

Short Communication

Optimizing the Accuracy of Cortical Volumetric Analysis in Traumatic Brain Injury

Bram R. Diamond,^{1,2} Christine L. Mac Donald,³ Samuel B. Snider,¹
Bruce Fischl,² Kristen Dams-O'Connor,^{4,5} * Brian L. Edlow^{1,2} *

* co-senior authors

¹⁰Center for Neurotechnology and Neurorecovery, Department of Neurology, Massachusetts General Hospital and
¹¹Harvard Medical School, Boston, MA.

12 ²Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital
13 and Harvard Medical School, Charlestown, MA.

14 ³Department of Neurological Surgery, University of Washington, Seattle, WA.

¹⁵Department of Rehabilitation Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

¹⁶Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY.

Correspondence to:

19 Kristen Dams-O'Connor, Ph.D.

20 Email: kristen.dams-o'connor@m Mountsinai.org

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29 **Author Contact Information**

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31 Bram R. Diamond: brdiamond@mgh.harvard.edu, Phone (617) 726-4050, Fax: (617) 726-7422, address:
32 Athinoula A. Martinos Center for Biomedical Imaging, 149 Thirteenth Street, Charlestown, MA 02129.

33

34 Christine L. Mac Donald: cmacd@uw.edu, Phone: (206) 897-4047, Fax: (206) 744-9942, address:
35 University of Washington School of Medicine, Department of Neurological Surgery, 325 9th Ave, Box
36 359924, Seattle, WA 98104.

37

38 Samuel B. Snider: ssnider@partners.org, Phone: (617) 724-6352, Fax: (617) 643-3939, address:
39 Massachusetts General Hospital, 175 Cambridge St – Suite 300, Boston, MA 02114.

40

41 Bruce Fischl: fischl@nmr.mgh.harvard.edu, Phone: (617) 726-3197, Fax: (617) 726 -7422, address:
42 Athinoula A. Martinos Center for Biomedical Imaging, 149 13th Street, Charlestown, MA 02129.

43

44 Kristen Dams-O'Connor: kristen.dams-o'connor@mountsinai.org, Phone: (212) 241-7587, Fax: (212)
45 241-0137, address: Brain Injury Research Center, Department of Rehabilitation Medicine, Department of
46 Neurology, Box 1163, One Gustave L. Levy Place, New York, NY 10029.

47

48 Brian L. Edlow: bedlow@mgh.harvard.edu, Phone: (617) 724-6352, Fax: (617) 643-3939, address:
49 Massachusetts General Hospital, 175 Cambridge St – Suite 300, Boston, MA 02114.

50 **Abstract**

51 Cortical volumetric analysis is widely used to study the anatomic basis of neurological deficits in
52 patients with traumatic brain injury (TBI). However, patients with TBI-related lesions are often
53 excluded from analysis, because cortical lesions may compromise the accuracy of reconstructed
54 surfaces upon which volumetric measurements are based. Here, we propose a novel FreeSurfer-
55 based lesion correction method and illustrate its impact on cortical volume measures in patients
56 with chronic moderate-to-severe TBI. We performed MRI in 87 patients at mean $+$ /SD 10.9 $+$ /
57 9.1 years post-injury using a T1-weighted multi-echo MPRAGE sequence at 1 mm resolution.
58 Following surface reconstruction, we parcellated the cerebral cortex into seven functional
59 networks using FreeSurfer's standard pipeline. Next, we manually labeled vertices on the cortical
60 surface where lesions caused inaccuracies and removed them from network-based cortical
61 volumetric measures. After performing this lesion correction procedure, we measured the surface
62 area of lesion overlap with each network and the percent volume of each network affected by
63 lesions. We identified 120 lesions that caused inaccuracies in the cortical surface in 46 patients.
64 In these 46 patients, the most commonly lesioned networks were the limbic and default mode
65 networks (95.7% each), followed by the executive control (78.3%), and salience (71.7%)
66 networks. The limbic network had the largest average surface area of lesion overlap (4.4 $+$ /3.7%)
67 and the largest percent volume affected by lesions (12.7 $+$ /9.7%). The lesion correction method
68 has the potential to improve the accuracy of cortical volumetric measurements and permit
69 inclusion of patients with lesioned brains in quantitative analyses, providing new opportunities to
70 elucidate network-based mechanisms of neurological deficits in patients with TBI.

