Biological Psychiatry: CNNI

Archival Report

Eigenvector Centrality Mapping Reveals Volatility of Functional Brain Dynamics in Anti-NMDA Receptor Encephalitis

Tim J. Hartung, Nina von Schwanenflug, Stephan Krohn, Tommy A.A. Broeders, Harald Prüss, Menno M. Schoonheim, and Carsten Finke

ABSTRACT

BACKGROUND: Anti-NMDA receptor encephalitis (NMDARE) causes long-lasting cognitive deficits associated with altered functional connectivity. Eigenvector centrality (EC) mapping represents a powerful new method for data-driven voxelwise and time-resolved estimation of network importance—beyond changes in classical static functional connectivity.

METHODS: To assess changes in functional brain network organization, we applied EC mapping in 73 patients with NMDARE and 73 matched healthy control participants. Areas with significant group differences were further investigated using 1) spatial clustering analyses, 2) time series correlation to assess synchronicity between the hippocampus and cortical brain regions, and 3) correlation with cognitive and clinical parameters.

RESULTS: Dynamic, time-resolved EC showed significantly higher variability in 13 cortical areas (familywise error $p < .05$) in patients with NMDARE compared with healthy control participants. Areas with dynamic EC group differences were spatially organized in centrality clusters resembling resting-state networks. Importantly, variability of dynamic EC in the frontotemporal cluster was associated with impaired verbal episodic memory in patients ($r = -0.25$, $p = .037$). EC synchronicity between the hippocampus and the medial prefrontal cortex was reduced in patients compared with healthy control participants (familywise error $p < .05$, $t_{max} = 3.76$) and associated with verbal episodic memory in patients ($r = 0.28$, $p = .019$). Static EC analyses showed group differences in only one brain region (left intracalcarine cortex).

CONCLUSIONS: Widespread changes in network dynamics and reduced hippocampal-medial prefrontal synchronicity were associated with verbal episodic memory deficits and may thus represent a functional neural correlate of cognitive dysfunction in NMDARE. Importantly, dynamic EC detected substantially more network alterations than traditional static approaches, highlighting the potential of this method to explain long-term deficits in NMDARE.

https://doi.org/10.1016/j.bpsc.2024.07.021

Anti-NMDA receptor encephalitis (NMDARE) is a severe neuroimmunological disease (1) that frequently leads to long-term cognitive deficits (2,3). While clinical magnetic resonance imaging (MRI) typically shows no or only mild structural abnormalities (4), NMDA receptor autoantibodies have been shown to induce extensive functional network changes. Thus, early neuroimaging studies have applied resting-state functional MRI to investigate the functional connectivity between blood oxygenation level–dependent (BOLD) signals of individual brain regions. These studies identified functional connectivity changes in most resting-state networks and found that hippocampal connectivity was particularly impaired, with strong associations to cognitive impairment and disease severity (5,6).

These early findings rested on the classical approach to estimate functional connectivity across the brain, in which pairwise BOLD time series correlation between any two brain regions is aggregated into a single connectivity matrix. This approach yields a static account of functional connectivity, in that regional BOLD activity is correlated across the entire resting-state scan of several minutes (yielding a single correlation coefficient between any 2 brain regions). This static approach has been applied in many neurological and psychiatric disorders, including NMDARE, and identified distinct patterns of functional connectivity alterations associated with major clinical symptoms (7). However, recent methodological advances now suggest that key aspects of functional brain network organization and dysfunction may not be adequately captured by purely static accounts of functional connectivity (8).

First, accumulating evidence shows that resting-state functional connectivity patterns are not stable over time, but rather fluctuate dynamically (9). Hence, static functional connectivity metrics disregard temporal information on the different connectivity patterns that emerge transiently during the resting-state recording (10). Second, recent research has

suggested that static functional connectivity may be driven by only a few time points of high interregional cofluctuation (11), indicating that static functional connectivity may only reflect a small proportion of all connectivity patterns that emerge over time. Third, resting-state functional connectivity is organized along a hierarchical spatial topology in which some regions are more important—or central—to the network than others. However, a single brain region may be involved in different functional systems at different times (12–14), requiring a time-resolved—or dynamic—analysis of centrality within the network. In this regard, eigenvector centrality (EC) mapping represents a novel and computationally efficient method that provides such time-resolved estimation of network centrality (15,16). EC refers to a graph-theoretical measure that quantifies the importance of a node in the network as its connection strength to other nodes that are themselves strongly connected.

