copy the letter presented on screen as many times as possible (letter copying trials) in a certain timeframe. Letter copying acted as a motor-control condition, allowing us to disentangle the motor from the linguistic part of written language when assessing cerebral lateralization of participants. Each picture contained three to four items starting with the same letter of the Greek alphabet. Twenty of the 24 Greek letters were used, according to Kondyli et al. (2017). More specifically, for each trial children w engaged in the following procedure:

I. A blurred background image of vivid colors appeared on screen for 10 seconds, in order to draw the attention of the participants

II. A figure of an astronaut and a galaxy portal sprung out and they moved up and down for 16 seconds

III. Stardust bursted on screen and another astronaut appeared at the centre for 10 seconds

IV. An auditory stimulus instructed participants to “Look carefully”

V. For the written language trials, the target picture was presented and participants were given 45 seconds to name “What came out of this portal?” For the letter copying trials, a letter appeared in a star-like shape and participants were asked to “Write with the hand the letter that is on the star” for 45 seconds. An ending sound followed.

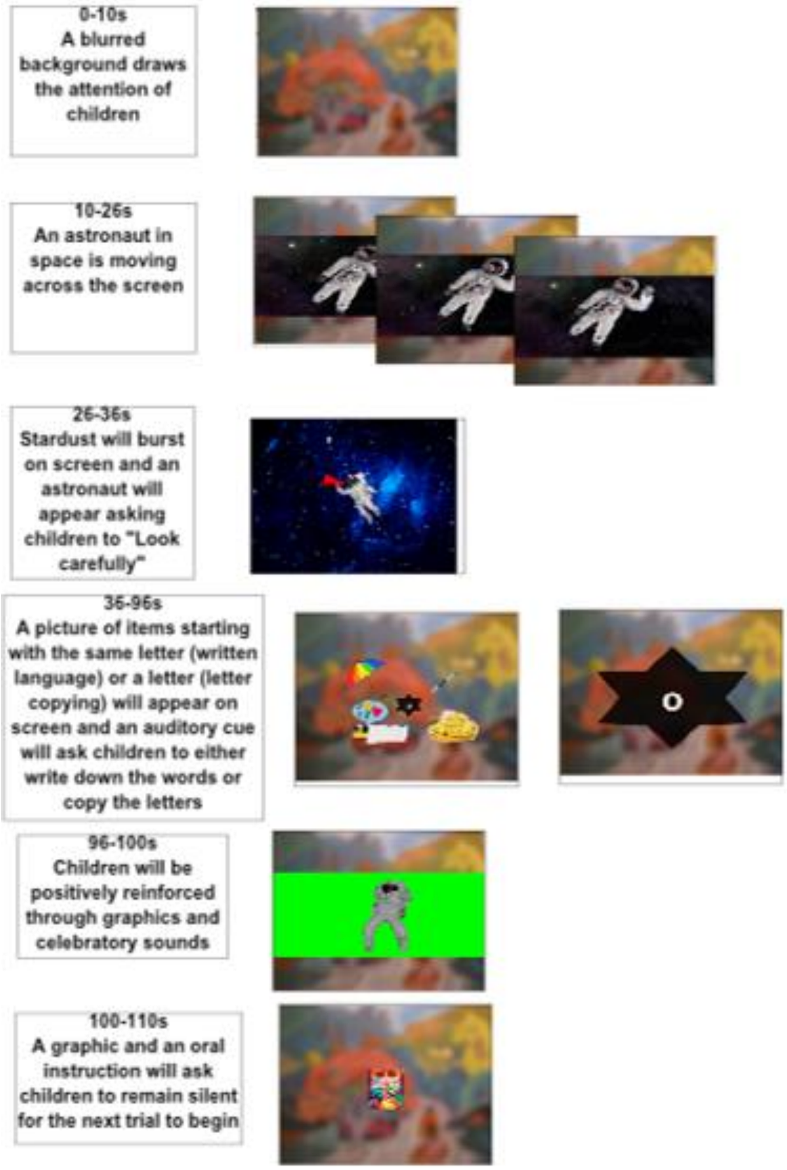
VI. Celebratory graphics and sounds positively reinforced children for four seconds, and

VII. A “shh” sound and graphic reinstated rest in order to prepare the participants for the next trial.

An example of one trial is presented in Figure 16. The task comprised 40 trials in total, a number that has been found to be adequate for measuring cerebral lateralization for oral language in 7-9 year old children (Badcock et al., 2018), 20 trials of written word generation (written language) and 20 trials of letter copying. Ten successive trials of one condition were altered with 10 successive trials of the other condition (e.g., 10 trials for written word generation, then 10 trials for letter copying, and again 10 trials for writing and 10 trials for copying).

Figure 16

Example of the "Space Portal Task"



3.2.10 FTCD data collection and analysis

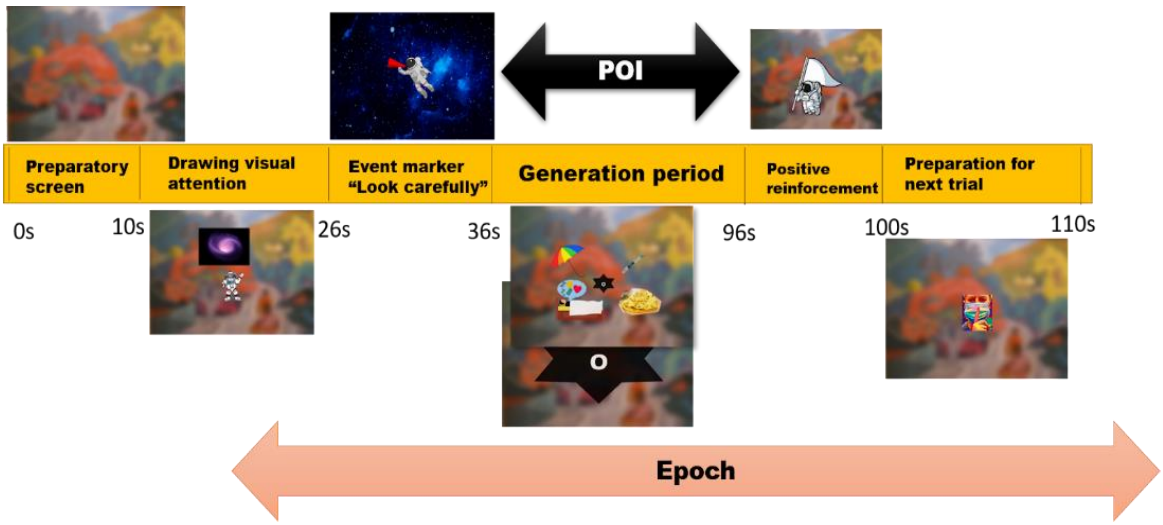
Neurophysiological data were collected with a commercially available Doppler ultrasound device (Delica EMS-9F). A flexible headset was fitted to participants so that the two

2-MHz robotic transducer probes were in contact with their left and right temporal windows. Maximal signal density was assured by adjusting the angles and the depth (30-62 mm for this age group; Reuter-Rice, 2017) of insonation of the left and right middle cerebral arteries according to each child's requirements. The freely available PsychoPy3 (Peirce et al., 2019) was used for visual and auditory stimulus presentation and for sending event markers to the Doppler device to signify the stimulus onset. The spectral envelope of the signal was recorded at 125 Hz and analyzed offline. Conditions that led to the replacement of participants were (i) the failure of penetrating the skull using Doppler ultrasonography and (ii) the occurrence of noise in data, meaning having less than 10 accepted epochs in a given task (based on the below criteria).

Data were analyzed using DopStep, a MATLAB-based toolbox (Badcock et al., 2012; available in https://github.com/nicalbee/dopStep). Unnecessary data were trimmed from the beginning and the end of the recording file and epochs lasted from 18 seconds prior to the event marker to 22 seconds after the disappearance of the target picture. The variability due to heart cycle was removed (Deppe et al., 1997; Knecht et al., 1998; Meyer et al., 2014) with the use of a linear correction, according to Badcock et al. (2018). Values beyond -3 SD to 4 SD from the mean (see Bishop et al., 2014), affecting less than 5% of the data, were corrected with a linear interpolation from 1.5 seconds either side of the extreme value. Left-channel and right-channel blood flow velocity were normalised to a mean of 100 at an epoch-by-epoch basis. Epochs with cerebral blood flow velocity lower than 50% or higher than 150% of the mean velocity or with an absolute left-minus-right-channel difference of 20 times each child's inter-quartile, affecting 1% of the data, were rejected. The remaining data were corrected for the baseline activation, measured from the beginning of each epoch until the cueing tone, at an epoch-by-epoch basis. The final data were averaged and the cerebral lateralization indices (LI) were calculated as the average of the left- minus right-channel difference during the period of interest. The periods of interest (POI) for the Space Portal task were 2 to 45 secs, that is, after the appearance of the stimulus until the stimulus disappears (Figure 17). Two LI were calculated for the Space Portal task: (a) $LI_{written}$, for written word generation and (b) $LI_{copying}$ for letter copying. A third LI representing the lateralization for the linguistic component of writing was calculated as the difference between the LI for written word generation and the LI for letter copying ($LI_{difference} = LI_{written} - LI_{copying}$). The validity of the measurements was secured with a split-half reliability test between odd and even trials (Bishop et al., 2021). Analysis proceeded only for the tasks that showed "moderate reliability" (rho ≥ 0.5; Koo & Li, 2016; Parsons et al., 2019).

Figure 17

Distribution of an epoch and a Period of Interest within a trial



3.2.11 Procedure

Accompanied by their guardians, participants visited the hospital/service facilities for the assessment of their academic performance by experienced special educators and pediatricians. The guardians of the participants received an information sheet 72 hours prior to the attendance to allow them time to decide if they wish their children to participate in this study. Moreover, they received an online questionnaire to prescreen children for the inclusion criteria, such as native language and vision. As soon as the participant and their guardian arrived at the laboratory, the researchers explained the aims and the process of the study and they invited the participant and the guardian to ask questions. The researchers reassured the participant and the guardian that they were free to leave the study at any time without providing a reason for doing so. As long as the guardian provided their written informed consent and the child provided their oral assent, the child was led to a quiet room, where the assessment of reading performance, of writing competence, and of non-verbal intelligence took place. Afterwards, they were requested to sit in front of a screen, watching a cartoon, while the ultrasound probes were fitted. The collection of the neurophysiology data ensued. Then, participants were assessed for behavioural laterality. As soon as their contribution was completed, participants were debriefed and given a memento and a diploma of participation.

3.2.12 Data analysis

Data were analyzed using R [Version 4.1.2; R Core Team (2021)] and the R-package *papaja* [Version 0.1.0.9997; Aust and Barth (2020)]. The hypotheses were analyzed using the Bayesian approach that compares existing knowledge (prior distribution) with observed data (posterior distribution) according to a likelihood (van de Schoot et al., 2021). Moreover, the Bayesian approach allowed to discriminate whether there was evidence of absence or absence of evidence (Keysers et al., 2020), which is of particular importance for our second hypothesis [*"Writing competence, (a) writing quality and (b) orthographic skills, will not be correlated with the cerebral lateralization for the linguistic component of written language over the whole sample (children at risk for dyslexia and typically developing children)"*], in which I am interested in calculating the probability of the null hypothesis (absence of correlation) over the alternative hypothesis.

Hypothesis 1: The first hypothesis (*"The linguistic component of written language will be less lateralized in children at risk for dyslexia compared to the control group."*) was tested using a Bayesian *t*-test for independent groups (children at risk for dyslexia and typically developing children). The dependent variable that was compared between groups was the $LI_{difference}$. The prior for the *t*-test was described with a half Cauchy distribution (Rouder et al., 2009) and with a scale parameter of 0.6 (Schmalz et al., 2021), which corresponds to Cohen's *d* for the difference in language lateralization between adults with dyslexia and neurotypical adults in Illingworth and Bishop (2009). The Bayes Factor (BF_{10}) indicated the probability for supporting the alternative hypothesis (difference in cerebral lateralization for the linguistic component of written language between children at risk for dyslexia and typically developing children) over the null hypothesis.

Hypothesis 2: The second hypothesis [*"Writing competence, (a) writing quality and (b) orthographic skills, will not be correlated with the cerebral lateralization for the linguistic component of written language over the whole sample (children at risk for dyslexia and typically developing children)"*] was analyzed using two Bayesian Spearman correlations, one for the $LI_{difference}$ and the score for writing quality and one for the $LI_{difference}$ and the score for orthographic skills. Spearman correlations minimize the influence of extreme data points commonly observed in fTCD studies (Papadatou-Pastou et al., 2022). The priors for these analyses were described by two Beta-distributions centered around zero and with parameters a=1/7 and β=1. The magnitude of the parameters a and β was suitable for this exploratory analysis, because small correlations ($-0.25<rho<0.25$; Mueller et al., 2015; Nair et al., 2019) were expected in 80% of a Beta (1/7,1) distribution.

Split-half reliability: The consistency of the measurements of LIs across trials of the same task were verified using a Bayesian Spearman correlation of the mean LIs between odd and even trials (Bishop et al., 2021) for each task ($LI_{written}$, $LI_{copying}$, $LI_{difference}$). Assuming equal probabilities for all possible correlations in order to be able to estimate any degree of reliability, the priors for the Spearman correlations were described by a Beta (1,1) distribution.

Exploratory (non-registered) analyses: The additional analyses that were performed to further explore the data are the following:

(a) Bayesian one-sample *t*-tests against zero for each condition in each group. For each of these *t*-tests priors were described by a half-Cauchy distribution (Rouder et al., 2009) and a width parameter of 0.6 (Illingworth & Bishop, 2009),

(b) Bayesian Spearman correlations centered around zero and with parameters a=1/7 and β=1 for all the quantitative variables assessed in this study,

(c) Bayesian *t*-test for independent groups (children at risk for dyslexia and typically developing children) with the non-verbal intelligence index as the outcome variable. Priors were described by a half-Cauchy distribution (Rouder et al., 2009) and the width parameter had the default value of 0.707,

(d) Bayesian *t*-tests for independent groups (children at risk for dyslexia and typically developing children) with the number of errors in writing competence (writing quality or orthography) as the outcome variables. Priors for each test were described by a half-Cauchy distribution (Rouder et al., 2009) and the width parameter had the default value of 0.707,

(e) Bayesian *t*-tests for independent groups of children according to their grade (second-graders and third-graders) with lateralization index for each condition as the outcome variable. Priors for each test were described by a half-Cauchy distribution (Rouder et al., 2009) and the width parameter had the default value of 0.707,

(f) Bayesian *t*-tests against zero for each condition in each handedness group defined by the EHI score of children (left-handers and right-handers). Priors for each test were described by a half-Cauchy distribution (Rouder et al., 2009) and the width parameter had the default value of 0.707, and

(g) Bayesian *t*-tests for independent handedness groups (left-handers and right handers) with the lateralization index for each condition as the outcome variable. Priors for each test were described by a half-Cauchy distribution (Rouder et al., 2009) and the width parameter had the default value of 0.707.

3.3 Results

There was extreme evidence for a moderate split-half reliability for the written word generation task (rho = 0.53, BF = 51.53) and a high reliability for the letter copying task (rho = 0.74, BF = 7.93×10^4). Therefore, the data were adequately reliable and analysis proceeded. Of note, there was no evidence regarding the reliability of the difference of the lateralization indices (rho = 0.31, BF = 1.14), a result potentially affected by the decrease of data due to exclusion of unaccepted trials.

The results for the lateralization for letter copying and written word generation are summarized in Table 2 and the mean lateralization indices are plotted in Figure 18. The mean lateralization indices for both letter copying and written word generation of typically developing children are positive, indicating a left lateralization, however, non-registered Bayesian *t*-tests against zero showed that there is moderate evidence for a clear left lateralization only for writing words (BF = 5.91) and only anecdotal evidence for a left lateralization for letter copying (BF = 2.01). On the other hand, marginally moderate evidence suggests a lack of lateralization for written word generation of children at risk for dyslexia (BF = 0.34) and there is not enough evidence for a lateralization pattern for letter copying in this group. When it comes to the lateralization for the linguistic component of written language, calculated as the difference of the lateralization index for letter copying from the lateralization index for word writing, the mean scores for both groups are close to zero and there is moderate evidence that for typically developing children $LI_{difference}$ is no different than zero (BF = 0.32).

Of note, when the same Bayesian *t*-tests against zero were performed in separate groups in terms of handedness, there was moderate evidence that both letter copying (BF = 3.22) and written word generation (BF = 4.38) was left-lateralized for right-handers irrespective of their reading skills. There was only anecdotal evidence for the lateralization for the linguistic component of writing in right-handers (BF = 0.35) and for the direction of lateralization for each condition in left-handers (letter copying: BF = 1.63; written word generation: BF = 0.85; linguistic component of written language: BF = 1.85).

Table 2

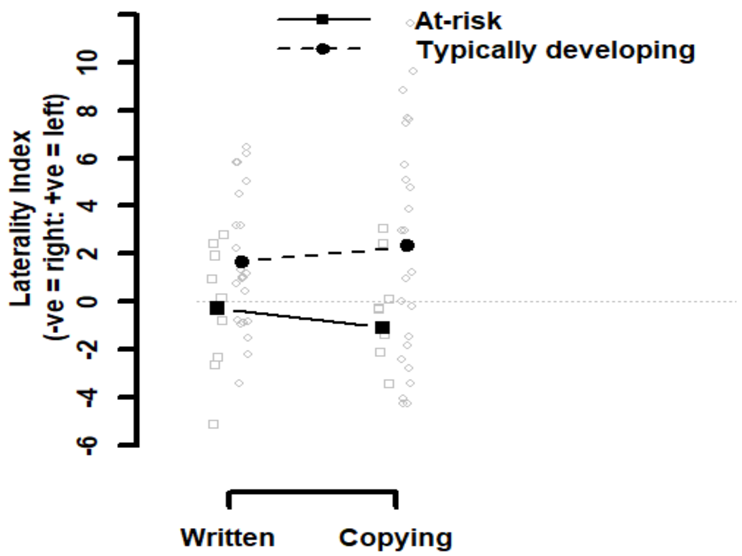
Descriptive statistics for cerebral lateralization in the different functional transcranial Doppler ultrasonography conditions.

Condition	Reading performance	Number	Number of epochs	Mean	SD	Median	Max/Min
Letter copying	At-risk	12	13.9	-1.09	3.28	-0.31	[-7.98, 3.05]
	Typically developing	24	16.8	2.32	4.88	2.11	[-4.27, 11.63]
Written word generation	At-risk	12	15.5	-0.29	2.67	0.15	[-5.13, 2.79]
	Typically developing	24	16	1.68	2.82	1.1	[-3.43, 6.47]
Word Letter	At-risk	12		0.81	2.81	1.08	[-3.19, 5.35]
	Typically developing	24		0.64	3.36	-0.27	[-6.42, 4.5]

Note: SD: Standard Deviation, Max: The maximum score observed in the handedness group for the condition, Min: The minimum score observed in the handedness group for the condition.

Figure 18

Lateralization indices per condition and reading performance group



Note: Different conditions are presented in different columns (right: written word generation, left: copying letters). The classification of participants according to the Reading Skills Assessment Test score is depicted as squares crossed by straight lines (at-risk) and circles crossed by dashed lines (typically developing). Grey symbols correspond to each participant's indices and black bold symbols correspond to the mean lateralization index of each group in each condition.

Regarding writing competence, the number of errors for each task is tabulated in Table 3. The errors observed in children's writing included aberrations from the typical letter shape and position on textbook lines in spontaneous and dictated writing, rather than in copying, confusion of capital and small letters in cases of names or following full stop and of graphemes whose phonemes were similar, lack of accentuation, reversals of graphemes (e.g., “E” to “3”), but also of the order of letters in words, and replacement of the dictated words due to automatic completion of words.

Table 3

Descriptive statistics for writing competence in terms of handwriting quality and orthography.

