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Research Article

Language and communication functioning in children and adolescents with agenesis of the corpus callosum

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ABSTRACT

The corpus callosum, the largest white matter inter-hemispheric pathway, is involved in language and communication. In a cohort of 15 children and adolescents (8–15 years) with developmental absence of the corpus callosum (AgCC), this study aimed to describe language and everyday communication functioning, and explored the role of anatomical factors, social risk, and non-verbal IQ in these outcomes. Standardised measures of language and everyday communication functioning, intellectual ability and social risk were used. AgCC classification and anterior commissure volume, a potential alternative pathway, were extracted from T1-weighted images. Participants with AgCC showed reduced receptive and expressive language compared with test norms, and high rates of language and communication impairments. Complete AgCC, higher social risk and lower non-verbal IQ were associated with communication difficulties. Anterior commissure volume was not associated with language and communication. Recognising heterogeneity in language and communication functioning enhances our understanding and suggests specific focuses for potential interventions.

1. Introduction

Agenesis of the corpus callosum (AgCC) is a prenatal alteration of callosal development, characterised by the complete or partial absence of the corpus callosum (Edwards, Sherr, Barkovich, & Richards, 2014; Paul, Corsello, Kennedy, & Adolphs, 2014; Siffredi, Anderson, Leventer, & Spencer-Smith, 2013; Tovar-Moll et al., 2014). It can present as an isolated condition or with other anomalies including other malformations of the brain or elsewhere in the body, sometimes as part of a genetic syndrome (Paul et al., 2007; Paul, 2011). In recent years, the clinical impact of AgCC has become increasingly recognised in both adults and children, with an increased risk of neuropsychological difficulties compared with their typically developing peers (Brown & Paul, 2019; Chadie et al., 2008; Folliot-Le Doussal et al., 2018; Guadarrama-Ortiz, Choreño-Parra, & de la Rosa-Arredondo, 2020; Romaniello et al., 2017; Siffredi, Anderson, Leventer, & Spencer-Smith, 2013; Siffredi et al., 2018).

Language and communication challenges have been a focus of research in individuals with agenesis of the corpus callosum, see Table 1 for a summary of previous studies (Bartha-Doering et al., 2021; Hinkley

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et al., 2016; Lawson-Yuen, Berend, Soul, & Irons, 2006; Paul, Van Lancker-Sidtis, Schieffer, Dietrich, & Brown, 2003; Rehmel, Brown, & Paul, 2016). Such interest in language and communication has been motivated by the long-held understanding that these functions are key neuropsychological domains that have important implications for adaptive functioning such as academic achievement and socio-emotional skills (Durkin & Conti-Ramsden, 2007; Schoon, Parsons, Rush, & Law, 2010). A further motivator for investigating language in children and adolescents with AgCC comes from contemporary neuro-imaging studies supporting what is commonly referred to as the dynamic dual pathway model (Friederici & Alter, 2004). Specifically, while neuropsychological research has traditionally argued that language in typical development is predominantly left-lateralised, this model suggests that language in typically developing children involves bilateral networks that are crucially dependent on the corpus callosum (Bartha-Doering et al., 2021; Emerson, Gao, & Lin, 2016; Friederici, von Cramon, & Kotz, 2007; Josse & Tzourio-Mazoyer, 2004; Sammler, Kotz, Eckstein, Ott, & Friederici, 2010). Accordingly, investigating language in children and adolescents with AgCC is a unique opportunity to obtain insight into neuropsychological domains that should manifest obvious deficits in the absence of callosal connectivity (Friederici & Alter, 2004; Friederici et al., 2007; Huber-Okrainec, Blaser, & Dennis, 2005).

Based on research to date, language and communication show considerable inter-individual variability in the AgCC population. In general, high rates of language difficulties have been reported in early childhood. Further, rates of language impairments in children with complex AgCC are higher (up to 55 %) than those for children with isolated AgCC (~20 %) (Chadie et al., 2008; Des Portes et al., 2018; Diogo et al., 2021; Glatter et al., 2021; Raile et al., 2020). Higher rates of language impairment are reported in samples where diagnosis of AgCC has not been based on prenatal diagnostics but on outpatient presentation in the context of functional symptoms (Romaniello et al., 2017). Several case studies of children with intellectual impairment have observed significant expressive and receptive language impairment, including a 2-year-old with complete isolated AgCC (Bayley Scale of Infant Development, Mental Developmental Index <50) (Lawson-Yuen et al., 2006), an 8-year-old with complete AgCC and associated brain malformations (Wechsler Intelligence Scale for Children (WISC)-III, Full-Scale IQ 63) (El Abd et al., 1997) and a 10-year-old with partial isolated AgCC (WISC-III, Full-Scale IQ 62) (Lamonica et al., 2009). Longitudinal assessment of an individual with complete AgCC and additional brain anomalies presenting with generally low average intelligence (age-appropriate Wechsler scales, Full Scale IQ range 79–84) showed a stable and pervasive language deficit from 8 years to 22 years (Stickles, Schilmoeller, & Schilmoeller, 2002). Conversely, in a sample of 6 children and adolescents with AgCC (n = 3 partial isolated AgCC, n = 3 complete AgCC and associated brain malformations) aged 6–15 years (general intelligence was not reported), receptive language was comparable to that of typically developing controls (Bartha-Doering et al., 2021). Similarly, receptive and expressive language abilities were average in a 10-year-old child with complete and isolated AgCC presenting with general intelligence within the average range (Bartha-Doering et al., 2024), and no evidence of receptive language impairment was identified in a 45-year-old individual with complete and complex AgCC with neuropsychological functioning within expectations (Kessler, Huber, Pawlik, Heiss, & Markowitsch, 1991).

