NeuroImage 243 (2021) 118471

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Large-scale functional network dynamics in human callosal agenesis: Increased subcortical involvement and preserved laterality

Vanessa Siffredi [a,b,c,d,1,*], Younes Farouj [a,b,1], Anjali Tarun [a,b], Vicki Anderson [c,e,f,g], Amanda G. Wood [c,h,i], Alissandra McIlroy [c], Richard J. Leventer [e,j,k], Megan M. Spencer-Smith [c,l], Dimitri Van De Ville [a,b]

[a] Institute of Bioengineering, École Polytechnique Fédérale de Lausanne, Switzerland
[b] Department of Radiology and Medical Informatics, University of Geneva, Geneva, Switzerland
[c] Brain and Mind Research, Clinical Sciences, Murdoch Children's Research Institute, Melbourne, Australia
[d] Division of Development and Growth, Department of Woman, Child and Adolescent, University Hospitals of Geneva, Geneva, Switzerland
[e] Neuroscience Research, Clinical Sciences, Murdoch Children's Research Institute, Melbourne, Australia
[f] School of Psychological Sciences, University of Melbourne, Melbourne, Australia
[g] Department of Psychology, Royal Children's Hospital, Melbourne, Australia
[h] School of Life and Health Sciences & Aston Neuroscience Institute, Aston University, Birmingham, B4 7ET UK
[i] School of Psychology, Faculty of Health, Melbourne Burwood Campus, Deakin University, Geelong, Victoria, Australia
[j] Department of Paediatrics, University of Melbourne, Melbourne, Australia
[k] Department of Neurology, Royal Children's Hospital, Melbourne, Australia
[l] Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University, Melbourne, Australia

ARTICLE INFO

Keywords:
Dynamic functional connectivity
Callosal agenesis
Subcortical networks
Brain plasticity

ABSTRACT

In the human brain, the corpus callosum is the major white-matter commissural tract enabling the transmission of sensory-motor, and higher level cognitive information between homotopic regions of the two cerebral hemispheres. Despite developmental absence (i.e., agenesis) of the corpus callosum (AgCC), functional connectivity is preserved, including interhemispheric connectivity. Subcortical structures have been hypothesised to provide alternative pathways to enable this preservation. To test this hypothesis, we used functional Magnetic Resonance Imaging (fMRI) recordings in children with AgCC and typically developing children, and a time-resolved approach to retrieve temporal characteristics of whole-brain functional networks. We observed an increased engagement of the cerebellum and amygdala/hippocampus networks in children with AgCC compared to typically developing children. There was little evidence that laterality of activation networks was affected in AgCC. Our findings support the hypothesis that subcortical structures play an essential role in the functional reconfiguration of the brain in the absence of a corpus callosum.

1. Introduction

With more than 190 million axon fibres, the corpus callosum is the largest white matter pathway and serves as a bridge to connect neurons between the two cerebral hemispheres of the human brain (Edwards et al., 2014). Its plays a crucial role in the transmission and integration of low-level sensory-motor, and higher-lever cognitive information between homotopic regions in the left and the right hemispheres (Gazzaniga, 2000; Hofer and Frahm, 2006; Hofer et al., 2008). Moreover, during prenatal and postnatal brain development, it is likely that the corpus callosum contributes significantly in the lateralisation and specialisation of function through the interplay of hemispheric interaction (Gazzaniga, 2000; Jeeves and Temple, 1987; Mancuso et al., 2019). In this context, studying individuals for whom the corpus callosum never develops or only develops partially can provide useful insights into how the two hemispheres communicate with each other and coordinate their functions (Karolis et al., 2019; Mancuso et al., 2019).

Abbreviations: AgCC, Agenesis of the corpus callosum; TDC, Typically developing controls; RCH, Royal Children's Hospital; iCAPS, Innovation-Driven Co-Activation Patterns; A-LI, Amplitude Laterality Index; O-LI, Occurence Laterality Index.

* Corresponding author.
E-mail address: vanessa.siffredi@unige.ch (V. Siffredi).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.neuroimage.2021.118471.
Received 1 February 2021; Received in revised form 20 July 2021; Accepted 11 August 2021
Available online 27 August 2021.

Developmental absence or agenesis of the corpus callosum (AgCC) is a congenital brain malformation and the most common disorder of axonal guidance (Owen et al., 2013). Starting 11–12 weeks' post-conception, neurobiological mechanisms regulating corpus callosum formation are complex (Edwards et al., 2014). Subsequently, AgCC can result from alteration of numerous neurodevelopmental events from early midline telencephalic patterning to neuronal migration and specification, axon guidance, and post-guidance development (Siffredi et al., 2021a). This complexity reflects the heterogeneous nature of clinical presentations of individuals with AgCC. It encompasses the complete or partial failure of the callosal fibres to cross the midline and form connections in the neocortex between the two hemispheres (Lassonde et al., 1991; Paul et al., 2007). Studies also show that individuals with AgCC are heterogeneous in terms of neurodevelopmental outcomes ranging from normal to individuals attending special developmental school and requiring assistance in daily living activities (D'Antonio et al., 2016; Siffredi et al., 2013; 2018).

