Université de Montréal

Profil neuropsychologique des enfants atteints de cardiopathie congénitale d'âge préscolaire : une perspective développementale

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Thèse présentée en vue de l'obtention du grade de PhD

en psychologie, option neuropsychologie clinique

Novembre, 2021

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Université de Montréal

Département de psychologie, Faculté des arts et des sciences

Cette thèse intitulée

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Résumé

Les cardiopathies congénitales (CC) sont les malformations congénitales les plus fréquentes, affectant 1% des nouveau-nés. Grâce aux avancées médicales des dernières décennies, le pronostic cardiaque d'enfants qui en sont atteint est généralement favorable. Or, les atteintes neurodéveloppementales sont courantes dans cette population, touchant environ la moitié des survivants à mesure qu'ils grandissent. À l'âge scolaire, une incidence plus élevée de difficultés langagières, académiques, sociales et comportementales sont rapportés chez les enfants nés avec une CC que chez leurs pairs en santé. On en sait toutefois relativement peu sur l'émergence de ces difficultés en âge préscolaire, de même que sur la trajectoire développementale et la stabilité des différentes fonctions cognitives au fil du temps. Dans ce contexte, cette thèse avait comme objectif général de caractériser le fonctionnement neuropsychologique et social des enfants d'âge préscolaire atteints de CC et d'identifier des marqueurs précoces permettant de dépister les difficultés pouvant survenir au moment d'entrer à l'école. La thèse est composée de trois articles principaux, soit une revue de la littérature et deux articles empiriques.

Le premier article visait à recenser les connaissances actuelles quant à la compréhension et la classification des troubles neurodéveloppementaux de manière globale. Ensuite, le second article de cette thèse avait pour but de dresser le profil neuropsychologique des enfants de 5 ans atteints de CC modérée à sévère (n=55) et de décrire leur trajectoire neurodéveloppementale entre 1 et 5 ans. Ultimement, cette étude visait à identifier des marqueurs prédictifs du fonctionnement préscolaire par l'entremise des habiletés en bas âge. Les résultats obtenus mettent en lumière une vulnérabilité importante au niveau des habiletés langagières, des prérequis à la lecture et aux mathématiques, ainsi qu'au niveau des fonctions attentionnelles et exécutives à l'âge de 5 ans. Nos données indiquent également des trajectoires développementales distinctes selon la sphère évaluée,

avec un retard qui semble s'accroitre entre 1 et 5 ans pour ce qui est du fonctionnement cognitif global et du langage expressif. À l'inverse, le langage réceptif s'amélior significativement au fil du développement, et, dans notre groupe d'enfants atteints de CC, le retard observé à 1 an n'était plus perceptible à l'âge de 5 ans. Par ailleurs, les résultats révèlent que les enfants à risque de présenter des difficultés langagières au moment de l'entrée à l'école peuvent être identifier avec précision par l'entremise de leurs habiletés langagières à l'âge de deux ans – contrairement aux autres difficultés neurodéveloppementales présentes à l'âge préscolaire.

Étudié à travers cette même cohorte d'enfants, le troisième article de cette thèse visait à évaluer la compétence et la cognition sociale des enfants de 5 ans atteints de CC, ainsi qu'à étudier les facteurs socio-cognitifs contribuant à la compétence sociale dans cette population. Cette étude montre une vulnérabilité de la cognition sociale chez notre cohorte d'enfants atteints de CC, tandis que la compétence sociale apparait préservée. Cette étude révèle aussi qu'ensemble, le langage, la cognition sociale (théorie de l'esprit) et le fonctionnement excutif permettent d'expliquer une proportion significative de la compétence sociale (R^2=0,62, p<0,001).

Globalement, les résultats de la thèse contribuent à établir un portrait plus complet des relations complexes et dynamiques s'opérant entre les diverses sphères du fonctionnement de l'enfant atteint de CC. Les résultats offrent des pistes novatrices quant à l'approfondissement des connaissances théoriques, empiriques et cliniques au sujet du développement neuropsychologique et social, et fournissent des fondements empiriques pour guider la prise en charge de ces enfants, en fonction des besoins auxquels ils sont confrontés à mesure qu'ils grandissent.

Mots-clés : cardiopathies congénitales, âge préscolaire, neurodéveloppement, profil neuropsychologique, cognition sociale, compétence sociale

Abstract

Congenital heart disease (CHD) is among the most common birth defects, affecting approximately 1% of all live births. Improvements in medical care have resulted in dramatically improved survival rates, however, rates of long-term neurodevelopmental disabilities and psychiatric comorbidities in this population remain relatively unchanged. Approximately one-half of children with CHD present with cognitive difficulties leading to higher rates of special education service use, poorer school outcomes, psychosocial maladjustment, as well as reduced earnings and employability in adulthood. Despite growing recognition of difficulties in early childhood and at school age, less is known regarding the presentation of these difficulties during preschool age. Moreover, the development of their neurodevelopmental profile over time has received relatively little attention.

To begin to address these issues, the overall objective of this thesis was to characterize the neuropsychological and social profile of preschoolers with CHD and to identify early markers for potential difficulties that may arise when entering school. This objective has been studied through three sub-objectives. First, we reviewed the literature regarding our current understanding and classification of neurodevelopmental disorders in children (article 1). In our second paper, we sought to characterize the neuropsychological profile of children with CHD at 5 years of age (N=55) and to describe their neurodevelopmental trajectory between 1 and 5 years of age. This work allowed us to identify potential predictive markers of poor neurodevelopmental outcomes (article 2). Finally, the third sub-objective, studied in the same cohort of children assessed for objective 2, was to evaluate the integrity of socio-cognitive skills (social cognition, language and EF) and to examine the contribution of these skills to social competence in preschool children (five years) with CHD (article 3).

Together, the results of our work provide new insight into the comprehensive neuropsychological profile of children with CHD, and help to guide our understanding of the complex and dynamic relationships between different developmental domains of following heart surgery. Our findings provide an empirical basis to guide future research into the development of optimal supports for young children with CHD.

Keywords: Congenital heart disease, preschool age, neurodevelopment, neuropsychological profile, social cognition, social competence

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Liste des sigles

ADHD	Attention deficit hyperactivity disorder
BRIEF	Behavior Rating Inventory of Executive Function
BSID	Bayley Scales of Infant and Toddler Development
CC	Cardiopathies congénitales
CHD	Congenital heart disease
CIM	Classification internationale des maladies
CINC	Clinique d'investigation neuro-cardiaque
CNOC	Cardiac Neurodevelopmental Outcome Collaborative
DSM	Diagnostic and Statistical Manual of Mental Disorders
EF	Executive functions
FE	Fonctions exécutives
GAI	General Ability Index
ICD	International Classification of Diseases
ROC	Receiver operating characteristic
TDAH	Trouble du déficit de l'attention avec hyperactivité
TDE	Théorie de l'esprit
TSA	Trouble du spectre de l'autisme
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

Liste des abréviations

c.-à-.d. : c’est-à-dire

e.g. : exempli gratia (par exemple / for example)

et al. : et alii (et collègues / and colleagues)

i.e. : id est (c’est-à-dire / namely)

p. ex : par exempe

Remerciements

Avant toute chose, j'aimerais remercier ma directrice de thèse, la Dre Anne Gallagher. Merci, Anne, pour la confiance que tu m'as accordée ces dernières années. Merci pour ton ouverture d'esprit, ta grande disponibilité et ta compréhension à mon égard, qui ont joué un rôle clé dans ma motivation. Ta rigueur, ta bonté et ton enthousiasme m'inspirent grandement. Ce fut un privilège immense d'apprendre à tes côtés et d'être si bien guidée ces dernières années.

Mes remerciements vont aussi à tous mes collaborateurs et collaboratrices de recherche sans qui cette thèse n'aurait pas pu voir le jour, ainsi qu'à toute l'équipe du LIONlab pour les beaux moments partagés. Un merci spécial à Solène, avec qui j'ai traversé les derniers miles du long marathon que représente la rédaction de cette thèse. Tu as été une coéquipière hors pair et nos discussions m'ont été très précieuses, tant sur le plan personnel qu'intellectuel. Natacha, j'aimerais aussi te remercier pour tes conseils, ta confiance et pour les opportunités que tu m'as offertes ces dernières années. Je t'en suis sincèrement reconnaissante et j'espère avoir la chance de travailler à tes côtés à nouveau dans le futur.

Je tiens également à remercier chaleureusement la merveilleuse équipe de la CINC. Votre dévouement, votre motivation contagieuse et votre grande considération pour la recherche clinique m'inspirent et m'aident à forger la professionnelle que je souhaite devenir. Une pensée particulière pour Amélie Doussau, qui a été d'une aide inestimable dans le bon déroulement de mon projet de recherche et — évidemment — hautement essentielle à la mise en œuvre du projet CINC-Yoga. Pour ta bienveillance, ta détermination et ton esprit rassembleur, merci du fond du cœur. Je remercie également toutes les familles ayant participé à mon projet de recherche pour leur confiance et leur précieuse collaboration. Votre résilience et votre courage sont de grandes sources d'admiration.

J’aimerais aussi remercier sincèrement ma cohorte du D.Psy (la meilleure, sans contredit) d’avoir ensoleillé mon chemin, même lorsque le temps était plus gris. Thaïna, Stéphany, Shirine, Josianne, Jennyfer, Cindy, Marianne et Delphine, merci pour ces beaux moments de folie et de complicité, mais aussi pour votre écoute et votre sensibilité. C’est une chance inouïe d’avoir développé de si belles amitiés avec vous ces dernières années. Je souhaite également remercier mes amies de plus longue date — notamment Marie Duchaine, Marie Dufour, Alex M., Alex G., Ariane, Sarah, Bianca et Cath — pour votre soutien inconditionnel, vos encouragements constants et pour m’avoir aidé à conservé un certain équilibre de vie au long de ce parcours. Les mots me manquent pour vous exprimer toute ma gratitude.

François, je ne pourrai jamais assez te remercier pour ton écoute, ta compréhension et ton support inébranlable pendant ce long périple ponctué d’embuches et de remises en question. Merci énormément pour ta patience et le réconfort que tu m’as offert. J’ai hâte d’entamer un nouveau chapitre avec toi.

Je tiens aussi à remercier ma famille exceptionnelle, à qui je dois beaucoup quant à l’aboutissement de mes études doctorales. À ma sœur, Gabrielle, et mes frères Alexandre et Dominique, merci pour votre bonté, votre humour, et votre présence ces dernières années. À mes parents, je tiens à vous remercier pour votre dévouement, vos nombreux encouragements et votre soutien infini. Merci de croire en moi et d’être de si beaux modèles de persévérance, de bienveillance et d’intégrité. Vous m’avez influencé plus que vous ne le pensez.

Chapitre 1 – Contexte théorique

Problématique

Les cardiopathies congénitales (CC) sont les anomalies congénitales les plus fréquentes, affectant environ 1 % des nouveau-nés au Québec (Marelli et al., 2014). Depuis quelques décennies, grâce au progrès de la médecine et des techniques chirurgicales, le taux de survie des enfants avec CC a nettement augmenté. Cette augmentation de la longévité est toutefois associée à une reconnaissance accrue du risque encouru sur le plan neurodéveloppemental (Cassidy et al., 2018; Kharitonova et Marino, 2016b; Marino et al., 2012). Ces difficultés affectent différentes sphères du fonctionnement au fil du développement de l'enfant, nécessitant une prise en charge appropriée à leurs besoins qui évoluent (Ilardi et al., 2020; Latal, 2016; Ware et al., 2020). Certaines difficultés ne sont dépistées que tardivement dans la petite enfance, alors que les demandes environnementales deviennent plus importantes. Une identification précoce des retards de développement et une prise en charge rapide permettraient à ces enfants d'optimiser leurs chances d'atteindre leur plein potentiel en dépistant, voire en prévenant, ces difficultés.

Malgré le nombre croissant d'études portant sur le neurodéveloppement des enfants atteints de CC, leur profil neuropsychologique global en âge préscolaire demeure à ce jour relativement peu connu. De même, la trajectoire de développement dans laquelle s'inscrivent les difficultés neuropsychologiques et les marqueurs prédictifs de difficultés au moment de l'entrée à l'école restent à élucider. Ainsi, la présente thèse a pour objectif principal de décrire le fonctionnement neuropsychologique et social de l'enfant d'âge préscolaire (5 ans) atteint de CC ainsi que la trajectoire neurodéveloppementale longitudinale entre 1 et 5 ans.

1. Cardiopathies congénitales

Les CC sont généralement définies comme des anomalies structurelles du cœur ou des vaisseaux intrathoraciques, présentes dès la naissance et ayant un impact réel ou potentiel sur le fonctionnement hémodynamique (Casey, 2016). Ces malformations apparaissent habituellement tôt durant la grossesse et couvrent un large spectre de sévérité, partant des formes mineures (asymptomatiques) à celles qui mettent en péril la survie du bébé. De tous les enfants nés avec une CC, environ le quart nécessiteront une ou plusieurs chirurgies cardiaques dans la première année de vie (Oster et al., 2013). À l'ère actuelle, l'avènement de nouveaux outils diagnostiques et le raffinement des méthodes d'interventions ont permis l'amélioration importante du pronostic vital des enfants qui en sont atteints (Hoffman et Kaplan, 2002). La plupart des conditions sont donc chirurgicalement traitables et le taux de survie jusqu'à l'âge adulte est maintenant supérieur à 85% (Cohen et Earing, 2018; Green, 2004; Marelli et al., 2014), de sorte qu'il y a maintenant plus d'adultes vivant avec une CC que d'enfants (Best et Rankin, 2016). Cette nette amélioration du taux de survie est associée à une augmentation de l'attention portée à la qualité de vie de ces survivants. Il est maintenant bien reconnu que les CC sont associées à un risque accru de comorbidités neurodéveloppementales. Cette vulnérabilité est attribuable à une pluralité de facteurs, qui seront abordés dans les prochaines sections.

1.1. Classification

De par la multitude et l'hétérogénéité des malformations cardiaques existantes, plusieurs échelles de classifications ont été proposées. Les CC peuvent être catégorisées en fonction de leur anatomie, de leur sévérité, ou de leurs conséquences hémodynamiques. Classiquement, elles sont groupées selon la présence (cyanogène) ou non (acyanogène) de cyanose. La cyanose se caractérise par la décoloration bleuâtre des lèvres, des gencives et de la peau, résultant d'une hypoxie (diminution du

taux d'oxygène sanguin transmis aux organes). Elle peut être causée par deux principaux mécanismes physiopathologiques, soit la dérivation de droite à gauche du sang dans le cœur (shunt droit-gauche) dans laquelle le sang oxygéné se mélange au sang non oxygéné (p. ex. tétralogie de Fallot ou sténose pulmonaire) engendrant une diminution du flux sanguin pulmonaire, ou par le mélange intracardiaque de sang oxygéné et désoxygéné (p. ex. transposition des grands vaisseaux ; Jacobs, 2013; Thiene et Frescura, 2010) augmentant le flot sanguin pulmonaire. À l'inverse, les CC acyanotiques n'engendrent pas de diminution du taux d'oxygène sanguin et, de ce fait, peu de symptômes de cyanose. Le plus souvent, elles sont causées par une dérivation de gauche à droite du sang dans le cœur (shunt gauche-droit ; p. ex. communication interauriculaire ou interventriculaire) ou par une lésion obstructive à gauche (p. ex. coarctation de l'aorte ou sténose aortique ; Jacobs, 2013; Thiene et Frescura, 2010).

On distingue également différents niveaux de sévérité (Hoffman et Kaplan, 2002). Dans le cas d'une CC modérée (p. ex. sténose aortique légère) ou sévère (p. ex. tétralogie de Fallot), une opération cardiaque est typiquement nécessaire dans les premiers jours ou mois suivant la naissance, généralement dans la première année de vie. Cependant, une CC de moindre sévérité peut être asymptomatique lors de la petite enfance et être détectée fortuitement par la découverte d'un murmure cardiaque lors d'un examen de routine plus tard dans la vie de l'individu. Les lésions dans cette catégorie incluent la petite communication interventriculaire ou interauriculaire ainsi que les sténoses valvulaires aortique ou pulmonaire légères, et certaines de ces conditions peuvent ne pas nécessiter d'intervention (Casey, 2016; Hoffman et Kaplan, 2002).

Finalement, les CC peuvent aussi être classifiées en fonction de leurs caractéristiques anatomiques, tel que proposé par le système de classification diagnostique élaboré par Clancy et ses collègues (2000), distinguant quatre catégories : Classe I, lésion biventriculaire sans obstruction de l'arche aortique ; Classe 2, lésion biventriculaire avec obstruction de l'arche aortique ; Classe 3, lésion

univentriculaire sans obstruction de l'arche aortique ; Classe 4, lésion univentriculaire avec obstruction de l'arche aortique. Ces caractéristiques anatomiques peuvent avoir différentes conséquences sur le développement cérébral et cognitif de l'enfant atteint de CC, qui seront d'ailleurs discutées dans les prochaines sections. Les lésions univentriculaires (Hoskoppal et al., 2010; Huisenga et al., 2020) et l'obstruction de l'arche aortique (Claessens et al., 2019; Feldmann et al., 2020) sont généralement associées à davantage d'atteintes cérébrales et neurodéveloppementales.

Dans le cadre de cette thèse, l'attention sera portée sur les enfants atteints de CC dites complexes, soit celles pour lesquelles une intervention chirurgicale est nécessaire dans les premiers mois de vie, et ce, en raison du risques auxquelles elles sont associées pour le neurodéveloppement.

1.2. Étiologies

Dans leur grande majorité, les troubles cardiaques affectant les nouveau-nés sont attribuables à une combinaison de facteurs génétiques et environnementaux (Goldmuntz et al., 2013). Parmi les facteurs environnementaux, il est reconnu que certains agents tératogènes (antiépileptiques, triméthadione, isotrétinoïne, lithium et alcool), infectieux (p. ex. rubéole) et certaines conditions de la mère (p. ex. diabète maternel) sont susceptibles d'entrainer une malformation s'ils sont présents dans les deux premiers mois de gestation (Fahed et al., 2013). Or, il semble que les facteurs génétiques aient un effet prédominant dans l'apparition de ce type de maladie, bien que l'identification précise de l'anomalie demeure incertaine (Gelb et Chung, 2014). On a néanmoins longtemps observé que les défauts chromosomiques et les affections monogéniques peuvent causer une cardiopathie, souvent dans le contexte d'une maladie multisystémique. Par exemple, le syndrome de Turner et le syndrome de Down sont liés à une incidence accrue de CC (Hoffman, 2018).

1.3. Diagnostic et prise en charge

Le diagnostic de CC est posé avant la naissance chez 50 à 70% des enfants par l'entremise d'une échographie fœtale (Bravo-Valenzuela et al., 2018; Lytzen et al., 2020; McQuillen et al., 2010; Suard et al., 2020; Waern et al., 2021). Dans la période prénatale, les CC sévères peuvent maintenant être diagnostiquées avec une précision aussi haute que 98 % dans les centres expérimentés (Qiu et al., 2020), permettant d'optimiser la prise en charge précoce. L'utilisation croissante de méthodes complémentaires telles que l'imagerie par résonance magnétique cardiaque, l'électrocardiographie fœtale et la magnétocardiographie fœtale contribue également à affiner le diagnostic et, par conséquent, à préciser et guider le plan d'intervention chirurgicale (Donofrio et al., 2014). Lorsqu'elle n'est pas identifiée dans la période prénatale, la CC complexe est souvent identifiée dans la période néonatale, permettant d'émettre un diagnostic dès la première semaine (46 %) ou année (88 %) suivant la naissance (Hoffman et Kaplan, 2002). En raison de la grande variété de CC, l'avenue de traitement varie et dépend du type particulier d'anomalie et de l'importance du dysfonctionnement qui lui est attribuable. Plus d'un quart de ces malformations cardiaques sont dites complexes, c'est-à-dire qu'elles requièrent une ou plusieurs interventions par cathéter et/ou par chirurgie pour assurer la survie de l'individu (Oster et al., 2013).

L'amélioration de la précision diagnostique et des techniques chirurgicales de pointe permettant de corriger ou pallier les malformations cardiaques font en sorte que le pronostic cardiaque à long terme est maintenant excellent (Latal, 2016). En contrepartie, des complications non cardiaques sont fréquentes dans cette population, et touchent principalement le neurodéveloppement.

1.4. Développement cérébral et facteurs de risque chez les CC

Ces vulnérabilités neurologiques peuvent résulter d'une combinaison de facteurs biologiques interagissant avec des facteurs environnementaux. Biologiquement, le développement *in utero* du cœur

et du cerveau se produit en interdépendance et simultanément, suivant un processus morphogénétique complexe (McQuillen et al., 2010). Ainsi, le développement cérébral dépend du cœur et du système sanguin pour l'apport en oxygène et en nutriments alors que le cœur dépend du système nerveux autonome pour son innervation et ses fonctions de pompage. Chez un fœtus avec CC, le développement cardiaque anormal peut donc affecter le développement cérébral, puisque celui-ci requiert des ressources métaboliques importantes délivrées par l'entremise du système cardio-vasculaire. Selon la sévérité de la CC, l'hypoxie qui en découle pourrait possiblement avoir un effet délétère sur le cerveau en développement. Ainsi, des facteurs prénataux (p. ex. hypoxie chronique ou intermittente) et périnataux (p. ex. poids à la naissance, interventions chirurgicales, convulsions) peuvent mener à des altérations cérébrales telles qu'une réduction du volume cérébral, des lésions de la matière blanche et une immaturité cérébrale, présentes dès la naissance (Birca et al., 2016; Hansen et al., 2017; Owen et al., 2011), et même en période prénatale (Limperopoulos et al., 2010; Rollins et al., 2021; Sun et al., 2015).

Par ailleurs, des anomalies génétiques ont non seulement été identifiés comme cause potentielle de la CC, mais aussi comme facteur de risque sur le plan cérébral. Certains syndromes génétiques connus (p. ex. syndrome de Down), associés à la fois à des déficits neurocognitifs et à un risque accru de CC, illustrent bien ce phénomène. Cependant, même en l'absence de tels syndromes, certaines mutations et polymorphismes génétiques contribueraient à augmenter la le risque d'anomalies neurologiques des enfants atteints de CC (Gaynor, Kim, et al., 2014; Gaynor et al., 2009; Homsy et al., 2015).

D'autres facteurs de nature environnementale, tels que le statut socio-économique ou sociodémographique et le stress parental, sont également associés à davantage d'anomalies cérébrales et neurdéveloppementales chez les enfants avec CC (Bucholz et al., 2020; Favilla et al., 2021; Hogan et al., 2020; Wu et al., 2020). Ces altérations cérébrales peuvent persister au cours de l'enfance et de

l'adolescence et sont associées susceptibles de se traduire en difficultés cognitives au cours du développement. Le profil neuropsychologique associé à la CC sera d'ailleurs détaillé à la section 2.2.

1.5. La Clinique d'investigation neuro-cardiaque du CHU Sainte-Justine

La clinique d'investigation neuro-cardiaque (CINC) du CHU Sainte-Justine a été créée en 2013 à la suite de la publication des lignes directrices de l'*American Heart association* (AHA) et l'*American Academy of Pediatrics* (AAP; Marino et al., 2012). L'AHA/AAP recommande un suivi neurodéveloppemental précoce et systématique de tout enfant né avec une CC nécessitant une chirurgie dans les premiers mois de vie. Basé sur ces recommandations, l'équipe multidisciplinaire offre des évaluations systématiques et standardisées à partir de l'âge de 4 mois. Le programme de suivi développemental de la CINC a pour mission dépister précocement les difficultés et retards développementaux afin de coordonner et faciliter l'accès aux traitements. La CINC est fondée sur un modèle interdisciplinaire incluant un fort arrimage recherche et clinique, permettant de bien caractériser la population, d'optimiser les évaluations en fonction de l'âge et du développement de l'enfant, ainsi que d'améliorer les interventions offertes.

En étroite collaboration avec la CINC et en lien avec les recommandations de l'AHA/AAP, la présente thèse a pour but de caractériser la trajectoire développementale des enfants nés avec une CC complexe et de dresser leur profil neuropsychologique à l'âge préscolaire afin de mieux comprendre les besoins à ce moment clé de leur développement. Ceci permettra potentiellement une détection précoce des enfants les plus à risque sur le plan neurodéveloppemental, d'optimiser la prise en charge clinique et, ultimement, l'amélioration du pronostic. L'étude du neurodéveloppement en contexte de CC nécessite toutefois une compréhension approfondie du neurodéveloppement de l'enfant de manière globale, de même que des troubles neurodéveloppementaux pouvant survenir (article 1). Ainsi, la prochaine section se concentrera sur le

neurodéveloppement de l'enfant et les difficultés susceptibles de survenir suite à une malformation cardiaque.

2. Neurodéveloppement de l'enfant

2.1. Développement cognitif de l'enfant et troubles neurodéveloppementaux

Le développement cognitif de l'enfant est caractérisé par des changements constants et importants, prenant appui sur la maturation cérébrale et l'environnement dans lequel il évolue (Ismail et al., 2017). Il s'agit d'un processus continu, qui s'entame dès les premières semaines de gestation et qui se poursuit et se raffine jusqu'au début de l'âge adulte (Anderson et al., 2019a). Cette période s'accompagne également de progrès considérable dans le fonctionnement cognitif et social de l'enfant.

Chez l'enfant dit neurotypique, ce développement cognitif suit un patron de maturation allant d'habiletés relativement simples et rudimentaires à un fonctionnement complexe et élaboré. Il est ainsi attendu que certaines fonctions se développent tôt dans la vie alors que d'autres, bien qu'elles émergent dans la petite enfance, seront en pleine expansion un peu plus tard. À titre d'exemple, le développement des fonctions langagières – qui fera l'objet de l'annexe II – s'entame avant même la naissance et peut être divisé en quatre grandes étapes chronologiques. La première étape s'effectue au cours de la première année de vie et représente la période préverbale. Durant cette période, l'enfant reconnaît certains mots et essaie de les verbaliser : il associe les mots et les utilise progressivement dans un contexte approprié. Vers deux ans, il maitrise les bases du langage : il utilise plusieurs types de mots (nom, verbe, etc.), s'exprime avec de courtes phrases (2-3 mots) et parvient à répondre à des questions simples. De deux à six ans, la compréhension et l'évocation lexicale vont croitre

exponentiellement, et ce, tant dans les systèmes phonologique, syntaxique, sémantique que pragmatique (AlSalehi et Alhifthy, 2020; Plaza, 2004; Plaza, 2014). En absence de retard ou de troubles de langage, ces processus vont se poursuivre et se raffiner au long de la vie.

L'étude des troubles neurodéveloppementaux, dont les systèmes de classification feront objet du premier article de cette thèse (Gaudet et Gallagher, 2020), doit donc s'opérer dans une approche développementale de l'enfant, c'est-à-dire en considérant le stade chronologique (AlSalehi et Alhifthy, 2020; Misheva, 2020). Les retards importants pouvant survenir en bas âges étant souvent annonciateurs de troubles neurodéveloppementaux, il s'avère essentiel de dépister rapidement les individus à risques de difficultés afin de leur offrir des interventions ou traitements appropriés.

Bien que certaines habiletés s'acquièrent généralement avant d'autres, le développement cognitif doit également être vu dans une perspective globale où les différentes fonctions cognitives interagissent entre elles pour supporter les progrès de l'enfant. Ainsi, le jeune enfant réalise des apprentissages différents dans tous les domaines simultanément et non de manière isolée (Anderson et al., 2019b). Par exemple, le développement adéquat des fonctions langagières supportera le développement social de l'enfant qui entrera plus aisément en relation avec autrui, et favorisera les apprentissages scolaires tels que la lecture et l'écriture. À leur tour, le développement de la lecture et l'augmentation des interactions sociales permettront à l'enfant d'affuter ses habiletés langagières. À l'inverse des difficultés dans une sphère peuvent avoir un effet en cascade sur d'autres domaines développementaux (Cassidy et al., 2016; Misheva, 2020). Cette influence mutuelle supporte la pertinence d'adopter une vision globale du développement neuropsychologique de l'enfant, et ce, tant pour le chercheur que le clinicien.

