

SCOPING REVIEW

Neuropsychological profiles of children with agenesis of the corpus callosum: A scoping review

Alice Wright¹ | Rhonda Booth² 

¹Child and Adolescent Mental Health Services, NHS Forth Valley, Stirling, UK

²Cognitive Neuroscience and Neuropsychiatry Section, Developmental Neurosciences Programme, UCL Great Ormond Street Institute of Child Health, London, UK

Correspondence

Rhonda Booth, Cognitive Neuroscience and Neuropsychiatry Section, Developmental Neurosciences Programme, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, UK.
Email: rhonda.booth@ucl.ac.uk

Funding information

NHS Forth Valley; Great Ormond Street Institute of Child Health

Abstract

Aim: To understand the wide variety of clinical outcomes in children with agenesis of the corpus callosum (AgCC) and examine evidence for the proposed neuropsychological syndrome reported in adults with primary AgCC.

Method: PsycINFO, PsycArticles, Medline, Embase, and Web of Science (January 2007–November 2021) were searched to identify studies reporting on cognitive or neuropsychological outcome in children with AgCC aged up to 18 years. Twenty-three articles investigating the cognitive profile were found; their methodology was evaluated against quality criteria.

Results: While there was a high degree of heterogeneity across studies, including the methodological quality, there was evidence for some features of the neuropsychological syndrome in children with AgCC. Vulnerabilities in executive function and social cognition were found, with particular difficulties on complex and novel tasks.

Interpretation: Data on the neuropsychological outcomes in children with AgCC are limited. Broad assessments are necessary to determine the extent to which core features of the neuropsychological syndrome may characterize children with AgCC and how additional neuroanatomical features contribute to outcome.

The corpus callosum is the largest connective structure in the brain, facilitating transfer of information between the hemispheres. The corpus callosum develops prenatally, with the major structures in place by 20 weeks of gestation; although pruning and myelination of the corpus callosum continues postnatally.¹ Agenesis of the corpus callosum (AgCC) is a congenital brain malformation in which the corpus callosum fails to develop, either completely or partially.² AgCC is one of the more common congenital neurological disorders, occurring in at least one in every 4000 live births³ and 2% to 3% of individuals with developmental disorders.⁴ The most common cause of AgCC is a genetic mutation with up to 45% of individuals having an identified genetic syndrome.³ AgCC can co-occur with another significant neurological abnormality or be the result of a viral infection during pregnancy, but for many the reason for the disruption in development of the corpus callosum remains unknown.

Despite being a relatively common neurological disorder, the impact of AgCC on neurocognitive functioning is highly variable and difficult to predict from the brain scan conducted at diagnosis.⁵ Whether the corpus callosum is completely absent (complete AgCC) or a remnant remains (partial AgCC) does not reliably determine outcome.² When AgCC is an isolated finding, that is, without accompanying neurological abnormalities, outcomes can be more favourable.^{4,6} However, a recent study with a relatively large and representative sample found no relationship between additional neurological factors (i.e. complex AgCC) and general cognitive ability.⁷ The definition of isolated AgCC can include the presence of interhemispheric cysts, enlarged ventricles, or hippocampal volume changes:⁸ all factors that may also determine outcome.

Recent work in the field has moved towards characterizing the neuropsychological profile of AgCC, despite the heterogeneity in outcome. Brown et al.³ were interested in the

Abbreviations: AgCC, agenesis of the corpus callosum; ASD, autism spectrum disorder; CNS, central nervous system; FSIQ, Full-Scale IQ.

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2023 The Authors. *Developmental Medicine & Child Neurology* published by John Wiley & Sons Ltd on behalf of Mac Keith Press.

impact of the absence of the corpus callosum itself, and therefore studied individuals with AgCC with few, if any, other structural brain abnormalities and Full-Scale IQ (FSIQ) within normal limits. AgCC was considered to be the *primary* contributor to cognitive outcome in these individuals who were identified as having 'primary AgCC'. In their synthesis of 25 years of anecdotal reports and research mainly with adults, Brown et al. proposed that primary AgCC may be understood as a core neuropsychological syndrome characterized by limited interhemispheric transfer of complex information, slow processing speed, and restricted ability to process novel and complex information. They propose the syndrome may be less pronounced in children than adults as the corpus callosum in typically developing children is still undergoing myelination, reducing the differences between children with AgCC and their peers.³ However, contrary to this hypothesis, a systematic review conducted by Siffredi et al.⁵ concluded that general intellectual function was lower in children than adults with AgCC; they also report wide variability and no 'characteristic profile' of neuropsychological outcomes in AgCC. The developmental trajectory of individuals with AgCC, as well as the proposed neuropsychological syndrome, therefore requires further study.