Brain connectivity can be explored using functional connectivity between distinct units within a nervous system (Rubinov and Sporns, 2010). Studies investigating functional connectivity using resting-state functional magnetic resonance imaging (fMRI) in individuals with AgCC have reported intact resting-state functional brain networks, with typical lateralisation (Owen et al., 2013; Tovar-Moll et al., 2014; Tyszka et al., 2011). A recent study also reported intra-hemispheric and inter-hemispheric functional connectivity in children with AgCC comparable to their typically developing peers (Shi et al., 2021; Siffredi et al., 2021a). These findings are in line with the view that resting-state functional connectivity reflects both direct and indirect anatomical connections and is usually mediated by more than just monosynaptic structural connectivity (Honey et al., 2009; Koch et al., 2002; Tarun et al., 2020). Therefore, it is possible that in the case of absence of callosal fibres, inter-hemispheric regions that are no longer directly connected will use indirect pathways to maintain their level of communication (Mancuso et al., 2019). In this context, evidence from callosotomy studies (i.e., studying patients who have undergone full callosotomy and described as split-brained) suggest that subcortical structures play a fundamental role in the functional reconfiguration of the brain (Funnell et al., 2000; Gazzaniga et al., 1987; Savazzi et al., 2007; Uddin et al., 2008).

To date, functional connectivity studies in AgCC have used only static functional connectivity; i.e., the correlation between the activation in different brain regions over the whole scanning time. A limitation of such static approaches is that they ignore the inherently dynamic nature of brain activity, with potentially valuable information contained in dynamic changes of activation and connectivity (Bolton et al., 2020; Christoff et al., 2016; Hutchison et al., 2013; Preti et al., 2017). Dynamic approaches are promising tools for the detection of subtle changes in brain functional organisation in children with AgCC compared to typically developing controls (TDC). This understanding could inform crucial questions about general cortical organisation and more particularly about potential functional reconfigurations.

In the present study, we extract, for the first time, dynamic properties of neural activity in AgCC and compared them to TDC. We extracted the so-called "innovation-driven co-activation patterns" (iCAPs) (Karahanoğlu and Van De Ville, 2015; 2017). These patterns are obtained based on *transient* brain activity, or moments of activity changes in the blood-oxygenation level dependent (BOLD) signal. These are recovered by undoing the effect of the haemodynamics through spatio-temporal deconvolution combined with a regular derivative (Farouj et al., 2017; Karahanoğlu et al., 2013; Karahanoğlu and Van De Ville, 2015). The result is a series of innovation frames that identify time-points for when the brain undergoes an increase or decrease in activity. By clustering these innovations, we obtain a decomposition of global brain dynamics. Using these properties, we assessed the spatial and temporal characteristics of networks in children with AgCC compared to TDC.

2. Methods and materials

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 was recruited from clinics and radiology records at The Royal Children's Hospital (RCH), Melbourne. Inclusion criteria were: 1) aged 8 years 0 months to 16 years and 11 months; 2) evidence of AgCC on MRI conducted as part of a routine clinical work-up; 3) English speaking; and 4) functional ability to engage in the assessment procedure. MRI findings were qualitatively reviewed by a paediatric neurologist with expertise in brain malformations (RJL), who confirmed diagnosis of AgCC, including complete and partial AgCC. A TDC group of 30 children comparable in age and sex to the AgCC group was recruited from the community.

2.2. Procedure

This project was approved by the RCH Human Research Ethics Committee. Caregivers provided written informed consent prior to participation. Consenting families were seen at a research clinic at the Murdoch Children's Research Institute.

2.3. Material

2.3.1. Neuroimaging measures

Magnetic Resonance Imaging acquisition Images were acquired on a 3T MAGNETOM Trio scanner (Siemens, Erlangen, Germany) at The RCH. A 32-channel head coil was used for transmission and reception of radio-frequency and signals. A high-resolution 3D anatomical images was acquired using a T1-weighted MP-RAGE sequence (TR = 1900 ms, TE = 2.71 ms, TI = 900 ms, FA = 9°i, FoV = 256 mm, voxel size = 0.7 x 0.7 x 0.7 mm). Resting-state gradient-echo EPI sequences was also acquired (196 frames, TR = 2000 ms, TE = 30 ms, voxel size= 2.6 x 2.6 x 4 mm, FA = 90 deg, FoV= 250 mm x 250 mm). During the resting-state fMRI sequence, participants were instructed to keep their eyes closed and engage in mind wandering.

Preprocessing MRI scans were preprocessed using SPM12 (Wellcome Centre for Human Neuroimaging, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/spm12) and functions of the Data Processing Assistant for Resting-State fMRI (Chao-Gan and Yu-Feng, 2010).

Resting-state fMRI data were converted from the native DICOM to NIFTI format using dcm2nii. We then followed the preprocessing pipeline described by Preti and Van De Ville (Preti and Van De Ville, 2017). For each participant, the first 5 (of the 196) volumes were discarded to ensure magnetisation equilibrium, and the remainder underwent spatial realignment and smoothing (5mm FWHM Gaussian kernel). For resting-state fMRI data, the mean framewise displacement for each frame was computed to quantify the extent of head motion from volume to volume for each participant (Power et al., 2012; 2014). Following Power and colleagues' recommendations, we implemented volume censoring ("scrubbing") for motion correction using a framewise displacement of 0.5 mm threshold for exclusion. Additionally, following Zöller and colleagues' preprocessing pipeline, participants with less than 125 frames remaining after scrubbing were excluded (Zöller et al., 2019). Following these recommendations, 6 AgCC and 1 TDC participants were excluded for head-motion. Moreover, 1 AgCC and 5 TDC participants were excluded because of bad coverage of the cerebellum; 3 AgCC participants were excluded due to mediocre registration to MNI that could potentially bias the results, especially the clustering phase of the iCAPs extraction; and 1 participant with AgCC was excluded due to atypical commissural elements. The following steps were performed on the scrubbed data of all remaining participants. Voxel-wise time-courses were first detrended (linear and quadratic trends). The 6 motion parameters, as well as the average white matter and cerebrospinal fluid signals

obtained from standard white matter and ventricular masks mapped to the subjects' fMRI space and masked with individual segmentation maps, were regressed out using the DPARSF toolbox (Leonardi et al., 2013). The time-courses were then band-pass filtered in the range of [0.01 0.15 Hz] to enhance resting-state fluctuations.

