Cortical thickness in adults with agenesis of the corpus callosum

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Agenesis of the corpus callosum (AgCC) is a congenital malformation that can occur in isolation or in association with other neurological conditions. Although the behavioral manifestations associated with AgCC have been widely studied, the effects of complete absence of the corpus callosum (CC) on cerebral cortex anatomy are not still completely understood. In this study, cortical thickness in adults with complete AgCC was compared to a group of healthy controls. Results showed highly variable patterns of cortical thickness in AgCC individuals, with few areas showing significant and consistent alterations including primary visual cortex, primary somatosensory cortex and primary motor cortex. These results suggest relatively limited effects of AgCC on cortical morphology, which are mostly restricted to primary sensory and motor areas.

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1. Introduction

The corpus callosum (CC) is the principal commissure of the brain connecting the two hemispheres with over 190 million axons (Tomasz, 1954). The maturation of the CC continues well after birth, and a fully mature and myelinated CC is generally seen in children at around 10 years of age (Armatas et al., 1994; Giedd et al., 1999; Mayston et al., 1999). The major role of this white matter bundle is to allow the transfer and integration of information between homologous regions of the cerebral hemispheres. Early disruption in the maturation of the CC can lead to a developmental condition known as agenesis of the corpus callosum (AgCC), a relatively frequent congenital malformation ranging from complete absence to hypogenesis (partial absence) of CC fibers (Paul et al., 2007). This condition occurs in 1:4000 individuals, making it one of the most common human brain malformations (Glass et al., 2008). The etiology of AgCC has an identifiable cause in about 25% of the cases (Paul et al., 2007), and is usually related to other neurological conditions, such as hydrocephalus (Schoner et al., 2013), microcephaly (Paciorowski et al., 2013), or fetal alcohol syndrome (Paul, 2011). Recent studies have highlighted the potential contribution of specific genetic elements in the occurrence of AgCC independently of other brain conditions. Among them, the Disrupted-in-Schizophrenia 1 (DISC1) gene, named because of its possible role in schizophrenia and related disorders (Millar et al., 2000), was found to be highly expressed in the developing CC of embryonic mice. Osbun and colleagues (2011) also identified a variant form of the DISC1 gene, possibly pathogenic, in 144 AgCC patients, further suggesting an important role of this gene in the development of the CC and in the etiology of AgCC (Osbun et al., 2011; Paul et al., 2007).

Since AgCC is an heterogeneous condition, symptoms can vary greatly between affected individuals, ranging from relative absence to severe impairment requiring special education and assistance in every day living (Paul et al., 2004; Siffredi et al., 2013). Nonetheless, although full-scale IQ can be lower than what is expected considering family history, global intelligence generally remains within normal limits (Chiarelli, 1980). Moreover, individuals with AgCC show relatively mild dysfunction in inter-hemispheric communication, as very few disconnection deficits are observed (Duquette et al., 2008; Lassonde et al., 1991; Saurwein et al., 1981). This contrasts sharply with what is observed in split-brain patients, for whom it is generally agreed that inter-hemispheric dysfunction is more severe and often present in the form of a disconnection syndrome (Sperry, 1968). Indeed, it is well established that complete section of the CC in adults abrogates or greatly impairs interhemispheric transfer of sensory information (Reuter-Lorenz et al., 1995). Patients with surgical section of the CC are unable to compare sensory information when it is sent...
separately to each hemisphere (Gazzaniga et al., 1965). In this population, although there seems to be a partial recovery of some of their deficits, most of these impairments are long-lasting (Goldstein et al., 1975; Sauerwein and Lassonde, 1997; Serrien et al., 2001). This suggests that the brain of individuals with AgCC is more efficient in its capacity to compensate and minimize the detrimental effects associated with the lack of its principal commissure, probably through neuroplastic adaptations during development.