Writing competence task	Reading performance	n	Mean number of errors	SD	Median	Min/Max
Luria-Nebraska Neuropsychological Battery	At-risk	12	8.1	1.05	9	[7, 9]
	Typically developing	24	4.4	1.79	4	[2, 7]
Orthography test	At-risk	12	19.3	5.63	19	[12, 28]
	Typically developing	24	10.8	5.76	9	[2, 22]

3.3.1 Registered analyses

<u>*Hypothesis 1*</u>*: The linguistic component of written language will be less lateralized in children at risk for dyslexia compared to the control group.*

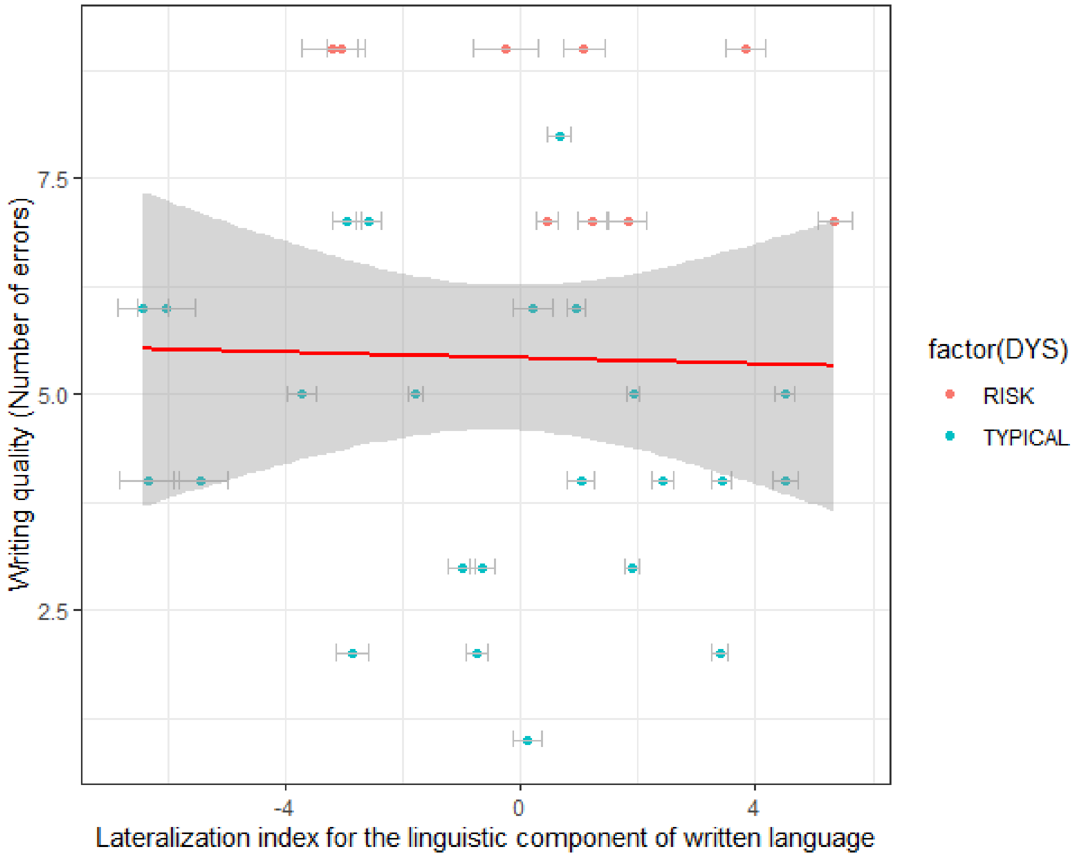
A Bayesian *t*-test for independent groups (at-risk and typically developing children; outcome variable: $LI_{difference}$; prior described by half-Cauchy distribution with a width parameter of $r = 0.6$) did not provide enough evidence (BF = 0.64) either in favor or against the first hypothesis, that the linguistic component of written language of children at-risk for dyslexia would be less left-lateralized compared to controls.

Hypothesis 2: Writing competence, as assessed by (a) writing quality and (b) orthographic skills, will not be correlated with the cerebral lateralization for the linguistic component of written language over the whole sample (children at risk for dyslexia and typically developing children).

The Bayesian Spearman correlations for each of the writing competence parameters over the whole sample (prior described by Beta (1,1) distribution; Figures 19 and 20) provided moderate evidence that the number of errors in writing quality was not correlated with the cerebral lateralization for the linguistic component of written language (rho = -0.02, BF = 0.218) and marginally moderate evidence that the number of errors in orthography was not correlated with the lateralization for the linguistic component of writing (rho = 0.16, BF = 0.338). Hence, the second hypothesis was confirmed.

Figure 19

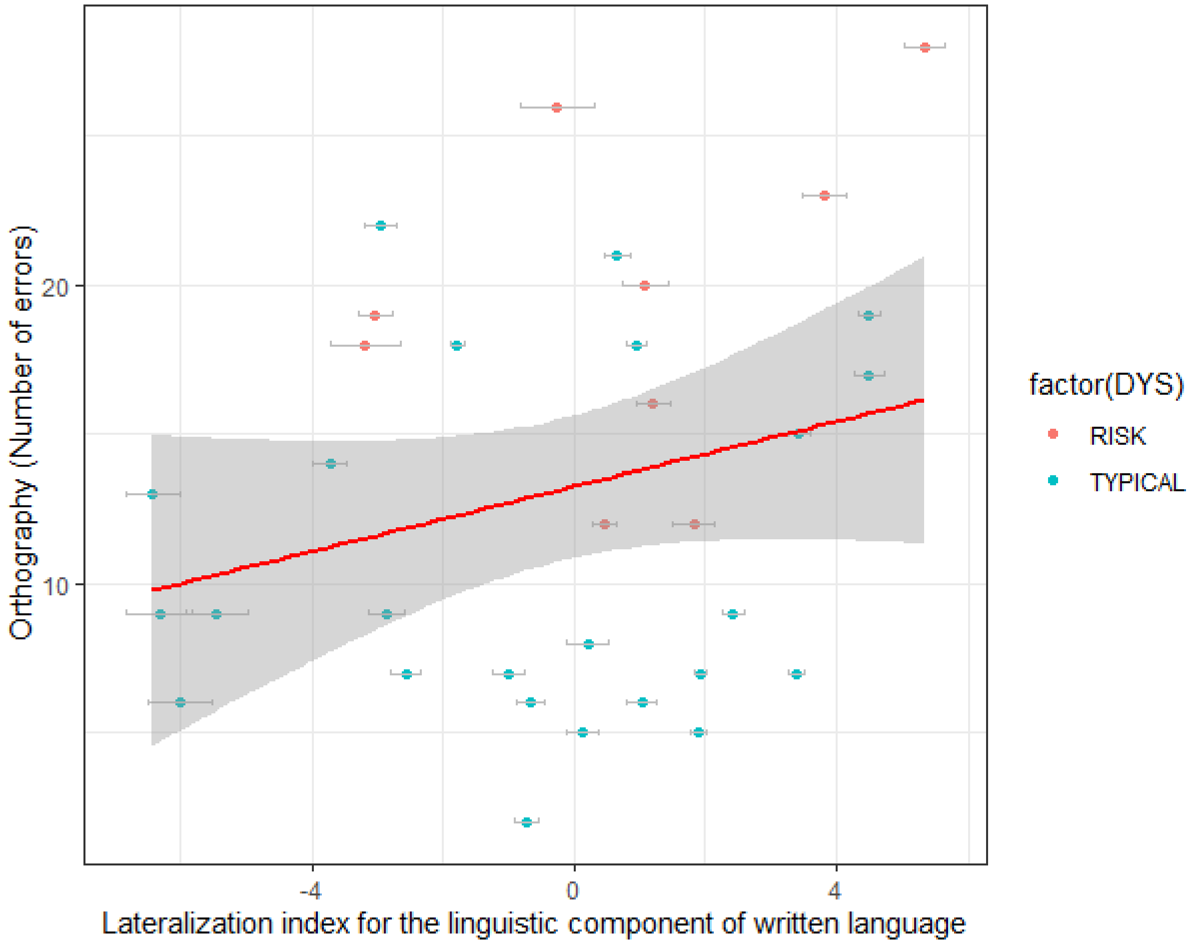
Scatter plot for the correlation of writing quality and the lateralization for the linguistic component of written language over the whole sample



Note: The horizontal bars correspond to the 95% confidence intervals for the $LI_{difference}$ of each participant. The different groups in terms of reading performance are depicted with different colours (red for at-risk and blue for typically developing children). The red line shows the linear trend of the correlation surrounded by the standard deviation of the values (grey area).

Figure 20

Scatter plot for the correlation of orthographic skills and the lateralization for the linguistic component of written language over the whole sample



Note: The horizontal bars correspond to the 95% confidence intervals for the $LI_{difference}$ of each participant. The different groups in terms of reading performance are depicted with different colours (red for at-risk and blue for typically developing children). The red line shows the linear trend of the correlation surrounded by the standard deviation of the values (grey area).

3.3.2 Exploratory analyses

Effect of age and intelligence on cerebral lateralization of children

Taking into consideration that children in different grades might rely on different aspects of language for reading and writing (second graders: phonological rehearsal; third graders: visuospatial processes) that correspond to different brain regions (Meyer et al. 2010), children of different grades in the sample of this study were assessed for their lateralization pattern. The lateralization indices for written word generation, letter copying, and the linguistic component of written language were compared between second- and third-grade children irrespective of their reading performance.

Bayesian *t*-tests for independent groups were conducted to examine the difference in lateralization for each condition between groups. There was not enough evidence to support either a difference or an absence of difference between second- and third-grade children in terms of lateralization for any of the assessed conditions (written word generation: BF = 0.36; letter copying: BF = 0.46; linguistic component of written language: BF = 1). Moreover, when the relationship of the lateralization indices with the actual age, rather than the grade of children, was explored, there was not enough evidence for any correlation, except for moderate evidence for a lack of correlation between age and the lateralization for written word generation (rho = 0.06, BF = 0.234).

When it comes to the intelligence of children, Bayesian *t*-tests for the same groups with the non-verbal intelligence index as an outcome variable, provided extreme evidence for lower non-verbal intelligence in children at-risk for dyslexia compared to typically developing children (BF = 148.85). However, Bayesian Spearman correlations showed moderate evidence that the level of non-verbal intelligence was not correlated with the lateralization for the linguistic component of written language, while only anecdotal evidence indicated a lack of correlation for the other two lateralization indices and non-verbal intelligence (Table 4).

Table 4

Relationship between the assessed variables

	$LI_{difference}$	LI_{word}	LI_{letter}	EHI	QHPT	PEG	Intelligence	Writing quality
LI_{word}	-0.19 (0.412)							
LI_{letter}	**-0.8 (1.19 X 10^{6})*****	**0.72 (2.72 X 10^{4})*****						
EHI	**-5.62 X 10^{-3} (0.22)***	-0.19 (0.425)	**-0.12 (0.273)***					
QHPT	**0.11 (0.269)***	**0.11 (0.273)***	**0.02 (0.221)***	**0.47 (11.83)****				
PEG	-0.29 (0.967)	0.21 (0.471)	0.33 (1.67)	**0.41 (4.68)***	**0.51 (41.07)*****			
Intelligence	**-0.1 (0.264)***	0.21 (0.473)	0.27 (0.772)	-0.18 (0.388)	**0.09 (0.247)***	**0.15 (0.322)***		
Writing quality	**-0.02 (0.218)***	**-0.1 (0.257)***	**-0.06 (0.233)***	0.21 (0.459)	**0.02 (0.219)***	**7.31 X 10^{-3} (0.217)***	**-0.42 (5.61)***	
Orthography	0.16 (0.338)	**-0.02 (0.217)***	**-0.15 (0.32)***	**-0.13 (0.29)***	**2.32 X 10^{-3} (0.217)***	**0.07 (0.233)***	**-0.43 (6.44)***	**0.71 (1.58 X 10^{4})*****

Effect of handedness on language lateralization of children

Importantly, none of the handedness measures, namely EHI, QHPT, and Peg-moving task, showed a positive correlation with either the experimental or the control fTCD task in terms of lateralization (Table 4). In fact, there was moderate evidence that EHI lacked correlation with the lateralization for both the letter copying and the linguistic component of writing, while QHPT lacked correlation with all lateralization indices.

Differences in writing competence and the risk for dyslexia

To assess the occurrence of problems in writing competence prior to the diagnosis of dyslexia in the present sample, the number of errors in writing quality and in orthography was compared between children at risk for dyslexia and typically developing children. Bayesian *t*-tests for independent groups provided extreme evidence that the number of errors for both writing quality and orthography was increased in children at risk for dyslexia compared to typically developing children (writing quality: BF = 5358, 89; orthography: BF = 44.28).

Relationship of writing competence with intelligence and age

Having conducted Bayesian correlations for all the quantitative variables assessed during this study, there was enough evidence for a relationship of the components of writing competence with several parameters across the sample (Table 4). There was moderate evidence that writing quality was not correlated with the lateralization pattern of any condition and with two out of the three handedness measures. Similarly, moderate evidence indicated lack of correlation of the orthographic skills with the lateralization for any condition and with all the handedness measures. Of note, there was moderate evidence that the number of errors for both writing quality and orthography was moderately negatively correlated with intelligence. In tandem, extreme evidence was found for a negative correlation of the number of orthographic errors and age (rho = -0.51, BF = 36). Thus, the difficulties in qualitative writing and orthography decrease with increasing intelligence and age.

3.4 DISCUSSION

This study was the first, to my knowledge, to assess the lateralization for written language in children. The specific aims of this study were to (i) compare the lateralization for the linguistic component of writing between children at-risk for dyslexia and typically developing children and to (ii) investigate the relationship of the lateralization for the linguistic component of writing with the writing competence of children, manifested by their handwriting quality and their orthographic skills. To isolate the activation that corresponds to the linguistic component of written language, letter copying was used as a motor control task, as it resembles the motor requirements of writing but without the linguistic demands for the generation of words. In other words, it was expected that if the lateralization for letter copying was subtracted from the lateralization for writing words, then the difference would represent the linguistic component of writing words.

According to the literature for the lateralization for covert word generation and reading in children with or at-risk for dyslexia (e.g., Heim et al., 2015), the first hypothesis was that the linguistic component of written language would be less left-lateralized in children at-risk for dyslexia compared to their typically developing peers. The data did not provide enough evidence either to confirm or to reject this hypothesis (BF = 0.64). In fact, a clear left lateralization pattern was evident only for the written word generation in typically developing children.

The lack of evidence for a clear lateralization for letter copying especially for typically developing children, a group that included only one left-hander, was surprising. If letter copying accounted only for the motor component of writing, then the direction of lateralization should have been contralateral to the hand used for writing. As it was also suggested in the *Discussion* of the previous chapter (2.4), letter copying might not simply represent the motor components of writing, but it could also engage functions that are controlled by the right hemisphere, such as suppression of working memory-related reflexive responses, rapid reaction, hyperarousal, or boredom (Aron et al., 2004; Comer et al., 2015; Joseph et al., 2009; Rogers, 2002). Another explanation for the absence of a clear lateralization pattern for any component of written language in children (potentially resulting in a non-lateralized linguistic component of written language) could be that such a pattern is yet to develop in the younger children of our sample. Next to studies suggesting that the lateralization for oral language comprehension and generation is apparent from birth, there are studies supporting that both hemispheres are equally involved in language processing during the first years of life and gradually one hemisphere dominates over the other (Labache et al., 2023; Olulade et al., 2020; Potdevin et al., 2023). Largely, there is evidence that even adolescents show more dispersed activation across brain hemispheres during oral language tasks compared to adults (Bates et al., 2001). This is why the effect of age on the cerebral lateralization of children was assessed in the context of exploratory analyses. There was moderate evidence that age did not affect the lateralization for written word generation, while there was not enough evidence for any of the other conditions to support either hypothesis. Moreover, only anecdotal evidence was found for a difference in lateralization between children of different grades. Hence, the lack of clarity in the lateralization patterns of children cannot be attributed to age.

Unlike the inconclusive findings for the first hypothesis, the second hypothesis claiming that writing competence and the lateralization for the linguistic component of written language would not be correlated across the whole sample was supported with moderate evidence. In other words, the lateralization for the linguistic component of writing cannot predict writing difficulties in children or vice versa. For completeness, the expected higher incidence of writing errors in children at risk for dyslexia compared to typically developing children was verified. Reading and writing difficulties in cases of dyslexia are opposite sides of the same coin, albeit reading problems are more easily managed compared to writing problems (Ishii, 2015; Otaiba et al., 2022), even though the current study provided extreme evidence that the number of errors in orthography decreased with age across the sample. Of note, writing errors could result from the fact that children younger than 8 years old tend to rely more on the perception of upper limb movement (proprioception) rather than on vision for writing, resulting in more reversals of letters (Mather, 2022).

Another important observation in our data was that lower non-verbal intelligence was found in children at-risk for dyslexia compared to typically developing children. Both genetic and environmental factors have been accounted for with regards to the strong correlation of academic performance and intelligence documented in literature ranging from 0.5 to 0.85 depending on the intelligence measure used and increasing with age (Cotton & Crewther, 2009; Thompson et al., 1991; Wainwright et al., 2005). When it comes to dyslexia, even the first cases described in the 19th century were characterized with at least average intelligence, while this prerequisite is set for all the currently used definitions of dyslexia (Kussmaul, 1877; Mather & Schneider, 2023). Of note, people with dyslexia with at least average intelligence and poor readers of low intelligence differ in their cognitive skills (Cotton & Crewther, 2009; Hoskyn & Swanson, 2000; Siegel, 1988; Thomson, 2003). However, early on researchers felt that employing tests that assess verbal intelligence would be inappropriate for the characterization of people with dyslexia, who have reduced vocabulary range and reading difficulties, leading to the use of non-verbal intelligence tests as an alternative source of information on their intelligence (Ferrer et al., 2010; Meyer, 2000; Monroe & Backus, 1937; Orton, 1925).

Of note, reduced non-verbal intelligence in dyslexia compared to children of typical development is evident not only in this study, but also in previous studies assessing children with or at-risk for dyslexia (Cowan et al., 2017; Snowling et al., 2003; van Bergen et al., 2013). A potential explanation is that children with higher non-verbal intelligence are more adaptable to compensate for reading deficits and they tend not to manifest strong signs of dyslexia (Alt et al., 2017; van Bergen et al., 2013). It is worth considering that in the present study, non-verbal intelligence was further strongly correlated with writing competence (handwriting quality: rho

= -0.42, BF = 5.61; orthography: rho = -0.43, BF = 6.44). This could be attributed to the correlation between phonological awareness and intelligence, which is associated with performance in writing competence in this study, with intelligence and working memory employed for the non-verbal intelligence assessment (Lopes-Silva et al., 2014). In any case, it is unclear whether the correlation between non-verbal intelligence with reading and writing performance is a general characteristic of dyslexia or it is the aftereffect of the low experience of children with dyslexia with brain-teasers as the ones included in Raven's CPM or texts. Taking into consideration children's cognitive abilities, the common practice is to match participants for mental age/intelligence (Callens et al., 2012; de Jong & van der Leij, 2003; Van Viersen et al., 2019).

Several strengths and limitations characterize this study. Importantly, it is the first study to investigate the lateralization for written language in children in general, and, notably, in children at-risk for dyslexia. Furthermore, it did so, using fTCD, which lends itself to studying language lateralization during writing in children due to the robustness of the measurement to the potentially relentless movement of this participant group, but most importantly, to movement that corresponds to writing itself. Moreover, the study is among the first to attempt to disentangle the linguistic and the motor component of writing, specifically emphasizing the lateralization for the linguistic component of written language. In addition, the adoption of the Bayesian approach allowed for the discrimination of the absence of evidence from the evidence of absence (which is what the frequentist approach offers) when examining for the first time in literature the relationship of writing competence and the lateralization for the linguistic component of written language. Another novel element of this study is that it is the first to investigate lateralization for written language in Greek students. The Greek language has a semi-transparent orthography, leading to a delay in the development of the symptomatology and the diagnosis of dyslexia. Therefore, we were able to recruit children at risk for dyslexia that had received adequate writing instruction.

Regarding the study's limitations, the sample size was too small to provide enough evidence for a clear lateralization pattern. The size of the sample was a corollary of the strict criteria that we applied during participant recruitment and of practical difficulties met during the recruitment and the participation of children. Future work including more participants of both groups might lead to more conclusive results. On this note, we should alert future researchers to the difficulties of recruiting children and particularly, those at risk for dyslexia, in a brain imaging study. Some of the challenges in this process include the difficulty in securing the consent of guardians, the high attrition rate between initially expressing interest in the study and the actual participation, the narrow time-window when children have been taught to read and write but are not yet at the age when they are at-risk but can be formally diagnosed, and the co-operation of participants. Additionally, to avoid misinterpreting results, future studies are encouraged to match participants for intelligence, after observing that the level of non-verbal intelligence differed between the groups of this study. Finally, taking into account the findings of Study 1 (see Chapter 2) and the lack of evidence in this study, letter copying may have been unsuitable as a motor control task due to engaging functions of the right hemisphere (for a discussion see Chapter 2).

To summarize, although there was moderate evidence that written word generation was left-lateralized in typically developing children, there was not enough evidence for a difference in the lateralization for the linguistic component of writing between groups. When it comes to the relationship of writing competence and the lateralization for the linguistic component of written language, there was moderate evidence for a lack of correlation especially for handwriting quality. Exploratory analyses showed that writing competence differed between groups and that it was correlated with non-verbal intelligence. More research is needed to shed light on the complex relationship of reading and writing difficulties, language and behavioral lateralization, and intelligence.

4 THE EFFECTS OF EDUCATIONAL INTERVENTIONS IN THE CEREBRAL LATERALIZATION FOR WRITTEN LANGUAGE IN CHILDREN AT RISK FOR DYSLEXIA: A PILOT INVESTIGATION

Abstract

Studies on the cerebral lateralization for oral language, meaning the differential activation of brain hemispheres during oral language tasks, have shown a left lateralization in the majority of neurotypical individuals. In the case of language disorders, such as dyslexia, this pattern is more symmetrical or even right-lateralized. Of note, appropriate educational interventions, especially in early childhood, could shift the oral language lateralization pattern in dyslexia to approximate the left-lateralization pattern of neurotypical individuals. However, there are no studies to date addressing the potential impact of an intervention on the cerebral lateralization for *written* language, despite the fact that written language is widely used in everyday life and dyslexia-related writing difficulties often persist even in adults. This pilot study aimed to investigate the effects of a phonological intervention in the pattern of the cerebral lateralization for the linguistic component of written language, as assessed using fTCD in five children at risk for dyslexia. Moreover, a non-phonological, pragmatic intervention was examined in one girl for feasibility as an active control intervention in larger studies in the future. Typically developing controls were also tested. It was hypothesized that the phonological intervention would result in a leftward shift to the pattern of cerebral lateralization for the linguistic component of written language, yet the results could not allow a reliable interpretation as the lateralization for the linguistic component of written language was shifted to the left or to the right in an individual-dependent manner, while the pragmatic intervention was successfully administered. Study findings highlight the impact of an early intervention used for the effective management of dyslexia on the amelioration of reading performance and

the different factors, such as responsiveness, that might affect the impact of an intervention on the cerebral lateralization for the linguistic component of written language in children.