71 **Introduction**

72 Cortical volumetric analysis with FreeSurfer^{1, 2} is widely used to study the neuroanatomic
73 basis of cognitive, behavioral, and motor deficits in patients with traumatic brain injury (TBI).³⁻⁶
74 However, cortical lesions caused by TBI pose major challenges to FreeSurfer's standard
75 automated magnetic resonance imaging (MRI) processing pipeline. Lesions often compromise
76 the accuracy of the cortical surfaces that are reconstructed and used by FreeSurfer to generate
77 volumetric measurements.^{4, 6, 7} As a result, TBI imaging studies have historically excluded
78 patients with large focal lesions.^{5, 8} Development of a tool that accounts for lesions in cortical
79 volumetric analysis is needed to prevent the systematic exclusion of patients with large cortical
80 lesions and to ensure that TBI imaging studies are generalizable across the full spectrum of
81 cortical pathology. Moreover, integration of such a tool into the FreeSurfer software platform
82 would create new opportunities to study network-based mechanisms of disease^{9, 10} using
83 canonical atlases.¹¹

84 Here, we propose a novel FreeSurfer-based lesion correction method and illustrate its
85 impact on cortical volumetric measures in patients with chronic TBI. The lesion correction
86 method differs in several ways from the standard FreeSurfer approach to editing reconstructed
87 cortical surfaces. Standard cortical segmentation using FreeSurfer relies on the assumption that
88 the brain has normal anatomy and that any surface inaccuracies are related to the FreeSurfer
89 processing pipeline. However, in patients with cortical lesions caused by TBI, FreeSurfer's
90 reconstruction of the cortical surface can be grossly inaccurate due to focal encephalomalacia
91 and distorted anatomy. This methodological limitation of the standard FreeSurfer editing
92 approach is the main motivation for the lesion correction method proposed here. The new

93 method makes no assumptions about lesioned cortical surface anatomy, and it minimizes bias by
94 requiring the manual rater simply to identify inaccuracies without changing the surfaces. In this
95 study, we use the lesion correction method to assess the topology of lesion overlap with
96 functional brain networks and to characterize inter-network differences in lesion burden. We
97 also distribute the lesion correction method to the academic community to facilitate future
98 studies of network-based mechanisms of neurological deficits in patients with TBI.

99

100 **Methods**

101 *Patients*

102 Between May, 2014 and January, 2019, we prospectively enrolled 141 patients with a history of
103 TBI at two academic medical centers as part of the Late Effects of TBI (LETBI) study.¹² Patients
104 were included if they had sustained a moderate-to-severe TBI at least one year prior to
105 enrollment. We characterized TBI severity based on the United States Department of Defense
106 classification system,¹³ as detailed in the Supplementary Material. Of the 141 enrolled
107 participants, 98 completed an MRI scan (see CONSORT diagram in Supplementary Fig. S1).

108

109 *MRI data acquisition*

110 Patients at Mount Sinai were scanned using a Siemens Skyra (Siemens Medical Solutions,
111 Erlangen, Germany) 3 Tesla (T) MRI scanner with a 32-channel head coil for signal reception,
112 and patients at University of Washington were scanned using a Philips Achieva 3T MRI scanner
113 with a 32-channel head coil.¹ Patients underwent standardized MRI using a T1-weighted multi-
114 echo MPRAGE (MEMPRAGE)¹⁴ sequence with 1mm isotropic voxels. All LETBI sequences

115 were designed to maximize consistency with the National Institutes of Health Common Data
116 Elements for TBI Neuroimaging.¹⁵

117

118 *MRI processing*

119 We first processed all MEMPRAGE data using the standard FreeSurfer pipeline (version 6.0) for
120 cortical surface reconstruction and cortical volume estimation.¹ We used the “big ventricles”
121 function to optimize automatic segmentation for a patient population with enlarged ventricles. In
122 accordance with FreeSurfer recommended best practices

123 (<https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingDataV6.0>), we visually
124 inspected output files, made manual edits to the white matter segmentation, and added control
125 points. To ensure that the lesion correction method would be tested in an unbiased manner, we
126 did not manually edit regions bordering cortical lesions. We then resampled the Yeo 7-Network
127 resting-state functional connectivity atlas¹¹ onto each patient’s reconstructed cortical surface
128 using FreeSurfer’s surface-based registration tool