Compensatory mechanisms in AgCC individuals have been associated with enhanced cerebral plasticity during childhood (Lassonde et al., 1991), possibly allowing the recruitment of alternative neural structures to enable interhemispheric communication. Indeed, other naturally occurring pathways could assume increased interhemispheric communication during ontogenesis in the absence of callosal fibers, such as the anterior and posterior commissures (Lassonde et al., 1991). There is also evidence from animal studies suggesting that nerve fibers can form synapses with atypical classes of cells when their conventional targets have unsuccessfully developed (Mariani, 1983; Wilson et al., 1981). Lassonde et al. (1991) have suggested that early absence of callosal connections can induce pathways that would not have been formed under normal circumstances, accounting for the greater interhemispheric communication that is observed in AgCC subjects compared to split-brain patients. In that regard, different alternative pathways have been suggested to play a role in this compensatory mechanism, namely the anterior commissure, the intercollicular or posterior commissures and/or the reinforcement of existing ipsilateral connections (Lassonde et al., 1991). Although these alternative pathways allow the maintenance of interhemispheric communication and possibly contribute to the superior performance of individuals with AgCC in comparison to split-brain patients, these compensatory mechanisms have their limits (Sauerwein and Lassonde, 1983). Indeed, in visual or sensorimotor tasks, when speed of response and error ratios are taken into account instead of accuracy, AgCC patients are impaired comparatively to healthy controls (Lassonde et al., 1988; Sauerwein and Lassonde, 1983). AgCC patients also have persistent deficits in bimanual coordination, characterized by slower performance and clumsiness (Chiarello, 1980; de Guise et al., 1999; Mueller et al., 2009). Other studies have reported that the congenital absence of the CC affects binaural listening performance (Hausmann et al., 2005; Lessard et al., 2002). A possible explanation for these results is that when the brain matures with total absence of the CC, it results in a lower level of cortical recruitment (Lassonde et al., 1988). Thus, changes in cortical pathways accounting for the lack of callosal connections could alter the responsiveness of each hemisphere (Duquette et al., 2008).

Animal research indicates that absence of the CC early in development can modify morphological characteristics of the brain. For example, Abreu-Villaca et al. (2002) found evidence of a reduction in neocortical thickness in genetically modified AgCC mice (BALB/cCF strain) in regions usually characterized by rich callosal afferent connections (Abreu-Villaca et al., 2002). These authors hypothesized that neurons that are normally intended to receive extensive callosal input died as a result of the loss of their afferents during the critical periods of cortical ontogenesis and synaptogenesis. This hypothesis is consistent with the well-established idea that neuronal survival relies upon activity-dependent processes during synaptogenesis (Jevtovic-Todorovic et al., 2003; Mennerick and Zorumski, 2000). Indeed, callosal projections are known to have excitatory influences over the contralateral hemisphere (Bloom and Hynd, 2005), and callosal deafferentation in the developing brain of AgCC mice may decrease the activity pattern of the neurons usually receiving strong callosal afferents, resulting in neuronal death (Ribeiro-Carvalho et al., 2006). In humans, maturation of the CC coincides with a period of plasticity in which children improve intermanual matching, are able to name tactile stimuli in either hand and show better accuracy in transferring the locus of touch between hands (Galin et al., 1979). At the same time, there seems to be great cortical development of the brain leading to the thinning of some cortical regions and thickening of others (Shaw et al., 2006). Thus, individuals with AgCC present a unique opportunity to gain insight on the relationship between the development of callosal pathways and the maturation of the cortex. In the present study, cortical thickness was measured in five individuals with complete AgCC and compared to a group of eleven healthy controls. Based on animal research, we hypothesize that the absence of CC would be associated with cortical thinning in numerous brain regions, predominantly located in primary sensorimotor areas.

