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# Pre-surgical features of intrinsic brain networks predict single and joint epilepsy surgery outcomes

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ABSTRACT

Despite the effectiveness of surgical interventions for the treatment of intractable focal temporal lobe epilepsy (TLE), the substrates that support good outcomes are poorly understood. While algorithms have been developed for the prediction of either seizure or cognitive/psychiatric outcomes alone, no study has reported on the functional and structural architecture that supports joint outcomes. We measured key aspects of pre-surgical whole brain functional/structural network architecture and evaluated their ability to predict post-operative seizure control in combination with cognitive/psychiatric outcomes. Pre-surgically, we identified the intrinsic connectivity networks (ICNs) unique to each person through independent component analysis (ICA), and computed: (1) the spatial–temporal match between each person's ICA components and established, canonical ICNs, (2) the connectivity strength within each identified person-specific ICN, (3) the gray matter (GM) volume underlying the person-specific ICNs, and (4) the amount of variance not explained by the canonical ICNs for each person. Post-surgical seizure control and reliable change indices of change (for language [naming, phonemic fluency], verbal episodic memory, and depression) served as binary outcome responses in random forest (RF) models. The above functional and structural measures served as input predictors. Our empirically derived ICN-based measures customized to the individual showed that good joint seizure and cognitive/psychiatric outcomes depended upon higher levels of brain reserve (GM volume) in specific networks. In contrast, singular outcomes relied on systematic, idiosyncratic variance in the case of seizure control, and the weakened pre-surgical presence of functional ICNs that encompassed the ictal temporal lobe in the case of cognitive/psychiatric outcomes. Our data made clear that the ICNs differed in their propensity to provide reserve for adaptive outcomes, with some providing structural (brain), and others functional (cognitive) reserve. Our customized methodology demonstrated that when substantial unique, patient-specific ICNs are present prior to surgery there is a reliable association with poor post-surgical seizure control. These ICNs are idiosyncratic in that they did not match the canonical, normative ICNs and, therefore, could not be defined functionally, with their location likely varying by patient. This important finding suggested the level of highly individualized ICN's in the epileptic brain may signal the emergence of epileptogenic activity after surgery.

*Abbreviations:* TLE, temporal lobe epilepsy; ICA, independent component analysis; ICN, intrinsic connectivity network; RS, resting state fMRI; RCI, reliable change index; DMN, default mode network; GM, gray matter; FSL, FMRIB Software Library; SOZ, seizure onset zone; AEM, anti-epileptic medication; SO, seizure outcome; MO, memory outcome; NO, naming outcome; SFO, semantic fluency outcome; PO, psychiatric outcome; FD, framewise displacement); DVARS, temporal derivative of time courses and root mean square variance over voxels; SPM, statistical parametric mapping.

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## 1. Introduction

### 1.1. Background

There is an extensive literature on medically intractable temporal lobe epilepsy (TLE), characterizing its functional and structural neuroimaging correlates prior to surgical interventions. Studies have focused on the connectome features predicting neurocognitive outcomes (Doucet et al., 2015) or post-surgical seizure control. (Bonilha et al., 0000; Doucet et al., 2015; Bernhardt et al., 2015; Asadi-Pooya et al., 2016; Keller et al., 2017; Bonilha et al., 2013; He et al., 2017; Keller et al., 2015) These two distinct outcomes are always investigated separately and are assumed to be independent of each other. In this project we provide the first report of the pre-surgical functional and structural brain features that share the ability to predict both neurocognitive and seizure control outcomes in TLE (referred to as joint outcomes). Evidence from a variety of whole-brain studies, across multiple levels of analysis, show that regions outside the epileptogenic temporal lobe respond to seizures (electrophysiology,(Khambhati et al., 2015) structural, (Pustina et al., 2014; Gross, 2011; Keller and Roberts, 2008; Tavakol et al., 2019) metabolic, (Tousseyn et al., 2015; Sequeira et al., 2013), functional imaging (Tavakol et al., 2019; Centeno and Carmichael, 2014). Moreover, there is a substantial body of evidence showing that seizure and neurocognitive outcomes after temporal lobe surgery depend upon the integrity of extra-temporal regions outside the epileptogenic focus (metabolism, (Tracy and Osipowicz, 2011; Yankam Njiwa et al., 2015) morphometry, (Bernhardt et al., 2015; Hong et al., 2016; Feis et al., 2013) electroencephalography, (Memarian et al., 2015; Antony et al., 2013) white matter, (Munsell et al., 2015) resting state connectivity, (He et al., 2017) and clinical/neurocognitive status (Armananzas et al., 2013). Based upon the importance of whole-brain integrity to outcomes, we chose a multi-network, macroscale approach that allowed us to capture key aspects of the biological and functional substrates that must be present prior to surgery to set the stage for good versus poor post-operative outcomes. More specifically, we utilized person-specific measures of intrinsic functional connectivity networks (ICNs) and the gray matter structure underlying these networks, choosing a sufficient number of networks to provide extensive whole brain coverage outside the epileptogenic temporal lobe. This extensive coverage allowed us to capture both the cognitive (functional) and brain (structural) reserve available in extra-temporal regions to test the role these substrates play in surgical outcomes. Such reserve has been defined as the cognitive and neurobiological capital (adaptability) that allows individuals to cope with brain pathology and obtain improved outcomes following therapeutic treatments. (Stern et al., 2020).

In our assessment of pre-surgical whole brain functional and structural network architecture, we leveraged the power of Independent Component Analysis (ICA) to identify the substantive intrinsic resting-state networks unique to each patient and computed: (1) the spatial–temporal match between an individual's ICA components and established, canonical intrinsic connectivity networks (ICNs), (Laird et al., 2011; Lu et al., 2017; Smith et al., 2009; Laird 2021) (2) the connectivity strength within each identified person-specific ICN, (3) the structural gray matter (GM) volume underlying the person-specific ICNs, and (4) the amount of variance not explained by the normative, canonical ICNs in each patient. Our idiographic, patient-centered approach allowed us to make no a priori assumptions about the topology (regional location, internal strength) of the intrinsic functional connectivity (FC) networks prominent in each patient. We operationalized seizure outcome (freedom versus recurrence) at 6 months or greater post-surgery, and, using reliable change indices, (Jacobson and Truax, 1991) classified outcomes (good versus poor) for several key cognitive functions potentially affected by temporal lobe surgery (verbal episodic memory, language [naming, semantic fluency] (Tavakol et al., 2019), as well as psychiatric status (depression). (Tracy et al., 2007) We then used random forest (RF) models to discover the distinct structural and functional brain features most valuable for discriminating good versus poor seizure control and cognitive/psychiatric status taken as a joint surgical outcome. Our goal was to identify the pre-surgical substrates shared by both seizure and cognitive/psychiatric outcomes, allowing us to address the following questions: (1) Are functional or structural features (as measures of, respectively, cognitive versus brain reserve) better for the prediction of joint surgical outcomes, (2) Are the structural and functional features predictive of good outcomes from the same pre-surgical network, (3) Are the pre-surgical features of some intrinsic networks more important than others for achieving good joint outcomes, (4) Is the amount of individual, idiosyncratic variance present prior to surgery (variance not captured by the normative ICNs) important to achieving good joint outcomes? We hypothesized that our empirically-derived measures customized to the individual will show that good joint seizure and cognitive/psychiatric outcomes depend upon higher levels of structural brain reserve (indexed by ICN GM volume) and functional/cognitive reserve (indexed by a strong match to functionally important ICNs and a high level of internal ICN strength), and that the predictive power of these features will be strongest when they are aligned (emerge from the same network). Moreover, based upon evidence that extra-temporal intrinsic connectivities provide the cognitive (Modi et al., 2021; He et al., 2015) and anti-seizure (He et al., 2015); (Tracy et al., 2014) functionalities that are adaptive in the setting of a deficient temporal lobe, we hypothesized that intrinsic networks encompassing regions outside the epileptogenic temporal lobe will play the largest role in predicting good joint outcomes.

