# Incorporation of Brain Connectomics for Stereotactic Radiosurgery Treatment Planning

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**BACKGROUND AND IMPORTANCE:** Neurosurgeons have integrated neuroanatomy-based tractography to avoid critical structures during dose planning. However, they have yet to integrate more comprehensive connectome networks for radiosurgical planning.

**CLINICAL PRESENTATION:** A young man presented with a Spetzler-Martin Grade 3 right temporal arteriovenous malformation.

**DISCUSSION:** As proof of concept, we incorporated connectomic networks including default mode network, optic radiation and central executive network into the Gamma Knife radiosurgical treatment planning workflow. Connectome networks were created from T1 anatomic and diffusion-weighted images magnetic resonance images using Quicktome software. The resulting networks were voxel-encoded in the magnetic resonance images, imported into GammaPlan, and segmented by image thresholding. The GammaPlan Lightning optimizer was used to create radiosurgical plans with a dose of 20 Gy to the 50% isodose line delivered to the arteriovenous malformation nidus both with and without treating these networks as risk structures. When taking into account the connectome networks, a maximum dose restriction of 14 Gy was placed on each network during lightning dose planning. With default mode network, optic radiation, and central executive network as risk structures, the maximum dose and $V_{12Gy}$ were reduced by 23.4% and 88.3%, 20% and 34.3%, and 29.8% and 63.2%, respectively.

**CONCLUSION:** We were able to incorporate connectomes into radiosurgical dose planning approaches. This allowed for dose reductions to the networks while still achieving delivery of a therapeutic dose to the target volume.

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Contemporary computational neuroscience increasingly hypothesizes that the brain is functionally organized as a series of interconnected networks.[1] Resting-state functional MRI (fMRI) and constrained spherical deconvolution fiber tracking have provided a window through which a functional view of the brain can be studied.[2] Connectomics use a big-data approach to constructing and identifying image-derived and computer-mapped functional and structural connections of the brain. Identification and prioritization of individual nodes within the brain and the connectome of white matter is now feasible for neurosurgical applications.

Functional MRI and MRI-based fiber tracking are critical tools for neurosurgeons to ascertain the safest possible pathway to a target. Although radiosurgery does not require physically traversing brain regions, it passes high-energy photon beams through cortical and subcortical structures. Dose tolerances for the anterior optic pathways and brainstem are defined in the literature and routinely applied to radiosurgical practice.[3] Using brain tractography for integrating corticospinal and optic tractography into dose planning has led to reduced radiosurgical complications.[4,5]

Most existing connectomic tools are heavily research-driven, with little integration into clinical radiosurgery systems.[6] As our knowledge matures, new tools become available, which standardize the data acquisition process and lower the technical barrier for using fMRI and tractography information in clinical situations.

In this report, we describe the use of one such software, Quicktome (Omniscient Neurotechnology Pty), to create and import patient-specific connectome data into the radiosurgical treatment planning system for Gamma Knife radiosurgery and demonstrate how this information can be used to constrain radiosurgical dose distributions.

**ABBREVIATIONS: CEN,** central executive network; **Dmax,** maximum dose; **DMN,** default mode network; **OR,** optic radiation.

## CLINICAL PRESENTATION

An otherwise healthy, 27-year-old right hand dominant male patient with a recent history of epilepsy was used as a test subject. The patient's epileptic episode prompted neuroimaging studies which revealed a Spetzler Martin Grade III arteriovenous malformation (AVM) involving the right lobe and measuring slightly more than 4 centimeters in maximum dimension. A subsequent angiogram revealed the AVM had feeders from the right middle cerebral artery and with both deep and superficial venous drainage.

The patient underwent Gamma Knife radiosurgery as previously described.[7] Treatment planning included acquisition of a volumetric brain MRI study, a stereotactic digital subtraction biplane angiography of the AVM nidus, and a stereotactic head computed tomography. The MRI study included volumetric T1 postcontrast images (FLASH 3D T1 with fiducial markers in place), as well as diffusion-weighted images (DWI) (2 mm slice thickness with 64 directions).

The AVM was targeted with a prescription dose of 20 Gy to the 50% isodose line using 13 isocenters. The prescription isodose volume was 8.4 $cm^3$. After the treatment plan was finalized, the treatment was delivered per the treatment plan using the Gamma Knife Icon.

