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Functional connectivity hemispheric contrast (FC-HC): A new metric for language mapping

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ABSTRACT

Development of a task-free method for presurgical mapping of language function is important for use in young or cognitively impaired patients. Resting state connectivity fMRI (RS-fMRI) is a task-free method that may be used to identify cognitive networks. We developed a voxelwise RS-fMRI metric, Functional Connectivity Hemispheric Contrast (FC-HC), to map the language network and determine language laterality through comparison of within-hemispheric language network connections (Integration) to cross-hemispheric connections (Segregation). For the first time, we demonstrated robustness and efficacy of a RS-fMRI metric to map language networks across five groups (total N = 243) that differed in MRI scanning parameters, fMRI scanning protocols, age, and development (typical vs pediatric epilepsy). The resting state FC-HC maps for the healthy pediatric and adult groups showed higher values in the left hemisphere, and had high agreement with standard task language fMRI; in contrast, the epilepsy patient group map was bilateral. FC-HC has strong but not perfect agreement with task fMRI and thus, may reflect related and complementary information about language plasticity and compensation.

1. Introduction

Twenty to thirty percent of children and adults who develop localization related epilepsy go on to develop medically refractory epilepsy (Ben-Menachem, 2014). For patients with medically refractory localization related epilepsy, surgery to remove the epileptic foci can be a viable option to achieve seizure control (Snead, 2001). The goal of epilepsy surgery is to achieve seizure freedom, while avoiding damage to eloquent cortex and preserving function (Gates & Dunn, 1999; Snead, 2001). Various techniques have been used to identify and localize eloquent cortex (Abou-Khalil, 2007). Task-based functional magnetic resonance imaging (fMRI) is an accepted noninvasive and reliable method for presurgical mapping of language function for epilepsy surgery (Gaillard et al., 2004). Pre-operative task fMRI predicts post-operative verbal memory (Bonelli et al., 2012) and naming performance (Sabsevitz et al., 2003; You et al., 2019). The American Academy of Neurology 2017 practice guidelines for the use of task fMRI in presurgical evaluation for epilepsy patients concluded that task fMRI may be considered an option for determining language laterality in patients with temporal epilepsy (Szaflarski et al., 2017). Once laterality is established, language function may be more specifically localized beyond fMRI by using other techniques such as intra, or extra, operative electrocortical stimulation. If language is ipsilateral to the seizure focus then we aim to identify if language regions activated by fMRI are close to, or overlap with, the seizure focus, as resection of language areas is associated with language impairment (Austermuehle et al., 2017; Ojemann, 1987; You et al., 2019). However, one challenge of fMRI is the patient must perform a task with expected engagement. This poses a

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Table 1
Subjects and Imaging Protocols.

	HCP 1	GUA1	GUA2	GUKids	CNH
N	100 Adults	12 Adults	45 Adults	55 Children	31 Pediatric Patients
Gender (females)	54 (54%)	7 (58%)	35 (78%)	30 (55%)	14 (33.3%)
Age (in years)	29.1 (22–36)	21.1 (18–29)	20.4 (18–22)	11.9 (7–18)	12.8 (7–18)
Handedness	11 left, 82 right, 7 mix Edinburgh Handedness Inventory (Oldfield, 1971), cutoff > 40	12 right Self-reported	2 left, 43 right Self-reported	3 left, 52 right Parent-reported	6 left, 19 right, 6 mix Edinburgh Handedness Inventory (Oldfield, 1971),cutoff > 40
Scanner (Tesla)	Siemens 3 T 32 channel Multiband	Siemens 3 T 12 channel Non-multiband	Siemens 3 T 12 channel Non-multiband	Siemens 3 T 12 channel Non-multiband	GE 3 T 8 channel Non-multiband
TR and Voxelsize	0.72 s, 2 mm	3 s, 3 mm	2 s,3mm	2 s,3mm	2 s,3mm
rsfMRI length	4800 volumes (56 min)	100 volumes (5 min)	150 volumes (5 min)	150 volumes (5 min)	150 volumes (5 min)
Language fMRI length and task contrast	732 volumes(~8min) Story vs Math (Binder et al.,2011)	100 volumes (5 min) Auditory Description Decision Task vs. Reverse Speech (Gaillard et al., 2007)	N/A	N/A	150 volumes (5 min) Auditory Description Decision Task vs. Reverse Speech(Gaillard et al., 2007)

limitation for very young patients or patients who are cognitively impaired and may be unable to perform the task.

Resting state functional MRI (RS-fMRI) with connectivity analysis is a task-free method that has been used to identify several cognitive networks including the default mode, somatosensory, visual, dorsal attention, ventral attention, frontoparietal control, and language (Lee et al., 2013; Tomasi & Volkow, 2012). The viability of RS-fMRI to evaluate language function has been demonstrated through various methods in Supplementary material, including direct comparisons of task-based fMRI maps, machine learning on a training set of task-based fMRI and RS-fMRI to enable prediction of task-based fMRI activation and laterality on a test set of unseen fMRI data (Parker Jones et al., 2017; Tie et al., 2014), and assessing asymmetry of language reorganization (Joliot et al., 2016; Pravatà et al., 2011). However, a limitation of these prior studies is that they applied methods to one, sometimes two, groups, thereby limiting the generalizability of their results. While RS-fMRI has shown promise, additional studies are needed to expand the validity of RS-fMRI method for identifying the language network.

In this study, we evaluate a new metric, Functional Connectivity Hemispheric Contrast (FC-HC), to map language function and laterality during RS-fMRI. Our approach uses a voxelwise evaluation of the asymmetry in recruitment of within-hemispheric language network connections (Integration) and suppression of cross-hemispheric connections (Segregation) to generate a whole brain connectivity map. Our method builds on prior work, which has established that the language network can be identified in healthy adults by its lateralized network properties (i.e., high within-hemisphere and low across-hemisphere connectivity (Gotts et al., 2013). We expand on Gotts' et al (2013) method by using a voxelwise approach instead of a seed-based whole brain ROIs approach to capture the language network with greater precision. Moreover, our whole brain voxelwise approach targets connections to all possible "language-ready" regions that have been identified through MRI meta-analysis of "language" (www.Neurosynth.org). Language-ready regions of the brain are those areas with the intrinsic anatomical neural structure necessary for underlying language functioning. Thus, they may not be active during a specific task, but could be invoked for a language task if demands change (Dehaene-Lambertz, 2002). Our approach provides information that extends beyond regional information obtained from a specific "language-seed" to a more distributed language network derived from compiled language studies.

The primary aim of this study is to establish the robustness of our FC-HC metric to map language networks, across five population groups (total N = 243) that differed in MRI scanning parameters, fMRI scanning protocols, age, and patient group. The inclusion of an epilepsy patient group bolsters the clinical viability of our methods. Importantly, patterns in pediatric epilepsy patients might provide insight into developmental plasticity if they differ from those in the healthy pediatric cohort despite no differences in language performance. Further, a unique aspect of our study is that three of these cohorts had both resting state and language task fMRI for comparison of both ROI level of laterality and spatial pattern similarity. Thus, the second aim of the study is to demonstrate the validity of our new FC-HC metric when compared to language task fMRI which is the current clinical "gold-standard." Three hypotheses that will support FC-HC as a metric of language lateralization include:

1) Language is lateralized to the left hemisphere in 95% of healthy right-handed participants. Thus, we hypothesize that FC-HC will reveal left-lateralized language connectivity patterns in all healthy groups (three adult and one pediatric) despite differences in demographics and imaging protocols.
2) Using the clinical standard as comparison, we hypothesize that there will be high agreement between language dominance determined by FC-HC compared to language task fMRI across healthy individuals.
3) Knowing that epilepsy populations have less lateralized language, we hypothesize that FC-HC will reveal less left lateralized in the pediatric patient group due to atypical language reorganization (Berl et al., 2014b).

2. Materials and methods

2.1. Overview

The current study used five different cohorts (Total N = 243) that differed in MRI scanning parameters, fMRI scanning protocols and age to determine the robustness and utility of FC-HC metric for language mapping (detailed in Table 1).

We applied the FC-HC method using resting state fMRI data across three independent healthy adult cohorts and one healthy pediatric cohort. Adult cohorts included "100 Unrelated Subjects" healthy adult cohort from the Human Connectome Project (HCP) (Van Essen et al., 2013) and two other adult cohorts that were independently collected from Georgetown University (GUA1 (n = 12) & GUA2 (n = 45)) for two different studies (PI Newport and Vaidya). The healthy adult cohorts were collected with different scanning parameters and the HCP data was also collected on a different scanner. The healthy pediatric cohort from Georgetown University (GUKids (n = 55), PI Vaidya) had the same scanner and scanning parameters as one of the adult cohorts (GUA2).

Comparison between FC-HC and language task fMRI was available for two of the healthy cohorts, HCP and GUA1 (language tasks described in Section 2.2). FC-HC comparison to language task fMRI was also available for the pediatric epilepsy patients from Children's National Hospital (CNH; n = 31) who underwent presurgical language task fMRI.

Data for the HCP group is available from the Human Connectome Project as part of their "S900 Subjects" dataset. Data for the other patient and subject groups may be made available if requested through a formal data sharing agreement with the author's institutions. The code developed for the analysis of the data in this study is available through the following resource: https://osf.io/w8g4n/?view_only=3386e755c8_614e369b7bbcaca5b29370).

