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BRIEF COMMUNICATION

New open-source ictal SPECT analysis method implemented in BioImage Suite

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Summary

Ictal single photon emission computed tomography (SPECT) is a powerful tool for noninvasive seizure localization, but it has been underutilized because of practical challenges, including difficulty in implementing ictal-interictal SPECT difference analysis. We previously validated a freely available utility for this purpose, ictal-interictal subtraction analysis by statistical parametric mapping (SPM) (ISAS). To further simplify and improve the difference imaging technique, we now compare a new algorithm, ISAS BioImage Suite (see http://spect.yale.edu and http://bioimagesuite.org), to the original ISAS method in 13 patients with known seizure localization. We found that ISAS BioImage Suite was in agreement with the original algorithm in all cases for which ISAS correctly identified a single unambiguous region of seizure onset. We also tested for possible effects of scan-order bias in the control group used for the analysis and found no significant effect on the results. These findings establish a simple, validated and objective method for analyzing ictal-interictal SPECT difference images for use in the care of patients with epilepsy.

KEY WORDS: Epilepsy, Single photon emission computed tomography, Surgery, Statistical parametric mapping, Localization.

Single photon emission computed tomography (SPECT) remains unique when compared to other neuroimaging modalities in its ability to image ictal cerebral blood flow (CBF) without movement artifact. Several processing techniques are available to analyze ictal SPECT images to predict the areas of epileptic foci (Zubal et al., 1995; O'Brien et al., 1998; Lee et al., 2000; Knowlton et al., 2004; Kim et al., 2009). These methods generally either compute the differences between an ictal SPECT and an interictal SPECT, or compare the ictal SPECT to a healthy normal database using methods such as statistical parametric mapping (SPM). One of the more advanced algorithms, ictal-interictal subtraction analysis by SPM (ISAS), compares the differences between a patient's ictal and interictal SPECT images to the normal variance of sequential SPECT images from a control group (Chang et al., 2002; McNally et al., 2005).

Although clinically successful, the ISAS algorithm is limited by non–user-friendly implementation with different SPM and MATLAB (The MathWorks, Inc., Natick, MA, U.S.A.) versions, and by imperfect image coregistration. In addition, ISAS was not tested for possible effects of scan-order bias in the estimate used for population standard deviation (SD). To reduce these limitations, a new algorithm based on ISAS was recently developed and implemented in a comprehensive, multiplatform, open-source image analysis suite, BioImage Suite (http://bioimagesuite.org) (Scheinost et al., 2009). This study provides clinical validation of the new method by comparing the results of ISAS BioImage Suite with the original ISAS algorithm.

Methods

We reutilized the same scans employed to validate the original ISAS algorithm. Full details of patients, SPECT image acquisition methods, and seizure localization have been published previously (McNally et al., 2005). This research received prior approval by the institutional review body and written informed consent was obtained from all human subjects.

Three analysis methods were compared: ISAS, ISAS BioImage Suite, and ISAS HN BioImage Suite. All three methods are based on first coregistering and subtracting ictal minus interictal SPECT images, and then computing the significance of any differences by using a standard dataset

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Table 1. Comparison of ISAS SPM, ISAS BioImage Suite, and ISAS-HN BioImage Suite algorithms in 13 patients with confirmed mesial temporal lobe or neocortical epilepsy