2.2. Profil neurodéveloppemental de l'enfant atteint de CC

Considérant les atteintes cérébrales mentionnées précédemment, les enfants atteints de CC présentent un risque plus élevé de déficits cognitifs et de difficultés scolaires par rapport à leurs pairs en bonne santé. Bien que la prévalence et la sévérité varient selon le type de CC, il est maintenant reconnu que la moitié des enfants présenteront des déficits moteurs et/ou cognitifs au cours de leur vie et nécessiteront des services éducatifs spécialisés (Latal, 2016; Marino et al., 2012; Riehle-Colarusso et al., 2015). Plus spécifiquement, les jeunes enfants atteints de CC présentent généralement un fonctionnement intellectuel légèrement plus faible que leurs pairs (Brosig et al., 2007; Martinez-Biarge et al., 2013) ainsi que des retards neurodéveloppementaux spécifiques touchants notamment la motricité globale et fine (39 et 49% respectivement; Majnemer, Limperopoulos, Shevell, Rosenblatt, et al., 2006) et les habiletés langagières (20-30%; Latal, 2016). Ce profil neurodéveloppemental se modifie typiquement avec l'âge, certaines difficultés étant davantage présentes lors de la petite enfance alors que d'autres apparaissent plutôt à l'âge scolaire avec le développement de l'enfant et l'augmentation des demandes de l'environnement (Figure 1).

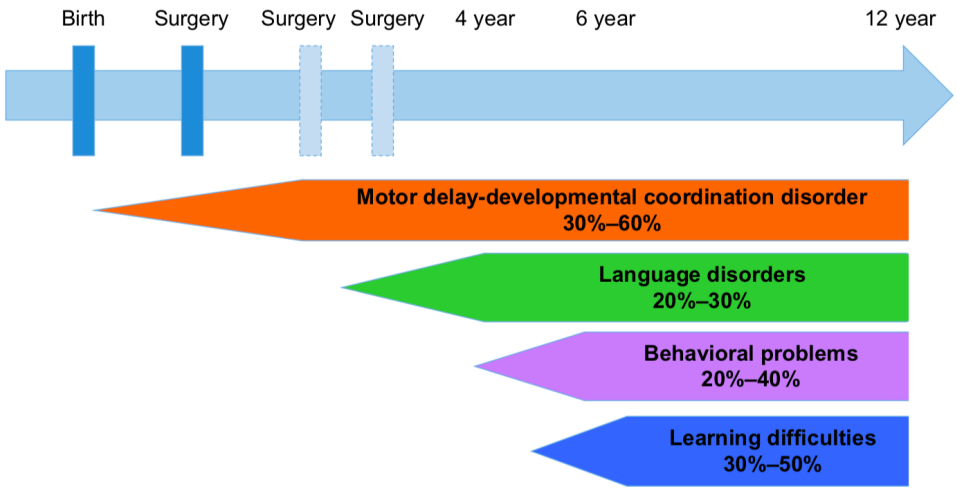

Figure 1. – Schéma des domaines de développement affectés chez les enfants avec CC, de l'apparition dans le temps et de la prévalence estimée. Tirée de Latal (2016)

L'ensemble des atteintes neurologiques survenues très tôt dans la vie (avant la naissance ou à la suite d'interventions chirurgicales dans la petite enfance) ne se manifeste donc pleinement que lorsque des tâches relativement plus complexes doivent être mises en œuvre plus tard dans l'enfance, notamment lors de l'entrée à l'école (Kharitonova et Marino, 2016).

Les fonctions cognitives dites d'ordre supérieur, tel que les fonctions exécutives (FE), ont été identifiées comme un domaine spécifiquement altéré chez les enfants d'âge scolaire et les adolescents atteints de CC (Calderon et al., 2019; Cassidy et al., 2015; Jackson et al., 2021; Kharitonova et Marino, 2016; Sanz et al., 2017; Sanz et al., 2018). Les FE consistent en un ensemble de processus neurocognitifs permettant de coordonner des d'actions en vue d'atteindre un objectif précis et de s'adapter à une situation complexe ou nouvelle (Meltzer, 2018). Celles-ci incluent l'autorégulation des pensées, la flexibilité mentale, l'inhibition des actions impulsives et automatiques ainsi que les capacités d'organisation et de planification (Guy et al., 2004). Les FE jouent par ailleurs un rôle critique dans le développement social et les apprentissages scolaires (Beauchamp et Anderson, 2010; Calderon et Bellinger, 2015; Calderon et al., 2019). Elles sont d'ailleurs plus étroitement associées au rendement académique que ne l'est le QI et s'avèrent être un prédicteur important des compétences en mathématiques et en lecture tout au long du parcours scolaire (Diamond, 2013; Diamond et al., 2007). Les fonctions attentionnelles sont elles aussi intimement liées aux FE et s'avèrent également fréquemment altérées chez les enfants avec CC. Chez les enfants d'âge scolaire, les seules études ayant employé des mesures objectives de l'attention mettent en lumière des difficultés au niveau de l'attention sélective (Miatton et al., 2007) et de l'attention soutenue (Bellinger et al., 2003; Hovels-Gurich et al., 2007; Kirshbom et al., 2005). Toutefois, à ce jour, très peu d'études ont utilisé des mesures directes du fonctionnement attentionnel et des questionnaires parentaux ou autorapportés, portants sur le comportement au

quotidien, sont généralement utilisés. Par l'entremise de ces questionnaires, des symptômes d'inattention et d'impulsivité ont été identifiés, tant chez les enfants d'âge préscolaire et scolaire (Gaynor, Ittenbach, et al., 2014; Sanz et al., 2017; Shillingford et al., 2008) qu'à l'adolescence et à l'âge adulte (Areias et al., 2013; Murphy et al., 2017). Les difficultés comportementales sont d'ailleurs très fréquentes (jusqu'à 40% des enfants avec CC) et se caractérisent par la présence de symptômes internalisés (anxiété, dépression, retrait social) et externalisés (hyperactivité, agressivité et opposition; Brosig et al., 2007; Cassidy et al., 2018; Marino et al., 2012). En accord avec les difficultés exécutives, attentionnelles et comportementales rapportées, les enfants avec CC ont trois à quatre fois plus de risques que la population générale d'atteindre les critères diagnostiques d'un trouble déficitaire de l'attention avec ou sans hyperactivité (TDAH; DeMaso et al., 2017; Hansen et al., 2012; Hovels-Gurich et al., 2007).

Les mécanismes responsables des difficultés comportementales sont assurément multifactoriels. En plus des difficultés exécutives et des lésions cérébrales pouvant y être associées, des facteurs parentaux tels que l'anxiété maternelle, l'état de stress post-traumatique de la mère et la surprotection contribuent certainement aux problèmes comportementaux de ces enfants (Latal et al., 2009) .

À cet effet, les familles d'un enfant avec CC sont confrontées à un stress psychologique significatif, quel que soit l'âge de l'enfant ou le type de CC (Wei et al., 2015). Un indice de stress parental élevé ainsi que des symptômes anxieux et dépressifs sont d'ailleurs souvent rapportés chez ces parents, bien qu'ils soient suspectés être sous-diagnostiqués, et perdureraient plusieurs années après la naissance de l'enfant (Golfenshtein et al., 2017). En effet, la détresse émotionnelle a été rapportée chez des parents d'enfants de tous âges, allant d'une journée de vie à 21 ans, touchant 25 à 50% d'entre eux (Woolf-King et al., 2017). En période néonatale, la santé précaire de l'enfant,

les interventions chirurgicales et les hospitalisations sont des sources de stress considérables pour les parents qui auront par la suite à composer avec la condition médicale de leur enfant et/ou les difficultés neurodéveloppementales, sociales, comportementales et académiques qui lui sont associées (Kaugars et al., 2018). Plusieurs parents rapportent du stress et un impact négatif de la condition médicale de l'enfant sur l'ensemble du fonctionnement familial (Kaugars et al., 2018). De plus, la santé psychologique des parents est significativement associée aux comportements de l'enfant (Majnemer, Limperopoulos, Shevell, Rohlicek, et al., 2006; Toren et Horesh, 2007), l'indice de stress parental étant fortement corrélé avec la présence de difficultés comportementales de l'enfant avec CC (Majnemer, Limperopoulos, Shevell, Rohlicek, et al., 2006; Visconti et al., 2002).

En somme, ces enfants sont vulnérables sur le plan neuropsychologique, comportemental et psychiatrique. Davantage d'études sont toutefois nécessaires pour mieux caractériser l'évolution et la stabilité de ces enfants sur le plan cognitif et par le fait même de mieux cibler le suivi et d'optimiser la prise en charge. L'article 2 de la présente thèse vise d'ailleurs à décrire la trajectoire neurodéveloppementale de ces enfants, de la petite enfance jusqu'à l'âge préscolaire. Par ailleurs, en dépit d'une connaissance fleurissante sur le neurodéveloppement en contexte de CC, l'étude du fonctionnement social des enfants atteints de CC demeure peu étudiée, particulièrement à l'âge préscolaire.

3. CC et fonctionnement social

Les compétences sociales évoluent de la petite enfance à l'enfance et à l'adolescence, parallèlement à des périodes de développement neurologique rapide et important (Wiseman-Hakes et al., 2020). Elles ne représentent donc pas une qualité fixe, mais doivent être considérées comme une construction qui, en soi, marque le développement. Comme tout autre volet développemental, les attentes qui lui sont associées sont inhérentes à l'âge et au stade de développement de l'enfant.

L'étude des perturbations du fonctionnement social des enfants atteints de CC nécessite évidemment une compréhension du sain développement et fonctionnement social.

3.1. Développement sociocognitif de l'enfant

L'être humain est une espèce à caractère social unique et, à ce titre, les interactions sociales sont au cœur de ses activités (Blakemore, 2010). La compétence sociale, qui peut être définie comme l'efficacité d'un enfant à s'engager dans des interactions sociales avec autrui, en fonction de ce qui est attendu selon son âge (Junge et al., 2020) est essentielle à la formation et au développement de relations satisfaisantes et durables qui, à leur tour, sont essentielles au bien-être psychologique tout au long de la vie (Thompson et al., 2018). Le développement des compétences sociales commence dès les premières interactions du nourrisson et, à mesure qu'ils grandissent, les enfants sont confrontés à des contextes d'interaction diversifiés au-delà de l'environnement familial, et des interactions plus sophistiquées sont attendues de la part des enfants plus âgés (Junge et al., 2020). Pour être socialement efficaces ou compétents dans une variété de contextes, ils doivent ainsi maîtriser de nombreuses aptitudes qui sous-tendent la compétence sociale, tels que la régulation émotionnelle ou la communication sociale, qui peuvent également différer selon le stade de développement (Beauchamp et Anderson, 2010; Beaudoin et Beauchamp, 2020; Junge et al., 2020). De par sa complexité, le développement social est généralement conceptualisé dans une approche multifactorielle (Beauchamp, 2017). Ainsi, le *modèle d'intégration d'habiletés sociocognitives* (SOCIAL), élaboré par Beauchamp et Anderson (2010), offre une vision intégrative des facteurs déterminant la compétence sociale d'un enfant dans une perspective développementale (Figure 2). Par conséquent, la compétence sociale serait le fruit de l'interaction dynamique entre des facteurs internes (p. ex. âge, tempérament), externes (p. ex. niveau socioéconomique, culture), ainsi que les substrats neurobiologiques et les habiletés sociocognitives

qui interagissent ensemble pour façonner l'aptitude sociale lors du développement.

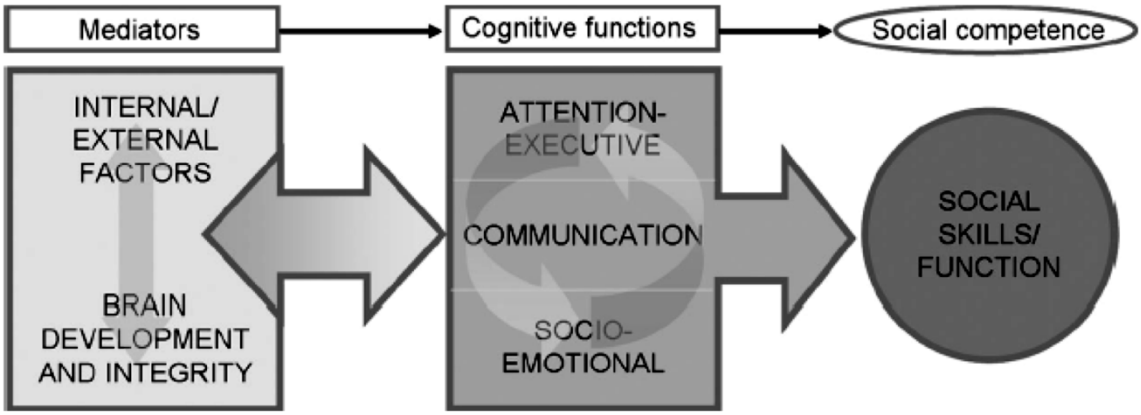

Figure 2. – Modèle d'intégration des habiletés sociocognitives. Tiré de Beauchamp et Anderson (2010)

Au cœur de ce modèle se trouvent les fonctions dites sociocognitives, qui comprennent les fonctions exécutives (p. ex. contrôle attentionnel, flexibilité cognitive, planification), la communication (p. ex. langage expressif ou réceptif) et la cognition sociale (p. ex. théorie de l'esprit, reconnaissance d'affects).

3.2. Développement sociocognitif de l'enfant atteint de CC

De par leur vulnérabilité sur le plan neuropsychologique, il a été suggéré que les enfants atteints de CC soient à risque sur le plan social (Bellinger, 2008). Or, en dépit de cette vulnérabilité et de l'importance indéniable de la sphère sociale dans le développement de l'enfant, l'intégrité des habiletés sociales des enfants atteints de CC reste relativement peu étudiée. À ce jour, la grande majorité des études s'étant penchées sur cette question a utilisé des questionnaires comportementaux. Par l'entremise de ces questionnaires, un taux plus élevé de difficultés socio-émotionnelles sont rapportés chez les enfants atteints de CC que dans la population générale (Abda et al., 2019; Clancy et al., 2019; Karsdorp et al., 2007; McCusker et al., 2013). Plus spécifiquement, les parents et les enseignants ont évalué les enfants atteints de CC comme étant renfermés

socialement, participant à moins d'activités sociales, n'étant pas acceptés par leurs pairs ou étant trop dépendants des autres (McCusker et al., 2013; Miatton et al., 2007; Schaefer et al., 2013; Sigmon et al., 2019). Ces enfants sont par ailleurs à haut risque de présenter des symptômes du trouble du spectre autistique (TSA) ou d'en rencontrer les critères diagnostic (Bean Jaworski et al., 2017; Razzaghi et al., 2015; Sigmon et al., 2019; Tsao et al., 2017).

Les mécanismes et facteurs responsables de telles difficultés restent à être élucidés. Néanmoins, même en l'absence d'un diagnostic formel de TSA, la vulnérabilité du fonctionnement social de ces enfants peut être attribuée à des déficits de la cognition sociale. Ainsi, des difficultés au niveau du traitement émotionnel et de la théorie de l'esprit ont été mises en lumière chez des enfants d'âge scolaire (7 ans; Calderon et al., 2014; Calderon et al., 2010) et des adolescents (Bellinger et al., 2015; Bellinger et al., 2011) atteints de CC complexe.

Alors que l'âge préscolaire est une période sensible au développement de certaines composantes de la cognition sociale telle que la théorie de l'esprit, aucune étude n'a, à notre connaissance, fait état de la cognition sociale les jeunes enfants atteints de CC à cet âge. Puisque l'entrée à l'école est une période où les compétences sociales sont sollicitées de manière exponentielle, et puisque les enfants atteints de CC sont à risque sur divers aspects de leur développement sociocognitif, il s'avère essentiel d'étudier la cognition et la compétence sociale de ces enfants dès l'âge préscolaire, ce qui est d'ailleurs l'objectif du troisième article de la présente thèse.

Chapitre 2 : Objectifs et hypothèses

L'objectif général de la présente thèse consiste à dresser le profil neuropsychologique des enfants nés avec une CC complexe d'âge préscolaire, afin de mieux cibler leurs besoins et d'orienter leur prise en charge au moment de l'entrée à l'école. Cet objectif a été exploré par l'entremise de trois objectifs secondaires, lesquels sont présentés à travers trois articles.

Article 1 : L'objectif du premier article était de décrire les troubles neurodéveloppementaux susceptibles de se manifester chez l'enfant et d'en présenter les différents systèmes de classifications. Considérant la nature de ce premier objectif, qui consiste à faire état des connaissances actuelles, aucune hypothèse n'y est associée. Ce travail a abouti en un chapitre publié dans le *Handbook of Clinical Neurology* (2020).

Article 2 : Le second article avait pour but de décrire le profil neuropsychologique et langagier des enfants atteints de CC âgés de 5 ans, de dresser la trajectoire développementale du fonctionnement cognitif et langagier entre 1 et 5 ans, ainsi que d'identifier des marqueurs précoces des difficultés mesurées à l'âge préscolaire. Il était attendu que les enfants ayant reçu une opération cardiaque en jeune âge présentent des difficultés affectant plusieurs domaines neurodéveloppementaux, et que le fonctionnement en bas âge (c.-à-d. à 1 ou 2 ans) soit prédictif du fonctionnement ultérieur (c.-à-d. à 5 ans). Les résultats de cette étude ont été publiés dans *The Journal of Pediatrics* (2021).

Article 3 : Finalement, le troisième article consistait à décrire le fonctionnement social des enfants de 5 ans atteints de CC. Plus précisément, cet article visait à faire état de la cognition et de la compétence sociale à l'âge préscolaire et à étudier la contribution des fonctions sociocognitives

sous-jacents à la compétence sociale dans cette population. Cet article est maintenant en révision dans le journal *Neuropsychology*.

Chapitre 3 – Article 1

Description and classification of neurodevelopmental disabilities (article 1)

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Chapitre publié dans *Handbook of Clinical Neurology*, Vol. 173 (3rd series). Neurocognitive Development: Normative Development https://doi.org/10.1016/B978-0-444-64150-2.00001-0

Abstract

Classification is a tool for communication so that when clinicians, policy-makers, or researchers refer to some features they are talking about the same thing. The classification of neurodevelopmental problems in children and adolescents is crucial to better understanding their prevalence and the intervention or treatment that should be provided. However, such classification might be challenging, especially when developmental aspects have to be taken into account. This chapter aims to provide a better understanding of the classification of neurodevelopmental disabilities. Thus, we provide an overview of the different classification systems that are most commonly used, such as the well-known Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD). Moreover, we address opportunities and challenges inherent to the classification of neurodevelopmental disorders and the implications for clinical practice and research areas.

Keywords: Classification system; Neurodevelopmental disabilities; Diagnostic and statistical manual of mental disorders (DSM); International classification of diseases (ICD).

Despite major advances in medicine, there is still a lack of valid biomarkers to accurately discriminate and diagnose most neurodevelopmental disorders (NDDs). Currently, NDD's diagnosis relies mainly on behavioral and cognitive manifestations. Different diagnostic scoring systems and classification algorithms have been developed over time and are used worldwide. NDDs classification and diagnosis may differ depending on the algorithm used. Despite their differences, almost all algorithms share the concept that NDDs arise in the developmental period and impair the child's development and functioning. NDDs can hence be defined as a heterogeneous set of chronic conditions, characterized by a delay or an impairment in cognition, communication, behavior, and/or motor development, having functional impacts in school or in social, family, or daily life (Mullin et al., 2013; Jeste, 2015).

Classification Systems for NDDs

Two of the most widely used classification systems are the Diagnostic and Statistical Manual of Mental Disorders (DSM), developed by the American Psychiatric Association (APA, 2013) and the International Classification of Diseases (ICD), developed by the World Health Organization (WHO, 2018). Both systems have a section on NDDs and provide criteria to identify different subtypes and to improve the accuracy of the diagnosis. Although the DSM is mainly used in North America and the ICD in Europe, these tools share internationally recognized references and consensus on diagnostic definitions, which provide guidance in informing and shaping clinical decisions at various levels. These levels include etiologic evaluation, rehabilitation referrals, service needs provision, programming access, counseling, and prognostics.

The first version of the ICD was published at the end of the nineteenth century and has been regularly updated since then. It is now published in 41 languages and is used for a wide range of purposes, including morbidity and mortality statistics, health services reimbursement, and

healthcare planning (Carr, 2015). Disorders of mental health were included in the ICD only since 1949 (IDC-6; WHO, 1962). The eleventh version, released in June 2018, includes a section on NDDs (WHO, 2018). In this latest version, NDDs are defined as impairments in the acquisition or exaction of functioning, either in the intellectual, social, or motor coordination areas (WHO, 2018).

The DSM is a North American classification system widely used internationally for both clinical diagnosis and research activities. Since its first publication in 1952, the DSM has been periodically revised until its fifth and most recent version was published in 2013. The writing of this fifth edition differed from previous editions. Specifically, health professionals and scientists defined the content first, and the final version incorporated input from hundreds of individuals, including numerous stakeholders, patients, families, lawyers, consumer organizations, and advocacy groups (APA, 2013).

According to the definition provided by the APA, NDDs usually arise in early childhood (preschool age) and involve significant difficulties in the social, academic, or personal functioning of the child (APA, 2013). Differences between NDDs can be more or less specific since in most cases differences are not clear-cut and it is not easy to segregate conditions. Clinical presentation is diversified and, among other features, may include deficits, delays in development, repetitive behaviors, or hyperactivity. Given this heterogeneity, the use of specifiers is needed to better characterize the clinical presentation, in terms of etiology (e.g., is it associated with a known medical condition, genetic susceptibility, or environmental factors), severity (from mild to severe), and symptomatology. More than one NDD may affect the same individual. The co-expression of two or more NNDs of different etiology and severity in the same child is often associated with more functional limitations and requires specific interventions, emphasizing the importance of an accurate diagnosis (APA, 2013).

Although the ICD and DSM classification systems are generally harmonized, the presence of two major classifications of mental disorders might sometimes represent a hurdle from a clinical standpoint or a scientific perspective. Indeed, it has been previously reported that using the two systems on the same patient population may occasionally lead to different diagnoses (APA, 2013). As a consequence, scientific results may be harder to replicate and, more importantly, impact treatment plans. To avoid discrepancies and harmful consequences, the APA and the WHO have agreed to harmonize their approaches and to collaborate closely in the next editions of the DSM and ICD. The next editions should thus reflect a consensual and harmonized understanding of NDD diagnosis and impact clinical approaches.

It should be noted that the ICD and DSM are not the only existing NDD classification systems. There remains some controversy in the clinical and scientific community related to the limited evidence on the validity of the current diagnostic categories (Carr, 2015). As a consequence, parallel classification systems have recently emerged, such as the Research Domain Criteria framework (RDoC), developed by the National Institute of Mental Health (NIMH) in 2009. Instead of being based on a categorical model, the RDoC aims to uncover and specify underlying mechanisms that influence cognitive, affective, and behavioral functioning, through a better understanding of the neurobiologic abnormalities that affect development throughout the lifespan (Patel et al., 2018), in the context of a neurodevelopmental perspective (Casey et al., 2014).

Currently, the RDoC identifies six major domains of functioning that are presumed to underlie core symptoms of psychopathology: cognition (e.g., attention, perception, language), positive (e.g., reward seeking) and negative (e.g., fear, anxiety) valence systems, social process systems (e.g., attachment, social communication), arousal and regulatory systems (circadian rhythms), and the sensorimotor system (National Institute of Mental Health, 2018). Autism research is a good example of how RDoC can be used while searching for biomarkers or specific

neural circuitry abnormalities underlying NDDs (Campos et al., 2018; Preckel and Kanske, 2018). In a recent review, Hennesey and colleagues explain the involvement of the amygdala in RDoC domains (negative valence systems, positive valence systems, cognitive systems, social processes, and arousal and regulatory systems) and the association between amygdala dysfunction and altered development with autism symptomatology (e.g., social deficit, rigidity of thinking, impaired attention; Hennessey et al., 2018). The use of the RDoC framework, therefore, exposes a relationship between an altered brain function or structure and the phenotype related to a NDD.

Benefits and Challenges Related to the Use of Classification Systems

Although there are some differences and discordances between the classification systems, they are essential as they provide a common language through which clinicians and researchers communicate with one another. Moreover, they allow for the application of research to clinical problems and provide guidance to clinical practice, explanations to patients, and criteria for clinical reimbursement (Carr, 2015). Classification systems also facilitate the development of epidemiologic information about the incidence, prevalence, and course of disorders, which can be used to plan services (Garralda, 2017). However, since diagnoses need to adapt and change in the light of new knowledge and expertise, the fact that diagnostic criteria change over time may lead to concerns about comparability between past and future studies (Van Herwegen et al., 2015). A recent example relates to important discussions raised since 2013, with the publication of the new DSM-V. This version groups together the five pervasive development disorders (autism, Asperger's syndrome, pervasive developmental disorder-not otherwise specified, Rett's syndrome, child disintegrative disorder) into a single diagnosis of autism spectrum disorder, whereas they were treated individually in the DSM-IV (Nemeroff et al., 2013; Kulage et al., 2014; Maenner et al., 2014).

The Diagnosis of NDDs: A Challenging Process

Even though the accurate recognition of a child's NDD is essential at many levels, it may also be challenging in clinical practice for several reasons. Diagnostic criteria for NDDs are based on a constellation of behavioral or cognitive manifestations that contribute to their clinical heterogeneity and represent an important clinical challenge. For one NDD subtype, the symptomatology regularly varies between affected individuals (Van Herwegen et al., 2015), while several clinical expressions overlap between different subtypes (McCary et al., 2012). In addition, NDDs are not always mutually exclusive and having one may increase the likelihood of having another. Hence, especially since these disorders often overlap, a differential diagnosis is necessary to provide appropriate services. For example, a 3-year-old child with language impairment may experience social integration difficulty at day care or school, which increases their communication disability and limits the development of adaptive behavior. As a consequence, if the NDD (language disorder) is not accurately diagnosed at the earliest stage, the patient's symptoms at age five might be seen as a different subtype of NDD, such as autism spectrum disorder or behavioral disorder (Toppelberg and Shapiro, 2000).

Many factors contribute to the significant heterogeneity within each subtype of NDD (intraclass heterogeneity). Age, neurologic development, maturation, mode and timing of presentation, etiology, and environmental modifiers are among the factors contributing to this heterogeneity and constitute a challenge for the clinician and the care team. Variability in the amount of support and intervention required, challenges faced by the patient and family, and long-term outcomes also factor in the classification of NDD. In addition, given that the first 18 years of life span the period during which the most profound changes occur in physical, cognitive, and social development, the predominant signs and symptoms of atypical development will vary depending on the age of the child, which must be accounted for. The developmental trajectory and

expectations associated with maturation imply that the manifestation of most NDD subtypes evolves over time and the clinical expression of NDDs differs in relation to the developmental process and from one individual to another (Racine et al., 2013; Ball and Karmiloff-Smith, 2015).

Conclusion

There is an international consensus for the definition of NDDs inherent in the two main classification systems used in the United States and Europe even if there is variety within the available tools. Despite a certain amount of heterogeneity, early identification of NDDs is essential to allow for access to specialized healthcare services at an early stage to promote optimal neurodevelopmental and functional outcomes. Since lifelong morbidity is often associated with a NDD diagnosis, additional medical, rehabilitation, educational, occupational, and supportive care are usually needed and may place a burden on the individual, the family, and society (Shevell, 2010).

Better consensus among classification systems is expected in the future which will be valuable to clinical and research fields. Classification will certainly remain an arduous task, in particular because of the implicit diversity in the clinical presentation of these disorders. This challenge is also significant given the presence of different schools of thought, each offering strong theoretical models that are difficult to integrate. Young adults with NDDs require particular consideration, as the issue of transition from the pediatric to the adult-oriented healthcare system, remains a challenge in clinical practice, and should be taken into account (Patel and Greydanus, 2011). Clinical awareness and judgment (Shevell, 2010) and close monitoring of the clinical trajectory over time using a dynamic approach is essential to deal with the clinical heterogeneity of NDDs and to assure optimal management of NDD subtypes (Thomas et al., 2009).

