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Title: *Networks underlie temporal onset of dysplasia-related epilepsy- a MELD study*

Running Head: *FCD NETWORKS*

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Summary for Social Media If Published:

1. Twitter: @NathanTCohen
2. What is the current knowledge on the topic? (one to two sentences)

   Focal cortical dysplasia is the most common cause of surgically-remediable, pharmacoresistant epilepsy in children. Predictors of age of epilepsy onset in FCD-related epilepsy are inconsistent.

3. What question did this study address? (one to two sentences)

   To evaluate if FCD co-localization to distributed cortical functional networks underlies the temporal distribution of epilepsy onset in FCD.

4. What does this study add to our knowledge? (one to two sentences)

   FCD co-localization to distributed functional cortical networks is associated with age of epilepsy onset: sensory neural networks (somatomotor, visual) with earlier onset, and limbic latest onset. This may be due to synaptic, white matter, or network maturation.

5. How might this potentially impact on the practice of neurology? (one to two sentences)
   These findings provide a potential biological basis for the developmental differences in the variable age of epilepsy onset seen in children with FCD-related epilepsy. They also contribute to the growing understanding of focal epilepsy as a network disorder.

Draft Tweet of Essential Message (<180 characters): Focal cortical dysplasia co-localization to distributed functional networks is associated with age of epilepsy onset: earliest in sensory neural networks, latest in limbic network.

Abstract:

Objective : To evaluate if focal cortical dysplasia (FCD) co-localization to cortical functional networks is associated with the temporal distribution of epilepsy onset in FCD.

Methods: International (20 center), retrospective cohort from the Multi-centre Epilepsy Lesion Detection project. Patients included if >3y, had 3D-preoperative-T1 MRI (1.5 or 3T) with radiologic or histopathologic FCD after surgery. Images processed using MELD protocol, masked with 3D regions-of-interest (ROI) and co-registered to fsaverage_sym (symmetric template). FCDs were then co-localized to one of seven distributed functional cortical networks. Negative binomial regression evaluated effect of FCD size, network, histology, and sulcal depth on age of epilepsy onset. From this model, predictive age of epilepsy onset was calculated for each network.

Results: 388 patients had median age seizure onset 5y (IQR 3-11y), median age at preoperative scan 18y (IQR 11-28y). FCDs co-localized to the following networks: limbic (90), default mode (87), somatomotor (65), frontoparietal control (52), ventral attention (32), dorsal attention (31), and visual (31). Larger lesions were associated with younger age of onset ($p=0.01$); age of epilepsy onset was associated with dominant network ($p=0.04$) but not sulcal depth or histology. Sensorimotor networks had youngest onset; the limbic network had oldest age of onset ($p_s<0.05$).

Interpretation: FCD co-localization to distributed functional cortical networks is associated with age of epilepsy onset: sensory neural networks (somatomotor, visual) with earlier onset, and limbic latest onset. These variations may reflect developmental differences in synaptic/white matter maturation or network activation and may provide a biological basis for age-dependent epilepsy onset expression.

Introduction:

Focal cortical dysplasia (FCD) is the most common cause of pharmacoresistant, surgically-remediable epilepsy in children. FCD-related epilepsy often begins at a young age with onset before five years old in many patients.[1] However, adult-onset epilepsy is reported in up to 10% of patients, and may occur as late as 55 years.[2] Studies have sought predictors of age of onset of FCD-related epilepsy but findings are inconsistent. Cortical lobar lesion location (e.g. frontal, temporal) is not associated with clear difference in age of onset in some studies.[3-5] Larger lesions are associated with earlier onset of epilepsy.[4] FCDs are currently classified by ILAE into three types with subcategories.[6] Types IB, IIA, and IIB may be associated with earlier onset than type IA.[7] The international, Multi-centre Epilepsy Lesion Detection (MELD project) of 580 patients found that FCD Type II are more commonly frontal and Types I and III are more commonly temporal; larger lesions and lesions in primary somatosensory or motor areas have earlier age of epilepsy onset compared to lesions in higher-order regions.[8] Sulcal depth may play a role in FCD epileptogenesis. Functional connectivity variability correlates with sulcal depth variability with increased gyrification in association areas and decreased gyrification in older unimodal cortex; whereas cortical thickness is not related to network functional connectivity.[9] Association areas that continue to mature in later adolescence and adulthood have increasing sulcal depth variability.[10, 11] Recent quantitative imaging has shown that MRI abnormalities tend to be sulcal in Type II FCD, suggesting they may be rooted in the sulcal depth.[12] Interictal high frequency oscillations and seizure onset zones are most common in the bottom of the sulcus in Type II FCD.[13] Therefore, we included lesion sulcal depth as a predictor as it might reflect the degree of developmental disruption, lesion connectivity, and/or electrophysiological characteristics.

