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The effects of left or right hemispheric epilepsy on language networks investigated with semantic decision fMRI task and independent component analysis

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Abstract

Chronic and progressive brain injury, as seen in epilepsy, may alter brain networks that underlie cognitive functions. To evaluate the effect of epilepsy on language functions we investigated the neuroanatomical basis of semantic processing in patients with left (LHE) or right (RHE) hemispheric onset epilepsy using semantic decision fMRI paradigm and group independent component analysis (ICA); we then compared the results of our investigations to language network in healthy subjects examined with the same language task (1). Group ICA is a data-driven technique capable of revealing the functional organization of the human brain based on fMRI data. In addition to providing functional connectivity information, ICA can also provide information about the temporal dynamics of underlying networks subserving specific cognitive functions. In this study, we implemented two complementary analyses to investigate group differences in underlying network dynamics based on associated independent component (IC) time courses (*a priori* defined criterion or *a posteriori* identified maximum likelihood descriptor). We detected several differences between healthy controls and patients with epilepsy not previously observed with standard fMRI analysis methods. Our analyses confirmed the presence of different effects of LHE or RHE on the behavior of the language network. In particular, a major difference was noted in the nodes subserving verbal encoding and retrieval in the bilateral medial temporal regions; these effects were dependent on the side of the epilepsy onset i.e., effects were different with left or right hemispheric epilepsy. These findings may explain the differences in verbal and non-verbal memory abilities between the left and right hemispheric epilepsy patients. Further, while the

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effects on other nodes of the network were more subtle, several deviations from normal network function were observed in patients with LHE (e.g., alterations in the functions of the primarily left fronto-temporal network module) or in patients with RHE (e.g., differences in the medial retrosplenial module responsible for mental imagery or in the anterior cingulate module subserving attention control). These findings highlight the negative effects of epilepsy not only on the main left hemispheric language network nodes in patients with LHE but also document the effects of epilepsy on other language network nodes whether exerted by LHE or RHE. Further, these results document the advantages of using group ICA for investigating the effects of disease state (e.g., epilepsy) on the network subserving cognitive processing and provide an interesting avenue for further exploration.

INTRODUCTION

Epilepsy, as a chronic disorder, frequently impacts the cognitive skills including language (2–7). The severity of language impairment may vary depending on the type of epilepsy and its severity. On one end of the spectrum, patients with acquired epileptic aphasia (Landau-Kleffner syndrome; LKS) usually present with severe language dysfunction that predominantly involves comprehension while nonverbal intellectual functions are preserved (2,4,8,9) while patients with electrical status epilepticus during slow wave sleep (ESES) usually suffer from low lexical, morphosyntactic, and pragmatic skills (4). On the other end of the spectrum are patients with benign epilepsies, e.g., benign epilepsy with centrotemporal spikes (BECTS), but even these patients have been reported to have language deficits (6,10).

Previous studies have documented atypical language representation in patients with epilepsy usually via showing atypical language lateralization (e.g., bilateral or right-hemispheric). For example, one study used intracarotid amobarbital procedure (IAP) to show a relatively high incidence of atypical language representation in epilepsy patients with early brain injury when compared to patients without evidence of such damage (11–17). The differences between healthy and epilepsy subjects may be related to an early seizure onset, atypical handedness and the location and nature of pathology (18–20). Overall, in the previous IAP studies, the incidence of atypical language dominance ranged from 14.5% to 42.7% (12–17). The results of the invasive studies were recently confirmed by several fMRI reports (19–24).

The underlying cortical architecture that preferentially supports language within the left hemisphere is clearly disrupted in patients with epilepsy (25). The presence of such disruption is, in part, supported by the previously mentioned findings of patients with LHE having higher proportion of atypical language dominance when compared to RHE (e.g., (26)). Further, a comparison between adult controls and patients with left temporal lobe epilepsy (TLE) has revealed a much lower lateralization index (LI) in the adult (21) and pediatric (20) patients with epilepsy. Finally, a within patient comparison revealed that LI is highest (most left-lateralized) in right TLE, followed by the healthy controls and the left TLE group (23). Such an inter- and intrahemispheric language function transfer was suggested in both, patients with left and right TLE (24). The presence of function transfer ability in chronic models of brain injury (e.g., epilepsy) is partly supported by the results of language recovery after acute brain injury (e.g., after perinatal left hemispheric stroke) (27,28). Further, the presence of brain's ability to reorganize language networks in epilepsy can be inferred from animal studies showing neurogenesis after seizure (29). In clinical situations, the observed ictal or postictal language dysfunction (30–32) suggests that the seizure itself has a negative effect on language network.

In the present investigation, we perform an in-depth analysis of the network subserving semantic decision in patients with right- or left- hemispheric epilepsy using a semantic/tone decision (SDTD) fMRI task (33). This task specifically targets the retrieval of previously stored semantic information and the perceptual analysis of speech sounds. Retrieval of semantic information can activate the syntactic processing and verbal working memory networks. In addition, mental resources required for low-level auditory processing and attentional maintenance must be recruited for correct performance of the task (33). This task has previously been used to investigate the language processing in healthy left- and right-handed adults (19,34) and to estimate language lateralization in epilepsy patients undergoing presurgical evaluation (26,35,36); it showed superior correlation with IAP when compared to a verb generation fMRI task which is frequently used in the presurgical evaluation of the patients with epilepsy (26). In the companion paper, we have presented a theoretical framework for the STDT task based on an extended version of the Wernicke-Lichtheim-Geschwind model for language processing and the data from 49 healthy participants (1,37).