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Chapitre 4 – Article 2

Neurodevelopmental outcome of children with congenital heart disease: a cohort study from infancy to preschool age (article 2)

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Article publié dans *The Journal of Pediatrics* (2021). https://doi.org/10.1016/j.jpeds.2021.08.042

Objective : To characterize the neuropsychological outcome of children with congenital heart disease (CHD) at age 5 years; the stability of cognitive and language abilities across childhood; and to identify early neurodevelopmental markers of neuropsychological outcomes in these children.

Study design : Five-year-old children (n = 55) with complex CHD were assessed using standardized and comprehensive neuropsychological measures. Stability of language and cognitive performance was assessed by comparing standardized scores between ages 1, 2, and 5 years old. Association between 5-year-old skills and scores obtained in early childhood was studied to identify potential early markers of preschool performance. Receiver operating characteristic curves were used to evaluate the classification accuracy of Bayley Scales of Infant Development, Third Edition scales in identifying later impairments.

Results: At age 5 years, our cohort obtained scores significantly below the norms on most developmental domains, with 35% to 65% of participants showing impaired short-term/working memory, attention, and preacademic skills. Developmental patterns measured between ages 1 and 5 years were different for cognitive and language domains, with a decline with age for cognitive functioning and stable results for expressive language. The Bayley Scales of Infant Development, Third Edition language scores at age 2 years provided good predictive value in identifying children with impaired language at age 5 years.

Conclusions: In our cohort, we found a high prevalence of impairments affecting higher-order cognitive domains. Although language difficulties can be detected as early as 2 years of age, other neuropsychological impairments, such as attention and pre-academic skills, only appear later during development, which reinforces the need for long-term monitoring and systematic assessment before school entry.

Keywords

congenital heart disease

children

preschool

neurodevelopmental outcomes

Abbreviations

ADHD – Attention deficit hyperactivity disorder

AUC – Area under the curve

CELF-4 – Clinical Evaluation of Language Fundamentals, Fourth Edition

CHD – Congenital heart disease

CINC – Clinique d'Investigation Neuro-Cardiaque

BSID-III – Bayley Scales of Infant Development, Third Edition

ICU – Intensive care unit

ROC – Receiver operating characteristic

WPPSI – Wechsler Preschool and Primary Scale of Intelligence

Technological advancements in medical and surgical care have led to improved survival rates of infants with complex congenital heart disease (CHD; Hoffman et al., 2004; Marelli et al., 2014; van der Linde et al., 2011). However, these improvements have been associated with alarming rates of comorbidities and long-term consequences in survivors, with neurodevelopmental disabilities affecting approximately one-half of surviving children (Latal, 2016; Marino et al., 2012). Children with complex CHD are at higher risk of motor, language, and cognitive delays as well as behavioral problems (Howell et al., 2019; Kharitonova et Marino, 2016; Liamlahi et Latal, 2019). These neurodevelopmental disabilities are in turn associated with high rates of academic underachievement, special education services use, psychosocial and affective maladjustment, as well as reduced earnings and employment potential in adulthood (Cassidy et al., 2018; Cohen et Earing, 2018; Kaugars et al., 2018; Latal et al., 2009; Mulkey et al., 2016). Although major impairments (eg, intellectual disability, severe motor, and language disorders) are often detected during early childhood, other neurodevelopmental dysfunctions (eg, learning disabilities, attention and executive deficits) become more salient when children grow older (ie, at preschool or school ages), when environmental demands exceed the developmental abilities of the child. This is of particular clinical interest because a successful first few years of school has been associated with better long-term academic, social, and economic outcomes (Entwisle et al., 2005). Despite growing awareness of neurodevelopmental impairments in children with CHD in early childhood (Brosig et al., 2018; Fourdain, Simard, et al., 2020; Fourdain et al., 2019; Hicks et al., 2016; Mussatto et al., 2014), and at school age (Bellinger et al., 2003; Calderon et al., 2010; Calderon et al., 2014; Cassidy et al., 2015, 2016; Hövels-Gürich et al., 2002; Hövels-Gürich, 2008; Hovels-Gurich et al., 2007), less is known regarding the global neuropsychological profile and the emergence of specific impairments in children with CHD in the preschool period.

Previous studies in preschoolers with CHD highlighted lower IQ than the general population, poorer fine and gross motor performance, and lower expressive language (Bellinger et al., 1999; Brosig et al., 2013). However, few studies have investigated higher-order cognitive functions in these children around the age of 5 years (Bellinger et al., 1999; Brosig et al., 2013; Calderon et al., 2012), or the stability of their neuropsychological profile over time (Brosig et al., 2018; Creighton et al., 2007; Naef et al., 2019). Furthermore, studies examining the predictive value of early neurodevelopmental assessment on later neuropsychological outcomes in the CHD population are scarce. It is of clinical interest to characterize the detailed neuropsychological profile of children with CHD before school entry and identify potential predictive markers of neurodevelopmental outcomes to provide more appropriate and personalized interventions to these children and their family and identify children at higher risk of neurodevelopmental problems.

In this study, we thus aimed to characterize the detailed neuropsychological profile of children with CHD at preschool age (5 years); elucidate the developmental patterns of cognitive and language abilities in our cohort between 12 months and 5 years; and identify early markers predictive of cognitive and language impairments at preschool age. It was hypothesized that preschoolers with CHD would exhibit impairments on several cognitive domains, notably attention, executive functions, language, and pre-academic skills. It was also expected that language deficits would partly resolve with development, as seen in younger children (Fourdain et al., 2019). Finally, we hypothesized that impairments at age 5 years could be identified through 1- to 2 -year-old assessments using the, Bayley Scales of Infant Development, Third Edition (BSID-III).

Methods

Five-year-old patients followed at our cardiac neurodevelopmental clinic, the *Clinique*

d'Investigation Neuro-Cardiaque (CINC), of the Sainte-Justine University Hospital Centre were recruited to receive an interdisciplinary evaluation (mean age 5.55 ± 0.26 years). All participants recruited for this cohort study were born between December 2012 and July 2015 and presented various CHDs (Table 1 shows detailed demographic and clinical information). As patients at the CINC, all have been enrolled in the systematic, multidisciplinary, and standardized developmental follow-up program since the age of 4 months (Fourdain, Caron-Desrochers, et al., 2020). During the completion of this study, 112 children with CHD followed at the CINC were 5 years of age. Of these, 19 did not meet our inclusion/exclusion criteria and were, thus, excluded (Figure 1). Inclusion criteria were having undergone at least 1 invasive procedure for correction or palliation of a major heart defect. Exclusion criteria were the presence of any comorbid genetic syndrome known to impact neurodevelopment (eg, Turner syndrome, Turner syndrome with 22q11 deletion) or a severe neurologic condition (eg, cerebrovascular accident). Children with nonsyndromic genetic mutations were included. Patients diagnosed with neurodevelopmental disorders that would preclude them from completing the standardized assessment (eg, autism spectrum disorder and/or severe global developmental delay) prior to their fifth birthday were also excluded from this study.

Procedures and materials

All children included in this study attended a single 4-hour visit at the Sainte-Justine University Hospital Center to participate in a cognitive and language evaluation. Assessments were performed by either a neuropsychology or a speech therapy graduate student blinded to the child's medical history, neurodevelopmental profile, and demographic information at the time of the assessment. As part of our systematic developmental follow-up program at the CINC, most participants previously received a neurodevelopmental examination using the BSID-III (Bayley, 2006) at both 12 and 24 months (n=46; mean ages 12.24 ± 0.43 months and 24.69 ± 1.10 months,

Figure 1). Each of these neurodevelopmental assessments were performed in a single visit by an accredited developmental psychologist or occupational therapist. All assessments were performed in French except for 2 children (1 English speaker and 1 English-Italian bilingual) for whom the assessment was completed in English.

Preschool 5-Year-Old Neuropsychological Assessment

Preschoolers, aged 5 years completed a comprehensive battery of standardized and validated tests. General intelligence was estimated using the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV) *General Ability Index* (GAI), which includes the following subtests: *Information* (general knowledge), *Similarities* (verbal reasoning, concept formation), *Block design* (nonverbal reasoning, visuospatial organization and *Matrix reasoning* (abstract reasoning, problem-solving). Language assessment included core subtests of the French-Canadian version of *Clinical Evaluation of Language Fundamentals edition* (CELF-4; Wiig et al., 2009). Expressive language was assessed using the main subtests of the CELF-4 battery (*Recalling Sentences, Word Structure, Expressive Vocabulary*), from which the *Expressive Language* index can be derived. Receptive language assessment included subtests of the CELF-4 (*Following Directions* and *Understanding Spoken Paragraphs*), used to measure more complex discourse, and the French version of the *Peabody Picture Vocabulary Test* used to measure receptive vocabulary knowledge (Dunn et al., 1993). Because the Peabody Picture Vocabulary Test has been shown to overestimate the language abilities of francophone preschoolers in Quebec (Thordardottir et al., 2011; Thordardottir et al., 2010) we used more recent norms based on a sample of monolingual French-speaking children in Montreal, age 5.5 year-old (Thordardottir et al., 2010). The assessment of pre-academic skills included a measure of phonological awareness (*Phonological Processing subtest,* NEPSY-II; Korkman et al., 2007) and measures of pre-math

abilities (*Numeration* and *Measurement* subtests, KeyMath-3; Connolly, 2007). We also assessed attention (Conners' Kiddie Continuous Performance Test – 2nd edition; Conners, 2015), verbal short-term and working memory (*Numbers* subtest, Children's Memory Scale; Cohen, 1997), and planning skills (*Tower* subtest, NEPSY 1st edition; Korkman, 1998). Parents also completed a locally developed demographic and developmental questionnaire. Data on a large number of medical variables (e.g., cardiac diagnosis, age at first surgery, length at Intensive Care Unit [ICU] stay) were collected from the patient's medical chart.

Statistical Analyses

Global Neuropsychological Profile of Children with CHD at 5-Years-old

Mean values of neuropsychological scores were compared with normative data from the general population using 1-sample t tests. For increased clinical relevance, scores obtained at age 5 years were categorized as being within the norm (within 1 SD or above the test mean), showing mild-to-moderate impairment (between 1 and 2 SD below the test mean), or severe impairment (≥2 SD below the test mean) range. A 1-sample χ^2 test was performed to examine whether the prevalence of neuropsychological impairment observed in our sample was significantly different from that expected in the general population. As a reference, in a normal distribution, 84.1% of a given sample should fall within or above the normal range, 13.6% within the mild-to-moderate impairment range (below −1 to −2 SD), and approximately 2.3% within the severe impairment (≤-2 SD) range. We performed comparisons across all the neuropsychological data using z scores, calculated by subtracting the score from the normative mean, divided by the normative SD. Z scores provide an average of 0 and a SD of 1, with higher scores indicating better performance. Z scores between −1 and −2 (corresponding to the 15th and 2nd percentile of typically developing children, respectively) were considered to reflect mild-to-moderate impairment, whereas z scores

below −2 were considered to reflect severe impairment.

Developmental Patterns of Cognitive and Language Abilities in Our Cohort Between 12 months and 5 Years

To measure the stability of cognitive and language functions across development, a 3 × 2 repeated measure ANOVA was performed with age (12 months vs 24 months vs 5 years) and neurodevelopmental domain (cognition vs language) as within subject factors. The cognitive domain was measured using the BSID-III cognitive score at ages 12 and 24 months, and using the WPPSI's general ability index score at age 5 years, whereas the global language domain was examined using the BSID-III global language score at 12 and 24 months, and the core language score obtained with the CELF battery at 5 years. We also compared the developmental stability of receptive and expressive language scores separately, using the BSID-III's receptive and expressive language scores obtained at ages 12 and 24 months, and the CELF's following directions subtest (receptive language) and expressive language index (expressive language) at 5 years of age. The Following Directions subtest was selected as a measure of receptive language because it is included in the same battery as the expressive language measure; thus allowing for more accurate comparison between the 2 language domains at age 5 years. Again, a 3 × 2 repeated measures ANOVA was performed, with age (12 months vs 24 months vs 5 years) and language modality (receptive vs expressive) as within subject variables. Effect sizes were estimated using partial eta squared (η_p^2) from the target variable.

Early Neurodevelopmental Markers of Higher Risks of Impairments at Age 5 Years

To determine the interrelatedness of different neuropsychological measures at 5-years and early cognitive abilities (BSID-III scores obtained at 12 and 24 months of age), we computed partial

correlations, controlling for the influence of gestational age, CHD anatomic classification (univentricular vs biventricular), ICU length of stay, and maternal education level. The strength of correlations were determined according to the Cohen criteria (Cohen, 1992). Receiver operating characteristic (ROC) curves were used to evaluate the classification accuracy of BSID-III scales in identifying impairments (≤-1 SD) at preschool age. An area under the curve (AUC) value of .9-1 is considered excellent, .80-.89 is good, and .70-.79 is fair. Values below .70 are poor, and tests with values close to .50 are of no value (Carter et al., 2016). The optimal cut point (based on the best combination of sensitivity and specificity) was calculated with the Youden index.

The SPSS v 25 (IBM) was used for statistical analyses. All statistical tests were 2-tailed with a significance level set to $P < .05$. To minimize the likelihood of type I errors, correction for multiple was applied (Benjamini et Hochberg, 1995).

Results

Figure 1 shows the recruitment process and follow-up flow chart for participants. During the recruitment period, 93 eligible children were identified in the database. Of these, 6 families could not be contacted, and 20 declined participation due to lack of time (n = 9) or interest (n = 11). The remaining 67 families (72%) agreed to have their child participate, but 10 were not seen due to the coronavirus disease 2019 pandemic shutdown. A total of 57 children completed the preschool assessment. Of them, 2 were subsequently excluded from the present research: 1 turned 6 years by the time of the evaluation, and 1 was diagnosed with Turner syndrome. Hence, a total of 55 children are included in this study. Demographic and clinical characteristics of the participants are presented in Table I; 52% of the participants were male and approximately two-thirds had cyanotic heart defects. Most children had a biventricular heart defect (87.3%). On average, children underwent their cardiac repair at the age of 3.7 ± 6 months. Mean ICU and

hospital length of stay were 8 ± 8 and 20 ± 14 days, respectively. Eight children (14.5%) were born prematurely. No differences were found between participants (n = 55) and nonparticipants (n = 36) for all medical-related variables (P > .05) including sex ratio, time of CHD diagnosis, age at first cardiac surgery, duration of cardiopulmonary bypass, ICU stay, gestational age, and birth weight.

Neurodevelopmental Outcomes at Age 5 years in Preschool Children with CHD

Detailed results from the 5-year-old assessment are presented in Table II. In comparison with published test norms, our cohort of survivors of complex CHD had significantly worse mean scores across almost all cognitive and language domains, while their performance on a simple receptive language task (Following Directions subtest), nonverbal reasoning (Block Design, Matrix Reasoning), and planning skills (Tower) did not significantly differ from published norms. At the same time, a higher prevalence of mild-to-moderate impairments (1-2 SD below test mean) and severe impairments (>2 SD below test mean) was observed for several cognitive and language functions (Figure 2; available at www.jpeds.com). Specifically, difficulties affecting short-term memory, working memory, and attention skills were particularly prevalent, with 40%-65% of children having lower functioning than their peers (>1 SD below test mean). This was followed by prevalence of difficulties in preschool abilities (35%-40%), receptive language (27%-39%), expressive language (25%-31%), and verbal reasoning (30%).

Neurodevelopmental Stability in Children with Complex CHD Between 1 and 5 years of Age

Among the 46 children who completed neurodevelopmental assessment at all 3 time points, only 39 had a valid global language score at the 5-year-old assessment. Three participants who were already being closely followed in speech therapy did not complete the language evaluation to minimize assessments received. Two children could not be assessed because they were not French

speaking and an additional 2 children had incomplete subtests due to time constraints. The cognitive and language developmental stability of the 39 children with complete examinations at all 3 time points (12 months, 24 months, and 5 years) are illustrated using boxplots (Figure 3). The results of the 2-way repeated measures ANOVA revealed a significant interaction between age and neurodevelopmental domain (F [2, 76] =1 4.757, P < .01, ηp2 =.280), as well as a main effect of neurodevelopmental domain (cognition vs global language; F (1, 38) = 12.633, P < .01, ηp2 =.249). Participants scored significantly lower in the global language than the cognitive domain at ages 12 and 24 months (P < 05), however, this difference was no longer significant at age 5 years (P = .482). Cognitive performance was significantly lower at age 5 years compared with age 12 months (P < .01) and tended to be lower at 5-year-old compared with 24-month-old (P = .08). Conversely, no significant differences were found for global language domain scores between the 3 time points. The developmental stability across age for expressive and receptive language skills separately are shown in Figure 3. Results showed an interaction between age and language modality (F [2, 76] = 8.605, P < .01, ηp2 =.185), and a main effect of language modality (F [1, 38] = 4.171, P <. 05, ηp2 =.099). Specifically, receptive language scores were significantly lower than expressive language scores at 12 months of age (P = .01). Inversely, a statistical tendency pointed toward better receptive than expressive language abilities at age 24 months (P = .053). At 5-years, the receptive language score was significantly higher than the expressive language score (P < .01). This indicates an improvement in receptive language skills, which were higher at age 24 months (P < .05) and 5 years (P < .01) than at 12 months of age. In contrast, no differences were found in expressive language scores with age (P > .05).

Associations Between Early Functioning and 5-Year-old Neuropsychological Outcomes

Partial correlation coefficients between scores at 12- and 24-months with scores at 5-years

are presented in Tables III and IV (both available at www.jpeds.com), respectively. Included covariables were gestational age, CHD classification (univentricular vs biventricular), ICU length of stay, and maternal education level. Results identified few significant and moderate correlations between BSID-III scores at age 12 months and neuropsychological scores at age 5 years. The false discovery rate multiple testing correction discarded all of the significant P values. At 24 months, the majority of scores were significantly and positively correlated with 5-year-old scores after controlling for multiple comparisons. Specifically, the global language scale at 24 months was positively associated with intelligence ($r = .499$, $P < .01$), receptive ($r = .401$, $P < .05$ to $r = .483$, $P < .01$), expressive ($r = .465$, $P < .01$ to $r = .625$, $P < .001$), and core language functioning ($r = .610$, $P < .001$), premath abilities ($r = .471$, $P < .01$ and $r = .556$, $P < .001$), and working memory ($r = .373$, $P < .05$) at age 5 years. Significant but slightly weaker correlations were found between the 24-month receptive and expressive language scores and most of these domains at age 5 years. The BSID-III cognitive score was moderately to highly associated with pre-math skills ($r = .542$, $P < .001$ and $r = .612$, $P < .001$), working memory ($r = .464$, $P < .01$), expressive ($r = .382$, $P < .05$), and core language ($r = .428$, $P < .01$) scores at 5 years of age. However, no significant relationship was identified between functioning at 24-months and later attentional skills.

Optimum Cut Points for BSID-III Scales as a Predictor of Impairments at Age 5 Years

Table V, Figures 4, and 5 depict the ROC analysis of BSID-III scores used to identify delays at age 5 years. Given the strong association between the performance at 24 months and 5 years of age, we assessed the relevance of BSID-III scores obtained at 24 months in identifying individuals who developed difficulties at 5-years, focusing on the variables with the highest correlation scores ($r > .6$) as early markers for preschool functioning. BSID-III global language score at 24 months of age significantly identified delays in expressive language (AUC = .820), and core language

scores (AUC =.856) at 5 years. A cut-off value of 92.5 on BSID-III global language score provided the optimal balance between sensitivity and specificity. BSID-III cognitive scale scores allowed for the identification of impairments on the measurement subtest (AUC =.749), with an optimal cut point of 97.5. Although the correlation between receptive language at 24 months and expressive language at 5 years, as well as between global language at 24 months and the 5-year word structure score were higher than .6, we did not assess ROC curves for these scores as they are already included within global scores at ages 2- and 5-years respectively.

Discussion

The main objective of this study was to characterize the neuropsychological profile of preschoolers born with CHD. Although the overall average scores obtained by children with CHD fell within 1 SD of test norms at age 5 years, our cohort demonstrated significantly poorer performance and an increased prevalence of impairments relative to the normative sample on multiple cognitive and language domains, pointing to weaknesses in their development. These difficulties primarily affect higher order domains, such as immediate and sustained attention as well as working memory, which highlights the great vulnerability of attentional and executive functions in this population. Such impairments have previously been described in school-aged children (Bellinger et al., 2003; Calderon et al., 2010; Calderon et al., 2014; Hovels-Gurich et al., 2007; Miatton et al., 2007) and in adolescents with CHD (Bellinger et al., 2011; Cassidy et al., 2015; Schaefer et al., 2013). Our results confirm that struggles with attention and executive functions are already apparent at age 5 years, reinforcing the need for long-term follow-up and increased vigilance in monitoring these abilities, as impairments in these domains are core features of neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD; Barkley, 1997). Because the prevalence of ADHD or ADHD-related symptoms is much higher in children

with CHD (Calderon et al., 2016; Hansen et al., 2012; Shillingford et al., 2008), early surveillance could play a crucial role in the early identification of at-risk children. Parent behavior training (Charach et al., 2013), mindfulness-based interventions (Chimiklis et al., 2018; Lo et al., 2020) and physical activity (Ng et al., 2017) are among the interventions that have been shown to decrease ADHD-related symptoms. Given the central role that executive functions plays in quality of life (Sanz et al., 2018) and findings that poorer executive abilities have been associated with increased use of remedial services in school-age children with CHD (Calderon et al., 2013) it would be of significant clinical interest to study the impactof early intervention on these skills. In the general population, executive functions at preschool age have also been identified as an important indicator for school readiness (Blair, 2002; Fitzpatrick et al., 2014), predicting later math and reading achievement (Blair et Razza, 2007; Bull et al., 2008; Clark et al., 2010). Consistent with the executive function and attention difficulties we highlighted, our population demonstrated vulnerability in the acquisition of basic concepts in mathematics, and lower performance on a task assessing phonological awareness. Our findings are in line with previous studies in older children with CHD, which reported lower math and reading achievement (Blair et Razza, 2007; Bull et al., 2008; Clark et al., 2010). The emergent difficulties we identified as measurable at the age of 5 years might be precursors of later academic underachievement (Bellinger et al., 2003; Mulkey et al., 2016; Oster et al., 2017) and specific learning disorder (Razzaghi et al., 2015; Riehle-Colarusso et al., 2015). In fact, literacy and math skills measured in kindergarten represent the 2 strongest indicators of children's later academic achievement (Duncan et al., 2007; Pagani et al., 2010). Finally, our findings confirm long-term difficulties in language functioning, affecting predominantly the expressive domain, as observed in older children with CHD (Hovels-Gurich et al., 2008).

Analysis of the developmental pattern of cognitive and language outcomes in children with CHD from 12 months through preschool ages revealed that cognitive abilities declined during this time period, in comparison with normative data, and that global language remained stable. These results suggest slower cognitive development in our cohort of children with CHD compared with the general population, thus the gap between our cohort and their healthy peers widens with age. Other studies have found an upward trend in cognition through development (Creighton et al., 2007; Naef et al., 2019). Despite potential differences in population demographics and neurodevelopmental stages of comparison, these findings may diverge from the current study due to the use of different neurodevelopmental assessment tools. Previous studies used the second edition of the BSID as a measure of early cognitive functioning. Here, the use of BSID-III instead of BSID Second Edition may partly explain differences in neurodevelopmental trajectory, as the third version of the test may overestimate neurodevelopmental abilities when compared with earlier versions of the measure (Acton et al., 2011; Anderson et al., 2010). The BSID III was also used by Brosig et al who found, similarly to the current study, a lower global cognitive functioning in children with CHD age 4 years compared with age 2 years (Brosig et al., 2018). Although global language scores remained stable during development, divergent trajectories were identified for expressive and receptive modalities. Receptive language improved throughout development while expressive language remained stable. Our findings align with those of a previous study showing a similar developmental shift in expressive and receptive language performance between 12- and 24-month-olds (Fourdain et al., 2019). Here, we illustrated that this pattern persists until age 5 years.

The ultimate objective of our work was to better identify children at higher risk of neuropsychological impairments and to provide them with resources targeted to their specific needs. This raises important questions about which developmental domain places a child at higher

risk for disabilities, and about best determining when these difficulties emerge, to act preventively. Results from the 24 month assessment were more predictive of the preschool neuropsychological profile than the 12-month-old assessment, as the majority of scores at 24 months were significantly correlated with the 5-year-old functioning. Language scores at 24 months were highly associated with expressive and global language performances at 5 years, and allowed for the accurate prediction of global and expressive language difficulties at preschool age, illustrating again the good stability in language performance measured at this age. A cut-off score of 92.5, which still falls within the normal range, provided a good sensitivity and fairly good specificity, suggesting that the official cut point of 85 for developmental delay might be too low (Creighton et al., 2018; Johnson et al., 2014; Spencer-Smith et al., 2015). Although language deficits persisted at age 5 years, these difficulties could be identified through systematic clinical assessment at age 2 years using this more appropriate threshold. For children performing at the lower bound of the average range (29th percentile or less), vigilance and a personalized care is suggested at the preschool age. In addition, a strong relationship was demonstrated between cognitive scores at 24 months and pre-math skills at 5 years, suggesting an important association between these developmental processes. However, this scale only provided moderate accuracy in identifying children with pre-math impairments. Importantly, the weak associations between BSID-III scores and some skills measured at age 5 years including attention, executive functions and prereading skills suggest that children who struggle with these functions would not have be identified at earlier ages, further confirming the need to systematically evaluate children with CHD prior to school entry.

This study has several limitations. First, we report results from a single center and not all patients who were eligible for the developmental assessments participated. Thus, findings may not be generalizable to the whole population of children with CHD. Similarly, given the predominance

of biventricular CHD in this sample, our results may not generalize to all single ventricle patients for whom poorer neurodevelopmental outcomes are generally reported (Gaynor et al., 2014; Hoskoppal et al., 2010; Huisenga et al., 2020). Although we controlled for the potential effect of preterm birth in our analyses, the inclusion of children born prematurely may have impacted the neurodevelopmental phenotype observed because these children are known to be at higher risk for neurodevelopmental delays (Goff et al., 2012; Sanz et al., 2018). Furthermore, we compared our results with test norms, not with a control group, which would afford more precise analysis. Our longitudinal examination involved age-appropriate assessment tools that differed at 1-, 2-, and 5-years. Although each measure was validated for age and developmental stage, some variation in test results may be attributed to the fact that different tests were used. Overall, careful attention was paid to ensure the use of clinically relevant tools that would provide comparable information on language and cognitive abilities across age groups, using age-specific norms. Lastly, neurodevelopmental assessments were not completed by the same examiner at each age and because these were clinical assessments examiners were not blinded as to the child's medical history and neurodevelopmental findings at previous ages, which may have resulted in an assessment bias.

Despite these limitations, our findings document the particular importance of preschool monitoring in children with CHD, even if early evaluations do not identify any significant delays or concerns. The identification of preschool skills that can be targeted to reduce educational challenges represents an important step in minimizing the burden associated with CHD. Our findings have directly impacted our clinical practice as we have discontinued the systematic 12-month evaluation of our clinical follow-up program at the CINC to best focus our clinical time and resources on the systematic 24-month and 5-year evaluations.

We thank the parents and children for participating in our study and all the staff of the CINC of the Sainte-Justine University Hospital Center for their dedication

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Figure 1. – Flow chart of patients included in the study.

