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Multiple-brain systems dynamically interact during tonic and phasic states to support language integrity in temporal lobe epilepsy

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ABSTRACT

An epileptogenic focus in the dominant temporal lobe can result in the reorganization of language systems in order to compensate for compromised functions. We studied the compensatory reorganization of language in the setting of left temporal lobe epilepsy (TLE), taking into account the interaction of language (L) with key non-language (NL) networks such as dorsal attention (DAN), fronto-parietal (FPN) and cingulo-opercular (COpN), with these systems providing cognitive resources helpful for successful language performance.

We applied tools from dynamic network neuroscience to functional MRI data collected from 23 TLE patients and 23 matched healthy controls during the resting state (RS) and a sentence completion (SC) task to capture how the functional architecture of a language network dynamically changes and interacts with NL systems in these two contexts.

We provided evidence that the brain areas in which core language functions reside dynamically interact with non-language functional networks to carry out linguistic functions. We demonstrated that abnormal integrations between the language and DAN existed in TLE, and were present both in tonic as well as phasic states. This integration was considered to reflect the entrainment of visual attention systems to the systems dedicated to lexical semantic processing. Our data made clear that the level of baseline integrations between the language subsystems and certain NL systems (e.g., DAN, FPN) had a crucial influence on the general level of task integrations between L/NL systems, with this a normative finding not unique to epilepsy. We also revealed that a broad set of task L/NL integrations in TLE are predictive of language competency, indicating that these integrations are compensatory for patients with lower overall language skills.

We concluded that RS establishes the broad set of L/NL integrations available and primed for use during task, but that the actual use of those interactions in the setting of TLE depended on the level of language skill. We believe our analyses are the first to capture the potential compensatory role played by dynamic network reconfigurations between multiple brain systems during performance of a complex language task, in addition to testing for characteristics in both the phasic/task and tonic/resting state that are necessary to achieve language competency in the setting of temporal lobe pathology. Our analyses highlighted the intra- versus inter-system communications that form the basis of unique language processing in TLE, pointing to the dynamic reconfigurations that provided the broad multi-system support needed to maintain language skill and competency.

1. Introduction

The presence of an epileptogenic focus in the dominant temporal lobe often results in the reorganization of language-relevant systems in the brain (Tracy et al., 2009; He et al., 2018). In the setting of focal left temporal lobe epilepsy (TLE) such potential reorganization has been associated with atypical patterns of representation as revealed by fMRI, (Gaillard et al., 2007; Thivard et al., 2005; Dijkstra and Ferrier, 2013; Bell et al., 2002; Mbwana et al., 2009; for reviews see Balter et al., 2019). To yield competent task output these compensatory systems must interact with the core computational regions for language, which themselves are regionally distributed in the brain ("dual stream" model)

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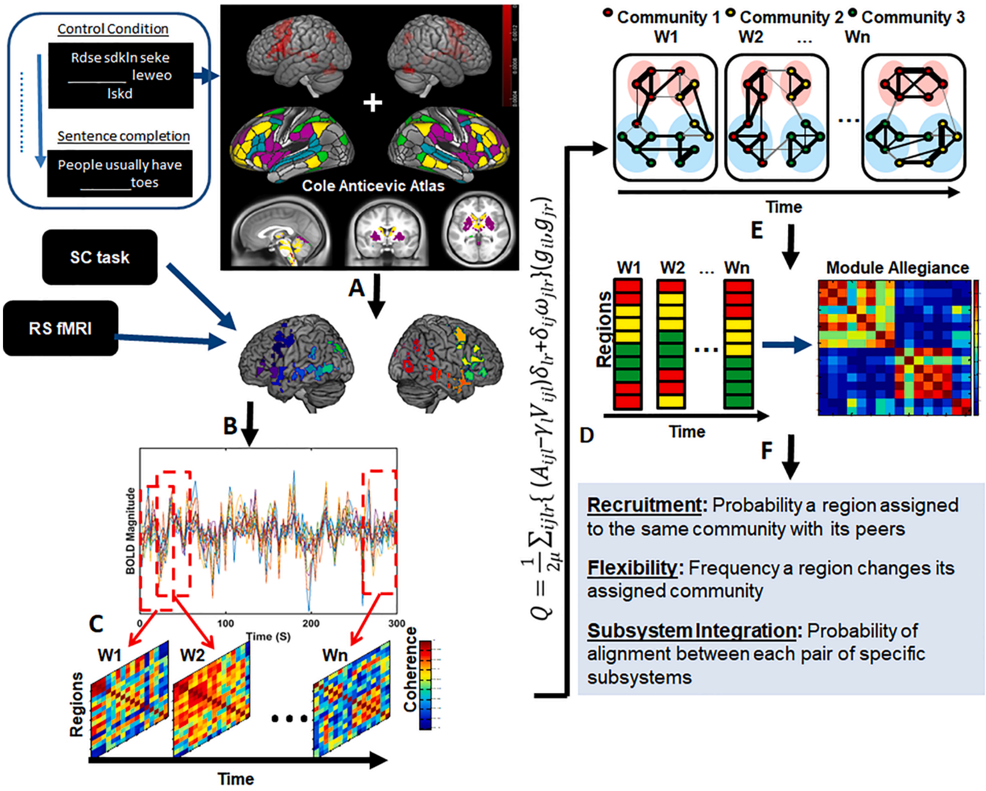
(Hickok and Poeppel, 2007; Fridriksson et al., 2018). In the setting of a complex language task, it is highly likely that competent performance requires a broader set of non-language functions. When pathology compromises the core language areas one might suspect that these non-language functions take on a larger role, becoming crucial to achieving compensatory language reorganization. One could argue that it might be impossible to capture the essence of compensatory reorganization if one does not account for these interactions with non-language functions. In this project we examined compensated, intact language status in TLE, with a focus on the interaction of language systems with key non-language networks such as dorsal attention network (DAN) (Osher et al., 2019), fronto-parietal attention network (FPN) (Sheffield et al., 2015) and cingulo-opercular network (COpN) (Vaden et al., 2013). We chose a language task (sentence completion, SC) that required a complex set of computations such as understanding the meaning of individual words, constructing the overall meaning of the sentence, and generating the appropriate word to fit the sentence. Because SC is an open-ended task requiring the subject to both hold on to and analyze a pool of candidate words before selecting a response, successful performance depends upon other functions. Such functions would include working memory, selective/sustained attention, stimulus salience, top down cognitive control and flexibility, lexical/semantic search and retrieval strategies, and error monitoring (Ashtari et al., 2005; Just et al., 1996; Price, 2010).

Computational tools from network science were used to capture how the functional architecture of language dynamically changed and interacted with non-language systems during SC task performance (He et al., 2018; Chai et al., 2016; Bassett et al., 2011; Bassett et al., 2013; Fedorenko and Thompson-Schill, 2014). Prior work from our lab has suggested that dynamic analyses of a language network may be superior to static depictions of task-relevant activity in the setting of a neurologic disease such as epilepsy (He et al., 2018). That investigation, however, omitted from analysis the potential role of non-language systems in language performance. More specifically, this prior work failed to examine whether these additional functionalities interacted with language systems only in a transient manner during a task, or if long-standing intrinsic interactions existed between language and non-language systems. It is certainly possible that such transient or long-standing interactions are important, perhaps even necessary, to achieve compensated task performance, as well as a general language competency.

We sought to answer two questions. One, in the face of pressures to reorganize language networks due to TLE, do patients demonstrate abnormal patterns of language/non-language interaction compared to controls, and are any such abnormal network dynamics evident only during task performance or are they also present and, perhaps even influenced, by the level of dynamic activity present in the baseline, tonic state? Two, do brain system dynamics differ depending on an individual's level of overall language competence, and does this point to the specific language/non-language interactions that support compensated language in the setting of temporal lobe disease?