FCD-related epilepsy perturbs neural networks and can cause extensive changes in the brain despite the apparent focal pathology. Whole-brain structural connectivity is altered in patients with FCD compared to controls.[14] Similarly, there is widespread reduction in thalamocortical network connectivity and FCD-hemispheric thalamic volume loss in children with FCD-related epilepsy.[15]

The human brain is organized into distinct distributed functional networks that can be identified using functional MRI connectivity analysis.[16] There is a known differential maturation[11, 17, 18] of the seven distributed functional cortical networks that occurs earliest in primary sensory and motor regions (visual and somatomotor) and latest in higher-order association areas (latest in default mode and limbic).[11] Given this maturational gradient and the wide-scale network changes associated with FCD-related epilepsy, we sought to evaluate if FCD co-localization into distributed cortical networks is a factor in age-dependent clinical epilepsy expression. We hypothesized that FCD MRI co-localization to one of these seven distributed cortical networks and their maturation explains the age-dependent manifestations of FCD-related epilepsy.

Methods:

This is an international, multicenter (20 experienced epilepsy centers (7 adult, 6 pediatric, 7 combined)), retrospective cohort design study from the MELD project. Patients were included using the following criteria: >3 years old, had 3D preoperative T1 MRI (1.5 or 3T) with radiologic diagnosis of FCD, or histopathological confirmation (underwent epilepsy surgery). Radiologic confirmation of FCD was per each MELD epilepsy center's acquisition protocol using established radiologic features to diagnose FCD. We used medical records to track age of epilepsy onset, age at preoperative scan, duration of epilepsy, and ILAE histopathologic classification. MRIs were collected at the 20 participating MELD sites as reported previously.[8] Ethical approval was granted by each center's ethics committee and/or institutional review board. Anonymized, retrospective data was shared with the consortium with local IRB approval.

Image Processing Protocol: Images were processed using a standardized pipeline (MELD protocol[19]) and FCDs masked with manually drawn 3D regions of interest (ROI) on T1 or FLAIR images. The ROIs were projected onto individual FreeSurfer[20] surfaces then registered to fsaverage_sym,[21] a bilaterally symmetrical template.

Determining FCD co-localization to functional network: Yeo's seven distributed functional cortical networks[16] were projected on the fsaverage_sym template. The percentage of

co-localization of FCD (overlap) with each of the seven networks was calculated. FCD dominant (top) network co-localization was determined. The network with maximal overlap with FCD was designated as the dominant network for that FCD. To examine whether partial FCD overlap to a specific network could have an effect on age of epilepsy onset, each FCD was categorized as associated or not for each of the seven networks. Associated network was defined as overlap 10% or greater to account for margin of error for hand drawing of FCD. Multiple network FCD was defined as having more than one associated network.

