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Cerebral language networks and neuropsychological profile in children with fronto-temporal lobe epilepsy : a multimodal neuroimaging and neuropsychological approach

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Résumé

L'enfance et l'adolescence sont des périodes uniques de la vie où les changements neuronaux favorisent l'établissement de réseaux cérébraux matures et le développement des capacités intellectuelles. Le langage est un domaine cognitif qui est, non seulement essentiel pour la communication interhumaine, mais qui contribue également au développement de nombreuse capacités et prédit de manière significative la réussite académique. Les régions cérébrales frontotemporales sont des régions clés du réseau langagier du cerveau. Il a été démontré que les neuropathologies telles que l'épilepsie des lobes frontal et temporal (ELF et ELT) interfèrent avec le développement des réseaux cérébraux du langage et provoquent des circuits cérébraux aberrants. Les patrons exacts de réorganisation des réseaux cérébraux fonctionnels ne sont toutefois, pas entièrement compris et l'association avec le profil neuropsychologique reste spéculative. Par conséquent, l'objectif principal de cette thèse est d'accroître la compréhension des altérations du réseau langagier et d'améliorer les connaissances de l'association de l'architecture du réseau et des capacités cognitives chez les enfants et les adolescents avec ELF ou ELT.

La présente thèse est composée de trois articles scientifiques, les deux premiers présentant des travaux méthodologiques qui ont permis d'optimiser les méthodes appliquées dans le troisième article, l'étude empirique principale menée auprès d'enfants avec ELF et ELT. Le premier article présente le bilan neuropsychologique pédiatrique comme un outil important pour estimer les capacités cognitives et dresser un profil cognitif avec ses forces et ses faiblesses. Dans le deuxième article, l'analyse factorielle parallèle (PARAFAC) est présentée et validée comme une nouvelle technique employée pour corriger les artefacts de mouvement qui contaminent le signal hémodynamique évalué par la spectroscopie fonctionnelle proche infrarouge (fNIRS). Une meilleure qualité du signal permet une interprétation fiable de la réponse cérébrale en plis de déduire des métriques d'organisation du réseau cérébral. Le troisième article consiste en une étude empirique, où le traitement cérébral du langage, est comparé entre des enfants avec ELF et ELT, et des pairs neuroptypiques. Les schémas de connectivité fonctionnelle indiquent que le groupe de patients présente moins de connexions intra-hémisphériques dans l'hémisphère gauche et entre les hémisphères, et des connexions accrues dans l'hémisphère droit par rapport au groupe témoin. Les mesures de l'architecture du réseau révèlent en outre une efficacité de traitement local plus élevée dans l'hémisphère droit chez les enfants atteints de ELF et ELT par rapport aux enfants en bonne santé. L'architecture du réseau local de l'hémisphère gauche et la capacité intellectuelle globale dans le groupe de patients sont négativement liées, tandis que dans le groupe contrôle, aucune association de ce type n'est identifiable. Ces résultats suggèrent que la réorganisation du

réseau de langage chez les enfants avec ELF ou ELT semble dans certains cas soutenir un meilleur résultat cognitif, soit lorsque l'efficacité du traitement local dans l'hémisphère gauche est diminuée. Au contraire, une plus grande efficacité de traitement local semble être une caractéristique d'un réseau de langage cérébral associé à de moins bonnes capacités cognitives.

Les travaux de recherche de cette thèse de doctorat fournissent des lignes directrices pour l'utilisation de l'évaluation neuropsychologique pédiatrique, à la fois dans un contexte clinique et scientifique. L'introduction de PARAFAC pour corriger les artefacts de mouvement dans le signal fNIRS est un ajout important au pipeline de prétraitement qui permet d'augmenter la qualité du signal pour une analyse ultérieure. De futurs projets pourront s'appuyer sur cette validation initiale et étendre l'utilisation de PARAFAC pour les analyses du signal fNIRS. Sur cette base méthodologique solide, le travail empirique confirme l'incidence accrue de circuits cérébraux aberrants liés au traitement du langage chez les enfants atteints de ELF et de ELT, et soutient en outre l'efficacité du réseau local en tant que déterminant clé de l'impact de la plasticité cérébrale précoce sur les capacités cognitives. Afin de mieux comprendre les altérations du réseau en réponse aux neuropathologies et leur impact, des études avec des échantillons plus grands et de différents groupes d'âge, devraient étudier plus spécifiquement le rôle des facteurs cliniques (e.g., le type d'épilepsie, la latéralisation de l'épilepsie, le contrôle des crises, etc.) et aborder leurs influences sur le développement. À long terme, cela augmentera le pronostic des phénotypes cliniques chez les patients pédiatriques atteints de ELF et de ELT, et offrira des opportunités d'interventions précoces pour soutenir un développement typique.

Mots-clés : Neurodéveloppement, réseau cérébral du langage, plasticité cérébrale précoce, neuropsychologie, spectroscopie fonctionelle proche infrarouge-éléctrophysiologie (fNIRS-EEG), corréction des artefacts de mouvement, analyse des réseaux, épilepsie pédiatrique, épilepsie du lobe frontotemporal, relation cerveau-comportement.

Abstract

Childhood and adolescence are unique periods in life where neuronal changes support the establishment of mature brain networks and the development of intellectual capacities. Language is one cognitive domain that is not only an essential part of inter-human communication but also contributes to the development of other capacities and significantly influences academic achievement. Frontotemporal brain areas are key regions of the brain's language network. Neuropathologies such as frontal and temporal lobe epilepsies (FLE and TLE) have been shown to interfere with developing brain language networks and cause aberrant cerebral circuits. The exact patterns of functional brain network reorganization are not fully understood and the association with the neuropsychological profile remains speculative. Therefore, the main objective of this thesis was to increase comprehension of language network alterations and enhance the knowledge on the association of network topology and cognitive capacities in children and adolescents with FLE or TLE.

This thesis consists of three scientific articles, with the first two presenting methodological work that allowed for the optimization of the methods applied in the third article, which is the main empirical study conducted on children with FLE and TLE. The first article presents the pediatric neuropsychological assessment as a valuable tool to estimate cognitive capacities and draw a cognitive profile with strengths and weaknesses. In the second article, parallel factor analysis (PARAFAC) is presented and validated as a novel technique to correct motion artifacts that contaminate the hemodynamic signal assessed with functional near-infrared spectroscopy (fNIRS). A better signal quality is the basis for a reliable interpretation of the cerebral response and derive metrics of brain network organization. The third article consists of an empirical study where cerebral language processing is compared between children with FLE and TLE, and neuroptypical peers. Patterns of functional connectivity indicate that the patient group demonstrates fewer intra-hemispheric connections in the left hemisphere and between hemispheres, and increased connections within the right hemisphere as compared to the control group. Metrics of network architecture further reveal a higher local processing efficiency within the right hemisphere in children with FLE and TLE compared to healthy peers. Local network architecture of the left hemisphere and the overall intellectual capacity in the patient group is negatively related, while in the control group no such association is identifiable. These findings suggest that language network reorganization in children with FLE or TLE in some cases seems to support a better cognitive outcome, namely when local processing efficiency in the left hemisphere is decreased. On the contrary, a higher local processing efficiency seems to be a characteristic of a brain language network that goes along with worse cognitive capacities.

The research work of this doctoral thesis provides guidelines for the use of pediatric neuropsychological assessment both in a clinical and scientific context. The introduction of PARAFAC to correct motion artifact in the fNIRS signal is an important add-on to the preprocessing pipeline that allows to increase signal quality for subsequent analysis. Future projects will be able to build on this initial validation and extend PARAFAC's use for fNIRS analysis. On this solid methodological foundation, the empirical work confirms the increased incidence of aberrant brain circuits related to language processing in children with FLE and TLE, and further supports local network efficiency as a key determinant of the impact of early brain plasticity on cognitive capacities. In order to further understand network alterations in response to neuropathologies and their impact, studies with larger samples sizes and different age groups should further investigate the specific role of clinical factors (e.g., epilepsy type, epilepsy lateralization, seizure control, etc.) and address developmental influences. Ultimately, this will increase prognosis of clinical phenotypes in pediatric patients with FLE and TLE, and offer opportunities for early interventions to support a healthy development.

Keywords: Neurodevelopment, cerebral language network, early brain plasticity, neuropsychology, functional near-infrared spectroscopy-electrophysiology (fNIRS-EEG), motion artifact correction, network analysis, pediatric epilepsy, frontotemporal lobe epilepsy, brain-behavior relationship.

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List of Acronyms and Abbreviations

AAL	Automated anatomical labeling
AC	Amplitude modulation
ADHD	Attention deficit hyperactivity disorder
ANOVA	Analysis of variance
ASD	Autism spectrum disorder
ASM	Anti-seizure medication
aSTG	Anterior superior temporal gyrus
aSTS	Anterior superior temporal sulcus
AUC	Area under the curve
BOLD	Blood-oxygen-level-dependent
BYD	Beck youth inventory
BSID	Bayley scales of infant development
CHD	Congenital heart disease
Corcondia	Core Consistency Diagnostic
DC	Light intensity
DPF	Differential pathlength factor
EC	Effective connectivity
EEG	Electroencephalography
e.g.	Exempli gratia (*for example*)
$\mathbf{E_{local}}$	Local processing efficiency
$\mathbf{E_{global}}$	Global processing efficiency
EOWPVT	One-word picture vocabulary test
EPT	Extremely prematurely born

ERP	Event-related potential
et al.	And colleagues
EVT	Expressive Vocabulary Test
F	Female
FC	Functional connectivity
FLE (ELF)	Frontal lobe epilepsy (*épilepsie du lobe frontal*)
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
γ	Clustering coefficient
GLM	General linear model
HbO	Oxyhemoglobin
HbR	Deoxyhemoglobin
HR	High risk
HRF	Hemodynamic response function
ICA	Indepencent component analysis
ID	Intellectual disability
i.e.	Id est (*that is*)
IFG	Inferior frontal gyrus
ILAE	International league against epilepsy
IQ	Intelligence quotient
K-ABC	Kaufman assessment battery for children
λ	Characteristic path length
LH	Left hemisphere
LLD	Language-based learning disorder
LLI	Language learning impairment

LPA	Left pre-auricular
LR	Low risk
MBLL	Modified Beer-Lambert law
M	Male
MCDI	Mac-Arthur communicative developmental inventory
MEG	Magnetoencephalography
MFG	Middle frontal gyrus
mSTG	Middle superior temporal gyrus
NA	Not available
N/A	Not applicable
n.s.	Not significant ($p > .05$)
δ**OD / dOD**	Delta optical density
PARAFAC	Parallel factor analysis
PLI	Phase lag index
PLV	Phase locking value
PSI	Phase slope index
PPVT	Peabody picture vocabulary test
PRD	Percent root difference
PRI	Perceptual reasoning index
pSTG	Posterior superior temporal gyrus
pSTS	Posterior superior temporal sulcus
R	Pearson's product-moment correlation coefficient
RH	Right hemisphere
RMSE	Root mean square error
ROI	Region of interest

RPA	Right pre-auricular
SD	Standard deviation
SES	Socio-economic status
SNR	Signal-to-noise ratio
σ	Small-world index
SPM	Statistical parametric mapping
TB	Term-born
TD	Typically developing
TLE (ELT)	Temporal lobe epilepsy (*épilepsie du lobe temporal*)
(t)PCA	(Target) principal component analysis
VCI	Verbal comprehension index
WASI	Wechsler abbreviated scale of intelligence
WAIS	Wechsler intelligence scale for adults
WHO	World health organization
WISC	Wechsler intelligence scale for children
2D	Two-dimensional
3D	Three-dimensional

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Preface

Childhood is a unique period in life where major cerebral and cognitive development occurs. Neuronal growth and maturation during the first years of life are complex and happen at an impressive speed (Accogli et al., 2020; Paus, 2022). These cerebral changes accompany the establishment of numerous skills that are essential for a healthy cognitive, behavioral and socioaffective functioning (Cattell, 1987; Colom, 2020). Throughout childhood and adolescence, cerebral development remains dynamic and brain networks become more and more intricately intertwined (Gozdas et al., 2019; Koenis et al., 2018). This accompanies more efficient and integrated information processing that supports fine tuning of previously acquired skills (Skeide & Friederici, 2016) and ultimately leads to a mature and adult-like cerebral organization and functional state.

Brain lesions and neurological disorders have been shown to interfere with normal cerebral and cognitive development. They can cause the neurodevelopment to stagnate at a premature stage, slow-down, recess or take atypical pathways, and cause alterations in the establishment of mature cerebral networks (Smith, 2010). Childhood epilepsy is the most common pediatric neurological disorder (Behr et al., 2016; Berg et al., 2013). Focal epilepsy, in particular, has long served as a clinical model to investigate the human brain and its adaptive capacities (Banks et al., 2014; Milner, 1982; Nasif et al., 2021; Penfield & Jasper, 1954). Pediatric frontal and temporal lobe epilepsy (FLE, TLE) represent the most diagnosed clinical entities and have been associated with a wide range of cognitive, behavioral and socioaffective difficulties (Hernandez et al., 2002; Law et al., 2018; Smith, 2016; Wilson et al., 2015). Although certain neuropsychological particularities have often been reported for each type of epilepsy, FLE and TLE also share common patterns of difficulties. Language impairment is frequent in both of these focal epilepsies (Bear et al., 2019; Metternich et al., 2014).

Previous studies, including the work from our lab, have further shown that cerebral language processing in children with FLE or TLE is associated with a more frequent atypical hemispheric dominance compared to neurotypical children (Gallagher et al., 2016; Vannasing et al., 2016), altered network synchronization (Balter et al., 2019; Bear et al., 2019; Sepeta et al., 2015) and deviant network topology (Slinger et al., 2022). Neuroimaging techniques, especially the sophisticated acquisition methods and analysis approaches that have been refined in the last few decades, have significantly contributed to characterize cerebral language processing and identify alterations such as in children with FLE or TLE. Functional near-infrared spectroscopy (fNIRS) is a particularly useful tool to study language processing in pediatric epilepsy patients, because it does not require the participant to remain still during

data acquisition, is relatively tolerant to movement, and thus allows the child to keep contact with the accompanying caregiver during the recording.

Although an increased incidence of aberrant brain circuits that support language functions in children with FLE or TLE has been reported in studies using functional magnetic resonance imaging (fMRI) and fNIRS, the patterns of brain reorganization and their associations with cognitive impairment in the context of the developing brain are still unclear. Precisely, it remains speculative whether early brain plasticity allows for a cerebral reorganization that promotes the development of language functions or whether the cerebral reorganization is a sign of malfunctioning and is associated with an unfavorable development of language skills.

The main objective of this thesis is to map out functional brain language network organization in association with the neuropsychological profile in children with FLE or TLE using fNIRS and neuropsychological assessment. Prior to this empirical study, we conducted two methodological projects to optimize our methods and data analysis procedure. Article one underlines the relevance of pediatric neuropsychological evaluations to identify developmental alterations. Article two was conducted to refine an important preprocessing step in fNIRS data analyses, precisely motion artifact correction, to improve interpretation of the fNIRS signal and have a better characterization of brain networks. These two methodologies (neuropsychological assessment and fNIRS) are employed in the last and main article three of this thesis on pediatric FLE and TLE.

This thesis is organized in six parts. First, chapter one provides the theoretical background, including a literature review on the normal development of language functions and their cerebral correlates, the epidemiology and clinical characteristics of pediatric epilepsy, the current knowledge on the impact of FLE and TLE on cognitive and cerebral development, and the background and methodological challenges of fNIRS. Chapter two lays out the detailed research objectives and hypotheses of this doctoral research work. Part three to five form the core of this thesis and include three publications. A book chapter on the pediatric neuropsychological assessment published in the Handbook of Clinical Neurology, Volume *Neurocognitive Development: Disorders and Disabilities,* in 2020, a validation study on a novel method for signal processing in fNIRS published in Neurophotonics (2022), and an empirical study on cerebral language networks and cognitive profiles in children with FLE or TLE. Part six is a general discussion including a summary of the main findings, the strengths and limitations of this research work, and future perspective. Two additional articles that I co-authored are included in the appendices: 1) a systematic review published in Frontiers in Human Neuroscience (2020) on cerebral language networks in children that built an important theoretical foundation for the concepts used in the research of language development, and 2) an article published in the Journal of Neuroscience Methods (2022) presenting a fNIRS data analyses toolbox developed in our lab and used in articles 2 and 3.

Chapter 1

Theoretical background

1.1. Language

Language is a key instrument of human communication and a cornerstone for successful and efficient social interactions. Broadly speaking, language serves information transfer and includes perception and production of both verbal, i.e., spoken, signed or written words, and non-verbal, i.e., body language, mimic, gestures, expressions (Crystal & Robins, 2022; Hauser et al., 2002). In this thesis, a narrower definition is applied with a focus on spoken verbal language. Receptive language processing in the form of human speech is composed of a coordinated analysis and integration of basic acoustic, phonetic (single characters), syllabic (character units), morphologic (word units), lexic (word category), semantic (meaning), syntactic (sentence structure), and prosodic (intonation) characteristics of spoken language (e.g., Skeide & Friederici, 2016). Expressive language is based on the knowledge of all of the above characteristics but further includes motor components to produce language (e.g., Skeide & Friederici, 2016). The cornerstones of the neurobiology of language processing and the major developmental steps of language acquisition during childhood and adolescence are presented in the next two sections.

Neurobiology of language

Most of the current knowledge of cerebral language processing originates from the findings of early lesional studies by pioneers such as Paul Broca (1861) or Carl Wernicke (1969). During the last decades however, sophisticated neuroimaging techniques and analytical approaches have enabled more precise investigations of functional brain organization and allowed deeper insight of cerebral correlates of language processing. Based on these findings Hickok and Poeppel (2004) proposed their dual stream model, which considers the complex facets of language processing and cerebral networks. Comparable with other sensory domains (e.g., visual), two processing streams, a ventral temporal stream and a dorsal parietofrontal stream, are differentiated (Hickok & Poeppel, 2007; Matchin & Hickok, 2020). The ventral stream is mainly involved in processing speech input and the dorsal stream is predominant in speech production. While the model promotes the long-known left-hemispheric language dominance, it also underlines that language comprehension incorporates a complex distributed network involving bilateral temporal areas. Receptive language processing thus involves a myriad of linguistic and nonlinguistic processes including acoustic analysis in bilateral primary auditory

cortices, phonological analysis in bilateral middle to posterior superior temporal areas, lexico-semantic attribution predominantly, yet not exclusively, in left middle to posterior temporal areas and a more complex sentence-level semantic integration in the left anterior temporal lobe. Expressive language, generally represented in the dorsal stream, is assumed to require a transfer of phonologic knowledge from bilateral posterior superior temporal regions via parietotemporal connections (e.g., angular and supramarginal gyrus, arcuate fasciculus) to elicit speech articulation in the left premotor cortex and inferior frontal gyrus (IFG). The dorsal pathway further enables multisensory integration to improve speech processing during comprehension. The right hemisphere seems to play a tangential role for speech production. Despite revisions (Hickok & Poeppel, 2007) and extensions to speech production (Hickok et al., 2021), and sentence level processing of syntax (Matchin & Hickok, 2020), the dual stream model has remained unchanged in its core and has seen wide acceptance since its first proposal (e.g., Bornkessel-Schlesewsky & Schlesewsky, 2013; DeWitt & Rauschecker, 2013; Fedorenko & Thompson-Schill, 2014; Hickok, 2009; Hickok et al., 2021; Matchin & Hickok, 2020; Poeppel et al., 2012; P. Tremblay & Dick, 2016).

Development of language

The development of language abilities is an important achievement of early childhood. The comprehension of human speech and the ability to express one's needs and thoughts pave the way for the acquisition and maturation of many cognitive and social abilities and can have a predictive value for later academic achievement (Berwick et al., 2013; Gervain, 2020). While the first meaningful words are usually expressed around one year of age, language skills knowingly start to develop much earlier (Skeide & Friederici, 2016). Neonates born prematurely during the last trimester of pregnancy, already show advanced phonetic differentiation capacities (Mahmoudzadeh et al., 2013). Fullterm newborns are already sensitive to pitch variations (Perani et al., 2011), discriminate speech in their mother tongue (Dehaene-Lambertz et al., 2002; May et al., 2011; Moon et al., 2013; Vannasing et al., 2016) or a language they were regularly exposed in utero from speech in foreign languages or from non-speech auditory stimuli (Caron-Desrochers, 2022; Partanen et al., 2013; Vannasing et al., 2016). Even though early language development often refers to speech perception, specific prosodic characteristics of the infant's mother tongue have been identified in infant cries shortly after birth, potentially representing early precursors of speech articulation (Gervain, 2018; Gustafson et al., 2017; Mampe et al., 2009; Manfredi et al., 2019).

Language capacities in neonates are still universal and specialization as well as maturation is shaped by the first months and years of life experience (Dehaene-Lambertz & Houston, 1998; Gervain, 2018, 2020). Skeide and Friederici (2016) provide an extensive graphical summary of language development and its cerebral correlates in childhood and adolescence

(Fig. 1). Overall, language abilities develop gradually, and many also sequentially, such that lower-level skills serve as a foundation for the development of more complex abilities. Some basic receptive capacities precede the development of expressive language skills such as passive phonetic discrimination that is established in utero, compared to the articulation of syllables (babbling), which only arises during the first year of life. Around the age of three, the basic language skills for a child's native language(s) seem to have developed and henceforth mainly undergo qualitative changes.

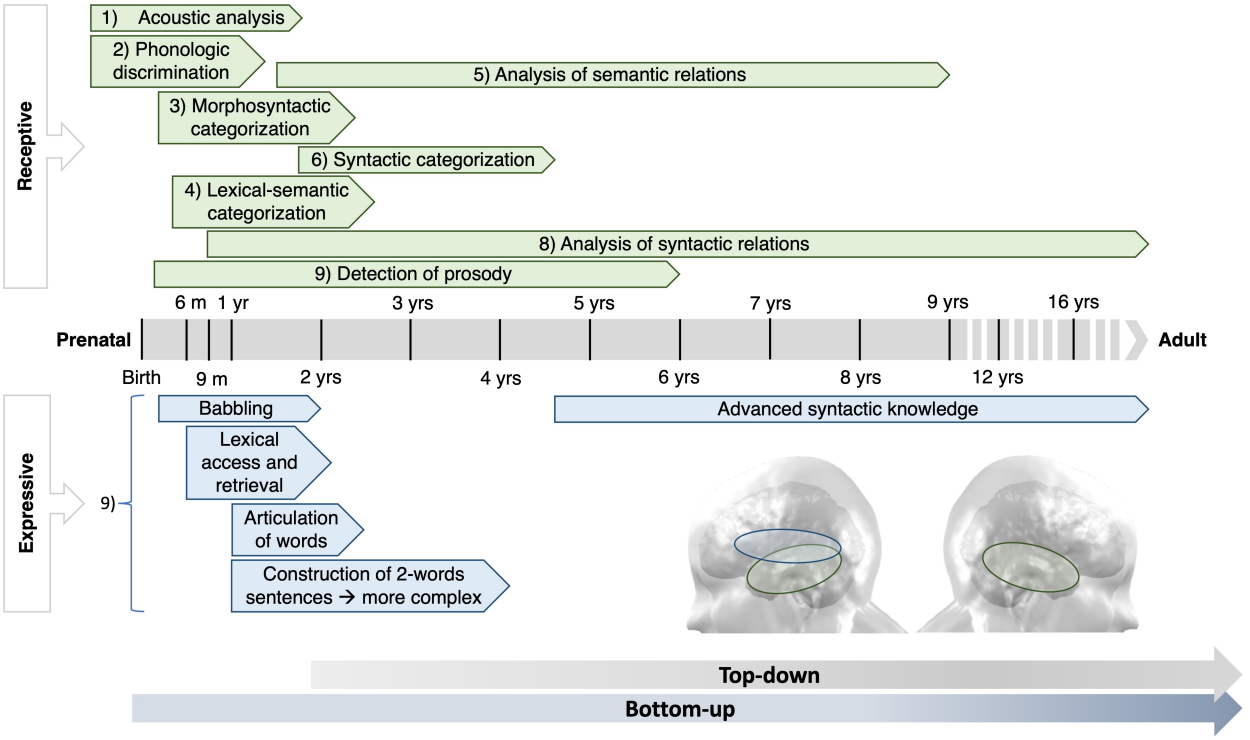

Figure 1 – Developmental of language capacities from the prenatal period until late adolescence and early adulthood inspired by (Skeide & Friederici, 2016). The numbers one to eight indicate the rough course of receptive language processing, though certain parts may also occur in parallel.

The specialization of the brain's left hemisphere for language processing is well-recognized. Whether this left hemispheric dominance is present at birth remains debatable. Many studies confirm this hypothesis (**CaronDesrochers:submitted**; Peña et al., 2003; Vannasing et al., 2016), while others suggest that the left-hemispheric specialization establishes later during development (May et al., 2011; Perani et al., 2011). The exact properties of language stimuli may explain certain differences between these studies. Nevertheless, there is a common agreement that the left hemispheric dominance is established early in life suggesting that the brain possesses an innate predisposition for language processing (Cai et al., 2019).

In their model, Skeide and Friederici (2016) differentiate between bottom-up, i.e., stimuli driven, and top-down, i.e., higher-order or experience based, processing. Bottom-up processing arises as soon as language input is being processed and dominates the early phase of language acquisition, where the mental representations serving top-down processing have yet to be established. As shown in Fig. 1, after the initial processing of acoustic features in bilateral auditory cortices (1), the analysis of phonologic features and word form (2), morphosyntactic (3) and lexico-semantic (4) categorization and sentence level understanding (5, 6 and 8) in infants mainly involve the posterior, middle and anterior superior temporal gyrus (pSTG, mSTG, aSTG) and anterior to posterior superior temporal sulcus (aSTS, pSTS) of the left hemisphere. Only processing of intonation (7) is thought to involve the posterior superior temporal areas of the right hemisphere, which shows a certain differentiation between mature and developing language networks. Around the age of three, the rise of top-down processing allows for a more advanced lexico-semantic categorization and analysis of syntactic relations. It extends the language network into the IFG involving more higher-order control mechanisms. Thus, in line with the developmental trajectory of language functions, after 3 years of age, the main cornerstones of the cerebral language network are established and largely resemble the adult's network organization. This early network maturity goes along with other metrics of cerebral development (e.g., gray and white matter), which after a rapid increase during infancy knowingly level off (Bethlehem et al., 2022; Gilmore et al., 2018; Paus, 2022).

Henceforward, increasing top-down processing accompanies the qualitative changes of language capacities and enables more efficient processing of complex human speech (Höhle et al., 2004; Skeide & Friederici, 2016). Simultaneously the need for slower stimuli-driven bottom-up decoding decreases. It seems inherent that meanwhile related cerebral networks are being refined too (Bruchhage et al., 2020). Regional differences of functional connectivity (FC) in the pSTG and the IFG during sentence-level speech comprehension have been observed in younger (three-year-old) compared to older (six-year-old) children (Vissiennon et al., 2017). Precisely, in younger children the activation in the pSTG showed a stronger association with the activation in the pars triangularis, while the older children demonstrated more dominant FC between the pSTG and the pars opercularis. Since older children demonstrate better comprehension, the difference in network synchrony seems to be an indicator for more mature language abilities. These findings are complemented by investigations of hemodynamic correlates during language processing as assessed with fNIRS (Paquette et al., 2015). The amplitude of the hemodynamic response during an expressive language paradigm increased between the age of 3 to 16 years (Paquette et al., 2015). This modulation of the brain's response goes along with better performance during the task paradigm, suggesting that the amplitude of the hemodynamic response may be an index of language maturation. An EEG study further investigated acoustic and phonetic processing in individuals aged between 3 and

32 years (Paquette et al., 2013). They showed that phonetic processing differs between young children (3 to 7 years), older children (8 to 16 years) and adults (18 years and over), while acoustic processing between the age of 8 and 16 years is comparable to adult participants. The difference of discriminatory capacities for speech sounds between children and adults suggests continuing maturation throughout childhood and adolescence for linguistic processing. In school-aged children cerebral language networks have been characterized by more inter-hemispheric connections, in contrast to adults where language comprehension elicited a network predominated by intra-hemispheric connections within the left hemisphere (Friederici et al., 2011). Again, these differences in FC probably reflect a more mature language network organization in adults. The changing patterns of FC in language related brain regions indicate continuous development of cerebral language processing during childhood and adolescence. During this period, brain networks generally undergo substantial topological changes whereby functional brain networks become more globally integrated with age, while their local specialization decreases (Gozdas et al., 2019; Supekar et al., 2009). These changes in network architecture probably aim at building robust brain networks enabling efficient information processing and are accompanied by structural changes (e.g., gray matter pruning, continuing myelination) (Giedd et al., 1999).

Neuropathologies during childhood and adolescence can interfere with the establishment of functional brain networks and cognitive development. As a result, the developmental cascade may stagnate at a premature stage, slow-down, recess or take atypical pathways, which in consequence can alter global and specific cerebral networks (Smith, 2010). The structural and functional organization of cerebral language networks, can be altered in children with cerebral lesions (e.g., tumors, hemorrhages) or neurologic disorders (e.g., epilepsy), especially when they affect brain regions associated with language processing (Anderson et al., 2006; Berl et al., 2005; Gallagher et al., 2012; Gallagher et al., 2013; Hamberger & Cole, 2011; Ilves et al., 2014; Slinger et al., 2022). Epilepsy has long served as a clinical model to study the brain and its adaptive capacities and is used again in the current thesis to study adaptive capacities of the brain's language networks.

1.2. Epilepsy

Epidemiology, definitions, classification and etiologies

The phenomenon of epileptic seizures has long interested man kind and has been described as early as 1000 B.C. on Babylonian tablets and by Hippocrates 450 B.C. (Wolf, 2014). For many centuries epilepsy was however a great mystery causing people to assume a sacred or even demonic origin. In the 19th and 20th century epilepsy played an important role in the

development of modern neurological diagnostic and interventions, such as the refined localization techniques with EEG, cortical stimulation, neuroradiology, presurgical mapping and neuropsychology (Meador et al., 1989). Epilepsy today remains an important clinical model to investigate cerebral network organization and its association with neuropsycholological functions to better understand the brain's adaptive mechanisms.

In 2020, the prevalence of epilepsy among the general Canadian population was estimated to be around 300 000, thus about 0.8 % of the Canadian population were living with an epilepsy diagnosis (« Canada [country] (table) », 2016; « Canada Population », 2023; « Canadian Chronic Disease Surveillance System [CCDSS] », 2021; « Epilepsy in Canada », 2017; « General information: epidemiology », n.d.). Out of the 17 000 newly diagnosed individuals every year, 25 % are under the age of nineteen (« Canadian Chronic Disease Surveillance System [CCDSS] », 2021). Epilepsy is in fact one of the most common neuropediatric disorders worldwide (Berg et al., 2013).

Epilepsy is a heterogeneous brain disease that involves one of the following manifestations: a person has had at least two unprovoked seizures that are more than 24 hours apart; if they have had one unprovoked seizure and a probability of 60 % for having another seizure within the next ten years; or if they are diagnosed with an epilepsy syndrome such as the Dravet or West syndrome (Fisher et al., 2014). The term non-provoked means that the seizure occurred spontaneously and is not associated with a factor that temporarily affects cerebral activation such as a traumatic brain injury, during an episode of fever or in the context of a substance withdrawal. Under some conditions, a specific stimulus provokes seizures and the diagnosis of epilepsy is still appropriate, for instance in case of reflex seizures (e.g., photic or reading). Epilepsy is considered as being resolved when patients have an age-dependent syndrome and have outgrown the critical age or if they have not had a seizure during the past ten years out of which during five years they did not receive anti-seizure medication (ASM) (Fisher et al., 2014).

> An epileptic seizure is the transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain and epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures (Fisher et al., 2005, p. 471).

The various etiologies of epilepsy, the different seizure semiologies and the numerous comorbidities, underline the complex clinical pathology of epilepsy. A systematic classification is important for the clinical care of these patients, to plan appropriate interventions and facilitate coordination among the interdisciplinary health professionals (Bracchi et al., 1990). In 2017, the ILAE proposed a classification system based on four different factors: 1) the

type of seizures, 2) the type of epilepsy, 3) the nature of the syndrome, and 4) the underlying etiology (Scheffer et al., 2017). Based on the electroencephalogram (EEG) results (Berg et al., 2010; Engel, 2006; Fisher et al., 2017), three types of seizures have been identified: *focal* seizures with an onset in one cerebral hemisphere, *generalized* seizures originating from both hemispheres and seizures with *unknown* onset. Whenever possible, the brain lobe or even more precise cerebral region where the epileptic activity presumably initiates, is specified (e.g., frontal, temporal, or mesial temporal) (Berg et al., 2010). The description of the type of seizures leads to the classification of the type of epilepsy: *focal epilepsy* (focal or multifocal seizures), *generalized epilepsy* (generalized seizures), *combined epilepsy* (focal and generalized seizures) and *unknown epilepsy* (Scheffer et al., 2017). In some cases, the characteristics of the clinical picture, i.e., the seizure semiology, the cerebral activity measured with the EEG, neuroimaging data, the age of epilepsy onset, and neuropsychologic or psychiatric comorbidities, allow the identification of a specific epilepsy syndrome (e.g., juvenile absence epilepsy, juvenile myoclonic epilepsy, Dravet syndrome). Recently, it has been proposed that in underaged patients, these syndromes should be subdivided into 1) self-limited focal epilepsies, 2) generalized epilepsies, and 3) developmental and/or epileptic encephalopathies (Scheffer et al., 2017; Specchio et al., 2022). Finally, epilepsy can also be categorized based on the underlying etiology(ies). It may originate from a *structural* abnormality, such as a brain tumor or a cerebral hemorrhage, an assumed (e.g., family history of epilepsy) or identified *genetic* mutation (e.g., FLE with nocturnal seizures), an *infectious* disease (e.g., tuberculous), a *metabolic* dysfunction (e.g., porphyria) or the cause can be *unknown* (Berg et al., 2010; Fisher et al., 2014; Scheffer et al., 2017). A good characterization of the precise seizures and epilepsy type provides clinicians with a theoretical framework and significantly guides the treatment.

The treatment of choice for epilepsy is a pharmacotherapy with ASM, which efficiently eliminates or significantly reduces seizure occurrence in 70 % of all patients. To achieve a satisfactory control of seizures, trials with different ASM or even a combination of several ASM may be necessary (Holmes et al., 2013). Some patients are however refractory to a pharmacologic treatment and alternative options such as the implantation of a vagus nerve simulation, a ketogenic diet or a neurosurgical intervention may be considered.

Frontal and temporal lobe epilepsy

The most common types of epilepsies are frontal and temporal lobe epilepsies (FLE, TLE; Téllez-Zenteno & Hernández-Ronquillo, 2012). If FLE and TLE originate from the left cerebral hemisphere, they are prone to interfere with widely distributed brain networks involved in language processing and consequently may cause language impairment. Although FLE and TLE are two rather heterogeneous clinical entities, the following sections will include

a more detailed description of the specific characteristics of these two syndromes and their impact on cerebral organization and cognitive functioning.

FLE is a focal epilepsy where the epileptogenic zone is located in the left, right or bilateral frontal lobe. It is the second most common form of epilepsy in children and adolescents (Behr et al., 2016; Deonna et al., 1986; Gallagher & Lassonde, 2005; Hermann et al., 2002; Téllez-Zenteno & Hernández-Ronquillo, 2012). A general characteristic of seizures in patients with FLE is that they often rapidly spread from the onset localization and lead to secondary generalization, which is probably due to the involvement of the frontal brain regions in many cerebral networks (Y. Hu et al., 2012; Lawson et al., 2002; Smith, 2016). Seizures often occur during the night, manifest as involuntary movements and vocalizations, are preceded by a non-specific aura and patients often show post-ictal aphasia (Manford et al., 1996; Quesney et al., 1990). Children who suffer from FLE are often (up to 40 %) refractory to pharmacotherapy and account for 23 to 25 % of patients that are candidates for a surgical removal of the epileptogenic zone, thus making them the second most represented cases in epilepsy surgery (Braakman et al., 2011; Rasmussen, 1991; Rougier et al., 1992; Téllez-Zenteno & Hernández-Ronquillo, 2012).

TLE is a focal epilepsy where the epileptogenic zone is located in the left, right or bilateral temporal lobe. It is the most common form of epilepsy in children and adolescents (Behr et al., 2016; Deonna et al., 1986; Gallagher & Lassonde, 2005; Hermann et al., 2002; Téllez-Zenteno & Hernández-Ronquillo, 2012). TLE is often associated with an early onset of seizures and earlier studies have reported high prevalence of febrile seizures in the history of children with TLE (Commission on Classification and Terminology of the International League Against Epilepsy [ILAE], 1989; Engel, 1996; Holmes et al., 2013). TLE seizures are often announced by an aura such as the feeling of déjà-vu, psychiatric symptoms, epigastric sensations and accompanied by oral or manual automatisms (Holmes et al., 2013; Manford et al., 1996; Ray & Kotagal, 2005). Further, 30 % of patients with TLE are refractory to a pharmacological treatment (Téllez-Zenteno & Hernández-Ronquillo, 2012; Wiebe, 2000). Depending on various clinical variables such as the EEG trace, the presence of cerebral lesions, the presence of a genetic syndrome, the localization of cerebral language processing, patients with TLE may be candidates for a surgical removal of the epileptogenic zone (Helmstaedter, 2001; Téllez-Zenteno & Hernández-Ronquillo, 2012; Wiebe, 2000). They in fact account for a majority, up to 73 % of cases, in epilepsy surgery.

Neuropsychological profile of children with FLE or TLE

The presence of epilepsy does not only have an important impact on the daily life of children but often leads to cognitive, behavioral, psychological and social impairments. Even though the neuropsychological profile in children with FLE or TLE is often heterogeneous

and cognitive difficulties are complexly intertwined, there are certain cognitive characteristics in each of the subgroups (Kellermann et al., 2016).

Children with FLE often have an overall reduced intelligence quotient (IQ) probably partly caused by important attentional and executive deficits (Gallagher & Lassonde, 2005; Orduña et al., 2021). Difficulties in attentional and executive functions such as planning, inhibition, working memory, and cognitive flexibility are in fact typical in these patients and attention-deficit hyperactivity disorder is a common comorbidity in pediatric FLE, with more than 50 % of patients having this diagnosis (Gallagher & Lassonde, 2005; Gonzalez-Heydrich et al., 2007; Hernandez et al., 2003; Hernandez et al., 2002; Nickels et al., 2016; Prévost et al., 2006; Smith, 2016; D.-Q. Zhang et al., 2014). Reduced performance in memory tasks has also been reported, particularly during learning (encoding) and retrieval of information. The underlying cause may therefore not be a deficit in memory capacities but rather represent a consequence of attentional and executive difficulties (Hernandez et al., 2003).

Children with TLE commonly have an IQ within the norm although at the lower limit of the average (Gallagher & Lassonde, 2005; Orduña et al., 2021). Evidence from adult patients however, suggests that depending on the specific type of TLE, especially the level of neuronal atrophy and hippocampal sclerosis, these patients may also have a mild to moderate reduction of their IQ (Hermann et al., 2002; Jokeit & Schacher, 2004). Even though attention and executive deficits are particular concerns in children with FLE, children with TLE can face similar challenges in tasks with attentional and executive demands (Smith, 2016). Memory difficulties (e.g., episodic memory, semantic memory) however are the most typical characteristics of the neuropsychological profile of children with TLE (e.g., Gallagher & Lassonde, 2005; Hermann et al., 2002; Hernandez et al., 2003; Menlove & Reilly, 2015; Nickels et al., 2016; Smith, 2016). Mnesic impairments may be driven by the lateralization of the epileptogenic zone, i.e., left or right, leading to difficulties in a specific modality, i.e., verbal or visual memory, specifically (Gallagher & Lassonde, 2005; Jambaqué et al., 1993; Menlove & Reilly, 2015; Nolan et al., 2004). However, this hemispheric-dependent memory impairment type is not as clear as in the adult population (Golby et al., 2001; T. M. C. Lee et al., 2002).

Although limited studies evaluate and compare the performance between patients with FLE as opposed to TLE, difficulties in language functions (e.g., impaired comprehension, reading, vocabulary, verbal fluency) have been reported in both patient groups (Gallagher & Lassonde, 2005; Hermann et al., 2002; Hermann et al., 2007; Hernandez et al., 2002; Vanasse et al., 2005). In adults with focal epilepsies, a meta-analysis regrouped 39 scientific publications that investigated language capacities (Metternich et al., 2014). Most participants in the included studies received their diagnosis before 18 years of age, thus the results of the meta-analysis reveal to some extent the impact of childhood epilepsy on language.

In comparison to neurotypical controls, patients with TLE presented difficulties in both semantic and phonemic verbal fluency tasks, while those with FLE only had reduced word production in the phonemic condition. The direct comparison between patient groups revealed poorer phonemic verbal fluency in patients with FLE compared to those with TLE, while their semantic word production did not differ. The authors argue that the higher demands on executive processes during the phonemic verbal fluency task may explain the poorer performance in patients with FLE. Even though similar results have been found independent of epilepsy lateralization, difficulties were more pronounced in patients with left hemispheric frontal or temporal seizure onset than those with right hemispheric onset in homologous brain regions. In pediatric patients, language has also been identified as a vulnerability, though results are less consistent (Braakman et al., 2011; Braakman et al., 2012; Caplan et al., 2009; Hermann et al., 2006; Law et al., 2018; Orduña et al., 2021; Verche et al., 2018). In children with FLE exclusively, language is typically impaired, but this seems to be part of a broad reduction of the neuropsychological functioning rather than a domain specific effect (Braakman et al., 2011; Braakman et al., 2012). In contrast, a study on pediatric patients with drug-resistant FLE or TLE, language was not identified as a specific domain of concern (Orduña et al., 2021). Differences between studies are probably partially due to the heterogeneous methods used to assess language functions and the previously emphasized confounding measures of attentional and executive functions. Law and colleagues (2018) recently compared the performance of an extensive neuropsychological assessment in executive functions, verbal semantics, motor, nonverbal cognition and impulsivity, and verbal cognition and attention between children with FLE and TLE, and their healthy peers. Children with FLE had reduced performance in all domains with the exception of motor functions, while those with TLE only had deviant performances in executive functions and verbal capacities, in comparison to the neurotypical control group. The comparison between both patient groups further revealed poorer executive functions and verbal capacities in children with FLE than in those with TLE. Language may thus not be the only domain of concern in children with FLE or TLE, but it is a common difficulty in both types of epilepsies, as expected given the neurobiology of language. The neuropsychological evaluation is a key instrument to assess cognitive, behavioral and socioaffective functions including language capacities, allows to draw conclusions about a patient's individual profile of strengths and weaknesses, and hypothesis about the underlying neuropathology (Berl et al., 2017; Jones-Gotman et al., 2010; Smith, 2010; Wilson et al., 2015). Therefore, the first article of this thesis aimed to introduce the pediatric neuropsychological assessment, with a detailed description of the methodological procedures, present its relevance for the diagnostic process of neurodevelopmental disorders such as pediatric FLE or TLE, specify how it can guide the therapeutic approach and elaborate its prognostic value.

Structural and functional brain alterations in children with F/TLE

The focal onset of FLE and TLE imply that pathologic processes emerge from a specific cerebral region. However, cerebral alterations associated with FLE and TLE go beyond frontal or temporal areas (Gao et al., 2012; Meng et al., 2010). Widespread structural abnormalities such as cortical thinning in both hemispheres (Widjaja et al., 2011) and alterations in fiber pathways outside the frontal lobe (Lawson et al., 2002; Widjaja et al., 2014) have been found in children with FLE irrespective of the lateralization of the epileptogenic zone. In children with TLE, some structural variations are more localized and lateralized, such as the disruption of gray matter in ipsilateral hippocampal and parahippocampal areas (Guimarães et al., 2007), while alterations in white matter have also been reported in both hemispheres, though ipsilateral fibers seem slightly more affected (Gao et al., 2012; Meng et al., 2010). These deviations also seem to affect overall network architecture as well as regional organization of structural networks as it has been shown in adult patients with TLE (Larivière et al., 2022; Slinger et al., 2022; van Diessen et al., 2014). How these structural abnormalities potentially affect functional brain networks of language processing is elaborated in the following sections.

Patients with cerebral lesions or neurologic disorders localized in the left hemisphere often present an atypical hemispheric dominance for language processing (e.g., Berl et al., 2014; Gallagher et al., 2013; Gallagher et al., 2007; Hamberger & Cole, 2011; Mbwana et al., 2008; Vannasing et al., 2016). In fact, several studies of our lab that applied fNIRS show that language processing in children with left lateralized FLE or TLE yields in a cerebral reorganization, i.e., a more bilateral cerebral activation or a shift towards homologous frontotemporal regions of the right hemisphere (Gallagher, Bastien, et al., 2008; Gallagher et al., 2007; Vannasing et al., 2016). In a case of a nine-year-old child with left hemispheric F-TLE, expressive language has elicited an altered cerebral response within posterior temporoparietal areas of the left hemisphere, suggesting an intra-hemispheric reorganization (Gallagher, Bastien, et al., 2008). Similarly, in adult patients with FLE or TLE, semantic verbal fluency has yielded in a more bilateral activation of homologous temporal areas as compared to a more left dominant activation in healthy controls (Tung et al., 2021). Phonemic verbal fluency has however remained dominant within frontotemporal regions of the left hemisphere underlining that alterations in cerebral language processing may be different for specific linguistic processes.

In recent years, neuroimaging techniques and new FC data analyses enabled a paradigm shift from hemispheric dominance and localization towards more complex investigations of cerebral networks. Distinct patterns of FC in cerebral language networks have been observed both in pediatric (Chou et al., 2018; Foley et al., 2020; Sepeta et al., 2015; Vannest et al., 2019) and adult patients with epilepsy (Balter et al., 2019; Caciagli et al., 2023; Trimmel et al.,

2018). In particular, children with left lateralized focal epilepsy show reduced FC between homologous frontal, i.e., IFG and middle frontal gyri (MFG), and posterior temporal, i.e., pSTG, as well as lower bilateral intra-hemispheric coupling between IFG and MFG during a semantic decision task (Sepeta et al., 2015). Children with TLE specifically, show decreased FC within the left IFG compared to neurotypical children while listening to a passive story listening task (Vannest et al., 2019). Such reduced FC indicates that certain components of the cerebral language network in children with FLE and TLE are less synchronized compared to neurotypical children. Although studies on network alterations in children with FLE or TLE are still scarce, many adult patients have had a disease onset during childhood and adolescence, and thus adult findings provide some guidance and allow to uncover long-term effects of childhood epilepsy. A recent fMRI study specifically evaluated disruptions of cerebral language processing in a large sample of adults ($n = 172$) with FLE or TLE (Caciagli et al., 2023). A majority of this sample had epilepsy onset during childhood or adolescence. Compared to healthy controls, patients with FLE show reduced activation of frontal (left MFG to IFG) and large parts of the middle temporal lobe during a phonemic verbal fluency task, while those with TLE only have reduced activation in the left IFG. In contrast to healthy controls, both patient groups demonstrate less deactivation of cortical regions associated with the default-mode network, though in those with FLE, this appears in bilateral anterior (prefrontal cortex) and posterior (temporal and angular gyrus) areas, while in those with TLE it mainly affects the precuneus. Similarly, cerebral activation during a verb generation task, reveals reduced activation of inferior frontal areas in the left hemisphere and less deactivation of the right angular gyrus in patients with FLE compared to healthy controls, while those with TLE exhibit a whole-brain reduction of hemodynamic response. Consequently, comparisons between both patient groups reveals a widespread increase of activation in left, and to some extent bilateral posterior areas, and less deactivation within the right angular gyrus and bilateral precuneus in patients with FLE compared to those with TLE. These findings illustrate how both task-dependent language networks and large-scale brain networks are affected by FLE and TLE, and that even though overall both groups have similar alterations, there are also some subgroup specificities.

Graph theory has become a popular approach to better characterize the specific brain network topology in patients with epilepsy (e.g., Bernhardt et al., 2015; Farahani et al., 2019; Rodríguez-Cruces et al., 2020; Slinger et al., 2022; Tavakol et al., 2019; Tung et al., 2021). The graphical representation of a network is commonly based on the FC matrix, where each measurement of cerebral activation (e.g., voxel in fMRI, channels in fNIRS) represents a node and the coupling between two nodes represents an edge (Rubinov & Sporns, 2010). The graphical illustration of a network's nodes and edges forms the basis for numerous metrics to interpret the networks local and global processing efficiency. There are three

main characteristics describing the network: i) the degree centrality, which is the number of connections each node has where a higher value implies a node is highly connected; ii) segregation, which refers to the tendency of a network to build local clusters, hence the level of cerebral activation in proximal nodes synchronizes, which is an indicator of local efficiency in a network; and iii) integration, which describes how well distinct parts of the network are connected, thus how efficient information is transferred between distant cerebral regions, which is an indicator of global efficiency in a network (Fornito et al., 2016; Latora & Marchiori, 2003; Latora & Marchiori, 2001; Sporns, 2018; Watts & Strogatz, 1998). The small-world index further specifies the ratio between a network's segregation and integration, thus the balance between efficient local and global information processing (Watts & Strogatz, 1998). A small-world topology has been shown to be a key network feature in healthy individuals (e.g., Asis-Cruz et al., 2015; Fornito et al., 2016; Fransson et al., 2011). Graph analysis represents a data-driven network approach, and the network metrics are based on the entire data set. This results in fewer statistical comparisons than in traditional analysis of individual nodes, and therefore reduces the risk of false positive results. A meta-analysis recently evaluated the results of 45 studies using graph theory to assess cerebral network topology in pediatric and adult patients with different focal epilepsies (Slinger et al., 2022). Their analyses revealed that compared to healthy controls, the overall epilepsy group as well as the subgroup of those with TLE, had lower network segregation. This is in contrast to findings of an earlier meta-analysis by the same group, where functional brain networks showed higher local segregation, but reduced global integration (van Diessen et al., 2014). Similarly, structural network topology in patients with TLE compared to that of healthy adults, suggests higher network segregation and reduced network integration (Larivière et al., 2022; van Diessen et al., 2014). The heterogeneity of the individual results probably precluded the identification of other robust network alterations. Nevertheless, these results suggest that one of the main brain network topology patterns in patients with focal epilepsy is local information processing.

Associations between cognitive and cerebral alterations in children with F/TLE

The previous sections revealed cognitive and cerebral alterations in children with FLE or TLE. The following question remains: how is the neuropsychological profile associated with the neural network characteristics of individuals with FLE or TLE? In healthy children, the precise links between the developmental trajectories of language functions and cerebral language processing is yet to be fully understood. There is some evidence for a positive association between visual, motor and language abilities and FC in the visual, dorsal attention and frontoparietal brain networks in healthy children (Bruchhage et al., 2020). This suggests

a global effect of increasing functional abilities and reinforcement of different brain networks, rather than a specific functional association between for instance language abilities and language brain networks. The developmental trajectory of network topology in healthy individuals does show that global integration increases, while local segregation decreases during childhood and adolescence (Gozdas et al., 2019; Supekar et al., 2009). Therefore, while cognitive processes become more complex and interrelated with age, cerebral networks similarly become more sophisticated and globally integrated. In children and adolescents with focal epilepsy, resting-state graph network analyses reveal a mixed relationship between global intellectual functioning and alterations in network architecture (Songjiang et al., 2021). Precisely, higher full-scale, verbal and performance IQ were associated with both higher network integration, degree centrality and network segregation of resting-state brain networks, suggesting an atypical development of network topology that may enable better cognitive outcome in these patients. In pediatric patients with FLE or TLE specifically, reduced neuropsychological functions reportedly went along with lower FC across different resting-state networks (Widjaja et al., 2013). This extends to language abilities in particular, where naming was associated with lower FC among bilateral frontotemporal language areas (Sepeta et al., 2015). In adult patients with FLE or TLE, a well-integrated and sufficiently active cerebral language network with an adequate deactivation of the default-mode network are indicators for better language performance (Caciagli et al., 2023). The relationship between brain activity and cognitive performance thus seems to go beyond language networks. It remains however speculative whether alterations of brain network structure in children with FLE or TLE reflect an aberrant development or a compensatory effect, especially since cerebral organization in these patients seems dynamic and the association between cerebral organization and the neuropsychological profile may change over time (Helmstaedter et al., 2006; Vannasing et al., 2016).

1.3. Functional neuroimaging

Numerous neuroimaging techniques have been used to study cerebral language networks in pediatric patients with epilepsy (e.g., Balter et al., 2019; Gallagher et al., 2012; Pirmoradi et al., 2016). fNIRS is a very well adapted technique for pediatric populations, in whom collaboration is often limited, is non-invasive, does not require a complete immobilization as it is relatively tolerant to movements and thus allows a more natural setting and constant contact between the child, the assessor and caregiver (Gervain et al., 2011; Lloyd-Fox et al., 2010). fNIRS uses light in the near-infrared spectrum between 650 and 1000 nm to measure cerebral hemodynamic changes (Delpy & Cope, 1997; Ferrari & Quaresima, 2012; Jobsis, 1977). Each wavelength has individual absorption properties specific to oxy- and deoxyhemoglobin (HbO, HbR). Therefore, depending on the photon variation measured with each wavelength (Δ of

emitted to detected light), it is possible to determine relative changes of HbO and HbR to estimate the hemodynamic response in different cerebral regions (Ferrari & Quaresima, 2012; Huppert et al., 2009). Another advantage of fNIRS is that it can be easily combined with other brain recording techniques, such as EEG, which in the case of patients with epilepsy is essential to monitor interictal epileptic discharges and screen for potential subclinical or rather discreet epileptic seizures (Obrig, 2014). The value of fNIRS for localizing cerebral language networks in children with epilepsy is well established (Gallagher, Bastien, et al., 2008; Gallagher, Lassonde, et al., 2008; Gallagher et al., 2007) and fNIRS is now often part of the presurgical clinical assessment of children with refractory epilepsy. Figure 2 summarizes the principles of fNIRS and the origin of its signal (A), and the derived interpretation of cerebellar activity (B).

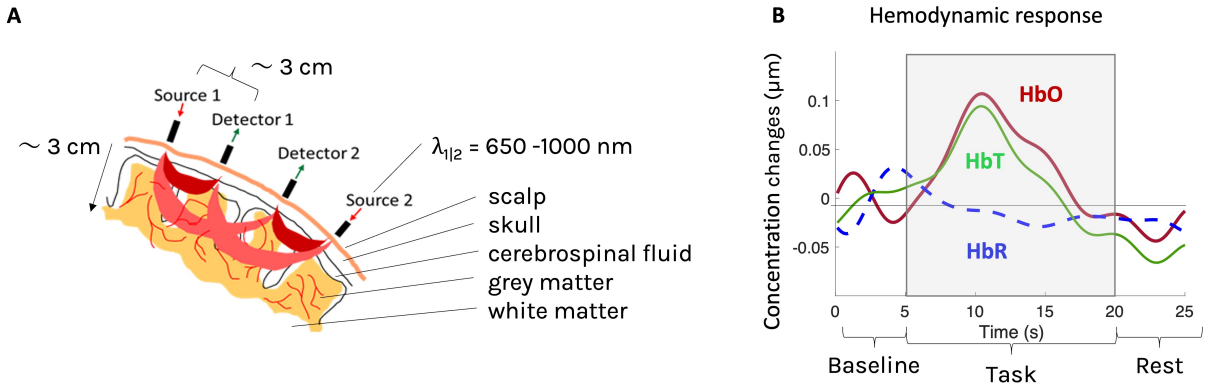

Figure 2 – Functional neuroimaging with near-infrared spectroscopy and composition of the cerebral signal adapted with permission (« Our story: fNIRS and NIRx », 2023)

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Even though, fNIRS is relatively tolerant to motion compared to other neuroimaging techniques, motion can cause abrupt changes in the fNIRS signal (Yücel et al., 2014), and is an important source of noise. Several artifact correction methods have been proposed in the literature, but to date, none fully take advantage of the complexity of the fNIRS signal. The dynamic between the signal of the two wavelengths is one valuable source of information to detect and correct such movement artifacts (Cui et al., 2010). Currently, two-dimensional techniques for artifact correction do not allow to exploit this advantage (Brigadoi et al., 2014; Cooper et al., 2012; Tak & Ye, 2014). A multidimensional decomposition approach called parallel factor analysis (PARAFAC) represents an interesting alternative for motion artifact detection since it allows to simultaneously consider the time course, space (channels) and wavelength ($\lambda 1|2$) signatures to extract the characteristics of the motion artifact (Bro, 1998; Harshman, 1970). PARAFAC has shown promising results for multidimensional (>2 dimensions) EEG and joint fMRI-EEG neuroimaging data analysis (Acar et al., 2007;

Martínez-Montes et al., 2004; Miwakeichi et al., 2004), yet has not been used for analysis of the fNIRS signal. Therefore, we conducted a methodological study to validate PARAFAC for fNIRS data analysis (article two). Based on the promising results of article two for the use of PARAFAC to detect motion artifacts in the fNIRS signal, PARAFAC has also been used in article three.