Innovation-Driven Co-Activation Patterns (iCAPs) We tailored the openly available MATLAB code (https://c4science.ch/source/iCAPs/) MATLAB vR2016a (The MathWorks, Inc., Natick, MA) to apply the iCAPs framework on children with AgCC. The overall routine is composed of 4 steps (details can be found in the Supplementary Methods):

- **Spatio-temporal deconvolution**: In this first step a hemodynamically-informed deconvolution (Farouj et al., 2017; Karahanoğlu et al., 2013) was applied to the fMRI timeseries in a way that promotes the rareness of activity transients and spatially coherent activations.
- **Significant transients detection**: *Innovation* signals are computed as the temporal derivative of the deconvolved signals. The obtained signals can be seen as a representation in terms of transients in neural activity, where large amplitude transients implicitly identify change-points. Significant transients were determined using a two-step thresholding procedure. A temporal threshold estimated from a surrogate distribution that keeps only transient larger than 95% or lower than 5%. Then, a spatial thresholding procedure was applied, in which a frame was considered significant if at least 5% of the gray matter voxels were active. The frames showing significant transients are called *innovation* frames, and allow to identify time-points when a given region in the brain undergoes an increase or decrease in activity.
- **Aggregation**: The significant frames were warped into MNI (Montreal Neurologic Institute) space via a specific DARTEL (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) template (Klein et al., 2009). This normalisation method has been demonstrated to be robust to age differences in participants of 7 years and above, as well as in abnormal brain development such as AgCC (Ashburner and Friston, 1999; Burgund et al., 2002; Tyszka et al., 2011). All frames were then aggregated for clustering.
- **Clustering**: The retained *innovation* frames, underwent K-means clustering that resulted in K centroids that are the spatial maps. The optimum number of clusters was obtained using consensus clustering (Monti et al., 2003), a resampling-based technique for optimal class discovery.

Static Analysis of iCAPs We extracted an activity time course for each iCAP by spatio-temporal back-projection of the spatial maps onto the activity-inducing signals (Zöller et al., 2018). This resulted in a set of K signals for each run describing activity segments of each of the k iCAPs. Afterwards, we then computed a static measure of inter-iCAPs interactions, i.e., temporal correlation. The inter-iCAPs kxk correlation matrices of each participant were then used for group comparisons.

Extraction of Temporal Properties For each iCAP, we computed the number of contributing significant innovations and their percentage out of the total nonmotion scanning time. By measuring the percentage of innovations, we measured purely the contribution of each network in resting-state in terms of spontaneous engagement while removing the effect of BOLD signal variability.

Laterality of Brain Networks The standard MNI template space is not symmetric and thus not suitable for laterality assessment. Therefore, we co-registered the iCAPs maps to an MNI symmetrical template, available at http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin2009, before extracting two different laterality measures:

- **Laterality of activity maps**: The first measure of laterality aimed at exploring possible asymmetry effect between the two hemispheres by comparing lateralised amplitude maps of the iCAPs. The amplitudes of these patterns reflect the mean activity amplitude for each voxel when contributing to a certain network. Such measure have been used previously in the literature (see for example Karolis et al., 2019). We flipped the left hemisphere maps and subtracted them from unflipped right hemisphere maps in order to obtain an Amplitude Laterality Index (A-LI) for each voxel. Positive and negative values in these A-LI maps reflect, respectively, right and left lateralisation. These maps were then averaged for each iCAPs in order to obtain one A-LI for each iCAPs and each participant.
- **Laterality of activity occurrences** : The second measure of laterality aimed at extracting possible asymmetries in terms of occurrences rather than amplitude. To this end, we computed for each voxel the number of times it was active when a given iCAP was active. The obtained percentage of voxel-iCAP contribution was then used as an Occurrence Laterality Index (O-LI) for comparisons. Similarly to the first measure, we subtracted the left hemisphere maps from right hemisphere maps and averaged then to obtain a global O-LI.

2.4. Statistical analyses

All analyses were performed using R software, version 3.5.2 (Allaire, 2012; Team et al., 2013). Given the small number of participants in the partial AgCC group, we completed primary analyses on comparing the complete AgCC and the TDC groups; and secondary analyses compared the partial AgCC group to the complete AgCC and TDC groups.

Primary analyses: comparison of the complete AgCC and TDC groups Group comparisons between complete AgCC and TDC were conducted for the inter-iCAPs correlations (i.e., static analysis of iCAPs), as well as for the percentage of innovations on the 12 retrieved networks (i.e., temporal properties) using Wilcoxon signed rank test. P values were corrected for multiple comparisons with the false discovery rate (FDR, q values <0.1) (Benjamini and Hochberg, 1995). Effect size were assessed using Wilcoxon effect size (r). Linear models were used to evaluate whether network laterality was different across groups for both laterality of activity maps and laterality of activity occurrences. We modelled the effects of network laterality using laterality indices, i.e., A-LI and O-LI, as dependent variables and groups (i.e., complete AgCC, partial AgCC and TDC) as independent variables. Considering the importance of handedness in networks laterality (Amunts et al., 1996; Kirsch et al., 2018; Mazoyer et al., 2014), handedness was used as covariate in the model. P values were corrected for multiple comparisons with the false discovery rate (FDR, q values <0.1). Effect size were assessed using Cohen's f.