Additional variables: We examined three other FCD factors postulated to explain epilepsy onset: lesion size, histologic subtype, and sulcal depth. Size of FCD (number of surface vertices/total number of cortical vertices) was derived from 3D ROI (above). Pathology for each patient is reported per MELD protocol as FCD Type I (and not further subcategorized), Type IIA, Type IIB, or Type III. We evaluated the influence of a lesion's sulcal depth on age of epilepsy onset. Mean sulcal depth within the lesion mask was calculated from the individual T1 Freesurfer output for each FCD. A positive mean sulcal score across the FCD mask is deeper (more sulcal) and a negative score is more gyral (less sulcal). Epilepsy duration (years) was defined as (age at preoperative scan – age at seizure onset). We also performed a subgroup analysis of patients who had ever been reported MRI negative compared to the MRI positive (MRI confirmed) patients.

Statistical Analysis: Two-way Chi-square test examined association between dominant network and binned age of epilepsy onset (<3y, 3 to <10y, 10 to <16y, ≥16y). These age bins represent infancy (<3y), childhood (3 to <10y), adolescence (10 to <16y), and late adolescence/adult (≥16y). The association between other categorical variables was also examined using Chi-square test. We examined the effect of individual predictors on the age of epilepsy onset (as a continuous variable) using ANOVA for categorical variables and Pearson's coefficient for continuous variables. Negative binomial regression was used to generate a predictive model to evaluate the effect of FCD dominant network on the age of epilepsy onset (as continuous variable instead of categorical age onset bins), controlling for the lesion size, as well as sulcal depth and histology type. We assumed, based on previous work[4] that FCDs in the somatomotor network are associated with earliest onset of epilepsy, and this network used as the

reference for the dominant network variable in the model. From this model, predictive age of epilepsy onset was calculated for each network across the lesion size range. We also tested the relationship between FCD dominant network and epilepsy duration, using negative binomial regression controlling for lesion size. We also evaluated the effect of FCD being associated with a network or multiple networks on the age of epilepsy onset using negative binomial regression due to the same nature of non-normal distribution of age at onset.

Results:

Of the 388 patients meeting inclusion criteria, 47% were female (n=185). 324 MRIs were acquired at 3T, 64 were 1.5T. Median age of seizure onset was five years old (interquartile range (IQR) 3-11 years; range 0-56 years). Median age at preoperative scan was 18 years old (IQR 11-28 years). Mediation duration of epilepsy was 10.7 years (IQR 4.9 to 18.9 years). Pathology was available for 345 patients: Type I (n=39); Type IIA (n=107); Type IIB (n=182); Type III (n=17). The sulcal depth values range from -0.59 (highest gyral point) to 1.1 (deepest sulcal point). Figure 1 shows FCD dominant network distribution (median 64% overlap of FCD to one of the seven networks) by binned age of epilepsy onset.

Relationship between individual predictors: To generate our negative binomial regression, we examined any interaction between the individual predictors. *Sulcal depth versus FCD location***:** There was a difference of sulcal depth by dominant cortical network (ANOVA, $p<0.001$). Ventral attention network FCDs were more sulcal (with most positive sulcal depth scores) while limbic FCDs were more gyral (only network with negative sulcal depth scores) which may reflect differences in lobar folding anatomy. *FCD dominant network and histology*: FCD histology subtype varied by dominant network (Chi-square, $p<0.001$). 71% (n=12) of Type III FCD were limbic. Most Type I FCDs were limbic (n=20, 51%) or default mode network (n=9, 23). 68% (n=21) of FCDs in ventral attention network are Type IIB. *FCD dominant network and lesion size*: FCD lesion size varies by dominant network (ANOVA, $p<0.05$). The visual network has the largest lesions. Given these findings, these individual predictors (FCD dominant network, lesion size, sulcal depth, and histology) were included in the negative binomial regression model.

Individual predictors and age of epilepsy onset: We evaluated the individual predictors for association with age of epilepsy onset (continuous). Dominant network (ANOVA, p=0.01), lesion size (r=-0.14, p=0.006) and histopathology subtype (ANOVA, p=0.036) were all independently associated with age of epilepsy onset. Larger lesions were associated with earlier epilepsy onset. The limbic network was associated with the oldest epilepsy onset. Sulcal depth score (r=-0.04, p=0.38) was not associated with age of epilepsy onset. Figure 2 shows the FCD dominant network distribution (number of patients per network) by age of epilepsy onset group. Age of epilepsy onset was associated with the dominant distributed cortical network to which the FCD co-localizes ($p = 0.042$).