Keywords: cerebral lateralization, writing, functional Transcranial Doppler, dyslexia, intervention

4.1 INTRODUCTION

In the majority of neurotypical individuals the left cerebral hemisphere is more activated during oral language production tasks compared to the right hemisphere (e.g., Braga et al., 2020; Manilla & de Braga, 2017; Nielsen et al., 2013; Olulade et al., 2020; Packheiser et al., 2020; Pennisi, 2023; Potgieser et al., 2015; van Setten et al., 2016), a phenomenon known as cerebral lateralization. Reading difficulties, such as those met in case of dyslexia, have been associated with atypical (more symmetrical or right-lateralized) cerebral lateralization (Démonet, et al., 2004; Gallagher et al., 2000; Horowitz-Kraus et al., 2024; Pennington & Lefly, 2001; Quin-Conroy et al., 2024), while interventions that improve reading tend to reorganize the cerebral lateralization pattern for oral language tasks of students with dyslexia to approximate that of neurotypical individuals (e.g., Costanzo et al., 2019; Heim et al., 2015; Meyler et al., 2008; Nugiel et al., 2019; Odegard et al., 2008; Rezaie et al., 2011; Richards & Berninger, 2008; Romeo et al., 2017; Spironelli et al., 2010). However, to our knowledge, no study has assessed the effect of such interventions on the cerebral lateralization for written language.

Producing, reading, and interpreting written language are widely practiced in everyday life for communication and education (Share, 2021). Moreover, children's writing skills are related to their reading skills (Kim et al., 2013; Shanahan et al., 2006), which in turn are crucial for educational success by promoting language development and enhancing vocabulary acquisition (Boakye, 2017; Hargrave & Sénéchal, 2000). Handwriting during note-taking further appears to be beneficial for any aspect of language recruited during reading comprehension (Richards et al., 2016). What is more, writing problems appear more difficult to overcome compared to reading problems (Berninger & Richards, 2010; Morken et al., 2014; Richards et al., 2017). Therefore, understanding the neurobiological underpinnings of written language and whether they are affected in the same way that oral language underpinnings are affected by intervention could allow us to improve education and life outcomes for individuals with writing difficulties. In the present pilot study, I aimed to compare the pattern of cerebral lateralization for written language between children at risk for dyslexia, prior and after an intervention (phonological or pragmatics), and typically developing children tested in the same time points, using fTCD.

As above-mentioned, dyslexia is a Specific Learning Disorder that affects 3% to 10% of the world's population, with the prevalence ranging across different orthographies and depending on diagnostic criteria (Miles, 2004; van Setten et al., 2016). Dyslexia affects individuals in spite of having received adequate education and not suffering from intellectual disability, as a result of a neurobiological dysfunction. Depending on whether this neurobiological dysfunction is attributed to a sudden event following typical development or it is innate, dyslexia cases are distinguished in acquired or developmental dyslexia, respectively (Temple, 2006); for the purposes of this pilot study, I focused on developmental dyslexia. It is characterized by difficulties in spelling, reading accuracy, and fluency (International Dyslexia Association; Lyon et al., 2003); in the fifth edition of the DSM-V, poor reading comprehension is included as a characteristic of dyslexia (American Psychiatric Association, 2013). Although dyslexia is a multidimensional disorder, the majority of children with dyslexia face problems in naming as well as in matching speech sounds (phonemes) to visual representations in written language (letters), and in memorizing, categorizing, and consciously using these correspondences, all problems reflecting deficits in phonological awareness (Archer, 2020; Boets et al., 2013; Chaubet et al., 2014; Gori et al., 2016; Lieder et al., 2019; Manilla & de Braga, 2017; Marchesotti et al., 2020; Peterson & Pennington, 2012; Snowling & Hulme, 2012;

Vieira et al., 2013). In addition, children with dyslexia may struggle with deficient writing, audiovisual, and attentional skills, as well as in executive functions (Archer et al., 2020; Ashburn et al., 2020; Chaubet et al., 2014; Dresler et al., 2018; Gori et al., 2016, 2020; Jagger-Rickels et al., 2018; Nachshon & Horowitz-Kraus, 2019; Ramus et al., 2013; Salvador et al., 2019). Early signs of these problems before reading and writing acquisition, often accompanied by family history (familial risk) of dyslexia (Gerrits & de Bree, 2009; Lyytinen et al., 2004; Torppa et al., 2010), are risk factors for dyslexia. The associated deficits affect their social and emotional state by diminishing their self-esteem, self-concept, and self-efficacy, oftentimes resulting in peer rejection and even causing comorbid anxiety disorders and depression (Berninger et al., 2019; McArthur et al., 2022; Nachson & Horowitz-Kraus, 2019). Hence, an appropriate intervention might aid these children both at an educational and at an emotional level.

According to the "dyslexia paradox" (Ozernov-Palchik & Gaab, 2016), interventions are usually administered after the official diagnosis of dyslexia, when the impairments in reading might have become severe and persistent, and, hence, the individuals who receive intervention may not experience the maximum benefit (the "waiting to fail effect"; Van den Bempt et al., 2021; Verwimp et al., 2020; Wanzek & Vaughn, 2007). For instance, Lovett et al. (2017) showed that reading intervention was more beneficial in terms of acquired basic reading skills and of reading rate if children at risk for reading difficulties received the intervention during the first two years of elementary school rather than later. In contrast, early, preventive, intensive interventions are quite successful; 56% to 92% of children at risk for dyslexia who received early instruction in six studies reached the average reading ability of fluent peers (for reviews see Gabrieli, 2009; Torgesen, 2004). Therefore, detecting the risk for dyslexia and intervening early can improve reading outcomes.

Cerebral lateralization for language refers to the differential activation of the two brain hemispheres during language tasks (Bradshaw et al., 2017; Ocklenburg et al., 2017). For the majority of neurotypical individuals, oral language production is left-lateralized (Nielsen et al., 2013; Papadatou-Pastou et al., 2017; Petit et al., 2020; van Setten et al., 2013). The dominant hemisphere for the production of oral language could be established in early infancy in typically developing children (Gurunandan et al., 2021; Lawrence et al., 2021), while the degree of lateralization becomes stronger over time (Berl et al., 2014; Olulade et al., 2020).

In cases of SLD, such as dyslexia, cerebral lateralization for oral language differs from that of typically developing children, with (i) decreased activation of left hemispheric regions (Richlan, 2020; Richlan et al., 2009; Scerri et al., 2011; van der Mark et al., 2010; for a review see Vlachos & Avramidis, 2020) and/or (ii) increased activation of homologous right hemispheric regions (Berninger & Richards, 2010; Richards & Berninger, 2008; Richards et al., 2006; Simos et al., 2002), potentially for compensatory purposes (Jagger-Rickels et al., 2018; Morken et al., 2014, 2017; Richlan et al., 2009; Siok et al., 2008). Areas showing differences in cerebral language lateralization between children with dyslexia and typically developing children include the left temporoparietal cortex (Ashburn et al., 2020; Chen et al., 2014; James & Engelhardt, 2012; Linkersdörfer et al., 2012; Longcamp et al., 2011; Purcell et al., 2011; Richlan, 2020; Yuan & Brown, 2014) and the left inferior frontal gyrus (Ashburn et al., 2020; James & Engelhardt, 2012; Linkersdörfer et al., 2012; Longcamp et al., 2011; Purcell et al., 2011; Richlan, 2020), both involved in phonological processing, as well as the left medial frontal gyrus (Richlan, 2020), the left inferior temporal gyrus (Scerri et al., 2011), and the left occipito-temporal cortex (Ashburn et al., 2020; Linkersdörfer et al., 2012; Richlan, 2020; Richlan et al., 2011; van der Mark et al., 2011). All these left-hemispheric areas are also typically activated during writing tasks in neurotypical individuals (Araújo et al., 2012; Berninger, 2009; Kircher et al., 2011; Potgieser et al., 2015; Purcell et al., 2011a,b; Rapp & Lipka, 2011; Seghier & Price, 2011; Tsapkini & Rapp, 2010). These differences in cerebral lateralization for language between individuals with dyslexia and neurotypical individuals could –to some extent– explain the behavioral differences in terms of reading difficulties between these groups (for a review see Farah et al., 2021).

Atypicalities in the cerebral lateralization for language can often be observed prior to the development of the behavioral symptoms of dyslexia. For instance, children at familial risk for dyslexia show the same pattern of atypical lateralization of regions involved in phonological processing as individuals diagnosed with dyslexia (Debska et al., 2016). These atypicalities have been attributed to the underactivation of the language production regions of the left hemisphere during language tasks (Powers et al., 2016; Raschle et al., 2014; Sarkari et al., 2002; van Leeuwen et al., 2007). Notably, the degree of the activation of the left hemisphere of children at risk for dyslexia has been shown to provide an indication of the responsiveness of children to age-appropriate educational interventions (Davis et al., 2011; Pleisch et al., 2019).

Following educational intervention addressing early symptoms of dyslexia, cerebral lateralization for language is shifted leftwards approximating the pattern of age-matched neurotypical individuals (Dresler et al., 2018; Goswami, 2006; Heim et al., 2015; Munzen et al., 2020; Peck et al., 2018; Simos et al., 2000a, b, 2002b; Temple et al., 2003; Ylinen & Kujala, 2015). This shift in lateralization affects regions involved in phonological awareness, among others (Berninger & Richards, 2010; Démonet et al., 2004; Elbro & Jensen, 2005; Gabrieli, 2009; Manilla & de Braga, 2017; Richards & Berninger, 2008; Richards et al., 2006; Shaywitz et al., 2006; Temple et al., 2003). Of note, the studies addressing the effect of interventions on cerebral lateralization for language use oral language tasks. The impact of interventions on the cerebral lateralization for written language is yet to be studied.

The association between reading improvement after phonological intervention and the cerebral lateralization for oral language in individuals with dyslexia has received attention during the last two decades. The large majority of such studies has sampled children and adolescents (e.g., Hasko et al., 2014; Shaywitz et al., 2004), with only one study sampling adults with dyslexia (Eden et al., 2004). Brain activation has been assessed using a variety of techniques: functional magnetic resonance imaging (fMRI; Eden et al., 2004; Gaab et al., 2007; Heim et al., 2015; Richards et al., 2007; Shaywitz et al., 2004); event-related potentials (ERP; Hasko et al., 2014; Jucla et al., 2009; Molfese et al., 2013; Spironelli et al., 2010); MRI (Richards et al., 2000, 2002); MEG (Simos et al., 2007a,b); and magnetic source imaging (Simos et al., 2002).

In most of these studies, prior to intervention, the right-hemisphere shows increased activation, which is attributed to older age in adults (Eden et al., 2004) and to compensatory mechanisms in children (Shaywitz et al., 2004; Simos et al., 2002; Spironelli et al., 2010). Phonological intervention shifted the typically hypoactive left-hemispheric language areas in dyslexia to typical levels, including the left-hemispheric prefrontal, (Gaab et al., 2007), temporal (Gaab et al., 2007; Simos et al., 2002, 2007a,b), parietal (Eden et al., 2004; Simos et al., 2002, 2007a,b), and subcortical regions (Gaab et al., 2007). In addition, phonological intervention led to the hyperactivation of the, previously normally activated, left (Shaywitz et al., 2004; but see Richards et al., 2000, 2002 for contradictory evidence) and right inferior frontal gyrus (Richards et al., 2007; Shaywitz et al., 2004), and the left inferior occipitotemporal cortex (Heim et al., 2015; Simos et al., 2002).

The abovementioned studies provide evidence that the earlier the intervention the better the outcome; however, only five studies have included children at risk (Molfese et al., 2013; Shaywitz et al., 2004; Simos et al., 2007a,b; Yamada et al., 2011). In Shaywitz et al. (2004), the brain activity of 8-year-old children at risk for dyslexia and controls was measured using fMRI during a letter identification task, prior and after two types of intervention, a phonologically-based intervention and a community intervention administered at school with no phonological component. The phonologically-based intervention resulted in short-

(immediately after intervention) and long-term (one year after the completion of intervention) (i) increase in the activation of frontal, temporal, and occipitotemporal regions of the left hemisphere and (ii) reduction in the activation of right cortical and subcortical regions, which were initially hyperactivated, potentially for compensatory purposes. The community intervention did not improve behavioral or neurophysiological traits of children at risk for dyslexia, a parameter potentially dissuading parents from including their children in the post-test (Shaywitz et al., 2004). Simos et al. (2007a, b) used MEG to measure the spatiotemporal brain activity of 7- to 9-year-old children at risk for dyslexia during oral word reading (Simos et al., 2007a) or rapid word recognition (Simos et al., 2007b), before and after a phonological awareness intervention. Prior to the intervention, the activation of temporal (Simos et al., 2007a,b), parietal (Simos et al., 2007a,b), and occipitotemporal (Simos et al., 2007b) regions of the left hemisphere was decreased, while the bilateral activation of the inferior frontal gyrus was either early (Simos et al., 2007a) or increased (Simos et al., 2007b) in children at risk for dyslexia compared to controls. Following intervention, the children at risk for dyslexia who responded adequately to the intervention showed normalized activity, in terms of duration and degree, with the pattern of activation of the above-mentioned regions resembling the pattern of typically developing children.

Yamada et al. (2011) sampled participants as young as kindergarten of typical pre-literacy level and at-risk for reading difficulties. Using fMRI, they studied the changes in brain activity for letter processing relative to false font processing following (i) three months of kindergarten (typically developing toddlers) or (ii) a supplementary intervention with a phonological component (toddlers at risk for reading difficulties). Before the intervention, typically developing toddlers showed bilateral activation of posterior dorsal regions during letter processing compared to false font processing, while at-risk toddlers did not display any differential activation during these tasks. Regular education resulted in a left-lateralized activation of temporoparietal regions, accompanied by the decreased recruitment of right homologue regions in typically developing toddlers. Regular education supplemented by an intervention led at-risk children to develop a pattern similar to the initial pattern of typically developing children along with the engagement of frontal regions of the left hemisphere, potentially for compensation. This study was limited by the fact that the usable fMRI data was reduced due to the excessive motion of participants (i.e., n = 3 children at-risk of the available sample of 7).

Unlike previous studies, Molfese et al. (2013) did not compare children at risk for dyslexia before and after an intervention, but they investigated differences in early ERP during rhyming tasks between responders and non-responders to an intervention with a phonological awareness component and controls. Potentials in the right hemisphere showed larger amplitudes in responders compared to controls, while for the left hemisphere, increased amplitudes were observed in responders compared to non-responders.

Based on the above findings, it appears that interventions with a phonological component have the potential to reorganize the activation patterns of language-related regions across hemispheres in children at risk for dyslexia, in order to approximate the pattern of typically developing children. However, as only one of the studies sampling children at risk for dyslexia provided an exclusively phonologically-based intervention (Shaywitz et al., 2004), there is inadequate evidence to attribute these effects to the phonological component of the interventions. This question has been rather studied in children diagnosed with dyslexia (Hasko et al., 2014; Heim et al., 2015; Richards et al., 2002, 2007).

In their 2002 study, Richards et al. showed that a morphological intervention (focusing on the etymology of words) rather than a phonological intervention was more efficient in normalizing the lactate elevation, representing metabolism, in the left frontal gyrus of children with dyslexia. In 2007 they compared a phonological intervention –administered to children with dyslexia– and a non-phonological intervention, including training on non-verbal response to a virtual reality task -administered to both children with dyslexia and typically developing controls. Heim et al. (2015) administered three types of intervention, one phonologically-based, one focusing on visual word recognition (reading), and one attention-driven, with the former two affecting regions related to phonological processing. In both Richards et al. (2007) and Heim et al. (2015), the interventions with a phonological component led to increased activation of the previously underactive left parietal regions, while children who received the control intervention focusing on visual attention, showed increased activation of left-hemisphere regions associated with attention. Of note, Hasko et al. (2014) assigned children with dyslexia to one of two types of intervention, focusing on phonological awareness or on grapheme (written representation)-phoneme correspondence. However, they reported that the small sample (14 children in each group) only allowed for comparison of the differences pre- and post-intervention, but not the effect of the type of intervention. Overall, in the studies on children with dyslexia, the control intervention either included a phonological component itself (Hasko et al., 2014; Heim et al., 2015; Richards et al., 2002) or it was ineffective (Richards et al., 2007; Shaywitz et al., 2004). Therefore, the phonological component appears to have a critical role in the efficiency of the intervention in shifting the language lateralization towards the typical pattern.

To summarize, the effects of phonological interventions on the cerebral lateralization for language seem to be:

(i) a normalized pattern of activation, translating into an increase in activation of previously underactive left-hemispheric regions related to phonological processing and a reduction in activation of previously hyperactive homologous regions of the right hemisphere during oral language tasks;

(ii) observed even before the diagnosis of dyslexia, although only four studies have assessed at-risk children, and their results are inconclusive and

(iii) possibly attributed to the phonological component of the interventions.

Given that no study has assessed the impact of a phonological intervention on cerebral lateralization for language during writing tasks, the aim of the present study was to investigate the effects of a phonological intervention on cerebral lateralization for written language in children at-risk for dyslexia.

Language can be analyzed in five constituent parts: phonology, morphology, syntax, semantics, and pragmatics (Adlof & Hogan, 2018; Roesch, 2019). The latter component, pragmatics, represents the ability to comprehend the language used in a given communicational interaction or social context and to manipulate language properly to respond in such contexts (Ferrara et al., 2020; Roesch, 2019). Pragmatic skills include performing and interpreting different functions of messages (e.g., apologizing, requesting, thanking) and conversational codes, according to the roles of each communicator (speaker or listener) and to the context of conversation, while employing the appropriate strategies (e.g., initiating a discussion, changing or keeping to a topic; Cappelli et al., 2018; Cardillo et al., 2018; Wong et al., 2021). Additionally, a pragmatics-competent individual is capable of assuming information that is not explicitly reported by the speaker (i.e., inference) and of providing enough detail to help the listener refer to the discussed subject (i.e., reference; Cappelli et al., 2018; Cardillo et al., 2018; Wong et al., 2021). In fact, Grice (1975) proposed a list of maxims regarding pragmatic competence that should govern human communication, in terms of the relativity, the sufficiency and the validity of provided information, and the manner of providing this information, clearly and decently. It is evident that adequate pragmatic skills are important for social inclusion and generally in everyday life (Cappelli et al., 2022).

The inadequate pragmatic competence that characterizes neurodevelopmental disorders, such as high-functional autistic spectrum disorders (Bishop, 2000; Perkins, 2000), is also apparent in dyslexia (Griffiths, 2007), though it is not a primary difficulty (Cardillo et al., 2018;

Vellutino et al., 2004). Of note, pragmatic impairment is suggested to result from difficulties in language processing at a more basic level (Cappelli et al., 2022), being assigned to reduced working memory (Griffiths, 2007; Miles et al., 2006), automatization (Cappelli et al., 2018), and vocabulary (Cappelli et al., 2022), all induced by the core phonological deficit. Some of the struggles related to pragmatics that individuals with dyslexia might cope with throughout their lives include: (i) difficulties in selecting the right words and in keeping to a topic or changing between cohesive topics while attempting to orally communicate their ideas (Cardillo et al., 2018; Griffiths, 2007; Norbury & Bishop, 2003; Troia, 2011), (ii) lack of grammatical and lexical cohesion and incorrect punctuation in their written texts (Norbury & Bishop, 2003; Troia, 2011), (iii) hardship in comprehending and interpreting idioms, jokes, and metaphors (Cappelli et al., 2022; Cardillo et al., 2018; Ferrara et al., 2020; Mashal & Kasirer, 2011; Nippold, 2007; Troia, 2011), and (iv) inference problems (Cappelli et al., 2018; Cardillo et al., 2018). These deficits in pragmatic competence can lead to misunderstandings and misjudgments in various social environments causing social and emotional inconvenience for individuals with dyslexia who struggle with these problems (Cappelli et al., 2022; Ferrara et al., 2020; Griffiths, 2007; Troia, 2011).

In the present pilot study, a pragmatics intervention was administered to a girl at risk for dyslexia to test the feasibility of an active control intervention for application in a larger study. Such an intervention does not include a phonological component and, although pragmatics interventions were originally developed for children with other neurodevelopmental disorders, they are considered promising for children with dyslexia in improving their communication skills (Cappelli et al., 2018). Therefore, children receiving either intervention would benefit from participating in the study.