2.2. Data collection

2.2.1. HCP

HCP dataset consists of "100 Unrelated Subjects" who were randomly selected from the 900 subjects in the S900 Subjects dataset. The use of 100 unrelated individuals' datasets is widely used and more appropriate for statistical analyses intended to represent the general population (Cole et al., 2016; Shine et al., 2016; Wang et al., 2015). Details regarding randomization can be found in the relevant HCP paper (Van Essen et al., 2013). Each participant underwent a 56 min long RS-fMRI (eyes open with fixation) collected over two days. During each visit, 28 min of eyes open resting-state fMRI data were collected across two runs (56 min total, 4800 volumes). Participants also completed a block design auditory language fMRI task over two consecutive runs (3.5 min) with two different conditions: "Story" block vs. "Math" block. During the Story block subjects heard auditory stories (5–9 sentences) followed by 2-alternative forced-choice questions about the topic of the story, while during the Math block subjects were shown arithmetic operations followed by "equals" and then two choices. Resting state and language task fMRI data collection details can be found (Barch et al., 2013; Smith et al., 2013). Briefly, whole-brain echo-planar imaging (EPIs) were acquired with a 32-channel head coil on a modified 3 T Siemens Skyra with TR = 720 ms, TE = 33.1 ms, flip angle = 52°, in-plane FOV = 208 × 180 mm, 72 slices, 2.0 mm isotropic voxels, with a multi-band acceleration factor of 8. Subjects also underwent neuropsychological testing and performed in the average range. 82 out of 100 subject were right handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971), cutoff > 40). As part of the Washington University-Minnesota Consortium participants were recruited from Washington University (St. Louis, MO) and the surrounding area. All participants gave informed consent consistent with policies approved by the Washington University Institutional Review Board.

2.2.2. GUA1, GUA2 and GUKids

Data from three healthy cohorts (GUA1, GUA2, GUKids) was collected at Georgetown University from two independent labs. GUA1 (PI Newport) consisted of twelve healthy adult controls (7 female, mean age 21 years old; range 18–29, all right handed), GUA2 and GUKids (PI Vaidya) consisted of 45 healthy adult (35 female, mean age 20.4 years old, range 18–22, 43 right handed) and 55 healthy children control subjects (52 right handed). GUA2 and GUKids were included in previous studies (Gordon et al., 2012; Loewenstern et al., 2019; Lynch et al., 2017; Yerys et al., 2015; You et al., 2013). Handedness was self-reported or parent-reported. All participants gave written informed consent consistent with policies approved by the Institutional Review Boards of Georgetown University Medical Center.

Subjects in these three groups underwent image acquisition with a similar protocol and imaging parameters at Georgetown University with the exception of using a TR of 2 s for GUA2 and GUKids as opposed to a TR of 3 s for GUA1 (see Table 1). All subjects underwent one RS- fMRI scan (5 min, eyes open, with a fixation cross and the instruction to "not to think of anything in particular"). Resting state fMRI data collection details can be found in previous studies (Gordon et al., 2012; Lynch et al., 2017; Loewenstern et al., 2019; You et al., 2013; Yerys et al., 2015). Briefly, whole brain EPIs were acquired with a 12-channel head coil on a 3 T Siemens Trio scanner with flip angle = 90°, in-plane FOV = 192 × 192 mm, 3.0 mm isotropic voxels.

In addition, GUA1 cohort had collected 5 min block designed Auditory Description Decision Task (ADDT) language task fMRI with same scanning parameters as resting state scans except TR = 3 s. The ADDT is a semantic decision task based on the Boston Naming Task which has been previously described (Gaillard et al., 2007). Briefly, during the task session word definitions (e.g. "a long yellow fruit is a banana") were presented aurally, and subjects instructed to press a button for true statements (70% of items) and not to press for false statements (30% of items). The control condition was reverse speech with tone identification; subjects were asked to press a button when hearing the tone (70% with tones, 30% with foils). The paradigm was presented as a block design of five, one-minute cycles (30 s of control condition followed by 30 s of active condition) with total duration of five minutes. ADDT was adjusted for skill level. Performance during both task and control conditions were monitored. The number of push-button responses for task and control conditions was matched.

The ADDT task was designed for use in presurgical epilepsy populations which has been previously published and validated (Austermuehle et al., 2017; Berl et al., 2014a; Gaillard et al., 2007; You et al., 2019). Importantly ADDT elicits strong and reliable activation in both the frontal and temporal language processing network and has been the most reliable language task out of the full panel to identify language dominance in the clinical setting (Gaillard et al., 2004). It has been used in over 400 patients and 100 controls (Berl et al., 2014a), has been validated by the Wada test and extra operative cortical stimulation, and predicts post-operative language outcomes (Austermuehle et al., 2017; Rolinski et al., 2019; You et al., 2019).

2.2.3. CNH pediatric epilepsy sample

The clinical sample had 31 patients (14 female, mean age = 12.8 years old, range 7–18) diagnosed with focal unaware epilepsy and had undergone evaluation for epilepsy surgery. All had ictal video EEG and high-resolution MRI epilepsy protocol. Twenty-three patients had seizure focus in the left hemisphere and eight in the right; ten had focal cortical dysplasia (FCD) (two with mesial temporal sclerosis) , eight had a tumor, four had a vascular malformation, five were normal, two had other MCD (malformations of cortical development), two had encephalomalacia (Table S1 in Supplementary Material, which includes detailed patient demographic and epilepsy information stating their detailed etiology, handedness, age of onset, seizure duration, gender, medication and age at scan information. Of the patient cohort, 19 out of 31 were right-handed as determined by the Edinburgh Handedness Inventory (cutoff > 40). All patients underwent fMRI as part of the presurgical evaluation for epilepsy surgery, including one 5 min RS-fMRI run (eyes open with fixation) and a panel of language task fMRI which includes same ADDT task collected in GUA1. For details and rationale of using ADDT in our clinical setting see the description for the GUA1 language task. Both RS-fMRI and ADDT were collected using a gradient echo pulse sequence with an 8-channel head coil on a 3 T General Electric scanner with TR = 2 s, flip angle = 90°, in-plane FOV = 192 × 192 mm, 3.0 mm isotropic voxels. Studies were approved by CNH Institutional Review Boards and written informed consent was obtained from all patients.

2.3. fMRI data processing

2.3.1. HCP pipelines

The HCP fMRI data underwent spatial normalization to a standard MNI template, which includes gradient unwarping, motion correction, field map-based EPI distortion correction, brain-boundary-based registration of EPI to structural T1-weighted scan, non-linear registration into MNI152 space and grand-mean intensity normalization, as part of the HCP's minimal preprocessing pipeline (Glasser et al., 2013). Preprocessed volumetric (rather than the surface) resting-state fMRI was denoised using the aCompCor strategy (Behzadi et al., 2007) implemented in the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). Data were also "scrubbed" to remove spurious variance unlikely to reflect neuronal activity (Power et al., 2011). aCompCor in combination with scrubbing is collectively effective for mitigation of residual motion and distance-dependent artifact (Ciric et al., 2017). Denoising steps included linear de-trending and nuisance regression (5 principal components from white matter and cerebrospinal fluid masks derived from T1 segmentation, point-regressors to censor time points with mean frame-wise displacement > 0.04 mm) (Gordon et al., 2017). Residual time-series were first band-pass filtered (0.01 Hz < f < 0.1 Hz). Motion-contaminated volumes were then identified by frame-by-frame displacement (FD) calculated as the sum of absolute values of the differentials of the three translational motion parameters and three rotational motion parameters. Previous work reported that temporally filtering movement parameters derived from HCP resting-state fMRI data allowed for identification of an appropriate FD threshold (Gordon et al., 2017). Denoised resting-state time-series within the cortical ribbon (those situated between the white and pial surfaces) were mapped onto each individual's 32K_fs_LR mid-thickness surfaces and spatially smoothed ($\sigma = 2.55$). Sigma of 2.55 is equal to 6 mm FWHM (Gordon et al., 2017). We used the workbench command "wb_command —volume-to-surface-mapping" from the Human Connectome Project, which provided a way to sample the voxels' value between the pial and white matter surface. The voxel values are sampled using the ribbon mapping method, which constructs a polyhedron from the vertex's neighbors on each surface (pial or white). Vertex refers to the intersection of three triangles on a tessellated surface, which is similar to voxel in 3D volumetric space, but a point of representation on 2D surface space. The algorithm then estimates the amount of the polyhedron's volume that falls inside any nearby voxels. The volume overlap with each nearby voxel is used to weight the voxel values when they are mapped to the surface. Both left and right surfaces were combined into the Connectivity Informatics Technology Initiative (CIFTI) format using Connectome Workbench (Glasser et al., 2013), yielding time courses representative of the entire cortex, excluding non-gray matter tissue and sub-cortical structures. Denoised time-series in CIFTI format were submitted for FC-HC calculation (see section 2.4 below). For the HCP datasets that had four runs of RS-fMRI data, we computed FC-HC for each run and averaged the FC-HC map across all four runs to have a stable measure as to overcome the LR and RL different phase encoding bias on each hemisphere.

Task-based fMRI from the HCP is already fully processed and the activation map (Story vs Math) is readily available to be used for further analysis. Detail processing steps can be found elsewhere (Barch et al., 2013) which includes the similar minimal preprocessing pipeline as RS-fMRI (Glasser et al., 2013). Activation beta estimates were then computed from the preprocessed functional time series using a general linear model (GLM) implemented in FSL's FILM (FMRIB's Improved Linear Model with autocorrelation correction (Woolrich et al., 2001). Predictors (Story and Math blocks) were convolved with a double gamma "canonical" hemodynamic response function (HRF, Glover, 1999) to generate the main model regressors with temporal derivative terms derived from each predictor as confounds of no interest. The key contrast of interest is Story > Math for language function.

2.3.2. GU and CNH pipeline

All fMRI data from GU and CNH underwent a similar processing pipeline as HCP datasets except the initial standard preprocessing was done in SPM12 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK) with motion correction, unwarping, and indirect normalization to MNI space using a deformation field generated through T1 segmentation. RS-fMRI data then followed by similar denoising process as HCP data in CONN toolbox (version 19.c) with the aCompCor strategy but with "scrubbing" criteria for high motion volumes FD > 0.5 mm as suggested for non-multiband fMRI data to remove spurious variance (Power et al., 2015). Final samples included in current study had <20% high movement volumes. Denoised volumetric time-series within the cortical ribbon were mapped onto standard 32K_fs_LR mid-thickness surfaces, after which the left and right hemispheres were combined into CIFTI format through the same method as HCP datasets and spatially smoothed ($\sigma = 2.55$). For the method of FC-HC calculation see section below 2.4.