Several limitations can be identified in articles that have reviewed the neuropsychological profile of individuals with AgCC. Studies that report favourable outcomes with children with isolated AgCC often base this on IQ alone. There is evidence that children with AgCC have multiple cognitive difficulties such as in executive functioning and social cognition despite having IQ scores within the typical range.⁷ Furthermore, categorizing developmental outcome as 'normal' versus 'abnormal' can be limiting.⁹

A comprehensive review was completed by Paul et al.,² however, the review was descriptive, non-systematic, and did not provide detail on neuropsychological profiles in AgCC. The systematic review conducted by Siffredi et al.⁵ only included published research up to 2011. A recent systematic review on neurodevelopmental outcomes by Bernardes da Cunha et al.⁴ only included children with a prenatal diagnosis of isolated AgCC, omitting current studies on neuropsychological outcomes that include individuals with a postnatal diagnosis.⁷

In this scoping review, we aim to extend these earlier reviews by (1) identifying articles characterizing the neuropsychological profile of children with AgCC published from January 2007 to November 2021, and (2) map the evidence for the proposed neuropsychological syndrome of AgCC in a variety of clinical outcomes.³ As the neuropsychological syndrome of AgCC is primarily an adult-based model, the current review will appraise published research on children aged 18 years and below, with either a prenatal or postnatal diagnosis of AgCC, to establish whether the syndrome is evident across all ages of development and level of general functioning. Secondary explorations will be made on whether the heterogeneity in the neuropsychological profile of AgCC can be explained by (1) the presence of other neurological abnormalities, (2) if the AgCC is partial or complete,

What this paper adds

- Features of the proposed neuropsychological syndrome of primary agenesis of the corpus callosum (AgCC) are evident in children.
- Broad assessments of neuropsychological outcome in AgCC are needed throughout the lifespan.

and (3) age effects. The overarching aim of this review was to provide greater clarity of the neuropsychological profile of children with AgCC to help inform the direction of assessment and intervention.

METHOD

The scoping review was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) criteria¹⁰ and the methodology described in the online JBI reviewer's manual.¹¹

Search strategy

Five electronic databases (Embase, Medline, PsycINFO, PsycArticles, Web of Science) were systematically searched using subject headings and keywords selected based on the research question and those used by Siffredi et al.⁵ Two searches were made using terms related to AgCC and neuropsychological/cognitive assessment; the searches were then combined using the Boolean operator 'AND' to retrieve relevant articles published between January 2007 and November 2021 (see Table S1 for search terms used). No a priori protocol was registered, but further information on the process can be obtained from the corresponding author on request.

Study selection and synthesis

The first author was solely responsible for conducting the review and collecting all data from articles. As the review was originally submitted in partial fulfilment of an MSc degree, it was a requirement for the review to be entirely the result of their own work.

After the removal of duplicates, titles were reviewed removing those where the title indicated the article did not relate to AgCC or included only those with an identified genetic syndrome. Abstracts of all remaining articles were reviewed and studies not meeting the inclusion and exclusion criteria (Table 1) were removed. If there was any uncertainty the full article (including online supplementary data

TABLE 1 The eligibility (inclusion and exclusion) criteria employed for the review.

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> Published between January 2007 and November 2021 Includes children under the age of 18 years Participants have a diagnosis of AgCC Reports a neuropsychological outcome (i.e. general cognitive ability, social cognition/social skills, attention, memory, or executive functioning) 	<ul style="list-style-type: none"> Includes children but does not report their results separately from adult participants Includes only those with AgCC and another neurological condition not typically associated with AgCC Only includes those with a specific genetic syndrome (i.e. Aicardi syndrome) Single-case studies Only reports non-specific neuropsychological outcomes (i.e. developmental delay) with no details on measure or uses a non-standardized measure such as review of clinical notes to determine outcome Conference abstracts and posters

Abbreviation: AgCC, agenesis of the corpus callosum.

if available) was reviewed for eligibility. All data relevant to inform the scoping review objectives were extracted and summarized in [Table S2](#).

Appraisal criteria

The methodological quality of the selected articles was appraised using an adapted version of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria for methods and results.¹² Recommendations relevant to the topic were selected along with additional criteria relating to the method used to diagnose AgCC (magnetic resonance imaging [MRI] is considered criterion standard)⁵ and reporting comorbidities (e.g. other neurological conditions, neurodevelopmental disorders, and mental health concerns). An assessment of whether articles considered sources of potential bias in recruitment was also included in the appraisal (i.e. only including individuals with a prenatal diagnosis or certain IQ level). Criteria were rated as being completely covered, partly covered, absent, or not applicable because of study design or aims. Full details of the quality criteria are provided in [Table S3](#).

RESULTS

The database search identified 16 823 records in 2020 and an additional 2298 records when updated in 2021. Similar to Siffredi et al.,⁵ the broad keyword and subject heading searches had high sensitivity and after removing 8074 duplicates, 11 047 titles were reviewed, from which 173 abstracts were identified for further review. This identified 66 articles eligible for full-text review from which 23 articles met the inclusion and exclusion criteria. The study selection

process and reason for exclusion at each stage are detailed in [Figure S1](#).

Methodological quality

Most studies reported key criteria relating to the setting and participants including confirming diagnosis by MRI scan, except for Badaruddin et al.¹³ who confirmed diagnosis through parental report and Raile et al.¹⁴ where diagnosis was based on postnatal imaging using MRI or ultrasound. Describing the neuropsychological assessment was less comprehensive with only 10 from 23 studies providing full details including relevant psychometric properties of the instruments used. A significant weakness highlighted in the quality review was in the declaration of comorbidities in participants with AgCC. All studies covered this criterion to some extent; however only Folliot-Le Doussal et al.¹⁵ and Uccella et al.¹⁶ were comprehensive in detailing associated neurological and genetic abnormalities, neurodevelopmental disorders, and how these were detected. Other studies^{6,7,17–20} provided information on the presence of comorbidities, but did not detail the method of assessment. Reporting the presence of neurodevelopmental disorders, such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder, was limited, with studies not stating if these additional conditions were included/excluded in their sample and how this was confirmed. This is a particular concern as des Portes et al.²¹ found 40% of their participants with apparently isolated AgCC had attention difficulties while Lau et al.²² reported 33% of their participants with isolated AgCC met criteria for ASD. Children with ASD and attention-deficit/hyperactivity disorder have a range of neuropsychological weaknesses²³ and therefore declaring the presence of additional diagnoses is important when interpreting findings specific to AgCC.