Secondary analyses: comparisons including the partial AgCC group Group comparison between partial AgCC and complete AgCC, and partial AgCC and TDC were conducted using Wilcoxon signed rank test, for inter-iCAPs correlations and for the percentage of innovations on the networks that show significant difference between complete AgCC and TDC. P values were corrected for multiple comparisons with the false discovery rate (FDR, q values <0.1) (Benjamini and Hochberg, 1995). Effect size were assessed using Wilcoxon effect size (r). Linear models described above were used to evaluate whether network laterality on A-LI and O-LI was different across groups, including the partial AgCC group.

3. Results

3.1. Sample characteristics

After quality checking, the current analyses included 12 children with AgCC, including 8 with complete AgCC and 4 with partial AgCC, as well as 23 TDC. Characteristics of the study participants in the AgCC and the TDC groups are presented in Table 1 and in Supplementary Table S1. Supplementary Table S2 also shows anatomical images of AgCC participants. Considering the small number of children with partial AgCC, group comparisons were conducted primarily with the complete AgCC and TDC groups. In secondary analyses, we then explored differences with the partial AgCC group.

Table 1
Characteristics of the study participants in the Complete AgCC, Partial AgCC and TDC groups .

	Complete AgCC	Partial AgCC	TDC
n	8	4	23
Age in years, mean (SD)[range]	11.43 (1.79)[8.67-14.42]	13.08 (3.68)[9.67-17.08]	11.65 (2.46)[8–16.42]
Sex, n	2 females, 6 males	2 females, 2 males	10 females, 13 males
Handedness, n	5 R, 2 L, 1 M	3 R, 1 L	20 R, 3 L
Full-Scale IQ, mean (SD)[range]	73 (5.66)[67–84]	95.25 (23.37)[73–126]	111.96 (11.86)[88–136]

Note: Full-scale Intellectual Quotient (IQ) was measured using the Wechsler Abbreviated Intelligence Scale (WASI) or the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV; n=3) where the mean standardized score is M= 100 and SD=15; Handedness was estimated using the Edinburgh Handedness Inventory where right-handed (R)= + 40 to + 100, left-handed (L)= - 40 to - 100, and mixed handed (M)= - 40 to + 40

3.2. Extracted spatial maps correspond to known resting-state networks

The iCAPs framework was applied to resting-state fMRI scans of both AgCC (complete and partial) and TDC children. We identified 12 iCAPs that corresponded to well-known resting-state networks, including: a) sensory-related networks such as primary visual, secondary visual, sensorimotor/auditory networks; b) default-mode network (DMN) decomposed into ventral, anterior and precuneus/ventral DMN; c) attention and executive related network, including the frontoparietal network (FPN) and visuospatial (VSN) network; d) networks implicating regions commonly considered as the salience network (SN) such as the anterior insula (AntI) and dorsal anterior cingulate cortex together with dorsolateral prefrontal cortex (dACC/dlPFC), e) subcortical structures networks including cerebellum and amygdala/hippocampus (AMY/HIP), see Fig. 1 and Supplementary Table S4. These well-known networks were identified in both the AgCC (complete and partial) and the TDC groups.

3.3. Static properties of inter-iCAPs interactions

To probe alterations in the static properties of the networks, we compared the complete AgCC group to the TDC group in terms of inter-iCAPs temporal correlation for the 12 identified networks. There was no group difference for all of the inter-iCAPs interactions, see Supplementary Table S3.

3.4. Temporal properties of networks

3.4.1. Comparison of the complete AgCC and TDC groups

To investigate alterations in the temporal properties of the networks, we compared the complete AgCC group to the TDC group in terms of the innovation frames as percentage of the total nonmotion scanning time for the 12 identified networks, see Fig. 2 and Supplementary Table S4. The percentage of innovation corresponds to the engagement in a given brain state. In comparison to the TDC group, children with complete AgCC showed a significant increase in the percentage of innovation for both subcortical networks, including the cerebellum (iCAP4: Complete AgCC median = 13.5 ; TDC median = 7.33) and the amygdala/hippocampus (iCAP10: Complete AgCC median = 3.53; TDC median = 8.06) compared to the TDC group (W = 142, Z = -2.27, p = 0.023, q (FDR adjusted p-value) = 0.093, r = 0.41; W = 39, Z = -2.42, p = 0.016, q = 0.093, r = 0.43). A significant reduction in the engagement of the frontoparietal network was also observed in complete AgCC compared to TDC (iCAP9: Complete AgCC median = 10.4; TDC median = 7.62; W = 148, Z = -2.57, p = 0.01, q (FDR adjusted p-value) = 0.093, r = 0.45).

3.4.2. Group comparisons including the partial AgCC group

We compared the complete AgCC group to the partial AgCC group, as well as the partial AgCC to the TDC group on the percentage of innovation for the networks that show a significant difference in engagement between the complete AgCC and the TDC groups, i.e., iCAP4 - amygdala/hippocampus, iCAP8 - frontoparietal and iCAP10 - cerebellum. We found no significant differences in terms of engagement in these 3 networks between the complete and the partial AgCC groups, as well as between the partial AgCC and the TDC groups, see Fig. 2 and Supplementary Table S5.