Chapter 2

Research objectives and hypotheses

Although basic and key aspects of language abilities and cerebral language processing develop during infancy, their maturation continues throughout childhood and adolescence. Neuropathologies, such as pediatric FLE and TLE, can disrupt language and cognitive brain processes as well as impair language and cognitive abilities. However, the patterns of reorganization of cerebral language networks in the context of pediatric FLE and TLE are not yet well understood, and the association with language and cognitive abilities remains unclear. The ultimate objectives of this thesis were thus to characterize cerebral language network patterns in children and adolescents with FLE or TLE using fNIRS, and to better understand the associations between cognitive and language abilities, and brain networks. This thesis includes one handbook chapter and two scientific articles. The first two manuscripts were necessary steps to establish the optimal methodology of the third article, which is the main article of this doctoral work. The objectives of each manuscript are briefly presented here:

Article 1: The **first article** is a methodological manuscript that underlines the relevance of the neuropsychologic assessment for the estimation of the functional impact of neurodevelopmental disorders such as pediatric FLE and TLE, and to better understand the brain-behavior relationship. This manuscript consists of a book chapter on the specific goals, background, methods and clinical values of a pediatric neuropsychologic evaluation and has been published in the *Handbook for Clinical Neurology*, Volume *Neurocognitive Development: Disorders and Disabilities* (Hüsser et al., 2020). The handbook provides extensive guidelines to clinicians and researchers alike regarding typical and atypical neurodevelopment and the commonly used methods to assess deviations.

Article 2: fNIRS is the neuroimaging technique of choice to address cerebral processing of language in pediatric patients with FLE or TLE. Despite its relatively high tolerance to movement, motion induced signal variations can reduce signal quality. The **second article** aimed to validate a multidimensional decomposition approach, PARAFAC, to correct movement artifacts in fNIRS data under controlled conditions. We hypothesized that a multidimensional decomposition and subtraction of components related to the artifact's signature would lead to a significant increase in signal quality. Our results confirmed this hypothesis and PARAFAC has therefore been used for fNIRS data pre-processing analyses of article three. Article two has been published in *Neurophotonics* (Hüsser et al., 2022), the journal of the international society for fNIRS.

Article 3: The main objectives of the **third article** were to characterize cerebral language network patterns in children and adolescents with FLE or TLE using fNIRS, and to better understand the associations between cognitive and language abilities, and brain networks in these patients. Therefore, the hemodynamic response of 20 patients with FLE or TLE and 29 healthy controls was assessed using fNIRS during a resting-state paradigm and a receptive language task. We hypothesized that epilepsy patients would demonstrate altered FC within frontotemporal regions compared to the control group, and that this would reflect in less efficient network topology of cerebral language processing. We further assumed that higher cerebral abnormalities would be associated with more neuropsychological impairments in these patients and that the relationship between cerebral language networks and cognitive abilities in the patient group would differ from that observed in the healthy children group. Since the current literature on the developmental impact of pediatric FLE and TLE is non-conclusive, a data-driven approach with few a priori hypotheses was employed. This study allows to better understand the adaptive capacities of the developing brain, and the impacts of cerebral alterations on cognitive and language functioning. The third article has been published in the special issue *Bridging Cognitive Neuroscience and Neurosurgery for Effective Brain Mapping* in *Frontiers in Human Neuroscience* (Hüsser et al., 2023).

Two additional publications representing relevant work conducted during this doctoral thesis are presented in Appendices I and II. Appendix I includes the **fourth article**, which is a second-author systematic review on functional brain networks of language functions in children that introduces important research concepts about language brain networks development. Article four has been published in *Frontiers of Human Neuroscience* (Gaudet, Hüsser, Vannasing, & Gallagher, 2020). The **fifth article** (Appendix II) presents a fNIRS analysis toolbox developed in our lab that was used for data analysis of articles two and three. Article five has been published in the *Journal of Neuroscience Methods* (J. Tremblay, Martínez-Montes, Hüsser, Caron-Desrochers, Lepage, Pouliot, Vannasing, & Gallagher, 2022).

First Article.

Neuropsychologic Assessment

by

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A.H. set up the concept of the publication, conducted the literature search and wrote the manuscript. S.F. revised and complemented the concept and the bibliography, and she thoroughly revised the manuscript. A.G. was the supervisor and revised both the concept and the manuscript.

Abstract. The purpose of a pediatric neuropsychologic assessment is to evaluate cognitive, behavioral, sensory-motor, perceptual and socioaffective functioning. A standardized, validated set of tools, questionnaires, and qualitative methods is applied to this end. The neuropsychologist integrates the results of the formal assessment, the case history, and third-party observations to interpret the individual findings across disciplines and draw conclusions about brain–behavior relationships.

Various indications for neuropsychologic assessment include the identification of neurodevelopmental difficulties and the characterization of the impact of medical conditions or a pharmaceutical treatment. Prior to the evaluation, as much information as possible must be gathered about the child for efficient and accurate planning. In the context of pediatric neuropsychologic assessments, special challenges may arise, requiring more flexibility as regards the duration of the assessment, the use of different age-specific tools, or particular sensitivity when interacting with the child may arise.

Neuropsychologic assessment is a cornerstone in the process of diagnosing neurodevelopmental disabilities in children and is frequently one component of a multidisciplinary evaluation. From it can be derived recommendations for the different contexts of a child's life (e.g., family, care team, school).

Keywords: Pediatric population, neuropsychologic evaluation, psychometric tests, standardized cognitive assessment, brain–behavior relationship, cognitive functioning.

1. General Aspects of Pediatric Neuropsychologic Assessments

Neuropsychologic assessment is a cornerstone in the process of diagnosing neurodevelopmental disabilities in children and adolescents based on known or presumed brain–behavioral relationships. It includes the formal evaluation of a variety of cognitive, sensory-motor and perceptual functions as well as behavior and socioaffective functioning using a standardized, validated set of tools and questionnaires (Baron, 2010; Evans, 2003; Glasel & Mazeau, 2017b, 2017c; Goldstein & McNeil, 2004; Heffelfinger, 2014; Schoenberg & Scott, 2011). The standardized and observational results of the assessment provide a detailed picture of the child's intellectual capacities and an overall cognitive profile covering strengths, weaknesses, and sometimes deficits in domains such as attentional and executive functioning, learning and memory, language functions, visuospatial abilities, and overall characteristics of work behavior (e.g., motivation, endurance, performance anxiety) (Evans, 2003; Gorske & Smith, 2009; Reynolds & Fletcher-Janzen, 2009). To draw conclusions on potential dysfunctions, the neuropsychologist interprets the results by factoring in data from several sources: 1) the child's behavior during the evaluation; 2) the child's socioaffective well-being; 3) observations reported by caregivers and family members (parents, siblings and teachers); 4) the case history, including previous neuropsychologic or other neurodevelopmental assessments, like occupational or speech therapy, and other clinical examinations, like hearing and vision tests, imaging data or laboratory analyses (Baron, 2010; Schoenberg & Scott, 2011; Snyder et al.,

2006). For a clinical neuropsychologist, the challenge extends beyond simply describing cognitive functioning based on test scores: it involves interpreting all relevant findings from a range of health disciplines (Aylward, 2010; Schoenberg & Scott, 2011). Thus, broad knowledge of basic neuroscience, functional neuroanatomy, neurobiology, neuropathology, clinical psychology, and, in particular, neuro- and psychological development is vital to properly incorporating neuropsychologic findings into the diagnostic process. This leads to accurate assumptions on brain–behavior relationships. Only an integrative approach such as this allows for proper identification of the neurologic pathologies that may be responsible for the particular pattern and degree of functional impairments in cognition, behavior and emotions (Aylward, 2010; Baron, 2010; Heffelfinger, 2014; Koziol & Budding, 2010; Rae-Grant & Parsons, 2014; Reynolds & Fletcher-Janzen, 2009; Schoenberg & Scott, 2011; Vanderploeg, 2000). Finally, detecting and specifying cognitive impairment is the foundation for introducing appropriate intervention strategies.

1.1. Indications

Many indications may lead to a referral for a neuropsychologic evaluation (see Table 1 for an overview of these). These indications are significant in determining the scope of the assessment and establishing the principle hypothesis (Rae-Grant & Parsons, 2014).

Table 1 – Main indications for a pediatric neuropsychologic assessment.

• Cognitive and behavioral difficulties	• Brain surgery
• Impact of medical conditions	• Scientific documentation of normal neurodevelopment
• Effects of pharmaceutical treatment	• Liability and causal relationships of legal forensic context
• Guidance for interventions	

First, a neuropsychologic assessment is indicated whenever cognitive or behavioral difficulties are observed and neurodevelopmental alterations are suspected. Hence, such an assessment contributes substantially to the diagnosis of pathologies with varying etiologies. In this context, the neuropsychologist must consider different causes and clinical conditions that may be associated with the specific neuropsychologic profile (pattern of cognitive and behavioral strengths and impairments), including neurodevelopmental disorders, functional or structural cerebral pathologies, psychiatric disorders, metabolic malfunctioning, and pharmacologic treatment (Heilbronner et al., 2009; Lezak et al., 2012c; Snyder et al., 2006). In some cases, the clinical picture may require a differential diagnosis and the neuropsychologist must specifically address the differentiation between various disorders (e.g., between attention deficit hyperactivity disorder (ADHD) and a learning disorder, an autism spectrum disorder (ASD) and a language disability, ADHD and anxiety). In addition, numerous scientific publications (Baron, 2010; Giedd, 2004; Goldstein & McNeil, 2004; Paquette et al., 2015;

Skeide & Friederici, 2016) outline the ongoing neuronal maturation that occurs throughout childhood until late adolescence. These maturational processes may, on one hand, show significant alterations due to pathologic events and thus enhance impairments or, on the other hand, allow the child or adolescent to outgrow or compensate for impairments despite the pathologic influence. Thus, the neuropsychologic assessment can contribute to understanding the complex interactions between cognitive impairment, the underlying pathology, and the child's (neuro-) development and can be used to track developmental trajectories (Aylward, 2010; Baron, 2010; Goldstein & McNeil, 2004; Reynolds & Fletcher-Janzen, 2009).

Second, a neuropsychologic assessment may be requested to identify and document the impact of a clinical condition (e.g., traumatic brain injury, cerebral hemorrhages, brain tumor, cerebral malformation) on the child's cognitive abilities and behavior (Schoenberg & Scott, 2011; Snyder et al., 2006; Vanderploeg, 2000). This type of assessment will provide a comprehensive cognitive profile of the child that can guide the clinical team in his or her care. In some cases, the impact of a known clinical condition can only be estimated through follow-up evaluations as part of long-term neurodevelopmental monitoring (Aylward, 2010; Glasel & Mazeau, 2017b; Snyder et al., 2006).

A third indication is associated with specific pathologies that require pharmaceutical treatment. In these cases, the neuropsychologic assessment aims to demonstrate pharmaceutical effectiveness or document adverse side-effects on cognitive functioning. For example, in children with ADHD, it may be of interest to evaluate the potential improvement of attentional and executive functions related to the medication (Brown & Daly, 2009; Faraone & Buitelaar, 2010). Also, patients with epilepsy must be monitored for the potential side-effects of anti-epileptic drugs on processing speed, attention and memory functions (Bennett & Ho, 2009; Lagae, 2006; Yu et al., 2015).

Although the neuropsychologic assessment itself is not an intervention, its conclusions will lead to recommendations that may include intervention strategies and professional follow-up (Aylward, 2010; Baron, 2010; Lezak et al., 2012b; Schoenberg & Scott, 2011). The interventions will be personalized to each child based on his or her strengths and deficits. One core element of the intervention is to build on the individual's intact functions and strengths to reduce dysfunctions (Aylward, 2010; Baron, 2010; Lezak et al., 2012c; Schoenberg & Scott, 2011). Another important point is early diagnosis for the purpose of early intervention (Nadel & Poss, 2007). In several pediatric clinical populations (e.g., ASD, children born prematurely or with congenital heart disease), early intervention has been shown to improve neurodevelopmental outcomes, probably due to brain plasticity in children (Gallagher et al., 2017; Kern et al., 2013; Procianoy et al., 2009). Ultimately, follow-up evaluations are used to monitor the efficacy of intervention programs and make individual adjustments.

Neuropsychologic assessment may also be part of pre-surgical protocols. For example, children with refractory epilepsy (i.e., who have not experienced a significant reduction in

seizures despite several forms of treatment) may be candidates for surgical removal of the epileptic zone (Holmes et al., 2013; Téllez-Zenteno & Hernández-Ronquillo, 2012; Wiebe, 2000). In this situation, a neuropsychologic assessment will be useful in investigating language function lateralization and in identifying the location of the cerebral area to be removed or spared, resulting in a targeted evaluation. In these cases, the neuropsychologist should understand the general scope of the surgical procedure. Furthermore, the pre- and post-surgical assessments can be compared to estimate the impact of the surgery on the child's cognitive functioning (Berl et al., 2017).

In a scientific context, a neuropsychologic assessment has various applications. It can be used to: 1) detect potential neuropsychologic markers for the development or course of a disease, and thus to identify at-risk populations; 2) determine the effectiveness of interventions or treatments; 3) document the child's development; 4) establish a referent group of healthy children to develop normalized data for adequate interpretation of clinical data and detect altered functions in clinical populations; or 5) study the behavioral aspects that influence the child's performance during neuropsychologic evaluation, such as task engagement (Lezak et al., 2012b; Schoenberg & Scott, 2011).

Finally, there may also be forensic/legal indications for a neuropsychologic assessment. Here, the formal assessment of cognitive functioning and behavior is considered an expert report for estimating cause-and-effect relationships (e.g., cognitive impairments or behavioral alterations related to injuries) or the potential alteration of liability due to dysfunctions known to affect behavior, emotion and cognition, and thus decision-making capacity (e.g., intellectual disabilities that alter comprehension of social interactions and other people's needs or the expression of the child's own needs; psychological conditions associated with an altered perception of reality; brain injuries with significant impact on a behavior and personality) (Lezak et al., 2012b; Schoenberg & Scott, 2011).

1.2. Minimum information required to efficiently plan an assessment

While the attending physician or another professional is often the referring party, the evaluation may also be requested by the child's parents based on their observations or at the school's recommendation, in which case there is no referral letter. Whoever requires the assessment, the following information should be obtained before an evaluation to efficiently plan and conduct the assessment (Table 2 for an overview of guidelines; Annett & Dencoff, 2010; Snyder et al., 2006). In addition to the specific indications, complaints and questions, the neuropsychologist would benefit from knowing about previously diagnosed clinical conditions, suspected developmental alterations or behavioral/cognitive regression (e.g., learning disorders, ADHD, ASD, language disabilities, epilepsy syndromes) or physical handicaps (e.g., blindness or hearing loss; any conditions requiring a bedside assessment). In fact, these conditions

may influence the child's performance or explain a discrepancy between chronologic and developmental age that may require a modified protocol and thus the use of alternative tools, such as non-verbal intelligence tests (Glasel & Mazeau, 2017a, 2017c; Heffelfinger, 2014; Nadel & Poss, 2007; Yeates et al., 2010). Any information that may guide the hypotheses and interpretation is useful. For example, if a differential diagnosis is necessary and the range of potential pathologies is already restricted, these pathologies should be named in order to address specific hypotheses (Noël, 2007; Rae-Grant & Parsons, 2014).

As children and adolescences grow continuously and quickly, within a short age range they show significant differences in their cognitive performance levels. Consequently, there is a need for adapted tools that are sensitive to minor developmental changes as well as for specific norms (Baron, 2010; Giedd, 2004; Goldstein & McNeil, 2004; Paquette et al., 2015; Skeide & Friederici, 2016). Knowing the child's chronologic age prior to the assessment is crucial to properly planning the first appointment. Doing so means the neuropsychologist is able to choose tests designed for the child's age group, including appropriate types of stimuli (i.e., non-verbal stimuli or more playful activities for younger children) and the availability of age-specific norms. Finally, the attention span differs significantly within age groups, younger children having shorter attention span. It is thus necessary to adjust the duration of the assessment and the number of separate meetings based on the age of the child to allow measuring a valid performance. Knowledge of any previous evaluations conducted in other settings, such as private or public health care facilities or at school, greatly supports the neuropsychologist in planning the evaluation. For instance, if the last assessment was carried out shortly before the current one, some parts of it may not need to be repeated (e.g., a thorough intellectual assessment may not be necessary), while certain tests may have to be replaced to prevent repetition effects (Matson et al., 2009). If the child performed specific tasks a few weeks or months ago, his or her performance would not be valid if the same tests were repeated, because the enhanced performance may be attributable to a repetition (or learning) effect rather than to actual improvement in the functions. Further, for a follow-up evaluation, the interpretation mainly focuses on comparing the current and previous assessments to address individual progress or regression. In such cases, the neuropsychologist benefits from insight into previous report(s).

Pharmaceutical treatment can affect a child's performance during the neuropsychologic assessment. Without knowledge of the child's pharmaceutical record and current medication, the neuropsychologist may falsely attribute underperformance to pathologic processes or overestimate certain functions that are improved due to medication. That is why it is essential to know the list of medications a child is currently taking. In some cases, the effectiveness of a medication may also be of particular interest or constitute the main indication for the assessment. The neuropsychologist may thus consider comparing the child's performance

with and without medication (e.g., in children with ADHD) (Rae-Grant & Parsons, 2014; Reynolds & Fletcher-Janzen, 2009; Snyder et al., 2006).

Table 2 – Information that contributes to appropriate planning of the neuropsychologic assessment.

• Indications, complaints, and questions	• Previous neuropsychologic evaluation(s)
• Child's chronologic age	• Pharmacologic treatment
• Clinical pathology/pathologies and developmental alteration(s)	

2. Specific Stages and Considerations of the Pediatric Neuropsychologic Assessment

The following section will give readers a better understanding of the various information sources available for a neuropsychologic assessment. These include the child's case history, the evaluation of cognitive and behavioral functions, and a screening of the socio-affective well-being. The overall duration of the formal assessment ranges from 2 to 6 hours, but can last as long as 8 hours. The duration depends on variables like the child's age, his or her medical condition and developmental status, case complexity, the indications, the depth of evaluation required, and the patient's cooperation and motivation.

2.1. Case history

Neuropsychologists begin gathering information for their interpretation as soon as a patient is referred for or books a neuropsychologic assessment. The indication for the assessment helps the neuropsychologist draft specific questions that will be addressed during the process (Noël, 2007). Several sources of information must then be consulted to reconstruct the case history, allowing for different perspectives on the child's cognitive, behavioral and socioaffective condition, both previous and current (Table 3).

To begin, the patient's medical record (e.g., public health service) or earlier clinical reports include the findings of previous clinical examinations conducted by other professionals (e.g., neuropsychologists, psychologists, neurologists, speech or occupational therapists) and the record summary can guide the hypothesis for the assessment.

The evaluation itself starts with the anamnesis, or initial interview, which is guided by the referral question leading to the neuropsychologic assessment (Heffelfinger, 2014; Noël, 2007; Snyder et al., 2006). The purpose of the anamnesis is to understand and gather information on the child's general development and the milestones met. It specifically addresses past and current cognitive or behavioral difficulties in the varied contexts of daily life (e.g., at home,

Table 3 – Sources of information for the case history.

• Medical record, including previous evaluations
• Attending physician and other allied health professionals
• Patient
• Parent/primary caregiver
• Teachers
• Siblings or extended family
• Developmental questionnaires

school or daycare, with peers) (Heffelfinger, 2014; Matson et al., 2009). When conducted with the pediatric population, this process differs significantly from that conducted with adults. In fact, the child may be unable to recover precise time-related personal information and may have trouble describing symptoms. Parents and caregivers must therefore be involved. Nevertheless, the child's own point of view on present difficulties, examples of daily challenges, and the level of suffering should be given a great deal of consideration, whenever possible. As children age and mature and as their introspective abilities and verbal skills grow, their personal perspective carries greater and greater weight (Bauer et al., 2010; Bergen & Woodin, 2010; Bronk, 2010).

Parents or primary caregivers usually provide a great deal of information, giving the neuropsychologist a broad picture of the child's behavior in ordinary, day-to-day contexts (Heffelfinger, 2014; Noël, 2007). These observations are the main source of information and should be incorporated into the anamnesis for deeper insight into the child's early development and the family's medical history. Furthermore, the caregiver's perspective reveals how the child's dysfunctions affect family dynamics. It is sometimes a good idea to conduct a separate meeting or phone interview with the caregivers/parents before or after the neuropsychologic evaluation in order to discuss sensitive information that may affect the child or that may take up too much time during the initial assessment session.

Developmental questionnaires filled out by the primary and external caregivers (e.g., teachers) are another source of information. These provide a standardized approach to address factual, specific information about the child's developmental milestones and behavioral traits with peers and adults, as well as a summary of additional medical records (Matson et al., 2009). Whenever possible, such questionnaires should be completed before the date of the assessment to free up significantly more time for the anamnesis and to adapt the protocol to the child's specific needs.

Apart from the primary caregivers, it can also be useful to consider other sources of information, such as siblings and members of the extended family who are in regular contact

with the child. If the child already attends daycare or school, the teacher will add another valuable perspective. This is also an opportunity to identify behavioral incongruences between home and school. Only a profound knowledge of the child's environment will result in realistic, effective recommendations for intervention strategies that will support his or her development and further involve members of his or her social environment.

Now that the neuropsychologist has consulted multiple sources of information to elucidate the grounds for the referral or appointment, the case history, and a range of perspectives on the child's difficulties, he or she is ready to formally evaluate the patient's cognitive and behavioral functioning.

2.2. Cognitive assessment

The assessment of cognitive and behavioral functioning will start with the child alone while the family is usually asked to wait outside. Meanwhile, they can complete questionnaires given by the neuropsychologist. The use of quantitative and qualitative tools make up the core of the evaluation process.

2.2.1. *Quantitative assessment*

Quantitative tools are among the fundamental elements that neuropsychologists use to estimate a child's functioning in various domains (Table 4). However, quantitative assessment of cognitive and behavioral function is far from a purely dichotomic categorization: functions are not just labelled "normal" or "abnormal," but are estimated on a continuous scale from impaired to gifted. Further, the neuropsychologic assessment is a patient-centered and hypothesis-oriented approach, not just the administration of a single battery of tests that overlooks certain cognitive functions. Each standardized psychometric test or group of tests should be carefully chosen to answer a specific question, based on the nature, the intensity, the mechanisms and the potential causes of the child's difficulties (Glasel & Mazeau, 2017a). Even when the assessment is properly planned, the list of selected tools is often modified during the evaluation by adding or removing tests based on the child's performance and behavior during the clinical interview or the assessment. Thus, the neuropsychologist must be highly flexible and remain ready to change the plan at any time.

Table 4 – Cognitive and motor functions commonly evaluated in a neuropsychologic assessment.

General intellectual functioning	Global capacity to act purposefully, think rationally and deal effectively with the environment (Wechsler, 1944, p. 3)
Attention	Immediate, selective, sustained, or divided: allocation of resources and efforts towards an object or a task (Naglieri & Otero, 2010, p. 320)
Executive functions	Inhibition, flexibility, planning, working memory, etc.: Capacity to respond in an adaptive manner to novel situations and coordinate cognitive, emotional and social skills (Lezak et al., 2012c, p. 666)
Memory and learning	Verbal and nonverbal, short- and long-term: capacity to retain information and utilize it for adaptive purposes (Fuster, 1995; Lezak et al., 2012a)
Academic learning	Reading, writing, mathematics
Visual and visuospatial capacities	Ability to visually perceive the size and color of objects as well as their spatial orientation and relation (« Les fonctions cognitives », 2018)
Motor functions	Fine and gross motor coordination, handwriting skills, handedness as an index for hemispheric dominance of language functions
Visuomotor skills	Coordination of visual perception and motor functions, including eye-hand coordination
Social cognition	Perception and processing of social interactions and own behavior during it, and about the social norms and procedures (Beer & Ochsner, 2006)

The main advantages of using standardized, valid and reliable tools are: 1) cognitive functions are conceptualized based on widely used theoretical concepts, which facilitates communication among clinical professionals and allows comparability; 2) standardization of the administration procedure (e.g., detailed verbatim instructions and non-verbal procedures for exact introduction and administration, if necessary; guidelines on how many times a task should be explained, how one should react to the child's questions, or how much the neuropsychologist can push the child in order to receive an answer) allows inter-individual comparisons; 3) each test or subtest has been designed to assess specific functions or abilities, which leads to precise interpretation of the results; and, finally, 4) the results are scored in a systematic process that maps individual results based on standardized scores.

Until recently, pediatric psychometric tests were based on theoretical concepts developed

for adults. It has only been a few decades since standardized tests for the pediatric population, deduced from specific scientific findings in children, began to be developed in a significant manner. Today, child neuropsychologists have access to several batteries of tests that have been standardized on substantial normative pediatric samples (Snyder et al., 2006). Hence, standardized assessment tools establish acceptable statistical limits of inter-individual variability and can be used to categorize a child's individual performance in relation to an age-specific normative sample (impaired, below average, average, above average, exceptional) (Glasel & Mazeau, 2017a). For certain neuropsychologic test batteries, language- or culture-specific norms supplement age-specific references for even more accurate measurement of the child's functioning.

Despite important advances in standardized age-specific neuropsychologic assessments as well as major advances in the documentation of developmental patterns in the pediatric population, it remains a challenge to differentiate between developmental delay and permanent impairment (delay *vs.* disorder, e.g., Baron, 2010; Giedd, 2004; Goldstein & McNeil, 2004; Paquette et al., 2015; Skeide & Friederici, 2016). This is also due to the individual variability of functional development among children, the different developmental courses within cognitive domains, and the maturation rates of different brain areas. In some cases, only repeated neuropsychologic assessments provide adequate interpretations of an individual developmental trajectory.

Further, there also remain certain statistical challenges regarding the availability of well standardized assessment tools. First, some tools are based on very small samples, therefore limiting generalization in terms of statistical means. Second, the sample may be drawn from individuals who do not accurately represent the patient's population, introducing potential distortion for the distribution. These limits may prevent the neuropsychologist from assessing the effect of demographic and socioeconomic factors on cognitive performances. Some standardized tests are based on samples of children diagnosed with various neuropsychologic conditions, allowing for classification of a child's performance within the normative sample of a specific pathologic population, which can be highly relevant for some children. However, these clinical normative samples are still scant and their number should increase considerably in the future.

2.2.2. *Qualitative assessment*

In the neuropsychologic assessment process the qualitative assessment is as important as the quantitative assessment. In addition, when a child cannot complete the quantitative assessment due to age or to developmental, medical or motivational restrictions, qualitative observations are of particular value. This part of the evaluation will be discussed in the next section.

While the quantitative assessment is a standardized process, the qualitative assessment is

based mainly on the neuropsychologist's observation and requires a high degree of expertise. The child's behavior must be observed from the first direct contact with the child and the family (Snyder et al., 2006). Throughout the clinical interview, the neuropsychologist must be alert to the child's verbal, motor (e.g., pencil grasp) and attentional abilities (e.g., whether the child understands questions and responds appropriately), the family dynamics, the child's temperament and behavioral particularities (e.g., anxious, approachable, calm, nail biting) and interaction with the neuropsychologist (e.g., eye contact, extroverted or reserved) (Noël, 2007). Throughout the sessions, the neuropsychologist must continuously observe how the child approaches tasks and understands instructions, whether the child is confident in his or her performance or how fast he or she finishes tasks (working speed). With respect to age and developmental stage, it is also of particular importance to pay attention to the child's expressive and receptive language, including vocabulary, syntax, morphology, comprehension, grammar, pragmatics, articulation, pronunciation, speed of speech or fluidity of speech, and lexical access. Regarding attentional skills, the focus should be on distractibility, the capacity to sustain attention, the tolerance to mental effort, hyperactivity, and the capacity to sit still for a long period. Further, the observations include fine motor functions such as comprehension, pencil grasp maturity, motor control while writing and the handling of toys and testing material (e.g., blocks), as well as gross motor skills such as coordination, walking, running and general body language. The qualitative assessment of cognitive and behavioral function illustrates that the neuropsychologic assessment is far from a purely psychometric assessment. In particular, when quantitative assessment produces surprising or inconsistent results, the qualitative assessment contributes to a better understanding (e.g., fatigue indexes during a task administered right before the break or anxiety indexes during a challenging task).

2.2.3. *Behavioral and socioaffective functioning*

The impact of socioaffective well-being on cognitive functions has been widely investigated. As such, the child's psychological state at the time of the evaluation must be considered in order to properly interpret the aetiology of the identified phenotype, i.e., the pattern of cognitive strengths and impairments (Glasel & Mazeau, 2017a). For example, it is widely known that anxiety or depression symptoms are frequently associated with distractibility, concentration problems, or memory problems (Gualtieri & Morgan, 2008; Rock et al., 2018). On the other hand, socioaffective dysfunction may also be a consequence of cognitive impairment or developmental delay (Tavano et al., 2007). In fact, cognitive impairment can result in reduced academic performance, altered social relationships and limited social participation, or a disruptive family dynamic, which in turn may lead to anxiety symptoms, feelings of helplessness, low self-esteem, and depressive mood. The neuropsychologic assessment should therefore screen for specific behavioral and socioaffective difficulties that would require further

psychological consultation. However, the neuropsychologic assessment does not include a complete psychological evaluation, i.e., a detailed exploration of the child's emotional and relational experiences, unresolved unconscious conflicts, or personality development. Usually, a variety of questionnaires is used to screen for socioemotional characteristics like aggressive behavior, disobedience, anxiety, and depression symptoms. It is important to emphasize that screening does not always allow for a final psychological diagnosis nor does it replace a comprehensive psychological evaluation. However, it does help identify whether the child's performance may have been hampered by a psychological condition, and the interpretation of the assessment should take this information into account. If socioaffective deviations are observed, the child should be referred to a clinical psychologist.

2.3. Interpretation

Once the formal neuropsychologic assessment is completed, the neuropsychologist must organize and summarize all results in order to interpret the findings (Table 4). By integrating quantitative findings (the performance in the psychometric assessment of cognitive and behavioral functioning) with qualitative findings (observations of the behavior during the direct contact with the child), the neuropsychologist is able to determine whether the child's performance for a specific subfunction is within, above, or below the norm—respectively representing the norm, a strength or a weakness. The combination of results for each cognitive function (e.g., flexibility, inhibition, organization skills) leads to an integrated estimation of the cognitive level within a class of functions (e.g., executive functions). The overall picture of the results gives a global profile of the child's cognitive capacities and allows for identification of individual strengths and weaknesses and, in some cases, deficits. The established performance profile should be interpreted in the context of the normative sample, as well as in consideration of intra-individual variability. Different tests assessing the same function may result in contradictory findings. The neuropsychologist must then identify potential explanations for these discrepancies: assessment using different modalities (e.g., verbal versus non-verbal memory functions); timing of administration within the assessment session, which can affect the child's level of fatigue or anxiety (e.g., at the beginning or end of the session or before or right after a break); or other explanations (e.g., motivational or attentional fluctuations).

Overall, the interpretation process requires the neuropsychologist to consider the patient's entire history, including: 1) the case history, i.e., medical records, developmental reports and questionnaires, third-party observations; 2) the profile of the child's performance revealed by the quantitative and qualitative assessment; and 3) his or her socioaffective well-being. The final step is the integration of the individual findings across disciplines, i.e.,

neuroscience, functional neuroanatomy, neurobiology, neurology, neuropathology, clinical psychology, and, in particular, neuro- and psychological development. This leads to conclusions about brain–behavior relationships that enable the neuropsychologist to identify possible underlying neurologic processes and potential pathologic conditions. The conclusion should reflect the initial indication and specific questions. This emphasizes yet again the importance of specifying the indications, complaints and questions from the outset in order to maximize the efficiency of the neuropsychologic assessment.

The findings of the assessment will be summarized in a neuropsychologic report, allowing third parties to be informed of and to understand the conclusions (Rae-Grant & Parsons, 2014). This report is also intended for clinical professionals in other disciplines, the child's primary caregivers, and significant individuals in regular contact with the child (e.g., teachers). The report must be written in plain, objective language. Usually, it contains the following sections: a) the indications, complaints and questions; b) the case history; c) the findings of the qualitative assessment; d) the results of the formal evaluation; e) the conclusions regarding cognitive and behavioral functions, the assumptions, and the diagnosis of underlying pathologies; and f) personalized recommendations for interventions to address the difficulties identified.

3. Pediatric Neuropsychologic Assessment in Specific Situations

Although there are certain well known similarities between pediatric and adult neuropsychologic assessment, different approaches and techniques must be applied to each population (Baron, 2010; Reynolds & Fletcher-Janzen, 2009). A number of factors influence the interpretation of a pediatric assessment, and expertise on adult brain–behavior relationships does not apply to children in the same way. The following paragraphs explore the distinctive characteristics and challenges that are met when conducting assessments of children, and these will be illustrated with examples of pathologic conditions.

First, various behavioral dysfunctions can affect the child's cooperation and motivation. In this case, if the neuropsychologist wishes to properly assess the child's best performance, he or she will need to have strategies at hand to keep the child interested. Depending on the extent and severity of the behavioral dysfunctions, the neuropsychologic protocol requires substantial adjustments. For example, in children with an intellectual disability (ID), frequently alternating between the evaluation and play-breaks to reward them for their efforts is crucial. Thus, the duration of the formal assessment is limited and the assessment requires a rather narrow protocol with a focus on the most important functions.

Second, language abilities can be limited and the comprehension of instructions may be challenging. Standardized administration therefore requires adjusted instructions. Tools that

use simple, non-verbal instructions can be used to overcome this challenge. These are often used for children with ID to assess cognitive functioning despite limited verbal skills.

Third, a limited attention span can have significant effects on the neuropsychologic assessment, as it affects more aspects than just the tasks assessing attentional functions. It is often challenging for the neuropsychologist to keep the child's attention during the evaluation, thus flexibility to adjust the protocol (e.g., the need to break down a task into several blocks, taking numerous short breaks) or creative strategies (e.g., running around and other physical activity between tasks) may be crucial to obtain valid results. Among others, the cognitive profile of children with ADHD is characterized by attentional and executive difficulties (American Psychiatric Association [APA], 2013; WHO, 1992). In these cases, there is often a frequent need for breaks, as attention and concentration decline and fluctuate, or because impulsive and hyperactive behavior causes interruptions. This may result in quite divergent results for similar tasks and functions, which the neuropsychologist should not only attribute to cognitive underperformance but also interpret as due to attentional difficulties. Overall, the validity of the psychometric results may be reduced, which emphasizes the importance of qualitative observations, in order to estimate the influence of attentional difficulties on all the neuropsychologic results.

Fourth, impaired social skills and altered communicative capacities can render the interaction during the assessment difficult and often unpredictable (e.g., children suspected to have or diagnosed with ASD). In these cases, the neuropsychologist's observations of social cues and elements of the interaction are of great importance. There are also certain standardized tools for evaluating specific social abilities, such as non-sense stories or stories with ironic content and real-life situations. During the entire assessment, the neuropsychologist should pay particular attention to his or her style of interacting with the child to maximize the extent and quality of the assessment. Children with ASD or with social difficulties may show reduced flexibility and ability to adapt to a social situation. Adjusting to a new setting demands significantly more time and cognitive resources of these children. The child's focus of attention can also be quite different; some aspects of the room or certain objects may attract unusual attention, while focus on the task itself is low. Finally, the child may also have trouble understanding implicit requests or may show a low underlying level of tolerance when trying to complete a task. The neuropsychologist should be aware of these particularities, limit the sources of distraction, allow more time for the child to become familiar with the setting, and be particularly clear when introducing a task.

Lastly, the selection of tests depends largely on the child's developmental age. Where there is a considerable developmental delay (e.g., ID, in some children with ASD), the developmental age may differ significantly from the child's chronologic age (Koziol & Budding, 2010; Mazeau & Pouhet, 2014). As a consequence, the neuropsychologist will have to adjust the choice of tests during the initial interview to include more playful tasks. For instance,

when evaluating a 6-year-old showing a developmental delay, the use of tools for pre-schoolers may be more appropriate than the school-age batteries normally applied. This generally requires the neuropsychologist to develop a broad range of expertise, a deep knowledge of the available tools, and a high degree of flexibility.

4. Conclusion

The main objective of the neuropsychologic assessment is to document neurodevelopmental alterations within various cognitive and behavioral domains, sensory-motor and perceptual functions, and socioaffective functioning. Subsequently, it aims to propose appropriate explanations for the specific pattern of impairments previously documented. To do so, the neuropsychologist not only integrates the results of the extensive formal quantitative and qualitative assessment, but also considers observational reports by caregivers and the case history. The main expertise of a clinical neuropsychologist lies in the integrative and multidisciplinary interpretation of the findings. This ultimately allows him or her to specify potential neurodevelopmental pathologies, to document the impact of structural abnormalities, and to draw profound assumptions about brain–behavior relationships. The neuropsychologic assessment is frequently part of a multidisciplinary evaluation, from which recommendations are derived for various contexts of the child's daily life (e.g., family, care team, school). In fact, it provides significant guidance in introducing or adjusting the appropriate therapeutic and intervention programs addressing the difficulties identified. Further, the assessment also finds application within a scientific context, where it contributes to documenting normal development or, in legal cases, to justifying conclusions about causal relationships.

Since the acquisition of valid, reliable performances that accurately reflect a child's cognitive potential depends largely on his or her motivation, cooperation and concentration, the pediatric neuropsychologic assessment in particular requires a high degree of flexibility on the part of the neuropsychologist (e.g., regarding the evaluation protocol, the duration of each session, and the interaction with the child). That is why efficient preparation for the evaluation is essential. This also depends on a range of information the neuropsychologist must know prior to the assessment (e.g., chronologic age, known pathologies, pharmaceutical treatment).

Future advances in pediatric neuropsychologic assessments should address the development of more sophisticated tools. This includes, for example, establishing larger normative samples that improve statistical power, building pathologic normative samples to facilitate the categorization of results, or augmenting sociocultural specific norms. Further, there should be a deeper understanding of the importance of pediatric neuropsychologic assessments to the child's neurodevelopment and an exchange of information with other disciplines. This

may pave the way for more holistic protocols and make diagnosis as well as intervention more effective.

Second Article.

Parallel factor analysis for multidimensional decomposition of functional near-infrared spectroscopy data

by

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A.M.H. and L.C.D. figure as co-first authors on this publication. They together initiated the project, were responsible for the recruitment of participants and data acquisition, conducted the initial preprocessing and the statistical analyses together. A.M.H. did the second round of preprocessing, ran the simulations and was the main writer of the article. L.C.D. thoroughly revised the analyses and the manuscript. P.V. supported the neuroimaging

acquisition, supervised initial preprocessing and revised the manuscript. J.T. implemented PARAFAC into the LIONirs toolbox enabling easy use for our data set, she accompanied the preprocessing, simulation analyses and statistics of the data, and revised the manuscript. E.M.M. introduced PARAFAC to the group and suggested its use for fNIRS data sets. He was the main supervisor for the methodological framework, he supervised the implementation of PARAFAC into the LIONirs toolbox, and the simulation analyses; E.M.M. also revised the manuscript and helped to properly integrate our findings into the current literature. A.G. was the secondary supervisor who set the larger scope of the article, ensured we would not loose track of it and she revised the manuscript.

ABSTRACT. **Significance:** Current techniques for data analysis in functional near-infrared spectroscopy (fNIRS), such as artifact correction, do not allow to integrate the information originating from both wavelengths, considering only temporal and spatial dimensions of the signal's structure. Parallel factor analysis (PARAFAC) has previously been validated as a multidimensional decomposition technique in other neuroimaging fields.

Aim: We aimed to introduce and validate the use of PARAFAC for the analysis of fNIRS data, which is inherently multidimensional (time, space, wavelength).

Approach: We used data acquired in 17 healthy adults during a verbal fluency task to compare the efficacy of PARAFAC for motion artifact correction to traditional 2D decomposition techniques, i.e., target principal (tPCA) and independent component analysis (ICA). Correction performance was further evaluated under controlled conditions with simulated artifacts and hemodynamic response functions.

Results: PARAFAC achieved significantly higher improvement in data quality as compared to tPCA and ICA. Correction in several simulated signals further validated its use and promoted it as a robust method independent of the artifact's characteristics.

Conclusions: This study describes the first implementation of PARAFAC in fNIRS and provides validation for its use to correct artifacts. PARAFAC is a promising data-driven alternative for multidimensional data analyses in fNIRS and this study paves the way for further applications.

Keywords: near-infrared spectroscopy, multidimensional decomposition, parallel factor analysis (PARAFAC), canonical decomposition, artifact correction, language paradigm

1. Introduction

Functional near-infrared spectroscopy (fNIRS) is a noninvasive neuroimaging technique that uses light of at least two different wavelengths in the near-infrared spectrum in order to assess brain activity based on neurovascular coupling. The specific absorption properties of oxygenated (HbO) and deoxygenated (HbR) hemoglobin allow individual assessments of concentration changes in both HbO and HbR separately (Jobsis, 1977). Although the fNIRS signal is considered to be relatively tolerant to movement (Lloyd-Fox et al., 2010), quality of data may be reduced due to abrupt changes in the light intensity caused by movement artifacts (Yücel et al., 2014). It has been shown that the dynamics of both wavelengths provide important information for artifact detection and correction (Cui et al., 2010). However, current techniques for movement artifact correction (e.g., wavelet filtering, decomposition, spline interpolation, and so on) typically assume that the behavior of both wavelengths is similar in time, thus do not take advantage of the structured information offered by both wavelengths (Brigadoi et al., 2014; Cooper et al., 2012; Tak & Ye, 2014). Two-dimensional (2D) analyses require that data with more dimensions, such as fNIRS data, undergo superficial unfolding before processing, e.g., treating both wavelengths or HbO and HbR independently. Hence, some of these 2D analysis tools are forced to impose other nonphysiological constraints, such as orthogonality in the case of principal component analysis (PCA) or statistical independence for independent component analysis (ICA).

Although there are several ways to approach PCA, e.g., dimensionality reduction (H. Zhang et al., 2011), classification (James et al., 2021), from the signal decomposition point of view, PCA aims at extracting the so-called principal components, i.e., those components that explain the greatest amount of variance of the signal (X. Zhang et al., 2017) activities in fNIRS (Cooper et al., 2012; Peng et al., 2014; Tak & Ye, 2014; X. Zhang et al., 2017). In temporal PCA, the data is decomposed into a sum of components, each one formed by the product of two vectors: one representing the temporal principal component and the other, the corresponding topography (scores for each channel). A basic problem with PCA is that the components defined by only two signatures (time and space) are not uniquely determined. Therefore, orthogonality is imposed between the corresponding temporal signatures of the different components (Becker et al., 2011; Miwakeichi et al., 2004; Tak & Ye, 2014). Orthogonality among brain signals is, however, a rather nonphysiological constraint. Even with this restriction, the extracted principal components are not completely unique, given that the arbitrary rotation of axes does not change the explained variance of the data. This has led researchers to use different mathematical criteria as the basis for choosing specific rotations (e.g., Varimax, Quartimax, and Promax). In fNIRS, PCA has also been applied to target time intervals (tPCA), that is only during periods where artifacts related to articulation or other head movements occurred, instead of during the entire unsegmented signal (Behrendt

et al., 2018; Yücel et al., 2014). This type of targeted correction resulted in better signal quality, as compared to wavelet-based filtering and spline interpolation, while also reducing the risk of altering the signal's global integrity (Yücel et al., 2014). Although PCA is very common and easy to use, some authors have already discussed its pitfalls and caveats as a method for artifact correction (Brigadoi et al., 2014; Jahani et al., 2018).

More recently, ICA has become another popular tool for data decomposition in fNIRS (Kamran et al., 2016; Tachtsidis & Scholkmann, 2016; H. Zhang et al., 2010). It has the benefit of preventing rotational freedom (Jung et al., 2001). However, uniqueness is achieved at the cost of imposing a constraint even stronger than orthogonality, namely, statistical independence of the temporal signatures (Comon, 1994; Jutten & Herault, 1991). Statistical independence is appropriate for identifying artifacts with spatio-temporal signatures that are very different to those of neural activity (e.g., ocular movements), but is less appropriate for artifacts that share spatio-temporal characteristics with neural signals. What is more, ICA is commonly applied to the entire signal in contrast to a target decomposition as introduced previously for tPCA (H. Zhang et al., 2010). It may thus be more challenging to achieve a satisfying correction of irregular movement artifacts. In ICA, the maximal number of components (hypothesized sources) equals the number of observations, which in neuroimaging is often rather high. It could therefore become difficult to identify the artifact's signature, which could be split into several components.

To overcome these limitations, a multidimensional ($\geq$ 3D) approach called parallel factor analysis (PARAFAC) (Bro, 1998; Harshman, 1970), or less frequently referred to as canonical decomposition (Carroll & Chang, 1970), could be considered as an alternative for the analysis of fNIRS data. PARAFAC is a decomposition technique applicable to any dataset that can be described in more than two dimensions (e.g., time, space, frequency, participants, conditions, signal characteristics) and allows for the extraction of different signatures present in the data. It assumes multilinear relations between the different dimensions and usually does not need any other mathematical constraints to find a unique decomposition of the data. It may therefore be used in the data preprocessing steps to isolate artifacts, as well as in the actual data analyses to extract a predominant brain activation, or other relevant characteristics of the signal. Such multidimensional decomposition was initially introduced in the field of psychometrics and linguistics as a tool for multifactorial analysis (Carroll & Chang, 1970; Harshman, 1970; Tucker, 1966). Over time, its use was extended to neuroimaging signals, such as the analysis of event-related potentials (ERPs) assessed by electroencephalography (EEG), in which time, space and participants were considered for the signal decomposition (Field & Graupe, 1991; Möcks, 1988). Multidimensional decomposition with PARAFAC is not limited to 3D and could potentially be applied to data with more dimensions. In the context of ERP data, PARAFAC as a five-way analysis has successfully been used to identify differences and common characteristics of intertrial phase coherence across conditions and

subjects, including the dimensions of time, channels, frequency, subjects, and conditions (Möcks, 1988). PARAFAC was also applied for data analysis in continuous EEG recordings, taking into account the temporal, spatial and frequency representation of the EEG signal (Martínez-Montes et al., 2004; Miwakeichi et al., 2004). Indeed, using a time-frequency wavelet transformation for each channel in EEG data, Miwakeichi and colleagues (2004) revealed PARAFAC as an appropriate tool for both the detection of ocular movement artifacts and the identification of dominant brain activation patterns. In their study, some of the artifact components identified using PARAFAC were highly similar to those extracted with principal component analysis (PCA), a well-established approach for 2D decomposition. Specifically, significant overlap was shown for eigenvalues and peaks of time/frequency components, as well as their topographical representations found with PCA and PARAFAC for activities that effectively fulfill the orthogonality requirement. PARAFAC, using the dimensions of time, space and frequency, has also been applied successfully to the EEG data of individuals with epilepsy, for the purposes of artifact detection and the identification of aberrant cerebral activation (Acar et al., 2007). The growing popularity of PARAFAC in neuroimaging stems from the intrinsic advantage of multidimensional decomposition, as it reflects the nature of most data gathered in neuroscience. Compared to 2D methods, the application of PARAFAC does not need to impose nonphysiological constraints (Martínez-Montes et al., 2004). What is more, since decomposition techniques represent data-driven approaches, PARAFAC could also contribute to enlighten new aspects of neuroimaging data compared to model-based techniques (Calhoun, 2018). Although PARAFAC has been applied for data analysis on NIRS data in the food industry (Bro, 1998), it has not yet been used in fNIRS in the field of neuroscience.

The current study aimed to introduce and validate PARAFAC as a multidimensional decomposition technique to extract and correct artifacts in fNIRS data. To account for the natural complexity and variability regarding motion artifacts, we first applied the PARAFAC technique in real cognitive fNIRS data. More specifically, data were acquired from participants that performed aloud a verbal fluency task, in which the main motion artifacts are known to be task-dependent and have characteristics that might confound the estimation of the hemodynamic response function (HRF) (Brigadoi et al., 2014). PARAFAC's performance to correct motion artifacts was compared to two traditional bidimensional decomposition techniques: tPCA and ICA. In doing so, we investigated differences in artifact correction efficacy related to the number of dimensions used in the decomposition techniques (i.e., treating both wavelengths as independent or as a dimension). As the true HRF was unknown and therefore did not allow to directly compare the recovered task activation to a ground truth, we used statistical analysis of correction performance based on various quality measures of the three different corrected signals.

Secondly, we investigated how artifact correction with PARAFAC performed in various controlled scenarios to disentangle in which cases a multidimensional decomposition approach that does not impose orthogonality constraints could become advantageous. For that purpose, a real artifact was extracted from a data set of the task condition and added to a clean resting-state signal. Different artifact parameters (e.g., amplitude, onset of overlapping artifacts) were controlled to produce various scenarios, including variation in the level of orthogonality among the signals combined in the simulated data. Further, the use of the resting-state signal allowed us to evaluate how artifact correction would affect the reconstruction of a synthesized HRF (HRF_{sim}), which has actually been named as one of the most suitable methods to validate artifact correction (Cooper et al., 2012). Artifact correction in these scenarios was performed with PARAFAC and tPCA only, both applied specifically during the artifacted interval (i.e., target decomposition), compared to ICA that is typically applied to the entire signal, and thus being more comparable methods. Indices for the similarity between the clean signal before adding artifacts and the signal after artifact correction, the signal's quality as well as the recovery of the HRF_{sim} after correction, were used to compare the performance of both correction approaches.

2. Methods

2.1. Sample and Data Acquisition

Eighteen healthy native French-speaking adults participated in this study. One participant was excluded from the analyses, as it showed continuous noise precluding the identification of individual artifacts. The final sample for the validation of using PARAFAC for artifact correction thus included 17 participants (mean age $\pm$ standard deviation = 22.8 $\pm$ 2.0 years; nine females and eight males). All were right-handed and presented no neurological or psychiatric disorders. Experimental procedures were approved by the local ethics committee.

fNIRS data was acquired with a multichannel Imagent Tissue Oxymeter (ISS Inc., Champaign, Illinois) frequency-domain fNIRS device using 14 light detectors and 60 laser light emitters, each regrouping two light sources of different wavelengths ($\lambda 1|2 = 690|830$ nm) with an average power of 10 mW. Emitters and detectors coupled at a distance of 3 to 4.5 cm allowed for the recording of 104 channels for each wavelength. Optodes were held in place perpendicularly, using a cap that was fitted on the head of participants in accordance with the 10-20 system (Klem et al., 1999). Optical intensity, including information regarding the average light intensity (DC), amplitude modulation (AC) and phase shift (ϕ), was measured with a sampling rate of 19.53 Hz (Boxy, ISS Inc., champaign, Illinois). The channel setup covered both hemispheres equally and included the regions of interest for the investigation of language functions, i.e., frontal, temporal and parietal lobes (Fig. 1A).

Participants sat comfortably in a soundproof room. They were instructed to relax, to avoid any intentional movements or muscular tension, and to fix their gaze on the center of a screen placed at a distance of 114 cm. Participants underwent fNIRS recording during two conditions (Fig. 1B): (1) a 12-min resting-state with eyes open and (2) a verbal fluency task previously validated for expressive language-related activation (Gaillard et al., 2003; Gallagher et al., 2016; Paquette et al., 2015). The task consisted of 11 different familiar semantic categories (e.g., animals, colors, fruits, and so on) that appeared one at a time on the screen. Participants were instructed to name as many words as possible belonging to the specified category and to continue as long as the category name appeared on the screen. We used a block design paradigm in which periods of rest (fixation cross presented on the screen) and task (semantic category) alternated (Presentations®, Neurobehavioral Systems, 2018). The inter-stimulus interval varied randomly between 25 and 29 s, while stimuli (one of the semantic categories) were always presented for 30 s. An audiovisual recording of the fNIRS session enabled visual support during offline preprocessing for the identification of movements and the timing of word articulation. Participants completed on average 10.4 ± 0.9 blocks of the verbal fluency task and named an average of 14 ± 2.2 words during each 30-s block. Data analysis was conducted with the use of a homemade toolbox (LIONirs) (J. Tremblay et al., 2022) adapted in SPM12 (Statistical Parametric Mapping) (Villringer & Dirnagl, 1995) in MATLAB® (The MathWorks, Inc., Massachusetts).

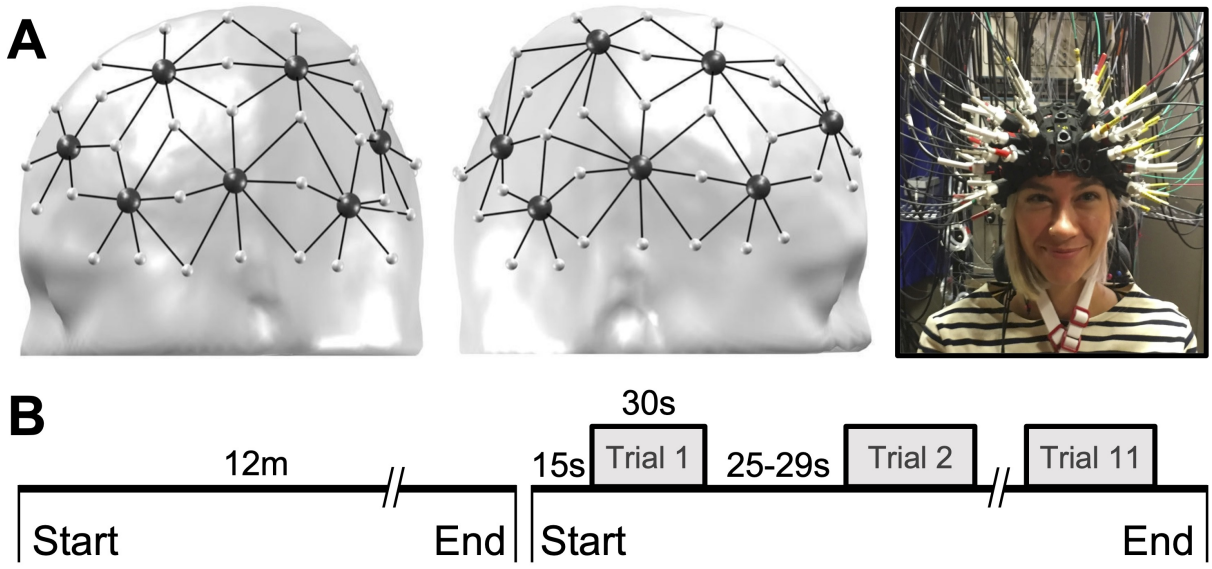

Figure 1 – fNIRS setup: (A) Probe placement (sources in small light gray dots, detectors in dark gray dots) as shown on an adult's head model. (B) Experimental design including a 12-min resting-state followed by an expressive verbal fluency task that included 11 trials. Trials lasted 30 s and inter-stimulus intervals varied pseudo-randomly between 25 and 29 s.

2.2. Validation Process

Validation of PARAFAC for artifact correction was done in two realistic applications as illustrated in Fig. 2. First, artifact correction with PARAFAC was tested on the real task-based signal of the whole sample, and its performance was compared with tPCA and ICA. Indices for the signal's quality were used to compare the three techniques (Sec. 2.6). Second, a simulation analysis was conducted to investigate the efficacy of PARAFAC to correct artifacts with controlled parameters. Similarity metrics, quality measures and reconstruction of the $\mathrm{HRF}_{\mathrm{sim}}$ were used to evaluate artifact correction with PARAFAC and tPCA both applied in a target manner (Secs. 2.6, 2.3 and 2.8).

2.3. Nonsimulated Task-related Motion Artifacts

Preprocessing of the task-condition data first included the automatic exclusion of channels with insufficient light intensity amplitude (average raw DC intensity across time < 100). The signal was afterwards segmented into blocks of 50 s (5 s resting-state baseline, 30 s task, and 15 s resting-state), and light intensity was converted to changes in optical density (normalization of each block). We then performed a semi-automatic artifact detection using a moving-window algorithm to automatically mark segments where an abrupt change of the signal's variance exceeded three times the average variance of the previous interval (Aarabi & Huppert, 2016) with a window duration of 0.8 s. Events that were 2 s or less apart were considered as one and channels that were strongly correlated with a noisy channel (Pearson correlation of ≥ 0.8) within the aberrant segment were also marked as artifacted. The automatic detection step was reviewed afterward and adjusted based on an inter-rater visual inspection of the signal's characteristics and the video recordings. Because the task required participants to name words aloud, artifacts in the current language paradigm were mostly due to facial movements related to the muscular contraction of articulation.