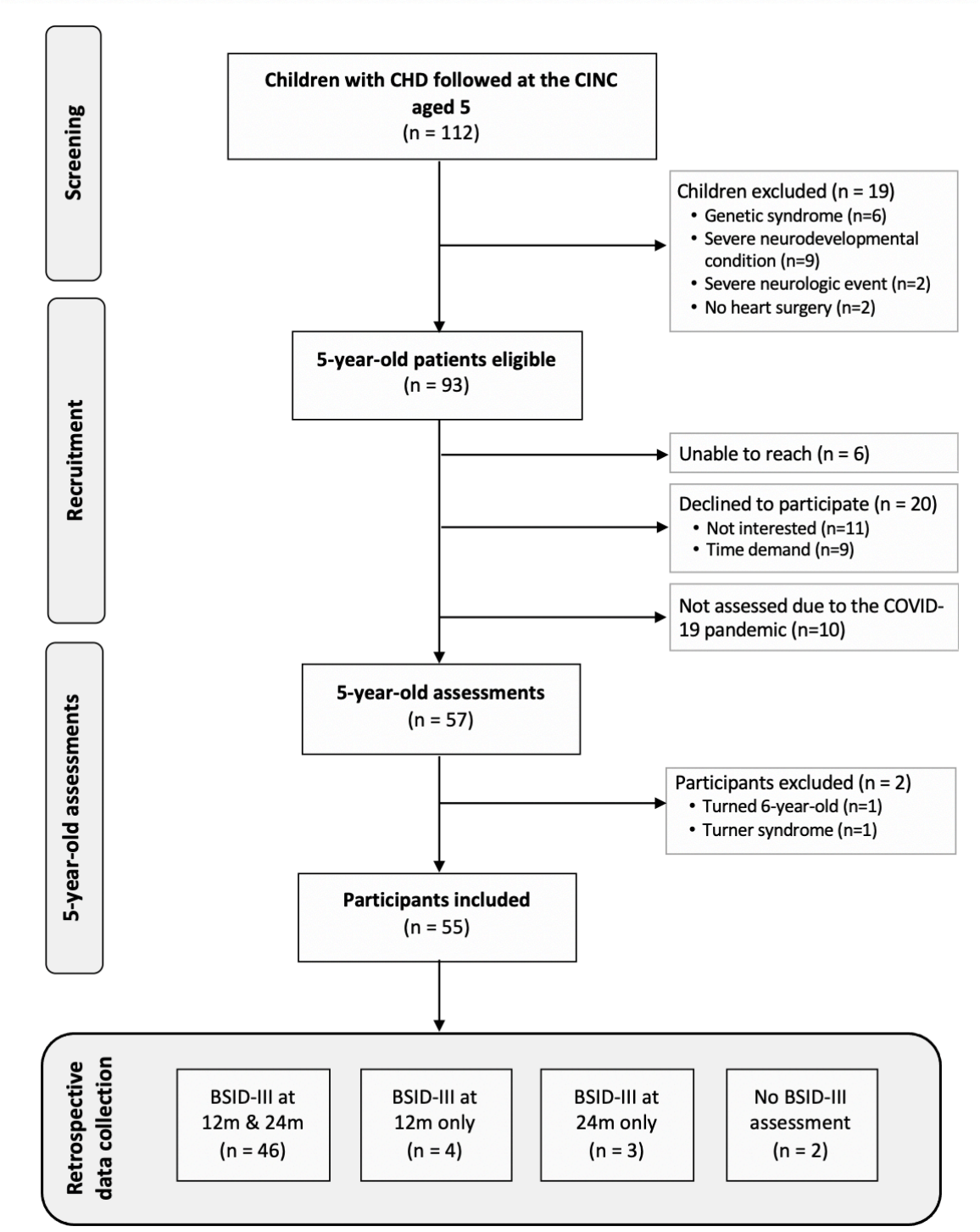


Table 1. – Demographic, perinatal, and cardiac characteristics of the participants

	N valid	n (%); *Mean* (SD)	Minimum	Maximum
Demographics				
Sex: male		29 (52.7%)	--	--
Maternal education				
High school or less		14 (25.5%)	--	--
College		16 (29.1%)	--	--
University		23 (41.8%)	--	--
Missing		*2 (3.6%)*	--	--
Family income				
<15 000$		1 (1.8%)	--	--
15 - 35 000$		4 (7.3%)	--	--
35 - 55 000$		6 (10.9%)	--	--
55 - 75 000$		4 (7.3%)	--	--
75 - 100 000$		11 (20.0%)	--	--
100-125 000$		12 (21.8%)	--	--
> 125 000$		15 (27.3%)	--	--
Missing		*2 (3.6%)*	--	--
Perinatal characteristics				
Prematurity (GA <37 wk)	55	8 (14.5%)	--	--
Gestational age (wk)	55	38.54 (1.9)	31.86	41.00
Birth weight (kg)	55	3.07 (0.6)	1.44	4.11
APGAR 1 min	54	7.72 (1.9)	1	9
APGAR 5 min	55	8.40 (1.4)	4	10
Cyanotic heart defect	55	37 (67.3%)	--	--
Biventricular heart defect	55	48 (87.3%)	--	--
Prenatal diagnosis	55	34 (61.8%)	--	--
Surgical characteristics (first surgery)				
Age at first surgery (months)	55	3.66 (6.0)	0.10	29.54
Length of ICU stay (days)	54	8.19 (8.0)	2	35
Length of hospital stay (days)	55	20.29 (14.0)	6	65
CPB time	53	143.55 (96.1)	0	410
Cross-clamp (min)	53	90.38 (68.2)	0	325
Surgical risk category (RACHS)[87]	55			
R1		1 (1.8%)	--	--
R2		21 (38.2%)	--	--
R3		24 (43.6%)	--	--
R4		8 (14.5%)	--	--
R5		0 (0%)	--	--
R6		1 (1.8%)	--	--

CPB, cardiopulmonary bypass; RACHS, risk adjustment for congenital heart surgery.

Mean ± SD are presented for continuous variables and frequency with percentages are presented for categorical variables.

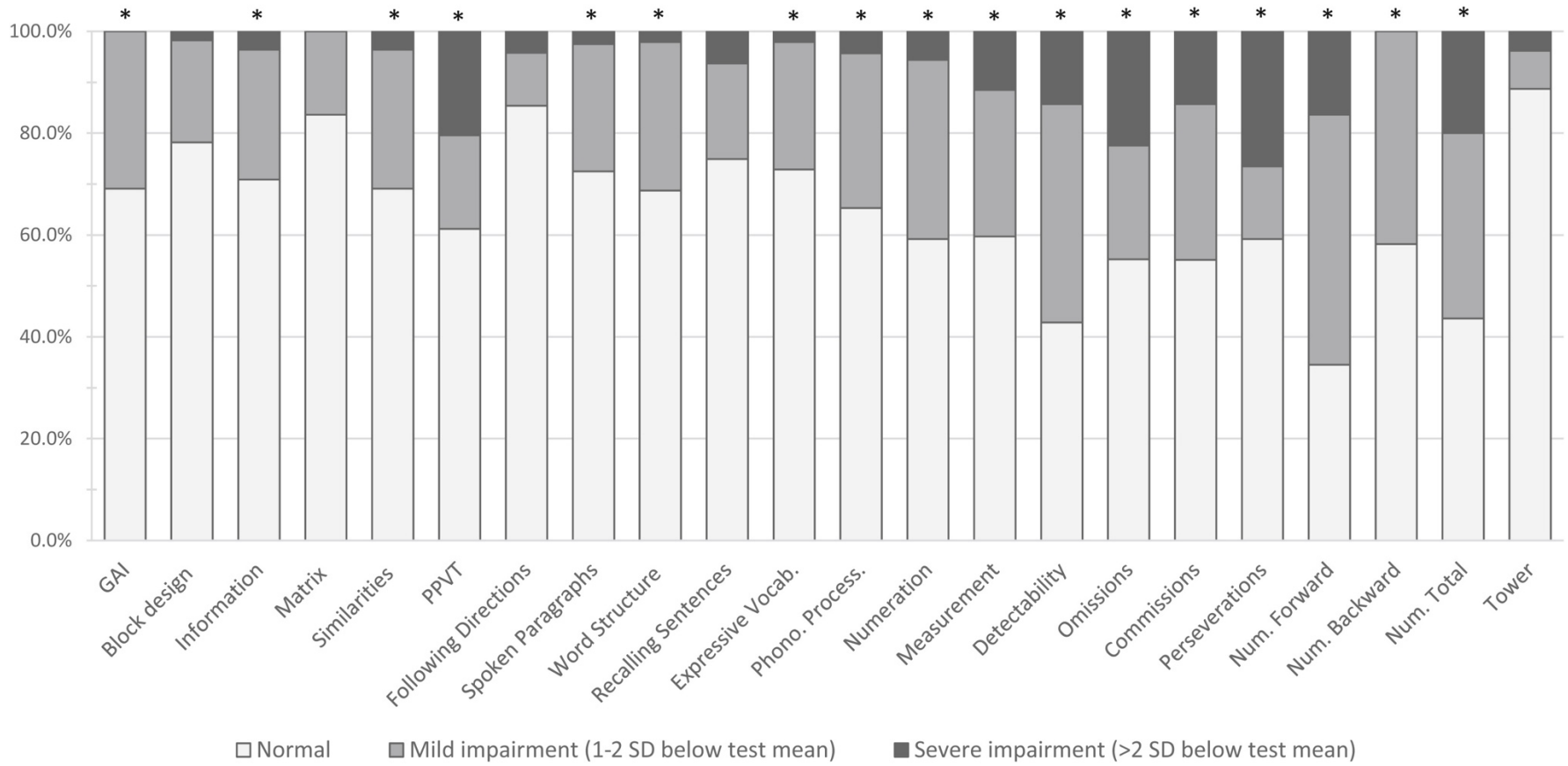
Table 2. – Results of the neuropsychological assessment at 5-year-old

Cognitive Domain	*n valid*	Mean ± SD		Sample mean vs norms		Prevalence of impairments[1]	
		Children with CHD	Published norms	t test	P	% difficulties	P
Intelligence							
Block design	*55*	9.4 ± 2.7	10 ± 3	-1.67	.100	21.8%	.187
Information	*55*	9.0 ± 2.4	10 ± 3	-3.11	**.003***	29.1%	**.006***
Matrix reasoning	*55*	9.9 ± 2.4	10 ± 3	-0.46	.649	16.4%	.339
Similarities	*55*	8.5 ± 2.3	10 ± 3	-4.98	**<.001***	30.9%	**.002***
VCI	*55*	92.3 ± 11.6	100 ± 15	-4.94	**<.001***	30.9%	**<.001***
GAI	*55*	93.5 ± 11.8	100 ± 15	-4.09	**<.001***	30.9%	**<.001***
Receptive language							
PPVT	*49*	110.6 ± 16.9	122 ± 14	-4.72	**<.001***	38.8%	**<.001***
Following Directions	*48*	9.5 ± 2.7	10 ± 3	-1.30	.199	14.6%	.661
Understanding Spoken Paragraphs	*40*	9.0 ± 2.3	10 ± 3	-2.84	**.007***	27.5%	**.040***
Expressive language							
Word Structure	*48*	8.9 ± 3.0	10 ± 3	-2.58	**.013***	44.8%	**<.001***
Recalling Sentences	*48*	8.9 ±2.5	10 ± 3	-3.24	**.002***	25.1%	.057
Expressive Vocabulary	*48*	8.7 ± 2.6	10 ± 3	-3.58	**.001***	27.1%	**.021***
Expressive language score	*48*	92.2 ± 12.8	100 ± 15	-4.24	**<.001***	31.3%	**.001***
Global language							
Core language score	*48*	93.9 ± 13.2	100 ± 15	-3.18	**.003***	27.1%	**.021***
Phonological Awareness							
Phonological Processing	*46*	8.1 ± 1.9	10 ± 3	-6.87	**<.001***	34.7%	**<.001***
Pre-Mathematics							
Numeration	*54*	8.4 ± 2.8	10 ± 3	-4.27	**<.001***	40.8%	**<.001***
Measurement	*52*	8.4 ± 3.4	10 ± 3	-3.34	**.002***	40.3%	**<.001***
Concentration (K-CPT-2)							
Detectability	*49*	60.6 ± 7.9	50 ± 10	9.4	**<.001***	57.2%	**<.001***
Omissions	*49*	61.1 ± 13.9	50 ± 10	5.80	**<.001***	44.8%	**<.001***
Commissions	*49*	58.2 ± 10.9	50 ± 10	5.22	**<.001***	44.9%	**<.001***
Perseverations	*49*	60.5 ± 13.9	50 ± 10	5.30	**<.001***	40.8%	**<.001***
Executive function							
Numbers Forward	*55*	7.4 ± 2.5	10 ± 3	-8.01	**<.001***	65.5%	**<.001***
Numbers Backward	*55*	8.7 ± 2.8	10 ± 3	-3.37	**.001***	41.8%	**<.001***
Numbers Total	*55*	7.4 ± 2.9	10 ± 3	-6.57	**<.001***	56.4%	**<.001***
Tower	*53*	10.5 ± 2.5	10 ± 3	1.43	.158	11.3%	.489

GAI, general ability index; K-CPT-2, Kiddie Continuous Performance Test, Second Edition; PPVT, Peabody Picture Vocabulary Test; VCI, verbal comprehension index.

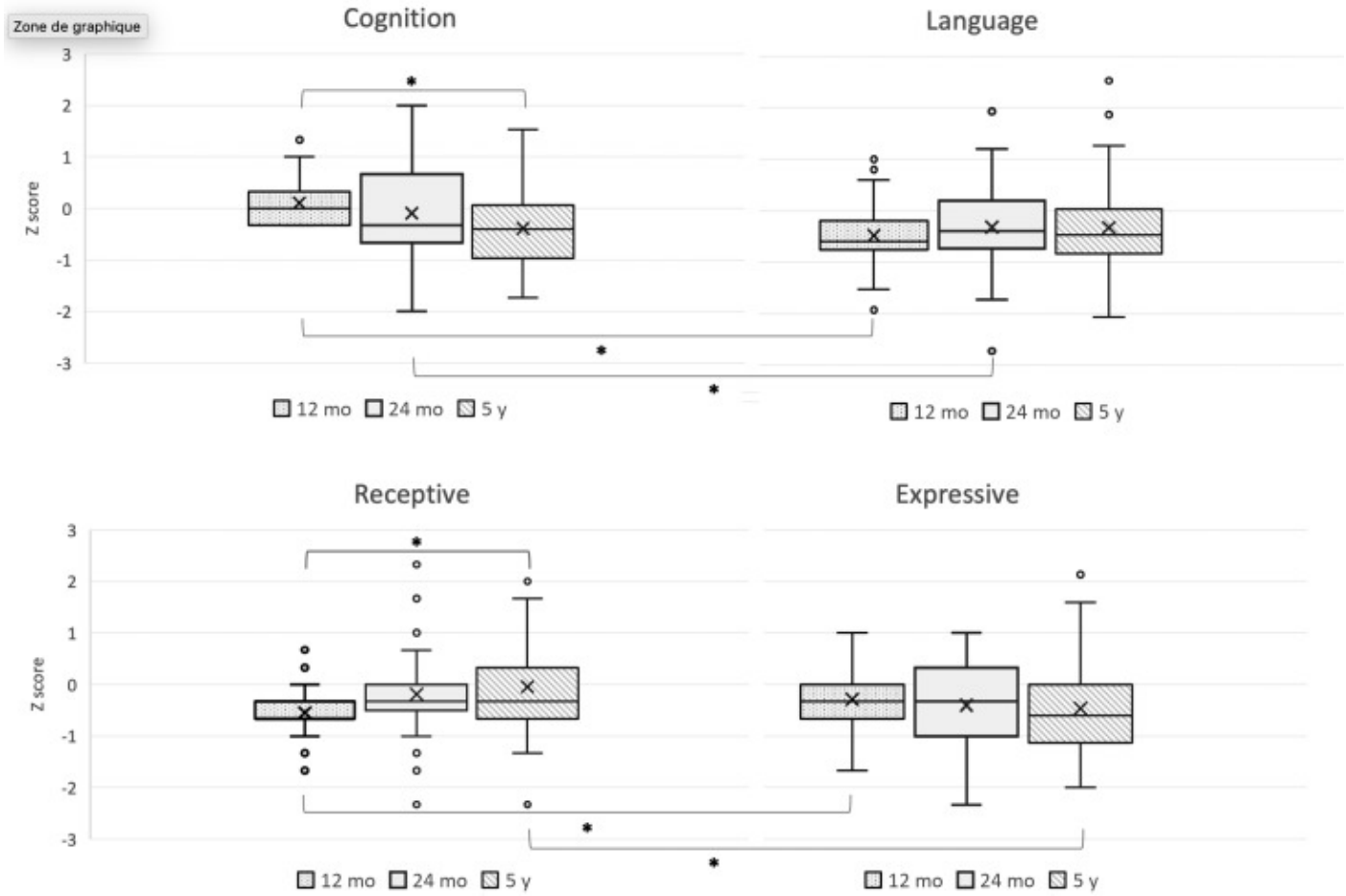
Analyses were calculated by using the 1-sample t test and $\chi 2$ tests. ∗P .05.

Figure 2. – Prevalence of patients in the normal, mild-to-moderate impairment and severe impairments ranges on cognitive and language measures at age 5 years.



Graphs present the percentage of children within the normal (*white*), mild-to-moderate impairment (*light gray*), and severe impairment (*dark gray*) ranges for each test. The expected values in a normal distribution are 84.1% (normal), 13.6% (mild-to-moderate impairment), and 2.3% (severe impairments). ∗Indicates significantly more impairments than expected with the norms ($P < .05$). *P* value calculated based upon independent-sample χ^2.

Figure 3. – Cognitive and language functioning at age 12 months, 24 months, and 5 years of age.



Global cognitive and language performance (*top row*) as well as expressive and receptive language abilities (*bottom row*) at ages 12 months, 24 months, and 5 years are represented as boxplots (n = 39 children who completed all measures at all 3 time points). The data are expressed as z scores (mean = 0 SD = 1 in typically developing children). The upper/lower borders of each box are third/first quartile, respectively. The thick line in the box is the median and the X represents the mean. Significant differences between developmental domains and between ages are represented by a ∗.

Table 3. – Partial correlation between BSID-III scores at age 12 months and neuropsychological performance at age 5 years

	Fine Motor	Gross motor	Global Motor Scale	Receptive language	Expressive language	Global Language Scale	Cognitive Scale
Intelligence							
Block design	-.146	-.047	-.103	-.168	-.204	-.203	-.253
Information	-.041	-.032	-.034	-.070	-.165	-.127	-.115
Matrix reasoning	-.092	.112	.053	-.160	-.181	-.189	-.042
Similarities	-.094	-.023	-.064	-.042	-.050	-.045	-.149
VCI	-.091	-.041	-.072	-.076	-.128	-.107	-.163
GAI	-.148	-.001	-.063	-.147	-.214	-.196	-.206
Receptive language							
PPVT	-.126	.140	.094	.317	.223	.284	.203
Following Directions	-.062	-.114	-.080	.330	.234	.302	.390
Und. Spoken Paragraphs	-.148	.035	.003	.318	.147	.241	.439
Expressive language							
Word Structure	-.115	.117	.078	.359	.190	.298	.152
Recalling Sentences	-.091	.099	.088	.169	.052	.123	.054
Expressive Vocabulary	-.336	.118	.020	.245	.048	.152	-.016
Expressive lang. score	-.174	.095	.067	.310	.110	.228	.148
Global language							
Core language score	-.234	.057	.009	.344	.164	.274	.164
Pre-academics							
Phonological Processing	-.029	-.095	-.095	.059	-.084	-.029	-.026
Numeration	-.230	.146	.030	.022	-.119	-.065	.068
Measurement	-.110	-.110	-.138	.053	.133	.109	-.056
Concentration							
Detectability	.258	.028	.125	.103	.155	.145	.156
Omissions	.023	-.086	-.075	.147	.108	.151	0
Commissions	.355	.162	.281	.014	.146	.085	.232
Perseverations	.166	-.086	.006	-.082	-.139	-.122	-.137
Executive function							
Numbers Forward	-.072	.153	.129	-.194	-.207	-.218	-.078
Numbers Backward	-.094	.083	.033	-.057	-.110	-.085	-.063
Numbers Total	-.093	.109	.075	-.141	-.179	-.170	-.077
Tower	.097	.063	.120	.005	.135	.079	.171

FDR, false discovery rate; GAI, general ability index; PPVT, Peabody Picture Vocabulary Test; VCI, verbal comprehension index. No correlations remained significant after FDR correction. Covariates were gestational age, CHD classification (univentricular vs biventricular), ICU length of stay, and maternal education level; VCI, Verbal Comprehension Index.

Table 4. – Partial correlation between BSID-III scores at age 24 months and neuropsychological performance at age 5 years

	Fine Motor	Gross motor	Global Motor Scale	Receptive language	Expressive language	Global Language Scale	Cognitive Scale
Intelligence							
Block design	.265	.162	.261	.116	.229	.183	.212
Information	.343	.186	.336	**.400****	**.490****	**.491****	.251
Matrix reasoning	.337	.348	**.458****	.311	.194	.314	.134
Similarities	.301	-.066	.144	.339	.260	.303	.224
VCI	.341	.069	.257	**.405****	**.405****	**.433****	.278
GAI	**.467****	.253	**.457****	**.455****	**.449****	**.499****	.321
Receptive language							
PPVT	**.587*****	.065	**.417****	.350	**.413****	**.401***	.282
Following Directions	**.494****	.113	**.402****	.295	.320	.341	.334
Und. Spoken Paragraphs	**.563****	.081	**.427****	**.478****	.409	**.483****	.205
Expressive language							
Word Structure	**.491****	.228	**.457****	**.548*****	**.550*****	**.612*****	**.382***
Recalling Sentences	.262	.143	.214	**.463****	**.407***	**.465****	.291
Expressive Vocabulary	**.435****	.112	.356	**.527****	**.446****	**.544*****	.378
Expressive lang. score	**.563*****	.204	**.484****	**.609*****	**.517****	**.625*****	.368
Global language							
Core language score	**.527****	.197	**.455****	**.580*****	**.524****	**.610*****	**.428****
Pre-academics							
Phonological Processing	.026	-.019	-.002	.051	.089	.071	-.018
Numeration	**.487****	.247	**.486****	**.562*****	**.428****	**.556*****	**.542*****
Measurement	.115	.118	.148	**.474****	**.377***	**.471****	**.612*****
Concentration							
Detectability	-.266	-.031	-.179	-.357	**-.360***	-.373	-.282
Omissions	-.234	-.208	-.270	-.232	-.268	-.277	-.249
Commissions	-.125	.120	-.006	-.259	-.149	-.203	-.068
Perseverations	-.341	-.110	-.236	-.300	-.210	-.243	-.251
Executive function							
Numbers Forward	.086	.054	.056	.316	.160	.245	.225
Numbers Backward	.318	.210	.307	.355	.353	**.373***	**.464****
Numbers Total	.215	.135	.187	**.371***	.308	.352	**.401****
Tower	.297	-.019	.133	.043	.178	.063	.097

∗P < .05,∗∗P < .01, ∗∗∗P <.001. Correlations that remain significant after FDR correction are in bold. Covariates were gestational age, CHD classification (univentricular vs biventricular), ICU length of stay, and maternal education level.

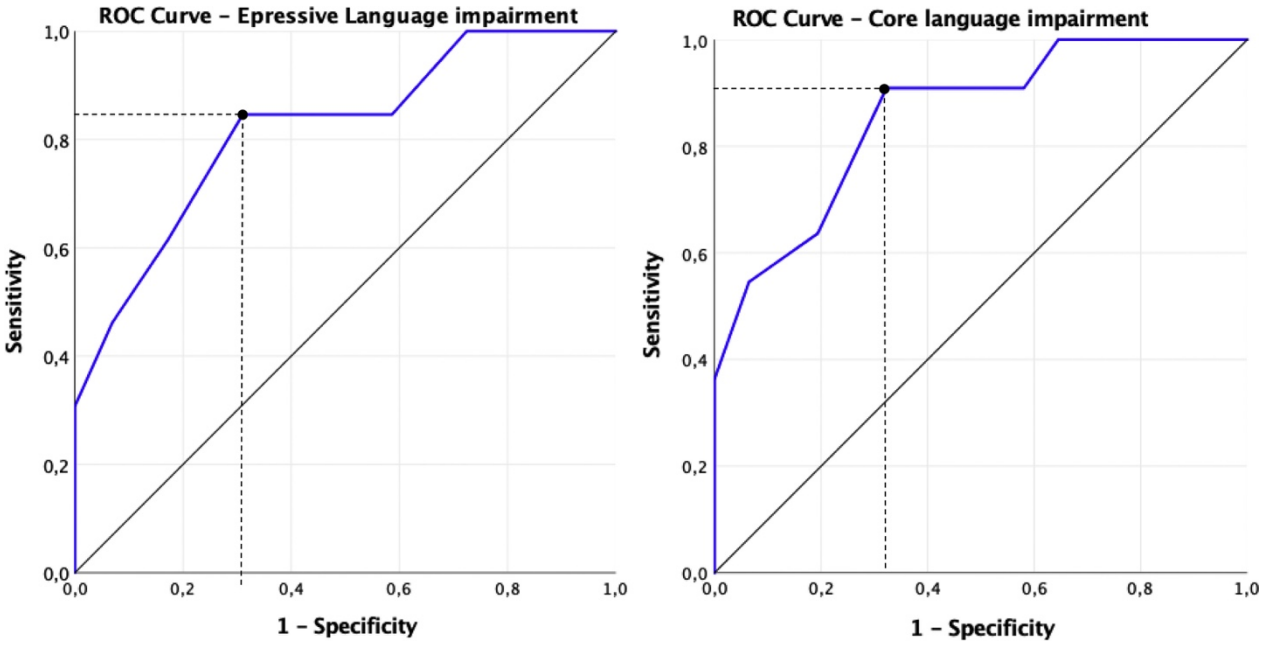
Table 5. – Receiver operating characteristic (ROC) curve for prediction 5-year-old impairments (<-1 SD) from 24-months Composite Score of the BSID-III.

	AUC	p	CI (95%) Lower bound	CI (95%) Upper bound	cut-off	sensitivity	specificity	J
Expressive language impairment (≤-1SD)								
BSID-III Scale: *Global language*	.820	**.001***	.678	.961	92.5	.85	.69	.536
Core language impairment (≤-1SD)								
BSID-III Scale: *Global language*	.856	**.001***	.729	.984	92.5	.91	.68	.587
Measurement impairment (≤-1SD)								
BSID-III Scale: *Cognition*	.734	**.007***	.589	.878	97.5	.74	.63	.366

J, Youden Index.

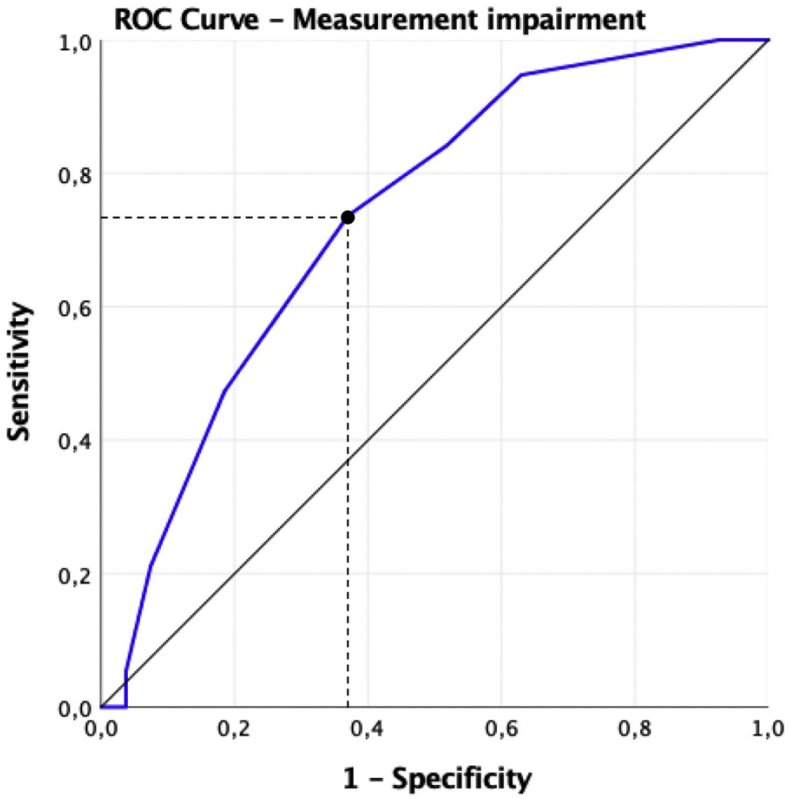
∗*P* .05.

Figure 4. – ROC curves identifying impairments on language at age 5 (score ≤-1 SD) through BSID-III Global language scale.