3.5. Laterality of brain networks

- **Laterality of activity maps**: There were no significant differences in Amplitude Laterality Index (A-LI) between the complete AgCC, the partial AgCC and the TDC groups for any of the O-LI of 12 iCAPs networks, see Supplementary Table S6.
- **Laterality of activity occurrences**: There were no significant differences in Occurrences Laterality Index (O-LI) between the complete AgCC, the partial AgCC and the TDC groups for any of the 12 iCAPs networks, see Supplementary Table S7.

4. Discussion

This is the first study to explore the dynamic features of network brain activity in individuals with AgCC. We used the iCAPs framework to go beyond static connectivity analyses which enabled examination of the dynamic engagement of different large-scale functional brain networks. Our findings suggest that comparable dynamic large-scale brain networks can be observed in children with AgCC and TDC, despite complete or partial absence of the major commissural track in the human brain, i.e., the corpus callosum. In line with the hypothesis of subcortical involvement in individuals with AgCC, examination of temporal properties of subcortical networks showed increased engagement of the cerebellum and amygdala/hippocampus networks in children with complete AgCC compared to TDC. Comparable laterality, both in terms of amplitude and occurences of activity, was found for each of the 12 extracted dynamic large-scale brain networks between the AgCC and the TDC groups.

Using innovation-driven coactivation patterns for dynamic large-scale brain network analysis, we uncovered comparable patterns of brain network activation in children with AgCC (complete and partial) and TDC. The qualitative spatial organisation of the 12 well-known dynamic networks retrieved were all bilateral. Moreover, using a static functional connectivity approach, inter-iCAPs interactions were comparable between the AgCC and the TDC groups. These results are in line with previous resting-state fMRI studies using static analysis methods and showing similar static spatial organisation of brain networks in individuals with AgCC and healthy controls (Owen et al., 2013; Tovar-Moll et al., 2014; Tyszka et al., 2011). These findings provide further evidence that despite major structural alteration with complete or partial absence of the corpus callosum, typical functional brain networks can be realised. It is likely that substantial reorganisation occurs and indirect pathways are found to maintain typical brain states, as well as inter-hemispheric functional communication in these atypically developing brains (Honey et al., 2009; Koch et al., 2002).

To explore potential functional reorganisation in individuals with developmental absence of the corpus callosum, we compared the temporal

Fig. 1. Spatial patterns of the 12 innovation-driven coactivation patterns (iCAPs) retrieved from all subjects. Locations denote displayed slices in Montreal Neurological Institute coordinates. For each iCAPs, pie charts show the innovation frames per group as a percentage of the total nonmotion scanning time, including complete AgCC, partial AgCC and TDC. Spatial patterns of the 12 iCAPs include: AntI, anterior insula; SecVIS, secondary visual; PREC/vDMN, precuneus/ventral default mode network; Cerebellum; VSN, visuospatial network; SM/AUD, sensorimotor/auditory; aDMN, anterior default mode network; FPN, frontoparietal network; vDMN, ventral default mode network; AMY/HIP, amygdala/hippocampus; dACC/dlPFC, dorsal anterior cingulate cortex/ dorsolateral prefrontal cortex; PrimVIS, primary visual.

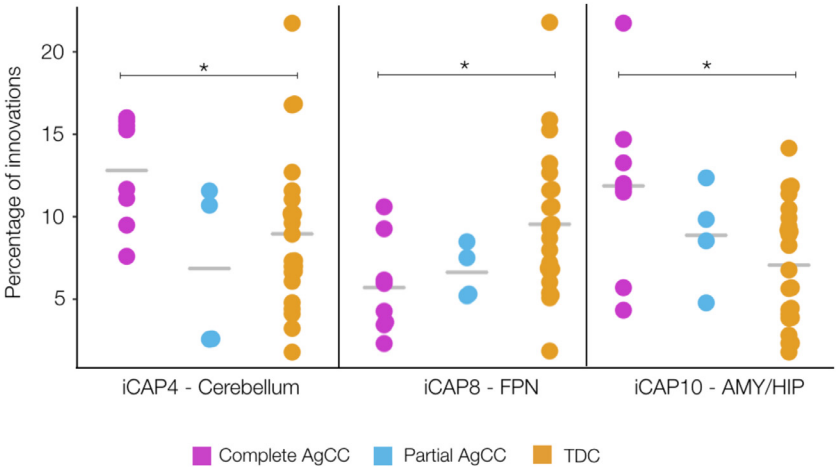

Fig. 2. Percentage of innovations showing significant group differences for iCAP4-Cerebellum, iCAP8-Fontoparietal network and iCAP10-Amygdala/Hippocampus. The mean for each iCAP and each group is represented by a grey line; * indicates significant difference between group with $p<0.05$ and $q<0.1$ (FDR adjusted p-value).

properties of the networks between the AgCC and the TDC groups. A significant and specific increase in network engagement was found for both subcortical networks, i.e., cerebellum and amygdala/hippocampus networks, in children with complete AgCC compared to TDC. These findings support the hypothesis of the contribution of subcortical structures to functional reorganisation in AgCC. Callosotomy studies provide strong evidence that subcortical structures play a fundamental role in the functional reconfiguration of the brain (Funnell et al., 2000; Gazzaniga et al., 1987; Savazzi et al., 2007; Uddin et al., 2008). According to the theory of Sperry (1984), because of the absence of the CC, the functional organisation of the two hemispheres have become independent and appear to bifurcate from a unified root of subcortical structures (Sperry, 1984). Notably, this pattern of increased subcortical engagement was specific to complete AgCC and was not observed in children with partial AgCC. In complete AgCC, disruption of programmed callosal formation processes occurs very early in brain development; while in partial AgCC, callosal formation begins and the disruption occurs after the pioneering axons cross the midline and grow into the contralateral hemisphere towards their designated target region (Paul et al., 2007). It is possible that the earlier the disruption occurs, the more likely that brain reorganisation takes place through subcortical networks (Anderson et al., 2011; Kennard, 1938).

