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The organization of functional neurocognitive networks in focal epilepsy correlates with domain-specific cognitive performance

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Abstract

Understanding and diagnosing cognitive impairment in epilepsy remains a prominent challenge. New etiological models suggest that cognitive difficulties might not be directly linked to seizure activity, but are rather a manifestation of a broader brain pathology. Consequently, treating seizures is not sufficient to alleviate cognitive symptoms, highlighting the need for novel diagnostic tools. Here, we investigated whether the organization of three intrinsic, resting-state functional connectivity networks was correlated with domain-specific cognitive test performance. Using individualized

Abbreviations: AAL, Automated Anatomical Labeling; ASM, anti-seizure medication; CANTAB, Cambridge Neuropsychological Test Automated Battery; CEN, central-executive network; CWIT, Color-Word Interference Test; DMN, default mode network; DS, Digit Span; ERT, Emotion Recognition Task; FE, focal epilepsy; FDR, false discovery rate; HC, healthy control; OTS, One Touch Stockings of Cambridge; PLV, phase locking value; PRM, Pattern Recognition Memory; RTI, Reaction Time; RVP, Rapid Visual Processing; SN, salience network; SSP, Spatial Span; SW, small world.

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EEG source reconstruction and graph theory, we examined the association between network small worldness and cognitive test performance in 23 patients with focal epilepsy and 17 healthy controls, who underwent a series of standardized pencil-and-paper and digital cognitive tests. We observed that the specific networks robustly correlated with test performance in distinct cognitive domains. Specifically, correlations were evident between the default mode network and memory in patients, the central-executive network and executive functioning in controls, and the salience network and social cognition in both groups. Interestingly, the correlations were evident in both groups, but in different domains, suggesting an alteration in these functional neurocognitive networks in focal epilepsy. The present findings highlight the potential clinical relevance of functional brain network dysfunction in cognitive impairment.

KEYWORDS

cognitive impairment, focal epilepsy, functional connectivity, graph theory, neurocognitive networks, RRID:SCR_002510, RRID:SCR_003550, RRID:SCR_004841, RRID:SCR_004849, RRID:SCR_007037, RRID:SCR_007292, RRID:SCR_013202, source EEG

Significance

Although epilepsy is most commonly associated with seizures, the disease is more often than not accompanied by non-seizure symptoms, such as cognitive deficits. Interestingly, even in focal epilepsies, the cognitive challenges often extend beyond the seizure onset brain area's classical cognitive expression, suggesting a wide-reaching perturbation of peripheral networks. In the present study, we demonstrate, using source-space electroencephalography, functional connectivity, and graph theory concepts, that the organization of neurocognitive brain networks is associated with domain-specific neuropsychological test performance. These findings might hold clinical relevance with regard to the identification, monitoring, and treatment of cognitive symptoms in epilepsy.

1 | INTRODUCTION

Fundamental physiological processes in the human brain, such as those supporting control of movement (King et al., 2018), autonomic functions (Fan et al., 2012), and cognition (Shine et al., 2019), are sustained and regulated by complex interactions both within and between functional networks. Thus, network disruptions are likely to amount to an important role in mediating physiological dysfunction and associated behavioral manifestations, such as cognitive impairment (Stam, 2014; Uhlhaas & Singer, 2006). Importantly, in contrast to the traditional modular paradigm, the hypothesis that cognition arises from the activity of large-scale networks (Bressler & Menon, 2010; Mesulam, 1990) can account for the presence of cognitive dysfunction beyond local structural pathology (Tailby et al., 2018). Thus, the impact of functional brain networks on cognitive dysfunction has attained increased focus, both in nonclinical (Douw et al., 2011; Langer et al., 2012) and clinical groups (Hassan et al., 2017; van Dellen et al., 2015; Vlooswijk et al., 2011).

Epilepsy is considered the epitome of brain network dysfunction (Kramer & Cash, 2012), putatively caused by hypersynchronous neuronal network activity (Engel et al., 2013). During the past decade, the functional connectivity (Bastos & Schoffelen, 2015) and graph theory (Behrens & Sporns, 2012) frameworks have successfully been applied to delineate network alterations in focal epilepsy (FE) using electro- and magnetoencephalographic (EEG/MEG) methods (Horstmann et al., 2010; Niso et al., 2015; Vecchio et al., 2015). Importantly, concurrent with functional network changes, patients with epilepsy are often burdened with cognitive impairment (Henning et al., 2019; Lin et al., 2012). Intriguingly, such impairment is increasingly understood as a distinct manifestation of underlying brain network pathology, rather than being directly linked to seizure activity (Helmstaedter & Witt, 2017). This notion lines up with evidence that FE often manifests with widespread cognitive impairment extending beyond the seizure onset area's classical cognitive expression (Oyegbile et al., 2004). Furthermore, network disruptions, manifested as interictal epileptiform discharges in EEG peripheral to the seizure onset zone, are associated with impaired short-term memory encoding (Ung et al., 2017). Also, cognitive dysfunction in FE patients may change over time, possibly reflecting the dynamic nature of brain networks and their disturbance, and may even persist after successful seizure remission has been achieved with anti-seizure medication (ASM; Hermann et al., 2007).

The idea that cognitive functions are embedded in neuronal networks is not new (Geschwind, 1965; Verzeano & Negishi, 1960), and today, the cognitive relevance of intrinsic, resting-state networks is well established (Ito et al., 2017). Moreover, with the advent of

non-invasive highly specialized experimental technology, such as functional magnetic resonance imaging (fMRI), research has begun delineating distinct intrinsic neurocognitive brain networks (Deco et al., 2011; Uddin et al., 2019). Consistently reported among such functionally and spatially distinct networks are the default mode network (DMN), the central executive network (CEN), and the salience network (SN). The DMN is anchored in the medial prefrontal and posterior cingulate cortices, and the posterior extent of the inferior parietal lobule (Andrews-Hanna et al., 2010; Buckner et al., 2008), whereas the CEN relies on the lateral prefrontal cortex and the anterior inferior parietal lobule reaching into the intraparietal sulcus, and the SN on anterior insular and anterior middle cingulate cortices (Seeley et al., 2007; Uddin, 2015; Yeo et al., 2011). Together, these have been suggested to comprise a triple network model of human cognition (Menon, 2011; Seeley et al., 2007; Uddin, 2015), in which the DMN and CEN maintain antagonistic activity mediated by the SN (Chand et al., 2017; Goulden et al., 2014). These network constellations may sustain a broad spectrum of cognitive functions (Uddin et al., 2019), where the DMN is most closely associated with internally directed and self-generated cognitive processes (Andrews-Hanna et al., 2014), the CEN with higher order executive functioning, and the SN with an identification of salient information with regard to current goal states (Seeley et al., 2007). Cognitive deterioration is accompanied by altered connectivity within this large-scale system, both in pathological (Agosta et al., 2012; Damoiseaux et al., 2012) and normal aging (Chand et al., 2017). In FE, such network reorganization could reflect a compensatory mechanism to sustain an adequate level of cognitive functioning, possibly at the expense of brain health and longevity (Helmstaedter & Witt, 2017; Sen et al., 2018).

The investigation of brain networks is methodologically challenging, albeit fMRI has made significant contributions in characterizing spatial properties of functional brain networks (Uddin et al., 2019). However, to expand on the temporal dynamic nature of brain networks (Fox & Raichle, 2007), the millisecond timescales provided by EEG and MEG are necessary for insights into oscillatory activity in specific frequency bands associated with differential neuronal processing of information (Rossini et al., 2019). Neuronal oscillations in different frequency bands have consistently been shown to perform differential roles in cognition (for a review, see Lopes da Silva, 2013). However, sensor-level electrophysiological connectivity estimates are ubiquitously perturbed by noise and volume conduction effects (Brunner et al., 2016), and sophisticated source reconstruction methods (Hassan & Wendling, 2018; Schoffelen & Gross, 2009; Vorwerk et al., 2014) are needed to mitigate these effects and, consequently, enhance reliability (Besserve et al., 2011). Currently, sensor-level EEG/MEG measurements play an important role in epilepsy diagnostics, and, with further methodological development, EEG/MEG source-space connectivity estimation may in future contribute significantly to the refinement of both individualized diagnostics and treatment of epilepsy (van Mierlo et al., 2019).

However, the role of distinct intrinsic neurocognitive network disruptions and their correlation with the observable cognitive deficits in epilepsy remains unclear, and warrants further investigation. The present study aimed to address this issue by examining whether the graph theoretical organization of intrinsic neurocognitive brain networks during rest can reliably predict performance on a broad spectrum of cognitive tests in a cohort of well-functioning chronic FE patients in middle adulthood and age-matched healthy controls. The investigated networks were constructed with bivariate estimates of source-level functional connectivity derived from scalp EEG. With this approach, our objectives were to (a) compare the patients and controls on cognitive test performance and (b) on graph metrics indexing the organization of the DMN, CEN, and SN networks, and (c) correlate cognitive test performance, global and domain-wise, with DMN, CEN, and SN organization. Considering the well-functioning epilepsy patients included in this study, we hypothesized that the overall cognitive test performance would not differ between groups; yet, we expected the groups to exhibit subtle differences in network organization, and that the network organization metric would predict cognitive test performance, thus highlighting the clinical relevance of functional network analysis.

2 | MATERIALS AND METHODS

2.1 | Participants

Twenty-three patients diagnosed with uni- or bilateral FE (15 females, age 54.7 ± 5.9 years) were recruited to the study from neurological outpatient clinics in the Oslo region, Norway, in connection with routine follow-up visits. In addition, 17 age-matched healthy control (HC) subjects (12 females, age 55.9 ± 6.7 years) participated. The HC participants were recruited from the FE patients' social networks, providing controls with similar socioeconomic background to the patients. All FE subjects had used the same ASM for at least 6 months before they participated in the study. The patients were all considered to be in a chronic phase of epilepsy (duration of epilepsy 24.4 ± 13.7 years). Neither FE nor HC subjects had any history of epilepsy surgery, psychiatric disorders, developmental disorders, or any other debilitating diseases. The patients' clinical data, including ASM therapy, etiology, EEG/MRI pathology, and focus localization, are listed patient-wise in Table 1. Of the seven patients with MRI-verified pathology, two had mesial temporal sclerosis, whereas the remaining five had other local structural pathology. None had indications of progressive neurological disease nor tumor. All patients presented with past or present focal seizures. Thirteen of whom also had focal seizures with secondary generalization. Neither FE nor HC participants were compensated for their study participation. Ethical approval for the study was granted by the Regional Committees for Medical Research Ethics – South-East Norway. Following the Declaration of Helsinki, all participants provided informed written consent.

2.2 | Cognitive testing

All participants underwent a standardized cognitive assessment constituent of both paper-and-pencil and digital tests.

TABLE 1 Clinical data of the patients

ID	Age	Sex	Duration	ASM	Etiology	MRI pathology	EEG pathology	Epilepsy focus
1	55	F	21	LEV	Structural	Yes	Yes	Temporal, left
2	62	F	20	LEV, CBZ	Unknown	Yes	Yes	Temporal, right
3	47	F	11	OXC	Unknown	No	Yes	Focal, unknown
4	49	F	24	LTG, CBZ	Unknown	No	Yes	Temporal, left
5	45	F	10	LTG	Unknown	No	Yes	Temporal, left
6	56	F	49	VP, PRG, LEV	Structural	Yes	Yes	Temporal, left
7	62	M	44	OXC, LEV	Structural	Yes	Yes	Temporal, left
8	52	M	20	LEV, ESC	Unknown	No	No	Temporal, left
9	53	F	16	LEV	Unknown	No	Yes	Temporal, right
10	59	M	11	OXC	Structural	Yes	No	Temporal, right
11	58	M	44	CBZ, PB	Unknown	No	Yes	Temporal, left
12	58	M	38	LEV, CBZ	Unknown	No	No	Temporal
13	61	F	13	LEV	Unknown	No	No	Focal, unknown
14	54	F	13	None	Unknown	No	Yes	Temporal, left
15	64	F	10	LTG	Unknown	No	No	Focal, unknown
16	57	M	36	VP	Unknown	No	Yes	Temporal, right
17	54	F	12	LEV	Unknown	No	Yes	Temporal, left
18	59	M	38	CBZ	Structural	Yes	No	Temporal, right
19	46	M	9	LTG	Unknown	Yes	Yes	Temporal, left
20	57	F	48	LTG, TPM	Unknown	No	Yes	Temporal, right
21	58	F	18	LTG	Unknown	No	Yes	Frontal, left
22	51	F	35	LEV	Unknown	No	No	Temp.-occip., right
23	42	F	22	None	Unknown	No	Yes	Temporal, right

Note: Age given in years. Sex: *F* = female; *M* = male. Duration of epilepsy is defined as years since the patient's first seizure. The MRI/EEG pathology columns denote whether the patient presents with pathological findings. Epilepsy focus reflects the clinical diagnosis made on the basis of all available information.