ROC curves for sensitivity and 1-specificity of Bayley-III Global language scores predicting expressive language (*left*) and global language (*right*) scores ≤1 SD below the norms at age 5 years. The black dot denotes optimal predictive value (Youden Index; BSID-III score of 92.5).

Figure 5. – ROC curves identifying impairments on measurement at age 5 years (score ≤-1SD) through BSID-III Cognitive scale.



ROC curves for sensitivity and 1-specificity of Bayley-III Cognitive scores predicting measurement) scores ≤1 SD below the norms at age 5 years. The black dot denotes optimal predictive value (Youden Index; BSID-III score of 97.5).

Chapitre 5 – Article 3

Social cognition and competence in preschoolers with congenital heart disease

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Article en révision dans *Neuropsychology* (2021)

Abstract

Objective: Children born with congenital heart disease (CHD) are at increased risk for various neurodevelopmental impairments. However, little is known regarding social outcomes associated with CHD, particularly during early childhood. The current study aimed to characterize the socio-cognitive profile and to assess the contribution of language, executive functions (EF), social cognition to social competence in preschoolers with CHD. ***Methods:*** Five-year-old children with CHD (n=57) completed a standardized neuropsychological assessment. Performance on socio-cognitive skills was compared to test norms using one-sample T-tests. Hierarchical regression was conducted to examine the associations between language skills, Theory of Mind (ToM), EF (performance-based and parent-rated), and social competence. Adjustments for length of hospital stay and maternal educational level were taken into account. ***Results:*** Children with CHD performed significantly worse than norms in language and ToM, whereas EF and social competence appeared generally preserved in our sample. In hierarchical regression analysis, socioeconomic and medical factors did not contribute to social competence, however, adding cognitive functions (language score, ToM, EF performance) accounted for a significant 29.3% of the variance. Parent-rated EF added another 32.0% to the total explained variance. ***Conclusions:*** These findings provide new evidence for understanding social cognition and competence among preschoolers with CHD, showing vulnerability in social cognition and language skills, but not in social competence more generally. The model suggests a combined contribution of social cognition, language, and EF on social outcomes. Remedial programs addressing these intervention targets could be useful in promoting social development in this vulnerable population.

Key Points

Question: Is social cognition and competence altered in preschoolers with congenital heart disease? ***Findings:*** By the time of school entry, children with CHD are already at risk for difficulties in language and social cognition, whereas EF and social competence seem to be preserved. Socio-cognitive skills significantly contribute to explaining outcomes in social competence. ***Importance:*** These findings provide, for the first time, a socio-cognitive profile of preschoolers with CHD, and the underlying socio-cognitive substrates associated with social competence after heart surgery. ***Next Steps:*** Longitudinal studies are required to explore the development of socio-cognitive skills over time and infer causal relationships between the variables explored.

Introduction

Congenital heart disease (CHD) is the most commonly occurring birth defect, affecting approximately 1% of children (Marelli et al., 2014). Of these, more than one-third present with complex heart conditions and undergo surgical procedures early in their developmental course either to correct or to palliate their defect (Go et al., 2013). The survival rate of children born with CHD has considerably improved over the last two decades due to progresses in diagnosis and surgical care, and most infants now survive into adulthood (Dearani et al., 2007; Marelli et al., 2014). However, increased survival comes at a cost in terms of morbidity and CHD is considered a chronic and lifelong condition, which necessitates complex and specialized care through the lifespan, and places a significant burden on children and their caregivers (Celermajer et al., 2016; Cohen & Earing, 2018; Strange et al., 2020; Zomer et al., 2012).

It is now established that individuals with complex CHD are at high risk for neurodevelopmental delays (Gaudet et al., 2021; Ilardi et al., 2020; Ware et al., 2020), due to reduced fetal cerebral blood flow or oxygenation, sequelae of the heart condition itself (e.g. severe cyanosis, cardiac arrests), and medical and surgical therapies required (e.g. perioperative hypoxic ischemic injury, prolonged hospitalization) (Marelli et al., 2007; McQuillen et al., 2010; Nattel et al., 2017). Developmental delays arise in multiple domains, such as gross and fine motor skills (Bolduc et al., 2020; Fourdain et al., 2020; Majnemer et al., 2006), language and core communication skills (Fourdain et al., 2019; Hovels-Gurich et al., 2008; Majnemer et al., 2008; Sananes et al., 2012; Sommariva et al., 2020), attention and executive abilities (Calderon, Jambaque, et al., 2014; Cassidy et al., 2015; Jackson et al., 2021; Sanz et al., 2017; Sanz et al., 2018), and global intellectual functioning (Bellinger, Wypij, et al., 2003; Forbess et al., 2001; Gaynor et al., 2014; Majnemer et al., 2008) leading to academic underachievement (Bellinger, Bernstein, et al., 2003; Hövels-Gürich et al., 2002; Oster et al., 2017; Wypij et al., 2003) and behavioral maladjustment (internalizing and externalizing problems) (Abda et al., 2019; Bellinger et al., 2009; Hövels-Gürich et al., 2002; Sarrechia et al., 2016). While an extensive body of literature addresses neurocognitive delays in this population, very few studies have explored the implications of CHD for social cognition and competence especially in early childhood (Clancy et al., 2019).

Social interaction is a fundamental component of human development that requires the recruitment of underlying socio-cognitive skills and enables the proper development of social competence. Appropriate social skills are the basis for the creation of satisfying relationships, which in turn are essential to psychological well-being across the lifespan (Amati et al., 2018; Bronk et al., 2020; Segrin & Taylor, 2007). Social functioning has

implications beyond the social sphere and is associated with school readiness and success (Bernier et al., 2020; Blair, 2002; Curby et al., 2015; Denham et al., 2014; Vitiello & Williford, 2016), as well as quality of life (Helgeson, 2003; Wehmeier et al., 2010). Poor social skills in childhood can have lasting consequences on long-term outcomes, including academic problems (DeRosier & Lloyd, 2011; Gallardo et al., 2016), peer rejection (DeRosier & Lloyd, 2011), drug misuse (Jones et al., 2015; Scheier et al., 1999), antisocial behavior (Beelmann & Lösel, 2006), mood disturbances (Goldstein et al., 2006; Huber et al., 2019), and suicide (Spirito et al., 1990).

Social competence, defined as the degree to which children are effective in their social interactions with others (Junge et al., 2020), emerges during early childhood as a function of increased brain specialization and environmental interactions, making this period the cornerstone of adequate social development (Denham et al., 2009). Social maturation is a highly complex process involving the consolidation of a broad range of cognitive and affective functions recognized under the umbrella term social cognition and their underlying neural substrates. Key components of social cognition include both basic processes, such as affect recognition, and more complex ones, such as theory of mind (ToM) (Bora & Pantelis, 2016; Miranda et al., 2017). The former involves the ability to perceive and correctly distinguish emotions displayed by others (Phillips, 2003), whereas the latter refers to the understanding of another's mental state (desires, beliefs, feelings, intentions) that shape and predict how they will act (Wellman et al., 2011).

According to the *SOcio-Cognitive Integration of Abilities modeL* (SOCIAL; Beauchamp & Anderson, 2010), social competence requires intact attention and executive functioning (EF), communication skills, and social cognition (e.g. affect recognition, theory of mind). These socio-cognitive functions are moderated by a range of factors either

intrinsic to the individual (e.g. age) or reflecting their environment (e.g. socio-economic status). Given the multiple processes involved, it is not surprising that social competence is vulnerable to disruption in youth with chronic illness (Martinez et al., 2011), epilepsy (Caplan, 2019; Stewart et al., 2019), acquired brain injury (Anderson et al., 2017; Ganesalingam et al., 2011; Ryan et al., 2014; Ryan et al., 2019), preterm birth (Alduncin et al., 2014; Marleau et al., 2020) or neurodevelopmental disorders (Berard et al., 2017; Brinton & Fujiki, 2005; Nixon, 2001; Staikova et al., 2013; Stichter et al., 2010).

Socio-behavioral difficulties have previously been reported in children with CHD (Bellinger et al., 2009; Clancy et al., 2019; Mussatto et al., 2018; Werninger et al., 2020), and there is emerging evidence showing that CHD survivors have increased risk of autism spectrum disorder (ASD) symptoms (Bean Jaworski et al., 2017) or of meeting ASD diagnostic criteria (Razzaghi et al., 2015; Sigmon et al., 2019; Tsao et al., 2017). Even in the absence of an ASD diagnosis, some studies have reported adverse outcomes in domains closely related to social cognition. For example, executive dysfunction has repeatedly been reported in individuals with CHD from the preschool period and beyond (Calderon, Jambaque, et al., 2014; Cassidy, 2020; Cassidy et al., 2015; Hovels-Gurich et al., 2007; Sanz et al., 2017). Receptive, expressive, and pragmatic language difficulties are also documented in children with surgically corrected CHD (Fourdain et al., 2019; Hovels-Gurich et al., 2008; Sommariva et al., 2020). However, few studies have directly assessed social cognition in this population. Those that do report alterations in emotion perception in children (Calderon, Angeard, et al., 2014) and adolescents (Bellinger et al., 2015; Bellinger et al., 2011) with complex CHD. Some evidence suggests that school-aged children with CHD have poorer ToM compared to healthy-matched peers (Sarrechia, Miatton, et al., 2015). Calderon and colleagues (2010) also found that ToM was more

impaired in 7-year-old children with transposition of the great arteries, a type of critical congenital heart defect, than their healthy peers. Importantly, this study found that ToM skills correlated with EF, with cognitive and behavioral inhibition being main contributors (Calderon et al., 2010). Given the vulnerabilities in domains argued to support social competence, it is likely that children with CHD would exhibit difficulties in this developmental sphere. However, the characterization of social competencies in a more formal way remains to be addressed.

The current study

Despite documented manifestation of behavioral and social difficulties in children with CHD, little is known regarding the underlying socio-cognitive substrates associated with social competence after cardiac surgery. The aim of this study was to evaluate the integrity of socio-cognitive skills (social cognition, language and EF) and to examine the contribution of these skills to social competence in preschool children (five years) with CHD. The preschool period was selected because it corresponds to a sensitive period for the development of both ToM and EF (Korkman et al., 2007) and represents the timing of entry into the formal education system where social skills are exponentially solicited. It was expected that 5-year-old children with CHD would display poorer language, ToM, EF and social competence than their peers, as per normative data. We also hypothesized that social cognition, language and EF would jointly predict social competence when accounting for medical (hospital stay) and environmental (socioeconomic status) factors.

Methods

Participants

The data are from a single center prospective cohort study of neurocognitive outcomes in 5-year-old children born with CHD between 2012 and 2015. Here we report only on the social, executive and language outcomes drawn from the larger cohort study, the methods of which are more fully described elsewhere (Gaudet et al., 2021). Briefly, a sample of 93 eligible children followed at the Clinique d'Investigation Neuro-Cardiaque (CINC) of the Sainte-Justine University Hospital who underwent at least one invasive procedure for correction or palliation of a complex heart defect were identified and invited to participate in the study. Exclusion criteria were the presence of genetic syndromes (e.g. Down syndrome) and diagnosis of severe neurological condition (e.g. cerebrovascular accident, traumatic brain injury) or severe neurodevelopmental disorder (e.g. autism spectrum disorder; severe global developmental delay) that would better explain their cognitive and behavioral profile.

Among all eligible patients, parents of 67 (72%) agreed to their child's participation. Neurodevelopmental assessment could not be completed for 10 out of the 67 participants due to the COVID-19 pandemic shutdown. A total of 57 children completed the preschool assessment. Two were subsequently excluded from the present study: one had turned 6 years by the time of the evaluation, and one was diagnosed with Turner syndrome. Consequently, 55 children are included in this study. No significant differences were found between participants (n=55) and non-participants (n=38) in terms of sex ratio,

gestational age, birth weight, time of CHD diagnosis, anatomic CHD classification, age at first cardiac surgery, duration of cardiopulmonary bypass and hospital stay (p>.05).

Neuropsychological assessment

Neuropsychological assessment included a comprehensive battery of tests assessing a range of developmental domains (Gaudet et al., 2021). Among these, variables that best fit the SOCIAL model structure were considered as candidate predictors for social competence (SC) in preschoolers with CHD. Hence, the present study used a subset of data including measures of language, social cognition and EF. Social competence was assessed using the PEERS-Q, a standardized parent questionnaire. All measures are validated and have normative values based on typically developing children. If not otherwise indicated, raw scores were used in all regression analyses as they provide a larger range of values compared to standard scores. Sociodemographic and clinical factors (i.e., maternal level of education and hospital length of stay) were also taken into account.

Sociodemographic and medical information

Parents completed questionnaires documenting their child's development and sociodemographic context, including information on mother's highest level of education and family income. Medical information (e.g. cardiac diagnosis, age at first surgery, length of Intensive Care Unit [ICU] stay) were gathered from the patient's chart.

Intellectual Functioning

To accurately portray our cohort of children, the *General Ability Index* (GAI; mean = 100 ± 15) from the WPPSI-IV was used to provide an estimate of general intellectual ability (IQ) based on scores on the *Information* (general knowledge), *Similarities* (verbal

reasoning, concept formation), *Block design* (non-verbal reasoning, visuospatial organization) and *Matrix reasoning* subtests (Wechsler, 2012).

Language

The Core Language score from the French-Canadian version of *Clinical Evaluation of Language Fundamentals—4th edition* (CELF-4) (Wiig et al., 2009) was used (mean = 100 ± 15) as a measure of general language ability. This score is derived by summing the scaled scores from the subtests that are known to best discriminate typical language performance from disordered language performance (i.e., *Following Directions, Recalling Sentences, Word Structure* and *Expressive Vocabulary*).

Social cognition

The Affect Recognition (AR) and Theory of Mind (ToM) subtests from the *Developmental Neuropsychological Assessment-Second Edition* (NEPSY-II) were used to reflect social cognition (mean = 10 ± 3) (Korkman et al., 2007). The AR task assesses the ability to recognize and compare emotional expressions (happy, sad, anger, fear, disgust, and neutral) from photographs of children's faces. This task was added later in the research protocol and some children (18%) did not complete it.

The ToM task is designed to assess the ability to understand mental functions and another's point of view, and is divided into two parts: *Verbal tasks* and *Contextual tasks* (Korkman et al., 2007). For the verbal items, the child is provided with verbal or pictorial descriptions of various social situations and is then asked questions about the characters' thoughts, ideas, and the child's understanding of figurative language. The *Contextual tasks* measure the child's ability to relate emotion to the social context. They

evaluate the child's ability to understand how certain emotions are linked to given social situations and to correctly recognize the emotions generated in the various social settings.

Executive functions (EF)

The Tower subtest from the NEPSY battery (Korkman, 1998) was used as a performance-based measure of EF. This subtest evaluates nonverbal planning and problem solving. On this task, the child moves three colored balls onto target positions on three pegs in a prescribed number of moves (1-7), based on specific task rules. The overall score reflects the number of correctly achieved target positions, within the move and time limit (mean = 10 ± 3).

Parent-rated everyday EF was assessed using the Behavior Rating Inventory of Executive Function — Preschool version (BRIEF-P) (Gioia et al., 2003). On this 63-item questionnaire, item responses are summed to create composite indices of inhibitory control, shifting, working memory, emotional regulation, and planning, as well as a Global Executive Composite score (GEC), composed of all items (mean = 50 ± 10). A T-score of 65 or above is considered clinically significant.

Social competence

The *Paediatric Evaluation of Emotions, Relationships, and Socialisation Questionnaire* (PEERS-Q; Thompson et al., 2018) was used to measure general social competence in children with CHD. The PEERS-Q is a 55-item questionnaire based on the SOCIAL theoretical framework (Beauchamp & Anderson, 2010). This questionnaire describes child behavior and social skills in everyday situations when interacting with others, providing information on a range of social competencies, such as friendships and

social participation (Tuerk et al., 2020). A total social skills score is generated (mean = 50 ± 10), with higher scores indicating lower social competence.

Statistical analyses

Statistical analyses were completed using the Statistical Package for the Social Sciences (SPSS) version 25 with the significance level set at 5%. Descriptive analyses were computed on developmental data to describe the study group. With regard to our first objective, mean performance on IQ, language, social cognition, EF and social competence scores of children with CHD were compared with those from the general population (normative data) using one sample t-tests. Prevalence of children having a performance between 1 and 2 standard deviations [SD] below the test mean (mild-to-moderate impairments) and having a performance ≥2 SD below the test mean (severe impairments or deficits) was compared to expectations based on a normal distribution, using one-sample Chi-Squared tests.

For the second objective, multiple hierarchical regression analyses were conducted to examine the extent to which cognitive factors (i.e. language skills (CELF-4 *Core Language* score), social cognition (ToM) and EF [performance-based (Tower) and parent-rated (BRIEF-P)]), contribute to the prediction of social competence, above and beyond socioeconomic (i.e. maternal educational level) and medical (i.e. length of hospital stay) factors. Given the high rate of missing data for the Affect Recognition task (18%), this measure was not included in the regression model in order to increase statistical power.

Given that environmental and clinical factors, such as socioeconomic status (Hackman & Farah, 2009; Pluck et al., 2021; Ursache & Noble, 2016) and postoperative length of hospital stay (Eichler et al., 2019; Fuller et al., 2009; Marino et al., 2012;

Newburger et al., 2003; Sananes et al., 2012), are known to impact neurodevelopment, they were first entered in the regression analysis (Block 1). Cognitive factors, that is raw scores on core language, ToM and EF subtests, were subsequently added (Block 2). Finally, parent-rated EF, as measured with the GEC score of the BRIEF-P, was entered in the third step (Block 3). A total of 10 participants (18%) had missing data for at least one variable and were thus excluded from the regression models.

Results

Table 1 displays participants' demographic, perinatal clinical and surgical (first surgery) characteristics. Male and female sex was represented in similar proportions whereas parental questionnaires were primarily completed by the child's mother (83.6%). The proportion of participating families with low (< $ 55 000) annual family income was less than 20%. Most children had received an antenatal diagnosis for complex CHD (62%) and eight (15%) were born preterm. On average, children underwent their first cardiac surgery at the age of 3.7 ± 6 months and were hospitalized for 20.29 ± 14 days.

Univariate descriptive statistics for the core study variables, including cognitive factors are presented in Table 2, and multivariate hierarchical regression results are presented in Table 3. Relative to standardized norms, children with CHD exhibited lower performance on intellectual ability, language and ToM tests ($p<.05$), although mean scores remained within the average range (see Table 2). Further, the rate of children displaying mild-to-moderate impairments in these three domains was significantly higher than that of the normative population ($p<.05$, see Figure 1). No significant differences were found for EF skills (performance-based and parent-rated; $p>.05$), or performance on the measure of AR ($p>.05$). Interestingly, 9% of children had severe deficits on the AR subtest which

significantly exceeds the expected rate of 2% ($p<.05$), despite a normal rate of mild-to-moderate impairments and an average overall group performance. Finally, significantly fewer social competence problems were reported on the parent questionnaire compared to norms ($p<.05$).

In the regression analysis, maternal education and length of hospital stay, entered in Block 1, did not contribute significantly to social competence (R-squared changes = .007, $F(2, 42)=0.141$, $p=.869$; Table 3). Adding cognitive functions to the model (CELF-4 core language score, ToM, tower scores) significantly accounted for 29.3% of the variance in social competence ($\Delta F(3, 39)=5.450$, $p=.003$) with poorer planning skills (tower score, $p=.036$) and lower ToM performance ($p=.036$) predicting poorer social competence. In Block 3, parent-rated EF (BRIEF-P – GEC) added another 32.0% to the total explained variance ($\Delta F(1, 38)=32.040$, $p<.001$). Both performance based and parent-rated EF scores were significant independent predictors of PEERS-Q, with lower planning skills (tower score, $p=.032$) and more overall EF problems reported by the parent (BRIEF-P – GEC; $p<.001$) associated with lower social competence. Overall, the hierarchical regression model accounted for 62.0% of the variance in parent-rated social competence as measured by the PEERS-Q ($F(6, 38)= 10.345$, $p<.001$).

Discussion

This study examined social cognition and social competence in 5-year-old children with CHD and their association with language and executive skills. The results highlight difficulties in the cognitive functions underpinning social competence in CHD survivors even in the absence of deficits in intellectual functioning (estimated IQ > 70 for all children

assessed). Overall, better socio-cognitive skills (language, EF, ToM) contributed to higher parent-reported social competence.

Consistent with the existing literature, children with CHD exhibited lower global language abilities compared with normative data (Fourdain et al., 2019; Hovels-Gurich et al., 2008; Sommariva et al., 2020). Moreover, the current study identified lower average group performance on ToM tasks compared to norms with a significant proportion of patients showing difficulties (1 SD or more below test norms). These findings align with results previously reported in older children with CHD (Calderon, Angeard, et al., 2014; Calderon et al., 2010; Sarrechia, De Wolf, et al., 2015). To our knowledge, this is the first time that vulnerability in ToM has been shown in the preschool period in the CHD population. As a group, children with CHD tended to perform adequately when compared to the general population in terms of affect recognition, despite the finding of a greater prevalence of facial affect recognition deficits (> 2 SD below the test norm) observed in a subset of patients. These significant difficulties in affect recognition observed in some children could be associated with the long-lasting problems in emotion processing that have been reported at school age (Calderon, Angeard, et al., 2014; Sarrechia, Miatton, et al., 2015) and adolescence (Bellinger et al., 2015; Bellinger et al., 2011). The medical and socio-demographic characteristics that might explain findings related to affect recognition remain to be elucidated. Together, our results add to the evidence for disruptions in social cognition in CHD, especially with regard to complex skills, and show that difficulties previously identified in older children may already be present during the preschool years.

Contrary to our expectations, neither parent-rated nor performance-based EF were affected in preschoolers with CHD in comparison with population norms. These findings contrast with the current literature suggesting that CHD survivors are at increased risk for

EF deficits throughout childhood (Bellinger, Wypij, et al., 2003; Calderon, Jambaque, et al., 2014; Sanz et al., 2017) and adolescence (Bellinger et al., 2015; Bellinger et al., 2011; Cassidy et al., 2015). The discrepancy between our results and previous studies may be due, in part, to heterogeneity in the CHD population studied (e.g., diagnosis, surgical procedure) or differences in samples and assessment tools. First, others have noted that the NEPSY Tower subtest is not clinically sensitive (Brooks et al., 2009; McCormack & Atance, 2011; Schmitt & Wodrich, 2004); use of this measure may therefore have limited the identification of planning problems in our cohort. Alternatively, it is possible that five-year-old children with CHD have problems in other EF domains not tested here, such as inhibitory control, working memory or cognitive flexibility (Calderon, Jambaque, et al., 2014; Jackson et al., 2021). Future research should consider a more comprehensive assessment of EF using more sensitive measures. Moreover, the young age of children included in this study (i.e., 5-year-old) may, in part, explain discrepancies with other studies. Though EF emerge during the preschool period, they develop and refine through school age and adolescence. Thus, deficits in EF might be less apparent at an age where expectations remain relatively low. Similarly, it is possible that, at this age, the functional and behavioral impacts of poorer EF are not overtly apparent to parents (parent-rated EF using BRIEF-P). At school entry, EF problems may become more salient because the school setting requires children to be more organized, to stay focused, and to follow classroom rules and instructions (O'Meagher et al., 2017). As suggested in children born preterm whose neurodevelopmental outcomes are similar to those of children with CHD (McQuillen et al., 2010), the assumption that these children are vulnerable because they survived and overcame a disease may reduce parent expectations regarding their child's development (O'Meagher et al., 2017; O'Meagher et al., 2020; Schappin et al., 2013). Thus,

parents whose outlook on their child's prognosis was dim may feel encouraged by their preschooler's progress and overestimate their executive functioning in day-to-day contexts (O'Meagher et al., 2017; O'Meagher et al., 2020). This limitation could be rectified in future research by obtaining ratings of executive functions and social competence from other sources (e.g., teacher ratings).

Surprisingly, when compared to normative values, better social competence was reported by parents of preschoolers with CHD. This may seem counterintuitive given literature suggesting more problems in social behavior in this population (Abda et al., 2019; Clancy et al., 2019) or no differences compared to controls in terms of social skills (Werninger et al., 2020). However, several reasons may explain why the CHD participants in this study were rated as more socially competent by their parents. First, deficits in social competence may not be fully evident for parents at the age of 5, where social demands remain relatively simple without exceeding the limited capacities of the child. It is also possible that ToM vulnerability in preschoolers with CHD only translates into difficulties in more global or daily aspects of social competence later in development (Barreto et al., 2018; Caputi et al., 2012; Devine et al., 2016). Longitudinal follow-up is needed to test this hypothesis. Alternatively, parents may, consciously or not, depict a favorable impression of their child, presumably to enhance their perceived parenting skills or because they see their child as vulnerable (Clancy et al., 2019; Gaynor et al., 2009), as suggested with regard to parent-reported EF. Findings from a large study on preschoolers (4-5-year-old) with CHD revealed that a high proportion of parents (35%) tended to display defensive responses on parent questionnaires, thus presenting their child positively and minimizing problems (i.e., socially desirable responses) (Gaynor et al., 2009). Specifically, these parents tended to underreport their child's social impairments compared to nondefensive

parent reporters (Gaynor et al., 2009). Similarly, several studies in youth with CHD report fewer parent-rated behavioral problems compared to normative samples (Bellinger et al. 1997; Claessens et al., 2018; Sterken et al. 2016). Thus, it is unclear whether the greater social competence observed in this study reveals a true strength in this population or rather differing thresholds for identifying behaviors as problematic among parents of children with CHD (Bellinger et al., 1997). Again, gathering information from more than one respondent (e.g., teacher, both parents) could be considered in future research.

The second aim of this study was to better understand the factors that contribute to social competence in preschoolers with CHD. Examination of predictors of social competence reveals that multiple factors need to be considered to understand children's social outcomes in the context of CHD. Our model, that included child factors, cognitive skills and day-to-day EF, explained a significant amount of variance in social competence.

Maternal education level and length of hospitalization did not make a significant contribution to parent-rated social competence, but this may be attributable to the relative homogeneity between participants as very few children came from disadvantaged socioeconomic backgrounds (<$55,000/year) and nearly half of the mothers had a university degree. While the negative impact of a prolonged hospital stay on neurodevelopment has been well described in this population (Eichler et al., 2019; Fuller et al., 2009; Marino et al., 2012; Sananes et al., 2012), less is known about its consequences on social competence specifically. Hence, its impact on parent-rated social skills at preschool age may be negligible and thus, undetectable.

Performance-based cognitive factors (language, ToM, performance-based EF) did contribute to social competence. Executive skills and ToM accounted for significant unique variance in PEERS-Q, with higher performance related to higher levels of social

competence. This reinforces the close association between EF and social domains even during the preschool period (Calderon et al., 2010; Tuerk et al., 2020). Moreover, language performance may not individually contribute to parents' perceived social competence, but when all cognitive functions are considered together, they explain a significant portion of variability in social competence in 5-year-old children with CHD. This reflects the importance of taking into account the interplay between several developmental domains in the understanding of social outcomes.

Notably, parent behavioral ratings of EF accounted for the most significant proportion of social competence (32%), suggesting that poorer behavioral expression of executive skills may result in reduced social competence, even though no significant differences were observed between children with CHD and test norms in these two domains. This strong relationship, however, must be interpreted in light of the potential effect of shared assessment modality (i.e., parent-rating questionnaire), because parents rated both executive functions and social competence. Nevertheless, although the causal nature of the observed links remains to be demonstrated, the final model explained substantial variance in social competence, with both parent-rated EF and performance-based EF as unique independent predictors. Even though our cohort of preschoolers did not have significantly lower EF nor social competences compared to norms, our results underline the intimate relationship between these two areas of development, as previously reported in healthy children at age 5 (Tuerk et al., 2020). EF are critical to everyday functioning and provide a basis for successful social interactions and relationships by allowing children to integrate feedback, react flexibly to changes in routine, respect turn-taking, or inhibit negative reactions (Ganesalingam et al., 2011). These skills are directly

linked to establishing socially appropriate behaviors and meaningful social relationships (Ganesalingam et al., 2011; Ryan et al., 2019).

