

# Independent component analysis of resting-state fMRI reveals diminished functional connectivity in callosal dysgenesis

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## Introduction

The corpus callosum is the major white matter tract connecting the left and right cerebral hemispheres. Using seed voxel correlation analysis of resting state fMRI in three patients with agenesis of the corpus callosum (AgCC), it has been shown that there is diminished interhemispheric functional connectivity (FC) in motor and auditory cortex compared to normal controls [1]. However, the FC of intrinsically connected cortical networks has not previously been systematically investigated throughout the brain in AgCC. In this work, we perform a data-driven whole-brain analysis of resting state fMRI using independent component analysis (ICA) in a much larger sample of patients with partial or complete AgCC in order to determine which resting state networks have the greatest alterations in FC relative to controls. We hypothesize that the most highly interconnected cortical regions such as the precuneus and posterior cingulate cortex, which are the "hubs" of the default mode network (DMN), will be among the areas with the most reduced FC. The results of the data-driven ICA analysis were verified using hypothesis-driven seed voxel correlation analysis.

## Methods

**Subjects:** The 12 patients consisted of 8 complete AgCC and 4 partial AgCC (mean age 27±10 years, 10 male, 7 right-handed, mean IQ 93±12), and there were 12 controls (mean age 30±10 years, 9 male, 12 right-handed, mean IQ 105±10). **Imaging:** 3T BOLD fMRI was acquired using a 2D gradient echo echoplanar acquisition with FOV 22x22 cm, 64x64 matrix, 4 mm slices with no gaps, and TR of 2 sec and TE of 28 msec. After 10 dummy brain volumes to reach equilibrium magnetization, two hundred (T=200) brain volumes were collected with eyes closed to minimize exogenous visual activation (total 7 minutes scan time). **Preprocessing:** Data preprocessing included motion correction, spatial normalization, and smoothing using the functions provided in the FMRIB FSL toolbox [2]. For seed voxel correlation analysis, high-pass filtering and regression of the white matter and CSF signals was performed on the voxel-wise time series in the fMRI data. For Group ICA, each fMRI volume is registered to the subject's 3D T1-weighted image volume and then to the MNI152 2mm template by FSL FLIRT. **Extraction of resting-state networks:** The Group ICA of fMRI toolbox (GIFT) [3] was used to extract 25 independent components (ICs). After ICA decomposition on group-aggregated data, GIFT reconstructs the ICs estimated for each individual subject, hence, making it convenient to perform inter-group comparisons on the spatial maps. Eleven ICs were manually selected as representing intrinsically connected cortical networks by their localized spatial connectivity patterns with reference to reported resting state networks [4]. Voxel-wise nonparametric permutation testing using the "randomise" function in FSL was employed for statistical inference on the FC maps, with threshold-free cluster enhancement [5] to control for multiple voxel-wise comparisons. **Voxel based morphometry (VBM):** To exclude the possibility that structural differences may account for the observed FC differences between the AgCC group and the normal group, we performed voxel based morphometry on the 3D T1-weighted images in SPM to determine group differences in tissue

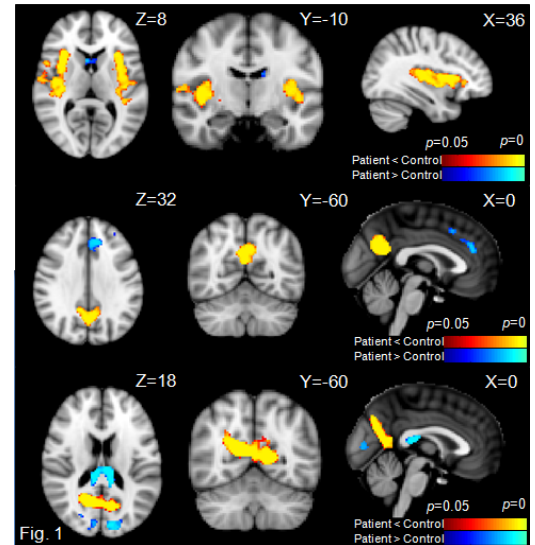
density. **Interhemispheric seed voxel correlation test:** To verify the difference of connectivity in the resting-state networks identified by Group ICA and permutation testing, we used spatial maps that show significant difference between AgCC patient and controls as the masks to extract the actual time series from the preprocessed fMRI data. The mean time series is calculated for the

masked regions in the right and the left hemisphere separately and correlation coefficients are calculated between the two mean time series. Therefore, for each network and subject, we get a correlation score for the interhemispheric FC. A two sample t-test is performed on the correlation scores between the patient group and control group of each network.

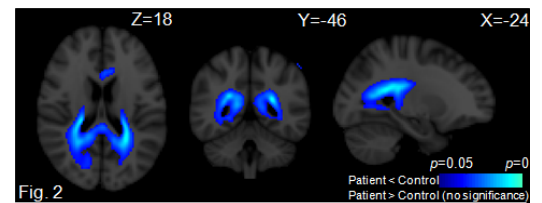
**RESULTS:** The 11 observed resting state networks included the default mode network, bilateral motor cortex and bilateral visual cortex, among others. Three of the ICs showed significant FC differences between AgCC and controls, as shown in the Group ICA results of Figure 1. The VBM results in Figure 2 demonstrate that the regions of greatest structural differences in AgCC vs controls are peritrial white matter areas that do not overlap with the cortical networks with reduced FC in AgCC. Table 1 provides FC values from the interhemispheric seed voxel correlation analysis, confirming the reduced interhemispheric FC of the 3 resting state networks identified from the data-driven Group ICA analysis.

**DISCUSSION** In this work, we perform the first exploratory whole-brain investigation of altered functional connectivity in AgCC using resting state fMRI. Two of the three cortical networks with significantly reduced FC localized to the precuneus and the posterior cingulate, which are the two most highly interconnected regions of the cerebral cortex and constitute the hubs of the default mode network [6]. The additional finding of strongly decreased FC of a bilateral insular/perisylvian network in AgCC may help explain the diminished pain sensitivity and altered emotional processing commonly found in these patients [7], since the insula is a limbic structure well known to be a central component of the "pain network". These initial observations demonstrate the great potential of resting state fMRI to reveal abnormal function in the malformed brain and thereby also help elucidate the function of the normal human brain.

**References and Acknowledgements:** [1] Quigley M et al., AJNR, 2003; 24:208–212. [2] [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl) [3] Calhoun VD et al., Hum. Brain Map, 2001; 14,140-151. [4] Damoiseaux, JS. et al., PNAS 2006; 103 (37) 13848-13853. [5] Smith SM, Nichols TE. Neuroimage 2009; 44:83-98. [6] Hagmann P et al., PLoS Biol 2008; 6:e159. [7] Moes P et al., Child Care Health Dev 2009; 35:656-72.



**Figure 1.** Three resting-state networks show significant group differences between AgCC and controls: insular/perisylvian (top), posterior cingulate (middle), and precuneus/posterior cingulate (bottom)



**Figure 2.** Voxel-based morphometry show decreased T1-weighted contrast in AgCC patients

**Table 1:** Comparison of interhemispheric functional connectivity in regions identified by ICA group comparison

Resting-State Network	AgCC	Normal	P-Value
Insular/ perisylvian	0.62	0.87	0.004
Posterior cingulate	0.76	0.89	0.01
Posterior cingulate and precuneus	0.74	0.88	0.07