As above-mentioned, most of the techniques used to study the effects of phonological interventions on the cerebral lateralization for language (namely electroencephalography, MEG, mass spectrometry imaging, and MRI) do not allow for assessing the performance of participants in writing tasks. Only fMRI has been applied for the measurement of brain activity during writing (e.g., Richards et al., 2015, 2017). However, the additional fMRI-compatible equipment that is needed to assess writing in a scanner increases the cost of an already expensive technique, while the position of participants during writing tasks (laying on their back) does not simulate the natural position for writing (but see also Baumann et al., 2022). In this pre-registration, I used fTCD (see Section 1.9 of this thesis for details). Lateralization indices computed using fTCD for oral language tasks show good test-retest reliability when different test sessions are separated from three to 434 days (Bruckert et al., 2021; Woodhead et al., 2021). This is an essential feature for the scope of this pre-registration in order to ensure that the expected effect of the phonological intervention on cerebral lateralization for written language in children at risk for dyslexia does not reflect variability in measurements between sessions.

The main aim of this pilot study was to compare the cerebral lateralization for the linguistic component of written language in children at risk for dyslexia at two time-points (before and after a phonological intervention) versus that of typically developing children (who did not receive an intervention). The cerebral lateralization for the linguistic component of written language was computed by taking the difference in the cerebral lateralization as assessed during a Written Word Generation task and a Letter Copying task. I further administered a pragmatic intervention to one child at risk for dyslexia to test the feasibility of this intervention, to be used in future studies investigating whether the effects of the targeted (phonological) intervention are specific to phonology. For the purposes of the current study, I did not take into consideration the familial risk for dyslexia, but risk was assessed by the presence of early symptoms.

The following hypothesis was put forward:

Hypothesis: The cerebral lateralization for the linguistic component of written language of children at risk for dyslexia compared to that of typically developing children will show larger differences prior than following the phonological intervention.

4.2 METHODS

4.2.1 Participants

A total of 12 participants from Study 2 were recruited for this pilot study, 6 children at risk for dyslexia and 6 typically developing children. Six children at risk for dyslexia were administered an intervention: (a) 5 at-risk children were administered a phonological intervention and (b) 1 at-risk child received a pragmatic intervention.

Children at risk for dyslexia and typically developing children were matched for age, intelligence, and gender. The inclusion criteria were the same as described in Chapter 3. In addition, children at risk for dyslexia had a score lower than the 25th percentile (mean score lower than 37 for the boys and mean score lower than 44 for the girls) in the pragmatic domain of the Logometro tool (Mouzaki et al., 2017).

Participants were considered typically developing, if they had:

(a) A score higher than the 25th percentile in the Reading Skills Assessment Test (Panteliadou et al., 2019), verifying the absence of risk for reading difficulties and

(b) A score higher than the 50th percentile in the pragmatic domain of the Logometro tool.

Five boys and one girl (2 left-handed boys, mean age = 8.1 years old) were administered the phonological intervention and one right-handed girl (8.4 years old) was administered the pragmatic intervention.

Assessment of non-verbal intelligence, comorbidities, the risk for dyslexia, and cerebral lateralization was conducted according to Chapter 3.

4.2.2 Assessment of pragmatic skills

Logometro: Logometro is a digital tool, standardized for the Greek population (Mouzaki et al., 2017), that evaluates the linguistic skills of children in kindergarten and first school years. For the purposes of this study, only the pragmatic skills of the participants were assessed using this tool. The pragmatic competence of children is estimated according to their ability to (a) understand and interpret communicational contexts, (b) to express their intention to communicate, (c) to respond to a communicational interaction, and (d) to react properly in different communicational contexts. A series of communicational contexts familiar to children is presented on screen as pictures or videos. Auditory messages describe the contexts and what is requested from children. An example inducts children to each one of the assessed skills. Their responses are recorded and a score is computed according to the number of correct answers.

4.2.3 Educational interventions

Each intervention was completed in 22 30-minute one-on-one training sessions, administered twice per week. The nature of sessions alternated between in-person meetings at a familiar and emotionally safe place for children, and online meetings. The first session always took place in person.

The teaching principle of reducing guidance (Rosenshine, 1983) was employed. During each session children were introduced to the aim of the session, then the strategy to achieve this aim was provided to children using examples; the researcher showed the children how she would apply the strategy in one (pragmatics) or two to three (phonological) examples. Children were then asked to apply the strategy with the guidance of the researcher and, finally, practice the instructed skill independently. Children's independence was further encouraged through self-monitoring (at the beginning of the last step) and self-assessing (at the end of the session) of their performance. Self-evaluation has been shown to help students analyze and review their skills resulting in improved performance (Vasileiadou & Karadimitriou, 2021).

4.2.3.1 Phonological intervention (experimental group)

The phonological intervention had the following goals:

A. Recognition of rhyming (e.g., children learnt to select two words that rhyme from a list of three pictures)

B. Detection of similarities at the level of the first or last syllable or phoneme (e.g., children learnt to group words that start or end with the same phoneme)

C. Segmentation of words into syllables, and of syllables into phonemes (e.g., children learnt to separate the word entities of a sentence)

D. Synthesis of syllables or phonemes into words (e.g., children learnt to form words by combining syllables)

E. Detection of the location (first, last, or any other) of syllables or phonemes in words using the Elkonin method. This method raises awareness through the segmentation of the components of words into sequential boxes (e.g., children learnt to recognize the place of a syllable in a word; Elkonin, 1973)

F. Addition or removal of a syllable or a phoneme, at the beginning, the end, or any place within the word (e.g., children learnt to add a syllable at the beginning of a word to form a new one)

G. Reversal of syllables or phonemes in words (e.g., children learnt to spell a four-letter word backwards)

H. Replacement of a syllable or a phoneme (e.g., children learnt to recognize a specific syllable and place a new, named syllable in its place) and

I. Detection of the place of a grapheme within a word using the Elkonin method (e.g., children learnt to correspond the written representation of a letter to its sound and to detect its place in a word).

4.2.3.2 Pragmatic intervention (active control group)

The pragmatic intervention is based on McGinnis and Goldstein's (1984) trainings named "Classroom Survival skills" and "Friendship Making skills", which have the following goals:

(a) Active listening and keeping order in a conversation

(b) Starting, keeping up with, changing subject, and ending a conversation

(c) Following the four maxims (Quantity, Quality, Relativity, & Manner; Grice, 1989)

(d) Asking for clarifications

(e) Requesting or providing help and reasons for actions, situations or choices

(f) Making or accepting compliments

(g) Requesting and reacting to any change of actions

(h) Apologizing and thanking

(i) Joining group activities and conversations

4.2.4 Procedure

An information sheet was sent 72 hours prior to participation to the guardians of the prospective participants to ensure that they would have adequate time to consider participation of the children. Upon agreement, an online questionnaire was administered to pre-screen children (e.g., language, vision). On the day of the first data-collection session, guardians and children arrived at the lab, the study was described to them, and they were encouraged to ask questions. Guardians were then asked to provide informed written consent and children to orally declare their assent, while being reassured that they are free to discontinue the project at any time without explanation. Next, non-verbal intelligence, pragmatic skills, and reading performance were assessed in a quiet room. Participants watched a few minutes of a cartoon while the fTCD headset was fitted. The neurophysiological data for each participant ensued. The first data collection session was completed with the assessment of behavioral lateralization. In the following days, the educational interventions were administered to the children at risk for dyslexia. After the completion of the 22 training sessions, children were reinvited to the laboratory, where they were reassessed for cerebral lateralization for language, pragmatic skills, and reading performance. After the completion of the second data collection session, participants were given a memento and a diploma of participation and they were debriefed.

4.2.5 Data analysis

Data were analyzed using R Studio [Version 4.1.2; R Core Team (2021)]. The hypothesis was tested using a Bayesian approach that allows to estimate the probability of the alternative over the null hypothesis according to pre-determined prior effect-size assumptions and the observed data (posterior probability) even when there is no prior evidence over one of the two conditions (Wei et al., 2022).

The hypothesis was tested using a Bayesian paired *t*-test of children at risk for dyslexia before and after receiving the phonological intervention with the LI for the linguistic component of writing as the dependent variable. The prior for this test was set as the default (0.707) because there is no prior knowledge for the effect of an exclusively phonological intervention on the lateralization for the linguistic component of written language.

4.3 RESULTS

The data of children prior to intervention were derived from Study 2. Within one week following intervention the fTCD task and reading skills evaluation were repeated. The mean lateralization indices of each group in each condition prior and after intervention are plotted in Figure 21. Performance of children on the assessment of reading skills (Table 5) indicated that two of the children administered the phonological intervention did not progress, while the score on pseudoword and word decoding was increased for the rest of participants.

Table 5

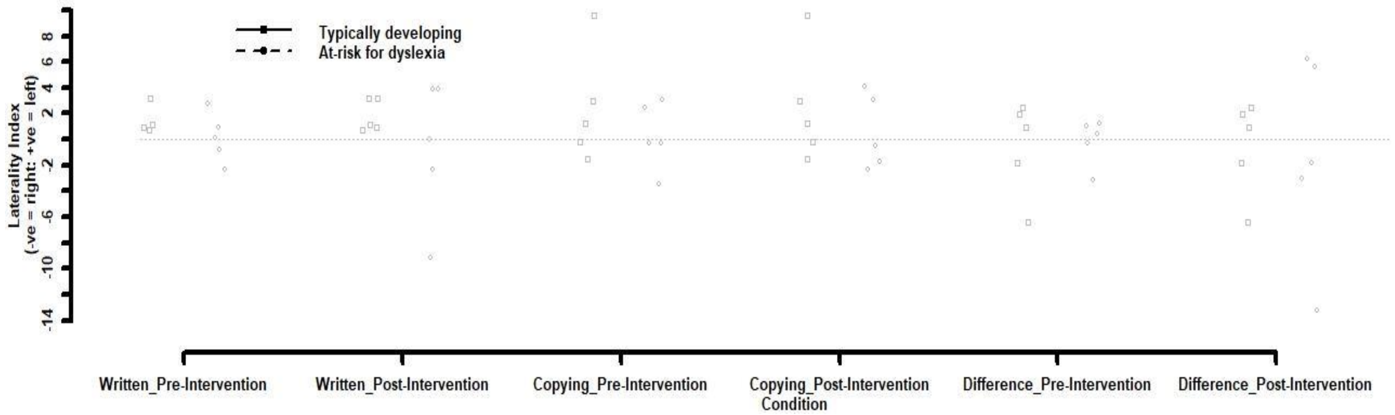
Typical scores in Reading Skills Assessment Test of children at risk for dyslexia prior and after the phonological intervention

	Grade	Pseudoword decoding prior	Pseudoword decoding after	Word decoding prior	Word decoding after
P1	**B**	**5**	**5**	**5**	**5**
P2	**B**	**9**	**25**	**16**	**50**
P3	**C**	**2**	**50**	**5**	**37**
P4	**C**	**16**	**16**	**5**	**9**
P5	**B**	**2**	**9**	**1**	**25**

Note: The table includes the typical scores of the participants administered the phonological intervention in the two assessed tasks of the Reading Skills Assessment Test prior and after the intervention. Participants were anonymized and coded as P1, P2, P3, P4, and P5 for the purposes of this table.

Figure 21

Lateralization indices prior and after intervention in children at-risk for dyslexia and typically developing children



4.3.1 Registered analysis

Hypothesis: The cerebral lateralization for the linguistic component of written language of children at risk for dyslexia compared to that of typically developing children will show larger differences prior than following the phonological intervention.

The Bayesian paired *t*-test could not provide enough evidence in favor either of the null or of the alternative hypothesis (BF = 0.42)

4.3.2 Exploratory analysis

Exploring the shift in the direction of lateralization

Inspection of the data (see Supplementary Table 6) led to the realization that for three of the children, who received the phonological intervention, lateralization for the linguistic component shifted to the left following intervention (positive difference of indices), while for the remaining two it shifted to the right (negative difference of indices). However, the small size of the sample could not allow to conduct any further analyses to test for other differences between the groups.

Exploring responsiveness

The occurrence of adequate and inadequate responders raised the question whether there was a difference in lateralization between these two groups. Among children whose lateralization shifted to the right, one boy (P3) was an adequate responder and one girl (P1) was an inadequate responder. The number of participants in each group could only allow to visually inspect that the lateralization for the linguistic component of written language was similar in both responders and inadequate responders.

4.4 DISCUSSION

The present study was a pilot study investigating for the first time the effect of an intensive exclusively phonological intervention on the lateralization for writing in children at-risk for dyslexia. Moreover, a pragmatic intervention was piloted for its feasibility as an active control intervention in a larger study.

Previous studies assessing the outcome of administering interventions with a phonological component to children at-risk for dyslexia on the lateralization for speaking and listening have shown that the involvement of the left hemisphere increases, while the involvement of the right hemisphere decreases, following intervention (Shaywitz et al., 2004; Simos et al., 2007a, b; Yamada et al., 2010). With this knowledge, it was hypothesized that the lateralization for writing would become more leftward, to approximate that of typically developing children, following phonological intervention. The findings could not provide enough evidence for this hypothesis. In fact, there was not a clear trend for the shift of the lateralization pattern across children who received the phonological intervention for any of the conditions assessed. Therefore, there is inadequate evidence to support that an exclusively phonological intervention can reorganize the representation of writing in the brain of children at-risk for dyslexia. However, it should be noted that a dispersed lateralization pattern of the group was also apparent prior to intervention (see Chapter 3). This might indicate that the lateralization for writing of children at-risk for dyslexia as well as their potential for brain reorganization is inconsistent on a group level.

The response of a student to an intervention is influenced by individual traits with 2 to 6% chance of failure to ameliorate children's performance (Simos et al., 2007b; Torgesen, 2000; Torgesen et al., 2001; Wise et al., 2000). Several parameters influence children's response to intervention, including differences in academic skills except for the ones used to classify children as at-risk for dyslexia, in behavior, in intelligence, and in brain structure and function (Al Otaiba & Fuchs, 2006; Barquero et al., 2014; Fletcher et al., 2011). Adequate response to a phonological intervention is evidenced by an amelioration of phonological awareness skills, such as elevated scores in decoding words and pseudowords (Odegard et al., 2008). In the present study, the scores of three out of five children that received the phonological intervention rendered them adequate responders, while for the remaining two (inadequate responders) scores were similar prior and after intervention. Gathering additional data could allow us to test whether the phonological intervention on reading performance is linked to a change in the lateralization for the linguistic component of written language.

Following inspection of the findings, another explanation related to the aberrations in the lateralization pattern across individuals could be that the absence of a clear effect of the phonological intervention was the different direction that the lateralization shift took following intervention in different individuals. Specifically, phonological intervention led three participants to be more left-lateralized following intervention and two participants to be more right-lateralized following intervention. Therefore, the same type of intervention could have different impacts on hemispheric specialization in different children. However, this notion needs further evidence and support.

The current pilot study is the first to include an exclusively phonological intervention. Interventions previously used targeted phonological awareness but also assess graphophonemic correspondence and morphological awareness (e.g., Simos et al., 2002, 2007a,b). Moreover, this pilot study was pioneer in the field of lateralization as it was the only one to my knowledge that has investigated the effect of educational interventions on the lateralization for writing (as opposed to oral language) and, in particular, in children at risk for dyslexia.

Another important quality of this study was the inclusion of a pragmatic intervention. This type of intervention was assessed for feasibility to be employed as an active control intervention in future, larger studies. The pragmatic intervention designed for this study was administered successfully. The girl that received the pragmatic intervention advanced both in terms of reading performance and of self-esteem according to personal observations and what was reported by children themselves, parents, and school teachers. Notably, it is important for the potential use of this intervention as an active control in the future (Shaywitz et al., 2004) that the girl completed her training despite the fact that the pragmatic intervention did not address the phonological difficulties in reading. Thus, the pragmatic intervention described in this study lends itself as a promising active control intervention for future larger studies.

However, these strengths were accompanied by some limitations. This was a pilot study and, hence, the sample size was small. Having secured that the pilot administration of both types of intervention was successful, inclusion of more children at-risk for dyslexia (and matched controls) could potentially lead to more robust findings regarding the effect of the phonological intervention on lateralization. Moreover, as previously discussed in Chapters 2 and 3, letter copying might have failed to adequately isolate the motor component of writing, and, hence, a better motor control task might be required to disentangle the linguistic component of writing in future studies.

In conclusion, even though this pilot study did not yield enough evidence for the effect of a phonological intervention on the shift in lateralization for the linguistic component of writing at a group level, it was successful in terms of the cooperation of the participants, their interest for the contents of the interventions, and the amelioration of reading performance. Testing for the responsiveness effect or the direction of lateralization could not be analysed in this small sample, but this methodology provides a proof of concept for future work. Given the effectiveness of the interventions in improving the reading skills of specific children, it would be intriguing to explore further the characteristics of these children in future studies.

Supplementary Table 6

Cerebral lateralization indices of children at risk for dyslexia prior and after the phonological intervention

	$LI_{written}$ (prior)	$LI_{written}$ (after)	LI_{letter} (prior)	LI_{letter} (after)	$LI_{difference}$ (prior)	$LI_{difference}$ (after)	Shift in $LI_{difference}$
P1	2.79	-9.15	3.05	4.08	-0.26	-13.23	-12.97
P2	0.94	3.86	-0.27	-2.34	1.21	6.2	4.99
P3	0.15	0.04	-0.31	3.03	0.46	-2.99	-3.45
P4	-0.77	2.37	2.42	-0.53	-3.19	-1.84	1.35

P5	-2.32	3.9	-3.4	-1.71	1.08	5.61	4.53

Note: The table includes the lateralization indices of the participants administered the phonological intervention, for each condition, prior and after the intervention. Participants were anonymized and coded as P1, P2, P3, P4, and P5 for the purposes of this table. The last column indicates the difference in the lateralization indices of the examined variable, the lateralization for the linguistic component of writing before and after the intervention, or alternatively the shift in lateralization for the linguistic component of writing

5 GENERAL DISCUSSION

More or less, life relies on asymmetry (Geschwind & Galaburda, 1985; Quack, 1989). The most well-known manifestations of asymmetry that show a pattern at a population-level in humans are the cerebral lateralization for language and handedness (Schmitz et al., 2017). Handedness is an umbrella term, referring to both the preference for using one hand for unimanual tasks but also the skill in using one hand relative to the other (Papadatou-Pastou et al., 2020). Oral language comprehension and generation have been widely studied in terms of lateralization and there is a consensus that these are associated with left lateralization for the majority of individuals (Baynes & Long, 2007; Braga et al., 2020; Friederici & Alter, 2004; Frost et al., 1999; Josse & Tzourio-Mazoyer, 2004; Josse et al., 2008). Deviations from the typical language lateralization pattern are in part linked to handedness (Khedr et al., 2002; Knecht et al., 2000; Ocklenburg et al., 2014; Papadatou-Pastou, 2011; Pujol et al., 1999). More specifically, left-lateralization for language has been found to be the case in 83-96% of right-handers, but 64-85% of left-handers (Bartha et al., 2003; Bishop & Bates, 2020; Carey & Johnstone, 2014; Clarke et al., 2016).

Another parameter that has been related to differential language lateralization is dyslexia (Annett, 1996; Galaburda, 1983; Hiscock & Kinbourne, 1995; Kershner, 2020; Kershner & Graham, 1995). Children with or at-risk for dyslexia show decreased activation of language-related regions of the left hemisphere during oral and reading language tasks, which is accompanied by an increase in activation of the homologous right-hemispheric regions, potentially as a compensatory mechanism (Banfi et al., 2019; Kershner & Stringer, 1991; Leonard & Eckert, 2008; Papadopoulou et al., 2022). Notably, as a result of neuroplasticity, interventions, especially those including a phonological component, can shift the language lateralization of children with or at-risk for dyslexia to the left to approximate that of typically developing children (Hasko et al., 2014; Helland et al., 2011; Kershner, 2020; Odegard et al., 2008).

All the findings mentioned above are derived from studies on oral language or reading. Written language, albeit critical for everyday communication and work, across time and geographical locations, is significantly understudied in terms of lateralization (Herron et al., 1979; Keene, 1981; Kerckhove & Lumsden, 2013; Kershner & Stringer, 1991; Planton et al., 2017). Of note, potentially due to the multifactorial nature of writing, only four studies had assessed the lateralization for writing in both left-handed and right-handed adults (Kondyli et al., 2017; Papadatou-Pastou et al., 2022; Siebner et al., 2002; Zaman et al., 2002) and, before this thesis, no study had examined lateralization for writing in children. In the four preceding studies, despite noting distinctions in the lateralization for writing between left-handers and right-handers, the results were inconclusive in establishing a consistent pattern for both groups. This could be attributed to a number of limitations, such as small sample sizes, using nominal hand to determine handedness, and neglecting the complex nature of writing (Siebner et al., 2002; Zaman et al., 2002), or lacking an appropriate motor control task (Kondyli et al., 2017; Papadatou-Pastou et al., 2022).

These limitations were addressed in Study 1 of this thesis in which the lateralization for the linguistic component of written language was compared between left-handers and right-handers. Letter copying was used to disentangle the motor component of written language as a control task for written word generation. The lateralization for the linguistic component of writing was then assessed by subtracting the lateralization for letter copying from the lateralization for written word generation. If this difference indeed removed the motor component of writing, then we expected that the linguistic component of written language would simulate the processes also subserving oral word generation. Therefore, a second aim of Study 1 was to assess the relationship of the linguistic component of written language and oral word generation in terms of lateralization.