Impairments in pragmatic language abilities have also been reported, including in children with partial AgCC and spina-bifida meningomyelocele (n = 8, Full-Scale IQ mean=93.25 (SD=10.79), range 76–110) compared with a typically developing control group (n = 11) (Huber-Okrainec et al., 2005), and in adolescents, young adults and adults with complete and partial AgCC and presenting with general intelligence within the average range (Brown & Paul, 2000, n = 2; Paul et al., 2003, n = 10; Rehmel et al., 2016, n = 19; for a review see Brown & Paul, 2019). Variability in performance on verbal naming tasks has been documented in the AgCC population (Bartha-Doering et al., 2021; El Abd et al., 1997; Moutard et al., 2003; Stickles et al., 2002). Performance comparable to typically developing individuals was observed in a study

Table 1
Summary of previous studies reporting on language and communication functioning in children and adolescents with AgCC.

Studies	N AgCC	Age (in years)	Type of AgCC	Measured IQ (or similar scale)	Language functioning
Bartha-Doering et al., 2021	6	M = 11 (SD = 3.35), range from 6 to 15	Complete isolated and complex AgCC, n = 3 Partial isolated AgCC, n = 3	Not reported (note: individuals were able to complete a functional MRI task)	Expressive and receptive language significantly reduced compared to the control group
Bartha-Doering et al., 2024	1	10	Complete isolated AgCC	Within average	Expressive and receptive language within average
Brown & Paul, 2000	2	Case 1: 16–18 Case 2: 18	Case 1: Complete isolated AgCC Case 2: Complete complex AgCC	Within average for both cases	Pragmatic language impairments
El Abd et al., 1997	1	8	Complete complex AgCC	FSIQ = 63	Expressive and receptive language impairments
Hinkley et al., 2016	25	M = 32.6 (SD = 13.8), range from 14 to 70	Complete AgCC, n = 13 Partial AgCC, n = 12	FSIQ: M = 100.4 (SD = 12.4)	Expressive language significantly reduced compared to the control group
Huber-Okrainec et al., 2005	8	SBM: M = 12.9 (SD = 3.1)	Partial, with SBM	FSIQ: M = 88.97 (SD = 13.97)	Pragmatic language impairments
Kessler et al., 1991	1	45	Complete complex AgCC	Within average	Receptive language impairment
Lamonica et al., 2009	1	10	Partial isolated AgCC	FSIQ = 62	Expressive and receptive language impairments
Lawson-Yuen et al., 2006	1	2	Complete isolated AgCC	Mental Developmental Index < 50	Expressive and receptive language impairments
Moutard et al., 2003	17	2, 4 and 6 years	Complete AgCC, n = 11 Partial AgCC, n = 6	IQ: range from 80 to 109	Overall verbal performance comparable to typically developing individuals
Paul et al., 2003	10	M = 22.1, range from 16 to 31	Complete AgCC	FSIQ: M = 93.1, range from 83 to 105	Pragmatic and paralinguistic language impairments
Rehmel et al., 2016	19	M = 25.9 (SD = 9.5)	Complete AgCC, n = 15 Partial AgCC, n = 4	FSIQ: M = 98.26 (SD = 13.3), range from 83 to 131	Pragmatic language impairments
Stickles et al., 2002	1	8–22 (single case longitudinal study)	Complete complex AgCC	FSIQ: range from 79 to 84	Expressive and receptive language impairments

Note: FSIQ = Full-scale IQ, M = mean; SD = standard deviation, SBM = spina bifida meningomyelocele.

of 17 children and adolescents with complete AgCC and median general intellectual ability in the average range (Full-Scale IQ range 78–120) compared with typically developing individuals (Moutard et al., 2003), and in an 8-year-old boy with complete AgCC and associated brain anomalies presenting with generally low average intelligence across childhood (Full Scale IQ range 79–84) (Stickles et al., 2002). However, poorer verbal fluency and naming was observed in 3 children and adolescents with complete AgCC aged 6–15 years (general cognitive ability not reported) (Bartha-Doering et al., 2021), and also in an 8-year-old with complete AgCC and associated brain malformations presenting with intellectual impairment (Full Scale IQ 63) on a picture naming task (El Abd et al., 1997). In summary, while some individuals show age-appropriate language and everyday communication functioning, others experience difficulties that range from mild to severe in one or many aspects of language and everyday communication. Based on research to date, the level of association between non-verbal intelligence with language and communication is unknown.