Regression model with all individual predictors: Finally, we generated the negative binomial regression with the individual predictors. The predictive model including lesion size, FCD dominant network, sulcal depth, and histology identifies lesion size (p=0.01) and FCD dominant network (p=0.039) as factors in age of onset expression. Sulcal depth (p=0.98) and histology (p=0.09) are not predictive of age of epilepsy onset. Using somatomotor as the reference network, the predictive model (Fig 3) incorporating lesion size and FCD dominant network showed that FCD co-localization to the limbic network is associated with oldest age of epilepsy onset (p=0.015). The ventral attention, frontoparietal control and default mode networks were associated with older age of onset (all $p<0.05$). The similar model showed no relationship between FCD dominant network and epilepsy duration.

Analyses using varied FCD network overlap definitions and age of epilepsy onset: *Any limbic or somatomotor network overlap*: Negative binomial regression showed that FCDs with any limbic overlap are associated with older age of epilepsy onset compared to lesions without any limbic overlap ($p<0.001$, Fig 4). In contrast, FCDs with any somatomotor network overlap are associated with a younger age of epilepsy onset compared to lesions without any somatomotor overlap (p=0.02, Fig 4). *Multiple network overlap*: Similar analysis showed FCD with multiple network overlap (multiple associated networks) or single network did not differ in age of onset (p=0.28). Ninety-two patients (24%) had dominant FCDs in a single network; 146 (37%) had one associated network;109 (28%) had two associated networks; 34 (9%) had three

associated networks; and 7 (2%) had four or more associated networks. The extent of FCD overlap within each dominant network median (range): visual, 80.3% (27.8-100%); somatomotor, 70.2% (29.9-100%); dorsal attention, 58.1% (32.3-90.4%); ventral attention, 53.7% (26.1-100%); limbic, 68.9% (30.9-100%); frontoparietal, 58.3% (25.4-100%); DMN, 58.9% (22-100%). For FCDs with limbic network dominance, younger age of epilepsy onset was associated with higher number of associated networks while controlling for lesion size (p=0.01). The distributions of associated networks for each dominant network are shown in Table 1.

Subgroup analysis of patients ever reported MRI Negative: 145 patients were classified as ever reported MRI negative. The dominant network and lobar distributions were similar between ever reported MRI negative and MRI positive patients (Chi-square, p=0.22 and p=0.21 respectively (Supplemental Table 1).

Discussion:

In this large, multicenter, international cohort investigating predictive factors of the age of onset of focal cortical dysplasia-related epilepsy, we demonstrate that there is an association of FCD network co-localization within one of seven canonical, distributed functional cortical networks and the age of epilepsy onset. We confirm that FCD in sensorimotor neural networks (somatomotor and visual) are associated with earliest age of epilepsy onset.[4, 8] We demonstrate the novel finding that FCD in the limbic network are associated with the latest age of epilepsy onset. This study also confirms the prior finding that larger FCDs are associated with earlier age of epilepsy onset independent of network overlap.[4, 8]

The ontogenetic emergence of functional networks occurs earliest in sensorimotor regions and latest in higher order association areas. Sensorimotor systems are known to myelinate earliest, and associative/higher order networks latest.[4, 22, 23] The sequential regional myelination of the brain parallels the time-dependent epilepsy onset in our cohort in a time course comparable to the functional system maturation. Myelination progression mirrors the attainment of sequential developmental milestones[24] (e.g. basic sensorimotor areas myelinate first, and more complex cognition, language and memory systems are attained and refined later).

FCDs are intrinsically epileptogenic[25] and we postulate that functional network maturation may allow for the "escape" of epileptic activity, and the ensuing clinical expression of seizures.