The linguistic component of written language was left-lateralized for both left-handers and right-handers, as expected (Papadatou-Pastou et al., 2022). However, there was not enough evidence for a difference in the lateralization for the linguistic component of written language between left-handers and right-handers. Of note, letter copying was in general more right-lateralized than expected, especially in right-handers. If letter copying indeed isolated the hand motion of writing, then the direction of its lateralization should be contralateral to the hand used for writing. The most plausible interpretation for this result was that the motor control task could not adequately isolate the motor component of writing. Letter copying might have engaged more right-hemispheric functions than hypothesized. For example, the right hemisphere can be activated for letter-by-letter reading or to inhibit the innate urge to write the next letter of the alphabet or words starting with this letter (Aron et al., 2004; Hellige et al., 1989; Lindell, 2006; Van Ettinger-Veenstra et al., 2011; Völlm et al., 2006). When it comes to the relationship of oral language generation and the linguistic component of written language in terms of lateralization, again there was not enough evidence for a correlation between the two variables across the whole sample, but extreme evidence confirmed a strong correlation specifically for the left-handers of the sample. Taken together, the findings underscore the challenge of accurately assessing the components of writing in terms of lateralization, which is made even more daunting by the variability that handedness introduces in data.

Studies 2 and 3 assessed the lateralization for written language in children, including children at-risk for dyslexia. This is important taking into consideration that writing difficulties is an integrant characteristic of dyslexia, persisting through ages (Berninger et al., 2008; Sumner et al., 2014). Again, analyses focused on the linguistic component of written language that was calculated as previously described for adults. To begin with, the lateralization for the linguistic component of written language was compared between children at-risk for dyslexia and typically developing children. Moreover, based on the knowledge that academic performance is correlated with language lateralization (Hirnstein et al., 2014), this was the first study to investigate the relationship between the lateralization for the linguistic component of written language and writing competence. Writing competence was assessed according to the number of errors in handwriting quality and orthography.

Not enough evidence was collected to support a difference between children at-risk for dyslexia and typically developing children in terms of the lateralization for the linguistic component of written language. Two probable interpretations for this result are either the unsuitableness of the motor control task to isolate the motor component of writing or that the number of participants was not enough to support a clear pattern of lateralization. Regarding the relationship of writing competence and the lateralization for the linguistic component of written language, moderate evidence revealed an absence of correlation between the variables across the sample. Nevertheless, what is noteworthy is the divergence in non-verbal intelligence between the two groups of children, where writing competence showed a robust correlation with the level of non-verbal intelligence. This correlation can be elucidated by the connection between phonological awareness and intelligence, especially involving working memory, which is integrated into non-verbal intelligence (Lopes-Silva et al., 2014).

Finally, Study 3 was a pilot study assessing the effect of an exclusively phonological intervention on the lateralization for writing of five at-risk children from Study 2. In addition, to assess for feasibility for future use as an active control against the phonological intervention, an at-risk girl was also administered a pragmatic intervention that lacked any phonological component and the difference of lateralization prior and after intervention was assessed. Despite the general effectiveness of the phonological intervention for three out of the five children in reading improvement, there was not enough evidence to support an impact of the phonological intervention on the lateralization for the linguistic component of written language. However, the initial disperse pattern of lateralization for these children should be taken into account, when interpreting these findings. Relying on the literature for the differences in the activation pattern of children at-risk for dyslexia depending on their responsiveness to intervention (Davis et al., 2011; Molfese et al., 2013; Pleisch et al., 2019), children were grouped according to their response to intervention. The small sample size could not render data analyses possible, but no clear effect of responsiveness to the shift in lateralization could be visually inspected.

The common thread linking the discoveries throughout this thesis is the challenge of identifying a consistent lateralization pattern for the linguistic component of written language, a complexity evident in both adults and children, being more challenging in the latter group. Focusing on the group means, written language, either as a whole or with regards to its linguistic component in particular, seems to engage more the left hemisphere in children compared to adults, in accordance with the literature (Berl et al., 2014; Byars et al., 2002; Everts et al., 2009; Gaillard et al., 2000, 2003; Hadač et al., 2007; but also see Paquette et al., 2015, for contradictory findings). In fact, this difference is more profound for right-handed participants. A potential explanation is that the right hemisphere becomes less involved from childhood to adulthood or even adolescence (Haag et al., 2010; Olulade et al., 2020). An alternative explanation is that experience rather than age shifts oral language lateralization leftwards (Olulade et al., 2020). With written language being acquired several years later than oral language, children that participated in the two studies of this thesis had limited experience in written language and, hence, according to the latter notion, the right hemisphere was expected to be more involved in children than in adults during writing. In Study 3, experience in phonological processing of words at different levels was gained through the phonological intervention administered to five children at risk for dyslexia. In fact, for three of them this experience led to a leftward shift of the lateralization for the linguistic component of written language. This shift could not be attributed to age, as in Chapter 3, there was no difference in the lateralization pattern between children with an age gap of one year. Future studies including more children at risk for dyslexia could shed more light on this observation.

The lack of experience in writing might also have accounted for the children's errors in handwriting quality and orthography presented in Chapter 3. Children at risk for dyslexia had a written text with more errors than typically developing children. Nevertheless, the number of errors was not correlated with the lateralization for the linguistic component of written language. Olulade et al. (2020) demonstrated that, from 4-year-old to 13-year-old children, the number of errors in language task performance is not linked to the extent of engagement of the right hemisphere during the task. Therefore, it could be assumed that training in phonological processing can lead to a more localized hemispheric activation regardless of the quality of the outcome, which could be linked to the differential lateralization shift of adequate responders in this thesis.

As discussed in Chapter 2, letter copying might have failed to adequately isolate the motor component of writing by inducing the activation of right hemispheric regions. Conversely, in right-handed children letter copying was more left lateralized than in adults. This could indicate that children, unlike adults, might not engage into the meta-cognitive approaches discussed above (e.g., inhibiting the generation of words starting with the given letter) that are related to the activation of the right hemisphere during letter copying, but they might simply perform the repetitive formation of the letter as many times as possible. Another interpretation for the age difference is that children and adults seem to adopt different patterns of cerebral activation across the development of language function (Gogtay et al., 2004; Luna et al., 2001; Moore & Linthicum, 2007). Different patterns of hemispheric activation could also be adopted by the two handedness groups, justifying the inconsistency in the correlation of oral language and the linguistic component of written language in terms of lateralization between left-handed and right-handed adults, described in Chapter 2.

5.1 LIMITATIONS

"There are lots of opportunities in limitations, but it takes a positive mindset to recognize them."

Israelmore Ayivor, (1989-)

Recognizing some caveats and limitations in the present thesis is necessary to address them in future studies. The most important limitation is the failure to adequately disentangle the linguistic and the motor components of writing using letter copying as a motor control task. At least in adults, letter copying was more right-lateralized than expected, while in children, this phenomenon was weaker. However, the disperse lateralization pattern of children could not allow us to draw any firm conclusions. Copying letters within the fTCD task context could be linked to right-hemispheric functions regardless of the hand movement involved.

In relation to the previous limitation, the low spatial resolution of fTCD might have hindered some further observations. Functional transcranial Doppler ultrasonography measures and compares the changes in blood flow velocity in the territories supplied by the left and the right medial cerebral arteries respectively. These territories include the temporal and parietal regions of the left hemisphere that are related to phonological processing of language (Kovelman et al., 2012; Oo et al., 2021). This did not allow us to determine the specific regions of each hemisphere that were more or less activated when comparing left-handers and right-handers, children at risk for dyslexia and typically developing children, and children prior and after an intervention. Notably, considering the ease, applicability, and low cost of fTCD, if a clear difference in the lateralization pattern at the level of brain hemispheres is detected, this could serve as a baseline for assessing lateralization for written language using techniques with higher spatial resolution, for instance, fMRI. However, it is important to acknowledge the limitations of such techniques, including issues related to sample size and the ecological validity of the task.

When it comes to the studies on children, the most important limitation was the small sample at risk for dyslexia. The stringent criteria applied for participant inclusion, aimed at avoiding comorbidities and identifying pronounced signs of dyslexia, coupled with practical challenges in recruitment, resulted in a sample size of only twelve children at risk for dyslexia. Of note, other fTCD studies have provided reliable findings recruiting such small sample sizes for experimental groups that are difficult to recruit (e.g., Knake et al., 2003, who assessed language lateralization in 11 patients with temporal lobe epilepsy), while in Study 2 the control group was larger compared to the experimental group to avoid statistical errors and to facilitate drawing reliable results at a population-level. Even though the ratio of children at risk for dyslexia to typically developing children in the sample exceeds the prevalence of dyslexia in the population (50% compared to 3-17%, Wagner et al., 2020), such a small experimental group limited the analytical power of the study. The size of the sample was even smaller, by default, for the pilot study, not allowing to safely conduct analyses to explore the effect of responsiveness to the intervention and of the direction of the shift in lateralization. For the investigation of the feasibility of the pragmatics intervention in particular, only one participant was examined. Therefore, it would not be secure to draw any conclusions based on these results yet.

5.2 IMPLICATIONS

"I alone cannot change the world, but I can cast a stone across the waters to create many ripples."

Mother Teresa (1910-1997)

In terms of theory formation, this thesis has several implications. Firstly, it supports the hypothesis that oral and written language are left lateralized for the majority of individuals (e.g., Braga et al., 2020; Knecht et al., 2000; Szaflarski et al., 2012). Even though I expected that oral language would be similarly lateralized as the linguistic component of written language, this was only true for left-handers. Hence, varied patterns of activation for oral language and the linguistic component of written language between left-handers and right-handers are implied, aligning with the findings in Kondyli et al. (2017) and Papadatou-Pastou et al. (2022).

Hand preference has been widely considered as a proxy for oral language lateralization (Groen et al., 2013; Papadatou-Pastou, 2011; Woodhead et al., 2019). When it comes to written language, this thesis provides evidence that the best behavioral lateralization index associated with the lateralization for the linguistic component of written language is the relative hand skill assessed by the Peg-moving task. This finding stands for adults, while for children no handedness measure correlated with language lateralization indices.

This thesis was the first to assess the lateralization for written language in children, be it typically developing or not. It confirmed previous suggestions that language lateralization becomes more left-sided in an age-dependent or experience-dependent manner from childhood to adulthood (e.g., Gaillard et al., 2000; Holland et al., 2007; Olulade et al., 2020; Ressel et al., 2008). However, as also suggested by Olulade et al. (2020), in children, the number of errors in performance was not correlated with the predominant activation of the right hemisphere. This underscores the distinctive nature of language lateralization in the developmental stages of childhood, as it is important to take into consideration the developmental milestones of children together with their level of experience when examining the relative activation of the brain hemispheres during language tasks.

When it comes to the assessment of the risk for dyslexia, this thesis provided evidence consistent with the theory that writing difficulties are more frequent in children with (risk for) dyslexia compared to typically developing peers (e.g., Berninger et al., 2008; Bogdanowicz, 2003; Thompson et al., 2015). Another assumption in the literature that was supported by this thesis was that children at risk for dyslexia are characterized by decreased non-verbal intelligence compared to age-matched controls (e.g., van Bergen et al., 2013). Finally, training with a phonological intervention can shift lateralization either to the left (e.g., Odegard et al., 2008; Shaywitz et al., 2004; Spironelli et al., 2010) or to the right (see Molfese et al., 2013 for potential explanation), thus contributing valuable insights for intervention strategies in dyslexia related to the different etiological hypotheses that have been suggested for dyslexia (Ramus et al., 2003) or to target different language functions during remediation (Taskov & Dushanova, 2022).

In terms of research design, the implications of this thesis are also important for future projects. The one that played the most critical role was the adoption of the registered reports approach. Registering the study design, objectives, and methodology before data collection enabled us to obtain feedback from reviewers and editors specializing in each respective field. This, in turn, facilitated timely adjustments to the work plan. Additionally, securing in principle acceptance for a Registered Report Stage 1 was crucial for this thesis because the null hypothesis was put forward for a number of hypotheses and journals that adopt the traditional publication strategy are typically reluctant to publish research papers with negative or null findings (Bespalov et al., 2019). Furthermore, following the open access practices that are endorsed by registered reports, all the raw data, analysis codes, and results have been uploaded to an open access platform. This is particularly important for the data from different handedness measures collected throughout this thesis that can be included in future larger studies or meta-analyses and help researchers conclude on which handedness measure is optimal depending on the research question. Keeping in mind the transparency and detail in the methods that is encouraged by Registered Reports (Stage 1), we also provided a detailed account for the methods to be used, which further helped us clarify what we were going to do. In addition to these advantages which are specific for this thesis, registered reports are considered good practice because they minimize controversial tactics in scientific publications, such as *p*-hacking, which is the manipulation of data to achieve the desirable *p*-value and/or HARKing (Hypothesizing After the Results are Known), meaning modifying hypotheses to better fit with the results (Weinhardt et al., 2019). Overall, registered reports help increase transparency and replicability of findings across space and time (Weinhardt et al., 2019).

Study 1 showed that letter copying is not the optimal motor control task for the removal of the motor component of written language because meta-cognitively, it leads participants to activate the right hemisphere at a larger degree than expected (among other interpretations discussed in 2.4). Similarly, the novelty of the symbols used in the motor control task in Papadatou-Pastou et al. (2022) led to the increased activation of the right hemisphere. Hence, the isolation of the motor component of written language in adults proved to be more challenging than anticipated. The findings from both aforementioned studies emphasize the necessity of designing a motor control task that excludes properties independent of hand movement, preventing the activation of the right hemisphere.

Regarding the design of studies with children, whether at risk for dyslexia or typically developing, this thesis provided insights into the variability of the lateralization for writing or letter copying of children, especially those at risk for dyslexia. Larger samples could potentially counteract this variability and allow for a better analytical power. However, a parameter that should be taken into consideration when designing a cerebral lateralization study for children is the difficulty in persuading guardians and children to participate and in keeping them motivated during the process. The way that the studies in this thesis were designed and conducted achieved to minimize attrition at any stage of the procedure.

In particular, the design of the educational interventions allowed children both to enjoy or even to look forward to each session and to evolve in their academic performance progressively. Following a pandemic and lockdown era, during which children were tutored through distance learning, web sessions were expected to facilitate the learning process and be familiar to children. However, the lack of more involved interaction or the possibility of internet connection difficulties or device malfunctions led the experimenter to try harder to retain the attention of some children depending on their personality. It is important to note that, despite inter-individual differences, the skills were uniformly taught to all children following a pre-established protocol. Hence, this thesis demonstrated that thoughtfully crafted and implemented educational interventions can become advantageous for both the academic proficiency and the engagement of children at risk for dyslexia. This holds true even when the interventions are delivered in a hybrid format (combining in-person and web meetings), provided that the children actively engage in the interaction.

5.3 Future directions

"The future is always beginning now"

Mark Strand (1934-2014)

The findings, constraints, and insights from this study lay the groundwork for future projects. Taking into consideration the complexity of disentangling the linguistic and the motor component of written language in terms of lateralization, an important direction for future studies would be to design the motor control task that would achieve the dissociation of the components of written language. This could potentially be implemented by comparing the two motor control tasks tested in Papadatou-Pastou et al. (2022) and this thesis with other similar tasks, which would lack the limitations found in the former ones, which are linked to the activation of the right hemisphere. This comparative analysis aims to determine the distinctive qualities of each task, as reflected in the brain activation. For example, an alternative task could request participants to draw a series of shapes that mimic the movements performed to design each letter of the alphabet. This condition would lack the parameter of the novelty of the shapes, the meta-cognitive functions that arise when being requested to copy a letter instead of writing a word discussed in Chapter 4, and it would decrease the feeling of boredom of having to copy the same letter. A future project that would identify a motor control task that would isolate the motor component of written language would be crucial for the research inquiry of the lateralization for the linguistic component of writing.

Considering the impact of the writing hand on the lateralization for written language, future studies could explore assessing the linguistic component of written language with bimanual writing tasks. For instance, typing is a form of writing that is being largely practiced during the last decades for education, work, and communication and the vast majority of keyboard users type with both their hands. Therefore, assessment of typing could remove the effect of the movement of a single writing hand on the lateralization for written language facilitating the isolation of the linguistic component of written language and the comparison between different handedness groups.

A profound future direction derived from the findings of this thesis is the application of the pilot study described in Chapter 4 in a larger sample. Future studies assessing the impact of the risk for dyslexia on cerebral lateralization for writing in a larger sample of children should precede. Once a group difference in the lateralization for written language between children at risk for dyslexia and typically developing children has been confirmed by a larger study, examining the impact of educational interventions on the lateralization pattern of children at risk for dyslexia becomes particularly intriguing. In fact, the interventions of this thesis shifted the language lateralization of children at risk for dyslexia to the left in some cases. Under this note, a promising future direction is to apply the pilot project of this thesis to compare the lateralization shift between adequate and inadequate responders, similar to the research focus of previous studies on brain activation during reading (Molfese et al., 2013). A future large study providing evidence that the adequate response of children at risk for dyslexia to a phonological intervention can shift the lateralization pattern towards the pattern of typically developing children can confirm the importance of the phonological deficit in dyslexia and point to the direction of an additional screening tool for the investigation of the risk for dyslexia.

5.4 General conclusions

The lateralization for written language is influenced by at least two components: language lateralization and motor lateralization. Disentangling these two components was extremely difficult especially for groups where atypical lateralization appears to be more frequent, such as left-handers and children at-risk for dyslexia. Throughout the studies of this thesis, the intricate relationship between language lateralization, handedness, dyslexia, and educational interventions unfolded. The findings underscored the challenges of identifying consistent lateralization patterns, emphasizing the need for nuanced approaches tailored to assess the differences between different age and handedness groups. Importantly, this research contributes to the ongoing dialogue on the developmental aspects of language lateralization, paving the way for future studies to refine testing methods and deepen our understanding of the complex interplay between motor and linguistic components in written language. As a concluding remark, future inquiries should include written language generation in their research aims, taking into consideration the importance of writing in education, work, and communication and in particular, for cases of individuals with dyslexia that struggle with writing throughout their lives.

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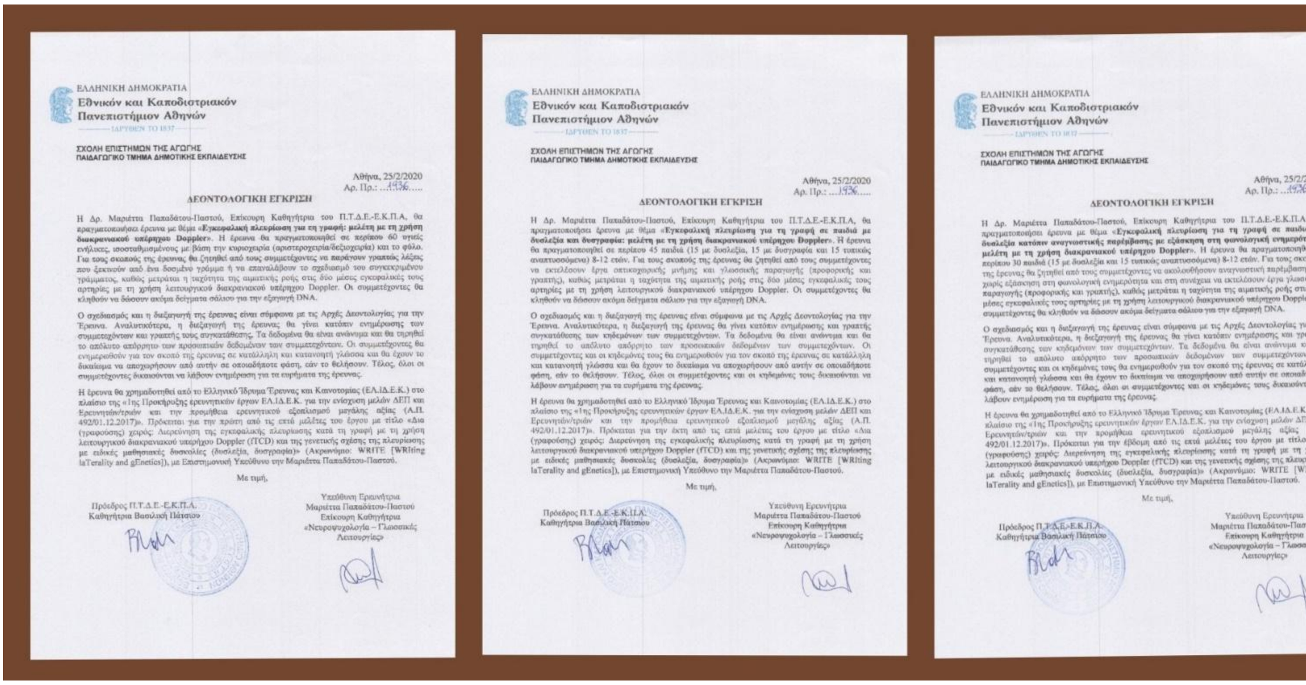
6 APPENDIX

Ethical approval by the School of Education (NKUA) for the elaboration of the three studies of this thesis



ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν
Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΤΗΣ ΑΓΩΓΗΣ
ΠΑΙΔΑΓΩΓΙΚΟ ΤΜΗΜΑ ΔΗΜΟΤΙΚΗΣ ΕΚΠΑΙΔΕΥΣΗΣ

Αθήνα, 25/2/2020
Αρ. Πρ.: ...1936....