### Creation of Connectomic Data Using Quicktome

Patient consent was waived because of the retrospective nature of the study. For the purposes of this study, the patient's pretreatment MRI, including the T1 postcontrast and DWI, was exported in DICOM format to the Quicktome software. Quicktome follows the processing pipeline as described by Doyen et al.[8] Specifically, Quicktome preprocesses the DWI images to correct for motion and gradient artifacts. These are then coregistered to a skull-stripped version of the T1 anatomic images. Fiber tractography is determined using the constrained spherical deconvolution method described by Tournier et al.[9] A machine-learning model then computes the most likely parcellation on a voxel-by-voxel basis based on structural connectivity and a match

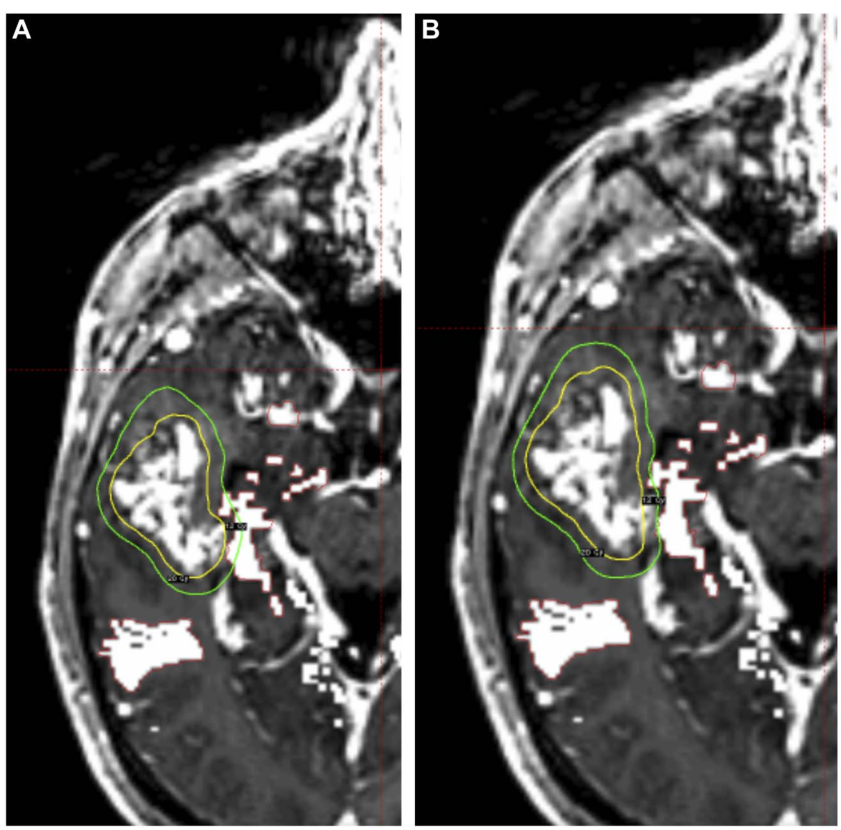


**FIGURE 1.** *A T1 post contrast axial view of the patient's brain MRI demonstrating the right temporal arteriovenous malformation 20 Gy (yellow isodose line) and the 12 Gy isodose line in green. The DMN network is outlined in brown.* **A**, *The radiosurgical dose plan without protection and* **B**, *the effect on the dose plan after using a 14 Gy risk protection of the DMN network in Gamma Plan's Lightning software. DMN, default mode network.*