Inconsistent findings in the literature may be explained by variations in anatomical presentations, general intelligence, social risk, and/or methodological shortcomings, such as sample selection, present in the literature. In atypically developing populations, anatomical, non-verbal intelligence and social risk factors (pertaining for example to economic status and family structure) are known to have important influences on the development of language and communication (Bartha-Doering et al., 2021; Bornstein, Hahn, & Putnick, 2016; Conti-Ramsden & Durkin, 2015; Howard et al., 2011; Kuhl, 2010; Nguyen et al., 2019; Rosselli, Ardila, Matute, & Vélez-Uribe, 2014).

Earlier research has indicated that the absence of the corpus callosum, whether partially or entirely, as well as the isolated occurrence of AgCC or its association with other complex brain malformations, is linked to overall multiple skills: cognitive functions (language and communication, executive functions, attention), school performance and socio-emotional skills (Bedeschi et al., 2006; Edwards et al., 2014; Moutard et al., 2003; Paul et al., 2007). Additionally, characteristics of alternative interhemispheric conduits such as the anterior commissure may contribute to our understanding of the variability in neuropsychological outcomes in this population (Hannay, Dennis, Kramer, Blaser, & Fletcher, 2009; Siffredi et al., 2019, 2021; Tovar-Moll et al., 2007, 2014). The anterior commissure contains fibres connecting the anterior and lateral portions of the temporal lobes (Catani & Thiebaut de Schotten, 2008), and is considered involved in interhemispheric communication between language areas in typically developing individuals (Northam et al., 2012). In individuals with AgCC, the anterior commissure has been proposed to undergo structural modifications on account of neuroplasticity, with an increase in size and aberrant homotopic bundles crossing the midline via the anterior commissure and connecting parietal cortices (Siffredi et al., 2019, 2021; Tovar-Moll et al., 2007, 2014; van Meer et al., 2016). Thus, the volume of these commissures in children and adults with AgCC may differentially influence language and communication outcomes.

Language and communication development is strongly influenced by early socio-economic risks, such as younger maternal age at birth, a single caregiver and/or lower primary caregiver education (Basit, Hughes, Iqbal, & Cooper, 2015; Hackman & Farah, 2009; Nguyen et al., 2019). However, in the context of AgCC, few studies have examined associations between such social risks and neuropsychological outcomes. Evidence to date suggests that social risk has an impact on children's cognitive outcomes in this population (Siffredi et al., 2018).

This study aimed to describe language and everyday communication in a sample of school-aged children and adolescents with AgCC compared with test norms and explored the role of anatomical factors (i.e., complete vs partial; complex vs isolated; volume of the anterior commissure), non-verbal intelligence and social risk in understanding language and communication this population. We hypothesised that children and adolescents with AgCC would demonstrate poorer language and everyday communication compared with normative data, with poorer functioning in children and adolescents with complete compared with partial AgCC and in those with complex compared with isolated AgCC. We expected that larger anterior commissure volume and/or lower social risk would be associated with better language and everyday communication functioning in children and adolescents with AgCC. It was unclear whether non-verbal intelligence would be associated with language and everyday communication in children with AgCC.

1.1. Data availability

Ethical restrictions prevent us from making anonymised data available in a public repository. Data may be accessed from the Royal Children's Hospital Data Access/Ethics Committee for researchers who meet the criteria for access to confidential data by direct request to the Agenesis of the Corpus Callosum Project Data Committee: Vicki.Anderson@rch.org.au. There are restrictions on data related to identifying participant information and appropriate ethical approval is required prior to release. Only de-identified data will be available.

2. Methods

2.1. Sample

This study used data from the "Paediatric Agenesis of the Corpus Callosum Research Project" (Siffredi et al., 2018). Twenty-eight participants (85 % of those eligible; $n = 33$), aged 8–17 years (M = 11.54; SD = 2.35) were ascertained following from the radiology database at The Royal Children's Hospital (RCH) Melbourne, Australia, a statewide tertiary paediatric hospital. Participants completed a standard protocol including language and neuropsychological measures and brain MRI, either generally on the same day, or within a maximum interval of one month. Inclusion criteria were: (1) aged 8.0–16.11 years at recruitment; (2) prior evidence of AgCC on MRI; (3) English speaking; and (4) ability to engage in neuropsychological testing. All participants had normal or corrected-to-normal hearing and vision. The study was approved by The RCH Human Research Ethics Committee. Written informed consent was given by caregivers and participants over 10 years of age.

To be eligible for the current study, participants needed to have completed the Clinical Evaluation of Language Fundamentals – 4th Edition (CELF-4), Australian Standardised Edition (Semel, Wiig, & Secord, 2006) resulting in the inclusion of 15 children and adolescents with AgCC. Out of the 15 participants who completed the CELF, 3 did not complete the MRI scan and were therefore excluded from the analyses involving anterior commissure measures.

2.2. Measures

2.2.1. Language and communication

Language functioning was assessed with the Clinical Evaluation of Language Fundamentals, Fourth Edition (CELF-4), Australian Standardised Edition, designed to screen language difficulties in individuals 5–21 years of age (Semel et al., 2006). The Core Language Index (CLI), the Receptive Language Index (RLI) and the Expressive Language Index (ELI) were calculated based on different subtests depending on age (see Table 2). Standard scores were used (mean = 100, SD = 15).