Limitations

The current study has some limitations that must be considered. First, the small sample size reduces the statistical power and did not allow for testing the effects of all medical variables (e.g., gestational age, cardiac class) or cognitive factors (e.g. IQ, attentional skills) on social outcomes. In addition, the inclusion of a control group would have allowed for a better understanding of the impact of CHD on socio-cognitive skills. Moreover, measures of social competence and day-to-day EF were assessed using parental questionnaires, which are prone to subjective bias. However, by including both performance-based and behavioral measures of EF we gathered a broader range of information about the child's functioning. Finally, the present findings are correlational in nature precluding conclusions about causal relationships. Further studies using a longitudinal design could more accurately explore the progression of socio-cognitive skills during childhood and enable the exploration of causal relationships.

Conclusions and future directions

This study reveals vulnerability in social cognition and language skills in preschoolers with CHD, providing new evidence for understanding social cognition and competence at the time of school entry. Given the concurrent relationship between language, ToM, EF and social functioning, it is essential that these children have access to interventions that will allow them to develop their socio-cognitive skills, in order to establish healthy and satisfying relationships. Developmental investigation of these

children and adolescents will allow us to better understand the trajectory of socio-cognitive skills, and to better target the interventions that are appropriate to their needs and developmental stage.

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Table 1. – Participants' demographic, perinatal and cardiac characteristics

Characteristics	N valid	n (%); *Mean* (SD)	Minimum	Maximum
Demographics				
Age at testing	55	5.57 (0.26)	5.12	5.99
Sex: male	55	29 (52.7%)	--	--
Questionnaire respondent				
Mother		46 (83.6%)		
Father		7 (12.7%)		
Both parents		2 (3.6%)		
Maternal education				
College or less		32 (58.2%)	--	--
University		23 (41.8%)	--	--
Family income				
<15 000$		1 (1.8%)	--	--
15 - 35 000$		4 (7.3%)	--	--
35 - 55 000$		6 (10.9%)	--	--
55 - 75 000$		4 (7.3%)	--	--
75 - 100 000$		11 (20.0%)	--	--
100-125 000$		12 (21.8%)	--	--
> 125 000$		15 (27.3%)	--	--
Missing		2 (3.6%)	--	--
Perinatal characteristics				
Prematurity (GA <37 wk)	55	8 (14.5%)	--	--
Cardiac class	55			
Class 1: 2V, no aortic obstruction		38 (69.1%)	--	--
Class 2: 2V, aortic obstruction		11 (20.0%)	--	--
Class 3: 1V, no aortic obstruction		2 (3.6%)	--	--
Class 4: 1V, aortic obstruction		4 (7.3%)	--	--
Prenatal diagnosis	55	34 (61.8%)	--	--
Surgical characteristics				
Age at first surgery (months)	55	3.66 (6.0)	0.10	29.54
Length of ICU stay (days)	54	8.19 (8.0)	2	35
Length of hospital stay (days)	55	20.29 (14.0)	6	65

Note. Mean ± standard deviation (SD) are presented for continuous variables and frequency with percentages are presented for categorical variables.

GA=gestational age; 2V= two-ventricle cardiac anatomy; 1V=single ventricle cardiac anatomy; ICU=Intensive Care Unit.

Table 2. – Descriptive statistics for main study variables (n=55)

Cognitive Domain	*n valid*	Mean ± SD		Sample mean vs norms	
		Children with CHD	Published norms	t test	*P*
Intelligence					
Global ability index	*55*	93.5 ± 11.8	100 ± 15	-4.09	**<.001***
Global language					
Core language score	*48*	93.9 ± 13.2	100 ± 15	-3.18	**.003***
Social cognition					
Affect recognition	*45*	10.0 ± 3.5	10 ± 3	0.04	.966
Theory of mind	*54*	8.8 ± 2.3	10 ± 3	-3.76	**<.001***
Executive functions					
Tower	*53*	10.5 ± 2.5	10 ± 3	1.43	.158
Parent rated EF	*54*	50.6 ± 10.1	50 ± 10	0.42	.679
Social competence					
PEERS-Q	*53*	46.1 ± 8.9	50 ± 10	-3.19	**.002***

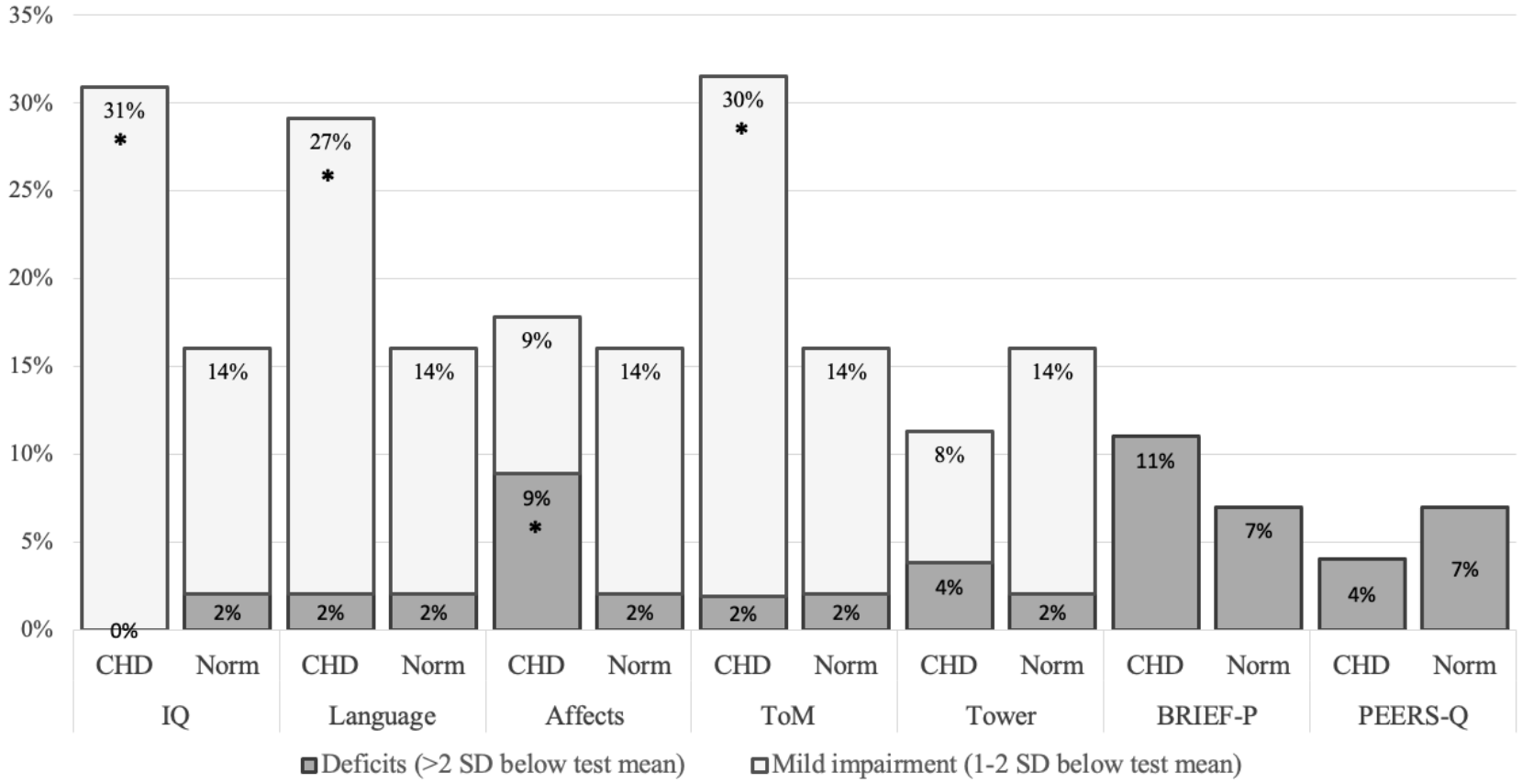
Note. Standardized scores were used.
EF = Executive Function; PEERS-Q = Paediatric Evaluation of Emotions, Relationships, and Socialisation Questionnaire.
*Statistical significance, $p<0.05$

Table 3. – Hierarchical regression analyses predicting social competence (PEERS-Q)

Candidate predictors	β	*p*	$\mathbf{R^2}$	$\mathbf{\Delta R^2}$	ΔF	*p*
Step 1: Child factor			.007	.007	0.141	.869
Length of hospital stay	-.026	.878				
Maternal education	-.087	.599				
Step 2: Cognitive factors			.300	.293	5.450	**.003***
Length of hospital stay	-.084	.586				
Maternal education	-.068	.654				
Language	-.126	.454				
ToM	-.360	**.036***				
Tower	-.304	**.036***				
Step 3: Behavioral factors			.620	.320	32.040	**<.001***
Length of hospital stay	-.007	.955				
Maternal education	-.006	.956				
Language	-.107	.395				
ToM	-.125	.345				
Tower	-.234	**.032***				
Parent-rated EF	.622	**<.001***				

Note. Raw scores of language (*Core language* subscale), theory of mind (*ToM* subscale), performance-based EF (*Tower* subtest) and parent-rated EF (BRIEF-P) were used. *N*=45. EF = Executive Function.
*Statistical significance, $p<0.05$.

Figure 1. – Proportion of children with difficulties compared to test norm.



Note. *Indicates significantly higher proportion of children with mild-to-moderate impairments or deficits than the test norm ($p<0.05$). IQ = Estimation of intellectual ability; BRIEF-P = Behavior Rating Inventory of Executive Function – Preschool version (Global Executive Composite score); PEERS-Q = Paediatric Evaluation of Emotions, Relationships, and Socialisation Questionnaire.

Chapitre 6 – Discussion

Il est maintenant indéniable que les enfants atteints de cardiopathie congénitale sont à risque sur le plan neurodéveloppemental et une prise en charge conséquente est dorénavant attendue. Partout à travers le monde, des cliniques spécialisées sont d'ailleurs graduellement mises en place pour répondre aux besoins de ces enfants. Malgré les avancées fulgurantes des connaissances acquises dans ce domaine au cours de la dernière décennie, des questions persistent concernant l'optimisation de la prise en charge en fonction de l'âge et du stade de développement de l'enfant. Cette thèse visait à participer aux discussions scientifiques liées à ces questions ainsi qu'à offrir des éléments de réponses cliniques quant au devenir neuropsychologique et la prise en charge à privilégier dans le contexte de CC.

L'âge de 5 ans a été ciblé, puisqu'il constitue une période clé dans le développement de l'enfant qui fait son entrée dans le système scolaire, où les habiletés sociales et cognitives sont sollicitées de manière exponentielle. Ainsi, il apparait particulièrement important de mieux comprendre le fonctionnement des survivants à la malformation cardiaque à cet âge charnière dans leur développement.

Dans les sections suivantes, les résultats des trois articles de cette thèse seront résumés et mis en commun afin d'en abstraire certaines interprétations et constats généraux, le tout en lien avec la littérature existante. Les retombées cliniques de la thèse de même que les principales limites et les avenues de recherche futures seront également discutées.

1. Retour sur les principaux objectifs et résultats

1.1. Premier article

L'objectif du premier article était de faire état de la littérature actuelle quant à la description des troubles neurodéveloppementaux (TND) et des outils d'évaluations de ces derniers. Précisément, nous avons décrit les principaux outils de classification des TND, soit la *Classification statistique internationale des maladies et des problèmes de santé connexes* (CIM) et le *Manuel diagnostique et statistique des troubles mentaux* (*Diagnostic and Statistical Manual of Mental Disorders*; DSM), et leur pertinence dans l'élaboration d'un langage universel entre les chercheurs et les cliniciens de divers horizons. Une cohérence entre les différents outils de classification s'avère ainsi primordiale.

Rappelons que tant la CIM que le DSM permettent aux cliniciens de poser un diagnostic (catégoriel) basé sur la nature et le nombre de symptômes ainsi que la présence d'une détresse ou d'une déficience. Certains défis peuvent être rencontrés dans l'identification précise du diagnostic neurodéveloppemental d'un enfant. Ceux-ci incluent l'hétérogénéité et la variabilité interindividuelle et intra-individuelle (selon l'âge) dans la manifestation de symptômes associés au diagnostic (deux enfants peuvent être diagnostiqués avec le même trouble alors qu'ils ont peu de symptômes en commun), le chevauchement de certains symptômes entre les diagnostics ainsi que la fréquence élevée des comorbidités qui constitue d'ailleurs davantage la norme que l'exception.

Visant à pallier ces limites, le *Research Domain Criteria* (RDoC) développé par le *National Institute of Mental Health*, a vu le jour en 2009 (Insel et al., 2010). Plutôt que de prendre appui sur un modèle de catégorisation, le RDoC vise à découvrir et à spécifier les mécanismes qui sous-tendent et influencent le fonctionnement cognitif, affectif et comportemental, au moyen d'une

meilleure compréhension des anomalies neurobiologiques affectant le développement. Le RDoC peut ainsi être utilisé comme cadre pour l'examen de la psychopathologie en termes de construits comportementaux et cognitifs mesurables qui transcendent les catégories de diagnostic, qui incluent la variation normale et qui tiennent compte de l'évolution et du changement au cours du développement.

1.2. Deuxième article

La seconde étude de cette thèse avait trois objectifs, soit : 1) caractériser le profil neuropsychologique des enfants atteints de CC à l'âge de 5 ans, 2) dresser la trajectoire du développement cognitif et langagier de ces enfants entre 1 et 5 ans et 3) identifier des marqueurs précoces des difficultés neuropsychologiques à l'âge préscolaire.

D'abord, les résultats de cette étude mettent en lumière des difficultés significatives touchant de nombreuses sphères du fonctionnement neuropsychologique à l'âge préscolaire. Les fonctions de plus haut niveau, soit les fonctions exécutives (mémoire de travail) et attentionnelles (attention immédiate et soutenue), s'avèrent particulièrement affectées dans notre cohorte d'enfants. Des difficultés affectant les prérequis scolaires (à la lecture et aux mathématiques) et du langage expressif sont également notables à cet âge.

Par ailleurs, des trajectoires développementales distinctes sont observées selon la sphère cognitive étudiée. Ainsi, le langage global apparait stable au fil du temps, contrairement à la cognition globale qui elle, diminue par rapport à ce qui est attendu pour l'âge. De même, en étudiant la progression développementale du langage réceptif et expressif de manière distincte, on observe que le versant expressif demeure stable entre les trois temps de mesure (1, 2 et 5 ans), alors que le langage réceptif s'améliore avec l'âge. Par conséquent, bien que les difficultés en langage réceptif

s'amenuisent au cours du développement, celles affectant le langage expressif persistent jusqu'à l'âge préscolaire.

Enfin, nos résultats révèlent que le fonctionnement langagier global mesuré à 2 ans permet d'identifier avec justesse les enfants présentant des difficultés langagières à 5 ans, et ce, tant au niveau du langage global que de l'expression langagière. Dans une moindre mesure, le score de fonctionnement cognitif obtenu à 2 ans présente à son tour une valeur prédictive dans l'identification des enfants à risque au niveau des prérequis en mathématiques à 5 ans. Dans les deux cas toutefois, notons qu'une performance située dans les bornes de la moyenne était nécessaire afin d'identifier adéquatement les enfants qui présentent des difficultés à 5 ans. Par ailleurs, il importe de mentionner que certaines autres fonctions, telles que les prérequis à la lecture, l'attention et les FE, qui sont pourtant largement affectées dans notre cohorte d'enfants à 5 ans, étaient peu associées aux performances mesurées en bas-âges, et ne pouvaient ainsi pas être détectées précocement.

1.3. Troisième article

La troisième étude de cette thèse a été conduite au sein de la même cohorte d'enfants que l'étude 2 et a permis, pour la toute première fois en si jeune âge, de décrire le fonctionnement sociocognitif des survivants à une CC âgés de 5 ans. Plus précisément, elle visait à faire état de la cognition et de la compétence sociale à l'âge préscolaire ainsi qu'à étudier la contribution de fonctions sociocognitives dans la compétence sociale chez ces enfants.

En premier lieu, les résultats de cette étude ont permis de mettre en lumière des difficultés au niveau de la cognition sociale (c.-à-d. théorie de l'esprit et reconnaissance d'affects), qui sont donc déjà apparentes à l'âge de 5 ans. Pour sa part, la compétence sociale semble préservée. En

outre, nous avons montré qu'à l'instar de ce qui est rapporté chez les enfants neurotypiques, un ensemble de fonctions sociocognitives (c.-à-d., langage, FE et théorie de l'esprit) permettent d'expliquer la compétence sociale en contexte de CC, au-delà des facteurs propres à la maladie de l'enfant (durée d'hospitalisation) et de l'environnement dans lequel il évolue (éducation de la mère). Ceci illustre bien l'intime relation entre les différentes sphères du développement de l'enfant atteint de CC et leur contribution dans le fonctionnement social.

2. Profil neuropsychologique de l'enfant atteint de CC: une perspective globale

Dans l'ensemble, le cadre conceptuel adopté dans les deux articles empiriques (articles 2 et 3) permet de rendre compte du fonctionnement de l'enfant atteint de CC en adoptant une perspective globale, dans laquelle divers aspects de son développement sont considérés. Cette approche, qui correspond aux constats découlant du premier article de cette thèse, n'est pas sans rappeler celles préconisées par le *Cardiac Neurodevelopemental Outcome Collaborative (CNOC)*, un regroupement d'experts qui allie chercheurs et cliniciens de différents horizons (psychologie, neuropsychologie, cardiologie, neurologie, sciences infirmières, ergothérapie, etc.) provenant de partout dans le monde. Le CNOC vise l'avancement, la promotion et l'optimisation de la recherche clinique en neuro-cardiologie. Par le biais de comités de travail et de publications de style *white papers*, les membres proposent des lignes directrices sur la prise en charge à favoriser et identifient les manques importants de connaissances à combler dans la littérature sur le neurodéveloppement des individus avec CC.

Très récemment, un regroupement d'experts du CNOC a publié des recommandations quant aux pistes de recherche futures à adresser afin de mieux caractériser les pronostics neurodéveloppementaux et psychologiques de cette population (Sanz et al., 2021). Dans ce papier, le manque d'études intégrant diverses dimensions du fonctionnement de l'enfant, plutôt que des fonctions isolées, est clairement identifié comme une lacune dans l'état des connaissances actuelles (Sanz et al., 2021). Ces recommandations s'accordent avec l'approche adoptée dans les articles empiriques de cette thèse (articles 2 et 3). De plus, en lien étroit avec l'article 1 de la présente thèse, les auteurs soulignent également la pertinence d'étudier les profils qui sont en dehors des classifications diagnostiques strictes telles que définies par le DSM-V ou la CIM-10 par exemple, surtout dans le contexte où les mêmes symptômes sont observés dans différents diagnostics. Une approche visant à concevoir les troubles neurodéveloppementaux comme un enchevêtrement de symptômes qui coexistent et qui sont interreliés, plutôt que comme des entités catégorielles distinctes, a plus récemment vu le jour (voir article 1 pour un résumé des approches de classification diagnostic) et son utilisation a plutôt été proposée dans l'étude du neurodéveloppement de la CC (Sanz et al., 2021). Bien que le RDoC n'ait pas été utilisé dans nos études, l'approche globale adoptée dans l'étude du neurodéveloppement de l'enfant atteint de CC permet de diriger notre regard vers une constellation de caractéristiques neuropsychologiques et interreliées. Les résultats issus de l'article 3, portant sur le fonctionnement social, en sont un bon exemple, puisqu'ils illustrent que la compétence sociale est tributaire de fonctions cognitives sous-jacentes (adoption d'une approche biopsychosociale). Ceci sera discuté plus en détail dans la section 3.

Enfin, le fort ancrage clinique dans lequel cette thèse s'est déployée a aussi motivé à détailler les sphères de fonctionnement les plus vulnérables chez ces enfants, afin d'orienter au

mieux les suivis et la prise en charge clinique. Aux vues de ces résultats, il apparait clair que le moment de l'entrée à l'école est associé à des difficultés neuropsychologiques plus ou moins sévères chez grand nombre de patients suivis à la CINC. Ces dernières seront détaillées dans les sections subséquentes.

2.1. Vulnérabilités mises en évidence à 5 ans.

Le profil neuropsychologique dressé à l'âge préscolaire, autour de l'entrée à l'école, montre des difficultés affectant la presque totalité des sphères évaluées. Parmi elles se trouvent les fonctions langagières, telles que précédemment rapportées dans plusieurs études portant sur des enfants de différents âges (Fourdain et al., 2019; Hicks et al., 2016; Hoffman et al., 2016; Hovels-Gurich et al., 2008; Mussatto et al., 2015; Sommariva et al., 2020). Un fonctionnement intellectuel (indice d'aptitudes globales ; GAI) plus faible est également mis en évidence bien qu'aucun des participants ne présentait un retard global de développement ou une déficience intellectuelle (GAI>70 pour tous les participants évalués), ce qui concorde avec l'état des connaissances actuelles sur le neurodévelppement en contexte de CC (Bellinger et al., 1999; Cassidy et al., 2018). De manière plus novatrice, nos résultats permettent aussi de mettre en lumière des difficultés touchant les fonctions attentionnelles, exécutives (mémoire de travail) ainsi que les fondements du langage écrit et des mathématiques, lesquelles sont typiquement rapportées chez des enfants atteints de CC plus âgés (âge scolaire et adolescence) (Calderon et al., 2010; Cassidy et al., 2015; Gerstle et al., 2016; Hovels-Gurich et al., 2007; Ilardi & LaMotte, 2021; Marijke Miatton et al., 2007; Shillingford et al., 2008). Des fragilités au niveau de la cognition sociale sont par ailleurs mises en évidence ce qui, à notre connaissance, n'avait encore jamais été rapporté à un si jeune âge dans cette population.

Globalement, il importe de souligner le rôle primordial des fonctions susmentionnées dans l'intégration et le fonctionnement scolaire du jeune enfant (Best et al., 2011; Burchinal et al., 2020; Einarsdóttir et al., 2016; Pace et al., 2019; Rhoades et al., 2011; Shaul & Schwartz, 2013; Simanowski & Krajewski, 2017). Alors que le succès de la première année d'école a été démontré comme cruciale dans la réussite scolaire ultérieure (Duncan et al., 2007; Entwisle et al., 2005) et sachant que l'âge de 5 ans constitue le point d'entrée dans le système scolaire québécois, il s'avère essentiel de dépister adéquatement les enfants atteints de CC (c.f. section 2.2.) étant donné le risque accru de difficultés qu'ils présentent à cet âge.

2.1.1. Fonctionnement attentionnel et exécutif en contexte de CC

L'ampleur des difficultés attentionnelles et exécutives mise en lumière dans notre cohorte à un âge charnière de leur développement mérite une attention particulière. D'abord, cette forte prévalence de difficultés mesurée à l'âge de 5 ans est cohérente avec l'état des connaissances actuelles, voulant que ces sphères développementales soient particulièrement à risque chez les enfants et adolescents atteints de CC (Calderon, Bellinger, Hartigan, et al., 2019; Cassidy, 2020; Jackson et al., 2021).

À ce jour, très peu d'auteuts se sont penchés sur l'évaluation directe des fonctions attentionnelles et exécutives des enfants atteints de CC d'âge préscolaire. Alors qu'une étude précédente conduite chez des enfants de 5 ans a montré un fonctionnement attentionnel préservé chez les enfants atteints de CC (Brosig et al., 2013), d'autres montrent des vulnérabilités à cet âge (Calderon, Jambaque, et al., 2014; Sterken et al., 2016). Davantage d'études sont nécessaires pour mieux caractériser le fonctionnement exécutif et attentionnel des enfants atteints de CC, sachant que les vulnérabilités peuvent varier en fonction de la composante évaluée et que la maturation de ces composantes semble suivre un patron qui lui est propre (Calderon, Jambaque, et al., 2014;

Sterken et al., 2016). Plus précisément, les travaux conduits par Calderon et ses collègues (2014) ont montré des difficultés d'inhibition chez des enfants atteints de transposition de grands vaisseaux (TGV) âgés de 5 ans, qui n'étaient toutefois plus observables à l'âge de 7 ans. À l'inverse, l'écart entre la performance des jeunes atteints de TGV et celle des de leurs pairs en santé s'était accentué entre 5 et 7 ans, au niveau de la flexibilité cognitive. Finalement, contrairement aux résultats issus de la présente thèse, cette même étude a montré que la mémoire de travail était préservée dans cette population, tant à 5 ans qu'à l'âge de 7 ans (Calderon, Jambaque, et al., 2014).

Dans notre cohorte, un suivi à plus long terme est nécessaire afin de savoir si les difficultés observées tendront à se normaliser, à s'aggraver ou encore si elles demeureront stables à l'âge scolaire et à l'adolescence. Néanmoins, des plusieurs études conduites chez des enfants plus âgées ont montré des difficultés affectant la performance attentionnelle et en mémoire de travail en contexte de CC (Bellinger & Newburger, 2010; Bellinger et al., 2003; Hovels-Gurich et al., 2007; M. Miatton et al., 2007; Naef et al., 2017), laissant présager que les fragilités observées à 5 sont susceptibles de perdurer.

Par ailleurs, l'altération des FE et de l'attention constituent des symptômes prédominent dans le trouble trouble du déficit de l'attention avec ou sans hyperactivité (TDAH) (Barkley, 1997), duquel les enfants atteints de CC sont connus pour être spécialement à risque (Calderon et al., 2016; Hansen et al., 2012; Shillingford et al., 2008). L'identification précoce des vulnérabilités attentionnelles et exécutives est particulièrement importante compte tenu de la fréquence élevée de recours aux traitements pharmacologiques (psychostimulants et traitements non stimulants) dans cette population (Batra et al., 2012; Berger, 2016). Le dépistage en bas âge de telles difficultés permettrait d'initier des interventions alternatives et/ou complémentaires aux traitements

pharmacologiques, ces derniers devant être surveillés chez l'enfant à risque cardiaque (Batra et al., 2012; Berger, 2016).

Bien que la mise en place d'interventions ciblant spécifiquement les habiletés attentionnelles et exécutives soit nécessaire la population atteinte de CC (Cassidy, 2020; Cassidy et al., 2021), aucune étude n'a, à ce jour, été conduite chez des enfants d'âge préscolaire. Dans la population générale, diverses avenues prometteuses ont été proposées. Entre-autres, des interventions basées sur l'activité physique (Ng et al., 2017), la pleine conscience (Chimiklis et al., 2018; Lo et al., 2020) et le yoga (Cohen et al., 2018; Jarraya et al., 2019; Sun et al., 2021) ont été montrés bénéfiques dans la prévention et la réduction des symptômes liés au TDAH. Chez des adolescents atteints de CC, un programme informatisé (Cogmed) a montré des bénéfices sur le contrôle inhibiteur (Calderon et al., 2020). Davantage d'études sont nécessaires d'orienter, aux mieux, les jeunes atteints de CC leurs familles vers les ressources appropriées.

La prise en charge des difficultés exécutives et attentionnelles est d'autant plus importante, sachant que ces fonctions sont connues pour avoir des implications dans diverses sphères développementales. Notamment, elles joueraient un rôle central dans les apprentissages scolaires (Best et al., 2011; Montoya et al., 2019; Mulder et al., 2017). Ainsi, de bonnes habiletés exécutives ont été associées à de meilleurs résultats en lecture et mathématiques dans la population générale (Blair, 2002; Blair & Razza, 2007; Bull et al., 2008; Clark et al., 2010) et chez des enfants (Cassidy et al., 2016; Ilardi & LaMotte, 2021) et des adolescents (Cassidy et al., 2016) atteints de CC. Par conséquent, il est possible que les faiblesses aux prérequis à la lecture et aux mathématiques dans notre cohorte soient intimement liées aux difficultés attentionnelles et exécutives également présentes.

Qui plus est, l'importance des FE dans la qualité de vie (Sanz et al., 2018) et le fonctionnement social (c.f. section 2.1.2) (Calderon et al., 2010; Ryan et al., 2019; Tuerk et al., 2020) a été documentée antérieurement, laissant présager que les vulnérabilités attentionnelles et exécutives mises en lumière dans notre cohorte pourraient avoir des répercussions plus larges dans le fonctionnement quotidien de l'enfant.