To accomplish these goals, we analyzed dynamic changes in communication among the core language subsystems and between language and three distinct, well-established intrinsic non-language systems, systems that likely provide the additional cognitive computations and resources needed for successful language performance (DAN; FPN; COpN). We acquired functional MRI data from TLE patients and matched healthy controls (HCs) during both the SC task and a resting state (RS) condition. Time series of the BOLD response were extracted for various brain subsystems at the individual level using the Cole-Anticevic Brain-wide Network Partition (CAB-NP) (Ji et al., 2019). Using a sliding-window strategy, we generated cross-region coherence matrices over time for both the task and rest conditions. We then applied dynamic network analysis methods to detect community structures over time (Mucha et al., 2010), and quantified the aforementioned language and non-language network reconfigurations (Fig. 1). We focused on the dynamic measures of 'recruitment' (the probability of intra-communication with peer regions from the same subsystem), 'flexibility' (frequency with which a region changes its assigned community over time) and 'integration' (probability of inter-communication with



Recruitment: Probability a region assigned to the same community with its peers

Flexibility: Frequency a region changes its assigned community

Subsystem Integration: Probability of alignment between each pair of specific subsystems

Fig. 1. Schematic overview of the approach. (A) BOLD signal was extracted from the parcels corresponding to the language network, and three non-language networks – dorsal attention network, fronto-parietal network and cingulo-opercular network – at individual level using the Cole-Anticevic Brain-wide Network Partition (CAB-NP). Color codes: Language network (teal), dorsal attention network (lime), fronto-parietal network (yellow), cingulo-opercular network (magenta). (B) Time series were extracted from the CAB-NP parcels using both SC task and RS functional MRI data, with the subsequent processing steps identical for both modalities. (C) A sliding window strategy (length/step = 40/20 s, 14 windows in total) was used to generate inter-regional coherence matrices over time. (D) Dynamic community structure was detected by maximizing a multilayer modularity quality function (Mucha et al., 2010). (E) Community identities were sorted for each functionally-defined region of interest over time (Module Allegiance) (Chai et al., 2016; Bassett et al., 2015). (F) Dynamic properties were estimated separately (Bassett et al., 2011; Bassett et al., 2015; Mattar et al., 2015) for the SC and RS conditions. SC = Sentence Completion task; RS fMRI = resting state functional MRI.

regions from other subsystems) (Bassett et al., 2015; Mattar et al., 2015). The above designated group comparison (TLE versus matched healthy controls) was undertaken, followed by a partial least square (PLS) analysis of specific dynamic variables during both the SC task and RS to identify the most important predictors of language competence.

We believe our analyses are the first to capture the potential compensatory role played by dynamic network reconfigurations between multiple brain systems during performance of a complex language task, in addition to testing for characteristics in both the phasic/task and tonic/resting state that are necessary to achieve language competency in the setting of temporal lobe pathology. Our analyses specified the communication reconfigurations affected by a temporal lobe disease, highlighting the degree to which intra- versus inter-system communications form the basis of unique language processing in TLE, pointing to the dynamic reconfigurations that provided the broad, multi-system support needed to maintain language skill and competency.

2. Materials and methods

2.1. Participants

A total of twenty-three patients with refractory unilateral TLE were recruited from the Thomas Jefferson Comprehensive Epilepsy Center. All patients were surgical candidates for either a standard anterior temporal lobectomy or thermal ablation of the ictal mesial temporal lobe, determined by a multimodal evaluation including neurological history and examination, scalp video-EEG, MRI, PET, and neuropsychological testing (Sperling et al., 1996) (See Supplementary Section for more details). Given that the functional profile of the language system is associated with handedness (Knecht et al., 2000), patients with left handedness (Oldfield, 1971) were excluded to ensure comparability. Accordingly, all patients were right-handed, demonstrated left hemisphere language dominance through a task-fMRI verb generation task (He et al., 2018), and obtained a verbal IQ of 80 or greater (Verbal Comprehension Index, VCI) (Lange, 2011). The latter ensured that all participants had the cognitive capacity to follow instructions and perform the functional MRI SC task. A total of 23 age-, and gender-matched right-handed HCs also participated (Table 1 for sample demographic and clinical characteristics). All controls were free of psychiatric or neurological disorders based on a health screening measure. All study participants gave written informed consent before participating in the study. The study was approved by the Ethics Committee of the Thomas Jefferson University and was conducted in compliance with the Declaration of Helsinki.

2.2. Neuropsychological testing

All participants were assessed for verbal fluency competency through the Controlled Oral Word Association Test (COWA). Scores for the phonemic (letter) and semantic (animal naming) fluency subtests of the COWA were combined to produce a measure of language competency (LC, mean COWA score) (Gladsjo et al., 1999; Benton and Sivan, 1994).

Table 1
Sample demographic and clinical characteristics.

	Left TLE (23)	Healthy controls (23)	t/χ^2	*P*
Age	41.39 ± 14.82 (Range: 20–69 years)	35.96 ± 8.13 (Range: 27–60 years)	−1.542	0.132
Gender (M/F)	(8/15)	(13/10)	2.190	0.139
Education	14.87 ± 2.40	17.35 ± 2.48	3.445	0.001
Edinburgh Handedness	97.83 ± 7.36	95.87 ± 23.35	−0.657	0.534
Phonemic Fluency[a]	43.56 ± 11.47	47.89 ± 7.99	1.359	0.182
Semantic Fluency[b]	43.83 ± 14.04	48.39 ± 10.16	1.160	0.253
Language Competence Score[c]	43.70 ± 11.57	48.14 ± 7.29	1.421	0.163
Verbal Comprehension Index[d]	102.13 ± 12.43	NA		
Age at epilepsy onset	27.71 ± 16.75	NA		
Duration of epilepsy	14.37 ± 13.75	NA		
Seizure focality (with/without GS or 2nd GS)	(14/9)	NA		
Interictal spike (ipsilateral/bilateral)	(22/1)	NA		
Temporal pathology (NB/HS/TT/TD/E/O)	7/8/1/1/2/4	NA		
Seizure type				
SPS	1			
CPS	3			
CPS/SPS	5			
SPS + 2nd GS	0			
CPS + 2nd GS	10			
CPS/SPS + 2nd GS	2			
CPS + GS	2			
CPS/SPS + GS	0			
Anti-epileptic drugs		NA		
VGNC	11			
GABA$_a$ agonist	1			
SV2$_a$ receptor mediated	11			
CRMP2 receptor mediated	12			
Multi-action	2			

Continuous variables are presented in mean ± SD.
Temporal pathology was diagnosed by neuroradiologists specializing in epilepsy based upon presurgical MRI scans: NB = normal brain; HS = hippocampal sclerosis; TT = temporal tumour; TD = temporal dysplasia; TE = temporal encephalocele, O = Other MR signal abnormality (e.g., encephalomalacia, cavernoma).
Seizure type: SPS = simple partial seizure; CPS = complex partial seizure; 2nd GS = secondary generalized tonic-clonic seizure; GS = generalized tonic-clonic seizure.
Anti-epileptic drugs: VGNC = voltage-gated Na + channel blockage, e.g. phenytoin, carbamazepine, oxcarbazepine, lamotrigine (plus T Type Ca2 + channel blockage); GABAa agonist, e.g. diazepam, clonazepam, clobazam, lorazepam, traxene, phenobarbital; SV2a receptor mediated, e.g. levetiracetam; CRMP2 receptor mediated, e.g. lacosamide (plus VGNC blockage); Multi-action: e.g. Na + valproate (VGNC + GABAa agonist), topiramate (VGNC + GABAa agonist + AMPA/kainate receptor blockage + carbonic anhydrase inhibitor).
For continuous variables, independent sample t-tests were carried out. For categorical variables, χ^2 tests were carried out.

[a] Measured by Controlled Oral Word Association (COWA) letter fluency score. Five Controls did not have valid data.

[b] Measured by Animal Naming score of COWA. Five Controls did not have valid data.

[c] An average of Phonemic Fluency and Semantic Fluency.

[d] Measured by Wechsler Adult Intelligence Scale-Version IV (WAIS-IV).

2.3. Imaging data acquisition and preprocessing of resting state and task conditions

All participants underwent a structural scan along with two functional MRI scans (Siemens 3 T). An SC Task (5 min) with five 30 s alternating experimental and control epochs with instructions to covertly generate a single word that meaningfully completed a viewed sentence, or to passively view random letters arrayed in a word and sentence like format (control condition). The second fMRI scan with identical imaging parameters involved a five-minute RS scan when participants viewed a crosshair with no task requirements. The fMRI data was collected with a single shot echoplanar gradient echo imaging (EPI) sequence acquiring T2* signals (120 volumes; 34 axial slices acquired parallel to the anterior, posterior commissure line; TR = 2.5 s, TE = 35 ms; FOV = 256 mm, 128 × 128 data matrix voxels, flip angle = 90°, in-plane resolution = 2 mm × 2 mm, slice thickness = 4 mm). Each EPI imaging series started with three discarded scans to allow for signal stabilization. See Supplementary Section for details on task design and data preprocessing. Of note, subjects with more than 10% of outlier volumes (frame-wise displacements (Jenkinson et al., 2002); Derivatives of rms VARiance over voxelS (Power et al., 2012) during either the RS or SC task conditions were excluded from analyses. All the participants in the study (23 left TLE group and 23 controls) satisfied this criterion (8 subjects from the initially recruited 31 TLE patients and 6 from the initially recruited 29 controls did not satisfy this criterion and, therefore, were not included in the analyses). Prior to collection of the T2* images, T1-weighted images (180 slices) were collected using an MPRAGE sequence (256×256 isotropic 1 mm voxels; TR = 640 ms; TE = 3.2 ms, FOV = 256 mm, flip angle = 8°) in positions identical to the functional scans to provide an anatomical reference. The in-plane resolution for each T1 slice was 1 mm^3 (axial oblique).

