RESEARCH NOTE

The first 3D printed multiple sclerosis brain: Towards a 3D era in medicine [version 1; referees: awaiting peer review]

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Abstract

Conventional magnetic resonance imaging (MRI) studies depict disease of the human brain in 2D but the reconstruction of a patient's brain stricken with multiple sclerosis (MS) in 3D using 2D images has not been attempted.
Using 3D reconstruction algorithms, we built a 3D printed patient-specific brain model to scale. It is a first of its kind model that depicts the total white matter lesion (WML) load using T2 FLAIR images in an MS patient. The patient images in Digital Imaging and Communications in Medicine (DICOM) format were imported into Mimics inPrint 2.0 (Materialise NV, Leuven, Belgium) a dedicated medical image processing software for the purposes of image segmentation and 3D modeling. The imported axial images were automatically formatted to display coronal and sagittal slices within the software. The imaging study was then segmented into regions and surface rendered to achieve 3D virtual printable files of the desired structures of interest.
Rendering brain tumor(s) in 3D has been attempted with the specific intent of extending the options available to a surgeon but no study to our knowledge has attempted to quantify brain disease in MS that has, for all practical purposes, no surgical options.

Keywords

3D printing, multiple sclerosis, DICOM files, image segmentation, reconstruction algorithms, patient education, disease modeling, neurodegenerative diseases

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Introduction

Multiple sclerosis (MS) is a chronic, white and gray matter disease of the central nervous system. Gray matter disease in MS is poorly visualized in conventional MRI but has been increasingly studied in recent years using high strength magnets (de Graaf *et al.*, 2013). The use of MRI in tracking disease of the human brain and spinal cord in patients with MS is central to the diagnosis and treatment of the disease.

Development of computational models for patient-specific requirements based on human pathophysiology individualized to patient-specific data is needed as we move forward with advanced techniques such as 3D printing in medicine. For starters, the potential to improve diagnosis and optimize clinical treatment by predicting outcomes of therapies is attainable. For instance, the accurate prediction of rupture of abdominal aortic aneurysm is possible through patient-based diagnostic tools coupled to medical imaging (Ricotta *et al.*, 2008). However, most results might not apply directly to individual patients yet because they are based on averages (Kent & Hayward, 2007). As an alternative, patient-specific modeling (PSM) can be used as an analytical tool to optimize an individual's therapy. Our study could potentially be useful in building a platform for patient-specific treatment options based on 3D analysis of brain disease, particularly in acute settings such as stroke, mass effect of tumors, midline shift in patients with acute intracerebral hemorrhage, among others.

With rapid strides made in computer-based technologies, brain atlases are 'constructed' by computers. This enables such atlases to become plastic or deformable to fit the size/shape of individual brains. To construct brain atlases, collections of micrographs or schematic drawings of brain sections from one or a few brains are used in which anatomical structures such as nuclei, cortical ribbon or tracts, are identified (Roland & Zilles, 1994). To make assumptions about localization of function and structure at both the macroscopic and microscopic levels, computerized brain atlases are needed. Computerized brain atlases are also used for topographically defined data from the literature (Roland & Zilles, 1994). The spatial resolution is about 1 mm for structural imaging and is below the cellular scale (Roland & Zilles, 1994). For understanding the interaction between brain areas and regions, subcortical nuclei, gyri and sulci, the resolution appears to be sufficient (Toga *et al.*, 2006).

Image segmentation is crucial in medical image analysis and is perhaps the most critical step in many clinical applications (Despotović *et al.*, 2015). In brain MRI analysis, image segmentation is used for measuring and visualizing the brain's anatomical structures, analyzing changes and identification of pathological regions, as well as for surgical planning and image-guided interventions. Recent advances in brain MRI have provided large amount of data with an increasingly high level of quality but analysis of large and complex MRI datasets is onerous for clinicians, who still extract information manually. Since errors due to inter- or intra-operator variability studies rack up when manual analyses are done, brain MRI data analysis requires inventions in computerized methods to improve disease diagnosis. Increasingly, computerized methods for MR image segmentation, registration, and visualization have been extensively used to assist doctors in qualitative diagnosis (Despotović *et al.*, 2015).