À cet égard, soulignons toutefois que, malgré les difficultés importantes révélées par l'évaluation directe des FE, celles-ci ne ressortent pas de manière significative au questionnaire rempli par le parent (Behaviour Rating Inventory of Executive Function – Preschool; BRIEF-P). Plusieurs pistes d'interprétation peuvent ici être considérées pour expliquer ce phénomène. D'abord, bon nombre d'auteurs ont montré une corrélation très faible, voire nulle, entre la performance de l'enfant aux tâches directes et le BRIEF (Gross et al., 2015; McAuley et al., 2010; Nordvall et al., 2017; Soto et al., 2020), suggérant que ces mesures (tâches directes et BRIEF) ne devraient pas être utilisées de façon interchangeable, mais devraient plutôt être vus comme des outils mesurant des aspects complémentaires du FE (Soto et al., 2020). Ainsi, des difficultés dans des tâches exécutives formelles ne se traduisent pas nécessairement par des difficultés identifiables dans ce questionnaire.

Ceci étant dit, plusieurs études ayant employé cet outil (BRIEF) ont révélé des déficits exécutifs chez des enfants d'âge scolaire et des adolescents atteints de CC (Bellinger et al., 2011; Gerstle et al., 2016; Sanz et al., 2017; Sanz et al., 2018; Sarrechia et al., 2015). Par conséquent, il est également possible que le jeune âge des participants inclus dans cette étude contribue à ces résultats. Ainsi, les impacts fonctionnels et comportementaux d'un faible FE ne sont possiblement pas si apparents pour les parents en âge préscolaire, mais pourraient le devenir avec l'entrée à

l'école, où il est attendu que l'enfant soit plus organisé, qu'il demeure concentré et qu'il suive les instructions en classe (O'Meagher et al., 2017).

2.1.2. Devenir social de l'enfant atteint de CC

Tel que mentionné précédemment, des vulnérabilités touchant la cognition sociale ont été observées dans notre population. Celles-ci se reflètent par une proportion plus de quatre fois plus importante d'enfants présentant des déficits au niveau de la reconnaissance d'affects (9 %, comparativement à 2 % dans la population générale), ainsi que par une performance en TDE se situant globalement en dessous de ce qui est attendu pour l'âge (norme de tests) et une incidence accrue (30 %) de difficultés légères à modérées (-1 à -2 écarts-types sous la norme des tests). À cet égard, soulignons qu'aucun des enfants recrutés dans l'étude n'a reçu de diagnostic de TSA, ce qui concorde avec les résultats d'études précédentes montrant un traitement de l'information sociale moindre chez les enfants atteints de CC, même en l'absence de diagnostic formel de TSA (Calderon, Bellinger, & Newburger, 2019).

Par ailleurs, en vue de bien décrire le fonctionnement social, les résultats de la présente thèse ont également permis d'illustrer que la compétence sociale des enfants avec CC est tributaire de fonctions cognitives sous-jacentes.

D'abord, rappelons qu'une approche biopsychosociale basée sur le modèle théorique SOCIAL (Beauchamp & Anderson, 2010) fût préconisée dans l'étude du développement social de l'enfant atteint de CC. Les résultats du **3e article** de cette thèse illustrent ainsi l'apport d'une pluralité de facteurs, incluant diverses fonctions cognitives, dans la compréhension de la compétence sociale des enfants atteints de CC. Cette vision prend appui sur l'idée que des difficultés touchant notamment le langage, les FE et la cognition sociale peuvent miner la compétence sociale.

Plus spécifiquement, le langage est une sphère de vulnérabilité largement documentée dans la population atteinte de CC (Bellinger et al., 2003; Fourdain et al., 2019; Hicks et al., 2016; Hovels-Gurich et al., 2008; Mussatto et al., 2015; Sommariva et al., 2020) et la cohorte d'enfants étudiée dans la présente thèse n'y fait pas exception. Cependant, le langage à lui seul ne constitue pas un facteur contribuant significativement à la compétence sociale, contrairement à ce à quoi on pourrait s'attendre, à la lumière d'études dans diverses populations cliniques pédiatriques. On peut toutefois se questionner sur la composante du langage à préconiser dans la compréhension du fonctionnement social, qui reste d'ailleurs sujet à débat dans la littérature actuelle. Dans notre étude, nous avons opté pour le langage global (score du langage fondamental de la CELF) regroupant différents aspects du langage réceptif et expressif, étant donné que les deux versants du langage ont montré une influence dans le fonctionnement social lors de diverses études antérieures (Bellerose et al., 2015; Calderon, Angeard, et al., 2014; Caplan, 2019; Ryan et al., 2014). En revanche, les sous-échelles qui composent le score de langage fondamental concernent des éléments de connaissances (vocabulaire) et fonctionnels (syntaxe, grammaire) du langage. Il est néanmoins possible que des aspects plus raffinés du langage, tels que la pragmatique (Caplan, 2019; Junge et al., 2020), voire même certains aspects de la communication non-verbale (Raissadati et al., 2020) contribuent davantage à la compétence sociale que le score de langage global utilisé ici.

Le fonctionnement exécutif, tant au niveau de la performance directe que des résultats issus des questionnaires parentaux, constitue un prédicteur important dans la compétence sociale, de sorte qu'un bon fonctionnement exécutif est associé à de bonnes compétences sociales et vice-versa. Ce résultat s'ajoute au bassin de littérature actuelle ayant mis en lumière l'intime relation entre le développement des FE et le fonctionnement social dans la population pédiatrique

(Alduncin et al., 2014; Bernier et al., 2020; Ganesalingam et al., 2011; Gomes et al., 2012; Tuerk et al., 2020; Vera-Estay et al., 2016) et chez les enfants atteints de CC spécifiquement (Calderon et al., 2010).

Enfin, la cognition sociale, plus précisément la TdE constitue également un prédicteur indépendant significatif de la compétence sociale, de sorte qu'une meilleure performance en TdE est associée à une meilleure compétence sociale rapportée par les parents. Ceci est cohérent avec d'autres études issues de diverses populations pédiatriques, voulant que des difficultés en TdE aillent de pair avec des difficultés en compétence sociale (Beaudoin & Beauchamp, 2020; Bellerose et al., 2017; Huber et al., 2019; Stewart et al., 2019). Le fait que la compétence sociale apparait préservée dans notre cohorte nous pousse cependant à nous questionner sur l'implication concrète ou pratique de cette relation statistique. D'abord, il est possible que l'impact d'une faible TdE ne soit pas tangible à l'âge préscolaire, où les demandes de l'environnement demeurent relativement peu exigeantes en matière d'habiletés sociales, mais qu'elles deviennent plus saillantes avec l'âge. Les difficultés identifiées en TdE pourraient ainsi se traduire en une moindre compétence sociale seulement plus tard dans le développement des enfants avec CC, tel que proposé pour le FE. Alternativement, il est également possible que d'autres facteurs soient impliqués et permettent d'expliquer la préservation de la compétence sociale, malgré la faible cognition sociale chez les enfants de notre cohorte. Ainsi, certains facteurs de protections, tels que le tempérament de l'enfant ou le style parental, pourraient favoriser le déploiement de bonnes compétences sociales chez l'enfant atteint de CC, malgré les vulnébilités sociocognitives qu'il présente (Lalonde et al., 2018; Tuerk et al., 2020). Ces hypothèses demeurent spéculatives et devraient faire l'objet d'investigation empirique.

2.2. Trajectoire neurodéveloppementale chez l'enfant atteint de CC

Au-delà de la caractérisation du profil neuropsychologique des enfants atteints de CC, l'adoption d'une perspective globale implique également une vision ou une approche développementale. Alors que la majorité des connaissances relatives au développement neurologique des personnes atteintes de CC ont été acquises à partir d'études transversales (Sanz et al., 2021), la seconde étude de cette thèse offre ainsi une vision longitudinale du neurodéveloppement d'une cohorte d'enfants atteints de CC.

En plus de contrer le manque de données longitudinales dans la littérature actuelle, l'adoption d'une vision développementale, s'inscrivant donc dans une trajectoire, nous apparait essentielle à plusieurs égards. D'abord, le manque de données quant à la stabilité du fonctionnement rend le pronostic difficile à révéler pour le clinicien œuvrant auprès de cette population (Naef et al., 2019). Alors que certaines étapes développementales peuvent être acquises normalement, de nouvelles difficultés peuvent survenir avec la complexité croissante des demandes de l'environnement. À l'instar des résultats issus de la présente thèse, qui montrent que l'écart entre le fonctionnement cognitif des enfants atteints de CC et la population générale s'accroit avec l'âge (c.-à-d. diminution du fonctionnement à travers le temps), des études précédentes ont aussi montré des difficultés ou retards qui s'accentuent en vieillissant (Brosig et al., 2018; Goldberg et al., 2014). Ainsi, l'idée qu'un enfant présentant des problèmes de développement rattrapera éventuellement ses pairs en santé et qu'il est souhaitable d'attendre et de voir comment l'enfant se développe pourrait s'avérer un pari risqué chez les enfants avec CC (Ware et al., 2020). Autrement dit, un examen rassurant pendant la petite enfance n'est pas toujours synonyme d'un développement typique à long terme, car les enfants sont confrontés à des tâches et des activités de plus en plus complexes à mesure qu'ils grandissent. Alors que le cerveau et la

cognition se développent, de nouvelles habiletés et sphères de vulnérabilités voient le jour. Par conséquent, le respect des protocoles de suivi planifiés est important pour tous les enfants atteints de CC, quelle que soit leur présentation au début de leur vie (Ware et al., 2020).

De nombreuses études effectuées dans diverses populations pédiatriques ont d'ailleurs démontré les bénéfices d'une prise en charge clinique précoce et rapide sur le pronostic neurodévelppemental (Britto et al., 2017; Estes et al., 2015; Gallagher et al., 2017; Spittle et al., 2015). Ce genre de suivi permet en effet d'identifier rapidement les enfants qui présentent des difficultés dans un ou plusieurs domaines, même si celles-ci n'ont pas été mises en évidence par l'entremise d'un suivi antérieur. Ceci est d'autant plus essentiel sachant que des difficultés non identifiées peuvent non seulement s'exacerber, mais aussi avoir des répercussions dans d'autres domaines de développement, phénomène mieux connu sous le concept de « cascade développementale » (Cassidy et al., 2016; Misheva, 2020)..

Cette idéologie de prise en charge clinique précoce et systématique, bien qu'appuyée par de multiples études, ne va pas sans se heurter aux contraintes d'accessibilités de ressources auxquelles sont confrontés la majorité des établissements du Québec. Alors que la responsabilité d'offrir des services appropriés s'impose, il est tout aussi primordial de cibler judicieusement les besoins en fonction de l'âge ; et ultimement, d'identifier les enfants ou les sphères développementales les plus à risque. Ceci dans le but de dépister rapidement les difficultés afin de limiter leur impact dans le fonctionnement quotidien et d'éviter une cascade développementale de problèmes.

À cet égard, le second article de cette thèse visait précisément l'identification de marqueurs précoces des difficultés identifiées à l'âge de 5 ans. Deux constats découlent de ces résultats.

2.2.1. Efficacité du dépistage langagier.

Les résultats de l'**article 2** de cette thèse montrent des difficultés langagières qui persistent à l'âge préscolaire (5 ans) et qui touchent principalement le versant expressif du langage. Ceci est cohérent avec d'autres études dans cette population montrant que les difficultés touchant l'expression langagière persistent au cours de l'enfance (Bellinger et al., 2003; Brosig et al., 2007; Hovels-Gurich et al., 2008). Malgré qu'une vulnérabilité persiste dans cette sphère de développement, et malgré l'importance incontestable du bon développement langagier dans l'intégration sociale et scolaire de ces enfants, il convient de rappeler que ces difficultés peuvent être identifiées avant l'âge de 5 ans.

Alors que la trajectoire du développement du langage réceptif est marquée par une amélioration du fonctionnement entre 1 et 5 ans, conformément à ce qui a d'ailleurs été rapporté dans une étude précédente de notre laboratoire portant chez des enfants plus jeunes (Fourdain et al., 2019), le langage global, tout comme son versant expressif, demeurent stables mais légèrement en deçà des attentes par rapport aux pairs entre 1, 2 et 5 ans.

Par ailleurs, considérant le bon apport prédictif du langage mesuré à deux ans pour identifier les enfants qui présentent des difficultés langagières à 5 ans, l'évaluation systématique du fonctionnement langagier au moment de l'entrée à l'école apparait moins essentielle dans le cadre d'un suivi longitudinal. De par la surveillance en bas âge (12 et 24 mois), les enfants qui présentent des difficultés légères à modérées (-1 à -2 É.T. sous la norme des tests) et des déficits langagiers (<-2 É.T. sous la norme des tests) à l'âge de 5 ans bénéficiaient généralement déjà d'une prise en charge en orthophonie depuis un plus jeune âge. Ainsi, bien que des difficultés langagières persistent à 5 ans, l'évaluation systématique du fonctionnement langagier ne nous semble pas

essentielle à cet âge dans le cadre du suivi clinique à la CINC. Cependant, une vigilance devrait être portée et le jugement clinique est de mise afin de référer, au besoin, des enfants qui présentent des difficultés langagières qui n'auraient pas été identifiées dans le cadre d'un suivi antérieur.

2.2.2. Inefficacité du dépistage attentionnel, exécutif et préacadémique.

Les autres résultats neurodéveloppementaux en bas âge sont peu ou pas associés aux différentes sphères de fonctionnement neuropsychologique mesurées à 5 ans. Une exception concerne toutefois la forte association entre l'échelle cognitive à 2 ans et l'acquisition des concepts de bases en mathématiques à 5 ans, permettant une identification des enfants à risque de difficultés en mathématiques avec le suivi antérieur. Ce résultat s'accorde d'ailleurs avec ceux de précédentes études montrant l'importance de divers aspects du fonctionnement cognitif sur les habiletés ultérieures en mathématiques (Ilardi & LaMotte, 2021; Mulder et al., 2017; Simanowski & Krajewski, 2017). À l'inverse, aucune composante du fonctionnement en bas âge n'a permis de prédire les difficultés aux prérequis à la lecture. De plus, bien que les difficultés d'ordre attentionnelles et exécutives (mémoire de travail) soient hautement prévalentes dans notre cohorte à 5 ans (affectent 40 à 66 % des enfants), elles ne peuvent être identifiables autrement que par l'évaluation directe de ces enfants et fonctions étant donné leur faible association avec les résultats neurodéveloppementaux antérieurs.

2.3. Implications sur la prise en charge clinique

Dans un premier temps, nos résultats sont cohérents avec ceux des études antérieures voulant que le neurodéveloppement précoce (<18 mois) ait une valeur prédictive limitée pour les années d'âge préscolaire et au-delà (Sanz et al., 2021; Ware et al., 2020). Ces conclusions abondent dans le même sens que ceux de Fourdain et ses collaborateurs (2019), qui ont montré qu'une évaluation systématique à 12 mois n'était pas essentielle pour dépister les enfants les plus à risque

sur le plan langagier. Nos résultats élargissent ce constat à d'autres sphères neurodéveloppementales et, ensemble, ont mené à l'abandon de l'évaluation systématique des enfants de 12 mois suivis à la CINC afin d'optimiser l'utilisation des ressources de la clinique.

Lorsque les plus récents consensus d'experts (Ilardi et al., 2020; Ware et al., 2020) et le profil neuropsychologique des enfants illustré dans le second article de la présente thèse sont mis en relation, nous sommes confrontés au fait qu'une évaluation systématique est primordiale à l'âge de 5 ans. Ce constat est ainsi aligné avec les plus récentes recommandations du CNOC qui, en novembre 2020, a publié des lignes directrices faisant suite à celles initialement élaborées par Marino et ses collègues (Marino et al., 2012), afin de préciser les batteries d'évaluation à privilégier chez les enfants atteints de CC de différents âges (Ilardi et al., 2020; Ware et al., 2020).

Globalement, ces recommandations veulent que les enfants atteints de CC bénéficient d'un suivi neurodéveloppemental longitudinal permettant de répondre à leurs besoins qui évoluent avec l'âge (Ilardi et al., 2020; Marino et al., 2012; Ware et al., 2020), ce qui implique aussi l'évaluation de diverses sphères de fonctionnement à mesure qu'ils grandissent. Par l'entremise de ce suivi longitudinal, l'adoption d'une vision biopsychosociale du développement de l'enfant est d'ailleurs préconisée afin de tenir compte d'une multiplicité de facteurs propre à l'enfant (sexe, race), à son histoire médicale (facteurs périnataux, cardiaques, chirurgicaux et génétiques) et à l'environnement dans lequel il évolue (éducation des parents, statut socioéconomique, multilinguisme).

Ces recommandations du CNOC impliquent l'évaluation du fonctionnement cognitif, moteur et langagier (Bayley Scales of Infant & Toddler Development) vers l'âge de 2 ans (entre 13 et 29 mois), ainsi que l'évaluation du fonctionnement intellectuel (Wechsler Preschool and Primary Scale of Intelligence ; WPPSI) entre 3 et 5 ans (Ware et al., 2020). D'autres mesures, telles que des mesures de croissance de l'enfant, mais aussi des questionnaires visant à dépister la

présence de problèmes comportementaux (Behaviour Assessment Scale for Children; BASC), exécutifs (BRIEF), adaptatifs (Adaptive Behaviour Assessment Scale; ABAS) et socio-communicatifs (Social Responsiveness Scale et Infant-Toddler Social and Emotional Assessment) au quotidien, en plus de la santé psychologique du parent (Depression, Anxiety & Stress Scale - 21), y sont recommandées. À l'âge scolaire, des évaluations sont prescrites par ce regroupement d'experts lors de certaines périodes clés, telles qu'au moment de l'entrée à l'école (5 ans), entre 8 et 10 ans, au moment où différents concepts se consolident, vers 13 ans ou au début du secondaire, et à 18 ans, soit lors de la transition à l'âge adulte. Alors que de futures études sont nécessaires (et actuellement en cours) afin de caractériser plus spécifiquement les besoins et défis auxquels sont confrontés les patients suivis à la CINC, les conclusions du profil neuropsychologique observé à l'âge de 5 ans renforcent la nécessité de ce suivi.

À l'âge de 5 ans, les recommandations du CNOC quant à la prise en charge de base de ces enfants incluent l'évaluation du fonctionnement intellectuel, la préparation à la scolarisation (*school readiness*) et des habiletés de bases à la lecture et aux mathématiques ; ainsi que la motricité fine. Bien que l'évaluation directe de l'attention et du fonctionnement exécutif n'y soit pas mentionnée pour les enfants en bas âge, celle-ci nous apparait primordiale dès 5 ans, compte tenu de l'ampleur des difficultés qui ressortent dans notre cohorte et de l'importance de ces habiletés dans le fonctionnement scolaire mentionné plus haut.

À ce stade, il convient de mentionner que, à la lumière des résultats issus de l'article 2, les gestionnaires de la clinique ont été rencontrés et les besoins mis en relief ont été présentés. Ceci a conduit à orienter la prise en charge clinique et des évaluations systématiques de tous les enfants suivis à la CINC à l'âge de 5 ans devraient être mises en place (Annexe 1).

3. Limites

Les résultats issus de la présente thèse doivent être interprétés à la lumière de certaines limites méthodologiques, lesquelles sont détaillées dans chacun des articles. Tout d'abord, les études présentées dans cette thèse ont été conduites dans une population très hétérogène en termes sociodémographique (ethnie, genre, statut socioéconomique) et médical (facteurs liés à la CC et à la chirurgie), et ce, sur un nombre limité de participants. Par conséquent, elles les analyses statistiques employées n'intègrent qu'un petit nombre de variables en lien avec le fonctionnement neuropsychologique et social. Or, une pluralité de facteurs est susceptible d'influencer le fonctionnement observé et ainsi, certains facteurs n'ayant pas été considérés dans nos analyses statistiques ont pu jouer un rôle dans les résultats mesurés. D'autres facteurs pourraient donc être incorporés dans des études futures, notamment d'autres variables médiatrices individuelles, familiales, sociales et culturelles décrites dans le modèle SOCIAL (p.ex. : le tempérament, la position dans la fratrie, la qualité de la relation parent-enfant, le stress parental, etc.). Enfin, l'évaluation d'une plus grande diversité de FE (p.ex. inhibition, flexibilité, auto-régulation) auraient permis de capter avec plus de finesse l'émergence de ces fonctions à l'âge préscolaire en contexte de CC. Cela reste toutefois difficile à effectuer sur le plan méthodologique compte tenu le nombre restreint d'outils valides et standardisés disponibles pour les enfants de cet âge.

4. Avenues futures

En dépit des défis méthodologiques, la présente thèse a permis de spécifier le fonctionnement neuropsychologique et social de l'enfant atteint de CC jusqu'à l'âge préscolaire. Les besoins qui ressortent du profil neuropsychologique observé démontrent la nécessité d'offrir des interventions appropriées en vue de permettre à ces enfants d'atteindre leur plein potentiel. À cet effet, notons

que l'efficacité d'une intervention de yoga parent-enfant sur les habiletés attentionnelles est actuellement étudiée chez les enfants de 4 à 6 ans atteints de CC qui sont suivis à la CINC. En parallèle, d'autres avenues d'intervention et de prise en charge devraient être étudiées dans cette population vulnérable, particulièrement au moment de l'entrée à l'école.

Par ailleurs, l'inclusion des parents des enfants CC s'avère essentielle afin que les avenues de recherches futures s'accordent avec les besoins exprimés par la famille (Williams et al., 2019). À cet égard, un groupe de parents partenaires a été mis en place à l'été 2021, afin de mieux connaître les défis auxquels ont fait face les parents d'enfants atteints de CC à partir du moment où ils ont appris le diagnostic et par la suite.

De plus, l'ajout de diverses mesures évaluant le fonctionnement de l'enfant dans son quotidien (p.ex. qualité de vie, fonctionnement à l'école ou à la garderie, etc.) et leurs liens avec les mesures directes des habiletés permettrait de mieux saisir l'impact concret du profil neuropsychologique observé chez l'enfant d'âge préscolaire. De même, l'évolution neurodéveloppementale des enfants suivis à la CINC au-delà de l'âge préscolaire reste à élucider. Des études allant jusqu'à l'âge scolaire (8-12 ans), l'adolescence (13-18 ans) et même jusqu'à l'âge adulte sont nécessaires afin de mieux comprendre l'impact réel des difficultés mesurées en bas âge sur le fonctionnement à plus long terme.

Enfin, il serait nécessaire d'investiguer les mécanismes cérébraux sous-jacents à ces retards et/ou dysfonctionnements observés chez les enfants atteints de CC, à l'aide de techniques de neuroimagerie. Précisément les corrélats neuronaux associés au développement sain et atypique du langage dans la population pédiatrique ont été détaillés dans une étude précédente, faisant l'objet de l'annexe II (Gaudet et al., 2020). Les résultats de cette revue systématique pourraient être étendus à l'évaluation langagière de l'enfant atteint de CC, voir même potentiellement à l'étude du

fonctionnement neuropsychologique de manière plus globale, permettant ultimement de mieux identifier les enfants à risque ainsi qu'à adapter et préciser les cibles d'intervention qui leur sont offertes.

5. Conclusion

Cette thèse s'inscrit dans le souci de mieux comprendre les besoins neuropsychologiques chez les enfants d'âge préscolaire atteints de CC. Plusieurs changements cérébraux et neuropsychologiques s'opèrent pendant la période et le jeune enfant réalise des progrès considérables. Chez le survivant à la CC, cette période en est aussi une où les vulnérabilités neurodéveloppementales peuvent être plus apparentes. Considérant les besoins flagrants qu'ils présentent à cet âge, un suivi approprié s'avère essentiel pour optimiser leurs chances d'atteindre leur plein potentiel et atténuer l'impact des difficultés sur leur fonctionnement scolaire et social.

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ANNEXES

Annexe I – Proposition des épreuves d'évaluations des fonctions cognitives et langagières des enfants de 5 ans suivis à la CINC

Durée totale : 1h25 (+45 min si le CELF est administré)

Tests	Sous-tests	Fonctions	Durée (min)	CINC5?	CNOC protocol ?
WPSSI-IV	Connaissances Similitudes Blocs Matrices Reconnaissance d'images Repérage d'insectes	Fonctionnement global	45	oui	*core*
K-CPT		Attention soutenue, inhibition	10	oui	non
NEPSY	Processus phonologiques	Conscience phonologique	7	oui	non
NEPSY	Production de mots	Accès lexical, organisation	3	oui	*extended*
CMS	Empan de chiffres	Attention immédiate, mémoire de travail	5	oui	non
Key-Math	Numération Mesure	Concept du nombre Estimation des quantités et comparaison d'objets	10 10	oui oui	oui, mais autres ss-tests
Évaluation en orthophonie au besoin[1]					
CELF	Concepts et exécution de directives Morphologie Répétition de phrases Vocabulaire expressif Compréhension paragraphes à l'oral	Compréhension de consignes Structure des mots Mémoire verbale à court terme, habiletés morphosyntaxiques Dénomination Langage réceptif	45	oui	*extended*
Questionnaires parentaux					
BRIEF		Fonctionnement exécutif/comportement		oui	*core*
BASC[2]	Version parent Version enseignant ou éducateur	Comportement à la maison Comportement à l'école		oui	*core*
PSI		Stress parental		oui	*extended*
SCQ		Habiletés sociales		oui	non (SRS)
ABAS[3]		Comportements adaptatifs		oui	*core*

[1]Seulement pour les enfants chez qui des difficultés langagières sont observées lors de l'évaluation et qui n'ont pas de suivi en orthophonie en CR

[2]Le BASC est plus sensible que le CBCL et est recommandé par le CNOC. Toutefois, comparativement au CBCL il ne se retrouve pas sur AIDE.

[3]seulement si l'échelle globale (QI) du WPPSI est < 75.

Annexe II : Article 4

Functional Brain Connectivity of Language Functions in Children Revealed by EEG and MEG: A Systematic Review

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Article publié dans *Frontiers in Human Neuroscience*, *Vol. 14* (issue 62) https://doi.org/10.3389/fnhum.2020.00062

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 effective connectivity 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

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., 2015; Tremblay and 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, functional connectivity 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, 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, 2011). With the sharp increase of studies on brain connectivity, researchers have developed and applied increasingly sophisticated analytic strategies that highlight functional or effective connectivity (EC) and that allow a more advanced exploration of interactions between

regional structures and networks involved in language development (Bastos and Schoffelen, 2016). In the past few years, novel neuroimaging techniques and methods of analysis have enabled the examination of functional connectivity 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 (~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 millisecond). 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 and Friederici, 2016).

So far, neuronal accounts of language system development largely rely on EEG data (Skeide and 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 functional connectivity between electrodes.

In order to perform functional connectivity 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 (4–7 Hz), alpha (8–12 Hz), beta (13–30 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 and 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 (Vértes and Bullmore, 2015; Meng and Xiang, 2016; Oldham and Fornito, 2018). 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 and 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 and 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 and Van Wassenhove, 2017; Meyer, 2018). More specifically, delta range (<4 Hz) has been associated with intonational processing and syntactic comprehension (Kösem and 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 (4–7 Hz) synchronizes with syllabic rates (Giraud and Poeppel, 2012; Meyer, 2018) and that theta coherence increases in tasks involving verbal information retrieval and verbal working memory (Friederici and Singer, 2015; Meyer, 2018). Alpha (8– 12 Hz) oscillations may also play a role in verbal working memory (Friederici and Singer, 2015; Meyer, 2018). Beta activity (13– 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 and 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 functional connectivity 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., Kida et al., 2015; Bastos and Schoffelen, 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 and 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 (Nolte et al., 2008; Bastos and Schoffelen, 2016). 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 (Sporns et al., 2004; Stam, 2004; Bullmore and Sporns, 2009). Subsequent connectivity metrics of all paired electrodes can then be explored between regions, using the Graph theory approach (Stam and 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 (2015) 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 and 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 functional connectivity 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.

METHODS

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.

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) functional or EC analysis was performed based on EEG or MEG data. We verified whether the described methods allowed actual interpretation of functional connectivity or applied different techniques such as intertrial synchronization, ERP timing, or time-frequency analysis, which were sometimes referred to as functional connectivity, but do not in fact fall in this category (Sakkalis, 2011; Bastos and Schoffelen, 2016). (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 **Figure 1**.