2.4. Simulated Motion Artifacts

A real resting-state dataset from one of the participants in which we could identify a 180-s segment without any motion artifact was employed for the simulated artifact experiment. As for the task-based data, channels with insufficient raw light intensity amplitude were first excluded based on the previously mentioned criteria, yielding a total of 82 channels. The data was then converted to changes in optical density (normalization based on the whole 180-s segment). It served as the initial signal baseline ($\mathrm{NIRS}_{\mathrm{ini}}$) for similarity and quality signal assessments.

To add a motion artifact with controlled parameters, we first used PCA to decompose all channels of a task-based fNIRS signal during a typical motion artifact (A) with a duration of 7 s. The obtained temporal signature of the first component was then added to the $\mathrm{NIRS}_{\mathrm{ini}}$.

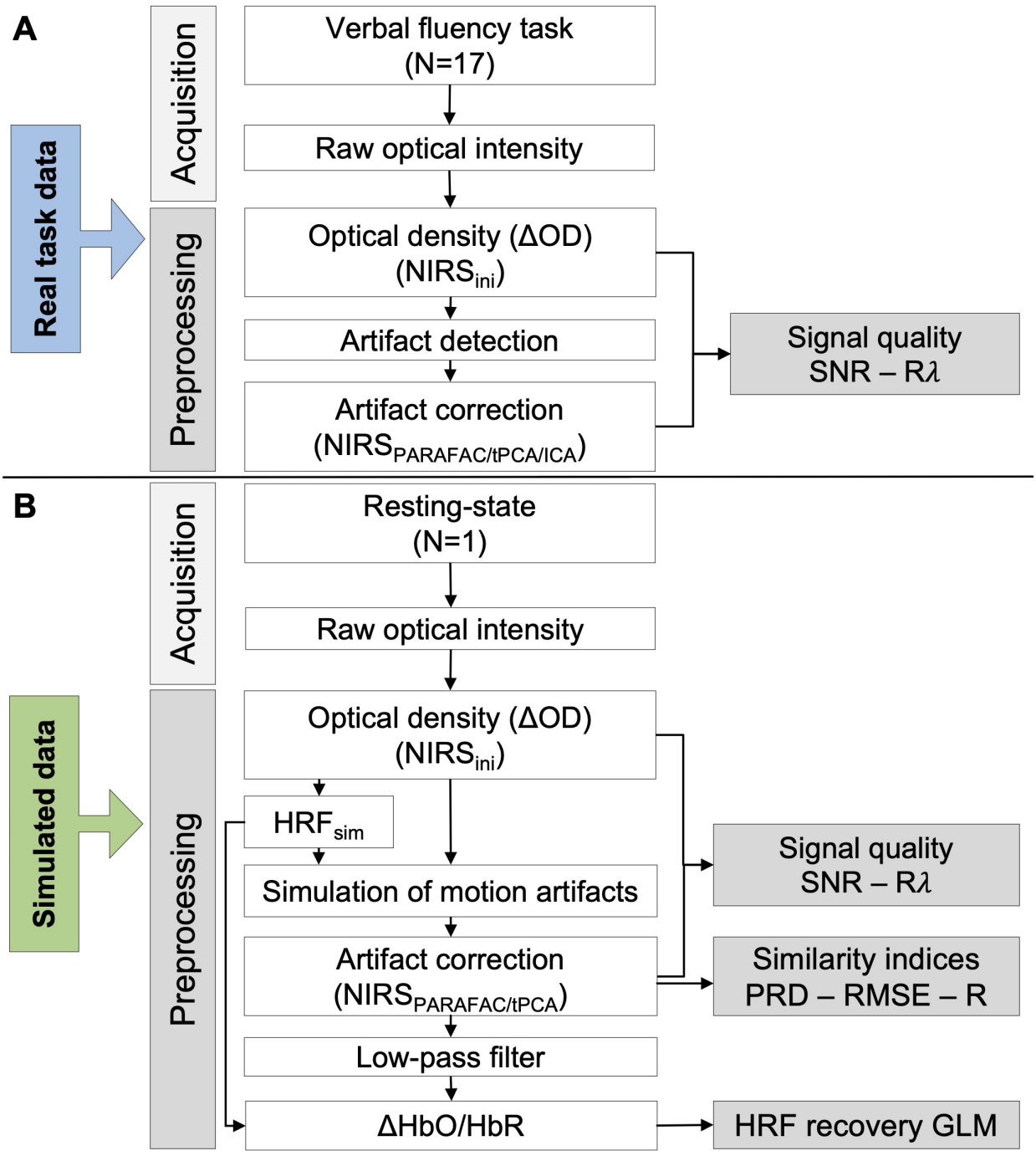

Figure 2 – Processing streams to validate PARAFAC as a multidimensional artifact correction technique for fNIRS data. (A) The processing of the real task data derived from 17 subjects, and (B) of the simulated data based on a single-subject, respectively. The metric(s) used to evaluate correction performance of each stream are presented on the right side. $NIRS_{ini}$ = initial signal used for comparison (with artifacts for the real task data; before artifact simulation for the resting-state data). PRD, Percent root difference; RMSE, root mean square error; R, Pearson product-moment correlation coefficient; SNR, signal-to-noise ratio; $R\lambda$, Pearson's correlation between wavelengths; GLM, general linear model; HRF_{sim}, simulated hemodynamic response function.

The spatial distribution of A, i.e., the weight of each channel was randomized, but the same distribution was added to both wavelengths with only a different overall scale. Figure 3 provides an overview of the set of simulations and their parameters, while more details are provided in Fig. S1 of the Supplemental Material. For the first simulation, the amplitude of the original artifact was modulated and scaled to five different amplitudes in order to produce artifacts with various signal-to-noise ratio (SNR) (simulations 1a to 1e). For the second simulation, we aimed to produce artifacts with more complex signatures (simulations 2a to 2f). The idea emerged from observations of artifact correction in the task-related signal and also aimed at exploring the decomposition when different artifacts are not completely orthogonal in the data. To do so, two individual artifacts (A_1, A_2) with varying time intervals between the onset of A_1 and A_2 led to different temporal orthogonality (r) which was evaluated for each simulation. The levels of orthogonality between the time courses of the raw signal and the first artifact r_a ($Raw \times A_1$) and between the time courses of the artifacted signal and the second artifact r_b ($(Raw + A_1) \times A_2$), were derived from the angle between both signals (i.e., taking the time course of each signal as a vector of time points and computing the angle between both vectors). A normalized measure of the orthogonality level is then computed such that when the angle between the signals is 90 deg, the measure is maximum and equal to one, while when the angle departs from 90 deg (both higher or lower) the measure linearly decreases to zero. Then, r values of one indicate perfect orthogonality between the two time courses, while r values lower than one, specifically those closer to zero indicate that the two time courses are not orthogonal to each other. Additionally, an HRF was synthesized (HRF_{sim}) in SPM by the linear combination of two gamma functions as proposed in the literature (Glover, 1999). That is, gamma functions one and two had a time-to-peak of 5.4 and 10.8 s respectively, a full-width-at-half maximum of 5.2 and 7.36 s respectively, and a scaling coefficient for the second gamma function of 0.35. The amplitude of the HRF_{sim} was scaled by 14 % for the 830 nm signal and 0.6 % for the 690 nm signal, which approximately produces an HRF with an 15µM increase in HbO concentration and a 5µM decrease in HbR concentration (Cooper et al., 2012; Gagnon et al., 2012; Gagnon et al., 2011; Glover, 1999). The response was simulated as a convolution of the HRF with a stimulus duration of 30 s resulting in a simulated physiological signal (HRF_{sim}) of $\sim$40 s. The HRF_{sim} was then added to the signal along with an artifact (A), so as to produce different overlaps between both time courses (simulations 3a to 3d).

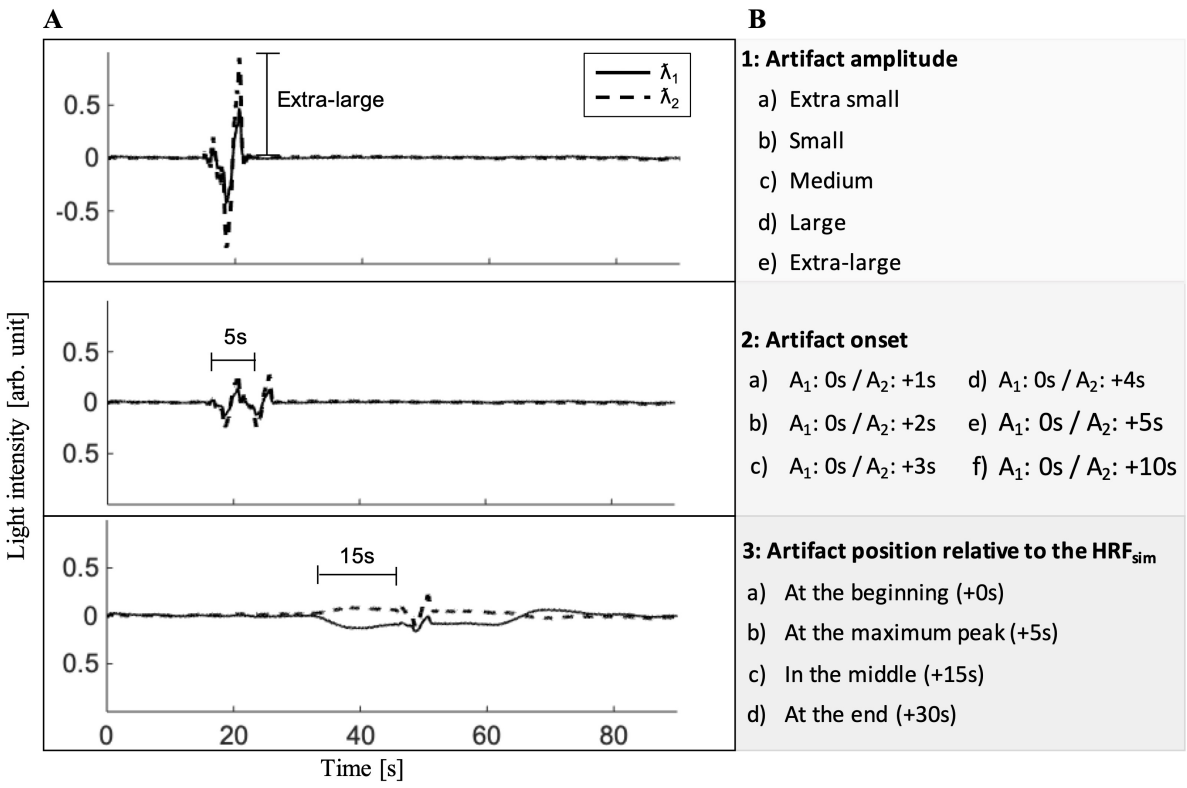

Figure 3 – Simulated fNIRS signals: (A) One example of the simulated fNIRS signal for each simulation condition one to three. (B) The details of the varying parameters of all simulations. Five scaling factors (0.4, 0.8, 1.0, 1.5, 3.0) were used to create simulated artifacts with different amplitudes. $\lambda 1|2 = 690|830$ nm; A, artifact; $\mathrm{HRF}_{\mathrm{sim}}$ = simulated hemodynamic response function.

2.5. Artifact Correction

In the task-based data set, artifact correction with PARAFAC and tPCA was applied in a target manner, i.e., to the segments identified during artifact detection as described in Sec. 2.3; while, with ICA the analysis was applied to the entire continuous signal. In the simulated signals, target correction was applied to a time interval of ±2 s around the simulated artifacts. More details on each decomposition technique will be presented in the following sections (Secs. 2.5.1 and 2.5.2).

2.5.1. *Two-dimensional Signal Decomposition for Artifact Correction*

For both ICA and tPCA, the decomposition of the 2D data matrix X (whose elements x_ij are indexed by channel i and time points j), leads to N_f components as defined in Eq. 1 and illustrated in Fig. 4A

$$x_{ij} = \sum_{f=1}^{Nf} a_{if} b_{jf} + \mathcal{E}_{ij}. \tag{1}$$

The matrix concatenates two separate data matrices (X_1,X_2) corresponding to the 2D structure for both wavelengths. The maximum number of components N_f could be equal to or less than the smaller dimension of the X matrix dimension, i.e., twice the number of channels or number of time points. Each component is modeled as the product of two factors/vectors which represent signatures of the space (a_f) and time (b_f) dimensions. The temporal signatures are constrained to be orthogonal among components, and rotated in order to obtain those signatures that offer the highest variance explanation (Varimax) from all the infinite solutions of the decomposition. The unexplained part of the data is considered irrelevant activity or noise ($\mathcal{E}$).

Artifact correction with tPCA was performed on each time interval containing artifacts as specified by the time interval of the simulated artifacts or the identified artifact detection of the task-based data set. From the obtained components we subtracted the first, which explains most of the variance based on the assumption that the highest variance in the data for each segment is assumed to be caused by the artifact.

Artifact correction with ICA, was done using BrainVision Analyzer (Brain Products GmbH, Gilching, Germany), and followed the steps proposed by Plank (2013). First, optical density fNIRS data were exported and ICA was applied on the entire unsegmented signal, as for the method commonly reported in the literature (H. Zhang et al., 2010). Noisy intervals reflecting artifacts were identified by semi-automatic inter-rater artifact detection (Sec. 2.3). We visually selected the ICA components reflecting the artifact, based first on their time course, i.e., high variation of light intensity similar to the artifact signature. Secondly, we rejected those whose subtraction would induce artificial artifacts elsewhere. Data was subsequently imported back into the LIONirs toolbox (J. Tremblay et al., 2022) in order to apply segmentation (Sec. 2.3).

2.5.2. *Multidimensional Signal Decomposition*

The fNIRS data naturally offers the time courses of all channels for two wavelengths, i.e., two separate data matrices. This data can be arranged in a tridimensional array, as illustrated in Fig. 4B. The dimensions of this 3D array are time (indexed by the time points in the analyzed segment), space (indexed by channels) and wavelength (indexed by the two wavelengths). As explained above, PARAFAC establishes a trilinear decomposition of each element of the fNIRS data array (X_tsw) in N_f components, each being the product of three factors (Bro, 1998) as defined in Eq. 2:

$$X_{tsw} = \sum_{f=1}^{Nf} a_{tf} b_{sf} c_{wf} + \mathcal{E}_{tsw}. \tag{2}$$

The estimated factors, a_{tf}, b_{sf} and c_{wf} are the elements of the so-called loading matrices A, B and C, whose column vectors $a_f = a_{tf}$, $b_f = b_{sf}$, $c_f = c_w f$, represent the temporal,

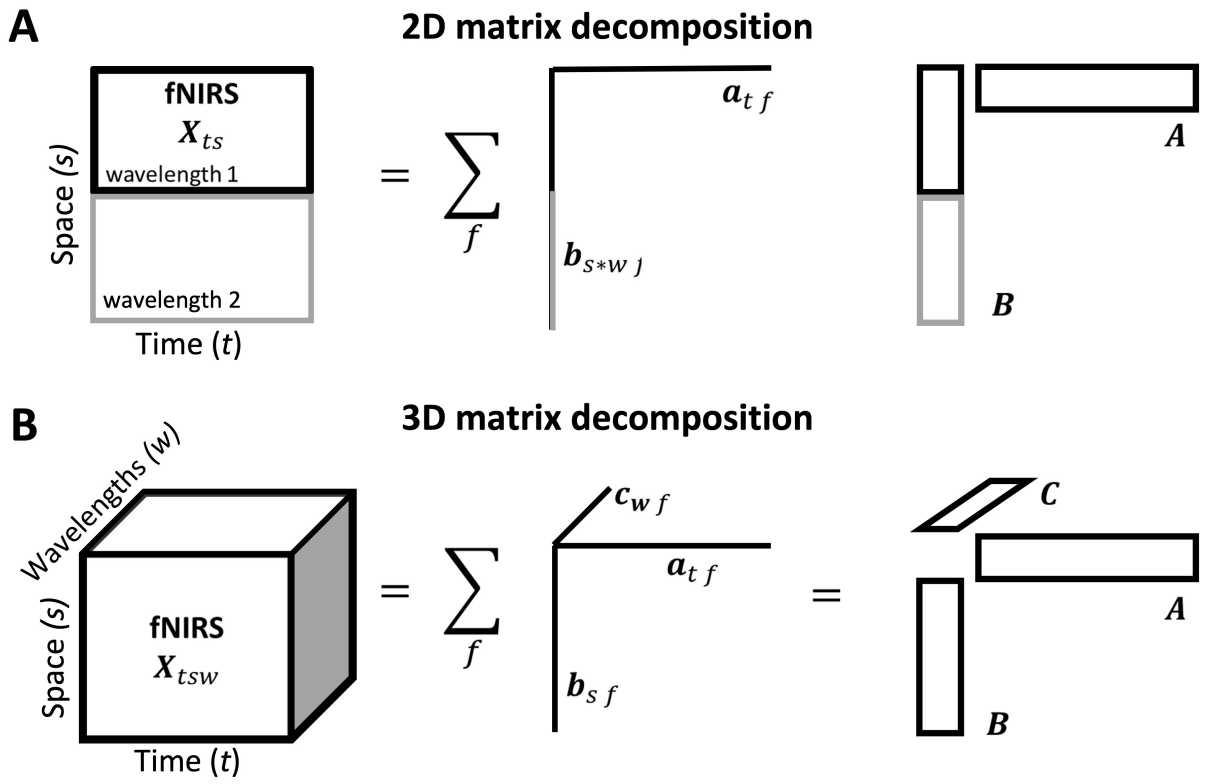

Figure 4 – Schematic representation of the decomposition models applied to fNIRS data. (A) The data X is arranged as a 2D data array by vertically concatenating the 2D matrices with dimensions being space (s) and time (t) for each wavelength (w). tPCA/ICA decomposes the array into components, each being a bilinear product of the loading vectors representing temporal (a_{tf}) and spatial signatures (b_{swf}). The latter is formed by the spatial signatures for the different wavelengths, which are represented in components without taking into account their spatial dependence, i.e., for the same temporal signature of each component, there will be two topographies corresponding to the two wavelengths. Matrices $A = \{a_f\}$ and $B = \{b_f\}$, contain as columns the temporal and spatial signatures for all components, respectively. (B) The data X is arranged as a 3D data array with dimensions being time (t), space (s) and wavelengths (w). PARAFAC decomposes this array into the sum of components, each being a trilinear product of loading vectors representing temporal (a_{tf}), spatial (channel, b_{sf}) and spectral (wavelength, c_{wf}) signatures. In practice, the decomposition consists of finding the matrices $A = \{a_f\}$, $B = \{b_f\}$ and $C = \{c_f\}$ that explain X with minimal residual error.

spatial and wavelength signatures of each component. The main advantage of this method is that it provides a unique decomposition of the fNIRS data into components reflecting different activities that do not need to be orthogonal or statistically independent in any of the dimensions. As long as an activation shows a different behavior in one of the dimensions, it can be extracted as a separate component. In this application, the spatial dependency between wavelengths is therefore exploited in order to perform the decomposition. The uniqueness of the solution is guaranteed when the number of components (N_f) is smaller than the sum of

the ranks of the three loading matrices. In the case of noisy data, it is very likely that the loading matrices are always full rank. Uniqueness is thus guaranteed as long as the number of components (N_f) is smaller than half the sum of the number of time points (N_t), number of channels (N_c), and number of wavelengths (N_w: $Nf \leq \frac{(N_t+N_C+N_w)}{2-1}$). For instance, even in a small array of 20 time points and eight channels at two different wavelengths, a unique decomposition could be achieved, using up to 14 components ($\frac{20_{(t)}+8_{(s)}+2_{(w)}}{2} - 1 = 14(Nf)$). Computationally, the decomposition is achieved by the Alternating Least Squares algorithm, as it has been used in previous studies on neuroscience data (Acar et al., 2007; Martínez-Montes et al., 2004; Miwakeichi et al., 2004; Mørup et al., 2006). The only indeterminacies in the least-squares solution are trivial and easy to handle: the order of the additive components and the relative scaling of the signatures (Bro, 1998).

In this work, we used the PARAFAC implementation from the N-way Toolbox (Andersson & Bro, 2000), which was included into the LIONirs toolbox (J. Tremblay et al., 2022) so as to visualize and apply the decomposition exclusively during selected time intervals and channels. Calculation with PARAFAC can be obtained in < 1 s for a dataset size of $\sim$50 channels x 100 time points x two wavelengths (typical dataset size in our experiments), which is as fast as comparable techniques such as tPCA. Components were ordered according to their importance in explaining the data's variance (similar to tPCA). The scale of the data was kept in the temporal signatures, while the other dimensions were normalized so as to have Frobenius norms equal to one. Since measures from both wavelengths are sampled simultaneously at each specific position on the scalp, movement artifacts affect their amplitudes similarly. During time intervals containing artifacts, the time courses of the signal from the two wavelengths commonly show a drastic and correlated increase as compared to the task-related or baseline signal (Cui et al., 2010). By using multidimensional PARAFAC decomposition, we can take advantage of this information for the adequate selection of components of the artifact's signature. PARAFAC decomposition was specified to extract between two to four components, allowing a clear separation of the artifact signatures representing the artifacts characteristics from the rest of the signal. This was associated with a Core Consistency Diagnostic (Corcondia) of more than 90 %, indicating that the model accurately described the data (Bro & Kiers, 2003). The appropriate components were selected based on (1) a visual inspection of their temporal overlap with the artifact, (2) the smallest number of possible components that would sufficiently correct the artifact, and (3) components showing similar weights for both wavelengths. In simulations, a standardized PARAFAC decomposition with three components was applied. Two components that clearly showed evidence of an amplitude change typically related to a movement artifact, i.e., short impulses, were discarded as reflecting the artifact in the original signal.

2.6. Signal Quality

The signal's overall quality was estimated by two quality measures (Cooper et al., 2012; Cui et al., 2010; Sweeney et al., 2012):

(1) Signal-to-noise-ratio: For each data segment with an artifact we estimated the SNR, as defined by Sweeney and colleagues (2012):

$$SNR = 10log_{10}\frac{\sigma_x^2}{\sigma_{e^2}}, \tag{3}$$

where σ_{x^2} represented the signal's variance computed in segments of data without an artifact. In case of the real task-based data set, σ_{x^2} was computed in a 5-s interval during the baseline of the task condition. For the simulations, σ_{x^2} was computed in a 5-s interval at the beginning of the resting-state signal. σ_{e^2} represented the variance of a segment where an artifact was identified or simulated. Therefore, our SNR works more like a constrast metric indicating how much the signal's variance of a noisy segment differs from the signal's variance of a clean segment. Whenever an artifact contaminated the signal, σ_{e^2} would usually be higher than σ_{e^2} because it comprised both the variance of the physiological signal and the variance of the artifact. It was therefore expected that the SNR of the signal before artifact correction would be negative. After artifact correction, a negative SNR ($\sigma_x < \sigma_e$) would indicate that the artifact had not been entirely removed, a positive SNR ($\sigma_x > \sigma_e$) would imply overcorrection meaning that artifact correction removed the artifact as well as parts of the relevant physiological activity, and an SNR of about zero ($\sigma_x = \sigma_e$) would suggest that the artifact had been eliminated to the extent that the variance of the corrected signal would not differ from the baseline segment without an artifact. In case of the task-based data set, the SNR of the uncorrected signal served as a baseline, thus the more the SNR of the corrected signal differed from the baseline value and approached zero, the better the artifact had been corrected. Since the ground truth of the signal's variance was unknown and besides the artifact also the hemodynamic response may contribute to the signal's variance, no further interpretation of a negative or positive SNR would have been appropriate. For the simulations, the SNR of the initial signal before artifact simulation ($NIRS_{ini}$ and $NIRS_{ini}$ + HRF_{sim}) served as a reference and the more the SNR of the corrected signal would approach this value, the better the performance of artifact correction was assumed to be.

(2) Pearson's correlation coefficient ($R\lambda$) between the time courses of both wavelengths from the same site were used as a subsequent quality measure to evaluate artifact correction performance (Cui et al., 2010). This was based on the assumption that a high correlation coefficient indicates the presence of artifactual signals measure simultaneously by both wavelengths, since in a clean signal these temporal courses appear much less correlated. Similar to how it was previously done for the SNR, we computed $R\lambda$ for all segments with identified or simulated artifacts before (i.e., uncorrected artifact reference) and after artifact

correction (i.e., corrected signal). For the task-based data, $R\lambda$ was additionally calculated for artifact-free baseline intervals (i.e., artifact-free reference) and in case of the simulations for the intervals of the initial signal ($NIRS_{ini}$ and $NIRS_{ini}$ + HRF_{sim}) before artifact simulation (i.e., artifact-free reference).

2.7. Similarity Indices

For the analysis of simulated data, three additional metrics were used to evaluate performance of artifact correction: (1) the percent root difference (PRD), (2) the root mean square error (RMSE) and (3) the Pearson product-moment correlation (R). These allowed us to estimate the degree of correspondence between the initial signal without simulated artifacts ($NIRS_{ini}$ and $NIRS_{ini}$ + HRF_{sim}) and the signal after correction of the simulated artifacts (Gagnon et al., 2012; S. Liu et al., 2008; Scholkmann et al., 2010). PRD, RMSE and R were defined as follows:

$$PRD = 100\% \sqrt{\sum_{i=1}^{N}(x(t_i) - y(t_i))^2 (\sum_{i=1}^{N} x^2(t_i))^{-1}}, \tag{4}$$

$$RMSE = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(x(t_i) - y(t_i))^2}, \tag{5}$$

$$\begin{gathered} R = \frac{1}{N-1}\sum_{i=1}^{N}(\frac{x(t_i) - \bar{x}}{s_x})(\frac{y(t_i) - \bar{y}}{s_y}, \\ \text{where } s_x = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(x(t_i) - \bar{x})^2},\ s_y = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(y(t_i) - \bar{y})^2}. \end{gathered} \tag{6}$$

For all three indices, $x(t_i)$ and $y(t_i)$ represented the i-th point of the time courses of the corrected signal and of the initial artifact-free signal ($NIRS_{ini}$ and- $NIRS_{ini}$ + HRF_{sim}), respectively. N corresponded to the duration of the time courses and $\bar{x}$ and $\bar{y}$ to their respective mean values along time. An ideal artifact correction would have been achieved when the artifact was completely removed, and the corrected signal maximally resembled the initial signal. As PDR and RMSE inform on the difference of the two signals, the smaller they were, the more accurate the performance of artifact correction was. On the contrary, the R index represents the similarity of both signals, hence a higher value suggested better artifact correction.

2.8. HRF Recovery

In order to investigate how artifact correction would affect the interpretation of the hemodynamic response, in the last simulations (3a to 3d) we aimed to recover a previously

synthesized HRF. Therefore, a Butterworth low-pass filter (filter order = 4, cut-off frequency = 0.2 Hz) was applied to the signal to remove oscillations caused by heartbeat and respiration. The optical intensity changes of the two wavelengths were then transformed into relative concentration changes of HbO and HbR, done so by using an age-adapted differential pathlength factor (DPF) and the modified Beer-Lambert Law (Kocsis et al., 2006; Scholkmann & Wolf, 2013). A general linear model (GLM) with the $\mathrm{HRF_{sim}}$ as a predictor was then applied. The GLM assumes that a linear relation exists between different inputs (Friston et al., 2011), and has already been applied in several fNIRS studies to specify the HRF (Minagawa-Kawai et al., 2011; Schroeter et al., 2004; Tak & Ye, 2014). The cerebral activation of the signal (y) is defined as:

$$y = \beta_0 + \beta_{HbO/HbR} x + \mathcal{E}, \tag{7}$$

where y referred to the analyzed signal, β_0 was a constant, $\beta_{HbO/HbR}$ represented the predictive value of the simulated hemodynamic response represented by x ($\mathrm{HRF_{sim}}$) for both concentration changes of HbO and HbR, respectively, and $\mathcal{E}$ represented the error or the unexplained part of the signal. GLM was applied to a 60-s interval that was set to 15 s before and 45 s after the onset of the $\mathrm{HRF_{sim}}$. The GLM allowed us to estimate how much of the signal's variance (R_2) could be predicted by the $\mathrm{HRF_{sim}}$. This estimation was conducted for the initial signal without artifacts ($\mathrm{NIRS_{ini}}$ + $\mathrm{HRF_{sim}}$), the uncorrected signal with a simulated artifact, and for the corrected signal.

2.9. Statistical Analysis

Quality and similarity measures were computed for each channel separately and then averaged across channels for statistical analysis. Prior to statistical analysis, correlation coefficients (R and $R\lambda$) were standardized using Fisher's transformation to obtain values following a normal distribution. For the real task-based data, we conducted statistical analysis to compare the signal quality metrics among the motion artifact correction techniques. A repeated measures ANOVA including PARAFAC, tPCA, ICA and the uncorrected reference signal as the within factor, was performed independently for the mean of each metric across all channels (i.e., SNR, $R\lambda$). In case of the $R\lambda$, the reference of the baseline (nonartifacted signal) was included as another condition. Follow-up paired contrasts were conducted with a critical alpha of 0.05. For the simulations, we applied a repeated measures ANOVAs to compare the mean outcome of the quality and similarity metrics between the different simulations, i.e., 1a to 1e for the amplitude scaling, 2a to 2f for the complex artifacts and 3a to 3d for the $\mathrm{HRF_{sim}}$, and within correction condition, i.e., PARAFAC, tPCA, and the uncorrected signal. Tukey correction for multiple comparisons was applied for posthoc analysis.

3. Results

3.1. Correction of Nonsimulated Task-related Motion Artifacts

First, decomposition with PARAFAC was applied for the correction of real task-based motion artifacts. The signal's quality (SNR, $R\lambda$) after correction with PARAFAC was evaluated and compared to the signal before correction (uncorrected), the signal after correction with two 2D decomposition techniques (i.e., tPCA and ICA), and a reference signal of a segment without artifacts (Rλ). Figure 5 provides an example of target artifact correction with PARAFAC illustrating the 3D decomposition for a motion artifact detected in the real task-based signal. The time course of the three components obtained with PARAFAC allowed to differentiate between the two components with distinct artifact signatures, and the one component representing the clean signal. Spatial distribution of each component is shown as a loading matrix and helps to identify in which channels (localization) the artifact's signatures were most important. The two components that appear to represent the artifact showed similar scores for both wavelengths, as represented in the wavelength signatures. Subsequently, removal of PARAFAC first and second components resulted in a less noisy time interval and satisfyingly corrected signal.

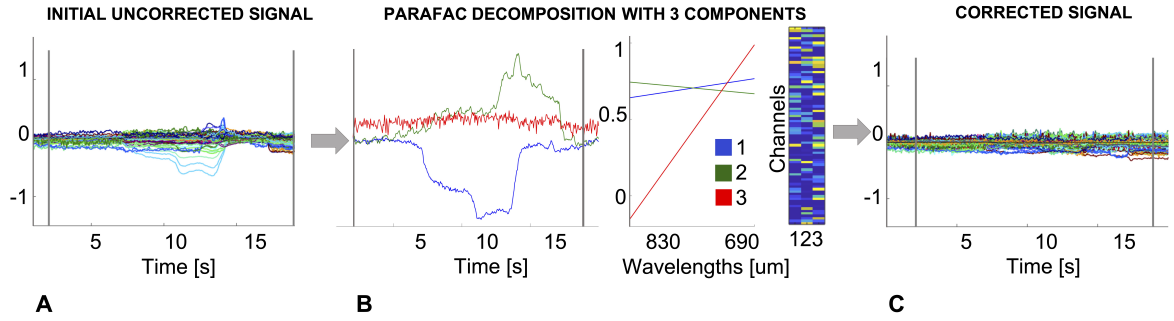

Figure 5 – Example of target 3D PARAFAC decomposition to correct motion artifacts in a task-based fNIRS data set. (A) The initial uncorrected data segment. (B) The temporal, spatial (channel) and wavelength ($\lambda 1|2 = 690|830$ nm) signatures of the components identified with PARAFAC decomposition are presented, respectively. (C) The corrected signal, illustrating the efficacy of movement artifact correction with PARAFAC after subtraction of two components (1 and 2). Y-axis is presented in arbitrary units.

Automatic and manual artifact detection agreed on a majority of the signal with an average concordance of 92.8 %, so only minor manual adjustments had been applied. A total of 585 different artifactual events, on average 66 events per subject with a mean, minimal and maximal duration of 5, 0.7 and 21.2 s, respectively, were considered for correction. Comparison of the SNR included measures of every channel of both wavelengths. Repeated-measures ANOVA with Greenhouse-Geisser correction for the SNR of all conditions (uncorrected,

PARAFAC, tPCA and ICA) revealed a significant main effect, $F(2.3, 44966.3) = 7550.7$, $p < 0.001$, $\eta = 0.28$. The uncorrected signal had the largest ratio of noise (-0.69), followed by the signal after ICA correction (-0.50), tPCA correction (-0.33), and PARAFAC correction (-0.31) (Table 1). Pairwise contrasts (Cohen, 1988) revealed that PARAFAC correction resulted in a significantly higher SNR compared to the uncorrected signal ($\eta = 0.45$), and the signal after correction with ICA ($\eta = 0.13$), both having a large effect size. Comparison of PARAFAC and tPCA, though statistically significant, revealed only a small effect size ($\eta = 0.002$). Repeated-measures ANOVA with Greenhouse-Geisser correction for the $R\lambda$ revealed a significant difference between the five conditions: $F(3.2, 30999.0) = 2686.46$, $p < 0.01$, $\eta = 0.22$. Mean $R\lambda$ coefficients showed the highest association between wavelengths for the uncorrected signal (0.74), followed by the signal after ICA correction (0.67), tPCA correction (0.53), PARAFAC correction (0.51) and the artifact-free reference signal (0.47) (Table 1). Contrasts of $R\lambda$ coefficients between PARAFAC and ICA ($\eta = 0.14$, large effect) as well as the uncorrected signal ($\eta = 0.35$, large effect) suggested that wavelengths were greatly less correlated after PARAFAC correction. Correction with PARAFAC resulted in slightly higher $R\lambda$ coefficients compared to segments without artifacts (artifact-free reference, $\eta = 0.01$, small effect), and slightly lower $R\lambda$ coefficients compared to correction with tPCA ($\eta = 0.01$, small effect).

Table 1 – Mean quality metrics for evaluation of artifact correction in the task-based data set.

Mean $\pm SD$	Artifact-free reference	PARAFAC	tPCA	ICA	Uncorrected artifact reference
Signal-to-noise ratio (dB)	N/A	-0.31 ± 0.58	-0.33 ± 0.57	-0.50 ± 0.64	-0.69 ± 0.65
Pearson's correlation between wavelengths ($R\lambda$)	0.47 ± 0.33	0.51 ± 0.38	0.53 ± 0.38	0.67 ± 0.38	0.74 ± 0.29

Results are displayed for the three decomposition techniques, parallel factor analysis (PARAFAC), target principal component analysis (tPCA) and independent component analysis (ICA), as well as for two reference signals, an artifact-free segment retrieved from the baseline before task onset, and the uncorrected signal consisting of all artifact segments before correction was applied.

3.2. Correction of Simulated Motion Artifacts

As a second step, we evaluated the performance of PARAFAC to correct simulated artifacts with varying parameters, see Fig. 3 for the composition of the different scenarios. Three similarity indices (PRD, RMSE, R) for the agreement of the initial (NIRS_{ini}) and the

corrected signal ($\text{NIRS}_{\text{PARAFAC/tPCA}}$), two quality measures (SNR, $R\lambda$) and the reconstruction of the synthesized HRF were used to quantitatively compare performance of PARAFAC to tPCA. The sample for each index (PRD, RMSE, R, SNR) consisted of 164 measures, corresponding to channels of both wavelengths. Since $R\lambda$ is a correlation coefficient between both wavelengths, the sample consisted of 82 values. For each simulation condition (1a to 1e, 2a to 2f, 3a to 3d), indices were computed for three correction conditions (=within-subject factor), i.e., the signal corrected with PARAFAC or tPCA and the uncorrected signal. Table 2 shows the results of the interaction effects between simulations and corrections as revealed by the repeated measures ANOVA. Results of post-hoc comparisons with Tukey correction are illustrated in Fig. 6 using the example of PRD. The results of the other indices are mostly in line with those. Detailed results for the RMSE, R, SNR and $R\lambda$ can be found in Fig. S 2-S 5 in the Supplemental Material, respectively.

Simulations 1a to 1e included artifacts with extra small, small, medium, large and extra-large amplitudes. Similarity indices (PRD, RMSE, R) revealed that both PARAFAC and tPCA resulted in a significant higher resemblance of the corrected signal and the initial signal compared to the uncorrected condition for all amplitude sizes except for the artifact with an extra small amplitude where tPCA did not lead to a significant improvement compared to the uncorrected signal. Similarly, both correction methods led to a significantly higher signal quality, i.e., lower SNR and $R\lambda$, compared to the uncorrected signal with the same exception for tPCA in the extra small amplitude, where no difference was observed to the uncorrected signal. When artifacts had a small, medium or extra-large amplitude, correction methods obtained comparable results over all indices and did not statistically differ. The most consistent differences between correction methods can be observed for the artifact with extra small and large amplitudes. While similarity metrics and quality measures revealed that PARAFAC achieved significantly better results than tPCA for the correction of artifacts with an extra small amplitude, for artifacts with a large amplitude tPCA seemed to have a slight but statistically significant advantage as compared to PARAFAC.

Table 2 – Interaction effects of the statistical comparisons between simulations and within correction methods

$[F(\text{df}), \eta^2_{partial}]$	Amplitude size (1a-1e)	Onset delay of second artifact (2a-2f)	Onset of the artifact relative to the HRF_{sim} (3a-3d)
PRD	67.14 (8, 1630)**, 0.248	4.98 (10, 1956)**, 0.025	26.67 (6, 1304)**, 0.109
RMSE	132.35 (8, 1630)**, 0.394	8.93 (10, 1956)**, 0.044	52.74 (6, 1304)**, 0.195
R	94.01 (8, 1630)**, 0.316	7.82 (10, 1956)**, 0.038	63.23 (6, 1304)**, 0.225
SNR	214.90 (8, 1630)**, 0.513	7.18(10, 1956)**, 0.035	61.31 (6, 1304)**, 0.220
$R\lambda$	115.96(8, 810)*, 0.534	2.36(10, 972)*, 0.024	22.06(6, 648)*, 0.170

The table shows the results for the five metrics, i.e., PRD, percent root difference, RMSE, root mean square error, R, product-moment correlation, the SNR, the signal-to-noise ratio and the $R\lambda$, Pearson's correlation coefficient, that were used to compare artifact correction with PARAFAC and targeted PCA among the different simulated noise scenarios. See Sect. 2.4 and Fig. S1 in the Supplemental Material for details regarding the simulations' parameters. *$p < 0.01$, **$p < 0.001$.

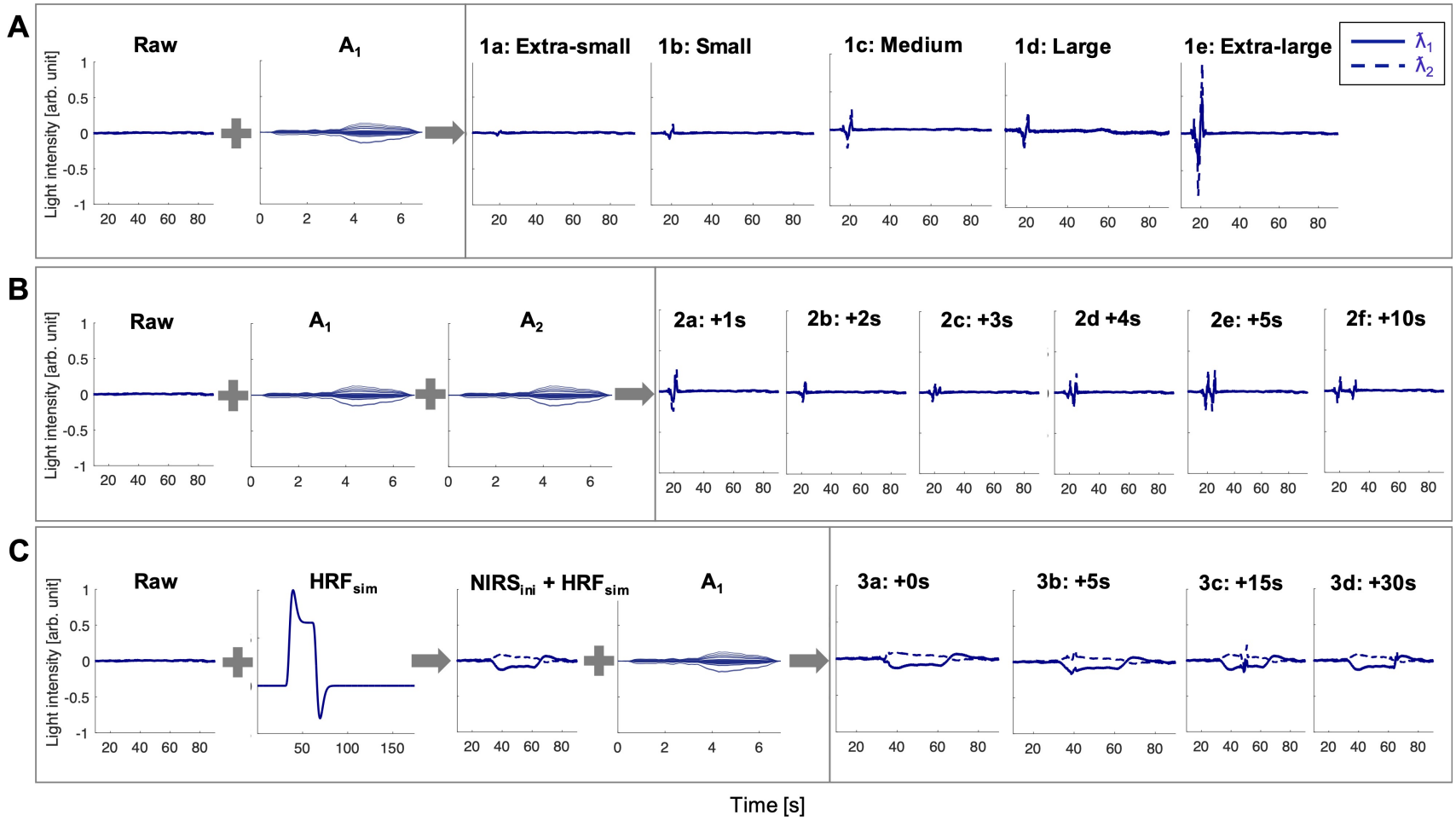

Figure 6 – Evaluation of correction in simulated motion artifacts based on signal similarity. Simulations are identified on the x-axis. (A) 1a to 1e: artifacts with different amplitude sizes; (B) 2a to 2f: complex artifacts with two superimposed artifacts and an onset delay between the first (A_1) and second artifact (A_2); and (C) 3a to 3d: the onset of the artifact relative to the beginning of a simulated HRF. Performance of artifact correction is illustrated by the use of the similarity index percent root difference (PRD), where a lower value represents higher resemblance between the corrected and the initial clean fNIRS signal, hence a better correction of the artifact. Results are displayed separately for the correction with PARAFAC (light gray bars) and tPCA (gray bars). The PRD of the uncorrected signal is not displayed in this figure but differed significantly from both correction techniques in all conditions, except where specified (n.s.) otherwise inside the bar. Significance level are based on post-hoc tests with Tukey correction. $^{***}p \leq 0.001$, n.s. $p > 0.05$. Uncorrected = NIRS_{ini} + artifact (A_1) without correction, PARAFAC = NIRS_{ini} + artifact (A_1/A_2) after artifact correction with PARAFAC, tPCA = NIRS_{ini} + artifact (A_1/A_2) after artifact correction with tPCA.

Simulations 2a to 2f led to signals with different onset delays (1-5 s and 10 s) between two superimposed artifacts, which allowed to create different complex artifacts. Over all conditions, notwithstanding their onset delay, similarity indices indicated a significantly higher overlap with the initial signal for the signal corrected with PARAFAC as compared to the one corrected with tPCA and the uncorrected signal. Similarly, quality metrics revealed a significantly higher signal quality after correction with PARAFAC compared to the correction with tPCA and the uncorrected signal. Nevertheless, tPCA also resulted in statistically significant better results as compared to the uncorrected signal in all conditions both with regard to the similarity metrics and the quality measures.

In simulations 3a to 3d the onset of an artifact varied relative to the beginning of a simulated HRF_{sim}: +0 s, +5 s, +15 s, and +30 s. Independent of the onset of the artifact, correction with PARAFAC resulted in a signal that showed a significantly higher overlap with the initial signal compared to the uncorrected condition. Similarly, quality measures showed a significant improvement of the signal's quality after correction with PARAFAC compared to the uncorrected signal. tPCA achieved almost identical results as PARAFAC in comparison to the uncorrected signal, except when the artifact was placed shortly after the beginning of the HRF_{sim} (+5 s) for which PRD and RMSE did not show a significant difference between the uncorrected signal and the one corrected with tPCA. Further, for artifacts at the very beginning (+0 s), shortly after (+5 s) or at the very end (+30 s) of the HRF_{sim} (at the same time than the low-frequency increase or decrease that is intrinsic to the HRF_{sim}), similarity indices revealed a significant better overlap of the corrected signal with the initial signal after correction with PARAFAC as opposed to tPCA. In contrast, tPCA compared to PARAFAC seemed to have a significant advantage for the correction of artifacts during the plateau of the HRF_{sim} (+15 s), which might be explained by a higher orthogonality between the artifact and the signal at this onset. Quality measures however only partially support these findings, namely in favor of correction with tPCA for the artifact at the beginning (+0 s) and in favor of PARAFAC for the artifact shortly after (+5 s) the beginning of the HRF_{sim}. When the artifact is at the very beginning of the HRF_{sim} (+0 s), signal quality is however significantly higher after correction with tPCA as compared to PARAFAC. There is no statistically significant difference between signal quality for any of the correction methods when the artifact is placed at the very end of the HRF_{sim} (+30 s). Further, results of the GLM revealed that in none of the conditions the simulated artifact led to an important reduction of the variance explained by the HRF_{sim} as compared to the initial signal (Table 3). In line with the results of the similarity metrics, reconstruction of the HRF after correction with PARAFAC was qualitatively better as compared to tPCA when the artifact occurred at the beginning (+0 s), shortly after (+5 s) and at the end (+30 s) of the HRF. In particular, for the artifact 5 s after the onset of the HRF, reconstruction after correction with tPCA

seemed disturbed. There was no important difference between correction methods for the reconstruction of the HRF when the artifact was during the plateau of the HRF (+15 s).

Table 3 – Percentage of explained variance by the HRF_{sim} based on the R^2 of the GLM.

Mean ± SD	Initial	Uncorrected	PARAFAC	tPCA
3a: HRF + 0 s	95.16 ± 16.24	94.88 ± 16.49	95.18 ± 15.68	94.23 ± 18.33
3b: HRF + 5 s	95.16 ± 16.24	94.43 ± 7.84	94.54 ± 7.78	86.96 ± 12.81
3c: HRF + 15 s	95.16 ± 16.24	95.00 ± 16.16	95.10 ± 16.27	95.18 ± 16.20
3d: HRF + 30 s	95.16 ± 16.24	95.14 ± 16.25	94.92 ± 16.26	91.83 ± 15.89

Results are displayed for the three decomposition techniques, parallel factor analysis (PARAFAC), target principal component analysis (tPCA) and independent component analysis (ICA), as well as for two reference signals, an artifact-free segment retrieved from the baseline before task onset, and the uncorrected signal consisting of all artifact segments before correction was applied.

Orthogonality measure for the relation of the time courses of the raw signal and the artifact signal (Raw x A_1: r_a) were calculated for all simulations, orthogonality for the time courses of the raw signal with the first artifact and the second artifact (RawA_1 x A_2: r_b) was only computed for simulations of complex artifacts (2a to 2f). A value of one, represented maximum orthogonality between both signals meaning they are in a 90 deg angle to each other. Any value smaller than one or even zero indicated nonorthogonality meaning that they are in any other angle than 90 deg, maximally zero or 180 deg to each other. Results of r_a revealed consistently high orthogonality for all simulations with varying amplitudes (Min = Max = 0.97) and with complex artifacts (Min = 0.97, Max = 0.98). Orthogonality for the simulations with the HRF revealed more variations (Min = 0.88, Max = 0.97) where the artifact 30 s after the HRF_{sim} created the least orthogonal condition (Median ± standard error: 0.88 ± 0.03), followed by the simulation with the artifact at 0s (Median ± standard error: 0.93 ± 0.05), 5 s (Median ± standard error: 0.96 ± 0.01) and 15 s (Median ± standard error: 0.97 ± 0.01) of the HRF_{sim}. Results of the second orthogonality measure r_b indicated that the onset delay of 2 s led to the least orthogonal condition (Median ± standard error: 0.75 ± 0.07), followed by the delay of 3 s (Median ± standard error: 0.93 ± 0.02) and 5 s (Median ± standard error: 0.98 ± 0.02). When the second artifact had a delay of 1 s, 4 s or 10 s, there was equally high orthogonality for all three conditions (Median ± standard error: 0.99 ± 0.02).

4. Discussion

Promising results have been reported by using parallel factor analysis (PARAFAC) for multidimensional ($n \geq 3$) data analysis in EEG data (Martínez-Montes et al., 2004; Miwakeichi et al., 2004; Mørup et al., 2006). Since the fNIRS signal has inherently three dimensions, time × space × wavelength, we aimed to extend the application of PARAFAC to fNIRS and validate its use for artifact correction. First, we explored the usefulness of PARAFAC to correct movement artifacts in a data set of task-related fNIRS signals acquired during an expressive language paradigm. Performance of artifact correction was evaluated by the use of two signal quality metrics, (1) the SNR considering the signal's variance during the simulated intervals after correction; and (2) the temporal similarity between both wavelengths during the simulated intervals after correction ($R\lambda$). Quality measures after correction with PARAFAC were compared to those obtained after the use of two commonly used decomposition methods in fNIRS (i.e., tPCA and ICA). Second, several scenarios with simulated artifacts in a clean resting-state signal were computed to assess the performance of artifact correction with PARAFAC and its homologue 2D target decomposition technique (tPCA) in a controlled setting. Simulated artifacts had five amplitude sizes, six levels of temporal overlap with a second artifact to create complex artifactual events and were added at four different time points of a simulated HRF. We compared the performance of both correction methods using (1) similarity indices describing the degree of correspondence between the corrected signal after removal of simulated artifacts and the artifact-free signal before simulation (RMSE, PRD, and R); and (2) the two quality measures, SNR and $R\lambda$, already used for the task-related signal.

With regard to motion artifact correction in the task-based data set, the signal after artifact correction with PARAFAC had the smallest SNR among the three methods (PARAFAC, tPCA, ICA), suggesting that more of the variance related to the artifact had been removed and a better signal quality was achieved. Similarly, correction with PARAFAC led to the lowest correlation between HbO and HbR indices, as well as the correlation index that most resembled the nonartifactual resting-state baseline reference. Even though the resting-state signal has been reported to show slightly different hemodynamic changes as compared to a stimuli-induced cerebral activity (T. T. Liu, 2013; H. Zhang et al., 2010), we consider it a suitable reference for a time interval without artifacts, because it was not affected by articulation. In line with previous findings, our analyses also revealed a robust advantage in applying target corrections (tPCA and PARAFAC) instead of whole-block (ICA) correction, resulting in a better signal quality (Behrendt et al., 2018; Kamran et al., 2016). ICA was indeed applied to the entire signal as reported in the literature (H. Zhang et al., 2010), while tPCA and PARAFAC were used in a target manner, i.e., only decomposing the signal during specific intervals where artifacts had been detected. As proposed by Yücel and colleagues

(2014), target artifact correction prevents large changes in the overall composition of the signal, and exclusively corrects the noisy time interval of the artifact. It allows the decomposition to clearly sort a component representing the artifact signature, without considering the characteristics of these channels during the intervals without artifacts. Target decomposition is thus beneficial for a precise identification of the artifact's signatures and PARAFAC for artifact correction in fNIRS should also be applied in a target manner.

Results of the conducted simulations with controlled parameters suggest that artifact correction with PARAFAC led to a signal that corresponded more closely to the initial signal, as compared to the uncorrected signal. Similarly, PARAFAC yielded a significant better signal quality as compared to the uncorrected signal. This result is a preliminary validation of the use of PARAFAC for artifact correction in fNIRS signals and similarity measures show that the signal comes close to the original signal, thus it does not remove large parts of the physiological or relevant activity. While correction with tPCA in most cases also led to better results compared to the uncorrected signal, it has to be mentioned that its performance was less consistent over conditions. tPCA correction of an artifact with an extra small amplitude for instance did not lead to a significant improvement compared to the uncorrected signal. This is probably due to the ability of the numerical engine to extract a component that explains a small portion of the data variance and list such a component among the first one or two components, which is related to the signal-to-noise ratio of the signals. In a real data set, such a small artifact might however not have been detected and it might not even have disturbed the interpretation of the hemodynamic signal. This result's significance is thus limited. Further, in almost all scenarios correction with PARAFAC compared to tPCA led to either better or comparable results. Especially, when the artifact was simulated along with a simulated HRF, PARAFAC showed superior and more robust results compared to tPCA. According to the applied orthogonality measure, those conditions where tPCA showed a poor performance were exactly those where the artifact and the simulated HRF were less orthogonal. This is in line with the assumption that decomposition with PARAFAC is not affected by nonorthogonality given there is enough information in the wavelength dimension to differentiate nonorthogonal artifacts due to their different profile in both wavelengths. Only in two simulations, namely when the artifact had a large amplitude or was during the plateau of the simulated HRF (where the orthogonality between the $\mathrm{HRF}_{\mathrm{sim}}$ and the artifact was the highest), correction with tPCA outperformed PARAFAC. It does not come as a surprise that tPCA outperforms PARAFAC when a perfectly orthogonal artifact is added to the physiological signal, as this is exactly its main assumption, which is not for PARAFAC. Finally, results of the GLM indicate that artifact correction with PARAFAC did not negatively affect the recovery of the simulated HRF, which suggests that it successfully targeted the artifact signature and did not induce changes of the signal that would alter interpretation of the underlying hemodynamic response. Even though this is an encouraging result, it has

to be mentioned that similar results were achieved for the HRF_{sim} of the uncorrected signal, suggesting that the simulated artifact did not have a very strong impact on the signal and the interpretation of the HRF_{sim}. This could be different for more complex artifacts where correction may not sufficiently work or more likely, when not using the same linear model to simulate and subsequently recover the HRF. In most cases correction with tPCA allowed a similarly good recovery of the simulated HRF, but was strongly affected when an artifact was placed shortly after the beginning of the HRF_{sim}, i.e., when the assumption of orthogonal artifact is not perfectly met. This is in line with the findings for the similarity and quality metrics for this scenario.

Regarding the comparison of both targeted decomposition techniques, the small effect size of the difference between tPCA and PARAFAC in the task-based data set suggests that both target correction techniques led to a similar reduction of the variance induced by motion artifacts and to an equal reduction of correlation between both wavelengths. Even though correction of simulated artifacts outlined certain advantages of PARAFAC compared to tPCA in some conditions, there was no consistent difference between both methods when applied to large data sets of real movement artifacts in a verbal fluency task. Since it was previously emphasized that performing accurate simulations of real motion artifacts is challenging, validation of an artifact correction technique in real data is a crucial step (Brigadoi et al., 2014). We can conclude that its performance both in real and simulated data was generally equally good as tPCA and slightly better under certain conditions, suggesting the validation of PARAFAC as a new tool for artifact correction in fNIRS data.

What is more, PARAFAC's core strength compared to tPCA is mainly related to its conceptualization. The use of a decomposition approach considering the multidimensional structure of the fNIRS signal where a unique decomposition is achieved with few constraints, i.e., without imposing orthogonality nor independence, is appropriate and seems advantageous compared to tPCA as well as ICA (Mørup, 2011; Mørup et al., 2006). Even though the results of the simulations provide some support that artifact correction with PARAFAC was not affected by nonorthogonality, orthogonality did not sufficiently vary among simulations and mostly reached a high orthogonality as we used resting state as background data. Nevertheless, given that in real data, the ground truth about the signal's composition of noise is unknown and orthogonality cannot be verified, it is safe to say that PARAFAC represents a robust approach for artifact correction in fNIRS. Two-dimensional decomposition, such as ICA and tPCA, analyzes both wavelengths as independent measures of the fNIRS signal, even though they are in fact highly related, since they are acquired at the same location (Cui et al., 2010). Since the estimation of the hemodynamic signal is based on the signal of both wavelengths (Kocsis et al., 2006), reliable conclusions require the signal to be clean in both of them. It is also worth to notice that for artifact correction, we have followed in all our simulations the assumption that both wavelengths are affected by artifacts equally across channels (just with

a different general scale). This is in fact the worst case for PARAFAC, as it will give better results if there are larger differences in all dimensions of the data. Therefore, we could expect an improved performance when artifacts have even small differences between the spatial distributions for the two wavelengths.