To help the patient understand the extent of the disease is probably cathartic and revealing although each individual patient may react differently. The primary goal of our endeavor is to educate patient(s) and physician (s) alike regarding the magnitude of a medical disease and the immediacy of treating such a ravaged brain. Our concept borrows from the design and modeling of normal, anatomically-detailed, 3D representations of the normal male and female human bodies and acquisition of transverse CT, MR and cryosection images of representative male and female cadavers in the Visible Human Project.

From a patient's perspective, holding one's own brain that is built to scale in the palm of a hand delves into a hitherto unknown and previously unexplored dimension. Looking *en face* at the disease, particularly for a condition that has minimal or no surgical options probably gives patients a better perspective about their disease, but could also evoke fear. With 3D modeling, we enter a novel but untouched world in disease presentation to patients. Only time can tell if more patients embrace such an idea and wish to explore the unknown.

Data acquisition and segmentation

We obtained routine MRI images of the brain from a young Caucasian woman in her early 20s who came to our neurology clinic for the first time following a hospital visit for headache, mild gait problems and visual impairment in her right eye that she had developed over the two days prior to presentation. Her MRI images (Phillips 3T TX, software 3.2 version) had the following parameters: Sag T1 SE 5 Thick x 1 gap DWI 5 Thick x 1 gap, Axial FLAIR 5 Thick x 1 gap, Axial T1 SE 5 Thick x 1 gap, Axial PD 5 Thick x 1 gap, Sag FLAIR (reconstructed to Sagittal, Coronal, and Axial 1.0 mm thick x 0 gap, and Sagittal 3D T1 FFE (reconstructed to Sagittal, Coronal, Axial 1.0 mm thick x 0 gap), respectively. The MRI images showed typical white matter lesions that raised concern for MS; her diagnosis was established after ruling out mimics. Since her brain contained an unusually high lesion load, we opted to print a 3D model to fully ascertain the extent of white matter involvement by total lesion volume. We chose T2 FLAIR lesions to compute lesion load and manually identified lesions within each 1 mm slice of the MRI scan in sagittal, coronal and axial planes, respectively. The total combined lesion load was 95,774 mm^3, suggesting axonal transection in this volume of brain tissue. A seminal publication (Trapp *et al.*, 1998) showed that active MS lesions, defined on a histological basis, had 11,236 transected axons per mm^3 of tissue. This underscores the importance of the burden of disease and the therapeutic challenges that accompany repairing each mm^3 of tissue lost to disease. Our patient had a total white matter lesion load of 95,774 mm^3 corresponding to a loss of 10^9 axons. Since no study had characterized a patient's total lesion volume loss in 3D in MS, comparison of our results to any published literature is not possible.

3D reconstruction

Using 3D reconstruction algorithms, we built a highly accurate 3D printed patient-specific brain model to scale. It is a first

of its kind that depicts the total white matter lesion (WML) load using T2 FLAIR images in an MS patient. The patient images in Digital Imaging and Communications in Medicine (DICOM) format were imported into Mimics inPrint 2.0 (Materialise NV, Leuven, Belgium) a dedicated medical image processing software for the purposes of image segmentation and 3D modeling. The imported axial images were automatically formatted to display coronal and sagittal slices within the software to aid in the visualization and segmentation process. The imaging study was then segmented into regions and surface rendered to achieve 3D virtual reconstructions in addition to 3D printable files of the desired structures of interest – the brain, ventricles and white matter lesions.

The cortical surface of the brain was segmented via Thresholding operations which isolates tissue based on gray value in the images corresponding to the cortical brain surface. The ventricles of the brain and lesions were also segmented using Thresholding combined with 3D interpolation to manually refine the accuracy of the segmented regions as shown in Figure 1. After the images were segmented into the defined regions of interest in the images, 3D tessellated surface models were calculated and rendered from the segmented regions (Figure 2). Upon segmentation and reconstruction, accurate brain and lesion volumes can then be calculated.

