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Anterior and posterior commissures in agenesis of the corpus callosum: alternative pathways for attention processes?

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Abstract

Developmental absence (agenesis) of the corpus callosum (AgCC) is a congenital brain malformation resulting from disruption of corpus callosum formation, a structure that is crucial for the transfer and integration of information, including attention processes, across the brain. This study aimed to investigate previously proposed candidates for alternative inter-hemispheric pathways in AgCC by examining (1) white matter volume and microstructure of the anterior and posterior commissures in children with AgCC compared to typically developing controls (TDC), and (2) in children with AgCC, examine the associations of white matter volume and microstructure of the anterior and posterior commissures and any remaining corpus callosum with attention processes. Participants were 21 children with AgCC (13 complete, 8 partial) recruited from The Royal Children’s Hospital, Melbourne, and 30 TDC aged 8 to 17 years. T1- and diffusion-weighted MR sequences were used to calculate volume and microstructural parameters. Neuropsychological testing assessed attention processes. We found the anterior commissure was significantly larger in volume in children with AgCC than TDC (p = 0.027), with reduced mean FA (p = 0.001) associated with increased mean RD (p < 0.001). In children with AgCC, we found microstructural properties of the anterior commissure associated with attentional processes, specifically, mean FA of the anterior commissure was associated with better divided attention (p = 0.03), and the association between alerting attention and mean AD and RD was found to be moderated by age (p = 0.027, p = 0.008) and the degree of corpus callosum agenesis (p = 0.025, p = 0.016). Furthermore, in partial AgCC, larger posterior commissure volume was associated with better orienting attention (p = 0.035). In conclusion, we provide evidence that the volume and microstructure of the anterior commissure are altered in children with AgCC, and this neuroplastic response might have an influence on attention processes.
Keywords: agenesis of the corpus callosum; alternative inter-hemispheric pathway; anterior and posterior commissures; attention processes; development

Abbreviations:

AD axial diffusivity
AgCC Agenesis of the corpus callosum
CNS Central Nervous System
DTI Diffusion tensor MR imaging
FA Fractional Anisotropy
RD radial diffusivity
ROIs regions of interest
TEA-Ch Test of Everyday Attention for Children
TDC typically developing controls
1. Introduction

The corpus callosum is the largest white matter pathway connecting homologous structures of the two cerebral hemispheres (Aboitiz & Montiel, 2003; Banich, 1995; Barkovich & Kjos, 1988). With over 190 million axons, it plays a crucial role in interhemispheric communication, and in the integration and control of motor, sensory and cognitive information (Fratelli et al., 2007; Lassonde & Jeeves, 1994; Paul et al., 2007; Schulte & Müller-Oehring, 2010). Developmental absence (agenesis) of the corpus callosum (AgCC) refers to the complete or partial failure of the callosal fibres to cross the midline and form connections in the neocortex between the two hemispheres (dos Santos et al., 2002). Its estimated prevalence, varying as a function of both diagnostic techniques and sample populations, is 1 to 7 per 4000 births (Chiappedi & Bejor, 2010; Glass, Shaw, Ma, & Sherr, 2008; Guillem, Fabre, Cans, Robert-Gnansia, & Jouk, 2003; Wang, Huang, & Yeh, 2004). The absence of the corpus callosum may be complete or partial. In complete AgCC, interruption of callosal development occurs at an early stage in embryological development, before gestational week 6 (Edwards, Sherr, Barkovich, & Richards, 2014). In partial AgCC, disruption to callosal development occurs slightly later in gestation, so that a portion of the corpus callosum is present (Huang et al., 2009; Paul, 2011; Richards, Planchez, & Ren, 2004).

AgCC may present as an isolated condition with recognised secondary brain anomalies including colpocephaly, Probst bundles and cingulate gyrus alteration (Booth, Wallace, & Happe, 2011). It may also be associated with other central nervous system (CNS) anomalies known to impact cognition, and attention in particular, such as hydrocephalus, grey matter heterotopia, holoprosencephaly, interhemispheric cyst, gyral abnormalities (Bedeschi et al., 2006); neurological conditions, for example epilepsy, macro or microcephaly (Moes, Schilmoeller, & Schilmoeller, 2009); or genetic conditions including single-gene and
Chromosomal abnormalities (Edwards et al., 2014). Consistent with the heterogeneity of this population, neurobehavioural functions range from normal (Caillé et al., 1999) to impaired (Graham et al., 2008; Graham et al., 2003). Recent studies show that, on average, intellectual abilities in individuals with AgCC are significantly below those of the general population, and within the low average range, although individuals show abilities ranging from extremely low to superior (Siffredi, Anderson, Leventer, & Spencer-Smith, 2013; Siffredi et al., 2018).

The ability to effectively attend to information is a core cognitive ability important for the development of a range of other cognitive, academic and behavioural functions (P. J. Anderson, 2008; V. Anderson, Northam, Hendy, & Wrennall, 2001; Aylward, 2002; Gathercole & Pickering, 2000; Gathercole, Pickering, Knight, & Stegmann, 2004; Kyllonen & Christal, 1990). Separable neural networks have been proposed to underpin the key attention processes of orienting, alerting and executive attention (Petersen & Posner, 2012). Orienting represents the ability to engage, disengage and shift attention. Alerting is the ability to achieve and maintain a state of alertness (i.e. sustained attention). Executive attention is a more self-generated component of attention, which is goal-directed and planned, and has also been linked to working memory processes including active manipulation and updating of task-relevant contents (Awh, Vogel, & Oh, 2006; Engle, 2002). These different processes are subserved by distinct, but partly overlapping neural networks of interacting left and right hemisphere brain regions, including prefrontal, anterior cingulate and parietal regions (Klingberg, 2006; Klingberg, Forssberg, & Westerberg, 2002; Petersen & Posner, 2012; Siffredi, Barrouillet, et al., 2017; Siffredi, Spencer-Smith, et al., 2017; Spencer-Smith et al., 2013). To effectively deploy attention, transfer and integration of information has to occur both within and across, the cerebral hemispheres through the corpus callosum (Culham, Cavanagh, & Kanwisher, 2001; Haxby, Petit, Ungerleider, & Courtney, 2000; Hillary et al.,
2011). Associations between white matter microstructural properties of the corpus callosum (fractional anisotropy and/or apparent diffusion coefficients) and components of attention have been identified in typically developing adults and children. For example, individual differences in white-matter microstructure within the splenium and genu of the corpus callosum have been related to orienting (Bennett, Motes, Rao, & Rypma, 2012; Niogi, Mukherjee, Ghajar, & McCandliss, 2010), within the posterior body and on streamline traversing the corpus callosum have been associated with alerting (Klarborg et al., 2013; Mabbott, Noseworthy, Bouffet, Laughlin, & Rockel, 2006; Takahashi et al., 2010), and within the anterior and posterior parts of the corpus callosum have been related to executive attention including working memory (Lebel et al., 2013; Nagy, Westerberg, & Klingberg, 2004; Peters et al., 2014). Therefore, the corpus callosum may play an important role in attention processing, which may be explored in the context of AgCC and the efficacy of plasticity in the developing CNS. Interestingly, a study from Tovar-Moll and colleagues showed the existence of long-distance plasticity with atypical white-matter tracts connecting parietal cortices homotopically via the anterior and the posterior commissures in individuals with AgCC (Tovar-Moll et al., 2014). Given the crucial involvement of interhemispheric parietal cortex communication for attention processes, this raises the question of the role of the anterior and posterior commissures in AgCC for higher order cognitive functions.

Plasticity in the developing brain can be observed at the level of neurobehavioural functions (V. Anderson, Spencer-Smith, & Wood, 2011; Hannay, Dennis, Kramer, Blaser, & Fletcher, 2009; Tovar-Moll et al., 2007). In the case of AgCC, the anterior and posterior commissures, as well as integrity of the corpus callosum (i.e. complete vs. partial AgCC), are suggested as potential candidates for plasticity in AgCC. The anterior commissure contains approximately 3.5 million fibres in humans (Guénot, 1998) and extends from one hemisphere to the other in
the anterior portion of the basal ganglia and between the amygdalae, above and behind the septal nuclei (Raybaud, 2010). In typical development, the anterior commissure contains olfactory fibres, as well as non-olfactory fibres, which are further subdivided into an anterior part connecting the temporal poles, and a posterior part connecting the inferior temporal cortex, including the parahippocampal, fusiform, and inferior occipital gyri (Kollias, 2012). The anterior commissure is thought to be enlarged in around 10% of individuals with AgCC (Hetts, Sherr, Chao, Gobuty, & Barkovich, 2006; Loeser & Alvord, 1968) and, as mentioned earlier, may constitute an alternative inter-hemispheric pathway (Barr & Corballis, 2002; Brown, Jeeves, Dietrich, & Burnison, 1999; Fischer, Ryan, & Dobyns, 1992; Hannay et al., 2009; Lassonde, Sauerwein, Chicoine, & Geoffroy, 1991; Paul et al., 2007; Tovar-Moll et al., 2014; van Meer et al., 2016). In typical development, the posterior commissure is an exclusively subcortical, mesodiencephalic bundle that makes direct connections with the nucleus of Darkschewitsch and the red nucleus, as well as with the habenular nuclei (Keene, 1938; Tovar-Moll et al., 2014). Alternative pathways through the posterior commissure have remained relatively unsuspected so far, with the exception of the study of Tovar-Moll and colleagues, mentioned earlier (Tovar-Moll et al., 2014). Finally, the degree of integrity of the corpus callosum in AgCC has been proposed as a potential mechanism for functional compensation. In comparison to complete AgCC, in partial AgCC white matter fibres still cross the midline. Therefore an increased number of interhemispheric connections might play a role in the preservation of cognitive outcomes in partial AgCC compared to complete AgCC (Huber-Okrainec, Blaser, & Dennis, 2005).

