Title: "How important is the corpus callosum in resting-state networks?"

Running Title:
Callosum and rsBOLD

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Summary (120 words, actual 112)

The human brain appears to have a reproducible set of intrinsic functional networks. Each network consists of several brain regions whose activity patterns are temporally correlated with one another when the individual is not doing any particular task. Most of these networks are bilaterally symmetric, therefore requiring some form of interhemispheric coordination. Evidence from individuals who had callosotomy and individuals born with callosal agenesis suggests that although the corpus callosum is heavily involved in the resting networks of healthy human brains, typical bilateral resting-state networks can also emerge in the absence of callosal connections. Understanding how and why this is possible will provide important insights into development and plasticity in brain function.

Article (1500 words, actual 1567)

Introduction

Resting-state functional magnetic resonance imaging (rs-fMRI) examines spontaneous, low frequency (<0.08 Hz) fluctuations in blood oxygenation level-dependent (BOLD) signal in the absence of a specific task. Temporal correlations between different brain regions in the resting-state BOLD (rsBOLD) signal are widely interpreted as an index of intrinsic functional brain connectivity at the neuronal level [1-3]. Interestingly, connectivity analyses of rsBOLD data reveal consistent and reproducible resting state networks (RSNs) in healthy humans with normal cognition [3-5]. These RSNs are, with few exceptions, bilaterally symmetric and show similarity to networks subserved by known white matter connections [6]. Moreover, homotopic regions (the equivalent region in the left and in the right hemisphere) have a much higher temporal rsBOLD correlation than that seen between heterotopic regions (different regions in left and right hemisphere) [7, 8]. If direct structural connections provide the necessary foundation for functional networks, then we would expect to find reduced interhemispheric functional connectivity, revealed as fewer or more asymmetric RSNs, in individuals who do not have the primary interhemispheric white matter tract -- the corpus callosum.

The human corpus callosum consists of ~190 million nerve fibers which primarily connect homotopic areas of the left and right hemispheres. In the following sections we review all of the current published information regarding rsBOLD in individuals who had an intact callosum that was surgically severed (“split-brain”) and individuals who never developed callosal connections at all (callosal agenesis).

Callosotomy

Surgical sectioning of the corpus callosum, callosotomy, is an intervention to address intractable epilepsy [9] .The callosotomy may have varying extent, sometimes severing all or part of the corpus callosum, and in some cases the sectioning extends to minor commissures (commissurotomy). Post-callosotomy “split-brain” patients offer unique insights into the callosum’s role in cognitive systems. To date within-subject comparison of pre-callosotomy and post-callosotomy rsBOLD activation patterns have been reported for 3 patients [10, 11] and rsBOLD has been examined in one patient who was at least 40 years post-callosotomy [12].

Taken together, these studies indicate that the impact of callosotomy on interhemispheric functional connectivity may change across time following surgery.

A pediatric case study reported dramatic reduction of functional connectivity between homotopic cortical regions following callosotomy [10]. The 6-year-old child underwent surgical severing of the corpus callosum and dorsal hippocampal commissure, leaving the anterior and posterior commissures intact. The child was anesthetized during BOLD fMRI, which was conducted immediately prior to and within 5 days following surgery. Effective connectivity was determined by correlating activity in 12-mm regions of interest (ROIs) with all other voxels. The ROIs were selected in regions commonly activated in rsBOLD.

Since the follow-up MRI was conducted within 5 days of surgery in this case, the brain had limited time to make significant adaptations and the resulting rsBOLD activity reflected only the acute impact of the callosotomy. Shared variance between left & right cortex and between left and right thalami diminished by 88.5% and 54% respectively. Callosotomy had the least impact on temporal BOLD correlations between cortex and ipsilateral thalamus, with a somewhat stronger reduction in correlation between cortex and contralateral thalamus.

ROI-analyses revealed the variable impact of callosotomy, with marked decreases in functional connectivity of dorsal attention (FEF), default (LP), and primary visual (V1) systems and relative sparing of interhemispheric connectivity of the somatomotor (hand region) and rostral temporal cortices (including memory systems). In this case, the anterior commissure was left intact, thus allowing its extensive projections to the rostral temporal cortex to maintain interhemispheric connectivity in that region. As a result, the reduction of interhemispheric connectivity post-callosotomy was minimal in rostral regions of the temporal lobes and became more pronounced moving caudally.

In contrast to the regionally specific loss of interhemispheric connectivity reported immediately post-callosotomy [10], resting interhemispheric correlation was relatively preserved in two adult callosotomy patients tested both prior to and 4-months following surgery [11]. One patient had a complete callosotomy and one had severing of the anterior two-thirds of the callosum. Although both participants exhibited attenuated levels of interhemispheric coherent activity following surgery, they retained the typical pattern of greater interhemispheric coherence during sleep relative to when awake. The authors suggest that thalamo-cortical circuits facilitate the shift to greater interhemispheric coherence during sleep.