Everyday communication in home and school settings was assessed using the Communication subscale from the Adaptive Behavior Assessment System – II (ABAS-II; (Harrison & Oakland, 2003)) rated by parents and teachers respectively. The ABAS-II is designed for individuals from birth to 21-years-old and the Communication subscale consists of 24 items for the parent-reported form and of 22 items for the teacher-reported form. Standard scores were used (mean = 10, SD = 3).

For all language and communication subscales, level of functioning was classified using the CELF-4 manual cut-offs: a) average or above average: > -1 SD of the test mean; b) borderline: ≤ -1 to < -2 SD; c) moderate to severe impairment: ≤ -2 SD).

Table 2
CELF-4 administration by age.

CELF-4 Indices	Subtests for 8-year-olds	Subtests for 9–12-year-olds	Subtests for 13-year-olds and older
Core Language Index (CLI)	Concepts and following directions	Concepts and following directions	Recalling sentences
	Word structure	Recalling sentences	Formulated sentences
	Recalling sentences	Formulated sentences	Word classes – total
	Formulated sentences	Word classes – total	Word definitions
Receptive Language Index (RLI)	Concepts and following directions	Concepts and following directions	Word classes – receptive
	Word classes – receptive	Word classes – receptive	Understanding spoken paragraphs
	Sentence structure		Semantic relationships
Expressive Language Index (ELI)	Word structure	Recalling sentences	Recalling sentences
	Recalling sentences	Formulated sentences	Formulated sentences
	Formulated sentences	Word classes – expressive	Word classes – expressive

2.2.2. Intellectual functioning

Intellectual functioning was estimated using the Wechsler Intelligence Scale for Children – 4th Edition (WISC-IV; Wechsler, 2003) for participants who had recently completed a clinical neuropsychological assessment, or the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) for participants assessed only for research purposes. Both measures generate a Full-Scale IQ (general intelligence) and Performance IQ (non-verbal intelligence) (mean = 100, SD 15) and have high concurrent validity (Saklofske, Caravan, & Schwartz, 2000).

2.2.3. Social risk

The Social Risk Index was used to estimate family and economical social risk. The Social Risk Index is a composite score based on information collected from the primary caregiver in a questionnaire regarding family structure, education of primary caregiver, occupation of primary income earner, employment status of primary income earner, language spoken at home and maternal age at birth. Scores range from 0 to 12, with higher scores representing greater socio-economic risk (Roberts et al., 2008).

2.3. Neuroimaging

2.3.1. Magnetic resonance image acquisition

Images were acquired on a 3T MAGNETOM Trio scanner (Siemens, Erlangen, Germany) at The RCH, Melbourne, Australia. A 32-channel head coil was used for transmission and reception of radio-frequency and signals. Data acquired included high-resolution 3D anatomical images acquired using a T1-weighted MP-RAGE sequence (Magnetization Prepared Rapid Gradient Echo) with the parameters set at: repetition time = 1900 msec, echo time = 2.71 msec, inversion time = 900 msec, flip angle = 9°, field of view = 256 mm, voxel size = .7 × .7 × 0.7 mm.

2.3.2. MRI features

Structural T1-weighted images were qualitatively reviewed by a paediatric neurologist with expertise in brain malformations (R.J.L.). A specially modified protocol (Anderson et al., 2009; Leventer et al., 1999; Siffredi et al., 2018) was used to characterise AgCC: (a) AgCC type: partial (section of the corpus callosum absent) or complete (entire corpus callosum absent); (b) CNS anomalies: isolated or complex (excluding common concomitant anatomical changes due to the absence (complete or partial) of the CC such as Probst bundles, cingulate gyrus alteration, and colpocephaly (Booth, Wallace, & Happe, 2011; Lee, Kim, Cho, & Lee, 2004; Paul et al., 2007).

2.3.3. Volume of the anterior commissure

Given differences in gross anatomy among individuals with AgCC, the anterior commissure was manually defined for each participant's native T1-weighted image using MRIcron (https://www.mccauslandcenter.sc.edu/mricro/mricron/) and MRview (https://github.com/MRtrix3) on native space T1-weighted images (Siffredi et al., 2019). Two independent researchers performed the drawings of these ROIs. The drawings were restricted to five slices in the sagittal plane, and there was no restriction for the axial and coronal directions. One drawer was consistently used as the reference drawer. First, the number of voxels for each drawing was calculated using SPM functions running on Matlab (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007). Second, the number of voxels overlapping in terms of location between the two drawings was computed. Third, the "percentage of overlap" of the reference drawer was calculated: number of voxels of the reference drawer/number of voxel overlapping between the two drawings × 100. If there was an overlap of more than 80 % in terms of number of voxels and location for the reference drawer, the ROIs of the reference drawer was used. If the overlap was less than 80 %, the ROIs were redrawn by both researchers until there was 80 % overlap. The final ROI used was the reference drawing. To adjust for differences in total brain volumes, measures of volume of the anterior commissure were calculated using the total number of voxels in the ROI corrected as a ratio to total brain volume (ROI volume divided by total brain volume; O'Brien et al., 2011).

