RESEARCH NOTE

UPDATE The first 3D printed multiple sclerosis brain: Towards a 3D era in medicine [version 2; referees: 3 not approved]

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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

Open Peer Review

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UPDATE **Updates from Version 1**

Information regarding patient consent for the publication of the study was not included in the first version; a statement has now been added.

See referee reports

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

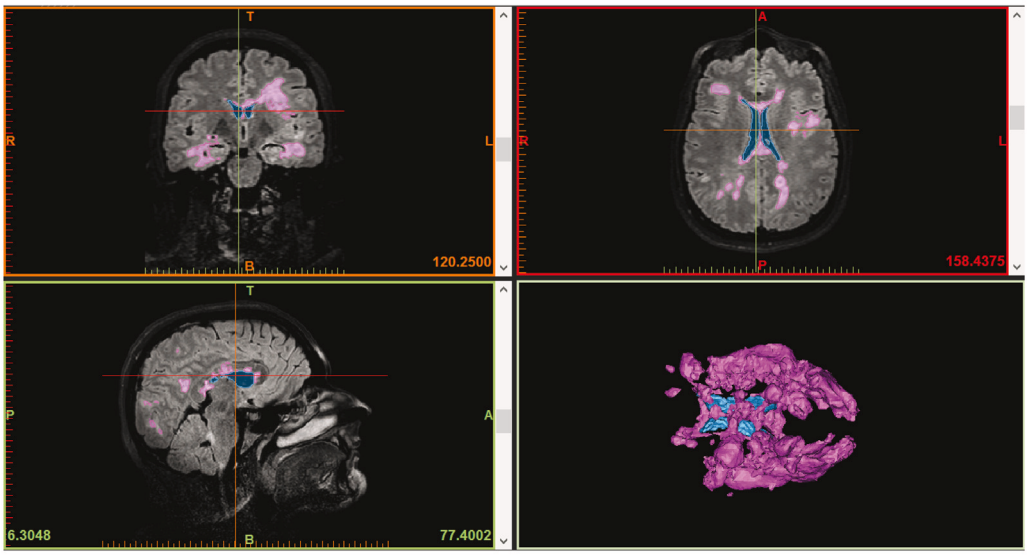

Figure 1. MRI images segmented into brain regions of interest in coronal, axial and sagittal planes, respectively. The pink represents the total lesion load when amalgamated from all the 3 different slices and planes.

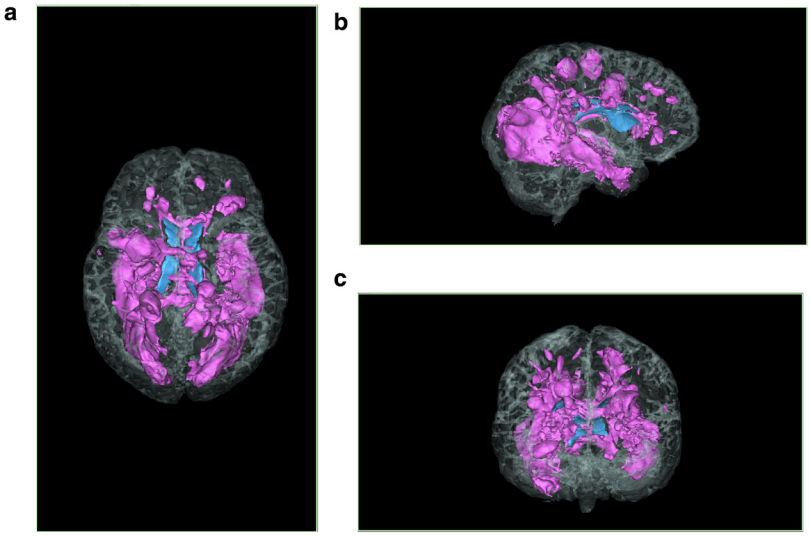

Figure 2. Reconstructed 3D brain images depicting axial, sagittal and coronal views with amalgamated lesions shown in pink and ventricles displayed in blue.