Decomposition with PARAFAC offers a rather easy way to make a selection of relevant components that differentiate between signatures related to artifacts or other relevant characteristics of the signal. Even if fNIRS is considered to be less sensitive to movements -as compared to other neuroimaging techniques such as fMRI and signal quality should be controlled during data acquisition as much as possible, appropriate tools for artifact correction are an essential part of preprocessing in fNIRS, particularly for data acquired in populations where cooperation is limited, such as children and clinical populations (Brigadoi et al., 2014; Tak et al., 2015; Yücel et al., 2021). PARAFAC thus appears to be a suitable and robust alternative to the currently used approaches and will be a valuable add-on for fNIRS studies and clinical examinations by minimizing the amount of nonusable data and improving data quality. That being said, the researcher always has to weigh the means of applying artifact correction and should not do so without visual inspection of the decomposition signature. It is the overall quality of a data set, i.e., the amount of clean signal, and the duration, extent and moment of the artifact that ought to influence the researcher's choice to reject data sets, to apply artifact correction and to proceed with analysis.

4.1. Usefulness and Limitations of PARAFAC

PARAFAC is a data-driven approach based on the linear relations of the three dimensions of the fNIRS signal (Bro, 1998; Martínez-Montes et al., 2004; Möcks, 1988). PARAFAC has the advantage of allowing for the three-way arrays of data to be uniquely decomposed into a sum of components, each of which is a trilinear combination of factors or signatures. The only statistical requirements of PARAFAC is that of a moderate linear independence across components, i.e., their time course, topography and wavelength characteristics. This is a less stringent requirement than previous models that underlie space/time decompositions (PCA or ICA). Each component provides characteristics of a particular pattern identified within the mixed measured fNIRS signal. When there are empirical or theoretical reasons to expect more than one relevant component (e.g., resting state functional connectivity analysis, epileptic activity, physiological aspects, and so on), PARAFAC would also allow disentangling several components. Moreover, when there are reasons to include other constraints such as orthogonality, nonnegativity, smoothness and sparseness of the signatures, it has been shown that PARAFAC can also include them in the decomposition procedure (Bro, 1998; Martínez-Montes, Sánchez-Bornot, et al., 2008; Martínez-Montes, Vega-Hernández, et al., 2008).

Different from ICA, PARAFAC components can be ordered according to their importance in explaining the data's variance (Poeppel et al., 2012). This is why many studies using ICA apply data reduction or clustering techniques such as PCA prior to the execution of ICA (Makeig, 2002; H. Zhang et al., 2010). Moreover, when using PARAFAC, the description of the data is based on more dimensions, and with less theoretical constraints (orthogonality, independence) which lead to the identification of fewer relevant components (Deburchgraeve. et al., 2009; Martínez-Montes et al., 2004; Miwakeichi et al., 2004; Sidiropoulos & Bro, 2000). Compared to ICA, the selection of the relevant components is thus simplified. Importantly, when using PARAFAC, it is not recommended to ask for more than five components, as this increases the risk of overfitting the data with the decomposition model. Even though the issue of selecting the optimal number of components should be better explored and standardized in future studies, based on our experience and previous studies, usually, three to five components sufficiently describe the signal's relevant characteristics (Acar et al., 2007; Bro, 1998; Harshman, 1970; Martínez-Montes et al., 2004; Miwakeichi et al., 2004). The Corcondia index provides further information regarding a good fit of the PARAFAC model and the analyzed data. Precisely, a satisfying decomposition should have a core consistency of 85% or higher and usually drops below 80% if an extra component is extracted, suggesting overfitting (Bro & Kiers, 2003). Similar to PCA, a typical choice made when using PARAFAC analysis, is that of ordering the extracted components according to their contribution to explaining the variance of the data. In this sense, it can be expected that the first PARAFAC component will always represent the highest activity, which, in the case of target artifact correction, will correspond to the artifact activity. This makes PARAFAC also a promising choice to explore the development of simple automatic methodologies for the detection and correction of such artifacts. Relevant components for artifact correction could for instance be selected based on the amplitude size or the differences between scores for the two wavelengths. Despite being a time efficient and promising approach, we believe that at the current state visual verification cannot be ceased, because depending on the paradigm, noise may have characteristics that render automatic processing inadequate. Future studies should be devoted to this specific aim.

Some challenges of PARAFAC have already been discussed in previous studies (Martínez-Montes et al., 2004; Miwakeichi et al., 2004). One limitation is related to PARAFAC's assumption of linear relations of the temporal characteristics between different channels (which also applies to (t)PCA and ICA). Despite being one of the most common and simple models, imposing linearity may not entirely reflect complex cerebral processes (Huppert, 2016). Some attempts have been made to introduce approaches that tolerate nonlinear relations (Freiwald et al., 1999; M. Hu & Liang, 2014). However, to date, linear models remain the most popular and adequate approach for analysis of macroscopic data in neuroscience. Thus, it represents a general limit of the domain, rather than one specific to PARAFAC. Another

potential limitation of our implementation of PARAFAC might arise from the specific use of the simple alternating least-squares algorithm to perform the decomposition. Other methods have been proposed for estimating PARAFAC models, but some studies have shown that, given the uniqueness of the solution, they do not usually outperform the simple least-squares technique (Faber et al., 2003).

The need for careful preprocessing of data before characterizing brain activity constitutes another limitation. When PARAFAC was introduced for the analysis of EEG data, the authors emphasized the importance of searching for constant factors, outliers, and degeneracy (Field & Graupe, 1991; Miwakeichi et al., 2004). Detailed information on how to deal with these aspects can be found in previous literature (Miwakeichi et al., 2004). In the current study, the implementation of PARAFAC into the LIONirs toolbox (J. Tremblay et al., 2022), gave us a certain flexibility regarding the channels and time segments to be included. Thus, we were able to exclude deviant channels prior to use PARAFAC.

Finally, among the applications of PARAFAC not yet tested in fNIRS, is its use to identify patterns of brain activity in the hemodynamic response as it has been applied in EEG data analysis (Acar et al., 2007; Miwakeichi et al., 2004; Mørup et al., 2006). Compared to other techniques such as GLM or global averaging who treat each channel independently and provide a narrower spatial representation of the dominant activation, PARAFAC analysis could reveal a wider distributed activation pattern. This would strongly correspond to the current understanding of cerebral processing, whereby mostly large-scale networks, and not isolated regions, are considered to be involved in various cognitive processes (Jasdzewski et al., 2003; T. Sato et al., 2016; Tak et al., 2015). PARAFAC could thus appear to be suitable for reflecting cerebral processes occurring in distributed networks, rather than for the identification of a specific core region. This is obviously given a sufficient fNIRS covering. Moreover, the topographic signature would correspond to a whole time course of the extracted activations and can easily be subjected to diffusion optical tomography in order to locate the HbO and HbR concentration changes in the brain cortex (J. Tremblay et al., 2018). Another potential application is using PARAFAC as a screening tool. For instance, Miwakeichi and colleagues (2004) applied PARAFAC to an EEG dataset in order to extract one component related to ocular movement artifacts, and subsequently used the PARAFAC analysis fixing spatial and spectral signatures of that component to screen a second dataset in order to identify and correct similar artifacts. This application can also support the development of a detection method as has already be done in other fields such as detection of epileptic seizures (Acar et al., 2007; Ontivero-Ortega et al., 2015) and for brain-computer interfacing (Cichocki et al., 2008; Eliseyev & Aksenova, 2013; Eliseyev et al., 2012; Nazarpour et al., 2006). Although this can be useful for correcting artifacts that have consistent topographical and wavelength profiles, movement artifacts were mostly related to articulation in our study,

often showing quite different signatures. A different paradigm may enable the testing of this application of PARAFAC in fNIRS.

Our findings also encourage the general application of PARAFAC for multidimensional decomposition in neuroimaging, where data can often be described in more than two dimensions. PARAFAC could for instance be of interest for fNIRS data acquired with a multi-wavelength ($>$ 2 wavelengths) system (Bale et al., 2016; Highton et al., 2018). Beyond the obvious dimensions of a technique such as that of time $\times$ space $\times$ wavelength (fNIRS) or frequency (EEG), characteristics of the task paradigm or group variables could also be considered in the decomposition model (Mørup et al., 2006). For instance, if a "group" dimension was to be included, groups could be compared regarding their relative weight over the main cerebral activation component that would have been outlined from the PARAFAC model.

4.2. Limits of the Current Study

The use of a language paradigm allowed for the induction of artifacts that were mainly related to articulation and often overlapped with the stimulus onset. This makes identification and correction of artifacts particularly challenging and may limit the generalization of our results. From video recordings, however, we were able to acknowledge that swallowing, jaw or tongue movements, eye blinks, and frowning also induced artifacts in our data set. Our results particularly contribute to an improved artifact correction in a paradigm where artifacts can pose a significant problem for interpretation. The validation of PARAFAC in a realistic scenario represents an important advantage because simulated artifacts either completely artificial or by instruction of participants to make certain movements, rarely live up to the complexity and variability of real spontaneous artifacts (Brigadoi et al., 2014). Even though the simulated artifacts were also based on one identified during the task-condition, parameters were modified and allowed to create noise with different characteristics. Further fNIRS studies using PARAFAC, and including different task paradigms, resting-state, and recording in naturalistic environments when participants are moving or are instructed to perform specific movements, could show its utility for a wider range of artifacts (e.g., baseline shifts or physiology).

The validation of PARAFAC for artifact correction was conducted by comparing results with two other decomposition techniques. This could be considered one limit of the present study, because we did not consider other correction approaches for comparison. The objective of this study was not to conduct exhaustive and systematic comparisons in order to identify the best method for artifact correction, but rather to introduce PARAFAC as an alternative and adequate method in fNIRS analysis. Future studies could therefore expand the validation of PARAFAC and extend comparisons of its performance to other tools that do not necessarily use decomposition, such as spline interpolation or wavelet filtering. With relation to that,

even if there were to be a slight advantage of PARAFAC over tPCA in artifact correction results, the small difference might not have a concrete impact on the applicability of those two methods. Qualitative differences between tPCA and PARAFAC regarding the type of artifacts and corrected signal should be further assessed and described in subsequent studies to better understand how their efficacy may vary according to the artifact's characteristics.

Last but not least, PARAFAC's components related to artifacts were selected during a visual inspection based on their temporal overlap with the artifact, i.e., sudden change of amplitude, and those showing similar weights for both wavelengths. The smallest number of possible components that sufficiently corrected the artifact were selected. Even though our results show that this procedure led to satisfying correction, it is not a fully standardized procedure which may hamper an easier, automatic correction that would reduce the need of the researcher's expertise in detecting and adequately applying correction. This issue could be addressed using the screening procedure mentioned in the previous section or using other templates for the artifacts of interest or by applying the usual automatic rules based on amplitude characteristics to the temporal signatures obtained by PARAFAC instead of the original mixed data. The goal of the current study was not to propose a method for artifact detection but to validate the relative efficacy of these methods in artifact correction. It would be interesting for future studies to address the development of a more automatic procedure based on PARAFAC analysis contributing to a faster and standardized processing pipeline.

5. Conclusion

PARAFAC has the advantage to simultaneously treat both wavelengths or HbO and HbR during fNIRS data analyses. Our findings from real task-related signals and controlled simulations validate previous results in EEG data and promote multidimensional decomposition with PARAFAC as a promising new tool for the correction of movement artifacts in fNIRS. Precisely, PARAFAC achieves comparable results as tPCA when the artifact's signature is simple and clearly distinguishable from the signal. It outperforms tPCA mainly when artifacts have small amplitude, show a complex temporal signature or when they co-occur during an HRF. These results can partially be attributed to low orthogonality between signal and noise. The advantages of PARAFAC and tPCA, as compared to ICA, are consistent and seem to be due to the target application. Further, PARAFAC has a strong advantage compared to both 2D decomposition techniques because it offers a unique decomposition without orthogonality or independence constraints, hence represents a robust decomposition technique. The validation of its use paves the way for future use in fNIRS research to extract relevant signatures represented in the fNIRS signal.

6. Disclosures

We have nothing to disclose.

7. Acknowledgments/Funding sources

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8. Code, Data, and Materials Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

9. Supplemental Material

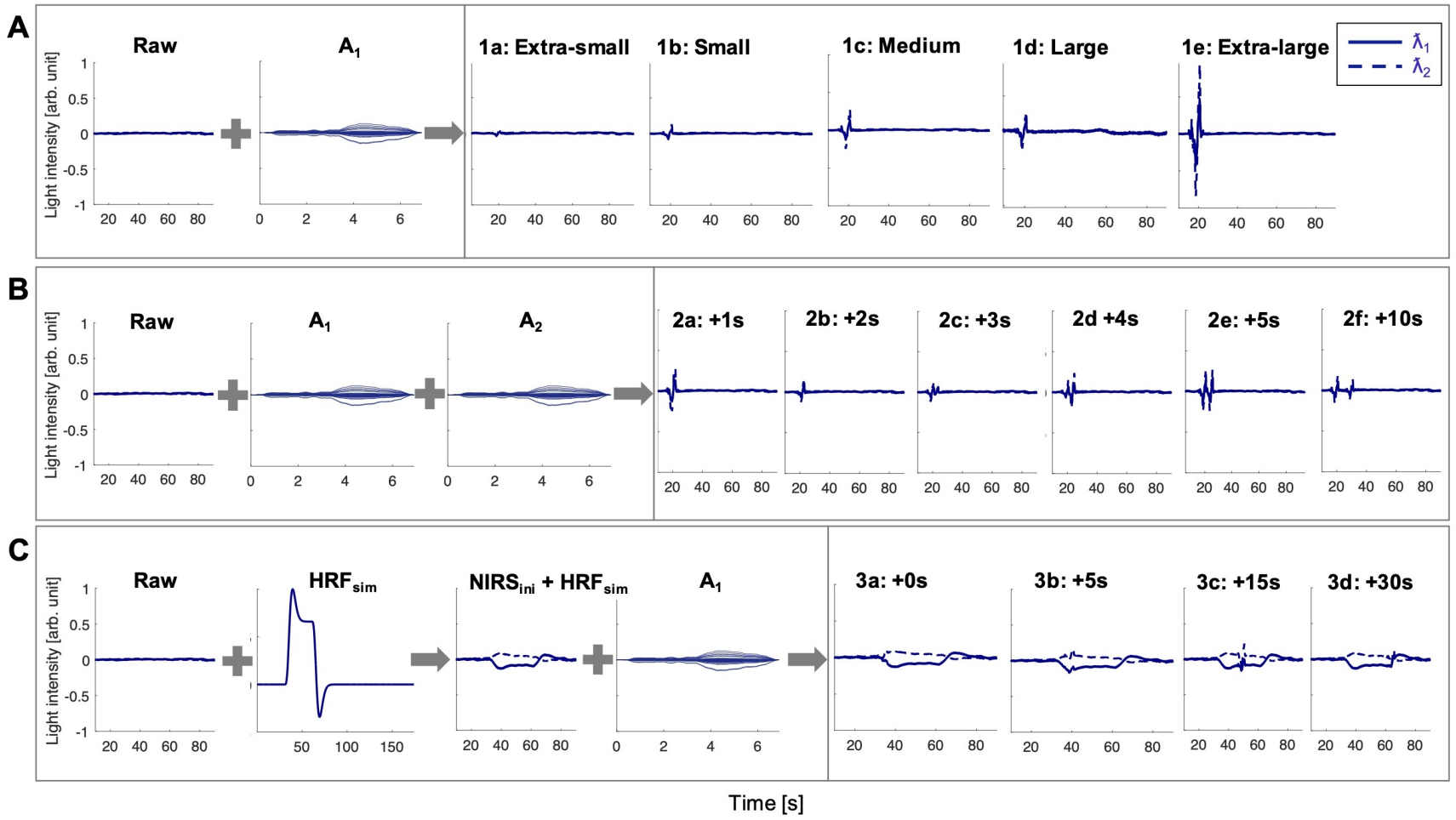

Figure S 1 – Parameters of all simulations. One or two real motion artifact(s) ($A_{1/2}$) and a synthesized HRF (HRF_{sim}) were added to a normalized resting-state fNIRS signal (Raw). (A) shows simulations 1a to 1e with an artifact of varying amplitude sizes, (B) simulations 2a to 2f with a complex artifact where the onset of the second artifact (A_2) was varied relative to the onset of the first artifact (A_1), and (C) simulations 3a to 3d with varying onset of the artifact relative to the beginning of the HRF_{sim}. $\lambda 1|2 = 690|830$ nm.

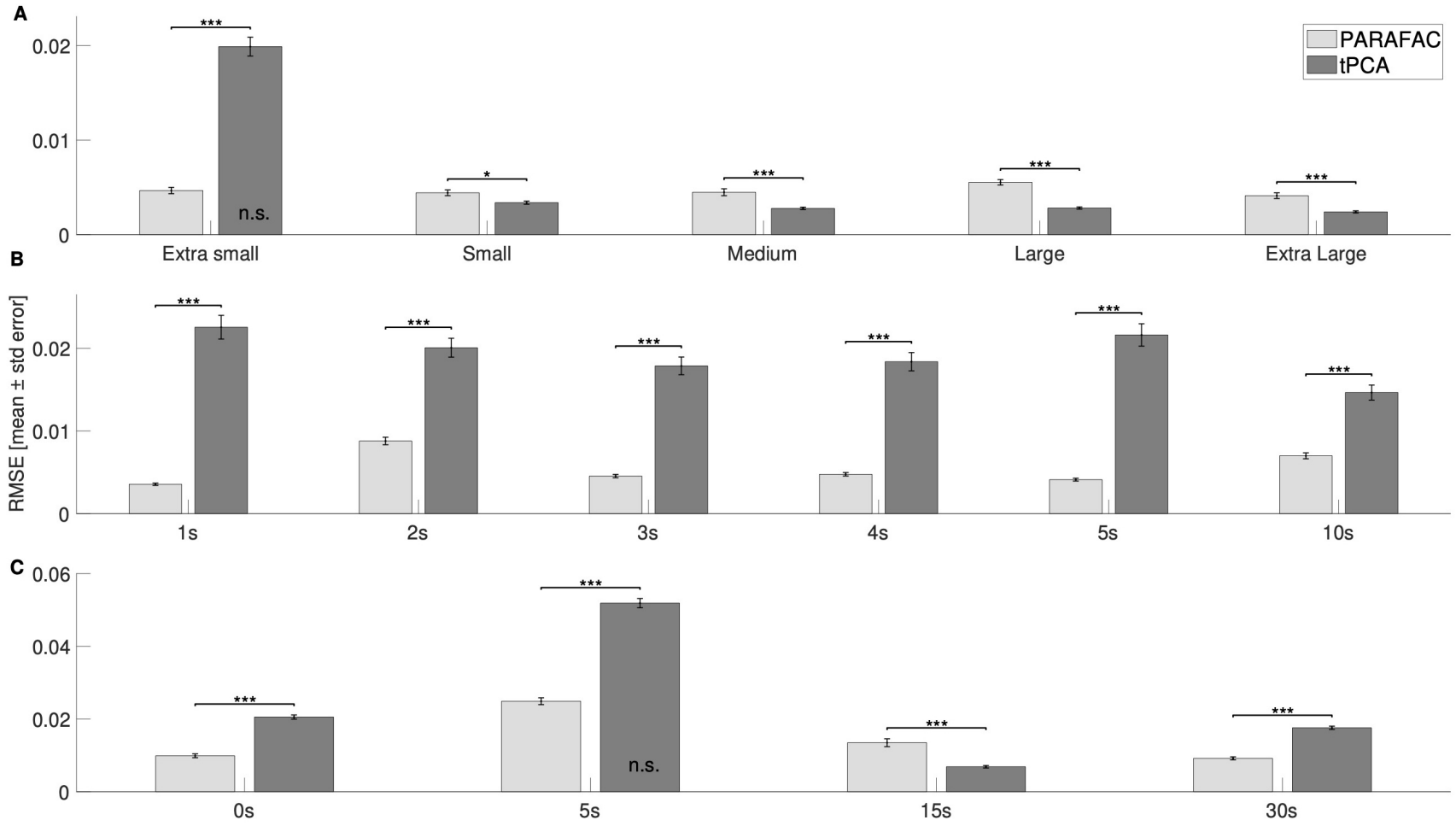

Figure S 2 – Evaluation of correction in simulated motion artifacts based on signal similarity by the use of the root mean square error (RMSE). Simulations are identified on the x-axisis. (A) 1a to 1e: artifacts with different amplitude sizes; (B) 2a to 2f: complex artifacts with two superimposed artifacts and an onset delay between the first (A_1) and second artifact (A_2); and (C) 3a to 3d: the onset of the artifact relative to the beginning of a simulated HRF. A lower RMSE represents higher resemblance between the corrected and the initial clean fNIRS signal, hence a better correction of the artifact. Results are displayed separately for the correction with PARAFAC (light gray bars) and tPCA (gray bars). The RMSE of the uncorrected signal is not displayed in this figure but differed significantly from both correction techniques in all conditions, except where specified otherwise inside the bar. Significance level are based on post-hoc tests with Tukey correction. $^*p \leq 0.05$, $^{***}p \leq 0.001$, n.s. $p > 0.05$. Uncorrected = NIRS_{ini} + artifact (A_1) without correction, PARAFAC = NIRS_{ini} + artifact ($A_{1/2}$) after artifact correction with PARAFAC, tPCA = NIRS_{ini} + artifact ($A_{1/2}$) after artifact correction with tPCA.

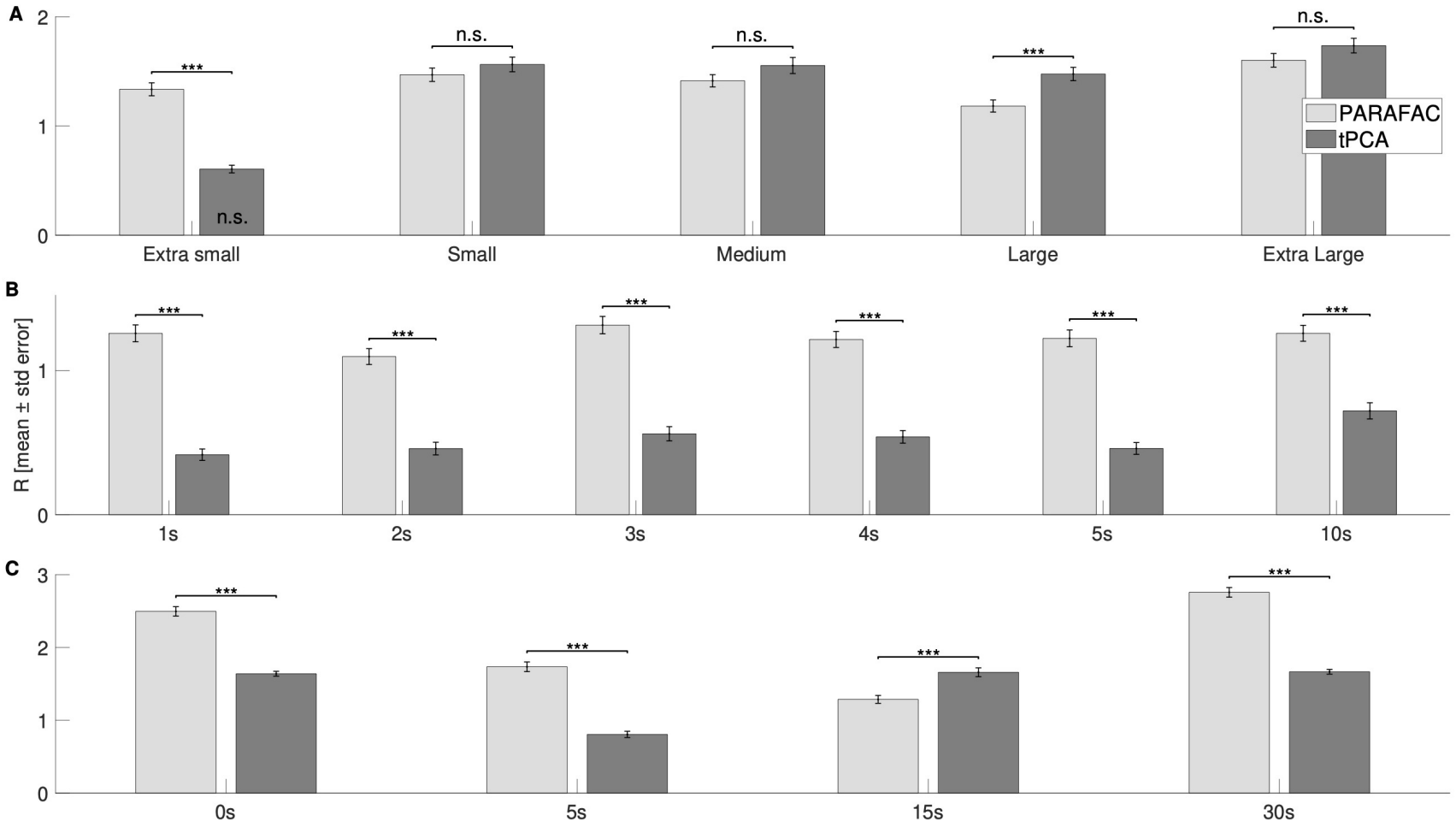

Figure S 3 – Evaluation of correction in simulated motion artifacts based on signal similarity by the use of the Pearson product-moment correlation coefficient (R). Simulations are identified on the x-axis. A: 1a-e) artifacts with different amplitude sizes; B: 2a-f): complex artifacts with two superimposed artifacts and an onset delay between the first (A_1) and second artifact (A_2); and C: 3a-d) the onset of the artifact relative to the beginning of a simulated HRF. A higher R represents higher resemblance between the corrected and the initial clean fNIRS signal, hence a better correction of the artifact. Results are displayed separately for the correction with PARAFAC (light gray bars) and tPCA (gray bars). The R of the uncorrected signal is not displayed in this figure but differed significantly from both correction techniques in all conditions, except where specified otherwise inside the bar. Significance level are based on post-hoc tests with Tukey correction. $^*p \leq 0.05$, $^{***}p \leq 0.001$, n.s. $p > 0.05$. Uncorrected = NIRS_{ini} + artifact (A_1) without correction, PARAFAC = NIRS_{ini} + artifact ($A_{1/2}$) after artifact correction with PARAFAC, tPCA = NIRS_{ini} + artifact ($A_{1/2}$) after artifact correction with tPCA.

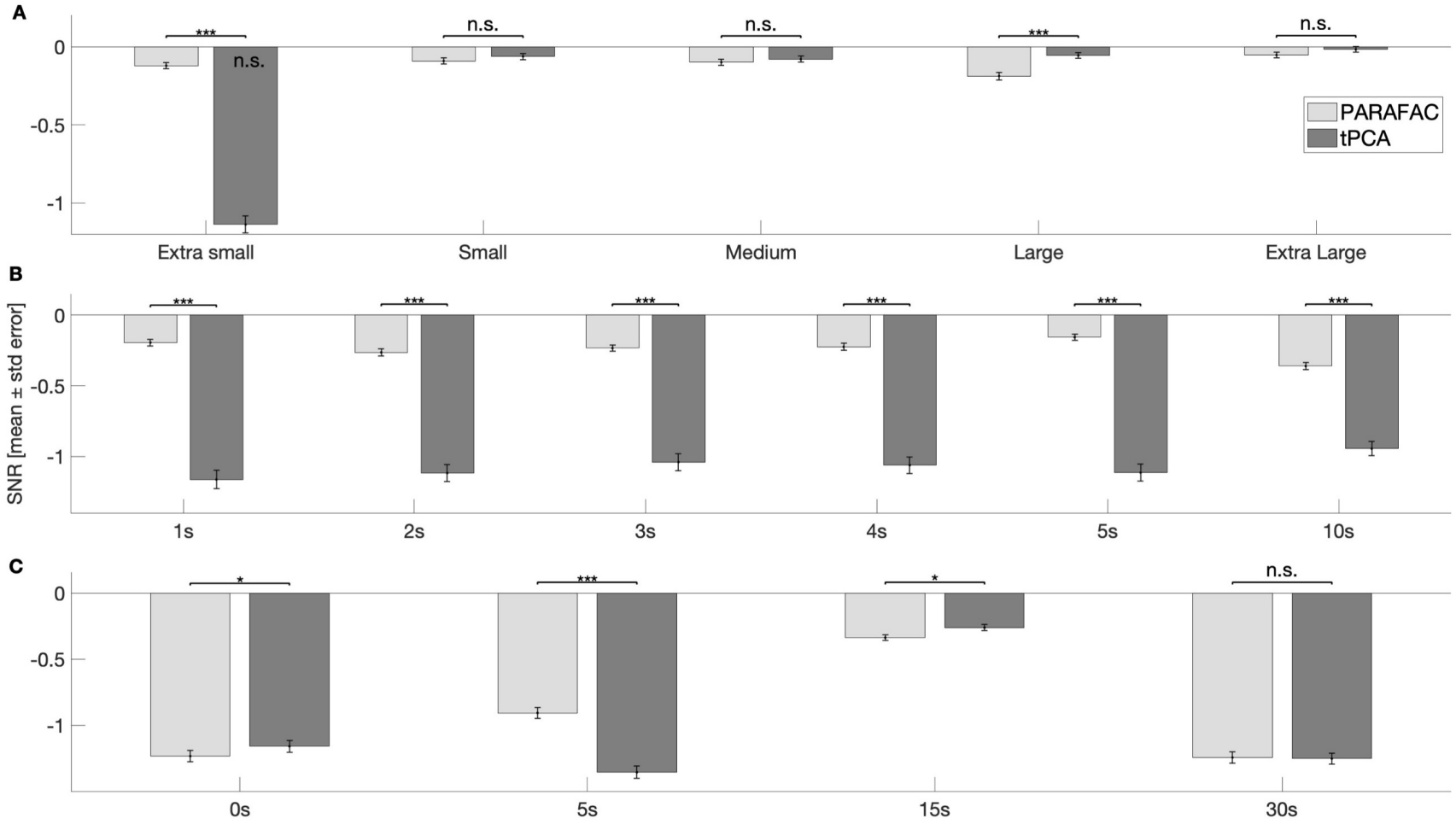

Figure S 4 – Evaluation of correction in simulated motion artifacts based on signal similarity by the use of the signal-to-noise ratio (SNR). Simulations are identified on the x-axis. (A) 1a to 1e: artifacts with different amplitude sizes; (B) 2a to 2f: complex artifacts with two superimposed artifacts and an onset delay between the first (A_1) and second artifact (A_2); and (C) 3a to 3d: the onset of the artifact relative to the beginning of a simulated HRF. An SNR closer to 0 represents a more equal ratio between the signal's variation during the artifact period and the clean signal. Results are displayed separately for the correction with PARAFAC (light gray bars) and tPCA (gray bars). The SNR of the uncorrected signal is not displayed in this figure but differed significantly from both correction techniques in all conditions, except where specified otherwise inside the bar. Significance level are based on post-hoc tests with Tukey correction. $^*p \leq 0.05$, $^{***}p \leq 0.001$, n.s. $p > 0.05$. Uncorrected = NIRS_{ini} + artifact (A_1) without correction, PARAFAC = NIRS_{ini} + artifact ($A_{1/2}$) after artifact correction with PARAFAC, tPCA = NIRS_{ini} + artifact ($A_{1/2}$) after artifact correction with tPCA.

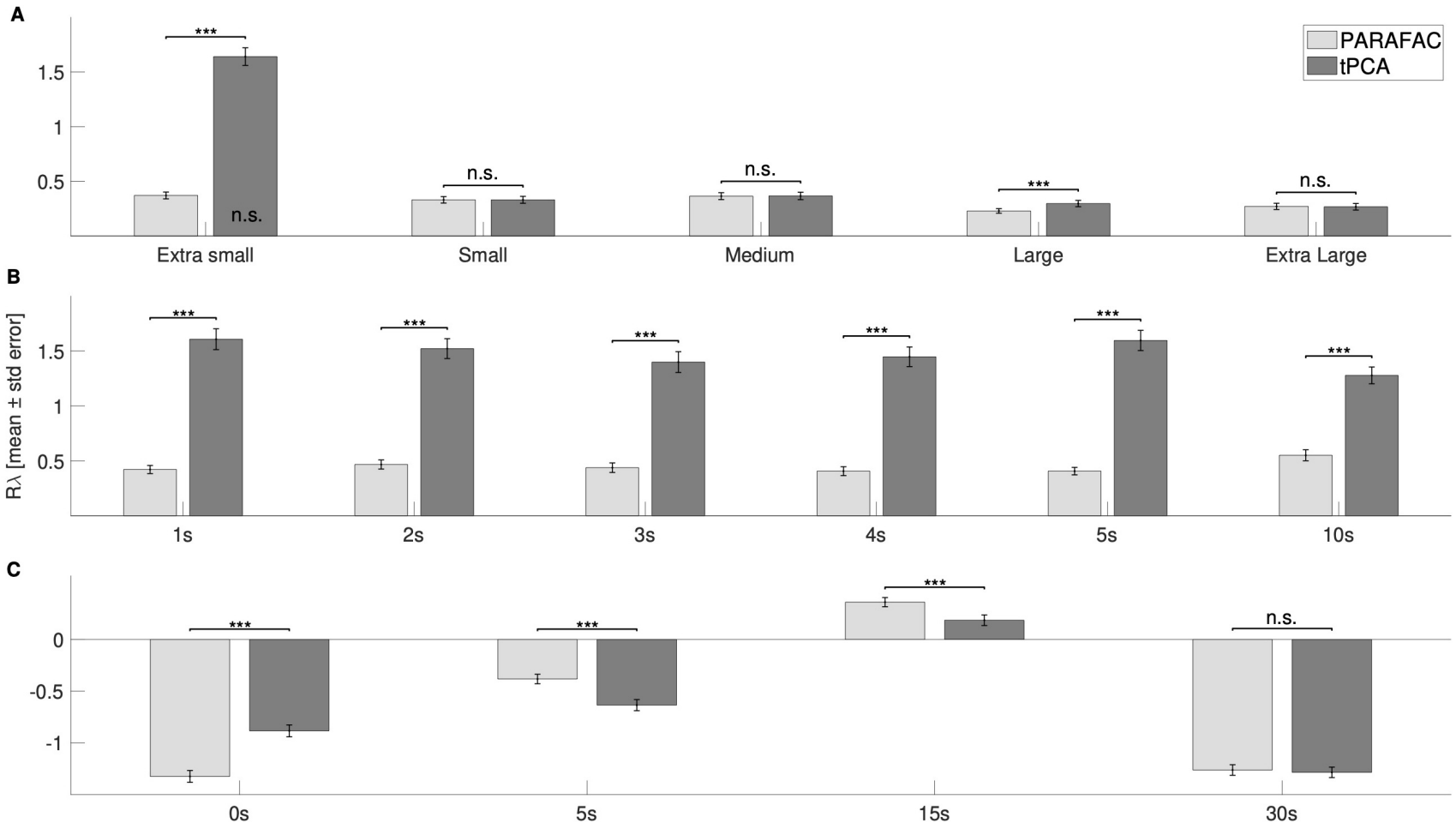

Figure S 5 – Evaluation of correction in simulated motion artifacts based on signal similarity by the use of the Pearson's correlation between wavelengths ($R\lambda$). Simulations are identified on the x-axis. (A) 1a to 1e: artifacts with different amplitude sizes; (B) 2a to 2f: complex artifacts with two superimposed artifacts and an onset delay between the first (A_1) and second artifact (A_2); and (C) 3a to 3d: the onset of the artifact relative to the beginning of a simulated HRF. $R\lambda$ in a clean signal is usually lower than in artifacted signals. Results are displayed separately for the correction with PARAFAC (light gray bars) and tPCA (gray bars). The $R\lambda$ of the uncorrected signal is not displayed in this figure but differed significantly from both correction techniques in all conditions, except where specified otherwise inside the bar. Significance level are based on post-hoc tests with Tukey correction. $^*p \leq 0.05$, $^{***}p \leq 0.001$, n.s. $p > 0.05$. Uncorrected = NIRS_{ini} + artifact (A_1) without correction, PARAFAC = NIRS_{ini} + artifact ($A_{1/2}$) after artifact correction with PARAFAC, tPCA = NIRS_{ini} + artifact ($A_{1/2}$) after artifact correction with tPCA.

Third Article.

Brain language networks and cognitive outcomes in children with frontotemporal lobe epilepsy

by

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Abstract. Introduction: Pediatric frontal and temporal lobe epilepsies (FLE, TLE) have been associated with language impairments and structural and functional brain alterations. However, there is no clear consensus regarding the specific patterns of cerebral reorganization of language networks in these patients. The current study aims at characterizing the cerebral language networks in children with FLE or TLE, and the association between brain network characteristics and cognitive abilities. Methods: Twenty (20) children with FLE or TLE aged between 6 and 18 years and 29 age- and sex-matched healthy controls underwent a neuropsychological evaluation and a simultaneous functional near-infrared spectroscopy and electroencephalography (fNIRS-EEG) recording at rest and during a receptive language task. EEG was used to identify potential subclinical seizures in patients. We removed these time intervals from the fNIRS signal to investigate language brain networks and not epileptogenic networks. Functional connectivity matrices on fNIRS oxyhemoglobin concentration changes were computed using cross-correlations between all channels. Results and Discussion: Group comparisons of residual matrices (=individual task-based matrix minus individual resting-state matrix) revealed significantly reduced connectivity within the left and between hemispheres, increased connectivity within the right hemisphere and higher right hemispheric local efficiency for the epilepsy group compared to the control group. The epilepsy group had significantly lower cognitive performance in all domains compared to their healthy peers. Epilepsy patients' local network efficiency in the left hemisphere was negatively associated with the estimated IQ ($p = .014$), suggesting that brain reorganization in response to FLE and TLE does not allow for an optimal cognitive development.
Keywords: Language networks; receptive language; functional near-infrared spectroscopy (fNIRS); functional connectivity; electroencephalography (EEG); pediatric frontotemporal lobe epilepsy; neurodevelopment.

1. Introduction

Focal epilepsy of the frontal (FLE) or temporal lobe (TLE) is the most frequent diagnosis in pediatric epilepsy (Behr et al., 2016; Beleza & Pinho, 2011; Gallagher & Lassonde, 2005; Hermann & Seidenberg, 2002; Téllez-Zenteno & Hernández-Ronquillo, 2012). Pediatric FLE and TLE have been shown to interfere with brain development and can result in altered functional cerebral networks including reorganization of brain circuits that support language functions (Berl et al., 2005; Berl et al., 2014; Gallagher et al., 2013; Hamberger & Cole, 2011; Mbwana et al., 2008). For instance, a more frequent bilateral hemispheric speech representation or right-hemispheric language dominance have been found in these children (Baciu & Perrone-Bertolotti, 2015; Foley et al., 2020; Gallagher, Lassonde, et al., 2008; Gallagher et al., 2016). Moreover, there is evidence of intra-hemispheric reorganization in patients with left FLE or TLE, where regions within the left hemisphere typically not involved in language production (e.g., posterior areas) are recruited during an expressive language task (Gallagher et al., 2007; Vannasing et al., 2016). Such alterations in children with FLE and TLE may reflect either language network reorganization allowed by early brain plasticity (Hamberger & Cole, 2011; Staudt et al., 2002; Staudt et al., 2001) or aberrant development of language brain networks due to early neuropathology (Bear et al., 2019; Hermann et al., 2002; Sepeta et al., 2015; Vannest et al., 2009).

Major advances in neuroimaging data acquisition and functional connectivity (FC) analysis have allowed a more thorough investigation of brain network reorganization (Friston et al., 2011). Children (Chou et al., 2018; Foley et al., 2020; Sepeta et al., 2015; Vannest et al., 2019) and adults (Balter et al., 2019) with FLE or TLE show different FC patterns within their cerebral language networks compared to healthy controls. Precisely, reduced FC between homologous inferior (IFG) and middle (MFG) frontal gyri and posterior superior temporal gyri (pSTG) as well as decreased intra-hemispheric FC between the IFG and MFG in both hemispheres has been reported in children with left hemispheric focal epilepsy during a semantic congruency task compared to typically developing controls (Sepeta et al., 2015). In children with TLE specifically, FC within the left IFG during a story listening task was significantly lower than in healthy peers (Vannest et al., 2019). The strength of FC among language-related brain areas might therefore be an index of altered brain network in children with FLE or TLE.

The graph theory approach has gained increasing recognition as a mean to characterize brain networks in patients with epilepsy of all ages (e.g., Bernhardt et al., 2015; Farahani et al., 2019; Rodríguez-Cruces et al., 2020; Slinger et al., 2022; Tavakol et al., 2019; Tung et al., 2021). Graph theory allows the rederivation of common network properties from the FC matrices. Notably, it provides the network's segregation and integration properties (Rubinov & Sporns, 2010), which refer to a network's tendency to have locally specialized subnetworks

(segregation), and to the efficacy of a network to efficiently globally integrate information from distinct parts of the network (integration; Rubinov & Sporns, 2010). A recent meta-analysis addressed the question of network alterations in pediatric and adult patients with focal epilepsy (Slinger et al., 2022). The authors included the results of 45 studies (n > 1400) published between 2006 and 2020 that used a graph theoretical approach. Although the structural integration of neural networks was lower in patients with epilepsy than healthy controls, the network integration and segregation characteristics did not statistically differ between groups. The authors hypothesized that the high heterogeneity of individual results notably due to methodological or technological differences probably precluded the identification of network differences between groups. To reduce this heterogeneity, they performed sub-analyses that included only recent studies (2013 and after) and found a significantly lower network segregation for the epilepsy group compared to healthy controls. This difference was even more striking when comparing patients with TLE only, i.e., the largest subgroup of patients, to healthy controls. Lower network segregation suggests reduced local processing efficiency (Rubinov & Sporns, 2010), which may be a specific characteristic of cerebral networks in epilepsy patients.

In addition to altered brain networks, pediatric FLE and TLE have been associated with many behavioral, cognitive, and psycho-affective deficits impacting the well-being and quality of life of these children and their families (Berg et al., 2008; S. W. Goodwin et al., 2017; Hernandez et al., 2002; Karrasch et al., 2017; Law et al., 2018; Smith, 2016; Wilson et al., 2015). Although most children with FLE and TLE have intellectual abilities within the norms, some children have an overall decrease of their intellectual profile (Gallagher & Lassonde, 2005). Also, children with FLE and TLE often present deficits in specific cognitive domains including attention, executive functions, memory, language, and social cognition (Fuentes & Smith, 2015; Gallagher & Lassonde, 2005; Helmstaedter, 2001; Hermann & Seidenberg, 2002; Hernandez et al., 2003; Hernandez et al., 2002; Jokeit & Schacher, 2004; Prévost et al., 2006; Reuner et al., 2016). Although some cognitive difficulties are more specific to FLE (e.g., impaired executive functions) or TLE (e.g., memory problems), the neuropsychological profiles of these children are often heterogeneous and complexly intertwined (Hermann et al., 2021; Law et al., 2018; Smith, 2016). Common and frequent difficulties in children with FLE and TLE are language impairments affecting expressive (e.g., phonetic or semantic verbal fluency, naming) or receptive (e.g., phonological awareness, comprehension) language functions, or verbal problem-solving skills (Bear et al., 2019; Metternich et al., 2014; Teixeira & Santos, 2018). This is not surprising since language processing in healthy humans is thought to be organized in a complex cerebral network predominantly in the left hemisphere including posterior inferior frontal regions, large parts of the temporal lobe, the angular and supramarginal gyri in the parietal lobe, and white matter fiber pathways connecting

frontotemporoparietal and occipitotemporal regions (Hickok, 2022; Hickok et al., 2021; P. Tremblay & Dick, 2016).

Typical development of language brain networks is a long process that starts in utero and evolves throughout infancy, childhood and even into late adolescence (Paquette et al., 2015; Paquette et al., 2013; Skeide & Friederici, 2016; Weiss-Croft & Baldeweg, 2015). Overall, brain network topology in typically developing children is characterized by a decrease of network segregation with age, while global integration increases (Giedd et al., 1999; Supekar et al., 2009). The establishment of language-related neuronal networks is accompanied by the development of language abilities that are crucial for later social, academic, and daily functioning. In children with focal epilepsies, the strength of left intra-hemispheric FC between the IFG and pSTG during a language task has been positively associated with language skills (Sepeta et al., 2015). This suggests that reductions of FC within regions of the brain's language network might represent suboptimal cerebral reorganization associated with language impairments. Furthermore, graph theoretical studies in children and adolescents with focal epilepsies have shown that higher resting-state network segregation and integration are associated with higher general intellectual capacities (Paldino et al., 2017; Songjiang et al., 2021). A positive association between segregation and cognitive capacities differs from the typical developmental trajectory of network topology reported in healthy children (Giedd et al., 1999; Supekar et al., 2009). However, whether a similar atypical relationship exists between brain language network characteristics and language and cognitive functions in children with FLE or TLE specifically remains unknown.

Despite numerous studies reporting cerebral alterations in pediatric focal epilepsies, specific patterns of brain network reorganization are still unpredictable and the precise impact on cerebral language networks is not clear. Also, there is no consensus yet on the functional impact of specific language network alterations. The current study aims at characterizing the cerebral networks related to language processing in children with FLE or TLE as compared to healthy controls, using functional near-infrared spectroscopy (fNIRS) and a graph theoretical approach. Qualitative comparisons of fNIRS FC patterns between epilepsy subgroups (FLE vs. TLE, left vs. right epilepsy) and graph theory characteristics will also be explored. fNIRS has been widely used to investigate cerebral language processing because it allows to capture hemodynamic changes in cortical regions. It is particularly adapted for pediatric patients because it is non-invasive, relatively tolerant to movements, and offers the flexibility to acquire data when the caregiver remains close by. The secondary aim of this study is to characterize the association between language brain network characteristics and the neuropsychological profile of children with FLE and TLE.

This is the first study to explicitly focus on pediatric FLE and TLE, the two most common types of focal epilepsies. Based on the overlap between the epileptogenic network of these patients and the typical organization of cerebral language processing, children with FLE

and TLE have a higher risk of alterations in brain language networks. Our findings will strengthen the current knowledge on FC alterations of brain language networks in these patients. Moreover, graph network analysis allows to uncover how alterations of FC translate to characteristics of graph network architecture. To our knowledge this is the first study that applies graph theory to characterize functional brain network topology in children with FLE and TLE. Moreover, this study will contribute to a better understanding of the cerebral alterations and cognitive abilities in children with FLE and TLE, i.e., the specific brain-behavior relationship under neuropathologic conditions.

2. Materials and methods

2.1. Participants

Between 2017 and 2020, we recruited 20 children with FLE ($n = 9$) or TLE ($n = 11$) and 29 healthy controls. All participants were French speakers, aged between 6 and 18 years, born at term, and had no history of previous neurosurgery, metabolic disorder, traumatic brain injury or intellectual disability. Medical files of patients with epilepsy followed at the Neurology Division of the Mother and Child University Hospital Center Sainte-Justine (CHUSJ, Montreal, QC, Canada) were screened. For children with epilepsy, exclusion criteria were: multifocal epilepsy, significant structural abnormalities with mass effect, genetic syndrome known to significantly affect neurodevelopment, autism spectrum disorder, multiple (≥ 3) comorbidities (e.g., attention deficit hyperactivity disorder, dyslexia, dyspraxia, and so on). Patients and their caregivers were approached by their neurologist (BO, AL, PD, PM, ER) and subsequently contacted by the research coordinator (AMH). The study's protocol (2014-664, 3876) was approved by the research ethics board of the Sainte-Justine Mother and Child University Hospital. All parents and children provided written informed consent. Descriptive statistics of the sample's sociodemographic and clinical characteristics are presented in Table 1.

2.2. Procedure

Participation in the study included 1) a combined functional near-infrared spectroscopy (fNIRS) and electroencephalography (EEG) data acquisition at rest and during a receptive language task, and 2) a neuropsychological assessment. Both are described in the following sections.

2.2.1. *fNIRS-EEG data acquisition*

The fNIRS-EEG data acquisition was performed using a continuous-wave fNIRS system (NIRScout, NIRx Medical Technologies, LLC, Berlin, Germany) equipped with 16 detectors and 16 sources emitting light at two-different wavelengths ($\lambda 1|2 = 760|850$ nm), yielding to a

total of 50 channels per wavelengths. The hemodynamic signal was recorded at a sampling rate of 7.8 Hz. Detectors and sources were held in place on an elastic cap (NIRScap, EASYCAP GmbH, Woerthsee-Etterschlag, Germany) and arranged according to the 10-20 system to cover frontal, temporal, and part of the parietal and occipital areas bilaterally (Fig. 1A). Spatial localization of all probes was digitalized on a head model using fiducial points (nasion, inion, LPA and RPA) as reference landmarks (Polaris stereotaxic system, Northern Digital

Table 1 – Descriptive statistics of the socio-demographic and clinical characteristics of participants who completed the neuropsychological assessment, the resting state and the passive story listening task during the fNIRS-EEG recording.

	Epilepsy patients	**Healthy controls**	**Group comparison**
	(Number of missing data)		(p-value)
N	13	26	
Sex [female/male]	4/9	11/15	.728
Age [$M \pm SD$]	11.2 ± 3.9	12.9 ± 4.1	.203
Socio-economic status [Median]			
Family income	5/5	5/5(3)	.793
Parental education	5/6	5.8/6	.311
Socio-affective well-being[a] [$M \pm SD$]			
Self-concept	50.2 ± 7.1(1)	52.1 ± 6.0	.439
Symptoms of depression	49.8 ± 8.2(1)	47.5 ± 5.5	.343
Symptoms of anxiety	49.8 ± 8.5(1)	48.1 ± 8.5(1)	.057[1]
Handedness [right/left/ambidexter]	9/3/1	21/1/4	-
Epilepsy diagnosis			
Type [FLE or TLE]	5/8[b]	-	-
Lateralization [left/right/bilateral]	3/6/3	-	-
Age of epilepsy onset [$M \pm SD$]	6.4 ± 3.1(1)	-	-
	Median = 5.7		
Epilepsy duration [$M \pm SD$]	4.8 ± 3.1(1)	-	-
	Median = 4.1		
Number of ASM [$M \pm SD$]	1.3 ± 0.48	-	-
Seizure control [yes/no]	9/4	-	-

*Critical alpha = .05, [1]statistical tendency ($.05 < p < .08$), [a]measured with the Beck Youth Inventory (BYD-II) who was only completed by participants aged ≥ 7 years, $n_{epi/ctrl} = 10/23$, [b]left/right/bilateral FLE: 1/3/1, left/right/bilateral TLE: 3/3/2. FLE: frontal lobe epilepsy. TLE: temporal lobe epilepsy, ASM: anti-seizure medication.

Inc., Waterloo, ON, Canada; Brainsight Frameless 39 software, Rogue Research Inc., Montreal, QC, Canada). Digitalized coordinates were projected onto a structural MRI template (Fonov et al., 2011; Fonov et al., 2009) and visualized with the 3DMTG interface from the LIONirs toolbox (J. Tremblay et al., 2022), allowing to project individual fNIRS data into a 3D MRI space.

Simultaneously to fNIRS data acquisition, EEG signal was acquired to identify potential subclinical seizures in patients, remove these time intervals from the fNIRS signal, and ensure we investigate language brain networks and not epileptogenic networks. EEG recording (BrainVision Recorder, Version 1.2, Brain Products GmbH, Gilching, Germany) included 21 active electrodes placed between the fNIRS fibers and arranged according to the 10-20 system, with FCz as the reference (actiCHamp system, Brain Products GmbH, Gilching, Germany). The electrophysiological signal was acquired at a sampling rate of 500 Hz.

The fNIRS-EEG recording took place in a dimmed-soundproof room. Participants sat in a comfortable armchair and were instructed to relax, avoid any intentional movements or muscular tension, and keep their gaze on the fixation cross presented in the center of a screen (placed at 114 cm in front of them). Throughout the entire session, a member of the research team sat next to the participant to give instructions and ensure that the participant remained engaged. Meanwhile the quality of the fNIRS-EEG signal and the state of alertness of the participant were monitored by a senior NIRS-EEG technician (PV). fNIRS-EEG data was acquired during two conditions (Fig. 1B): (1) a consecutive 12-min resting-state with eyes open, and (2) a 12-min passive story listening task previously validated for receptive language-related brain activation (Bassett et al., 2008; Gallagher, Bastien, et al., 2008; Gallagher et al., 2012; Gallagher et al., 2016; Vannasing et al., 2016). This paradigm had the advantage to minimize movements, minimizing signal artifacts and the need for signal preprocessing and modifications. The story was an abbreviated version of Snow White narrated in French and presented throughout 18 individual segments in a block design paradigm, where periods of rest and task alternated (Presentations®, Neurobehavioral Systems, 2018, Berkeley, CA, USA). The interstimulus interval was pseudo randomized between 15 and 20 s and stimulus presentation was ∼20 s. After the fNIRS-EEG recording, participants responded to 12 questions verifying if they followed the storyline. A video recording of the fNIRS-EEG session enabled visual support during offline preprocessing for the identification of movements and potential epileptic seizures.

2.2.2. *Neuropsychological assessment*

All participants underwent a neuropsychological evaluation that included an estimation of the general intellectual functioning (estimated IQ) and the assessment of the receptive and expressive language abilities. As proposed in the Wechsler Abbreviated Scale of Intelligence (WAIS-II; Wechsler, 2011), the estimated IQ was computed based on four subtests of the

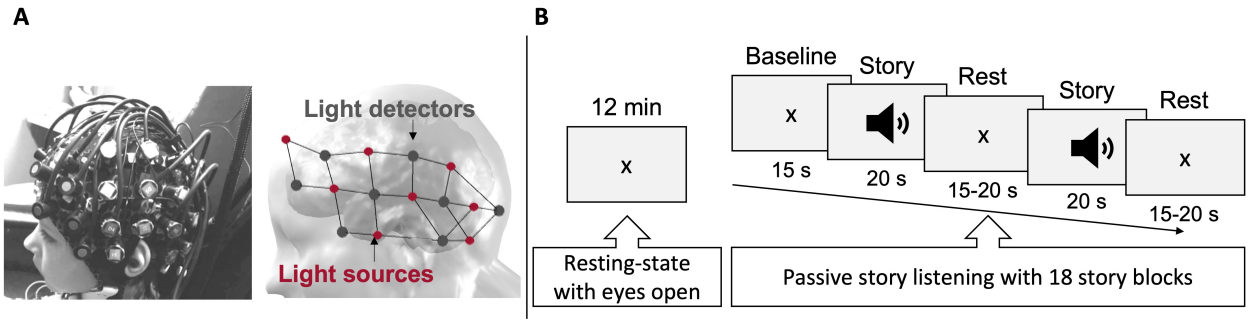

Figure 1 – fNIRS-EEG recording set-up. (A) fNIRS-EEG montage as it was placed on a participant's head (left), and the arrangement of 16 emitting light sources (λ 1|2 = 760|850 nm, red dots) and 16 light detectors (dark grey dots) covering regions of interest over both hemispheres (right). This resulted in 50 measurement channels. (B) The two behavioral paradigms, i.e., 12-minute resting-state period and the 12-minute receptive language task, performed during combined fNIRS-EEG data collection.

Wechsler intelligence scale for children (6 to 16 years, WISC-IV; Wechsler, 2005) and adults (16 years and over, WAIS-IV; Wechsler, 2010): Vocabulary (word knowledge), Similarities (verbal reasoning), Block design (visuo-constructive abilities) and Matrix reasoning (non-verbal problem solving). The receptive and expressive language abilities were assessed using the Peabody Picture Vocabulary Test, revised version (PPVT-R; Dunn et al., 1993) and the One-Word Picture Vocabulary Test (EOWPVT-2000; Brownell, 2000), respectively. All these tests are standardized validated tools frequently used for neuropsychological assessment of children with epilepsy. Individual test results were transformed into T scores based on the norms for the French-Canadian population.