Improved methods are urgently needed to better understand brain dysfunction in NMDARE. The lack of solid biomarkers for brain repair after encephalitis impairs decisions regarding the continuation of immunotherapy, estimation of prognosis, and repeated unbiased measures of recovery. However, only very few studies have begun to unravel the temporal patterns of functional connectivity in NMDARE. One recent study on resting-state dynamics found characteristic functional connectivity alterations within connectivity states (i.e., transient connectivity patterns) and increased temporal dynamics (17). Remarkably, these alterations were not detectable in conventional static functional connectivity analyses. Furthermore, this study showed increased volatility of resting-state dynamics that were correlated with disease severity and psychiatric symptoms, highlighting that altered resting-state dynamics may carry meaningful clinical information about the disease. However, this and other previous studies were based on functional connectivity differences within predefined regions (17). Importantly, such predefined anatomical regions may not necessarily match the components of functional networks (10), or the involvement of a particular voxel may itself change dynamically over time. EC mapping overcomes this issue by allowing for a fine-grained spatial resolution on the voxel level—without the need to predefine particular regions.

Against this background, the current study aims to investigate dynamic changes in network centrality in patients with NMDARE in order to elucidate ongoing brain dysfunction in this disease. To this end, we 1) assessed static and dynamic functional network centrality patterns in patients with NMDARE compared with matched healthy control participants, 2) investigated whether altered centrality and its dynamic changes were associated with cognitive impairment, and 3) evaluated seed-to-whole-brain centrality dynamics for the hippocampus as a region whose connectivity is particularly affected by NMDARE.

METHODS AND MATERIALS

Participants

We included 73 patients with NMDARE as part of a prospective observational cohort study at Charité – Universitätsmedizin Berlin. All patients had a confirmed NMDARE diagnosis according to current criteria, including the detection of IgG NMDA receptor antibodies in cerebrospinal fluid (CSF) (18). Patients' mean time since diagnosis was 2.8 years, and most patients were severely affected during the acute disease stage (median modified Rankin Scale [mRS] 4) but had improved clinically by the time of MRI (median mRS 1). Patients most frequently showed deficits in verbal episodic memory (Table 1). Healthy control participants (n = 73) were recruited as part of several neuroimaging studies and matched to patients by sex (exact match) and age (t = 0.31, p = .755) using the MatchIt package in R software (version 4.3.2; R Foundation for Statistical Computing).

Ethics

All patients and healthy control participants provided written informed consent according to the Declaration of Helsinki, and the study was approved by the Charité – Universitätsmedizin Berlin ethics committee (ref. no. EA4/011/19). Some of the study participants were included in previous studies (5,6,17,19).

Cognitive and Clinical Measures

Cognitive impairment was assessed in patients in the following domains known to be impacted by NMDARE: working memory (digit span backward), verbal episodic memory (Auditory

Table 1. Sample Characteristics

Characteristic	Patients With NMDARE, n = 73	Healthy Control Participants, n = 73
Sex, n (%)		
Female	62 (85%)	62 (85%)
Male	11 (15%)	11 (15%)
Age, Years, Mean (SD)	28.6 (8.7)	29.0 (8.5)
Education, Years, Mean (SD)	13.3 (2.3)	–
Time Since Diagnosis, Years, Mean (SD)	2.8 (2.4)	–
Peak mRS, n (%)		
2	9 (13%)	–
3	16 (24%)	–
4	14 (21%)	–
5	28 (42%)	–
mRS at rs-fMRI, n (%)		
0	18 (25%)	–
1	31 (43%)	–
2	19 (26%)	–
3	3 (4%)	–
4	1 (1%)	–
Cognitive Deficits by Domain		
Digit span backward	13 (18%)	–
AVLT delayed recall	16 (23%)	–
ROCF delayed recall	12 (17%)	–
Alertness tonic	6 (9%)	–
Go/no go	9 (15%)	–

AVLT, Auditory Verbal Learning Test; mRS, modified Rankin Scale; NMDARE, anti-NMDA receptor encephalitis; ROCF, Rey-Osterrieth Complex Figure; rs-fMRI, resting-state functional magnetic resonance imaging.

Verbal Learning Test [AVLT], delayed recall), visuospatial episodic memory (Rey-Osterrieth Complex Figure test, delayed recall), alertness (Test of Attentional Performance tonic alertness, median reaction time), and executive function (Test of Attentional Performance go/no go, median reaction time). In accordance with the test manual of the AVLT, participants were given a break of 25 minutes in which they were asked not to practice the 15 words. After the break, they were asked to recall as many of the words as possible to determine the delayed recall score. A patient was considered to have a cognitive deficit in a given domain if the test score representing this domain was 1.5 SD below the mean from normative data of the patient's age group. In addition, the mRS was used to assess disability ranging from 0 (no symptoms) to 5 (bedbound) both at peak severity and on the day of the MRI scan.