ΔΕΟΝΤΟΛΟΓΙΚΗ ΕΓΚΡΙΣΗ

Η Δρ. Μαριέττα Παπαδάτου-Παστού, Επίκουρη Καθηγήτρια του Π.Τ.Δ.Ε.-Ε.Κ.Π.Α, θα πραγματοποιήσει έρευνα με θέμα «**Εγκεφαλική πλευρίωση για τη γραφή: μελέτη με τη χρήση διακρανιακού υπέρηχου Doppler**». Η έρευνα θα πραγματοποιηθεί σε περίπου 60 υγιείς ενήλικες, ισοσταθμισμένους με βάση την κυριοχειρία (αριστεροχειρία/δεξιοχειρία) και το φύλο. Για τους σκοπούς της έρευνας θα ζητηθεί από τους συμμετέχοντες να παράγουν γραπτώς λέξεις που ξεκινούν από ένα δοσμένο γράμμα ή να επαναλάβουν το σχεδιασμό του συγκεκριμένου γράμματος, καθώς μετράται η ταχύτητα της αιματικής ροής στις δύο μέσες εγκεφαλικές τους αρτηρίες με τη χρήση λειτουργικού διακρανιακού υπέρηχου Doppler. Οι συμμετέχοντες θα κληθούν να δώσουν ακόμα δείγματα σάλιου για την εξαγωγή DNA.

Ο σχεδιασμός και η διεξαγωγή της έρευνας είναι σύμφωνα με τις Αρχές Δεοντολογίας για την Έρευνα. Αναλυτικότερα, η διεξαγωγή της έρευνας θα γίνει κατόπιν ενημέρωσης των συμμετεχόντων και γραπτής τους συγκατάθεσης. Τα δεδομένα θα είναι ανώνυμα και θα τηρηθεί το απόλυτο απόρρητο των προσωπικών δεδομένων των συμμετεχόντων. Οι συμμετέχοντες θα ενημερωθούν για τον σκοπό της έρευνας σε κατάλληλη και κατανοητή γλώσσα και θα έχουν το δικαίωμα να αποχωρήσουν από αυτήν σε οποιαδήποτε φάση, εάν το θελήσουν. Τέλος, όλοι οι συμμετέχοντες δικαιούνται να λάβουν ενημέρωση για τα ευρήματα της έρευνας.

Η έρευνα θα χρηματοδοτηθεί από το Ελληνικό Ίδρυμα Έρευνας και Καινοτομίας (ΕΛ.ΙΔ.Ε.Κ.) στο πλαίσιο της «1ης Προκήρυξης ερευνητικών έργων ΕΛ.ΙΔ.Ε.Κ. για την ενίσχυση μελών ΔΕΠ και Ερευνητών/τριών και την προμήθεια ερευνητικού εξοπλισμού μεγάλης αξίας (Α.Π. 492/01.12.2017)». Πρόκειται για την πρώτη από τις επτά μελέτες του έργου με τίτλο «Δια (γραφούσης) χειρός: Διερεύνηση της εγκεφαλικής πλευρίωσης κατά τη γραφή με τη χρήση λειτουργικού διακρανιακού υπέρηχου Doppler (fTCD) και της γενετικής σχέσης της πλευρίωσης με ειδικές μαθησιακές δυσκολίες (δυσλεξία, δυσγραφία)» (Ακρωνύμιο: WRITE [WRIting laTerality and gEnetics]), με Επιστημονική Υπεύθυνο την Μαριέττα Παπαδάτου-Παστού.

Με τιμή,

Πρόεδρος Π.Τ.Δ.Ε.-Ε.Κ.Π.Α.
Καθηγήτρια Βασιλική Πάτσιου

Υπεύθυνη Ερευνήτρια
Μαριέττα Παπαδάτου-Παστού
Επίκουρη Καθηγήτρια
«Νευροψυχολογία – Γλωσσικές Λειτουργίες»

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ΔΕΟΝΤΟΛΟΓΙΚΗ ΕΓΚΡΙΣΗ

Η Δρ. Μαριέττα Παπαδάτου-Παστού, Επίκουρη Καθηγήτρια του Π.Τ.Δ.Ε.-Ε.Κ.Π.Α, θα πραγματοποιήσει έρευνα με θέμα «**Εγκεφαλική πλευρίωση για τη γραφή σε παιδιά με δυσλεξία και δυσγραφία: μελέτη με τη χρήση διακρανιακού υπέρηχου Doppler**». Η έρευνα θα πραγματοποιηθεί σε περίπου 45 παιδιά (15 με δυσλεξία, 15 με δυσγραφία και 15 τυπικώς αναπτυσσόμενα) 8-12 ετών. Για τους σκοπούς της έρευνας θα ζητηθεί από τους συμμετέχοντες να εκτελέσουν έργα οπτικοχωρικής μνήμης και γλωσσικής παραγωγής (προφορικής και γραπτής), καθώς μετράται η ταχύτητα της αιματικής ροής στις δύο μέσες εγκεφαλικές τους αρτηρίες με τη χρήση λειτουργικού διακρανιακού υπέρηχου Doppler. Οι συμμετέχοντες θα κληθούν να δώσουν ακόμα δείγματα σάλιου για την εξαγωγή DNA.

Ο σχεδιασμός και η διεξαγωγή της έρευνας είναι σύμφωνα με τις Αρχές Δεοντολογίας για την Έρευνα. Αναλυτικότερα, η διεξαγωγή της έρευνας θα γίνει κατόπιν ενημέρωσης και γραπτής συγκατάθεσης των κηδεμόνων των συμμετεχόντων. Τα δεδομένα θα είναι ανώνυμα και θα τηρηθεί το απόλυτο απόρρητο των προσωπικών δεδομένων των συμμετεχόντων. Οι συμμετέχοντες και οι κηδεμόνες τους θα ενημερωθούν για τον σκοπό της έρευνας σε κατάλληλη και κατανοητή γλώσσα και θα έχουν το δικαίωμα να αποχωρήσουν από αυτήν σε οποιαδήποτε φάση, εάν το θελήσουν. Τέλος, όλοι οι συμμετέχοντες και οι κηδεμόνες τους δικαιούνται να λάβουν ενημέρωση για τα ευρήματα της έρευνας.

Η έρευνα θα χρηματοδοτηθεί από το Ελληνικό Ίδρυμα Έρευνας και Καινοτομίας (ΕΛ.ΙΔ.Ε.Κ.) στο πλαίσιο της «1ης Προκήρυξης ερευνητικών έργων ΕΛ.ΙΔ.Ε.Κ. για την ενίσχυση μελών ΔΕΠ και Ερευνητών/τριών και την προμήθεια ερευνητικού εξοπλισμού μεγάλης αξίας (Α.Π. 492/01.12.2017)». Πρόκειται για την έκτη από τις επτά μελέτες του έργου με τίτλο «Δια (γραφούσης) χειρός: Διερεύνηση της εγκεφαλικής πλευρίωσης κατά τη γραφή με τη χρήση λειτουργικού διακρανιακού υπέρηχου Doppler (fTCD) και της γενετικής σχέσης της πλευρίωσης με ειδικές μαθησιακές δυσκολίες (δυσλεξία, δυσγραφία)» (Ακρωνύμιο: WRITE [WRIting laTerality and gEnetics]), με Επιστημονική Υπεύθυνο την Μαριέττα Παπαδάτου-Παστού.

Με τιμή,

Πρόεδρος Π.Τ.Δ.Ε.-Ε.Κ.Π.Α.
Καθηγήτρια Βασιλική Πάτσιου

Υπεύθυνη Ερευνήτρια
Μαριέττα Παπαδάτου-Παστού
Επίκουρη Καθηγήτρια
«Νευροψυχολογία – Γλωσσικές Λειτουργίες»

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν
Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΤΗΣ ΑΓΩΓΗΣ
ΠΑΙΔΑΓΩΓΙΚΟ ΤΜΗΜΑ ΔΗΜΟΤΙΚΗΣ ΕΚΠΑΙΔΕΥΣΗΣ

Αθήνα, 25/2/
Αρ. Πρ.: ...193

ΔΕΟΝΤΟΛΟΓΙΚΗ ΕΓΚΡΙΣΗ

Η Δρ. Μαριέττα Παπαδάτου-Παστού, Επίκουρη Καθηγήτρια του Π.Τ.Δ.Ε.-Ε.Κ.Π.Α
πραγματοποιήσει έρευνα με θέμα «**Εγκεφαλική πλευρίωση για τη γραφή σε παιδι**
δυσλεξία κατόπιν αναγνωστικής παρέμβασης με εξάσκηση στη φωνολογική ενημερότ
μελέτη με τη χρήση διακρανιακού υπέρηχου Doppler». Η έρευνα θα πραγματοποιηθ
περίπου 30 παιδιά (15 με δυσλεξία και 15 τυπικώς αναπτυσσόμενα) 8-12 ετών. Για τους σκο
της έρευνας θα ζητηθεί από τους συμμετέχοντες να ακολουθήσουν αναγνωστική παρέμβαση
χωρίς εξάσκηση στη φωνολογική ενημερότητα και στη συνέχεια να εκτελέσουν έργα γλωσ
παραγωγής (προφορικής και γραπτής), καθώς μετράται η ταχύτητα της αιματικής ροής στι
μέσες εγκεφαλικές τους αρτηρίες με τη χρήση λειτουργικού διακρανιακού υπέρηχου Dopple
συμμετέχοντες θα κληθούν να δώσουν ακόμα δείγματα σάλιου για την εξαγωγή DNA.

Ο σχεδιασμός και η διεξαγωγή της έρευνας είναι σύμφωνα με τις Αρχές Δεοντολογίας γι
Έρευνα. Αναλυτικότερα, η διεξαγωγή της έρευνας θα γίνει κατόπιν ενημέρωσης και γρ
συγκατάθεσης των κηδεμόνων των συμμετεχόντων. Τα δεδομένα θα είναι ανώνυμα κ
τηρηθεί το απόλυτο απόρρητο των προσωπικών δεδομένων των συμμετεχόντω
συμμετέχοντες και οι κηδεμόνες τους θα ενημερωθούν για τον σκοπό της έρευνας σε κατάλ
και κατανοητή γλώσσα και θα έχουν το δικαίωμα να αποχωρήσουν από αυτήν σε οποια
φάση, εάν το θελήσουν. Τέλος, όλοι οι συμμετέχοντες και οι κηδεμόνες τους δικαιούντ
λάβουν ενημέρωση για τα ευρήματα της έρευνας.

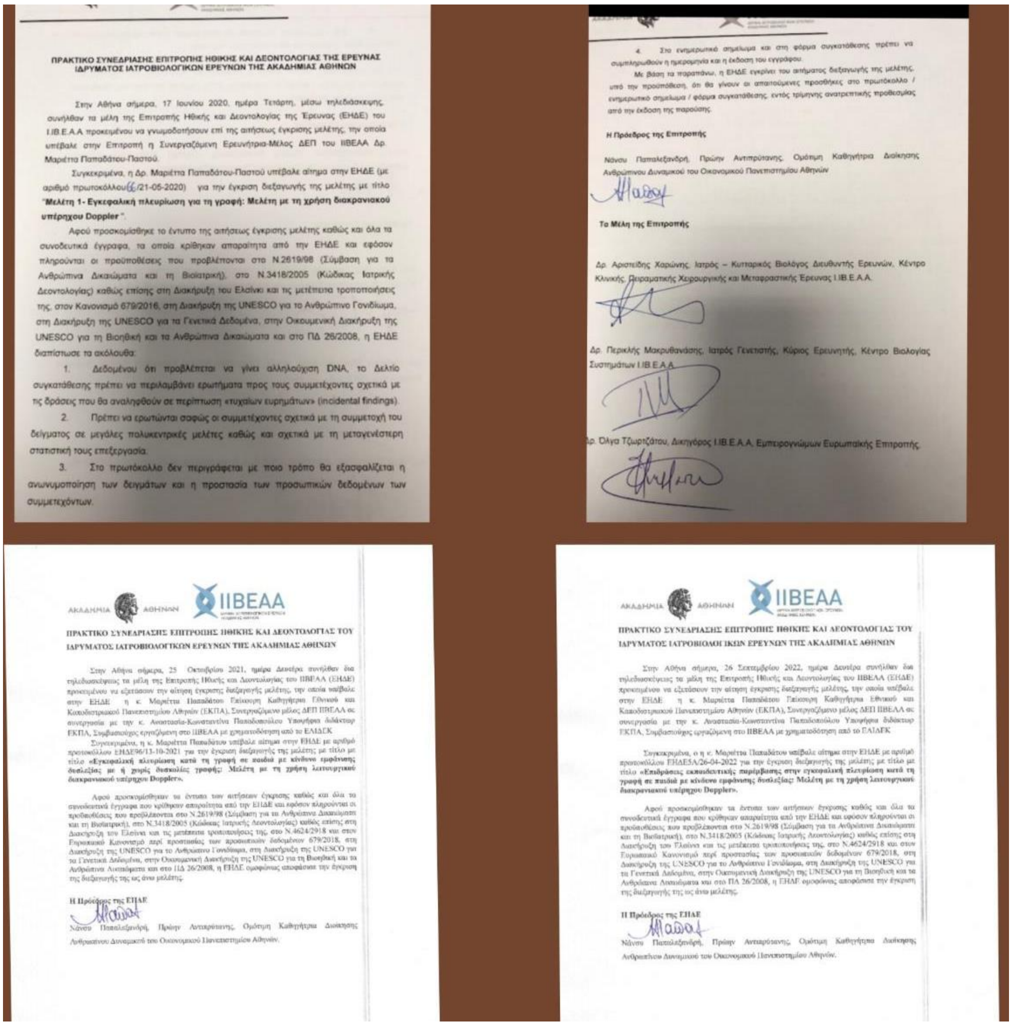
Η έρευνα θα χρηματοδοτηθεί από το Ελληνικό Ίδρυμα Έρευνας και Καινοτομίας (ΕΛ.ΙΔ.Ε.Κ
πλαίσιο της «1ης Προκήρυξης ερευνητικών έργων ΕΛ.ΙΔ.Ε.Κ. για την ενίσχυση μελών ΔΕ
Ερευνητών/τριών και την προμήθεια ερευνητικού εξοπλισμού μεγάλης αξίας
492/01.12.2017)». Πρόκειται για την έβδομη από τις επτά μελέτες του έργου με τίτλο
(γραφούσης) χειρός: Διερεύνηση της εγκεφαλικής πλευρίωσης κατά τη γραφή με τη
λειτουργικού διακρανιακού υπέρηχου Doppler (fTCD) και της γενετικής σχέσης της πλευρ
με ειδικές μαθησιακές δυσκολίες (δυσλεξία, δυσγραφία)» (Ακρωνύμιο: WRITE [W
laTerality and gEnetics]), με Επιστημονική Υπεύθυνο την Μαριέττα Παπαδάτου-Παστού.

Με τιμή,

Πρόεδρος Π.Τ.Δ.Ε.-Ε.Κ.Π.Α.
Καθηγήτρια Βασιλική Πάτσιου

Υπεύθυνη Ερευνήτρια
Μαριέττα Παπαδάτου-Παστ
Επίκουρη Καθηγήτρια
«Νευροψυχολογία – Γλωσσ
Λειτουργίες»

Ethical approval by the Ethical Committee of the Biomedical Research Foundation of the Academy of Athens



ΠΡΑΚΤΙΚΟ ΣΥΝΕΔΡΙΑΣΗΣ ΕΠΙΤΡΟΠΗΣ ΗΘΙΚΗΣ ΚΑΙ ΔΕΟΝΤΟΛΟΓΙΑΣ ΤΗΣ ΕΡΕΥΝΑΣ ΙΔΡΥΜΑΤΟΣ ΙΑΤΡΟΒΙΟΛΟΓΙΚΩΝ ΕΡΕΥΝΩΝ ΤΗΣ ΑΚΑΔΗΜΙΑΣ ΑΘΗΝΩΝ

Στην Αθήνα σήμερα, 17 Ιουνίου 2020, ημέρα Τετάρτη, μέσω τηλεδιάσκεψης, συνήλθαν τα μέλη της Επιτροπής Ηθικής και Δεοντολογίας της Έρευνας (ΕΗΔΕ) του Ι.ΙΒ.Ε.Α.Α προκειμένου να γνωμοδοτήσουν επί της αιτήσεως έγκρισης μελέτης, την οποία υπέβαλε στην Επιτροπή η Συνεργαζόμενη Ερευνήτρια-Μέλος ΔΕΠ του ΙΙΒΕΑΑ Δρ. Μαριέττα Παπαδάτου-Παστού.

Συγκεκριμένα, η Δρ. Μαριέττα Παπαδάτου-Παστού υπέβαλε αίτημα στην ΕΗΔΕ (με αριθμό πρωτοκόλλου 66/21-05-2020) για την έγκριση διεξαγωγής της μελέτης με τίτλο "**Μελέτη 1- Εγκεφαλική πλευρίωση για τη γραφή: Μελέτη με τη χρήση διακρανιακού υπέρηχου Doppler**".

Αφού προσκομίσθηκε το έντυπο της αιτήσεως έγκρισης μελέτης καθώς και όλα τα συνοδευτικά έγγραφα, τα οποία κρίθηκαν απαραίτητα από την ΕΗΔΕ και εφόσον πληρούνται οι προϋποθέσεις που προβλέπονται στο Ν.2619/98 (Σύμβαση για τα Ανθρώπινα Δικαιώματα και τη Βιοϊατρική), στο Ν.3418/2005 (Κώδικας Ιατρικής Δεοντολογίας) καθώς επίσης στη Διακήρυξη του Ελσίνκι και τις μετέπειτα τροποποιήσεις της, στον Κανονισμό 679/2016, στη Διακήρυξη της UNESCO για το Ανθρώπινο Γονιδίωμα, στη Διακήρυξη της UNESCO για τα Γενετικά Δεδομένα, στην Οικουμενική Διακήρυξη της UNESCO για τη Βιοηθική και τα Ανθρώπινα Δικαιώματα και στο ΠΔ 26/2008, η ΕΗΔΕ διαπίστωσε τα ακόλουθα:

1. Δεδομένου ότι προβλέπεται να γίνει αλληλούχιση DNA, το Δελτίο συγκατάθεσης πρέπει να περιλαμβάνει ερωτήματα προς τους συμμετέχοντες σχετικά με τις δράσεις που θα αναληφθούν σε περίπτωση «τυχαίων ευρημάτων» (incidental findings).
2. Πρέπει να ερωτώνται σαφώς οι συμμετέχοντες σχετικά με τη συμμετοχή του δείγματος σε μεγάλες πολυκεντρικές μελέτες καθώς και σχετικά με τη μεταγενέστερη στατιστική τους επεξεργασία.
3. Στο πρωτόκολλο δεν περιγράφεται με ποιο τρόπο θα εξασφαλίζεται η ανωνυμοποίηση των δειγμάτων και η προστασία των προσωπικών δεδομένων των συμμετεχόντων.
4. Στο ενημερωτικό σημείωμα και στη φόρμα συγκατάθεσης πρέπει να συμπληρωθούν η ημερομηνία και η έκδοση του εγγράφου.

Με βάση τα παραπάνω, η ΕΗΔΕ εγκρίνει του αιτήματος διεξαγωγής της μελέτης, υπό την προϋπόθεση, ότι θα γίνουν οι απαιτούμενες προσθήκες στο πρωτόκολλο / ενημερωτικό σημείωμα / φόρμα συγκατάθεσης, εντός τρίμηνης ανατρεπτικής προθεσμίας από την έκδοση της παρούσης.

Η Πρόεδρος της Επιτροπής

Νάνσυ Παπαλεξανδρή, Πρώην Αντιπρύτανης, Ομότιμη Καθηγήτρια Διοίκησης Ανθρώπινου Δυναμικού του Οικονομικού Πανεπιστημίου Αθηνών

Τα Μέλη της Επιτροπής

Δρ. Αριστείδης Χαρώνης, Ιατρός – Κυτταρικός Βιολόγος Διευθυντής Ερευνών, Κέντρο Κλινικής, Πειραματικής Χειρουργικής και Μεταφραστικής Έρευνας Ι.ΙΒ.Ε.Α.Α.

Δρ. Περικλής Μακρυθανάσης, Ιατρός Γενετιστής, Κύριος Ερευνητής, Κέντρο Βιολογίας Συστημάτων Ι.ΙΒ.Ε.Α.Α.

Δρ. Όλγα Τζωρτζάτου, Δικηγόρος Ι.ΙΒ.Ε.Α.Α, Εμπειρογνώμων Ευρωπαϊκής Επιτροπής.

