NeuroImage: Clinical 8 (2015) 483–492

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Abnormal structural connectivity in the brain networks of children with hydrocephalus

Weihong Yuan[a,d,*], Scott K. Holland[a,d], Joshua S. Shimony[e], Mekibib Altaye[b,d], Francesco T. Mangano[c,d], David D. Limbrick[f], Blaise V. Jones[a,d], Tiffany Nash[a], Akila Rajagopal[a], Sarah Simpson[a], Dustin Ragan[f], Robert C. McKinstry[e]

[a]Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[b]Div. of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[c]Division of Pediatric Neurosurgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[d]University of Cincinnati College of Medicine, Cincinnati, OH, USA
[e]Mallinckrodt Institute of Radiology, Washington University School of Medicine, Saint Louis, MO, USA
[f]Department of Neurological Surgery, Washington University School of Medicine, Saint Louis, MO, USA

ARTICLE INFO

Article history:
Received 30 December 2014
Received in revised form 18 March 2015
Accepted 26 April 2015
Available online 29 April 2015

Key words:
Graph theoretical analysis
Network
Pediatric hydrocephalus
Small-worldness

ABSTRACT

Increased intracranial pressure and ventriculomegaly in children with hydrocephalus are known to have adverse effects on white matter structure. This study seeks to investigate the impact of hydrocephalus on topological features of brain networks in children. The goal was to investigate structural network connectivity, at both global and regional levels, in the brains in children with hydrocephalus using graph theory analysis and diffusion tensor tractography. Three groups of children were included in the study (29 normally developing controls, 9 preoperative hydrocephalus patients, and 17 postoperative hydrocephalus patients). Graph theory analysis was applied to calculate the global network measures including small-worldness, normalized clustering coefficients, normalized characteristic path length, global efficiency, and modularity. Abnormalities in regional network parameters, including nodal degree, local efficiency, clustering coefficient, and betweenness centrality, were also compared between the two patients groups (separately) and the controls using two tailed t-test at significance level of $p < 0.05$ (corrected for multiple comparison). Children with hydrocephalus in both the preoperative and postoperative groups were found to have significantly lower small-worldness and lower normalized clustering coefficient than controls. Children with hydrocephalus in the postoperative group were also found to have significantly lower normalized characteristic path length and lower modularity. At regional level, significant group differences (or differences at trend level) in regional network measures were found between hydrocephalus patients and the controls in a series of brain regions including the medial occipital gyrus, medial frontal gyrus, thalamus, cingulate gyrus, lingual gyrus, rectal gyrus, caudate, cuneus, and insular. Our data showed that structural connectivity analysis using graph theory and diffusion tensor tractography is sensitive to detect abnormalities of brain network connectivity associated with hydrocephalus at both global and regional levels, thus providing a new avenue for potential diagnosis and prognosis tool for children with hydrocephalus.

1. Introduction

Normal brain function requires the integrity of neuronal function and connectivity, globally and regionally. In HCP, data from both human research and experimental research have suggested that a wide range of WM networks connecting various functionally important cortical and subcortical regions are primary targets for disruption due to enlarged ventricles and/or increased intracranial pressure (Assaf et al., 2006; Hassan et al., 2008; Yuan et al., 2009; Yuan et al., 2010; Scheel et al., 2012; Ginat et al., 2013; Yuan et al., 2013). Although surgery can significantly reduce the mortality and morbidity, HCP remains as an incurable lifelong disorder (Mataro et al., 2001). The damage to neuroanatomy sustained prior to the surgical treatment may remain or continue to progress after the surgery, leading to long term behavioral and neuropsychological deficits in visuospatial skills, visuomotor skills, and a series of other important neurocognitive domains (Erickson et al., 2001; Mataro et al., 2001; Frank et al., 2003; Bakar et al., 2009).

Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; GM, gray matter; HCP, hydrocephalus; ROI, region of interest; WM, white matter.

* Corresponding author at: Pediatric Neuroimaging Research Consortium, Department of Radiology, Cincinnati Children's Hospital, 3333 Burnet Avenue, ML 5033, Cincinnati, OH 45229, USA. Tel.: +1 513 636 2864; fax: +1 513 636 3754.
E-mail address: Weihong.Yuan@cchmc.org (W. Yuan).

http://dx.doi.org/10.1016/j.nicl.2015.04.015

DTI is an advanced neuroimaging technique that can measure in vivo WM structural integrity (Basser and Jones, 2002; Beaulieu, 2002). A growing body of literature has shown the success of DTI in investigating WM structural abnormality in pediatric HCP (Assaf et al., 2006; Hassan et al., 2008; Yuan et al., 2009, 2013; Air et al., 2010; Jang and Kim, 2011; Sheel et al., 2012; Jiang et al., 2013; Rajigopal et al., 2013). A series of regions, e.g., corpus callosum and posterior internal capsule, have been reported to show different degrees and patterns of abnormality in the directionality as well as the magnitude of water diffusion parameters. In these studies, in order to extract DTI parameters, a predefined list of ROIs needs to be delineated based on the hypotheses of the study. However, this approach does not provide a global quantification for the integrity of the entire brain network, nor does it allow for detecting any abnormalities outside the hypothesized brain regions. Hydrocephalus, a neurological disorder with heterogeneous etiologies, often presents with regionally specific damage, and this damage is also expected to extend to wider areas throughout the brain. ROI-based DTI analysis alone is clearly not sufficient to meet all the challenges in studying this patient population.