Emerging evidence expands the role of myelin in activity-dependent circuit plasticity.[26] This study augments prior network connectivity analyses by correlating the dominant functional network with age of epilepsy onset. Similar to prior work, we find the somatomotor and visual areas are associated with earliest epilepsy onset.[4, 8] Despite numerous reports of its abnormal connectivity in FCD-related epilepsy, the default mode network is associated with relatively older epilepsy onset than the earlier myelinating somatomotor network. We find that FCD co-localization to the limbic network is associated with older age of epilepsy onset. There are maturational changes in limbic cortico-cortical connectivity such that children exhibit weaker limbic connectivity and that subsequently strengthens in adults.[27]

Normal cortical development occurs in a hierarchical fashion along a sensorimotor to association (S-A) axis incorporating diverse processes such as white matter maturation (myelination), intracortical myelination, synaptic pruning, interneuron maturation, and functional refinement among others that follow this spatiotemporal gradient.[11] Cortical thickness expands rapidly in early life and then exhibits regional pruning, reaching mature thickness first in somatomotor cortex and latest in association cortex.[22, 28] The patterned cortical thinning reflects a complex interplay of dynamic changes in synaptogenesis, synaptic pruning, vascular, and glial changes. Due to frequent head motion artifact and methodologic inconsistencies in image acquisition and/or processing across studies, there are limited imaging based morphometric data in early childhood regarding cortical developmental courses[29, 30] Some studies show inverted U-shaped cortical thickness from childhood to adulthood[31] while others find monotonic decreases in cortical thickness starting in childhood or early adolescence.[32] The thinning process occurs regionally and heterogeneously across the cortex following the S-A axis pattern; while perhaps related, the majority of cortical thinning usually occurs later in childhood after most FCD-related epilepsy has begun.[11, 33] A recent, large study of 778 patients from the PING cohort showed that while there is global thinning across childhood/adolescence, there is accelerated thinning in certain areas (mesial/lateral anterior frontal cortex, precuneus and lateral inferior parietal cortex) and slowest thinning in motor/premotor, temporal pole and superior temporal cortices. The

differential thinning rates did not correlate to average regional cortical thickness.[34] Functional imaging studies using FDG-PET show local cerebral glucose metabolic rates reflect synaptic activity and correlate with synaptic density and pruning. After a rapid increase in cortical FDG uptake in the first year of life with subsequent plateauing, regional cortical glucose metabolic rates decrease in mid-childhood and reach adult levels in mid-adolescence, also too late to describe the time-dependence of epilepsy onset seen in FCD-related epilepsy.[35] Maturation is a complex process that involves these many complex features. Overall, the pattern of epilepsy onset best matches the sequence of network maturation in myelination but further work is needed. Furthermore, the cortical cellular maturation of the FCDs remains unknown.

We, and others, do not find evidence of differences in age of onset from FCD histological classification. There may be genetic causes of differential FCD network expression that relate to age of epilepsy onset that are not studied in our sample. FCDs are thought to be derived, in some cases, from somatic or germline variants[36], that result in abnormalities in migration and post-migrational development[37, 38] The pathogenesis remains elusive but FCD Type II appear to be related to variants in the mammalian target of rapamycin (mTOR) pathway whereas FCD Type I are associated with a wider range of genetic variants and epigenetic modifications that require further characterization.[39] One hypothesis is that FCD Type I arise in late stages of corticogenesis, when inter- and intra-hemispheric commissural and association networks are established, and therefore may exhibit more widespread global network alterations than FCD Type II, which develop from earlier abnormalities with radial glial migration and therefore may have more constricted network alterations.[40]