Abbreviations: ASM, anti-seizure medications; CBZ, carbamazepine; ESC, Eslicarbazepine acetate; LEV, Levetiracetam; LTG, Lamotrigine; OXC, oxcarbazepine; PB, Phenobarbital; PRG, Pregabalin; TPM, Topiramate; VP, Valproate.

The assessments were administered and supervised, respectively, by a trained clinical psychologist, and covered executive functioning, including working memory, selective and sustained attention, visual recognition memory, manual reaction time, mental and motor speed, and social cognition. The digital cognitive tests were administered on an iPad (Apple, Inc.) with Cambridge Neuropsychological Test Automated Battery (CANTAB®; Cambridge Cognition) software. In addition, the participants were asked to report their subjective memory complaints in their daily life (compared to individual expectations and ambitions).

Executive functioning was assessed with the One Touch Stockings of Cambridge (OTS; CANTAB®) spatial planning/working memory task, and the inhibition and inhibition/switching tasks of the Color-Word Interference Test (CWIT; Delis et al., 2001). Attention and working memory were indexed in the verbal modality with the Wechsler's Adult Intelligence Scale-IV Digit Span (DS; Wechsler et al., 2008) task and in the visual modality with the Spatial Span (SSP; CANTAB®) task. The Pattern Recognition Memory (PRM; CANTAB®) task, a test of visual pattern recognition in a two-choice forced discrimination paradigm, was used to probe memory. Manual reaction time was measured with the Reaction Time (RTI; CANTAB®) task, which relies on the ability to react on a visual cue, whereas processing speed was assessed with the word reading task from CWIT. Social cognition was measured with performance on the Emotion Recognition Task (ERT; CANTAB®), which indexes the ability to identify six basic emotions in facial expressions. Sustained attention was assessed with the Rapid Visual Processing (RVP; CANTAB®) task, a test requiring the participant to identify a specific series of digits in a continuous visual stream. A total of 17 cognitive test scores were obtained. Global level of cognitive functioning was estimated based on the participant's performance on the individual tests compared to the other participants. Points in the range 1–4 were allocated per test depending on the quartile in which the participant's performance resided (below 25th percentile = 1 point; between 25th and 50th percentile = 2 points, and so on).

2.3 | EEG acquisition and electrode localization

EEG was recorded with a BioSemi 128-channel system with a sampling rate of 2,048 Hz during a task-free (i.e., resting-state) paradigm. The participant was comfortably seated in a chair, resting with his or her eyes closed, but awake, for 4 min. To minimize between-subject variation regarding task comprehension, instructions were given in written form on a computer monitor, as recommended by van Diessen et al. (2015).

High-precision information on the spatial locations of the EEG electrodes was acquired using an IO Structure Sensor (Occipital, Inc.) scanner device for iPad (Apple, Inc.). From the 3D head model, the electrodes were spatially identified by an operator using MATLAB (The MathWorks, Inc.) and FieldTrip (ver. 2019-01-16, RRID:SCR_004849; Oostenveld et al., 2011). For enhanced accuracy in the manual alignment of electrode positions and head model (see below), the head shape surface was also extracted. For nine subjects (five patients and four controls; all females), we were unable to obtain the individual head shape and electrode positions, and instead used a set of electrode positions based on the average of the other participants.

2.4 | EEG preprocessing and source-space functional connectivity

Here, we give a condensed summary of the EEG preprocessing and subsequent calculation of source-space functional connectivity. For a comprehensive account of the procedures, the reader is referred to Hatlestad-Hall et al. (2021).

The EEG data were preprocessed, including downsampling to 512 Hz, band-pass filtering between 1 and 45 Hz, and cleaning for ocular and muscle activity, in MATLAB (ver. 2019b; The MathWorks, Inc.) with functions from EEGLAB (ver. 2019.1, RRID:SCR_007292; Delorme & Makeig, 2004), ZapLine (from NoiseTools; de Cheveigné, 2020), Second Order Blind Identification (SOBI; Belouchrani et al., 1993), and ICLabel (Pion-Tonachini et al., 2019). The EEG source reconstruction used an SPM12 (RRID:SCR_007037) segmentation of the individual T1-weighted MRI (Ashburner & Friston, 2005; Huang et al., 2016) to construct a three-layer boundary element model (BEM; iso2mesh, RRID:SCR_013202; Qianqian Fang & Boas, 2009). The BEM model was combined with the digitized electrode positions and a source model consisting of a homogenous regular grid of dipoles to obtain the individual lead fields (OpenMEEG, RRID:SCR_002510; Gramfort et al., 2010). A spatial filter based on linearly constrained, minimum variance beamformers (Van Veen et al., 1997) was used for inverse modeling. Finally, source-space functional connectivity was defined as the phase locking value (PLV; Bruña et al., 2018; Lachaux et al., 1999; Rosenblum et al., 1996) between the cortical brain areas of the Automated Anatomical Labeling atlas (AAL, RRID:SCR_003550; Tzourio-Mazoyer et al., 2002). PLV was computed separately for four distinct frequency bands: theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–45 Hz).

2.5 | Network analysis

The network analysis was conducted with functions available from the Brain Connectivity Toolbox (BCT; ver. 2019-03-03, RRID:SCR_004841; Rubinov & Sporns, 2010) and with in-house MATLAB code (available upon request). Network nodes were defined as AAL regions and network edges as the PLV estimate between regions. The three neurocognitive networks were composed of distinct sets of nodes, defined in approximate accordance with current anatomical definitions of these networks (Uddin et al., 2019). The selection of networks for analysis was *a priori* defined, based on the relatively strong consensus regarding their anatomical definitions and their consistently described relevance to cognition (for a review, see Uddin et al., 2019). The mapping of the networks to AAL regions is presented in Figure 1 and Table 2.

In terms of network analysis, the functional connectivity matrices were *weighted* (PLV) and *undirected*. The matrices were analyzed under a fixed density threshold of 65%, constrained by the requirement of the matrices to remain fully connected. As no basis exists on which to define an ecologically valid threshold level (Fornito et al., 2012; van Wijk et al., 2010), the 65% threshold was selected as it was previously demonstrated to maximize the group difference in graph metrics in FE (Hatlestad-Hall et al., 2021). To implement this, we first computed the minimum spanning tree (MST; Stam et al., 2014; Tewarie et al., 2015) of the inverse functional connectivity matrix, and then added edges to the MST backbone incrementally by descending weight order until the density threshold was reached. For each functional connectivity matrix, 100 rewired null models with preserved weight, degree, and strength distributions were generated from the dense matrix (BCT: null_model_und_sign; Rubinov & Sporns, 2011). These null models were processed identical to the empirical network, and the mean global network metrics calculated from them were used to normalize the corresponding metric for the empirical network.

We calculated the *small world index*, which was defined as the ratio between the network's normalized clustering coefficient and normalized characteristic path length (Humphries & Gurney, 2008; Watts & Strogatz, 1998):

$$SW = \frac{CC_{obs}/\,CC_{rand}}{CPL_{obs}/CPL_{rand}}$$

where CC is the clustering coefficient and CPL is the characteristic path length, and the subscripts *obs* and *rand* denote the metric of the observed (empirical) network and the mean metric calculated from the randomly rewired networks, respectively. The terms SW index and SW-ness are used interchangeably.

Differences in the overall level of functional connectivity between subjects or groups can generate spurious differences in network

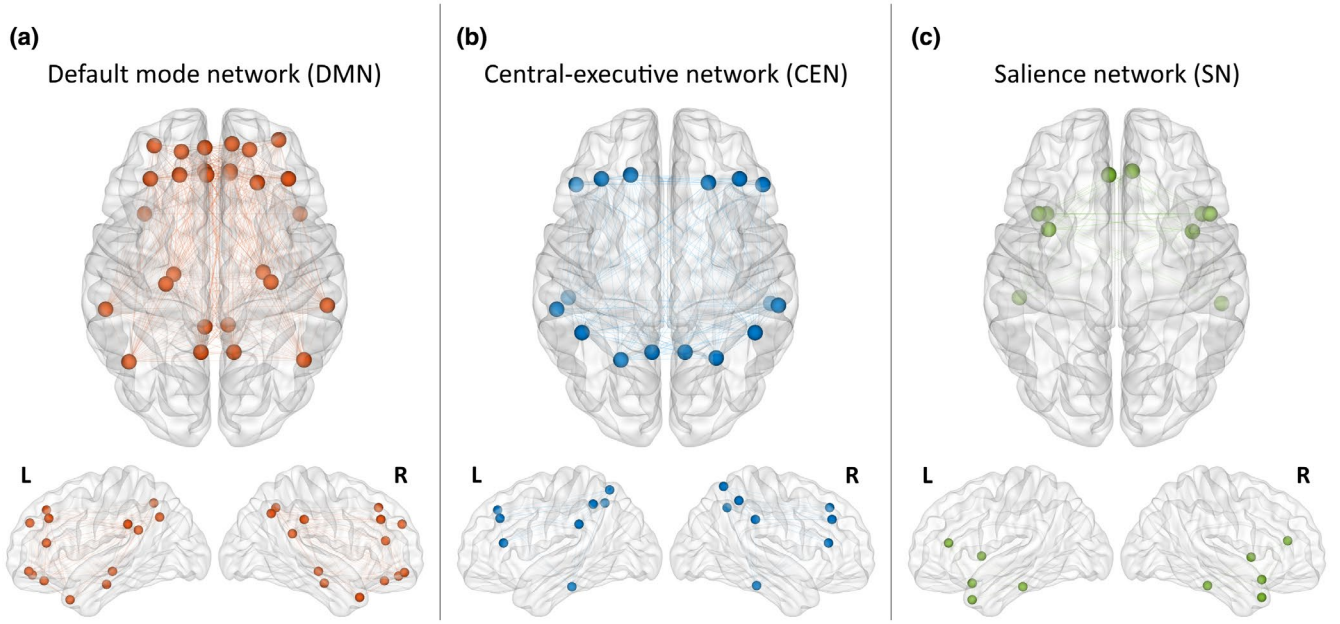

FIGURE 1 Maps of AAL regions included in the neurocognitive networks. Top row: Axial view. Bottom row: Left and right medial view

metrics (van den Heuvel et al., 2017). In this context, overall functional connectivity was defined as the mean PLV in the individual connectivity matrix, discarding intraregional estimates, and calculated separately for each frequency band. We explored possible differences in overall functional connectivity for each of the three neurocognitive networks in a post hoc group comparison. As these values did not differ between groups, the potential effect of overall functional connectivity differences between groups was disregarded.

2.6 | Statistical tests

Associations between small world (SW) indices of the neurocognitive networks and cognitive test performance were analyzed using partial linear correlation coefficients, where the effects of the SW indices of two other neurocognitive networks were held constant. The partial correlation coefficients were computed separately for the patient and control groups. For the significant partial correlations, post hoc ANOVAs were performed to test for significant interactions between the factors group and SW index of the corresponding network, while controlling for the SW of the other two networks. Group differences in SW indices and cognitive test scores were analyzed using the Student *t* test. For both the partial correlation coefficients and the *t* tests, *p* values were obtained via a nonparametric permutation test approach (Legendre, 2000; Maris & Oostenveld, 2007). For each test, 100,000 permutations were carried out. The *p* values associated with partial correlation coefficients and *t* statistics reflecting SW indices were corrected for multiple comparisons (across neurocognitive networks; three comparisons) with the Benjamini–Yekutieli false discovery rate with assumed positive test correlation (FDR) procedure (Benjamini & Yekutieli, 2001; Genovese et al., 2002). FDR-adjusted two-tailed *p* values (i.e., *q* values) below 0.1 (Niso et al., 2015) were considered statistically significant; however, uncorrected two-tailed *p* values below 0.05 were considered trend-significant. Group differences were quantified as the corrected standardized mean difference, with the effect size estimate termed *Hedges' g* (Lakens, 2013). The directionality of effects is consistently reported so that positive values of *g* indicate larger values for the FE group than for the HC group. To assess the potential effect of epilepsy duration (years since first seizure) on SW-ness and cognitive test scores, post hoc two-tailed Pearson correlation analyses were conducted in the patient sample. The group differences in the subjective memory complaint measures were analyzed using a chi-squared test for comparing proportions. The post hoc test of group differences in overall FC was conducted in an identical Student *t* test permutation procedure, as described above. All statistical analyses were performed with MATLAB and SPSS Statistics (ver. 26/27; IBM, Inc.).