Most studies sampled a subgroup of children with AgCC by only including those diagnosed prenatally, with a minimum ability level, or sufficient clinical need for an MRI scan (i.e. because of epilepsy or head injury), all sample selection biases which may limit the generalizability of findings.²² Of the 10 studies that included children with a prenatal diagnosis, only three studies referred to this subgroup when drawing conclusions from their results.^{18,24,25} Furthermore, of the 10 studies that limited the sample by ability level (e.g. by applying a minimum IQ or capacity to engage in neuropsychological testing), six considered the potential of this to limit generalization.^{7,13,15,22,26,27}

General intellectual function

Seventeen studies assessed general intelligence in their sample. Of these studies, 13 reported FSIQ, Performance IQ, or Verbal IQ scores from the Wechsler intelligence tests^{28–30} or Stanford Binet Intelligence Scales.³¹ There was a wide range in FSIQ scores reported, ranging from 'extremely low' (30)

to 'superior' (126). Six studies reported average FSIQ of their sample more than one SD below the normative mean for the general population (i.e. FSIQ <85).^{6,7,14,26,32,33} The remaining seven studies reported average FSIQ (or Performance/Verbal IQ) within one SD of the normative mean.^{15,17,19,21,27,34,35} However, two of these studies^{17,19} included participants with prenatally-diagnosed isolated AgCC with FSIQ above 70, thereby restricting their sample IQ range.

In preference to reporting IQ scores, four studies^{8,16,24,25} stated the number of children falling within a classification (see Table S2). This classification was determined by a combination of general intelligence and developmental assessments, with atypical development being defined differently across studies. Three further studies reported developmental quotients (see Table S2 for details of measure used). Mangione et al.¹⁸ reported an average developmental quotient of 89 in their sample of 22 children with prenatally diagnosed isolated AgCC (with four participants later identified as complex AgCC). Raile et al.¹⁴ reported a mean mental developmental index of 87 in young children with both complex and isolated AgCC. Yeh et al.²⁰ did not include a mean score but reported 45% of participants were in the typically developing range on standardized assessments of infant development with the majority (70%) having complex AgCC.

In summary, the general intellectual abilities of individuals with AgCC were found to vary widely. At a group level, mean FSIQ were reported to be within average range (within one SD of the normative mean) in seven of the articles reviewed. The method of reporting of intellectual function varied across studies, with the inclusion criteria applied in some studies constraining the true range of IQ/developmental quotient scores in the AgCC population.

Evidence for the neuropsychological syndrome

Of the 23 studies under review, only 12 considered aspects of neuropsychological functioning beyond general intellectual ability. No study fully examined the pattern of neuropsychological weaknesses consistent with the proposed neuropsychological syndrome.³ Only Folliot-Le Doussal et al.¹⁵ reported on processing speed, with this found to be in the average range in their sample of 15 4- to 14-year-olds with prenatally diagnosed isolated AgCC, although scores varied widely (mean Processing Speed Index from the Wechsler Intelligence Scale for Children: 92.5, range 64–106). Nine studies investigated executive functioning and/or social skills, where impairments could be seen to reflect difficulties processing complex and novel information and these are detailed below.

Social skills

When assessing social competence, most studies relied on parent or teacher report, with AgCC experiencing greater

difficulty in this area compared to controls. In the Siffredi et al.^{7,32} and Shi et al.³³ studies (with 60%, 63%, and 32% of participants having complex AgCC respectively), more than half of parents and teachers reported clinical levels of ASD symptoms using the Social Skills Improvement System³⁶ which included ratings of communication, cooperation, assertion, responsibility, empathy, engagement, and self-control. Similarly, Lau et al.²² found a high percentage of individuals with isolated AgCC (45% of children aged 4–11 years, 35% of adolescents aged 12–15 years) scored beyond the autism-screening cut-off on the Autism-Spectrum Quotient,^{37,38} a parent-report questionnaire measure of autistic traits including socio-communication skills, imagination, attention to detail, and attention switching/tolerance of change.

Badaruddin et al.¹³ assessed behavioural difficulties, including social competence, using the Child Behaviour Checklist³⁹ in their sample of 61 children (2–11 years; 51% with potentially complex AgCC). They found 39% of their older sample (6–11 years) were rated by parents as having a clinically significant level of problem in social interactions. Main difficulties included initiating and sustaining conversation, developing peer relationships, showing social and emotional give-and-take, and understanding nonverbal communication.

Zhan et al.⁴⁰ administered the Chinese version of the Infant-Toddler Social and Emotional Assessment to assess the socio-emotional development young children with AgCC aged 12 to 36 months (70% with isolated AgCC). They found a significant proportion of children (43%) were reported as having problems by parents, particularly on the Competence domain (30%) which rated prosocial peer relations, empathy, imitation in play, attention, and compliance.

Labadi et al.¹⁷ went beyond parent/teacher report and directly assessed elements of social cognition. In their sample of 18 children with prenatally diagnosed isolated AgCC aged 6 to 8 years, Labadi et al. found impairments in recognizing emotions and understanding theory of mind compared to age- and IQ-matched typically developing children. They concluded that reduced callosal connectivity may contribute to the development of social-cognitive deficits, particularly when required to process complex and rapidly presented social information. This aligns closely to the neuropsychological syndrome proposed by Brown et al.³ where core deficits in processing novel and complex information quickly may negatively impact social and emotional cognition.