Previous studies utilized general linear modeling (GLM) to analyze the contrast between semantic decision and tone decision and to show robust activations in the left lateralized language networks including frontal, posterior superior temporal and angular gyri (26). Although GLM confirmed the results of original SDTD studies, this type of analysis is only able to reveal a fairly unidimensional picture that does not allow a precise evaluation of multiple components (nodes) of the language network or their temporal dynamics and relationships. In contrast, independent component analysis (ICA), as a data-driven analysis technique, allows detecting additional brain regions involved in semantic processing when compared to the standard GLM analysis (1,38). Therefore, in this study, we exploit both the spatial and temporal information provided by ICA to lay the foundation for a comprehensive analysis of network differences between the patients with left (LHE) and right hemispheric (RHE) epilepsy; the results of similar analysis in the healthy controls presented in the companion paper are used here as reference (1). The main goal of the present study was to investigate group differences in network dynamics associated with semantic decision between patients with LHE and RHE. Further, we propose a timecourse analysis method in which the hemodynamic response function (HRF) is allowed to vary in order to account for the maximum variability between healthy controls and groups of patients with epilepsy. We hypothesized that this approach would detect significant differences in proposed cognitive modules for semantic decision.

METHODS

Subjects

A total of 107 subjects took part in this study after signing an IRB-approved informed consent. We enrolled 30 patients with LHE and 28 with RHE; first 38 of these patients were included in our previous publication (26). The LHE group consisted of 20 female and 10 male patients (age = 38.1 ± 9.8 years; 27 were right-handed). There were 25 patients with temporal lobe epilepsy (TLE) and 5 with extra-temporal, neocortical epilepsy (ETLE); 19/30 LHE patients had focal seizures with secondary generalization and 11/30 had only focal onset seizures. This group included 4 patients with lesions – one frontal arachnoid cyst, one hippocampal dysembryoplastic neuroepithelial tumor (DNET), one medial frontal glioma and one anterior temporal cortical dysplasia. Twenty of the RHE group were females and 8 were males (age = 36.5 ± 11.9 years; 26 of were right-handed). Of the RHE group, 25 had TLE and 3 had ETLE, 17/28 had secondary generalized seizures while 11/18 had only focal onset seizures. In this group were included one patient with a small posterior temporal DNET, one with temporal tip ring enhancing lesion and one with posterior hippocampal lesion. As in our previous studies, the diagnosis and lateralization/localization of epilepsy onset was established in all patients via prolonged video/EEG monitoring and review of ancillary data

including neuroimaging and neuropsychological testing (5,39). Patients with generalized epilepsies or unclear lateralization of seizure onset were excluded from this study (in some patients seizure onset was confirmed during intracranial EEG monitoring). Additionally, data on previously presented 49 healthy controls (37 males, 12 females; mean age 39.3 ± 12.4 [range: 23–59 years]) were included in this study only for comparison purposes (1,26). All included subjects were native English speakers. Forty seven of the healthy controls were right-handed and 2 were left-handed according to the Edinburgh Handedness Inventory (40).

Functional MRI (fMRI) task

As in the original version of the SDTD task, there are two intervening conditions: the control condition (tone recognition) and the active condition (semantic recognition) (34). Each fMRI block (condition) lasts 30 seconds (except for the first tone recognition block that lasts 15 seconds) and is repeated 7 times (tone recognition condition is repeated 7 times plus the additional 15 seconds block used for MR signal equilibration) (1,26). The total duration of the entire task is 7 minutes and 15 seconds. In the tone condition, subjects hear brief sequences of four to seven 500- and 750-Hz tones every 3.75 seconds and respond with the non-dominant hand button press for any sequence containing either two 750-Hz tones (“1”) or other than two 750-Hz tones (“2”). Similarly, in the active condition, subjects hear spoken English nouns designating animals every 3.75 seconds and respond “1” with a non-dominant hand button press to stimuli that met two criteria: “native to the United States” and “commonly used by humans”. In all other cases, they respond by pressing “2”. Understanding of the task is tested before subjects enter the scanner. Intra-scanner behavioral responses are recorded for further analyses via a button box that is also used in case of emergency to alert the MRI technologist to a problem during scanning.

Functional MRI scanning and imaging data post-processing

The imaging was done either using a 3T Bruker Biospec 30/60 (Bruker Medizintechnik, Karlsruhe, Germany, at the Cincinnati Children’s Hospital Medical Center) or a 4T Varian (Oxford Magnet Technology, Oxford, UK, in the Center for Imaging Research, University of Cincinnati) MRI scanner. The differences between the two imaging protocols and the subsequent data merging methods have been discussed in detail elsewhere and the reader is referred to the relevant articles describing this methodology (1,26,41). Briefly, the data from the 3T and 4T scanners were merged only after we assured that there were no differences in activation distribution or intensity patterns between the scanners (1). The fMRI image post-processing and ICA decomposition were performed using in-house developed software implemented in the IDL environment (IDL 6.3; Research Systems Inc., Boulder, CO, USA) (42). Geometric distortion due to B0 field inhomogeneity was corrected during reconstruction using a multi-echo reference scan (43). Data were then co-registered and motion corrected using a pyramid iterative algorithm (44) and transformed into Talairach reference frame prior to statistical and ICA analysis (45).