3 | RESULTS

3.1 | Cognitive test performance and self-reported deficits

The complete list of group-level performance on the cognitive tests is presented in Table 3. Although the control group achieved higher mean performance on 76.5% of the test measures, suggesting that the patients were relatively more likely to achieve lower test scores, we did not observe significant group differences in performance on any single cognitive test, nor on the overall cognitive performance composite. This similarity between groups was expected, considering the generally high quality-of-life and work

TABLE 2 AAL regions composing the neurocognitive networks

Brain region	Corresponding AAL area	AAL indices
Default mode network		
Ventral medial prefrontal cortex	Superior frontal gyrus, orbital	5, 6
	Middle frontal gyrus, orbital	9, 10
	Gyrus rectus	27, 28
	Anterior cingulate and paracingulate gyri	31, 32
Posterior cingulate cortex	Posterior cingulate gyrus	35, 36
Posterior inferior parietal lobule and temporoparietal junction	Angular gyrus	65, 66
	Supramarginal gyrus	63, 64
Middle temporal gyrus and superior temporal sulcus	Middle temporal gyrus	85, 86
Parahippocampal cortex	Parahippocampal gyrus	39, 40
Precuneus	Precuneus	67, 68
Hippocampus	Hippocampus	37, 38
Superior/middle frontal gyrus	Superior frontal gyrus, medial	23, 24
	Superior frontal gyrus, dorsolateral	3, 4
	Middle frontal gyrus	7, 8
Anterior temporal lobes	Temporal pole, middle temporal gyrus	87, 88
Central-executive network		
Dorsolateral prefrontal cortex	Superior frontal gyrus, dorsolateral	3, 4
	Middle frontal gyrus	7, 8
	Inferior frontal gyrus, triangular	13, 14
Posterior parietal cortex	Supramarginal gyrus	63, 64
	Superior parietal gyrus	59, 60
	Inferior parietal gyrus	61, 62
Posterior inferior temporal cortex	Inferior temporal cortex	89, 90
Dorsal precuneus	Precuneus	67, 68
Salience network		
Anterior insula	Insula	29, 30
Dorsal anterior cingulate cortex	Anterior cingulate and paracingulate gyri	31, 32
Temporal pole	Temporal pole, superior temporal gyrus	83, 84
	Temporal pole, middle temporal gyrus	87, 88
Inferior parietal cortex	Inferior temporal cortex	89, 90

Note: All networks are bilaterally mirrored.

participation among all participants. Yet, 52.2% of the patients, and none of the controls, reported subjective memory complaints ($\chi^2 = 12.67$, $p < 0.001$).

Among the cognitive test scores, only the social cognition task (ERT number of hits) displayed a trend-significant negative correlation with the duration of epilepsy ($r = -0.479$, $p = 0.021$, $q = 0.378$), reflecting lower task performance with increasing time since the debut of epilepsy.

3.2 | Neurocognitive network small worldness

Interestingly, we observed subtle group differences in SW indices in all three neurocognitive networks across several frequency bands (Figure 2). In the DMN, patients displayed higher SW indices relative to the healthy controls across all frequency bands, with the difference being most pronounced in the theta band ($d = 0.652$, $p = 0.045$, $q = 0.135$), followed by the alpha band ($d = 0.480$, $p = 0.134$, $q = 0.202$).

In contrast to the DMN, for the other neurocognitive networks, the direction of the observed group differences was dependent on the frequency band. In the CEN, the group differences were most pronounced, yet not significant, in the theta ($d = -0.313$, $p = 0.326$, $q = 0.489$) and alpha bands ($d = -0.312$, $p = 0.324$, $q = 0.324$), where patients displayed relatively lower levels of the SW index. The SN showed relatively lower SW indices for the patients in the alpha ($d = -0.605$, $p = 0.061$, $q = 0.182$) and beta ($d = -0.655$, $p = 0.043$, $q = 0.129$) bands as the largest group differences. None of the observed group differences in the SW index in either neurocognitive network retained statistical significance after FDR correction for multiple comparisons.

We observed significant negative correlations between the duration of epilepsy and SW indices of the SN in the patients (Figure 3). These associations were observed for the alpha ($r = -0.550$, $p = 0.007$, $q = 0.042$) and beta bands ($r = -0.674$, $p < 0.001$, $q < 0.001$), and were specific to the SN. A trend-significant relationship was evident in the theta band ($r = -0.461$, $p = 0.027$, $q = 0.108$).

3.3 | Correlation of network small worldness with cognitive test performance

In both groups, positive and negative robust correlations between the levels of the SW index and cognitive test performance were observed in all neurocognitive networks and among all frequency bands.

3.3.1 | Default mode network

In the DMN (Figure 4), the patient group's SW index of the theta band displayed a significant negative correlation of moderate magnitude with memory performance ($r = -0.658$, $p = 0.001$, $q = 0.005$), and a trend-significant lower magnitude positive correlation with the latency measures in the same task ($r = 0.454$, $p = 0.038$, $q = 0.153$). For the former relationship, a significant interaction effect between group and SW index in predicting test

TABLE 3 Group characteristics and cognitive test performance

Characteristics	Focal epilepsy	Healthy controls	
Group size	$n = 23$	$n = 17$	
Female	65.2%	70.6%	
Age, years	54.7 ± 5.9	55.9 ± 6.7	
Higher education, years	4.3 ± 3.3	5.3 ± 3.1	
Handedness, right-handed	95.7%	94.1%	
Subjective memory complaints	52.2%	0.0%	
Cognitive test scores	**Focal epilepsy**	**Healthy controls**	***Hedges' g***
Color-Word Interference Test (CWIT)			
Reading speed (s)	23.1 ± 4.5	20.7 ± 3.3	0.59
Inhibition (s)	60.3 ± 18.5	55.9 ± 8.7	0.29
Inhibition/switching (s)	71.9 ± 28.3	60.3 ± 10.1	0.51
Digit Span (DS)			
Forward (span length)	9.0 ± 2.5	8.2 ± 1.6	0.39
Backward (span length)	8.0 ± 2.8	8.9 ± 1.7	−0.36
Sequencing (span length)	8.1 ± 2.0	8.4 ± 2.4	−0.12
Spatial Span (SSP)			
Forward (span length)	5.9 ± 1.4	5.5 ± 0.8	0.36
Pattern Recognition Memory (PRM)			
Correct, hits (%)	81.9 ± 15.4	88.2 ± 8.9	−0.48
Mean latency (s)	2.51 ± 0.72	2.42 ± 1.23	0.09
One Touch Stockings of Camb. (OTS)			
Correct first choice	10.7 ± 2.9	10.1 ± 3.6	0.20
Mean latency (s)	28.92 ± 13.21	29.27 ± 12.07	−0.03
Emotion Recognition Task (ERT)			
Correct, hits	26.5 ± 5.4	27.8 ± 3.7	−0.28
Median latency (s)	1.87 ± 0.45	1.92 ± 0.64	−0.10
Reaction Time (RTI)			
Mean reaction lat. (s)	0.413 ± 0.039	0.407 ± 0.034	0.17
Errors	1.39 ± 2.54	0.77 ± 1.72	0.28
Rapid Visual Processing (RVP)			
Detection rate (prop.)	0.956 ± 0.095	0.965 ± 0.095	−0.09
Mean latency (s)	0.51 ± 0.12	0.47 ± 0.10	0.33
Overall cognitive performance			
Sum of quartile points	44.0 ± 9.9	46.9 ± 9.5	−0.30

Note: Group means and standard deviations. In the column "Effect size," blue font color indicates better performance by the healthy controls compared to the patient group, and vice versa for red font color.

score was observed ($F = 4.549$, $p = 0.040$). Together, these results suggest that higher SW of the DMN is associated with poorer memory performance, both in terms of recognition hits and selection latency.

3.3.2 | Central-executive network

In the CEN (Figure 5), robust partial correlations were evident between the SW indices and cognitive test scores in healthy controls, but not in patients. In particular, the theta band SW index displayed the correlations of moderate magnitude with multiple test scores in the domains of working memory and executive functioning, specifically in the DS sequencing condition ($r = 0.730$, $p = 0.001$, $q = 0.005$) and the CWIT inhibition/switching task ($r = -0.641$, $p = 0.010$, $q = 0.020$). Thus, better performance on tests of working memory and executive functioning was associated with higher levels of SW in the theta frequency range of the CEN, but only in the healthy controls. The association between the CWIT inhibition/switching and the SW index was also evident in

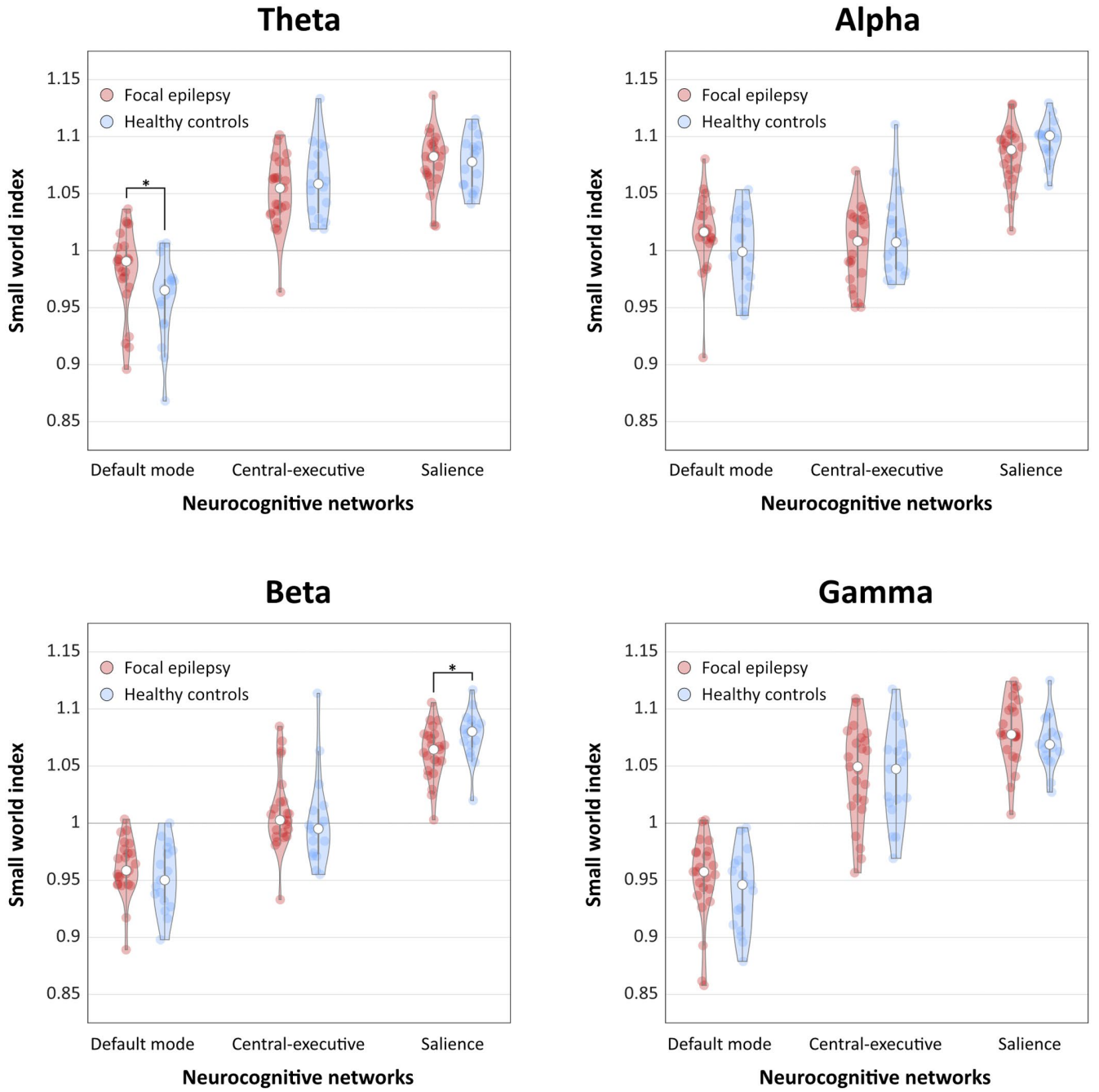

FIGURE 2 Network-wise SW index comparison between groups. An asterisk marks trend-significant group differences ($p < 0.05$); however, none of the observed group differences survived FDR adjustment. The violins represent a kernel density estimate. Box plot components: White dot = median; vertical thin gray bar = upper/lower adjacent value; vertical thicker gray bar = first/third quartile; colored dots = individual observations

the alpha band ($r = -0.693$, $p = 0.005$, $q = 0.018$). Furthermore, relationships were seen between the CEN theta band SW index and the composite score for overall cognitive performance ($r = 0.680$, $p = 0.005$, $q = 0.021$), CWIT measure of word reading ($r = -0.591$, $p = 0.021$, $q = 0.092$), and the latency measure of the social cognition task ($r = -0.704$, $p = 0.003$, $q = 0.013$). In all of the latter associations, significant group-SW index interactions were observed (overall performance: $F = 6.788$, $p = 0.014$; CWIT reading speed: $F = 6.761$, $p = 0.014$; ERT latency: $F = 5.565$, $p = 0.024$). The social cognition latency score was also associated with the SW indices of the CEN in the alpha ($r = -0.593$, $p = 0.019$, $q = 0.037$) and gamma ($r = -0.523$, $p = 0.045$, $q = 0.060$) bands. The latter displayed a significant interaction effect between group and SW index ($F = 5.120$, $p = 0.030$).