The potential roles of the anterior and posterior commissures and remaining corpus callosum as alternative pathways in AgCC have been rarely studied, and only in small samples (Tovar-Moll et al., 2014). In AgCC, commissure volumes have not been explored quantitatively.
Furthermore, associations between volumetric and white matter microstructural measures of the anterior and posterior commissures and remaining corpus callosum with higher cognitive functions, such as attention, have not yet been investigated. Therefore, the current study investigated the volume and white matter microstructure (fractional anisotropy, axial and radial diffusivity) of the anterior and posterior commissures in a cohort of children with AgCC. White matter microstructural metrics can be measured using diffusion tensor MR imaging (DTI). A derivative of these measures, fractional anisotropy (FA), is derived from a combination of the estimates of axial (AD) and radial (RD) diffusivity (Wozniak & Lim, 2006). FA is believed to reflect the degree of myelination and axonal density and/or integrity (Arfanakis et al., 2002; Harsan et al., 2006). Studies have suggested that directional diffusivities such as AD and RD are more specific to underlying biological processes, such as myelin abnormalities and axonal changes (Song et al., 2003; Song et al., 2002). In this study, we firstly aimed to compare these volumetric and white matter microstructure measures in children with AgCC and typically developing controls (TDC), and in children with complete and partial AgCC. The impact of associated CNS anomalies on these measures was also explored. The second aim was to examine in children with AgCC potential associations of the volume and white matter microstructure in the anterior and posterior commissures and any remaining corpus callosum, with a range of attention processes. As AgCC represents atypical brain development, we expected differences in volume and white matter microstructural properties between the AgCC and TDC groups, and in children with AgCC expected that these properties would be associated with attention processes. Presence of such atypical neuroplastic responses might facilitate inter-hemispheric transfer of information. We also expected differences in white matter microstructure between isolated AgCC and AgCC with associated CNS anomalies as these anomalies might create myelin and axonal changes across the brain.
2. Materials and Methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. Sample

This study used data from the “Paediatric Agenesis of the Corpus Callosum Project” (Siffredi et al., 2018). A cohort of 28 children with AgCC, diagnosed on MRI, were recruited from clinic and radiology records at The Royal Children’s Hospital in Melbourne, Australia. Inclusion criteria were: 1) aged 8 years 0 months to 16 years and 11 months; 2) documented evidence of AgCC on MRI conducted as part of routine clinical work-up; 3) English speaking; and 4) functional ability to engage in the neuropsychological assessment procedure. A TDC group of 30 children, comparable in age and sex to the AgCC group, was recruited through advertisement in local schools and through staff at The Royal Children’s Hospital. TDC children were aged 8 to 16 years 11 months, English speaking, and had no documented history of a brain lesion, neurological disability or neurobehavioural disorders. Structural brain images of the TDC group were reviewed to ensure that there were no incidental findings that would warrant a clinical referral. Participants in the AgCC and TDC groups had normal or corrected-to normal vision and hearing.

The Royal Children’s Hospital Human Research Ethics Committee approved the study. Caregivers, and when appropriate, participants (above 10 years), provided informed written consent. No part of the study procedures and analyses were pre-registered prior to the research being conducted. Participants completed a neuropsychological assessment and, if consent was
given, a brain MRI. In the current study, six participants with AgCC were excluded, as they did not complete the diffusion-weighted sequences of the MRI. The final sample for the current study comprised 21 children with AgCC and 30 TDC. Seven children were assessed on two separate occasions, and in this study we chose to include the assessment for that child with the most complete dataset. One child was recruited below 16 years and 11 months but was assessed at 17 years and 1 month.

2.2. Neuroimaging

2.2.1. Image acquisition

Images were acquired on a 3T MAGNETOM Trio scanner (Siemens, Erlangen, Germany) at The Royal Children’s Hospital. 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 ms, echo time =2.71 ms, inversion time=900 ms, flip angle=9°, field of view=256mm, voxel size=0.7 x 0.7 x 0.7 mm. Single-shell echo planar diffusion-weighted images were also acquired with the following parameters: axial slices=2.3 mm, echo time=112 ms, field of view=240 mm, matrix size=104*104*54, voxel size =2.3 x 2.3 x 2.3 mm, and the following diffusion-weighting scheme: b-value=3000s/mm$^2$, 50 gradient directions, repetition time = 8200ms, including one scan without diffusion weighting (b-factor = 0) as part of the single diffusion acquisition.

2.2.2. Volumetric analysis of ROIs

Given differences in gross anatomy among individuals with AgCC, regions of interest (ROIs) were manually defined for each participant’s image from the AgCC and TDC groups using MRIcron (http://www.mccauslandcenter.sc.edu/micro/mricron/) and MRview
on native space T1-weighted images. ROIs included: the anterior commissure, the posterior commissure, and remnant of the corpus callosum in the case of partial AgCC. 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 voxel for each drawings was calculated using SPM functions running on Matlab (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007; The MathWorks, 2012). Second, the number of voxel 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 x 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 as such. If the overlap was less than 80%, the two drawers had to make an agreement for the final ROI. Volume was then extracted from these ROI images in mm$^2$ (Fig. 1). To adjust for differences in total brain volumes, anterior and posterior commissures volumes, as well as remaining corpus callosum volumes, were corrected as a ratio to total brain volume (ROI volume divided by representative brain volume; O'Brien et al., 2011).

<Insert Figure 1 about here>

2.2.3. DTI parameters analysis of ROIs

Diffusion volumes were eddy current and motion corrected using the Eddy tool from the FSL package in order to minimize distortions due to eddy currents and to reduce simple head motion (Andersson & Sotiropoulos, 2016). The T2-weighted low-b ($b = 0$) image was extracted from the DW-images using MRtrix (i.e. the image with no diffusion encoding). In order to remove non-brain tissue components and background noise, brain-only images were
extracted using the Brain Extraction Tool (BET2) compiled in FSL (Jenkinson, Pechaud, & Smith, 2005; Smith, 2002). The diffusion tensor model was fitted using MRtrix software and relevant diffusion image maps were generated, including FA and the three eigenvalues ($\lambda_1$, $\lambda_2$, $\lambda_3$) of the diffusion tensor (Tournier, 2010; Tournier et al., 2008). The FA maps were transformed into T1 space using the bbregister and mri_vol2vol co-registration tools from FreeSurfer (Fischl, 2012). Each co-registration was carefully inspected and if necessary an additional manual correction of the automated co-registration was completed to ensure accurate alignment. The ROI images in T1 space were then used to extract the key measures of diffusivity from the FA image transformed to T1 space: mean FA, AD $\lambda_\parallel = \lambda_1$ and RD $\lambda_\perp = (\lambda_2 + \lambda_3)/2$ (Smith et al., 2006; Smith et al., 2007).

### 2.3. Attention measures

Child testing was conducted by a trained child psychologist using standardised tests to estimate attention processes. For all measures, standard scores have mean of 10 and standard deviation of 3. i) Orienting: Two aspects of Orienting were examined, selective and shifting attention. The Sky Search subtest from the Test of Everyday Attention for Children (TEA-Ch; Manly et al., 1999) was used to assess selective attention, which requires the child to circle target spaceships among distracters as quickly as possible and the number of correctly identified targets was the variable of interest. The Trail Making Test from the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001) was used to assess shifting. The Number-Letter Switching condition requires the child to switch back and forth between connecting numbers and letters as quickly as possible (i.e., 1 - A - 2 - B), while the Motor Speed condition requires the child to trace over a dotted line connecting circles on the page as quickly as possible. The difference in speed of performance on these conditions removes the motor speed element from the test score to ascertain a measure of cognitive flexibility (Lezak
, Howieson, Bigler, & Tranel, 2012), and this difference score was used as a measure of shifting. ii) Alerting was measured using the Score! subtest (TEA-Ch) which involves the child counting beeps on an audiotape for 10 games, and the number of correct games was the variable of interest. iii) Executive attention measures assessed divided attention and working memory. Divided attention was measured using the Sky Search DT subtest (TEA-Ch), which requires the child to simultaneously complete the Sky Search and Score! Tasks and the dual task decrement score was the variable of interest. Working memory was assessed using the Digit Span Backward subtests from the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV; Wechsler, 2003), which requires the child to immediately repeats a spoken string of digits in the reverse order, and the number of correct trials was the variable of interest.