Executive functions

Siffredi et al.⁷ found children with AgCC (aged 8–17 years, 60% with complex AgCC) scored significantly below what would be expected on parental and teacher ratings of everyday behaviours indicative of difficulties with executive function (Behavioral Rating Inventory of Executive Function).⁴¹ Shi et al.³³ and Siffredi et al.³² further reported that children with AgCC (aged 8–17 years, 32% and 63% with complex AgCC

respectively) were significantly lower than typically developing controls on measures of cognitive inhibition, flexibility, and processing speed as measured by the Stroop Color–Word Interference Test and Trail Making Test from the Delis–Kaplan Executive Function System.⁴² Poor verbal fluency and cognitive switching have also been reported in several studies.^{7,32,33,40}

Moutard et al.¹⁹ reported all children with isolated AgCC in their sample (followed-up at age 10 years) experienced difficulties on the Rey–Osterrieth Complex Figure Test, with 50% demonstrating severe impairment on this measure of visuo-construction ability, visual memory, and executive planning.⁴³ In sum, the executive difficulties found in fluency, planning, inhibition, flexibility, and processing speed may all stem from the core deficits outlined by Brown et al.³

Other cognitive/sensory difficulties

Difficulties on other measures, not necessarily accounted for by the proposed syndrome were also identified. Demopoulos et al.³⁴ used the Adolescent/Adult Sensory Profile⁴⁴ reporting that 57% of their sample (which included adults) with isolated AgCC had atypically high scores indicating challenges with sensory processing. Siffredi et al.²⁶ reported that children with AgCC (62% with complex AgCC) had poorer attention (switching and selective) than controls. Furthermore, Siffredi et al.³² and Shi et al.³³ (63% and 32% with complex AgCC respectively) reported difficulties with short- and long-term verbal memory when compared to typically developing controls. In contrast, Siffredi et al.²⁷ (44% complex AgCC) and Moutard et al.¹⁹ (all isolated AgCC) both reported short-term memory scores falling within the typically developing range. Moutard et al.¹⁹ also assessed long-term memory, reporting that delayed recall of a list of words was in the typical range for all participants.

Although evidence for the neuropsychological syndrome was not explicitly examined, there was indication of difficulties in processing complex and novel information in the studies reviewed. This was observed across measures of executive function, attention, social cognition, and visuospatial perception and construction.

Factors impacting neuropsychological outcome

Presence of other neuroanatomical abnormalities

Only three articles systematically explored differences in outcome between those with isolated AgCC and those with additional neuroanatomical abnormalities of the central nervous system (CNS) not considered secondary to AgCC. Additional neuroanatomical abnormalities of the CNS (i.e. complex AgCC) included hydrocephalus, grey matter heterotopia, holoprosencephaly, microcephaly, interhemispheric cyst, and gyral abnormalities.

Bayram et al.⁶ found general intelligence was significantly higher in children with isolated AgCC (mean IQ 82) compared to complex AgCC (mean IQ 60, age range

6 months–16 years). Siffredi et al.⁷ reported additional neurological abnormalities were associated with poorer teacher ratings on the Strengths and Difficulties Questionnaire⁴⁵ and, alongside social risk, poorer math computation scores in their sample of school-aged children (8–17 years) diagnosed with AgCC. Siffredi et al.²⁶ reported that children with isolated AgCC (8–17 years) had better attention scores compared to those with other neurological abnormalities. Chadie et al.,²⁴ Folliot-Le Doussal et al.,¹⁵ Glatter et al.,²⁵ and Mangione et al.¹⁸ (all samples between 2 and 16 years) also considered the comparison of complex versus isolated AgCC, but only report descriptive data which suggested that significant disabilities were more common in those with additional neurological abnormalities.

In contrast to these findings, Yeh et al.²⁰ found no significant differences in the presence of other neurological abnormalities for those with typical compared to delayed development (9 months–5 years). Raile et al.¹⁴ further reported more children with other CNS abnormalities were classified as having typical outcomes than those with isolated AgCC (8 months–9 years). However, both studies assessed very young children; Yeh et al.²⁰ only considered the developmental quotient in children at an average of 2 years and for Raile et al.,¹⁴ the mean age for those with other CNS malformations was 2 years 11 months.

Findings from neuroimaging studies

Diogo et al.⁸ conducted a qualitative assessment of the structural features of fetal MRI scans of those with isolated AgCC. Using an anatomical scoring system which considered factors such as gyration, asymmetry, lamination, and ventricular size, Diogo et al. found a significant correlation with postnatal neurodevelopmental outcome with those with fewer abnormalities having better cognitive, motor, and language skills (as assessed between 6 months and 6 years). Using the same scoring system, Glatter et al.²⁵ reported that a cut-off score was 91% accurate in predicting outcomes in young children with AgCC (mean age 3 years 1 month, SD = 2.1; 82% with isolated AgCC).

Three recent studies using both structural and functional MRI methods examined the impact of neurological connectivity on cognitive outcome. Bartha-Doering et al.⁴⁶ studied the functional organization of the language network in six children with AgCC (aged 6–15 years, one child with complex AgCC). Using a linguistic task-based functional MRI paradigm, where participants judged whether a definition accurately described a given noun, Bartha-Doering et al. found reduced interhemispheric and right intrahemispheric language network connectivity in children with AgCC as compared to controls. Interestingly, they also found better language abilities were associated with stronger functional connectivity between the left and right temporal areas in AgCC but not in controls.