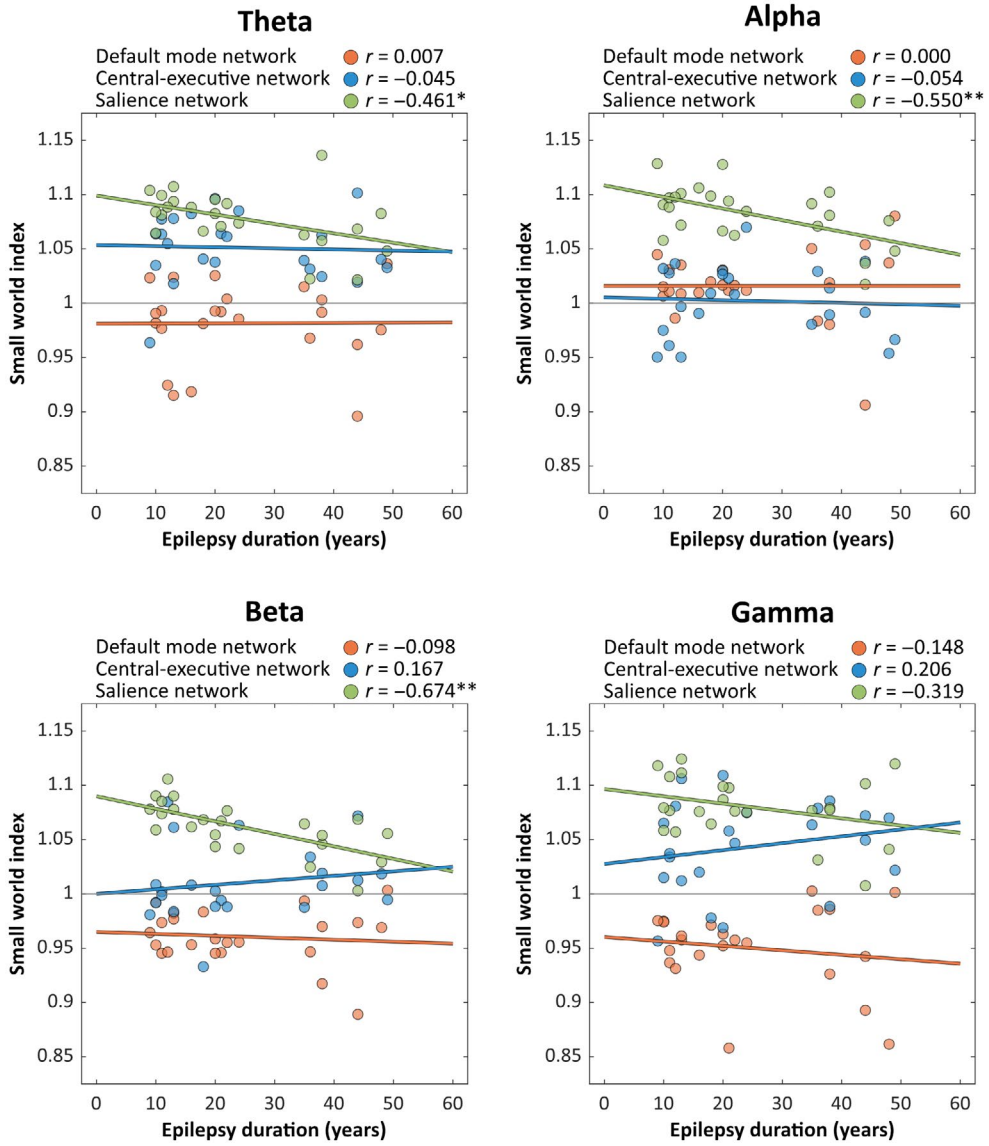

FIGURE 3 Correlation between the SW index and time living with epilepsy. A single asterisk marks trend-significant correlations ($p < 0.05$). A double asterisk marks significant correlations after FDR adjustment ($q < 0.1$)

3.3.3 | Salience network

In the SN (Figure 6), associations between test scores and SW indices were observed for both patients and controls, and were most prominent in the alpha band. In the social cognition task, the patients' scores were positively correlated with task performance ($r = 0.456$, $p = 0.038$, $q = 0.075$), whereas the controls' scores were negatively correlated with task latency ($r = -0.610$, $p = 0.016$, $q = 0.063$). Moreover, the same directionality pattern was evident in the opposite constellation, although the correlations were weaker. A similar pattern was observed for the SW index in the beta band, exemplified by a moderate positive correlation with ERT performance in the patients ($r = 0.569$, $p = 0.007$, $q = 0.029$). Also, the alpha band SW index of the SN displayed significant or trend-significant associations with subscores of the CWIT, including reading speed (patients: $r = -0.530$, $p = 0.013$, $q = 0.052$), inhibition (patients: $r = -0.503$, $p = 0.019$, $q = 0.077$) and inhibition/switching (controls: $r = -0.566$, $p = 0.028$, $q = 0.111$), and the composite overall performance score (patients: $r = 0.578$, $p = 0.006$, $q = 0.024$). No significant interaction effects between group and SW index were observed in the SN.

4 | DISCUSSION

In recent years, EEG-based functional network abnormalities have been consistently reported in epilepsy (Horstmann et al., 2010; Quraan et al., 2013; Vecchio et al., 2015), and such network-level dysfunctions are increasingly considered crucial mechanisms in sustaining non-seizure symptoms, such as cognitive impairment (Kramer & Cash, 2012; Uhlhaas & Singer, 2006). However, to our

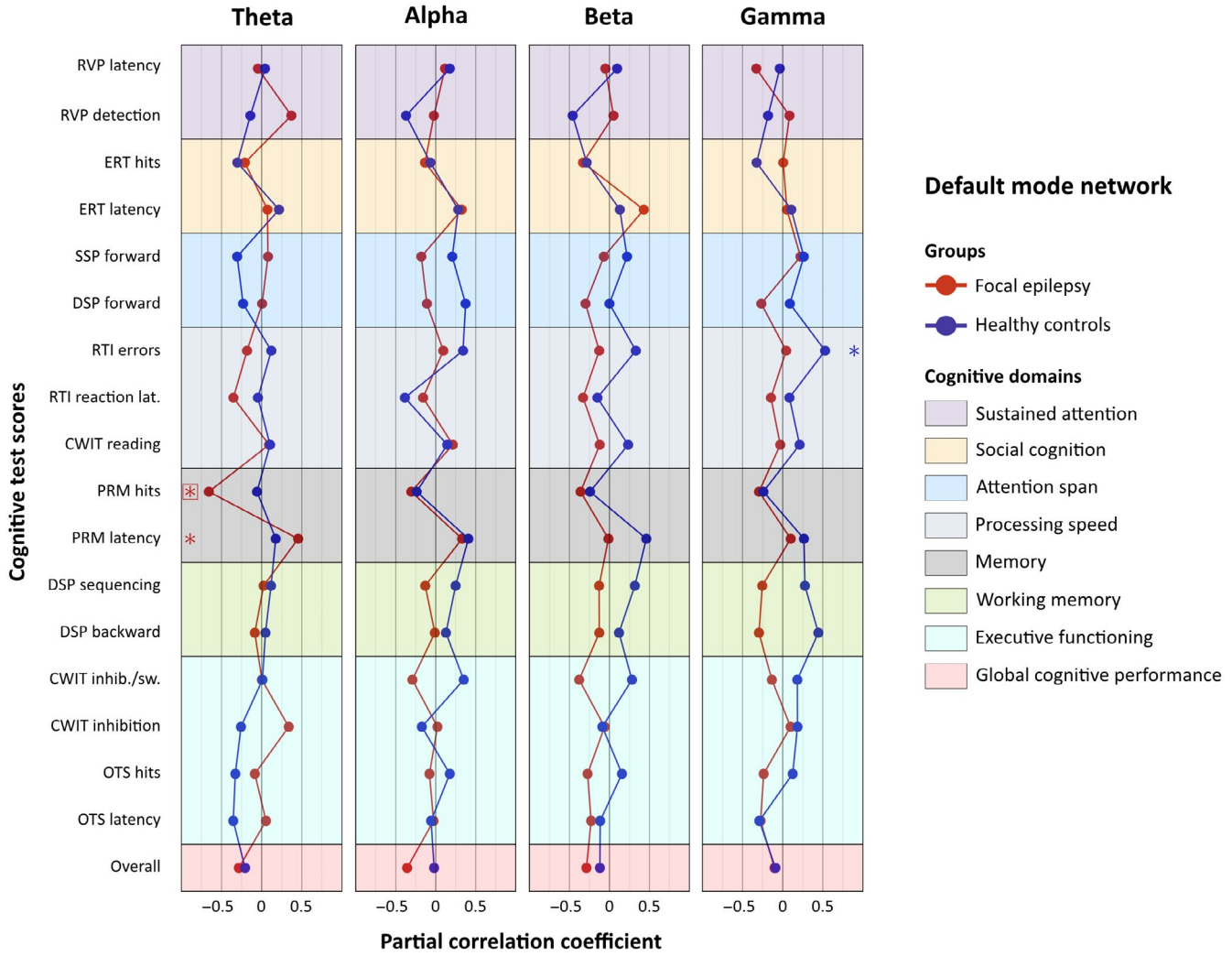

FIGURE 4 Partial correlation coefficients between SW-ness of the default mode network and cognitive test performance. Significant coefficients are marked with an asterisk. Significant coefficients which survived FDR correction are framed

knowledge, their association with distinct measures of cognitive test performance in epilepsy has not been highlighted before. Here, we investigated whether functional network organization, as reflected in source-level EEG and quantified as the SW index, was associated with performance on a range of cognitive tests. Specifically, we targeted three well-established neurocognitive networks, that is, the DMN, CEN, and SN, and examined to what degree their SW-ness would predict domain-specific cognitive performance in middle-aged patients with chronic FE and in healthy controls. Interestingly, although we only observed minor group differences in cognitive test performance and SW-ness separately, we were able to demonstrate that associations between them depended on the examined neurocognitive network, the EEG frequency band, and the presence or absence of epilepsy. Our analyses revealed that SW-ness of the DMN was associated with memory performance in patients, whereas the CEN organization was closely related to working memory and executive functioning in controls. For both groups, a significant correlation between the SW index of the SN and performance on a social cognition task was evident. Interestingly, for the latter network specifically, SW-ness across several frequency bands varied in relation to the patients' time living with epilepsy. In the following, we discuss how these findings relate to the existing literature, and the clinical relevance of the relationship between neurocognitive network organization and cognitive functioning in epilepsy.