The digital 3D model of the brain and structures was then virtually sliced on a sagittal plane into its two hemispheres to achieve

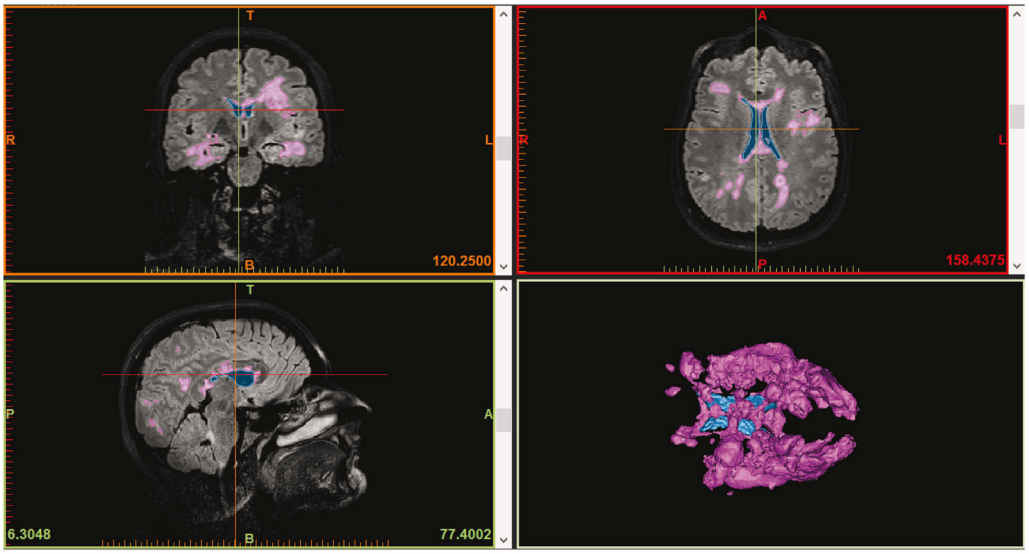

Figure 1. MRI images segmented into brain regions of interest in coronal, axial and sagittal planes, respectively. The pink represents the total lesion load when amalgamated from all the 3 different slices and planes.

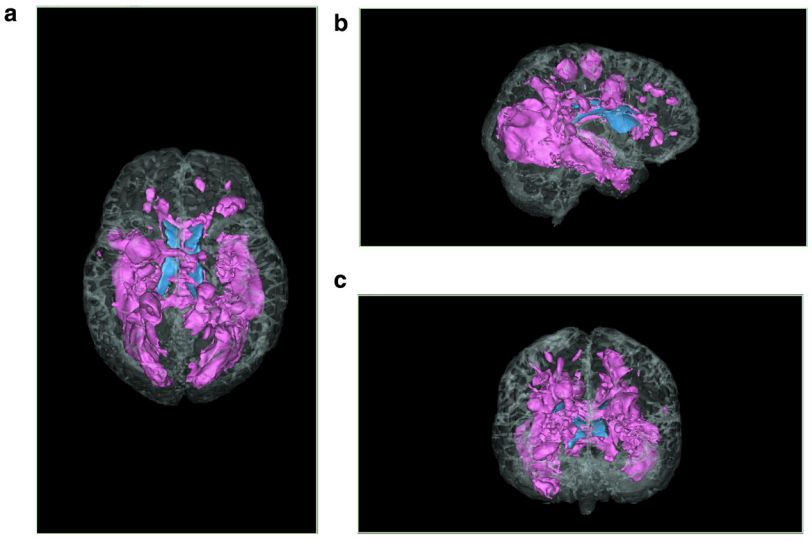

Figure 2. Reconstructed 3D brain images depicting axial, sagittal and coronal views with amalgamated lesions shown in pink and ventricles displayed in blue.

optimal visualization of the lesions in the eventual 3D printed model. To assist with the utility of the printed model and allow optimal visualization, small holes were created in the mating surfaces of the brain along the sagittal planes to support the insertion of magnets post-3D printing. This enables the brain hemispheres to be separated and then easily assembled using the magnets placed in the corresponding landmarks of each hemisphere. After the completion of the 3D model, STL files of each brain hemisphere were exported for 3D printing on a Connex3 (Stratasys, Eden Prairie, MN, USA) 3D printer. Material-jetting technology was chosen to 3D print the model in order to leverage the need for a combination of transparency and colored regions in the printed models. This technology works by extruding microscopic droplets of curable photopolymer through many jetting heads, building the region one thin layer at a time. The brain cortex was printed using transparent material, with blue representing the ventricles and lesions as depicted in pink (Figure 2).