MRI Acquisition

Structural and functional MRI data of all patients and healthy control participants were acquired at the Berlin Center for Advanced Neuroimaging at Charité – Universitätsmedizin Berlin on a 3T Tim Trio scanner (Siemens) using a 20-channel head coil. The protocol included a high-resolution T1-weighted structural magnetization-prepared rapid acquisition gradient-echo sequence (1 mm isotropic voxels) and a resting-state echo-planar imaging sequence (repetition time = 2.25 seconds, echo time = 30 ms, 260 volumes, 3.4 mm isotropic voxels).

MRI Preprocessing

We used the ICA-AROMA+2Phys-Pipeline for preprocessing (20), which included discarding the first 4 of the scan, slice time correction, realignment to the first volume, spatial normalization to Montreal Neurological Institute space (voxel size 2 × 2 × 2 mm), brain extraction, detrending, intensity normalization, motion correction via ICA-AROMA, denoising using motion parameters, mean white matter and CSF time series regression, bandpass filtering (retaining 0.008–0.08 Hz), and spatial smoothing with a 6-mm full width at half maximum smoothing kernel. We then applied an Montreal Neurological Institute space gray matter mask excluding the cerebellum and the brainstem in line with previous studies (21).

Statistical Procedures

EC Mapping. EC represents a graph-theoretic measure that attributes a value of importance to each node in a network. In EC mapping for network neuroimaging, nodes correspond to voxels and have high EC if they are strongly connected (i.e., their BOLD signals are highly correlated) to many other voxels that are themselves highly connected (15). EC mapping is sensitive to relatively subtle changes in connectivity (22) and has revealed network alterations associated with cognitive impairment and disability in multiple sclerosis (MS) (21,23–25) and biomarkers of Alzheimer's disease (26,27). An illustration of the current methodology, including a comparison with our 2 previous resting-state functional MRI studies in patients with NMDARE, is shown in Figure S1.

Voxelwise EC maps were calculated using the fastECM toolbox (https://github.com/amwink/bias) (16) in MATLAB (version R2019b; The MathWorks, Inc.). Static EC was computed using the whole resting-state functional time series for each voxel (across 255 volumes). Dynamic EC was assessed using a sliding window approach with a window length of 20 volumes (45 seconds) and a shift length of 1 volume, resulting in 236 windows per resting-state recording. EC maps were computed for each time window and concatenated to create a 4-dimensional dynamic centrality map. Dynamic variability of centrality was computed as the standard deviation across time of each concatenated 4-dimensional dynamic centrality map—analogous to a study by Eijlers *et al.* (23). Thus, this approach resulted in voxelwise maps of static centrality as well as dynamic variability of centrality, which were subjected to the following further analyses.

Group Comparisons. We first assessed differences between patients with NMDARE and control participants in static and time-resolved EC using a voxelwise approach. Group differences in static EC maps and in the variability (standard deviation) of time-resolved EC maps were assessed using FSL randomise (version 6.0.4; https://fsl.fmrib.ox.ac.uk) for independent samples with threshold-free cluster enhancement and 5000 permutations.

Hierarchical Clustering of Eigenvector Dynamics. Next, we explored spatial patterns of group differences using a clustering approach. Voxels with significant group differences were grouped according to the threshold-free cluster enhancement method, yielding 13 voxel clusters with more than 50 voxels each. To label these voxel clusters in an anatomically meaningful way, we assigned an atlas-based anatomical label to each cluster using FSL atlas query. For each of the 13 voxel clusters, we extracted the mean window-wise EC values in each participant. The resulting time series were then spatially grouped via hierarchical clustering, in which the similarity of EC fluctuations over time was quantified by the Euclidean distance (*pdist* function in MATLAB).

Associations between dynamic EC and clinical or cognitive outcomes were computed for each of the 4 clusters: We first extracted the average standard deviation across all voxels in a cluster from the dynamic EC maps and then computed Kendall's tau correlation with mRS at the time of scan and the product-moment correlation (r) with each cognitive test score.

Hippocampal Synchronicity of EC

Because previous studies in patients with NMDARE found particularly strong changes in functional connectivity for the hippocampus (5,6,17), we studied seed-to-whole-brain associations in dynamic centrality to investigate the functional dynamics of the hippocampus in more detail. To this end, a sphere was created for the left and right hippocampus (diameter: 5 mm) as the seed region of interest. To avoid partial volume effects with CSF, the spheres were subsequently masked with the gray matter mask used for the computation of the EC maps (see Table S1 for coordinates and Figure S2 for seed masks). For all voxels in each seed, we extracted the mean window-wise dynamic EC values for each participant.