Statistical analysis

ICA analysis—In order to examine group differences between the epilepsy patients and the healthy controls, we performed the ICA decomposition by combining all subjects into one dataset. Other than this additional concatenation step, the ICA decomposition followed the same basic steps as described and explained in our previous publications including the companion paper that focuses on healthy controls performing the same language task (1,46,47). Briefly, the ICA decomposition employed here is based on the method proposed by Calhoun et al. (48) and includes several steps described below. During the first step, timecourses of all voxels were normalized to a percent signal change from the mean. This was followed by a two stage data reduction step using principal component analysis (PCA).

Each individual dataset (subject level) was reduced to 40 principal components and then concatenated across subjects prior to the 2nd data reduction step at group level. The first 50 PCA components were retained for the subsequent ICA decomposition. The decomposition, based on the Fast ICA algorithm (49) was run 25 times before performing hierarchical agglomerative clustering (50) in order to estimate the most reliable components resulting in retaining 53 of them. All networks included in the current report were identified in multiple runs (≥ 20 out of 25) of the FastICA algorithm which assured high reliability. Next, using the back propagation method, IC timecourses were estimated for each subject before a time domain analysis to determine the task-related IC components for each group (i.e. healthy, RHE and LHE subjects). Briefly, the corresponding timecourse of each individual IC map was Fourier transformed and the component at the on-off task frequency was subjected to a separate group analysis (46,51). This post hoc time domain analysis of all subjects enrolled in the study resulted in retaining 16 components of which 8 were later rejected following visual inspection as motion-related artifacts based on their spatial and temporal characteristics. We assumed that these IC maps captured the behavior of the brain networks underlying the SDTD task in both, the healthy controls and the patients with epilepsy (these results were later compared with the findings from the companion paper that specifically focused on examining the networks underlying semantic decision in healthy controls (1)). As a next step, a one-sample t-test was performed on each IC map on a voxel-wise basis to determine whether a given voxel intensity was significantly different from zero across the group. Finally, separate timecourse analyses of RHE and LHE patients were carried out to identify specific group differences in the networks subserving semantic decision. This complementary analysis investigated the Fourier transform of each IC timecourse at the task frequency and phase following previously described routines (see below and (46,51,52)). Based on ICA formalism, we hypothesized that ICA would identify separate networks (maps) exhibiting significantly different dynamics corresponding to each group (46,51,53,54).

Time course analysis—The group differences in selected IC maps were investigated by extending a previously developed procedure in which the task-relatedness of each individual IC map was investigated based on associated timecourses (51). As mentioned above, these individual IC timecourses were estimated using a back propagation method following the group ICA decomposition at the group level. For this analysis, we assumed that individual IC timecourses are capable of capturing temporal characteristics that are unique to each subgroup even though they themselves do not represent absolute BOLD signal intensities. To be more specific, we hypothesized that the associated temporal dynamics of each selected IC map may relate to the underlying pathology in the case of patients with epilepsy facilitating a group difference investigation. On the other hand, the scaling ambiguity associated with standard ICA methods precludes one from directly testing for any group differences on the individual IC maps (54,55). However, methods have been proposed to scale IC maps to percent signal changes facilitating direct correlation analyses (56). Therefore, in this study, group differences were analyzed and tested using associated individual IC timecourses based on similar methods described by our group previously (51).

In order to assess the group differences, we implemented two complementary data analysis methods. In the first approach we fitted each individual timecourse (from a given component) to the on-off task reference function. The t scores (representing task-relatedness of each network) from the first level were then incorporated into a second-level group differences analysis. A significant result in the second-level analysis implies a group difference in associated network dynamics subserving semantic decision. However, as pointed previously (46), most IC timecourses do not exhibit strong correlations (overall fit) with the on-off task reference timecourse with a fixed phase and period. Poor overall fit may capture differences in hemodynamic responses over such variables as age, pathological

differences or, up to a certain extent, performance of included subjects. Specifically, lack of fit in this method could simply represent a measurable change in BOLD responsiveness between subjects due to age, brain region, pathology and other physiological/attentional differences. Therefore, in this study, it is reasonable to assume that differences in underlying pathology (side of epilepsy onset) are the leading contributor to the above mentioned differences in BOLD responsiveness which warrants the use of a flexible hemodynamic response function (HRF). Consequently, to accurately separate group differences in correlations associated with language-related ICs, we used an alternative and more flexible data-driven method where the hemodynamic response function was allowed to vary across subjects, prior to testing for any group effects in the second level analysis. The second method that entails allowing the HRF to vary during the first level analysis is also based on investigating group differences in task-relatedness (t score) derived from the first level analysis. However, in this approach the HRF is modified iteratively between the first and second level analyses in order to maximize the group differences in t score for each of the eight independent components tested. Specifically, the on-off reference timecourse is allowed to vary in order to capture maximum group differences. This optimization was performed using the downhill simplex method (57). To regularize the optimization (i.e. to prevent the algorithm from converging to an exact match to the time course from the subject with the largest group difference, resulting in a huge t score for that subject), an upper bound of $t = 25$ was set for the fit with each individual time course. The regularization corresponded to setting a lower bound on the variance of each associated time course which is an equivalent to incorporating a Bayesian theorem (e.g., zero prior probability of zero variance). The null distribution for the slope was found via Monte Carlo simulation via repeatedly performing the algorithm on random Gaussian noise of the same dimensionality (a significant difference in the slope from the null distribution indicates a significant effect).