In parallel to the increased engagement of subcortical networks, we observed a significant reduction of engagement of the frontoparietal network in the complete AgCC group compared to TDC. Tyszka and colleagues (2011) also observed an atypical pattern in the frontoparietal network in adults with AgCC, with the frontoparietal network split into anterior and posterior networks (Tyszka et al., 2011). In typically developing brains, bilateral frontal and parietal cortices are highly connected by the corpus callosum (Hofer and Frahm, 2006). In the absence of the corpus callosum, it is possible that these regions are less able to engage in a functional network that is comparable to typically developing brains.

As the major inter-hemispheric connections in the human brain, callosal connectivity has long being considered a key contributor to the architecture of functional lateralisation in the human brain (Gazzaniga, 2000; Jeeves and Temple, 1987; Mancuso et al., 2019). In the present study, the 12 dynamic large-scale brain networks retrieved showed comparable laterality between the AgCC and the TDC groups, both in terms of amplitude and occurences of activity. Findings are consistent with a previous resting-state study showing similar laterality of static networks between individuals with AgCC and healthy controls (Tyszka et al., 2011). This suggests that inter-hemispheric functional integration can occur in the absence of the corpus callosum.

In the current study, findings showed an increased engagement of the contribution of subcortical networks in brain reorganisation in the AgCC compared to the TDC group. Other neuroplastic responses have also been proposed, in particular, the contribution of the anterior and posterior commissures as alternative commissural pathways is of interest (Hung et al., 2019; Siffredi et al., 2021b; 2019; Tovar-Moll et al., 2014). It is possible that these structures also play a role in the establishment of typical large-scale functional brain networks and their functional lateralisation, but further studies are needed to explore these questions. Furthermore, in future works, extracting networks separately from the two hemispheres could allow the investigation of asymmetries. Another potential advantage of performing the analysis at the hemisphere level, is the possibility to assess the couplings between activity patterns in homotopic regions using state-of-the art methods for information flow analysis (Frässle et al., 2021). Such analyses will certainly benefit from the continuous improvement of fMRI data acquisition speed. On the structural level, there was an important variability in terms of anatomical profiles. In particular, some children have isolated AgCC, while others have AgCC with additional brain malformations (i.e., complex AgCC). Further investigations with larger samples of each phenotypic group, possibly achieved through recruitment across multiple sites, are necessary to better understand the impact of such additional malformations on brain functioning.

4.1. Conclusion

The present findings showed typical spatial patterns of large-scale functional brain networks in children with complete and partial absence of the corpus callosum. Increased engagement of subcortical networks in children with complete AgCC are in line with the hypothesis of functional brain reconfiguration through subcortical routes. Moreover, despite the loss of callosal connectivity, the laterality of brain networks retrieved were comparable in the AgCC and the TDC groups. This work provides novel evidence that comparable dynamic resting-state functional networks can be realised on different structural architectures, at least in a developmental context that permits substantial reorganisation, such as AgCC.

Funding

This study was supported by the Boninchi Foundation from the University of Geneva; the Victorian Government's Operational Infrastructure Support Program; and the Murdoch Children's Research Institute. Younes Farouj and Anjali Tarun are supported by the Swiss National Science Foundation Project [205321_163376]. Professor Amanda G. Wood is supported by a European Research Council Consolidator Fellowship [682734]. Associate Professor Richard J. Leventer is supported by a Melbourne Children's Clinician Scientist Fellowship. Professor Vicki Anderson was supported by the Australian National Health and Medical Research Council Senior Practitioner Fellowship.

Data/code availability statement

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 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: 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. Codes used in the context of this study are openly available https://c4science.ch/source/iCAPs/.

Ethics statement

This study was approved by the Royal Children's Hospital Human Research Ethics Committee. Written informed consent was obtained from the principal caregiver and from the participant

Competing interests

The authors declare that they have no competing interests.

Credit authorship contribution statement

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

acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Dimitri Van De Ville:** Conceptualization, Investigation, Resources, Software, Supervision, Validation, Writing – review & editing.

Acknowledgments

We gratefully acknowledge the families who participated in this study and Kate Pope for her assistance in recruitment of the families.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at 10.1016/j.neuroimage.2021.118471

References

Allaire, J., 2012. Rstudio: integrated development environment for r. Boston, MA 770, 394.

Amunts, K., Schlaug, G., Schleicher, A., Steinmetz, H., Dabringhaus, A., Roland, P.E., Zilles, K., 1996. Asymmetry in the human motor cortex and handedness. Neuroimage 4 (3), 216–222.

Anderson, V., Spencer-Smith, M., Wood, A., 2011. Do children really recover better? neurobehavioural plasticity after early brain insult. Brain 134 (8), 2197–2221.

Ashburner, J., Friston, K. J., 1999. Spatial normalization in: Toga AW, editor., editor. brain warping.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal statistical society: series B (Methodological) 57 (1), 289–300.

Bolton, T.A.W., Morgenroth, E., Preti, M.G., Van De Ville, D., 2020. Tapping into multi-faceted human behavior and psychopathology using fMRI brain dynamics. Trends Neurosci..

Burgund, E.D., Kang, H.C., Kelly, J.E., Buckner, R.L., Snyder, A.Z., Petersen, S.E., Schlaggar, B.L., 2002. The feasibility of a common stereotactic space for children and adults in fMRI studies of development. Neuroimage 17 (1), 184–200.

