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## Sink into the epileptogenic zone: findings from directed SIEG functional connectivity decomposition

This scientific commentary refers to ‘The interictal suppression hypothesis is the dominant differentiator of seizure onset zones in focal epilepsy’ by Doss *et al.* (<https://doi.org/10.1093/brain/awae189>).

For patients with medically refractory focal epilepsies, epilepsy surgery represents the most effective treatment option. Many of these patients require intracranial EEG investigation to delineate the epileptogenic zone (EZ, the zone primarily responsible for generating seizures) and its relationship with eloquent cortices. Advances in intracranial EEG investigation, most notably in signal analysis and quantification, have led to the discovery that the EZ often includes multiple brain regions with simultaneous discharges during both interictal and ictal periods.<sup>1</sup> This has led to a paradigm shift, with the EZ now thought of as a network of interconnected regions rather than as a single focus from which epileptic activity spreads to surrounding areas.<sup>1</sup>

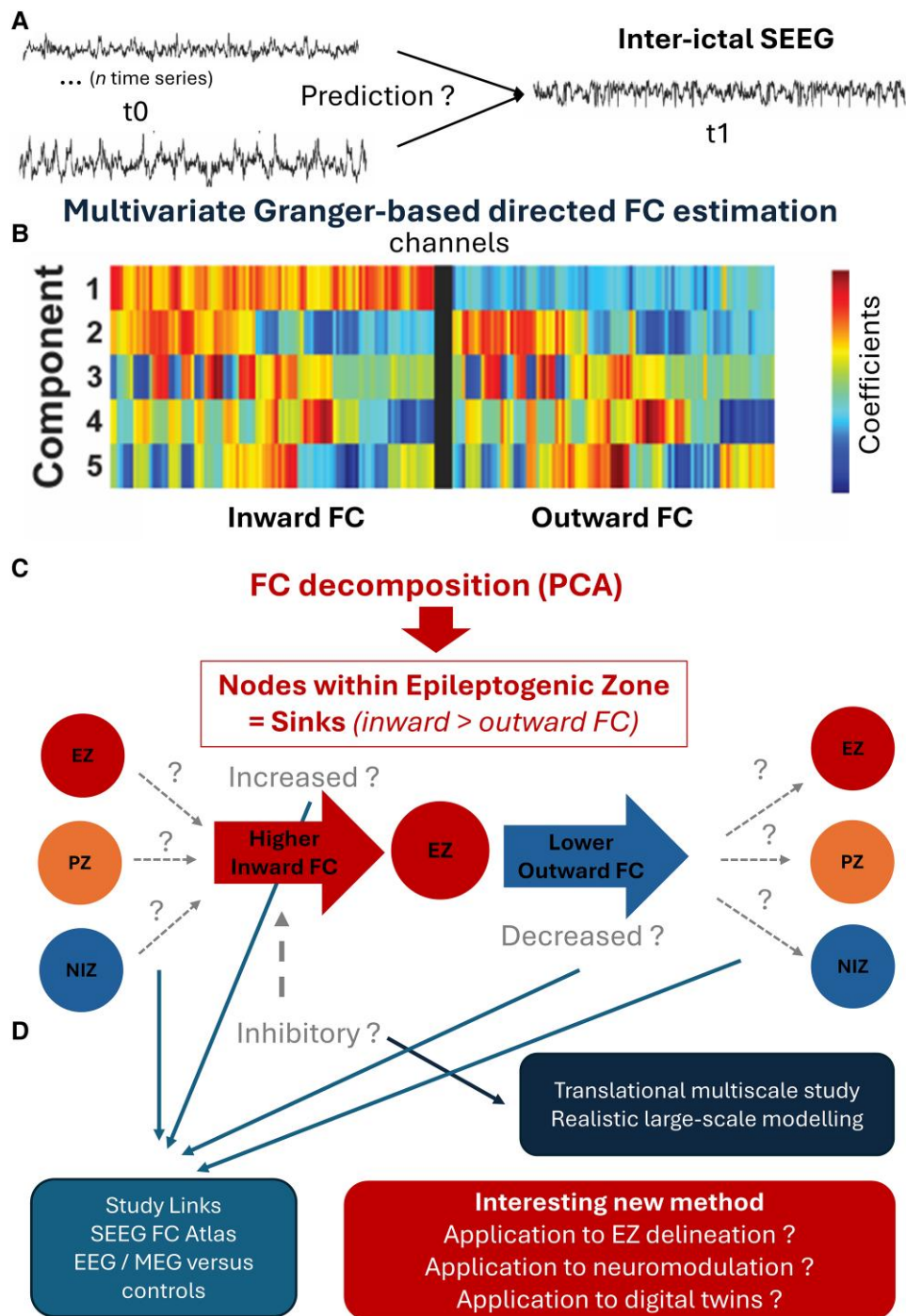
In addition, numerous methods have been developed to assess the synchronization of brain electrophysiological signals, in order to evaluate cerebral functional connectivity. Altered functional connectivity during the interictal period has been linked to epileptogenicity.<sup>2</sup> It is now well established that, in various forms of focal epilepsy, regions within the EZ are more highly interconnected than regions outside.<sup>2</sup> Furthermore, zones where seizures initiate show greater functional connectivity with seizure propagation zones than with zones not involved in seizures.<sup>2</sup> Patterns of interictal functional connectivity also correlate with surgical outcomes: greater functional connectivity within the resected zone is associated with favourable outcomes, while greater functional connectivity outside the EZ is linked to unfavourable outcomes.<sup>2</sup> Assessing interictal functional connectivity has shown promise as a means of delineating the EZ.<sup>3</sup>