Finally, the data-driven optimal reference timecourse was tested in order to determine whether the observed effects were, in fact, task-related. This method, with slight modifications has also been used to investigate any performance effects on the underlying neural networks subserving semantic decision. In essence, this approach entailed varying the on-off reference function iteratively between the first and second level analyses in order to maximize the performance effects in t score for each network (46,51). To simplify, the difference between the two complementary approaches can be summarized as follows. In the first method, the significant group differences in task-relatedness and shape of the timecourses are tested as determined by an *a priori* criterion (e.g., correlation with the task reference) while the second method finds a maximum likelihood descriptor of any group differences present, and then analyzes it *a posteriori*.

RESULTS

The mean percentage of correct answers for the semantic decision was 81 ± 12.0 (range 46 – 96), 70 ± 11.7 (range 50 – 96) and 71 ± 11.2 (range 52–96) for healthy, LHE and RHE subjects, respectively. There were no significant effects of age on task performance.

Figure 1 shows the results of a random effects GLM analysis of each group performing the STDT task. For healthy controls (Figure 1a), activation was detected in the bilateral inferior frontal gyrus (IFG), left middle frontal gyrus, medial frontal gyrus and superior frontal gyrus, bilateral parahippocampal and angular gyri, left superior temporal gyrus, lingual gyrus, posterior cingulate and precuneus consistent with our prior report [this is similar to Figure 1 in (26) and in (58)]. Figures 1b and 1c represent the GLM maps of LHE and RHE patients. On visual inspection, these activation patterns do not appear to be substantially different from the healthy controls suggesting that the standard GLM approach to detecting group differences may be suboptimal (healthy controls have higher intensity of the BOLD

signal response likely related to a larger number of subjects enrolled in this group). Further, a previous study utilizing the same dataset tested for the differences in language lateralization indices between patients with LHE and RHE and found a significant effect (26). Again, while this effect is present here, it does not appear to be reflected in the GLM activation patterns depicted in Figure 1.

Figure 2 shows the ICA maps (networks) sub-serving the semantic decision task, selected based on a post hoc analysis of timecourses of all enrolled subjects; the corresponding average IC timecourses are displayed in Figure 3. All IC maps were detected at least in 20 (out of 25) runs of the ICA decomposition assuring a high degree of reliability. We assume that these IC maps represent the underlying brain networks that subserve the SDTD task in both, controls and patients with epilepsy as discussed in detail elsewhere (1). The brain areas encompassed in IC maps (Figure 2) relevant to semantic decision aspects of the SDTD task are tabulated in Table 1A. The inter-subject variability was calculated using previously established methods and is presented in Table 2 (column 4) (51,52). In brief, this method captures the variability of each IC time course when fitted to an optimal time course representing group effects (e.g., underlying pathology or performance effects). Accordingly, for the semantic decision, the components shown in Figures 2c, 2g and 2h show considerable variability in the epilepsy group compared to the healthy-control subjects. Based on a previously proposed model for STDT task (1), the network shown in Figures 2c pertains to semantic decision making while the networks shown in Figures 2g and 2h pertain to speech production and general attentive processes subserving the STDT task.

The laterality index (LI) was calculated for all subjects using the previously described formula $LI = ((L-R)/(L+R))$ where L is the number of voxels in the left hemisphere and R is the number voxels in the right hemisphere with all IC maps scaled to unity variance (1,26,46). As previously (46), we chose hemispheric ROIs to minimize the contributions (influence) of epilepsy on LI calculations. Nevertheless, the overall left laterality associated with semantic decision is readily observed in this population even when the atypical contributions of epilepsy patients are taken into account.

Average IC timecourses of the semantic decision were correlated with the on-off task reference function resulting in correlation coefficients of $|r| \geq 0.22$ for healthy controls. The inherent drawback of this method (even in the case of average IC timecourses) is the assumption of a fixed hemodynamic response function (HRF) for all three groups. To circumvent this problem, we implemented a more flexible Bayesian approach in which the HRF was allowed to vary (46). The resulting optimal timecourse capturing maximum amount of group differences (or performance/age effects) in the BOLD signal was then tested for the task-relatedness with the on-off reference function. A significant correlation provides confidence that the observed effects are, in fact, task-related and can justify the use of a simple on-off task reference function in further characterization of IC timecourses (or brain networks). This approach can be identified with typical optimization algorithms in machine learning applications (59). Based on this more flexible method, for the healthy-controls, only IC maps shown in Figure 2a, 2b, 2c, 2f and 2g resulted in a significant correlation coefficient ($p < 0.05$). Similarly, language networks in patients with LHE shown in Figures 2a, 2c, 2e, and 2g and language networks in patients with RHE shown in Figures 2b, 2e, 2g, and 2h were significantly correlated ($p < 0.05$) with the task reference function.