2. Material and methods

2.1. Participants

Two groups of participants were recruited: 1) an experimental group comprising five participants with AgCC, and 2) a control group of eleven neurologically intact participants. The study was approved by the local ethics committee and all participants provided written informed consent prior to testing. The AgCC group had a mean age of 37.6 years (range 22–42) and an average IQ of 76. The control group had a mean age of 33.8 years (range 23–51) and consisted of six men and five women, three of which were left-handed. The average IQ of the control group was 111 based on the revised Wechsler Adult Intelligence Scale. The patients are described individually below.

2.1.1. M.G.

Case M.G. is a 34 year-old, left-handed man and the youngest child of a French Canadian family of four children, three of which have AgCC. He experienced respiratory difficulties at birth. At the age of 4, he had prolonged enuresis, impoverished motor coordination and delayed speech acquisition that lead him to be referred to a neurologist; agenesis of the CC was then detected with pneumoencephalography. At age 8, a complete agenesis of the corpus callosum was confirmed with CT and MRI scans with preservation of the anterior commissure. M.G. global IQ was 77 based on the Ottawa–Wechsler Intelligence Scale; he finished high school and is unemployed.

2.1.2. L.G.

Case L.G. is a 41 year-old, right-handed woman and is the third child from the family of M.G. She was born prematurely in the 7th month of gestation following a laborious breach birth. When she was 3.5 years, she suffered a light cranial trauma caused by a fall on the head, which required hospitalization. An EEG was then performed revealing a slow dysrhythmia without epileptic foci. She was re-hospitalized at 6 years for elective mutism and ataxia. No neuropsychological deficits were observed, but pneumoencephalography revealed agenesis of the corpus callosum, which was later confirmed by CT and MRI when she was 17 years old. The scans revealed a normal anterior commissure. As a child, she had to attend special classes for children with learning disabilities. Mutism and ataxia vanished, and she seemed socially well adjusted. L.G.'s full scale IQ is 78 based on the Ottawa–Wechsler Intelligence Scale.

2.1.3. S.G.

Case S.G. is a 42 years-old, right-handed woman. She is the oldest sister of M.G. and L.G. Like her siblings, she was born following a breach delivery. She was asymptomatic with the exception of a slow acquisition of walking related to motor incoordination usually noticed in callosal agenesis during development. Her milestones were otherwise considered normal. She volunteered with her parents to have a CT scan to investigate the presence of the congenital abnormality in her family. It was then discovered that she had complete callosal agenesis and an intact anterior commissure. S.G. has a global IQ of 84 based on the WAIS-R, graduated from high-school and is employed in a home for the elderly.

2.1.4. S.P.

Case S.P. is a 35 years-old, left-handed man. S.P reports that he suffered several concussions as a child, but these events were not registered in his medical file. He quit school when he was in sixth grade and started working when he was 13 years old. When he was 23 years old, he suffered ventriculoperitoneal derivation for hydrocephaly, which provoked absence seizures. The MRI showed complete absence of the corpus callosum with an intact anterior commissure. S.P.'s global IQ is 75 based on the WAIS-R.
2.1.5. J.P.L.
Case J.P.L. is a 22 years-old, right-handed man. When he was born he had an abnormal cardiac rhythm and suffered from anoxia. J.P.L. was diagnosed with a complete callosal agenesis and colpocephaly. At the time of the scan he was living with both his parents and had a part-time job. He has finished high school and his global IQ is 65 based on the WAIS-R.

2.2. MRI acquisition and analysis
Magnetic resonance images were acquired on a Siemens 3T Magnetom TIM Trio scanner with a 12-channel head coil (Siemens, Erlangen, Germany) with the following acquisition parameters: three-dimensional high-resolution T1-weighted images of the brain, sagittal MP-RAGE sequence (number of slices: 176; 1 mm³ resolution; repetition time: 2300 ms; echo time: 291 ms).