2.4. Statistical Analyses

Two-tailed statistical analyses were performed on data extracted from each ROI and on attention measures mean scores using SPSS 22.0 (IBM, Released 2013). Independent sample t-tests (or Mann-Whitney tests in the case of violation of normality) were used with 95% confidence intervals, to examine differences between the following groups: a) AgCC and TDC, b) complete AgCC and partial AgCC, and c) isolated AgCC and AgCC with associated CNS anomalies. To address type I error, multiple testing corrections using the Benjamini–Hochberg false discovery rate (i.e. q-value) (Benjamini & Hochberg, 1995) was applied for the different group comparisons; (a) for attention measures, and (b) for volume and DTI parameters (FA, AD, RD) in the anterior and posterior commissures. A p-value < 0.05 and a q-value < 0.05 was considered significant.

To examine associations between volume and DTI parameters (FA, AD, RD) in the anterior and posterior commissures and attention processes a series of linear regressions was
performed. Given the importance of developmental changes in white-matter micro-structure across childhood (Dubois et al., 2008; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008) as well as the heterogeneity of our cohort in terms of age and degree of corpus callosum agenesis (complete / partial), age at testing and degree of agenesis were examined as moderators in each model. In partial AgCC, a series of linear regressions was used to examine associations between volume and DTI parameters (FA, AD, RD) of the remnant of the corpus callosum and attention processes, and age at testing was examined as moderators of this association. To test for an interaction effect, the independent variable (e.g. volume of the anterior commissure) and the interaction terms (e.g. volume of the anterior commissure x age, and volume of the anterior commissure x degree of agenesis) were centred and included in the linear model. The variables age at testing and the degree of agenesis were identified as a moderator if the interaction term was significant. Assumptions for linear regression were checked and in the case of heteroscedasticity, bootstrapped linear regressions were used (1000 repetitions) (Field, 2013). Multiple testing corrections using the Benjamini–Hochberg false discovery rate was applied for the different group comparison according to each of the attentional measure tested. A p-value < 0.05 and a q-value < 0.05 was considered significant.

Results are interpreted based on p-values, q-values and effect sizes (Sullivan & Feinn, 2012), using Cohen’s d or Glass’s Δ in the case of inhomogeneity of variance. These two measures of effect size were interpreted in the same way: small effect size = 0.2, medium effect size = 0.5, and large effect size = 0.8.

2.5. Data Availability

Ethical restrictions prevent us from making anonymised data available in a public repository. Data may be available from the Royal Children's Hospital Data Access / Ethics Committee at
rch.ethics@rch.org.au for researchers to researchers who meet the criteria for access to confidential data by direct request to the Agenesis of the Corpus Callosum Project Data Committee. Data are from the Agenesis of the Corpus Callosum Project whose authors may be contacted at 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.

The study materials are part of a commercial test battery and cannot be publicly archived due to legal restrictions. Users seeking access to these materials can contact the commercial providers: Pearson Clinical (TEA-Ch, D-KEFS, WISC-IV).

3. Results

3.1. Sample characteristics

Participants were 21 children with AgCC (13 complete, 8 partial) and 30 TDC children aged 8 to 17 years (Table 1). The AgCC group was slightly older and had more males than the TDC group, but groups were not statistically different for age or sex. There was a high percentage of left-handedness in the AgCC group (52%) (measured by the Edinburgh Handedness Inventory using the following thresholds: right-handed=+40 to +100, left-handed=-40 to -100, mixed handed=-40 to +40; (Groen, Whitehouse, Badcock, & Bishop, 2012; Oldfield, 1971), which is consistent with previous AgCC studies that have reported a higher proportion of left-handedness than in the general population, ranging from 24% to 56% (e.g., Chiarello, 1980; Labadi and Beke, 2017; Sauerwein and Lassonde, 1994, Ocklenburg, Ball, Wolf, Genc, & Gunturkun, 2015; for further examination of underlying mechanisms see Genç et al., 2015).

The Full-Scale IQ was significantly lower in the AgCC than the TDC group (p < 0.001).
Detailed demographic characteristics and associated CNS anomalies of children with AgCC can be found in Table 2.

<Insert Table 1 and Table 2 about here>

### 3.2. Volume and DTI parameters of the anterior and posterior commissures in AgCC compared with TDC

For the anterior commissure, the mean volume, corrected as a ratio of total brain volume, was significantly greater in the AgCC group compared with the TDC group ($q = 0.025$) with a medium effect size ($d = -0.729$), see Fig. 2 and Table 3. There was variability within the AgCC group, with 52.4% (n = 11) having an anterior commissure bigger than the mean volume in the TDC group. In the AgCC group the mean FA was also significantly reduced ($q = 0.0188$, $d = 1.114$), while medians AD and RD were significantly increased ($q = 0.0125$ and $q = 0.0063$), relative to the TDC group with large effect sizes ($\Delta = -3.449$ and $\Delta = -3.467$). For the posterior commissure there was a pattern of increased mean AD and RD in the AgCC compared with the TDC group with medium effect sizes ($\Delta = -0.523$ and $-0.637$), however these differences did not reach statistical significance. There was no group difference for volume and mean FA of the posterior commissure and effect sizes were small ($d = -0.22$ and $0.277$).

<Insert Figure 2 and Table 3 about here>

The complete AgCC and partial AgCC subgroups did not differ statistically in the volume and DTI parameters for either the anterior or posterior commissures with negligible effect sizes. The isolated AgCC and AgCC associated with CNS anomalies subgroups did not differ statistically in the volume, FA or RD of the either the anterior or posterior commissures, or in the AD of the posterior commissure with small effect sizes. However, AD of the anterior
commissure was significantly higher in isolated AgCC (median = 0.0012) compared with AgCC associated with CNS anomalies, with a medium effect size (median = 0.0011; U = 74.5, z = 2.424, p = 0.019, q = 0.0063, d = 0.542).

### 3.3. Attention scores

The AgCC group had poorer scores on all attention measures compared to the TDC group (all \( p < 0.01 \)), with the exception of Score! which did not reach statistical difference (Table 1). While children with partial compared with complete AgCC generally showed better attention scores (with the exception of Score!), these differences did not reach statistical significance and had small effect size with the exception of Digit Span Backward which had a medium effect size (Table 4). Children with isolated AgCC compared with AgCC and associated CNS anomalies showed better attention scores, although group differences were significant only for Sky Search and Digit Span Backwards with large effect size (Table 4).

<Insert Table 4 about here>

### 3.4. Volume and DTI parameter associations with attention in AgCC

For executive attention, in the cohort of children with AgCC increased mean FA in the anterior commissure was associated with increased Sky Search DT score (\( \beta \) [with 95% bias corrected and accelerated confidence interval] = 28.084 [27.44, 28.728], standard error = 12.073 , \( p = 0.03, q = 0.0025 \)). This association was not moderated by age at testing or degree of agenesis of the corpus callosum.
For alerting, there were associations between mean AD and RD of the anterior commissure and the Score! subtest, which were moderated by age at testing and degree of agenesis of the corpus callosum (mean AD x age at testing: $\beta = 5844.801 \ [5527.5, \ 6162.102]$, standard error = 2960.745, $p = 0.027$, $q = 0.01$; mean AD x degree of agenesis: $\beta = -30576.536 \ [-30022.237, \ -31130.835]$, standard error = 15358.858, $p = 0.025$, $q = 0.007$; mean RD x age at testing: $\beta = 5689.809 \ [5379.29, \ 6000.328]$, standard error = 2000.584, $p = 0.008$, $q = 0.0025$; mean RD x degree of agenesis: $\beta = -33067.743 \ [-30904.006, \ 35231.48]$, standard error = 11632.341, $p = 0.016$, $q = 0.005$). Simple slope analyses showed that for both the mean AD and RD of the anterior commissure, younger children with AgCC showed a positive association between these DTI parameters and alerting, whereas older children showed a negative association between these DTI parameters and alerting. In addition, simple slope analyses showed a positive association between mean AD of the anterior commissure and alerting scores in partial AgCC. For mean RD of the anterior commissure, simple slope analyses showed a positive association in children with complete AgCC ($n = 13$) and alerting scores, and a negative association in children with partial AgCC ($n = 8$) and alerting scores.

Furthermore for orienting, the association between volume of the posterior commissure and Sky Search score was moderated by the degree of agenesis of the corpus callosum (volume of the posterior commissure x degree of corpus callosum agenesis: $\beta = 2846369.82 \ [2764880.3, \ 2927859.34]$, standard error = 1675843.8, $p = 0.035$, $q = 0.025$). Simple slope analysis showed a positive association between volume of the posterior commissure and orienting scores in partial AgCC ($n = 8$); and in contrast, a negative association between volume of the posterior commissure and orienting scores in complete AgCC ($n = 13$).
There were no significant associations between volume and DTI parameters in either the anterior or posterior commissure with any of the other studied attentional scores (regression coefficient of the models ranging from $p = 0.56$ to $p = 0.967$). In the partial AgCC subgroup, there were no significant associations identified between volume and DTI parameters in the remnant corpus callosum with any of the studied attention processes (regression coefficient of the models ranging from $p = 0.56$ to $p = 0.916$).