For ADDT task based fMRI, we first spatially smoothed the normalized images using a Full Width Half Maximum 8 mm Gaussian kernel and submitted the smoothed images for single subject first-level activation analyses in SPM12 using GLM (Friston et al., 1994). The delta function of the block onsets for task and control conditions were convolved with the canonical HRF. The key contrast of interest is Task > Reverse speech for language function.

2.4. Resting state fMRI language FC-HC calculation

2.4.1. Rationale

We propose that the language cortex in an individual's language dominant side of the brain will exhibit more/a higher degree of functional connections to all the canonical language areas during resting state fMRI. Based on graph theory's concept of network efficiency in which an efficient network should have high integration within network and high segregation across networks (Fair et al., 2007; Gotts et al., 2013; Yerys et al., 2015), we aimed to derive a vertex-wise/voxelwise measure that would capture both integration and segregation of the lateralized language network. We therefore built upon the concept of Gotts's study and adapted the voxelwise hemispherical contrast metric used by Lee et al (H. W. Lee et al., 2014) , which aimed to identify a lateralized effect of the seizure focus. We inferred that functional connectivity associated with a lateralized function (e.g. language) would have differences in within-hemispheric compared to across-hemispheric connections. Our definitions of Integration and Segregation are slightly different from others (Gotts et al., 2013). In their case integration is high both within and across hemisphere connectivity strength, while "Segregation" is high within relative to across hemisphere, and mainly relying on low across hemisphere connections. Thus their "Segregation" is essentially what FC-HC is capturing. But due to our unique usage of degree of connections in a graph theory network fashion, we opt to call high within hemisphere integration, and call low across hemisphere FC segregation. In our application, we are interested in language cortex which prior studies demonstrate are largely constrained to canonical areas in either hemisphere that comprise a frontal-temporal language network (Mbwana et al., 2009; Rosenberger et al., 2009; You et al., 2019). When there is reorganization of language networks due to epilepsy, stroke, or other neurological factors, language remains in these traditional frontotemporal areas. Thus, we defined our target as an unbiased symmetric language network derived from a language meta-analysis (this network delineation will be described below) to identify functionally meaningful voxels that have strong connections to the dominant language areas (high Integration), preferentially over the connections to nondominant language areas (high Segregation).

2.4.2. Calculation of language FC-HC metric:

The language FC-HC map is computed based on the following: first, we computed the whole brain vertex to vertex connectivity matrix using a Pearson Correlation (r). After the whole-brain vertex-wise correlations were obtained, correlation thresholds were set to decide whether voxels were "connected". Then, for each vertex within the gray matter we computed the degree of within hemisphere connectivity by calculating the number of ipsilateral connections in a comprehensive language mask at a threshold r (Intra-hemispheric FC; hereafter referred to as Within hemisphere connections, which represents Integration). The 'ipsilateral connections' were values established per every gray matter voxel, in relation to the language meta-analysis mask. Similarly, we computed the degree of across hemisphere connectivity by calculating the number of

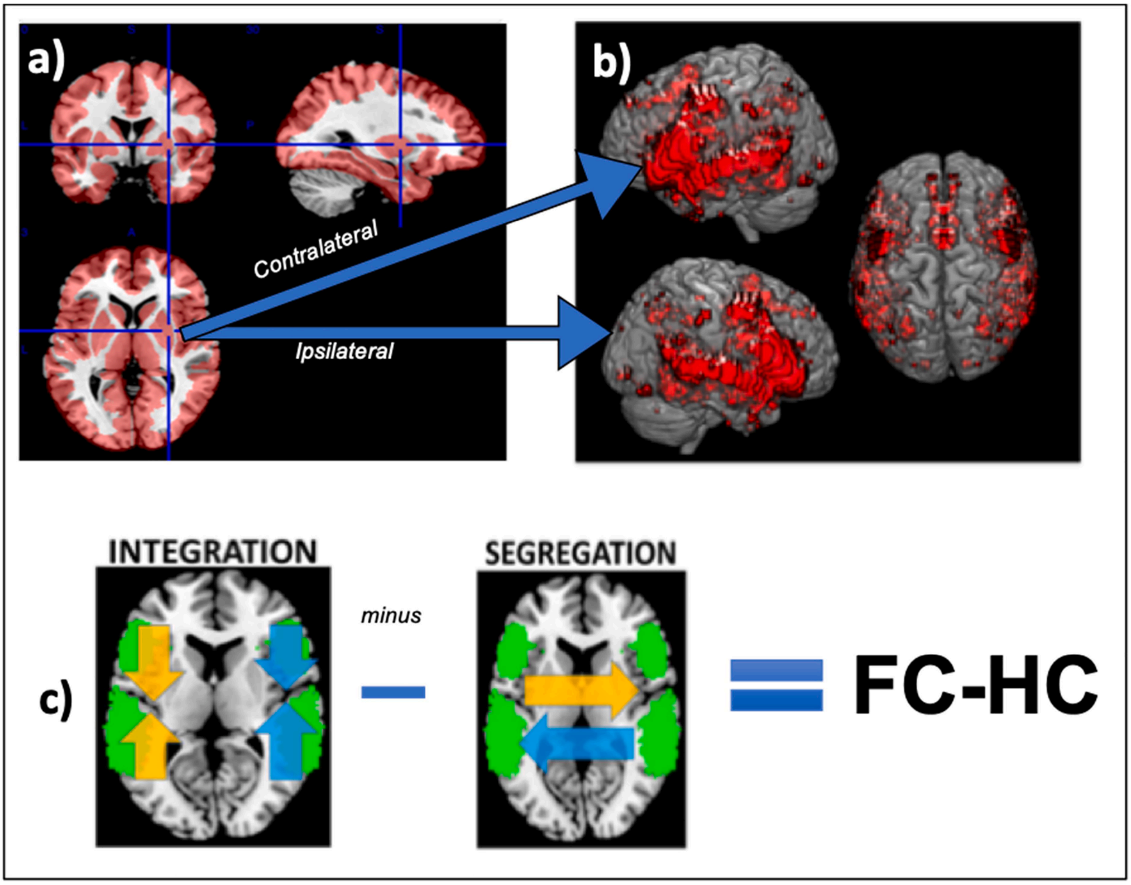

Fig. 1. FC-HC calculation schema. For each voxel within the gray matter mask (a), the number of connections to the union language target masks (b) was calculated, separately to the ipsilateral side (Within hemisphere FC representing "Integration"), and to the contralateral side (Across hemisphere FC representing "Segregation"). Voxelwise/vertexwise FC-HC is then derived from Within (Integration) minus Across (Segregation) (c). The union language masks were created by Neurosynth.org from a meta-analysis of language-related studies (FDR corrected at p = 0.01), after which we flipped this overall left-lateralized language mask to create a mirrored version, and then combined both to create a union mask.

contralateral connections in the same language mask (Inter-hemispheric FC; hereafter referred to as Across hemisphere connections, which represents Segregation). At that point, the Within and Across FC values consisted of raw counts of connections, which are dependent on image resolution. Therefore, to make comparable across studies with different resolution, we proposed to scale these FC metrics, the number of Within and Across hemispheric connections for each vertex was converted to 0–1 range through dividing it by total number of vertices in the language mask in one hemisphere (i.e. the largest possible number of Within or Across hemisphere connections for any vertex). Then the FC-HC for each vertex was calculated by subtracting the Across FC from Within FC (Within – Across, Fig. 1), where FC-HC > 0 suggests greater FC within hemisphere and FC-HC < 0 indicates greater FC across hemispheres. A whole brain vertex-wise map of language network FC-HC (maximum range −1 to 1) was then generated to indicate each individual's laterality. Since the FC-HC is dependent upon r thresholds, the above analysis was conducted at 1) different r thresholds, determined from a stepwise edge density (ED) incrementally from ED = 0.1 (i.e. 10%) with a step of 0.1 to 0.5, (2) each threshold's resulting FC-HC was then multiplied by 0.5/ED (3) the results from the previous step were averaged. The highest ED was set to 0.5 to maintain r thresholds higher than 0.1 for all individuals. This weighted mean FC-HC ensured that different levels of contributions were weighted by the strength of connections, as stronger connections should be more meaningful biologically, and carry more weight and influence. Edge Density within the language network is defined as how many actual edges/connections between all nodes/vertices exist compared to how many edges/connections between all nodes/vertices are possible. We used Edge Densities (ED) over r correlation thresholds because the ED method maintains a biologically plausible amount of connections that should reasonably be present in any given subject's language system, while r thresholds can be susceptible to baseline differences in connectivity, easily resulting in few or no connections within a language system when r threshold is high, causing unstable laterality. See Supplementary Material (Figures S6, S7, S10) for the comparisons between mean language FC-HC Group mean maps and LI across Edge Density steps and R thresholds, as well as individual subject maps displaying the differences between the weighted ED and weighted R methods.

To ensure that FC-HC is language specific, we used a comprehensive and representative language mask obtained from Neurosynth.org for the FC-HC calculation above. Specifically, search term of "language" produced an FDR corrected (p = 0.01) mask through the meta-analysis of 1101 "language" related studies. We flipped this overall left-lateralized language mask to create a mirrored version, and combined them to create a union mask. Note this union mask contains over 99% of voxels that were present in the union masks of other language related search terms in Neurosynth, such as "semantic", "speech", "Phonics". Thus this comprehensive and representative union mask included all the possible language regions in both hemispheres and is large enough to include language areas reported in epilepsy populations with intra-hemispheric reorganization (Mbwana et al., 2009; Rosenberger et al., 2009; You et al., 2019). We then mapped the volumetric union language mask to the standard 32K_fs_LR surface (see Figure S1) for vertex-wise FC-HC calculation.

