NeuroImage 82 (2013) 170–181

Contents lists available at ScienceDirect

NeuroImage

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

Digital reconstruction and morphometric analysis of human brain arterial vasculature from magnetic resonance angiography

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ARTICLE INFO

Article history:
Accepted 16 May 2013
Available online 28 May 2013

ABSTRACT

Characterization of the complex branching architecture of cerebral arteries across a representative sample of the human population is important for diagnosing, analyzing, and predicting pathological states. Brain arterial vasculature can be visualized by magnetic resonance angiography (MRA). However, most MRA studies are limited to qualitative assessments, partial morphometric analyses, individual (or small numbers of) subjects, proprietary datasets, or combinations of the above limitations. Neuroinformatics tools, developed for neuronal arbor analysis, were used to quantify vascular morphology from 3 T time-of-flight MRA high-resolution (620 μm isotropic) images collected in 61 healthy volunteers (36/25 F/M, average age = 31.2 ± 10.7, range = 19–64 years). We present in-depth morphometric analyses of the global and local anatomical features of these arbors. The overall structure and size of the vasculature did not significantly differ across genders, ages, or hemispheres. The total length of the three major arterial trees stemming from the circle of Willis (from smallest to largest: the posterior, anterior, and middle cerebral arteries; or PCAs, ACAs, and MCAs, respectively) followed an approximate 1:2:4 proportion. Arterial size co-varied across individuals: subjects with one artery longer than average tended to have all other arteries also longer than average. There was no net right–left difference across the population in any of the individual arteries, but ACAs were more lateralized than MCAs. MCAs, ACAs, and PCAs had similar branch-level properties such as bifurcation angles. Throughout the arterial vasculature, there were considerable differences between branch types: bifurcating branches were significantly shorter and straighter than terminating branches. Furthermore, the length and meandering of bifurcating branches increased with age and with path distance from the circle of Willis. All reconstructions are freely distributed through a public database to enable additional analyses and modeling (cng.gmu.edu/brava).

Introduction

Cerebrovascular disorders are the leading cause of death, devastating morbidity, and long-term disabilities in humans, worldwide. Individual and group variations in the neurovascular structure–function relationship have not yet been comprehensively investigated. Quantitative characterization of cerebrovascular architecture from modern magnetic resonance angiography (MRA) may lead to a better understanding of physiological function and pathological dysfunction of the cerebrovascular system. MRA is a non-invasive technique for three-dimensional visualization of cerebral arteries. It is based on the contrast between rapidly moving arterial blood and stationary tissues that surround the vessel. To date, most MRA studies have been limited to qualitative or semi-quantitative assessments (El-Barhoun et al., 2009), partial morphometric analyses (Bullitt et al., 2009; Chen et al., 2011), small numbers of subjects (Canham and Finlay, 2004), and proprietary datasets (Nowinski et al., 2009a). A more comprehensive structural characterization of the cerebral arterial tree can be achieved by reconstructing the vascular arborization into an explicit 3D representation (Bullitt et al., 2005; Passat et al., 2006). In addition to enabling extensive morphometric analysis, these reconstructions can be used for subject-specific assessment of individual risks of vascular malformation using fluid dynamics modeling (Cebral et al., 2003; Oshima et al., 2001). These approaches require specification of appropriate boundary conditions and constraints related to arterial branch geometry and bifurcation characteristics (Onate et al., 2000; Olufsen, 1999). However, the difficulties of manually reconstructing extensive vascular structure limited numerical simulations to synthetic arterial tree models (Bui et al., 2010;

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http://dx.doi.org/10.1016/j.neuroimage.2013.05.089

Dokoumetzidis and Macheras, 2003; Karch et al., 1999; Olufsen et al., 2000).

Here, we show that 3D reconstruction of the cerebral arterial vasculature can be achieved using existing methods originally developed for digital tracing and quantitative analysis of neuronal trees (Brown et al., 2005; Halavi et al., 2012; Scorcioni et al., 2008). Further, we demonstrate how the existing analysis methods can be used to study individual and population differences in cerebral vasculature at the level of the entire vasculature, specific arteries or single branches. Age-related changes, hemispheric lateralization, and gender-related difference in cerebral circulation may all be important risk factors in cerebrovascular disorders (Zanatta et al., 2012; Zurada et al., 2011). For instance, increase in tortuosity of right arterial trees during normal aging may have clinical implications (Zurada et al., 2010, 2011), while higher rate of subarachnoid hemorrhages in women may be caused by hormonal differences (Ghods et al., 2012).

This report provides the most extensive quantification to date of the global and local anatomical features of arterial vasculature, including size, symmetry, branching characteristics, bifurcation angles, and path meandering, for a representative sample of the normal human population. We reconstructed the entire cerebral arterial trees visible in the MRA images, including basilar and the internal carotid arteries that feed the circle of Willis (CoW) and the six major arteries stemming from CoW, including the middle, anterior, and posterior cerebral arteries (MCAs, ACAs, and PCAs, respectively). These six arteries were followed and reconstructed for ~300 mm from the CoW, through ~15 bifurcation points along the paths. We focused on morphological measures most relevant to common pathological conditions and least affected by potential imaging limitations. In addition to characterizing normative statistics for this representative population sample, we systematically compared arterial geometry between hemispheres, genders, and branch types; and among arteries, along the path, and across subject ages. Our analysis reproduced and extended previous knowledge of the human cerebrovascular architecture. In addition to the tools to reconstruct, visualize, and analyze the vascular arbors, the entire dataset is freely shared with the greater research community (http://cng.gmu.edu/brava).