Chao-Gan, Y., Yu-Feng, Z., 2010. Dparsf: a matlab toolbox for "pipeline" data analysis of resting-state fmri. Front Syst Neurosci 4.

Christoff, K., Irving, Z.C., Fox, K.C.R., Spreng, R.N., Andrews-Hanna, J.R., 2016. Mind-wandering as spontaneous thought: a dynamic framework. Nat. Rev. Neurosci. 17 (11), 718.

D'Antonio, F., Pagani, G., Familiari, A., Khalil, A., Sagies, T.-L., Malinger, G., Leibovitz, Z., Garel, C., Moutard, M.L., Pilu, G., et al., 2016. Outcomes associated with isolated agenesis of the corpus callosum: a meta-analysis. Pediatrics 138 (3), e20160445.

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 (6), 1579–1613. doi:10.1093/brain/awt358. https://academic.oup.com/brain/article-pdf/137/6/1579/13797191/awt358.pdf

Farouj, Y., Karahanoğlu, F.I., Van De Ville, D., 2017. Regularized spatiotemporal deconvolution of fMRI data using gray-matter constrained total variation. In: 2017 IEEE 14th International Symposium on Biomedical Imaging (ISBI 2017). Ieee, pp. 472–475.

Frässle, S., Harrison, S.J., Heinzle, J., Clementz, B.A., Tamminga, C.A., Sweeney, J.A., Gershon, E.S., Keshavan, M.S., Pearlson, G.D., Powers, A., et al., 2021. Regression dynamic causal modeling for resting-state fMRI. Hum Brain Mapp 42 (7), 2159–2180.

Funnell, M.G., Corballis, P.M., Gazzaniga, M.S., 2000. Cortical and subcortical interhemispheric interactions following partial and complete callosotomy. Arch. Neurol. 57 (2), 185–189.

Gazzaniga, M.S., 2000. Cerebral specialization and interhemispheric communication: does the corpus callosum enable the human condition? Brain 123 (7), 1293–1326.

Gazzaniga, M.S., Holtzman, J.D., Smylie, C.S., 1987. Speech without conscious awareness. Neurology 37 (4). 682–682

Hofer, S., Frahm, J., 2006. Topography of the human corpus callosum revisited-comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. Neuroimage 32 (3), 989–994.

Hofer, S., Merboldt, K.-D., Tammer, R., Frahm, J., 2008. Rhesus monkey and human share a similar topography of the corpus callosum as revealed by diffusion tensor MRI in vivo. Cerebral cortex 18 (5), 1079–1084.

Honey, C.J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J.-P., Meuli, R., Hagmann, P., 2009. Predicting human resting-state functional connectivity from structural connectivity. Proceedings of the National Academy of Sciences 106 (6), 2035–2040.

Hung, S.-C., Lee, C.-C., Chen, H.-H., Chen, C., Wu, H.-M., Lin, C.-P., Peng, S.-J., 2019. Early recovery of interhemispheric functional connectivity after corpus callosotomy. Epilepsia 60 (6), 1126–1136.

Hutchison, R.M., Womelsdorf, T., Allen, E.A., Bandettini, P.A., Calhoun, V.D., Corbetta, M., Della Penna, S., Duyn, J.H., Glover, G.H., Gonzalez-Castillo, J., et al., 2013. Dynamic functional connectivity: promise, issues, and interpretations. Neuroimage 80, 360–378.

Jeeves, M.A., Temple, C.M., 1987. A further study of language function in callosal agenesis. Brain Lang 32 (2), 325–335.

Karahanoğlu, F.I., Caballero-Gaudes, C., Lazeyras, F., Van De Ville, D., 2013. Total activation: fMRI deconvolution through spatio-temporal regularization. Neuroimage 73, 121–134.

Karahanoğlu, F.I., Van De Ville, D., 2015. Transient brain activity disentangles fMRI resting-state dynamics in terms of spatially and temporally overlapping networks. Nat Commun 6 (1), 1–10.

Karahanoğlu, F.I., Van De Ville, D., 2017. Dynamics of large-scale fMRI networks: deconstruct brain activity to build better models of brain function. Current Opinion in Biomedical Engineering 3, 28–36.

Karolis, V.R., Corbetta, M., De Schotten, M.T., 2019. The architecture of functional lateralisation and its relationship to callosal connectivity in the human brain. Nat Commun 10 (1), 1–9.

Kennard, M.A., 1938. Reorganization of motor function in the cerebral cortex of monkeys deprived of motor and premotor areas in infancy. J. Neurophysiol. 1 (6), 477–496.

Kirsch, V., Boegle, R., Keeser, D., Kierig, E., Ertl-Wagner, B., Brandt, T., Dieterich, M., 2018. Handedness-dependent functional organizational patterns within the bilateral vestibular cortical network revealed by fMRI connectivity based parcellation. Neuroimage 178, 224–237.

Klein, A., Andersson, J., Ardekani, B.A., Ashburner, J., Avants, B., Chiang, M.C., Christensen, G.E., Collins, D.L., Gee, J., Hellier, P., Song, J.H., Jenkinson, M., Lepage, C., Rueckert, D., Thompson, P., Vercauteren, T., Woods, R.P., Mann, J.J., Parsey, R.V., 2009. Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. Neuroimage 46 (3), 786–802. doi:10.1016/j.neuroimage.2008.12.037.

Koch, M.A., Norris, D.G., Hund-Georgiadis, M., 2002. An investigation of functional and anatomical connectivity using magnetic resonance imaging. Neuroimage 16 (1), 241–250.