We also investigated how the performance in semantic decision is influencing the task-related behavior of networks shown in Figure 2. The more flexible optimal time course approach capable of representing the maximum amount of performance-effects on BOLD signal revealed that the IC maps shown in Figure 2a, 2b, 2c and 2g had significant influence on the task-related behavior ($p < 0.05$). Previously, we used a similar approach to investigate

developmental trajectories associated with a covert verb generation (46). Interestingly, the IC map shown in Figure 2g (highly left lateralized network) did not show significant performance-related BOLD signal changes reemphasizing the fact that this network subserving semantic decision is the dominant one as discussed elsewhere (1). The alternative approach (first method) in which one investigates how the task performance is related to the task-relatedness (correlation coefficient) of each IC time course did not yield any significant results.

The group differences in task-relatedness were investigated between the three groups using similar methods as described above. In the first approach, group differences were investigated in the task-relatedness based on correlation coefficients between IC timecourses and the on-off task reference function. When LHE patients were compared with healthy controls, significant differences were detected in both left lateralized networks as shown in Figures 2d and 2g; the former was more active (task-related) in the LHE while the latter was more active in the healthy-controls. Similarly, in the RHE group, networks shown in Figures 2f, 2g and 2h were significantly less active when compared to the healthy controls. However, this method did not detect any statistically significant differences between the left and right epilepsy groups. This was a surprise as we anticipated significant group differences between the LHE and RHE groups due to the chronic nature of the epilepsy and the highly left lateralized nature of the SDTD task. A possible explanation for this finding may be our assumption of an invariant HRF for all three groups irrespective of the underlying pathology. While the alternative Bayesian approach detected significant task-related differences in several networks (Figure 2a, 2b, 2e, 2f, and 2h) between LHE and RHE groups, this method did not detect significant task-related differences between the epilepsy groups in the network shown in Figure 2g which is the main network subserving semantic decision (1). The detected differences in networks shown in Figure 2e, 2f, and 2h pertain to reasoning, semantic memory retrieval and general attentive control according to the hypothesized cognitive model for semantic decision discussed elsewhere (1). The other differences are in the verbal encoding and mental imagery module (Figures 2a and 2b) which are related to stored mental image activation as described in detail elsewhere (1). Using the Bayesian approach we also examined task-related differences between healthy controls and LHE patients. Significant differences were detected in networks shown in Figures 2a, 2b, 2c, 2d, 2e and 2g. More significantly, we detected highly significant group differences in the task-relatedness of the main network (Figure 2g) subserving semantic decision. As mentioned earlier, the anticipated group differences (in the temporal dynamics) between the healthy controls and LHE patients were detected in the highly left lateralized network of the SDTD task when analyzed using the Bayesian approach. The assumption of a variable HRF between the two groups effectively provided the necessary detection power to decipher the effects of chronic LHE on the main network (Figure 2g) subserving semantic decision. In a similar way, this data-driven approach also detected significant differences between healthy-controls and RHE patients in networks shown in Figures 2c, 2d, 2e, 2f, 2g and 2h. The main findings in this comparison are the detected differences in the highly left lateralized networks as shown in Figures 2g and 2h. Thus, irrespective of the epilepsy focus, (in this case the right hemisphere) the chronic nature (or the underlying pathology) of this disease affects the main left lateralized networks subserving semantic decision as seen in healthy controls.

Additional IC maps and corresponding timecourses detected in patients with epilepsy are shown in Figures 4 and 5. These differences were detected based on the ICA timecourse analysis described in the methods section with few additional steps. In addition to the standard analyses, a separate ICA analysis of the LHE group detected the IC map shown in Figure 4a while the maps shown in Figures 4b and 4c were detected in the RHE group. This additional analysis provided further evidence to support our findings of different effects of

LHE and RHE on language circuitry. Briefly, this complementary analysis investigated how the phase of the average Fourier component of each IC map (at the frequency) compared to the phase of the on-off task reference function (shifted by 3 seconds relative to the task itself to account for the hemodynamic delay) (60). A paired t test revealed that the IC maps shown in Figure 4 are not significantly different between LHE (4a) and RHE (4b and c combined) patients when compared to healthy controls. This suggests that the nodes shown in Figure 4 correspond to the nodes shown in Figure 2f, the main module subserving semantic memory encoding and retrieval in healthy controls as described previously (1). An additional analysis was performed to investigate any group differences in task-relatedness of these networks using the first method (i.e., correlating with the on-off task reference function). The task-relatedness of all three networks in the epilepsy group (both, left and right hemispheric epilepsy) did not differ when compared to healthy controls. Finally, the task-relatedness of these three nodes (Figure 4) did not differ significantly between the two epilepsy groups even after taking into account the 3 seconds shift as described above.

The Bayesian method detected significant differences in the task-relatedness between the LHE and the healthy-controls (Figure 4a). In evaluating the maximum likelihood reference time course, the null distribution for the slope found via the Monte Carlo simulation (repeatedly performing the algorithm on Gaussian noise) yielded a result of 2.77842 ± 0.183569 for the null distribution. As indicated above, this significant difference in the slope from the null distribution indicates a significant group difference effect in the task-relatedness of the network shown in Figure 4a between the LHE and the healthy-controls. In addition, the temporal differences were also task-related in the network shown in Figure 4a when calculated by correlating the optimal group difference reference function with the on-off task reference function ($p < 0.05$). Likewise, the RHE group showed significant task-related differences in all networks (Figures 4b and 4c) when compared to the healthy-controls; the null distribution yielded a result of 2.87054 ± 0.200004 for this contrast. Finally, when LHE (Figure 4a) and RHE groups were compared (Figures 4b and 4c, combined), all three networks showed temporal differences [when compared with the null distribution (3.19832 ± 0.208003)], while two networks shown in Figures 4a and 4c showed additional task-related behavior.