4.1 | Neurocognitive networks in epilepsy

The DMN supports a range of cognitive functions, including memory (for a review, see Uddin et al., 2019). Altered functional connectivity in the DMN or its constituent regions has been shown to predict memory deficits in neurological disease such as amnestic mild cognitive impairment (Dunn et al., 2014; Wang et al., 2013). Importantly, DMN connectivity aberrancies, as measured by fMRI, have been implicated in the sustenance of epilepsy symptoms with regard to seizure propagation (Ofer et al., 2019),

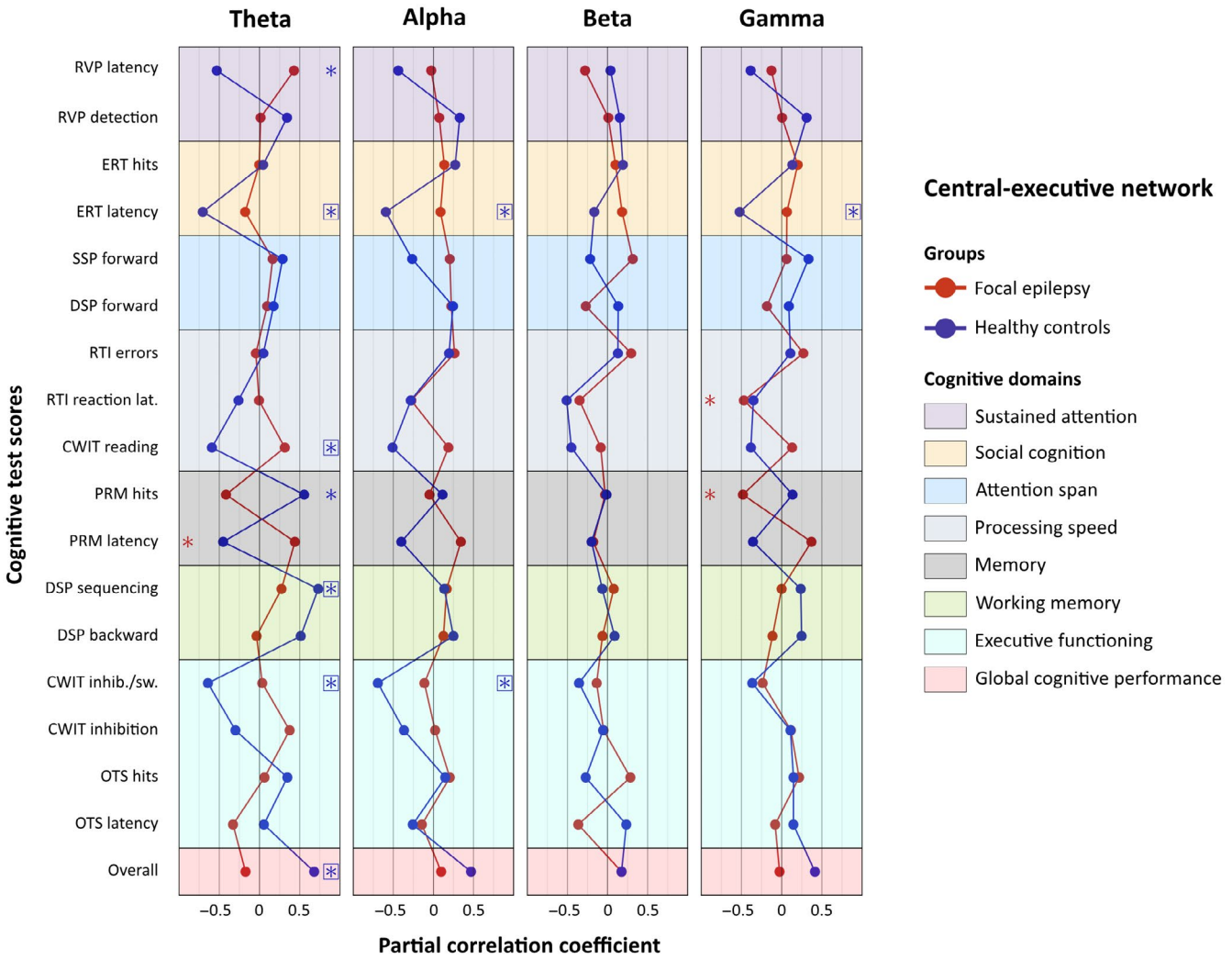

FIGURE 5 Partial correlation coefficients between SW-ness of the central-executive network and cognitive test performance. Significant coefficients are marked with an asterisk. Significant coefficients which survived FDR correction are framed

memory (McCormick et al., 2013), and executive dysfunction (Zhou et al., 2019). In keeping with this, we demonstrate that increased SW-ness of the DMN in the theta band is associated with poorer memory performance in patients. The fact that this finding is specific to the theta band is interesting, as theta oscillations are closely related to memory processes (Axmacher et al., 2008; Raghavachari et al., 2006; Sauseng et al., 2009). Furthermore, several studies suggest the global network alterations in FE to be relatively prominent in the theta band (Horstmann et al., 2010; Quraan et al., 2013). This is further supported by the observation in the current study that, among the investigated frequency bands, theta showed the most robust group difference in DMN SW-ness (Figure 2, top-left), with patients displaying the larger SW indices. Interestingly, the association between memory and the DMN was not found in the healthy controls, suggesting that the SW-ness of the network does not index global memory integrity, but rather the degree of deterioration, a notion further reinforced by a significant interaction effect between SW-ness and group.

Consistent with the established role of the CEN as a neural substrate for executive functioning (Markett et al., 2014; Seeley et al., 2007), here the network's SW-ness in the theta band robustly predicted performance on tasks relying on mental flexibility and working memory. However, in contrast to the DMN, the CEN-specific associations were only evident for healthy controls, and not for patients. One potential interpretation of this discrepancy may be that the CEN is adversely affected in epilepsy, leading to dysfunctional regulation of the network in response to current goal states. Indeed, in a study of newly diagnosed FE patients, network functional connectivity alterations were found selectively in the CEN (Alonazi et al., 2019), suggesting that this network might be particularly susceptible to disruption by epileptic neuronal activity. However, from our data, this potential disruption does not appear to be reflected in the network's SW-ness, which was similar across the groups. Conversely, this similarity may suggest the presence of compensatory mechanisms in the patients, reducing the discrepancy of the network's SW-ness and cognitive performance relative to the healthy controls. In this scenario, such compensatory

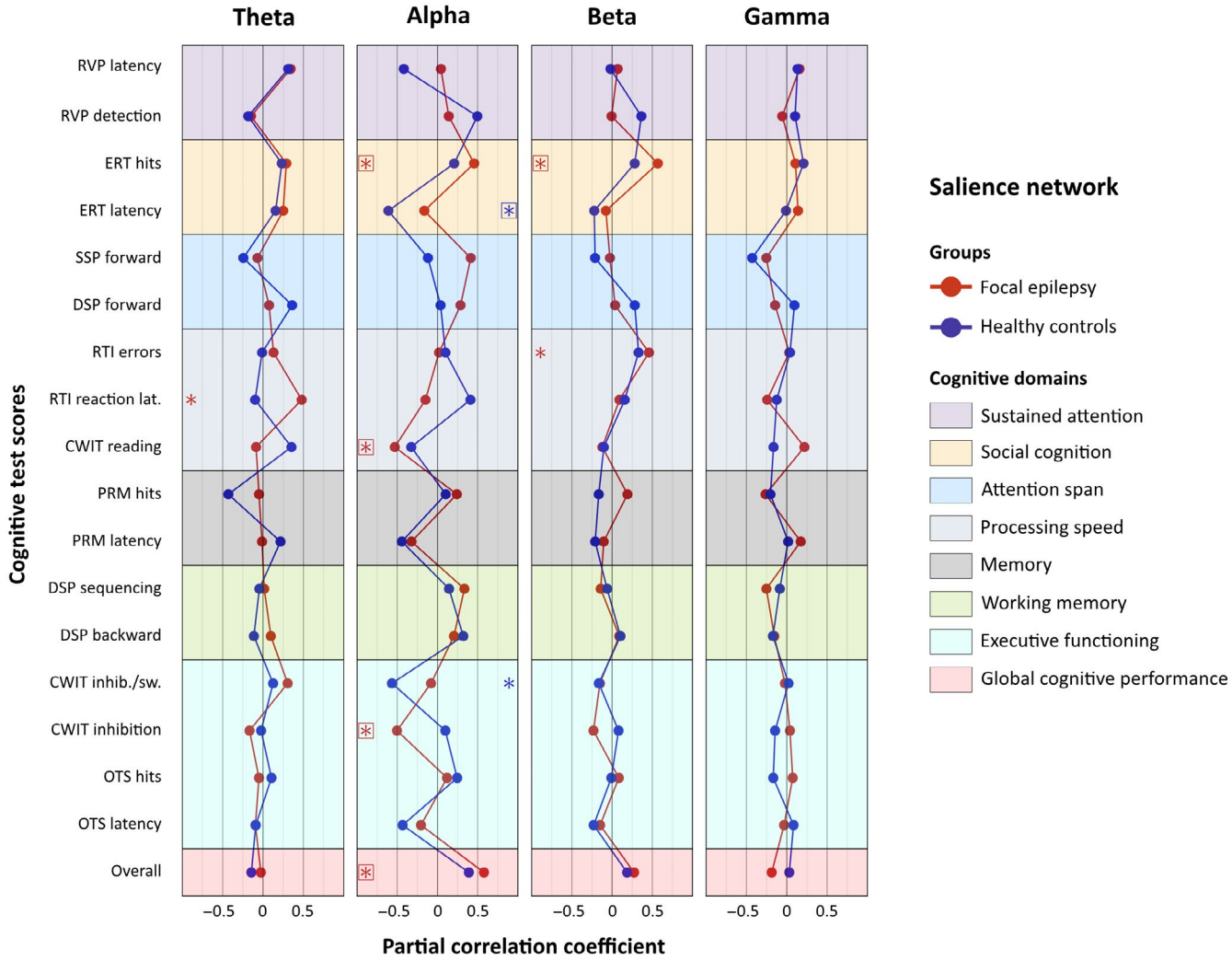

FIGURE 6 Partial correlation coefficients between SW-ness of the salience network and cognitive test performance. Significant coefficients are marked with an asterisk. Significant coefficients which survived FDR correction are framed

measures may suppress the direct relationship between network SW-ness and executive functioning observed in the controls. Behaviorally, executive dysfunction is prevalent in several syndromes of epilepsy, such as FE with frontal or temporal origin (Hermann et al., 1997; Oyegbile et al., 2004). Moreover, in a study employing graph theory on cognitive test scores in a large cohort of temporal lobe epilepsy patients, a test of mental flexibility and rapid set switching (Trail Making Test B) comprises a central hub in the network of tests (Kellermann et al., 2016), implicating that other test results are relatively likely to be correlated with it. Following this notion, it is possible that prevalent cognitive issues, such as memory impairment (Taylor et al., 2010), are caused either directly by disruption of the CEN, or indirectly via behavioral executive dysfunction as a mediator. We encourage future research to investigate additional characteristics of the CEN in order to delineate its role in cognitive dysfunction in epilepsy.

The SN is attributed with the task of identifying the most relevant among the continuous stream of internal and external inputs to the brain, including emotional information (Kennedy & Adolphs, 2012; Menon, 2011; Seeley et al., 2007). In line with this, we observed in our data a robust association between the patients' SW-ness of the SN in the alpha and beta bands, and their ability to identify emotions from rapid presentation of human faces (the ERT). The higher the SW-ness, the more correct responses were made. Moreover, in both these frequency bands, patients displayed a trend toward lower SW-ness of the SN relative to the controls. These observations, in light of the firmly established evidence that patients with epilepsy, predominantly with temporal origin, suffer impairment of social cognition and facial recognition (Bora & Meletti, 2016; Edwards et al., 2017; Monti & Meletti, 2015), suggest that an alteration in the SN's functional organization might amount to a crucial mechanism in sustaining these deficits in epilepsy. Furthermore, the regulation of alpha and beta oscillations has been found to be involved in face perception (Popov et al., 2012, 2013). However, in our data, the alpha band SW-ness of the SN was also predictive of processing speed, inhibitory control, and overall cognitive performance in the patients, suggesting that SN organization might be implied in a broader range

of cognitive domains. Indeed, considering the hypothesis of accelerated cognitive aging, which postulates that cognitive decline in epilepsy follows a normal trajectory, but at an increased rate (Breuer et al., 2016, 2017), the SN might be among several intrinsic brain networks which, in a compensatory effort, alters their intra- and inter-network organization in response to pathological processes (Bernas et al., 2020). Our finding of an association between SW-ness of the SN and the patients' number of years living with epilepsy might lend further support to this notion.

4.2 | Clinical relevance

Cognitive impairment remains a prominent personal and diagnostic challenge in epilepsy, with approximately 70% of patients reporting subjective memory problems, independent of age, medication, and seizure status (Henning et al., 2019). In objective measures, about half of newly diagnosed patients over the age of 15 present with abnormal performance in the memory and psychomotor speed domains, regardless of seizure type and epileptogenic brain area (Taylor et al., 2010). Currently, seizure control with ASM is the prioritized aim in epilepsy treatment (Schmidt & Schachter, 2014; Sørensen & Kokaia, 2013). However, new etiological models increasingly consider the possibility that cognitive dysfunction arises as an independent manifestation of a complex underlying pathology that also provokes seizures (Bjørke et al., 2021; Hermann et al., 2008; Lin et al., 2012). Thus, in many clinical cases, achieving freedom from seizures will not be sufficient for treating cognitive dysfunction (Witt & Helmstaedter, 2017), introducing the need for additional diagnostic, monitoring, and treatment tools to be developed. Considering recent findings, including those of the present study, clinical application of source-level functional network analysis should be considered a viable candidate in this regard (Stefan & Lopes da Silva, 2013; van Mierlo et al., 2019).