2.4. Identification of language (L) and non-language (NL) systems

To capture the regions representative of individual language and non-language functionalities, we utilized the CAB-NP (Ji et al., 2019), that includes cortical parcels developed by Glasser et al. (Glasser et al., 2016) and extends into subcortex by labeling each subcortical voxel based upon the cortical network with which it obtained the strongest average Pearson correlation. Compared to traditional structurally-defined or group-activation defined regions of interest, the CAB-NP defined brain systems have been shown to demonstrate highly robust functional networks (Ji et al., 2019). The CAB-NP is the most accurate estimate of discrete, whole-brain functional network organization in humans to date, providing demonstration of the existence of novel functional networks, such as the lateralized language network.

2.5. Network construction

Detailed methodology is described in the Supplementary Section. Briefly, head motion influence was removed from the preprocessed functional MRI data by regressing out: (1) signals from six CompCor components, (2) 24 motion parameters, their temporal derivatives, and quadratic terms of both, (3) SC task effects and their temporal derivatives, and (4) any general linear trend. Denoised functional data (cifti) files were parcellated into 718 regions of interest (CAB-NP ROIs). Out of the 718 parcels, the BOLD signal from the parcels corresponding to the language, and three non-language networks were extracted (DAN; FPN; COpN (Fig. 1A). We further applied wavelet decomposition to extract information in the frequency interval of $0.05 \sim 0.1$ Hz (scale 2) (Percival and Walden, 2000). A sliding-window approach (length/step = 40/20 s, 14 windows in total) was applied to parse the decomposed time-series for each condition. We then used wavelet coherence to estimate the adjacency matrix for each window and coupled all 14 windows into a multilayer network (Bassett et al., 2011; Braun et al., 2016).

2.6. Dynamic community detection

For each participant, both their SC task and RS multilayer networks were partitioned using a multilayer community detection algorithm to extract groups of brain regions (i.e. communities) that were functionally connected with one another at each layer (Supplementary Section for description of algorithm) (Mucha et al., 2010). The quality of multilayer community detection was equivalent across experimental groups for both conditions (Supplementary Section, Table 1).

2.7. Dynamic network statistics

For each dynamic community structure detected from each multilayer network during each condition, three dynamic network statistics were estimated to characterize the functional reconfigurations among various subsystems of the language network, as well as the interaction between the language and the non-language subsystems (details in the Supplementary Section).

2.7.1. Module allegiance

We used this measure to summarize the consistency with which the parcels of the language and non-language subsystems were assigned to communities over time (Chai et al., 2016; Bassett et al., 2015).

2.7.2. Flexibility, recruitment and integration

The CAB-NP parcels of the language network were categorized into the following six subsystems: left frontal, right frontal, left temporal, right temporal, subcortical, and cerebellar (Supplementary Section, Data Processing). The non-language systems (DAN, FPN, COpN) were chosen to capture key functionalities that might be utilized to process the language stimuli of the SC task and carry out its requirements (see (Friederici, 2002; Gabrieli, 1998; Poldrack et al., 1999) for further discussion of language/non-language system interactions). These functionalities included: working memory, initiating goals, modulating cognitive control, lexical search and retrieval (FPN) (Sheffield et al., 2015; Welsh et al., 1991; Zanto and Gazzaley, 2013), stimulus salience, maintaining task-relevant goals, tonic alertness, error monitoring (COpN) (Vaden et al., 2013; Sadaghiani and D'Esposito, 2015; Dosenbach et al., 2008; Cocchi et al., 2013), and selective and sustained top-down control of external attention (DAN) (Osher et al., 2019; Vossel et al., 2014). These networks were divided into left and right hemisphere forms, combining all the left and right hemispheric parcels of each system. Based upon prior work on community detection (Bassett et al., 2011), we utilized the following measures of community membership change and interaction: (1) flexibility, capturing the frequency with which a particular parcel changed its assigned community over time, (2) recruitment, quantifying for each parcel in the language and non-language subsystems, the probability with which it was assigned to the same community as parcels from the same subsystem, or (3) with other subsystems over time (referred to as integration) (Bassett et al., 2015; Mattar et al., 2015).

2.8. Identifying the dynamics within language and between language/non-language systems

We utilized repeated measures multivariate analysis of variance (MANOVA) on our three dynamic measures (recruitment, flexibility, and integration) with L subsystems alone (or L combined with the NL systems) and condition (SC task, RS) as within-subject factors. Experimental group (TLE versus HC) served as a between-subject factor. Our goal was to determine if there were experimental group differences in network dynamics as a function of context (RS versus SC task), dynamic effects for specific subsystems (recruitment and flexibility solely within the L subsystems, or the L/NL subsystem combinations of L/DAN, L/FPN, and L/COpN), and, lastly, integration effects between the L and NL subsystems (dynamic integration measure between the L/DAN, L/FPN, and L/COpN; see Supplementary Section for further details).

2.9. The relationship between RS and SC task integrations

To more specifically identify the ability of RS dynamics to influence and predict language task dynamics, we conducted repeated measures MANOVA models on our three L/NL integration measures, run separately for the three L/NL combinations (L/DAN, L/FPN, L/COpN). The SC task integration measures served as the dependent variable. The relevant L/NL integration variables during the RS served as independent variables, with experimental group as a between subject factor (TLE, HCs). Our goal was to determine if SC integration levels for each of the L/NL integration sets (L/DAN, L/FPN, L/COpN) could be predicted by their RS integration values, and whether such associations varied by experimental group (TLE, HCs).

2.10. Relationship between dynamic integration and language competence in TLE

Since COWA measures of phonemic and semantic fluency were highly correlated (Pearson $r = 0.64$, $P = 0.001$), we averaged these to produce a more general measure of language competency (LC) with greater construct validity. To determine whether any observed dynamic L/NL integrations in the TLE patients, either in the RS or SC task, were adaptive or maladaptive, we tested whether they were associated with LC. If the association reflected an adaptive, language enhancing, and potentially compensatory dynamic process, one would expect the compensatory integration effects to be associated with the subgroup of individuals whose language system is most compromised and in need of help (i.e., those with lower LC scores). In this analysis we utilized partial least squares regression (PLS) on the LC measure. This allowed us to determine which specific L/NL integrations occurring during the SC task or RS were most strongly associated with language competency. The PLS model accounted for the effects of age and gender by including them in the PLS model. We utilized the latent factors that cumulatively explained a substantial portion of the variance in LC (80%), and the predictors with a variable importance value of 1.5 or greater (see Supplementary Section for further details).

2.11. Relationship between RS and SC dynamics and clinical variables

We report univariate Pearson correlations between the dynamic measures and key clinical variables (age of disease onset and illness duration) using a permutation method (mult_comp_perm_corr, 2021) to control for family-wise error rate.

2.12. Statistical analysis

Statistical analyses were conducted using MATLAB functions or IBM® SPSS® v23 with alpha level set at $p < 0.05$ for both multivariate and univariate effects in our repeated measures MANOVA's with appropriate correction for multiple comparisons. Preliminary assumption testing checked for independence of observations, normality, and sphericity. Independence of observations and normality were met. If sphericity was violated, the Huynh–Feldt correction was applied (epsilon > 0.75) to determine significant univariate effects. Tables 2A and 2B present the significant univariate effects ($p < 0.05$ or less), with notations indicating if the multivariate test (Wilks' Lambda) was significant ($p < 0.05$ or less). Post hoc pairwise comparisons were applied to the significant univariate effects to delineate the nature of the finding.

3. Results

3.1. Demographical, behavioral, and clinical comparisons

The experimental groups (TLE, HC) did not differ in age, gender, or handedness. The groups, however, did differ in the years of education attained, with controls having higher years of education than the TLE group (Table 1). No significant differences were found between the two experimental groups in either the separate phonemic and semantic fluency scores, or the composite language competency variable (LC). The language performance scores, however, were higher in the HCs compared to the patients (Table 1).