2.4. Statistical analyses

Analyses were performed using the R software version 4.0.3, and R studio version 1.3.1093 (Team, 2020; Team, 2013). To examine differences in language and everyday communication scores between the AgCC cohort mean scores and test norms and given that the assumptions to use parametric testing were violated, Wilcoxon signed-rank tests were used. To examine within group differences between expressive and receptive language, as well as between the ABAS parent- and teacher-reports, Wilcoxon test for paired samples was used. Effect sizes were calculated using $r = Z/\sqrt{N}$ (Fritz, 2011); with $r = 0.1$–0.3 considered a small effect, $r = 0.3$–0.5 a medium effect, and $r \geq 0.5$ a large effect size. Given the small sample size, both p-values and effect sizes were used to interpret the results. Secondary analyses were performed excluding participants with a Full-Scale IQ < 70 (n = 2).

Multiple linear regression models were used to examine the contribution of anatomical, non-verbal intelligence and socio-economic factors in language and everyday communication functioning in children and adolescents with AgCC. Language and communication scores were modelled as dependent variable and anatomical factors, Performance IQ and social risk entered as independent variables, including: a) AgCC type (complete or partial AgCC); b) presence or absence of associated CNS anomalies (isolated or complex AgCC); c) volume of anterior commissure; d) Performance IQ, and e) Social Risk Index. Assumptions for regression linear models, including normality of the residuals, were checked through visual inspection of plots of residuals. While Full Scale, Verbal and Performance IQs were all collected, only Performance IQ (not Full-Scale IQ or Verbal IQ) was used in the linear regression models as it is known to be more directly related to non-verbal cognitive abilities (Wechsler, 2003).

The p-values were corrected for multiple comparisons using Bonferroni correction (Field, Field, & Miles, 2012): α altered = α original 0.05/5 comparisons = 0.01.

3. Results

3.1. Sample characteristics

This study included a cohort of 15 children and adolescents with AgCC aged 8–15 years who were mostly male, with similar numbers of participants with complete and partial AgCC, and fewer participants with isolated than complex AgCC (Table 3). The mean full-scale IQ of the sample was in the borderline range (2 participants scored below 70) and the mean Performance IQ was in the low average range (3 participants scored below 70). Detailed characteristics of children and adolescents with complete/partial AgCC and isolated/complex AgCC, including Full-Scale and Performance IQ, are provided in Supplementary Table S1 and Table S2.

3.2. Language and communication in children and adolescents with AgCC compared with test norms

Children and adolescents with AgCC had significantly lower language index scores than the normative test mean with large effect sizes, Table 4 and Fig. 1. On the Core Language Index, one third of the participants with AgCC had scores in the borderline range and 40 % in the moderately to severely impaired range. Children and adolescents with AgCC tended to have better scores on the Receptive Language Index (26.7 % moderate to severe impairment, 40 % borderline) than the Expressive Language Index (66.7 % moderate to severe impairment, 13.3 % borderline). Expressive language was significantly lower than receptive language ($W = 465$, $p < 0.001$, $r = 1.23$).

Everyday communication in children and adolescents with AgCC rated by parents and teachers reached large effect size but did not differ significantly from normative test means after Bonferroni correction. Parents rated communication in their children with AgCC significantly more positively than teachers ($W = 186$, $p = 0.002$, $r = -1.15$). It was found that 57.1 % of parents reported their children's communication abilities to be within the average or above-average range, whereas teachers rated these abilities within the moderate to severe impairment range in 60 % of cases.

Results of secondary analyses including only participants with a Full-Scale IQ of 70 or above, were generally comparable to results of the main analyses, Supplementary Table S3. Children and adolescents with AgCC had significantly lower scores than the normative test mean on the Expressive and Receptive Language Indexes with large effect size. The Core Language Index and Communication subscale rated by both parents and teachers were not significantly different from normative expectations after Bonferroni correction but reached large effect size.

Table 3
Characteristics of participants with agenesis of the corpus callosum (AgCC, n = 15).

	AgCC, n = 15
Female, n (ratio, %)	5 (ratio: 5/15, 33.3 %)
Age at testing in years, mean (SD) [range]	12.0 (2.13) [8.58, 15.7]
Right-handed/Left-handed, n (ratio, %)	9 (ratio: 9/15, 60.0 %)/6 (ratio: 6/15, 40.0 %)
Complete/Partial AgCC, n (ratio, %)	7 (ratio: 7/15, 46.7 %)/8 (ratio: 8/15, 53.3 %)
Isolated/Complex AgCC, n (ratio, %)	6 (ratio: 6/15, 40 %)/9 (ratio: 9/15, 60 %)
Full-Scale IQ, mean (SD) [range]	75.7 (13.6) [40—100]
Performance IQ, mean (SD) [range]	82.0 (16.6) [45—107]
Social Risk, mean (SD) [range]	3.67 (2.41) [0, 7]

Note: Handedness was estimated using the Edinburgh Handedness Inventory (Groen, Whitehouse, Badcock, & Bishop, 2012; Oldfield, 1971). Based on the laterality coefficient, participants were classified as right-handed (+40 to +100), left-handed (−40 to −100), or mix-handed (−40 to +40). Full-scale IQ was measured using the Wechsler Abbreviated Intelligence Scale (WASI; Wechsler, 1999) or the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV; Wechsler, 2003). Full-Scale IQ and Performance IQ are reported using age-standardised scores (M = 100, SD = 15). Social risk was measured using the Social Risk Index (Roberts et al., 2008). SD = standard deviation: AgCC = agenesis of the corpus callosum.