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 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.

Consent

Written informed consent was obtained from the patient for the publication of the patient's details and accompanying images.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Current Referee Status: ✗ ✗ ✗

Version 2

Referee Report 27 December 2017

doi:10.5256/f1000research.13796.r26540

✗ **Ramin Javan**
Dept of Radiology, George Washington University, Washington, DC, USA

This article I believe is better suited as a “technical note” rather than a “research note” as it predominantly describes the methodology of creating a novel 3D printed model along with discussion of possible or presumed future implications and uses. There is no comparison, no survey data, no statistical data or analysis, or any p-values that ate pertinent in this paper for it to be a research note. That being said, the model is extremely visually appealing and can certainly be used for patient counseling, trainee education and interdisciplinary decision making.

The underlying technique though may be applied in many other applications where an internal pathology is to be demonstrated within a normal structure or an organ, with many publications describing it either using Polyjet technology or through stereolithography with transparent resin. With respect to multiple sclerosis, however, the vast majority of cases do not have such a heavy load of white matter disease as demonstrated here, except for cases of primary progressive MS or advanced MS. So this model, exaggerates the possible use of 3D printing in MS, as authors themselves describe the case presentation to have an unusually high load of white matter disease.

Another consideration is the cost of the model (which would help readers if it was described either ordered through Materialise or the cost of the Connex printer and material) and whether it adds benefit for that cost and the time needed for segmentation and 3D printing. However, as authors mention, this can and will likely change in the future both in terms of automation of segmentation as well as the cost.

One consideration to take into account to improve upon the current model would be to also add another color mask that shows enhancement of lesions demonstrating degree of active disease (especially with newer multicolor Polyjet 3D printers that can print up to 6 non-support material colors). This may help clinicians in the acute setting determining the severity, extent or percentage of plaques involved in active demyelination. It can also be helpful in determining predominance in certain areas of the brain (as mentioned by authors) or for comparing to prior white matter lesion load or comparing with other previous acute presentations.

With respect to the authors’ statement regarding the need for automated quantitative analysis of white matter disease, the specific role of 3D printings is questionable while the actual 3D volumetric measurement is of the essence, readily provided by the software. A 3d model may help clinicians determine whether the progression has occurred predominantly in a certain region of the brain for example. This, however, can also be done through virtual 3D visualization but also with the use of software calculations, probably even more accurately, if desired.

Lastly, financial disclosure must be detailed under “Competing Interest” since second author is an employee of Materialise.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Referee Report 30 October 2017

doi:10.5256/f1000research.13796.r26539

Toshihiro Mashiko
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[Overall comments]
The authors have described an extremely interesting three-dimensional (3D) model for MS, with precise segmentation of the MS lesion. However, the usefulness and applicability of this model is unclear. Although the authors have mentioned various points in the “Conclusions and Future Directions section,” they have not emphasized on the necessity to use 3D models in their study. Research is to discover the unknown. However, in this paper, it has not been thoroughly achieved. The authors must initially apply a suitable research design to demonstrate the usefulness of a 3D model for MS. For “Future Directions,” the basis shall be stated in each item.

[Is the work clearly and accurately presented and does it cite the current literature?]
The method of fabrication of the model is clearly and accurately presented. However, the purpose and results of this study are unclear. In addition, the authors have stated that the 3D models assist in increasing patient awareness and knowledge without providing substantial evidence. This study has essentially succeeded in fabricating a 3D model for MS; however, there is no new knowledge.

[Is the study design appropriate and is the work technically sound?]
There is no description regarding the study design.

[Are sufficient details of methods and analysis provided to allow replication by others?]
No analysis has been conducted.

[Are all the source data underlying the results available to ensure full reproducibility?]
The results are not described.

[Are the conclusions drawn adequately supported by the results?]
Because the results are not shown, the conclusion cannot be evaluated.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 01 Nov 2017

Jagannadha Avasarala, Greenville Hospital System University Medical Center, USA

The authors thank Toshihiro Mashiko for his comments.