3.2. Group differences in dynamics both within language and between the language/non-language systems

Utilizing repeated measures MANOVA, we tested for group differences in dynamic network reconfigurations during both task and RS conditions, capturing these reconfigurations through our measures of recruitment, flexibility, and integration (Tables 2A and 2B). We first examined our dynamic measures within the language subsystems. For recruitment, there was a significant effect of group with the TLE group showing reduced recruitment within the language subsystems compared to controls ($p = 0.047$). Flexibility displayed a significant condition by group effect ($p = 0.037$) with the TLE group showing a general reduction in flexibility during the SC task (univariate effect, $p = 0.067$). As noted, there was a difference in years of education between the TLE patients and HC's. This did account for some of the observed group differences in dynamics, reducing some of the statistical effects to trends, particularly for the reduced recruitment effect seen in the patients. These reduced statistical effects and trends were low powered, suggesting that larger samples may be required to observe dynamic recruitment differences between TLE patients and HC's.

We then shifted to experimental group differences in dynamics between the (L) and non-language (NL) subsystems (DAN, FPN and COpN; split into left and right subsystems), using models similar to above, but in these models the subsystem factor included not just the L subsystems but also the NL subsystems. For recruitment, all three sets of L/NL subsystem dynamics showed a significant group effect, with HC showing greater recruitment across the subsystems (L/DAN, $p = 0.037$); (L/FPN, $p = 0.041$); (L/COpN, $p = 0.049$). The L/COpN model also revealed a significant condition X group interaction ($p = 0.032$), with HCs showing greater recruitment during the RS condition.

With regard to flexibility, for the L/DAN subsystems model, a significant condition X subsystem X group interaction emerged ($p = 0.026$) with left frontal ($p = 0.029$), left temporal ($p = 0.045$), and right temporal ($p = 0.008$) language subsystems showing increased flexibility during RS in TLE as compared to the HCs. The L/FPN subsystem model showed a main effect for condition with greater flexibility across the subsystems during RS compared to the SC task ($p = 0.034$). No flexibility effects were observed for L/COpN subsystem model.

With regard to subsystem integration, out of the three L/NL subsystem models, effects emerged most clearly for the L/DAN model. Overall, a condition effect was present with greater L/DAN integration present during the SC condition. There was a significant subsystem X group interaction ($p < 0.003$), revealing greater integration in the TLE group between the right DAN and left temporal ($p < 0.001$), as well the right DAN/right temporal language subsystem ($p = 0.009$) (Fig. 2). Integration for L-FPN subsystems showed a condition effect, with greater integration during the SC task than RS ($p = 0.014$). For the L-COpN subsystem integration model there were no significant experimental group, condition, or subsystem integration effects.

3.3. The relationship between RS and SC task dynamic integrations

To better understand the relationship between RS integration values as a baseline context that potentially influences the level of SC task integration, we ran a repeated measures MANOVA with the L/NL subsystem integration measures as the dependent measure, and their corresponding RS measures as independent variables, along with experimental group as a between subject factor.

The results showed a RS L/DAN integration main effect indicating that the combined level of SC task integration varied as a function of integration values involving the RS right frontal/left DAN ($p = 0.042$) (Table 3A). This right frontal/left DAN integration effect was related to overall task integration. Also, specific RS language/DAN interactions with SC integration values were demonstrated, (see Table 3A) involving the RS cerebellar/right DAN ($p = 0.006$) predicting the SC left temporal/right DAN ($p = 0.05$) and subcortical/right DAN ($p = 0.007$) integrations. Also, the RS cerebellar/left DAN ($p < 0.001$) predicted the SC left frontal/right DAN ($p = 0.015$) and subcortical/right DAN ($p = 0.001$) integrations.

A similar repeated measures MANOVA's on the SC task integration values involving the L/FPN revealed that three RS /FPN integration main effects were present indicating that the level of the left frontal/left FPN ($p = 0.017$), left temporal/left FPN ($p = 0.033$), and cerebellar/left FPN ($p = 0.005$) communication at RS influenced the broad level of SC

Table 2A

Results of Two-way Repeated-Measures MANOVA for recruitment and flexibility within the language and between the language/non-language subsystems (L/DAN, L/FPN, L/COpN).

Source	df or Hypothesis df/ error df	F	Sig	Partial Eta Squared	Observed Power	Source	df or Hypothesis df/ error df	F	Sig	Partial Eta Squared	Observed Power
RECRUITMENT Within Language subsystems FLEXIBILITY											
WS Condition	1	0.654	0.423	0.015	0.124	WS Condition	1	0.297	0.588	0.007	0.083
WS Condition X Group	1	1.947	0.170	0.042	0.276	WS Condition X Group[b]*	1	4.639	0.037	0.095	0.558
WS Subsystems X Group	3.662	0.368	0.815	0.008	0.129	WS Subsystems X Group	4.373	0.616	0.666	0.014	0.208
WS Condition X Subsystem X Group	4.172	1.424	0.226	0.031	0.448	WS Condition X Subsystem X Group	4.303	0.890	0.477	0.020	0.290
BTWS Group[a]	1/44	4.160	0.047	0.086	0.514	BTWS Group	1/44	0.119	0.731	0.003	0.063
RECRUITMENT Among Language/DAN subsystems FLEXIBILITY											
WS Condition	1	0.711	0.404	0.016	0.131	WS Condition	1	3.430	0.071	0.072	0.441
WS Condition X Group	1	0.236	0.629	0.005	0.076	WS Condition X Group	1	1.878	0.177	0.041	0.268
WS Subsystems X Group	4.807	0.953	0.445	0.021	0.330	WS Subsystems X Group	5.279	1.277	0.273	0.028	0.463
WS Condition X Subsystem X Group	4.623	1.772	0.126	0.039	0.578	WS Condition X Subsystem X Group[d]	5.824	2.459	0.026	0.053	0.816
BTWS Group[c]	1/44	4.620	0.037	0.095	0.557	BTWS Group	1/44	1.743	0.194	0.038	0.253
RECRUITMENT Among Language/FPN subsystems FLEXIBILITY											
WS Condition	1	0.316	0.577	0.007	0.085	WS Condition[f]*	1	4.783	0.034	0.098	0.571
WS Condition X Group	1	0.928	0.341	0.021	0.156	WS Condition X Group	1	0.490	0.488	0.011	0.105
WS Subsystems X Group	4.539	1.538	0.185	0.034	0.505	WS Subsystems X Group	5.319	0.937	0.462	0.021	0.344
WS Condition X Subsystem X Group	3.889	1.980	0.092	0.043	0.618	WS Condition X Subsystem X Group	5.798	0.935	0.468	0.021	0.361
BTWS Group[e]	1/44	4.416	0.041	0.091	0.538	BTWS Group	1/44	0.105	0.748	0.002	0.062
RECRUITMENT Among Language/COpN subsystems FLEXIBILITY											
WS Condition	1	3.419	0.071	0.072	0.440	WS Condition	1	0.418	0.521	0.009	0.097
WS Condition X Group[g]*	1	4.920	0.032	0.101	0.583	WS Condition X Group	1	1.218	0.276	0.027	0.191
WS Subsystems X Group	4.618	0.599	0.688	0.013	0.209	WS Subsystems X Group	5.300	0.948	0.454	0.021	0.347
WS Condition X Subsystem X Group	4.385	1.166	0.328	0.026	0.381	WS Condition X Subsystem X Group	4.611	1.454	0.211	0.032	0.483
BTWS Group[h]	1/44	4.117	0.049	0.086	0.510	BTWS Group	1/44	0.010	0.920	0.000	0.051

The univariate test results showing main effects and interactions of condition, experimental group, and subsystems for recruitment, flexibility (2a) and integration (2b). Pairwise comparisons were also tested for the results showing a significant univariate effect to determine the nature of the differences between those variables.
WS – Within-subject effect, BTWS – Between-subject effect.

*Multivariate effect is significant at $p < 0.05$ or less.

Within language system

Recruitment:

[a] Group effect: Healthy controls higher recruitment than TLE.

Flexibility:

[b] Multivariate effect for Condition × Group: Wilk’s lambda: 0.905; F(1,44) () = 4.639, p = 0.047; partial eta squared = 0.095; power = 0.558. Pairwise comparison indicated during task healthy controls had a greater flexibility as compared to the TLE group (F(1,44) = 3.535, p = 0.067).

Among Language/DAN subsystems

Recruitment:

[c] Group effect: Healthy controls higher recruitment than TLE.

Flexibility:

[d] Multivariate effect for Condition × Subsystem X Group: Wilk’s lambda: 0.737; F(7,38) () = 1.939; p = 0.090, power = 0.683, with a high epsilon (0.832) indicating that the univariate test may be more sensitive to this effect. Pairwise comparison indicated during rest TLE group had a greater flexibility as compared to controls for left frontal language (F(1,44) = 5.096, p = 0.029), Left temporal language (F(1,44) = 4.252, p = 0.045), right temporal language (F(1,44) = 7.663, p = 0.008) and RDAN (F(1,44) = 3.219, p = 0.080) subsystems.