2.5. FC-HC stability across cohorts and agreement with activation

To examine the robustness and stability/usability of FC-HC metric, mean FC-HC maps were compared first across all cohorts, then against activation maps within cohorts that had language task fMRI. We did not apply cluster correction for rest FC-HC and task activation maps at both the individual and group levels, as we aim to provide unbiased group level maps. We used spatial correlation to quantify the similarity at the group level. To facilitate visual comparison, we presented both the raw maps as well as top 10% thresholded maps. The top 10% criterion was not applied to the r value, but applied to both the resulting 3D FC-HC map and task activation map. To calculate the spatial similarity between maps, we used the Brodmann Area surface masks provided in Human Connectome Project (Van Essen, 2005; Van Essen et al., 2012) intersected with the union language mask we used for FC-HC calculation to obtain a comprehensive language network described at the BA-level. Our union mask had a total of 16 BAs from each hemisphere that extended beyond traditional Broca's area (BA 44, 45) and Wernicke's area (BA 21, 22, 39), by also including BA 6, 9,40,41,42,46,47 in frontal, and BA 13,20,37,38 in extra-frontal areas. We then extracted the mean signal within each BA from each hemisphere in the union language mask, and performed the Pearson correlation of BAs between FC-HC maps across cohorts, as well as between the FC-HC maps and task activation maps (t statistic map from SPM) within each cohort. Similar to visual inspection steps, we calculated spatial correlation on both the raw maps and thresholded top 10% maps. We used BA level spatial correlation instead of voxel level as we wanted to place emphasis on the general pattern of BA distribution within and across hemispheres between task activation and FC-HC, rather than the variance of voxels within BA areas across the two.

The rationale for inspecting results on unbiased raw maps as well as at a specific threshold is that unbiased raw FC-HC maps allow for inspection of the full range of FC-HC, since there is no prior knowledge of FC-HC value distribution in the population. We then operationalized threshold by using the top 10% (You et al., 2019) as has been discussed with task activation (Wilke & Lidzba, 2007). Using a thresholded map is important for interpretation, as raw data is often too inclusive of low-level signal in all regions of the brain. Using the top 10% is advantageous because it creates individualized thresholded maps based on the amount of connections (or activation) present in each patient/group, which is more stable than just using a single arbitrary cutoff (You et al 2019).

Another way to quantify the robustness and stability of FC-HC is calculating a Laterality Index (LI) to measure similarity in terms of language dominance for each cohort's FC-HC maps and task activation maps (t statistic map from SPM) when available, which is commonly performed in clinical practice (Szlaflarski et al 2017). First, we used the anatomical AAL atlas frontal lobe mask to extract the frontal language component/ROI, then used the temporal-parietal lobe mask to extract the temporal-parietal language component. We then quantified the LI on each of the frontal and temporal ROI by extracting signals from left and right hemisphere separately and used the formula of (L-R)/(L + R), with > 0.2 being left lateralized, $<$-0.2 right, and otherwise bilateral (Berl et al., 2014a; Gaillard et al., 2007) for FC-HC/task activation maps from each cohort.

In order to have comparable LI measures between task activation and FC-HC maps, we used the top 10% positive signal from both maps for LI calculation based on the rationale mentioned above. We thresholded each individual raw/uncorrected map at the top 10% level, and used the total strength of those remaining voxels within each ROI to calculate LI.

To analyze the agreement of language lateralization between task LI and language FC-HC LI in the HCP cohort, we first plotted the task LI against the language FC-HC LI for each subject using the gold standard thresholds for language lateralization in task LI: Left dominant language if $LI > 0.2$, Bilateral language if $|LI| < 0.2$, Right dominant language if LI < -0.2. To further examine the effect of FC-HC LI threshold on language dominance concordance rates between FC-HC LI and task activation LI, the left dominance cutoff for the FC-HC LI was increased from –1 to 1, while the left dominance cutoff for task LI was held constant at $LI \geq 0.2$ in the HCP cohort. Concordance rates were defined as the number of subjects designated as left language dominant by FC-HC LI /number subjects designated as left language dominant by task LI.

We used surface-based FC-HC as the main approach instead of volume-based because surface analysis is more accurate in optimizing the alignment of anatomical and functional data across individuals and increases the specificity of cortical activation patterns and connectivity results (Brodoehl et al., 2020). Moreover, neighboring voxels in 3D space often represent locations that are distant in cortical (2D) space, thus smoothing in surface space can avoid signal bleeding to seemingly adjacent voxels that are actually remote on the cortical sheet (Anticevic et al., 2008). However, in addition to conducting surface-based analyses on all cohorts, we added volume spaced based FC-HC results for patients in the supplementary material (Figure S11).

2.6. Understanding the variance of FC-HC/sub-component analysis

As FC-HC is a new metric, we report many measures to describe better the metric overall, and how the four components that comprise the FC-HC calculation, i.e., how the left/right integration and left/right segregation components influence the overall FC-HC. To capture variance across individuals, we calculated LI of FC-HC maps for each individual within each cohort and provided their group distribution with standard error. Similarly, we also calculated each subject's LI for the Within hemisphere FC map, as well as the LI for Across hemisphere FC map separately to understand the extent of their respective contribution to the laterality of FC-HC. Lastly, we examined the value in each hemisphere for FC-HC, Within and Across hemisphere FC maps that contributed to the LI calculation. We tested group differences through one-way ANOVA across all cohorts for FC-HC LI. We compared task activation LI and FC-HC LI through paired *t* test in each cohort (HCP, GUA1, CNH).

2.7. Clinical utility and functional meaning of FC-HC

To further establish the validity of the language FC-HC LI we investigated the relationship between rest FC-HC LI and the age adjusted score on the Picture Vocabulary neuropsychology measure in the HCP cohort. We tested whether language FC-HC LI explains more variance than task activation LI in the HCP sample, which is the largest sample that also has language measures. The non-patient cohorts were not designed to investigate language function, thus we have limited language measures for investigating the relationships between language FC-HC and language function. To demonstrate that the robustness of our language FC-HC findings in the HCP cohort is stable regardless of preprocessing pipeline choices, we re-calculated the FC-HC maps using the Minimally preprocessed ICA-FIX denoised data (Glasser et al. 2013), by downloading them directly from HCP AWS database using the neurohcp R package.

We have also included individual surface and volumetric FC-HC maps from two patients in Supplementary Materials to demonstrate the stability of the FC-HC metric at the individual level in a clinical population.

3. Results

3.1. FC-HC across healthy cohorts

FC-HC group maps across the four healthy cohorts were all left-lateralized (Fig. 2). Visually FC-HC values are higher on the left hemisphere in both frontal and temporal-parietal areas. This left dominance is more evident using the top 10% threshold for the FC-HC maps. This observation is also supported by calculated mean FC-HC LI within each

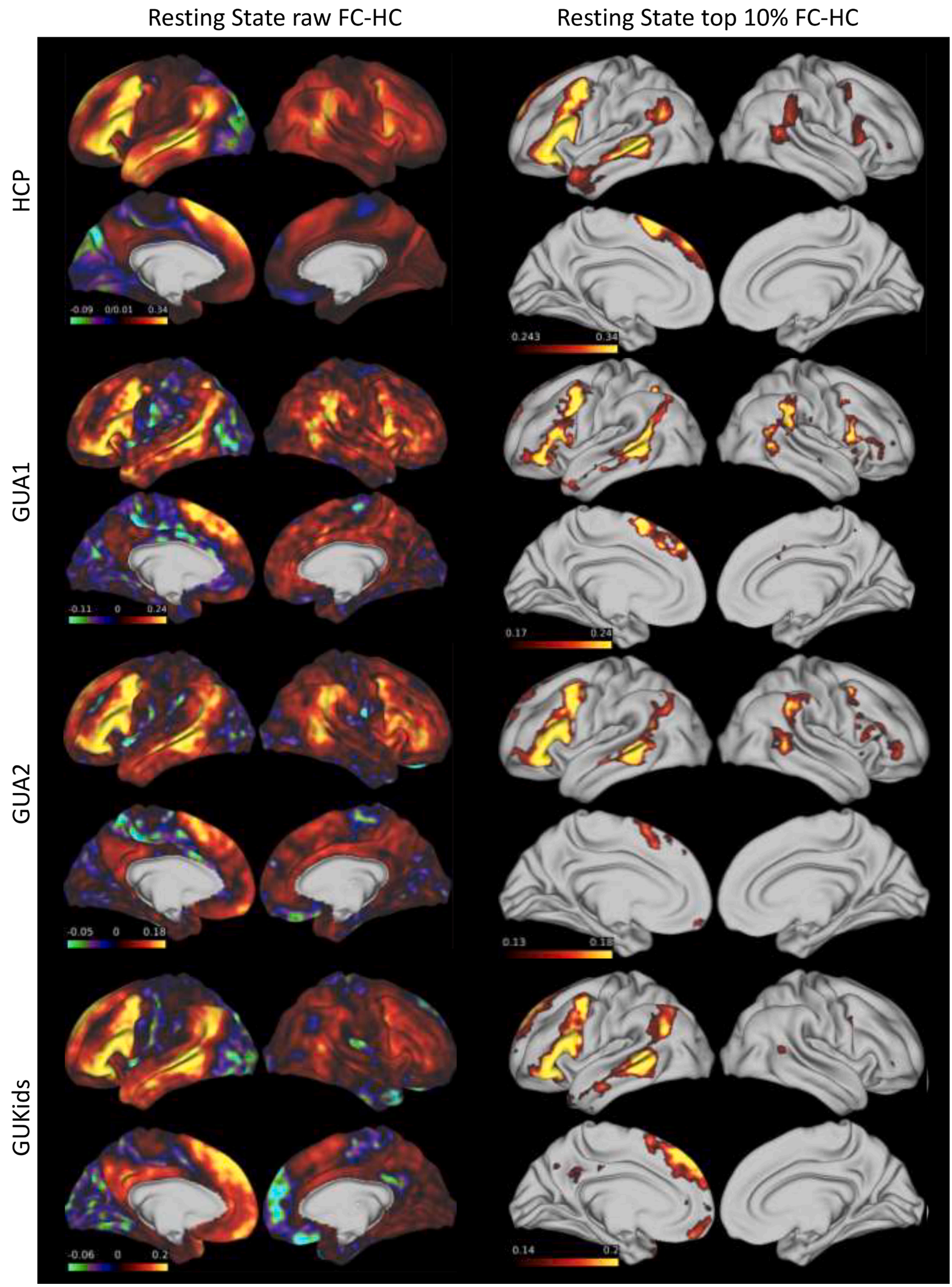

Fig. 2. Stability of FC-HC across healthy cohorts at the raw and top 10% level. The resting state FC-HC maps of the two Georgetown University adult groups showed a high degree of visual similarity. All healthy cohorts demonstrated left dominant language FC-HC. (HCP = Human Connectome Project, GUA1 = Georgetown University Adults 1, GUA2 = Georgetown University Adults 2, GUKids = Georgetown University Kids).