Conclusions and future directions

We emphasize that our model (Figure 3) is primarily educational but can be modified to document the progression or regression of lesions over time. As well, quantification of T1 black hole volume loss, particularly with the development of automated algorithms, is possible (Datta *et al.*, 2006). Hopefully, our work will trigger research into the study of regional/global atrophy, focal/total cortical thickness assessment and deep gray matter changes in 3D, a field that is increasingly coming to light in conventional studies using Structural Image Evaluation Using Normalization of Atrophy software and statistical parametric mapping analysis (Pagani *et al.*, 2005). Additionally, a platform to document changes accurately using computer-assisted automated algorithms that are universally accepted and standardized will be developed. This is critical given the recent EPIC study findings that showed a disappointing trend in how disease-modifying drugs fail to arrest or impact disability in MS patients (Cree *et al.*, 2016) since no drug, if any, affects atrophy measures in a meaningful way. For longitudinal studies, it is crucial that research methods are automated, validated, universally accepted, standardized and based on computer-based image analysis tools that can sift through large data sets. Additional enhancements for our 3D model could include such innovations as Cold Spring Harbor's G2C interactive normal brain models, funded by the Dana Foundation and Hewlett Foundation, wherein structure/function relationships can be gleaned when a 3D brain with disease is superimposed on an interactive normal 3D brain model giving patients and physicians a new perspective on how different anatomical structures are involved and affected in health and disease. Since no two patients are similar, scan quality can vary but so do their file formats. Yet, if the end goal is improvement in quality patient care, one would want to ensure that the 3D models accurately represent the patient's anatomy which is what one would expect as 3D technologies continue to evolve.

Figure 3. A 3D brain, modeled to size. Ventricles are shown in blue and white matter lesions are depicted in pink.

Many automated segmentation methods that detect brain lesions have been developed in MS (Udupa *et al.*, 2001; Wu *et al.*, 2006; Zijdenbos *et al.*, 2002) but no study has been validated for commercial or routine use, nor has the depiction of the impact of lesion load in a 3D printed model been published. If such technology can be developed and transferred to the ICU settings, medical and surgical decisions could perhaps be handled better, particularly in acute neurological disorders that cause rapid clinical changes and worsening mass effect and midline shift following intracerebral bleeding, hydrocephalus or cerebral edema owing to mass effect of tumors. New guidelines could be developed for therapeutic and surgical interventions. Could 3D printing introduce a new angle to how lesion load is defined? Can one visualize 3D printing becoming a teaching, diagnostic and decision-making tool in the ICU setting? We think that to accurately document changes that occur in acute neurological diseases such as hemorrhagic strokes with or without mass effect, or cerebral edema from varied causes, a 3D model would be ideal if not mandatory, particularly if available in real time for decision-making in treatment options and patient education.

Since no radiological markers accurately quantify disability in MS, how does one assess objectively, the effect of disease modifying drugs on MS outcomes research? As technology evolves, a routine CT and MRI scan can probably be converted instantly into a 3D model with the help of automatic segmentation algorithms that could be used to document volumetric changes both global, regional and deep gray matter structures. We hope our study is the first step towards such a goal.

Quantitative analysis of WML in large clinical trials assumes a major role particularly in cerebrovascular disease, diabetes mellitus and Alzheimer's disease, wherein 30% of patients could have some degree of vascular pathology. In population studies, such as the Cardiovascular Health Study (CHS) or the Rotterdam Scan Study (RSS) WMLs have been shown to be associated with age, clinically silent stroke, higher systolic blood pressure, hypertension, atrial fibrillation, among others (de Groot *et al.*, 2000; de Groot *et al.*, 2000; Longstreth *et al.*, 1996). An urgent unmet need is the assessment of MRI data of WML load in various disease states that is standardized, automated and followed longitudinally. Hopefully,

this study is a first of many such attempts in that evolutionary path moving forward.

Data and software availability

The MRI files underlying the 3D model of this patient's brain have not been included to maintain patient anonymity.

Alternative software packages that are available include Slicer (open source) or Osirix (free demo available) to segment the imaging data, and Meshmixer (open source), a digital CAD software, to prepare the 3D model for printing.

Supplementary material

Supplementary Movie 1: Video of 3D brain with multiple sclerosis. Click here to access the data.

Author contributions

JA: Concept, data collection, MRI analysis, manuscript preparation; TP: 3D printing, presentation and development of the model, MRI data extraction from DICOM files.

Competing interests

No competing interests were disclosed.

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