3.3. Factors associated with language and communication in AgCC

There were no significant associations between any of the studied anatomical factors (AgCC type, CNS anomalies, volume of anterior commissure) or social risk and the Core, Receptive and Expressive Language Indexes or teacher-rated Communication subscale score (Table 5). However, parent-rated Communication was associated with AgCC type (complete vs partial, $t(8) = 5.585$, $p = 0.003$), Performance IQ ($t(8) = -2.642$, $p = 0.046$) and social risk ($t(8) = -8.485$, $p = 0.0003$), with lower parent-rated communication scores associated with complete AgCC, higher social risk and to a lesser extent Performance IQ.

4. Discussion

This study sheds light on language and communication functioning in school-age children and adolescents with AgCC. Our cohort of participants who presented to a tertiary hospital showed poorer language than test norms, with a significant pattern of better receptive than expressive language. While everyday communication functioning appears comparable for children and adolescents with AgCC and test norms, high rates of communication impairment were reported by parents and teachers. Complete AgCC, non-verbal IQ and higher social risk were associated with increased communication difficulties rated by parents. However, none of the studied anatomical factors of AgCC (i.e., AgCC type; presence or absence of associated CNS anomalies; volume of the anterior commissure), non-verbal IQ or social risk were found to be strongly associated with language or teacher-rated communication outcomes.

Overall our cohort of children and adolescents with AgCC had poorer language functioning than normative expectations with large effect size in core expressive and receptive language functions, consistent with several previous studies (El Abd et al., 1997; Lamonica et al., 2009; Lawson-Yuen et al., 2006). Our results highlight great heterogeneity in language functioning in this population, with around 20–30 % of participants with AgCC performing within the average range. In line with the literature in children and adolescents with AgCC (Bartha-Doering et al., 2021; El Abd et al., 1997; Kessler et al., 1991), significantly poorer expressive language compared to receptive language was observed. This difference between receptive and expressive language could be interpreted through the lens of developmental models of the ventral and dorsal pathways and their lateralization. At birth, the ventral pathway, primarily associated with receptive language, is bilaterally organised (Perani et al., 2011). Conversely, the dorsal pathway, which is more involved in expressive language, undergoes development later in childhood and shows a predominantly left-lateralised pattern (Hickok & Poeppel, 2004). While both pathways are typically left-hemisphere dominant in typical adult brains, the ventral stream exhibits less pronounced asymmetry than the dorsal stream. Furthermore, during typical childhood development, increased white-matter microstructural asymmetry of the posterior segment of the dorsal pathway has been associated with enhanced language skills (Eichner, Berger, Klein, & Friederici, 2024). In adolescents and adults with AgCC, studies have shown bilateral language organisation for receptive and expressive language (Bartha-Doering et al., 2021; Hinkley et al., 2016; Pelletier et al., 2011). It is possible that this bilateral organisation of language in individuals with AgCC may have a lesser impact on receptive language functioning, which is typically more bilaterally represented and initially bilaterally organised at birth. In contrast, expressive language may be more affected, as the strong left-lateralisation typically observed of the dorsal pathway may not developed optimally in the absence of the corpus callosum.

Table 4
AgCC children and adolescents compared with test norms for language and communication scores, as well as impairment rates and ratio.

	n	Median	Mean group difference	Wilcoxon signed-rank tests			Percentage impaired		
				W	p-value	Effect size (r)	Average or above	Borderline	Moderate to severe
Language									
Core index*	15	78	22.67	10	0.005*	0.73	26.70 % ratio: 4/15	33.30 % ratio: 5/15	40.00 % ratio: 6/15
Receptive index*	15	79	20.73	5	0.002*	0.8	33.30 % ratio: 5/15	40.00 % ratio: 6/15	26.70 % ratio: 4/15
Expressive index*	15	65	30.87	4	0.002*	0.81	20.00 % ratio: 3/15	13.30 % ratio: 2/15	66.70 % ratio: 10/15
Communication									
Parent-reported	14	8	3	11	0.017	0.61	57.10 % ratio: 8/14	21.40 % ratio: 3/14	21.40 % ratio: 3/14
Teacher-reported	10	3.5	4.8	4	0.019	0.61	40.00 % ratio: 4/10	0.00 % ratio: 0/10	60.00 % ratio: 6/10

Note: Language functioning was evaluated using the CELF-4 (M =100, SD = 15); Communication functioning was evaluated using the ABAS parent and teacher-reported questionnaires (M = 10, SD = 3). Impairment rates were defined as follow: a) average or above average: > −1 standard deviation (SD) of the test mean; b) borderline: ≤−1 to <−2 SD; moderate to severe impairment: ≤−2 SD). Significant difference with normative expectation that survived Bonferroni correction are indicated with *.