## 2. Materials and methods

### 2.1. Study characteristics and key measures

Participants were dug-resistant unilateral left temporal lobe epilepsy patients from the Thomas Jefferson Comprehensive Epilepsy Center (n = 56) who under went either a standard en bloc anterior temporal lobectomy (n = 40) or MR-guided stereotactic laser interstitial thermal therapy of the hippocampus (LaRiviere and Gross, 2016) (n = 16) as treatment for their medically intractable TLE. All patients had a seizure onset zone (SOZ) in the left temporal lobe, established through the use of scalp EEG, MRI, PET, and other clinical data, as part of a presurgical algorithm that determined this lobe harbors the seizure focus. (Sperling, 1993; Sperling et al., 1989; Sperling et al., 1992) We included pathology beyond classic hippocampal sclerosis to broaden the applicability of the study, as loss of connectivity or reserve is not dependent upon the presence of a gross macroscopic epileptogenic lesion. (Modi et al., 2021) All participants were assessed both pre- and approximately one year post-surgery for verbal episodic memory, confrontation naming, verbal (semantic) fluency, and psychiatric status (depression) using well-established neuropsychological measures. Verbal memory scores were obtained from the California Verbal Learning Test II (long delay free recall). (Delis et al., 2000) Confrontation naming was assessed using the Boston Naming Test. (Goodglass et al., 2001) Verbal (semantic) fluency was assessed through the Controlled Oral Word Association Test. (Benton et al., 1994; Gladsjo et al., 1999) These specific measures were chosen because their implementation relies heavily on the language dominant temporal lobe, putting them at risk with temporal lobe surgery. (Lezak et al., 2004; Tracy et al., 2010; Tracy and Tinker, 2017) Depression was assessed through the Beck Depression Inventory-II, a self-report measure. (Beck et al., 1996; Beck et al., 1961; Button et al., 2015) Surgical outcomes were measured with a modified Engel scale (Engel et al., 1993).

### 2.2. Seizure, Cognitive, and psychiatric outcome classification

Surgical outcomes were categorized according to seizure status at six months or greater post-surgery (no seizure, "good outcome"; any seizure activity, "poor outcome"). (Engel et al., 1993) For memory and naming

outcomes (good = no change or improvement; poor = performance declined), Reliable Change Indices (RCI) were utilized based upon prior work in left temporal lobe epilepsy surgical samples. (Hermann et al., 1996; Sawrie et al., 1996) RCI's take into account the normative variability in measurements across time, along with the auto-correlation of the two measured time points. (Jacobson and Truax, 1991) As no published RCI value for semantic fluency in epilepsy was available, a change greater than one standard deviation from pre-surgical levels was utilized. Psychiatric status [depression] utilized RCI values from a randomized controlled clinic trial for the management of depression. (Button et al., 2015).

### 2.3. Imaging methods

All participants underwent an anatomical structural scan along with a functional MRI (resting state, RS) on a Phillips Achieva 3.0 T scanner (see Supplement for scanning and processing details). During the RS scan (five minutes) the participants viewed a crosshair with no task requirements. The structural T1-weighted and functional-BOLD data were pre-processed together in the fmriprep V20.2.0 pipeline, which is based on accumulated best practices and protocols for pre-processing functional MRI data. (Esteban et al., 2018) Our image processing, variable construction, and analytic methods pipeline is summarized in Fig. 1 (details in Supplement). Briefly, the steps included anatomically guided intensity corrections, spatial transformations and signal processing, and the pre-processed output was used for subsequent feature analysis. The RS run was slice-time corrected and consistent with prior work, (Bassett et al., 2013; Bassett et al., 2011; Bassett et al., 2014; He et al., 2018), we examined wavelet scale (0.05 ~ 0.1 Hz), which is thought to be particularly sensitive to functional brain architecture, minimizing the impact of high frequency physiological noise stemming from cardiac function and respiration.

#### 2.3.1. Structural Post-Processing

The pre-processed T1-weighted image, was intensity normalized (Fischl et al., 2004) de-skulled using BET in FSL. (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009) It was then automatically segmented using the FAST algorithm in FSL (Zhang et al., 2001) to provide the patient's uniquely delineated gray matter masks.

#### 2.3.2. Resting state Post-Processing

The functional data was smoothed after pre-processing. We employed a 7 mm smoothing kernel, and implemented the SUSAN smoothing algorithm from FSL, which groups similar intensities together in order to preserve anatomical information and guide the smoothing. (Mikl et al., 2008; Smith and Brady, 1997) The confounds calculated during the fmriprep pre-processing step were regressed out of the functional series using partial least squares regression. Thirty-six confounds in total were used (including temporal derivatives of FD and DVARS). Three patients were dropped for excessive head motion based upon our FD and DVARS criteria.

### 2.4. Individualized intrinsic connectivity network construction

In the ICA, the RS dimensionality was estimated using multiple dimensions, d = 20,30,40,50 on initial pass, then the optimal number (d = 30) was chosen based on having the highest mean template match across patients and networks. (Wang and Li, 2015) Thirty components provided the best balance between fragmenting versus combining regions to form coherent networks, ultimately yielding the highest level of ICN matches across patients and networks. The total variance explained by the whole ICA decomposition (30 components) is the sum of all the individual component variances explained, calculated on an individual level. Supplement Figure S1 plots the total variance explained by the 30 components (average across patient sample, 77%), as well the lower level of variance explained by the final 11 components (average across patient sample, 28%) utilized in our analyses (described below). This plot also shows that higher dimensionalities beyond 30 added only a modicum of variance explained, and these 30 dimensions were present in over 90% of patients (n.b., at higher dimensionalities this dropped). Dimension reduction to 30 components is consistent with other human literature. (Laird et al., 2011; Smith et al., 2009; Laird, 2021; Wang and Li, 2015).