The synchronicity of centrality dynamics between regions was assessed as the product-moment correlation between the EC time series of the seed and every other gray matter voxel in the brain. The result was a brain map of seed-to-whole-brain

synchronicity of EC for each participant. These represent the synchronicity in centrality between the region of interest and the rest of the brain, which may be disrupted in neurological diseases that functionally or structurally affect the respective region of interest.

To assess whether EC synchronicity is altered in patients with NMDARE, we compared seed-to-whole-brain EC synchronicity maps between patients and control participants using FSL randomise for independent samples with threshold-free cluster enhancement and 5000 permutations. For voxels with significant group differences, the association between EC synchronicity and each cognitive test was assessed using product-moment correlations.

Missing Values. There were <5% missing values for any of the analyzed variables. Missing values were removed pairwise for correlations.

RESULTS

EC Group Differences Between Patients With NMDARE and Healthy Control Participants

Significantly higher variability (i.e., standard deviation) of dynamic EC was observed in patients compared with control participants in the bilateral parahippocampal gyrus, bilateral precuneus, bilateral superior frontal gyrus, right thalamus, right frontal pole, inferior lateral occipital cortex, right temporo-occipital fusiform cortex, right superior lateral occipital cortex, left temporo-occipital fusiform cortex, bilateral posterior cingulate gyrus, left occipital pole, bilateral posterior temporal fusiform cortex, and left superior lateral occipital cortex (familywise error p [p_{FWE}] $< .05$) (Figure 1A). These regions were further investigated in the hierarchical clustering analysis. In static EC analyses, patients with NMDARE showed higher EC in the left intracalcarine cortex compared with healthy control participants ($p_{FWE} < .05$) (Figure 1B).

Hierarchical Clustering of Eigenvector Dynamics

Areas with significant group differences in EC dynamics hierarchically clustered into 4 spatial clusters based on the similarity of EC fluctuations over time. These centrality clusters resembled components of the salience, precuneus/default mode, frontotemporal, and frontal resting-state networks and were labeled accordingly (Figure 2A). In patients with NMDARE, the variability (i.e., standard deviation over time) of dynamic EC in the temporal cluster was negatively correlated with verbal episodic memory as assessed with the delayed recall task of the AVLT ($r = -0.25$, $p = .037$) (Figure 2B). There was no significant correlation between the other clusters and cognitive domains (Table S2).

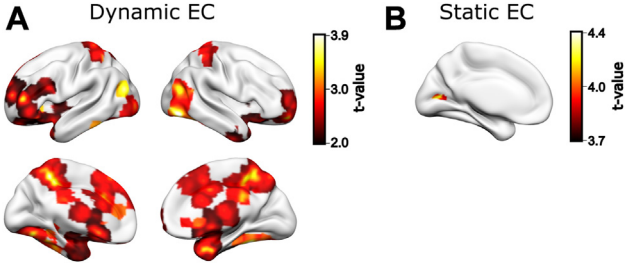

Figure 1. Voxels with **(A)** significantly higher variability in dynamic eigenvector centrality (EC) and **(B)** significantly higher static EC in patients with anti-NMDA receptor encephalitis compared with healthy control participants (familywise error $p < .05$).

Hippocampal Synchronicity of EC

Time-resolved EC of the right hippocampus was significantly less correlated with the EC time series of the left medial prefrontal cortex (mPFC) in patients, indicating reduced EC synchronicity ($p_{FWE} < .05$) (Figure 3A). In patients with NMDARE, reduced synchronicity between the right hippocampus and the left mPFC was significantly associated with impaired verbal episodic memory, as assessed with the delayed recall task of the AVLT ($r = 0.28$, $p = .019$) (Figure 3B). There was no significant correlation between hippocampus-mPFC synchronicity and the other cognitive tests (Table S3).

DISCUSSION

In this prospective functional neuroimaging study, we found that NMDARE is characterized by widespread alterations in brain network centrality dynamics compared with healthy control participants. Brain areas with significantly increased centrality dynamics in NMDARE clustered in spatial patterns consistent with established functional brain networks. In addition, we observed a desynchronization of brain network centrality between the hippocampus and the medial mPFC in patients. Importantly, both EC variability in a spatial cluster of frontotemporal cortical areas and hippocampal-prefrontal desynchronization were associated with deficits in verbal episodic memory. These findings show that dynamic EC mapping can reveal clinically meaningful changes in network organization in NMDARE—beyond those detectable with conventional static functional connectivity analyses.