FCD-related epilepsy is associated with complex functional network alterations. Connectome-based modeling shows that FCD pathologic subtype is associated with differing levels of intra-network and inter-network connectivity with type IIB less locally connected and type IIA more locally connected. Those "hypoconnected' FCD with more obvious structural abnormalities had fewer alterations in widespread network connectivity whereas those with subtle, hyperconnected lesions had more diffuse network abnormalities.[41] Independent component analysis, seed-based functional connectivity, and graph theory analyses (n=34 with FCD) show increased connectivity in the anterior default mode network, sensorimotor and dorsal

attention networks compared to normal controls.[42] Similar network abnormalities are seen in focal epilepsy- a study of 19 patients with mixed etiology found (using resting state fMRI) that frequent seizures may lead to network disruption in the default mode network and dorsal and ventral attention networks.[43] Our data suggest that location within specific networks may, in part, explain the age dependence of FCD-related epilepsy onset. We found no difference in age of epilepsy onset for those FCDs with single or multiple network overlap. However, within the limbic network dominant FCDs, having multiple associated networks was associated with a younger epilepsy onset, whereas a purely dominant single network limbic FCD was associated with older epilepsy onset. This might explain the bimodal distribution seen in the limbic network in Figure 1. Further work is necessary to examine altered structural and functional network connectivity in relation to age of epilepsy onset.

There are several limitations to this study. Our method uses a projection of structural location onto maps of functional networks collected from 1,000 normal adult subjects so we are unable to test more specific connectivity hypotheses using this paradigm as they are not age-matched. Despite the existence of various network parcellation schemes, we chose the seven-network Yeo atlas for its stability across populations, spatial normalization accuracy of mapping the FCDs onto the adult brain, and more direct correspondence to general cognitive domain functions. As the Yeo atlas is based on adult networks, there may be developmental differences in network maturation, as well as minor age-based co-registration differences that are in part mitigated by including only patients over three years old. FCDs are congenital static lesions that do not grow with development. Lesion registration from native space to the template uses a surface-based process based on gyrification/sulcation pattern that is developmentally established for the patients included in this study and should not limit the registration. Adult pattern resting state functional networks are established by two years old[44, 45], and all patients in this study had scans from three or older. Seizures arising from frontal or mesial temporal regions may be clinically difficult to diagnose and this may delay epilepsy diagnosis, potentially confounding accurate age of onset determination in this subset. Another limitation is that we did not track seizure burden (frequency of seizures) which may be a confound. Our study may have referral bias given patients are treated at mostly tertiary epilepsy centers, which might limit the broader generalizability of these data. The number of patients with ictal EEG confirmation is unknown,

but many patients underwent epilepsy surgery so most likely had ictal confirmation; for those without surgery, the number with ictal EEG confirmation is unknown. All MELD centers are experienced epilepsy centers. The study population includes patients from all continents (except Africa) and although more diverse than many studies (with representation from Europe, China, Australia, Brazil and the United States), it is not representative of all ethnicities. Due to the database design, we report on a subgroup of patients who were ever reported MRI negative, but do not have final data on how many of these patients ultimately had MRI confirmation (all were confirmed by surgical pathology). Initial studies may be interpreted as normal, either because of resolution of MRI, skill in reading MRI, or because of subtlety of findings that require a second look based on additional information even in skilled hands.[46]

Our study demonstrates a temporal relationship between FCD cortical co-localization in distributed functional networks and the development of epilepsy. We postulate this may reflect the different maturational trajectories in myelination, and connectivity of these distributed networks.[11] FCD location in earlier myelinating functional networks (somatomotor and visual) is associated with earlier onset of epilepsy; and co-localization in later myelinating functional networks (limbic) with later onset of epilepsy. This observation may help to explain the differential onset of seizures in patients with focal cortical dysplasia and may provide insight into the development of pharmacoresistant epilepsy, which is more common in those with earlier onset epilepsy.

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Author Contributions:

NTC, XY, AZ, TB, KW, SA, and WDG contributed to the conception and design of the study. NTC, XY, MK, LNS, AZ, CO, MTW, TG, TB, KW, SA, WDG contributed to the acquisition and analysis of data. NTC, XY, LNS, AZ, CO, MTW, TG, TB, KW, SA, WDG contributed to drafting a significant portion of the manuscript or figures.