To label or match a patient's individual components with established

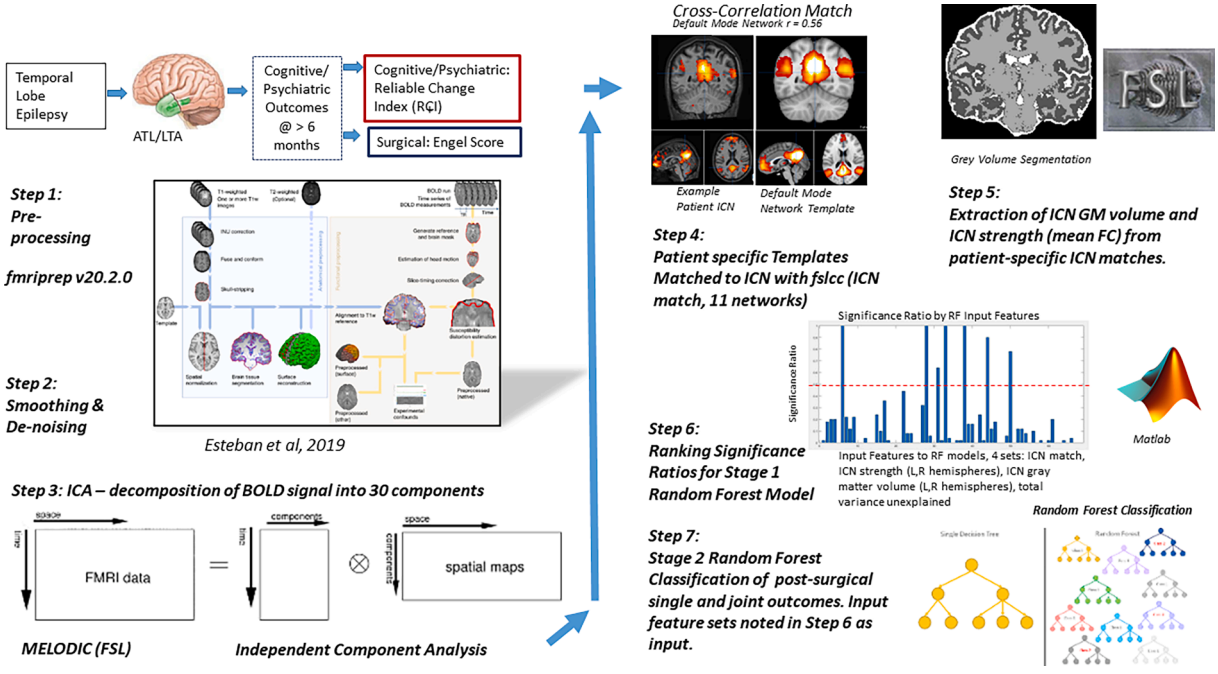


**Fig. 1. Image Processing, Variable Construction, and Analytic Methods Pipeline**. Legend: ICA = independent component analysis; FSL = FMRIB Software Library; RCI = reliable change index; ICN = intrinsic connectivity network; fslcc = fsl cross correlation; GM = gray matter; FC = functional connectivity; ATL = anterior temporal lobectomy; LITT = laser interstitial thermal therapy; L = left; R = right.

and functionally defined intrinsic RS systems, we used as templates the 20 common networks reported by Smith et al., (Smith et al., 2009) Laird et al., (Laird et al., 2011; Laird, 2021) and utilized by others (Ghasemi et al., 2021) (see Fig. 2). Based upon the matching process provided in FSL (fsl cross correlations [cc]), and using a criteria of at least cc[r] $\geq$ 0.2, we found that nine of the 20 templates could not be matched to individual patient components in a consistent manner across the sample. As a result, we dropped these templates, yielding a total of 11 templates. This is consistent with Smith et al. (Smith et al., 2009) (also (Laird et al., 2011; Laird, 2021) who suggested several of the original 20 represented systematic but unidentifiable signal that should not necessarily be considered one of the normative, healthy brain functional networks. The Supplement displays the sample mean ICN match values (cc) by ICA dimensionality (Figure S2), a patient example of a strong ICN match (Figure S3), and the sample mean ICN match values for the final 11 ICN's (Figure S4).

### 2.5. Individualized functional and structural intrinsic connectivity network Measures.

We computed four metrics from our RS functional data: ICN match, ICN strength, ICN GM volume (structural measure), and total ICN variance unexplained. The ICN match measure was constructed using the fsl cross correlation in the manner described above. Regarding the ICN strength measure, after labelling and measuring the correspondence to a normative template, the patient's own network was then used to calculate the average connectivity. This was done by thresholding the individual's ICA component map for all significantly connected voxels (fdr corrected, $p < .05$) based upon Pearson correlation of all the inter-regional edges within each unique ICN for each patient. Next, we calculated the mean of the voxel-wise correlation of these ICN inter-regional edges for each patient for each network. Regarding the ICN GM volume measure, after the labeled component was thresholded for significantly connected voxels ($Z > 2.0$), the resulting mask was overlaid with the whole brain gray matter mask to calculate total GM volume of these person-specific ICN regions (n.b., each gray matter mask was created during the pre-processing step). The patient's individual total brain GM volume was used to normalize the ICN gray matter values associated with the person-specific ICNs, allowing us to account for brain size. The difference between the amount of variance explained by the patient's original 30 ICNs and their 11 labelled ICNs comprised our measure of total ICN variance unexplained (Supplement Figure S1). This total ICN variance unexplained measure reflects coherent, systematic, but idiosyncratic variance in the resting state signal whose function is highly individual and undefined as it does not match, nor get captured, by any of the 11 canonical ICNs.

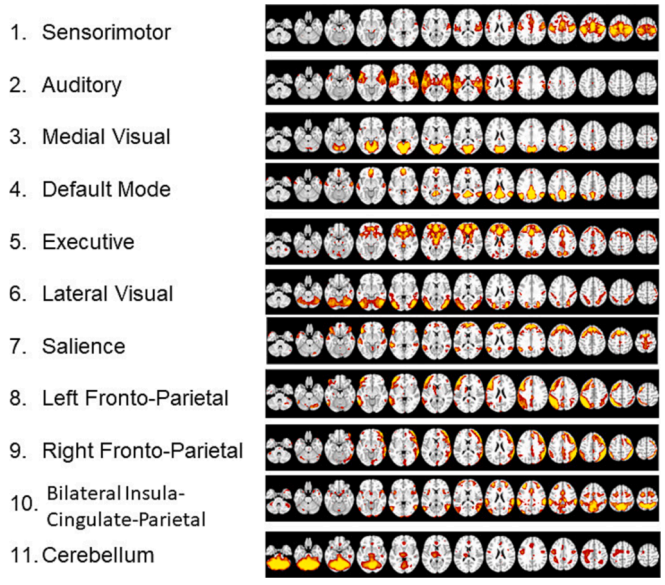


**Fig. 2. Canonical Intrinsic Connectivity Networks (ICN's) and their Brain Topography.** Legend: ICN = Intrinsic Connectivity Network.

Utilizing the Engel scale post-surgical seizure classifications we co-classified seizure control with the other four singular, reliable-change based outcomes (verbal memory, semantic fluency, naming, psychiatric status [depression]). We focused our analyses on the comparison of joint good versus poor outcomes.