Table 2
Group mean FC-HC LI and Peak information across all cohorts.

Group		Motion	Frontal Language Mask					Temporal-parietal Language Mask				
			LI	Peak Value	Peak X	Peak Y	Peak Z	LI	Peak Value	Peak X	Peak Y	Peak Z
HCP	Task	0.18	0.340	4.482	−41.250	29.927	−14.073	0.293	5.256	−45.570	−63.515	24.650
	Rest	0.35	0.459	0.007	−51.951	21.291	17.171	0.341	0.007	−51.965	−38.706	0.069
GUA1	Task	0.16	0.788	6.023	−49.912	20.099	37.447	0.815	4.473	−37.553	−29.851	−23.502
	Rest	0.22	0.288	0.001	−50.586	24.871	6.569	0.206	0.001	−54.890	−39.604	−0.448
GUA2	Rest	0.16	0.255	0.007	−47.579	21.210	20.437	0.274	0.007	−55.607	−38.983	−0.985
GUKids	Rest	0.15	0.395	0.008	−51.137	21.353	18.339	0.440	0.008	−55.461	−40.930	0.197
CNH	Task	0.13	0.575	1.916	−41.541	22.255	23.018	0.542	1.401	−54.627	−41.140	7.172
	Rest	0.24	−0.054	0.002	−49.810	33.898	0.664	−0.035	0.002	54.465	−49.354	10.924

*LI values are calculated based on top 10% maps.

group across individual maps, as well as the peak location for group mean maps in frontal and temporal-parietal ROIs in these cohorts (Table 2). Mean LI values exceeded the 0.2 definition of left lateralization for all four cohorts. Moreover, spatial correlation results showed there was shared spatial variance for the raw FC-HC across cohorts (r_s > 0.6, p < 0.001) for both raw and top 10% FC-HC group mean maps.

3.2. Agreement between FC-HC and task fMRI in healthy cohorts

Both healthy groups with task and RS-fMRI (HCP and GUA1) showed left-lateralized patterns in group maps of FC-HC and task activation for raw data (Fig. 3A) and top 10% thresholded data (Fig. 3B). Although overall group mean LI values exceeded the 0.2 definition of left lateralization for both FC-HC and task activation, the LI values for FC-HC were not as high as activation mean maps for GUA1 in both frontal (Paired *t* test: t = 3.62, df = 11, p = 0.004) and temporal-parietal ROIs (Paired *t* test: t = 4.11, df = 11, p = 0.002), while HCP had comparable temporal-parietal LI between task and FC-HC (Paired *t* test: t = -1.07, df = 99, p = 0.29), but higher frontal FC-HC LI (Paired *t* test: t = -2.66, df = 99, p = 0.009) than task activation LI (Table 2 and see Supplementary Fig. S2 for LI bar plots showing task activation and rest FC-HC LI). In addition, spatial correlation for group mean maps showed there was shared spatial variance between raw FC-HC and raw activation maps (r_s > 0.6, p < 0.001) as well as for the top10% thresholded maps (r_s > 0.8, p < 0.001).

The scatter plot of task LI against the language FC-HC LI in the HCP (Human Connectome Project) cohort showed majority subjects agreed with language dominance (62% for frontal ROI and 56% temporal ROI) using the gold standard thresholds for language lateralization in task LI (Fig. 4).

Using the left lateralized HCP subjects (task activation LI > 0.2) as the base for a concordance analysis (Frontal N = 70. Temporal N = 67), the concordance between FC-HC and task LI generally declined as FC-HC LI threshold for left language dominance increased from − 1 to 1 (Fig. 5). Concordance rates were above 87% when then cutoff for left, typical language dominance was set from − 1 to 0. The average concordance rate for calculating FC-HC LI when left language dominance was defined as 0<=FC-HC LI<= 0.2 across masks was 85% (range 74%–92%).

3.3. FC-HC vs task activation in pediatric epilepsy cohort

In contrast to healthy cohorts, the group level FC-HC map showed a bilateral pattern in the pediatric epilepsy cohort (Fig. 6A and 6C). Of note, bilateral FC-HC occurred in the context of left dominant task activation (Fig. 6B and 6D). A bilateral pattern was also supported by group mean LI values (<0.1 and > -0.1, Table 2). Paired T test showed reduced LI for FC-HC than task maps in both frontal (t = 3.79, df = 20, p < 0.001) and temporal-parietal (t = 3.82, df = 30, p = 0.003) ROIs (see Supplementary Fig. S2). Differences between FC-HC and task activation were also reflected by the moderate spatial similarity correlation (r = 0.379, df = 31, p = 0.03) between their group mean maps, considerably lower than those of HCP and GUA1.

3.4. FC-HC sub-component analysis

Average FC-HC LI in each healthy cohort were left dominant in both frontal ROI and temporal ROI while CNH patients were bilateral in both ROIs (Fig. 7). The ANCOVA controlling for motion (mean framewise-displacement) showed significant difference in FC-HC LI between cohorts in both frontal (F(4,237) = 6.357, p < 0.001) and temporal (F (4,237) = 5.699, p = <0.001) ROIs. The pediatric epilepsy cohort was lower than all healthy cohorts in the frontal ROI (adjusted p_s < 0.02), except GUA1 (adjusted p = 0.1) as revealed by a Bonferroni-corrected post-hoc pairwise comparisons test. In the temporal FC-HC LI ROI, a post-hoc pairwise comparisons test demonstrated that the FC-HC LI of the epilepsy cohort was significantly lower than the GUKids cohort (adjusted p < 0.05). Same ANCOVA controlling for motion across healthy cohorts showed no differences in FC-HC LI across healthy cohorts for both ROIs (adjusted p_s > 0.05). Motion is not correlated with FC-HC LI nor absolute FC-HC LI in any cohort.

Group level summary of Within, Across, and FC-HC LIs across the four healthy cohorts revealed that left laterality pattern of FC-HC is mainly driven by left dominant Within-hemisphere FC, especially for the frontal region. This is less evident for the temporal-parietal ROI, of which FC-HC is more dependent upon the preferential degree of Within over Across hemisphere FC. In contrast, the pediatric patient group's bilateral FC-HC LI in the frontal region was driven by slightly right dominant Within hemisphere FC. Their temporal ROI's bilateral FC-HC LI was driven by a similar level of Within and Across FC, albeit slightly more on the left hemisphere. These observations are supported by group level Within-hemisphere and Across-hemisphere maps, as well as the plots of left and right mean value of the top 10% voxels that constituted the LI calculation (Supplementary Material Figs. S3, S4). Left and right sub components revealed that there was more right hemisphere integration in the CNH pediatric group than in all healthy cohorts. Specifically, the left dominant FC-HC LI in both frontal and temporal-parietal ROIs across all healthy cohorts was driven by much stronger integration on the left than the right hemisphere (Within FC map), as there is less distinction between the left and right for Across hemisphere FC. For the patient cohort, there is an opposite pattern for FC-HC in frontal ROI which is driven by stronger right-side integration. For the temporal-parietal ROI, the patient cohort had equal Within Hemisphere FC and FC-HC in left and right hemispheres, albeit slightly stronger right integration than the other cohorts, while healthy cohorts still had higher Within Hemisphere FC and FC-HC in the left hemisphere.

The mean FC-HC map for the patient cohort in volumetric space was also atypical (non-left dominant compared to healthy cohorts), which is supported by the bilateral volumetric language FC-HC LI summary for all patients (Fig. S12).