In recent years, graph theory analysis has emerged as a promising tool that provides information on brain connectivity, structural and functional, at both global and regional levels (Rubinov and Sporns, 2010). The brain is modeled as a network composed of a number of nodes and edges connecting these nodes. The nodes and edges respectively represent individual gray matter regions responsible for various brain functions and white matter fibers responsible for transferring information among these regions. This method of graph theory analysis has been applied in characterizing the developmental trajectory of network connectivity as well as for investigating the disruption of network connectivity in various neurological disorders (Liu et al., 2008; Bernhardt et al., 2011; Kim et al., 2011; Shi et al., 2012; Ottet, 2013). So far, however, no study has used graph theory approach in the analysis of white matter integrity in hydrocephalus brain networks.

In the present study, graph theory is applied to analyze the structural connectivity based on DTI tractography in children with hydrocephalus. The hypothesis of the present study is that the brain network integrity is affected in hydrocephalus patients as reflected in the aberrant topological features at both the global and regional levels. More specifically, we aim to investigate whether brain networks in children with hydrocephalus exhibit small-world properties and to evaluate whether small-worldness, a parameter derived from the graph theoretical analysis, is a sensitive measure for detecting global network alteration in this patient population. Specifically, we hypothesize that the small-worldness, and other global network measures, including normalized clustering coefficient, normalized characteristic path length, global efficiency, and modularity, are abnormal in both hydrocephalus patient groups. In addition, we aim to assess abnormalities of regional network measures, including nodal degree, local efficiency, clustering coefficient, and betweenness centrality, in hydrocephalus patients at both pre-surgery and post-surgery in comparison to normal controls.

2. Materials and methods

2.1. Patients

This was a retrospective analysis with all the data selected from an ongoing prospective neuroimaging project of children with hydrocephalus before and within 1 year after CSF diversionary surgery. At the time of data analysis, 61 normal children and 58 children with hydrocephalus were recruited into the study. It was decided that we would need to (1) exclude datasets from children younger than 11 months because the image normalization did not generate consistent results due to the poor image contrast in very young children; and (2) exclude datasets that presented image artifact because of the programmable valves in the shunts. In addition, five participants (3 controls and two HCP patients) were initially eligible for the study but were also needed to be excluded due to excessive head motion ($n = 4$) or image distortion ($n = 1$). Combining these factors, three groups of children were included in the study: Group 1 were controls, $n = 29$, age range: 13.1–197.8 months, median age 48.7 months; Group 2 were preoperative (PreOp) HCP patients, $n = 9$, age range: 11.0–194.5 months, median age 38.5 months; and Group 3 were postoperative (PostOp) HCP patients, $n = 17$, age range: 12.0–207.2 months, median age 41.4 months. No statistically significant difference was found in age between the control group and either one of the two patient groups ($p > 0.1$). The demographic information for patients is included in Table 1.

All the participants were recruited from two hospitals, Cincinnati Children's Hospital (CCHMC) and St. Louis Children's Hospital (SLCH). The study was approved by the Institutional Review Board at both CCHMC and SLCH (Washington University). Families of participants gave written informed consent when enrolled into the study, and children older than 11 years of age provided written assent.

2.2. MRI/DTI data acquisition

DTI data were acquired on 1.5 Tesla scanners with a single-shot echo planner imaging sequence at either CCHMC (GE, Signa, GE Healthcare, Milwaukee, Wisconsin) or SLCH (Siemens Avanto, Erlangen, Germany). The sequence specifications were: TR/TE = 9400/93.2 ms; in-plan resolution = 2.5 × 2.5 mm; slice thickness = 2.5 mm; 15 non-colinear diffusion-weighted directions ($b = 1000$ s/mm^2); 1 vol of images with no diffusion sensitization; ASSET or IPAT factor = 2; number of average = 2. Site compatibility was established before the study started and the quality assurance procedures involving both MR phantom and traveling human subject "phantom" were followed rigorously as reported elsewhere (Yuan et al., 2011; Rajagopal et al., 2013; Yuan et al., 2013).

2.3. DTI data preprocessing and brain parcellation

The DTI data were corrected for head motion and eddy current artifact using Automated Image Registration, an affine transformation method as described by Woods et al. (1998a,b). The B-matrix was rotated when correcting for subject motion (Leeman and Jones, 2009). To address the recent concerns in the literature about the potential confounding effect of head motion on fiber tracking (Yendiki et al., 2013) and graph theory based connectivity analysis (Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012), any datasets that had translational motion that exceeded 1.5 mm and/or rotational motion that exceeded 1 degree were discarded from further analysis. The translation motion in a scan was defined as the median of the frame-by-frame translation values determined by the translation motion in the x, y and z directions. The rotation in a scan was defined as the median of the frame-by-frame rotation values determined as the average of three Euler angles. As described earlier, data of four participants (3 controls, 1 HCP patient) who were initially eligible were discarded because the head motion exceeded 1.5 mm of translation and/or 1 degree of rotation (average of the three Euler angles). In the three groups of participants that were included in the final analysis, no statistically significant difference was found in head motion between the controls and either of the two HCP patient groups.

The DTI metrics maps were calculated with standard technique (Basser and Pierpaoli, 1998). Large deformation diffeomorphic metric mapping, a non-linear transformation (Miller, 2005), was used to normalize the images to MNI space to register with the JHU-DTI-WMPM II atlas (Oishi et al., 2008; Oishi et al., 2009; Djamanakova et al., 2013). DTI maps with multiple contrasts (FA and b0) were used to provide complementary contrast in the normalization. Mask of ventricles in b0 maps was used for HCP patients to improve registration. All the results of the normalization were visually reviewed (W.Y) to confirm accuracy of the procedure (see example in Fig. 1). The parcellation of gray and