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p 1 and Group 2) included in this study, had
dure MRI evaluations. Diffusion weighted images
ed before and within 48 h of the vascular intervention.
ent Diffusion Coefficient (ADC) maps were calculated based on these DW-images using the product software. Group 1 data were collected on a 1.5 T MRI (Signa Excite HD 12.0, GE Medical Systems, Milwaukee, WI, USA). Axial DWI echoplanar/spin echo images (TR/TE = 12,000/80 milliseconds, b = 1000, 5 mm thick slices, 5 mm gap, matrix size 128 × 128, FOV = 300 mm, acquired inplane resolution 2.344 mm). Group 2 data were collected on 3 T MRI (Discovery MR 750 Software Rev. 23, GE Medical Systems, Milwaukee, WI, USA). The protocol included 30 directional whole brain Axial DWI echoplanar/spin echo images with Asset (TR = 6600, TE minimum, 5 B0 images with B0 = 1000s/mm^2, 2 NEX, 2.5 mm thick slices, 0 mm gap, matrix size 96 × 96, FOV = 240 mm).

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Estimation (ALE) analysis (Glahn

imensional maps of probabilities of lesion

primarily been used for meta-analyses, and re-

convergence of points across sets of three-dimensional coordinates in standard space obtained from published studies of functional imaging (Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002) and voxel-based morphometry studies (Ellison-Wright et al., 2008; Glahn et al., 2008). The ALE statistical approach is also robust against false positives because it involves permutation testing and correcting for multiple comparisons using Family-wise-Error (FWE, Eickhoff et al., 2016).

Here we describe Convergence Analysis of Micro-Lesions (CAML), a new application of the ALE algorithms which is adapted for small lesions and surgical applications. Essentially lesions are defined manually, representative points are derived, and brains are compared based on what is known about the intervention. For example in this application, since procedure-related embolization tends to travel to the same side of the procedure, analyses were made more sensitive and informative by flipping brains so that hemispheres ipsilateral to the intervention are analyzed together. Results thus identify regions where lesions occur contralaterally, likely due to crossflow. In order to test the replicability and field robustness of these convergence maps, we collected data from two groups of patients from MRI's of different field strengths (1.5T, 3T) all scanned at a single institution over 12 years.

2. Material and methods

2.1. Participants

2.1.1. Selection

Indications for carotid revascularization procedures included severe asymptomatic stenosis (> 80%) of carotid arteries identified on carotid duplex ultrasound or moderate to severe stenosis (> 60%) with focal neurological symptoms. All patients who received CAS procedures were typically those deemed to be high-risk (Bates et al., 2007). All CAS and majority of CEAs were performed by a single operator (WZ) without changing in operative techniques. The study was approved by the Stanford Institutional Review Board and the R&D committee of the VA Palo Alto Health Care System (VAPAHCS). Procedures followed were in accordance with institutional guidelines. For some early data collected for Group 1, MRI data was obtained for clinical care and waivers of HIPAA authorization and consent were granted. For all later studies patients provided informed consent and HIPAA authorization.

2.1.2. Patient groups and procedures

The first group of patients was scanned on a 1.5 T MRI (Group 1) and the second group of patients was scanned on a 3 T MRI (Group 2), a

2.3. Image analyses

Lesions were defined by signal intensity, increases on DWI and decreases on ADC. Procedure associated lesions were defined as the lesions seen only in the post-procedure DWI and ADC images and not in the pre-procedural DWI and ADC images. These post-procedure lesions were traced manually on individual MRI slices by a rater using MRICron (http://people.cas.sc.edu/rorden/mricro/mricro.html) in both groups. Board certified neuroradiologists (B.L., S.S.), checked these lesion definitions and one (S.S.) checked both groups for continuity of rating and also the pre-procedure images to assure that lesions are new lesions related to procedures. Routines from University of Oxford's Center for Functional MRI of the Brain (FMRIB) Software Library (Jenkinson et al., 2012; Smith et al., 2004) were used to prepare regions of interest (ROI's) for the ALE analysis. The B0 images of the DWI were skull stripped using BET 2.1 to remove the tissue outside the brain. These skull stripped images were then warped to the template brain used in ALE (Colin T1 MNI) using a 12 parameter, affine transformation with FLIRT 5.5. No lesion tissue masking was required as the lesions did not seem to be affecting the normalization of these B0 images. To enable group analyses, warping parameters derived from warping the whole brain B0 images, were applied to the ROI's. Since lesion laterality was typically ipsilateral to the side of surgery, ROI's were collapsed on to one hemisphere based on whether they were ipsilateral (right) versus contralateral (left, using FSL fslswapdim) and single points were extracted. A point based analysis was performed to avoid bias from large lesions, thus, the ALE analysis was conducted on the centers of mass of the ROI's rather than their entire volume. A parallel analysis of the entire ROI volumes resulted in similar results. To extract the peak coordinates for the ALE analysis, an FSL cluster routine was applied to the normalized ROI image files, one for each patient, to derive a center of gravity for each ROI, and these points were submitted for further analysis to GingerALE (version 2.3.6, http://www.brainmap.org/ale/) (Laird et al., 2009). In ALE, these three-dimensional coordinates were blurred with a Gaussian distribution to approximate the original cluster extent, and pooled to search for convergence. GingerALE (Eickhoff et al., 2009) was applied to data from the individual patients to generate a digital convergence map (full width half max values for each Gaussian distribution were determined automatically by the software with no additional full width half max values applied) and clusters