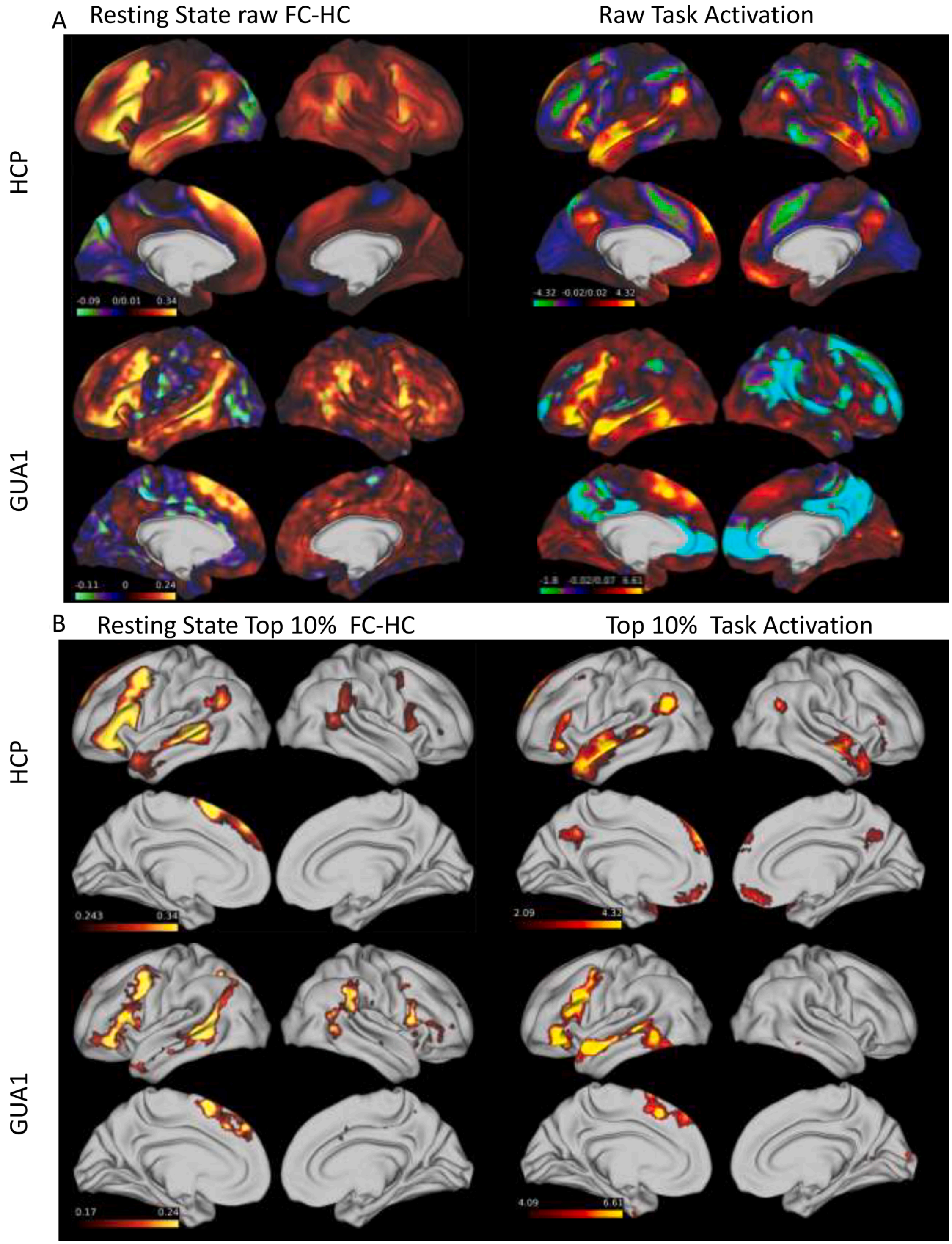

Fig. 3. Similarity between FC-HC and task activation maps at the raw (A) and 10% level (B) in 2 healthy adult cohorts: HCP (Human Connectome Project) and GUA1 (Georgetown Adults 1).

3.5. Clinical utility and functional implication of FC-HC

In the HCP (Human Connectome Project) cohort FC-HC LI is correlated with age adjusted score on the Picture Vocabulary language measure in the temporal ROI ($r = -0.23$, $p = 0.02$). Frontal and temporal FC-HC LI are both correlated with picture vocabulary measures in the right handed HCP subjects ($N = 84$) ($r = -0.27$, $p = 0.01$), while task LIs are not correlated with Picture Vocabulary score in the full cohort or in the right handed subjects (Fig. 8, $p_s > 0.4$). Through an ANOVA of linear regression models, we found that a model of handedness, task LI, and FC-HC LI explained more variance than a model of handedness and task LI in predicting Picture Vocabulary score (ANOVA, $F = 5.32$, $p = 0.02$).

The correlation between age adjusted Picture Vocabulary score and language FC-HC LI is driven by the right-handed subjects ($N = 84$). Mean group FC-HC maps (Fig. S8) and FC-HC LIs (Fig. S9) generated from the HCP data processed by the ICA-FIX pipeline were consistently left dominant, similar to our current stringent motion correction pipeline in

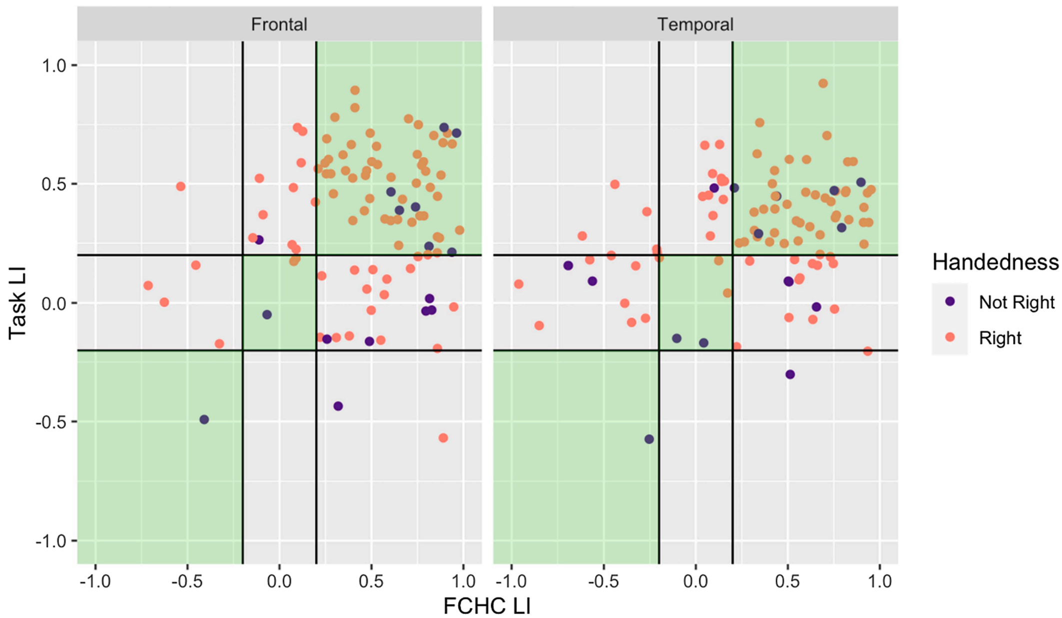

Fig. 4. Scatter plot visualizing all subjects (N = 100) from the HCP (Human Connectome Project) cohort categorized by handedness (Right = Pink, Not right = Purple), highlighting in green the language dominance quadrants where task activation LI and resting state FC-HC LI agree. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

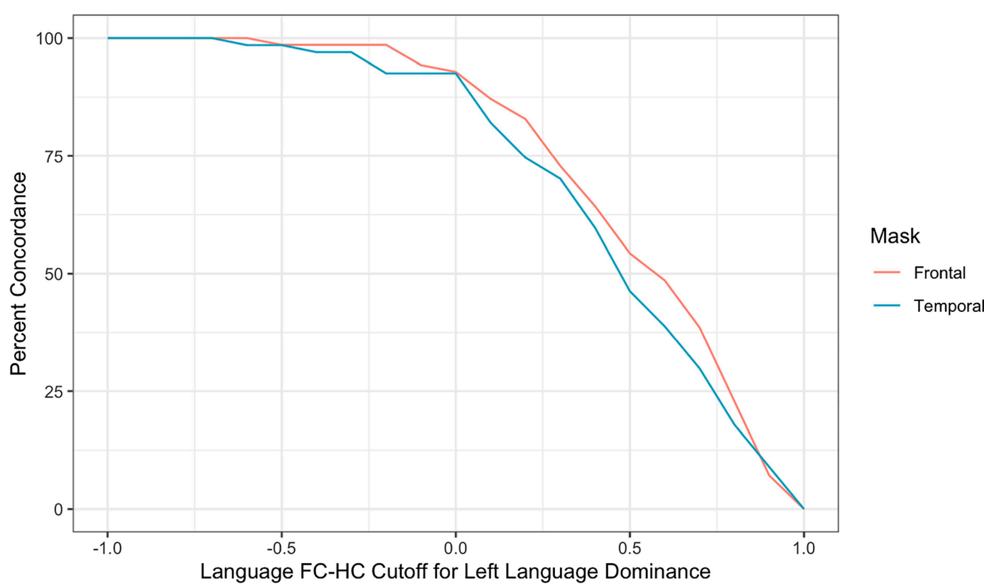

Fig. 5. Rate of concordance between resting state language FC-HC LI and task activation LI as the cutoff for FC-HC left language dominance is increased from –1 to 1 from the HCP (Human Connectome Project) cohort. This is using the left lateralized HCP subjects (task activation LI > 0.2) as the base (Frontal N = 70. Temporal N = 67).

the HCP (Human Connectome Project) cohort. The two individual subject FC-HC maps from the HCP cohort (Fig. S10) also demonstrated the robustness of the language FC-HC metric regardless of processing pipeline. We have also provided two individual patient maps to demonstrate the potential clinical utility of the FC-HC metric (Fig. S13) to lateralize and localize language area.

4. Discussion

We demonstrate the potential of using RS-fMRI to determine language laterality with a novel adaptation of a metric, Functional Connectivity Hemispheric Contrast (FC-HC), that quantifies language dominance through the number and strength of connections within a hemisphere compared to those across hemispheres on a voxel-wise basis. At the group level, FC-HC revealed the expected left-lateralized language pattern across healthy adult and pediatric populations. The finding was robust across cohorts with different scanning parameters and ages, and held at different thresholds. In a subset of healthy adults, there was high agreement between resting state FC-HC and the current clinical standard of language task fMRI activation; however, the degree of laterality was consistently lower for FC-HC when compared to the highly lateralized ADDT language task. The pediatric epilepsy group, had strongly left lateralized standard fMRI language activation, yet the FC-HC was bilateral. Decomposing FC-HC components revealed that