2.2.1. Cortical thickness analysis
High-resolution T1-weighted images were preprocessed using the CIVET pipeline (McConnell Brain Imaging Center, McGill University, Canada). Preprocessing included non-uniformity corrections, brain extraction, segmentation of gray/white matter tissues, and computation of white and gray matter surfaces using 81,920-polygon meshes. Cortical thickness was computed from the distance between corresponding nodes in the gray and white matter surface meshes. After registration to a standard MNI space, patients/controls comparisons were carried out using the SurfStat toolbox (www.math.mcgill.ca/keith/surfstat/) running on Matlab®. Analysis of cortical thickness was conducted using three methods. First, individual patient differences with the control group were assessed following the method of Boes et al. (2012). This comparison was performed by computing a 95% confidence interval around the mean thickness of the control group for every node, and testing the null hypothesis that each corresponding node in individual patients is included within this confidence interval ($P < 0.05$, uncorrected). Following this, the consistency of cortical thickness patterns among the AgCC group was evaluated by conducting a conjunction analysis, where nodes that were statistically different in every patient and displayed the same direction of change (i.e. patient < controls, or patient > controls) were labeled and visualized on an average surface map to identify common differences in cortical thickness among patients. Second, between-group differences were assessed using a general linear model with group contrasts (i.e. patients–controls) at each node, corrected for multiple comparisons using false discovery rate (Storey, 2002). Thirdly, variations in cortical thickness were assessed in regions of interest (ROI) consisting of the main primary cortices using false discovery rate (Storey, 2002). Thirdly, variations in cortical thickness were assessed in regions of interest (ROI) consisting of the main primary cortices using false discovery rate (Storey, 2002).

3. Results
The total absence of a corpus callosum was confirmed in all 5 AgCC participants using anatomical MRI (Fig. 1). At the individual level, each AgCC patient showed numerous, albeit heterogeneous, areas of cortical thickness abnormalities compared to the normative group (Fig. 2 and Table 1). To establish the presence of consistent morphological differences amongst the AgCC group in comparison to controls, a conjunction analysis was performed, revealing cortical areas that were either consistently thicker or thinner in all of the AgCC patients (Fig. 3). This analysis revealed the presence of very small areas of consistent thickness abnormalities in the anterior-cingulate cortex bilaterally, left primary somato-sensory cortex, left primary visual cortex and left orbitofrontal cortex, all of which where thicker. Between-group whole-brain analysis showed small areas of significant cortical thickening located in the medial part of the brain, namely in the posterior-cingulate, the anterior portions of the cingulate cortex bilaterally, and the left calcarine sulcus (Fig. 4). Finally, an analysis was performed on regions of interest (ROIs) defined a priori. No significant difference in cortical thickness was observed in primary motor cortex and primary auditory cortex. Significant areas of cortical thickening were found in the M1 hand area ($F = 4.92_{1,14}$, $P = 0.044$), primary somatosensory cortex ($F = 4.83_{1,14}$, $P = 0.045$) and primary visual cortex ($F = 5.22_{1,14}$, $P = 0.039$).

4. Discussion
The primary aim of the present study was to determine whether congenital absence of the corpus callosum is associated with aberrant cortical morphology in adults. This was achieved by individually comparing cortical thickness of subjects with AgCC to a group of healthy controls, investigating between-group differences at the whole-brain level and, based on previous behavioral evidence (Moes et al., 2009; G. Schilmoeller and K. Schilmoeller, 2000), of comparing cortical thickness in predefined ROIs. In general, results showed very few and limited effects of AgCC on cortical structure. Whole-brain analysis yielded subtle differences between groups, mostly located on the medial portion of the brain, while conjunction analysis revealed the presence of cortical thickening in spatially restricted areas that included somatosensory and visual regions. Finally, the ROI approach revealed cortical thickening in S1, V1 and the hand region of M1 in AgCC patients.