Our responses are

1. The single most important aspect(s) of our paper is that a) feasibility of printing a 3D brain with disease is do-able, and b) that the applicability of such technique(s) can be extended to the ICU provided progress in technology developments are attained.

2. The 3D technology applications in the SURGICAL field are nothing new and are, in fact, routine - 3D printing techniques are practical and anatomically accurate methods of producing patientspecific models for surgical planning, simulation and training, tissueengineered implants, and secondary devices is well described and almost universally

applied in select cases, probably well known to Dr Mashiko. Our idea is extend this thought process to the MEDICAL field, and in particular, neurology, as an example.

3. The purpose of this study and results are presented to demonstrate feasibility of the above 'idea'. All it takes is to utilize the capabilities of companies that can turn 2D data such as MRI images into definable, patient-education-friendly models in 3D that can augment what is conventionally being presented the world over in a 2D data format.

Competing Interests: None

Referee Report 16 October 2017

doi:10.5256/f1000research.13796.r26575

Daniel S. Reich , **Nicholas J. Luciano**
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This article demonstrates the creation of a 3D printed model of the brain of a multiple sclerosis patient, allowing for enhanced visualization of white matter lesions. This technique may be useful for medical education and may provide patients with a more tangible representation of their disease pathology. By utilizing clinically relevant MRI sequences and an imaging segmentation tool designed for a clinical workflow, the authors present a method that can be implemented by clinicians at other institutions. However, the article has several weaknesses that must be addressed:

1. The authors report that the patient provided written consent for publication of his/her images, however there is no information about whether the study was approved by the local IRB, or, instead, a waiver was received. IRB approval, or a waiver of IRB approval, is required, by law, prior to commencing a medical research study.

2. The paper is classified as a “Research Note,” which, per the F1000Research guidelines, “include single-finding papers that can be reported with one or two illustrations (figures/tables), descriptions of unexpected observations, and lab protocols. Posters from conferences or internal meetings may be summarized as Research Notes. In many cases, some additional detail, particularly in the methods, description of the results, and/or discussion/conclusions will be required to make sure that readers (and referees) have enough information to understand the description of the work.” There is no research in this paper; rather, it is an educational demonstration, as the authors themselves report. In fact, it is not clear that this report falls under any of the F1000Reserach article categories.

3. The patient’s diagnosis of multiple sclerosis (MS) is not entirely clear based on the presented information. As it is noted that the patient has an unusually large lesion load (with bilateral temporal lobe symmetry, per Figures 1, 2, and Supplementary Movie 1), we would ask that the authors clarify if the patient met the 2010 McDonald criteria (*Polman et al., 2011*), specifically dissemination in time (DIT). Further, if DIT was apparent based on the hospital visit MRI as compared to the images collected at the neurology clinic, printing a 3D model for each of these time points would strengthen the author's argument that the brain model could be used to demonstrate disease progression. But in that case, they would need to quantify the change using their approach. We also ask that the authors clarify the clinical measures used to reach the

diagnosis of MS for this patient.

4. The authors state that “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.” This is clearly not the case. Indeed, the segmentation in this paper was done on 2D slices of the 3D image volumes, and that is routine in the field.

5. The discussion of axonal transections, based on data from *Trapp et al., 1998*, is bizarre. As the authors themselves note, no two MS cases are identical, and therefore precise estimates of the number of transected axons in the current patient’s brain are not justified. Moreover, the authors provide no information about how they determined whether lesions in their patient’s brain were active or chronic, which is highly relevant in this regard. This entire section should be removed.

6. The authors should discuss a recent publication relevant to this article: Newton, Braeden D., *et al.* "ThreeDimensional Shape and Surface Features Distinguish Multiple Sclerosis Lesions from Nonspecific White Matter Disease." *Journal of Neuroimaging* (2017).

7. While the authors emphasize the utility of automated/computational algorithms in MRI in both the introduction and the discussion, the method presented here is based entirely on manual segmentation and thresholding. Given this emphasis, we ask that the authors explain why they chose not to use an automated method for segmentation of lesions, such as those presented in *Carass et al., 2017*.