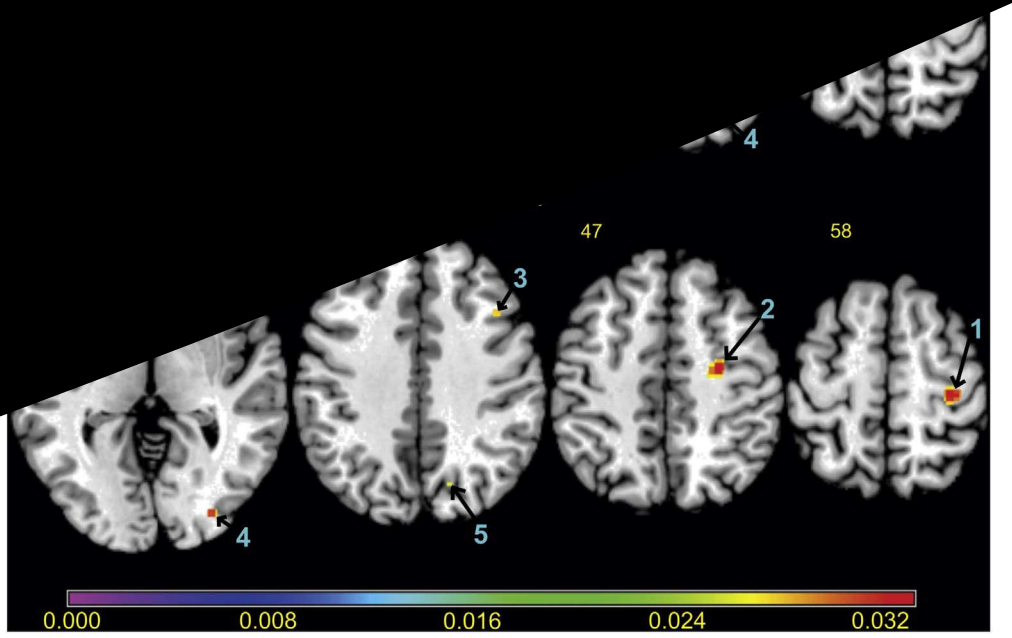

Fig. 1. ALE Statistics map for all clusters in Group 1 (top) and Group 2 (bottom) as seen in Table 1. Color scheme in the images represents the degree of convergence of lesions across patients in each group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(corrected for multiple comparisons with Voxel-level Family-wise Error, $p < 0.05$, number of permutations = 1000). The threshold was chosen to be adequately conservative to avoid false positive findings (Eklund et al., 2016).

3. Results

3.1. Overview

We present in Fig. 1 an image displaying the brain regions most vulnerable to the lesions in the two groups. Table 1 represents the separate ALE analyses of Group 1 (1.5T MRI) and Group 2 (3T MRI). Note that emboli ipsilateral to the side of the procedure were collapsed on to the right hemisphere, so the x coordinate only reflects the degree of lateralization with respect to the procedure. Brodmann Areas reported were derived by ALE using the Talairach Daemon atlas (http://www.talairach.org/daemon.html) and the icbm2tal transform (Lancaster et al., 2007). Each label was checked by the investigators and when a Brodmann Area was not reported in ALE results (typically for a white matter region), other maps were used including, those provided by FSL (http://fsl.fmrib.ox.ac.uk/fsl/fsl4.0/fslview/atlas-descriptions.html) which include the Johns Hopkins WM/LONI 81 DTI Atlas and the Harvard-Oxford atlas.

3.2. Rates of lesions

General trends in overall lesion rates were consistent with the previously established findings. For example, more lesions were detected

Table 1
Separate group analyses for Group 1 and Group 2.