Patient data		ISAS SPM Results			ISAS BioImage Suite results			ISAS-HN BioImage Suite Results		
Patient no.	Localization[a]	Location of most significant hyperperfusion cluster	Cluster significance[b] (p-value)	Cluster volume[c] (*k*)	Location of most significant hyperperfusion cluster	Cluster significance[b] (p-value)	Cluster volume[c] (*k*)	Location of most significant hyperperfusion cluster	Cluster significance[b] (p)	Cluster volume[c] (*k*)
Mesial temporal										
1	L Temporal	**L Temporal**	<0.001	22717	**L Temporal**	<0.001	25862	**L Temporal**	<0.001	25645
2	R Temporal	**R Temporal**	<0.001	10429	**R Temporal**	<0.001	13165	**R Temporal**	<0.001	11233
3	R Temporal	**R Temporal**	<0.001	28444	**R Temporal**	<0.001	29098	**R Temporal**	<0.001	27496
4	R Temporal	**R Temporal**	<0.001	17538	**R Temporal**	<0.001	17612	**R Temporal**	<0.001	17166
5	R Temporal	**R Temporal**	<0.001	31298	**R Temporal**	<0.001	30818	**R Temporal**	<0.001	30908
6	L Temporal	L Temporal, L occipital	<0.001	19246	L Temporal, bilateral occipital	<0.001	18443	L Temporal and Bilateral Occipital	<0.001	18882
7	L Temporal	L Temporal, L parietal, bilateral occipital	<0.001	22799	**L Temporal**	<0.001	18055	**L Temporal**	<0.001	18864
Neocortical										
8	R Temporal neocortex	**R Temporal**	<0.001	19963	**R Temporal**	<0.001	18279	**R Temporal**	<0.001	18365
9	L Temporal neocortex	**L Temporal**	<0.001	30233	**L Temporal**	<0.001	28618	**L Temporal**	<0.001	29860
10	R Superior temp, inferior parietal	No significant clusters	0.117	1013	**R Temporal**	0.011	2002	No Significant Clusters	0.055	1436
11	L Rolandic	**L Rolandic**	<0.001	2961	**L Rolandic**	<0.001	15450	**L Rolandic**	<0.001	15930
12	R Superior frontal	**R Superior frontal**	<0.001	4203	**R Superior frontal**	<0.001	6302	**R Superior Frontal**	<0.001	6559
13	R Frontal	**R Frontal**	<0.001	7726	**R Frontal**	<0.001	8927	**R Frontal**	<0.001	9778

[a]Seizure localization was confirmed in all patients by seizure free outcome for at least one year following resective surgery. Preoperative evaluation was as described previously (McNally et al., 2005).
[b]Cluster level significance (p) corrected for multiple comparisons for the entire brain.
[c]Cluster size (k) in voxels (voxel size = 2 × 2 × 2 mm).
Bolded text indicates a correspondence between the location of the most significant hyperperfusion cluster and the known region of seizure onset.

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of normal controls to estimate the variation of sequential SPECT imaging for an individual at two different time points. SPECT seizure localization for each patient was then determined based on the voxel cluster with the most significant ictal CBF increases.

ISAS in SPM was performed with MATLAB 6.1 and SPM2 using the standard ISAS algorithm described previously (http://spect.yale.edu/) (McNally et al., 2005).

ISAS BioImage Suite analysis was performed with BioImage Suite 2.6 (http://bioimagesuite.org). This method uses the same processing steps used by the original ISAS algorithm but simplifies the calculations of voxel by voxel significance by determining estimates of the variation of sequential SPECT imaging once, rather than recalculating them for each patient analysis. BioImage Suite also uses improved image coregistration (Papademetris et al., 2004), which differs slightly from SPM2.

ISAS HN BioImage Suite was used to test for any possible effects of scan-order bias in the control population. Both ISAS and ISAS BioImage Suite treat the first scan as ''ictal'' and the second as ''interictal'' for each subject in the healthy normal cohort, although in fact both scans were ''interictal.'' To eliminate this effect, ISAS HN BioImage Suite estimates the normal variation of sequential SPECT images using a half-normal distribution rather than a standard normal distribution (Scheinost et al., 2009). Full details and instructions for all analysis methods can be found at http://spect.yaleedu.

Results

We found that ISAS BioImage Suite was in agreement with the original algorithm in all cases for which ISAS correctly identified a single unambiguous region of seizure onset (Table 1). In addition, eliminating scan-order bias in the estimation of the normal variation (ISAS HN BioImage Suite) had no major effect on the results.

All three methods provide a high level of correspondence between the known region of seizure onset and the location of the most significant ictal hyperperfusion cluster. For the mesial temporal lobe epilepsy group, the new algorithms agreed with the region correctly identified by ISAS in SPM for patients 1–5 (Table 1). In patient 6, unambiguous localization was not attained by any method, since hyperperfusion extended into the occipital lobe(s). For patient 7, the ISAS SPM algorithm indicated a cluster of hyperperfusion spreading into several lobes, failing to give a correct localization. However, both algorithms in BioImage Suite produced correct localization of the left temporal lobe. Fig. 1A,B shows typical clusters of hyper- and hypoperfusion produced by the two BioImage Suite algorithms in a patient with right mesial temporal epilepsy. The clusters produced by each algorithm localized to the confirmed area of seizure onset (right temporal) and have similar shapes and sizes.