4. Discussion

To our knowledge, this is the first study to explore commissural volume and microstructure in individuals with AgCC compared with TDC, and associations with higher order cognitive functions. We found evidence of larger volume and altered microstructure of the anterior commissure in children with AgCC, and little evidence of major alterations in the posterior commissure. In our cohort, mean FA of the anterior commissure was associated with better divided attention (an executive attention process), in line with the presence of atypical inter-hemispheric parietal tracts crossing through the anterior commissure (Tovar-Moll et al., 2014). For alerting attention the association between microstructural measures of the anterior commissure was found to be moderated by age and the degree of corpus callosum agenesis. Specifically, for younger compared with older children there was a positive association found between mean AD and RD and alerting, and for children with partial AgCC there was a positive association between mean AD and alerting, as well as a negative association between mean RD and alerting. Moreover, in children with partial AgCC, a larger posterior commissure was associated with better orienting attention, in line with the presence of atypical inter-hemispheric parietal tracts crossing through the posterior commissure (Tovar-Moll et al., 2014).
Indeed, our study revealed that volume and microstructure of the anterior commissure differs in children with AgCC compared with their typically developing peers. Our cohort of children with AgCC had a larger volume of the anterior commissure compared with the TDC group, confirming previous reports in the AgCC literature that are based on qualitative review of scans to estimate anterior commissure size (Hannay et al., 2009; Hetts et al., 2006; Loeser & Alvord, 1968). Consistent with the heterogeneity of the AgCC population, there was large variability in anterior commissure volumes in our cohort, but despite this, 52.4% had an anterior commissure bigger than the mean volume of the TDC. Our AgCC children also had reduced mean FA and increased AD and RD in the anterior commissure compared with TDC. In light of the findings of Genç and colleagues (2011a, 2011b) in typically developing adults, the association between a reduction in FA values with an increase in RD in AgCC children could reflect a group difference in myelination in the anterior commissure, such as reduced myelinisation (Beaulieu, 2002; Song et al., 2003). Alternatively, it is possible that in highly coherent streamlines such as cerebral commissures, increased RD is produced by larger axon diameters that lead to faster nerve-conduction velocity in those connections (Genc et al., 2011a; 2011b). In children with complete and partial AgCC, there were no significant differences in volume and DTI parameters for the anterior commissure, which is consistent with our finding of an absence of significant differences in attention processes between these subgroups. Children with isolated AgCC compared with AgCC with associated CNS anomalies had increased AD in the anterior commissure, possibly reflecting increased axonal integrity (Kumar, Chavez, Macey, Woo, & Harper, 2013), which is in line with higher performance on specific attention measures (orienting and executive attention) in children with isolated AgCC.
We found no evidence that volume or DTI parameters in the posterior commissure were not significantly altered in children with AgCC compared with TDC. Furthermore, there were no differences between subgroups of children with complete and partial AgCC, or isolated AgCC and AgCC associated with CNS anomalies for the posterior commissure. Alternative pathways in AgCC through the posterior commissure has remained relatively unsuspected so far. However, recently Tovar-Moll and colleagues (2014) identified atypical crossing of tracts in parietal cortices in a sample of four individuals with AgCC aged 6 to 33 years of age. In light of this recent study and our findings, it is possible that a neuroplastic response in the posterior commissure may be subtle at the level of white matter volume and microstructure, but could be more evidence at a tract pathway level, which was not examined in this study.

We showed that children with AgCC experience variability in their attention profile. Our cohort performed similar to TDC children in alerting attention, but more poorly across orienting, shifting and executive attention including working memory. Previous work in adults suggests that attentional processes (orienting, shifting, inhibition and flexibility) seem to rely on the microstructural integrity of specific subregions of the corpus callosum and not only on the microstructural integrity of transcallosal fibres (Niogi, Mukherjee, Ghajar, & McCandliss, 2010). This pattern of variability in attention processes is consistent with the findings of a previous review of the AgCC literature (Siffredi et al., 2013). While previous studies have suggested better cognitive functioning in individuals with partial compared with complete AgCC (Huber-Okrainec et al., 2005; Siffredi et al., 2018), we found no such difference in our cohort for a range of attention processes. However, children with isolated AgCC showed better orienting and executive attention processes than children with AgCC with associated CNS anomalies, consistent with previous studies examining a range of cognitive functions (Pilu et al., 1993; Siffredi et al., 2018; Vergani et al., 1994).
Our findings revealed a positive association between mean FA in the anterior commissure with divided attention (an executive attention process), suggesting that the anterior commissure might act as an alternative pathway for divided attention. Tovar-Moll and colleagues (2014) found that early failure of callosal development might lead to anomalous inter-hemispheric parietal connections in the anterior commissure. Therefore, it is possible that increased mean FA in the anterior commissure compensates for absence of the corpus callosum, which has been involved in the modulation of cortico-subcortical interactions involved during divided attention (Iacoboni, 2005). An increased mean FA in the anterior commissure could increase hemispheric symmetry and therefore parallel processing during a divided attention task, as previously observed during dichotic listening in individuals with AgCC (Ocklenburg, Ball, Wolf, Genc, & Gunturkun, 2015). However, this needs to be investigated further.

We also observed associations between mean AD and RD of the anterior commissure with altering attention, which was moderated by a) the age at testing, with a positive association between these DTI parameters and alerting in younger children but not in older children; and b) the degree of corpus callosum agenesis, with a different pattern of association for children with complete and partial AgCC: in partial AgCC we observed a positive association between mean AD with altering, and a negative association between mean RD and altering; whereas in complete AgCC, a positive association was observed between mean RD and altering. These different patterns of association highlight the importance of taking into account developmental factors. Despite the occurrence of disruption in callosal development very early during embryological life (before the 20th gestational week), it is possible that developmental pathways across childhood and adolescence of associations between brain
structural and microstructural features with specific behaviour and cognitive processes in children with AgCC differ from typically developing children. Furthermore, our results suggest different neuroplastic responses occurring in the context of complete and partial AgCC. The disruption of callosal development occurring at different stages, very early during embryological callosal development in the case of complete AgCC and slightly later in gestation in the case of partial AgCC (Huang et al., 2009; Paul, 2011; Richards et al., 2004), might lead to distinct neuroplastic responses.

Finally, our findings suggest that the posterior commissure might act as an alternative pathway for specific attention processes in subgroups of children with AgCC, specifically in children with partial AgCC but not in all children with complete AgCC. In children with partial AgCC, larger volume of the posterior commissure was associated with better visual orienting. Tovar-Moll and colleagues (2014) found that early failure of callosal development might lead to anomalous inter-hemispheric parietal connections in the posterior commissure. Therefore, it is possible that larger posterior commissure volume allows for an increased number of inter-hemispheric connections in parietal cortices underpinning visual orienting abilities, and compensates for absence of the splenium of the corpus callosum, which is specifically involved in orienting abilities (Han et al., 2004). It will be important for future studies to test this hypothesis, and to verify and explain why this is specific to partial AgCC.

The findings of this study should be considered in the context of some limitations. Our cohort may be considered small and somewhat heterogeneous in terms of associated brain malformations, reflecting the clinical and anatomical presentation of children with AgCC. Nevertheless, cognitive and neuroimaging studies in this population are sparse and sample sizes are typically smaller than in the present study (Lum et al., 2001, n = 3; Owen et al.,
Further research with larger samples and larger subgroup of AgCC (e.g. complete / partial), possibly achieved through participation of multiple sites, is needed to replicate our findings. This approach would also enable exploration of the heterogeneity in clinical and anatomical presentations of children with AgCC, and a range of factors that might contribute to understanding neurodevelopmental outcomes. Given important developmental changes in brain (Dubois et al., 2008; Lebel et al., 2008) and cognitive maturation (Siffredi et al., 2013) during childhood, studies of children with AgCC should consider the influence of age at testing. Longitudinal studies with large samples would allow to capture better structural and functional brain maturation in parallel to cognitive maturation in the context of this brain malformation. In addition, future studies using fibre-tracking techniques are necessary to better understand the properties of the fibres crossing though the anterior and posterior commissures. Using a ROI approach on the midline point of the anterior and posterior commissure, our findings are limited to that specific portion of the streamline and may not capture the anterior and posterior commissures white matter pathways as a whole. Tractography reconstruction could generate further information about brain structural and functional organisation reflecting neuroplastic responses in AgCC. However, reconstruction of these small streamlines in the atypically developing brain can be highly challenging methodologically and the possibility of false positive bundles needs to be taken into account (Maier-Hein et al., 2017). Finally, enlargement of the hippocampal commissure has previously been hypothesised to be an alternative interhemispheric conduit (Hannay et al., 2009). Even though the hippocampal commissure is quite small and usually difficult to visualise on MRI (Rauch & Jinkins, 1994; Barkovich, 2000), rapid advances in neuroimaging might offer an opportunity to explore the role of the hippocampal commissure as an alternative pathway and its association with functional outcomes in AgCC.
5. Conclusion

In conclusion, we provide evidence of significant volume enlargement and microstructural changes in the anterior commissure, but not in the posterior commissure, in children with AgCC. In the anterior commissure, this neuroplastic response does not appear to play a major role in attention processes. However, in children with partial AgCC only, a larger posterior commissure may play a role in better orienting attention, in line with the recently discovered atypical inter-hemispheric parietal tracts crossing through the posterior commissure (Tovar-Moll et al., 2014). Furthermore, in partial AgCC a smaller remaining part of the corpus callosum may play a role in better divided attention. This work progresses the understanding of the properties and role of potential structural organisation and alternative pathways in individuals with AgCC and their role in understanding the heterogeneity in neurodevelopmental outcomes.