Cluster #	Descriptor center (peaks)	Brodmann area	Volume (mm^3)	ALE statistic	Peak[a]		
					x	y	z
Group 1							
1	Motor/premotor	4/6	1664	0.027	36	−18	56
2	Frontal WM		984	0.025	24	−24	38
3	Premotor/DLPFC	6/9	208	0.020	36	12	48
4	Parietal	7	8	0.018	26	−64	46
Group 2							
1	Motor/premotor	4	456	0.037	34	−26	60
2	Frontal WM	6	384	0.035	28	−12	46
3	DLPFC	9	128	0.031	42	18	38
4	Occipital	18	112	0.031	32	−86	−2
5	Parietal	7	8	0.026	16	−72	36

ALE = Anatomic likelihood estimate; WM = White Matter.
[a] Montreal Neurological Institute (MNI) co-ordinates.

ocated in the carotid bi- to common carotid arteries. or occlusion was present in Group 1 in roup 2 in 19.56% (9/46). Rate of preoperative Group 1 was 74.4% (32/43) and Group 2 was 76% (35/ ate of new focal neurological symptoms for Group 1 was 16.2% (7/43, 2 CAS) and for Group 2 was 6.52% (3/46, 3 CAS). Screening for depression using the Geriatric Depression Scale was available for Group 2 and 33% (13/46) screened positive (i.e. > 9) preprocedure and 16.2% (6/46) screened positive postprocedure.

3.4. Locations of lesions

Table 1 shows the locations of lesions reaching significance. Fig. 1 displays these regions with cluster numbers corresponding to the table indicated in turquoise. Only lesions ipsilateral to the side of surgery reached significance. One of the most obvious differences across the groups was that results were more robust and consistent in Group 2 at the higher field strength than in Group 1, hence in Fig. 1 those clusters appear in warmer colors on Group 2. For both studies, the peak of the largest cluster (cluster 1) was in motor/premotor cortex (BA 4/6), Group 1 (36, −18, 56), and Group 2 (34, −26, 60). Cluster 2 was in the white matter, deep to the motor/premotor cortex. In Group 1, cluster 2 was deeper and larger than in Group 2. The next largest cluster (cluster 3) was in the dorsolateral prefrontal cortex (DLPFC) for both the groups. One other cluster common to both groups (cluster 4 in Group 1 and cluster 5 in Group 2) was in the dorsal/medial, parietal lobe region. Group 2 also included a cluster (cluster 4) in the occipital lobe.

4. Discussion

Across these two, patient groups, scanned on different MRI systems, CAML generated highly consistent, probabilistic maps that identified regions vulnerable to lesions from carotid revascularization. As expected, the higher field strength MRI increased sensitivity to detect these lesions. The motor/premotor cortex was the most likely to be affected. Other consistent regions included subcortical white matter deep to motor/premotor cortex, dorsolateral prefrontal cortex, and medial/superior parietal cortex. At the higher field strength an occipital cluster was also detected. In addition to being consistent across acquisitions, the analysis technique was thus quite sensitive in detecting patterns in approximately only 40 patients per group.

The finding that the region most vulnerable to these lesions was the motor/premotor area (BA 4/6) is consistent with other studies of carotid revascularization. Heyer et al. (2015) studied 374 patients undergoing CEA and found that post-procedure changes in hand dexterity were associated with the side of the surgery. Specifically, procedures contralateral to the nondominant hand (e.g. right hemisphere for right

al., of studies vascular cogni- et al., 2017) and/or Concerto et al., 2013; Pennisi tor cortex excitability alone cannot from other forms of degenerative burden disease (Pennisi et al., 2015), a logical follow-up e of changes in motor cortex excitability following lesions tor cortex occurring during endovascular procedures. More recent theories of cognitive aging and memory have also implicated the motor system in inhibitory processes in memory (Rae et al., 2015; Schilling et al., 2014).