Supplementary Table 2 lists the contributing collaborators of the Multi-centre Epilepsy Lesion Detection (MELD) Project who all contributed to data collection for this multicenter consortium.

Potential Conflicts of Interest:

The authors have no relevant conflicts of interest.

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Figure Legends

Figure 1: Age of Epilepsy Onset by Dominant Network
1A) This figure shows the binned (1 year bins) age of epilepsy onset (years) broken down by dominant FCD network (All networks combined are shown in brown at bottom). 1B) 7-network parcellation map of 1,000 subjects adapted from Yeo et al.[16] Each network is color-matched to Fig 1A.

Figure 2 FCD dominant network by binned age of epilepsy onset
This figure shows the number of patients in FCD dominant network by binned age of epilepsy onset (years).

Figure 3: Predicted age of epilepsy onset versus lesion size by each dominant FCD network through negative binomial regression model

This graph shows the predicted age of epilepsy onset (years) versus lesion size for each dominant FCD network. Lesion size is reported as percentage of cortical vertices such that 0.1=10%, 0.2=20%, etc.

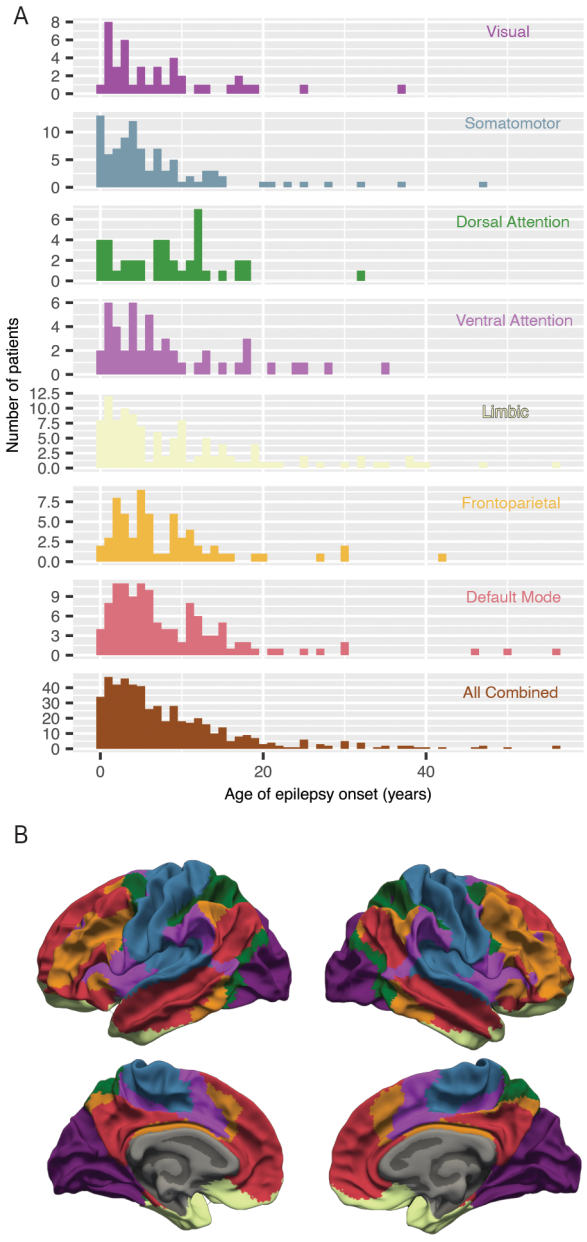
Figure 4: Age of epilepsy onset (years) by associated network
The grouped bars on the left half shows all FCDs evaluated as having any limbic overlap (>10%,) or not. Limbic overlap is associated with older age of epilepsy onset.
The grouped bars on the right half shows all FCDs evaluated as having any somatomotor overlap (>10%) or not. Somatomotor overlap is associated with younger age of epilepsy onset.