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References

Aboitiz, F., & Montiel, J. (2003). One hundred million years of interhemispheric communication: the history of the corpus callosum. *Braz J Med Biol Res, 36*(4), 409-420.

Anderson, P. J. (2008). Towards a developmental model of executive function. In V. Anderson, R. Jacobs, & P. J. Anderson (Eds.), *Executive functions and the frontal lobes: A lifespan perspective* (pp. 3-21). Philadelphia, PA US: Taylor & Francis.

Anderson, V., Northam, E., Hendy, J., & Wrennall, J. (2001). *Pediatric Neuropsychology: A Clinical Approach*. London.

Anderson, V., Spencer-Smith, M., & Wood, A. (2011). Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain, 134*, 2197-2221.

Andersson, J. L. R., & Sotiropoulos, S. N. (2016). An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *Neuroimage, 125*, 1063-1078. doi:10.1016/j.neuroimage.2015.10.019

Arfanakis, K., Haughton, V. M., Carew, J. D., Rogers, B. P., Dempsey, R. J., & Meyerand, M. E. (2002). Diffusion tensor MR imaging in diffuse axonal injury. *American Journal of Neuroradiology, 23*(5), 794-802.

Awh, E., Vogel, E. K., & Oh, S. H. (2006). Interactions between attention and working memory. *Neuroscience, 139*(1), 201-208. doi:10.1016/j.neuroscience.2005.08.023

Aylward, G. P. (2002). Cognitive and neuropsychological outcomes: more than IQ scores. *Ment Retard Dev Disabil Res Rev, 8*(4), 234-240. doi:10.1002/mrdd.10043
Banich, M. T. (1995). Interhemispheric processing: Theoretical considerations and empirical approaches. In R. J. Davidson & K. Hugdahl (Eds.), *Brain Asymmetry* (pp. 427–450). Cambridge: MIT Press.

Barkovich, A. J., & Kjos, B. O. (1988). Normal postnatal development of the corpus callosum as demonstrated by MR imaging. *AJNR Am J Neuroradiol, 9*(3), 487-491.

Barr, M. S., & Corballis, M. C. (2002). The role of the anterior commissure in callosal agenesis. *Neuropsychology, 16*(4), 459-471. doi:10.1037/0894-4105.16.4.459

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed, 15*(7-8), 435-455. doi:10.1002/nbm.782

Bedeschi, M. F., Bonaglia, M. C., Grasso, R., Pellegrini, A., Garghentino, R. R., Battaglia, M. A., . . . Borgatti, R. (2006). Agenesis of the corpus callosum: clinical and genetic study in 63 young patients. *Pediatr Neurol, 34*(3), 186-193.

Bennett, I. J., Motes, M. A., Rao, N. K., & Rypma, B. (2012). White matter tract integrity predicts visual search performance in young and older adults. *Neurobiology aging, 33*(2), 433 e421-431. doi:10.1016/j.neurobiolaging.2011.02.001

Booth, R., Wallace, G. L., & Happe, F. (2011). Connectivity and the corpus callosum in autism spectrum conditions: Insights from comparison of autism and callosal agenesis. *Gene Expression to Neurobiology and Behavior: Human Brain Development and Developmental Disorders, 189*, 303-317. doi:Doi 10.1016/B978-0-444-53884-0.00031-2

Brown, W. S., Jeeves, M. A., Dietrich, R., & Burnison, D. S. (1999). Bilateral field advantage and evoked potential interhemispheric transmission in commissurotomy and callosal agenesis. *Neuropsychologia, 37*(10), 1165-1180. doi:10.1016/s0028-3932(99)00011-1
Caillé, S., Schiavetto, A., Andermann, F., Bastos, A., de Guise, E., & Lassonde, M. (1999). Interhemispheric transfer without forebrain commissures. *Neurocase, 5*(2), 109-118. doi:10.1093/neucas/5.2.109

Chiappedi, M., & Bejor, M. (2010). Corpus callosum agenesis and rehabilitative treatment. *Ital J Pediatr, 36*, 64. doi:10.1186/1824-7288-36-64

Chiarello, C. (1980). A house divided? Cognitive functioning with callosal agenesis. *Brain Lang, 11*(1), 128-158. doi:10.1016/0093-934x(80)90116-9

Culham, J. C., Cavanagh, P., & Kanwisher, N. G. (2001). Attention response functions: characterizing brain areas using fMRI activation during parametric variations of attentional load. *Neuron, 32*(4), 737-745.

Delis, D., Kaplan, E., & Kramer, J. (2001). *Delis-Kaplan Executive Function System (DKEFS)*. San Antonio, TX: The Psychological Corporation.

dos Santos, A. C. E., Midleton, S. R., Fonseca, R. L., dos Santos, S. R., Llerena, J. C., & Vargas, F. V. (2002). Clinical, neuroimaging and cytogenetic findings in 20 patients with corpus callosum dysgenesis. *Arq Neuropsiquiatr, 60*(2-B), 382-385.

Dubois, J., Dehaene-Lambertz, G., Perrin, M., Mangin, J. F., Cointepas, Y., Duchesnay, E., . . . Hertz-Pannier, L. (2008). Asynchrony of the early maturation of white matter bundles in healthy infants: quantitative landmarks revealed noninvasively by diffusion tensor imaging. *Hum Brain Mapp, 29*(1), 14-27. doi:10.1002/hbm.20363

Edwards, T. J., Sherr, E. H., Barkovich, A. J., & Richards, L. J. (2014). Clinical, genetic and imaging findings identify new causes for corpus callosum development syndromes. *Brain, 137*, 1579-1613. doi:10.1093/brain/awt358

Engle, R. W. (2002). Working memory capacity as executive attention. *Current Directions in Psychological Science, 11*(1), 19-23. doi:10.1111/1467-8721.00160
Fischer, M., Ryan, S. B., & Dobyns, W. B. (1992). Mechanisms of interhemispheric transfer and patterns of cognitive function in acallosal patients of normal intelligence. *Arch Neurol, 49*(3), 271-277.

Fischl, B. (2012). FreeSurfer. *Neuroimage, 62*(2), 774-781. doi:10.1016/j.neuroimage.2012.01.021

Fratelli, N., Papageorghiou, A. T., Prefumo, F., Bakalis, S., Homfray, T., & Thilaganathan, B. (2007). Outcome of prenatally diagnosed agenesis of the corpus callosum. *Prenat Diagn, 27*(6), 512-517.

Friston, K. J., Ashburner, J. T., Kiebel, S., Nichols, T., & Penny, W. D. (2007). *Statistical Parametric Mapping (SPM): The analysis of functional brain images, 2nd Edition.* London: Academic Press.

Gathercole, S. E., & Pickering, S. J. (2000). Working memory deficits in children with low achievements in the national curriculum at 7 years of age. *Br J Educ Psychol, 70*, 177-194.

Gathercole, S. E., Pickering, S. J., Knight, C., & Stegmann, Z. (2004). Working memory skills and educational attainment: Evidence from national curriculum assessments at 7 and 14 years of age. *Applied Cognitive Psychology, 18*(1), 1-16. doi:10.1002/Acp.934

Genc, E., Bergmann, J., Singer, W., & Kohler, A. (2011). Interhemispheric connections shape subjective experience of bistable motion. *Curr Biol, 21*(17), 1494-1499. doi:10.1016/j.cub.2011.08.003

Genc, E., Bergmann, J., Tong, F., Blake, R., Singer, W., & Kohler, A. (2011). Callosal connections of primary visual cortex predict the spatial spreading of binocular rivalry across the visual hemifields. *Front Hum Neurosci, 5*, 161. doi:10.3389/fnhum.2011.00161
Genc, E., Ocklenburg, S., Singer, W., & Gunturkun, O. (2015). Abnormal interhemispheric motor interactions in patients with callosal agenesis. *Behav Brain Res.*, 293, 1-9. doi:10.1016/j.bbr.2015.07.016

Glass, H. C., Shaw, G. M., Ma, C., & Sherr, E. H. (2008). Agenesis of the corpus callosum in California 1983-2003: a population-based study. *Am J Med Genet A*, 146A(19), 2495-2500.

Graham, J. M., Jr., Visootsak, J., Dykens, E., Huddleston, L., Clark, R. D., Jones, K. L., . . . Stevenson, R. E. (2008). Behavior of 10 patients with FG syndrome (Opitz-Kaveggia syndrome) and the p.R961W mutation in the MED12 gene. *Am J Med Genet A*, 146A(23), 3011-3017.

Graham, J. M., Jr., Wheeler, P., Tackels-Horne, D., Lin, A. E., Hall, B. D., May, M., . . . Cox, T. C. (2003). A new X-linked syndrome with agenesis of the corpus callosum, mental retardation, coloboma, micrognathia, and a mutation in the Alpha 4 gene at Xq13. *Am J Med Genet A*, 123A(1), 37-44.