In addition, three questionnaires were completed. First, a homemade demographic, developmental and socio-economic inventory was completed by the primary caregiver prior to the first meeting to confirm the eligibility of the child and determine the family socio-economic status (SES). The family's income (scaled from one to five) and the parental education as defined by the mean of the maternal and paternal level of education (scaled from one to six) served as indices for the SES (« APA Dictionary of Psychology », 2022). Second, the assessor completed the Beck Youth Inventory (BYI-II; Beck et al., 2005) with the child (aged seven and over) to assess three factors of the participants' psychological-wellbeing: self-concept, depression, and anxiety. Since impaired self-concept and psychological problems have been shown to be more prevalent in the epileptic population (Puka et al., 2020; Reilly et al., 2014) and can have an impact on the cognitive profile (Rock et al., 2018), these scores allowed to detect symptoms of psychological distress and control for differences between study groups if needed. Third, a French version of the Edinburgh Handedness Inventory (Oldfield, 1971) was also completed by the child to determine each participant's handedness based on self-reported

daily activities. Left-handedness and ambidexterity have been associated with an increased incidence of atypical hemispheric representation of language functions (Knecht et al., 2000).

2.3. fNIRS-EEG data preprocessing

The raw EEG signal was filtered (bandpass range: 0.3-35 Hz, notch: 60 Hz) and screened for potential neurophysiological abnormalities by a clinical epileptologist (BO) (BrainVision Analyzer, Version 2.2, Brain Products GmbH, Gilching, Germany). This aimed to identify sub-clinical seizures in the participants with epilepsy and assure the absence of pathological findings within the control group. fNIRS data recorded simultaneously to a subclinical seizure identified on the EEG were excluded from further analyses to avoid contamination of the epileptogenic networks when mapping the language brain networks.

Raw fNIRS data was imported into the LIONirs toolbox (J. Tremblay et al., 2022), which is embedded in SPM12 (Statistical Parametric Mapping) and operates in MATLAB (The MathWorks, Inc., 2019b, Natick, MA, USA). Signal coherence among channels for the peak frequency commonly related to the cardiac beat (0.8-2.3 Hz) allowed to exclude channels with poor optode-to-scalp coupling (Fourdain et al., 2023; Yücel et al., 2021). Intervals with aberrant signal variation based on moving average criteria were identified using an automatic algorithm. An artifact was identified if a) changes in light intensity within a time interval of 6 s exceeded three standard deviations, b) the noise lasted for more than 3 s, and c) at least 5 % of channels were affected. Temporally correlated ($r > 0.8$) channels within the same interval were considered as artifacts and intervals less than 2 s apart were considered as one event. A visual inspection was also performed, and minor manual adjustments were applied. Subsequently, parallel factor analysis (PARAFAC), i.e., a multidimensional decomposition method (Bro, 1997; Harshman, 1970) which has recently been validated for fNIRS data (Hüsser et al., 2022), was used to correct the signal during relatively isolated artifact intervals. Noisy periods that lasted for a relatively long interval and where no clear signature could be extracted were excluded. Optical density of the signal between uncorrected noisy intervals, was transformed into delta optical density to normalize the signal. A fourth-order zero-phase Butterworth band-pass filter with cut-off frequencies 0.001-0.5 was applied to reduce confounds of systemic physiology related to respiratory or cardiac pulsation, while keeping the low frequencies presumably related to the hemodynamic response (Pinti et al., 2019; Santosa et al., 2020). Optical density was then transformed into relative oxy-/deoxyhemoglobin (HbO/HbR) concentration changes using the modified Beer-Lambert Law (Kocsis et al., 2006) with age-appropriate differential pathlength factors (Scholkmann & Wolf, 2013). The averaged signal of all channels was regressed from every channel, a procedure which has been shown to successfully remove remaining physiologic confounds appearing in frequency bands

that are in the range of the hemodynamic signal and thus hard to filter (Saager & Berger, 2008). See Fig. 2 for an overview of the fNIRS preprocessing pipeline.

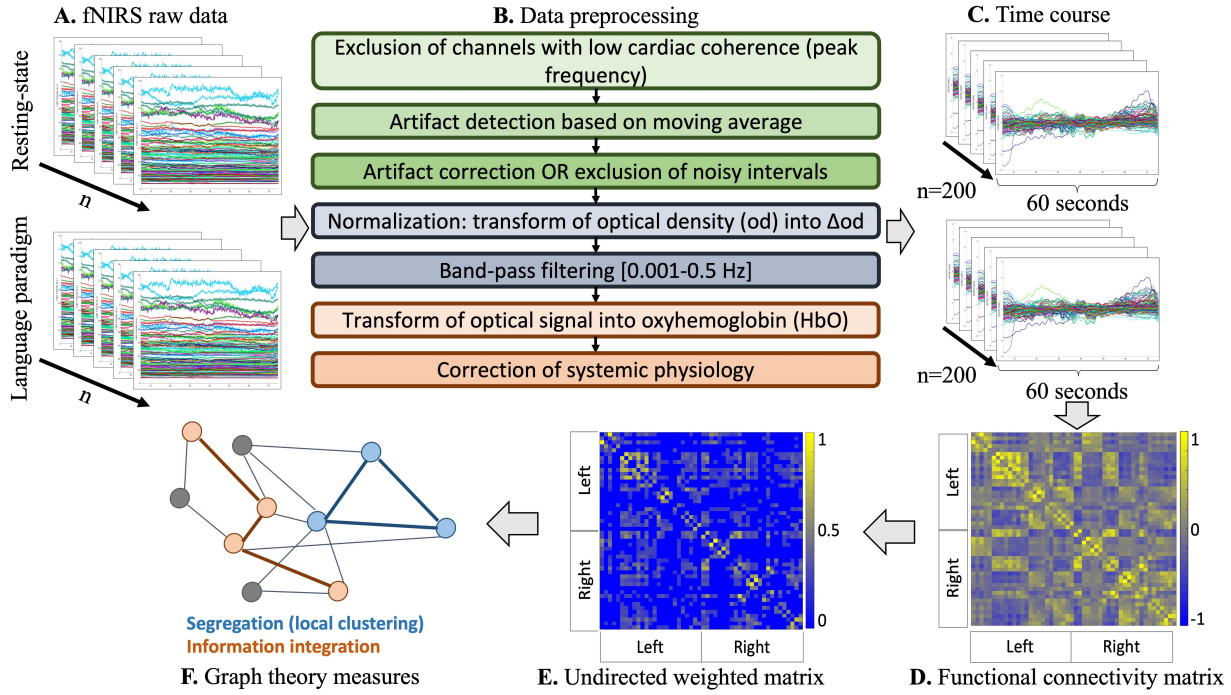

Figure 2 – Processing pipeline for the fNIRS signal. (A) Individual raw data of the resting-state and receptive language task; (B) preprocessing steps applied to ensure signal quality and transform raw optical density into relative HbO and HbR concentration changes; (C) extraction of random samples of 60 s; (D) computation of cross-correlations between all channels of each sample to produce averaged individual functional connectivity matrices on HbO signal (A_n); (E) thresholding of individual matrices over a sparsity range to produce undirected weighted graphs; (F) derivation of graph theoretical metrics to describe network properties. fNIRS: functional near-infrared spectroscopy, HbO: oxyhemoglobin.

2.4. Functional connectivity analysis

FC and network analyses were conducted on HbO matrices only, which is considered a sensitive indicator of regional oxygenation differences in response to cerebral activation (Homae et al., 2007) and has a good concordance with the fMRI BOLD signal (H. Sato et al., 2013; Tung et al., 2021). Circular bootstrapping was used to extract 200 random 60-s samples from each data set (resting-state and task) of each participant (Bellec et al., 2010). For each valid sample, we computed cross-correlations, i.e., pairwise Pearson's correlations (ρ) between the time course of all measurement channels (y_i,y_j = 1,...50). The symmetric matrix of each subject (A_n) included the averaged ρ_{ij} of all possible pairs (k = 1225) over all samples. Correlation coefficients underwent Fisher's transformation to obtain normally distributed values (z_{ij}). Developmental effects were removed by estimating and regressing

the contribution of age from A_n with a general linear model (GLM): $A_n = \beta_0 + \beta_1(age) + \epsilon$, resulting in B_n. The hemodynamic signal related to receptive language processing was isolated by subtracting the FC matrix computed using the resting-state data from the FC matrix computed using data gathered during the story listening task ($B_{n(task)} - B_{n(resting-state)}$). The subtraction allowed to control for inter-ictal epileptic or default mode network activity and yielded in a residual matrix (R_n) specific to language comprehension.

The brain networks were characterized with common graph theoretical measures of local and global processing efficiency. Segregation is the network's tendency to build local clusters and refers to local information processing. It is measured with: 1) the clustering coefficient (γ), which is the level a node's neighbors are directly connected to each other and describes the clustering density around each node; and 2) the local efficiency (E_{local}) index, which considers direct and indirect paths to describe a node's integration among its neighbors (Achard & Bullmore, 2007; Fornito et al., 2016; Latora & Marchiori, 2003; Latora & Marchiori, 2001; Newman, 2003; Sporns, 2018; Watts & Strogatz, 1998). Integration describes a network's ability to efficiently integrate information from distinct parts and refers to global information processing. It is commonly assessed using: 1) the characteristic's path length (λ), which quantifies the averaged shortest path between all possible nodes - a lower λ implies more rapid and efficient information processing; and 2) the global efficiency (E_{global}) index, which also refers to the network's global information exchange and is the reciprocal of the λ ($1/\lambda$) (Farahani et al., 2019; Fornito et al., 2016; Latora & Marchiori, 2001; Tavakol et al., 2019; Tung et al., 2021). Additionally, the small-world index (σ), which is a network characteristic that considers the normalized balance of a network's segregation and integration $\sigma = \gamma/\lambda$ (Watts & Strogatz, 1998), was considered. A network with small-world properties is characterized by a good balance of global and local processing efficiency, which is inherent for a healthy brain network architecture since early infancy and throughout adulthood (Fornito et al., 2016; Fransson et al., 2011; Liao et al., 2017).

Network metrics (γ, E_{local}, λ, E_{global}, σ) were computed with in-house Matlab scripts incorporating functions from The Brain Connectivity Toolbox (Rubinov & Sporns, 2010). In the graph theoretical framework, each measurement channel (i,j) of the fNIRS data represents a node and every correlation pair (ρ_{ij}) is an edge. Individual connectivity matrices ($B_{n(task)}$) computed from the language task signal only that were corrected for developmental effects, were transformed into undirected weighted graphs (W_n) using a range of absolute correlation thresholds (τ). The ideal range is commonly achieved when a fully connected network, that is each node is at least connected with one other node (degree centrality (K) ≥ 1), is accompanied by a small-world topology ($\gamma > 1, \lambda > 1, \sigma > 1$ or in small networks when $\gamma > \gamma_{rand}$) (Bassett et al., 2008; Montoya & Solé, 2002; Rubinov & Sporns, 2010). These criteria were most appropriate for our set of data and have been tested in other studies (Provost et al., 2023; Roger et al., under review). In the current study, a satisfying mean minimal K of

one was maintained from a threshold of 0.01 to 0.17 for the task matrices. Within that range, the average normalized γ and λ also fulfilled the criteria of 1. Small-world topology based on the criteria for small networks was also fulfilled for this range; the actual index was however only greater than one for thresholds above 0.12. Given the size of the cerebral network, i.e., < 3000 nodes, analyses were conducted for threshold ranges of $\tau_1 = 0.01$, to $\tau_{(m(task))} = 0.17$, with $\triangle\tau = 0.01$. Correlations fulfilling the threshold criteria kept their absolute value ($|\rho_i j|$). Correlations on the principal diagonal representing each channel's correlation with itself and correlations below the threshold were set to zero. For every threshold, we extracted 100 random graphs, derived network metrics and calculated a group mean over all graphs and subjects (M_{rand}). We then divided individual metrics, derived from the real graph, by M_{rand} resulting in normalized metrics. Finally, we calculated the area under the curve (AUC) for the normalized network metrics over the sparsity range, which provided a valuable alternative to analyzing metrics for each threshold individually (Ding et al., 2017; Lei et al., 2015; Suo et al., 2015; H. Zhang et al., 2011).

2.5. Statistics

The statistical analyses were conducted using the R statistical software and Matlab functions integrated in the LIONirs toolbox. Between group analysis (epilepsy vs control group) allowed to: 1) detect potential differences regarding the sample's demographic characteristics (age, sex and SES) and socio-affective wellbeing measure with the BYD-II questionnaire; 2) ensure equal fNIRS signal quality (the number of good trials included for FC matrices); and 3) statistically compare graph network metrics as well as cognitive performance. Student's t-tests, or the non-parametric Mann-Whitney-U test when normality was violated, were used for continuous variables and Fisher's exact tests were used to analyze categorical variables.

Due to the high number of connectivity links ($n = 1225$), 2000 unpaired permutation tests based on student t-test statistic were computed to compare the residual FC matrices of the epilepsy group to the control group (Galán et al., 1997; Lage-Castellanos et al., 2010). Insufficient power precluded quantitative analyses of patient subgroups (FLE vs. TLE, left vs. right epilepsy). Therefore, the mean and standard deviation of the control group's residual FC matrices were used to transform the patients' residual FC matrices into z-scores. The z-scores of four different patient subgroups, i.e., FLE, TLE, left and right lateralized epilepsy, were averaged to qualitatively evaluate the impact of epilepsy lateralization and localization on organization of cerebral language networks.

Pearson's correlation analysis between cognitive measures (estimated IQ, expressive and receptive language skills) and the AUC of the graph metrics were used to better understand the associations between network organization and the neuropsychological profile. Subsequently, linear regression models with the cognitive measures and the group factor (epilepsy and healthy

control) as predictor variables, were tested to evaluate their relative explanation of the different network properties, i.e., the AUC of the network's segregation (γ, E_{local}) of each hemisphere, the network's integration (λ, E_{global}), and its small-world topology (σ). Post-hoc analyses were applied to disentangle the moderating effect of the group factor on the association between cognitive measures and the AUC of the different brain network. Explorative correlation analyses between clinical factors and the AUC of the graph metrics of epilepsy patients were computed to explore the impact of the type of epilepsy (frontal/temporal), epilepsy lateralization (left/right/bilateral), age of epilepsy onset, epilepsy duration and seizure control on the language brain network topology. Pearson's correlation coefficients and Spearman rank correlations were used for continuous and categorical variables, respectively. Results are all interpreted with a critical alpha level of .05 and common effect size measures, i.e., Cohen's *d*, partial eta squared (η_p^2), and Varga and Delaney's *A* (Cohen, 1988; Vargha & Delaney, 2000).

3. Results

All 49 participants completed the neuropsychological assessment and the resting-state fNIRS-EEG recording. However, fNIRS-EEG recording during the passive story listening task was not done or not completed in 9 participants (seven epilepsy patients and two healthy controls) due to participant discomfort, limited collaboration or time restrictions. Since it was not possible to compute the residual matrix in those participants, they were excluded for all cerebral network analyses (Secs. 3.2 and 3.4). The EEG of one healthy control suggested potential epileptiform abnormalities. Consequently, this participant was excluded from the study. The neurologist did not identify subclinical seizures in any epilepsy or control participant. Indicators of inter-ictal activity, such as spikes or slow waves, were identified in the resting-state signal of five patients and in the task signal of three patients. These events were short ($\approx$ 0.002 s) and mostly limited to a single channel, thus minimally affecting the hemodynamic signal. The sample characteristics and neuropsychological results for the final sample are reported in Sec. 3.1.

3.1. Socio-demographic and clinical characteristics of the final sample

The final sample was composed of 13 children with epilepsy and 26 healthy controls (Table 1 for socio-demographic and clinical characteristics). Comparisons between healthy controls and epilepsy patients regarding their socio-demographic characteristics revealed no significant differences for sex (Fisher's exact test: $p = .728$), age ($t(37) = 1.30$, $p = .203$, $d = 0.44$, small effect), socio-economic status operationalized as the family income ($W = 155.5$, $p = .793$, A=0.46, very small effect) nor the mean parental education ($W = 202.0$, $p = .311$,

$A = 0.60$, small effect). The BYD-II was only completed by participants aged ≥ 7 years i.e., 10 epilepsy patients and 23 healthy controls. Both groups have a socio-affective well-being within the normative range, with no statistically significant differences between groups for any of the three dimensions of the BYI-II, i.e., self-concept ($t(31) = 0.78$, $p = .439$, $d = 0.30$, small effect), depression ($t(31) = -0.93$, $p = .343$, $d = 0.37$, small effect) and anxiety ($t(31) = -2.00$, $p = .056$, $d = 0.75$, medium effect). We thus considered both groups as being comparable and did not include any of the socio-demographic nor the socio-affective factors as covariables for primary statistical analysis. The etiology of epilepsy was unknown in eight patients, potentially structural (e.g., atrophy, cyst, sclerosis) in three, though one had incomplete signs of a hippocampal sclerosis, and an auto-immune disease was suspected in one. Etiology could not be verified for one. None of the patients presented a self-limited epilepsy syndrome (Specchio et al., 2022). Nine patients received a monotherapy, and four a combination of two ASMs. Carbamazepine and levetiracetam were the most common ASMs in this study group and anyone received treatment with topiramate, which is known to affect language functions (S. Lee et al., 2003; Szaflarski & Allendorfer, 2012). See Table S1 in the supplemental material for details on individual patients.

3.2. Cerebral networks

On average, we recorded 12.2 (*SD*: ± 2.8) and 12.3 (*SD*: ± 2.1) min of resting-state and task data, respectively. After the bootstrapping of 60-s trials, we extracted an average of 93.2 (*SD*: ± 59.5) and 121.6 (*SD*: ± 59.1) valid resting-state and 67.2 (*SD*: ± 51.9) and 95.3 (*SD*: ± 54.2) task segments for the epilepsy and control groups, respectively. The number of valid segments for the resting-state ($t(46) = 1.63$, $p = .109$, $d = 0.48$, small effect) nor the language paradigm ($t(37) = 1.54$, $p = .131$, $d = 53$, medium effect) statistically differed between groups. When the comprehension of the story line presented during the receptive language task was assessed, epilepsy patients gave significantly fewer correct answers (40 %) as compared to the healthy controls (90 %, $W = 181$, $p = 0.002$, $A = 0.54$, very small effect).

Permutations were conducted at a channel-level, for visualization and interpretation purposes, channels were attributed to four regions of interest (ROI), i.e., frontal, temporoparietal, temporal and temporooccipital areas of both hemispheres (Fig. 3A, Koessler et al., 2009; T. Nguyen et al., 2018). Averaged residual connectivity matrices (R) of epilepsy patients and healthy control children are illustrated in Fig. 3B. Student's t-test statistics after 2000 permutations revealed numerous significant differences ($p < .05$) between residual matrices of patients with epilepsy and healthy control children (Fig. 3C). Group differences indicated that, compared to their healthy peers, children with FLE or TLE overall had decreased frontotemporal FC within the left hemisphere, increased frontotemporal FC within the right hemisphere, and mixed results regarding FC alterations of inter-hemispheric FC ($p < .05$,

d |Min-Max|: 0.74-2.81, medium to large effect, Fig. 3D). Precisely, the epilepsy group predominantly had reduced FC between homologous regions (e.g., fronto-frontal connections) and a few stronger long-range inter-hemispheric connections (e.g., right frontal-left temporal) compared to the control group. The averaged z-score matrices for the four patient subgroups implied that children with FLE and right lateralized pathology, as compared to healthy controls, had the most different frontotemporal FC (Fig. 4). These patients had particularly increased FC of posterior temporal areas. Strikingly, children with left lateralized epilepsy had mainly left hemispheric and inter-hemispheric FC alterations, while their right hemisphere seemed almost unaffected and comparable to their healthy peers. The sample size prevented further statistical analyses between the subgroups.

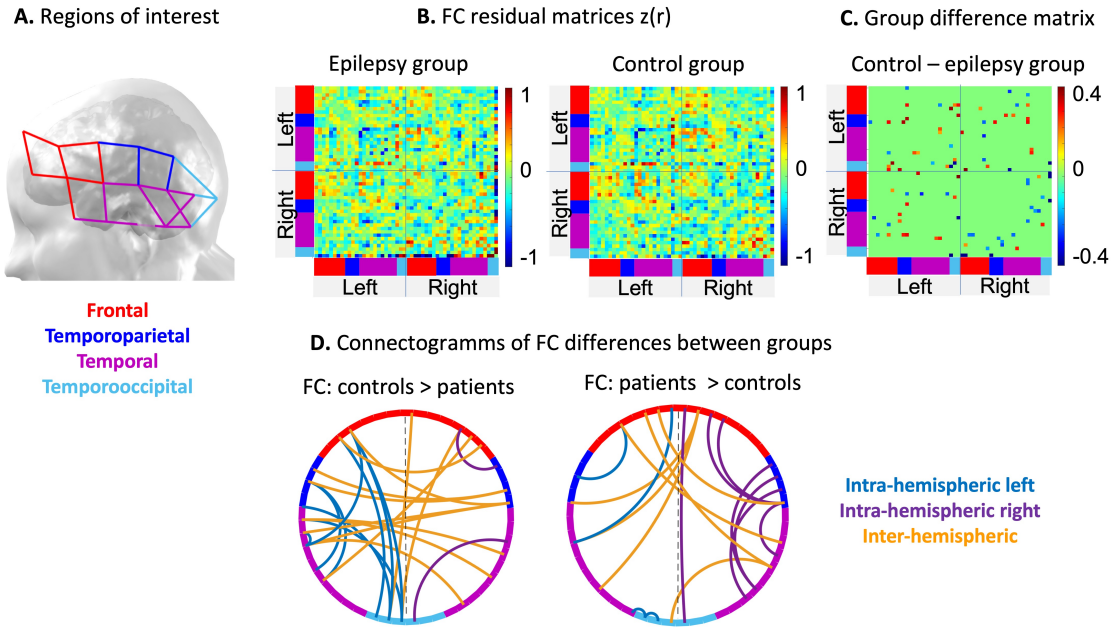

Figure 3 – Results of functional brain networks involved in language processing: (A) Specifies how channels were regrouped into four regions of interest. The color codes of these regions are used to indicate regions in the connectivity matrices and the connectograms; (B) the averaged residual matrices (FC story – FC resting-state) are illustrated for the patient (left) and the control (right) group; (C) the group difference matrix shows the correlation pairs that differed significantly ($p < 0.05$) between both groups; (D) the connectograms separately show the significantly positive (left, patients < controls, Cohen's d Min-Max: |0.74-2.81|, medium to large effect) and negative (right, patients > controls, Cohen's d Min-Max: |0.74-2.07|, medium to large effect) differences of functional connections between groups, respectively.

Connectivity strengths across all channels showed overall a similar distribution of FC. Averaged FC in the epilepsy and control group was 0.11 and 0.12, respectively (Fig. 5A). Weighted graph networks of children with FLE or TLE and healthy controls revealed a small-world topology ($\gamma > 1, \lambda > 1, \gamma > \gamma_{rand}$) for the language brain network over the sparsity range of $\tau_1 = 0.01$, to $\tau_{(m(task))} = 0.17$. Figure 5B displays the averaged AUC for

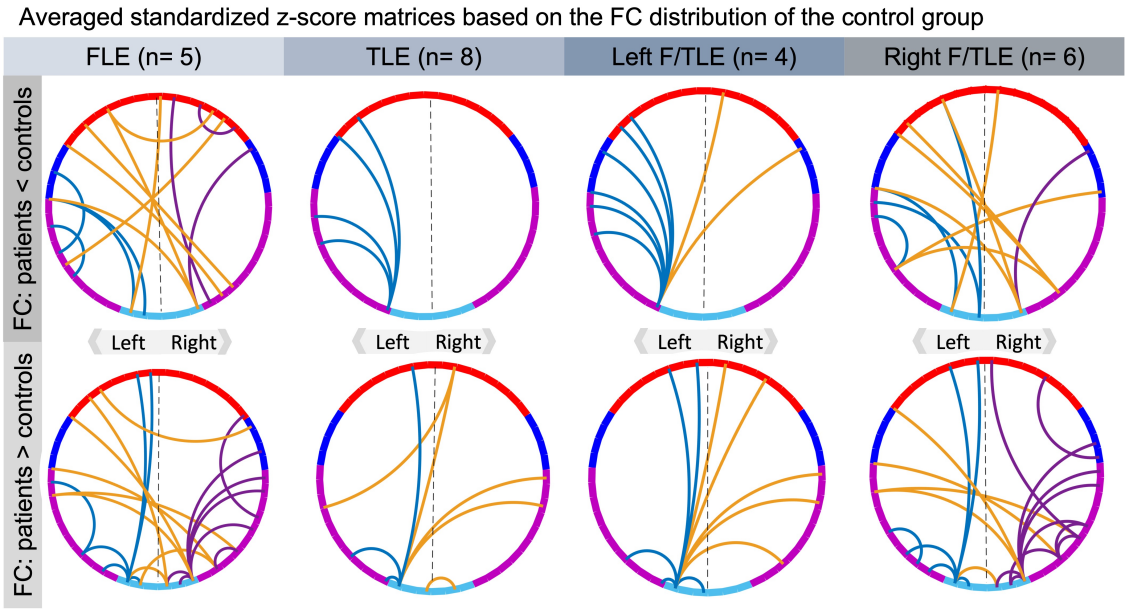

Figure 4 – Qualitative results of averaged standardized residual matrices of patients' subgroups. The upper part contains connections that are ≥ 2 *SD* lower in the epilepsy group than in the control group, while those in the bottom illustrate connections that are ≥ 2 *SD* higher in the epilepsy group compared to the control group. For all connectograms, the intra-hemispheric connections within the left and right hemisphere are displayed in blue and purple, respectively, and inter-hemispheric connections in orange. The color code of the regions of interest is specified in Figure 3A, where channels in red refer to frontal, blue to temporoparietal, purple to temporal and turquoise to temporoccipital areas of the brain.

each graph network metrics. We found a significant group difference for the AUC of E_{local} in the right hemisphere ($t(37)$ = -2.07, p = .046, d = -0.70, medium effect) and a relevant but not significant difference between groups for the clustering coefficient for the same hemisphere ($t(37)$ = -2.07, p = .059, d = -0.66, medium effect), but no differences between patients and controls for any of the other network metrics ($p > .05$).

Explorative correlation analysis between clinical factors and the AUC of the graph metrics of epilepsy patients revealed that overall epilepsy type showed the highest correlation across the AUC of all network metrics (Spearman r = |0.58-0.69|), followed by seizure control (Spearman r = |0.32-0.54|). Age of epilepsy onset (Pearson r = |0.20-0.33|) had a small to moderate correlations with network metrics. Lateralization (Spearman r = |0.05-0.28|) and epilepsy duration (Pearson r = |0.00-0.10|) did not show any strong associations with the AUC of network metrics (Table 2).

3.3. Cognitive profile

Results of the neuropsychological evaluation revealed that, compared to children of the control group, children of the patients group had a significantly lower estimated global IQ

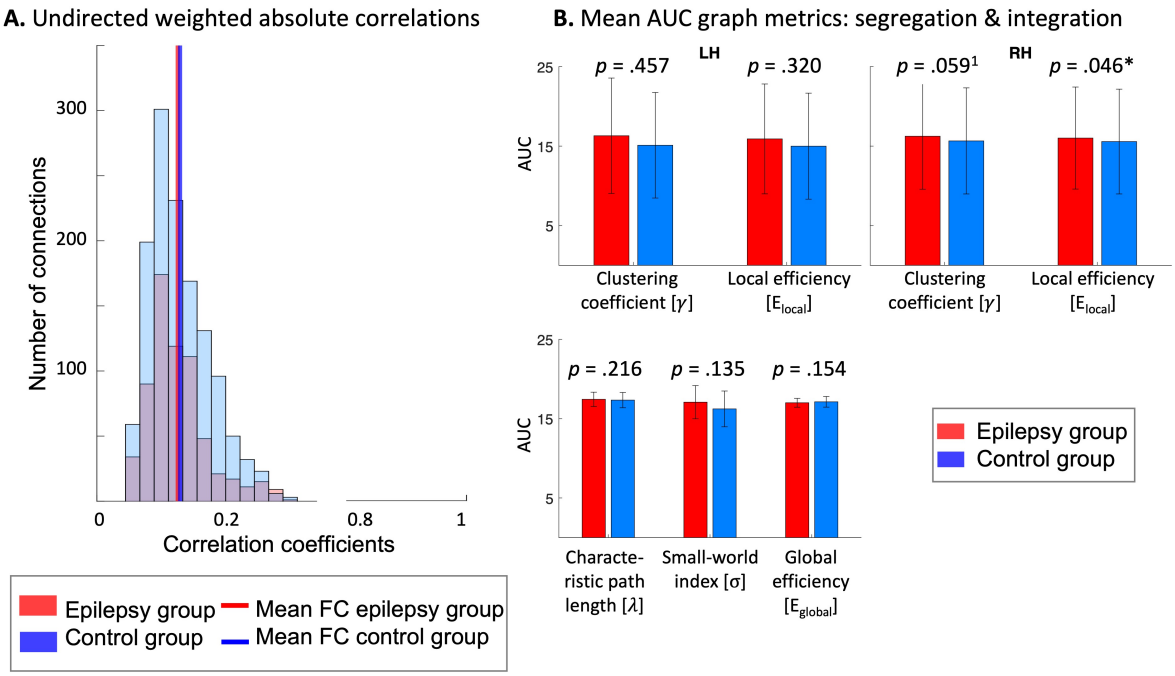

Figure 5 – Graph analysis of functional brain networks involved in language processing: (A) The distribution of the functional connectivity strength and the mean functional connectivity as indicated by the undirected weighted absolute correlation coefficients across all channels of the receptive language task for the epilepsy (red) and control (blue) group. The overlap between the distribution of both groups appears purple; (B) the mean AUC of the local and global graph metrics respectively over the sparsity range of 0.01-0.17. Local metrics are displayed for the left and right hemisphere individually. AUC: area under the curve, FC: functional connectivity, LH: left hemisphere, RH: right hemisphere. *Critical alpha: $p = .05$, [1]statistical tendency ($.05 < p < .08$).

($t(35) = 5.43$, $p < .001$, $d = 1.91$, large effect, missing $n_{\text{epi/ctrl}}$: 1/1), reduced overall verbal capacities (verbal comprehension index of the Wechsler intelligence scale, VCI: $t(35) = 3.37$, $p = .002$, $d = 1.19$, large effect, missing $n_{\text{epi/ctrl}}$: 1/1), lower receptive ($t(36) = 3.64$, $p < .001$, $d = 1.27$, large effect, missing n_{epi}: 1), and expressive language abilities ($t(37) = 2.94$, $p = .006$, $d = 1.00$, large effect) as well as decreased non-verbal skills (perceptual reasoning index of the Wechsler intelligence scale, PRI: $t(37) = 4.78$, $p < .001$, $d = 1.62$, large effect). Detailed results of the subtests are illustrated in Fig. 6.

Table 2 – Correlation analysis to assess the association of clinical factors and metrics of brain network organization.

	Clustering coefficient LH	Clustering coefficient RH	Local efficiency LH	Local efficiency RH	Characteristic path length	Global efficiency	Small-world index
Epilepsy type [FLE or TLE][1]	-0.65	-0.58	-0.60	-0.58	0.69	-0.66	-0.66
Epilepsy lateralization [left, right, bilateral][1]	-0.10	0.13	-0.05	0.18	-0.25	0.28	0.09
Age of epilepsy onset[2]	-0.20	-0.30	-0.24	-0.27	0.33	-0.30	-0.29
Epilepsy duration[2]	0.10	0.07	0.00	-0.09	-0.05	-0.01	0.07
Seizure control [yes, no][1]	0.49	0.42	0.54	0.41	-0.36	0.32	0.47

[1]Spearman rank correlation, [2]Pearson correlation coefficient, light grey, light blue/pale orange and dark blue/orange indicate small (r = |0.029|, medium (r = |0.30-0.49|), and large (r = |0.50-1.0|) correlations, respectively. Orange and blue stand for positive and negative correlations, respectively. LH: left hemisphere, RH: right hemisphere.

3.4. Association of brain network organization and the cognitive profile

Correlation coefficients revealed high correlations between the different cognitive measures ($r > 0.70$). Table S2 in the Supplemental Material provides the correlation coefficients between all variables. Due to multicollinearity between cognitive measures and because the estimated IQ had the most relevant and consistent association with network metrics across different metrics (r = |0.18-0.29|), we opted for a linear model that included the centered estimated IQ, the group factor and their interaction term to predict the AUC of the brain network metrics. Statistical results of this model are summarized in Table 3. 14.4 % of the E_{local} variance in the left hemisphere ($F(3,33) = 3.02$, $p = .044$, $d = 0.08$, small effect) was explained by this model. 13.0 % of the E_{local} variance in the right hemisphere ($F(3,33) = 2.79$, $p = .056$, $d = 0.02$, small effect) was explained by the included variables, which was however not statistically significant. We did not find any main effects of the group nor the estimated IQ, but there was a significant interaction effect between the group and estimated IQ for E_{local} of the left hemisphere (Beta = -1.46, $p = .014$, $\eta_p^2 = 0.16$, large effect) and an equally large but not significant effect for E_{local} of the right hemisphere (Beta = -1.29, $p = .055$, $\eta_p^2 = 0.10$, medium to large effect). The F-statistics of all the other metrics did not reveal a significant model fit.

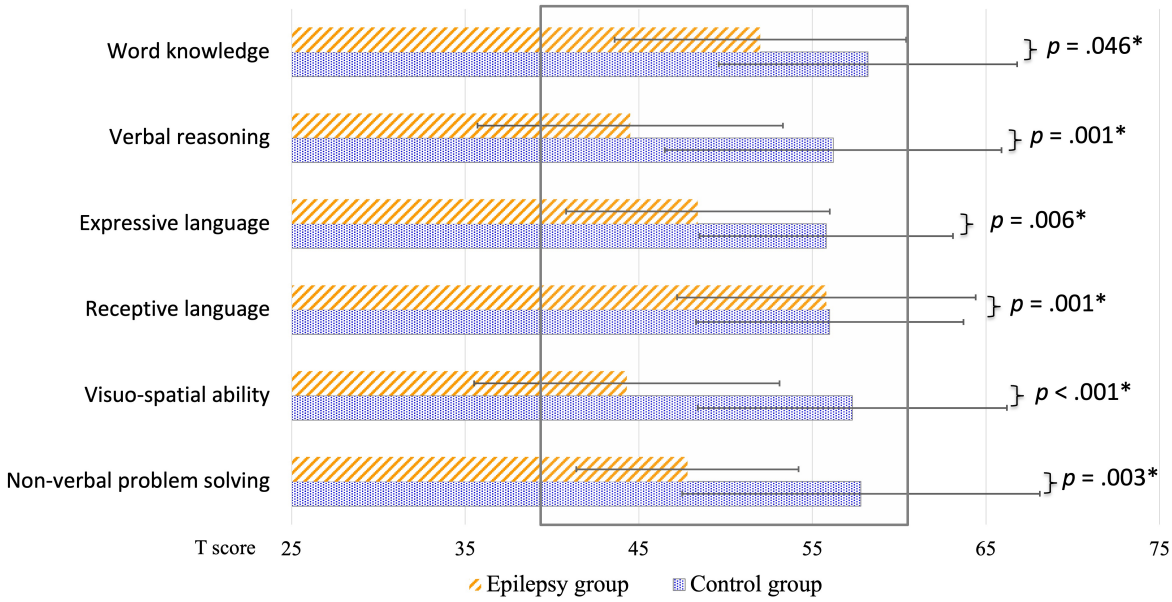

Figure 6 – Group comparisons of cognitive performance: children with frontal or temporal lobe epilepsy (orange stripes) and healthy control children (blue dotted) are illustrated separately. Results are expressed as t-scores. The normative range is indicated with the grey rectangle ($M \pm SD = 50 \pm 10$). All comparisons had a medium to large effect size ($d \geq 0.7$). *Critical alpha: $p = .05$.

Post-hoc simple slope analyses revealed that the association between the estimated IQ and E_{local} of the left hemisphere differed significantly between groups ($p = .014$) and at trend level for the E_{local} of the right hemisphere ($p = .055$). Precisely, an increase in the estimated IQ was associated with a significant decrease of E_{local} in the left (-1.43, $p = .006$) and the right hemispheres (1.17, $p = .046$) in the epilepsy group. In the control group, an increase of the estimated IQ did not relate to any changes of the E_{local} in the left (+0.03, $p = .915$) nor the right (+0.12, $p = .714$) hemispheres (Fig. 7).

Table 3 – Regression analysis to assess the association of cognitive measures and metrics of brain network organization and to detect potential moderating effects of the group factor.

Dependent variables	Clustering coefficient		Local efficiency		Characteristic path length	Global efficiency	Small-world index
	LH	RH	LH	RH			
Model fit $AUC = \beta_0 + \beta_1(Est.IQ) + \beta_2(Group) + \beta_3(Est.IQ * Group)$							
$F(3,33)$	1.47	1.95	**3.02**	**2.79**	1.66	1.11	2.19
Adjusted R^2	0.04	0.07	**0.14**	**0.13**	0.05	0.01	0.09
Estimated IQ							
β	-0.14	0.01	0.03	0.12	-0.04	0.03	0.02
p	.745	.984	.915	.714	.816	.745	.972
Group							
β	-0.49	0.53	-0.19	0.49	-0.06	0.09	0.10
p	.489	.492	.676	.360	.819	.489	.890
Group*Estimated IQ							
β	-1.41	-1.37	**-1.46**	**-1.29**	**0.59**	-0.20	**-1.80**
β	.112	.149	**.014***	**.055[1]**	**.080[1]**	.223	**.057[1]**

*Critical alpha: $p = .05$, [1]statistical tendency ($.05 < p < .08$). Significant effects and statistical tendencies are emphasized in bold. LH: left hemisphere, RH: right hemisphere.

4. Discussion

Developing language brain networks are vulnerable to neuropathologies, which may interrupt or disturb their normal development. At the same time, the developing brain benefits from great plasticity, offering a unique window for adaptive processes in response to neuropathologies (Smith, 2010). Differences in cerebral networks involving language processing have been reported in children with focal epilepsies compared to healthy controls (e.g., Hamberger & Cole, 2011; Sepeta et al., 2015; Slinger et al., 2022). However, specific patterns of language brain network alterations in pediatric patients with FLE and TLE are unknown and their associations with cognitive and language abilities are not fully understood. Therefore, it is not clear if the differences found in children with FLE or TLE compared to healthy controls represent positive adaptive reorganization or if they constitute pathological

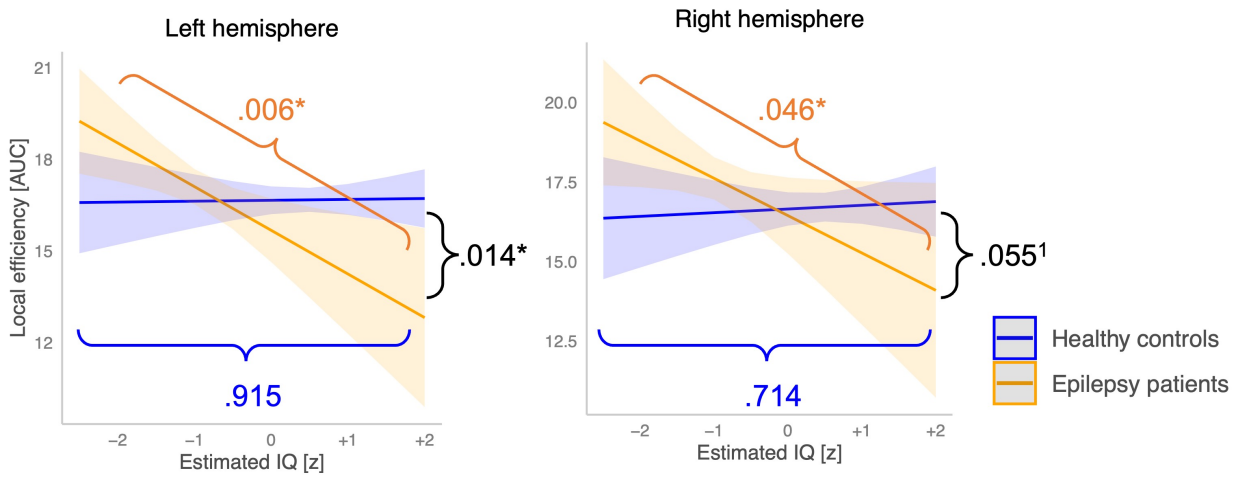

Figure 7 – Moderation of the association between the estimated IQ and local network topology by the group factor. Black brackets indicate the between group differences in the slope, orange lines show the slopes of the epilepsy group, and the blue lines represent the slopes of the control group. *Critical alpha = .05, [1]statistical tendency ($.05 < p < .08$).

brain reorganization in response to epilepsy. The main objectives of this study were to characterize the cerebral language network organization and to study the associations of these networks' characteristics with the cognitive and language profiles in children with FLE or TLE.

4.1. Cerebral networks

In the current study, the healthy control group presented typical cerebral language networks characterized by a joint recruitment of left temporoparietal, temporal and temporooccipital areas as well as of bilateral frontal and temporal areas (Hickok, 2022; Skeide & Friederici, 2016). Compared to healthy controls, children with FLE and TLE demonstrated weaker left hemispheric and inter-hemispheric FC as well as increased right frontotemporal connections. These group differences support the known incidence of atypical functional language networks in pediatric focal epilepsy (Baciu & Perrone-Bertolotti, 2015; Berl et al., 2014; Marcelle et al., 2022; Vannest et al., 2019). While the enhanced recruitment of right hemispheric frontotemporal regions is a frequent and well-established cerebral alteration of language processing in epilepsy patients, the impact on long-distance connections is less documented. In a recent fNIRS study in adult patients with frontotemporal epilepsy, Tung and colleagues (2021) investigated brain FC during a semantic and a phonemic verbal fluency task and found weaker inter-hemispheric FC in adult epilepsy patients compared to healthy controls. Our findings thus suggest that weaker inter-hemispheric FC between homologous frontotemporal regions in patients with FLE and TLE compared to controls is a characteristic of cerebral

language network reorganization across ages and different language domains (Sepeta et al., 2015; Tung et al., 2021).

Graph theory analysis revealed that global network topology of language processing was comparable between both groups, but that local network properties, i.e., local processing efficiency, in the right hemisphere was increased in the patient group compared to the control group. This suggests that the altered FC patterns in our epilepsy group only marginally affected the network's overall architecture and that the increase of right intra-hemispheric FC results in more segregation of right hemispheric frontotemporal regions. The reduction of FC within the left hemisphere does not however lead to significant changes in network architecture within this hemisphere. The typical developmental timeline of network architecture indicates that local network topology, i.e., network segregation, tends to decrease with age, while global network efficiency usually increases (Gozdas et al., 2019; Supekar et al., 2009). Hence, the above reported alteration could indicate a certain immaturity of brain language networks in children with FLE and TLE. Similarly, local network organization seems a common area of alterations in patients with epilepsy as the results of the meta-analysis by Slinger and colleagues (2022) underline. In contrast to our findings, they report however a lower clustering coefficient, suggesting a reduction of network segregation in adolescent and adult patients with focal epilepsy. Alterations of local network properties appear to be a key characteristic of brain network topology in patients with focal epilepsy such as FLE and TLE, and this both for large-scale brain networks as well as specific functional brain networks such as cerebral language networks. The direction of reorganization, i.e., whether fewer or more subnetworks are built, seems to depend on the patients' age.

Exploratory analyses of cerebral language networks in patient subgroups revealed that, compared to healthy controls, children with right lateralized epilepsy had overall more altered FC in cerebral language networks than patients with left lateralized epilepsy. The latter mainly had reduced FC among ipsilateral frontotemporal regions, suggesting that their language networks demonstrate primarily local deviations from the FC of healthy controls. Although epilepsy lateralization reportedly causes distinct differences in language networks, the literature rather suggests that patients with left lateralized FLE and TLE, i.e., seizure onset in the dominant hemisphere for language processing, experience more important alterations in their language networks compared to those with right hemispheric lateralization (Hamberger & Cole, 2011; Rodríguez-Cruces et al., 2020; Tung et al., 2021). Our data and others show that right hemispheric epilepsy does however not seem to prevent reorganization of cerebral language networks, causing a distinct pattern of alteration (Smith, 2016; Tung et al., 2021). This is in line with the current understanding of the typical neurobiology of cerebral language networks that suggests that despite a left hemispheric dominance, bilateral frontotemporal areas are involved in language processing (Hickok, 2009, 2022; Hickok & Poeppel, 2007). Regarding the role of epilepsy type, our results indicate that FC in children with FLE was

more strongly affected compared to those with TLE with much more differences in intra- and inter-hemispheric FC in FLE than TLE compared to healthy controls. A distinct pattern of FC for epilepsy type has recently also been identified in adult patients with FLE and TLE (Caciagli et al., 2023). Precisely, fMRI data acquired during two expressive language tasks indicate that patients with FLE compared to those with TLE demonstrate increased FC within left temporooccipital and bilateral occipital areas. In our data set, epilepsy type and to some extent seizure control, showed the strongest associations with graph metrics of network topology. Epilepsy type and lateralization seem relevant predictors for the organization of cerebral language networks, though more studies are necessary to better characterize the specific pattern of reorganization associated with each subgroup. In this context, it is also important to emphasize the heterogeneous seizure semiology. Precisely, cerebral language network organization may be affected differently when seizures are purely unilateral, or epileptic activity propagates to the other hemisphere or seizures commonly result in a secondary generalization. Future studies with larger samples size should consider more precise characteristics of seizure semiology.

4.2. Cognitive profile

The neuropsychological results indicated that children with FLE or TLE had an overall cognitive performance and receptive and expressive language capacities within the normative range, however significantly lower than their healthy peers. In our sample, FLE and TLE seem to have a general impact on the cognitive capacities rather than a specific effect on language abilities. This is in line with the current state of the literature on pediatric FLE or TLE, which shows that focal epilepsy is a network disorder and affects multiple cognitive domains (Garcia-Ramos et al., 2015; Hermann et al., 2017; Kellermann et al., 2016; Rodríguez-Cruces et al., 2020; Verche et al., 2018).

4.3. Relationships between brain network organization and cognitive profile

During the fNIRS-EEG recording, patients with epilepsy demonstrated reduced task performance at the passive story listening task, i.e., lower comprehension of the story line, compared to the control group. This suggests that the diffuse FC alterations and increased local processing efficiency in the right hemisphere measured during language processing seem to represent aberrant network organization. Specific regression analysis revealed however a more complex pattern. The estimated IQ alone did not predict any of the network's characteristics. However, we found a moderation effect of the group factor (patients vs. controls) on the association between the estimated IQ and the network's local processing efficiency in the left hemisphere and at a trend level in the right hemisphere. Precisely, the estimated IQ was

negatively related to the level of local processing efficiency in the patient's group, while no such relationship was identified for the control group. No moderation effect was found for the clustering coefficient nor any of the global network metrics. Although current findings from neurotypically developing children suggest that the direction of the association between intellectual capacities and graph theoretical measures differs between cerebral regions (Gozdas et al., 2019), network segregation generally decreases during childhood and adolescence (Supekar et al., 2009). The association of a lower network segregation with higher cognitive functioning may imply that compensatory mechanisms in the left hemisphere enabled a more mature and therefore more efficient cerebral language network.

4.4. Strengths and limitations

This study has several methodological strengths that can be highlighted here. First, epileptic activity can significantly affect hemodynamic fluctuations and mislead the interpretation of cerebral language processing. The simultaneous acquisition of the electrophysiological data (EEG) with the hemodynamic signal (fNIRS) thus allowed to monitor epileptic activity and ensure a good quality of the hemodynamic signal without contamination of seizure activity. In future studies, the joint multimodal analysis of EEG and fNIRS FC would certainly also offer rich information to characterize language brain networks in individuals with epilepsy. However, a task paradigm better adapted to both signals (slow fNIRS hemodynamic and fast EEG neuronal signals) and a greater number of EEG electrodes should be used. This nevertheless constitutes interesting paths for future research. Another methodological strength of this study is the subtraction of the resting-state FC matrices from the task FC matrices allowing to maximally isolate cerebral activation related to receptive language processing. Finally, a third strength is the use of a graph theoretical approach to characterize brain language networks in children with FLE and TLE, where such literature on this specific group of patients is still scarce.

This study also has several limitations that must be considered when interpreting its results. First, the heterogeneous clinical phenotype of epilepsy and the high number of comorbidities makes the recruitment of a homogeneous sample challenging and resulted in the current study in a relatively small sample. We carefully considered the sample size while performing statistical analysis and emphasize the value of effect sizes. The impact of clinical factors (e.g., epilepsy type and lateralization, age at onset, duration of epilepsy, seizure frequency and control) on brain functional connectivity could only be addressed in an explorative manner and the sample size precluded their consideration for advanced analysis. Due to high heterogeneity, other clinical variables (e.g., etiologies, number, and type of ASM, etc.) could not be considered for analyses. It has however been shown that these clinical factors correlate with the extent and type of cognitive difficulties (Gallagher &

Lassonde, 2005; Jambaqué et al., 1993; Verche et al., 2018). Therefore, their role for cerebral language processing and the neuropsychological outcome should be specifically addressed in upcoming research with larger samples. This will allow to shed light on differences in brain network architecture of epilepsy patients and enhance the understanding of the role of clinical characteristics on the association between neuropsychological profiles and cerebral network organization. Finally, the current findings are deducted based on a story listening task. Therefore, whether they represent specific cerebral characteristics of receptive language, or rather a general effect of language processing must be analyzed in a study applying different language task paradigms. This would for instance allow us to compare neuronal response between receptive and expressive language processing or other distinct linguistic processes.

4.5. Conclusion

This is the first study that specifically focused on children with FLE and TLE, the most common types of focal epilepsies where epileptogenic networks are more likely to interfere with cerebral language processing. Another novelty is the use of graph theory measures to characterize network architecture of brain language networks and identify their relationship with cognitive measures. We found distinct patterns of FC for cerebral language processing in children with FLE or TLE compared to typically developing children. Precisely, children with FLE or TLE had decreased left frontotemporal connections, fewer inter-hemispheric connections between homologous regions and increased right intra-hemispheric frontotemporal connections compared to their healthy peers. This suggests an atypical cerebral representation of language networks, with greater involvement of the right hemisphere and less left and inter-hemispheric interactions in these children. The patients' brain architecture was also characterized by higher local processing efficiency predominantly in the right hemisphere. These large-scale language network alterations in the epilepsy group were accompanied by a reduction of cognitive capacities both in verbal and non-verbal domains. In children with FLE or TLE, local efficiency in the left hemisphere was negatively associated with global intellectual functioning. Reduced network segregation, i.e., the tendency to build locally specialized clusters, especially in the left hemisphere, may thus be a specific aspect of cerebral reorganization allowed by early brain plasticity that overall seems to favor a better cognitive outcome. Future studies will allow to shed light on the associations between different measures of brain network alterations and the neuropsychological profile, and particularly address the complex impact of clinical factors on functional brain network organization, including factors such as epilepsy lateralization and localization, the age of epilepsy onset, epilepsy duration, seizure control or medication, on functional brain network organization. Understanding the developing brain's adaptive capacities in response to neuropathologies and the long-term functional impact in the context of development has important fundamental and clinical

implications. Our findings contribute to a better understanding of cerebral alterations in response to pediatric FLE or TLE and their functional impact and pave the way for further investigations. Epilepsy is a network disorder and understanding the broader picture of cerebral and cognitive alterations would enable the installation of more adequate interventions and individual support for these patients.

5. Conflict of interest and disclosures

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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8. Contribution to the field statement

Focal epilepsies, particularly those with seizures propagating from frontal and temporal lobes, are among the most common neuropediatric disorders. Various verbal and non-verbal cognitive difficulties are commonly reported in these patients and relate to lower academic achievement and reduced quality of life. Moreover, cerebral language networks in these patients are often characterized by an atypical organization in comparison to healthy controls. The specific patterns of alterations are however not fully understood and their relationship to cognitive and language capacities is often speculative. This study strengthens the current knowledge of network characteristics related to cerebral language processing in this group

of patients and extends the understanding of the functional impact of network alterations. This contributes to a better understanding of the developing brain's adaptive capacities in response to neuropathologies and might increases prediction of an unfavorable development and early detection of children at high-risk for neurodevelopmental impairments. Consequently, appropriate interventions can be installed to support the development of these children and the risk of procedures such as epilepsy surgery can be better estimated. Finally, this study paves the way for future investigations of the association between brain network organization and cognition, and the role of clinical factors such as epilepsy type and lateralization.

9. Code, Data and Materials Availability

The anonymized data that support the findings of this study are available from the corresponding author upon reasonable request.

10. Supplemental Material

Table 1 – Detailed clinical characteristics of patients with epilepsy.

EPILEPSY LOCALIZATION	ETIOLOGY	STRUCTURAL ABNORMALITIES	ASM AT TIME OF TESTING
FRONTAL LEFT	Auto immune	Cerebral atrophy	Phenytoin, Clobazam
TEMPORAL RIGHT	Unknown	None	Carbamazepine, Levetiracetam
TEMPORAL LEFT	Structural	Hippocampal sclerosis	Oxcarbazepine
TEMPORAL LEFT	Structural	Incomplete signs of hippocampal sclerosis	Carbamazepine
FRONTAL RIGHT	Unknown	None	Levetiracetam
TEMPORAL RIGHT	Unknown	None	Carbamazepine
FRONTAL RIGHT	Unknown	None	Levetiracetam, Carbamazepine
FRONTAL BILATERAL	Unknown	None	Levetiracetam
TEMPORAL BILATERAL	Unknown	Arachnoid cyst	Acid valproic
TEMPORAL BILATERAL	Unknown	None	Levetiracetam
TEMPORAL LEFT	Unknown	None	Carbamazepine
FRONTAL RIGHT	N/A	N/A	N/A
TEMPORAL RIGHT	Structural	White matter lesion, dysplasia	Lamotrigine

ASM: antiseizure medication; N/A: not available.

Table 2 – Correlation analysis (r) on the association of cognitive measures and metrics of brain network organization.

		Cognitive measures				**Network organization**						
Estimated IQ		1.00										
Receptive language		0.76	1.00									
Expressive language		0.71	0.63	1.00								
fNIRS task performance		0.49	0.20	0.46	1.00							
Clustering coefficient	LH	-0.19	-0.18	-0.15	-0.29	1.00						
	RH	-0.28	-0.09	-0.20	-0.39	0.77	1.00					
Local efficiency	LH	-0.23	-0.19	-0.22	-0.36	0.93	0.75	1.00				
	RH	-0.29	-0.07	-0.23	-0.43	0.74	0.95	0.81	1.00			
Characteristic path length		0.21	0.04	0.09	0.29	-0.53	-0.52	-0.63	-0.61	1.00		
Global efficiency		-0.18	0.02	-0.07	-0.24	0.25	0.25	0.44	0.43	-0.91	1.00	
Small-world index		-0.26	-0.11	-0.19	-0.37	0.91	0.92	0.91	0.91	-0.73	0.48	1.00
						LH	RH	LH	RH			
		Estimated IQ	Receptive language	Expressive language	fNIRS task performance[1]	Clustering coefficient		Local efficiency		Characteristic path length	Global efficiency	Small-world index

Light gray: r = |0-0.29|, pale blue/orange: r = |0.30-0.49| medium, blue/orange: r = |0.50-1.0| large, orange: positive correlations, blue: negative correlations. r, Pearson correlation coefficient, LH, left hemisphere, RH, right hemisphere, fNIRS, functional near-infrared spectroscopy, [1]estimated as percentage of correct responses regarding the comprehension of the storyline.

Chapter 3

Discussion

Pediatric FLE and TLE are among the most common neuropediatric disorders (Behr et al., 2016; Berg et al., 2013). Neuropsychological difficulties have long been reported in these patients (e.g., Law et al., 2018; Wilson et al., 2015). Traditionally, certain difficulties, i.e., impaired executive functions or memory capacities, are more common in patients with FLE and TLE, respectively (Smith, 2016). The clinical phenotype of focal epilepsies and the resulting neuropsychological profile is however very complex and it has been shown that difficulties in distinct domains are often intertwined (Kellermann et al., 2016). Nevertheless, a common concern in both groups is language (e.g., Metternich et al., 2014). Language functions influence many other cognitive and social abilities, and are highly relevant for later academic achievement (Berwick et al., 2013; Gervain, 2020). In case of atypical language capacities, interventions should start early in order to maximally support the normal progression during childhood and adolescence. Cerebral language processing in patients with FLE or TLE is reportedly marked by an atypical hemispheric dominance, altered patterns of FC among frontotemporal brain areas and distinct network topology such as reduced processing efficiency (e.g., Gallagher et al., 2016; Law et al., 2018; Slinger et al., 2022), given the neurobiology of the brain's language network that involves large parts of the frontotemporal cortex (Hickok & Poeppel, 2007; Skeide & Friederici, 2016). To date, there is however no clear consensus on the exact pattern of cerebral alterations of language networks in children with FLE or TLE and the brain-behavior relationship for language functioning remains speculative.

