NeuroImage 70 (2013) 340–355

Contents lists available at SciVerse ScienceDirect

NeuroImage

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

The structural connectome of the human brain in agenesis of the corpus callosum

Julia P. Owen [a,b], Yi-Ou Li [a], Etay Ziv [a], Zoe Strominger [c], Jacquelyn Gold [c], Polina Bukhpun [c], Mari Wakahiro [c], Eric J. Friedman [d], Elliott H. Sherr [c], Pratik Mukherjee [a,b,*]

[a] Department of Radiology & Biomedical Imaging, University of California, San Francisco, CA, USA
[b] Department of Bioengineering & Therapeutic Sciences, University of California, San Francisco, CA, USA
[c] Department of Neurology, University of California, San Francisco, CA, USA
[d] International Computer Science Institute, University of California, Berkeley, CA, USA

ARTICLE INFO

Article history:
Accepted 17 December 2012
Available online 23 December 2012

Keywords:
Structural connectivity
Diffusion-weighted imaging
Tractography
Congenital brain malformation
Brain development

ABSTRACT

Adopting a network perspective, the structural connectome reveals the large-scale white matter connectivity of the human brain, yielding insights into cerebral organization otherwise inaccessible to researchers and clinicians. Connectomics has great potential for elucidating abnormal connectivity in congenital brain malformations, especially axonal pathfinding disorders. Agenesis of the corpus callosum (AgCC) is one of the most common brain malformations and can also be considered a prototypical genetic disorder of axonal guidance in humans. In this exploratory study, the structural connectome of AgCC is mapped and compared to that of the normal human brain. Multiple levels of granularity of the AgCC connectome are investigated, including summary network metrics, modularity analysis, and network consistency measures, with comparison to the normal structural connectome after simulated removal of all callosal connections ("virtual callostomy"). These investigations reveal four major findings. First, global connectivity is abnormally reduced in AgCC, but local connectivity is increased. Second, the network topology of AgCC is more variable than that of the normal human connectome, contradicting the predictions of the virtual callostomy model. Third, modularity analysis reveals that many of the tracts that comprise the structural core of the cerebral cortex have relatively weak connectivity in AgCC, especially the cingulate bundles bilaterally. Finally, virtual lesions of the Probst bundles in the AgCC connectome demonstrate that there is consistency across subjects in many of the connections generated by these ectopic white matter tracts, and that they are a mixture of cortical and subcortical fibers. These results go beyond prior diffusion tractography studies to provide a systems-level perspective on anomalous connectivity in AgCC. Furthermore, this work offers a proof of principle for the utility of the connectome framework in neurodevelopmental disorders.

Introduction

Recent advances in imaging technology, computational power and mathematical tools for network analysis have enabled the investigation of brain organization at the systems level, creating a new field of neuroscience known as "MR connectomics." The structural connectome framework in particular provides a potent method for assessing the global white matter connectivity of the human brain (Sporns et al., 2005). The application of connectomics to healthy volunteers has elucidated the large-scale topology of the normal adult brain (Bullmore and Sporns, 2009; Gong et al., 2009; Hagmann et al., 2007; Hagmann et al., 2010; Iturria-Medina et al., 2007; Li et al., 2012a,b; Sporns, 2011; van den Heuvel and Sporns, 2011). There are consistent findings across these publications, including the presence of highly connected brain regions, referred to as hubs. Building on this initial success, structural connectomics is now being applied to human brain development (Fan et al., 2011; Hagmann et al., 2012; Tymofiyeva et al., 2012; Yan et al., 2011; Yap et al., 2011) and to neurological and psychiatric disorders (Alstott et al., 2009; Irimia et al., 2012; Shu et al., 2009; Verstraete et al., 2011). Borrowing techniques from graph theory, summary metrics can be calculated to quantify key characteristics of the networks (Rubinov and Sporns, 2010). Community detection or modularity analysis has also been applied to the structural connectome to find groups of nodes that