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.

Leonardi, N., Richiardi, J., Gschwind, M., Simioni, S., Annoni, J.-M., Schluep, M., Vuilleumier, P., Van De Ville, D., 2013. Principal components of functional connectivity: a new approach to study dynamic brain connectivity during rest. Neuroimage 83, 937–950.

Mancuso, L., Uddin, L.Q., Nani, A., Costa, T., Cauda, F., 2019. Brain functional connectivity in individuals with callosotomy and agenesis of the corpus callosum: a systematic review. Neuroscience & Biobehavioral Reviews.

Mazoyer, B., Zago, L., Jobard, G., Crivello, F., Joliot, M., Perchey, G., Mellet, E., Petit, L., Tzourio-Mazoyer, N., 2014. Gaussian mixture modeling of hemispheric lateralization for language in a large sample of healthy individuals balanced for handedness. PLoS ONE 9 (6), e101165.

Monti, S., Tamayo, P., Mesirov, J., Golub, T., 2003. Consensus clustering: a resampling-based method for class discovery and visualization of gene expression microarray data. Mach Learn 52 (1–2), 91–118.

Owen, J.P., Li, Y.-O., Yang, F.G., Shetty, C., Bukshpun, P., Vora, S., Wakahiro, M., Hinkley, L.B.N., Nagarajan, S.S., Sherr, E.H., et al., 2013. Resting-state networks and the functional connectome of the human brain in agenesis of the corpus callosum. Brain Connect 3 (6), 547–562.

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.

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59 (3), 2142–2154.

Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage 84, 320–341.

Preti, M.G., Bolton, T.A.W., Van De Ville, D., 2017. The dynamic functional connectome: state-of-the-art and perspectives. Neuroimage 160, 41–54.

Preti, M.G., Van De Ville, D., 2017. Dynamics of functional connectivity at high spatial resolution reveal long-range interactions and fine-scale organization. Sci Rep 7 (1), 1–12.

Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52 (3), 1059–1069.

Savazzi, S., Fabri, M., Rubboli, G., Paggi, A., Tassinari, C.A., Marzi, C.A., 2007. Interhemispheric transfer following callosotomy in humans: role of the superior colliculus. Neuropsychologia 45 (11), 2417–2427.

Shi, M., Freitas, L.G.A., Spencer-Smith, M.M., Kebets, V., Anderson, V., McIlroy, A., Wood, A.G., Leventer, R.J., Van De Ville, D., Siffredi, V., 2021. Intra-and inter-hemispheric structural connectome in agenesis of the corpus callosum. NeuroImage: Clinical 102709.

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.

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.

Siffredi, V., Preti, M.G., Kebets, V., Obertino, S., Leventer, R.J., McIlroy, A., Wood, A.G., Anderson, V., Spencer-Smith, M.M., Van De Ville, D., 2021. Structural neuroplastic responses preserve functional connectivity and neurobehavioural outcomes in children born without corpus callosum. Cerebral Cortex 31 (2), 1227–1239.

Siffredi, V., Preti, M.G., Obertino, S., Leventer, R.J., Wood, A.G., McIlroy, A., Anderson, V., Spencer-Smith, M.M., Van De Ville, D., 2021. Revisiting brain rewiring and plasticity in children born without corpus callosum. Dev Sci.

Siffredi, V., Wood, A.G., Leventer, R.J., Vaessen, M., McIlroy, A., Anderson, V., Vuilleumier, P., Spencer-Smith, M.M., 2019. Anterior and posterior commissures in agenesis of the corpus callosum: alternative pathways for attention processes? Cortex 121, 454–467.

Sperry, R.W., 1984. Consciousness, personal identity and the divided brain. Neuropsychologia.
Tarun, A., Behjat, H., Bolton, T., Abramian, D., Van De Ville, D., 2020. Structural mediation of human brain activity revealed by white-matter interpolation of fMRI. Neuroimage 213, 116718.
Team, R. C., et al., 2013. R: A language and environment for statistical computing.
Tovar-Moll, F., Monteiro, M., Andrade, J., Bramati, I.E., Vianna-Barbosa, R., Marins, T., Rodrigues, E., Dantas, N., Behrens, T.E.J., de Oliveira-Souza, R., et al., 2014. Structural and functional brain rewiring clarifies preserved interhemispheric transfer in humans born without the corpus callosum. Proceedings of the National Academy of Sciences 111 (21), 7843–7848.
Tyszka, J.M., Kennedy, D.P., Adolphs, R., Paul, L.K., 2011. Intact bilateral resting-state networks in the absence of the corpus callosum. J. Neurosci. 31 (42), 15154–15162.
Uddin, L.Q., Mooshagian, E., Zaidel, E., Scheres, A., Margulies, D.S., Kelly, A.M.C., Shehzad, Z., Adelstein, J.S., Castellanos, F.X., Biswal, B.B., et al., 2008. Residual functional connectivity in the split-brain revealed with resting-state fMRI. Neuroreport 19 (7), 703.
Zöller, D.M., Bolton, T.A.W., Karahanoğlu, F.I., Eliez, S., Schaer, M., Van De Ville, D., 2018. Robust recovery of temporal overlap between network activity using transient-informed spatio-temporal regression. IEEE Trans Med Imaging 38 (1), 291–302.
Zöller, D., Sandini, C., Karahanoğlu, F.I., Padula, M.C., Schaer, M., Eliez, S., Van De Ville, D., 2019. Large-scale brain network dynamics provide a measure of psychosis and anxiety in 22q11. 2 deletion syndrome. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 4 (10), 881–892.