The other clusters are within regions consistent with vascular cognitive impairment and vascular dementia. The dorsolateral prefrontal cortex (BA 9/46) and deep white matter in the frontal lobe have long been invoked as a neural substrate of executive dysfunction in vascular based mild cognitive impairment and in models of functional compensation in stroke and aging (Cabeza et al., 2002; Hachinski et al., 2006; Rosen et al., 2002; Smith et al., 2011; Ward, 2006). This region is also known to be involved with “prefrontal vascular syndrome” (Bella et al., 2010), a clinical phenomenon that involves both cognitive dysfunction and depressive symptoms. Of note even before the procedure a third of our cohort screened positive on the Geriatric Depression Scale, though there was a slight decrease after surgery, a finding that deserves further study. The superior parietal region (Group 1, cluster 4; Group 2, cluster 5) is part of the superior default mode network and damage to this system has been demonstrated to be particularly disruptive of cognition in stroke patients (Warren et al., 2014). The default mode network is also a brain system involved in memory that is affected by Alzheimer's disease through amyloid deposition (Buckner et al., 2005), hence lesions may be affecting an already vulnerable network. Apolipoprotein E-epsilon4 polymorphism, a genetic mutation associated with amyloid deposition, is associated with cognitive decline in Alzheimer's but also increased risk of CEA related cognitive decline (Heyer et al., 2014). The occipital cluster appears to be located at the border zone between the MCA and PCA territories and likely still represents an embolus location in the very distal MCA territory (Kansagra and Wong, 2008). This analysis thus identifies brain regions of interest for future a priori studies of brain changes related to carotid vascular procedures.

By identifying regional vulnerabilities in standard space, CAML thus represents a new, quantitative, approach to compare subtle, multifocal brain pathologies to findings from functional and structural MRI studies and across different clinical populations. There have been attempts to derive systematic patterns using the MRI scans of stroke patients from different vessel territories with reasonable success (Min et al., 2000; Phan et al., 2010; Phan et al., 2005; Phan et al., 2006). Probabilistic mapping of imaging data of different blood vessel territories has been based on patients with large strokes (Bilello et al., 2012; Hillis et al., 2004; Phan et al., 2009; Phan et al., 2006) and typically the statistics depend on simple proportions of patients. In our initial tests, maps based on the proportion of patients with lesions in a given voxel were extremely low for these tiny lesions and hence most statistical tests were insensitive and underpowered.

This study identifies consistent brain regions likely to be affected by carotid procedures and thus enables new lines of investigation of pathologies with diffuse non-overlapping lesions; however, there are also important limitations and need for further study. The consistency of the lesion locations across Groups 1 and 2 is compelling, but more study is needed on the mechanisms underlying this regional vulnerability. For example there may be regional differences in vessel tortuosity (Wang et al., 2016) or flow rate that may predict risk factors for

...otid ...aps. These ...large lesions, and ...ypes, (e.g. Gensicke et al., ...nts per group and significant het- ...we were conservative in the numbers of ...d, however, with larger samples the correlation ...cal (plaque features, type of intervention, presence/ab- ...of focal deficits) and neuroradiological data (lesion load, location, severity) would disclose additional interesting findings. Since these patients will likely have lesions in multiple locations and these lesions are tiny, studying disruptions of resting state fMRI networks of regions may be most informative (e.g. Warren et al., 2014). The fact that the two patient groups differed most in the frontal subcortical white matter lesions (cluster 2 in Group 1 and 2) suggests that this area may account for variability in patient outcomes either due to advancements in interventional techniques or differences in the patient groups. There also needs to be further study of the neural substrates of functional improvements and resilience. For example with respect to memory, there are some studies that find declines (Aharon-Peretz et al., 2003; Heyer et al., 1998; Zhou et al., 2012) but an increasing number of studies demonstrate improvements or resilience against the lesions (Aleksic et al., 2006; Bossema et al., 2005; Crawley et al., 2000; Ghogawala et al., 2013; Incalzi et al., 1997; Kim et al., 2015; Kougias et al., 2015; Kuliha et al., 2015; Migliara et al., 2013; Mononen et al., 1990; Ortega et al., 2014; Pearson et al., 2003; Piccetto et al., 2013; Takahashi et al., 2013; Wang et al., 2015; Xia et al., 2015; Xu et al., 2007; Zhou et al., 2017).

CAML thus provides many new opportunities for the study of multifocal pathology. Our consistent findings across two different MRI's and patient cohorts from a real-world setting at a Veteran's hospital, where complex patients with cardiovascular risk factors and comorbidities are highly prevalent (Johnson et al., 2004; Medicine, 2014), over a decade of vascular surgeries, highlights the robustness of CAML.

5. Conclusions

The CAML approach used convergence analysis to identify replicable patterns of tiny lesions following carotid endovascular procedures. The motor/premotor cortex is highly vulnerable to these lesions. Other regions that also have a high likelihood of lesions include the dorsolateral prefrontal cortex and medial superior parietal lobe. There is variability in extension to the white matter deep to motor cortex and occipital lobe hence this may be a target of study of heterogeneous patient outcomes. Applying this technique to other multifocal pathologies may yield different, as yet undiscovered, patterns of regional vulnerability and new lines of research.

Acknowledgments and funding page

ACR was supported by a K award NIH NIA (K01AG025157) and the

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