### 2.6. Outcome prediction through random forest modelling

A major challenge in outcome prediction with clinical and neuroimaging data is that while the training sample size is always limited, the pool of features from which to draw potential predictors is quite large. In addition, these predictors often possess multi-collinearity and non-normal distributions. To overcome these issues, machine learning has come to the forefront as a powerful tool to establish prediction models. (He et al., 2017; Feldt Muldoon et al., 2013; Khambhati et al., 2016) Random forest (RF), in particular, is optimal for our strategy. RF provides functions for feature selection, cross-validation, and quantifying prediction success. More specifically, RF provided the following advantages (Altmann et al., 2010); (Breiman, 2001): (1) it allows for more variables than observations, (2) it makes no assumptions about the distribution of explanatory variables, (3) it accounts for both linear and non-linear interactions, and (4) it shows good resilience to model overfitting with small samples.

The predictors of our five distinct outcomes, as well as our four joint outcomes involving seizure control and the separate cognitive/psychiatric measures, were determined through a two stage RF model process. Inputs to the initial RF model included the 4 ICN measures described above (ICN match [calculated for the whole network], ICN strength [calculated separately for the left, right hemispheres], ICN GM [separate for the left, right hemispheres]), and the total variance unexplained by the 11 canonical components out of the 30 total components given by the individual's ICA, yielding a total of 56 input features. The response (dependent) variable for the RF model was the binary code representing good versus poor outcome. RF models on the various outcomes were run separately: seizure control (referred to as seizure outcome, SO), verbal memory (memory outcome, MO), semantic fluency outcome (SFO), naming outcome (NO), and psychiatric outcome (PO, i.e., depression). The joint outcome RF models included the binary seizure control outcome co-classified with each of the four singular outcomes. The RF binary response variable always compared joint good versus poor status (e.g., the joint RF on seizure control and verbal memory compared patients with both good seizure control and good verbal memory outcome [SO/MO, good/good or GG] with patients who obtained poor outcomes in both these respects [SO/MO, poor/poor or PP].

In the first stage, we aimed to identify the top predictive variables. One way to achieve this is by looking at the variable importance values provided by the RF model. However, these importance values can be affected by collinearity such that two correlated variables with high predictive value would share the importance together due to being randomly picked in the tree decision points. To avoid this issue and identify predictive variables independently of collinearity aspects, we used an in-house procedure that relied on repeated random permutations of RF models to extract p-values and ultimately a significance ratio (the number of times a variable is found to be a significant predictor at $p < 0.05$ out of 500 repetitions; details in Supplement). RF predictor variables meeting a 0.60 significance ratio criterion (significant 60% of the time) were then brought to a second stage RF model for each of the outcomes. These second stage models yielded a clearer calibration of a variable's predictive strength relative to the other significant features, and optimized further the level of outcome classification accuracy since some noisy, non-predictive variables were no longer present. To

determine the directional effect of a given predictor (whether the good versus poor outcome group possessed a higher score) two sample t-tests were run on each predictor with outcome group as the between subject variable. Table 2 lists the final predictor variables for each of our four joint RF outcome models with the significance ratio value and *t*-test results displayed. RF model results for singular outcomes are displayed in the Supplement.

Image processing and statistical analyses were performed in FSL (5.0.9), fMRIPREP v20.2.0 (Esteban et al., 2018); Matlab (MATLAB. MATLAB., 2018) or SPSS v27. (IBM Corp, 2020).

### 2.7. Data availability

De-identified data and analytic codes is available upon request.

## 3. Results

### 3.1. Demographic and clinical epilepsy characteristics

The demographic and clinical characteristics of the combined outcome groups are presented in Table 1. The pre- and post-surgical scores on the memory, language, and psychiatric measures are also shown. Parametric or non-parametric tests (Chi-square or Fisher's Exact Test), as appropriate, were run to compare the good/good versus poor/poor groups for each of the four joint outcomes (see Table 1). There were no significant differences with exception of age of seizure onset for GG/PP groups for SO-psychiatric outcomes (PBonferroni, p =.02). The mean pre-surgical scores of our left TLE sample as a whole were -0.44 standard deviation (sd) or more below the mean value of age, education, and gender matched healthy controls (Heaton, 2004) (CVLT-II, -0.44 sd; Boston Naming, -0.87 sd; Semantic Fluency, -0.47 sd).

### 3.2. RF models of outcome

The classification accuracy was strong for both the single and joint RF models of outcome. Outcome classification accuracy was always at 80% or higher, which is well above the random 50% mark of the two-group classification.

**Table 1**
Demographics and clinical characteristics of left temporal lobe epilepsy group (n = 56*).

| Characteristic/ Measure | SO/MO (n = 27) G/G (n = 12) | P/P (n = 15) | SO/SF (n = 30) G/G (n = 20) | P/P (n = 10) | SO/N (n = 29) G/G (n = 15) | P/P (n = 14) | SO/Psychiatric (n = 31) G/G (n = 20) | P/P (n = 11) |
|---|---|---|---|---|---|---|---|---|
| Age at scan | 34.6 ± 8.1 | 39.6 ± 15.6 | 39.0 ± 15.2 | 37.5 ± 15.1 | 34.8 ± 13.9 | 30.4 ± 17.8 | 42.7 ± 11.3 | 35.0 ± 13.5 |
| Sex (Female/Male) | 03/09 | 08/07 | 09/11 | 06/04 | 06/09 | 10/4 | 10/10 | 06/05 |
| Presurgical-Cognitive/ Psychiatric** | 7.4 ± 4.7 | 10.2 ± 2.8 | 14.6 ± 5.2 | 18.7 ± 4.9 | 45.6 ± 18.1 | 52.4 ± 3.8 | 15.7 ± 10.4 | 6.0 ± 5.7 |
| Postsurgical-Cognitive/ Psychiatric** | 8.3 ± 4.1 | 4.3 ± 2.6 | 18.0 ± 4.2 | 13.7 ± 5.3 | 54.6 ± 28.7 | 19.6 ± 24.1 | 7.6 ± 7.6 | 14.8 ± 10.1 |
| Seizure onset age (years) | 21.6 ± 15.2 | 17.5 ± 13.8 | 22.9 ± 16.4 | 17.3 ± 16.2 | 20.4 ± 15.1 | 14.5 ± 9.2 | 27.5 ± 13.6 | 17.2 ± 10.2** |
| Seizure duration (years) | 12.9 ± 9.7 | 22.1 ± 15.4 | 16.1 ± 12.6 | 20.2 ± 14.9 | 14.4 ± 11.7 | 15.9 ± 14.4 | 15.3 ± 13.1 | 17.7 ± 11.4 |
| Education (years) | 13.9 ± 1.8 | 14.3 ± 2.9 | 13.7 ± 4.1 | 14.4 ± 3.1 | 12.7 ± 4.3 | 12.0 ± 5.7 | 14.1 ± 2.3 | 14.9 ± 2.4 |
| Temporal Pathology (NB/HS/TE/TU/O) | 3/3/0/2/4 | 3/6/1/0/5 | 4/10/1/2/3 | 2/4/0/0/4 | 5/5/1/1/3 | 3/4/0/0/7 | 6/7/2/0/5 | 1/3/1/0/6 |
| Surgery type (LITT/ATL) | 03/09 | 05/10 | 08/12 | 03/07 | 07/08 | 3/11 | 8/12 | 03/08 |
| Seizure type | 04 FAS/ 08 FIAS | 03 FAS/ 09 FIAS/ 03 FBTCS | 07 FAS/ 12 FIAS/ 01 FBTCS | 03 FAS/ 05 FIAS/ 02 FBTCS | 03 FAS/ 10 FIAS/ 02 FBTCS | 03 FAS/ 08 FIAS/ 03 FBTCS | 08 FAS/ 09 FIAS/ 03 FBTCS | 01 FAS/ 08 FIAS/ 02 FBTCS |
| Medication | | | | | | | | |
| GABAa | 02 | 07 | 03 | 04 | 05 | 05 | 02 | 05 |
| Multiaction | 05 | 01 | 07 | 01 | 03 | 01 | 07 | 01 |
| VGNC | 04 | 08 | 09 | 05 | 07 | 07 | 06 | 06 |
| CRMP2 | 04 | 10 | 07 | 06 | 07 | 06 | 09 | 05 |
| SV2 | 03 | 03 | 06 | 02 | 03 | 05 | 05 | 03 |