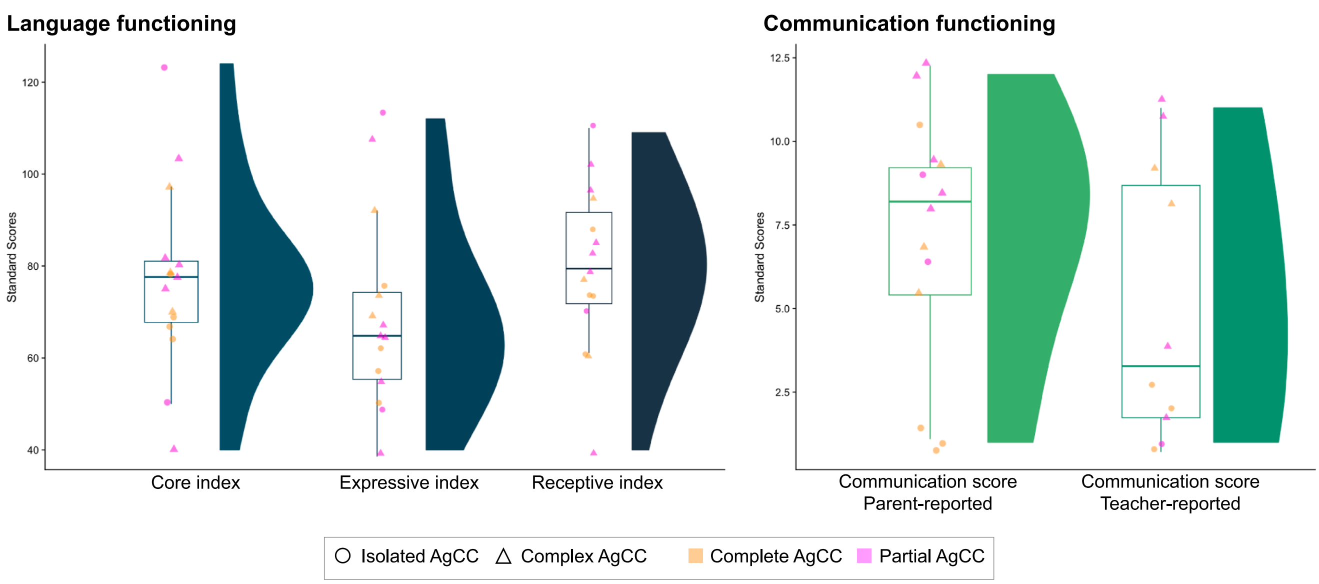

Fig. 1. Illustration of language and everyday communication in children and adolescents with AgCC based on the CELF-4 language indexes (normative mean = 100, SD = 15) and the ABAS communication subscale (normative mean = 10, SD = 3). Each dot represents a participant: circles represent participants with isolated AgCC, triangles represent participants with complex AgCC, orange dots represent participants with complete AgCC, and pink dots represent participants with complete AgCC.

Moreover, everyday communication functioning rated by parents and teachers, though not significantly different from normative expectation after correction for multiple comparisons, showed large effect size, with high rates of impairment. Notably, teachers reported significantly higher rates of communication impairments compared to parents. This pattern of results did not change when children and adolescents with a Full-Scale IQ below 70 were excluded, suggesting that our findings might not be driven by a subset of children and adolescents with significant intellectual impairment. Previous studies indicate that approximately 20 % of children and adolescents with isolated AgCC and up to 55 % with complex AgCC experience language impairments (Diogo et al., 2021; Glatter et al., 2021; Raile et al., 2020). In the current AgCC cohort, 10 of 15 children and adolescents (67 %) showed a language impairment. In the subgroups, 4 of 6 of the children and adolescents with isolated AgCC (67 %) and 7 of 9 children and adolescents with associated malformations (78 %) showed an impairment on at least one language measure. Additionally, deficits in pragmatic language abilities have been observed in children, adolescents and adults with complete/partial AgCC and also in those with isolated/complex AgCC, as well as in adolescents and adults with both isolated and complex AgCC (Brown & Paul, 2000; Huber-Okrainec et al., 2005; Paul et al., 2003).

Of the anatomical features, non-verbal IQ and social risk factors explored in our sample of children and adolescents with AgCC, only complete AgCC, higher social risk and to a lesser extent non-verbal IQ were associated with lower parent-rated communication functioning. Social risk is commonly recognised as contributing to language and communication outcomes in paediatric populations (Hartas, 2011; Kluczniok & Mudiappa, 2019; Letts, Edwards, Sinka, Schaefer, & Gibbons, 2013), and a key contributor to behavioural, executive and social functioning in children and adolescents with AgCC (Siffredi et al., 2018); our study, however, did not find an association with the other explored language outcomes. Previous studies have also observed poorer functioning in children and adolescents with complete AgCC compared to partial AgCC, in verbal naming and verbal fluency difficulties (Bartha-

Table 5
Multiple linear regression models showing associations between anatomical factors, Performance IQ and social risk, and language and communication functioning in children and adolescents with AgCC.

	Adjusted R^2	Estimate	Standard error	β	p
Language functioning					
Core index	0.444				0.125
Receptive index	0.001				0.488
Expressive index	0.599				0.052
Communication functioning					
Parent-reported *	0.933				**0.001**
Intercept		10.404	3.333		0.026
AgCC type		5.070	0.908	0.654	**0.003**
Associated with CNS anomalies		0.260	0.775	0.035	0.751
Volume of anterior commissure		73586.614	29856.735	0.291	0.057
Performance IQ		−0.100	0.038	−0.277	**0.046**
Social Risk Index		−1.056	0.124	−0.757	**0.0003**
Teacher-reported	0.863				0.315

Note: AgCC type, complete or partial AgCC; associated with CNS anomalies, isolated or complex AgCC; β, standardised beta estimate. Significant models that survived Bonferroni correction are indicated with * and in bold.