3.1. Recap of the main objectives

The broad objective of this thesis is to enhance the understanding of the neuropathological impact of FLE and TLE on cerebral language processing and the association with cognitive abilities during childhood and adolescence. Two methodological projects, preceded the main investigation and contributed to optimizing the research protocol. The first study aims to underline the value of the pediatric neuropsychological evaluation in estimating the overall cognitive profile, identifying potential abnormalities and to contribute to a better understanding of the brain-behavior relationship (Hüsser et al., 2020). The second study aims to optimize the applied methods and data analysis techniques that will be used in article three to improve fNIRS signal quality and increase characterization of brain networks (Hüsser et al., 2022). The empirical study in children and adolescents with FLE and TLE represents

the main project of this thesis and addresses cerebral language network organization and its relationship with the neuropsychological profile (Hüsser et al., 2023). In this discussion, the focus lies on summarizing and integrating the results of each article to derive a common outlook. First, the main methodological (Sec. 3.2) advances (articles one and two) and the findings on cerebral language networks as well as language and cognitive capacities in children with FLE and TLE (article three, Sec. 3.2) will be summarized and embedded in the current literature. The subsequent sections 3.3 will emphasize on the strengths and limitations of the presented publications, which will subsequently allow to draw the main implications of this doctoral thesis, provide directions for future research (Sec. 3.4), and a general conclusion. This thesis also includes as appendices two additional publications: the first introduces important concepts on research about the development of the brain's language networks (Appendix I, article four) and the second presents the fNIRS analysis toolbox that has been used for all fNIRS processing steps and parts of the statistical analyses (Appendix II, article five).

3.2. Summary and interpretation of the main findings

Methodological advances

The first publication of this doctoral thesis is a book chapter that presents the pediatric neuropsychological assessment as a tool to characterize the cognitive, behavioral and socioaffective profile of children. In this chapter, we underline the integrative work of qualitative and quantitative data to derive cognitive, motor, socioaffective and behavioral functioning. We review specific applications of the neuropsychological evaluation and how its results contribute to the diagnostic process, the planning of adequate interventions and monitoring of their progression, the surveillance of side effects related to pharmacotherapy and their prognostic value. The neuropsychological assessment is an important basis to derive hypothesis regarding the underlying cerebral correlates of cognitive functions and better understand the brain-behavior relationship. The more that is known about this association, the better neuropathologies and their clinical phenotype can be understood. In the context of this doctoral thesis, it guided the acquisition of the neuropsychological data to estimate general cognitive and specifical language abilities in children with FLE and TLE as well as in neurotypical children.

In the second publication, we investigate the use of PARAFAC for multidimensional data analysis of the fNIRS signal. The validation, under controlled conditions in a simulated fNIRS signal with simulated artifacts, allowed to refine the specific characteristics of artifact correction with PARAFAC. We also corrected real artifacts in a data set acquired in healthy adults during an expressive language task, which allowed to directly prove PARAFAC's use in a task paradigm mainly causing artifacts related to articulation. For simulated and real data, PARAFAC leads to a significant improvement of the signal quality. Furthermore,

compared to traditional 2D decomposition approaches (ICA and tPCA), it achieves similar results for artifact correction when the signal's dimensions, i.e., space (channels), time and wavelengths, were orthogonal to each other, and leads to a better signal quality, such as a lower signal-to-noise ratio, compared to two-dimensional decomposition methods when the signal's dimensions is not orthogonal. This thorough validation of PARAFAC as a multidimensional data analysis tool supports its use for movement artifact correction in fNIRS. Exploiting all three dimensions of the fNIRS signal rather than artificially unfolding them into two dimensions represents a valuable advantage and increases fNIRS data quality.

Cerebral language networks and cognitive capacities in pediatric FLE and TLE

The third publication consists of an empirical study on the organization of cerebral language networks and their association with cognitive measures in children with FLE or TLE in comparison to healthy controls. Hemodynamic fluctuations related to the brain's language processing were isolated and assessed by subtracting HbO FC matrices of the resting-state signal from the HbO FC matrices of the signal obtained during a passive story listening task. Residual FC matrices show a typical dominance of left hemispheric frontotemporal FC in the control group, while between group comparisons reveal intra- and inter-hemispheric differences of cerebral language networks. Precisely, stronger FC within right frontotemporal areas, and fewer FC within homologous left hemispheric regions as well as less inter-hemispheric connections are observed in the epilepsy group as compared to their healthy peers. Network topology derived from task matrices in epilepsy patients further show increased local processing efficiency in the right hemisphere compared to the control group. Global network metrics appear comparable between study groups. These findings replicate previous results of altered task-related FC in cerebral language networks (Baciu & Perrone-Bertolotti, 2015; Berl et al., 2014; Marcelle et al., 2022; Vannest et al., 2019) and underline the higher prevalence of atypical network organization in patients with FLE or TLE. Similarly to reports from adult patients (Slinger et al., 2022), the current research supports local network architecture as an important index of network alteration in response to pediatric FLE and TLE, though the direction of difference is not the same across adult and pediatric patients. Explorative subgroup analyses of FC patterns and network topology further support the relevance of clinical factors such as the type of epilepsy (FLE *vs.* TLE), epilepsy lateralization (left *vs.* right) and seizure control for the precise network alterations.

The differences in FC and the increased local processing efficiency within the right hemisphere in the patients group reveal an altered cerebral organization. The cognitive profile of children with FLE and TLE is characterized by reduced capacities in all assessed functions,

i.e., verbal and non-verbal general intellectual capacities, as well as expressive and receptive abilities, as compared to their healthy peers. This implies that the cerebral alterations do not favor normal cognitive development but rather represent a characteristic of an atypical development. Moreover, FLE and TLE further do not seem to have a specific impact on language capacities but rather cause a general reduction of intellectual functioning. Despite certain characteristics of the neuropsychological profile of children with FLE compared to those with TLE and common vulnerabilities in language capacities, recent findings reveal that their profile is often heterogeneous and complex (Hermann et al., 2021; Law et al., 2018; Smith, 2016). Consequently, focusing on one specific cognitive domain does not catch the full extent of the phenotype. This supports the notion of epilepsy as a network disorder, where the impact goes beyond the epileptogenic zone and is in line with the results of this study.

Task performance reveals that epilepsy patients had worse comprehension of the story presented during the fNIRS acquisition. This suggests that the above reported network alterations go along with worse task related cognitive capacities. Analysis of the association between indices of brain language network topology and cognitive measures allowed to refine this relationship. We have found a negative association between left and to some extent also right hemispheric local efficiency and general cognitive functioning in the epilepsy group, while for the controls no specific association between these measures has been identified. Patients with higher cognitive capacities thus present lower local processing efficiency compared to a higher local efficiency in those with lower cognitive capacities. In neurotypical children, network segregation, i.e., the level of local sub-networks, tends to decrease with age, while network integration, i.e., distant connections across the brain, tends to increase (Gozdas et al., 2019; Supekar et al., 2009). Local efficiency is one index of network segregation. Therefore, the reduction of local efficiency may represent a compensatory mechanism for some patients with FLE and TLE supporting a better cognitive development.

The current findings replicate and extend the current knowledge on cerebral and cognitive alterations in children with FLE and TLE and increase the understanding of the brain-behavior relationship. They show that FLE and TLE do have a broad impact on cerebral language processing as well as the neuropsychological profile in these children but also reveal that the developing brain is capable of adapting and partially compensating for the pathological influence. To the best of our knowledge, this study is the first to use graph network analysis to interpret functional brain network topology related to language processing in children with FLE and TLE.

3.3. Strengths and limitations

This doctoral thesis integrates fundamental concepts, methodological work and an empirical study. The extensive presentation of the neuropsychological assessment and its scope strongly

guided its application in the empirical study. Moreover, PARAFAC has been validated (article two) as a new methodological approach to correct movement artifacts in the fNIRS signal and can be added to the catalogue of applicable analytic methods for fNIRS. The use of PARAFAC for the correction of movement artifacts in the fNIRS signal allowed to increase data quality and improve network analysis of the empirical study. By following a strict acquisition protocol and assuring data quality during preprocessing analyses, the quality of the statistical sample is maximized. The main strength of this dissertation lies thus in the solid methodological foundation that leads to a refined approach for the principal study on pediatric FLE and TLE. The combination of reliable brain network and neuropsychological measures enhance robustness of the results on the brain-behavior relationship under neuropathological conditions.

The main limitation of the empirical study of article three, is the rather small sample size. This has been carefully considered for the choice of the statistical methods and results have been interpreted in the context of effect sizes. The findings of the current thesis generalize to all recruited patients with FLE and TLE independent of their clinical phenotype and provide preliminary indices for subgroup differences. The sample size has however prevented more advanced analysis to compare network alterations between patient subgroups, such as between left and right lateralized epilepsy or between FLE and TLE, and investigation of the precise role of different clinical factors. Although the role of clinical factors remains speculative, the present research work unravels certain similarities across different patient subgroups. Future studies with larger sample sizes will allow to address these issues and provide further insights into subgroup differences in children with epilepsy as well as enhance understanding of clinical factors.

A challenge of pediatric research is the dynamic cerebral and cognitive development. Studies in children and adolescents either must control for age differences between participants or recruit a large enough sample to provide a good representation of each developmental stage. In the case of epilepsy research, this applies both for the age of epilepsy onset as well as the age where cerebral processing and cognitive capacities are evaluated. There are reports of critical windows for the establishment of cerebral networks, such that reorganization of language networks differ depending on the age of epilepsy onset (Marcelle et al., 2022). In article three, we did control for age differences and did not interpret differences between younger or older patients. We explored how age of epilepsy onset relates to brain network organization but did not find any relevant association. Moreover, effects identified at a certain age may not persist, such that cerebral language networks change over time (Hertz-Pannier et al., 2002; Vannasing et al., 2016). It is commonly assumed that cognitive measures derived from a neuropsychological evaluation remain valid for at least a year, changes in patients with FLE or TLE may however follow a different dynamic. The current findings represent

a snapshot of brain network organization and neuropsychological performance and cannot provide prognosis of the developmental time course. Longitudinal follow-up would provide more insights into the dynamics of brain network organization and cognitive capacities in children with FLE or TLE.

3.4. Implications and perspectives

The developing brain is marked by dynamic changes of the nervous system (e.g., Paus, 2022). Under these circumstances the association between brain development and neuropsychological functioning is complex, and even more in the context of neuropathologies. Numerous metrics of cognitive capacities and cerebral correlates exist and methods such as the neuropsychological assessment, neuroimaging techniques, such as fNIRS, and advanced data analysis tools, such as PARAFAC, are essential to obtain reliable data. Article one and two of this thesis contribute to the continuous development of these tools and pave the way for more comprehensive data sets that allow to reliably interpret the brain-behavior relationship, and characterize the impact of pediatric FLE and TLE on neuronal and functional development.

Article one presents the neuropsychological evaluation in pediatric populations as a powerful and yet fairly available tool to characterize the neuropsychological profile and identify individual strengths and weaknesses in various pediatric populations. This chapter also presents how the neuropsychological results and interpretation allow to derive assumptions about cerebral correlates, which contributes to a better comprehension of the brain-behavior relationship. The current thesis contributes to enhance awareness and knowledge of the neuropsychological assessment and paves the way for its integration and appropriate use in future research protocols.

Article two presents the first application and validation of PARAFAC for artifact correction in fNIRS data and reveals its value for improving signal quality. The integration of PARAFAC into the LIONirs toolbox (J. Tremblay et al., 2022), developed by our group, allows for a rather straightforward application, where the decomposition can easily be adapted to the specific needs, characteristics of the components can be investigated and the effect of the correction can be monitored. As shown with other neuroimaging modalities (Martínez-Montes, Sánchez-Bornot, et al., 2008; Martínez-Montes et al., 2004), artifact correction represents however only one possible application of PARAFAC. Its potential to exploit the multidimensional structure of the fNIRS signal could in the future be extended for the correction of the physiologic signal, allowing to better isolate the relevant hemodynamic signal, and for network analysis, which would represent a valuable data driven approach to extract different network properties. Such data driven methods are particularly relevant for the identification of brain network alterations related to neuropathologies, where predictions about specific patterns are often challenging. PARAFAC could therefore complement currently used techniques such as FC

matrices and graph network analysis and provide a different perspective of network properties. PARAFAC would also be beneficial for multimodal neuroimaging analyses, such as combined fNIRS and EEG data, where the richness of both signals could be better exploited. Such research will increase PARAFAC's relevance for fNIRS data analysis and potentially allow to obtain new perspectives on brain network characteristics based on different measures of neuronal activity.

The investigations of characteristics of cerebral language networks and neuropsychological profile in children with FLE and TLE (article three) enhance the understanding of the pathological impact of focal epilepsy. Eventually, it could help clinicians to identify children at higher risks for cognitive and language dysfunctions. From a clinical perspective it would allow to provide appropriate interventions promoting long-term neuropsychological development, which have been associated with better academic achievement, psychosocial functioning and quality of life (Michaelis et al., 2018).

Explorative analyses revealed certain differences of cerebral network organization between patient subgroups, yet further investigation would require stronger statistical power with an increased sample size of sub-groups. The literature suggest however that clinical factors such as the type of epilepsy (Caciagli et al., 2023), epilepsy lateralization (Berl et al., 2005; Hamberger & Cole, 2011; Rodríguez-Cruces et al., 2020; Tung et al., 2021), age of epilepsy onset and disease duration (Ma et al., 2015; Marcelle et al., 2022), as well as seizure frequency and control (Caciagli et al., 2023), may account for differences of brain network organization between patients. The conditions and the extent to which early brain plasticity can counter pathological influences and whether there is a critical age remains to date unclear. Larger patient samples will allow to consider the influence of these clinical factors and better investigate the complex construct of cerebral and cognitive metrics in the developing brain. This is an important path for future research and will allow to better understand differences between patient subgroups and ultimately refine the identification of those at risk for an unfavorable development. Moreover, future studies should investigate whether the identified local and global network alterations manifest in other facets of cerebral language processing, i.e., expressive language.

Due to the high inter-individual variability in brain and cognitive development (Genon et al., 2022; Hüsser et al., 2020), differentiation between a normal variation or aberrant cerebral and cognitive maturation can thus sometimes be challenging. Moreover, an alteration may represent either a deficit or a delay (Baron, 2010; Giedd, 2004; Hüsser et al., 2020; Paquette et al., 2015; Skeide & Friederici, 2016), which cannot be differentiate in cross-sectional study designs. Therefore, only longitudinal data will allow to draw a precise developmental trajectory of cerebral organization in response to pathological influences such as in FLE and TLE. A refined understanding of early signs of developmental deviations is essential to install

appropriate interventions, support cerebral and cognitive maturation and optimize prognosis of children with neurodevelopmental disorders such as FLE and TLE.

Article three focuses specifically on functional brain networks and did not include structural brain data. In children with FLE, there has been evidence for increased cortical thinning (Widjaja et al., 2011), abnormal white matter tracts (Widjaja et al., 2014) as well as large-scale and specific functional network alterations (Braakman et al., 2013; Widjaja et al., 2013). Similarly, both grey (Guimarães et al., 2007) and white matter (Gao et al., 2012; Meng et al., 2010) abnormalities as well as structural brain network reorganizations have been reported in children with TLE. In future studies, integrating these metrics with functional network reorganization may provide more insights into the association between structural and functional brain network characteristics as well as into the brain-behavior relationship.

Epilepsy has long been an important clinical model and has contributed to advances in several domains of neuroscience beyond epilepsy. We believe the current findings further promote its role to study the association of brain network topology and neuropsychological functions under pathological conditions. Studies comparing cerebral alterations across different clinical populations will allow to derive common indices of cerebral and cognitive alterations across pathologies and provide further insights into the way the developing brain reacts to pathological influences, which enhances the understanding of the remarkable adaptive mechanisms related to early brain plasticity.

3.5. Conclusion

The development of language functions and cerebral language networks throughout childhood and adolescence are highly dynamic processes. Neuropathologies such as pediatric epilepsy have been shown to interfere with normal brain development and cause altered network structures. The exact mechanisms leading to such alterations and the association with the neuropsychological profile are however not yet fully understood. As shown in article one, the neuropsychological assessment is an important tool to assess the functional impact of neuropathologies such as pediatric FLE or TLE. Neuroimaging techniques allow to assess cerebral functioning and complement the understanding of the brain-behavior relationship by providing insights into the underlying brain architecture. Appropriate data analysis methods are essential to derive reliable findings and especially motion artifact correction techniques such as PARAFAC significantly improve the quality of data (article two). Empirical data on children with epilepsy reveal that there exist large-scale alterations in FC patterns that seem robust across studies. These lead to differences in local network structure, as shown in article three, with children with FLE and TLE demonstrating more local network segregation. The association between local processing efficiency further reveals that the association with the neuropsychological profile varies within the epilepsy group. Precisely,

lower local efficiency relates to better cognitive outcome, whereas higher local efficiency was associated with below average performance. This suggests that adaptive mechanisms have enabled network modifications that support a better neuropsychological outcome. The specific role of clinical characteristics that may explain differences between children with FLE and TLE remains unclear and needs to be addressed in future research. Overall, this thesis contributes to the improvement of methods detecting cognitive (article one) and cerebral (article two) alterations in children and to a better understanding of cerebral plasticity and the brain-behavior relationship in the developing epileptic brain (article three). Continuous research on patients with epilepsy will increase the understanding of this neuropathology, sensitize the knowledge on its functional impact and allow to further demystify it and therefore contribute to reduce its stigmatization.

Appendix A

Additional articles

Fourth Article.

Functional brain connectivity of language functions in children revealed by EEG and MEG: A systematic review

by

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I.G. developed search procedure, performed database searches and reviewed articles for inclusion/exclusion based on the title, and abstract. I.G. and A.H. reviewed articles for inclusion/exclusion based on the full text, extracted data from articles, analyzed the extracted data, and wrote the manuscript. P.V. contributed to intellectual content and provided comments on the manuscript. A.G. supervised all aspects of the systematic literature review, preparation of the manuscript, revision, editing, and final intellectual content.

Abstract. The development of language functions is of great interest to neuroscientists, as these functions are among the fundamental capacities of human cognition. For many years, researchers aimed at identifying cerebral correlates of language abilities. More recently, the development of new data analysis tools has generated a shift toward the investigation of complex cerebral networks. In 2015, Weiss-Croft and Baldeweg published a very interesting systematic review on the development of functional language networks, explored through the use of functional magnetic resonance imaging (fMRI). Compared to fMRI and because of their excellent temporal resolution, magnetoencephalography (MEG) and electroencephalography (EEG) provide different and important information on brain activity. Both therefore constitute crucial neuroimaging techniques for the investigation of the maturation of functional language brain networks. The main objective of this systematic review is to provide a state of knowledge on the investigation of language-related cerebral networks in children, through the use of EEG and MEG, as well as a detailed portrait of relevant MEG and EEG data analysis methods used in that specific research context. To do so, we have summarized the results and systematically compared the methodological approach of 24 peer-reviewed EEG or MEG scientific studies that included healthy children and children with or at high risk of language disabilities, from birth up to 18 years of age. All included studies employed functional and EC measures, such as coherence, phase locking value, and Phase Slope Index, and did so using different experimental paradigms (e.g., at rest or during language-related tasks). This review will provide more insight into the use of EEG and MEG for the study of language networks in children, contribute to the current state of knowledge on the developmental path of functional connectivity in language networks during childhood and adolescence, and finally allow future studies to choose the most appropriate type of connectivity analysis.
Keywords: functional connectivity, cerebral networks, language, language development, children, EEG, MEG, connectivity analysis

1. Introduction

Language is a highly complex function that is importantly involved in the development of human cognition and social functions (Berwick et al., 2013). With major advances in neuroimaging techniques, the language neural architecture has been increasingly studied in the past 20 years. While several brain regions have been identified as key areas for expressive and receptive language, it is now also widely recognized that the latter relies more on complex neural networks, requiring coordination between distinct neuronal populations and less on independent and specific brain areas (Ardila et al., 2016; P. Tremblay & Dick, 2016).

Over the past decades, functional brain connectivity (FC) has progressively captured the interest of scientists and clinical researchers working in the field of cognitive neuroscience, leading to the publication of numerous articles on the subject. On a general note, FC is defined as the statistical relationships between cerebral signals over time and thus potentially allows conclusions to be made regarding the functional interactions between two or more brain regions. Effective connectivity (EC), on the other hand, goes beyond the correlations between cerebral activity and aims at specifying causal relationships through the use of experimental paradigms

or models. This allows for an interpretation of the direction of interactions between different cerebral regions (Friston et al., 2011). With the sharp increase of studies on brain connectivity, researchers have developed and applied increasingly sophisticated analytic strategies that highlight functional or EC and that allow a more advanced exploration of interactions between regional structures and networks involved in language development (Bastos & Schoffelen, 2016). In the past few years, novel neuroimaging techniques and methods of analysis have enabled the examination of FC patterns. Namely, functional magnetic resonance imaging (fMRI) was the neuroimaging technique used in the first published study of brain spontaneous fluctuations, measured at rest (Biswal et al., 1995). Functional magnetic resonance imaging is widely used in brain connectivity studies, mostly due to its high spatial resolution (in millimeters). However, because it relies on the coupling between cerebral blood flow (hemodynamic response) and the underlying neuronal activation, this technique provides only an indirect measure of brain activity. Moreover, even though neuronal events occur within milliseconds, the induced blood-oxygenation changes spread out over several seconds, thereby severely limiting fMRI's temporal resolution ($\sim$2–3 s). Techniques such as electroencephalography (EEG) and magnetoencephalography (MEG), on the other hand, provide direct information on neuronal electrical activity and offer higher temporal resolution ($<$ 1 ms). This is particularly relevant for the study of language functions, because auditory processing and language processing occur within a short time interval of milliseconds (Skeide & Friederici, 2016).

So far, neuronal accounts of language system development largely rely on EEG data (Skeide & Friederici, 2016). Traditionally, electrophysiological data have been examined for vent-related potential (ERP), a method that reflects the brain's activity in response to a particular stimulus event. As of now, several metrics can be used to estimate FC between electrodes. In order to perform FC analysis, MEG and EEG (M/EEG) data are commonly transformed into the frequency domain. Measures are thus typically classified by five fundamental frequency bands, mostly defined by their spectral boundaries: delta ($<$ 4 Hz), theta (4 to 7 Hz), alpha (8 to 12 Hz), beta (13 to 30 Hz), and gamma ($<$ 30 Hz, Cacioppo et al., 2007), each of which has different functional characteristics and cortical topography (Herrmann et al., 2016). Despite the fact that the definitions of these bands may vary between studies, and the boundaries used in studies of early childhood may be lower (Saby & Marshall, 2012), the interpretation arising from the present systematic review is based on the above definition by Cacioppo et al. (2007).

What is more, development and maturation affect the frequency and synchronization of neural oscillations, both at rest and during a cognitive task. Globally, analyses of resting-state networks reveal that slow-wave activity (delta and theta) tends to decrease throughout childhood and adolescence, whereas oscillations in higher frequency (alpha, beta, and gamma) show an increase with age (Uhlhaas et al., 2010). Moreover, FC in childhood is dominated by short-distance local links, which are gradually replaced by long-distance functional connections

in adulthood, thus forming mature cerebral networks (Meng & Xiang, 2016; Oldham & Fornito, 2019; Vértes & Bullmore, 2015). The task-related developmental trajectory of neural oscillations is, however, less clear and varies widely depending on the nature of the task.

When it comes to the functional meaning of different frequency bands, previous studies have suggested that brain signals of each frequency band play a different role. First, the coherence of local neuronal populations and bottom-up processing are associated with high-frequency oscillations (Buzsáki et al., 2013; Friederici & Singer, 2015). Slower frequency ranges, on the other hand, are understood to represent the cooperative activity of large-scale neuronal networks and mediate top-down feedback information (Palva & Palva, 2018). Regarding language processing, the use of FC in the spectral domain is certainly important, but little is known about the association between frequency bands and language networks. Nevertheless, distinctions have been made regarding language processing and frequency band using spectral power analyses. It is argued that different stages of auditory and speech processing, language comprehension, and active speech itself do not rely on the same frequency bands (for an exhaustive review see Kösem & van Wassenhove, 2017; Meyer, 2018). More specifically, delta range (< 4 Hz) has been associated with intonational processing and syntactic comprehension (Kösem & van Wassenhove, 2017; Meyer, 2018). It plays a role in top-down processing and seems to contribute to the organization of the cortical speech system, which regulates auditory-cortical excitability. It is further implicated in language comprehension, more precisely in the grouping of words into syntactic phrases (Meyer, 2018). It has been pointed out that theta (4 to 7 Hz) synchronizes with syllabic rates (Giraud & Poeppel, 2012; Meyer, 2018) and that theta coherence increases in tasks involving verbal information retrieval and verbal working memory (Friederici & Singer, 2015; Meyer, 2018). Alpha (8 to 12 Hz) oscillations may also play a role in verbal working memory (Friederici & Singer, 2015; Meyer, 2018). Beta activity (13 to 30 Hz) in language processing has been associated with semantic predictions (top-down mechanisms), as well as in syntactic and semantic binding mechanisms. It has also been correlated with verbal memory processes and language production (Weiss & Mueller, 2012). Finally, the gamma band (> 30 Hz) has been associated with phonological perception and assessment of the contextual semantic fit of incoming words (bottom-up; Meyer, 2018). The association of FC based on frequency bands and the different stages of language processing are still subject to investigation.

Several techniques have been proposed in order to measure cerebral activity, thus allowing for the interpretation of brain connectivity. Even though a large range of FC metrics is available in the current literature, the present article is limited to those brain connectivity approaches used in pediatric electrophysiological language research. Thus, FC analysis will not be addressed exhaustively. Only the most commonly used metrics to quantify brain connectivity, such as coherence, phase locking value (PLV), Phase Lag Index (PLI), correlation, Granger causality, and Graph theory, will be briefly described in this review. Complementary

reviews on more detailed mathematical analyses of connectivity methods can be consulted elsewhere (e.g., Bastos & Schoffelen, 2016; Kida et al., 2016).

Connectivity analyses in M/EEG traditionally include the examination for changes in coherence between sources or sensors. Coherence can be defined as the covariation in amplitude and phase between two signals and quantifies the linear correlation between two time series, and this on the frequency domain (Bowyer, 2016). It is assumed that the higher the correlation, the more synchronized, and therefore integrated, the signals are. Thus, coherence is sensitive to changes in both power and phase relationships but cannot provide direct information on the true relationship between the two signals (Sakkalis, 2011).

As an alternative to traditional amplitude-based indices of coherence, metrics of phase synchronization have been developed, such as PLV and PLI. Both PLV and PLI compute the consistency of phase difference between two variables over a time period. They provide a measure of the two signals' temporal relationship, independent of their signal amplitude (Lachaux et al., 1999). The PLV approach evaluates the instantaneous phase difference of signals, assuming that the connected areas generate signals whose phases evolve together. Therefore, the phases of the signals are considered synchronous or locked if the difference between them is constant (Bruña et al., 2018). Similarly, PLI estimates the asymmetry of the distribution of phase differences between two signals, but this method is designed to reduce the effect of volume conduction (Stam et al., 2007). The central idea is that a consistent phase difference between two times series (asymmetric distribution, PLI > 0), cannot result from a single source (volume conduction). Overall, phase synchronization metrics are better used for short-duration events such as in event-related studies, to determine the coupling of two signals across trials (Aydore et al., 2013; Bowyer, 2016).

Recently, directed connectivity or EC metrics have been developed to determine the nature of the neural interactions that enable information flux, such as Granger causality in the time domain (Bressler & Seth, 2011) or phase slope index (PSI) in frequency domain (Nolte et al., 2008). Based on phase differences, PSI is a weighted average measure of phase coherency slope between two signals, over a frequency band (Bastos & Schoffelen, 2016; Nolte et al., 2008). Some EC measures rely on the concept of Granger causality, whereby one time series is said to "Granger cause" a second one if the past values of the first improve the prediction of the second. Originally, the concept of Granger causality was applied to time series, but this approach has been extended to the frequency domain (Geweke, 1982), and many multivariate measures can be derived from this model (Sakkalis, 2011).

Similar to fMRI or other neuroimaging techniques, M/EEG data used along with connectivity matrices can be used to construct brain networks from FC measures of the frequency domain (PLI, PLV, coherence), the source space domain, or the EC models (Bullmore & Sporns, 2009; Sporns et al., 2004; Stam, 2004). Subsequent connectivity metrics of all paired electrodes can then be explored between regions, using the Graph theory approach

(Stam & van Straaten, 2012). This method represents the brain as a collection of nodes, corresponding to recording sites or brain regions, and the pairwise relationship between them (edges). Taken together, nodes and edges enable the quantitative description of the local and global topological organization of brain networks (van Diessen et al., 2015). It has been shown that small-world topology is found at different frequency bands (Stam, 2004) and can be associated with cognitive performance and developmental changes in functional brain networks in young children (Boersma et al., 2013).

Despite the growing number of published studies on language brain connectivity, the establishment of functional patterns of language networks during childhood and adolescence is not yet fully understood. In 2015, Weiss-Croft and Baldeweg published the first and only systematic review of studies that used fMRI to explore the development of functional language networks. The authors identified both progressive (increasing) changes of FC with age, associated with cerebral specialization, and regressive (decreasing) changes of FC with age, associated with more automatized language processing and lower engagement of control mechanisms (Weiss-Croft & Baldeweg, 2015). Specifically, their review highlights four main findings. First, brain activity in regions that support semantic processing increased throughout development, reflecting specialization of the brain. Second, with age, there is an increased activation in sensory–motor regions, along with a decreased activation in higher–order cognitive regions. Third, an age-related decreased activation was found in regions implicated in the default mode network (posterior cingulate cortex and precuneus). Finally, their results demonstrate the establishment of language lateralization by the age of 5 years. Although this study is indeed interesting, there is currently in the literature no systematic review that includes M/EEG studies. Because of the excellent temporal resolution of MEG and EEG, such a study would greatly help to provide additional and important information on the establishment of functional patterns of language networks. Therefore, the main objectives of this article are to provide a state of knowledge on the investigation of language-related cerebral networks in children, through the use of M/EEG, and a detailed portrait of relevant M/EEG data analyses methods that have been used in the assessment of language FC in children. To do so, we conducted this systematic review on functional, and to some extent effective, connectivity patterns of spoken language in children, as revealed by EEG or MEG. Given the multitude of metrics used to quantify oscillatory interactions (e.g., coherence, phase locking, connectivity matrices, graph theory, PSI) and the diversity of methodological designs (e.g., resting-state vs. task recording, large variety of language tasks, longitudinal vs. cross-sectional study), the secondary objective is to synthesize and compare various method of connectivity analysis in the context of different pediatric populations (healthy and clinical) and a wide range of research objectives.

2. Methods

2.1. Search Strategy

The literature review was conducted using five databases: PubMed, PsycINFO, Web of Science, Scopus, and Linguistics and Language Behavior in order to find articles published between January 1995 and June 2018 inclusively. The key terms used were as follows: (magnetoencephalography OR electroencephalography OR MEG OR EEG) AND (resting state OR functional connectivity OR synchron∗ OR network∗ OR effective connectivity OR coherence) AND (Language OR Speech) AND (infant∗ OR infancy OR child OR children OR youth∗ OR toddler∗ OR schoolchild∗ OR teenager∗ OR adolescent∗ OR kid OR kids OR newborn). Additional reports were identified by handsearching the references cited in the retrieved articles.

2.2. Selection Criteria

This review is limited to empirical studies published in peer- reviewed journals in English or in French. Studies that adhered to the following inclusion criteria were considered: (1) The study included children or adolescents (< 18 years old), although the age range may extend into adulthood; (2) FC or EC analysis was performed based on EEG or MEG data. We verified whether the described methods allowed actual interpretation of FC or applied different techniques such as intertrial synchronization, ERP timing, or time-frequency analysis, which were sometimes referred to as FC, but do not in fact fall in this category (Bastos & Schoffelen, 2016; Sakkalis, 2011). (3) Studies that investigated language networks were included if either one of the following two conditions was met: (a) the authors used a behavioral assessment before or after the imaging acquisition, in order to evaluate language abilities; or (b) the authors applied expressive or receptive language paradigms (e.g., speech stimuli, story listening, or speech production) during MEG or EEG recording. In order to provide an exhaustive view of the connectivity patterns associated with language in childhood, this systematic review includes clinical pediatric samples as well as healthy children, as long as the methodology fit our selection criteria. Articles about written language only (reading or writing) without any association with verbal comprehension or expressions have been excluded. The lists of references of the selected articles were searched manually for additional relevant articles. The study selection process is summarized in Fig. 1.

2.3. Data Extraction

Following the database search, duplicates were removed. For all remaining articles, titles and abstracts were reviewed by the first author (I.G.) and selected for a second revision if they met at least one of the inclusion criteria. For the second revision, remaining articles were

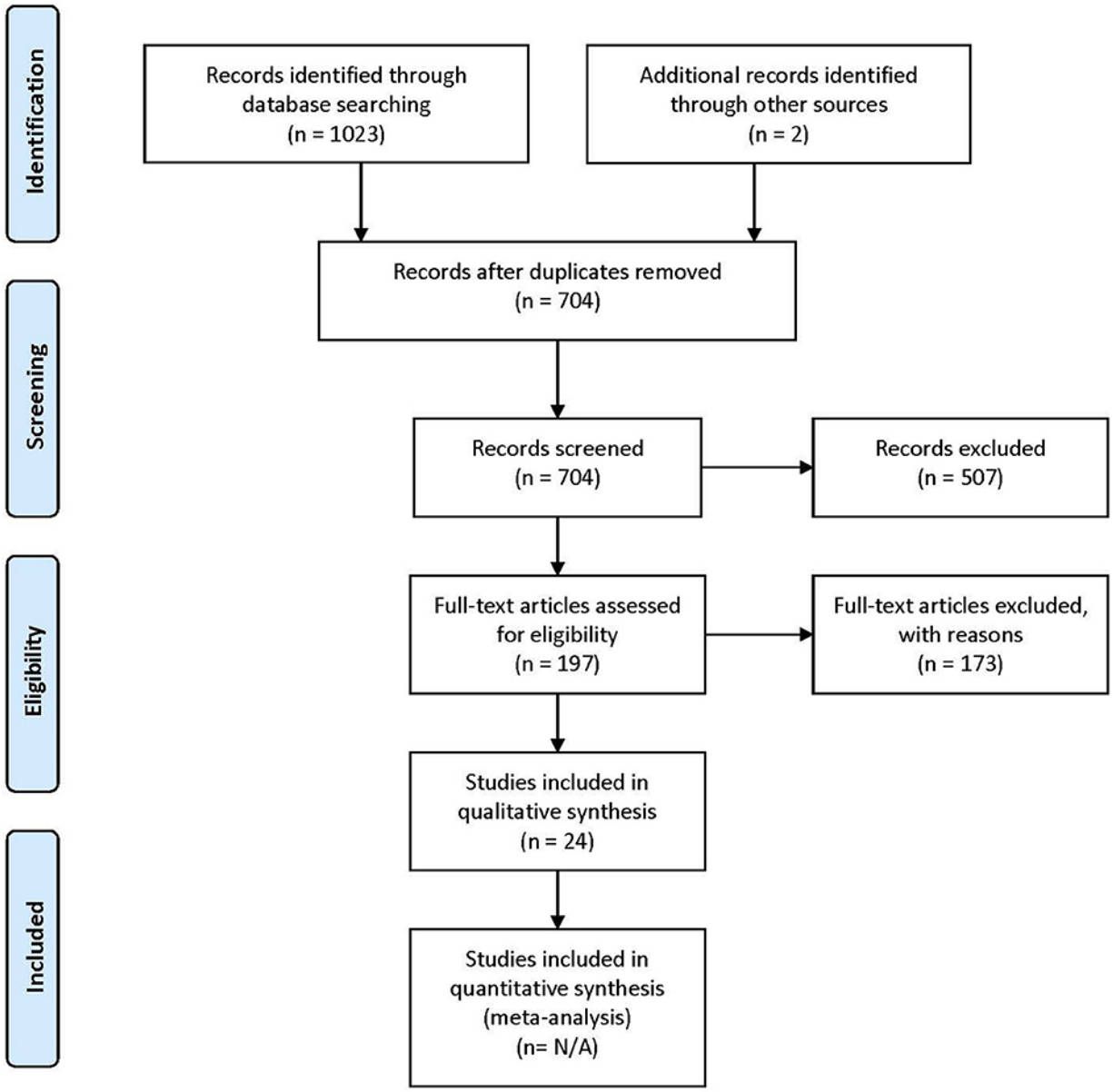

Figure 1 – PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram describing the paper selection process. Figure adapted from (Moher et al., 2009).

reviewed independently by two authors (I.G. and A.H.), in order to determine whether they matched the purpose of this study. When no consensus was reached, the consultation of a third-party expert in the domain (P.V.) helped make the ultimate decision on eligibility. Fig. 1 shows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) workflow diagram for study selection. Relevant information from each article was entered into a spreadsheet that included: (1) sample characteristics: age, gender, IQ, language evaluation

method, sample size; (2) experimental paradigms: resting-state, event-related experiments, sleep studies; (3) brain recording technique (EEG or MEG); (4) connectivity metrics.

The wide variability in study characteristics along these methodological dimensions precluded a meta-analysis. Instead, we synthesized and critically appraised findings made through the use of FC in the study of spoken language in children.

3. Results

A total of 704 articles were screened in the first step. Of these, 507 were excluded on the basis of their title or abstract, either because they were not experimental studies (e.g., review), they were conducted with adult participants only, or they did not conduct connectivity analysis using EEG or MEG. Following these exclusions, 197 articles were assessed for eligibility. Of these, 173 were excluded because they did not meet at least one of the selection criteria.

A total of 24 articles met the selection criteria, passed interrater revision (79 % agreement), and were confirmed by the third-party expert. All publications included in this work are peer-reviewed studies about FC of language functions in children, as revealed by EEG or MEG, and were published between 1999 and 2018. Detailed information was gathered about each study's population of interest, sample size, age of participants, design, imaging paradigm, type of language assessment, frequency bands considered for analyses, use of source or sensor analyses, and, finally, approach for connectivity analysis (Table 1 for studies including healthy children and Table 2 for those addressing clinical populations). Each table begins with studies using EEG followed by those employing MEG.

Table 1 – Descriptive data and methodological outline of articles focusing on healthy children.

Reference[1]	N (M/F)	Age	Design	EEG/MEG paradigm	Language assessment	Frequency band(s)	Source/ sensor	Connectivity analysis
EEG								
Asano, 2015	13/6	11 mo	Cross-sectional	Symbol-sound mismatch	N/A	Alpha, beta	Sensor	PLV
Hanlon, 1999	284/224	0-16.75 y	Cross-sectional	Resting	N/A	Theta	Sensor	Coherence
Kühn-Popp, 2016	15/17	14; 15 and 42 mo	Longitudinal	Resting	Declarative pointing and Verbal IQ	Theta-alpha	Sensor	Coherence
Marshall, 2008	48/42	30 and 42 mo	Longitudinal	Resting	RDLS	Theta, alpha, beta	Sensor	Coherence
Mundy, 2003	18/14	14-24 mo	Longitudinal	Resting	MCDI	Theta	Sensor	Coherence
Poblano, 2016	18/18	9-16 y	Cross-sectional	Resting; Lexical tonal discrimination	N/A	Theta	Sensor	Pearson correlation
Whedon, 2016	153/147	6-34 mo	Longitudinal	Resting	PPVT-III	Theta-alpha	Sensor	Coherence
Yang, 2005	23 (N/A)	6-8 y	Cross-sectional	Resting	Verbal IQ	Delta, theta, alpha, beta	Sensor	Pearson correlation
MEG								
Doesburg, 2016	31/42	4-18 y	Cross-sectional	Word generation	PPVT, EVT	Alpha, beta, theta	Source	PLV, PLI, graph theory
Doesburg, 2012	5/5	16-19 y	Cross-sectional	Word generation	N/A	Gamma, theta	Source	PLV
Kadis, 2016	13/8	5-18 y	Retrospective	Word generation	N/A	All	Source	PSI
Kikuchi, 2011	36/42	32-64 mo	Cross-sectional	Story listening	Expressive Vocabulary and Riddles (K-ABC)	Delta, theta, alpha, beta	Sensor	Coherence
Youssofzadeh, 2017	13/16	4-18 y	Cross-sectional	Word generation	N/A	Theta, alpha, beta, gamma	Source	PLV

Studies in the first and second part of the table used EEG and MEG, respectively. [1]First author, year; M, male; F, female; N/A; not applicable; PLV, phase locking value; PLI, phase lag index; PSI, phase slope index; RDLS, Reynell Developmental Language Scales; MCDI, Mac-Arthur communicative developmental inventory; PPVT, Peabody Picture Vocabulary Test; EVT, Expressive Vocabulary Test; K-ABC, Kaufman Assessment Battery for Children.

Table 2 – Descriptive data and methodological outline of articles focusing on children with or at risk for different clinical conditions.

Reference[1]	Population	N (M/F)	Age	Design	EEG/MEG paradigm	Language assessment	Frequency band(s)	Source/ sensor	Connectivity analysis
EEG									
Righi, 2014	Risk of autism	54 (N/A)	6 and 12 mo	Longitudinal	Discrimination of consonants	Subtest of MSEL	Gamma	Sensor	Coherence
Njiokiktjien, 2001	Nonverbal learning disorder/ Language disorder[2]	12/6 12/6	6-11 y	Cross-sectional	Resting	N/A	All	Sensor	Coherence
Zare, 2016	Risk of language disorder[2]	17/7	6 mo	Cross-sectional	Resting	N/A	Delta, theta, alpha1 and 2	Sensor	Connectivity matrix, graph theory
Kabdebon, 2015	Prematurity/ healthy	18/12 10/5	8m	Cross-sectional	Syllabic learning	N/A	Alpha, beta	Sensor	Coherence
Vasil'yeva, 2013	Stammering/ healthy	47/0 59/0	Preschool	Cross-sectional	Resting	N/A	All	Sensor	Coherence
Williams, 2012	CHD	14/2	0-18 mo	Longitudinal	Unknown	BSID	Beta	Sensor	Coherence
MEG									
Kovelman, 2015	Autism/ healthy	10 (N/A) 9 (N/A)	8-12y	Cross-sectional	Discrimination of native & foreign language	N/A	All	Source	Coherence
Mamashli, 2017	Autism/ healthy	29/0 17/0	9-15 y	Cross-sectional	Tonal discrimination	Social communication questionnaire	All	Source	Coherence

Reference[1]	Population	N (M/F)	Age	Design	EEG/MEG paradigm	Language assessment	Frequency band(s)	Source/ sensor	Connectivity analysis
Molinaro, 2016	Dyslexia/ healthy	9/11 10/10	8-14 y	Cross-sectional	Sentence listening	Verbal fluency, rapid automatized naming, pseudo-word repetition and phonemic deletion	Delta, theta	Sensor, source	Coherence, partial direct coherence based on Granger causality
Lizarazu, 2015	Language disorder[2]/ healthy	6/4 5/5	8-14 y	Cross-sectional	Listening of sounds	Reading of word and pseudoword lists, pseudoword repetition, and phonemic deletion	Delta, theta, beta, gamma	Source	PLV
Barnes-Davis, 2018	Extreme prematurity/ term born	9/6 7/8	4-6 y	Cross-sectional	Story listening	PPVT, EVT	Beta	Sensor	PSI, PLI

Studies in the first and second part of the table used EEG and MEG, respectively. [1]First author, year; [2]Language-based learning disorders (e.g., dyslexia, dysphasia). M, male; F, female; N/A, not applicable; MSEL, Mullen Scales of Early Learning; BSID, Bayley Scales of Infant Development; CHD, congential heart disease; PLV, phase lock value; PSI, phase sloe index; PLI, phase lag index; PPVT, Peabody Picture Vocabulary Test, EVT, Expressive Vocabulary Test.

Thirteen of the articles covered in this review addressed FC and language functions in healthy children, whereas 11 included children at risk of or suffering from various clinical conditions. Table 3 shows the different populations included in these studies. The most studied pathologies were related to language impairments such as dyslexia, language learning disorders, and stuttering (20 %), as well as autism spectrum disorder (ASD, 13 %).

Table 3 – Overall composition of samples included in all studies.

Study population	% (n)
Healthy	54 (13)
Autism spectrum disorder	13 (3)
Prematurity	9 (2)
Dyslexia	8 (2)
Language learning disorder	8 (2)
Stuttering	4 (1)
Congenital heart disease	4 (1)

Table 4 – Overview of all approaches applied to analyze functional or effective connectivity in included studies.

Connectivity analysis	% (n)$*$
Coherence	45 (13)
Phase locking value	21 (6)
Pearson correlation	7 (2)
Graph theory	7 (2)
Phase slope index	7 (2)
Phase lag index	7 (2)
Connectivity matrices	3 (1)
Granger causality	3 (1)

$*$Some studies applied multiple analysis; hence the total n outrages the number of studies included in this review.

Figure 2 shows the distribution of the number of participants per age group taken together for all studies, both in healthy and clinical populations. Infancy includes the first year after birth (0 to 12 months). Toddlers are children aged between 1 and 3 years; preschoolers include

the period from 3 to 5 years of age, gradeschoolers from 5 to 12 years, and adolescents are participants between 12 and 18 years of age. Each age group is subdivided into the number of children included in the studies addressing various clinical populations (green bars) and those interested in healthy children (blue bars), including those used as controls. Most of the healthy children studied were toddlers ($n > 350$), whereas studies interested in the impact of pathological conditions mostly included gradeschoolers ($n > 150$), although several studies on clinical populations also included infants and preschoolers. No data were available for any toddler or adolescent populations with clinical conditions. Overall, studies included in this systematic review total together a sample size of 728 in studies of healthy children and 394 in studies of clinical populations.

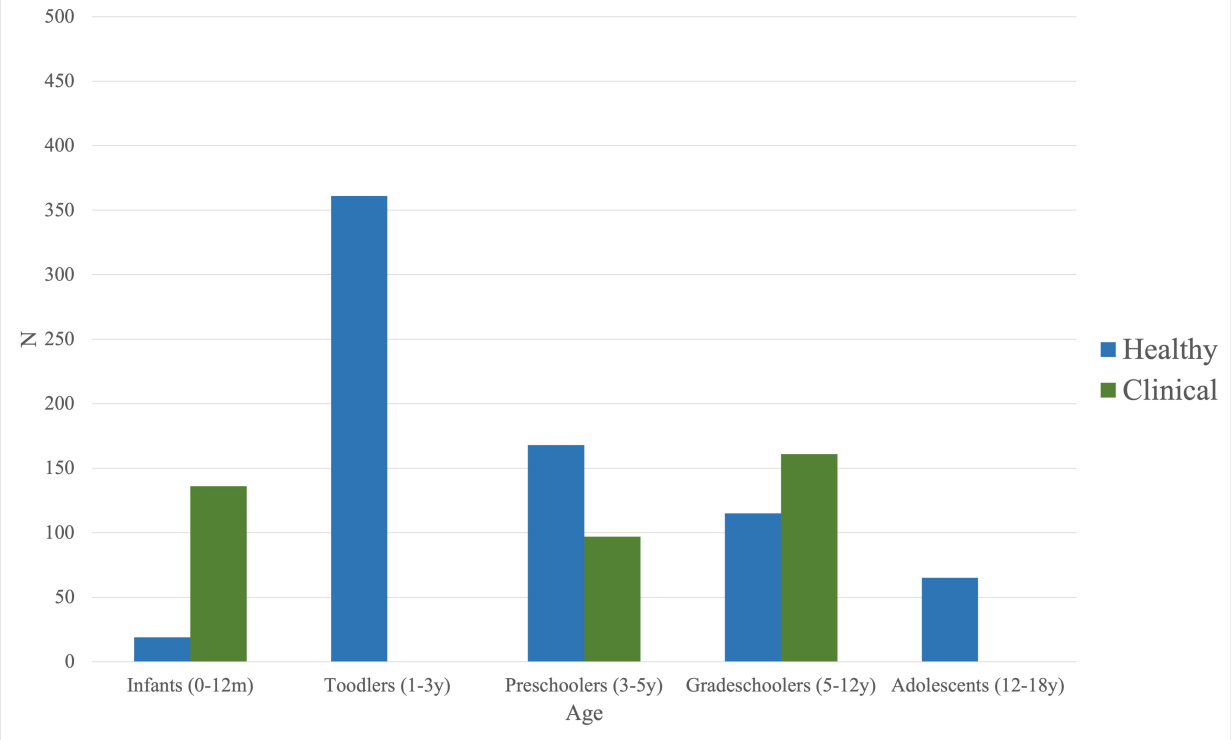

Figure 2 – Number of participants per age group of all included studies ($n = 24$). Blue bars represent number of participants included in the articles addressing healthy children; green bars stand for the number of participants included in studies investigating clinical populations (including control groups) such as autism spectrum disorder, dyslexia, language-learning impairment, or prematurity (Table 3).

Different methods of connectivity analyses were used in these studies; they are summarized in Table 4. Some studies combined or compared several methods for estimating cerebral connectivity. Phase coherence analysis was the most common method used (45 %), followed by PLV (21 %). The analyses were based on all frequency bands, as specified in Tables 1 and 2. The most studied frequency band was theta, and the least studied was gamma. Sixteen

studies used sensor information, and seven applied a source analysis. One study reported results for both source and sensor-based analyses.

Despite the fact that the scope of these studies differed, the aim of this review is to capture common findings concerning language-related FC. Therefore, we first present an overview of the results that emerged from the studies that investigated the association between language functioning and connectivity patterns, regardless of the task used during the EEG or MEG recording. Second, we illustrate, separately for healthy children and those in clinical populations FC and EC findings, while an expressive or receptive task was performed during the EEG and MEG recording. Finally, we display the results that emerge from all included studies organized according to the types of connectivity analyses used, beginning with those using FC, followed by those using EC. Again, the results will be indicated separately for healthy children and children with various clinical conditions.

3.1. Overview of All Results

From the 24 articles included in the review, only nine attempted to associate FC or EC patterns with objective measures of language functioning. Figure 3 shows the main results from these nine studies, for healthy subjects (eight studies) and for a clinical population (one study). Results are presented for each frequency band and organized according to age.

Only one study (Williams et al., 2012) investigated the relationship between FC networks and language abilities in a clinical population, that is, children with congenital heart disease (CHD), who are known to be at high risk of language delay (Fourdain et al., 2019; Hövels-Gürich et al., 2008; Hövels-Gürich & Mccusker, 2016). The authors did not find any significant association between FC during the neonatal period and their later language abilities as measured at 18 months of age. Additionally, Marshall et al. (2008) found no significant correlation between FC patterns and language performance in preschoolers under foster care. However, seven studies found a significant relationship between FC in the theta band and language performance. Positive correlations between FC and language score were also found in higher frequency bands: alpha (Doesburg et al., 2016; Yang et al., 2005) and beta (Doesburg et al., 2016; Yang et al., 2005). It should be noted that no study investigated the relationship between language skills and FC patterns in the gamma band.

In addition to articles that included a behavioral assessment of language functions, performed before or after an EEG or MEG recording, this systematic review also considers studies that included an expressive or receptive language paradigm (e.g., speech stimuli or speech production) during an MEG or EEG recording. The FC or EC patterns that arose from language paradigms are summarized in Fig. 4 (for healthy children) and Fig. 5 (for clinical populations).

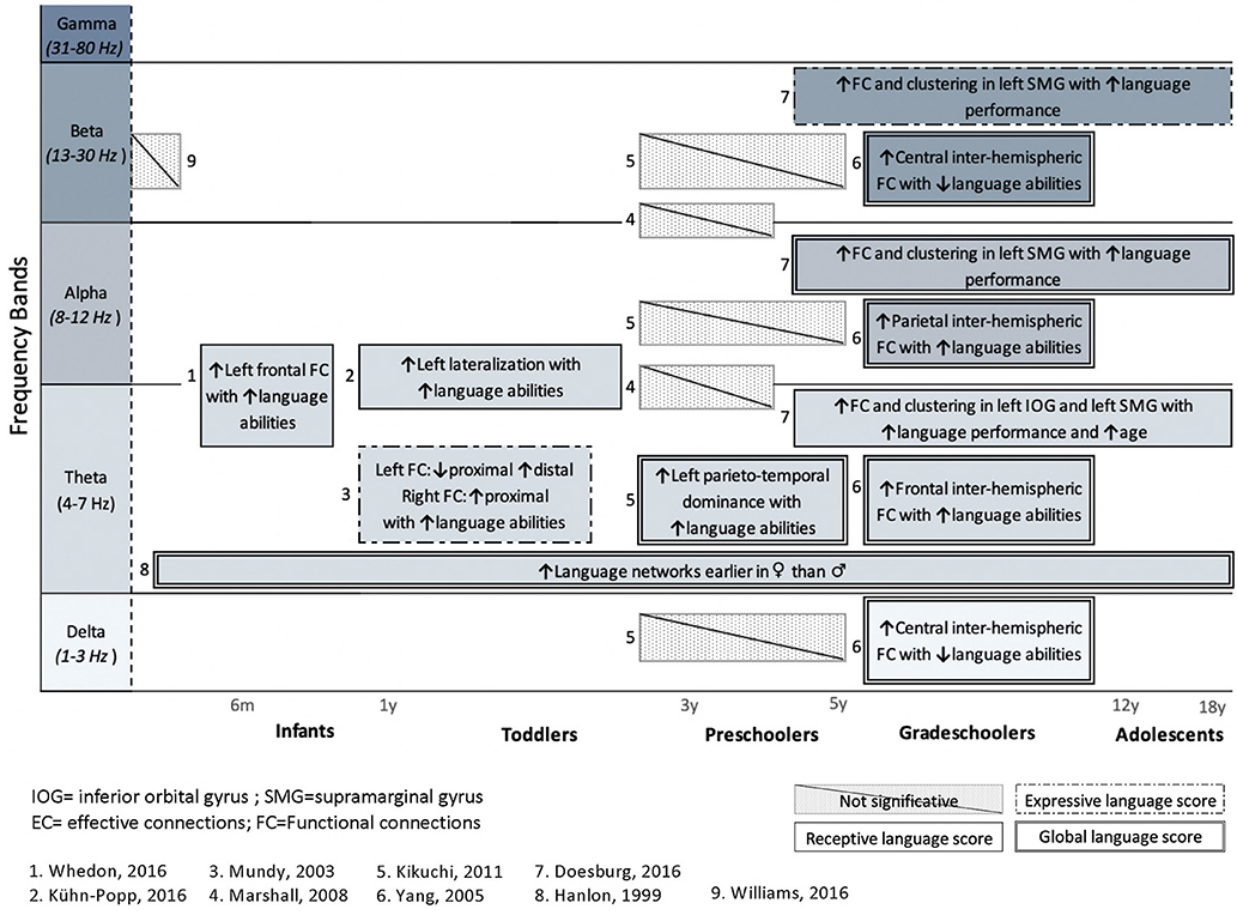

Figure 3 – Summary of studies investigating the association between language abilities, assessed with standardized tools, and cerebral language networks. Results are presented for each frequency band and organized regarding ages. Studies in healthy subjects ($n = 8$) and a clinical population ($n = 1$) are included. Upper arrows (↑) indicate a positive correlation with either receptive (simple solid line), expressive (dashed lines), or global language functioning (solid double lines), whereas downward arrow (↓) indicates negative correlation with language. Hatched areas represent non-significant correlations with language abilities.

In healthy children, the use of an expressive language paradigm (usually a verb generation task) was favored in four studies, whereas three studies used a receptive language task in order to examine the connectivity patterns that underlie language processing. These types of research paradigms have been performed mostly in research pertaining to gradeschoolers and adolescents, and the results are spread across all frequency bands.

In clinical populations, language tasks were mainly used to compare FC patterns between vulnerable children and healthy children. Here, only receptive language paradigms were used during M/EEG recording. Differences in FC between healthy and clinical subjects occur predominantly in the higher frequency bands (beta and gamma). Again, more details on the results of these studies are provided in section Results Derived From Connectivity Metrics.