Among Language/FPN subsystems

Recruitment:

[e] Group effect: Healthy controls higher recruitment than TLE.

Flexibility:

[f] Multivariate effect for Condition: Wilk’s lambda: 0.902; F(1,44) () = 4.783; p = 0.034; partial eta squared = 0.098; power = 0.571). Pairwise comparison indicated that flexibility was greater during rest than task condition.

Among Language/COpN subsystems

Recruitment:

[g] Multivariate effect for Condition × Group: Wilk’s lambda: 0.899; F(1,44) () = 4.920; p = 0.032; partial eta squared = 0.101; power = 0.583. Pairwise comparison

indicated that during rest controls had greater recruitment than TLE group (p = 0.006).

[h] Group effect: Healthy controls higher recruitment than TLE.

Table 2B

Results of Two-way Repeated-Measures MANOVA for subsystem integration within the language subsystems and between language/non-language subsystems (L/DAN, L/FPN, L/COpN).

Source	df or Hypothesis df/error df	F	Sig	Partial Eta Squared	Observed Power
Within language subsystems					
WS Condition	1	3.774	0.058	0.079	0.456
WS Condition X Group	1	1.114	0.297	0.025	0.178
WS Subsystems X Group	9.024	1.339	0.215	0.030	0.653
WS Condition X Subsystem X Group	8.890	1.260	0.258	0.028	0.615
BTWS Group	1/44	0.597	0.444	0.013	0.118
Between L/DAN subsystems					
WS Condition[i*]	1	5.205	0.027	0.106	0.607
WS Condition X Group	1	2.031	0.161	0.044	0.286
WS SSIntegration X Group[j*]	9.411	2.778	0.003	0.059	0.964
WS Condition X Subsystem X Group	8.910	0.696	0.711	0.016	0.344
BTWS Group	1/44	2.159	0.149	0.047	0.301
Between L/FPN subsystems					
WS Condition [k*]	1	6.501	0.014	0.129	0.703
WS Condition*Group	1	0.198	0.658	0.004	0.072
WS Subsystems*Group	9.597	0.878	0.550	0.020	0.457
WS Condition*Subsystem*Group	9.812	1.252	0.257	0.028	0.645
BTWS Group	1/44	0.949	0.335	0.021	0.159
Between L/COpN subsystems					
WS Condition	1	0.141	0.709	0.003	0.066
WS Condition X Group	1	0.392	0.534	0.009	0.094
WS SSIntegration X Group	9.891	1.201	0.289	0.027	0.625
WS Condition X Subsystem X Group	10.501	1.185	0.297	0.026	0.638
BTWS Group[l]	1/44	3.106	0.085	0.066	0.407

*Multivariate effect is significant at $p < 0.05$ or less.

Between L/DAN subsystems

[i] Multivariate effect for Condition: Wilk's lambda: 0.894; F(1,44) () = 5.205; p = 0.027; partial eta squared = 0.106; power = 0.607. Pairwise comparison indicated that L/DAN integration was greater during task as compared to rest.

[j] Multivariate effect for Condition X Group: Wilk's lambda: 0.425; F(11,34) () = 4.182; p = 0.001; partial eta squared = 0.575; power = 0.993. Pairwise comparison indicated that L/DAN integration was greater in the TLE group as compared to healthy controls for left temporal/right DAN (F(1,44) = 20.549, $p < 0.001$) and right temporal/right DAN (F(1,44) = 7.528, p = 0.009) integrations.

Between L/FPN subsystems

[k] Multivariate effect for Condition: (Wilk's lambda: 0.871; F(1,44) () = 6.501; p = 0.014; partial eta squared = 0.129; power = 0.703). Pairwise comparison indicated that L/FPN integration was greater during task as compared to rest.

Between L/COpN subsystems

[l] Group effect: TLE group had higher L/COpN integration than healthy controls.

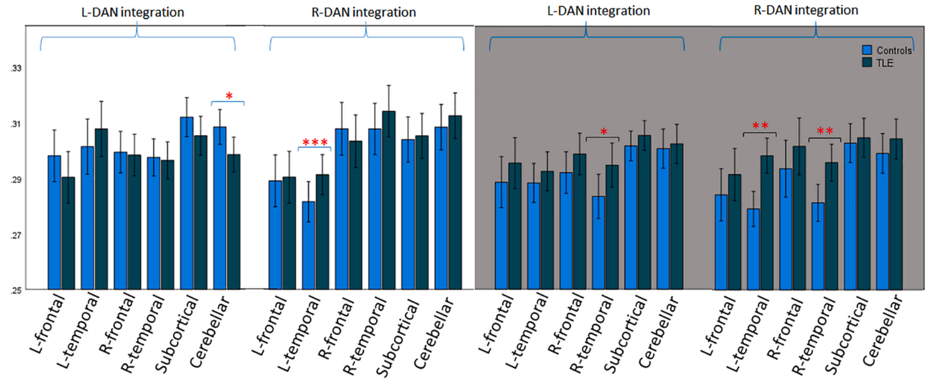


Fig. 2. Regional allegiance preference. Subsystem integration estimated during SC task (white background) and RS (gray background) condition: left (L) and right (R) dorsal attention network (DAN) integrations with each of six language subsystems. Asterisk indicates pairwise group differences, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.1$ (all Bonferroni corrected). Error bars reflect standard error (SE).

L/FPN integrations (Table 3B). Also, one specific RS language/FPN interaction with SC integration was present involving RS subcortical/right FPN integration (p = 0.045) (see Table 3B), with this showing a relationship with left frontal/left FPN integration during the SC task (p = 0.046). The results for L/COpN integration revealed no significant RS L/COpN integration main effects (Table 3C). One specific RS integration measure right frontal/left COpN (p = 0.009) (see Table 3C) demonstrated an interaction with two SC integrations (cerebellar/left COpN, p = 0.015; and left frontal/right COpN, p = 0.01).

Table 3A

Within-subject interactions involving SC language/non-language subsystem integrations and their matched RS language/non-language measures for L/DAN model.

Source	df	F	Sig.	Partial Eta Squared	Observed Power
SC L/NL integrations	11.000	1.651	0.083	0.049	0.824
SC L/NL integrations X RS L-Frontal/LDAN	11.000	1.644	0.085	0.049	0.822
SC L/NL integrations X RS L-Temporal/LDAN	11.000	1.446	0.150	0.043	0.758
SC L/NL integrations X RS R-Frontal/LDAN	11.000	0.818	0.622	0.025	0.458
SC L/NL integrations X RS R-Temporal/LDAN	11.000	0.788	0.652	0.024	0.441
SC L/NL integrations X RS Subcortical/LDAN	11.000	0.392	0.959	0.012	0.215
SC L/NL integrations X RS Cerebellar/LDAN *[a]	11.000	3.252	0.000	0.092	0.993
SC L/NL integrations X RS L-Frontal/RDAN	11.000	1.005	0.441	0.030	0.561
SC L/NL integrations X RS L-Temporal/RDAN	11.000	0.384	0.962	0.012	0.211
SC L/NL integrations X RS R-Frontal/RDAN	11.000	1.732	0.065	0.051	0.846
SC L/NL integrations X RS R-Temporal/RDAN	11.000	1.053	0.399	0.032	0.585
SC L/NL integrations X RS Subortical/RDAN	11.000	0.810	0.630	0.025	0.453
SC L/NL integrations X RS Cerebellar/RDAN *	11.000	2.444	0.006	0.071	0.959
SC L/NL integrations X Group	11.000	1.590	0.100	0.047	0.806

Between-subject effects for the above model

Source	F(1,32) ()	Sig.	Partial Eta Squared	Observed Power
RS L-Frontal/LDAN	0.645	0.428	0.020	0.122
RS L-Temporal/LDAN	0.109	0.744	0.003	0.062
RS R-Frontal/LDAN	4.508	0.042	0.123	0.540
RS R-Temporal/LDAN	0.279	0.601	0.009	0.081
RS Subcortical/LDAN	0.119	0.733	0.004	0.063
RS Cerebellar/LDAN	0.145	0.706	0.004	0.066
RS L-Frontal/RDAN	0.997	0.325	0.030	0.163
RS L-Temporal/RDAN	0.031	0.862	0.001	0.053
RS R-Frontal/RDAN	3.118	0.087	0.089	0.402
RS R-Temporal/RDAN	1.944	0.173	0.057	0.272
RS Subortical/RDAN	0.817	0.373	0.025	0.142
RS Cerebellar/RDAN	0.229	0.636	0.007	0.075
Group	0.268	0.609	0.008	0.079

*See abbreviations at the end of Table 3.

*Multivariate effect is significant at $p < 0.05$ or less.