Recent studies have used a variety of analytical techniques to assess static and dynamic functional connectivity in NDMARE and found disruptions in brain networks to be associated with cognitive deficits (5,6,17,19,28). Dynamic analyses revealed that patients with NMDARE differ from healthy control participants not only in functional connectivity, but also in the dynamic fluctuations between distinct brain connectivity states (17). Importantly, the dynamic approach showed stronger correlations with clinical and cognitive outcomes and was better at distinguishing patients from control participants than the traditional static analysis (17).

However, in the hierarchical spatial topology of a network, some regions are more important—or central—than others and a single brain region may be involved in different functional systems at different times (12–14). Therefore, a time-resolved, dynamic analysis of centrality within the network may be better suited to capture the dynamics of functional network organization in both health and disease (16). Dynamic EC mapping provides such a measure and has been successfully applied in MS (23). Therein, changes in EC dynamics in several resting-state networks as well as loss of interplay between these networks was identified as a substrate of impaired cognitive functioning in MS, providing new insights into the impact of the disease on brain function.

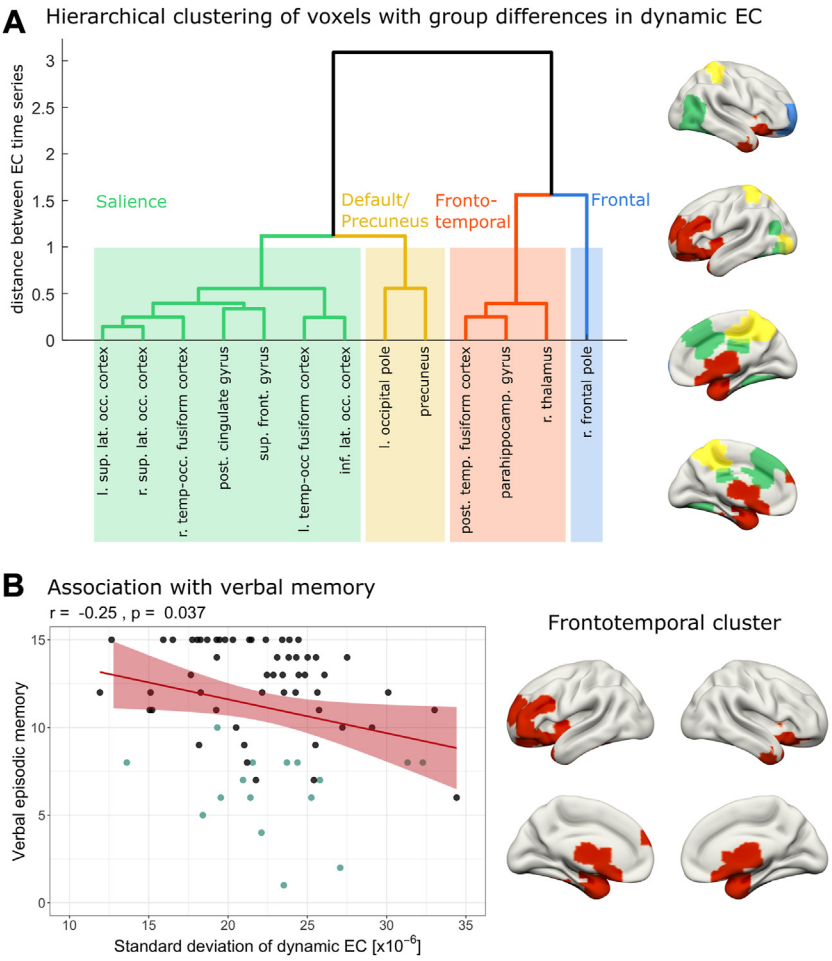

Figure 2. **(A)** Eigenvector centrality (EC) time series–based spatial hierarchical clustering of areas with significant group differences in EC dynamics (left). Surface mapping of the grouped clusters into a salience (green), precuneus (yellow), frontotemporal (red), and frontal (blue) centrality cluster (right). **(B)** Correlation between variability of EC dynamics in the frontotemporal cluster and verbal episodic memory as assessed with the Auditory Verbal Learning Test (delayed recall of X out of 15 words) in patients with anti-NMDA receptor encephalitis. The trend line slope represents the univariate linear regression coefficient (shaded area: 95% confidence interval). Patients with impairment in verbal episodic memory ($z < -1.5$) are colored in green. front, frontal; inf, inferior; l, left; lat, lateral; occ, occipital; parahippocamp, parrahippocampal; post, posterior; r, right; sup, superior; temp, temporal.