129 (https://surfer.nmr.mgh.harvard.edu/fswiki/mri_surf2surf).¹⁶

130

131 *Quality Assessments*

132 We performed visual quality assessment for all 98 scans based upon delineation of grey-white
133 matter boundaries and the accuracy of the FreeSurfer-generated surfaces. We defined scan
134 quality using an integer scale: 0 = scan excluded because FreeSurfer failed to complete the
135 processing pipeline; 1 = scan excluded because surface inaccuracies would have required major
136 manual edits; 2 = scan included because only minor manual edits required; 3 = scan included

137 without requiring manual edits. For any scan that received a score of 1 by the primary rater
138 (B.R.D.), a second rater (B.L.E.) reviewed the scan to achieve consensus. Our primary method
139 for determining scan inclusion was qualitative visual assessment because inaccurate FreeSurfer-
140 based segmentations can confound quantitative measurements. Nevertheless, we performed
141 quantitative assessments of signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) and
142 tested for correlations with visual assessments of scan quality, as detailed in the Supplementary
143 Materials.

144

145 *Lesion identification and classification*

146 We next assessed each MRI scan for focal lesions causing encephalomalacia of the cerebral
147 cortex (Fig. 1, top row).¹⁵ All such lesions were considered for subsequent lesion correction
148 analysis and classified according to the cortical network(s) with which they overlapped. To
149 ensure robust and reproducible methods for lesion identification, we performed an inter-rater
150 reliability analysis among three investigators who identified lesions in a randomly selected group
151 of 20 MRI scans and calculated lesion volumes using the standard ABC/2 method.¹⁷ Two
152 investigators were board-certified neurologists with fellowship training in Neurocritical Care
153 (B.L.E. and S.B.S.) and one was a research technician (B.R.D.).

154

155 *Implementation of the lesion correction procedure*

156 A detailed description of the methodological principles of the lesion correction procedure is
157 provided in the Supplementary Material. To implement the procedure, we visually identified
158 sites where FreeSurfer's modeled surface mesh erroneously passed through subcortical tissue

159 (Fig. 1, top row). Next, we manually labeled these surface-points to produce lesion-induced
160 inaccuracy labels (Fig. 1, middle row). Finally, we applied these labels as exclusion masks to
161 remove affected surface regions and calculate corrected cortical volumes (Fig. 1, bottom row).

162 After performing this lesion correction procedure, we used standard FreeSurfer tools to
163 measure the average surface area overlap of lesion-induced inaccuracies with each network of
164 the Yeo 7-Network atlas¹¹ and the average percent volume change of each network caused by the
165 lesion correction procedure (Fig. 2). There was no need to correct cortical volume measurements
166 by total intracranial volume in this study because all network-based measures (i.e. % change in
167 volume) were calculated at the single-subject level.

168 An overview of the lesion correction procedure is shown in Video 1, and additional
169 methodological details are provided in the Supplementary Material. We also release all code used
170 in the lesion correction procedure on https://github.com/ComaRecoveryLab/Lesion_Correction.

171

172 *Statistical analysis*

173 We used the intraclass correlation coefficient to test interrater reliability for lesion volume
174 measurements. We report descriptive statistics for the average percent cortical surface area and
175 the average percent cortical volume affected by lesions for each network.

176

177 **Results**

178 *Patient demographics and clinical characteristics*

179 Due to the presence of severe anatomic distortions, two of the 98 patients' scans did not complete
180 FreeSurfer's standard processing pipeline (visual assessment scores=0). Of the remaining 96

181 scans, nine received a visual assessment score of 1 by the two raters and were excluded, yielding
182 a final sample size of 87 patients. The 87-patient cohort was comprised of 60.9% men, with a
183 mean +/- SD age of 56.7 +/- 12.0 years. Injury severity was classified as mild (n=3), moderate
184 (n=42), and severe (n=32); in 10 participants duration of LOC was unknown and records were
185 not available. The duration from most recent TBI to MRI was 10.9 +/- 9.1 years. Additional
186 clinical and demographic data, as well as SNR and CNR data, are provided in Supplementary
187 Tables 1 and 2.