Siffredi et al.,³² using diffusion-weighted imaging and resting-state functional MRI, reported increased

*intra*hemispheric and reduced *inter*hemispheric structural and functional connectivity was associated with improved scores in memory, attention, and executive functioning in AgCC (8–17 years, 63% complex AgCC). In contrast Shi et al.³³ found no association between graph metrics of structural connectivity using diffusion-weighted imaging and a range of neuropsychological outcomes (8–17 years, 32% complex AgCC).

Despite some inconsistent findings, emerging evidence from structural and functional neuroimaging studies suggests that the presence of anatomical abnormalities, structural features, and the degree of functional connectivity, can impact on neuropsychological outcome in AgCC.

Impact of partial versus complete AgCC

Twelve studies considered if there was a difference in neuropsychological outcomes for partial AgCC versus complete AgCC, with five of these studies reporting no statistically significant difference between the subgroups.^{13,19–21,27} Three studies provide descriptive data for partial AgCC separately to complete AgCC but did not consider if any differences were significant.^{15,24,25}

In the four studies that report a difference, poorer performance was found in complete compared to partial AgCC. This pattern of performance was reported by Siffredi et al.⁷ on the Word Reading subtest from the Wide Range Achievement Test, Fourth Edition⁴⁷ and parent-rated Behavioral Rating Inventory of Executive Function scores⁴¹ in their participants aged 8 to 17 years (60% complex AgCC). Bartha-Doering et al.⁴⁶ detected impairments only in children with complete AgCC (6–15 years, 83% isolated AgCC) in specific language domains (verbal fluency on the Regensburger Wortflüssigkeitstest,⁴⁸ and naming on the Wortschatz- und Wortfindungstest).⁴⁹ Relatively better outcome for partial AgCC was also reported by Raile et al.:¹⁴ all participants with partial AgCC (8 months–9 years) were classified as having typical outcome (as defined by mental developmental index on the Bayley Scales of Infant Development, Second Edition⁵⁰ or a FSIQ greater than 85 and neither language nor motor impairment), while only 50% with complete AgCC met this classification. Finally, Siffredi et al.²⁶ found children with partial AgCC had better attention scores than children with complete AgCC (8–17 years; 62% complex AgCC), but the difference was not significant.

Overall, comparisons of the neuropsychological profiles of complete versus partial AgCC were inconclusive with studies either reporting no difference or relatively better outcome in partial compared to complete AgCC.

Impact of age

Six studies considered the impact of age on neuropsychological outcome in AgCC. Badaruddin et al.¹³ found

older children with AgCC (6–11 years) were reported to have problems in attention, social function, thought, and somatic complaints as rated by parents on the Child Behaviour Checklist,³⁹ whereas younger children with AgCC (2–5 years) were rated as primarily having sleep problems. Siffredi et al.⁷ reported that older age at testing (range 8–17 years, 60% complex AgCC) was associated with poorer parent ratings on the Behavioral Rating Inventory of Executive Function Behaviour Regulation Index (ability to shift cognitive set and modulate emotions and behaviour through appropriate inhibitory control) and the overall Global Executive Composite.⁴¹ In contrast, Lau et al.²² found proportionally more children (45%, 4–11 years) than adolescents (35%, 12–15 years) exceeded the autism-screening cut-off on the Autism-Spectrum Quotient^{37,38} suggesting that autistic traits such as poor social skills, imagination, and mind-reading may be more apparent in younger children with isolated AgCC.

Evidence for higher general intellectual ability with older age was also found in two studies. Uccella et al.¹⁶ reported 31% of children with complex AgCC and mild global developmental delay assessed during infancy had typical cognitive abilities when reassessed, on average, 7 years later. Des Portes et al.²¹ found younger children (3–5 years) had significantly lower Performance IQ (but not Verbal IQ) compared to older children (7 years), all with apparent isolated AgCC. Stable intellectual development was also evident, with Raile et al.¹⁴ reporting 86% of children (8 months–9 years, 61% isolated AgCC) for whom long-term data were available did not change outcome categorization, with one child shifting from moderate to severe delay over 3 years 6 months.

Overall, there was little converging evidence of a systematic change in the neuropsychological profile in AgCC with age; some studies report more evidence of behavioural and executive problems in older cohorts, while some cited improvements in social and intellectual functioning.

DISCUSSION

This review identified 23 articles reporting on neuropsychological outcomes in individuals with AgCC aged 1 month to 18 years. General intellectual function was found to vary widely in AgCC, with many studies quoting average FSIQ scores in the typically developing range in both complex and isolated AgCC. This is consistent with recent reviews,^{4,9} although the inclusion criteria set by several studies, such as a minimum IQ level or the ability to engage in neuropsychological testing, may mask the true reporting of intellectual functioning in AgCC.