[a] Multivariate effect for SC L/NL integrations X RS Cerebellar/LDAN: Wilk's lambda: 0.379; F(11,22) () = 3.279, p = 0.009; partial eta squared = 0.621; power = 0.939.

[b] Multivariate effect for SC L/NL integrations X RS Cerebellar/RDAN: Wilk's lambda: 0.463; F(11,22) () = 2.324, p = 0.044; partial eta squared = 0.537; power = 0.811.

Table 3B

Within-subject interactions involving SC language/non-language subsystem integrations and their matched RS language/non-language measures for L/FPN model.

Source	df	F	Sig.	Partial Eta Squared	Observed Power
SC L/NL integrations	11.000	0.856	0.584	0.026	0.480
SC L/NL integrations X RS L-Frontal/LFPN	11.000	1.447	0.150	0.043	0.758
SC L/NL integrations X RS L-Temporal/LFPN	11.000	0.716	0.723	0.022	0.399
SC L/NL integrations X RS R-Frontal/LFPN	11.000	2.201	0.014	0.064	0.933
SC L/NL integrations X RS R-Temporal/LFPN	11.000	1.560	0.109	0.046	0.797
SC L/NL integrations X RS Subcortical/LFPN	11.000	0.931	0.511	0.028	0.521
SC L/NL integrations X RS Cerebellar/LFPN	11.000	0.422	0.946	0.013	0.232
SC L/NL integrations X RS L-Frontal/RFPN	11.000	0.361	0.970	0.011	0.199
SC L/NL integrations X RS L-Temporal/RFPN	11.000	0.980	0.464	0.030	0.547
SC L/NL integrations X RS R-Frontal/RFPN	11.000	0.507	0.899	0.016	0.278
SC L/NL integrations X RS R-Temporal/RFPN	11.000	0.795	0.645	0.024	0.445
SC L/NL integrations X RS Subcortical/RFPN*[c]	11.000	1.848	0.045	0.055	0.873
SC L/NL integrations X RS Cerebellar/RFPN	11.000	1.745	0.062	0.052	0.849
SC L/NL integrations X Group	11.000	0.548	0.870	0.017	0.302

Between-subject effects for the above model

Source	F(1,32) ()	Sig.	Partial Eta Squared	Observed Power
RS L-Frontal/LFPN	6.317	0.017	0.165	0.683
RS L-Temporal/LFPN	4.988	0.033	0.135	0.582
RS R-Frontal/LFPN	1.272	0.268	0.038	0.194
RS R-Temporal/LFPN	0.086	0.771	0.003	0.059
RS Subcortical/LFPN	0.060	0.809	0.002	0.056
RS Cerebellar/LFPN	8.981	0.005	0.219	0.828
RS L-Frontal/RFPN	0.006	0.939	0.000	0.051
RS L-Temporal/RFPN	0.226	0.638	0.007	0.075
RS R-Frontal/RFPN	0.330	0.570	0.010	0.086
RS R-Temporal/RFPN	0.166	0.686	0.005	0.068
RS Subortical/RFPN	0.947	0.338	0.029	0.157
RS Cerebellar/RFPN	0.003	0.954	0.000	0.050
Group	0.389	0.537	0.012	0.093

[c] Multivariate effect for SC L/NL integrations X RS Subcortical,RFPN: Wilk's lambda: 0.456; F(11,22) () = 2.383, p = 0.040; partial eta squared = 0.544; power = 0.823.

*See abbreviations at the end of Table 3.

Table 3C

Within-subject interactions involving SC language/non-language subsystem integrations and their matched RS language/non-language measures for L/COpN model.

Source	df	F	Sig.	Partial Eta Squared	Observed Power
SC L/NL integrations	11.000	1.346	0.197	0.040	0.720
SC L/NL integrations X RS L-Frontal/LCOpN	11.000	1.437	0.154	0.043	0.755
SC L/NL integrations X RS L-Temporal/LCOpN	11.000	1.345	0.198	0.040	0.719
SC L/NL integrations X RS /R-Frontal/LCOpN*[d]	11.000	2.315	0.009	0.067	0.946
SC L/NL integrations X RS R-Temporal/LCOpN	11.000	0.974	0.469	0.030	0.544
SC L/NL integrations X RS Subcortcal/LCOpN	11.000	0.667	0.770	0.020	0.370
SC L/NL integrations X RS Cerebellar/LCOpN	11.000	1.292	0.227	0.039	0.697
SC L/NL integrations X RS L-Frontal/RCOpN	11.000	1.357	0.192	0.041	0.724
SC L/NL integrations X RS L-Temporal/RCOpN	11.000	1.392	0.175	0.042	0.738
SC L/NL integrations X RS R-Frontal/RCOpN	11.000	0.618	0.814	0.019	0.342
SC L/NL integrations X RS R-Temporal/RCOpN	11.000	0.994	0.451	0.030	0.555
SC L/NL integrations X RS Subcortical/RCOpN	11.000	0.606	0.824	0.019	0.335
SC L/NL integrations X RS Cerebellar/RCOpN	11.000	0.707	0.732	0.022	0.394
SC L/NL integrations X Group	11.000	0.841	0.599	0.026	0.471

Between-subject effects for the above model

Source	F(1,32) ()	Sig.	Partial Eta Squared	Observed Power
RS L-Frontal/LCOpN	2.263	0.142	0.066	0.309
RS L-Temporal/LCOpN	2.647	0.114	0.076	0.352
RS R-Frontal/LCOpN	1.323	0.259	0.040	0.200
RS R-Temporal/LCOpN	0.695	0.411	0.021	0.128
RS Subcortical/LCOpN	0.206	0.653	0.006	0.073
RS Cerebellar/LCOpN	0.039	0.845	0.001	0.054
RS L-Frontal/RCOpN	0.187	0.668	0.006	0.070
RS L-Temporal/RCOpN	0.000	0.993	0.000	0.050
RS R-Frontal/RCOpN	3.013	0.092	0.086	0.391
RS R-Temporal/RCOpN	3.671	0.064	0.103	0.460
RS Subortical/RCOpN	0.435	0.514	0.013	0.098
RS Cerebellar/RCOpN	0.179	0.675	0.006	0.069
Group	0.284	0.598	0.009	0.081

[d] Multivariate effect for SC L/NL integrations X RS R-Frontal/LCOpN: Wilk's lambda: 0.459; F(11,22) () = 2.358, p = 0.042; partial eta squared = 0.541; power = 0.818.

*SC – sentence completion task, RS – resting state, L-left, R-right, DAN – dorsal attention network, FPN – Frontoparietal network, COpN – Cingulo-opercular network.

3.4. *The relationship between dynamic integration and language competence in TLE*

Through our PLS model we explored the adaptiveness of integration measures in TLE, testing whether the dynamic integration measures either during the RS or SC contexts predicted language competence (LC). The results showed that one latent factor explained 54.9% of the variance in LC, with two latent factors explaining 82% of the variance (27.1% incremental gain). Thirteen integration features demonstrated substantive variable importance values across the two factors (Fig. 3 shows the substantive loadings on factors 1 and 2; Supplementary Section shows the list of predictors).

The results revealed that negatively weighted SC task integration measures dominated both factors (84.6%), indicating high integration during task predicted low LC. Selected left RS integrations were present (subcortical/left DAN, left frontal/left FPN), each with positive weights indicating high RS integration predicted high LC. The subsystems containing the well-established hubs of the language dominant hemisphere (left frontal and temporal) were strong contributors to both factors, with the left frontal subsystem showing both right and left hemisphere NL integrations in relation to LC. Two of the three predictive left temporal SC integrations involved the left hemisphere (left COpN, left DAN). The integrations involving the subcortical and cerebellar language subsystems comprised 38.4% (5 of 13) of the predictors of LC, with both right and left hemisphere NL subsystems involved. Also, the bilateral COpN communication with the language hubs and subcortical/cerebellar language subsystems held the most presence among the integration predictors, revealing a strong inverse relation to LC. Overall, this suggested that L/NL integrations during the phasic/task state, which all displayed an inverse relation to LC, best explained language competency. Selected RS integrations also made a contribution, but showed a positive relationship to LC. The left hemisphere language hubs played a