188

189 *Interrater Reliability*

190 The intraclass coefficient between the two physician raters across 20 datasets was 0.99 [95%
191 Confidence Interval 0.98, 0.99]. The intraclass coefficients between the physician raters and the
192 technician rater for these same datasets were 0.95 [0.91, 0.97] and 0.96 [0.93, 0.98], respectively.
193 Because sufficient inter-rater reliability was established in this test set (n=20; intraclass
194 correlation coefficient > 0.9), all subsequent lesion identification was performed by the
195 technician rater, B.R.D.

196

197 *Lesion characteristics and anatomic distribution*

198 Forty-six of the 87 patients had at least one lesion that affected the accuracy of the FreeSurfer-
199 modeled cortical surface. There were 120 total lesions, with a median of 2 lesions per patient
200 (range 1 to 10). On average, lesions overlapped with 4.6 +/- 1.6 of the 7 networks. A group-level
201 lesion topology map demonstrated an orbitofrontal and anterior temporal predominance of the
202 lesions (Fig. 2, Videos 2 and 3).

203

204 *Network-based cortical surface area measures*

205 The limbic and default mode networks were lesioned in the largest proportion of patients (44/46
206 scans, 95.7% incidence for both networks), followed by the executive control (78.3%), and
207 salience (71.7%) networks. This large limbic lesion burden was observed despite the limbic
208 network having the smallest average surface area of the seven functional networks across all
209 patients (Supplementary Fig. S2). The largest mean percentage of lesion-network surface area
210 overlap occurred within the limbic network (4.4 +/- 3.7% of total network surface area;
211 Supplementary Table 3).

212

213 *Network-based cortical volume measures*

214 When considering networks impacted by the lesion correction method in the 46 patients with
215 cortical lesions, we observed a median decrease in network-based cortical volume of 3.4%
216 (range <1.0% to 47.0%). The limbic network had the largest lesion-induced mean +/- SD
217 percentage decrease in cortical volume (12.7 +/- 9.7%; Supplementary Table 4).

218

219 **Discussion**

220 We introduce a new FreeSurfer-based method for cortical volumetric analysis in patients with
221 lesions caused by TBI. We apply this method in a cohort of 87 patients with chronic moderate-to-
222 severe TBI and show that lesion-induced cortical inaccuracies are not equally distributed within
223 the brain's functional networks. Rather, inaccuracies preferentially affected the limbic network,
224 an observation consistent with prior pathology^{18, 19} and MRI²⁰ studies showing that traumatic
10

225 contusions commonly affect the orbitofrontal and temporal nodes of the limbic network.
226 Implementation of the proposed lesion correction method will prevent the systematic exclusion
227 of patients with cortical lesions from MRI volumetric studies and improve the generalizability of
228 MRI studies across the full spectrum of cortical pathology.

229 These findings demonstrate the potential utility of the new lesion correction method for
230 studying network-based mechanisms of cognitive, behavioral, and motor deficits in patients with
231 TBI. For example, lesion-induced cortical volume changes within the limbic, default mode, and
232 frontoparietal networks (the three most frequently lesioned networks) can be tested for
233 correlations with symptoms that are putatively attributable to their dysfunction, such as
234 behavioral dysregulation, altered self-awareness, and executive dysfunction, respectively. From a
235 phenomenological standpoint, the application of the new lesion correction tool to large clinical-
236 radiological-pathological databases being acquired by the LETBI,¹² Transforming Research and
237 Clinical Knowledge in TBI (TRACK-TBI),²¹ Collaborative European NeuroTrauma
238 Effectiveness Research in Traumatic Brain Injury (CENTER-TBI),²² and other studies, has
239 potential to elucidate pathological signatures of TBI phenotypic classification, with implications
240 for clinical trial selection²³ and prognostication.¹⁰

241 Several limitations should be considered when interpreting the results of this study. The
242 lesion correction method relies upon an assumption whose validity is difficult to test: we assume
243 that at sites of tissue distortion and encephalomalacia, the cortex is non-functional and therefore
244 should be masked, or removed, from subsequent cortical volume measurements. This assumption
245 is made with the recognition that definitive determination of the functional status of lesioned
246 cortex is not possible solely with T1-weighted MEMPRAGE data. Nevertheless, the assumption

247 that lesioned cortex is non-functional in the population studied here is strongly supported by
248 visual inspection of the data, which reveals complete or near complete absence of cerebral
249 cortex, as shown in Figure 1. In future multimodal experiments, the lesion correction method can
250 be refined by analyzing the functional properties of lesioned cortex (e.g. with functional MRI or
251 EEG). In future work, it may also be possible to integrate the lesion correction method with
252 software programs that offer automated lesion detection, such as the ABC module extension of
253 3D Slicer.²⁴ Moreover, the method can be used to measure point-wise and region-wise estimates
254 of cortical thickness in unlesioned cortex by masking inaccurate regions of cortex.