The opportunity to map the wide variety of clinical outcomes and review evidence for the proposed neuropsychological syndrome in children with AgCC was limited by only half the studies reviewed going beyond general intellectual ability when reporting cognitive outcome. Only one study reported on the Processing Speed Index (from the Weschler

Intelligence Scale for Children) and no study considered if variability in test scores could be explained by slowed sensory and motor reaction times. As processing speed is highly vulnerable to disruptions in white matter connectivity, it seems pertinent for studies assessing children with AgCC to consider whether slow processing speed may impact social and cognitive development. This evidence is also needed to verify whether cognitive processing speed is a core deficit in children with AgCC, irrespective of overall level of functioning and additional neuroanatomical features (i.e. beyond those considered to have primary AgCC). There was some evidence across the reviewed studies for impairments in processing complex and novel information which was seen across domains of social cognition, executive functioning, and attention. More research is required to determine whether difficulties in complex reasoning and problem-solving are core deficits in children with AgCC, or whether underlying deficits in emotion recognition, inferring others' mental states, and limited imagination, are more fundamental (and akin to ASD; Happé et al.).⁵¹

Confirmation of the third aspect of the proposed syndrome, reduced interhemispheric transfer of sensory-motor information, was restricted by test selection (i.e. no studies reported on bimanual coordination or bilateral visual field matching to assess interhemispheric transfer at a behavioural level).³ However, recent studies of structural and functional MRI have enabled the study of interhemispheric and intrahemispheric connectivity and its relationship to neuropsychological outcome. Although the findings so far have been mixed in terms of whether the strength of functional interhemispheric connectivity reflects stronger or poorer cognitive outcome,^{32,33,46} the methods hold promise for future work into the efficacy of interhemispheric and intrahemispheric transfer of sensory-motor information in AgCC.

Brown et al.³ hypothesized that features of the neuropsychological syndrome would become more pronounced in later adolescence and adulthood as greater reliance is placed on the functional connectivity of the corpus callosum from this age. However, the current review identified several areas of weakness in individuals younger than 18 years compared to age- and ability-matched peers. While less than a third of studies reported on the developmental trajectory in AgCC, there was not a clear pattern of findings. Relatively more behavioural and executive problems (e.g. inhibitory control, ability to modulate emotions) were found in late childhood and adolescence compared to early childhood, whereas higher ratings of autistic traits and poorer intellectual functioning were found in younger cohorts of AgCC.

Of the studies that compared individuals with partial versus complete AgCC, around half found no differences in neuropsychological outcome. When a difference was reported, outcome was more favourable for those with partial AgCC. In line with previous findings,^{4,6} outcomes were also generally more favourable for individuals without accompanying neurological abnormalities to their AgCC. Interestingly, two studies of very young children found no

evidence of poorer outcomes in those with additional CNS abnormalities,^{14,20} although differences may become apparent with age. There is a clear need for more longitudinal follow-up studies in order to map the neurodevelopmental trajectories in AgCC and identify neurobiological factors that contribute to outcome.

Strengths and limitations

Strengths of this review included the number of databases searched for the identification of potentially eligible studies and the use of broad search terms. Selected search terms were more relevant to the core syndrome than secondary symptoms however, and specific terms relating to social and emotion processing were not included. This omission may have limited the final set of articles selected for the scoping review.

Further limitations included the rated quality of the articles with studies not always disclosing comorbidities in their sample or reporting relevant data such as mean scores. Differing inclusion criteria and how typical neurodevelopmental outcome was defined also limited the ability to make direct comparisons across studies.

Most studies under review recruited individuals with AgCC diagnosed through routine ultrasound screening. This recruitment method overcomes the bias towards only including individuals with sufficient clinical need for a scan to be requested. However, AgCC is not always detected prenatally. Zhan et al.,⁴⁰ for example, reported that for 8.7% of their participants, AgCC was diagnosed postnatally, despite having routine prenatal ultrasounds. A representative cohort should therefore include both prenatally and postnatally diagnosed individuals.

CONCLUSION

Assessing the neuropsychological profile of a child diagnosed with AgCC needs to go beyond the global measure of intellectual function. Cognitive and psychosocial difficulties were seen at an earlier age than suggested by the model proposed by Brown et al.³ and the profile may also change during childhood and the teenage years. Key areas to assess and monitor over time include processing speed, attention, and processing novel and complex information. These core skills are likely to impact the ability to follow social interactions and perform other cognitive 'online' tasks. Neuropsychological assessments should include both informant ratings and cognitive testing in order to obtain a full picture of the primary deficits seen in children with AgCC.

Further study into the developmental trajectory of AgCC is also needed to clarify the neuropsychological syndrome in children. It is encouraging that sample size and outcome measures have increased since the review by Siffredi et al.⁵ Advances in neuroimaging methods have also enabled the study of structural and functional factors

associated with neuropsychological outcome. Appropriate educational support for children with AgCC is often hindered by inconsistent understanding of the impact on functioning. Although the clinical outcomes for children with AgCC are highly variable, the proposed neuropsychological syndrome for adults with primary AgCC is a viable starting point to understanding the core deficits these children may encounter.

ACKNOWLEDGMENTS

Dr Alice Wright was funded to complete this research as part of a Masters in Clinical Paediatric Neuropsychology at UCL Great Ormond Street Institute of Child Health by NHS Forth Valley.

The authors have stated that they had no interests which might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Rhonda Booth  <https://orcid.org/0000-0003-0133-8110>