Methods

Subjects and data acquisition

Imaging data were collected at the Research Imaging Institute, University of Texas Health Science Center at San Antonio, using a Siemens TRIO, 3 T scanner and 12-channel head coil. 61 healthy, right-handed participants (36/25 F/M, average age = 31.2 ± 10.7, range = 19–64 years) recruited as part of the International Consortium for Brain Mapping (ICBM: Mazziotta et al., 1995, 2001). Exclusion criteria included endocrinal, neurological (stroke, TIA and history of aneurysms), and psychiatric illnesses, and MRI counter-indications as detailed elsewhere (Kochunov et al., 2009a,b).

Magnetic resonance angiography

MRA data were collected using a 3D, spoiled, gradient echo time-of-flight (TOF) sequence (Huettel et al., 2004) with 620 μm isotropic resolution and the following control parameters: TE/TR/flip angle = 4.4 ms/24.0 ms/18°. 3D-TOF sequence collects spatially contiguous data by performing 3D encoding of the entire imaging volume (Bernstein et al., 2004). To reduce saturation of TOF effects, the data were collected as two overlapping 200 mm thick slabs aligned with AC–PC and full brain coverage. Head motion was suppressed using expandable foam and mechanical head-holder. Slab thickness and excitation angles were varied in two healthy volunteers to optimize digital reconstruction reliability. A file with the final parameters used in this study can be downloaded from the reconstruction database. The study design was evaluated and approved by the Institutional Review Board at the University of Texas Health Science Center in San Antonio and all subjects signed an informed consent form.

Digital reconstructions

Digital reconstructions of arterial trees from 3D, TOF MRA images were carried out by the same person using the freeware Neuron_Morpho plugin (personal.soton.ac.uk/dales/morpho; Brown et al., 2005) for ImageJ (imagej.nih.gov; Collins, 2007). The Neuron_Morpho functionality provides for tracing the spatial course of the six major cerebral arteries starting at the circle of Willis. The arterial tree was quantified as a series of interconnected tapering cylinders characterized by their 3D coordinates, diameter, and link to the previous node. The results were saved as ASCII files in the SWC format (Ascoli et al., 2001). The SWC format fully describes branching structures as a parsimonious series of interconnected tapering cylinders characterized by their x, y, and z positions, radius, the identity of the parent cylinder, and an arbitrary numeric tag to label structures of interest. The application of a neuronal tree reconstruction and analysis method to 3D TOF scans is non-trivial, given the different nature and scale of data. However, such extension is not entirely original. Another recent method developed for neuronal tracing was deemed to be highly generalizable (Wang et al., 2011). That method was also successfully customized for digital tracing of MRA image stacks (Wang, 2011). These previous reports discuss the similarities and differences between neuronal and angiographic segmentation.

The arterial vasculature was reconstructed in each subject as a single arbor stemming from the basilar artery (BA). The first visible point along the BA was chosen as the origin for the vascular tree in every subject. The internal carotid arteries (ICAs) and all visible connecting vessels of the CoW were also reconstructed, with the exclusion of the anterior communicating arteries so as to unambiguously maintain a binary tree structure of the resulting reconstructions in all subjects, greatly aiding consistent comparisons within and across the population sample. All six major arteries stemming from the CoW (right and left MCAs, ACAs, and PCAs) were completely reconstructed through each visible ending. The vascular reconstructions were systematically validated by detecting defects such as intersecting branches, zero-diameter branches, spatially overlapping branches, disconnected branches, etc. (Halavi et al., 2008) followed by thorough visual inspection. Reconstructions for each subject were visually validated by overlaying the reconstructed arborization onto the original MRA image stack and 3D volume renderings.

Morphological analysis

Morphometric parameters were extracted from the digital reconstructions using L-Measure (http://krasnow1.gmu.edu/cn3), an open source tool originally developed to quantify axonal and dendritic morphology (Scorcioni et al., 2008). An expansive battery of variables was selected to yield a comprehensive statistical characterization of angiographic anatomy at both global and local levels, including measurements of size, distances, angles, and branching structure. In order to explain the definitions of the trivial metrics, we adopt the following standard terminological notation (e.g. Brown et al., 2008). Additional details, as well as diagrams accompanying each morphometric definition, are documented online on the L-Measure help page.

We refer to a *branch* as a sequence of reconstruction points starting from a bifurcation (or from the root) and ending at the next bifurcation (*bifurcating* branch) or at a termination (*terminating* branch). The *branch order* is the number of bifurcations between a given point in the arborization and the root. The branch path length or simply *branch length* is the geodesic distance between the beginning and ending of a branch (i.e., the sum length along the branch). Branch *tortuosity* is the