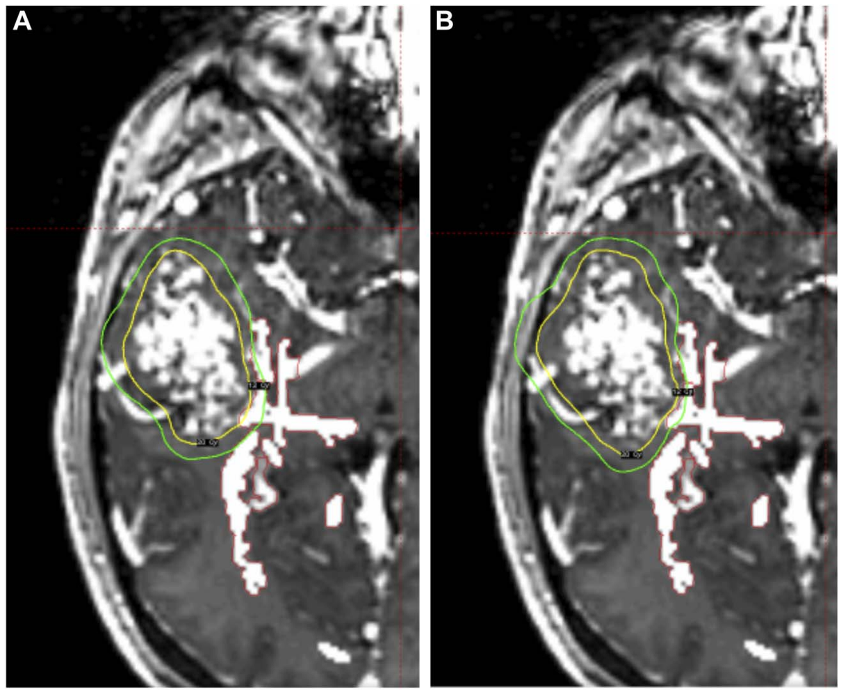

**FIGURE 2.** *A T1 post contract axial view showing the right temporal arteriovenous malformation targeted with a dose of 20 Gy yellow isodose line and the 12 Gy Isodose line in green. The OR network is outlined in brown.* **A**, *The dose plan without protection to the OR and* **B**, *the effect after a 14 Gy risk protection of the OR in Gamma Plan's Lightning software. OR, optic radiation.*



to an augmented Human Connectome Project atlas of task-based and resting-state fMRI. The result is a patient-specific parcellation and white matter fiber map for several well-known connectome networks, including the default mode network (DMN),[10,11] optic radiation (OR),[12] and central executive network (CEN).[13-15] The network data were in-turn converted to a set of "burn-in" images where the voxel data containing network parcellation or fiber tracts were set to the maximum voxel value for the data set. One series of burn-in images was created for each connectome network.

### Data Import Into GammaPlan

Each image series from the previous step as imported into GammaPlan and coregistered to the patient's existing imaging studies and treatment plan. The parcellation and fiber tract voxels for each network were segmented using GammaPlan's semiautomatic, threshold-based segmentation function. The results of this step were a set of 3D objects that could be used as risk structures in treatment planning.

### Comparative Treatment Planning

The GammaPlan Lightning optimization system was used to create treatment plans using the same margin dose (20 Gy) to the target as in the actual clinical plan.[16] Parameters for Lightning optimization were identical for all plans (low-dose weight = 0.50; beam-on-time weight = 0.50; max dose = 40 Gy, coverage = 100%, max dose to risk structure = 14 Gy). A baseline treatment plan without considering any connectome networks was created and compared with subsequent plans considering a single network as an avoidance structure.

### Evaluation

Differences between the baseline treatment plan and the plans with network consideration were evaluated using a set of common radiosurgical dose metrics, including the maximum dose to the connectome network and the volume of the temporal lobe component of each network that received 12 Gy ($V_{12Gy}$).

## RESULTS

### Default Mode Network

The original dose plan delivered a maximal dose of 19.7 Gy to the DMN and the $V_{12Gy}$ to the DMN was 0.207 cc. After using the DMN as a critical structure, the maximal dose and $V_{12Gy}$ to the DMN was 15.1 Gy and 0.045 cc, respectively. (Figure 1).

### Optic Radiations

The baseline dose plan delivered a maximal dose of 23.3 Gy to the OR and the $V_{12Gy}$ to the OR was 0.388 cc. After using the OR