Groen, M. A., Whitehouse, A. J., Badcock, N. A., & Bishop, D. V. (2012). Does cerebral lateralization develop? A study using functional transcranial Doppler ultrasound assessing lateralization for language production and visuospatial memory. *Brain Behav*, 2(3), 256-269. doi:10.1002/brb3.56

Guénot, M. (1998). Transfert interhémisphérique et agénésie du corps calleux, Capacités et limites de la commissure blanche antérieure. *Neurochirurgie, 44*(Suppl 1), 113-115.

Guillem, P., Fabre, B., Cans, C., Robert-Gnansia, E., & Jouk, P. S. (2003). Trends in elective terminations of pregnancy between 1989 and 2000 in a French county (the Isere). *Prenat Diagn.*, 23(11), 877-883. doi:Doi 10.1002/Pd.711

Han, S., Jiang, Y., Gu, H., Rao, H., Lihua, M., Cui, Y., & R., Z. (2004). The role of human parietal cortex in attention networks. *Brain, 127*(3), 650-659.
Hannay, H. J., Dennis, M., Kramer, L., Blaser, S., & Fletcher, J. M. (2009). Partial agenesis of the corpus callosum in spina bifida meningomyelocele and potential compensatory mechanisms. *J Clin Exp Neuropsychol, 31*(2), 180-194.

Harsan, L. A., Poulet, P., Guignard, B., Steibel, J., Parizel, N., de Sousa, P. L., . . . Ghandour, M. S. (2006). Brain dysmyelination and recovery assessment by noninvasive in vivo diffusion tensor magnetic resonance imaging. *J Neurosci Res, 83*(3), 392-402. doi:10.1002/jnr.20742

Haxby, J. V., Petit, L., Ungerleider, L. G., & Courtney, S. M. (2000). Distinguishing the functional roles of multiple regions in distributed neural systems for visual working memory. *Neuroimage, 11*(2), 145-156. doi:10.1006/nimg.1999.0527

Hetts, S. W., Sherr, E. H., Chao, S., Gobuty, S., & Barkovich, A. J. (2006). Anomalies of the corpus callosum: an MR analysis of the phenotypic spectrum of associated malformations. *American Journal of Roentgenology, 187*, 1343-1348.

Hillary, F. G., Medaglia, J. D., Gates, K., Molenaar, P. C., Slocomb, J., Peechatka, A., & Good, D. C. (2011). Examining working memory task acquisition in a disrupted neural network. *Brain, 134*, 1555-1570.

Huang, H., Xue, R., Zhang, J., Ren, T., Richards, L. J., Yarowsky, P., . . . Mori, S. (2009). Anatomical Characterization of Human Fetal Brain Development with Diffusion Tensor Magnetic Resonance Imaging. *The Journal of Neuroscience, 29*(13), 4263-4273.

Huber-Okrainec, J., Blaser, S. E., & Dennis, M. (2005). Idiom comprehension deficits in relation to corpus callosum agenesis and hypoplasia in children with spina bifida meningomyelocele. *Brain Lang, 93*(3), 349-368.
Iacoboni, M. (2005). Divided Attention in the Normal and the Split Brain: Chronometry and Imaging. In L. Itti, G. Rees, & J. Tsotsos (Eds.), *Neurobiology of Attention* (pp. 363-367). New York, NY: Academic Press.

IBM, C. (Released 2013). IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

Jenkinson, M., Pechaud, M., & Smith, S. (2005). *BET2: MR-based estimation of brain, skull and scalp surfaces*. Paper presented at the Eleventh Annual Meeting of the Organization for Human Brain Mapping.

Keene, M. F. (1938). The Connexions of the Posterior Commissure: A Study of its Development and Myelination in the Human Foetus and Young Infant, of its Phylogenetic Development, and of Degenerative Changes resulting from certain Experimental Lesions. *J Anat*, 72, 488-501.

Klarborg, B., Madsen, K. S., Vestergaard, M., Skimminge, A., Jernigan, T. L., & Baare, W. F. C. (2013). Sustained Attention is Associated with Right Superior Longitudinal Fasciculus and Superior Parietal White Matter Microstructure in Children. *Hum Brain Mapp*, 34(12), 3216-3232. doi:10.1002/hbm.22139

Klingberg, T. (2006). Development of a superior frontal-intraparietal network for visuospatial working memory. *Neuropsychologia*, 44(11), 2171-2177. doi:10.1016/j.neuropsychologia.2005.11.019

Klingberg, T., Forssberg, H., & Westerberg, H. (2002). Increased brain activity in frontal and parietal cortex underlies the development of visuospatial working memory capacity during childhood. *J Cogn Neurosci*, 14(1), 1-10. doi:10.1162/089892902317205276

Kollias, S. (2012). Insights into the connectivity of the human brain using DTI. *Nepalese Journal of Radiology*, 1(1).
Kumar, R., Chavez, A. S., Macey, P. M., Woo, M. A., & Harper, R. M. (2013). Brain axial and radial diffusivity changes with age and gender in healthy adults. *Brain Res, 1512*, 22-36. doi:10.1016/j.brainres.2013.03.028

Kyllonen, P. C., & Christal, R. E. (1990). Reasoning Ability Is (Little More Than) Working-Memory Capacity. *Intelligence, 14*(4), 389-433. doi:Doi 10.1016/S0160-2896(05)80012-1

Labadi, B., & Beke, A. M. (2017). Mental State Understanding in Children with Agenesis of the Corpus Callosum. *Front Psychol, 8*, 94. doi:10.3389/fpsyg.2017.00094

Lassonde, M., & Jeeves, M. A. (1994). *Callosal agenesis: A natural split brain?* New York, NY US: Plenum Press.

Lassonde, M., Sauerwein, H., Chicoine, A. J., & Geoffroy, G. (1991). Absence of disconnexion syndrome in callosal agenesis and early callosotomy: brain reorganization or lack of structural specificity during ontogeny? *Neuropsychologia, 29*(6), 481-495.

Lebel, C., Walker, L., Leemans, A., Phillips, L., & Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *Neuroimage, 40*(3), 1044-1055. doi:10.1016/j.neuroimage.2007.12.053

Lebel, C., Warner, T., Colby, J., Soderberg, L., Roussotte, F., Behnke, M., . . . Sowell, E. R. (2013). White matter microstructure abnormalities and executive function in adolescents with prenatal cocaine exposure. *Psychiatry Res, 213*(2), 161-168. doi:10.1016/j.pscychresns.2013.04.002

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological Assessment, 5th Edition*. New York, NY: Oxford University Press.

Loeser, J. D., & Alvord, E. C., Jr. (1968). Clinicopathological correlations in agenesis of the corpus callosum. *Neurology, 18*(8), 745-756.
Lum, C., McAndrews, M. P., Holodny, A. I., McManus, K. A., Crawley, A., Chakraborty, S., & Mikulis, D. J. (2011). Investigating agenesis of the corpus callosum using functional MRI: a study examining interhemispheric coordination of motor control. *J Neuroimaging, 21*(1), 65-68. doi:10.1111/j.1552-6569.2009.00430.x

Mabbott, D. J., Noseworthy, M., Bouffet, E., Laughlin, S., & Rockel, C. (2006). White matter growth as a mechanism of cognitive development in children. *Neuroimage, 33*(3), 936-946. doi:10.1016/j.neuroimage.2006.07.024

Maier-Hein, K. H., Neher, P. F., Houde, J. C., Cote, M. A., Garyfallidis, E., Zhong, J., . . . Descoteaux, M. (2017). The challenge of mapping the human connectome based on diffusion tractography. *Nat Commun, 8*(1), 1349. doi:10.1038/s41467-017-01285-x

Manly, T., Robertson, I., Anderson, V., & Nimmo-Smith, I. (1999). *Test of everyday attention for children.* Cambridge, UK: Thames Valley Test Company.

Moes, P., Schilmoeller, K., & Schilmoeller, G. (2009). Physical, motor, sensory and developmental features associated with agenesis of the corpus callosum. *Child Care, Health & Development, 35*(5), 656-672. doi:10.1111/j.1365-2214.2009.00942.x

Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of white matter is associated with the development of cognitive functions during childhood. *J Cogn Neurosci, 16*(7), 1227-1233. doi:10.1162/0898929041920441

Niogi, S., Mukherjee, P., Ghajar, J., & McCandliss, B. D. (2010). Individual Differences in Distinct Components of Attention are Linked to Anatomical Variations in Distinct White Matter Tracts. *Front Neuroanat, 4*, 2. doi:10.3389/neuro.05.002.2010

Ocklenburg, S., Ball, A., Wolf, C. C., Genc, E., & Gunturkun, O. (2015). Functional cerebral lateralization and interhemispheric interaction in patients with callosal agenesis. *Neuropsychology, 29*(5), 806-815. doi:10.1037/neu0000193
Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Owen, J. P., Li, Y. O., Ziv, E., Strominger, Z., Gold, J., Bukhpun, P., . . . Mukherjee, P. (2013). The structural connectome of the human brain in agenesis of the corpus callosum. *Neuroimage, 70*, 340-355. doi:10.1016/j.neuroimage.2012.12.031

Paul, L. K. (2011). Developmental malformation of the corpus callosum: a review of typical callosal development and examples of developmental disorders with callosal involvement. *J Neurodev Disord, 3*(1), 3-27. doi:10.1007/s11689-010-9059-y

Paul, L. K., Brown, W. S., Adolphs, R., Tyszka, J. M., Richards, L. J., Mukherjee, P., & Sherr, E. H. (2007). Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. *Nat Rev Neurosci, 8*(4), 287-299.