Data Extraction

Following the database search, duplicates were removed. For all remaining articles, titles and abstracts were reviewed by the first author (IG) and selected for a second revision if they met at least one of the inclusion criteria. For the second revision, remaining articles were reviewed independently by two authors (IG and AH), 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 (PV) helped make the ultimate decision on eligibility. **Figure 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 functional connectivity in the study of spoken language in children.

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 (see **Table 1** for studies including healthy children and **Table 2** for those addressing clinical populations). Each table begins with studies using EEG (Tables 1A, 2A) followed by those employing MEG (Tables 1B, 2B).

Thirteen of the articles covered in this review addressed functional connectivity 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%).

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– 12 months). Toddlers are children aged between 1 and 3 years; preschoolers include the period from 3 to 5 years of age, grade- schoolers 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 grade-schoolers (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.

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**, **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 functional connectivity. 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 functional connectivity, followed by those using EC. Again, the results will be indicated separately for healthy children and children with various clinical conditions

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 (Hövels-Gürich et al., 2008; Hövels-Gürich and Mccusker, 2016; Fourdain et al., 2019). 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

(Yang et al., 2005; Doesburg et al., 2016) and beta (Yang et al., 2005; Doesburg et al., 2016). 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 **Figure 4** (for healthy children) and **Figure 5** (for clinical populations).

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 grade-schoolers 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.

Finally, it should be noted that two studies (Njiokiktjien et al., 2001; Vasil'yeva and 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 and 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.

Results Derived From Connectivity Metrics

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 (Sakkalis, 2011; Van Mierlo et al., 2014; Hassan and Wendling, 2018). 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 (Van Mierlo et al., 2014; Bowyer, 2016). 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 (9–16 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 (Mundy et al., 2003; Marshall et al., 2008; Kikuchi et al., 2011; Kühn-Popp et al., 2016; Whedon et al., 2016) and grade-schoolers (Yang et al., 2005). Specifically, between 5 and 10 months of age, an increase in resting-state EEG coherence in the theta–alpha band (6–9 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 (4–6 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 (6–9 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 (6–8 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 (6–10 Hz) and alpha–beta (11–18 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 (Hövels-Gürich et al., 2008; Hövels-Gürich and Mccusker, 2016; Fourdain et al., 2019) 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 (Righi et al., 2014; Kovelman et al., 2015; Mamashli et al., 2017). 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 (8–12 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 (9–15 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 Figure 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 (6–11 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.

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 (12–15 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 ≤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 (13–18 Hz; during the first syllable) and later in alpha (8–12 Hz; after the word) over the left and right temporal areas (Kabdebon et al., 2015).

Using auditory stimuli in children (8–14 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.

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 (4–18 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 (4–6 years old) were compared to adolescents (16–18 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 (14–18 years old), compared to younger children (4–9 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 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 functional connectivity 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%).

Directionality of Language Networks (Effective Connectivity)

Effective connectivity reveals the directionality of information flow in particular brain regions and the causal and dynamic influences of one region on another (Stephan and Friston, 2010; Friston, 2011). 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 and 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 (4–6 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. Effective connectivity 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 grade-schoolers (8–14 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.

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.

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 (Mundy et al., 2003; Kühn-Popp et al., 2016; Whedon et al., 2016). In older children (grade-schoolers 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 (Figure 3), it is critical to look at all different frequency bands, especially in older children (grade-schoolers and adolescents).

Further, theta frequency band has been related to syllabic processing (Giraud and Poeppel, 2012; Meyer, 2018), and increases in theta activation have been found for tasks that include verbal working memory (Friederici and 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 and 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 (Kikuchi et al., 2011; Asano et al., 2015) and expressive (Doesburg et al., 2012, 2016; 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 (Righi et al., 2014; Lizarazu et al., 2015; Mamashli et al., 2017).

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 (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 (Mundy et al., 2003; Kikuchi et al., 2011; Kühn-Popp et al., 2016; 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 (Righi et al., 2014; Barnes-Davis et al., 2018) 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 (Kikuchi et al., 2011; Doesburg et al., 2016; Kadis et al., 2016). 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 and 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., Weiss-Croft and Baldeweg, 2015; Rimmele et al., 2018). 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 (Gur and Gur, 2016, 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.

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 and 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., 2015). 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.

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., Nunez et al., 1997; Sakkalis, 2011; Barzegaran and Knyazeva, 2017; Abreu et al., 2018, 2019). 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 and 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 and 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 and 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 functional connectivity, 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.

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.

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 (Kadis et al., 2016; Molinaro et al., 2016; Barnes-Davis et al., 2018) 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.

Conclusion and Future Directions

The analysis of brain functional connectivity 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.

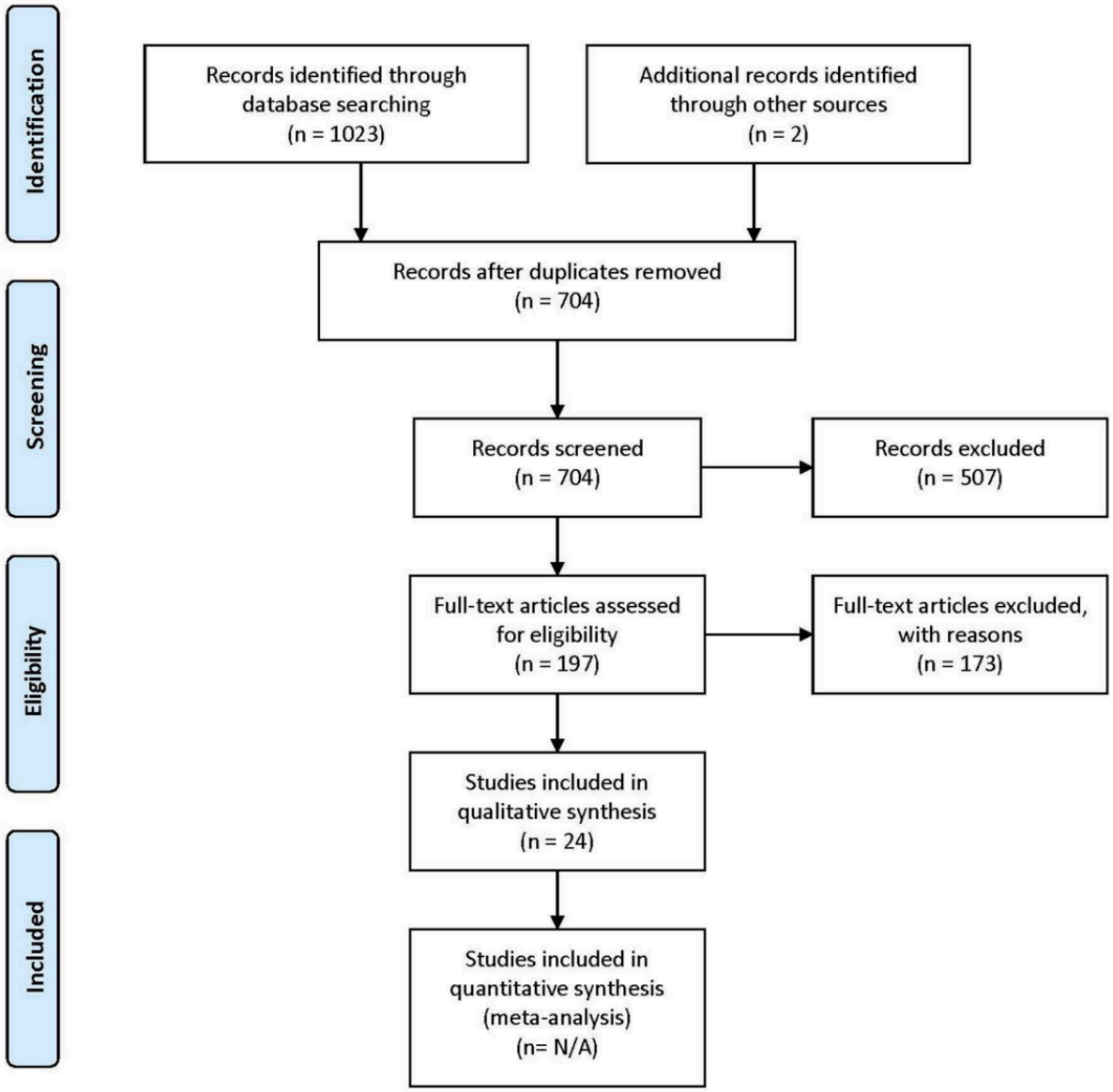

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram describing the paper selection process.

Figure adapted from Moher et al. (2009).

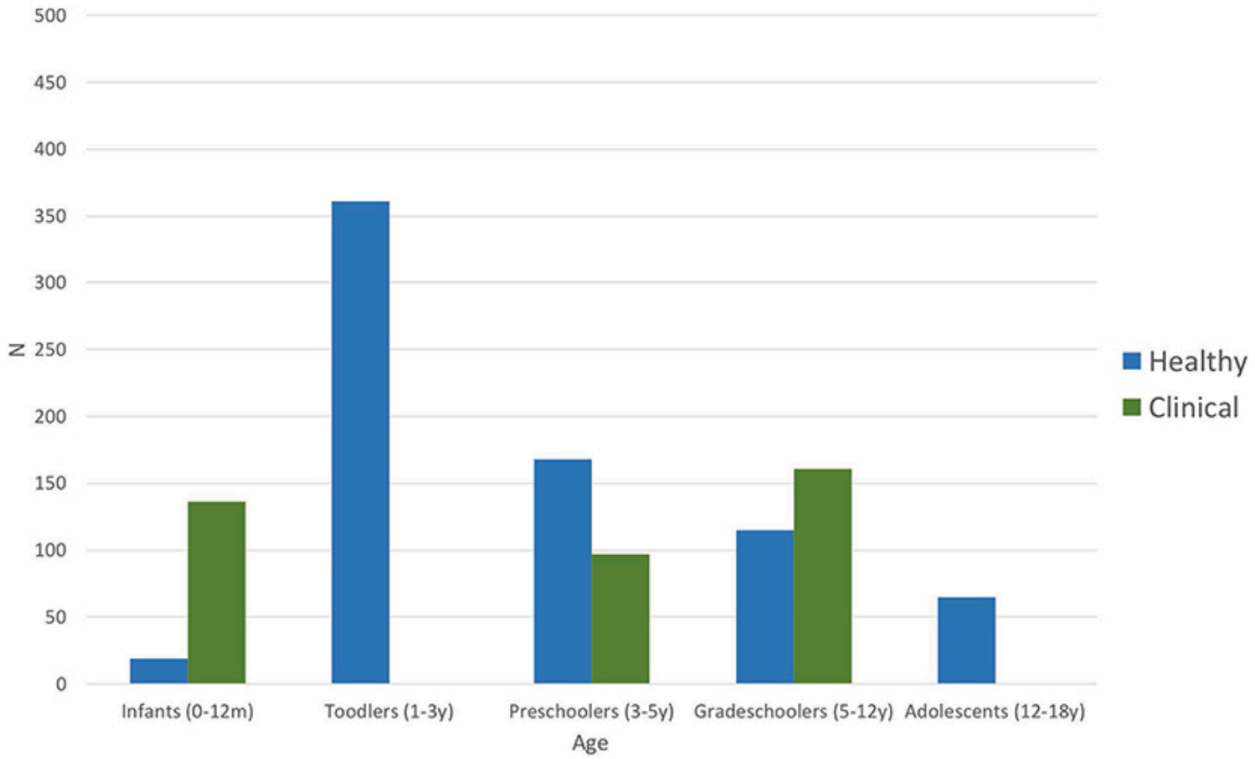

Figure 2. – Number of participants per age group of all included studies (n = 24).

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).

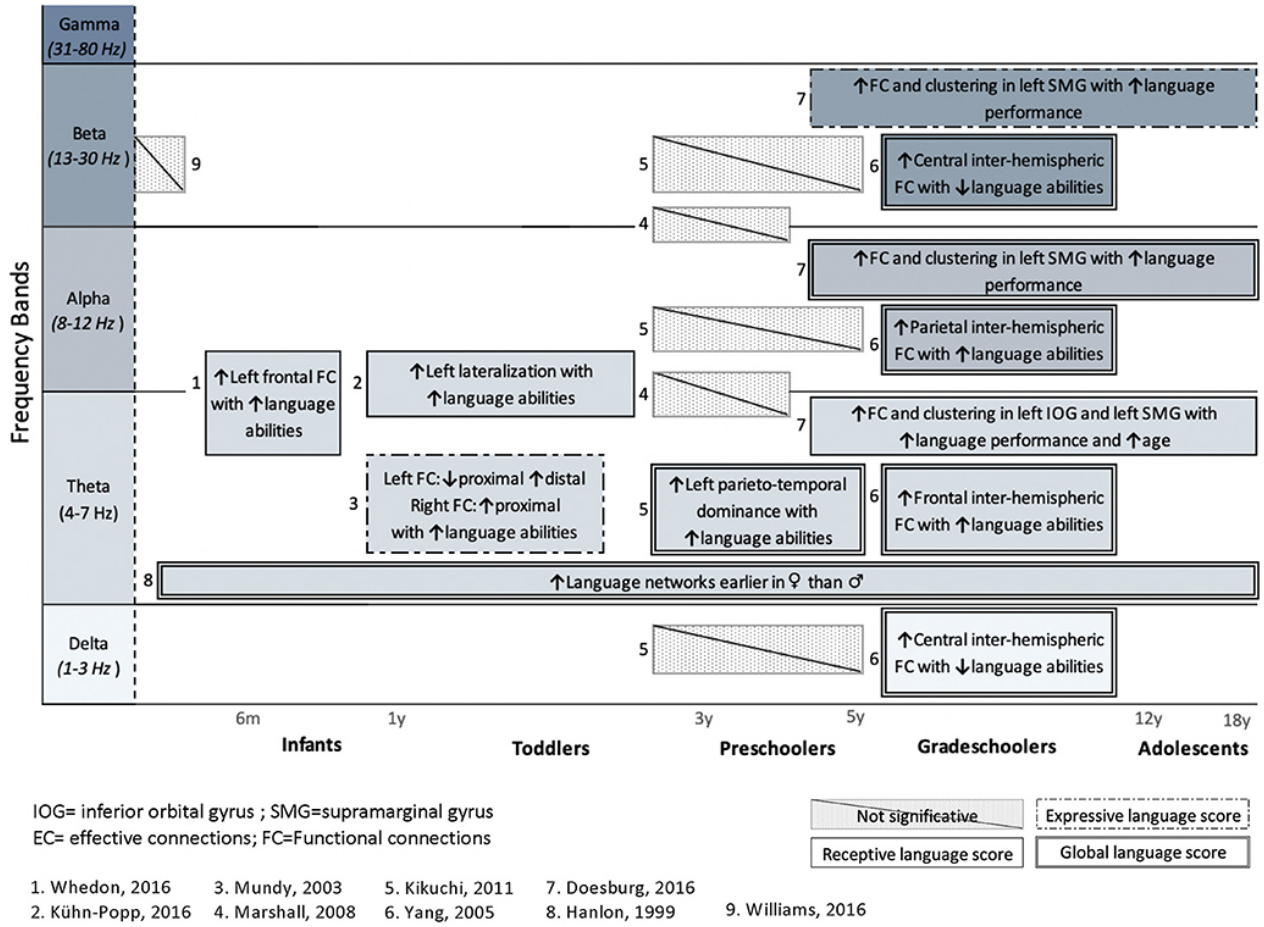

Figure 3. – Summary of studies investigating the association between language abilities, assessed with standardized tools, and cerebral language networks.

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 1), or global language functioning (solid double lines), whereas downward arrow (↓) indicates negative correlation with language. Hatched areas represent non-significant correlations with language abilities.

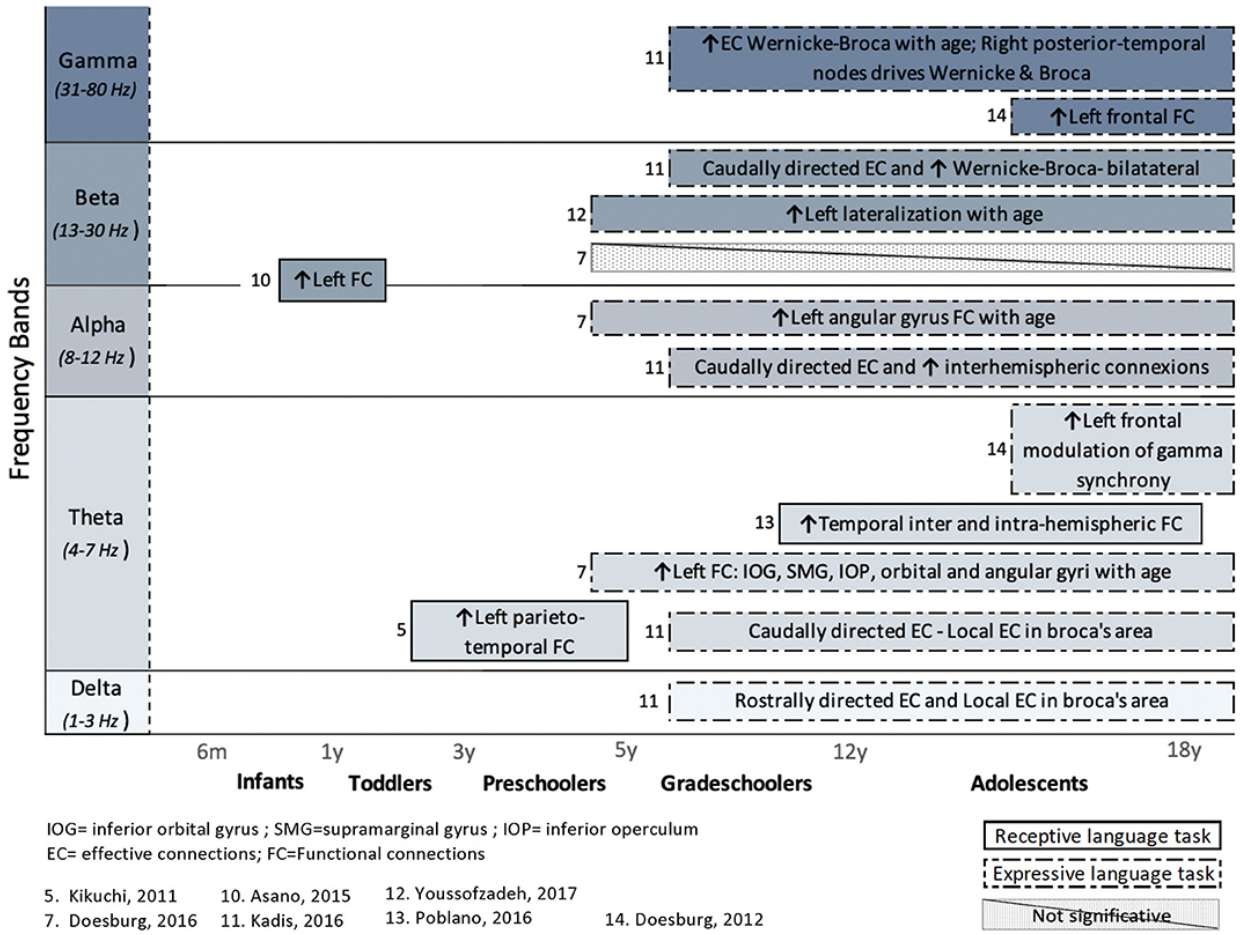

Figure 4. – Overview of task-related connectivity patterns in healthy subjects.

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

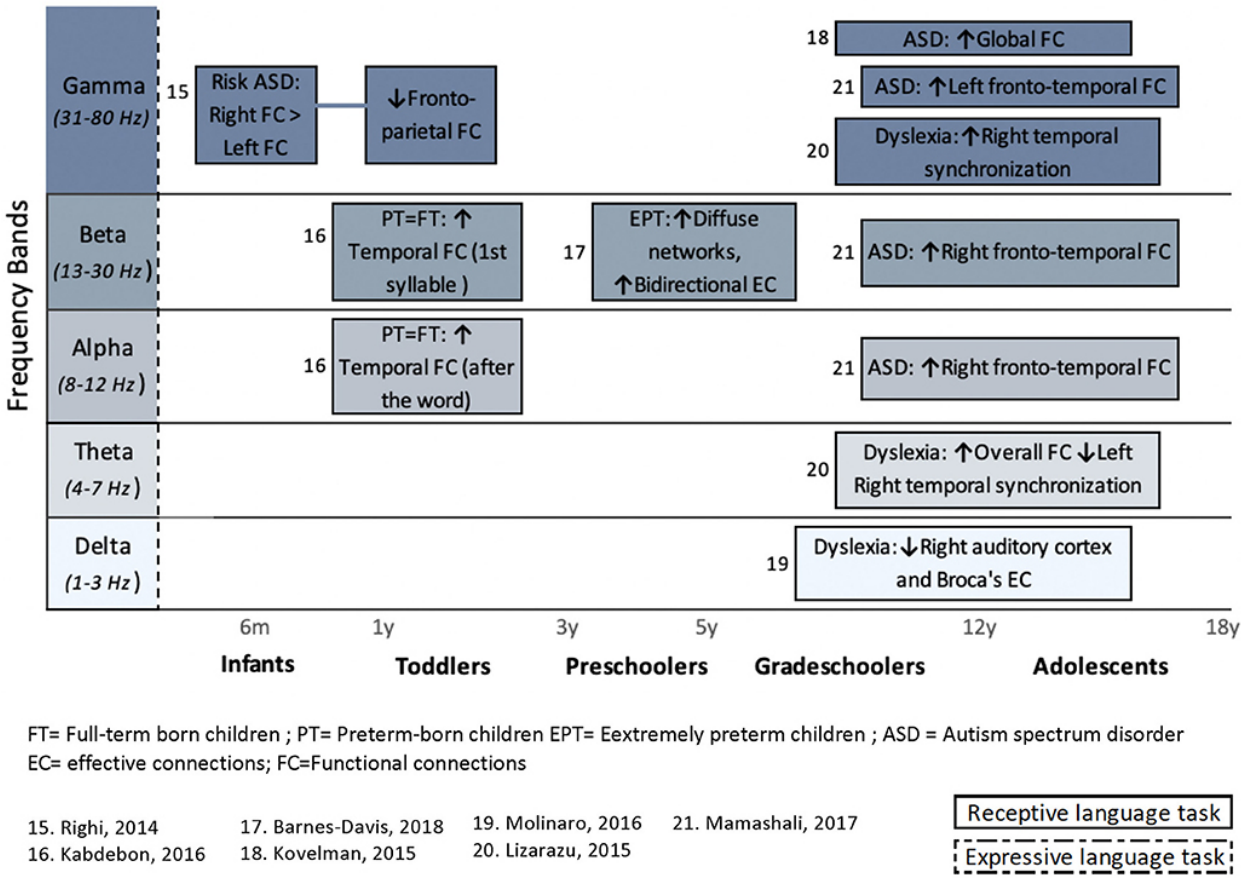

Figure 5. – Overview of task-related connectivity patterns in clinical populations compared to healthy subjects.

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.

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

References	*n* (M/F)	Age	Design	EEG/MEG paradigm	Language assessment	Frequency band(s)	Source/ sensor	Connectivity analysis
EEG								
Asano et al., 2015	13/6	11 mo	Cross-sectional	Symbol–sound mismatch	N/A	Alpha, beta	Sensor	Phase locking value
Hanlon et al., 1999	284/224	0–16.75 y	Cross-sectional	Resting	N/A	Theta	Sensor	Coherence
Kühn-Popp et al., 2016	15/17	14; 15 and 42 mo	Longitudinal	Resting	Declarative pointing and Verbal-IQ	Theta–alpha	Sensor	Coherence
Marshall et al., 2008	48/42	30 and 42 mo	Longitudinal	Resting	Reynell Developmental Language Scales	Theta, alpha, beta	Sensor	Coherence
Mundy et al., 2003	18/14	14–24 mo	Longitudinal	Resting	MCDI	Theta	Sensor	Coherence
Poblano et al., 2016	18/18	9–16 y	Cross-sectional	Resting; Lexical-tonal discrimination	N/A	Theta	Sensor	Pearson correlation
Whedon et al., 2016	153/147	6–34 mo	Longitudinal	Resting	PPVT-III[2]	Theta–alpha	Sensor	Coherence
Yang et al., 2005	23 (N/A)	6–8 y	Cross-sectional	Resting	Verbal-IQ	Delta, theta, alpha, beta	Sensor	Pearson correlation
MEG								
Doesburg et al., 2016	31/42	4–18 y	Cross-sectional	Word generation	PPVT, EVT	Alpha, beta, theta	Source	Phase locking value, phase lag index, graph theory
Doesburg et al., 2012	5/5	16–19 y	Cross-sectional	Word generation	N/A	Gamma, theta	Source	Phase locking value
Kadis et al., 2016	13/8	5–18 y	Retrospective	Word generation	N/A	All	Source	Phase slope index
Kikuchi et al., 2011	36/42	32–64 mo	Cross-sectional	Story listening	Expressive Vocabulary and Riddles (K-ABC)	Delta, theta, alpha, beta	Sensor	Coherence
Youssofzadeh et al., 2017	13/16	4–18 y	Cross-sectional	Word generation	N/A	Theta, alpha, beta, gamma	Source	Phase locking value

Studies in the first part of the table used EEG, whereas those in the second part applied MEG.
M, male; F, female; N/A, not applicable; MCDI, Mac-Arthur communicative developmental inventory; PPVT, Peabody Picture Vocabulary Test; ECT, Expressive Vocabulary Test; K-ABC, Kaufman Assessment Battery.

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

References	Pathology	*n* (M/F)	Age	Design	EEG/MEG paradigm	Language assessment	Frequency band(s)	Source/ sensor	Connectivity analysis
EEG									
Righi et al., 2014	Risk of autism	54 (N/A)	6 and 12 mo	Longitudinal	Discrimination of consonants	Subtest of Mullen Scales of Early Learning	Gamma	Sensor	Coherence
Njiokiktjien et al., 2001	Nonverbal learning disorder/ Language disorder[1]	12/6 12/6	6–11 y	Cross-sectional	Resting	N/A	All	Sensor	Coherence
Zare et al., 2016	Risk of language disorder[1]	17/7	6 mo	Cross-sectional	Resting	N/A	Delta, theta, alpha1, alpha2	Sensor	Connectivity matrix, graph theory
Kabdebon et al., 2015	Prematurity/ healthy	18/12 10/5	8 mo	Cross-sectional	Syllabic learning	N/A	Alpha, beta	Sensor	Coherence
Vasil'yeva and Shmalei, 2013	Stammering/ healthy	47/0 59/0	3–5 y	Cross-sectional	Resting	N/A	All	Sensor	Coherence
Williams et al., 2012	Congenital heart disease	14/2	0–18 mo	Longitudinal	Resting	Bayley Scales of Infant Development	Beta	Sensor	Coherence
MEG									
Kovelman et al., 2015	Autism/healthy	10 (N/A) 9 (N/A)	8–12 y	Cross-sectional	Discrimination of native and foreign language	N/A	All	Source	Coherence
Mamashli et al., 2017	Autism/healthy	29/0 17/0	9–15 y	Cross-sectional	Tonal discrimination	Social communication questionnaire	All	Source	Coherence
Molinaro et al., 2016	Dyslexia/healthy	9/11 10/10	8–14 y	Cross-sectional	Sentence listening	Verbal fluency, rapid automatized naming, pseudoword repetition, and phonemic deletion	Delta, theta	Sensor, Source	Coherence, partial direct coherence based on Granger causality
Lizarazu et al., 2015	Language disorder[a]/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, and gamma	Source	Phase locking value
Barnes-Davis et al., 2018	Extreme prematurity/term born	9/6 7/8	4–6 y	Cross-sectional	Story listening	PPVT, Expressive Vocabulary Test	Beta	Sensor	Phase slope and phase lag index

Studies in the first part of the table used EEG, whereas those in the second part applied MEG.
[a] Language-based learning disorders (e.g., dyslexia, dysphasia). M, male; F, female; N/A, not applicable; PPVT, Peabody Picture Vocabulary Test.

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

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

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

*Some studies applied multiple analyses; hence the total n outranges the number of studies included in this review.

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