8. The authors suggest that their work could stimulate research into cortical atrophy. We ask that the authors comment on the extent of atrophy required to notice an appreciable change in a 3D model and how that might compare with the known rate of cortical atrophy in MS literature.

9. The authors state that they believe a 3D printed model may become mandatory as a decision-making tool in some acute neurological diseases if provided in real time. Given the assumption that segmentation would be automated, we ask that the authors provide the approximate printing time and cost of the 3D model to provide context of the practicality of this use.

10. The references – particularly the ones that deal with segmentation of MS MRI scans – are out-of-date.

11. As a general point, the article is written in a very non-conventional format, and there are many extraneous details and a good bit of philosophizing, which really has no place in a scientific article.

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Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

We have read this submission. We believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 16 Oct 2017

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The authors thank the reviewer for his erudite observations. Our responses are as follows

1. IRB protocol was not a requirement at our institution (Avasarala J) but we are obtaining one now, to meet compliance standards. It is not our intent to do anything that is outside the rules of our institution.

2. Research note or technical note is, in theory, semantics. Software application to DICOM files was done as noted (Todd, P) in the paper. I am not sure that anything specific is being missing, but MRI data transformation was done, into DICOM files and data extracted into the software suite as described. We can expand on the technicalities of the software application, if need be.

3. The diagnosis was established based on T1 gad enhancing lesions **AND** T2 lesions present at the original time of diagnosis in the hospital (DIT and DIS) **AND** clinical examination **AND** clinical presentation **AND** exclusion of other mimcs as is the standard of care at our institution. The principal author is MS-fellowship trained (Washington U School of Medicine, 2000-03, St Louis, MO) and made the diagnosis based on evidence, clinical/radiological findings.

4. Segmentation in 2D is a very old technique but NO reconstruction of 3D volume losses in a 3D PRINTED model of human brain with MS was ever done or published, hitherto. There is no circumstance described in the literature that we could find that describes a physician presenting to his/her patient with a 3D brain (of the patient) with a goal of educating the patient (instead of showing lesions on a flat, 2D screen). Segmentation of MRI lesions is not new but collation of 2D data into a 3D model that is printable, is.

5 We disagree. This patient presented with *de novo* MS. The lesions, as described, are T2 lesions and were volumetrically assessed. Prior to the publication, one of us (JA) wrote to Dr Trapp and he agreed that ANY new T2 lesion or T1 enchanced lesion would represent a 'new lesion' and as noted, the patient was presenting for the first time. These lesions are not chronic, they are acute. Any clinical trial of any phase 3 drug trial for MS drugs notes two fundamental aspects of a new lesion definition on MRI - and they are a) T1-gad lesions and b) NEW T2 lesions. Using that definition and since the patient presented *de novo*, these are acute lesions. Acute lesion volumetric analysis (Trapp *et al*) shows that I cu mm3 destroys 11 K axons, from axonal transection. Unless this fundamental finding is being questioned, the axonal loss from the total volumetric loss in our patient corresponded to the number of axons transected, as noted. This section will not removed and is the core of this manuscript.

6 and 7. We can consider these suggestions. As for segmentation, there is NOT one standardized approach for ANY disease of the CNS, including those that claim automation, that everyone agrees on, or is a gold-standard. Manual automation does not disqualify the study, per se. Automated versions are fundamentally developed to look at massive amounts of data but to date, there is not even a single database in the world of MS that has defined brain atrophy using automated segmentation techniques. As well, no findings across multiple samples from various available datasets via normalization are published - some publications claim these findings, but again, no standard format exists. Therefore, no normalization techniques are available although numerous published data claim that one is better than the other.

8-11. There is no philosphical musing in our manuscript. Our references are what we felt were appropriate and relevant for the subject being discussed. As for points 8 and 9, they are well received and we can provide additional data on cost and time for using similar technology as it stands today.

Competing Interests: None