In NMDARE, autoantibodies directly alter receptor function and density across the whole brain but particularly so in regions with a high density of NMDA receptors such as the hippocampus, resulting in severe impairment of synaptic plasticity and network function (1). However, it has been difficult to assess such changes and their correlations to clinical

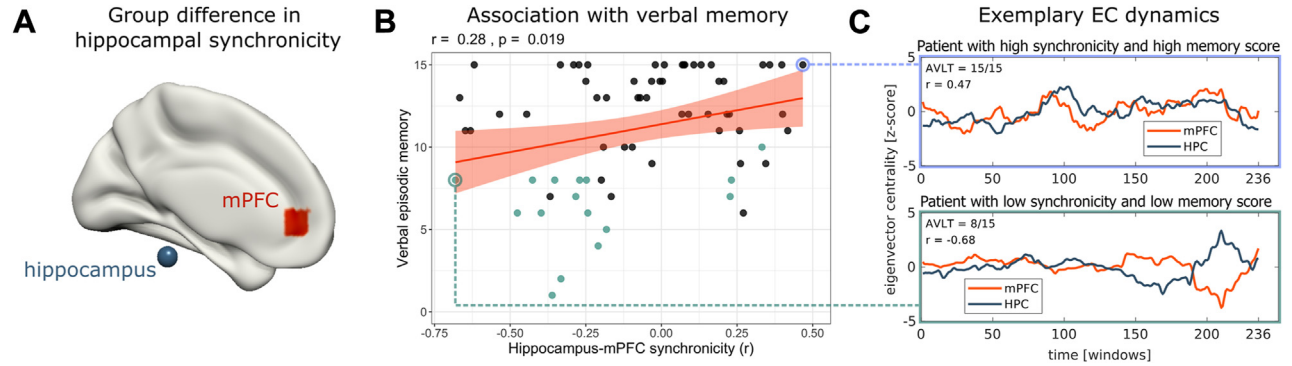

Figure 3. **(A)** Significantly decreased eigenvector centrality (EC) synchronicity between the right hippocampus (HPC) (blue sphere) and the left medial prefrontal cortex (mPFC) (red voxels) in patients with anti-NMDA receptor encephalitis compared with control participants (familywise error $p < .05$). **(B)** Reduced EC synchronicity (product-moment correlation r) between right HPC and left mPFC is significantly associated with lower verbal episodic memory performance in patients with anti-NMDA receptor encephalitis (Auditory Verbal Learning Test [AVLT], delayed recall of X out of 15 words). Patients with impairment in verbal episodic memory ($z < -1.5$) are colored in green. **(C)** EC dynamics in an exemplary patient with high HPC-mPFC synchronicity and high memory performance on the AVLT (top) and one with low synchronicity and low memory performance (bottom).

symptoms with objective measures of brain function. Dynamic EC mapping captures dynamic functional alterations and respects their hierarchical topological nature and is therefore particularly well suited to represent the pathophysiology of NMDARE. Here, we show that dynamic EC mapping indeed detects widespread alterations in NMDARE that were not observed with previous functional connectivity approaches. In addition, synchronicity of EC between the hippocampus and the mPFC was impaired and associated with cognitive performance on an individual patient level (Figure 3C). It is therefore plausible that dynamic EC analyses are particularly sensitive to network alterations in NMDARE, providing a deeper insight into the functional changes underlying cognitive symptoms of the disease.

Our finding that patients with NMDARE show significantly higher variability of dynamic EC compared with healthy participants suggests that network centrality dynamics are more volatile—or "unstable"—in NMDARE. Using hierarchical clustering analysis, these volatile areas could be grouped spatially into 4 centrality clusters. In analogy to known resting-state networks (29), these clusters were identified as salience, precuneus/default mode, frontotemporal, and frontal systems. While decreased connectivity in temporal networks was previously detected using conventional static methods (6), dynamic EC mapping now revealed changes in volatility in 3 further systems. This indicates the importance of considering the temporal dynamics of brain function when investigating diseases in which functional alterations may represent a key pathogenic factor—beyond structural damage alone. In this regard, the variability of EC in the frontotemporal cluster showed a significant negative association with verbal episodic memory in our study. This suggests that the volatility of network configuration may underlie cognitive dysfunction in NMDARE, highlighting the relevance of dynamic EC changes to explain long-term symptoms of NMDARE. Indeed, a link between network alterations in these regions and verbal memory deficits is plausible in light of previous research that demonstrated an association between alterations in hippocampal and parahippocampal connectivity and verbal memory dysfunction in NMDARE (6).