Abbreviations: AMG, amygdala; STS, bank of superior temporal sulcus; CAC, caudal anterior cingulate; CMF, caudal medial frontal; CAU, caudate; CUN, cuneus; ENT, entorhinal; FTP, frontal temporal pole; FUS, fusiform; HIP, hippocampus; IPT, inferior parietal sulcus; INS, insula; ISC, isthmus cingulate; LOC, lateral occipital; LOF, lateral orbital frontal; LIN, lingual; MOF, medial orbital frontal; MTP, medial temporal; ACB, nucleus accumbens; PRC, paracentral; PHP, pars hippocampus; POP, pars opercularis; POB, pars orbitalis; PTR, pars triangularis; PEC, pericalcarine; POC, postcentral; PCC, posterior cingulate; PRC, precentral; PCN, precuneus; PUT, putamen; RAC, rostral anterior cingulate; RMF, rostral medial frontal; SFT, superior frontal; SPT, superior parietal; STP, superior temporal; SMG, supramarginal gyrus; TPP, temporal pole; THL, thalamus; TTP, transverse temporal.

* Corresponding author at: Center for Molecular and Functional Imaging,Department of Radiology and Biomedical Imaging, University of California, San Francisco, UCSF Box 0946, 185 Berry Street, Suite 350, San Francisco, CA 94107, USA. Fax: +415 353 8593
E-mail address: pratik.mukherjee@ucsf.edu (P. Mukherjee).

1053-8119/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2012.12.031

are strongly interconnected and therefore likely to be functionally integrated as well (Hagmann et al., 2008). These analysis methods reduce the dimensionality of the human connectome and enable statistical inferences to be more specific and better powered (Meskaldji et al., 2011).

The connectome framework is ideal for studying congenital brain malformations, especially disorders of axonal pathfinding leading to aberrant structural connectivity (Engle, 2010; Nugent et al., 2012; Wahl et al., 2010). Agenesis of the corpus callosum (AgCC) is one of the most common human brain malformations, occurring in at least 1 in 4000 live births (Glass et al., 2008; Wang et al., 2004) and in 3–5% of individuals assessed for neurodevelopmental disorders (Bodensteiner et al., 1994; Jeret et al., 1985). AgCC can also be considered a prototypical human disorder of axon guidance, one in which fibers that would normally have crossed the midline as part of the corpus callosum instead form Probst bundles, large white matter tracts that course anterior-posterior parallel to the interhemispheric fissure within each cerebral hemisphere (Paul, 2011; Paul et al., 2007). These gross anatomical abnormalities are easily diagnosed with conventional MRI, but macrostructural images may only scratch the surface of the extensive white matter reorganization in axonal pathfinding disorders. Diffusion MR tractography studies have shown some alterations of white matter connectivity in AgCC (Lee et al., 2004, 2005; Nakata et al., 2009; Tovar-Moll et al., 2007; Wahl et al., 2009), but, to our knowledge, there has not been a systems-level investigation of connectivity in the acallosal brain. MR connectomics applied to AgCC may better characterize white matter abnormalities and potentially discover new anatomically subtle but functionally significant disruptions of connectivity that accompany this radiologically emblematic malformation. This could also serve as proof of principle for the utility of connectomics in more common neurodevelopmental disorders in which the underlying pathophysiological mechanism is also thought to be a "connectopathy," such as autism, dyslexia and schizophrenia (Seung, 2012).

In this paper, multiple levels of granularity of the connectome are investigated. The most granular level is analyzing the individual edges of the graphs. Next, sets of edges or modules are tested for consistency and for statistical differences in connection strengths within the modules between the AgCC and control cohorts. At a larger scale, graph theoretic metrics such as degree are used to distinguish hub nodes from less-connected nodes. Finally, summary metrics, such as mean degree, characteristic path length and mean clustering coefficient, are used to characterize the entire network and provide tractable measures on which to perform statistics to compare whole connectomes.

These systems-level computational approaches are particularly powerful for exploring the importance of missing tracts or ectopic tracts, which are the hallmarks of axonal guidance disorders, through studying the effect of simulated lesions on the whole-brain network. Here, a "virtual callosotomy" is performed on the healthy control brains, creating control connectomes without callosal connections. Using the virtual callostomy approach, we can assess the changes in the connectome of the normal brain due to the absence of interhemispheric callosal connections, and use these findings to generate specific hypotheses for the AgCC connectome. Similarly, a "virtual Probstotomy" is performed on the AgCC cohort to demonstrate the contribution of the Probst bundles to the AgCC connectome.