Likewise, intact interhemispheric functional connectivity was found in a 74-year-old female, who had received a complete commissurotomy at least 40-years prior to rsBOLD testing [12]. Two common bilateral RSNs were identified by spatial independent component analysis and left hemisphere ROIs selected from within these RSNs exhibited strong interhemispheric correlation. Neurological complications precluded interpretation of connectivity from right hemisphere ROIs. Unlike the callosotomy surgeries reported above, this individual retained no other commissures that could account for the residual interhemispheric connectivity.

Unfortunately, with only these few reported case studies and no longitudinal data tracking resting state activity from immediately post-callosotomy to many years thereafter, we can offer only a few tentative hypotheses: a) the callosum plays an important role in resting state interhemispheric correlation which is evidenced by a notable reduction within days following callosotomy (even when anterior and posterior commissures remain intact), b) when the

callosum is severed, the brain has a strong drive to re-establish bilateral resting state networks and does so over time, c) following callosotomy, the anterior commissure may facilitate interhemispheric connectivity of rostral temporal cortex and d) although attenuated following callosotomy, interhemispheric thalamo-cortical connectivity is less markedly impacted than cortical-cortical connectivity and may play an important role in the re-establishment of bilateral resting state networks.

Agenesis of the Corpus Callosum

Agenesis of the corpus callosum (AgCC), in contrast to "split-brain" callosotomy, is a congenital condition in which callosal fibers fail to migrate across the midline to form interhemispheric connections during prenatal development. If the callosum does not form *in utero* (complete AgCC) or only makes a fraction of the typical connections (partial AgCC), these connections will never be made later in life. For more information on this condition, see [13].

To date, two studies have reported resting state functional connectivity in AgCC [14, 15]; however, only one of these examined RSNs. The first study included three individuals with complete AgCC and a single neurotypical control [14] and restricted the analysis to functional connectivity from the sensory-motor and auditory cortices. They concluded that resting-state functional connectivity in the auditory and motor cortices was significantly diminished in AgCC. Although this case study is a valuable contribution to the literature on functional connectivity in callosal agenesis, generalization of these results is limited by methodology: data was acquired at relatively low spatial resolution and field strength, did not examine connectivity across the entire cortex and excluded many regions that are activated in RSNs of healthy humans.

Recently, in a more comprehensive study of this population, we reported largely intact RSNs and homotopic connectivity in eight adults with complete AgCC and normal intelligence, as compared with eight healthy matched controls [15]. This study included three main analyses: atlas-based BOLD temporal correlation to test homotopic functional connectivity, spatial independent component analysis (ICA) to explore functional networks using a data-driven approach, and ICA-based interhemispheric correlation analysis. Using atlas-based regions-of-interest covering the entire cortical surface, we found equivalently strong homotopic BOLD correlations in both the control and AgCC groups. Out of 48 homotopic pairings, only the intracalcarine cortex, precuneus and cuneal cortex (Harvard-Oxford atlas labels 23, 30 and 31) showed significant (uncorrected) group differences. Seventeen of 20 neuronal independent components (ICs) classified within the AgCC group were matched by spatial correlation with ICs from the control group. No significant (corrected) group difference in interhemispheric BOLD temporal correlations was observed within regions defined by spatial ICs.

In summary, our sample of eight adults with complete AgCC did not differ from matched neurotypical controls in terms of interhemispheric BOLD correlations, number or symmetry of neuronal ICs. These results argue that a normal complement of resting-state networks and intact functional coupling between the hemispheres can emerge in the absence of the corpus callosum.

Conclusion

Resting-state functional brain networks derived from BOLD fMRI data are known to bear important relationships to cognition: they are disrupted in neurodegenerative diseases and

dementia [16], and they correlate with IQ in healthy adults [17]. Bilateral RSNs are known to be present in infancy [18] and even at birth [19] when the corpus callosum has its adult complement of axons but is not yet fully myelinated [20], and show progressive changes throughout childhood [21] concomitant with changes in structural connectivity [22] and cognitive development [23]. All of these findings suggest that, just as structural connectivity forms the normal basis for functional networks, the latter form the basis for emergence of cognition. However, studies of callosal disconnection syndromes indicate that direct structural connectivity is not a strict determinant of the development of functional connectivity in human brains.

Future Directions

With respect to interhemispheric functional connectivity, including bilateral RSNs, we believe that the findings described above support two key hypotheses: a) the corpus callosum is heavily involved in interhemispheric functional connectivity in intact brains and b) when a brain loses or never develops callosal connections, it develops alternative routes to maintain bilateral RSNs and interhemispheric functional connections. Data from callosotomy patients suggests that minor commissures and thalamo-cortical pathways may play a key role in this adaptation. Identifying these compensatory systems in callosotomy patients and individuals with AgCC may provide unique insights regarding the compensatory drive toward specific functional systems in the human brain, as well as the functional plasticity of interhemispheric networks both during development and following brain injury.

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