Peters, B. D., Ikuta, T., DeRosse, P., John, M., Burdick, K. E., Gruner, P., . . . Malhotra, A. K. (2014). Age-related differences in white matter tract microstructure are associated with cognitive performance from childhood to adulthood. *Biol Psychiatry, 75*(3), 248-256. doi:10.1016/j.biopsych.2013.05.020

Petersen, S. E., & Posner, M. I. (2012). The attention system of the human brain: 20 years after. *Annu Rev Neurosci, 35*, 73-89. doi:10.1146/annurev-neuro-062111-150525

Pilu, G., Sandri, F., Perolo, A., Pittalis, M. C., Grisolia, G., Cocchi, G., . . . Bovicelli, L. (1993). Sonography of fetal agenesis of the corpus callosum: a survey of 35 cases. *Ultrasound Obstet Gynecol, 3*(5), 318-329. doi:10.1046/j.1469-0705.1993.03050318.x

Raybaud, C. (2010). The corpus callosum, the other great forebrain commissures, and the septum pellucidum: anatomy, development, and malformation. *Neuroradiology, 52*, 447–477.
Richards, L. J., Planchez, C., & Ren, T. (2004). Mechanisms regulating the development of the corpus callosum and its agenesis in mouse and human. *Clinical Genetics, 66*, 276-289.

Sauerwein, H. C., & Lassonde, M. (1994). Cognitive and sensori-motor functioning in the absence of the corpus callosum: neuropsychological studies in callosal agenesis and callosotomized patients. *Behav Brain Res, 64*(1-2), 229-240.

Schulte, T., & Müller-Oehring, E. M. (2010). Contribution of callosal connections to the interhemispheric integration of visuomotor and cognitive processes. *Neuropsychol Rev, 20*(2), 174-190. doi:10.1007/s11065-010-9130-1

Siffredi, V., Anderson, V., Leventer, R. J., & Spencer-Smith, M. M. (2013). Neuropsychological profile of agenesis of the corpus callosum: a systematic review. *Dev Neuropsychol, 38*(1), 36-57. doi:10.1080/87565641.2012.721421

Siffredi, V., Anderson, V., McIlroy, A., Wood, A. G., Leventer, R. J., & Spencer-Smith, M. M. (2018). A Neuropsychological Profile for Agenesis of the Corpus Callosum? Cognitive, Academic, Executive, Social, and Behavioral Functioning in School-Age Children. *Journal of the International Neuropsychological Society, 24*(5), 445-455. doi:10.1017/S1355617717001357

Siffredi, V., Barrouillet, P., Spencer-Smith, M., Vaessen, M., Anderson, V., & Vuilleumier, P. (2017). Examining distinct working memory processes in children and adolescents using fMRI: Results and validation of a modified Brown-Peterson paradigm. *PLoS One, 12*(7), e0179959. doi:10.1371/journal.pone.0179959

Siffredi, V., Spencer-Smith, M. M., Barrouillet, P., Vaessen, M. J., Leventer, R. J., Anderson, V., & Vuilleumier, P. (2017). Neural correlates of working memory in children and adolescents with agenesis of the corpus callosum: An fMRI study. *Neuropsychologia, 106*, 71-82. doi:10.1016/j.neuropsychologia.2017.09.008
Smith, S. M. (2002). Fast robust automated brain extraction. *Hum Brain Mapp, 17*(3), 143-155. doi:10.1002/hbm.10062

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., . . . Behrens, T. E. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage, 31*(4), 1487-1505. doi:10.1016/j.neuroimage.2006.02.024

Smith, S. M., Johansen-Berg, H., Jenkinson, M., Rueckert, D., Nichols, T. E., Miller, K. L., . . . Behrens, T. E. (2007). Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. *Nat Protoc, 2*(3), 499-503. doi:10.1038/nprot.2007.45

Song, S. K., Sun, S. W., Ju, W. K., Lin, S. J., Cross, A. H., & Neufeld, A. H. (2003). Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage, 20*(3), 1714-1722.

Song, S. K., Sun, S. W., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage, 17*(3), 1429-1436.

Spencer-Smith, M., Ritter, B. C., Murner-Lavanchy, I., El-Koussy, M., Steinlin, M., & Everts, R. (2013). Age, sex, and performance influence the visuospatial working memory network in childhood. *Dev Neuropsychol, 38*(4), 236-255. doi:10.1080/87565641.2013.784321

Takahashi, M., Iwamoto, K., Fukatsu, H., Naganawa, S., Iidaka, T., & Ozaki, N. (2010). White matter microstructure of the cingulum and cerebellar peduncle is related to sustained attention and working memory: a diffusion tensor imaging study. *Neuroscience Letters, 477*(2), 72-76. doi:10.1016/j.neulet.2010.04.031
The MathWorks, I., Natick. (2012). MATLAB and Statistics Toolbox. Massachusetts, United States.

Tournier, J. D. (2010). MRtrix package. Retrieved from http://www.brain.org.au/software/

Tournier, J. D., Yeh, C. H., Calamante, F., Cho, K. H., Connelly, A., & Lin, C. P. (2008). Resolving crossing fibres using constrained spherical deconvolution: Validation using diffusion-weighted imaging phantom data. *Neuroimage, 42*(2), 617-625. doi:10.1016/j.neuroimage.2008.05.002

Tovar-Moll, F., Moll, J., de Oliveira-Souza, R., Bramati, I. E., Andreiuolo, P. A., & Lent, R. (2007). Neuroplasticity in human callosal dysgenesis: a diffusion tensor imaging study. *Cerebral Cortex, 17*(3), 531-541.

Tovar-Moll, F., Monteiro, M., Andrade, J., Bramati, I. E., Vianna-Barbosa, R., Marins, T., . . . Lent, R. (2014). Structural and functional brain rewiring clarifies preserved interhemispheric transfer in humans born without the corpus callosum. *Proc Natl Acad Sci USA, 111*(21), 7843-7848. doi:10.1073/pnas.1400806111

van Meer, N., Houtman, A. C., Van Schuerbeek, P., Vanderhasselt, T., Milleret, C., & ten Tusscher, M. P. (2016). Interhemispheric Connections between the Primary Visual Cortical Areas via the Anterior Commissure in Human Callosal Agenesis. *Frontiers in Systems Neuroscience, 10*. doi:Art1 101
10.3389/Fnsys.2016.00101

Vergani, P., Ghidini, A., Strobelt, N., Locatelli, A., Mariani, S., Bertalero, C., & Cavallone, M. (1994). Prognostic indicators in the prenatal diagnosis of agenesis of corpus callosum. *Am J Obstet Gynecol, 170*(3), 753-758.

Wang, L. W., Huang, C. C., & Yeh, T. F. (2004). Major brain lesions detected on sonographic screening of apparently normal term neonates. *Neuroradiology, 46*(5), 368-373. doi:Doi 10.1007/S00234-003-1160-4
Wozniak, J. R., & Lim, K. O. (2006). Advances in white matter imaging: a review of in vivo magnetic resonance methodologies and their applicability to the study of development and aging. *Neurosci Biobehav Rev, 30*(6), 762-774. doi:10.1016/j.neubiorev.2006.06.003
Table 1. Characteristics of the agenesis of the corpus callosum (AgCC) and typically developing control (TDC) groups.

|                      | AgCC, \( n = 21 \) | TDC, \( n = 30 \) | Group comparison                      | Q-value | Effect size |
|----------------------|---------------------|-------------------|---------------------------------------|---------|-------------|
| Age in years         | 12.21 (2.63)        | 10.80 (2.44)      | \( t(49) = 0.42, p = 0.550 \)        | -       | -           |
| Age range in years   | 8.67 to 17.08       | 8 to 16.58        | -                                     | -       | -           |
| Sex                  | 14 males, 7 females | 16 males, 14 females | \( X^2(1, \ n=51) = 0.91, p = 0.341 \) | -       | -           |
| Handedness           | 11 R, 9 L, 1 M     | 26 R, 3 L, 1 M    | -                                     | -       | -           |
| Full-Scale IQ        | Median = 72.5       | Median = 109      | \( U = 1132.5, z = 6.14, r = 0.73, p < 0.001 \* \) | -       | -           |
| Orienting: Sky Search| 7.52 (3.43)         | 10.8 (3.09)       | \( t(49) = -3.56, p = 0.001 \* \)    | 0.01    | 1           |
| Orienting: Trail Making Test | 7.86 (3.75) | 9.77 (2.39) | \( t(49) = -2.23, p = 0.031 \* \)    | 0.03    | 0.62        |
| Alerting: Score!     | 8.76 (3.86)         | 10.13 (2.54)      | \( t(31.97) = -1.43, p = 0.163 \)    | 0.05    | 0.4         |
| Executive attention: Sky Search DT* | 5.1 (3.26) | 7.4 (2.87) | \( t(48) = -2.67, p = 0.010 \* \)    | 0.04    | 0.75        |
| Executive attention: Digit Span Backward | 8.19 (3.4) | 11.2 (2.77) | \( t(49) = -3.49, p = 0.001 \* \)    | 0.02    | 0.98        |