Despite considerable promise, several issues remain to be investigated with regard to network analysis in a clinical epileptology capacity. First, we observed that patients and controls presented with an intergroup discrepancy of network-cognition associations. This could possibly be an effect of the current small sample sizes (23 patients and 17 controls). However, a recent study employing fMRI-based effective connectivity concluded that epilepsy is associated with stronger connectivity *between* resting-state networks, and weaker connectivity *within* each network, possibly reflecting a compensation mechanism of overactive recruitment of network resources (Bernas et al., 2020). Following this notion, a possible consequence is that networks involved in higher cognitive processes (the CEN, in particular) may be predisposed for functional reorganization, and thus become less rigorously defined in epilepsy compared to the healthy brain. Consequently, it should not be ruled out that epilepsy patients and healthy controls differ on the degree of involvement of different networks in supporting cognitive functions. Indeed, in accordance with the hypothesis of accelerated cognitive aging in epilepsy (Breuer et al., 2016, 2017), research suggests that normal aging, with a corresponding normal trajectory for cognitive decline, is associated with increased distributed network function (Meunier et al., 2014). Another issue regards how epilepsy medication affects functional network connectivity. To date, few studies have investigated this potentially important relationship. However, there is some evidence that carbamazepine and oxcarbazepine are associated with changes to the brain's hub organization (Haneef et al., 2015), and that topiramate affects network connectivity to a larger extent compared to other medications (van Veenendaal et al., 2017).

Furthermore, the theoretical framework for the clinical application of graph methodology remains sparse. Graph theory has primarily developed describing theoretical and synthetic networks, and the translation of its concepts to clinically significant characterizations of complex biological systems, such as the human brain, is largely rudimentary (Douw et al., 2019; Papo et al., 2014). For example, the concept of increased SW-ness is, as a rule, associated with higher network efficiency. It reflects the system's ability to achieve integrated functioning through facilitation of long-range signal transmission between functionally specialized modules of short communication paths (Bassett & Bullmore, 2017; Bertolero et al., 2015). However, in the context of functional brain connectivity and clinical relevance, this notion is one of controversy (Papo et al., 2016). Provided the complexity of the human brain, it is perhaps more likely that SW-ness constitutes *one* relevant parameter of network organization, and that additional metrics are required for a more comprehensive characterization of brain networks (Hallquist & Hillary, 2019).

4.3 | Limitations

For the present study, some limitations should be outlined. First, compared to fMRI and MEG, EEG has inherent shortcomings regarding spatial resolution. Here, this limitation was mitigated by employing high-quality source reconstruction, based on individual anatomy. Nevertheless, the investigated resting-state networks were necessarily approximated by predefined composites of AAL regions. The selection of network regions was guided by an updated consensus definition of the networks (Uddin et al., 2019). Furthermore, electrophysiologically derived functional connectivity is subject to the effect of source leakage. If the leakage varies across groups, differences can arise in the connectivity matrices, and by extension, the graph metrics. While some functional connectivity measures eliminate the effects of leakage by removing zero-lag synchronization (Bruña et al., 2018; Ewald et al., 2012), these show low test–retest reliability, in contrast to PLV, which was used in the present study (Colclough et al., 2016; Garcés et al., 2016). Here, the effect of source leakage might have impacted the direct group comparisons of the SW index; however, its effect on the observed SW cognition correlations is presumed minimal. Finally, the current data are based on relatively small samples of patients with FE and healthy controls. The results should therefore see replication in larger samples. Also, due to the low number of participants, the patients were not stratified with regard to clinical factors such as epilepsy focus, ASM type

and dosage, and seizure frequency, which have previously been reported to affect network metrics (Haneef et al., 2015; van Dellen et al., 2009). It is important to note that the present patient sample is relatively homogeneously composed, reflecting people in middle adulthood and in a chronic phase of epilepsy.

4.4 | Conclusion

Here, we have demonstrated that graph characteristics of functional neurocognitive networks derived from source-level EEG display frequency- and domain-specific correlations with performance on cognitive tests. These findings highlight the role of functional brain network dysfunction in cognitive impairment, an important issue reiterated by revised etiological models suggesting that impaired cognition and epilepsy may arise independently from a shared pathology.

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

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PARTICIPANT INFORMED CONSENT

Following the Declaration of Helsinki, all participants provided informed written consent.

ETHICAL APPROVAL

Ethical approval for the study was granted by the Regional Committees for Medical Research Ethics - South-East Norway.

COMPETING INTERESTS

The authors report no competing interests.

AUTHOR CONTRIBUTIONS

All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization*, C.H., R.B., F.M., E.T., and I.H.H.; *Methodology*, C.H. and R.B.; *Investigation*, C.H., A.E., and V.A.; *Formal Analysis*, C.H. and R.B.; *Resources*, A.E., M.R.S., and E.T.; *Writing – Original Draft*, C.H., R.B., and I.H.H.; *Writing – Review & Editing*, M.R.S., A.H.S., H.R., C.M., F.M., K.H., E.T., and A.S.; *Visualization*, C.H.; *Supervision*, E.T., A.S., and I.H.H.; *Funding Acquisition*, I.H.H.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (or his affiliated institution) upon reasonable request.

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REFERENCES

Agosta, F., Pievani, M., Geroldi, C., Copetti, M., Frisoni, G. B., & Filippi, M. (2012). Resting state fMRI in Alzheimer's disease: Beyond the default mode network. *Neurobiology of Aging*, *33*, 1564–1578. https://doi.org/10.1016/j.neurobiolaging.2011.06.007

Alonazi, B. K., Keller, S. S., Fallon, N., Adams, V., Das, K., Marson, A. G., & Sluming, V. (2019). Resting-state functional brain networks in adults with a new diagnosis of focal epilepsy. *Brain and Behavior*, *9*(1), e01168. https://doi.org/10.1002/brb3.1168

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-anatomic fractionation of the brain's default network. *Neuron*, *65*, 550–562. https://doi.org/10.1016/j.neuron.2010.02.005

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences*, *1316*, 29–52. https://doi.org/10.1111/nyas.12360

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *Neuroimage*, *26*, 839–851. https://doi.org/10.1016/j.neuroimage.2005.02.018

Axmacher, N., Elger, C. E., & Fell, J. (2008). Ripples in the medial temporal lobe are relevant for human memory consolidation. *Brain*, *131*, 1806–1817. https://doi.org/10.1093/brain/awn103

Bassett, D. S., & Bullmore, E. T. (2017). Small-world brain networks revisited. *Neuroscientist*, *23*, 499–516. https://doi.org/10.1177/1073858416667720

Bastos, A. M., & Schoffelen, J.-M. (2015). A tutorial review of functional connectivity analysis methods and their interpretational pitfalls. *Frontiers in Systems Neuroscience*, *9*, 175. https://doi.org/10.3389/fnsys.2015.00175

Behrens, T. E. J., & Sporns, O. (2012). Human connectomics. *Current Opinion in Neurobiology*, *22*, 144–153. https://doi.org/10.1016/j.conb.2011.08.005

Belouchrani, A., Abed-Meraim, K., Cardoso, J. F., & Moulines, E. (1993). Second-order blind separation of temporally correlated sources. In *Proceedings of the International Conference on Digital Signal Processing* (pp. 346–351). Citeseer. .https://www.researchgate.net/profile/Adel_Belouchrani/publication/2699542_Second_Order_Blind_Separation_of_Temporally_Correlated_Sources/links/00463517ab

3e0aed06000000/Second-Order-Blind-Separation-of-Temporally-Correlated-Sources.pdf

Benjamini, Y., & Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency. *Annals of Statistics*, *29*, 1165–1188. http://www.jstor.org/stable/2674075

Bernas, A., Breuer, L. E. M., Lamerichs, R., de Louw, A. J. A., Aldenkamp, A. P., & Zinger, S. (2020). Accelerated cognitive ageing in epilepsy: Exploring the effective connectivity between resting-state networks and its relation to cognitive decline. *Heliyon*, *6*, e03951. https://doi.org/10.1016/j.heliyon.2020.e03951

Bertolero, M. A., Yeo, B. T. T., & D'Esposito, M. (2015). The modular and integrative functional architecture of the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *112*, E6798–E6807. https://doi.org/10.1073/pnas.1510619112

Besserve, M., Martinerie, J., & Garnero, L. (2011). Improving quantification of functional networks with EEG inverse problem: Evidence from a decoding point of view. *Neuroimage*, *55*, 1536–1547. https://doi.org/10.1016/j.neuroimage.2011.01.056

Bjørke, A. B., Østby, Y., Grahl, S. G., Larsson, P. G., Olsen, K. B., Johansen Nævra, M. C., Ringstad, G. A., Bjørnerud, A., Gjerstad, L., Taubøll, E., & Heuser, K. (2021). Cognition in adult patients with newly diagnosed non-lesional temporal lobe epilepsy. *Epilepsy & Behavior*, *116*, 107771. https://doi.org/10.1016/j.yebeh.2021.107771

Bora, E., & Meletti, S. (2016). Social cognition in temporal lobe epilepsy: A systematic review and meta-analysis. *Epilepsy & Behavior*, *60*, 50–57. https://doi.org/10.1016/j.yebeh.2016.04.024

Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: Emerging methods and principles. *Trends in Cognitive Sciences*, *14*, 277–290. https://doi.org/10.1016/j.tics.2010.04.004

Breuer, L. E. M., Boon, P., Bergmans, J. W. M., Mess, W. H., Besseling, R. M. H., de Louw, A., Tijhuis, A. G., Zinger, S., Bernas, A., Klooster, D. C. W., & Aldenkamp, A. P. (2016). Cognitive deterioration in adult epilepsy: Does accelerated cognitive ageing exist? *Neuroscience and Biobehavioral Reviews*, *64*, 1–11. https://doi.org/10.1016/j.neubiorev.2016.02.004

Breuer, L. E. M., Grevers, E., Boon, P., Bernas, A., Bergmans, J. W. M., Besseling, R. M. H., Klooster, D. C. W., de Louw, A., Mestrom, R. M. C., Vonck, K., Zinger, S., & Aldenkamp, A. P. (2017). Cognitive deterioration in adult epilepsy: Clinical characteristics of "Accelerated Cognitive Ageing". *Acta Neurologica Scandinavica*, *136*, 47–53. https://doi.org/10.1111/ane.12700

Bruña, R., Maestú, F., & Pereda, E. (2018). Phase locking value revisited: Teaching new tricks to an old dog. *Journal of Neural Engineering*, *15*, https://doi.org/10.1088/1741-2552/aacfe4056011

Brunner, C., Billinger, M., Seeber, M., Mullen, T. R., & Makeig, S. (2016). Volume conduction influences scalp-based connectivity estimates. *Frontiers in Computational Neuroscience*, *10*, 121. https://doi.org/10.3389/fncom.2016.00121

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, *1124*, 1–38. https://doi.org/10.1196/annals.1440.011

Chand, G. B., Wu, J., Hajjar, I., & Qiu, D. (2017). Interactions of the salience network and its subsystems with the default-mode and the central-executive networks in normal aging and mild cognitive impairment. *Brain Connectivity*, *7*, 401–412. https://doi.org/10.1089/brain.2017.0509

Colclough, G. L., Woolrich, M. W., Tewarie, P. K., Brookes, M. J., Quinn, A. J., & Smith, S. M. (2016). How reliable are MEG resting-state connectivity metrics? *Neuroimage*, *138*, 284–293. https://doi.org/10.1016/j.neuroimage.2016.05.070

Damoiseaux, J. S., Prater, K. E., Miller, B. L., & Greicius, M. D. (2012). Functional connectivity tracks clinical deterioration in Alzheimer's disease. *Neurobiology of Aging*, *33*, 828.e19–828.e30. https://doi.org/10.1016/j.neurobiolaging.2011.06.024

de Cheveigné, A. (2020). ZapLine: A simple and effective method to remove power line artifacts. *Neuroimage*, *207*, 116356. https://doi.org/10.1016/j.neuroimage.2019.116356

Deco, G., Jirsa, V. K., & McIntosh, A. R. (2011). Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nature Reviews Neuroscience*, *12*, 43–56. https://doi.org/10.1038/nrn2961

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). *Delis-Kaplan executive function system*. The Psychological Corporation. https://psycnet.apa.org/fulltext/9999-15082-000.pdf

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*, 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Douw, L., Schoonheim, M. M., Landi, D., van der Meer, M. L., Geurts, J. J. G., Reijneveld, J. C., Klein, M., & Stam, C. J. (2011). Cognition is related to resting-state small-world network topology: An magnetoencephalographic study. *Neuroscience*, *175*, 169–177. https://doi.org/10.1016/j.neuroscience.2010.11.039

Douw, L., van Dellen, E., Gouw, A. A., Griffa, A., de Haan, W., van den Heuvel, M., Hillebrand, A., Van Mieghem, P., Nissen, I. A., Otte, W. M., Reijmer, Y. D., Schoonheim, M. M., Senden, M., van Straaten, E. C. W., Tijms, B. M., Tewarie, P., & Stam, C. J. (2019). The road ahead in clinical network neuroscience. *Network Neuroscience*, *3*, 969–993. https://doi.org/10.1162/netn_a_00103