The three algorithms also had similar results in five of six of the patients with neocortical epilepsy (Table 1, patients 8–13). The ISAS BioImage Suite algorithm was the only algorithm to correctly localize seizure onset in patient 10, based on a hyperperfusion cluster just barely satisfying the significance threshold ($p < 0.05$). The other two algorithms, ISAS SPM and ISAS HN BioImage Suite, also had a hyperperfusion cluster in this region (right temporal) but it did not meet the significance threshold. Fig. 1C,D shows typical results from a neocortical epilepsy patient using the BioImage Suite–based algorithms.

Discussion

The original ISAS algorithm implemented in SPM provided a reliable statistical method for localizing focal epilepsy. We have shown that ISAS BioImage Suite has localizing ability similar to that of the original algorithm, and that scan order for the control population has no major effect on the results. ISAS BioImage Suite has advantages of easier implementation and improved registration methods over SPM2. BioImage Suite uses the same algorithm as the Image Registration Toolkit (IRTK), which has been shown to compare favorably to other registration methods (Klein et al., 2009). ISAS Bioimage Suite enables datasets across multiple techniques, including SPECT, magnetic resonance imaging (MRI), positron emission tomography (PET), functional MRI (fMRI), magnetic resonance spectroscopy (MRS), and computed tomography (CT) electrode maps to be easily combined in the same 3-dimensional space (3D) for a given patient.

ISAS-type analyses in both SPM and BioImage Suite involve several preprocessing steps (smoothing, nonlinear warping, and cropping), which if applied blindly can produce artifact from spurious signals outside the brain. We encourage users to not treat ISAS BioImage Suite as a ''black box'' system. We therefore include several checkpoints at the end of key steps (i.e., nonlinear registration) to allow the user to verify the accuracy of the data before continuing. In addition, we provide instructions on using difference imaging as a double check against preprocessing errors. Previously, other software (rview; http://www.colin-studholme.net/software/software.html) was needed to view difference images without preprocessing. However, another advantage of ISAS BioImage Suite is the automatic inclusion of simple difference images in the same package.

It was reassuring to find that results with ISAS HN BioImage Suite were very similar to those of the other algorithms, suggesting that scan-order effects in the normal population do not have any major effect on the results. Another important point is that the current validation study focused on SPECT signal increases, since these are most clinically relevant for ictal scans (McNally et al., 2005; Kim et al., 2009). However, ISAS BioImage Suite and other software including ISAS SPM can also be used to examine CBF