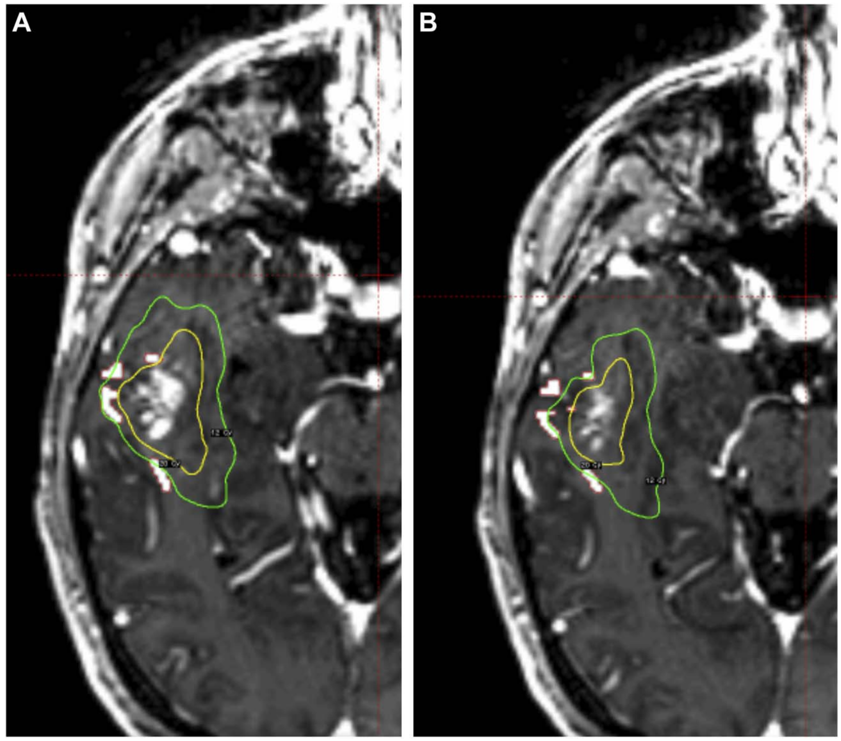


**FIGURE 3.** *A T1 post contract axial view showing the right temporal arteriovenous malformation 20 Gy (yellow isodose line) and the 12 Gy isodose line in green. The CEN network is outlined in brown.* **A**, *The dose plan without protection and* **B**, *the effect after a 14 Gy risk protection of the CEN in Gamma Plan's Lightning software. CEN, central executive network.*



as a critical structure, the maximal dose and $V_{12Gy}$ were 18.7 Gy and 0.255 cc, respectively (Figure 2).

### Central Executive Network

The original dose plan delivered a maximal dose of 24.2 Gy to the CEN and $V_{12Gy}$ was 0.372 cc. After using the CEN as a critical structure, the maximal dose and $V_{12Gy}$ to the CEN were 17 Gy and 0.137 cc, respectively (Figure 3).

## DISCUSSION

The importance of large-scale brain networks such as DMN, CEN, and OR in higher-order human functioning is well-established in neuroscience, but it has yet to deeply penetrate neurosurgical management.

$V_{12Gy}$ in normal brain has been associated with radiosurgical complications and adverse radiation effects for many different indications including intracranial AVM's.[17] Postradiosurgical white matter changes may have structural and clinical implications for the affected brain networks. Integrating brain network nodes and connecting white matter tracts into radiosurgical planning may help define their radiation tolerance limits.

In this proof-of-concept study, we integrated advanced techniques to define connectome networks that were anatomically close to a radiosurgical target volume. By considering the connectome networks as risk structures, the maximum dose (Dmax) and $V_{12Gy}$ to the fiber tracks can be substantially reduced. Although the dose tolerance of these connectomes is not fully defined, dose reduction to critical structures has long been a principle of radiosurgery. It would seem highly likely that reductions in Dmax and $V_{12Gy}$ to connectomes could similarly reduce adverse radiation effects and clinical neurological sequelae.

Concerning the clinical applications in radiosurgery, although we believe in the importance of integrating connectomics in radiosurgical planning, networks such as the DMN and CEN are involved in higher-level executive functions. It is unlikely that such patient outcomes have been captured in clinical follow-up for the majority of the patients and that they can be retrospectively retrieved and analyzed. A prospective study with standardized preoperative and postoperative neuropsychological assessment would be necessary to reliably capture and analyze these important data.

## CONCLUSION

Connectome mapping can be used to define critical neural networks. This information can be incorporated into radiosurgical planning systems to reduce the Dmax and V12 to nearby neural networks. Further studies are needed to define the tolerance of these fiber tracks and the clinical benefits of incorporating them into radiosurgical practice.

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