DISCUSSION

Epilepsy directly and indirectly impacts language functions; the immediate effects of seizure(s) can be seen as an ictal or early post-ictal language dysfunction (30–32) while long term language dysfunction is noted on detailed neuropsychological evaluation (61). In general, seizures originating from the dominant hemisphere usually are associated either with a speech arrest during the seizure or paraphasic errors after the seizure. Clinically, such information is frequently used as a diagnostic tool to determine the localization and lateralization of language dominance and, in certain cases, this information may be helpful in localizing the epileptic focus (32,61–63). While clinical testing during or after ictus has high predictive value for determining language dominance, cognitive assessments are less likely to provide detailed anatomical information regarding language center(s) location, especially in patients with preexisting anatomical or functional abnormalities as seen in epilepsy (64,65). Thus, the ability of fMRI to determine language lateralization and localization has become a very useful clinical tool in presurgical staging (26,66). Therefore, given the severity of language dysfunction seen in some patients with focal epilepsy syndromes one would expect that altered language networks in epilepsy patients can be detected using standard fMRI protocols and data analysis methods especially when a control group is available for comparison. However, as shown in Figure 1, such differences in fMRI may not be easily apparent and additional analyses may be necessary.

Standard fMRI analysis methods obviate investigating network dynamics and instead focus entirely on average brain activation patterns paying less attention to temporal characteristics of brain responses. While this makes reviewing individual imaging data relatively easy and is frequently used for clinical purposes (e.g., (18)), the detection power of brain activation differences between patients and healthy controls is, in part, related to task design, participant's age and thresholding method (67). Further, such analysis often fails to detect subtle network abnormalities which are clearly present in these patients. However, the present analysis deemphasizes the activation patterns while placing the emphasis on temporal behavior of language network(s). This novel approach to epilepsy fMRI data creates a foundation for superior detection power of brain response differences in patients compared to healthy controls. Developing sensitive analytical methods for fMRI may facilitate early detection of abnormalities in the language networks, and, therefore, implementation of early interventions especially that it has been shown that even patients with benign (e.g., BECTS) epilepsy (usually children below the age of 10 years), also suffer from language dysfunction. Although BECTS is a mild (and usually transient) form of epilepsy, detailed neuropsychological examination showed dysfunction in word comprehension in patients when compared to healthy controls (6). Development of such fMRI post processing methods is useful not only for testing the effects of epilepsy on brain function(s) but also for other types of brain injury that adversely disrupt the normal development patterns causing reorganization of brain areas resulting in atypical networks sub-serving language function (68). Additionally, developing methods to identify subtle network differences may be useful in devising clinical tests for epilepsy patients. Such methods, if properly tested, could replace traditional investigations such as IAT which has been extensively utilized to determine language dominance as a pre-surgical evaluation in intractable epilepsy patients (12,69).

The proposed Bayesian method was able to detect differences in the temporal characteristics of semantic decision processing with a very high degree of sensitivity. The advantage of this method is its flexibility that can easily be extended to investigating age-effects or performance effects of underlying network structures associated with cognitive (dys)function. In addition, availability of this analysis method could provide the researcher with the necessary insight into modifying or designing new paradigms capable of corroborating or testing new hypothesis regarding the language substrates in patient cohorts with specific pathologies.

As indicated previously, numerous IAP studies showed high incidence of atypical language dominance in epilepsy patients (12–17). In addition to these studies, many fMRI experiments have reported atypical language localization and lateralization in epilepsy patients (19–24). In particular, the first large scale study by Springer et al. compared epilepsy patients with a healthy group and reported a higher incidence of atypical language dominance in epilepsy patients (19). Many of the fMRI studies used lateralization index (LI) to quantify the degree of language dominance (19–24). While LI is probably not the most desirable way of presenting language dominance (e.g., (70)), in many studies left TLE groups have shown much lower LIs (more symmetric) than controls (20,21,23,24). In one other study, right TLE patients showed higher LIs than healthy controls (23). These and other fMRI studies provide preliminary evidence for language reorganization in the brain and the evidence for transfer of language functions to the contralateral homologues (interhemispheric transfer) in patients with chronic and progressive brain injury such as seen in epilepsy (5). Similar transfer is frequently observed in models of acute brain injury (e.g., stroke) but the efficacy of such transfer in acute brain injury has been questioned (28). Further, unlike IAP, fMRI can detect not only the lateralization but also the localization of language-related cortical areas. In this study, we found convincing activation differences in

language networks corroborating previously described differences in activated cortical regions in epilepsy patients compared to healthy controls (24).

The findings of this study suggest that the use of correlation coefficient (with the on-off task reference function) to describe the overall behavior of IC time courses may not be optimal in investigating group differences. However, the main network sub-serving SDTD task (Figure 2g) still showed the highest correlation and the lowest inter subject variability agreeing with the GLM results as shown in Figure 1. Albeit, this simple method lacks the required detection power to tease out any differences between epilepsy groups, it can detect clear differences between the healthy controls and the epilepsy patients.