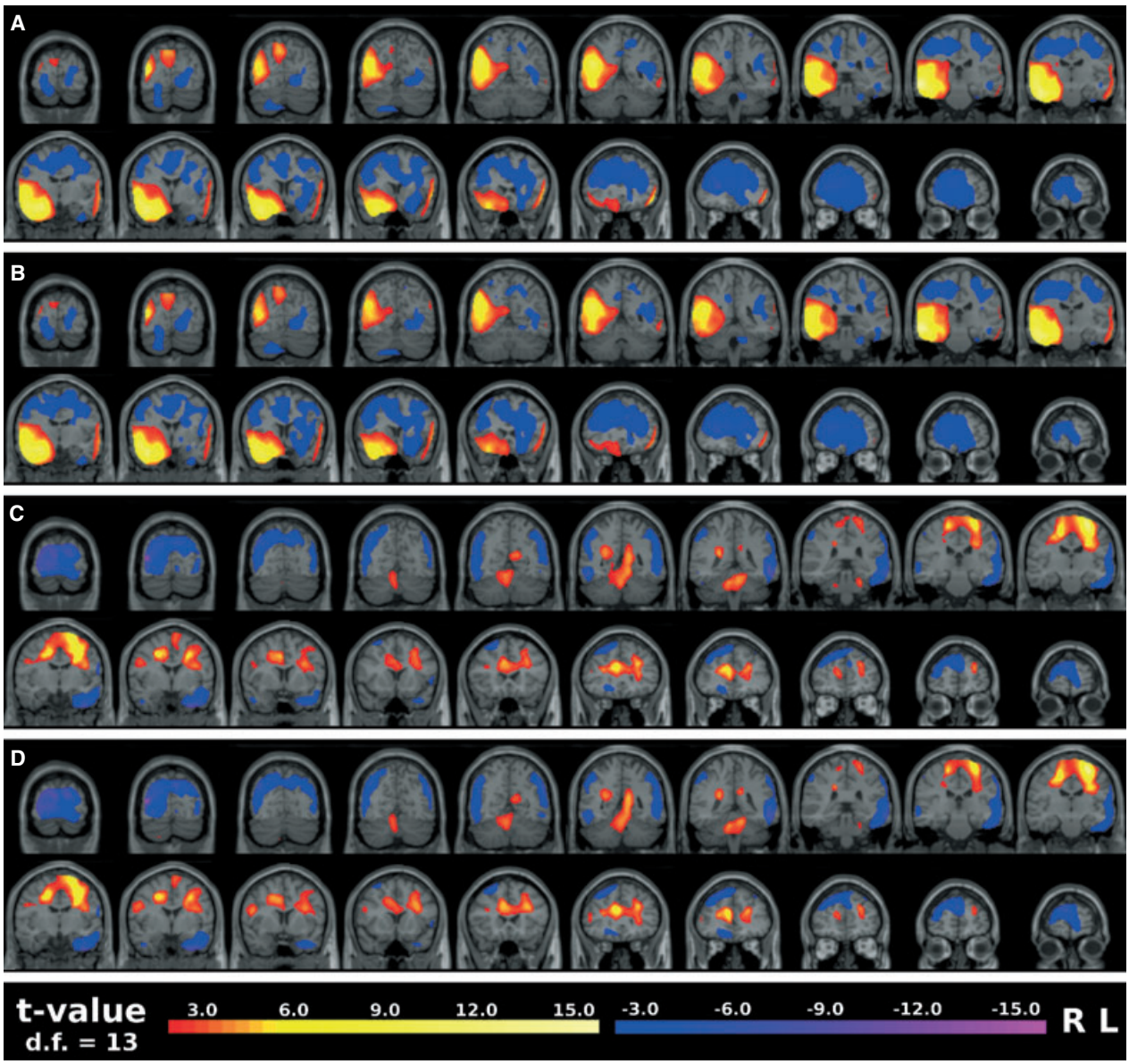

Figure 1.
Typical single photon emission computed tomography (SPECT) hyper- and hypoperfusion patterns for patients analyzed in BioImage Suite. Results obtained with ISAS BioImage Suite and ISAS HN BioImage Suite are generally similar, and agree with known region of seizure onset. (**A**, **B**) Results of ISAS BioImage Suite and ISAS HN BioImage Suite analyses for a patient with surgically confirmed right mesial temporal lobe epilepsy (Patient 5). (**C**, **D**) Results of ISAS BioImage Suite and ISAS HN BioImage Suite analyses for a patient with surgically confirmed left rolandic seizure onset (patient 11). Results for ISAS BioImage Suite and ISAS HN BioImage Suite were also very similar in appearance in all cases to analyses performed using the original ISAS algorithm (data not shown).

decreases, which can at least lateralize the side of seizure onset for postictal injections (McNally et al., 2005). It should be noted that ictal injections are critical for accurate localization, and to reduce the confounding effects of seizure propagation (McNally et al., 2005).

Although ictal SPECT analysis is a powerful tool in localizing seizures, the complexities of image analysis have caused the use of ictal SPECT to be limited except at specialized centers. We have now validated ISAS BioImage Suite HN, further reducing implementation problems and providing fully open-source implementation. We currently use ISAS BioImage Suite to analyze all ictal SPECT studies at our center. The ISAS (http://spect.yale.edu) and the BioImage Suite (http://bioimagesuite.org) websites have been updated to include a new step-by-step guide and sample analyses. Our hope is that these methods will con-

tinue to simplify the analysis of ictal SPECT making the technique more assessable to all centers providing care to patients with epilepsy.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure

None of the authors has any conflict of interest to disclose.

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