Progress in functional connectivity analysis has also led to the emergence of conceptual pathophysiological hypotheses. For instance, in multivariate and Granger-based assessments of functional connectivity (in which the history of multiple time series is used to predict the future of a time series of interest), methods like partial directed coherence (PDC) allow estimation of the directionality of functional connectivity and determination of whether one region leads another, controlling for indirect connections. By averaging all connections of a brain region (a node), it is possible to estimate whether that region behaves as a sender/source or receiver/sink within the network.

Interestingly, several studies have indicated that during the interictal period, the EZ acts predominantly as a sink, with greater inward functional connectivity than outward. This inward connectivity is stronger than that observed in regions outside the EZ, while the outward connectivity remains comparable.<sup>3–5</sup> Such directed functional connectivity has been shown to allow for better EZ determination than undirected functional connectivity.<sup>3</sup> However, it should be noted that this sink behaviour is not reproduced in all studies (for instance, studies using bivariate functional connectivity estimation and others on focal cortical dysplasia have suggested greater outward functional connectivity from the EZ<sup>2</sup>). Such divergence could stem from differences in the methods used, with multivariate analyses being mandatory to unravel such patterns, and/or from the impact of interictal epileptiform discharges (IEDs). Questions remain regarding the importance of these patterns within the overall functional connectivity and their consistency across patients, as previous studies were conducted at the group level. Furthermore, methods to extract the main patterns without prior assumptions are also needed. Doss and co-workers<sup>6</sup> begin to tackle these issues in a new study in *Brain*.

The authors assessed functional connectivity in 81 patients with various forms of epilepsy and locations of the EZ by performing multivariate analysis on the frequency domain (PDC) of stereo-EEG (SIEG) time series. From this directed functional connectivity analysis, they were able to estimate the relative strengths of outward and inward connections from each node (i.e. SIEG bipolar channel). The novelty of this study is the application of a data-driven (i.e. without a specific *a priori* hypothesis) decomposition technique, specifically principal component analysis (PCA), to the functional connectivity matrix to disentangle connectivity patterns (PCA components) that can be ranked in decreasing order in terms of the variance explained (Fig. 1). Notably, among the top five components, the authors found a component with high inward and low outward functional connectivity in all patients, which they termed the ‘interictal suppression hypothesis’ (ISH) component. This finding illustrates the consistency of functional connectivity patterns across patients, independent of the type of focal epilepsy. In ~80% of patients, the ISH component was ranked top, explaining the most variance in the data (~15%, PC 1 group), while in the other patients, it explained less variance (PC 2 group).

The authors then examined the spatial distribution of this ISH component, focusing on the relative participation of each node (i.e. the channel weight in the component). They found that nodes



**Figure 1** Overview of the study by Doss et al.<sup>6</sup> (A) From stereo-EEG (SEEG) interictal recordings (periods with and without spikes), Doss et al.<sup>6</sup> estimated multivariate directed functional connectivity (FC) by assessing how time series can predict the future of other time series using Granger-based squared partial directed coherence. (B) The authors decomposed their functional connectivity matrix into components using principal component analysis (PCA) with different weights for inward and outward functional connectivity for each channel. They consistently identified one component with high weights for inward and low weights for outward functional connectivity (Component 1). (C) The analysis of the channel weights within this component revealed that nodes within the epileptogenic zone (EZ) exhibit greater inward than outward functional connectivity compared to other zones. The authors hypothesize that this is due to increased surrounding inhibition toward the EZ. However, the source of this greater inward functional connectivity is unknown. (D) Further studies are needed: (i) to confirm that this stronger inward functional connectivity is truly due to increased functional connectivity from propagation (PZ) and non-involved zones (NIZ); (ii) to understand whether this inward functional connectivity is inhibitory; and (iii) to investigate the added value of this new method and findings in the diagnosis and treatment of focal medication-refractory epilepsies.

within the EZ were significantly over-represented in the ISH component compared to other regions, suggesting that the EZ has higher inward than outward functional connectivity. Information from

the PCA analysis allowed differentiation of the EZ from other zones in both patient groups, but particularly strongly in the PC 1 group. Although the main results were presented in the alpha band,

they remained robust across all sub-bands, confirming that the pattern is not frequency-specific.