Abbreviations: G/G = Good/Good; P/P = Poor/Poor. LITT = laser interstitial thermal therapy. ATL = Anterior Temporal Lobectomy.
Continuous variables are presented in mean ± SD.
Temporal pathology was diagnosed by neuro-radiologists based upon pre-surgical MRI scans: NB = normal brain; HS = hippocampal sclerosis; TE = temporal lobe encephalomalacia/gliosis, TU = tumor, O = Other MR abnormality (e.g., encephalocele, cavernoma).
Seizure types: FAS = focal onset aware; FIAS = focal onset impaired awareness; FBTC = focal to bilateral tonic clonic.
Anti-epileptic drugs (Medication): 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). Note, patients can be on more than one medication type. Patients may be on a medication regimen involving more than one drug type.
For continuous variables, independent sample t-tests were carried out comparing the G/G and P/P groups within each joint outcome. The pre-surgical cognitive/ psychiatric measures for the groups all differed significantly (PBonferroni **p <.05 or less) from their post-surgical values.
The GG/PP groups did differ on age of seizure onset for the joint SO-psychiatric outcome (PBonferroni, **p =.041). Therefore, we re-ran the SO-psychiatric RF model and the significant predictors/metrics remained the same (see Table 5). For categorical variables Fisher Exact or $\chi^2$ tests were carried out and there were no G/G versus P/P differences for sex or Surgery type.
Note, the joint groups classifications (GG, PP) were constructed on the basis of reliable change indices, or the sample standard deviation in the case of semantic fluency.
*Note: Patients could be represented in more than one joint outcome analysis.

### 3.3. RF model on seizure outcome (SO)

The RF model results for predicting good relative to poor seizure control (Supplement Table S1a) showed that seizure freedom was dependent upon increased GM volume in the bilateral cerebellum and right lateral visual ICNs, with two of three volume measures involving the side contralateral to the seizures. The internal strength of two networks mattered, but the direction of effect differed. Greater left-sided default model network (DMN) strength, a network encompassing the ictal left hippocampus in our LTLE sample, related to good outcome. Greater strength in the right medial visual network, an effect contralateral to the ictal temporal lobe, related to poor seizure outcome. Perhaps most notably, higher levels of the total variance not captured by our set of intrinsic ICNs was associated with poor outcome. This finding indicated the presence of higher levels of systematic, but idiosyncratic variance, potentially reflective of functional connectivity among regions that cohere because of shared potential for epileptogenic activity after surgery.

### 3.4. RF model on memory outcome (MO)

The RF model results for predicting MO (Supplement Table S1b) showed good episodic memory outcome had few reliable predictors. A higher match to the DMN, a network known to be involved in memory, (McCormick et al., 2014) was associated with poor verbal memory outcome. A higher match to the salience network, a network important to stimulus selection and mediating the interaction between networks, was associated with poor memory outcome. The left hemisphere GM of the salience network was also important (higher gray matter) to poor outcome. The DMN and salience networks both involve regions of the left temporal lobe and thus encompass part of the ictal lobe that is removed surgically in our LTLE sample. With this in mind, the weaker pre-surgical representation of these networks in association with good outcome may indicate cognitive reconfiguration (cognitive reorganization) in response to seizure activity within their network pathways, with the functionality of these ICNs shifting away from their prototypical brain locations.

### 3.5. RF models on language outcomes (SFO, NO)

Regarding the RF model for predicting SFO (Supplement Table S1c), good semantic fluency outcomes was associated with predictors reflecting weaker matches with the DMN, reduced internal strength in the salience network, as well as heightened GM in the left cerebellum network. The percent total variance unexplained by the set of ICNs was also higher for the good outcome group. As was noted above, the weaker pre-surgical representation of the DMN network in association with good SFO, suggested network reconfiguration; that is, a shift in the functionality of this ICN away from its prototypical brain location.

The RF model for predicting NO (Supplement Table S1d) produced the largest number of substantive predictors among the cognitive variables (six). Good confrontation naming outcomes relied on strong matches for ICNs (cerebellar and right fronto-parietal) and higher GM in the left auditory and executive function networks (i.e., ipsilateral to SOZ). The internal strength of the left cerebellar network was also important.

### 3.6. RF model on psychiatric outcome (PO-DEP)

The RF model results for predicting PO-DEP (Supplement Table S1e) revealed that good psychiatric outcome (reduced depression) relied upon reduced GM in the executive network bilaterally and reduced right cerebellar ICN GM. Also, intrinsic connectivity shifts away from the standard DMN and executive function ICN topography (i.e., poor ICN matches) prior to surgery was associated with good outcomes, suggestive of network reconfiguration. DMN functionality has been associated with theory of mind processing and social cognition,(Laird et al., 2011; Mars et al., 2012) and the executive network has inferior frontal coverage that has been implicated in functionality related to olfactory/gustatory and reward preference processing. As a consequence of such processing, a role in emotion has been proposed for these networks. (Laird et al., 2011; Castellazzi et al., 2014) In line with earlier comments about weaker presurgical representation of ICNs in association with good outcome, these data may indicate emotion system reconfiguration, with the functionality of these ICNs shifting away from their prototypical brain representations.

### 3.7. RF models on joint seizure and Cognitive/Psychiatric outcomes

Joint good SO/Memory outcomes (Table 2a; Fig. 3, panel A) relied upon ICN GM involving the lateral visual and cerebellum networks, similar to what was observed when predicting seizure outcomes alone. A high executive network match and high FC strength in the left (ictal) side of the right fronto-parietal network were also predictive of good outcomes. These findings indicated that GM integrity and internal network strength ipsilateral to the SOZ, and an intact executive function system, supported both seizure control and good memory outcomes. These findings differed from the predictors of good memory alone, which relied upon features of the DMN (weak match) and, in particular, the salience network (weak match; reduced left sided salience GM).

Joint good SO/semantic fluency outcomes (Table 2b, Fig. 3B) were predicted by higher GM of the cerebellar ICN (bilaterally) and the right lateral visual network, with both of these features also predictive of seizure outcome alone. The left GM cerebellar finding was also present for semantic fluency outcome alone. The features predictive of good semantic fluency outcome alone involved a poor match to the DMN and salience ICNs, and higher levels of the total ICN variance measure. Thus, these features appeared to be unassociated with post-operative seizure control.