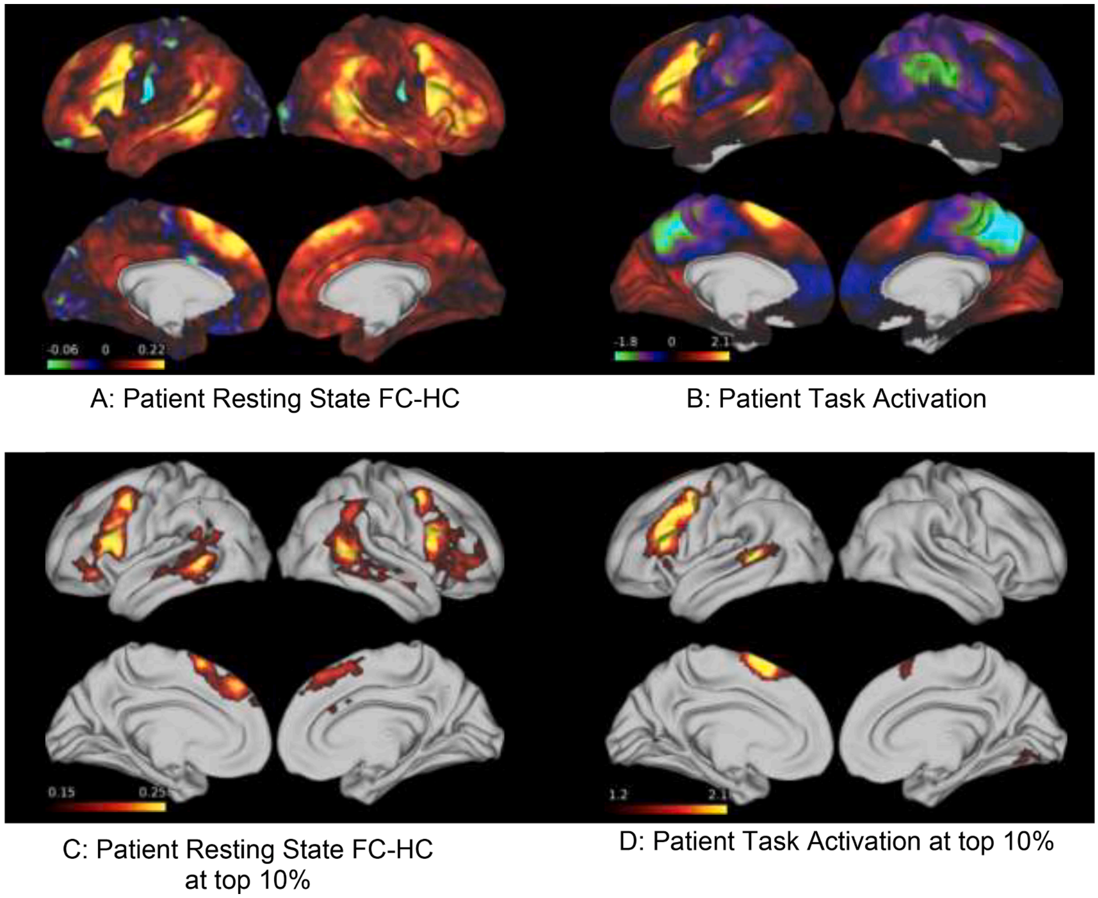

Fig. 6. Pediatric Patients (CNH) Resting State FC-HC and task activation maps. The pediatric patient group demonstrated left dominant language task activation (6B and 6D) but a more bilateral Resting State FC-HC both at raw (6A) and top 10% level (6C).

within hemisphere connectivity was consistently left among typical groups, while across hemisphere connectivity was more variable across all groups and by language region. Our results suggest that FC-HC is a metric that is related to language laterality given the high agreement with task-based LI, yet the differences and discrepancies also suggest that FC-HC may be a complementary measure to traditional activation LI, rather than a direct proxy.

The differences between the FC-HC metric and task-based metric may reflect different aspects of the neural bases of language. One possibility is that the more lateralized LI during task reflects the overt effort for active task processing. In comparison, the less lateralized FC-HC may reflect the inherent capacity of the network to perform language tasks, sometimes referred to as the "language ready" network (Doucet et al., 2017). For example, even typical adults activate language homologues in the contralateral hemisphere when they engage in more difficult language tasks, even though they remain left-hemisphere dominant for language (Just et al., 1996). There can be activation outside the language network because not all activation in language tasks is specific to language. Our resting state language FC-HC maps also showed strong FC-HC value in areas outside of the meta-analysis language mask, e.g. the HCP group map showed strong FC-HC in the angular gyrus, which is outside the language union mask (Fig. S1). This showed the robustness/lack of bias in the method in evaluating the number of connections to the target language meta-analysis mask for all the voxels/vertices on the cortex. Thus, FC-HC may reflect the capacity of the comprehensive language network (dominant areas and their homotopic areas in the other hemisphere) to be invoked for language processing. If true, this metric may provide insights about cognitive plasticity and inform our understanding of language reorganization in epilepsy. Our findings in the pediatric epilepsy group provide preliminary support for this notion. Specifically, this increased FC-HC on the right hemisphere is driven by an increased within-hemisphere connection and decreased across-hemisphere functional connectivity on the right hemisphere (Supplementary Figs. S3-4). The FC-HC in the healthy cohorts had a robust lateralized pattern against many changing parameters even though the raw number of within-hemisphere and across hemisphere connections may be influenced by different preprocessing steps especially level of smoothing (Supplementary Materials Figures S14-16).

Three prior studies compared task based-maps and resting state maps for language regions (Gaelle E. Doucet et al., 2017, 2015; Smitha et al., 2017). In 18 healthy adults, RS-fMRI seed-based analysis and task-based fMRI had correlated LI's with both methods showing left hemisphere dominance, especially in Broca's Area (Smitha et al., 2017). In a study that included epilepsy patients only, the correlation between the resting state and verb generation task varied depending on the seed region being used (Gaëlle E. Doucet et al., 2015). In a study with healthy adults and epilepsy patients, resting state maps were more bilateral than language activation maps that were left lateralized in both groups; however, the discrepancy was larger in the patient group. These authors were the first to propose that the difference between the functional network maps and task generated maps for language may be explained by language related functional networks involving a wider set of 'language ready' bilateral regions that are not all necessary for specific tasks (Doucet et al., 2017).

Our findings across combined datasets confirm previous findings that task-based and RS-fMRI are associated in terms of laterality, yet discrepancy is evident, more so, in a patient population. The divergence in pediatric patients (between task and rest and vs controls) might reflect intrinsic differences in what the patients were doing at rest. We also cannot exclude medication effects; however, we did not have

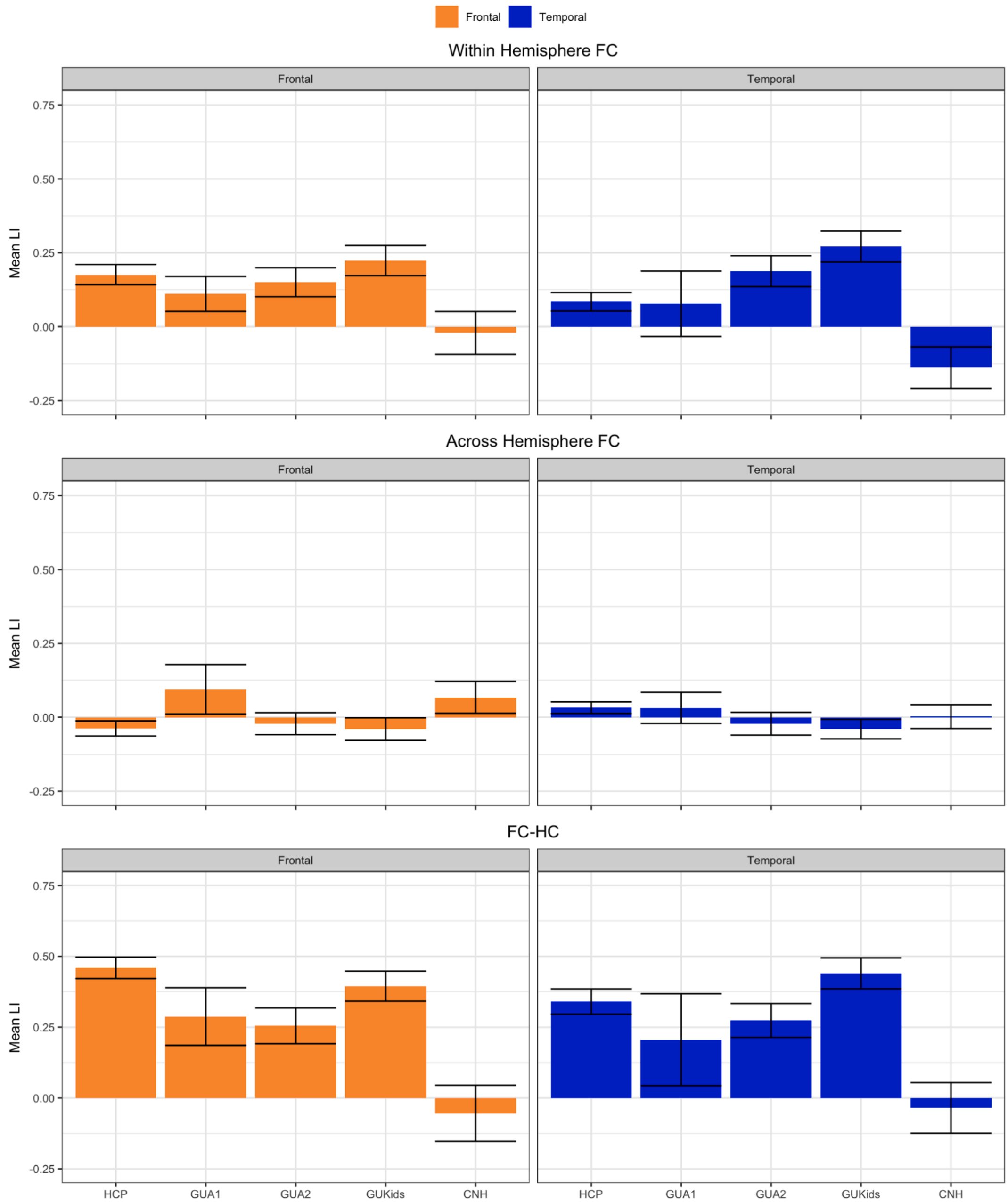

Fig. 7. Summary of FC-HC LI across different cohorts and relationship to Intra and Inter LI. Blue: Frontal ROI, Orange: Temporal ROI. FC-HC LI from the top 10% thresholded maps were left dominant in all healthy cohorts in both frontal ROI and temporal ROI (LIs > 0.2) except GUA1 temporal LI. CNH patients were bilateral in both frontal and temporal-parietal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

anyone obviously asleep during the scan which can be monitored through brain activation, the act of completing button presses for task fMRI, and their eyes being open. Theoretically, there are many factors that might influence FC-HC LI, as well as task activation LI, such as lesion location, whether present in language area or not, left or right focus, age of onset, age at resting state. There is a hypothesis that younger children exhibit more bilaterally based activation on task fMRI data (Berl et al., 2014a; Rasmussen & Milner, 1977; Szaflarski et al., 2006), but our findings did not suggest that younger healthy children exhibit more bilateral FC-HC metrics. Taken together, it may be that if bilateral FC-HC reflects adaptability or "readiness" of the broader language network to engage, then epilepsy might induce the brain to maintain that bilateral connectivity. It is unclear if bilateral FC-HC is advantageous in terms of language function or recovery of language. We do know that task-based fMRI is able to predict about 20–40% of the variance in language (You et al., 2019) and memory outcome (Bonelli et al., 2012; Sidhu et al., 2015), but there remains much unexplained variance in our prediction models for post-surgical outcomes. Prior studies in patients with epilepsy have found that a greater degree of connectivity between resected pathological regions of the temporal lobe and the rest of the language network is associated with greater post-operative decline in naming (language). Similarly, greater abnormal global language connectivity was found to be associated with a greater degree of post-operative naming (language) decline (Audrain et al., 2018).