Note: Mean and SD reported unless otherwise noted. Full-Scale IQ was measured using the Wechsler Abbreviated Intelligence Scale (WASI, \( n = 48, 94\% \); Wechsler, 1999) or the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV, Wechsler, 2003; \( n = 3, 6\% \)); Handedness estimated by the Edinburgh Handedness Inventory (Oldfield, 1971; Groen et al., 2012); Sky Search DT* only 20 children from the AgCC group completed the task; Q-value shows the adjusted p-value of 0.05 using the Benjamini–Hochberg false discovery rate to adjust for multiple comparisons. Group comparison that reached significance are indicated with asterisks.
| ID  | Age  | Sex | H | Associated CNS anomalies                                                                 |
|-----|------|-----|---|--------------------------------------------------------------------------------------------|
| 106 | 11.33| M   | L | Transmantle left frontal FCD                                                               |
| 011 | 11.67| M   | L | None                                                                                       |
| 017 | 8.83 | F   | R | Bilateral PNH / coronal synostosis                                                         |
| 105 | 14.42| M   | R | None                                                                                       |
| 103 | 11   | M   | R | None                                                                                       |
| 020 | 12.67| M   | L | Interhemispheric cyst lined by PMG, left frontal PMG, grey matter heterotopia lining medial right atrium |
| 021 | 10.67| M   | R | Right frontal PNH                                                                          |
| 102 | 12.67| M   | R | None                                                                                       |
| 107 | 11.58| M   | L | Interhemispheric cyst lined by PMG and extending into left frontal lobe                      |
| 108 | 10.17| M   | L | Interhemispheric cyst extending into left frontal and parietal lobes and lined by PMG, deep sulci lined by PMG left frontal lobe, PNH left atrium |
| 110 | 9    | M   | L | Interhemispheric cyst extending into left frontal lobe                                       |
| 022 | 8.67 | F   | A | Deep sulcus right posterior frontal lobe lined by PMG, asymmetric brainstem, PNH left atrium|
| 113 | 10   | F   | R | None                                                                                       |

| ID  | Age  | Sex | H | Associated CNS anomalies                                                                 |
|-----|------|-----|---|------------------------------------------------------------------------------------------|
| 104 | 15.58| M   | L | None                                                                                     |

**Table 2.** Demographic characteristics and associated central nervous system (CNS) anomalies of children with agenesis of the corpus callosum (AgCC) included in this study

**Complete AgCC**

**Partial AgCC**

**Status of the corpus callosum**

Part of the genu present
| ID  | Age  | Sex | Hand | Associated Anomalies                                                                 | CNS Anomalies                                      |
|-----|------|-----|------|--------------------------------------------------------------------------------------|---------------------------------------------------|
| 007 | 14.75| F   | L    | Agenesis of the septum pellucidum, semilobar holoprosencephaly                        | Thin rostrum, genu and anterior body present        |
| 012 | 15.33| F   | R    | Bilateral PNH                                                                        | Rostrum present                                    |
| 015 | 10.25| F   | L    | Right cerebellar hemisphere hypoplasia, bilateral parasaggital cortical thickening and grey matter heterotopia | Middle-posterior body, posterior body and splenium present |
| 111 | 16.17| F   | R    | None                                                                                 | Anterior body present                               |
| 101 | 14.83| F   | R    | Bilateral frontal PMG, right post fossa arachnoid cyst.                              | Thin middle anterior body, rostrum, genu and anterior Body present |
| 109 | 9.67 | F   | R    | Right parietal arteriovenous malformation                                            | Rhin rostrum, genu and anterior body present        |
| 112 | 17.08| M   | R    | Frononasal dysplasia, sphenoidal encephalocele, absent pituitary gland                | Rostrum present                                    |

Note: Age (in years); Sex: F female, M male; Handedness: L left, R right, A ambidextrous; Associated CNS anomalies: FCD focal cortical dysplasia; PNH periventricular nodular heterotopia; PMG polymicrogyria.
Table 3. Mean volume, FA, AD and RD of the anterior and posterior commissures and group comparisons for children with agenesis of the corpus callosum (AgCC) and typically developing controls (TDC).

|                      | AgCC         | TDC        | Group comparison | Q-value | Effect size |
|----------------------|--------------|------------|------------------|---------|-------------|
| **Anterior Commissure** |              |            |                  |         |             |
| Volume               | 0.00000114 (0.00000747) | 0.0000073 (0.00000273) | t (22.43) = 2.371, p = 0.027* | 0.0250  | 0.729       |
| FA                   | 0.14 (0.07)  | 0.20 (0.03) | t (26.978) = -3.767, p = 0.001* | 0.0188  | 1.114       |
| AD                   | Median = 0.0012 | Median = 0.00913 | U=16.5, z=-5.64, r=-0.7976, p < 0.001* | 0.0125  | -3.449     |
| RD                   | Median = 0.00098 | Median = 0.00702 | U=25, z=-5.447, r=-0.77032, p < 0.001* | 0.0063  | -3.467     |
| **Posterior Commissure** |              |            |                  |         |             |
| Volume               | 0.00000429 (0.0000014) | 0.00000402 (0.00000103) | t (32.23) = .726, p = 0.473 | 0.05    | 0.22        |
| FA                   | 0.098 (0.016) | 0.105 (0.024) | t (48.97) = -1.139, p = 0.260 | 0.0438  | 0.277       |
| AD                   | Median = 0.0011333 | Median = 0.001088 | U=220, z=-1.945, r=-0.27235, p = 0.052 | 0.0313  | -0.523     |
| RD                   | Median = 0.001 | Median = 0.00096 | U=232, z=-1.614, r=-0.226, p = 0.107 | 0.375   | -0.637     |

Note: Mean and SD reported unless otherwise noted. Q-value shows the adjusted p-value of 0.05 using the Benjamini–Hochberg false discovery rate to adjust for multiple comparisons. Cohen’s d was used as the effect size measure, if the standard deviations of the two groups were different, the Glass’ delta \( \Delta \) was used as the effect size measure. Group comparison that reached significance are indicated with asterisks.
Table 4. Attention scores and subgroup comparisons for children with a) complete and partial AgCC and, b) isolated AgCC and AgCC with associated CNS anomalies.

|                          | Complete vs Partial AgCC | Isolated AgCC vs AgCC with associated CNS anomalies |
|--------------------------|--------------------------|-----------------------------------------------------|
|                          | Complete \( n = 13 \) | Partial \( n = 8 \) | Group Comparison | Effect size | Isolated \( n = 7 \) | Not Isolated \( n = 13 \) | Group Comparison | Effect size |
| **Orienting: Sky Search** | 7.3 (3.2)               | 7.9 (4) | \( t(19) = -0.36, p = 0.720 \) | 0.166       | 10 (3)             | 6.3 (3) | \( t(19) = 2.7, p = 0.015 \) | 1.233       |
| **Orienting: Trail Making Test** | 7.3 (3.5) | 8.8 (4.2) | \( t(19) = -0.85, p = 0.405 \) | 0.388       | 8.6 (1.7) | 7.4 (4.4) | \( t(19) = 0.86, p = 0.401 \) | 0.360       |
| **Alerting: Score!**     | 9.1 (3.4)               | 8.2 (4.7) | \( t(19) = -0.47, p = 0.650 \) | 0.219       | 10.6 (3.2) | 7.9 (3.9) | \( t(19) = 1.58, p = 0.130 \) | 0.757       |
| **Executive attention: Sky Search DT*** | 4.9 (3.7) | 5.6 (2.4) | \( t(17.27) = -0.53, p = 0.600 \) | 0.189*      | 6.1 (3.5) | 4.5 (3.1) | \( t(18) = 1.05, p = 0.301 \) | 0.484       |
| **Executive attention: Digit Span Backward** | 7.5 (2.6) | 9.4 (4.3) | \( t(10.27) = -1.13 p = 0.280 \) | 0.731*      | 10.3 (3) | 7.1 (3.2) | \( t(19) = 2.18, p = 0.042 \) | 1.032       |
Note: Mean and SD reported; Cohen's d was used as the effect size measure, if the standard deviations of the two groups were different, the Glass' delta \( \Delta \) was used as the effect size measure; Sky Search DT\* only 7 children with partial AgCC, and only 13 children with AgCC and associated CNS anomalies completed the task. Q-value shows the adjusted p-value of 0.05 using the Benjamini–Hochberg false discovery rate to adjust for multiple comparisons.
Figure 1. The anterior and posterior commissures in yellow (images on the top are the original images, images at the bottom show the drawings) with a close up: a) anterior and posterior commissures on the sagittal view and b) anterior and posterior commissures on the axial view; c) anterior commissure on the coronal view and d) posterior commissure on the coronal view.
Figure 2. Volume of the anterior commissure as a ratio of the total brain volume (in mm$^3$) in children with agenesis of the corpus callosum (AgCC) and typically developing controls (TDC) (values adjusted at E-6).