In a hypothesis-driven approach, we further assessed hippocampal seed-to-whole-brain EC dynamics and found that the synchronicity between the right hippocampus and the left mPFC was significantly reduced in NMDARE. Moreover, reductions in EC synchronization between these areas were associated with deficits in verbal episodic memory in NMDARE. Recently, reduced functional connectivity of the hippocampus was also demonstrated in a mouse model of NMDARE (30). Notably, the importance of hippocampal-mPFC connectivity for memory consolidation and retrieval has long been established in animal models, lesion studies, and structural imaging (31). The reduction of hippocampal connectivity in NMDARE is indeed also plausible from a neurophysiological perspective, as the hippocampus is the brain region with the highest density of NMDA receptors (32,33).

With regard to previous studies using resting-state functional in patients with NMDARE, our current results corroborate prior findings while adding several novel insights. Consistent with earlier reports, we found systematically more volatile functional dynamics in NMDARE (17,19). In this context, a dynamic functional connectivity study from our group showed an increased volatility of transitions between functional connectivity states, i.e., states with high and low overall connectivity and states with high and low segregation, in patients compared with healthy control participants (17). In a complementary approach, we applied a new method to quantify the temporal trajectories of functional states across the whole brain with so-called transition networks (19). In line with the notion of increased functional volatility in NMDARE, we similarly observed a reduced resilience of these transition networks in patients compared with control participants (19), indicated, for example, by transitions between more distinct brain states in patients. In the current study, we also show increased volatility of functional dynamics in patients with NMDARE.

However, these earlier studies have quantified brain dynamics on the level of edges in the network (i.e., region-to-region connectivity). In contrast, the current study uncovers increased functional volatility on the level of individual voxels (i.e., the nodes in the network). Specifically, the current method of EC mapping allows voxelwise analysis of BOLD dynamics and quantifies the relative importance of each voxel within the whole network. This approach thus provides a more fine-grained topological analysis and accounts for the hierarchical nature of functional brain networks. Furthermore, our previous studies mostly showed alterations in the connectivity dynamics between the hippocampus and the mPFC, as well as within the default mode network and between frontal, visual, and subcortical areas (17). In the current study, we show that communication between the hippocampus and the mPFC is also impaired in terms of synchronicity of network importance. Our current findings thus corroborate the hypothesis that decreased hippocampal connectivity in general, and desynchronization of centrality dynamics between the hippocampus and the mPFC in particular, seems to be a key functional imaging correlate of cognitive deficits in NMDARE. However, our current study also revealed substantially more widespread increases in EC volatility in frontal, temporal, and parietal regions than previous studies. This suggests that NMDARE may affect a much wider range of functional brain systems than previously assumed.

Static EC group differences were observed in only 1 brain region, i.e., the left intracalcarine area. Alterations in this region were previously found in patients with optic neuritis but have not been associated with NMDARE so far (34). However, such visual network alterations could be associated with the subtle visual dysfunction reported in NMDARE (35). Indeed, a previous study observed decreased visual network connectivity to be associated with increased disability in NMDARE (6).

Following the established methodology, we focused on EC mapping in cortical gray matter. However, recently published studies show that BOLD signal from white matter can also be analyzed in terms of functional networks (36). Because there is a substantial body of research showing white matter changes in NMDARE, future studies could investigate EC in functional white matter networks in this disease (5,37,38).

EC mapping holds significant promise for extending our understanding of not only NMDARE, but also other neurological diseases characterized by network disruptions. For example, increased static centrality of the default mode network is associated with cognitive deficits in patients with

MS (21). Similar to our current study, dynamic EC analysis in MS showed substantially more widespread changes than the static approach, demonstrating that cognitively impaired MS patients exhibit reduced EC dynamics in the default mode, frontoparietal, and visual networks compared with cognitively preserved patients (23). Furthermore, changes in EC have been found to be associated with cognitive scores and CSF biomarkers in Alzheimer's disease (26), and these changes may precede the manifestation of dementia in *APOE* ε4 carriers (27). Thus, the application of EC mapping in clinical neuroscience could facilitate the development of targeted interventions and improve diagnostic accuracy across a variety of neurological conditions.

Limitations and Strengths

A limitation of our study is that patients were scanned at different time points after the acute phase of the disease. Future studies should investigate alterations in network centrality in both the acute phase and during long-term follow up. In addition, dynamic EC only explained a relatively small proportion of the variance in verbal episodic memory, suggesting that these cognitive deficits are best explained by an interplay of several factors, some of which are yet unknown.

However, considering the relative rarity of NMDARE, our study represents one of the largest cohorts to date. State-of-the-art voxelwise analysis of network centrality provides a powerful new and data-driven approach to investigate brain dynamics across the entire cerebral cortex and at a fine-grained resolution, overcoming some of the intrinsic limitations of traditional static functional connectivity analyses. The advantages of this method do not just apply to NMDARE, but also are promising to improve our understanding of brain function in other autoimmune encephalitides and neuropsychiatric disorders.