The presence of cortical thickening in human AgCC is at odds with animal studies that reported cortical thinning associated with congenital absence callosal fibers in regions normally richly innervated by the CC (Abreu-Villacorta et al., 2002; Ribeiro-Carvalho et al., 2006). Reductions in cortical thickness in these acallosal animal models may not be directly comparable to what is observed in human subjects, however. For example, Ribeiro-Carvalho et al. (2006) reported reduced thickness in layers V (area 6) and II–III (border of area 17/18a) of mice in which the corpus callosum was surgically sectioned on postnatal day 1, leading to probable axotomy-related cell death. More closely related to the present data, Ribeiro-Carvalho et al. (2006) found similar cortical thickness decreases in BALB/cCF mice, where 7% of the animals are born with complete AgCC. In this case, the BALB/cCF genetic mutation itself may have had an effect on cortical thickness. Nevertheless, the presence of increased cortical thickness in human AgCC is intriguing. It has been suggested that increased cortical thickness in congenital disorders may be related to groups of neurons missing their migrating targets in the cortex forming nodules of neurons lining the brain or ventricular surface, thus increasing cortical thickness (Guerrini and Marin, 2006; Guerrini et al., 2003; Hyde et al., 2007). Another possible explanation for increased cortical thickness is that aberrant neuronal migration can lead to faulty cortical organization, such as polymicrogyria (excessive

![Fig. 1. MRI of the five participants with AgCC in mid-sagittal view showing total absence of the corpus callosum.](image-url)
number of small and prominent convulsion gap by enlarged sulci) (Guerrini and Marini, 2006; Hyde et al., 2007). These aberrant cortical formations can manifest as epilepsy (Guerrini et al., 2003) or be associated with dyslexia (Chang, et al., 2005) and are suggested to occur in congenital amusia (Hyde et al., 2007). These hypotheses are coherent with AgCC since many neuronal targets during neuronal migration are sequestered into one hemisphere and could thus die during ontogenesis (as is suggested in mice) or form aberrant neuronal structures and artificially inflate cortical thickness.

Although patients with AgCC are surprisingly functional in everyday living, sensory and visual deficits can still be observed. For example, Schiavetto et al. (1993) found that AgCC patients have a higher threshold in a two-point discrimination task performed over the trunk (Schiavetto et al., 1993). Other studies have found higher pain tolerance in AgCC (Doherty et al., 2006; Moes et al., 2009). It was also reported that AgCC patients have difficulties in depth perception, distance perception, color perception and binocular vision (Corballis and Finlay, 2000; Lassonde et al., 1988; Moes et al., 2009; Saint-Amour et al., 2004). This is coherent with a study that found that 60% of their AgCC patient showed visual problems (Schell-Apacik et al., 2008). Moreover, according to Schilmoeller and Schilmoeller (2000), visual problems are the second most frequent clinical feature in patients with AgCC (prevalence of 33%), after mental retardation. Other studies suggest also that AgCC patients display impaired visuomotor learning in a bihemispheric condition (de Guise et al., 1999). Functional MRI data have also shown significant reorganization of visual cortical areas in individuals with AgCC (Bittar et al., 2000). Taken together, these studies suggest a possible link between the pattern of abnormal cortical thickness in visual areas of the brain reported here and specific dysfunctions related to the processing of sensory information.

In addition to dysfunctions in sensory cortices, individuals with AgCC showed abnormal cortical thickness in the hand knob of the primary motor cortex. This is in line with behavioral data where motor impairments have been reported in individuals with AgCC. Indeed, it has been shown that children with AgCC acquire gross and fine motor function later than healthy controls (Moes et al., 2009). Transferring motor information between hands is also

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Table 1
Areas of significant cortical thickness difference.