Doering et al., 2021) and parent-rated behavioural regulation (Siffredi et al., 2018), but not specifically for communication outcomes. Complex AgCC has generally been associated with poorer cognitive outcomes (Glatter et al., 2021; Siffredi et al., 2018); interestingly, we found no associations between language and communication and the presence of additional brain anomalies. The volume of the anterior commissure was also not found to be an important contributor to language and everyday communication functioning in our cohort of children and adolescents with AgCC. Recent studies have showed that language seems to be underpinned by increased bilateral hemispheric activity in individuals with AgCC compared to neurotypical individuals (Bartha-Doering et al., 2021; Hinkley et al., 2016). It is possible that language processing in AgCC relies on more global reorganisation processes related to functional connectivity and not only the use of the anterior commissure as an alternative pathway. Of interest, while non-verbal IQ was associated with parent (but not teacher) rated communication functioning, it did not appear as a major factor in understanding language outcomes in our sample of children and adolescents with AgCC. This finding suggests that overall, the language difficulties observed in our sample do not reflect difficulties in non-verbal intellectual functioning.

This study had several strengths. A combination of standardised and age-appropriate tests and ratings was used to measure children's and adolescents' language and everyday communication functioning, reflecting current clinical approaches to assessing these neuropsychological domains. Everyday communication was measured using both parent and teacher ratings to contribute valuable insights into the child's and adolescent's communication abilities across home and school settings. Including all children and adolescents who presented for clinical attention, rather than selecting children based on specific IQ cut points (e.g., within the average range) enabled us to describe language and communication outcomes in a more representative cohort of children and adolescents with AgCC, including those with lower intellectual functioning.

We acknowledge that our small and heterogeneous sample is a limitation, one that is commonly encountered in AgCC research in both paediatric and adult studies that reflects in part the rarity of the condition. Our sample may also present selection bias by including only individuals capable of participating in the cognitive assessment and excluding those with severe impairments and very poor functioning. Conversely, the cohort may be biased towards individuals who received an AgCC diagnosis, thereby excluding those who are asymptomatic and were not identified through diagnostic imaging (e.g., prenatal ultrasound). While our analyses lacked statistical power related to the small sample, we observed large effect sizes and comparisons with normative data contribute confidence that our study findings provide important understanding of language and communication functioning in children and adolescents with AgCC. Moreover, potential limitations may arise from the combination of the small sample and the inclusion of multiple independent variables in our linear regression models. These factors may affect the generalisability of the results and should be considered when interpreting the findings. Additionally, although the posterior commissure has not been implicated in language functioning to the best of our knowledge, it could have been included as an independent variable related to brain plasticity in this population. Nevertheless, due to our limited sample size, we chose not to add this variable to the linear regression models to maintain a balance between model complexity and statistical robustness. Further research with larger samples, possibly achieved through multiple site studies, is needed to replicate, and extend the current findings. This may support a transition from the current clinical approach to a more experimental one that can offer valuable theoretical insight into the specific role of the corpus callosum. Moreover, this approach would enable exploration of the heterogeneity in clinical and imaging features of children and adolescents with AgCC (e.g. studying subgroups with complete and partial as well as isolated and complex AgCC) and investigate factors that might contribute to understanding language and communication outcomes. Our study, however, offers insight into language and communication functioning in children and adolescents with AgCC presenting to paediatric neurology clinics. The study findings could also provide insights for clinicians and parents regarding language and communication outcomes in this population. Given important developmental changes during childhood, studies of children and adolescents with AgCC should consider the influence of age at testing. Longitudinal studies with large samples would provide the opportunity to capture cognitive maturation, in particular language and communication maturation, in parallel to brain maturation in the context of this brain malformation.

5. Conclusion

The current study highlights that many children and adolescents with AgCC experience language difficulties, with greater difficulties in expressive than receptive language. Unexpectedly, the anatomical factors we explored provided little insight into language and everyday communication outcomes in children and adolescents with AgCC, except for complete AgCC together with higher social risk and lower non-verbal IQ being associated with parent-rated communication difficulties. These findings could offer meaningful clinical insights for families and practitioners engaged with children and adolescents diagnosed with AgCC. The recognition of heterogeneity in language and everyday communication functioning, with expressive difficulties emerging as a prominent area of concern, and difficulties not reflective of non-verbal intelligence more generally, not only enhances our understanding but might also suggests a specific focus for potential interventions.

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CRediT authorship contribution statement

Charlene Moser: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Conceptualization. **Megan M. Spencer-Smith:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Peter J. Anderson:** Writing – review & editing, Validation, Supervision. **Alissandra McIlroy:** Writing – review & editing, Validation, Data curation. **Amanda G. Wood:** Writing – review & editing, Funding acquisition. **Richard J. Leventer:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization. **Vicki A. Anderson:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization. **Vanessa Siffredi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

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