Good joint SO/naming outcomes (Table 2c, Fig. 3C) mostly relied upon GM predictors. Relative to the joint poor outcome, the joint good outcome showed higher GM volume (right sided lateral visual, left sided cerebellum), but reduced GM volume for the left-side of the executive ICN. Reduced medial visual network internal strength ipsilaterally was associated joint good outcomes. Interestingly, prediction of naming alone involved none of these specific features, however, two of the GM features were also predictive of good seizure outcomes. This suggested that the features predictive of good naming alone were largely independent of those predictive of post-operative seizure control.

Good joint SO/psychiatric outcomes compared to joint poor outcomes (Table 2d, Fig. 3D) solely relied on the gray matter of two ICNs (cerebellum bilaterally, right lateral visual), with 2 of these 3 GM predictors involving the contralateral side. This suggested structural features of the non-ictal hemisphere were important to both seizure control and post-operative protection against depression. Note, these three features were predictive of seizure outcome alone, with only one (right cerebellum GM) predictive of depression as a singular outcome.

## 4. Discussion

In response to emerging evidence that focal epilepsies constitute a broad brain-network disorder, we sought to leverage the power of whole brain intrinsic connectivity to address a question absent in epilepsy outcome research to date: Are there functional and structural brain features predictive of *both* seizure control and cognitive/psychiatric outcomes? In doing so we showed that all ICN metrics are not equal in this regard, and that the gray matter associated with the visual lateral and cerebellar networks played the largest role in distinguishing good from poor joint outcomes. Neither ICN encompassed the seizure onset zone in our unilateral, focal left temporal epilepsy sample, suggesting, in line with our hypothesis, that these "extra-temporal" structural features, as opposed to the features directly encompassing the epileptogenic

**Table 2**
Random Forest Model Results.

**a.Joint Seizure and Memory Outcomes (Classification Accuracy = 85%)**

| ICN Network | ICN Metric | Seizure/Verbal Memory Outcome Code | *t*-test (p-val) | Significance Ratio |
|---|---|---|---|---|
| Executive | CC match | GG | 0.025 | 0.95 |
| Lateral Visual | Left Gray Vol | GG | 0.038 | 0.80 |
| Cerebellum | Left Gray Vol | GG | 0.00008 | 1.0 |
| Right fronto-parietal | Left Avg Z Strength | GG | 0.02 | 0.65 |
| Cerebellum | Left Avg Z Strength | PP | 0.033 | 0.75 |
| Cerebellum | Right Grey Vol | GG | 0.031 | 0.84 |

**b.Joint Seizure and Language (Semantic Fluency) Outcomes (Classification Accuracy = 80%)**

| ICN Network | ICN Metric | Seizure/Language Outcome (Semantic Fluency) Code | *t*-test (p-val) | Significance Ratio |
|---|---|---|---|---|
| Executive | CC match | GG | 0.04 | 0.92 |
| Cerebellum | Left Gray Vol | GG | 0.001 | 0.85 |
| Right fronto-Parietal | Left Avg Z Strength | GG | 0.009 | 0.90 |
| Cerebellum | Right Gray Vol | GG | 0.0005 | 1.0 |
| Lateral Visual | Right Gray Vol | GG | 0.05 | 0.68 |
| Cerebellum | Left Avg Z Strength | PP | 0.026 | 0.65 |

**c.Joint Seizure and Language (Naming) Outcomes (Classification Accuracy = 84%)**

| ICN Network | ICN Metric | Seizure/Language (Confrontation Naming) Outcome Code | *t*-test (p-val) | Significance Ratio |
|---|---|---|---|---|
| Executive | Left Gray Vol | PP | 0.05 | 0.85 |
| Cerebellum | Left Gray vol | GG | 0.01 | 0.9 |
| Medial Visual | Left Avg Z | PP | 0.006 | 0.76 |
| Lateral Visual | Right Gray Vol | GG | 0.0008 | 1.0 |

**d.Joint Seizure and Psychiatric (Depression) Outcomes (Classification Accuracy=84%)**

| ICN Network | ICN Metric | Seizure/Psychiatric (Beck Depression Inventory) Outcome Code | *t*-test (p-val) | Significance Ratio |
|---|---|---|---|---|
| Cerebellum | Left Gray Vol | GG | 0.027 | 0.62 |
| Lateral Visual | Right Gray Vol | GG | 0.0096 | 0.90 |
| Cerebellum | Right Gray Vol | GG | 0.011 | 0.98 |

pathology, are better determinants of more complex, multi-domain outcomes. Given the plethora of evidence linking verbally mediated memory, language (Banjac et al., 2021) and emotion processing (Doucet et al., 2013; Olson et al., 2007; Zhu et al., 2019) to the left temporal lobe, and the left temporal lobe to seizure generation, our data suggested these extra-temporal ICNs provided the neurobiological substrates (structural reserve) mutually beneficial for seizure prevention, verbal memory, expressive language, and psychiatric outcomes to compensate for the deficient temporal lobe.

Recent studies have implicated a cerebellar-thalamic loop in seizure activity and, therefore, as a potential therapeutic target for seizure control. (Blumenfeld et al., 2009; Kros et al., 2017; Streng and Krook-Magnuson, 2021) A role for the cerebellum in non-motor cognitive function has also been described. (Strick et al., 2009; Tracy et al., 2011) Accordingly, while the prior literature provides a basis for seeing the cerebellum as linked to separate seizure and cognitive outcomes, our data are the first to show that the cerebellum provides structural brain reserve for multiple types of surgical outcomes simultaneously. Moreover, our data provides new evidence that structural brain reserve is available through the cortical lateral visual ICN, which provided support for both adaptive cognitive and seizure control processes post-operatively.

Seizure control in combination with both verbal memory and semantic fluency outcomes demonstrated the most synergy, revealing shared features that go beyond the adaptive cerebellar and gray matter findings. For instance, these joint good outcomes also involved a strong match to the executive function ICN (a network with strong bilateral frontal representation). The role of the executive network in verbal memory and verbal fluency is well-established. (Wheeler et al., 1995) To the degree that this executive ICN finding reflected good integrity for executive functions, one can infer from our data that this network provided the functional reserve to resist recruitment into an epileptogenic network or possibly even provided an inhibitory surround against seizure spread or recurrence. (Tracy et al., 2014).

The joint good outcomes for SO/MO and SO/SFO were also predicted by low internal strength of the cerebellum ICN. Given that good compared to poor outcomes for both SO/MO and SO/SFO had a basis in higher GM in the cerebellar ICN (bilaterally), our data suggested that the adaptive versus maladaptive consequences of functional (ICN strength) and structural measures (GM volume) involving the same ICN can be dissociated. It is worth noting that these cerebellar findings were the only data suggesting that the predictive power of joint good outcomes depended on the structural or functional features of the same ICN. Thus, contrary to our initial hypothesis, we found very limited evidence that predictive power increases when the features of structural brain and functional/cognitive reserve emerge from the same network. Interestingly, the prediction of good SO/psychiatric outcomes was the only joint outcome that showed no reliance on a functional measure, showing association only with GM. With regard to the predictors of singular cognitive or psychiatric outcomes, most of these features were not among the features predictive of their respective joint outcome with seizure control. Thus, our datasuggested that cognitive and psychiatric outcomes are mostly driven by pre-surgical ICN features that are distinct from those that drive post-operative seizure control.