The use of a variable HRF method also did not detect significant task-related differences between epilepsy groups in the main network as shown in Figure 2g. However, this method detected significant differences in other networks based the hypothesized cognitive model for the SDTD task (1). Additionally, ICA also detected networks (Figure 4) that showed group differences between the LHE and RHE patients when investigated using the more flexible Bayesian method. Therefore, the proposed methods in this investigation lay the foundation for investigating group differences in general and may be more suitable for teasing out anticipated group differences between the LHE and RHE groups when compared to more conventional methods.

The current investigation provides additional evidence in support of intra- and inter-hemispheric transfer of language networks in epilepsy patients. The networks shown in Figure 4 and hypothesized to be part of the semantic decision process in epilepsy patients showed subtle differences in network dynamics when analyzed using more sensitive optimal time course method. However, the alternative complementary analysis provided evidence in support of a common global behavior by not detecting any significant differences in temporal dynamics between the LHE and RHE patients and healthy controls. We hypothesize that the disagreement between the methods is related to the fact that the networks shown in Figure 4 in fact correspond to the subnetwork shown in Figure 2f indicating similar function but different temporal characteristics of this network node between epilepsy patients and healthy controls or even different effects of epilepsy on this node in left or right hemispheric epilepsy patients. Further research such as brain connectivity analysis could shed more insight on language transfer processes in epilepsy patients.

LIMITATIONS

ICA is primarily a data-driven method capable of identifying spatially independent networks related to cognitive functions. We and others have previously shown how it can be further extended to determine the functional modularity of selected networks (1,71–73) by evaluating the biological relevance against the knowledge-base on human language circuitry. While the current approach provides additional information about network behavior, a better approach would be to establish functional specialization based on correlation analysis of relevant neuropsychological information in conjunction with neuroimaging data. Such approach becomes paramount when investigating patient populations where the pathology directly influences typical cognitive functions (e.g., language). The limited availability of neuropsychological data to fully characterize the hypothesized cognitive model for STDT task was a clear limitation in determining the functional modularity of each network.

In general, appropriate constraints must be incorporated into data-driven approaches to guide the analysis to extract plausible and relevant information. With ICA, this can be achieved at the decomposition stage (74) or at the post-hoc analysis stage of ICA results. In particular,

ICA can be combined with complementary information from other imaging modalities or network analysis techniques such as Granger causality (75), structural equation modeling (SEM) (47,76,77), or Dynamical Causal Modeling (DCM) (78) to decipher temporal dynamics (including the causal structure) in the semantic decision language task. The emphasis of the current study was to present method capable of establishing group differences in temporal/spatial dynamics that can be used as a basis for future epilepsy studies.

As mentioned in our previous investigations, ICA is not completely immune to movement artifacts. The issue of motion becomes relatively important especially when dealing with diseased and potentially cognitively impaired subjects. Although ICA and other preprocessing methods partially remove the motion artifacts, inherent sensitivity issues of fMRI to subject motion may not be completely eliminated in the current investigation. One additional potential source of variability in the current investigation may come from pooling data from two MRI scanners. To address this issue, we made sure that there were no differences in the distribution (or intensity) of activation patterns between the 3T and 4T scanners before ICA decomposition (41). In addition to motion related artifacts, scanner specific information can also be captured by IC maps that are later removed from further analyses. Finally, IC maps can be thresholding to eliminate both the motion and scanner specific artifacts from these maps (46). Therefore, these preprocessing steps coupled with the methodological advantages of ICA provided the means for investigating the common task-related spatial modes (networks) subserving STDT task within the entire cohort irrespective of the scanner. Further, a recent multi-scanner study of Alzheimer's Disease using Fast spin echo (FSE) imaging has revealed significant differences between different scanner platforms (79). Despite these differences, that study confirmed that the overall imaging properties (T2 relaxation) were related to the global dementia status of the subjects rather than to scanner differences. Therefore, in the present investigation, we have full confidence that different scanner data captures the global pathology of each group adequately facilitating a group investigation.

Finally, although we presume that the underlying network behavior (IC maps) is mainly related to pathology, it can be affected by differences in individual education level, handedness, age and sex or even anticonvulsant medications (80). Further, the results our study may be, at least partially, affected by including in our study patients with various etiologies of their epilepsies. Although, inter-subject variability calculations partially quantify or take into account such influences, adequate consideration must be given to minimize such variability in group fMRI investigations in the future.

CONCLUSION

The current study shows the advantage of investigating temporal dynamics of networks along with their spatial distributions in group ICA analysis. In particular, subtle differences in the temporal structure of underlying networks can be utilized to detect any group differences in fMRI investigations. More importantly, this study further highlights the significance of allowing the HRF to vary across groups substantially increasing the detection power of subtle group differences. Finally, while providing a different perspective of fMRI data, ICA can also provide information that is compatible with a standard GLM analysis. Thus, this approach is complementary to the existing approaches and provides an interesting avenue for further exploration. These results also emphasize the importance of both, left-right and bilateral subnets in semantic processing.

Research Highlights

We examine the effect of epilepsy on language circuits using independent component analysis.

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Figure 1.