Perhaps, FC-HC is a marker of the brain's potential to adapt to injury or disease. It is possible that the increased connectivity across hemispheres seen in epilepsy patients may be because the neurological disruption within the language ready regions results in persistence of connections to typically non-dominant regions as a protective measure

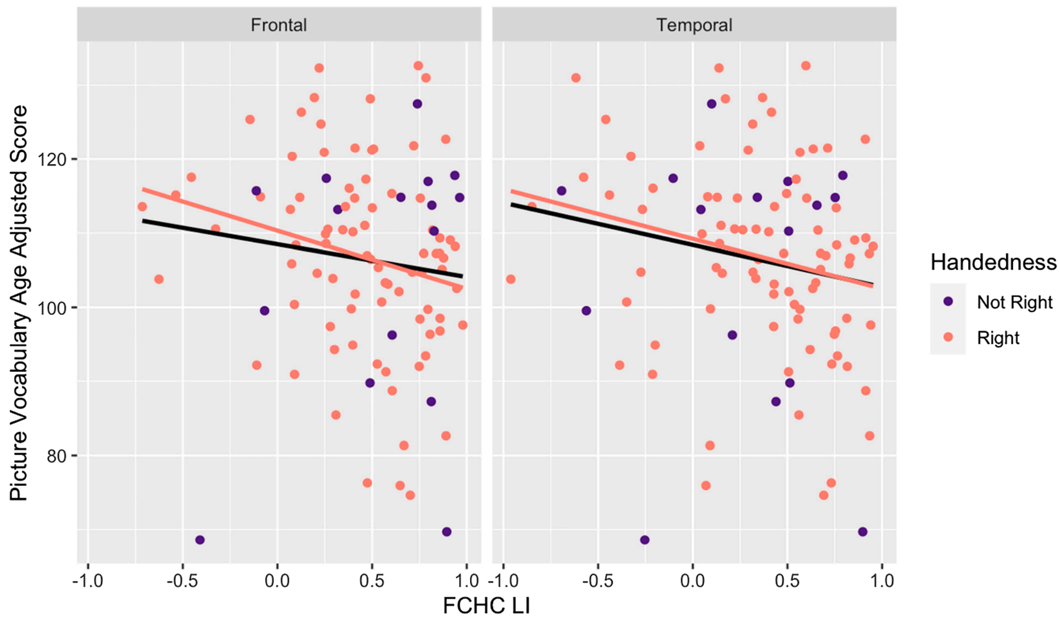

Fig. 8. HCP (Human Connectome Project N = 100) cohort age adjusted scores on the Picture Vocabulary language measure plotted against language FC-HC LI coded by handedness (Right-handed = pink, Non-Right-handed = purple). The regression line of the whole HCP cohort is shown in black while the regression line of the right-handed HCP subjects is shown in pink. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

against major language disruption. It will be important in the ongoing effort to validate FC-HC to determine its utility in predicting outcomes following epilepsy surgery. Our goal for adding the epilepsy cohort, is to demonstrate that there is a potential for brain insult to change the general left dominant language FC-HC pattern. Indeed the interpretations of the atypical FC-HC patients are speculative, it will be helpful to explore the patient subgroup further by investigating the effect of handedness, seizure focus side, and other clinical characteristics, such as age onset, seizure duration, medication effects, and outcomes. However, due to our small and heterogenous patient sample, (right hand right onset (N = 7), right hand left onset (N = 13), left hand left onset (N = 6), ambidextrous with left onset (N = 4), one ambidextrous patient with a right hemisphere seizure onset), we need a larger sample in the future to adequately address these questions.

In terms of applying our metric to pediatric populations, the FC-HC map from the resting state in the healthy children (GUKids) was left lateralized, similar to healthy adult findings. This suggests that there is applicability on the FC-HC metric in pediatric studies. However, there was no task-based fMRI in this group for direct comparison. In contrast, the resting state FC-HC map from the patient group (CNH) showed bilateral connectivity despite having a task-based activation map that was more left lateralized. The increased bilateral connectivity seen in the patient group is not likely a developmental effect, given that the healthy children did not demonstrate this finding. Moreover, in the prior study with adult epilepsy patients that compared RS-fMRI and task-based fMRI, patients had a bilateral resting state connectivity pattern compared to left lateralized activation during a verb generation language task (Gaelle E. Doucet et al., 2017). As suggested above, increased bilateral connectivity in both pediatric and adult epilepsy patients may reside in the potential for increased within- and across-hemispheric language reorganization often observed in epilepsy patients (Berl et al., 2014a; Mbwana et al., 2009).

The results of our study are compatible with those of prior studies investigating the use of RS-FMRI for language in that we established that with a task-free paradigm the expected lateralized pattern for language emerges. As hypothesized, we found that (1) FC-HC revealed overall left-lateralized language connectivity patterns in all healthy groups despite differences in demographics and imaging protocols (2) there was high spatial agreement between task and language FC-HC maps at the group level, with a moderate concordance rate at individual level across healthy cohorts and (3) FC-HC revealed diminished language lateralization in the pediatric patient group, even though their task activation overall showed left dominant, possibly reflecting a different aspect of atypical language reorganization. Our novel contribution is our method of quantifying functional connectivity of the distributed language network using integration and segregation measures, which aligns with general theories of brain development and language as a unique lateralized phenomenon. Our metric has the potential to probe the underlying mechanism that explains the differences in language outcome beyond task-based dominance. The generalizability of the FC-HC metric was validated by achieving similar results across the groups despite the different image acquisition parameters and task contrast. We included cohorts of children and an epilepsy patient group as an assessment of the developmental and clinical application of our methods. Our study included 243 subjects, higher than most studies using resting state connectivity analysis to map language networks. The number of subjects used in our study reinforces the robustness of our results. A limitation of our study is that we did not have all the conditions for comparison across all groups (task, imaging protocols etc) and therefore could not include all of the possible comparisons among the groups.

In our current study we have not assessed FC-HC results at the individual level to ascertain its utility in epilepsy surgical planning. Given the robustness and consistency of the FC-HC results in the healthy volunteer groups we believe further exploration of individual level FC-HC in epilepsy patients may provide insight to its potential use as an adjunct or replacement for current conventional methods of pre-surgical language localization. It will be important to determine the utility of the language FC-HC metric in predicting outcomes following epilepsy surgery in the ongoing effort to validate the metric. Future studies could explore the role of epilepsy and epilepsy treatment as factors in language functioning and recovery with FC-HC and traditional task-based metrics as predictors. It would be helpful to investigate whether a model could be created to predict surgical outcomes for language (presence or absence of post-operative deficits) based on pre-operative FC-HC as current task-based fMRI methods account for <40% of the variance. We used the ADDT task which reliably elicits both frontal ROI (Berl et al., 2014a,b), and temporal ROI activation in non HCP cohorts, while the HCP cohort demonstrated less frontal task activation. Future studies can evaluate the effect of choice of task on the agreement between FC-HC and task activation. Another area of study is to determine the evolution of FC-HC in healthy children over normal development as well as in newly diagnosed epilepsy patients over time. Finally, a next study includes looking at agreement at the individual level, which is important for establishing the metric as a clinical tool.

In summary, we developed the FC-HC metric to measure language laterality by measuring within-hemispheric connections (integration) and cross-hemispheric connections (segregation). Globally, at the group level, we demonstrated that RS-fMRI may be a useful tool to explore language function by giving complementary information to task-based fMRI. FC-HC may provide insights into language plasticity and compensation in the context of development and disease, but requires further study in patient cohorts and at the individual level. RS-fMRI offers an advantage over conventional fMRI because task performance is not required and thus it may be more readily used in younger or cognitively impaired populations. More studies are needed to validate this method for pre-surgical mapping of language for epilepsy surgery. In addition, our results and future studies may provide further insight into language reorganization patterns in epilepsy patients and prediction of post-surgical language outcomes.

CRediT authorship contribution statement

Juma S. Mbwana: Investigation, Writing - original draft, Writing - review & editing. **Xiaozhen You:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Supervision. **Alyssa Ailion:** Formal analysis, Investigation, Writing - review & editing. **Eleanor J. Fanto:** Investigation, Writing - review & editing. **Manu Krishnamurthy:** Investigation, Writing - review & editing. **Leigh N. Sepeta:** Investigation, Writing - review & editing. **Elissa L. Newport:** Investigation, Writing - review & editing. **Chandan J. Vaidya:** Investigation, Writing - review & editing. **Madison M. Berl:** Conceptualization, Investigation, Writing - review & editing, Supervision. **William D. Gaillard:** Conceptualization, Methodology, Investigation, Writing - review & editing, 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.2021.102598.

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