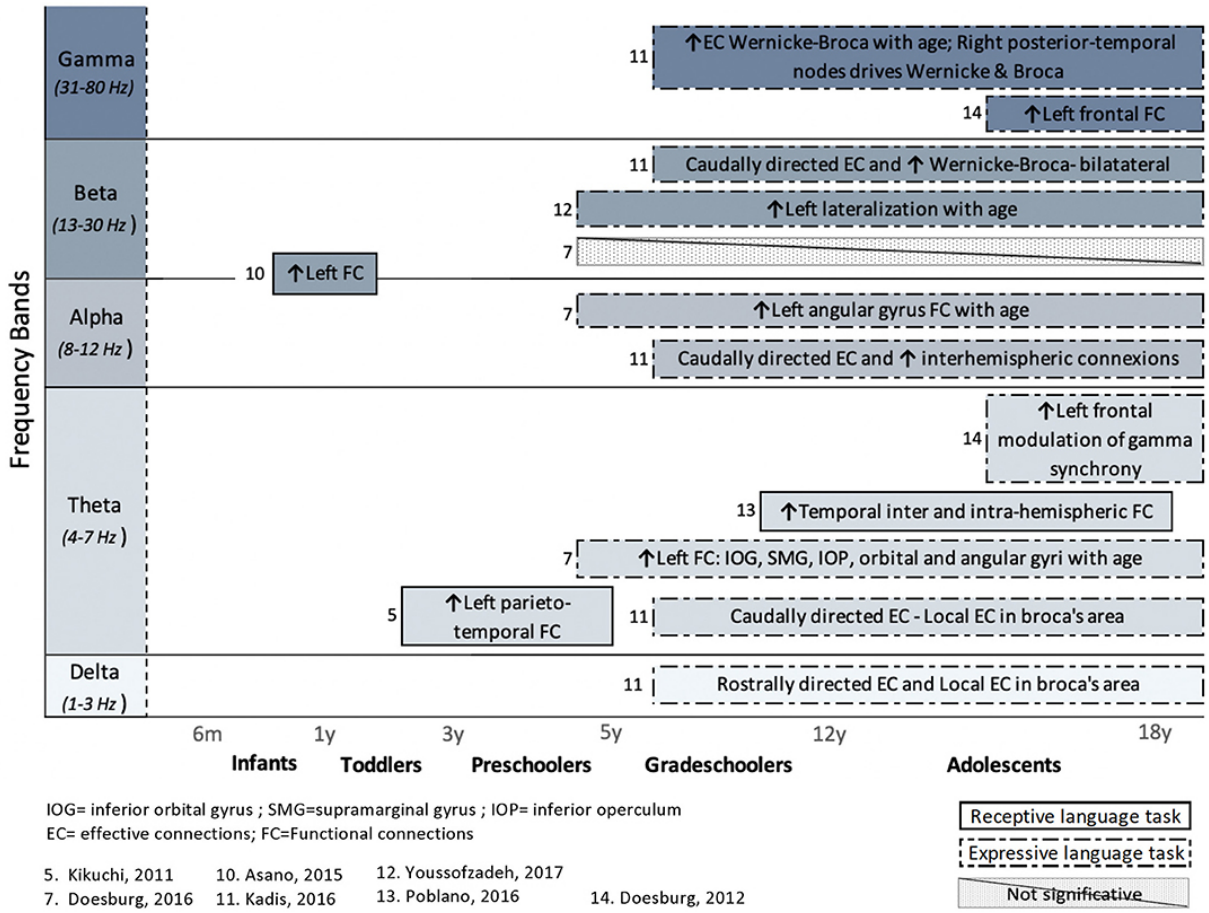

Figure 4 – Overview of task-related connectivity patterns in healthy subjects. Results are organized regarding frequency bands and age groups investigated. Upwards arrows (↑) indicate an increased connectivity during receptive (simple solid line) or expressive (dashed lines) language task, whereas downwards arrows (↓) indicate decreased connectivity.

Finally, it should be noted that two studies (Njiokiktjien et al., 2001; Vasil'yeva & Shmalei, 2013) done in resting-state FC in clinical populations were not presented in any of these figures. One of these studies looked at FC in children who received a diagnosis of language-based learning disorder (LLD), compared to children with non-verbal learning disorders (Njiokiktjien et al., 2001). The other looked at the FC patterns in children who stutter (Vasil'yeva & Shmalei, 2013). These studies did not use a language paradigm during EEG recording and therefore do not directly correlate connectivity patterns with behavioral language measures. The results of these two studies will nonetheless be discussed in section Results From Coherence in Clinical Population.

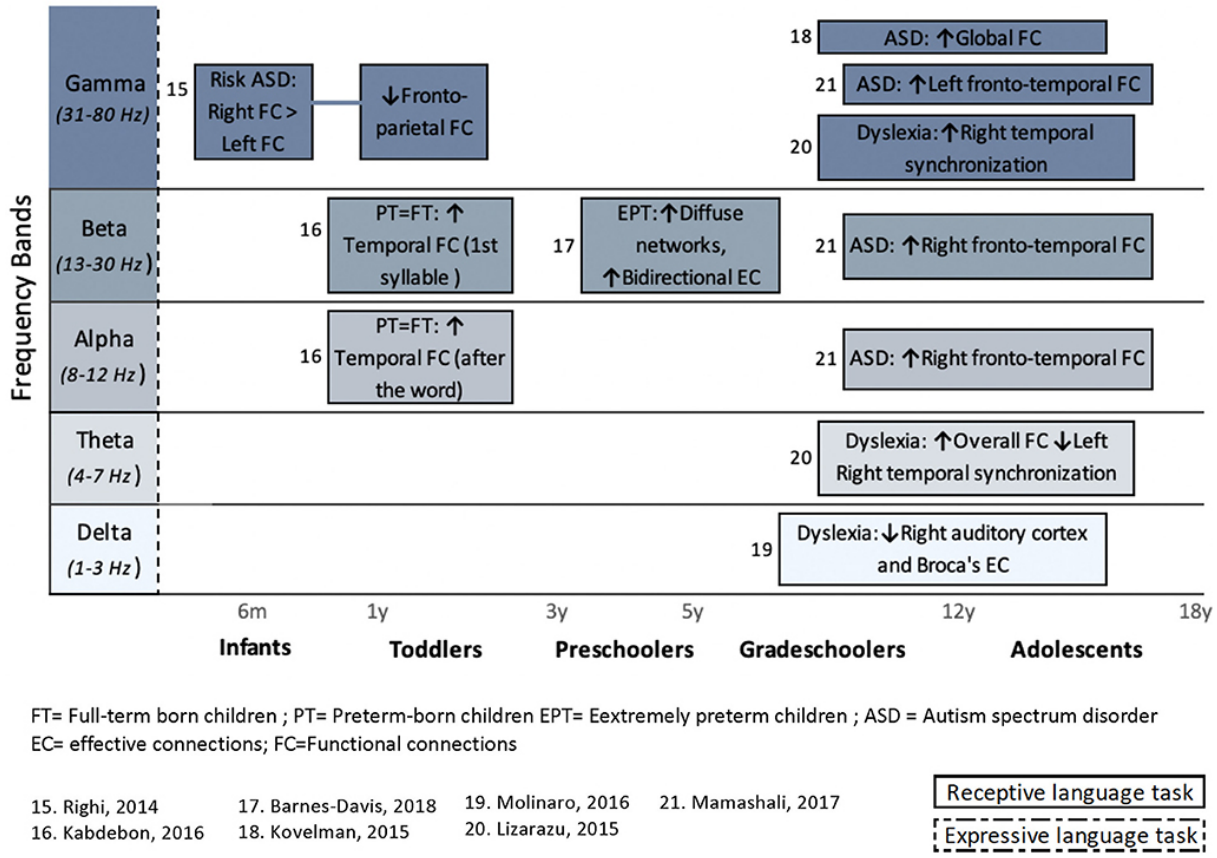

Figure 5 – Overview of task-related connectivity patterns in clinical populations compared to healthy subjects. Upper arrows (↑) indicate an increased connectivity during either receptive (simple solid line) or expressive (dashed lines) language task in this clinical population compared to healthy children, whereas downward arrow (↓) indicates decrease FC correlation in this clinical population compared to healthy children.

3.2. Results Derived From Connectivity Metrics

3.2.1. *Results From Correlation and Coherence Analyses*

The correlation coefficient and its analog in the frequency domain, coherence, are the classic measures of interdependence between two signals (Hassan & Wendling, 2018; Sakkalis, 2011; van Mierlo et al., 2014). Based on the amplitudes of the signals, the cross-correlation coefficient is a measure of the linear correlation between two time series and was utilized in one study using a tonal discrimination task (Poblano et al., 2016). Coherence, on the other hand, detects the linear relation between two electrophysiological signals at any particular frequency (Bowyer, 2016; van Mierlo et al., 2014). It is mainly used at rest and appears to be the most popular metric for M/EEG evaluation of functional language networks in children ($n = 13$). One other study used coherence and Granger causality and will therefore be discussed in the section on EC.

Results from correlation in healthy children. In a study on adolescents (9 to 16 years old, Poblano et al., 2016), correlation analyses were performed between several recording sites of the brain and were acquired during a lexical-tonal discrimination task of bisyllabic words in the Zapotec language (a tonal language, spoken by the participants). Results showed significant increases of interhemispheric and intrahemispheric correlations of the theta-relative power during a word discrimination task, predominantly between left frontal and right temporal sites.

Results from coherence in healthy children. In healthy infants, few studies ($n = 6$) investigated the association between measures of coherence and later language abilities of preschoolers (Kikuchi et al., 2011; Kühn-Popp et al., 2016; Marshall et al., 2008; Mundy et al., 2003; Whedon et al., 2016) and gradeschoolers (Yang et al., 2005). Specifically, between 5 and 10 months of age, an increase in resting-state EEG coherence in the theta–alpha band (6 to 9 Hz) within left frontal regions seems to be associated with higher cognitive functioning, including receptive language at 3 years of age (Whedon et al., 2016). This association, however, might not be specific to language functions because the authors reported a mediating influence of the level of attentional control at the age of 2 years. Another study showed that, in the theta band (4 to 6 Hz), a pattern of less proximal (left-frontal to left-central) but more distal (left-frontal to left-occipital) resting-state FC at 14 months old is negatively associated with the number of words expressed at the age of 2 years, as reported by the parents (lower vocabulary group; determined by the median split of the MacArthur Communicative Developmental Inventory (MCDI) results; (Mundy et al., 2003). The same group also showed that at 18 months of age a ratio of higher proximal synchrony in the right hemisphere (right-frontal to right-central) is positively associated with vocabulary outcome (MCDI; total words) at 2 years old (Mundy et al., 2003).

At 14 months of age, a theta–alpha band (6 to 9 Hz), FC pattern of more proximal and less distal coherence appears to be specifically and positively associated with later language functioning, regardless of the child's IQ (Kühn-Popp et al., 2016). Accordingly, those results indicate that maturation of EEG coherence in the left hemisphere, established by the ratio of short-distance/long-distance connections, is positively correlated with preverbal communicative abilities at 15 months of age (e.g., pointing at objects) and with verbal communication skills at 48 months of age (epistemic language; (Kühn-Popp et al., 2016). Congruently, left short-distance (parietotemporal) connectivity dominance in the theta band of preschoolers (32–64 months of age) during story listening shows exclusive positive correlation with language performance (no correlation with nonverbal cognitive performance or with chronological age), as assessed by the Kaufman Assessment Battery for Children at the same age (Expressive Vocabulary and Riddles subtests; Kikuchi et al., 2011).

In older children (6 to 8 years old), participants with high language functioning (verbal IQ > 110, as assessed by the Wechsler Intelligence Scale for Children III) had an increased

chance of higher correlations between homologous hemispheric regions (homologous interhemispheric correlations), compared to those who were classified as having a low verbal functioning (verbal IQ < 90; Yang et al., 2005). This was apparent in several regions (frontal, parietal) and mostly in the theta and alpha bands. In contrast, higher connectivity in interhemispheric central regions (delta and beta) was associated with lower language abilities.

However, one study reported non-significant correlations between coherence indices and language functioning. Marshall et al. (2008) highlighted environmental impacts on cerebral connectivity in young children, even though no significant correlation with language or cognitive functioning was found. They reported that EEG patterns in 42-month-old children placed in foster care before the age of 24 months differed from those of children placed in institutional care, the former showing lower short-distance connectivity. Specifically, in the foster-care group, intrahemispheric connections between frontal-central and frontal-temporal regions were characterized by lower connectivity in theta–alpha (6 to 10 Hz) and alpha–beta (11 to 18 Hz) bands. The authors did not link this difference to language abilities (no significant results) but instead to environmental conditions (foster care vs. institutional care).

Finally, an extensive longitudinal study including 508 children between 2 months and 16.5 years of age investigated developmental differences between sexes, using EEG coherence (Hanlon et al., 1999). However, no behavioral data were used to associate coherence patterns with language functioning. Results illustrated a sex difference in development, whereby girls presented earlier development of comprehensive language networks in theta neural networks than boys. Results also suggested that girls have more complex interconnection patterns between paired sites, particularly in those involving the temporal lobes.

Results from coherence in clinical population. Coherence for FC analyses was also used in several studies that included children with or at risk of neurodevelopmental conditions and therefore known to have vulnerable language functions. More specifically, included in this section are those studies using coherence as FC analyses and that focused on children with ASD, CHD, language learning impairment (LLI), stuttering, and dyslexia.

Children with CHD are known to be at higher risk of speech and language delays (Fourdain et al., 2019; Hövels-Gürich et al., 2008; Hövels-Gürich & Mccusker, 2016). It is in this context that Williams et al. (2012) investigated the predictive value of neonatal EEG frequency power analysis for later language development in children with CHD. Results revealed predictive value of the delta-relative power for language skills at 18 months of age, as assessed by the Bayley Scales of Infant Development (BSID). However, association between language functioning and coherence measures did not achieve significant results, despite the high correlation between BSID cognitive scores and beta's interhemispheric (left frontal polar to right frontal polar) and intrahemispheric (left frontal polar to left occipital) coherence. According to the authors, this may have been due to the small sample size ($n = 13$ participants).

Autism spectrum disorder is a neurodevelopmental disorder commonly associated with verbal and communicative dysfunctions (McDaniel et al., 2018). In three studies identified in this review, alteration of language task-related coherence was associated with ASD (Kovelman et al., 2015; Mamashli et al., 2017; Righi et al., 2014). However, no direct association was made with language functioning.

One publication aimed to identify an early electrophysiological biomarker for later ASD diagnosis (Righi et al., 2014). Electroencephalography recordings were performed for 6-month-old infants at high risk (HR, meaning siblings of children that were already diagnosed with ASD) and low-risk (LR) for ASD, done while listening to speech sounds. A higher right than left hemispheric coherence in the gamma band was observed in all children, with no difference between groups (HR vs. LR). At 12 months of age, analyses in LR and HR groups revealed no remaining hemispheric lateralization differences. Interestingly, HR infants showed significantly reduced task-related FC between frontal and parietal regions, compared to LR infants. Although these results must be replicated using a larger sample, this association seems to identify a potential 12-month predictive marker for clinical outcomes (Righi et al., 2014). These results also point out that genetic vulnerability for autism, that is, having a full sibling diagnosed with ASD, can potentially be assessed in the first year of life, based on differences in neural integration.

The two other published studies that used coherence involved older children with confirmed ASD diagnosis. Important differences were identified in FC patterns between healthy children and those diagnosed with ASD. Results of a preliminary study by Kovelman et al. (2015) indicated differences in cerebral coherence between ASD and control groups (8 to 12 years old) during a language task. In particular, EEG coherence measures during familiarization with a new language, including statistical learning for discrimination between adjacent syllables, were higher in children with ASD and had predictive value for ASD diagnosis. Coherence measures during the familiarization phase showed improved identification of ASD diagnosis, compared to coherence measure at rest, thus suggesting that language learning abilities are different in children with ASD, compared to typically developing (TD) peers.

Finally, Mamashli et al. (2017) used an MEG tonal mismatch paradigm in children (9 to 15 years old) with ASD. The MEG recording revealed an increase in frontotemporal coherence in the ASD group relative to the TD group, in response to both standard and deviant stimuli. This manifested in the gamma band for the left hemisphere and in the alpha and beta bands for the right hemisphere. When coherence was normalized with respect to the standard condition, the differences between groups were no longer significant. However, when the same stimuli were presented against a noisy background, the normalized coherence remained greater in ASD group, and this for the beta band in the left frontotemporal regions (not illustrated in Fig. 5). According to the authors, this may suggest that, for ASD children, reduced speech comprehension in noisy surroundings is due to a lower involvement of frontal

control mechanisms. These results imply that auditory processing, when done against a noisy background, results in altered functional networks in this group of patients.

Overall, studies in children with ASD demonstrated several distinct characteristics of functional neuronal networks associated with auditory and language processing, which are in line with typical difficulties in language functions associated with ASD. Knowing the characteristics of cerebral networks could potentially allow an early identification of children at higher risk of developing ASD.

Two studies involved participants with oral language disabilities, such as language disorder or childhood-onset fluency disorder (stuttering). Vasil'yeva and Shmalei (2013) were interested in brain coherence of male preschoolers (3–5-year-old boys) with neurosis-like stammering. These children showed generally stronger global coherence in delta and beta oscillations than did healthy children. Compared to healthy controls, theta band synchrony in interhemispheric frontal regions was also increased for the stammering group, although a smaller number of connections was observed in children who stutter than in healthy children. Finally, in all frequency bands, interhemispheric coherence was higher in preschoolers with neurosis-like stammering than in the control group. These results suggest that, in children with this kind of speech disturbance, the specialization of functions of the left and right hemispheres, as well as the interhemispheric asymmetry, is less expressed.

Finally, for children (6 to 11 years old) with non-verbal learning disorders, Njiokiktjien et al. (2001) reported a right lateralized decrease of intrahemispheric coherence, in contrast with children with LLI, who showed reversed lateralization. This difference was higher in the gamma band. Again, these M/EEG FC results suggest that hemispheric functional brain alterations are related to specific language development disorders.

3.2.2. *Results From Phase Synchronization*

Instead of investigating the relation between the amplitudes of the signals, one could also evaluate how the phases of the considered signals are coupled, the so-called phase synchronization measures. Among the many phase synchronization measures proposed in the literature, one of the most used is the PLV, which evaluates the phase difference between two signals (Lachaux et al., 1999). When two brain areas are functionally connected, the phases of their signals are assumed to evolve together; therefore, the difference in their phases should be constant (Bruña et al., 2018).

Results from phase synchronization in healthy children. Three studies combined phase synchronization metrics: two with an FC matrix (Doesburg et al., 2012; Youssofzadeh et al., 2017) and one with EC metrics (Barnes-Davis et al., 2018). Results from these three will be included in the sections on graph theoretical approaches and EC, respectively. Two other studies drew on phase synchronization metrics (PLV) in healthy children: one in a mismatch paradigm (receptive task) and the other in an expressive language task.

At around 1 year of age, results during an audiovisual paradigm revealed an increased large-scale communication between brain regions in the mismatch condition (a heard sound does not match the previously presented symbol), compared to the match condition (sound and symbol match; Asano et al., 2015). This occurred in the alpha–beta band (12 to 15 Hz) and was more prominent in the left hemisphere. According to the authors, this indicates that audiovisual integration requires a greater effort in the mismatch condition (Asano et al., 2015).

In adolescents (17 years old), an expressive language task (verb generation) resulted in an increased gamma-band synchronization among task-activated cortical regions (Doesburg et al., 2012). Moreover, there was a theta modulation of interregional gamma synchrony between several pairs of activated brain regions, mostly in the left frontal cortex. This reflects the involvement of gamma-band synchronization in language production and the role of low-frequency rhythms (theta), which modulate high-frequency connectivity in adolescents.

Results from phase synchronization in clinical population. One study used phase synchronization metrics (PLV) in task-related paradigms, in a vulnerable population, namely, children born prematurely. In fact, several studies report impairments of cognitive and behavioral functions, including language abilities, related to premature birth (weeks of gestation $\geq$ 37; e.g., Aarnoudse-Moens et al., 2009; de Kieviet et al., 2012). In our sample, one study used PLV for FC analyses in prematurely born children (27–30 weeks of gestation). Kabdebon et al. (2015) compared spatial synchrony and phase coincidence of EEG oscillations during syllabic learning in 8-month-old preterm-born and term-born children (corrected age for preterm-born). They did not find any differences between groups, suggesting similar language processing at 8 months of age. In both groups, an increase in the PLV was observed first in the beta band (13 to 18 Hz; during the first syllable) and later in alpha (8 to 12 Hz; after the word) over the left and right temporal areas (Kabdebon et al., 2015).

Using auditory stimuli in children (8 to 14 years old) and adults with dyslexia, another study found that, compared to a control group, dyslexic participants presented stronger synchronization and an absence of right hemispheric neural synchronization, related to low frequency (4 Hz; Lizarazu et al., 2015). On the other hand, for high frequencies (30 Hz), adults but mainly children with dyslexia show a rightward, instead of bilateral hemispheric lateralization. According to the authors, this may suggest that speech processing in dyslexic children relies more heavily on syllabic-rate information, compared to skilled reader peers.

3.2.3. *Results From Network Analysis*

Graph theory analysis looks at the brain as a complex network consisting of a collection of nodes connected by edges, in order to comprehend the topological organization of brain networks (Tahmasian et al., 2015).

Results from network analysis in healthy children. Two studies applied graph theoretical analysis into MEG results to investigate the organization of expressive language networks, from preschool age to adolescence (4 to 18 years old). Even though both used a verb generation task during MEG, and derived networks from phase synchronization metrics, their conclusions were not identical.

In the first of the two, results from a verb generation task revealed a developmental shift of the beta band lateralization in language production when children (4 to 6 years old) were compared to adolescents (16 to 18 years old): hubs were most lateralized in adolescents, whereas younger children showed a more bilateral distribution, or even a right-hemispheric pattern (Youssofzadeh et al., 2017).

The second study showed that connectivity within language-related areas (left angular gyrus, left precentral gyrus, right inferior orbital gyrus, and right rolandic operculum) increased with age (Doesburg et al., 2016). This was true for language production in the theta band. Increased FC during an expressive language task was also observed in higher frequency bands (alpha and beta). However, this increase was primarily found in brain areas associated with visual processing and thus might rather be associated with processing of the stimulus than to language-related task demands. Developmental analysis suggested significant differences between age groups: larger connectivity networks in adolescents (14 to 18 years old), compared to younger children (4 to 9 years old), and a stronger task-dependent increase of connectivity (expressed as theta coherence) in language-related areas, especially in frontal regions. Finally, theta-band connectivity measures showed a significant association with verbal language functioning (assessed with the Peabody Picture Vocabulary Test and the Expressive Vocabulary Test). Thus, the strength of task-dependent network connectivity was associated not only with a maturational pattern but also with language abilities (Doesburg et al., 2016).

Results from graph theoretical analysis in clinical population. Zare and colleagues Zare et al. (2016) developed a machine learning approach based on EEG network characteristics (efficiency and leaf number) in 6-month-old infants. They aimed at determining, based on family history, the risk of LLDs. Relying on FC measures, this work allowed for the accurate stratification of the children into low-risk (LR) and high-risk (HR) groups for LLD. Early brain networks revealed a reduced cortical communication capacity in HR infants, showing a network that was both decentralized (as revealed by the clustering index in the delta and alpha) and less efficient (as revealed by a decreased efficiency in the delta, theta, and alpha). Based on complex EEG patterns with support vector machine, it was possible to classify the children into HR and LR groups with approximately 80 % accuracy (specificity of 89 % and sensitivity of 92 %).

3.2.4. *Directionality of Language Networks (Effective Connectivity)*

EC reveals the directionality of information flow in particular brain regions and the causal and dynamic influences of one region on another (Friston et al., 2011; Stephan & Friston, 2010). Two methods of EC were used in the studies selected for review: partial directed coherence, a frequency-domain representation of the concept of Granger causality (Baccalá & Sameshima, 2001) and the PSI, a method based on phase differences in signals over a specified frequency range (Nolte et al., 2008).

Effective connectivity in healthy children. Only one study used EC metrics to study language networks in healthy children during an expressive language task. Kadis et al. (2016) reported an increased number of effective connections (PSI) with age, between 5 and 18 years. More importantly, different task-related EC patterns seemed to emerge among frequency bands. Analysis of lower frequency bands revealed more local, rostrally directed connectivity patterns in the left frontal region. At higher frequencies, EC increasingly involved distal and interhemispheric nodes. In alpha and gamma, bidirectional information transfer was observed between left and right frontal and posterior temporal nodes, whereas in the gamma band, the right posterior temporal region emerged as an important driver of Wernicke (left posterior temporal) and Broca (left frontal) regions.

Effective connectivity in clinical population. Phase slope index was also used to compare EC (PSI) and FC patterns (PLI) between extremely prematurely born children (EPT; $<$ 28 weeks of gestation) and their term-born (TB) peers (37–42 weeks of gestation; Barnes-Davis et al., 2018). At preschool age (4 to 6 years old), bilateral functional networks, including temporal and parietal regions, were revealed in both EPT and TB children during a receptive language task. On the other hand, the beta band indicated increased FC in language networks, as well as a more diffused network in EPT children, compared to TB. Moreover, analysis of EC suggested more bidirectional connections in EPT within bitemporal areas of the network, compared to TB, where fewer bidirectional networks or more unidirectional networks were identified. EC analysis also revealed that hyperconnectivity patterns in EPT were attributable to a greater information flux drive from the right hemisphere. Nevertheless, because those differences in connectivity patterns were not correlated with language performance, it was reported to be an effect of the clinical condition only (i.e., prematurity). Consequently, the authors assumed that their findings indicated an efficient reorganization of cerebral language networks, allowing the maintenance of language abilities in EPT children (Barnes-Davis et al., 2018).

Neuronal response while listening to low-frequency speech ($<$ 10 Hz), in gradeschoolers (8 to 14 years old) with dyslexia, was overall less synchronized, compared to normal readers (Molinaro et al., 2016). More specifically, during language stimulation (meaningful sentences),

reduced delta synchronization and impaired feed forward functional coupling (partial directed coherence) were found between the right auditory cortex and the left inferior frontal gyrus.

4. Discussion

We systematically reviewed 24 studies that assessed M/EEG functional networks associated with language in children. The great variability in study populations, sample size, and methodology precluded us from conducting a meta-analysis. Instead, we synthesized and critically appraised findings on the use of functional or EC in the study of spoken language in children.

4.1. Summary of the Main Observations

In order to characterize functional networks involved in language development, first considered were results reported in 13 articles on the study of TD children, and which used FC and EC analyses. The findings of most of the reviewed studies suggested that theta neural oscillations play a crucial role in healthy language development. In the theta band, a greater left resting-state coherence in early childhood seems to be associated with higher language functioning, either at the time of M/EEG recording (Kikuchi et al., 2011) or at a later age (Kühn-Popp et al., 2016; Mundy et al., 2003; Whedon et al., 2016). In older children (gradeschoolers to adolescents), associations between connectivity patterns and language abilities are not found only in theta, but in most frequency bands (delta, theta, alpha, and beta). The differences in frequency bands in relation to age might reflect typical brain maturation. Indeed, cerebral maturation in children has been associated with a global decrease of slow-wave activity, including theta oscillations, and an increase in higher frequencies (Uhlhaas et al., 2010). Thus, even though theta-band connectivity shows significant correlation with language abilities at all ages (Fig. 3), it is critical to look at all different frequency bands, especially in older children (gradeschoolers and adolescents).

Further, theta frequency band has been related to syllabic processing (Giraud & Poeppel, 2012; Meyer, 2018), and increases in theta activation have been found for tasks that include verbal working memory (Friederici & Singer, 2015; Meyer, 2018). Syllabic processing of human language constitutes one of the fundamental stages of bottom-up language processing, and there is evidence that it is established in utero, before term age (Mahmoudzadeh et al., 2013; Skeide & Friederici, 2016). The predictive value of theta coherence for early language comprehension in infants may thus be explained by the fundamental role of syllabic processing in later language acquisition. Given the assumed relation between theta band coherence and working memory, studies addressing language networks should also apply language paradigms that allow for the differentiation between higher-order cognitive functions and different stages of language processing.

The investigation of FC or EC networks using a language task during M/EEG recording reveals results distributed across all frequency bands. The involvement of the various frequency bands probably varies based on the nature of the task (e.g., active lexical discrimination vs. passive oddball paradigm), the language modality (expressive vs. receptive), and the level of language processing (e.g., syllabic vs. semantic). That being said, results from EC patterns in expressive language paradigm vary considerably depending on the frequency bands (Kadis et al., 2016). An age-related increase is shown in left effective connections, whereas higher frequencies reveal more bilateral effective connections with increasing age (Kadis et al., 2016).

For healthy children, the majority of studies using task-dependent connectivity analysis reveal increased left FC during receptive (Asano et al., 2015; Kikuchi et al., 2011) and expressive (Doesburg et al., 2016; Doesburg et al., 2012; Youssofzadeh et al., 2017) language paradigms. This occurs as early as 11 months of age (Asano et al., 2015) and appears to be constant throughout development. Interestingly, when it comes to examining the pattern of task-related FC in populations at risk of language disorders, in comparison with neurotypical children, differences are prominently characterized by a tendency for greater FC in the right hemisphere (Lizarazu et al., 2015; Mamashli et al., 2017; Righi et al., 2014).

Results from studies targeting clinical populations, mainly children at high risk of or suffering from language disabilities, also contribute to the understanding of the interactions between language abilities and the brain regions associated with language acquisition. In this review, we included 11 studies that addressed FC and EC patterns of language networks in different clinical populations. In children with speech disturbances (language learning disorders or stuttering), the functional specialization in the left and right hemispheres and the interhemispheric asymmetry typically seen in language networks seem altered (less hemispheric asymmetry observed). However, in populations at risk of language disabilities, such as ASD, preterm children, and infants with CHD, there are no clear or replicable FC profiles associated with language functioning that arise from the current literature. Although differences are observable between clinical and control groups, they seem to be more attributed to the signature of the underlying clinical condition, rather than to language functioning itself. More studies are needed to better understand the brain substrates of language alterations and vulnerabilities in these populations.

These results are consistent with the conclusion from Weiss-Croft and Baldeweg (Weiss-Croft & Baldeweg, 2015), who found that left language lateralization was well established by the age of 5 years. However, our results suggest that, before the first birthday, left lateralization is already apparent when a receptive language paradigm is performed (Asano et al., 2015). Moreover, a greater left connectivity before 5 years of age has been correlated with better language abilities (Kikuchi et al., 2011; Kühn-Popp et al., 2016; Mundy et al., 2003; Whedon et al., 2016). Thus, M/EEG research points toward an earlier implementation of left lateralization in language networks than was concluded from studies done with fMRI.

This is probably due to the suitability of electrophysiological techniques for studying young children. Furthermore, the impaired left lateralization in populations at risk of language impairments attests to the importance of the early development of left functional networks (Barnes-Davis et al., 2018; Righi et al., 2014) and its maintenance in later development (Lizarazu et al., 2015; Mamashli et al., 2017).

The developmental trajectory of FC of language networks evolves significantly with age, with the presence of greater connectivity networks in adolescents, compared to younger children (Doesburg et al., 2016; Kadis et al., 2016; Poblano et al., 2016; Youssofzadeh et al., 2017), but also more local and less bilateral networks as age increases (Doesburg et al., 2016; Kadis et al., 2016; Kikuchi et al., 2011). In line with findings of fMRI studies, strong local networks may actually reflect both processes related to cerebral specialization and automatized language processing, which require less top-down regulation and thus involves fewer network interactions (Weiss-Croft & Baldeweg, 2015).

Nonetheless, the exact timeline of maturational processes in language networks is not yet fully understood. This may be due in part to the great intervariability of typical development. Also, many studies included only a limited age range or did not have sufficient participants per age group to permit reliable conclusions regarding developmental changes. The importance of accounting for age-related changes has previously been emphasized in fMRI studies, in order to correctly interpret associations between network characteristics and language capacities (e.g, Rimmele et al., 2018; Weiss-Croft & Baldeweg, 2015). On the other hand, the methodological heterogeneity (e.g., language paradigms, cognitive assessments, connectivity algorithms) between developmental studies on brain correlates of language processing do not allow the drawing of a clear maturational timeline.

Finally, one should consider that sex differences may impact the development of FC patterns, as stated by Hanlon et al. (1999). In fact, the importance of integrating sex analysis in research is now well-established (Tannenbaum et al., 2019), and the sex differences of brain development have been documented (R. E. Gur & Gur, 2016; R. C. Gur & Gur, 2017; Kaczkurkin et al., 2019). In a recent systematic review, Etchell et al. (2018) highlighted sex differences in brain language structure and function. However, they concluded that these differences do not necessarily lead to differences in language task performance. It is therefore possible that boys and girls employ different but equally effective cognitive strategies for certain tasks, which leads to minor differences in performance as evidenced by brain function but not in the behavioral performance itself. Consequently, it is important that subsequent studies consider possible sex differences when characterizing language networks.

A better understanding of the association between language functions and the different characteristics of brain networks should include normal variation patterns that are not related to language difficulties. Understanding the normal development of functional language

networks would enable earlier identification of children at risk of language difficulties. Currently, language impairment is often detected only at an age at which evidence of healthy language functions can be formally assessed (Prelock et al., 2008). When a pathology is present, however, it could be crucial to initiate early intervention in order to support language development and increase quality of life for these children.

4.2. Methodological Considerations

This review shines light on the heterogeneity of methodological approaches used in the study of language functions in children, through the use of FC and EC. Beyond the neuroimaging method used (EEG vs. MEG), the type of analyses and their nomenclature vary greatly between research groups. Functional brain connectivity and EC analyses are indeed still recent, and to date, there is no consensus on which methods are to be advocated, highlighting the importance of summarizing the current state of knowledge and pursuing further research in this field. This would not only describe the various methods available, but also assess their respective pros and cons, in order to select the appropriate technique for specific experimental conditions and samples. This will ultimately support the production of more reliable and robust results and provide clear directions for future studies. Methodological heterogeneity is not only an issue in EEG and MEG, but also poses an obstacle to reliable conclusions about language networks estimated with other neuroimaging techniques, such as fMRI (Weiss-Croft & Baldeweg, 2015), hence the need to establish common standards of best practice.

Nevertheless, the number of M/EEG studies identified indicates that coherence and phase-locking measures may have high utility in language research, because these metrics were used in the majority of the published articles in the domain. These approaches achieved popularity because of their simple algorithms and fast computation. However, although coherence has been the most widely used FC method in this field, this does not necessarily mean it is the preferred method, nor the most fruitful. In fact, coherence may cause false-positive results, due to source leakage between local regions (Brookes et al., 2014; Kida et al., 2016). To overcome these challenges, many algorithms have been developed in the last few years. The Imaginary Part of Coherency (Nolte et al., 2008) and PLI are metrics that are less affected by the influence of common sources and active reference electrodes. They were introduced to facilitate the estimation of phase synchronization but have not been used much in the research of language development (none for Imaginary Part of Coherency and twice for PLI). Yet, the simplest method for reducing the influence of leakage on the estimation of connectivity is a leakage-invariant metric (O'Reilly et al., 2017).

Conversely, the use of task-evoked EC metrics such as Granger causality and PLI in this context is recent and remains limited, given that only three research teams have applied them

since 2016. Thus, little is known about the directionality (EC) of oral language networks in children.

To date, the use of EEG is more frequent than MEG for the investigation of language-related brain connectivity in children (14 and 10 articles, respectively), certainly because of the higher accessibility, lower cost, and ease of use of the EEG technique.

4.2.1. *Methodological Limitations of Reviewed Studies*

The primary methodological limitation of most studies reviewed was the failure to directly examine the association between brain FC patterns and objective language skills as assessed by standardized behavioral tests. In addition, in those studies that did evaluate language abilities, assessment of overall cognitive functioning was not always performed. Thus, the observed disturbance could indicate a lower global cognitive functioning, rather than a specific effect of language difficulties. A clear distinction between language and global cognitive functioning is therefore critical when investigating links between connectivity patterns and language performance. Relationships between brain activity and behavior must be addressed, especially in the context of clinical populations, where the disturbance in FC patterns associated with the neurodevelopmental condition must be distinguished from the disturbance specific to language functions alterations. For instance, in contrast to healthy children, M/EEG FC differences in children with CHD or born prematurely are not always associated with actual differences in language skills. The lack of attention to these relationships may be partially explained by the small sample sizes of the studies, which led to poor statistical power.

Finally, the results from various studies emphasized the difficulty of applying FC analysis derived from M/EEG data. Source localization of cerebral activity, captured on the surface of the scalp, represents a particular challenge for sensor-space analysis. This is known as the inverse problem, which may lead to inaccurate identification of cerebral networks (e.g., Abreu et al., 2018, 2019; Barzegaran & Knyazeva, 2017; Nunez et al., 1997; Sakkalis, 2011). Also, the effect of volume conduction, which is a mix of several signals within one sensor, and which originate from identical cerebral regions, makes critical a direct derivative from sensors to cerebral representation. Source-space analysis tries to overcome this downside and uses models that aim for a more accurate reconstruction of the true sources of the signal (Schoffelen & Gross, 2009). The conduction of source analyses seems particularly important when one is aiming to interpret FC, because the same cerebral activation is measured with different sensors and may potentially result in false conclusions regarding connected regions. Recently, it has been shown that source-space analyses seem accurate mostly when using high-density EEG, but result in limited interpretation of the more common low-density EEG (Barzegaran & Knyazeva, 2017). Also, some of the approaches to source analysis require certain assumptions be made about the underlying network, which may not be accurate for all data sets (Daunizeau & Friston, 2007). In particular, in children (where networks are

developing) or in clinical populations (where networks may be altered), it can be risky to assume a certain network composition. These limitations need to be taken into consideration when interpreting some of the findings on functional networks that are reported in this review. While studies that applied sensor-space analysis may overestimate FC, the interpretation of findings based on source-space analysis, especially in low-density EEG, may be less susceptible to this same overestimation. Finally, some studies might not have verified specific assumptions for their source-model, which limits their interpretation. This issue may occur especially in studies that include clinical populations, where characteristics of cerebral activation may be altered.

4.2.2. *General Utility of M/EEG Connectivity Analysis*

By providing information about temporal coupling between cortical areas (milliseconds time scale) and frequency bands of neural oscillations, both MEG and EEG are well-suited to study the development of language networks. They offer a quiet testing environment, which facilitates the use of language tasks. Moreover, they provide excellent temporal resolution, allowing analyses that target an immediate response to specific tasks or stimuli.

Because EEG is less sensitive to movement than other techniques (e.g., fMRI), thus allowing a certain mobility and tolerating articulatory movements, it is highly relevant for language assessment in pediatric populations. Furthermore, the low cost of EEG justifies its use for the investigation of developmental trajectories, which requires longitudinal design with multiple recordings over time. On the other hand, spatial and temporal data available from MEG allow the investigator to track both the neural timing and location associated with language and thus to efficiently map the trajectories of language networks. Regardless of the neuroimaging technique employed, the use of FC is highly relevant in research on children, because it allows acquisition at rest, without requiring that a task be performed, as it is in traditional ERP paradigms. Furthermore, the length of time required for data acquisition can usually be shorter, compared to task paradigms. Finally, a better understanding of FC M/EEG analysis and an evaluation of their usefulness are essential for future research and for the potential use of these techniques in clinical contexts.

4.3. Limits of This Review

Although this systematic review goes beyond a simple revision of the literature, it does not include any statistical analysis of the reviewed studies, as would have provided a meta-analysis. The reader should therefore take into account the fact that the current findings represent qualitative and not quantitative results. The methodological heterogeneity of the included studies, with respect to their paradigms, the types of FC and EC analysis, as well as the

large age range of the children investigated, is in itself a limitation for the generalization and integration of the results.

Compared to other neuroimaging techniques, both MEG and EEG stand out because of their high temporal resolution. This is of particular importance in language paradigms, where tonal differences occur at a fast rate. However, both methods have a relatively low spatial resolution, which leads to a rather large-scale localization of cerebral activity when compared to techniques such as fMRI. Thus, the present findings about functional language brain networks permit only limited spatial interpretation.

Finally, given that we mainly reviewed studies that considered FC as a measure of neuronal networks, we would like to acknowledge that FC bears an index of statistical dependency. More precisely, it allows the estimation of the correlation between cerebral activation, measured simultaneously with different electrodes or sensors located over different cerebral locations. Thus, it does not allow causal conclusions about brain networks. Only three studies (Barnes-Davis et al., 2018; Kadis et al., 2016; Molinaro et al., 2016) included EC analysis that allowed causal conclusions about interactions within functional language networks. Future studies should definitely include EC analysis that allows for more advanced characterization of cerebral language networks.

5. Conclusion and Future Directions

The analysis of brain FC and EC through the use of M/EEG data is a common emphasis of ongoing developmental research, but many unanswered questions remain regarding the brain correlates of language development. To our knowledge, this is the first systematic review to summarize the current state of knowledge on linguistic electrophysiological patterns of brain connectivity in the pediatric population. It provides a detailed portrait of the relevant MEG and EEG data analysis methods that have been used in that context. Future research should consider the different FC analyses available, in order to choose the appropriate tools and paradigms. Overall, the results of the reviewed studies are highly heterogeneous, precluding the possibility of drawing clear and quantitative conclusions and showing the importance of pursuing research in this field. Future work will enlighten on the brain substrates of language development and may also have important clinical impacts, for example, leading to the identification of early neuroimaging markers associated with altered language development in populations at high risk of language disabilities. It would also allow the identification of children at higher risk of language difficulties, in order to provide early and individualized intervention (Jeste et al., 2015). However, studies with significantly larger sample sizes, as well-normative data, are needed in order to be able to use these tools in a clinical context.

Fifth Article.

LIONirs: flexible Matlab toolbox for fNIRS data analysis.

by

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Abstract.

Background. Functional near-infrared spectroscopy (fNIRS) is a suitable tool for recording brain function in pediatric or challenging populations. As with other neuroimaging techniques, the scientific community is engaged in an evolving debate regarding the most adequate methods for performing fNIRS data analyses.

New method. We introduce LIONirs, a neuroinformatics toolbox for fNIRS data analysis, designed to follow two main goals: (1) flexibility, to explore several methods in parallel and verify results using 3D visualization; (2) simplicity, to apply a defined processing pipeline to a large dataset of subjects by using the MATLAB Batch System.

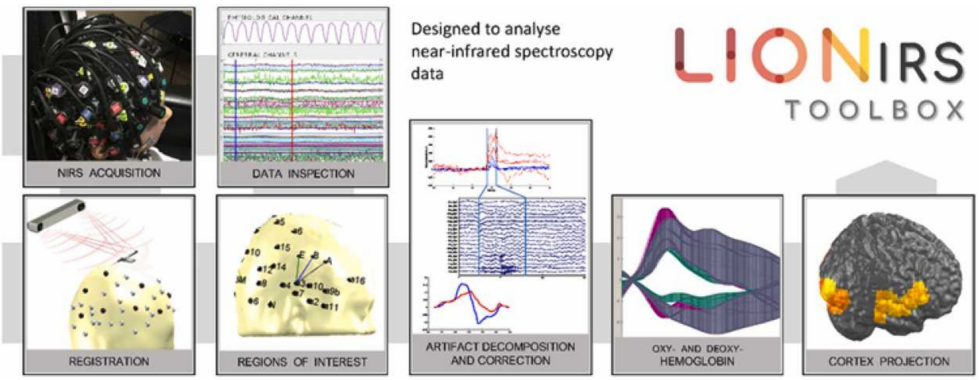
Results. Within the graphical user interfaces (DisplayGUI), the user can reject noisy intervals and correct artifacts, while visualizing the topographical projection of the data onto the 3D head representation. Data decomposition methods are available for the identification of relevant signatures, such as brain responses or artifacts. Multimodal data recorded simultaneously to fNIRS, such as physiology, electroencephalography or audio-video, can be visualized using the DisplayGUI. The toolbox includes several functions that allow one to read, preprocess, and analyze fNIRS data, including task-based and functional connectivity measures.

Comparison with existing methods. Several good neuroinformatics tools for fNIRS data analysis are currently available. None of them emphasize multimodal visualization of the data throughout the preprocessing steps and multidimensional decomposition, which are essential for understanding challenging data. Furthermore, LIONirs provides compatibility and complementarity with other existing tools by supporting common data format.

Conclusions. LIONirs offers a flexible platform for basic and advanced fNIRS data analysis, shown through real experimental examples.

Keywords: Matlab toolbox, functional Near Infrared Spectroscopy (fNIRS), semi-automated artifact correction, multimodal, task-based analysis, functional connectivity

Graphical abstract



Highlights

— The LIONirs toolbox is designed for fNIRS data inspection and visualization
— Methods are integrated for isolation of relevant activity and correction of artifacts.
— Multimodal auxiliary, EEG or audio-video are visualized alongside the fNIRS data.
— Task-based and functional connectivity measure analysis tools are available.
— The code structure allows to automated and standardized analysis of large data set.

1. Introduction

Functional near-infrared spectroscopy (fNIRS) is a non-invasive neuroimaging technique. Similar to functional magnetic resonance imaging (fMRI), it measures blood oxygenation fluctuations related to neuronal processes in cortical regions, but with several practical advantages. First, it is portable, allowing studies to be conducted in clinical settings where bedside acquisition is necessary (Kassab et al., 2018). Second, fNIRS is relatively tolerant to movement, which makes it suitable for language studies that require participants to speak aloud. Third, fNIRS is child-friendly because it allows the researcher or a parent to interact with the participant during data recording. Hence, it is a technique particularly useful for challenging populations, such as infants and toddlers, or individuals with cognitive or psychiatric conditions (Vannasing et al., 2016). Finally, fNIRS can easily be used in multimodal contexts, such as during simultaneous fNIRS-EEG acquisitions, which could, for example, contribute to a better understanding of neurovascular coupling and brain function in patients with epilepsy (Wallois et al., 2012; Wallois et al., 2010).

Since fNIRS is a relatively young modality, there exists a wide variety of approaches for the processing and analysis of its data, but no clear consensus on the best way to apply them. For instance, it is not yet clear which are the most appropriate and standardized pipelines through which to extract relevant information in specific experimental settings. Therefore, flexible neuroinformatics tools are needed, in order to allow the exploration of several options for the processing and handling of fNIRS data. It is important for such tools to provide user-friendly approaches for dealing with theoretical issues (e.g., which artifact-correction or data analysis method is the most appropriate), as well as practical concerns (e.g., definition of optode and data locations, visualization, multimodal integration, the handling of large datasets, performance of quality checks).

As with any other neuroimaging technique, a major challenge with fNIRS data analysis is the separation of the relevant signal from confounding signals (e.g., movement artifacts, physiological artifacts related to systemic fluctuations). Although a careful installation of the cap that holds the optodes and good cooperation from the participant during data acquisition can both significantly minimize artifacts, the fNIRS signal will always contain some confounding signals. For instance, in pediatric populations, young children or participants

with severe cognitive or behavioral deficits may be unable to stay still and focused for long periods of time; although the experiment is often temporarily interrupted to allow the child to move and relax, a large amount of data can sometimes be significantly corrupted by movements. Should this occur, it is crucial to proceed to artifact detection, and to then either correct or reject the contaminated data segments (Lorenzo et al., 2019). Appropriate methods should be used to reliably and efficiently detect and/or correct artifacts resulting from the participant's movements or physiology (e.g., heartbeat, respiration, Mayer waves). Compared to other neuroimaging techniques, fNIRS is still far from having standard data analysis procedures, and inadequate signal processing could lead to incorrect interpretation of the data and unreliable results (Brigadoi et al., 2014; Lorenzo et al., 2019).

Several methods have been suggested for dealing with motion or muscular artifacts in the fNIRS signal (Schecklmann et al., 2017), none being ideal and each having their own pros and cons (Hocke et al., 2018). Depending on the nature of the artifact itself, the mathematical assumptions made within a method for isolating the artifact may not be appropriate. Some methods reduce the interference caused by artifacts by using spline interpolation (Scholkmann et al., 2010), while others decompose the data using target principal component analysis (tPCA) and then remove the components related to the main artifacts (Yücel et al., 2014). More recently, parallel factor analysis (PARAFAC, Hüsser et al., 2020) has been used for decomposition, as this method takes advantage of the multidimensional nature of fNIRS data (time, space and wavelength), and the fact that movement artifacts equally affect both wavelengths at the same location (Cui et al., 2010). Independent component analysis (ICA) has largely been used in EEG, and magnetoencephalography (MEG) and has proven to be efficient for removing eye blinks, which generate systematic and reproducible artifacts that can be considered statistically independent from brain activity (Hyvarinen, 1999). The technique of ICA has also been used to unmix the independent components in fMRI and fNIRS (Beckmann & Smith, 2004; Hiroyasu et al., 2013). The use of wavelet decomposition has been proposed for reducing spike artifacts, by removing high-frequency outliers from the data (Molavi & Dumont, 2012). Recently, a hybrid two-step approach combining spline interpolation and wavelet decomposition has been applied to fNIRS data to correct artifacts caused by jaw movements related to articulation during the performance of a language paradigm (Novi et al., 2020). Finally, a least-squares regression method has also been used to measure, estimate and subtract physiological artifacts caused by systemic fluctuations (Pfeifer et al., 2018; Saager & Berger, 2005). It is not yet clear which method is best for fNIRS artifact detection and correction, and the method chosen certainly depends on the type of artifacts being dealt with.

Furthermore, many approaches can be applied for the subsequent analysis of the artifact-free data. A task-based paradigm will assess the overlap between the recorded brain response and the hemodynamic response function (HRF), which is modeled using a general linear

model (GLM) (Peng et al., 2016; Scholkmann et al., 2014; Uga et al., 2014). According to some studies, predefined theoretical HRF models can be problematic, notably in studies with clinical populations, infants or the elderly, or when focusing on complex cognitive functions (Buchsbaum et al., 2005; D. K. Nguyen et al., 2012, 2013; West et al., 2019). Moreover, there are some nonlinearity effects on the HRF response that are not yet completely understood (D.-Q. Zhang et al., 2014). The higher temporal resolution at the acquisition of ∼0.05 s for fNIRS in comparison to ∼1 s for fMRI (Glover, 2011; Witt et al., 2016) could help describe the HRF nonlinearity and bring additional information through its time course morphology. Other avenues may explore functional connectivity measures to describe cognitive brain function at rest. Considering this large range of existing methods, one could easily feel lost, especially as few of the methods require advanced programming skills.

The development of more user-friendly tools, notably through graphical interfaces for the processing and visualization of data, is critical for applied and clinical research teams. These tools should offer several flexible methods and functionalities, allowing the user to create the best pipeline for the analysis of their data set. Since the analysis of a sizeable number of subjects may be extremely laborious, and even unrealistic in very large studies, some parts of the process are best automated, once the ideal pipeline has been created. However, as described above, a fully automated method for removing artifacts from fNIRS data may not be the best option, as inadequate use of signal decomposition poses the risk of distorting or even removing the signal of interest itself. It is therefore crucial that the user have access to various artifact detection/correction methods, to be able to identify the most appropriate one for a given data set. The chosen method would then be applied in a semi-automated manner to the entire sample of subjects. However, a supervised application is especially important for noisier data sets. The user should be able to assess the signal quality with a visual inspection before, during, and after the application of artifact detection and correction. The optimal tool would also allow the user to simultaneously access the data acquired from multiple modalities (physiology, EEG, audio-video recording, etc.), which has been shown to help with the identification of different events in fNIRS data (movements, epileptic events, state of consciousness, etc. Louis et al., 2016). Finally, in fNIRS, the placement of optodes is not standardized, but is instead customized in function of the cap used, the number of optodes available in the equipment, and the experimental question being posed. A tool that allows the projection of data onto either a brain or scalp reconstruction or a template can therefore greatly help with the visualization of data.

Several good neuroinformatics toolboxes have been developed to help researchers perform fNIRS data analysis. One of the first and best known is HomER, which is publicly available on the NITRC website (Huppert et al., 2009). It is easy to use and offers a visual display of various options for motion correction and preprocessing. As of 2015, it also includes an external 3D interactive visualization of the data's spatial distribution in AtlasViewer (Aasted

et al., 2015). The Brain AnalyzIR toolbox is the most flexible tool available (Santosa et al., 2018); it offers various statistical methods for addressing the specific features of fNIRS data analysis (e.g., specific models for the noise covariance). However, AnalyzIR requires relatively advanced programming skills, which are not typically available in applied and clinical research teams. NIRS-SPM (Ye et al., 2009) applies the statistical GLM method, which leads to the creation of activation maps, but it does not include modules for artifact rejection, which is critical, especially in studies with infants and children. Finally, FC-NIRS focuses mainly on the computation of functional connectivity matrices, based on temporal correlations of fNIRS time series (Xu et al., 2015).

Table 1 – List of functionalities available (+) or not available (NA) in several popular open-source fNIRS tools.

Functionalities	**Homer**	**Atlas viewer**	**NIRS-SPM**	**NIR Storm**	**AnalyzIR**	**FC NIRS**	**LIONirs**
Batch processing	+	NA	+	+	+	+	+
Motion correction	+	NA	+	+	+	+	+
Quality control	+	NA	+	+	+	+	+
GUI design for piecewise artifact/data decomposition	NA	NA	NA	NA	NA	NA	+
Preprocessing dOD, filter, MBLL correction	+	+	+	+	+	+	+
GLM model	+	NA	+	+	+	NA	+
Window epoch averaging	+	NA	NA	+	+	NA	+
3D topography overlap MRI	NA	+	+	+	+	NA	+
2D datanavigation	+	NA	NA	NA	+	+	NA
FC measures	NA	NA	NA	+	+	+	+
Multimodal (EEG-video)	NA	NA	NA	+	NA	NA	+
No coding required	+	+	+	+	NA	+	+
Group level statistics	+	NA	+	+	+	+	+
Tomographic reconstruction	+	+	+	+	+	NA	NA

In summary, there is currently no available toolbox that provides transparency and flexibility for data quality control, and a single solution for all the challenges faced when performing fNIRS data analyses, such as the need for an interactive 3D visualization adapted for a large number of channels, the flexibility to explore different methods for building customized processing pipelines, and offering multimodal integration so as to fully benefit from any additional source of information acquired simultaneously. These elements are all crucial for data sets acquired from challenging populations, such as young children or patients,

where understanding the signal's structure requires efficient high-density data visualization at each step of processing.

In this article, we introduce the LIONirs toolbox as a new tool for the analysis of fNIRS data. LIONirs is intended to complement other existing software, by supporting compatible file formats. It offers the flexibility to explore and visualize the data at each step of its processing, and allows one to easily build a customized processing pipeline that can be applied to a large number of subjects. For this purpose, the LIONirs toolbox is embedded in the Matlab Batch System (http://sourceforge.net/projects/matlabbatch/), used in the SPM toolbox (Friston et al., 2011). This allows the inclusion of various modules for data handling and processing. It also provides the ability to easily standardize the analysis of large data sets by the use of processing pipelines or templates. In this paper, the reader will be guided through the organization of the LIONirs toolbox, and its applications are illustrated with examples. The toolbox is available under the General Public Licence (GNU) and maintained on the public github.com project (https://github.com/JulieTremblay3/LIONirs).

2. Methods and results

2.1. Software overview

The LIONirs toolbox is an open-source software written entirely in Matlab (The MathWorks, Inc., Natick, Massachusetts, United States; compatible with releases from 2014a). It was developed in Windows, using the batch data editor in SPM12, and offers a variety of either basic or more sophisticated functions for handling and processing fNIRS data. It is therefore a minimal requirement that the user install the Statistics and Machine Learning Toolbox and SPM12.

An important characteristic of the LIONirs toolbox is its modularity. It offers the user the possibility of performing data processing in a customized manner and to integrate all steps into a processing pipeline. The pipeline can be saved as a template to be used for subsequent analyses. The user can also prepare a hierarchical pipeline by creating different branches for testing alternative processing approaches. Branches could, for instance, correspond to two different conditions (e.g., resting state during different stages of alertness: sleep vs. awake) or to different types of artifact correction (e.g., PCA vs. PARAFAC). The corresponding Matlab structure for each branch is saved in separate subfolders, allowing the user to easily assess the results of each individual processing approach. All these operations and their corresponding parameters are codified and stored in a Matlab structure named NIRS.mat.

The main graphical interface in the toolbox is called DisplayGUI. This interface uses the NIRS.mat structure to help the user modify artifact selection, and to easily and simultaneously visualize fNIRS data and multimodal data (e.g., heartbeat, respiration, EEG, audio-video recordings), using topographical projections onto the skin or cortical surface. Moreover,

automatic script generation is available for creating a template, which can then be applied for multiple subjects [https://sourceforge.net/projects/matlabbatch/].

