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Convergence Analysis of Micro-Lesions (CAML): An approach to mapping of diffuse lesions from carotid revascularization

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Carotid revascularization (endarterectomy, stenting) prevents stroke; however, procedure-related embolization is common and results in small brain lesions easily identified by diffusion weighted magnetic resonance imaging (DWI). A crucial barrier to understanding the clinical significance of these lesions has been the lack of a statistical approach to identify vulnerable brain areas. The problem is that the lesions are small, numerous, and non-overlapping. Here we address this problem with a new method, the Convergence Analysis of Micro-Lesions (CAML) technique, an extension of the Anatomic Likelihood Analysis (ALE). The method combines manual lesion tracing, constraints based on known lesion patterns, and convergence analysis to represent regions vulnerable to lesions as probabilistic brain atlases. Two studies were conducted over the course of 12 years in an active, vascular surgery clinic. An analysis in an initial group of 126 patients at 1.5 T MRI was cross-validated in a second group of 80 patients at 3T MRI. In CAML, lesions were manually defined and center points identified. Brains were aligned according to side of surgery since this factor powerfully determines lesion distribution. A convergence based analysis, was performed on each of these groups. Results indicated the most consistent region of vulnerability was in motor and premotor cortex regions. Smaller regions common to both groups included the dorsolateral prefrontal cortex and medial parietal regions. Vulnerability of motor cortex is consistent with previous work showing changes in hand dexterity associated with these procedures. The consistency of CAML also demonstrates the feasibility of this new approach to characterize small, diffuse, non-overlapping lesions in patients with multifocal pathologies.

1. Introduction

Carotid revascularization procedures (carotid artery stenting [CAS] and endarterectomy [CEA]) are treatments for carotid occlusive disease that involve controlled manipulation of the carotid, and lead to multiple, tiny, brain lesions visible on diffusion weighted MR imaging (DWI). These lesions are clearly identifiable as procedure-related because they appear immediately after the procedure, are typically visible

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for only a few days, and have been related to particles flowing to the brain and detected on carotid ultrasound (Bonati et al., 2010; Ederle et al., 2010; Poppert et al., 2006; Rapp et al., 2007; Skjelland et al., 2009; Tedesco et al., 2009). Clinically, endovascular procedures are effective means of preventing stroke, and whereas serious associated complications are rare (Brott, 2010), there have been inconsistent studies suggesting these lesions may be linked to subtle post-procedural cognitive decline and increased vulnerability to future cognitive declines (Aharon-Peretz et al., 2003; Fink et al., 2015; Ghogawala et al., 2008; Heyer et al., 1998; Tiemann et al., 2009; van Dijk and Kalkman, 2009; Wasser et al., 2011; Zhou et al., 2017; Zhou et al., 2012). For example, one large study showed changes in hand dexterity related to side of intervention (Heyer et al., 2015). To identify potentially subtle dysfunction, it is crucial to have highly specific knowledge of which brain systems are affected in order to develop sensitive and focused assessment. Since lesions from endovascular procedures are small (100–200 mm^3), and diffuse, traditional analyses (e.g. Bates et al., 2003) are typically insensitive because they depend on lesions having spatial overlap.

In contrast, Anatomic Likelihood Estimation (ALE) analysis (Glahn et al., 2008) generates three dimensional maps of probabilities of lesion occurrence. ALE has primarily been used for meta-analyses, and represents the convergence of points across sets of three-dimensional peak 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 more sensitive acquisition protocol but one which was an opportunity to cross validate the initial results. The first group (Group 1) underwent successful carotid interventions between 2002 and 2009, a total of 126 patients (CAS = 55, CEA = 71). The second group (Group 2) underwent carotid interventions between 2009 and 2015, a total of 80 patients (CAS = 39, CEA = 41). A similar percentage of patients underwent stenting in Group 1 (44%) and Group 2 (49%).

2.2. Imaging acquisition

Both the groups (Group 1 and Group 2) included in this study, had pre and post-procedure MRI evaluations. Diffusion weighted images were collected before and within 48 h of the vascular intervention. Apparent 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).

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