A common thread for the prediction of singular verbal memory, semantic fluency, and psychiatric outcomes was that patients obtaining a poor outcome displayed a strong match to the DMN. This indicated that a good outcome in these domains relied on weak pre-surgical representation of the DMN. Given the evidence that the DMN is the most robust intrinsic networks in the healthy brain (Power et al., 2013; Raichle et al., 2001; van den Heuvel and Sporns, 2013), this finding potentially points to an important, adaptive reconfiguration of intrinsic connectivity prior to surgery. DMN functionality is a subject of debate, but there are strong indications it serves as the primary task negative intrinsic system,(Raichle et al., 2001) and plays a role in episodic memory. (Doucet et al., 2014; Huo et al., 2018) Most relevant to our LTLE sample, the DMN encompassed the hippocampus and other sections of the epileptogenic left temporal lobe. Thus, our data indicated that a weakening prior of a key intrinsic system encompassing the SOZ works in the service of adaptive cognitive and psychiatric outcomes post-surgery. Another ICN inclusive of regions involving the epileptogenic temporal lobe was the salience network (i.e., contains the parahippocampus, posterior temporal lobe). (Smith et al., 2009) The salience nettwork plays a role in selecting the external stimuli deserving of attention and mediating the function of other intrinsic networks. (Laird et al., 2011; Castellazzi et al., 2014; Seeley, 2019) In our data, the salience ICN also showed a weakened presence in the pre-surgical brain

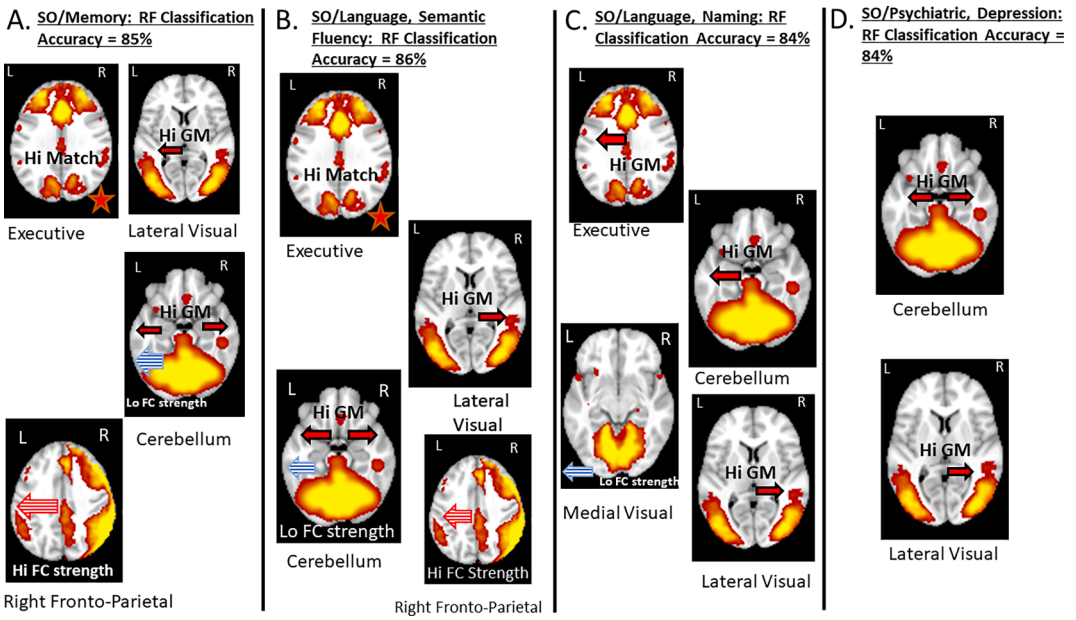


**Fig. 3. Panels A-D: Depiction of Random Forest Model Results for Joint Seizure and Cognitive/Psychiatric Outcomes. Panel A: Joint Seizure and Memory Outcomes. Panel B: Joint Seizure and Semantic Fluency Outcomes. Panel C: Joint Seizure and Naming Outcomes. Panel D: Joint Seizure and Psychiatric (Depression) Outcomes.** Legend: GM = gray matter; SO = seizure outcome; FC = functional connectivity; RF = random forest model; MO = memory outcome; SFO = semantic fluency outcome; NO = naming outcome; PO = psychiatric (depression) outcome. Red arrow indicates higher ICN GM volume in Good/Good (GG) relative to Poor/Poor (PP) outcomes. Direction of the arrow indicates side (hemispheric laterality) of the feature. Blue arrow indicates lower ICN GM volume in Good/Good (GG) relative to Poor/Poor (PP) outcomes. Direction of the arrow indicates side (hemispheric laterality) of the feature. Red star indicates higher ICN match in Good/Good (GG) relative to Poor/Poor (PP) outcomes. Red striped arrow indicates higher ICN strength in Good/Good (GG) relative to Poor/Poor (PP) outcomes. Direction of the arrow indicates side (hemispheric laterality) of the feature. Blue striped arrow indicates lower ICN strength in Good/Good (GG) relative to Poor/Poor (PP) outcomes. Direction of the arrow indicates side (hemispheric laterality) of the feature. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in association with good verbal memory and semantic fluency outcomes. The inference here is that these weakened pre-surgical representations of functionally important ICNs may reflect a shift of their functions to other brain locations. Alternatively, it may be that these ICNs were damaged because of their residing, at least in part, in the temporal lobe housing the SOZ. This form of damage may serve good outcomes by reducing the ability of these ICNs to carry epileptogenic signals. However, given that these weakened networks were predictive of positive cognitive outcomes, a shift in brain representation without a loss in function appeared more likely, indicating adaptive, compensatory cognitive reorganization occurred. Thus, our data indicated that this weakening of key ICN representations (DMN, salience) reflected truly comensatory presurgical reconfiguration, involving a shift away from the standard functional localization of these networks, taking advantage of cognitive reserve elsewhere in the brain. Unfortunately, our data does not allow us to specify where regional shifts in the actual implementation of verbal memory or semantic fluency occurred. Accordingly, these data demonstrated that in the setting of left TLE, certain ICNs developed an atypical architecture prior to surgery, an architecture that supports good cognitive functionality post-surgery to compensate for the deficient temporal lobe.

It is interesting to note that confrontation naming outcome was associated with a different set of predictive features. Good compared to poor naming outcomes were associated with greater GM volume in the left-sided portion of two networks (auditory and executive), and the right side of the left frontal-parietal network. A strong match to the right frontal-parietal and cerebellar ICNs was also present. The executive, cerebellar, auditory, and left frontal-parietal ICNs (Ang et al., 2020); (Cappa et al., 2002) could each potentially contribute to naming without necessarily reflecting a reconfiguration in the brain representation of left-hemisphere prominent naming processes. However, the separate right frontal-parietal finding (strong match; right sided left frontal-parietal GM) could potentially indicate some reconfiguration of the cognitive/functional and brain structural features implementing naming. The predictors for naming were quite different and more numerous than the other cognitive outcomes, suggesting it may have a more complex pre-surgical substrate.