Fig. 2. Cortical thickness results for the five AgCC patients, compared to healthy controls. Results are presented on the cortical surface of an average brain. Colors represent the magnitude of cortical thickness differences in millimeters for each AgCC participant. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
reported to be more difficult in individuals with AgCC (Chicoine, et al., 2000). Furthermore, de Guise et al. (1999) reported motor coordination deficits in AgCC patients that were more pronounced in tasks requiring rapid motor execution. Along the same lines, studies have shown speed deficits in AgCC individuals when a motor component is required (Franz and Fahey, 2007; Mueller et al., 2009; Silver and Jeeves, 1994). Interestingly, neurophysiological impairments have also been reported in the motor system of patients with AgCC. Using transcranial magnetic stimulation, Fecteau et al. (2006) found increased intracortical inhibition in the primary motor cortex of individuals with AgCC. Similarly to what was found for sensory areas, motor impairments in AgCC may be related to the abnormal pattern of cortical thickness found in primary motor cortex.

Although individuals with AgCC in the present study show significant abnormalities in cortical thickness in primary brain areas compared to healthy subjects, these differences are relatively mild when one considers the anatomical importance of callosal fibers. This is, however, in line with results from a recent study where the major white matter bundles of children with corpus callosum dysgenesis were found to be very similar to those of healthy controls in terms of morphology, fiber number and microstructure (Benezit et al., 2015). Interestingly, very similar patterns of white matter interhemispheric asymmetry were also found between controls and children with corpus callosum dysgenesis. For example, a right bias in the corticospinal tract and the superior longitudinal fasciculus was found for both healthy and dysgenetic children (Benezit et al., 2015). Along the same lines, Tyszka et al. (2011) have reported that patients with complete AgCC have, compared to healthy controls, nearly identical resting-state functional networks. Most notably, homotopic areas of the AgCC brain are highly correlated in terms of functional connectivity, suggesting the presence of interhemispheric interactions despite congenital absence of the corpus callosum (Tyszka et al., 2011). This should not be taken to imply, however, that the brain of patients with congenital AgCC follows identical anatomical developmental patterns to that of healthy individuals. For example, axons that do not cross the midline during development to become callosal fibers can form anterior–posterior tracts of white matter known as “Probst bundles” (Paul et al., 2007). Additionally, a recent connectomic study found reduced global connectivity, increased local connectivity, and greater variability of intrahemispheric connectivity in individuals with AgCC compared to healthy controls (Owen et al., 2013). It is important to note that in that same study, changes in the connectome were greater in AgCC individuals than what was predicted by a “virtual lesion” approach whereby the effects of removing callosal fibers are derived onto the normal connectome (Owen et al., 2013). This suggests that the core dysfunction leading to AgCC may also impact non-callosal areas and that plastic reorganization probably compensates for the absence of callosal fibers (Owen et al., 2013).

Further studies are needed to better characterize brain development and function in the absence of its principal commissure. For example, the conjunction analysis revealed a consistent thickening in the anterior-cingulate and the orbitofrontal cortex of AgCC patients. Although these regions did not appear as significantly different in whole brain analysis, it is interesting to note that these areas are involved in social behavior and introspection, two areas of known difficulties in AgCC patients (Paul et al., 2007). It should be noted, however, that the purported link between areas of abnormal cortical thickness and specific behavioral deficits in the present sample remains speculative in the absence of behavioral data. Future studies using larger sample sizes are necessary.
to clarify the link between structural abnormalities and motor, cognitive and social difficulties in AgCC patients.

5. Conclusion

Taken together, the present results suggest that the brain of AgCC individuals is characterized by distinct patterns of cortical abnormalities plasticity that may underlie the behavioral heterogeneity of the condition. Consistent differences in cortical thickness between individuals with AgCC and healthy controls were found to be relatively limited, however. Nevertheless, common areas of cortical abnormalities were present in primary motor, somatosensory and visual areas, paralleling some of the common behavioral deficits observed in AgCC. The mechanism underlying the possible vulnerability of primary areas to the loss of callosal fibers remains to be determined. The presence of large, fast-conducting fibers in the specific parts of the CC that connect motor, somatosensory and visual areas, as opposed to smaller slow-conducting fibers connecting higher-order association areas (Doron and Gazzaniga, 2008; Fabri et al., 2014), may offer some insight.

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