Finally, the authors compared the clinical features of the two patient groups without finding any significant differences, particularly regarding surgical outcomes. However, there were differences in SEEG spatial sampling, with fewer non-involved zones sampled in the PC 2 group, potentially explaining the greater difficulty in capturing the ISH pattern in this subgroup. Unfortunately, it remains unclear whether identifying nodes belonging to the EZ from the ISH component is easier than identifying them from the raw functional connectivity matrix, as this has not been formally tested. Nonetheless, some of the results showed a larger difference between the EZ and other zones using functional connectivity reconstructed from the ISH component, suggesting that future studies addressing this question would be worthwhile.

Overall, this work reinforces the observation of higher outward and lower inward functional connectivity in the EZ, demonstrating that such patterns are common across patients and often represent the most significant pattern in the functional connectivity matrix. This finding has conceptual implications, shifting our view of the EZ from being a source of excitatory or disruptive information for other brain areas (a view derived from temporal dynamics seen during seizures and IED propagation; in this study, the effect of IEDs is unknown) to the EZ being a receiver or sink during interictal states.

Interestingly, previous studies have shown that this pattern can reverse during seizures, with the EZ becoming the leading region.<sup>4</sup> The authors conceptualize this observation as inhibitory information sent from the non-EZ to the EZ to prevent seizures (ISH), mirroring the concept of surrounding inhibition observed during seizures.<sup>7</sup> However, it cannot be directly inferred that higher inward connectivity towards the EZ is inhibitory, as functional connectivity analyses cannot distinguish between inhibitory and excitatory transmission. Translational studies correlating directed functional connectivity with microscopic evaluation of neurotransmission in neural circuits, and large scale computational realistic neural mass modelling<sup>8</sup> could resolve this issue. Furthermore, as the observations are at the node level, it remains unclear whether this increased inward functional connectivity originates from regions outside the EZ or from other areas within the EZ, as no specific studies on these connections have been conducted to date.

In addition, as intracranial EEG studies do not include healthy control groups, it is uncertain whether the observed increase in inward functional connectivity within the EZ reflects a true enhancement compared to normal physiological conditions; it could also represent a reduction in inward functional connectivity in regions outside the EZ, which would produce a similar imbalance of higher inward and lower outward functional connectivity in the EZ relative to the entire SEEG-sampled network. Notably, the only intracranial EEG studies that compared functional connectivity between patients with and without epilepsy showed a disconnection of the EZ from the rest of the brain; scalp EEG studies have demonstrated decreased outward functional connectivity from the EZ, and diffusion MRI studies have shown preserved structural connectivity within the EZ and decreased structural connectivity outside.<sup>2</sup> Future studies should look at the links between areas within and outside the EZ, and between these zones. Non-invasive EEG or magnetoencephalography studies could also evaluate whether the inward functional connectivity towards the EZ truly increases compared to healthy controls. Another strategy could involve comparing normative atlases of functional connectivity from non-pathological



intracranial EEG channels, although no such atlas for directed functional connectivity has yet been developed.

Studies at various scales are thus needed to confirm the ISH and the current work opens up several new research avenues. First, using PCA and other decomposition techniques on the functional connectivity matrix is promising for generalizing findings from group level to patient level and enabling data-driven analyses without prior assumptions. It would undoubtedly be worth developing this approach for studies in patients with neurological conditions. However, the clinical value of these new metrics in delineating the EZ remains to be assessed, particularly in comparison to other ictal and interictal markers. Given the plethora of metrics suggested for localizing the EZ, comprehensive analysis of various metrics to disentangle the added value of each one is crucial, as well as proper statistical testing considering the class imbalance between EZ/non-EZ.

Another exciting research direction is to estimate how neuromodulation changes the functional connectivity pattern according to outcomes. Previous work has shown that decreasing functional connectivity during stimulation periods is associated with favourable outcomes.<sup>9</sup> Investigating whether responders to neuromodulation exhibit a pattern of reinforced inward functional connectivity towards the EZ would be valuable. It may even be worth considering tailoring a patient's stimulation parameters to maximize this effect using non-invasive functional connectivity data.

Another growing field is the use of 'digital twins', namely *in silico* modelling of brain epileptic behaviour from patient data (usually using structural connectivity and ictal excitability markers).<sup>10</sup> Currently, these models do not include information on the direction of connectivity. Integrating patterns of directed functional connectivity into the models may be interesting for exploring their impact on performance in delineating the EZ or in defining the optimal treatment strategy (*in silico* resection or neuromodulation).

Last but not least, despite significant advances in intracranial EEG quantification and functional connectivity analyses, there remains a need to integrate such metrics into clinical practice in epilepsy surgery centres, so that patients may benefit from these developments. Easy-to-use metrics that can be rapidly computed in user-friendly open software, and clinicians fully trained in their application, are greatly needed.

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## Competing interests

The authors report no competing interests.

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