REFERENCES

- Raybaud C. The corpus callosum, the other great forebrain commissures, and the septum pellucidum: anatomy, development, and malformation. *Neuroradiology* 2010; 52(6): 447–77.
- Paul LK, Brown WS, Adolphs R, Tyszka JM, Richards LJ, Mukherjee P, et al. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. *Nature Reviews Neuroscience* 2007; 8(4): 287–99.
- Brown WS, Paul LK. The neuropsychological syndrome of agenesis of the corpus callosum. *Journal of the International Neuropsychological Society* 2019; 25(3): 324–330.
- Bernardes da Cunha S, Carneiro MC, Miguel Sa M, Rodrigues A, Pina C. Neurodevelopmental outcomes following prenatal diagnosis of isolated corpus callosum agenesis: A systematic review. *Fetal Diagnosis and Therapy* 2021; 48(2): 88–95.
- Siffredi V, Anderson V, Leventer RJ, Spencer-Smith MM. Neuropsychological profile of agenesis of the corpus callosum: A systematic review. *Developmental Neuropsychology* 2013; 38(1): 36–57.
- Bayram AK, Kutuk MS, Doganay S, Ozgun MT, Gumus H, Basbug M, et al. An analysis of 109 fetuses with prenatal diagnosis of complete agenesis of corpus callosum. *Neurological Sciences* 2020; 41(6): 1521–1529.
- Siffredi V, Anderson V, McIlroy A, Wood AG, Leventer RJ, Spencer-Smith MM. A Neuropsychological profile for agenesis of the corpus callosum? Cognitive, academic, executive, social, and behavioral functioning in school-age children. *Journal International Neuropsychology Society* 2018; 24(5): 445–55.
- Diogo MC, Glatter S, Prayer D, Gruber GM, Bettelheim D, Weber M, et al. Improved neurodevelopmental prognostication in isolated corpus callosal agenesis: fetal magnetic resonance imaging-based scoring system. *Ultrasound Obstetrics & Gynecology* 2021; 58(1): 34–41.
- D'Antonio F, Pagani G, Familiari A, Khalil A, Sagies T-L, Malinger G, et al. Outcomes associated with isolated agenesis of the corpus callosum: a meta-analysis. *Pediatrics* 2016; 138(3): e20160445.
- Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of Internal Medicine* 2018; 169(7): 467–473.
- Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil, H. Chapter 11: Scoping Reviews (2020 version). In: Aromataris E, Munn Z (Editors). *JBIM Manual for Evidence Synthesis*. Adelaide: Joanna Briggs Institute; 2020. Available from <https://synthesismanual.jbi.global>. <https://doi.org/10.46658/JBIMES-20-12>
- Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Epidemiology* 2007; 18(6): 805–35.
- Badaruddin DH, Andrews GL, Bölte S, Schilmoeller KJ, Schilmoeller G, Paul LK, et al. Social and behavioral problems of children with agenesis of the corpus callosum. *Child Psychiatry and Human Development* 2007; 38(4): 287–302.
- Raile V, Herz NA, Promnitz G, Schneider J, Tietze A, Kaindl AM. Clinical outcome of children with corpus callosum agenesis. *Pediatric Neurology* 2020; 112: 47–52.
- Folliot-Le Doussal L, Chadie A, Brasseur-Daudruy M, Verspyck E, Saugier-Verber P, Marret S. Neurodevelopmental outcome in prenatally diagnosed isolated agenesis of the corpus callosum. *Early Human Development*, 2018; 116: 9–16.
- Uccella S, Accogli A, Tortora D, Mancardi MM, Nobili L, Berloco B, et al. Dissecting the neurological phenotype in children with callosal agenesis, interhemispheric cysts and malformations of cortical development. *Journal of Neurology* 2019; 266(5): 1167–81.
- Labadi B, Beke AM. Mental state understanding in children with agenesis of the corpus callosum. *Frontiers in Psychology* 2017; 8: 1–12.
- Mangione R, Fries N, Godard P, Capron C, Mirlesse V, Lacombe D, et al. Neurodevelopmental outcome following prenatal diagnosis of an isolated anomaly of the corpus callosum. *Ultrasound in Obstetrics & Gynecology* 2011; 37(3): 290–5.
- Moutard M-L, Kieffer V, Feingold J, Lewin F, Baron J-M, Adamsbaum C, et al. Isolated corpus callosum agenesis: a ten-year follow-up after prenatal diagnosis (How are the children without corpus callosum at 10 years of age?). *Prenatal Diagnosis* 2012; 32(3): 277–83.
- Yeh H-R, Park H-K, Kim H-J, Ko T-S, Won H-S, Lee M-Y, et al. Neurodevelopmental outcomes in children with prenatally diagnosed corpus callosal abnormalities. *Brain and Development* 2018; 40(8): 634–41.
- des Portes V, Rolland A, Velazquez-Dominguez J, Peyric E, Cordier M-P, Gaucherand P, et al. Outcome of isolated agenesis of the corpus callosum: a population-based prospective study. *European Journal of Paediatric Neurology* 2018; 22(1): 82–92.
- Lau YC, Hinkley LB, Bukshpun P, Strominger ZA, Wakahiro ML, Baron-Cohen S, et al. Autism traits in individuals with agenesis of the corpus callosum. *Journal of Autism Developmental Disorders* 2013; 43(5): 1106–18.
- Colombi C, Ghaziuddin M. Neuropsychological characteristics of children with mixed autism and ADHD. *Autism Research and Treatment* 2017; 2017: 5781781.
- Chadie A, Radi S, Trestard L, Charollais A, Eurin D, Verspyck E, et al. Neurodevelopmental outcome in prenatally diagnosed isolated agenesis of the corpus callosum. *Acta Paediatrica* 2008; 97(4): 420–4.
- Glatter S, Kasprian G, Bettelheim D, Ulm B, Weber M, Seidl R, et al. Beyond isolated and associated: A novel fetal MR Imaging-based scoring system helps in the prenatal prognostication of callosal agenesis. *American Journal of Neuroradiology* 2021; 42(4): 782–6.
- Siffredi V, Wood AG, Leventer R, Vaessen M, McIlroy A, Anderson V, et al. Anterior and posterior commissures in agenesis of the corpus callosum: Alternative pathways for attention processes? *Cortex* 2019; 121: 454–67.
- Siffredi V, Spencer-Smith MM, Barrouillet P, Vaessen MJ, Leventer RJ, Anderson V, et al. Neural correlates of working memory in children and adolescents with agenesis of the corpus callosum: An fMRI study. *Neuropsychologia* 2017; 106: 71–82.
- Wechsler D. Wechsler abbreviated scale of intelligence. San Antonio, TX: Psychological Corporation; 1999.
- Wechsler D. Wechsler Intelligence Scale for Children. 4. San Antonio, TX: Psychological Corporation; 2003.