Dunn, C. J., Duffy, S. L., Hickie, I. B., Lagopoulos, J., Lewis, S. J. G., Naismith, S. L., & Shine, J. M. (2014). Deficits in episodic memory retrieval reveal impaired default mode network connectivity in amnestic mild cognitive impairment. *Neuroimage Clinical*, *4*, 473–480. https://doi.org/10.1016/j.nicl.2014.02.010

Edwards, M., Stewart, E., Palermo, R., & Lah, S. (2017). Facial emotion perception in patients with epilepsy: A systematic review with meta-analysis. *Neuroscience and Biobehavioral Reviews*, *83*, 212–225. https://doi.org/10.1016/j.neubiorev.2017.10.013

Engel, J., Jr., Thompson, P. M., Stern, J. M., Staba, R. J., Bragin, A., & Mody, I. (2013). Connectomics and epilepsy. *Current Opinion in Neurology*, *26*, 186–194. https://doi.org/10.1097/WCO.0b013e32835ee5b8

Ewald, A., Marzetti, L., Zappasodi, F., Meinecke, F. C., & Nolte, G. (2012). Estimating true brain connectivity from EEG/MEG data invariant to linear and static transformations in sensor space. *Neuroimage*, *60*, 476–488. https://doi.org/10.1016/j.neuroimage.2011.11.084

Fan, J., Xu, P., Van Dam, N. T., Eilam-Stock, T., Gu, X., Luo, Y.-J., & Hof, P. R. (2012). Spontaneous brain activity relates to autonomic arousal. *Journal of Neuroscience*, *32*, 11176–11186. https://doi.org/10.1523/JNEUROSCI.1172-12.2012

Fang, Q., & Boas, D. A. (2009). Tetrahedral mesh generation from volumetric binary and grayscale images. In *2009 IEEE International Symposium on Biomedical Imaging: From Nano to Macro* (pp. 1142–1145). https://doi.org/10.1109/ISBI.2009.5193259

Fornito, A., Zalesky, A., Pantelis, C., & Bullmore, E. T. (2012). Schizophrenia, neuroimaging and connectomics. *NeuroImage*, *62*, 2296–2314. https://doi.org/10.1016/j.neuroimage.2011.12.090.

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, *8*, 700–711. https://doi.org/10.1038/nrn2201

Garcés, P., Martín-Buro, M. C., & Maestú, F. (2016). Quantifying the test-retest reliability of magnetoencephalography resting-state functional connectivity. *Brain Connectivity*, *6*, 448–460. https://doi.org/10.1089/brain.2015.0416

Genovese, C. R., Lazar, N. A., & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage*, *15*, 870–878. https://doi.org/10.1006/nimg.2001.1037

Geschwind, N. (1965). Disconnexion syndromes in animals and man. I. *Brain*, *88*, 237–294. https://doi.org/10.1093/brain/88.2.237

Goulden, N., Khusnulina, A., Davis, N. J., Bracewell, R. M., Bokde, A. L., McNulty, J. P., & Mullins, P. G. (2014). The salience network is

responsible for switching between the default mode network and the central executive network: Replication from DCM. *Neuroimage*, *99*, 180–190. https://doi.org/10.1016/j.neuroimage.2014.05.052

Gramfort, A., Papadopoulo, T., Olivi, E., & Clerc, M. (2010). OpenMEEG: Opensource software for quasistatic bioelectromagnetics. *BioMedical Engineering OnLine*, *9*, 45. https://doi.org/10.1186/1475-925X-9-45

Hallquist, M. N., & Hillary, F. G. (2019). Graph theory approaches to functional network organization in brain disorders: A critique for a brave new small-world. *Network Neuroscience*, *3*, 1–26. https://doi.org/10.1162/netn_a_00054

Haneef, Z., Levin, H. S., & Chiang, S. (2015). Brain graph topology changes associated with anti-epileptic drug use. *Brain Connectivity*, *5*, 284–291. https://doi.org/10.1089/brain.2014.0304

Hassan, M., Chaton, L., Benquet, P., Delval, A., Leroy, C., Plomhause, L., Moonen, A. J. H., Duits, A. A., Leentjens, A. F. G., van Kranen-Mastenbroek, V., Defebvre, L., Derambure, P., Wendling, F., & Dujardin, K. (2017). Functional connectivity disruptions correlate with cognitive phenotypes in Parkinson's disease. *Neuroimage Clinical*, *14*, 591–601. https://doi.org/10.1016/j.nicl.2017.03.002

Hassan, M., & Wendling, F. (2018). Electroencephalography source connectivity: Aiming for high resolution of brain networks in time and space. *IEEE Signal Processing Magazine*, *35*, 81–96. https://ieeexplore.ieee.org/document/8351910/ https://doi.org/10.1109/MSP.2017.2777518

Hatlestad-Hall, C., Bruña, R., Syvertsen, M. R., Erichsen, A., Andersson, V., Vecchio, F., Miraglia, F., Rossini, P. M., Renvall, H., Taubøll, E., Maestú, F., & Haraldsen, I. H. (2021). Source-level EEG and graph theory reveal widespread functional network alterations in focal epilepsy. *Clinical Neurophysiology*, *132*(7), 1663–1676. https://doi.org/10.1016/j.clinph.2021.04.008

Helmstaedter, C., & Witt, J.-A. (2017). Epilepsy and cognition—A bidirectional relationship? *Seizure*, *49*, 83–89. https://doi.org/10.1016/j.seizure.2017.02.017

Henning, O., Landmark, C. J., Henning, D., Nakken, K. O., & Lossius, M. I. (2019). Challenges in epilepsy—The perspective of Norwegian epilepsy patients. *Acta Neurologica Scandinavica*, *140*, 40–47. https://doi.org/10.1111/ane.13098

Hermann, B., Seidenberg, M., & Jones, J. (2008). The neurobehavioural comorbidities of epilepsy: Can a natural history be developed? *Lancet Neurology*, *7*, 151–160. https://doi.org/10.1016/S1474-4422(08)70018-8

Hermann, B., Seidenberg, M., Lee, E.-J., Chan, F., & Rutecki, P. (2007). Cognitive phenotypes in temporal lobe epilepsy. *Journal of the International Neuropsychological Society*, *13*, 12–20. https://doi.org/10.1017/S135561770707004X

Hermann, B. P., Seidenberg, M., Schoenfeld, J., & Davies, K. (1997). Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. *Archives of Neurology*, *54*, 369–376. https://doi.org/10.1001/archneur.1997.00550160019010

Horstmann, M.-T., Bialonski, S., Noennig, N., Mai, H., Prusseit, J., Wellmer, J., Hinrichs, H., & Lehnertz, K. (2010). State dependent properties of epileptic brain networks: Comparative graph-theoretical analyses of simultaneously recorded EEG and MEG. *Clinical Neurophysiology*, *121*, 172–185. https://doi.org/10.1016/j.clinph.2009.10.013

Huang, Y., Parra, L. C., & Haufe, S. (2016). The New York Head-A precise standardized volume conductor model for EEG source localization and tES targeting. *Neuroimage*, *140*, 150–162. https://doi.org/10.1016/j.neuroimage.2015.12.019

Humphries, M. D., & Gurney, K. (2008). Network "small-world-ness": A quantitative method for determining canonical network equivalence. *PLoS ONE*, *3*, e0002051. https://doi.org/10.1371/journal.pone.0002051

Ito, T., Kulkarni, K. R., Schultz, D. H., Mill, R. D., Chen, R. H., Solomyak, L. I., & Cole, M. W. (2017). Cognitive task information is transferred between brain regions via resting-state network topology. *Nature Communications*, *8*, 1027. https://doi.org/10.1038/s41467-017-01000-w

Kellermann, T. S., Bonilha, L., Eskandari, R., Garcia-Ramos, C., Lin, J. J., & Hermann, B. P. (2016). Mapping the neuropsychological profile of temporal lobe epilepsy using cognitive network topology and graph theory. *Epilepsy & Behavior*, *63*, 9–16. https://doi.org/10.1016/j.yebeh.2016.07.030

Kennedy, D. P., & Adolphs, R. (2012). The social brain in psychiatric and neurological disorders. *Trends in Cognitive Sciences*, *16*, 559–572. https://doi.org/10.1016/j.tics.2012.09.006

King, B. R., van Ruitenbeek, P., Leunissen, I., Cuypers, K., Heise, K.-F., Santos Monteiro, T., Hermans, L., Levin, O., Albouy, G., Mantini, D., & Swinnen, S. P. (2018). Age-related declines in motor performance are associated with decreased segregation of large-scale resting state brain networks. *Cerebral Cortex*, *28*, 4390–4402. https://doi.org/10.1093/cercor/bhx297

Kramer, M. A., & Cash, S. S. (2012). Epilepsy as a disorder of cortical network organization. *Neuroscientist*, *18*, 360–372. https://doi.org/10.1177/1073858411422754

Lachaux, J. P., Rodriguez, E., Martinerie, J., & Varela, F. J. (1999). Measuring phase synchrony in brain signals. *Human Brain Mapping*, *8*, 194–208. https://doi.org/10.1002/(sici)1097-0193(1999)8:4<194:aid-hbm4>3.0.co;2-c

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: A practical primer for t-tests and ANOVAs. *Frontiers in Psychology*, *4*, 863. https://doi.org/10.3389/fpsyg.2013.00863

Langer, N., Pedroni, A., Gianotti, L. R. R., Hänggi, J., Knoch, D., & Jäncke, L. (2012). Functional brain network efficiency predicts intelligence. *Human Brain Mapping*, *33*, 1393–1406. https://doi.org/10.1002/hbm.21297

Legendre, P. (2000). Comparison of permutation methods for the partial correlation and partial mantel tests. *Journal of Statistical Computation and Simulation*, *67*, 37–73. https://doi.org/10.1080/00949650008812035

Lin, J. J., Mula, M., & Hermann, B. P. (2012). Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. *Lancet*, *380*, 1180–1192. https://doi.org/10.1016/S0140-6736(12)61455-X

Lopes da Silva, F. (2013). EEG and MEG: Relevance to neuroscience. *Neuron*, *80*, 1112–1128. https://doi.org/10.1016/j.neuron.2013.10.017

Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG- and MEG-data. *Journal of Neuroscience Methods*, *164*, 177–190. https://doi.org/10.1016/j.jneumeth.2007.03.024

Markett, S., Reuter, M., Montag, C., Voigt, G., Lachmann, B., Rudorf, S., Elger, C. E., & Weber, B. (2014). Assessing the function of the fronto-parietal attention network: Insights from resting-state fMRI and the attentional network test. *Human Brain Mapping*, *35*, 1700–1709. https://doi.org/10.1002/hbm.22285

McCormick, C., Quraan, M., Cohn, M., Valiante, T. A., & McAndrews, M. P. (2013). Default mode network connectivity indicates episodic memory capacity in mesial temporal lobe epilepsy. *Epilepsia*, *54*, 809–818. https://doi.org/10.1111/epi.12098

Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*, *15*, 483–506. https://doi.org/10.1016/j.tics.2011.08.003

Mesulam, M. M. (1990). Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Annals of Neurology*, *28*, 597–613. https://doi.org/10.1002/ana.410280502

Meunier, D., Stamatakis, E. A., & Tyler, L. K. (2014). Age-related functional reorganization, structural changes, and preserved cognition. *Neurobiology of Aging*, *35*, 42–54. https://doi.org/10.1016/j.neurobiolaging.2013.07.003

Monti, G., & Meletti, S. (2015). Emotion recognition in temporal lobe epilepsy: A systematic review. *Neuroscience and Biobehavioral Reviews*, *55*, 280–293. https://doi.org/10.1016/j.neubiorev.2015.05.009

Niso, G., Carrasco, S., Gudín, M., Maestú, F., Del-Pozo, F., & Pereda, E. (2015). What graph theory actually tells us about resting state interictal MEG epileptic activity. *Neuroimage Clinical*, *8*, 503–515. https://doi.org/10.1016/j.nicl.2015.05.008

Ofer, I., LeRose, C., Mast, H., LeVan, P., Metternich, B., Egger, K., Urbach, H., Schulze-Bonhage, A., & Wagner, K. (2019). Association between seizure freedom and default mode network reorganization in patients with unilateral temporal lobe epilepsy. *Epilepsy & Behavior*, *90*, 238–246. https://doi.org/10.1016/j.yebeh.2018.10.025

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.-M. (2011). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational Intelligence and Neuroscience*, *2011*, 156869. https://doi.org/10.1155/2011/156869

Oyegbile, T. O., Dow, C., Jones, J., Bell, B., Rutecki, P., Sheth, R., Seidenberg, M., & Hermann, B. P. (2004). The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology*, *62*, 1736–1742. https://doi.org/10.1212/01.wnl.0000125186.04867.34