Good psychiatric outcome was dependent upon a unique set of features involving weakened representation of key ICNs (DMN and executive) and reduced GM volume in the executive and right cerebellar ICNs. The possible adaptive and maladaptive roles of a weakened DMN prior to surgery were discussed above. The reason reduced representation and GM for the executive ICN were conducive to a good psychiatric outcome is unclear. One possibility might be that compromise to the high-level cognitive functions of the executive ICN (abstract reasoning, insight, self-reflection monitoring)(Hofmann et al., 2012) might reduce the ruminations and negative thinking that are mainstays of depression. (Beck et al., 1996) Note, an association between abnormal functional connectivity (mesiotemporal/frontal circuit) and increased psychiatric symptoms in TLE has been reported by our lab (Doucet et al., 2013)and others (Rivera Bonet et al., 2020)but ours is the first report of functional connectivity (ICN) features predicting psychiatric outcome after surgery.

An important difference among the singular outcomes is worth noting. Seizure control was the only poor outcome that relied upon higher amounts of whole brain unexplained, idiosyncratic variance in

the resting state signal. Singular verbal memory, naming, or psychiatric outcomes did not appear to rely on systematic, idiosyncratic variance in any way that was found to be distinctive of good versus poor outcome groups. A prior study by Boerwinkle and colleagues (Boerwinkle et al., 2017) found that abnormalities in the rsfMRI signal can correlate with the seizure onset zone given by EEG. In contrast, we report an association between a highly individualized ICN feature drawn from the rsfMRI signal and poor seizure outcome.

### 4.1. Study limitations

Many clinical variables can potentially influence cognitive and seizure outcomes (age of disease onset, epilepsy duration in years, chronological age at surgery, surgery type, sex, education, Full Scale IQ, Interval between surgery and neuropsychological testing). (Sidhu et al., 2015) To address this, we examined correlations between the metrics found to be reliable predictors in our joint and singular RF models (Table 2 and S1) and the above variables using permutation testing in the sample as whole, within the combined or singular RF model subsamples, and within the separate outcome groups (good/good, poor/poor groups; good/poor groups). None of the clinical variables produced significant correlations ($P_{Bonferroni}$ $p < .05$) with any of the predictive RF metrics. Also, neither the joint nor singular outcome groups differed on any of the clinical variables with the exception of age at seizure onset (GG vs PP in the SO-psychiatric RF). We re-ran the SO-psychiatric RF with this seizure onset variable in the model, and the significant predictors remained the same.

We do not claim that the findings we report for our left TLE sample will hold for all forms of epilepsy, nor for other types of cognitive or psychiatric outcomes. We acknowledge that at the level of functional and structural networks there is no single way that the brain responds to seizures, and this, of course, is what motivated us to develop individualized measures of ICN match, ICN internal strength, ICN-linked gray matter volume, and total ICN unexplained variance. Also, we do not have data on the amount of tissue resected or ablated, thus this is an unmeasured, potentially influential variable.

Lastly, several networks found no representation in any of the joint models, but did appear to predict selected singular outcomes (e.g., DMN, salience, left fronto-parietal). This may have arisen from the fact that our singular and joint outcome models had different sample sizes and overlapping, yet different, mixes of patients. These factors may have played a role in these model discrepancies.

## 5. Conclusions

This is the first study to report on the brain functional and structural features that might serve as substrates for multiple types of *joint outcomes* following surgery for intractable TLE. Using our empirically derived ICN-based measures customized to the individual, we showed that good joint seizure and cognitive/psychiatric outcomes depend mostly upon higher levels of brain reserve (gray matter volume) in specific networks, but that more singular outcomes rely on indices of systematic, idiosyncratic variance in the case of seizure control, and indications of weakened pre-surgical representations of functional ICNs encompassing the ictal temporal lobe in the case of cognitive/psychiatric outcomes.

Our data make clear that the ICNs have a different propensity to provide the reserve needed to support adaptive outcomes, with some showing a tendency to provide structural (brain), and others to provide functional (cognitive) reserve following surgery. Most notably, greater GM volume in the lateral visual and cerebellar intrinsic networks were prominent predictors of all four of the seizure control and cognitive/psychiatric outcome combinations studied. In terms of cognitive/functional reserve, our data demonstrated that for joint seizure control and episodic verbal memory outcomes, selected features of internal ICN strength (high right frontal parietal; low cerebellar) and ICN match (high executive) delineated the key aspects of the reserve needed to drive these specific adaptive outcomes.

With regard to singular cognitive (verbal memory, semantic fluency) and psychiatric (depression) outcomes, stronger representation of the canonical intrinsic networks was not consistently associated with good outcomes, nor were higher levels of gray matter volume. In fact, weakened representation of ICNs encompassing parts of the epileptogenic temporal lobe (DMN, salience) were important to good memory and fluency outcomes, as well as good psychiatric outcome (DMN, executive; reduced depression). Given the association between these weakened ICNs and good outcomes, these data likely reflect a shift or reconfiguration of function to other brain locations prior to surgery to take advantage of cognitive reserve available elsewhere in the brain. Overall, most of the pre-surgical functional and structural features predictive of the singular cognitive/psychiatric outcomes appeared distinct and regionally independent from those predictive of seizure control.

In terms of features uniquely predictive of seizure outcome, our customized methodology allowed us to determine that there were substantive unique, patient-specific ICNs present prior to surgery. These idiosyncratic ICNs did not match the canonical, normative ICNs and therefore could not be defined functionally, and their location likely varied by patient. Higher levels of this idiosyncratic variance were reliably associated with poor post-surgical seizure control. While a pre-surgical structural network marker for TLE seizure outcome involving the bilateral parahippocampi,has been reported (Gleichgerrcht et al., 2020), here we demonstrate how an intrinsic, functional marker (prominent idiosyncratic resting state networks) may reflect aberrant plasticity prior to surgery that leads to the emergence of epileptogenic activity after surgery. Such intrinsic connectivity could represent occult, latent epileptogenic networks, untouched by the surgery, undetectable by current pre-surgical algorithms, yet capable of driving seizure activity even after removing the putative, primary epileptogenic region from the left temporal lobe. Accordingly, our data showed that there are limits to the effectiveness of using the features of the normative, canonical intrinsic networks when trying to account for post-surgical seizure control.

Future research will need to be directed at methods of determining on an individual basis the nature of the idiosyncratic networks we have found to be systematically related to seizure outcome. It will be important to broaden the measurement of both brain and cognitive reserve to include, for instance, white matter structural or electrophysiology measures, and to capture the impact of other cognitive systems (e.g., task activation networks) so as to better understand if brain and cognitive reserve need to be concordant (from same network) in order to drive adaptive surgical outcomes involving multiple life and health domains.

## 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.

## Data availability

Data will be made available on request.

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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.2023.103387.

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