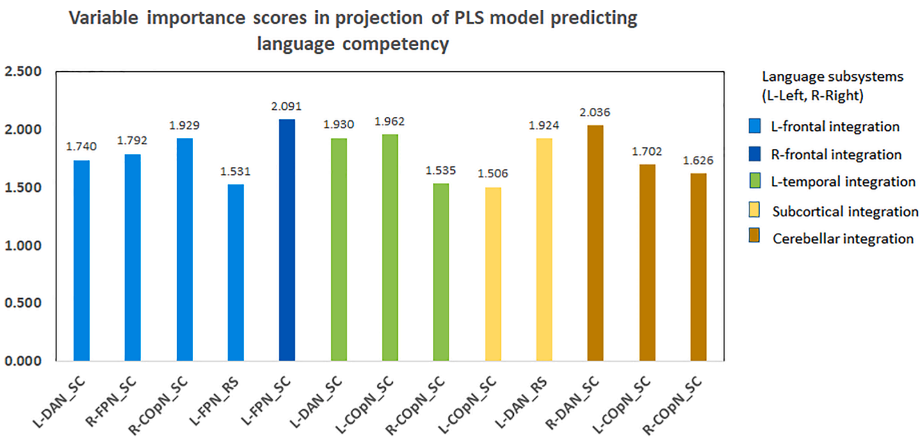


Fig. 3. Partial Least Squares (PLS) plot showing highest variable importance scores. PLS model predicting language competency indicated 2 latent factors explaining 82% of the variance in language competence. SC and RS indicate condition for integration value. Color code of the bars indicate the specific language subsystem (predictors) involved in the L/NL integration, with the linked NL subsystem indicated on × axis. L – Left, R – Right, DAN – dorsal attention network, FPN – fronto-parietal network, COpN – cingulo-opercular network, SC- sentence completion task, RS – resting state.

large predictive role, as did the bilateral COpN.

3.5. *Relationship between RS and SC dynamics and clinical variables*

We examined the potential association between key clinical characteristics (age of disease onset; disease duration) and the key dynamic properties within language system (recruitment, flexibility), and between the sets of L/NL integrations. Within the language system, earlier age of disease onset was associated with lower recruitment in the cerebellar subsystem during RS (r = 0.59, PBonferroni = 0.023). No reliable association with flexibility of the language subsystems was present.

Regarding integration, earlier age of disease onset was associated with lower integration during RS, involving the L/DAN subsystem (left DAN/ subcortical, r = 0.59, PBonferroni = 0.01; right DAN/ right temporal, r = 0.47, PBonferroni = 0.01; right DAN/cerebellar, r = 0.492, PBonferroni = 0.07) and one instance of higher integration involving the left COpN/left frontal, r=–52, PBonferroni = 0.04). No reliable associations between age of disease onset and the dynamic measures during the SC task emerged. Thus, overall, age of onset did influence the probability of intra-communication within language subsystems, as well as with the level of integration between certain L and NL subsystems, though this appeared only in the context of RS. Regarding disease duration, no reliable association with recruitment or flexibility involving the language subsystems was present. In contrast, longer disease duration was associated with higher levels of L/NL integrations during the SC, primarily involving the right temporal subsystem (right temporal/right DAN, r = 0.77, PBonferroni = 0.001; right temporal/ right FPN, r = 0.51, PBonferroni = 0.05; right temporal/right COpN, r = 0.52, PBonferroni = 0.05), suggesting the longer the disease impact the more the language subsystems depended on right hemisphere L/NL network integrations to maintain functionality.

As the cognitive reserve of the brain may be a feature that relates to the overall level of healthy functional dynamics in the diseased brain, we investigated whether our dynamic measures were related to overall verbal IQ, noting that IQ is often considered a surrogate of cognitive reserve (Stern, 2009). In this regard we utilized the WAIS-IV (VCI) and found that none of the language subsystem recruitment and flexibility measures, nor any of the various L/NL integration measures (L/DAN, L/FPN, L/COpN), during either RS or the SC, were associated with VCI in our TLE patients.

Lastly, we assessed whether the clinical epilepsy measures (e.g., age of onset) or cognitive reserve (VCI) mediated the relationship between the L/NL integrations and LC as observed in the PLS model (mediation analysis) (Wager et al., 2008). This analysis revealed that neither the clinical measures nor cognitive reserve mediated these relationships.

4. Discussion

In response to the first question we posed for this study regarding abnormal network dynamics in TLE, we utilized the emerging capabilities of dynamic network tools (Bassett and Sporns, 2017) to demonstrate that TLE patients do show a set of abnormal dynamics both during a language task and at rest. In so doing, we provided insight into the dynamic reconfigurations of multiple brain systems implementing language functioning in both TLE patients and matched healthy participants (see Fig. 4).

Overall, our TLE/HC comparisons revealed reduced recruitment in TLE relative to HCs, with this effect present when examined both within the language subsystems, and the broader L/NL subsystems. This suggested that over time during both the RS and SC conditions, community assignment was less fixed in TLE. However, subsequent analyses accounting for the role played by higher years of education in the HC's weakened the significance of these findings for recruitment (see Supplementary Section for more details). Our findings for flexibility also showed the TLE group had reduced flexibility during the SC task compared to RS within the L subsystems, but increased flexibility during RS involving the DAN and the language hubs (left frontal and temporal, also right temporal). This indicated that a background level of abnormal communication entrainment between language and attention was present in TLE. Given the abnormally reduced levels of intra-language dynamics, this background entrainment of the language and DAN subsystems appeared to be an adaptive feature of TLE network dynamics, helping to explain their overall intact language competency (n. b., no experimental group difference in LC).

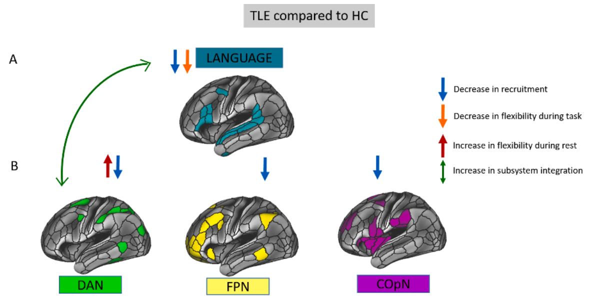


Fig. 4. Depiction of Key Group Effects. (1) (Row A, blue arrow): Decreased recruitment both within the language subsystems, and (row B, blue arrow) the broader Language/Non-Language systems in TLE (DAN, dorsal attention network; FPN, fronto-parietal network; COpN, cingulo-opercular network). Note, two of six Language subsystems are seen by this view (i.e., right frontal, right temporal, subcortical, and cerebellar not shown). (2) (Row A, orange arrow): Reduced flexibility within the language subsystems during task in TLE; (Row B, red arrow) increased flexibility during rest involving the DAN system and language hubs in TLE (Row A, left frontal and left temporal. Right temporal not shown). (3) (Row B, green double headed arrow): Increased integration between Language/DAN subsystems in TLE.

To determine the specific L/DAN communication accounting for this abnormality, we turned to our measure of integration and found striking differences in L/DAN subsystem integration, with the TLE patients showing increased integration compared to HCs between the right DAN and the left and right temporal lobe language subsystems. These increased integrations reflected a communication preference that was not related to condition (RS, SC). These L/DAN integrations were the only abnormal L/NL integrations seen in our data, suggesting these dynamics are specific and preferential to the L/DAN subsystems. Thus, the language-dominant temporal lobe pathology of TLE appeared to create a need to call upon functionalities involving top-down attentional control, perhaps with the goal of strongly linking the visual attention systems to the systems dedicated to lexical semantic processing.

Our finding on flexibility for TLE is consistent with a study by Chai et al. (2016) that showed greater flexibility for language ROIs in the resting state compared to a language task. The Chai results focused on healthy normals, thus our data extends this finding to TLE, but showed that this flexibility feature in TLE involved not just language ROI's but increased flexibility with a non-language system. Given that the preferential inter-network integration findings unique to TLE involved just the DAN, and not the FPN and COpN systems, our findings did not appear to be a domain-general effect related to a broad call for extra-temporal functionality because of their temporal lobe pathology (Braver et al., 2003; Cole and Schneider, 2007; Blank et al., 2014; Blumstein and Amso, 2013; Thompson-Schill et al., 2005). As the dynamic changes we report involved both language and non-language systems, our data goes beyond the concepts of 'core' and 'peripheral' language systems described in early work (Bassett et al., 2015). Thus, our data provided insight into the adaptive dynamics that may be present in TLE, taking advantage of the computational properties of a non-language system to compensate for the impact of their temporal lobe pathology.

Because our data showed some differences in L/NL dynamics during the different contexts of rest and task for TLE, we sought to determine more precisely the relationship between rest and task dynamics. We found that RS L/NL integrations, particularly for L/DAN and L/FPN, did influence the overall level of task L/NL integrations. Interestingly, if the RS integration involved a left (dominant) hemisphere language subsystem the relationship was positive (i.e., higher RS was associated with higher SC integrations). In contrast, if the RS integration involved a right hemisphere language subsystem (contralateral to the seizure focus) the influence of RS on SC integrations was mostly negative (i.e., higher RS integrations associated with lower SC integrations). Our data made clear that there is not a one-to-one correspondence between RS and SC task integrations, meaning that specific RS L/NL integrations did not predict the same pair of SC integrations. Lastly, it is important to note, in contrast to the above noted findings on flexibility and integration with the DAN which were specific to TLE, the influence of RS integrations on SC task integrations were present in both the TLE patients and HCs, indicating that these RS/SC effects were not linked to TLE pathology.