30. Wechsler, D. Wechsler Preschool and Primary Scale of Intelligence. 4. Bloomington, MN: Psychological Corporation; 2012.
31. Roid GH. Stanford Binet Intelligence Scales. Itasca, IL: Riverside Pub; 2003.
32. Siffredi V, Preti MG, Kebets V, Obertino S, Leventer RJ, McIlroy A, et al. Structural neuroplastic responses preserve functional connectivity and neurobehavioural outcomes in children born without corpus callosum. *Cerebral Cortex* 2021; 31(2): 1227–39.
33. Shi M, Freitas LGA, Spencer-Smith MM, Kebets V, Anderson V, McIlroy A, et al. Intra- and inter-hemispheric structural connectome in agenesis of the corpus callosum. *NeuroImage: Clinical* 2021; 31: 102709.
34. Demopoulos C, Arroyo MS, Dunn W, Strominger Z, Sherr EH, Marco E. Individuals with agenesis of the corpus callosum show sensory processing differences as measured by the sensory profile. *Neuropsychology* 2015; 29(5):751–8.
35. Cignini P, D'Emidio L, Padula F, Girgenti A, Battistoni S, Vigna R, et al. The role of ultrasonography in the diagnosis of fetal isolated complete agenesis of the corpus callosum: a long-term prospective study. *J Matern Fetal Neonatal Med* 2010; 23(12): 1504–9.
36. Gresham, FM, Elliott, SN. Social skills improvement system: Rating scales. Bloomington, MN: Pearson Assessments; 2008.
37. Auyeung B, Baron-Cohen S, Wheelwright S, Allison C. The Autism Spectrum Quotient: Children's Version (AQ-Child). *J Autism Dev Disord* 2008; 38(7):1230–40.
38. Baron-Cohen S, Hoekstra RA, Knickmeyer R, Wheelwright S. The Autism-Spectrum Quotient (AQ)--adolescent version. *J Autism Dev Disord* 2006; 36(3): 343–50.
39. Achenbach TM. Achenbach System of Empirically Based Assessment (ASEBA). In *The Encyclopedia of Clinical Psychology* (editors Cautin RL, Lilienfeld SO), 2015. <https://doi.org/10.1002/9781118625392.wbecp150>
40. Zhan D, Li H, Shi W, Zhao R. Social-emotional, sleep and feeding problems in young patients with agenesis of the corpus callosum and the life quality of their parents. *Soc Neurosci* 2021; 16(2): 166–73.
41. Gioia GA, Isquith PK, Retzlaff PD, Espy KA. Confirmatory factor analysis of the Behavior Rating Inventory of Executive Function (BRIEF) in a clinical sample. *Child Neuropsychol* 2002; 8(4): 249–57.
42. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan executive function system. San Antonio, TX: Pearson; 2001.
43. Meyers JE, Meyers KR. Rey Complex Figure Test and Recognition Trial (RCFT). Odessa, FL: Psychological Assessment Resources; 1995.
44. Brown C, Dunn W. Adolescent/Adult Sensory Profile manual. San Antonio, TX: Psychological Corporation; 2002.
45. Goodman R. The extended version of the Strengths and Difficulties Questionnaire as a guide to child psychiatric caseness and consequent burden. *J Child Psychol Psychiatry* 1999; 40(5): 791–9.
46. Bartha-Doering L, Schwartz E, Kollndorfer K, Fischmeister FPS, Novak A, Langs G, et al. Effect of corpus callosum agenesis on the language network in children and adolescents. *Brain Struct Funct* 2021; 226(3): 701–13.
47. Wilkinson GS, Robertson GJ. Wide Range Achievement Test-Fourth Edition (WRAT-4). Lutz, FL: Psychological Assessment Resources; 2006.
48. Aschenbrenner S, Tucha O, Lange KW. Regensburger Wortflüssigkeits-Test: RWT. Testzentrale: Goettingen): Hogrefe, Verlag für Psychologie; 2001.
49. Glück CW. Wortschatz- und Wortfindungstest für 6- bis 10-Jährige. München: Elsevier; 2011.
50. Bayley N. Bayley Scales of Infant Development Manual. 2. San Antonio, TX: The Psychological Corporation; 1993
51. Happé F, Frith U. Annual Research Review: Towards a developmental neuroscience of atypical social cognition. *J Child Psychol Psychiatry* 2014; 55(6): 553–7.

SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: PRISMA flow diagram of paper selection process.

Table S1: Search terms used in the scoping review.

Table S2: Studies exploring cognitive/neuropsychological functioning in children with agenesis of the corpus callosum.

Table S3: Rating of methodological quality based on adapted STROBE criteria.

How to cite this article: Wright A, Booth R. Neuropsychological profiles of children with agenesis of the corpus callosum: A scoping review. *Dev Med Child Neurol.* 2023;00:1–9. <https://doi.org/10.1111/dmcn.15532>