Table 1 Distribution of FCD dominant and associated networks

This table shows the number of FCDs in associated networks for each dominant network. The number of FCD in a given dominant network is highlighted in bold. The number in the far-right column (Total) is the total number of FCDs (dominant and associated) within a given dominant network. DMN=Default mode network; DA=Dorsal attention network; FP=Frontoparietal network; LIM=Limbic network; SM=Somatomotor network; VA=Ventral attention network; VIS=Visual network.

Supplemental Table 1 Subgroup analysis of ever reported MRI negative patients

This table summarizes the dominant network and cortical lobar location for the group of patients who were ever reported MRI negative (all with confirmed pathology) compared to the group of patients who were MRI positive.



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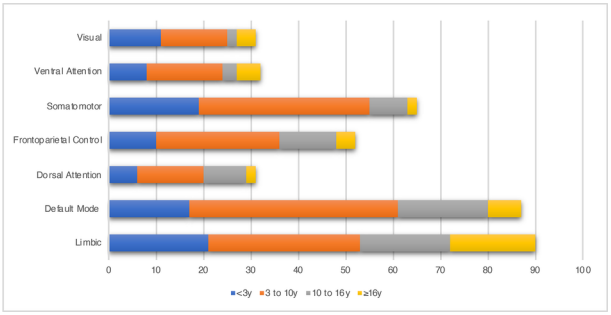

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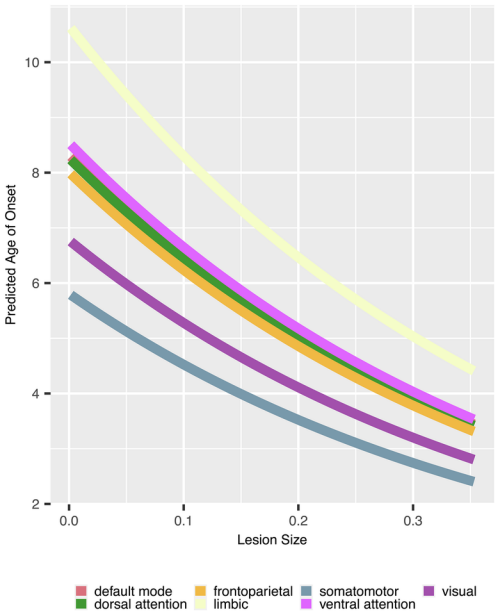

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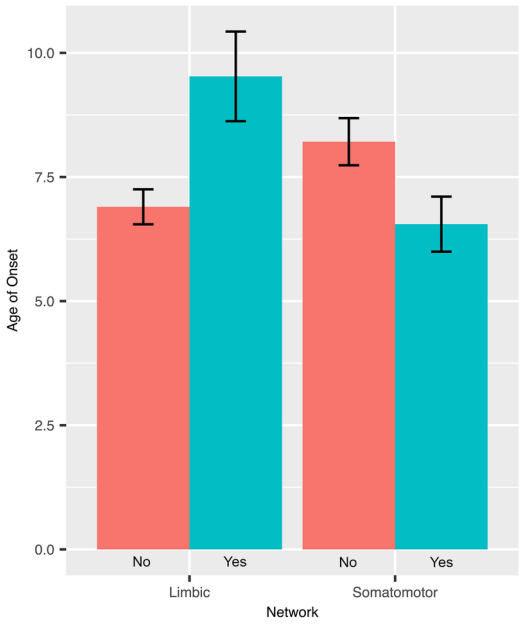

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		Associated Network							
		DMN	**DA**	**FP**	**LIM**	**SM**	**VA**	**VIS**	**Total**
Dominant Network	**DMN**	**87**	10	53	17	15	24	4	210
	DA	6	**31**	17	1	12	7	5	79
	FP	31	17	**52**	2	4	25	0	131
	LIM	54	2	12	**90**	6	9	5	178
	SM	13	18	5	1	**65**	37	0	139
	VA	13	6	13	1	20	**32**	0	85
	VIS	10	11	3	4	1	1	**31**	61