ΑΚΑΔΗΜΙΑ ΑΘΗΝΩΝ IIBEAA

ΠΡΑΚΤΙΚΟ ΣΥΝΕΔΡΙΑΣΗΣ ΕΠΙΤΡΟΠΗΣ ΗΘΙΚΗΣ ΚΑΙ ΔΕΟΝΤΟΛΟΓΙΑΣ ΤΟΥ ΙΔΡΥΜΑΤΟΣ ΙΑΤΡΟΒΙΟΛΟΓΙΚΩΝ ΕΡΕΥΝΩΝ ΤΗΣ ΑΚΑΔΗΜΙΑΣ ΑΘΗΝΩΝ

Στην Αθήνα σήμερα, 25 Οκτωβρίου 2021, ημέρα Δευτέρα συνήλθαν δια τηλεδιασκέψεως τα μέλη της Επιτροπής Ηθικής και Δεοντολογίας του ΙΙΒΕΑΑ (ΕΗΔΕ) προκειμένου να εξετάσουν την αίτηση έγκρισης διεξαγωγής μελέτης, την οποία υπέβαλε στην ΕΗΔΕ η κ. Μαριέττα Παπαδάτου Επίκουρη Καθηγήτρια Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών (ΕΚΠΑ), Συνεργαζόμενο μέλος ΔΕΠ ΙΙΒΕΑΑ σε συνεργασία με την κ. Αναστασία-Κωνσταντίνα Παπαδοπούλου Υποψήφια διδάκτωρ ΕΚΠΑ, Συμβασιούχος εργαζόμενη στο ΙΙΒΕΑΑ με χρηματοδότηση από το ΕΛΙΔΕΚ

Συγκεκριμένα, η κ. Μαριέττα Παπαδάτου υπέβαλε αίτημα στην ΕΗΔΕ με αριθμό πρωτοκόλλου ΕΗΔΕ96/13-10-2021 για την έγκριση διεξαγωγής της μελέτης με τίτλο με τίτλο **«Εγκεφαλική πλευρίωση κατά τη γραφή σε παιδιά με κίνδυνο εμφάνισης δυσλεξίας με ή χωρίς δυσκολίες γραφής: Μελέτη με τη χρήση λειτουργικού διακρανιακού υπέρηχου Doppler»**.

Αφού προσκομίσθηκαν τα έντυπα των αιτήσεων έγκρισης καθώς και όλα τα συνοδευτικά έγγραφα που κρίθηκαν απαραίτητα από την ΕΗΔΕ και εφόσον πληρούνται οι προϋποθέσεις που προβλέπονται στο Ν.2619/98 (Σύμβαση για τα Ανθρώπινα Δικαιώματα και τη Βιοϊατρική), στο Ν.3418/2005 (Κώδικας Ιατρικής Δεοντολογίας) καθώς επίσης στη Διακήρυξη του Ελσίνκι και τις μετέπειτα τροποποιήσεις της, στο Ν.4624/2918 και στον Ευρωπαϊκό Κανονισμό περί προστασίας των προσωπικών δεδομένων 679/2018, στη Διακήρυξη της UNESCO για το Ανθρώπινο Γονιδίωμα, στη Διακήρυξη της UNESCO για τα Γενετικά Δεδομένα, στην Οικουμενική Διακήρυξη της UNESCO για τη Βιοηθική και τα Ανθρώπινα Δικαιώματα και στο ΠΔ 26/2008, η ΕΗΔΕ ομοφώνως αποφάσισε την έγκριση της διεξαγωγής της ως άνω μελέτης.

Η Πρόεδρος της ΕΗΔΕ

Νάνσυ Παπαλεξανδρή, Πρώην Αντιπρύτανης, Ομότιμη Καθηγήτρια Διοίκησης Ανθρώπινου Δυναμικού του Οικονομικού Πανεπιστημίου Αθηνών.

ΑΚΑΔΗΜΙΑ ΑΘΗΝΩΝ IIBEAA

ΠΡΑΚΤΙΚΟ ΣΥΝΕΔΡΙΑΣΗΣ ΕΠΙΤΡΟΠΗΣ ΗΘΙΚΗΣ ΚΑΙ ΔΕΟΝΤΟΛΟΓΙΑΣ ΤΟΥ ΙΔΡΥΜΑΤΟΣ ΙΑΤΡΟΒΙΟΛΟΓΙΚΩΝ ΕΡΕΥΝΩΝ ΤΗΣ ΑΚΑΔΗΜΙΑΣ ΑΘΗΝΩΝ

Στην Αθήνα σήμερα, 26 Σεπτεμβρίου 2022, ημέρα Δευτέρα συνήλθαν δια τηλεδιασκέψεως τα μέλη της Επιτροπής Ηθικής και Δεοντολογίας του ΙΙΒΕΑΑ (ΕΗΔΕ) προκειμένου να εξετάσουν την αίτηση έγκρισης διεξαγωγής μελέτης, την οποία υπέβαλε στην ΕΗΔΕ η κ. Μαριέττα Παπαδάτου Επίκουρη Καθηγήτρια Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών (ΕΚΠΑ), Συνεργαζόμενο μέλος ΔΕΠ ΙΙΒΕΑΑ σε συνεργασία με την κ. Αναστασία-Κωνσταντίνα Παπαδοπούλου Υποψήφια διδάκτωρ ΕΚΠΑ, Συμβασιούχος εργαζόμενη στο ΙΙΒΕΑΑ με χρηματοδότηση από το ΕΛΙΔΕΚ

Συγκεκριμένα, ο η κ. Μαριέττα Παπαδάτου υπέβαλε αίτημα στην ΕΗΔΕ με αριθμό πρωτοκόλλου ΕΗΔΕ5Α/26-04-2022 για την έγκριση διεξαγωγής της μελέτης με τίτλο με τίτλο **«Επιδράσεις εκπαιδευτικής παρέμβασης στην εγκεφαλική πλευρίωση κατά τη γραφή σε παιδιά με κίνδυνο εμφάνισης δυσλεξίας: Μελέτη με τη χρήση λειτουργικού διακρανιακού υπέρηχου Doppler»**.

Αφού προσκομίσθηκαν τα έντυπα των αιτήσεων έγκρισης καθώς και όλα τα συνοδευτικά έγγραφα που κρίθηκαν απαραίτητα από την ΕΗΔΕ και εφόσον πληρούνται οι προϋποθέσεις που προβλέπονται στο Ν.2619/98 (Σύμβαση για τα Ανθρώπινα Δικαιώματα και τη Βιοϊατρική), στο Ν.3418/2005 (Κώδικας Ιατρικής Δεοντολογίας) καθώς επίσης στη Διακήρυξη του Ελσίνκι και τις μετέπειτα τροποποιήσεις της, στο Ν.4624/2918 και στον Ευρωπαϊκό Κανονισμό περί προστασίας των προσωπικών δεδομένων 679/2018, στη Διακήρυξη της UNESCO για το Ανθρώπινο Γονιδίωμα, στη Διακήρυξη της UNESCO για τα Γενετικά Δεδομένα, στην Οικουμενική Διακήρυξη της UNESCO για τη Βιοηθική και τα Ανθρώπινα Δικαιώματα και στο ΠΔ 26/2008, η ΕΗΔΕ ομοφώνως αποφάσισε την έγκριση της διεξαγωγής της ως άνω μελέτης.

Η Πρόεδρος της ΕΗΔΕ

Νάνσυ Παπαλεξανδρή, Πρώην Αντιπρύτανης, Ομότιμη Καθηγήτρια Διοίκησης Ανθρώπινου Δυναμικού του Οικονομικού Πανεπιστημίου Αθηνών.

Ethical approval by the Scientific board of the "Aghia Sofia" Children's hospital for Studies 2 and 3

ΕΘΝΙΚΟ ΣΥΣΤΗΜΑ ΥΓΕΙΑΣ
Α΄ΔΙΟΙΚΗΣΗ ΥΓΕΙΟΝΟΜΙΚΗΣ ΠΕΡΙΦΕΡΕΙΑΣ ΑΤΤΙΚΗΣ
ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΠΑΙΔΩΝ « Η ΑΓΙΑ ΣΟΦΙΑ »

ΕΠΙΣΤΗΜΟΝΙΚΟ ΣΥΜΒΟΥΛΙΟ
ΠΡΟΣ: κ.κ. ΠΑΝΑΓΙΩΤΑ ΠΕΡΒΑΝΙΔΟΥ, Αναπληρώτρια Καθηγήτρια Αναπτυξιακής & Συμπεριφορικής Παιδιατρικής Α΄ Παιδιατρικής Κλινικής Πανεπιστημίου Αθηνών και ΑΝΑΣΤΑΣΙΑ-ΚΩΝΣΤΑΝΤΙΝΑ ΠΑΠΑΔΟΠΟΥΛΟΥ, Υποψήφια Διδάκτωρ ΕΚΠΑ

ΑΠΟΣΠΑΣΜΑ ΠΡΑΚΤΙΚΟΥ ΣΥΝΕΔΡΙΑΣΕΩΣ 08-07-21

ΠΑΡΟΝΤΕΣ :
ΧΡΙΣΤΙΝΑ ΚΑΝΑΚΑ-GANTENBEIN, ΠΡΟΕΔΡΟΣ ΕΠΙΣΤΗΜΟΝΙΚΟΥ ΣΥΜΒΟΥΛΙΟΥ, Καθηγήτρια-Διευθύντρια Α΄ Παιδιατρικής Κλινικής Πανεπιστημίου Αθηνών
ΘΕΩΝΗ ΠΕΤΡΟΠΟΥΛΟΥ, ΜΕΛΟΣ, Δ/ντρια ΕΣΥ Παιδιατρικής
ΑΙΚΑΤΕΡΙΝΗ ΓΙΑΝΝΑΚΟΠΟΥΛΟΥ, ΜΕΛΟΣ, Δ/ντρια ΕΣΥ Καρδιολογίας
ΕΥΘΥΜΙΑ ΤΣΙΝΑ, ΜΕΛΟΣ, Επιμελήτρια Α΄ Οφθαλμολογίας
ΙΩΑΝΝΗΣ ΓΕΩΡΓΟΠΟΥΛΟΣ, ΜΕΛΟΣ, Ειδικευόμενος Χειρουργικής Παίδων
ΙΩΑΝΝΗΣ ΠΑΠΑΣΩΤΗΡΙΟΥ, ΜΕΛΟΣ, Δ/ντής Βιοχημικού Εργαστηρίου
ΕΥΦΡΟΣΥΝΗ ΒΛΑΧΙΩΤΗ, ΜΕΛΟΣ, ΠΕ Νοσηλευτικής

ΘΕΜΑ : Έγκριση διεξαγωγής μελέτης με τίτλο: «Εγκεφαλική πλευρίωση κατά τη γραφή σε παιδιά με κίνδυνο εμφάνισης δυσλεξίας με ή χωρίς δυσκολίες γραφής: Μελέτη με τη χρήση λειτουργικού διακρανιακού υπέρηχου Doppler»
Επιστημονικά Υπεύθυνη: κ. ΠΑΝΑΓΙΩΤΑ ΠΕΡΒΑΝΙΔΟΥ, Αναπληρώτρια Καθηγήτρια Αναπτυξιακής & Συμπεριφορικής Παιδιατρικής Α΄ Παιδιατρικής Κλινικής Πανεπιστημίου Αθηνών

ΣΧΕΤ. : Αρ.πρωτ. 13037/02.07.2021

Το Επιστημονικό Συμβούλιο κατά την συνεδρίασή του στις 08 Ιουλίου 2021 έλαβε υπόψη του την ανωτέρω αίτηση των κ.κ. Παναγιώτας Περβανίδου, Αναπληρώτριας Καθηγήτριας Αναπτυξιακής & Συμπεριφορικής Παιδιατρικής της Α΄ Παιδιατρικής Κλινικής του Πανεπιστημίου Αθηνών και της υποψήφιας διδάκτορος Νευροψυχολογίας του Παιδαγωγικού Τμήματος Δημοτικής Εκπαίδευσης του ΕΚΠΑ κ. Αναστασίας-Κωνσταντίνας Παπαδοπούλου, που αφορά στην έγκριση διεξαγωγής μελέτης με τίτλο «Εγκεφαλική πλευρίωση κατά τη γραφή σε παιδιά με κίνδυνο εμφάνισης δυσλεξίας με ή χωρίς δυσκολίες γραφής: Μελέτη με τη χρήση λειτουργικού διακρανιακού υπέρηχου Doppler».
Ύστερα από μελέτη και αναλυτική συζήτηση, διαπιστώθηκε ότι η ανωτέρω μελέτη, η οποία θα εκπονηθεί στα πλαίσια της διδακτορικής διατριβής της κ. Αναστασίας-Κωνσταντίνας Παπαδοπούλου, πληροί όλες τις προϋποθέσεις για τη διεξαγωγή της και όπως αναφέρεται δεν θα υπάρξει καμία οικονομική επιβάρυνση για το νοσοκομείο.
Κατόπιν τούτων, ομόφωνα το Επιστημονικό Συμβούλιο εισηγείται την έγκριση διεξαγωγής της ανωτέρω μελέτης, καθώς και την έγκριση των συνοδευτικών εγγράφων. Συγκεκριμένα:

1. Πρωτόκολλο μελέτης
2. Ερωτηματολόγια μελέτης
3. Έντυπο συναίνεσης

Η ΠΡΟΕΔΡΟΣ
ΤΟΥ ΕΠΙΣΤΗΜΟΝΙΚΟΥ ΣΥΜΒΟΥΛΙΟΥ
ΧΡΙΣΤΙΝΑ ΚΑΝΑΚΑ-GANTENBEIN
ΚΑΘΗΓΗΤΡΙΑ-ΔΙΕΥΘΥΝΤΡΙΑ
Α΄ ΠΑΙΔΙΑΤΡΙΚΗΣ ΚΛΙΝΙΚΗΣ ΠΑΝΕΠΙΣΤΗΜΙΟΥ ΑΘΗΝΩΝ

ΕΘΝΙΚΟ ΣΥΣΤΗΜΑ ΥΓΕΙΑΣ
Α΄ΔΙΟΙΚΗΣΗ ΥΓΕΙΟΝΟΜΙΚΗΣ ΠΕΡΙΦΕΡΕΙΑΣ ΑΤΤΙΚΗΣ
ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΠΑΙΔΩΝ « Η ΑΓΙΑ ΣΟΦΙΑ »

ΕΠΙΣΤΗΜΟΝΙΚΟ ΣΥΜΒΟΥΛΙΟ
ΠΡΟΣ: κ. ΠΑΝΑΓΙΩΤΑ ΠΕΡΒΑΝΙΔΟΥ
κ. ΜΑΡΙΕΤΤΑ ΠΑΠΑΔΑΤΟΥ- ΠΑΣΤΟΥ

ΑΠΟΣΠΑΣΜΑ ΠΡΑΚΤΙΚΟΥ ΣΥΝΕΔΡΙΑΣΕΩΣ 13-04-22

ΠΑΡΟΝΤΕΣ :
ΧΡΙΣΤΙΝΑ ΚΑΝΑΚΑ-GANTENBEIN, ΠΡΟΕΔΡΟΣ ΕΠΙΣΤΗΜΟΝΙΚΟΥ ΣΥΜΒΟΥΛΙΟΥ, Καθηγήτρια-Διευθύντρια Α΄ Παιδιατρικής Κλινικής Πανεπιστημίου Αθηνών
ΘΕΩΝΗ ΠΕΤΡΟΠΟΥΛΟΥ, ΜΕΛΟΣ, Διευθύντρια ΕΣΥ Παιδιατρικής
ΑΘΗΝΑ ΜΟΥΤΑΦΗ, ΜΕΛΟΣ, Επιμελήτρια Α΄ ΕΣΥ Παιδιατρικής
ΕΙΡΗΝΗ ΒΑΖΑΙΟΥ, ΜΕΛΟΣ, Επιμελήτρια Β΄ ΕΣΥ Ωτορινολαρυγγολογίας
ΚΛΕΟΠΑΤΡΑ ΣΠΑΝΟΥ, ΜΕΛΟΣ, ΠΕ Χημικών-Βιοχημικών-Βιολόγων
ΣΤΑΥΡΟΣ ΚΑΛΛΙΒΩΚΑΣ, ΜΕΛΟΣ, ΤΕ Ραδιολογίας-Ακτινολογίας
ΑΝΤΩΝΙΑ ΤΣΑΚΑΛΗ, ΑΝΑΠΛ. ΜΕΛΟΣ, Ειδικευόμενη ιατρός Ψυχιατρικής
ΑΓΓΕΛΙΚΗ-ΑΘΗΝΑ ΔΕΡΔΕΜΕΖΗ, ΜΕΛΟΣ, ΠΕ Νοσηλευτικής

ΘΕΜΑ : Έγκριση διεξαγωγής έρευνας με τίτλο «Επίδραση φωνολογικής παρέμβασης στην εγκεφαλική πλευρίωση κατά τη γραφή σε παιδιά με κίνδυνο εμφάνισης δυσλεξίας: Μελέτη με τη χρήση λειτουργικού διακρανικού υπερήχου Doppler»
Επιστημονικά Υπεύθυνη: κ. Παναγιώτα Περβανίδου Αναπληρώτριας Καθηγήτριας Παιδιατρικής - Αναπτυξιακής Παιδιατρικής της Α' Παιδιατρικής Κλινικής της Ιατρικής Σχολής ΕΚΠΑ.
Επιστημονικά Υπεύθυνη: κ. Μαριέττα Παπαδάτου-Παστού Επίκουρη Καθηγήτρια στο Παιδαγωγικό Τμήμα Δημοτικής Εκπαίδευσης ΕΚΠΑ συνεργαζόμενο μέλος ΔΕΠ με το Ίδρυμα Ιατροβιολογικών Ερευνών της Ακαδημίας Αθηνών.

ΣΧΕΤ. : Αρ.πρωτ 6627/29.03.2022

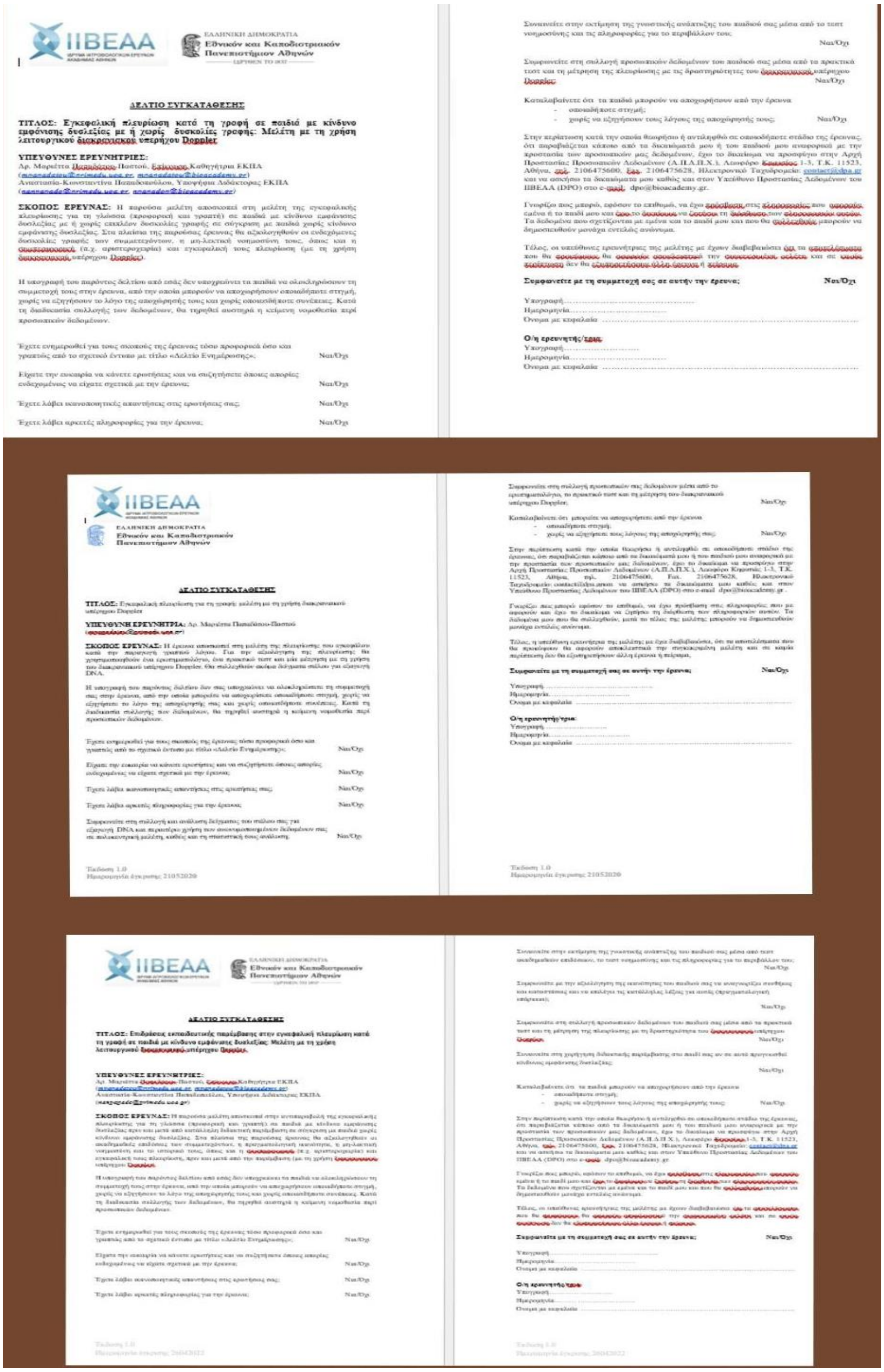
Το Επιστημονικό Συμβούλιο κατά την συνεδρίασή του στις 13 Απριλίου 2022 έλαβε υπόψη του την ανωτέρω αίτηση των κ. Παναγιώτα Περβανίδου Αναπληρώτριας Καθηγήτριας Παιδιατρικής - Αναπτυξιακής Παιδιατρικής της Α' Παιδιατρικής Κλινικής της Ιατρικής Σχολής ΕΚΠΑ και της κ. Μαριέττας Παπαδάτου-Παστού Επίκουρης Καθηγήτριας στο Παιδαγωγικό Τμήμα Δημοτικής Εκπαίδευσης ΕΚΠΑ συνεργαζόμενο μέλος ΔΕΠ με το Ίδρυμα Ιατροβιολογικών Ερευνών της Ακαδημίας Αθηνών που αφορά στην έγκριση διενέργειας έρευνας με τίτλο «Επίδραση φωνολογικής παρέμβασης στην εγκεφαλική πλευρίωση κατά τη γραφή σε παιδιά με κίνδυνο εμφάνισης δυσλεξίας: Μελέτη με τη χρήση λειτουργικού διακρανικού υπερήχου Doppler».
Ύστερα από μελέτη και αναλυτική συζήτηση, διαπιστώθηκε ότι η ανωτέρω μελέτη, η οποία θα εκπονηθεί στο πλαίσιο Διδακτορικής Διατριβής της Διδακτορικής Φοιτήτριας Αναστασίας-Κωνσταντίνας Παπαδοπούλου του Παιδαγωγικού Τμήματος Δημοτικής Εκπαίδευσης του ΕΚΠΑ, πληροί όλες τις προϋποθέσεις για τη διεξαγωγή της. Επισημαίνεται ότι οι απαραίτητες απεικονιστικές εξετάσεις (διακρανιακοί υπέρηχοι Doppler) θα λάβουν χώρα στο Ίδρυμα ΙΒΕΑΑ και όπως αναφέρεται δεν θα υπάρξει καμία οικονομική επιβάρυνση για το νοσοκομείο.
Κατόπιν τούτων, ομόφωνα το Επιστημονικό Συμβούλιο εισηγείται την έγκριση διεξαγωγής της ανωτέρω έρευνας, καθώς και την έγκριση των συνοδευτικών εγγράφων. Συγκεκριμένα:

1. Πρωτόκολλο μελέτης
2. Έντυπο πληροφορημένης συγκατάθεσης

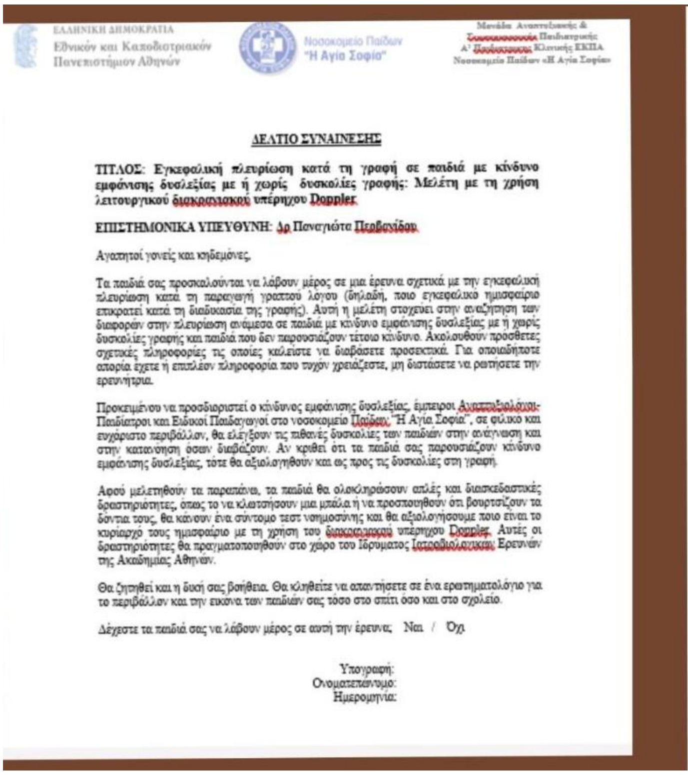
Η ΠΡΟΕΔΡΟΣ
ΤΟΥ ΕΠΙΣΤΗΜΟΝΙΚΟΥ ΣΥΜΒΟΥΛΙΟΥ
ΧΡΙΣΤΙΝΑ ΚΑΝΑΚΑ-GANTENBEIN
ΚΑΘΗΓΗΤΡΙΑ-ΔΙΕΥΘΥΝΤΡΙΑ
Α΄ ΠΑΙΔΙΑΤΡΙΚΗΣ ΚΛΙΝΙΚΗΣ ΠΑΝΕΠΙΣΤΗΜΙΟΥ ΑΘΗΝΩΝ

Information sheets for all three studies of this thesis according to the guidelines of the Biomedical Research Foundation of the Academy of Athens

Consent forms for all three studies of this thesis according to the guidelines of the Biomedical Research Foundation of the Academy of Athens



Consent form for Studies 2 and 3 according to the guidelines of the "Aghia Sofia" Children's hospital



ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν
Πανεπιστήμιον Αθηνών

Νοσοκομείο Παίδων "Η Αγία Σοφία"

Μονάδα Αναπτυξιακής & Συμπεριφορικής Παιδιατρικής
Α' Παιδιατρικής Κλινικής ΕΚΠΑ
Νοσοκομείο Παίδων «Η Αγία Σοφία»

ΔΕΛΤΙΟ ΣΥΝΑΙΝΕΣΗΣ

ΤΙΤΛΟΣ: Εγκεφαλική πλευρίωση κατά τη γραφή σε παιδιά με κίνδυνο εμφάνισης δυσλεξίας με ή χωρίς δυσκολίες γραφής: Μελέτη με τη χρήση λειτουργικού διακρανιακού υπέρηχου Doppler.

ΕΠΙΣΤΗΜΟΝΙΚΑ ΥΠΕΥΘΥΝΗ: Δρ Παναγιώτα Πervανίδου

Αγαπητοί γονείς και κηδεμόνες,

Τα παιδιά σας προσκαλούνται να λάβουν μέρος σε μια έρευνα σχετικά με την εγκεφαλική πλευρίωση κατά τη παραγωγή γραπτού λόγου (δηλαδή, ποιο εγκεφαλικό ημισφαίριο επικρατεί κατά τη διαδικασία της γραφής). Αυτή η μελέτη στοχεύει στην αναζήτηση των διαφορών στην πλευρίωση ανάμεσα σε παιδιά με κίνδυνο εμφάνισης δυσλεξίας με ή χωρίς δυσκολίες γραφής και παιδιά που δεν παρουσιάζουν τέτοιο κίνδυνο. Ακολουθούν πρόσθετες σχετικές πληροφορίες τις οποίες καλείστε να διαβάσετε προσεκτικά. Για οποιαδήποτε απορία έχετε ή επιπλέον πληροφορία που τυχόν χρειάζεστε, μη διστάσετε να ρωτήσετε την ερευνήτρια.

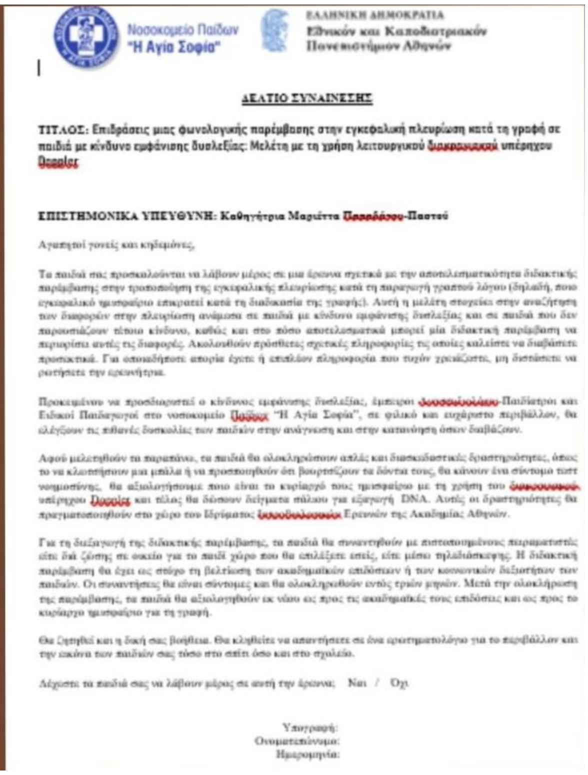
Προκειμένου να προσδιοριστεί ο κίνδυνος εμφάνισης δυσλεξίας, έμπειροι Αναπτυξιολόγοι-Παιδίατροι και Ειδικοί Παιδαγωγοί στο νοσοκομείο Παίδων "Η Αγία Σοφία", σε φιλικό και ευχάριστο περιβάλλον, θα ελέγξουν τις πιθανές δυσκολίες των παιδιών στην ανάγνωση και στην κατανόηση όσων διαβάζουν. Αν κριθεί ότι τα παιδιά σας παρουσιάζουν κίνδυνο εμφάνισης δυσλεξίας, τότε θα αξιολογηθούν και ως προς τις δυσκολίες στη γραφή.

Αφού μελετηθούν τα παραπάνω, τα παιδιά θα ολοκληρώσουν απλές και διασκεδαστικές δραστηριότητες, όπως το να κλωτσήσουν μια μπάλα ή να προσποιηθούν ότι βουρτσίζουν τα δόντια τους, θα κάνουν ένα σύντομο τεστ νοημοσύνης και θα αξιολογήσουμε ποιο είναι το κυρίαρχό τους ημισφαίριο με τη χρήση του διακρανιακού υπέρηχου Doppler. Αυτές οι δραστηριότητες θα πραγματοποιηθούν στο χώρο του Ιδρύματος Ιατροβιολογικών Ερευνών της Ακαδημίας Αθηνών.

Θα ζητηθεί και η δική σας βοήθεια. Θα κληθείτε να απαντήσετε σε ένα ερωτηματολόγιο για το περιβάλλον και την εικόνα των παιδιών σας τόσο στο σπίτι όσο και στο σχολείο.

Δέχεστε τα παιδιά σας να λάβουν μέρος σε αυτή την έρευνα; Ναι / Όχι

Υπογραφή:
Ονοματεπώνυμο:
Ημερομηνία:



Νοσοκομείο Παίδων "Η Αγία Σοφία"

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν
Πανεπιστήμιον Αθηνών

ΔΕΛΤΙΟ ΣΥΝΑΙΝΕΣΗΣ

ΤΙΤΛΟΣ: Επιδράσεις μιας φωνολογικής παρέμβασης στην εγκεφαλική πλευρίωση κατά τη γραφή σε παιδιά με κίνδυνο εμφάνισης δυσλεξίας: Μελέτη με τη χρήση λειτουργικού διακρανιακού υπέρηχου Doppler

ΕΠΙΣΤΗΜΟΝΙΚΑ ΥΠΕΥΘΥΝΗ: Καθηγήτρια Μαριέττα Παπαδάτου-Παστού

Αγαπητοί γονείς και κηδεμόνες,

Τα παιδιά σας προσκαλούνται να λάβουν μέρος σε μια έρευνα σχετικά με την αποτελεσματικότητα διδακτικής παρέμβασης στην τροποποίηση της εγκεφαλικής πλευρίωσης κατά τη παραγωγή γραπτού λόγου (δηλαδή, ποιο εγκεφαλικό ημισφαίριο επικρατεί κατά τη διαδικασία της γραφής). Αυτή η μελέτη στοχεύει στην αναζήτηση των διαφορών στην πλευρίωση ανάμεσα σε παιδιά με κίνδυνο εμφάνισης δυσλεξίας και σε παιδιά που δεν παρουσιάζουν τέτοιο κίνδυνο, καθώς και στο πόσο αποτελεσματικά μπορεί μία διδακτική παρέμβαση να περιορίσει αυτές τις διαφορές. Ακολουθούν πρόσθετες σχετικές πληροφορίες τις οποίες καλείστε να διαβάσετε προσεκτικά. Για οποιαδήποτε απορία έχετε ή επιπλέον πληροφορία που τυχόν χρειάζεστε, μη διστάσετε να ρωτήσετε την ερευνήτρια.

Προκειμένου να προσδιοριστεί ο κίνδυνος εμφάνισης δυσλεξίας, έμπειροι Αναπτυξιολόγοι-Παιδίατροι και Ειδικοί Παιδαγωγοί στο νοσοκομείο Παίδων "Η Αγία Σοφία", σε φιλικό και ευχάριστο περιβάλλον, θα ελέγξουν τις πιθανές δυσκολίες των παιδιών στην ανάγνωση και στην κατανόηση όσων διαβάζουν.

Αφού μελετηθούν τα παραπάνω, τα παιδιά θα ολοκληρώσουν απλές και διασκεδαστικές δραστηριότητες, όπως το να κλωτσήσουν μια μπάλα ή να προσποιηθούν ότι βουρτσίζουν τα δόντια τους, θα κάνουν ένα σύντομο τεστ νοημοσύνης, θα αξιολογήσουμε ποιο είναι το κυρίαρχό τους ημισφαίριο με τη χρήση του διακρανιακού υπέρηχου Doppler και τέλος θα δώσουν δείγματα σάλιου για εξαγωγή DNA. Αυτές οι δραστηριότητες θα πραγματοποιηθούν στο χώρο του Ιδρύματος Ιατροβιολογικών Ερευνών της Ακαδημίας Αθηνών.

Για τη διεξαγωγή της διδακτικής παρέμβασης, τα παιδιά θα συναντηθούν με πιστοποιημένους παρατηρητές είτε διά ζώσης σε οικείο για το παιδί χώρο που θα επιλέξετε εσείς, είτε μέσω τηλεδιάσκεψης. Η διδακτική παρέμβαση θα έχει ως στόχο τη βελτίωση των ακαδημαϊκών επιδόσεων ή των κοινωνικών δεξιοτήτων των παιδιών. Οι συναντήσεις θα είναι σύντομες και θα ολοκληρωθούν εντός τριών μηνών. Μετά την ολοκλήρωση της παρέμβασης, τα παιδιά θα αξιολογηθούν εκ νέου ως προς τις ακαδημαϊκές τους επιδόσεις και ως προς το κυρίαρχο ημισφαίριο για τη γραφή.

Θα ζητηθεί και η δική σας βοήθεια. Θα κληθείτε να απαντήσετε σε ένα ερωτηματολόγιο για το περιβάλλον και την εικόνα των παιδιών σας τόσο στο σπίτι όσο και στο σχολείο.

Δέχεστε τα παιδιά σας να λάβουν μέρος σε αυτή την έρευνα; Ναι / Όχι

Υπογραφή:
Ονοματεπώνυμο:
Ημερομηνία:

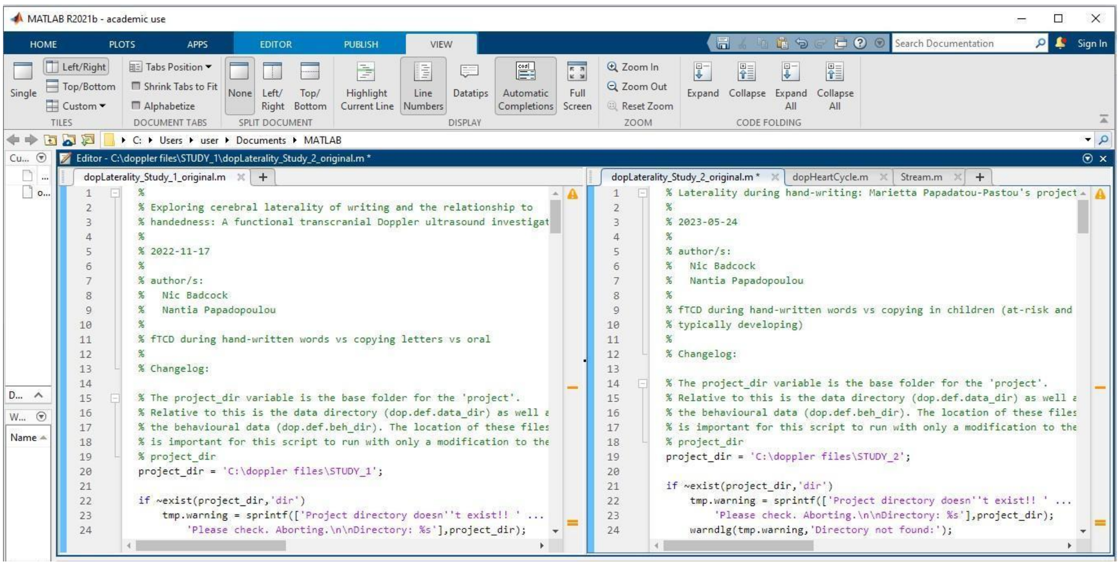
Brochure for the call for participation in Studies 2 and 3

Example of the PsychoPy code developed for this thesis

Example of a participant during the fTCD task in Study 1

Example of a participant during the fTCD task in Study 2

A part of the analysis code for the fTCD data using the MATLAB-based tool DopStep



The contents of the phonological intervention

ΕΚΠΑΙΔΕΥΤΙΚΗ ΠΑΡΕΜΒΑΣΗ ΦΩΝΟΛΟΓΙΚΗΣ ΕΠΙΓΝΩΣΗΣ ΓΙΑ ΜΑΘΗΤΕΣ Β' ΚΑΙ Γ' ΔΗΜΟΤΙΚΟΥ ΜΕ ΚΙΝΔΥΝΟ ΕΜΦΑΝΙΣΗΣ ΔΥΣΛΕΞΙΑΣ ΣΤΟ ΠΛΑΙΣΙΟ ΤΗΣ ΜΕΛΕΤΗΣ ΜΕ ΤΙΤΛΟ «**THE EFFECTS OF EDUCATIONAL INTERVENTIONS IN THE CEREBRAL LATERALIZATION FOR WRITTEN LANGUAGE IN CHILDREN AT RISK FOR DYSLEXIA: A FUNCTIONAL TRANSCRANIAL DOPPLER ULTRASOUND STUDY**»

Επιμέλεια:

Αναστασία-Κωνσταντίνα Παπαδοπούλου, υποψήφια διδάκτωρ Νευροψυχολογίας

Κωνσταντίνα Φραγκούλη, διδάκτωρ Ειδικής Αγωγής

Αθανάσιος Παπακώστας, διδάκτωρ Ειδικής Αγωγής

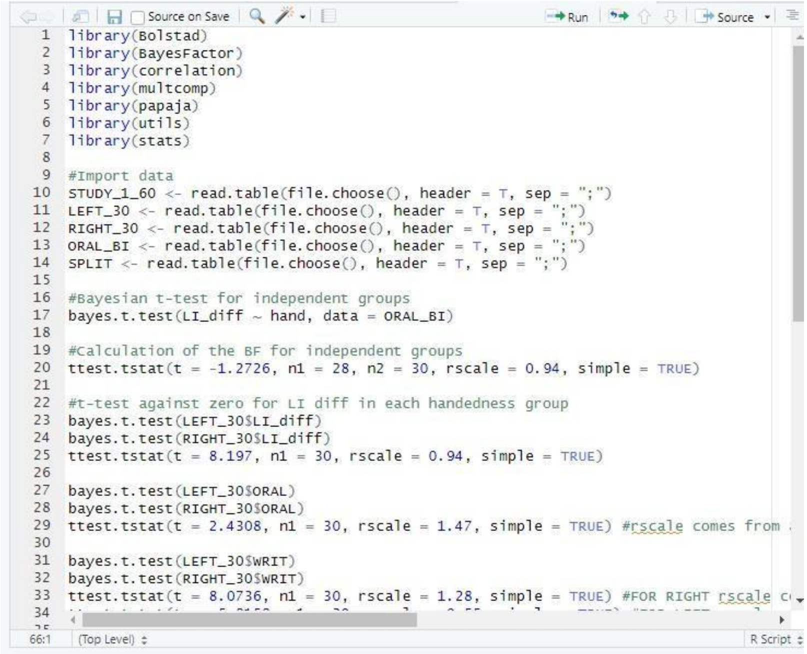
Περιεχόμενα:

The contents of the pragmatic intervention

Οι Κοινωνικοί Ντετέκτιβ

Περιεχόμενα

Part of the data analysis code in RStudio



```r
library(Bolstad)
library(BayesFactor)
library(correlation)
library(multcomp)
library(papaja)
library(utils)
library(stats)

#Import data
STUDY_1_60 <- read.table(file.choose(), header = T, sep = ";")
LEFT_30 <- read.table(file.choose(), header = T, sep = ";")
RIGHT_30 <- read.table(file.choose(), header = T, sep = ";")
ORAL_BI <- read.table(file.choose(), header = T, sep = ";")
SPLIT <- read.table(file.choose(), header = T, sep = ";")

#Bayesian t-test for independent groups
bayes.t.test(LI_diff ~ hand, data = ORAL_BI)

#Calculation of the BF for independent groups
ttest.tstat(t = -1.2726, n1 = 28, n2 = 30, rscale = 0.94, simple = TRUE)

#t-test against zero for LI diff in each handedness group
bayes.t.test(LEFT_30$LI_diff)
bayes.t.test(RIGHT_30$LI_diff)
ttest.tstat(t = 8.197, n1 = 30, rscale = 0.94, simple = TRUE)

bayes.t.test(LEFT_30$ORAL)
bayes.t.test(RIGHT_30$ORAL)
ttest.tstat(t = 2.4308, n1 = 30, rscale = 1.47, simple = TRUE) #rscale comes from

bayes.t.test(LEFT_30$WRIT)
bayes.t.test(RIGHT_30$WRIT)
ttest.tstat(t = 8.0736, n1 = 30, rscale = 1.28, simple = TRUE) #FOR RIGHT rscale c
```