Using a multi-scale connectomics analysis, we test three central hypotheses about the altered connectivity of AgCC subjects, garnered from the comparison of the controls to the virtual callosotomy case. First, we hypothesize that the AgCC brain has reduced long-range or global connectivity compared to the controls but increased short-range or local connectivity. Second, we expect to find that the AgCC connectome is less variable compared to the controls. Third, we postulate that the modular organization of the AgCC brain will not be altered due to the absence of the callosal fibers. While we do not assume that the virtual callosotomy will exactly replicate the AgCC brain, we do expect any deviations to provide insight into the structural alterations of AgCC beyond the lack of callosal connections.

Methods

Subjects

Written informed consent was obtained from all participants and/or their legal guardians under a study protocol approved by the institutional review board at our medical center. Seven subjects with AgCC (4 male, 3 female; mean age 24.3 ± 14.2, 5 right-handed) and 11 healthy volunteers (6 male, 5 female; mean age 24.9 ± 9.1, 11 right-handed) were included in this study. Full-scale IQ was obtained from the AgCC cohort (mean FS-IQ 102 ± 14) and control subjects (mean FS-IQ 109 ± 17). A two-sample Student's *t*-test revealed that there was no significant group difference in age ($p = 0.92$) or IQ ($p = 0.28$) and a two-sample Fisher's exact test showed that there was no significant group difference in handedness ($p = 0.14$) or gender ($p = 0.99$).

Image acquisition

All MR imaging was performed on a 3 T EXCITE MR scanner (GE Healthcare, Waukesha, WI, USA) using an 8-channel head phased-array radio-frequency head coil. High-resolution structural MR imaging of the brain was performed with an axial 3D inversion recovery fast spoiled gradient-recalled-echo T1-weighted sequence (TE = 1.5 ms, TR = 6.3 ms, TI = 400 ms, flip angle of 15°) with a 230 mm FOV, and one hundred fifty-six 1.0 mm contiguous partitions at a 256×256 matrix. Structural MR images of all subjects were interpreted by an attending neuroradiologist certified by the American Board of Radiology.

Whole-brain diffusion was performed with a multislice 2D single-shot spin-echo echo-planar sequence with 55 diffusion-encoding directions, the array spatial sensitivity encoding technique for parallel imaging with a reduction factor of 2, a diffusion-weighting strength of $b = 1000$ s/mm^2; TR/TE = 14,000/63 ms; NEX = 1; interleaved 1.8-mm axial sections with no gap; in-plane resolution of 1.8×1.8 mm with a 128×128 matrix; and a field of view of 230 mm. An additional image set was acquired with minimal diffusion weighting ($b = 10$ s/mm^2). The total acquisition time for diffusion imaging was 13 minutes.

Data pre-processing

After non-brain tissue was removed using the Brain Extraction Tool (BET; http://www.fmrib.ox.ac.uk/analysis/research/bet/) with a fractional intensity threshold of 0.3 (Smith, 2002), the diffusion-weighted images were corrected for motion and eddy currents using FMRIB's Linear Image Registration Tool (FLIRT; www.fmrib.ox.ac.uk/fsl/flirt) with 12-parameter linear image registration (Jenkinson et al., 2002). All diffusion-weighted images were registered to the reference $b = 10$ s/mm^2 image. From the transformation of every diffusion-weighted volume to the $b = 10$ s/mm^2 image, a scalar was derived, which reflects the amount each volume must be corrected. The mean of the parameter across volumes for each subject was used as the motion correction parameter in the *Data Quality Assurance* analysis. This procedure is described in a FMRIB technical report (Jenkinson, 1999). The fractional anisotropy (FA) image was calculated using FSL's DTIFIT.

Cortical parcellation

The T1-weighted MR images were automatically segmented using FreeSurfer 5.1.0 (Fischl et al., 2004) with the default settings of recon-all, resulting in 68 cortical regions, 34 per hemisphere, and 14 subcortical regions, 7 per hemisphere. These 82 regions represent