Papo, D., Zanin, M., Martínez, J. H., & Buldú, J. M. (2016). Beware of the small-world neuroscientist! *Frontiers in Human Neuroscience*, *10*, 96. https://doi.org/10.3389/fnhum.2016.00096

Papo, D., Zanin, M., Pineda-Pardo, J. A., Boccaletti, S., & Buldú, J. M. (2014). Functional brain networks: Great expectations, hard times and the big leap forward. *Philosophical Transactions of the Royal Society of London Series B, Biological Sciences*, *369*, 1–14. https://doi.org/10.1098/rstb.2013.0525

Pion-Tonachini, L., Kreutz-Delgado, K., & Makeig, S. (2019). ICLabel: An automated electroencephalographic independent component classifier, dataset, and website. *Neuroimage*, *198*, 181–197. https://doi.org/10.1016/j.neuroimage.2019.05.026

Popov, T., Miller, G. A., Rockstroh, B., & Weisz, N. (2013). Modulation of α power and functional connectivity during facial affect recognition. *Journal of Neuroscience*, *33*, 6018–6026. https://doi.org/10.1523/JNEUROSCI.2763-12.2013

Popov, T., Steffen, A., Weisz, N., Miller, G. A., & Rockstroh, B. (2012). Cross-frequency dynamics of neuromagnetic oscillatory activity: Two mechanisms of emotion regulation. *Psychophysiology*, *49*, 1545–1557. https://doi.org/10.1111/j.1469-8986.2012.01484.x

Quraan, M. A., McCormick, C., Cohn, M., Valiante, T. A., & McAndrews, M. P. (2013). Altered resting state brain dynamics in temporal lobe epilepsy can be observed in spectral power, functional connectivity and graph theory metrics. *PLoS ONE*, *8*, e68609. https://doi.org/10.1371/journal.pone.0068609

Raghavachari, S., Lisman, J. E., Tully, M., Madsen, J. R., Bromfield, E. B., & Kahana, M. J. (2006). Theta oscillations in human cortex during a working-memory task: Evidence for local generators. *Journal of Neurophysiology*, *95*, 1630–1638. https://doi.org/10.1152/jn.00409.2005

Rosenblum, M. G., Pikovsky, A. S., & Kurths, J. (1996). Phase synchronization of chaotic oscillators. *Physical Review Letters*, *76*, 1804–1807. https://doi.org/10.1103/PhysRevLett.76.1804

Rossini, P. M., Di Iorio, R., Bentivoglio, M., Bertini, G., Ferreri, F., Gerloff, C., Ilmoniemi, R. J., Miraglia, F., Nitsche, M. A., Pestilli, F., Rosanova, M., Shirota, Y., Tesoriero, C., Ugawa, Y., Vecchio, F., Ziemann, U., & Hallett, M. (2019). Methods for analysis of brain connectivity: An IFCN-sponsored review. *Clinical Neurophysiology*, *130*, 1833–1858. https://doi.org/10.1016/j.clinph.2019.06.006

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *Neuroimage*, *52*, 1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003

Rubinov, M., & Sporns, O. (2011). Weight-conserving characterization of complex functional brain networks. *Neuroimage*, *56*, 2068–2079. https://doi.org/10.1016/j.neuroimage.2011.03.069

Sauseng, P., Klimesch, W., Heise, K. F., Gruber, W. R., Holz, E., Karim, A. A., Glennon, M., Gerloff, C., Birbaumer, N., & Hummel, F. C. (2009). Brain oscillatory substrates of visual short-term memory capacity. *Current Biology*, *19*, 1846–1852. https://doi.org/10.1016/j.cub.2009.08.062

Schmidt, D., & Schachter, S. C. (2014). Drug treatment of epilepsy in adults. *BMJ*, *348*, g254. https://doi.org/10.1136/bmj.g254

Schoffelen, J.-M., & Gross, J. (2009). Source connectivity analysis with MEG and EEG. *Human Brain Mapping*, *30*, 1857–1865. https://doi.org/10.1002/hbm.20745

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*, *27*, 2349–2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Sen, A., Capelli, V., & Husain, M. (2018). Cognition and dementia in older patients with epilepsy. *Brain*, *141*, 1592–1608. https://doi.org/10.1093/brain/awy022

Shine, J. M., Breakspear, M., Bell, P. T., Ehgoetz Martens, K. A., Shine, R., Koyejo, O., Sporns, O., & Poldrack, R. A. (2019). Human cognition involves the dynamic integration of neural activity and neuromodulatory systems. *Nature Neuroscience*, *22*, 289–296. https://doi.org/10.1038/s41593-018-0312-0

Sørensen, A. T., & Kokaia, M. (2013). Novel approaches to epilepsy treatment. *Epilepsia*, *54*, 1–10. https://doi.org/10.1111/epi.12000

Stam, C. J. (2014). Modern network science of neurological disorders. *Nature Reviews Neuroscience*, *15*, 683–695. https://doi.org/10.1038/nrn3801

Stam, C. J., Tewarie, P., Van Dellen, E., van Straaten, E. C. W., Hillebrand, A., & Van Mieghem, P. (2014). The trees and the forest: Characterization of complex brain networks with minimum spanning trees. *International Journal of Psychophysiology*, *92*, 129–138. https://doi.org/10.1016/j.ijpsycho.2014.04.001

Stefan, H., & Lopes da Silva, F. H. (2013). Epileptic neuronal networks: Methods of identification and clinical relevance. *Front Neurol*, *4*, 8. https://doi.org/10.3389/fneur.2013.00008

Tailby, C., Kowalczyk, M. A., & Jackson, G. D. (2018). Cognitive impairment in epilepsy: The role of reduced network flexibility. *Annals of Clinical and Translational Neurology*, *5*, 29–40. https://doi.org/10.1002/acn3.503

Taylor, J., Kolamunnage-Dona, R., Marson, A. G., Smith, P. E. M., Aldenkamp, A. P., Baker, G. A., & SANAD Study Group. (2010). Patients with epilepsy: Cognitively compromised before the start of antiepileptic drug treatment? *Epilepsia*, *51*, 48–56. https://doi.org/10.1111/j.1528-1167.2009.02195.x

Tewarie, P., van Dellen, E., Hillebrand, A., & Stam, C. J. (2015). The minimum spanning tree: An unbiased method for brain network analysis. *Neuroimage*, *104*, 177–188. https://doi.org/10.1016/j.neuroimage.2014.10.015

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., & Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*, *15*, 273–289. https://doi.org/10.1006/nimg.2001.0978

Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction. *Nature Reviews Neuroscience*, *16*, 55–61. https://doi.org/10.1038/nrn3857

Uddin, L. Q., Yeo, B. T. T., & Spreng, R. N. (2019). Towards a universal taxonomy of macro-scale functional human brain networks. *Brain Topography*, *32*, 926–942. https://doi.org/10.1007/s10548-019-00744-6

Uhlhaas, P. J., & Singer, W. (2006). Neural synchrony in brain disorders: Relevance for cognitive dysfunctions and pathophysiology. *Neuron*, *52*, 155–168. https://doi.org/10.1016/j.neuron.2006.09.020

Ung, H., Cazares, C., Nanivadekar, A., Kini, L., Wagenaar, J., Becker, D., Krieger, A., Lucas, T., Litt, B., & Davis, K. A. (2017). Interictal epileptiform activity outside the seizure onset zone impacts cognition. *Brain*, *140*, 2157–2168. https://doi.org/10.1093/awx178

van Dellen, E., de Waal, H., van der Flier, W. M., Lemstra, A. W., Slooter, A. J. C., Smits, L. L., van Straaten, E. C. W., Stam, C. J., & Scheltens, P. (2015). Loss of EEG network efficiency is related to cognitive impairment in dementia with lewy bodies. *Movement Disorders*, *30*, 1785–1793. https://doi.org/10.1002/mds.26309

van Dellen, E., Douw, L., Baayen, J. C., Heimans, J. J., Ponten, S. C., Vandertop, W. P., Velis, D. N., Stam, C. J., & Reijneveld, J. C. (2009). Long-term effects of temporal lobe epilepsy on local neural networks: A graph theoretical analysis of corticography recordings. *PLoS ONE*, *4*, e8081. https://doi.org/10.1371/journal.pone.0008081

van den Heuvel, M. P., de Lange, S. C., Zalesky, A., Seguin, C., Yeo, B. T. T., & Schmidt, R. (2017). Proportional thresholding in resting-state fMRI functional connectivity networks and consequences for patient-control connectome studies: Issues and recommendations. *Neuroimage*, *152*, 437–449. https://doi.org/10.1016/j.neuroimage.2017.02.005

van Diessen, E., Numan, T., van Dellen, E., van der Kooi, A. W., Boersma, M., Hofman, D., van Lutterveld, R., van Dijk, B. W., van Straaten, E. C. W., Hillebrand, A., & Stam, C. J. (2015). Opportunities and methodological challenges in EEG and MEG resting state functional brain network research. *Clinical Neurophysiology*, *126*, 1468–1481. https://doi.org/10.1016/j.clinph.2014.11.018

van Mierlo, P., Höller, Y., Focke, N. K., & Vulliemoz, S. (2019). Network perspectives on epilepsy using EEG/MEG source connectivity. *Frontiers in Neurology*, *10*, 721. https://doi.org/10.3389/fneur.2019.00721

Van Veen, B. D., van Drongelen, W., Yuchtman, M., & Suzuki, A. (1997). Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Transactions on Biomedical Engineering*, *44*, 867–880. https://doi.org/10.1109/10.623056

van Veenendaal, T. M., IJff, D. M., Aldenkamp, A. P., Lazeron, R. H. C., Hofman, P. A. M., de Louw, A. J. A., Backes, W. H., & Jansen, J. F. A. (2017). Chronic antiepileptic drug use and functional network efficiency: A functional magnetic resonance imaging study. *World Journal of Radiology*, *9*, 287–294. https://doi.org/10.4329/wjr.v9.i6.287

van Wijk, B.C.M., Stam, C.J., & Daffertshofer, A. (2010). Comparing brain networks of different size and connectivity density using graph theory. *PLoS ONE*, *5*, e13701. https://doi.org/10.1371/journal.pone.0013701

Vecchio, F., Miraglia, F., Curcio, G., Della Marca, G., Vollono, C., Mazzucchi, E., Bramanti, P., & Rossini, P. M. (2015). Cortical connectivity in fronto-temporal focal epilepsy from EEG analysis: A study via graph theory. *Clinical Neurophysiology*, *126*, 1108–1116. https://doi.org/10.1016/j.clinph.2014.09.019

Verzeano, M., & Negishi, K. (1960). Neuronal activity in cortical and thalamic networks. *Journal of General Physiology*, *43*(6), 177–195. https://doi.org/10.1085/jgp.43.6.177

Vlooswijk, M. C. G., Vaessen, M. J., Jansen, J. F. A., de Krom, M. C. F. T. M., Majoie, H. J. M., Hofman, P. A. M., Aldenkamp, A. P., & Backes, W. H. (2011). Loss of network efficiency associated with cognitive decline in chronic epilepsy. *Neurology*, *77*, 938–944. https://doi.org/10.1212/WNL.0b013e31822cfc2f

Vorwerk, J., Cho, J.-H., Rampp, S., Hamer, H., Knösche, T. R., & Wolters, C. H. (2014). A guideline for head volume conductor modeling in EEG and MEG. *Neuroimage*, *100*, 590–607. https://doi.org/10.1016/j.neuroimage.2014.06.040

Wang, Y., Risacher, S. L., West, J. D., McDonald, B. C., Magee, T. R., Farlow, M. R., Gao, S., O'Neill, D. P., & Saykin, A. J. (2013). Altered default mode network connectivity in older adults with cognitive complaints and amnestic mild cognitive impairment. *Journal of Alzheimer's Disease*, *35*, 751–760. https://doi.org/10.3233/JAD-130080

Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of "small-world" networks. *Nature*, *393*, 440–442. https://doi.org/10.1038/30918

Wechsler, D., Coalson, D. L., & Raiford, S. E. (2008). *WAIS-IV technical and interpretive manual*. Pearson.

Witt, J.-A., & Helmstaedter, C. (2017). Cognition in epilepsy: Current clinical issues of interest. *Current Opinion in Neurology*, *30*, 174–179. https://doi.org/10.1097/WCO.0000000000000430

Yeo, B. T. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*, 1125–1165. https://doi.org/10.1152/jn.00338.2011

Zhou, X., Zhang, Z., Liu, J., Qin, L., & Zheng, J. (2019). Aberrant topological organization of the default mode network in temporal lobe epilepsy revealed by graph-theoretical analysis. *Neuroscience Letters*, *708*, 134351. https://doi.org/10.1016/j.neulet.2019.134351

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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