Results of a random effects GLM analysis of (a) 49 healthy controls (b) 30 LHE patients (c) 28 RHE patients where semantic decision was contrasted with tone decision (corrected $p < 0.001$). Slice range is between $Z = -20$ and $Z = +55$ mm (Talairach coordinates). All images are in radiologic orientation.

Figure 2.

Independent component maps of the semantic decision task common to all included subjects (controls, LHE and RHE). Slice range is between $Z = -29$ and $Z = +31$ mm (Talairach coordinates). All images are in radiologic orientation.

Figure 3.
Independent component time courses (average) for maps shown in Figure 2.

Figure 4.

Independent component maps of semantic decision task specific to epilepsy patients; a – components specific to the LHE patients; b and c – components specific to the RHE patients. Slice range is between $Z = -29$ and $Z = +31$ mm (Talairach coordinates). All images are in radiologic orientation.

Figure 5.
The corresponding average independent component time courses for maps shown in Figure 4.

Table 1

A. Task related brain regions subserving semantic decision in healthy and epilepsy subjects (combined).					
Figure 2	Anatomical area	Brodmann's area	Coordinates		
			x	y	z
a	R lingual gyrus	17/18	6	-49	-5
	L lingual gyrus	17/18	-10	-49	-5
	L cuneus	18	-2	-77	7
b	R cuneus	18	6	-77	7
	L lingual gyrus	18/19	-14	-69	-9
	R lingual gyrus	18	6	-77	-5
c	L inferior frontal gyrus	47	-38	15	-5
	R inferior frontal gyrus	47	34	15	-5
d	L parahippocampal gyrus	35/37	-22	-45	-13
	L superior temporal gyrus	41/22	-42	-29	7
	L lingual gyrus	18/19	-18	-61	-1
	L posterior cingulate	30/18	-22	-65	7
e	L parahippocampal/fusiform gyrus	20/36	-26	-33	-17
	L posterior cingulate	29/30	-10	-49	11
	R parahippocampal gyrus	18/30	14	-49	3
	R posterior cingulate	29/30	6	-49	11
	L middle temporal gyrus	22/39	-42	-57	11
	R middle temporal gyrus	22/39	42	-53	11
f	L amygdala		-22	-5	-21
	L hippocampus		-14	-21	-21
	R hippocampus		10	-17	-21
g	L inferior frontal gyrus	44/45	-42	11	19
	L medial frontal gyrus	32/10	-14	43	11
	L middle temporal gyrus	21/22	-46	-49	7
	L superior temporal gyrus	22	-46	-49	15
	L supramarginal/angular gyrus	39/40	-42	-49	23

A. Task related brain regions subserving semantic decision in healthy and epilepsy subjects (combined).					
Figure 2	Anatomical area	Brodmann's area	Coordinates		
			x	y	z
	R superior temporal gyrus	21/22	42	-21	-1
h	L anterior cingulate	32	-2	23	27
	R anterior cingulate	32	2	23	27

B. Brain regions subserving semantic decision specific to patients with epilepsy (left and right hemispheric epilepsy combined)						
Figure 4	Anatomical area	Brodmann's area	Coordinates			
			x	y	z	
a	L parahippocampal/fusiform gyrus	36/37	-26	-41	-9	
	R parahippocampal/lingual/fusiform gyrus	19/36/37	22	-45	-5	
b	L amygdala		-26	-5	-13	
	L hippocampus		-26	-9	-13	
	R hippocampus		22	-13	-13	
	L putamen		-26	-9	3	
	L thalamus		-22	-29	3	
c	R hippocampus/parahippocampal gyrus	36	14	-29	-17	

Table 2

Column three shows the correlation coefficients of the average time courses presented in Figures 3 and 5 (for components presented in Figures 2 and 4, respectively) of each of the components listed in Tables 1A and 1B with the task reference (on-off) function. Column four shows the inter-subject variability for each of the ICA time courses shown in Figures 3 & 5. Column five shows the lateralization indices (LIs) computed for each of the components shown in Figures 2 & 4.

Semantic Decision	Component	Correlation with the task (HC, LHE, RHE)	Variability (HC, LHE, RHE)	LI
Figure 2	Figure 2a	0.45, 0.70, 0.45	1.44, 1.61, 1.46	0.06
	Figure 2b	0.40, 0.62, 0.40	1.50, 1.52, 1.48	0.12
	Figure 2c	0.48, 0.28, 0.19	1.50, 2.06, 2.36	-0.09
	Figure 2d	-0.22, 0.26, 0.20	1.50, 1.51, 1.58	1.00
	Figure 2e	0.77, 0.86, 0.75	1.37, 1.43, 1.46	0.30
	Figure 2f	0.39, 0.39, 0.041 *	1.38, 1.42, 1.53	0.25
	Figure 2g	0.79, 0.63, 0.54	1.39, 2.00, 1.83	1.00
	Figure 2h	0.58, 0.54, 0.19	1.35, 1.68, 1.97	-0.10
Figure 4	Figure 4a	0.43, 0.62, 0.26	1.50, 1.53, 1.63	-0.29
	Figure 4b	0.72, 0.59, 0.55	1.34, 1.79, 1.74	1.00
	Figure 4c	0.53, 0.58, 0.25	1.44, 1.96, 2.15	-1.00

Asterisk (“**”) indicates IC map with a statistically not significant correlation coefficient at $p < 0.05$; all other were significant at $p < 0.05$.