255

256 **Conclusions**

257 We demonstrate the impact of a new FreeSurfer-based lesion correction tool on cortical
258 volumetric measures in 7 atlas-based functional networks, and we distribute this lesion
259 correction tool to the academic community. We show that cortical lesions are not evenly
260 distributed across networks, but rather preferentially affect the frontotemporal nodes of the
261 limbic network. This lesion correction method can facilitate inclusive, unbiased investigation
262 into the anatomic basis of neurological deficits in patients with TBI and other neuropsychiatric
263 diseases associated with focal lesions.

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285

286 **Author Disclosure Statement**

287 None of the authors has a conflicting financial interest. Dr. Fischl has financial interest in
288 CorticoMetrics, a company whose medical pursuits focus on brain imaging and measurement
289 technologies. His interests were reviewed and are managed by Massachusetts General Hospital
290 and Partners HealthCare in accordance with their conflict of interest policies.

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372 volumes. *J Neurotrauma* 28, 2287-2306.

373 **Figure Legends**

374 **Figure 1. Overview of Lesion Correction Method**

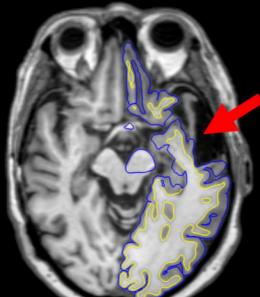
375 Row 1: Axial, coronal, and sagittal T1-weighted images of a representative patient with traumatic
376 brain injury. FreeSurfer reconstructions of the cortical surface (blue line) and grey-white surface
377 (yellow line) are used to visually identify regions where a cortical lesion (red arrows) caused
378 surface inaccuracies. Row 2: We manually outlined lesions by labeling inaccurate vertices on the
379 cortical surface (left image). This surface inaccuracy (labeled in red) is shown in the coronal
380 plane in the middle image and the right, zoomed image. The red label passes through lesioned,
381 encephalomalacic tissue. Row 3: To correct for the inaccuracy in the surface label at the site of
382 the lesion, we remove the volume of cortex within the lesion label and perform cortical
383 volumetric measures that exclude the lesioned tissue.

384

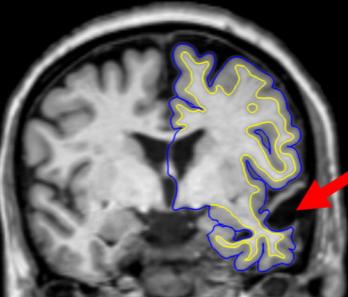
385 **Figure 2. Lesion Topology and Network-based Lesion Effects on Cortical Volume**

386 In the left panel, we show a heat map of cortical lesions for all 46 patients who had at least one
387 lesion. The anatomic regions most commonly affected by cortical lesions were the frontal and
388 temporal lobes, particularly the frontal poles, temporal poles and orbitofrontal regions. In the top
389 right panel, we show the 7 functional networks from the Yeo atlas¹¹ that were used to investigate
390 network-specific lesion effects. In the bottom right panel, we show a violin plot demonstrating
391 the changes in average cortical volume for each network after applying the lesion correction
392 method. Lesion effects on average cortical volume varied between networks, with the limbic
393 network showing the largest magnitude of decline in average cortical volume after application of
394 the lesion correction method.