Figure 1 gives an overview of the organization and functionalities of the LIONirs toolbox. One of the first steps in fNIRS data analyses is to provide a 3D representation of the association between the positions of the optodes and the anatomy of reference. The toolbox includes the 3DMTG graphical interface, which allows the user to associate the raw fNIRS data with the corresponding 3D representation of the montage and the anatomy. First and foremost, LIONirs offers a flexible and semi-automated artifact correction strategy by use of various data decomposition methods, such as tPCA or PARAFAC. Once the signal is considered clean, or without artifacts, transformation of the light intensity into concentrations of oxy- and deoxyhemoglobin is done using the Modified Beer-Lambert law (MBLL).

Hemodynamic analysis involves the identification of the task-related hemodynamic response (HRF), by averaging the time-lock events or estimating of the relevant activities using the HRF model in a GLM. Functional network organization can be estimated using several brain functional connectivity (FC) measures such as Pearson correlation, Hilbert joint phase probability distribution and magnitude squared coherence (Kida et al., 2016; Molavi et al., 2014; Xu et al., 2015). Finally, some basic statistical analyses (e.g., student t-tests, ANOVA, GLM) can be applied to task-based components or FC measures. A correction for multiple comparisons using false discovery rate adjustment or permutation tests is also implemented. These results can then be displayed as a topographical representation of all channels, or a selection of them.

In the next sections (Secs. 2.2 to 2.7), the main analysis steps and functionalities will be explained in detail and illustrated with examples. Several tutorials are available in the toolbox documentation, offering a step-by-step guide for some processing tools, along with data examples (https://github.com/JulieTremblay3/LIONirs).

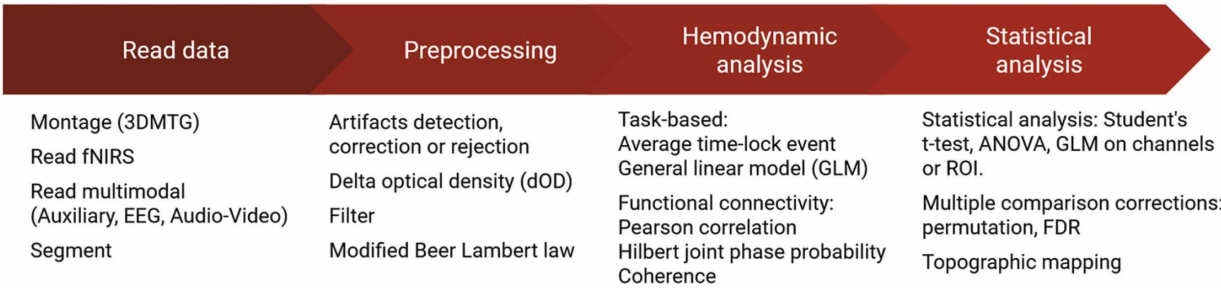


Figure 1 – Overview of the organization and functionalities of the LIONirs toolbox.

2.2. Montage configuration: 3DMTG interface

In fNIRS, the position of each source and detector (optodes), commonly called the montage, is not standardized and must be adjusted to fulfill the experimental requirements.

It is up to the user to associate sources and detectors with 3D coordinates, according to the specific montage of their study. Therefore, depending on the number of optodes available, the type of caps that is used, and the head sizes of the participants, the configuration is optimized in order to cover the regions of interest (ROIs). When determining a montage, it is important to match brain anatomy with the position of the optodes, in order to obtain reliable topographical and cortical projections. The optodes' locations on the head of a subject are recorded using a stereotactic system or a 3D localization system, and saved in a coordinates file (.elp file). The 3DMTG interface reads the coordinates file, allowing the visualization of the optodes' registered position on the 3D representation of the scalp or cortical surface (Fig. 2). The correspondence between optode location and anatomical representation is done with a rigid body transform method, or on a real subject using anatomical markers (nasion, inion, left and right pre-auricular points) identified through structural MRI images (Friston et al., 2011). The anatomy can be defined by either an MRI template or the subject's images (Richards et al., 2016). Optionally, MRI images include anatomical atlases such as a segmentation according to the Brodmann atlas or the automated anatomical labeling atlas (AAL), used to label functional cortical regions over the surface of the brain (Alemán-Gómez et al., 2006; Talairach, 1988; Tzourio-Mazoyer et al., 2002). The visualization of the atlas helps the user ensure that the montage adequately covers the ROI of the cerebral cortex. If the individual's MRI images are available, the anatomy of the brain and skin surface can be extracted using an external image processing software such as Neuronic Image Processor (http://www.neuronicsa.com/modulos/producto/imagic.html) or Brainsuite (Dogdas et al., 2005). The toolbox also provides a generic template in the required format for projection onto the skin and cortical surface (Collins et al, 1994). When no MRI data is available for an individual, the brain MRI template will likely require spatial rotation, translation, and scaling adjustments, in order to match the individual's optodes coordinates. Once all these steps are completed, the experimental project file can be saved. This allows the user to access the topographical representation of the data at any stage of the analysis and visualize the entire or partial data on the skin or cortex.

2.3. Data organization

LIONirs supports many raw data formats, including ISS, NIRx, .nirs, and SNIRF. It reads the data and uses the previously created 3DMTG anatomy to attribute each channel to the correct location on the scalp. Simultaneously acquired multimodal data, such as physiology, EEG, or audio-video recordings, can be integrated and synchronized, becoming accessible through the DisplayGUI. A trigger sent simultaneously to all equipment (e.g., fNIRS system and EEG amplifier) is essential for the proper synchronization of multimodal data. Any step of processing and adjustment taken in LIONirs can be saved to different

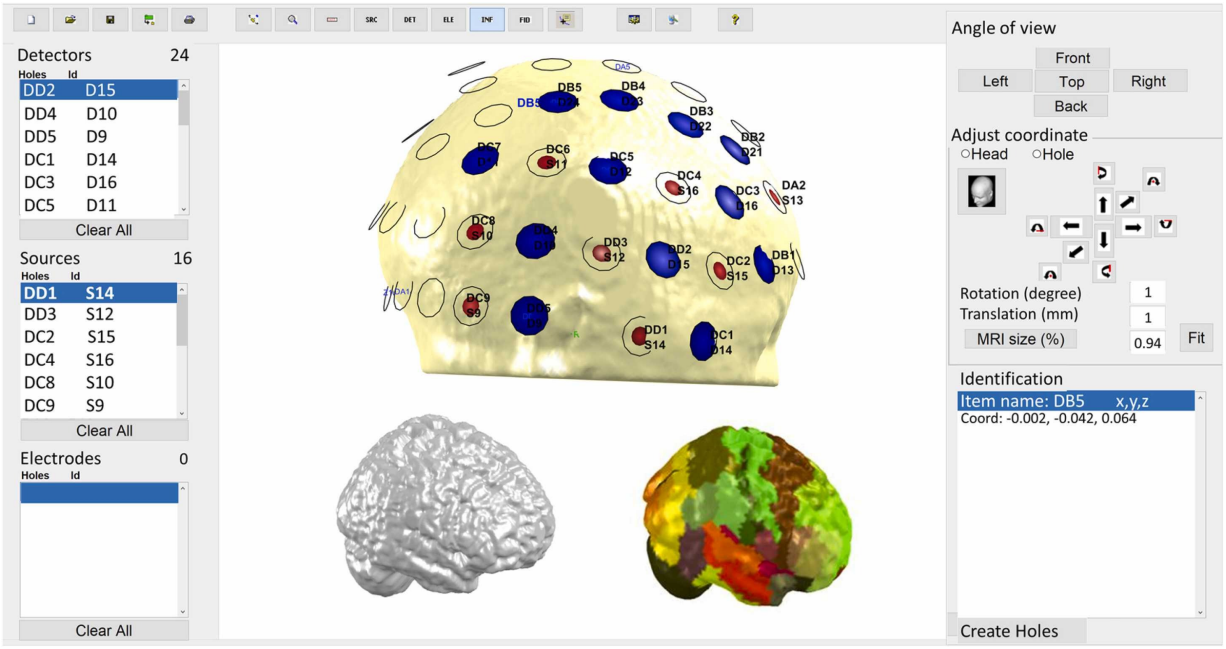


Figure 2 – 3DMTG interface for creating and visualizing the fNIRS optode localization. The skin (top image), cortical surface (bottom left image), or associated anatomical regions (bottom right image) can be used as anatomical landmarks to dictate the placement of the helmet holes. Each hole has a label that allows the identification of the physical holes on the cap. The right panels allow the user to select the angle of visualization (top), adjust the coordinates of the registered positions of hole(s) (middle) and provides information about exact coordinates (bottom). (a) The position of sources (S) and detectors (D) can be projected onto the head surface. (b) The three panels at the left list the associations between the labels of detectors (top), sources (middle) and electrodes (for simultaneous NIRS-EEG recordings; bottom) with the helmet holes. (c) The upper panel contains tools for moving the entire head, adding or removing sources, detectors and electrodes, and accessing parameter adjustments.

folders, organized in a tree structure for each subject, as depicted in Fig. 3. The necessary data and associated Matlab structure (NIRS.mat) are saved to each (sub)folder corresponding to the various stages of processing. This NIRS.mat structure allows one to easily keep track of all processed operations and apply modifications on one level, without having to start from the very beginning. The data structure NIRS.mat will open one data file at a time for visualization and processing. A computer with 8G Ram Memory should be sufficient to analyze and visualize an hour of data fluidly. Analyzed data are save in binary format to optimize speed and storage. It is possible to save intermediate analysis steps to review them if needed. However, a good practice to reduce data storage resources is to use the option to delete previous step by default. Folders and subfolders are also used to separate branches of a processing pipeline for parallel analysis of multiple conditions or different analytical approaches. Finally, at every stage, the data can be exported to the most common fNIRS format (.nirs or SNIRF), thereby facilitating compatibility with other software.

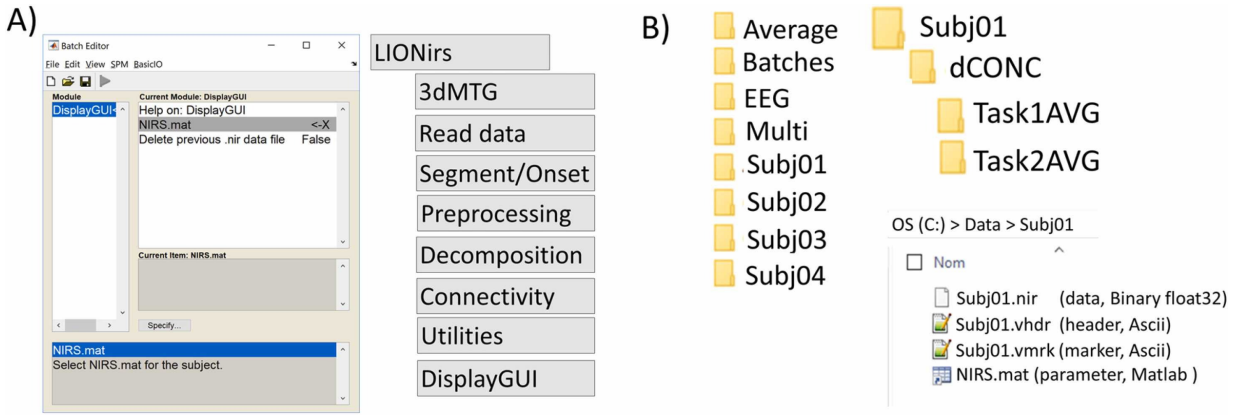


Figure 3 – Organization of the different stages of data analysis. A) The Matlab batch editor gives access to the LIONirs functions menu (e.g., artifact detection, filtering, averaging, etc.), allowing users to build up a processing pipeline for their specific needs. B) Example of folder and subfolder organization of the various processing steps applied at the subject or group-level. Each folder contains the NIRS.mat structure, to keep track of the operations applied and the analyzed data files. Subfolders can include separate branches for different parallel pipelines, for example, when analyzing multiple experimental conditions.

2.4. Visualization of the data (DisplayGUI)

One of the main objectives of this toolbox is to offer as much flexibility and transparency as possible, so that the user need not have programming skills in order to interact with the data. For this purpose, the DisplayGUI interface allows one to visualize the data at any step of the analysis. Figure 4 shows an overview of the DisplayGUI, including the multimodal display, different decomposition techniques, and the 3DMTG navigation. After synchronization with fNIRS, multimodal data such as respiratory signal, cardiac pulse, or other auxiliary channels are displayed in the upper window of the DisplayGUI. Video, EEG or 3DMTG topographic representation can be displayed on demand for a selected time interval. Specific spatial ROI can be selected in the 3DMTG interface to restrict visualization in the DisplayGUI and, inversely, channels of interest can be selected in the DisplayGUI, leading to a restricted visualization in the 3DMTG.

The user can either look at individual channels, select a group of channels based on the correlation of their time courses, or choose channels based on their amplitude or spatial localization. Subsequently, the user selects a specific time interval, such as the duration of an artifact or a task. Specific processing steps, such as rejection of noisy intervals or correction of artifacts, can be performed for the selected time interval and specific channels. Various data decomposition techniques are implemented in such a way that the user has the possibility to first extract one or several specific components, which will then be stored in the component list [Extract]. Because many of the decompositions can be influenced by the presence of outliers in the data, the customized time and channel selection within

the DisplayGUI is a particular advantage of the LIONirs toolbox, favoring a superior and more targeted decomposition. Visualization of the components' signatures in all considered dimensions, i.e., time, space, or wavelength, allows for easy identification of the components of interest. For instance, when aiming to correct an artifact, the user can identify those specific components with characteristics related to that artifact, and subtract it from the data. When decomposing a cerebral activation pattern, the visualization of the components allows for easy identification of those components that contain characteristics known to be related to a hemodynamic response, and should therefore be exported for statistical analysis (Sec. 2.7). If one has reason to exclude some or all channels of a specific interval, for example due to noise contamination, the DisplayGUI allows a manual rejection to be applied. Even though the DisplayGUI can visualize data from previous processing steps, the operations are done in a sequential manner. This means that any manual editing (e.g., artifact correction) is applied to the latest data stored to memory. However, the user has the option to overlay the data from the previous step onto the signal of the current module, to fully appreciate the effect of the procedure. This is, for example, useful during artifact correction, when overlaying the original onto the corrected one provides a better picture of the correction's effect on improving the signal's quality. If the corrections do not lead to satisfying results, it is possible to restore the previous data in the DisplayGUI.

2.5. Preprocessing tools

2.5.1. *Channel quality check*

In fNIRS data analysis, a common way to ensure signal quality is to detect the cardiac pulse, which is an easy-to-monitor physiological marker (Fekete et al., 2011; J. R. Goodwin et al., 2014; Pinti et al., 2019). Hence, in the absence of a cardiac pulse due to poor contact of the optodes with the skin, specific channels should be excluded. The frequency of the cardiac pulse varies with age, from 2 Hz at birth (Mortensen et al., 2017) to around 1 Hz in healthy adults (Fekete et al., 2011). In the software implementation, the user can adjust the sensitivity criteria in order to discard those channels that are without evidence of cardiac pulse, and thus ensure the quality of the fNIRS data. The toolbox offers the possibility to save a report that provides information about the peak frequency identified and which channels were excluded.

2.5.2. *Automated artifact detection and correction*

Abrupt variations in the raw fNIRS signal due to motion or muscular artifacts are often easy to detect (Schecklmann et al., 2017; Scholkmann & Wolf, 2013). The batch system has an artifact detection module that can automatically identify intervals and channels affected by a suspected artifact. The detection is performed using three criteria, whose sensitivity

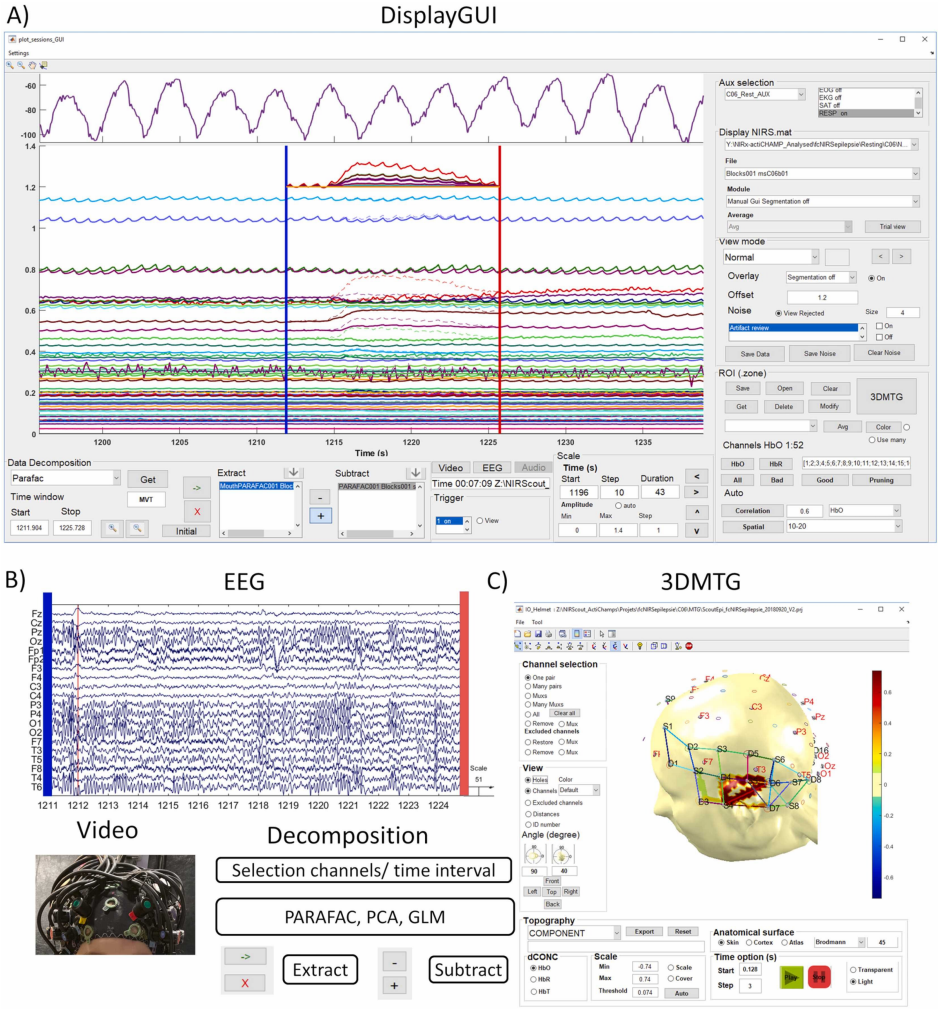


Figure 4 – Overview of the DisplayGUI interface for visualization of data at each processing stage. A) The upper panel shows the various multimodal recordings that can be synchronized with the fNIRS data, e.g., auxiliary for respiratory belt trace (purple line). The large panel below shows the fNIRS data at a specific stage, with different colors for each channel. Within this large panel, the right column includes different functions allowing the user to choose which fNIRS signal to display [Display NIRS mat], navigate between different blocks [File] and processing steps [Module], options to visualize channels using a butterfly or a standard view [View mode], and overlay the signal of a previous step with the current module [Overlay]. The user can also define [Get] and save a list [Save] of regions of interest [ROI zone], and use these to display a subset of channels. In the lower part of the large fNIRS data panel, one can access different data decomposition techniques, such as GLM, PARAFAC, and PCA, in order to identify components corresponding to artifacts or relevant physiological activities. The component of interest can subsequently be extracted for further analysis or, in case of artifacts, be subtracted from the data. Finally, the lower part of the panel at the right provides options to display [Trigger] or adjust [Scale]. B) Using the time start (blue vertical line) and time stop (red vertical line) options on the displayed fNIRS data (in A), one can select a window of time for which to quickly access the simultaneous EEG, audio-video recording, reject a section of data or apply a decomposition technique. C) Topographic visualization of the fNIRS signal using the [3DMTG]. The channels and hemodynamic activity can be projected onto a 3D representation of the skin (as shown on the figure), the helmet or the cortical surface. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

can be fine-tuned by the user. A first criterion uses a moving average technique to detect abrupt variations of amplitude that are abnormal; those intervals are identified when the variation is higher than a predefined normalized z-score threshold, computed on the channel's whole recording (Weinberg & Abramowitz, 2008). This method avoids over-sensitivity to background noise and, more specifically, detects excessively high variations of amplitude. A second criterion marks any artifact-free data segment that is between two artifacted segments, and shorter than a minimal time interval specified by the user. A third criterion uses the temporal correlation between channels with artifacted segments (detected using the two previous criteria) and any other channels. This implies that if the correlation between the time courses of a channel that contains an artifacted segment and another channel is higher than the threshold defined by the user, then the time interval of this other channel is also identified as containing an artifact. It is then up to the user to conduct a manual verification of the artifact detection and potentially apply adjustments to either reject the identified segments, or to proceed to one of the artifact-correction techniques provided in the toolbox. These corrections aim to minimize the overall effect of artifacts on the fNIRS signal, by avoiding the rejection of too many trials and thus maintaining adequate statistical power for further analyses.

LIONirs toolbox offers two data decomposition techniques specifically for artifact correction: the 2D PCA and the multidimensional PARAFAC. For both approaches, LIONirs allows the user to conduct an automated decomposition of segments previously identified as containing artifacts. Both have been proven to perform well for correcting movement artifacts in fNIRS (Hüsser et al., 2022; Yücel et al., 2014). The implementation of PCA uses a Matlab function to decompose time and channel into components that represent most of the variance, and classify these by percent of variability explained. With PCA, we assume that the component that explains most of the variance will reflect the artifact, and the user can remove the component up to a total percentage of variance explained (Brigadoi et al., 2014; Cooper et al., 2012). The implementation of PARAFAC is done by means of the external open-source package Nway Toolbox (Andersson & Bro, 2000). In PARAFAC, an automated decomposition selects the optimal number of components, based on the lowest residual error and the highest Concordia criteria (Andersson & Bro, 2000). The artifact component(s) retained for correction are the one(s) that explain the highest variance in the time course (similar to PCA) and also the lowest difference between wavelength, assuming that both wavelengths from the same site will perceive the artifact conjointly (Cui et al., 2010).

For both decomposition techniques, the user can choose between an automated subtraction using the batch system or a manual one using the DisplayGUI. Once the decomposition completed, the final effect of the correction can be reviewed visually in the DisplayGUI. There is also an offset adjustment available to force light intensity to return to the level it was at before the movement artifact, and thus avoid discontinuity in the signal. This procedure

greatly improves data quality, as illustrated in Fig. 5. In this case, the uncorrected artifact shows both wavelengths equally affected by an articulatory movement and an abnormal strong variation, while the corrected one shows the slow pattern of the HRF time-lock with the task event.

Although this article has laid out the different options for detecting, correcting and rejecting artifacts in the order in which they are typically performed for movement artifact correction, the LIONirs toolbox offers the flexibility to change that order, and to apply each method at any stage of processing.

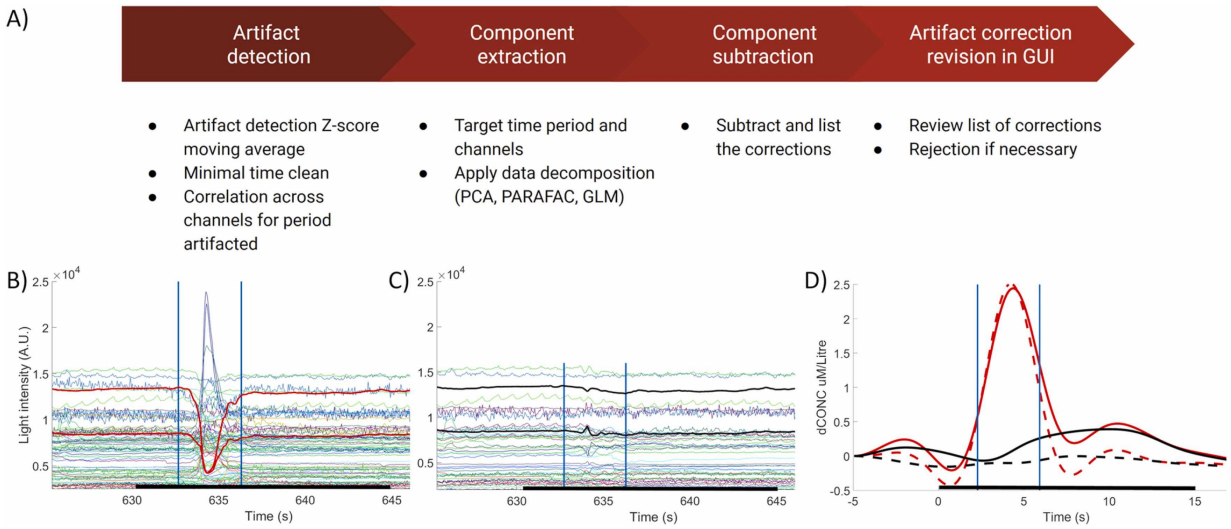


Figure 5 – Example of a movement artifact correction. A) The proposed sequence for the automated detection and correction of artifacts in the LIONirs toolbox. B) 15-s segment (black horizontal line) of raw fNIRS data recorded during a verbal fluency task, where the participant has to say out loud as many words as possible belonging to a given category during a specific time interval (Paquette et al., 2015). This task typically induces an articulatory movement artifact, expressed as an abrupt change in the fNIRS signal (shown on B between the two vertical blue lines). C) The same data segment after the subtraction of the artifact-related component, identified with PARAFAC decomposition. D) Concentration changes in HbO (solid lines) and HbR (dotted lines) from the channel which most prominently showed the artifact in the raw data, before correction (red lines) and after correction (black lines). HbO and HbR signals are both equally affected by the artifact (red lines) as they both show a strong abnormal variation, while the corrected data (black lines) reveals the slow pattern of the HRF time-locked with the task event in the Broca ROI typically recruited by the verbal fluency task.

2.5.3. *Systemic physiology artifacts*

fNIRS measures light attenuation as deep as a few centimeters under the surface of the skin (Haeussinger et al., 2011). Light absorption, however, is not specific to the cortex, as photons travel through skin, skull, and other superficial tissues. Thus, systemic hemodynamic

variations related to other physiological phenomena not directly related to cerebral activation, such as cardiac pulse, respiration, or slow-wave fluctuations around 0.1 Hz also known as Mayer waves (Julien, 2006), are part of the acquired signal and distort the hemodynamic response. Signals related to cardiac pulse or respiration can be filtered out, as their frequencies are not in the range of the hemodynamic activity (Fekete et al., 2011).

However, systemic slow hemodynamic fluctuations such as Mayer waves could be confounded with the hemodynamic response associated with brain activity. Multi-distance optodes, global average of all channels or PCA of the entire signal that includes the slow systemic fluctuations, can be used to identify and correct this type of noise (Erdoğan et al., 2016; Gagnon et al., 2012; J. R. Goodwin et al., 2014; Kirilina et al., 2012; Saager & Berger, 2005; Y. Zhang et al., 2005). The GLM (Sec. 2.6.1) can be applied, to estimate the regression coefficient corresponding to the slow systemic physiological noise, which can then be subtracted from the data. Regressing the confounding physiology increases the sensitivity of the subsequent analysis, thus improving the reliability of the results (Huppert, 2016; Y. Zhang et al., 2005). Figure 6 illustrates an example of such a regression using globally averaged data (all channels averaged) to estimate the effect of physiology artifact as a regressor (Fig. 6B). The HRF response is more stable after (Fig. 6C), compared to before (Fig. 6A) the extraction of the physiology.

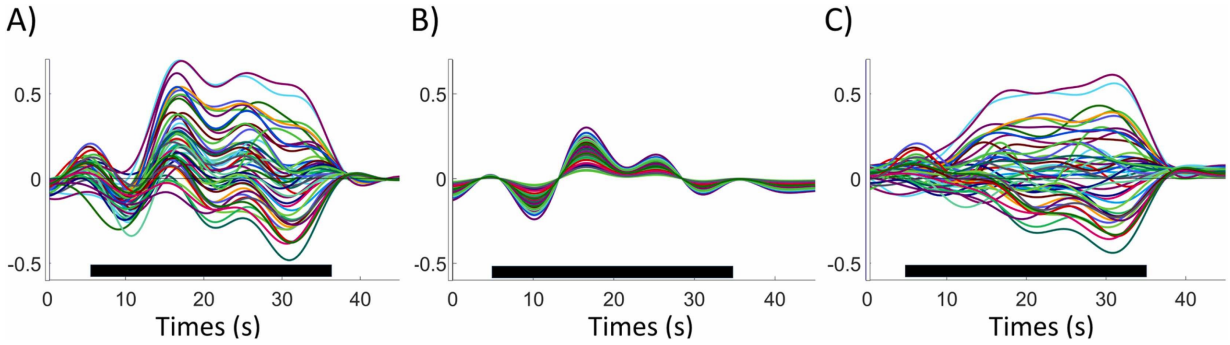


Figure 6 – Regressing out the effects of the physiology, as applied to a single trial of a fNIRS data set recorded during a 30-seconds visual stimulation (black horizontal bold line) with a flipping checkerboard. A) The raw data from the 54 fNIRS channels covering the occipital area; B) The extracted physiology artifact using a GLM regression in the same fNIRS channels. Slow-wave fluctuations around 0.1 Hz are clearly visible in the physiology extraction. C) fNIRS data after subtraction of the physiology artifact.

2.6. Hemodynamic analyses

Once data is corrected, by subtracting or rejecting confounding artifacts, the task-related brain activity or functional connectivity (FC) measures can be identified for each participant. LIONirs preprocessing modules handle the basic transformation of the data, such as delta

optical density (dOD), filtering, and transformation of light intensity into hemodynamic concentrations using the Modified Beer-Lambert law (MBLL) (Delpy et al., 1988). The differential pathlength factor (DPF) can be adjusted according to the participant's age (Duncan et al., 1995; Duncan et al., 1996; Scholkmann & Wolf, 2013) or be fixed manually. When the signal has been transformed into hemodynamic fluctuations, there are different ways of proceeding to the interpretation of cerebral activation. For example, it is possible to process task-based data in order to identify the specific characteristics of the task-related hemodynamic response. Functional connectivity data acquired at rest or during a specific task can also be processed in order to investigate brain network organization. In the next two sections, we will present task-related and functional connectivity analyses, respectively, using the LIONirs toolbox.

2.6.1. *Task-related hemodynamic response*

A typical way to estimate the HRF response is through a regression approach, namely the GLM, that allows the researcher to determine how well the data points match a set of predictions (Friston et al., 2011; Friston et al., 1995; Poline & Brett, 2012). A multiple linear regression based on the least-squares estimation has been implemented into the current toolbox, where the user must define the regressors to be considered (Draper, 1998). A tool is provided to convolve the modeled HRF based on the applied paradigm (Glover, 1999) and to create an event-related regressor. To improve performance of the GLM, the user has the flexibility to add relevant regressors to the model, i.e., factors that might be correlated with each other, such as auxiliary data (e.g., cardiac fluctuations or respiration) (Hillenbrand et al., 2016) or low-frequency oscillations (Tong and Frederick, 2010). For example, one or several short-distance channels (Gagnon et al., 2012), or the global average (Y. Zhang et al., 2005) can be used to estimate the physiological noise. Once the GLM estimation of the HRF response is obtained at the subject-level, individual regression weights, typically called beta coefficients, can be exported for use in group statistics. Decomposition using PCA or PARAFAC to extract the hemodynamic time course, could be explored as well. As a visual example, Fig. 7 shows a typical processing pipeline (7A) for data acquired during a visual stimulation (7B) and a data set acquired during a passive story listening paradigm (7C). Data were recorded using an Imagent Oxymeter (ISS, Champaign, Illinois, USA) on a healthy adult subject, at a sampling rate of 20 Hz. Experiments were approved by the ethical committee at the Sainte-Justine University Hospital. The following modules were applied to the data (see also Fig. 7A): read data, add multimodal data (e.g., HRF model response, video), segmentation to synchronize multimodal data, semi-automated artifact detection, and rejection, dOD, low-pass filtering at 0.1 Hz, and MBLL. Then, a GLM model, including global average (Y. Zhang et al., 2005) and the modeled HRF as regressors (Glover, 1999), was applied. The estimated physiology artifact was subtracted from the data, before averaging

across trials to obtain the time-locked response. The estimation of the HRF response was followed by a simple Student t-test against zero, applied to all coefficients that were estimated from multiple sessions for each channel (Uga et al., 2014). False discovery rate (FDR) was used to correct for multiple comparisons (Benjamini & Yekutieli, 2001). The response that differed significantly from zero was projected onto the cortical surface.

2.6.2. *Functional connectivity measures*

Functional connectivity (FC) is usually defined as the correlation between the time series of hemodynamic fluctuations measured at different locations on the scalp (Friston et al., 2011) FC has been largely studied in fMRI, and assumes that there is a direct relationship between neuronal activity and the hemodynamic fluctuations, measured as the BOLD signal. Research in this field has allowed the description of several consistent functional brain networks during resting state, including the default mode network, the somatosensory network, the dorsal attention network, the ventral attention network, and the auditory and visual networks (Bellec et al., 2010; Bijsterbosch et al., 2017; Damoiseaux et al., 2006; Raichle et al., 2001).

Many of the mathematical measures that are used to estimate FC from neuroimaging time series are also frequently applied in other modalities, such as fMRI or EEG (Friston et al., 2011; Smitha et al., 2017). Most of these approaches can be applied straightforwardly to the time series of fNIRS data (Gallagher et al., 2016; Molavi et al., 2014; T. Nguyen et al., 2018; Xu et al., 2015). However, fNIRS is limited to measuring hemodynamic fluctuations that occur in the cortical surface, thus precluding fNIRS data from informing about functional brain networks in deeper areas. Importantly, depending on the level of coverage of the montage used and duration of the recording, connectivity measures derived from fNIRS data should be interpreted carefully (Sun et al., 2018; Wang et al., 2017). Despite these limitations, FC measures can be applied to fNIRS data in order to answer specific questions regarding the characteristics of cortical functional networks in a specific population and/or condition.

The LIONirs toolbox allows the computation of functional brain connectivity measures within the predefined channels or ROIs, using Pearson's correlations (Xu et al., 2015), Hilbert joint phase probability (Molavi et al., 2014), and magnitude squared coherence (Kida et al., 2016). Figure 8A shows a typical processing pipeline for performing a FC analysis. In this example, we applied the magnitude squared coherence approach to fNIRS data recorded in 14 healthy adults during a 12-minutes resting-state period. Based on the 10-20 system (Klem et al., 1999) several ROIs were created in the DisplayGUI by assigning each channel to a specific ROI (Fig. 8B). For each participant, magnitude squared coherence measures are computed between the time series of each pair of channels and are presented by ROIs in a FC matrix (Fig. 8C) or a circular connectogram (Fig. 8D) using LIONirs GUI_LookMatrices and user-defined thresholds. FC measures could also be computed between each group of channel(s) representing ROIs (not illustrated in Fig. 8). The results of the resting-state coherence matrix

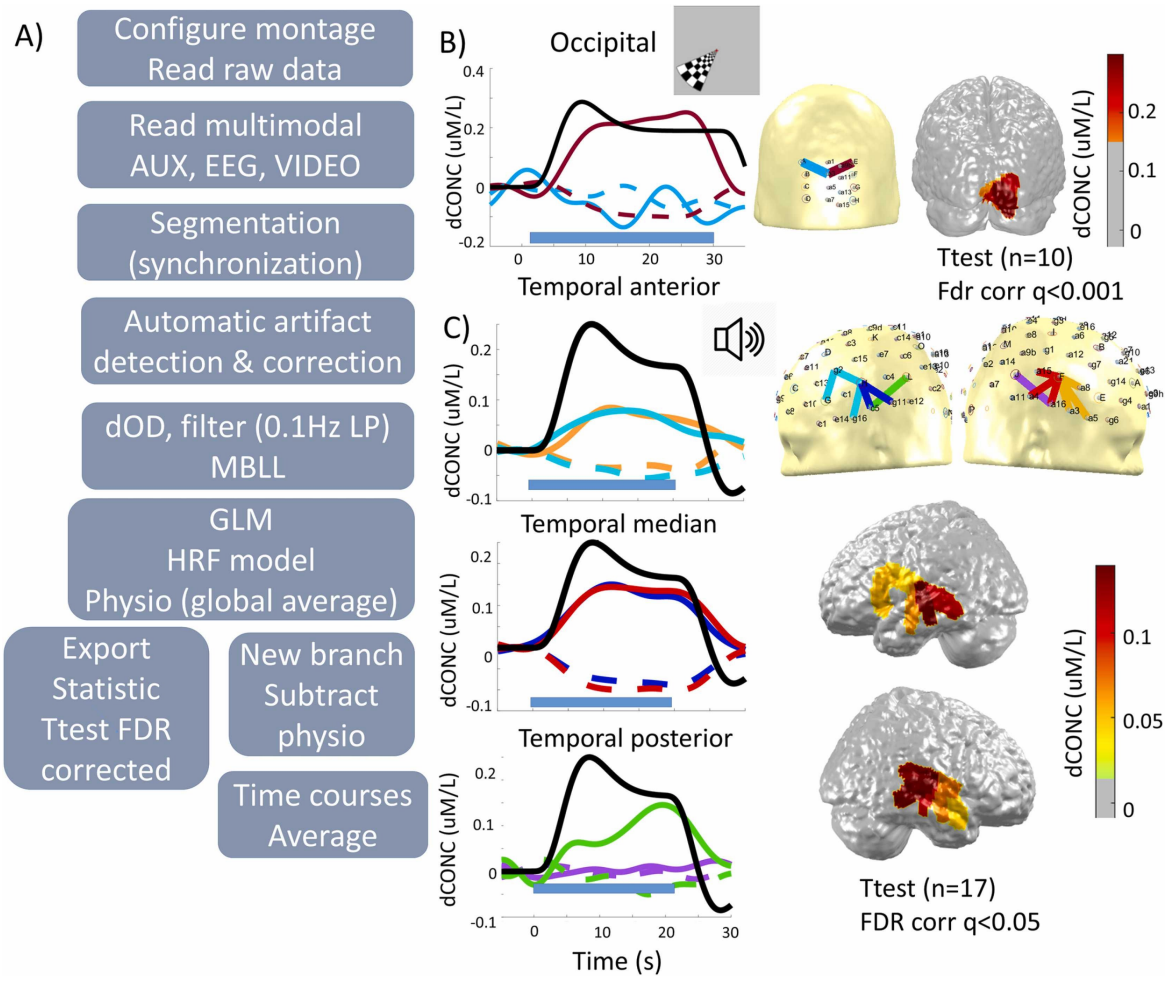


Figure 7 – Examples of subject-level analyses. In both cases, the results concord with previous fMRI analysis of similar experiments (Toronov et al., 2007; Vannest et al., 2009). A) Detailed hierarchical diagram of the different steps included in the processing pipeline. B) Visual stimulation. Fifty-four fNIRS channels covered the occipital cortex, measuring the cerebral activation in a healthy adult. Visual stimulation consisted of a flipping checkerboard that appeared for 30 s in the bottom-left corner of the stimulation screen (Bastien et al., 2012). The task included a total of 10 blocks. Averaged time courses of all blocks are shown by a solid line for HbO and a dotted line for HbR concentrations. The color of each curve associates with a channel(s) at a specific location on the head topography. The duration of stimulation for each paradigm is shown with a horizontal blue line below the timeline curve. The black line displays the expected HRF model. The significant response for HbO variations were projected onto the cortical surface (right panel). A strong statistical response was found in the right visual cortex (FDR corrected $q < 0.001$). C) Passive story listening task. One hundred ten channels covered the bilateral frontal, temporal and parietal areas. Hemodynamic fluctuations were recorded while the subject listened to a story presented in its native language. The story was presented in 18 individual blocks of 20 s each (Paquette et al., 2010). Note that the description used in B is also used here to illustrate HbO and HbR concentrations (solid and dotted lines, respectively), the duration of the task (horizontal blue line) and the expected HRF model (black line). Temporal anterior and temporal medial areas of both hemispheres showed significant responses related to the auditory response, while the temporal posterior area in the left hemisphere revealed cerebral activation most likely related to receptive language processing in Wernicke's area (FDR corrected $q < 0.05$).

for all healthy adults include the averaged coherence values for all subjects. Some connectivity clusters are observed in the prefrontal areas (FP1 and FP2), the somatosensory areas (F3, C3 and F4, C4) as well as the left-hemisphere language areas (F7 and T3, T5).

2.7. Statistical analyses

Statistical tools included in the LIONirs toolbox can be applied to specific channels or ROIs. Hence, prior to the analysis, it is essential that the user identifies homologous channels or ROIs for all subjects, to allow for proper inter-subject comparisons. Statistics can be applied to the averaged time course, to the components identified with a decomposition technique (e.g., the estimation of the hemodynamic response with the GLM model), or to FC measures.

2.7.1. *Task-related statistic*

Parametric statistical tools (one-sample, paired, unpaired student test and multiway analysis of variance (ANOVAN) are implemented using Matlab Statistics and Machine Learning Toolbox. The statistic is apply on exported components such as average hemodynamic amplitude or GLM estimate. In the case using a list of channels a statistical map are save and could be open in a 3DMTG to be visualized as a heatmap of the results: average contrast, Tmap or Fmap. These result maps are available uncorected or using FDR correction for multiple comparisons (Benjamini & Yekutieli, 2001) available in the Matlab bioinformatics toolbox. Export of predefine ROI or channels could be use in external specialized statistic softwares such as the Statistical Package for the Social Sciences (SPSS) or R (www.r-project.org).

2.7.2. *Functional connectivity*

Connectivity matrices statistics can be applied to specific channels or ROIs. First, a Fisher transform are implemented to be apply on brain connectivity measures. Non parametric permutation tests have been implemented using t statistic, which establishes the null distribution based on experimental data shuffle test repeated multiple times (Galán et al., 1997). A quick visualisation of these result and average groups matrices are available in the GUI_LookMatrices. Data could also be export to the specialized Network-Based Statistic (NBS) toolbox (Zalesky et al., 2010).

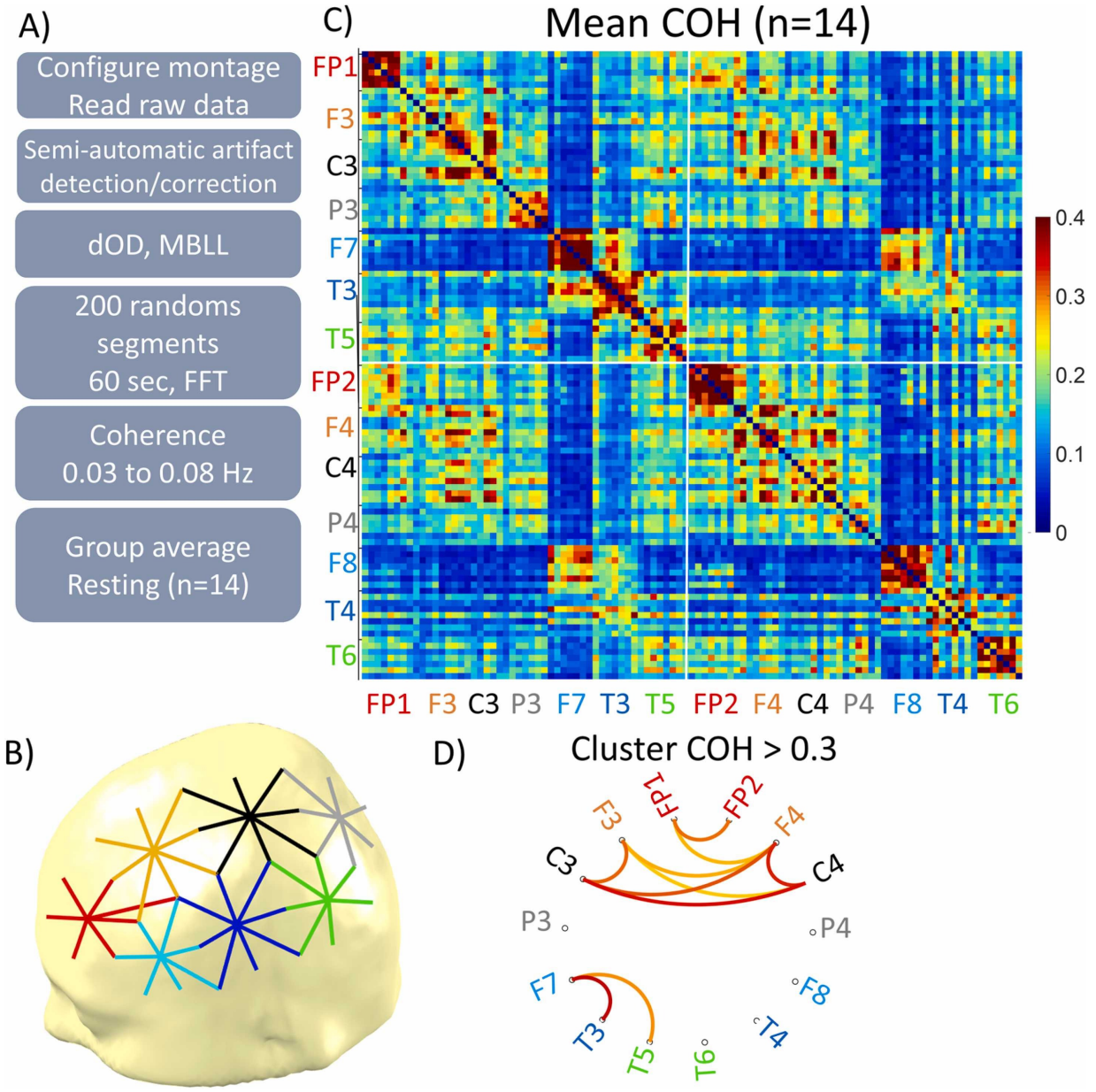


Figure 8 – Functional connectivity (FC) analysis for a fNIRS data set of 14 healthy adults during a resting-state data acquisition (eyes open, 12 min). A) A typical processing pipeline used to calculate FC using magnitude squared coherence of HbO hemodynamic concentrations. B) Regions of interest (ROIs) were defined manually using the DisplayGUI (the montage was identical for both hemispheres and the same for all participants). These ROIs were used to compute the connectivity matrix (shown in C). Red channels (B and C) are located around Fp1 and Fp2 from the 10–20 system; orange channels around F3 and F4; black channels around C3 and C4; gray channels around P3 and P4; cyan channels around Fp7 and Fp8; blue channels around T3 and T4; and green channels around T5 and T6. C) A coherence matrix between all pairs of ROIs is averaged for all 14 subjects (average matrix shown in this figure). In this matrix, the upper left quadrant corresponds to ROIs in the left hemisphere, the lower right part corresponds to the right hemisphere, while the lower left and upper right quadrants reflect inter-hemispheric connections. The color scale ranges from blue to red, where blue means there is no or weak functional connectivity and red suggests highly functionally connected regions. D) The connectogram reveals the stronger connections (COH $>$ 0.3) across the ROIs.

3. Discussion

LIONirs is a new open-source toolbox for the analysis of fNIRS data. The toolbox includes a variety of techniques and methods for data processing that have been used for fNIRS data analysis in many previous studies. Since there is currently no consensus on the standard procedures for fNIRS data recording, preprocessing and processing, one of the main objectives of this work was to design a toolbox that is as flexible as possible, and allows for easy handling of the data without requiring programming skills. Hence, the LIONirs toolbox makes it possible for the user to choose between several tools, explore and compare various methodological approaches, and easily build a customized data analysis pipeline adapted to their specific needs and data set characteristics. Most of the analysis modules need few seconds to compute. However, few modules such those allowing to compute connectivity measure, data decomposition, and artifact detection could take up to few minutes. The pipeline can subsequently be applied in either a fully or semi-automated manner to a large number of subjects. The second goal of the LIONirs toolbox was to provide an open-access and transparent tool for fNIRS data processing, thus avoiding the black-box phenomenon. To that end, two graphical interfaces (DisplayGUI and 3DMTG) provide 3D visualization of the fNIRS montage and the data at any stage of processing. It is thus possible to track each intermediate result across the entire data analysis process, allowing the user to modify, explore and compare the applied methods if necessary. fNIRS data acquired in children or clinical populations often includes a large number of movement artifacts that can rarely be fully corrected using an entirely automated procedure. A careful artifact detection and correction is critical for obtaining an interpretable fNIRS signal. The LIONirs toolbox enables a semi-automated artifact detection, correction, and rejection, allows the user to verify the quality of the preprocessing, make adjustments if needed, and combine different methods when applicable. LIONirs includes two data decomposition techniques for artifact correction, namely tPCA and PARAFAC, which are powerful tools for minimizing the impact of artifacts and increasing the quality of data (Hüsser et al., 2022; Yücel et al., 2014) A quality report can be produced to summarize the number and duration of the corrections applied for each subject. In some cases, poor signal quality may require the rejection of a channel or time interval instead of trying to correct it; an advantage of LIONirs is that it offers the user the flexibility to choose between either correction or rejection. Figure 5 illustrates the impact of non-corrected artifacts on the hemodynamic response, which could lead to misinterpretation of the data. The detection and correction or the rejection of artifacts are therefore crucial steps in fNIRS data analyses.

Another type of noise that often affects hemodynamic signals are slow-waves related to systemic physiological fluctuations (Chaddad et al., 2013; Masataka et al., 2015; Yücel et al., 2014). Several studies have shown that removing these slow-waves leads to a significant

increase of the specificity of the fNIRS signal (Erdoğan et al., 2016; Gagnon et al., 2012; J. R. Goodwin et al., 2014; Kirilina et al., 2012; Saager & Berger, 2005; von Lühmann et al., 2020; Y. Zhang et al., 2005). This correction is even more important when the hemodynamic response shows small amplitudes, due to a low signal to noise ratio (Tachtsidis & Scholkmann, 2016). To deal with this physiological noise, the LIONirs toolbox offers a simple regression of either short-distance channels or a global average of all channels. We have illustrated how useful a GLM regression is for extracting physiological noise, thereby improving the interpretability of the hemodynamic response (Fig. 6; Peng et al., 2016; Scholkmann et al., 2014; Uga et al., 2014).

Although the debate is ongoing as to which of the current methods is best, LIONirs incorporates some of the commonly applied techniques for analyzing hemodynamic response. They include epoch averaging (illustrated in Fig. 7) and multiple regression, which are mainly intended for task-related data sets. Several measures of functional connectivity, which can be applied to both resting-state and task-related data, are also available in the toolbox, namely Pearson's correlation, Hilbert joint probability distribution of the phase, and magnitude squared coherence (illustrated in Fig. 8, Kida et al., 2016; Molavi et al., 2014; Xu et al., 2015). Measures can be calculated to obtain individual and then group functional connectivity matrices (Xu et al., 2015). The LIONirs toolbox therefore offers a variety of hemodynamic responses and functional connectivity measures, which can be selected according to the research question.

In some studies, fNIRS acquisition is conducted simultaneously with other modalities such as physiologic measures (e.g., cardiac pulse, respiration), EEG, or audio-video recording. The LIONirs toolbox allows the integration and synchronization of multimodal signals, which can increase the fNIRS signal quality, help with fNIRS data interpretation, and provide rich information on neurovascular coupling. For instance, physiologic measures can significantly help detect physiological artifacts and remove them from the fNIRS signal. The movements of the participant during the fNIRS recording can be captured on audio-video monitoring, which can contribute to the identification of movement artifacts. EEG recorded simultaneously with fNIRS may provide precious information on the participants' state of consciousness (e.g., asleep, awake, drowsy or alert), or detect pathological alterations (e.g., epileptogenic activity) that can contaminate the fNIRS signal. Multimodal data acquisition is an important source of information for a better understanding of the neurovascular coupling (Lecrux et al., 2019). Extensive work on multimodal analysis in EEG and fMRI has shown that even if the electric signal from the EEG and the hemodynamic variations from the fMRI both evolve over a different time scale, subject-specific cerebral responses from both modalities can be useful for identifying relevant neuronal activity. Single-trial discrimination has also been used to construct EEG-derived fMRI activation maps (Philiastides & Heekeren, 2009), which could be applied to fNIRS. The concurrent analysis of these data can be helpful for the detection

of artifacts and the control of data quality, as variations in experimental design has been shown to cause complexities in the hemodynamic response (Issard & Gervain, 2018). Thus, multimodal data can contribute to a better understanding of the relationship between the time series and the evolution across time of EEG rhythmic activity such as alpha, theta and gamma frequency bands, and has provided important insights into the characteristics of brain activity (Goldman et al., 2002; Martínez-Montes et al., 2004).

LIONirs can be viewed as a complementary tool to currently available software packages. As described in the introduction, other well-designed and highly useful tools such as HomER TM (Huppert et al., 2009), NIRS-SPM (Ye et al., 2009), Brain AnalyzIR (Santosa et al., 2018) and FC-NIRS (Xu et al., 2015) have been publicly released in the last decades. While it also integrates some of the methods proposed by other toolboxes, LIONirs' development was mainly driven by the specific needs of processing artifacted data acquired from challenging populations (very young children or clinical populations), which are the populations we typically recruit in our lab. In these contexts, the signal's characteristics may be influenced by ongoing development or pathological phenomena, which have to be taken into account when processing and interpreting data. We therefore developed a highly flexible toolbox, allowing the user to apply various methods and visualize the data at any stage of the analysis. In addition, LIONirs includes PARAFAC, a new method for artifact correction and the extraction of relevant activities in fNIRS (Hüsser et al., 2022). Its integration into the Matlab Batch System, where processing pipelines can be customized, further contributes to this flexibility and enables the user to generate scripts that facilitate the automated analysis of large data sets. The DisplayGUI permits the visualization of data at any processing stage, thus contributing to both the transparency of the toolbox and to its flexibility, since alternative approaches can be explored and compared visually. Since montages are often not standardized across studies that use fNIRS, the 3DMTG GUI serves to create customized montages and associate them with a reconstruction of the brain's anatomy, using the subject's (or template) MRI images. Consequently, the user can, at any step during processing, organize the data by ROI. As do other fNIRS data processing toolboxes, LIONirs supports reading in and exporting to several data formats (e.g., .nirs, SNIRF, binary files), which allows the use of methods from other software packages.

As with other publicly available fNIRS data processing packages, LIONirs is in constant evolution, with new features and methods being continually added and improved. Novel functionalities will be progressively integrated into LIONirs and made publicly available. In its current version, the toolbox is designed to study the slow hemodynamic signal, not the Event-related optical signal (EROS) or the fast signal, which can help to understand interactions at different time scales between specific brain areas and the electrophysiological signal (Gratton, 2010; Gratton et al., 1997). Algorithms allowing to analyze the fast optical signal could be implemented in an upcoming version of the toolbox. LIONirs is also limited to

the visualization of the brain cortex by use of a simple radial projection from the corresponding channel position, because this provides an easy and fast ($<$ 1 sec) representation. Complete forward modeling and inverse estimation (diffusion optical tomography) are not yet supported, although they could be useful in studies that include high-density data acquisition. In a previous study, several methods were compared in a fNIRS context (J. Tremblay et al., 2018) and will be included in one of the upcoming versions of LIONirs. Nevertheless, the current version supports and provides several data formats; the integration of additional formats is planned, in order to make the toolbox available to a larger range of users. Finally, we also intend to integrate a technique for quantitative analysis of multimodal data, such as the N-way partial least-squares technique for a data-driven combination of neurophysiological EEG information and the hemodynamic response measured with fNIRS (Martínez-Montes et al., 2004)

Despite the examples used in this article to illustrate how a processing pipeline in LIONirs can be applied to real experimental data, we do not claim to establish a best-practice guideline for the analysis of fNIRS. The aim was rather to provide different options, so that researchers can build the processing pipeline that best suits their specific experiment and research question.

4. Conclusion

LIONirs is a new Matlab-integrated toolbox for fNIRS data analyses. It allows the user to deal with fNIRS data acquired with a wide range of optode montages, various correcting artifact methods, and multimodal data. The toolbox stands out because of its flexibility and transparency throughout the entirety of analysis processing. The user can explore and compare different methodological approaches and select the most appropriate technique for a particular data set. The toolbox provides the flexibility to build a customized processing pipeline, whereby the methods and order of analysis are completely determined by the user. Transparency is achieved via the DisplayGUI, that which allows one to visualize the continuous time series of the signal and a 3D projection of the data onto the scalp or cortex. The proposed semi-automated approach for artifact detection and data decomposition helps to efficiently reduce artifact contamination and promote quality of the fNIRS signal. LIONirs includes several techniques for the analysis of the hemodynamic signal, such as averaging, multiple regression, and FC measures, as well as a module for certain statistical analyses. The program is distributed under the GNU license and is open for further development and use in any third-party study, as long as this publication is cited. The current version, as well as detailed documentation on all its functionalities, can be downloaded from https://github.com/JulieTremblay3/LIONirs.

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7. Declaration of competing interest

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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