Previous work has suggested that brain activity and functional connectivity during rest and task have high overall correspondence (Smith et al., 2009; Cole et al., 2016; Krienen et al., 2014). There is also strong evidence that the human language system retains similar functional organization during both task (Fedorenko and Thompson-Schill, 2014; Blank et al., 2014; Doucet et al., 2017) and resting state conditions (Doucet et al., 2017; Tomasi and Volkow, 2012; Muller and Meyer, 2014). This has led to the notion that resting-state functional networks provide the pathways over which cognitive task activations flow (Cole et al., 2016). In contrast to our data, the above work has largely relied on static not dynamic measures of functional connectivity. Accordingly, our data shows that there are important differences in inter-network allegiances in the RS and SC contexts when examined through the lenses of more transient network allegiances. Our data is the first to show that the level of pre-existing inter-network dynamic activity laid down at rest is important for L/NL task integrations, perhaps establishing the types of L/NL integrations that are available for use during task if needed. Accordingly, our data addresses the normative relationship between tonic, background resting (intrinsic) activity and task-specific dynamics, providing an example of how increases in specific intrinsic inter-network integrations sets the stage and necessary conditions for potential task-driven network interactions.

In response to the second question we posed for this study, we described the specific language/non-language network dynamics that support language competence in TLE. In so doing, we showed that the dynamic abnormalities observed in TLE bring advantages to language performance, and are, therefore, compensatory. We established this connection between dynamic measures and language competency through PLS, which also allowed us to address the more general issue regarding the relationship between rest and task dynamics. Our data showed that left-hemisphere SC integrations were prevalent in the prediction of LC, indicating that lower levels of language competence were associated with higher levels of SC integration. Selected left RS integrations were also important for language competence, but in each case the RS integration indicated higher integration in association with higher levels of language competence. All three NL systems in interaction with L subsystems, played a role, in the prediction of LC. In short, these data on actual levels of language competency in TLE indicated that heightened L/NL integrations at rest may be a key feature of network dynamics that marks good language skills, but reduced use of the L/NL integrations during task seems to be characteristic of stronger language competence. This inverse relation between task integration and language competence has some basis in the literature, as Bassett et al. (2015) provided evidence that a well-trained brain relies less on inter-system integration during task performance. Combined with the results delineating the relationship between RS and SC task integrations, our data indicated that RS integrations may have a strong general effect on the mean level of SC integration, but these SC task integrations themselves bear the stronger relationship with actual language competence. Moreover, this combination of data suggested that baseline rest is a period where L/NL entrainment occurs to establish, prime, and influence the level of task L/NL integrations, but that the actual use of those interactions during a task, in the setting of TLE, is dependent on the level of language skill.

Finally, we examined the potential association between key clinical variables and RS or SC task dynamics. With regard to age of disease onset, only RS dynamics mattered. Specifically, younger age of disease onset was associated with lower recruitment and lower integration between the L/left DAN and L/right DAN subsystems. Thus, our data showed that when epilepsy strikes early in development there may be an alteration in the baseline, tonic levels of some intrinsic network dynamics. In light of our data suggesting that higher resting state integrations are associated with high levels of language competency, any disruption to tonic, baseline integration dynamics could have a negative cognitive impact (Kim and Ko, 2016). Illness duration was positively related to SC dynamics, specifically showing preferential language communications with the right hemisphere (DAN, FPN, COpN). This may be an indication that the longer epilepsy impacts the brain, the more likely the language system will be driven to integrate and rely on right hemisphere functionality.

Limitations and directions for future research

There are caveats to keep in mind with our study. The sample size is relatively small, reducing power and increasing the chance of type II error. Also, it is unclear the degree to which the preference in L/NL integrations reported here in TLE reflect biases in anatomical connectivity, and whether such biases are more important to language competence than RS or task dynamics. (Turken and Dronkers, 2011) It will be important to test the role of other ICN's for potential preferential integrations with language systems during task or rest.

Several methodological considerations are relevant to this study. First, although identical parameters were used in both the SC and RS scans, the length of 5 min was relatively short. In this light, it is important to note that the dynamic organization of the language system was originally discovered with tasks lasting from only 4 to 6 min (Chai et al., 2016). Second, the selection of window length and sliding steps could still potentially influence our measures of network dynamics (Telesford et al., 2016). The window length and sliding steps were selected based on an earlier published study from our group (He et al., 2018) where the task and rest scans were of identical length and alterations to the analytic pipeline of the main analyses (more windows, larger window length) produced identical results. Third, no individual responses to the covert SC task were recorded during performance. This limited our ability to link the dynamics with real-time performance profiles. Lastly, it is noteworthy that AEDs can influence the blood oxygen level-dependent signal (Jansen et al., 2006; Haneef et al., 2015; Wandschneider et al., 2017) that might have a potential influence on patient/control differences. It is also well known that anti-seizure medications can cause cognitive deficits in areas such as language (Witt and Helmstaedter, 2013; Witt et al., 2015; Ojemann et al., 2001) and such medication effects were not tested in our data. Unfortunately, AED regimen heterogeneity (type, dosage, number of AEDs) prevented further testing of these effects.

5. Conclusion

We provided evidence that the brain areas in which core language functions reside dynamically interact with non-language functional networks to carry out linguistic functions. We demonstrated abnormal language subsystem dynamics both at task and rest though the abnormalities differ for each context. We demonstrated that abnormal integrations between the language and a non-language system (DAN) exist in TLE, and these were present both in tonic as well as phasic states. This integration was considered to reflect the entrainment of visual attention systems to the systems dedicated to lexical semantic processing. Our data made clear that the level of tonic, baseline integrations between the language subsystems and certain task-relevant NL systems (e.g., DAN, FPN) had a crucial influence on the general level of task integrations between L/NL systems, with this a normative finding not unique to epilepsy. We also revealed that a broad set of task-shaped transient integrations in TLE are predictive of language competency, indicating that these integrations are compensatory for patients with lower overall language skills.

While the organizational structure of multiple cognitive domains have been studied in TLE (Kellermann et al., 2017), less is known about how cognitive systems interact, and whether such interactions are specific to a task, or also characteristic of the baseline state. While the degree and the profile of cognitive deficits in TLE and epilepsy syndromes has been well described, much less is known about the profile and brain organization of TLE patients who maintain function. This work contributes on both fronts. Also, it is worth noting that our integration findings involving the right DAN is consistent with data showing that left TLE is associated with adaptive right hemisphere activations and connections in order to compensate for a diseased language hub (Thivard et al., 2005; Powell et al., 2007; Tracy et al., 2021).

Our data argued that network dynamic abnormalities provide important insights into language processing in TLE, and perhaps other neurologic diseases affecting the temporal lobe. Our data implied that damage to a wider network of language/non-language interactions during the resting state may compromise the availability of those L/NL interactions for use under the demands of a language task. Our data reinforced other work showing that it is these language/non-language interactions that define the adequacy of language as much as its modular dedications (Catani and Mesulam, 2008; Catani and Mesulam, 2008). Indeed, a better understanding of the probability with which pathology might disrupt functions such as language will require an understanding of the dynamic language/non-language system interactions we have demonstrated here. We identified an important relationship between baseline/tonic and phasic/tasks contexts, and showed that the inter-network dynamics of both play a role in language competency, but have different purposes in establishing the network reorganizations that can be compensatory to performance. In so doing, we have advanced our understanding of the normative relationship between rest and task, and specified some of the network integrations and reorganizations that may be necessary to achieve compensated task performance and language competency in the setting of temporal lobe pathology. Through our focus on language/non-language interactions during both rest and task, we bring a new perspective to the characterization of language in TLE, increasing our understanding of language dysfunction and maladaptive seizure-driven plasticity in epilepsy, all toward advancing the process of developing personalized brain-based cognitive therapeutics.

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Shilpi Modi: Conceptualization, Methodology, Investigation, Writing – original draft. **Xiaosong He:** Investigation. **Kapil Chaudhary:** Investigation. **Walter Hinds:** Investigation. **Andrew Crow:** Investigation. **Ashithkumar Beloor-Suresh:** Investigation. **Michael R. Sperling:** Investigation. **Joseph I. Tracy:** Conceptualization, Methodology, Investigation, Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102861.

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