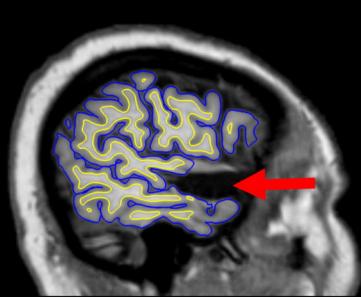
FreeSurfer
Reconstruction



Axial

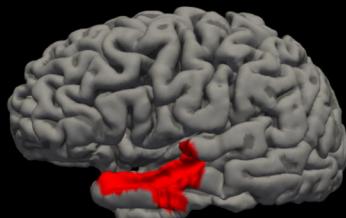


Coronal

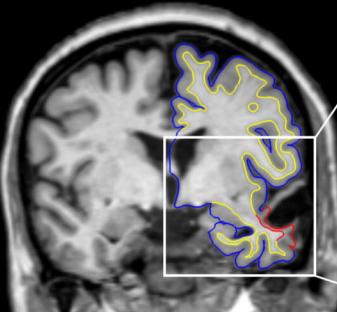


Sagittal

Lesion
Labeling

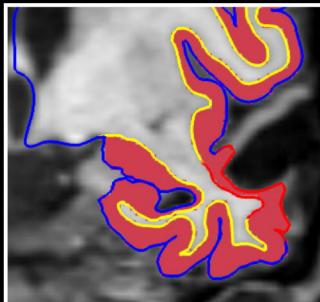


Lesion Label on 3D Surface

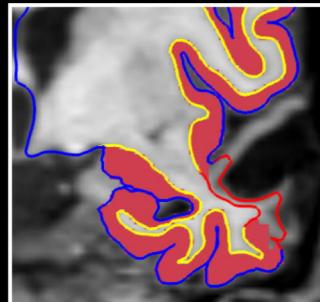


Lesion Label on Surface in Coronal Plane

Cortical
Volume
Correction



Inaccurate Cortical Ribbon

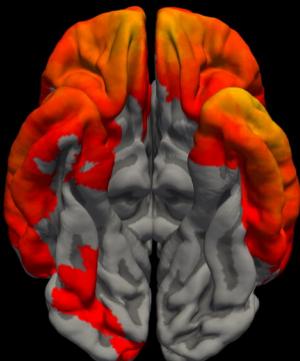
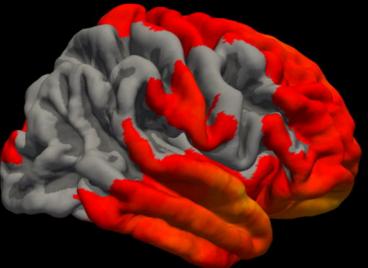
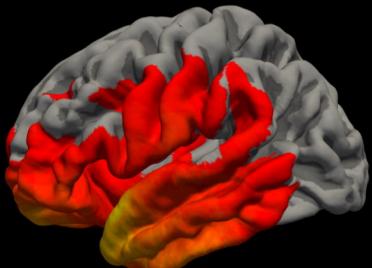


Corrected Cortical Ribbon



Cortical Volume

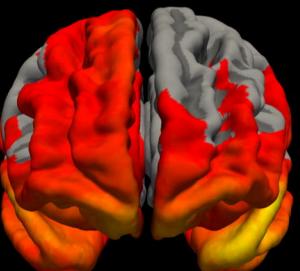
Contusions



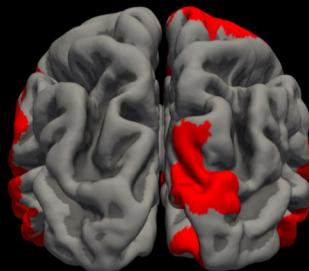
Inferior



Superior



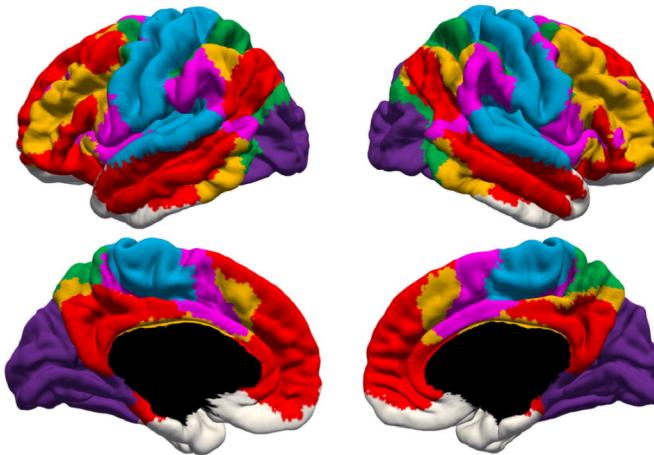
Anterior



Posterior

n=1

20



Networks

- Default Mode
- Salience
- Limbic
- Executive Control
- Dorsal Attention
- Somatomotor
- Visual

Contusion Effects on Network Volume