Conclusions

Dynamic EC mapping revealed widespread and clinically meaningful increases in the variability of functional brain network organization in patients with NMDARE. Time-resolved analyses uncovered widespread differences that were not detected by static approaches, suggesting that brain dynamics carry an increased sensitivity to functional alterations in NMDARE. Importantly, these alterations were associated with deficits in verbal episodic memory, potentially representing a functional neural correlate of cognitive dysfunction in NMDARE.

ACKNOWLEDGMENTS AND DISCLOSURES

The work was supported by the European Joint Programme on Rare Diseases (Grant No. EJPRD21-40 SAPIENCE); the German Federal Ministry of Education and Research, Grant Nos. 01GM210 (SAPIENCE) and 01GM1908D (CONNECT-GENERATE); and the German Research Foundation, Grant Nos. 327654276 (SFB 1315), 504745852 (Clinical Research Unit KFO 5023 "BecauseY"), FI 2309/1-1 (Heisenberg Program), FI 2309/2-1, PR1274/5-1, and PR1274/9-1. The funders were not involved in study design, data collection, data analysis, interpretation of data, writing of the report or decision to submit the paper for publication.

We thank all study participants for their time and all research assistants involved in data collection and entry.

TJH was involved in conceptualization, methodology, formal analysis, data curation, writing of the original draft, manuscript review and editing, visualization, and project administration. NvS was involved in conceptualization, methodology, formal analysis, data curation, manuscript review and editing, visualization, and project administration. SK was involved in methodology, providing resources, manuscript review and editing, and visualization. TAAB was involved in methodology, manuscript review, and editing. HP was involved in manuscript review and editing and providing resources. MMS was involved in methodology, manuscript review, and editing. CF was involved in conceptualization, methodology, data curation, manuscript review and editing, providing resources, project administration, and funding acquisition.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Neurology and Experimental Neurology, Berlin, Germany (TJH, NvS, SK, HP, CF); Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Berlin, Germany (NvS, CF); Department of Anatomy and Neurosciences, MS Center Amsterdam, Amsterdam Neuroscience, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands (TAAB, MMS); and German Center for Neurodegenerative Diseases, Berlin, Germany (HP).

Address correspondence to Carsten Finke, M.D., at carsten.finke@charite.de.

Received Apr 29, 2024; revised Jul 18, 2024; accepted Jul 21, 2024.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2024.07.021.

REFERENCES

1. Dalmau J, Armangué T, Planagumà J, Radosevic M, Mannara F, Leypoldt F, *et al.* (2019): An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: Mechanisms and models. Lancet Neurol 18:1045–1057.
2. Finke C, Kopp UA, Prüss H, Dalmau J, Wandinger K-P, Ploner CJ (2012): Cognitive deficits following anti-NMDA receptor encephalitis. J Neurol Neurosurg Psychiatry 83:195–198.
3. Heine J, Kopp UA, Klag J, Ploner CJ, Prüss H, Finke C (2021): Long-term cognitive outcome in anti–N-methyl-D-aspartate receptor encephalitis. Ann Neurol 90:949–961.
4. Bacchi S, Franke K, Wewegama D, Needham E, Patel S, Menon D (2018): Magnetic resonance imaging and positron emission tomography in anti-NMDA receptor encephalitis: A systematic review. J Clin Neurosci 52:54–59.
5. Finke C, Kopp UA, Scheel M, Pech L, Soemmer C, Schlichting J, *et al.* (2013): Functional and structural brain changes in anti–N-methyl-D-aspartate receptor encephalitis. Ann Neurol 74:284–296.
6. Peer M, Prüss H, Ben-Dayan I, Paul F, Arzy S, Finke C (2017): Functional connectivity of large-scale brain networks in patients with anti-NMDA receptor encephalitis: An observational study. Lancet Psychiatry 4:768–774.
7. Fornito A, Zalesky A, Breakspear M (2015): The connectomics of brain disorders. Nat Rev Neurosci 16:159–172.
8. Douw L, van Dellen E, Gouw AA, Griffa A, de Haan W, van den Heuvel M, *et al.* (2019): The road ahead in clinical network neuroscience. Netw Neurosci 3:969–993.
9. Smith SM, Vidaurre D, Beckmann CF, Glasser MF, Jenkinson M, Miller KL, *et al.* (2013): Functional connectomics from resting-state fMRI. Trends Cogn Sci 17:666–682.
10. Calhoun VD, Miller R, Pearlson G, Adalı T (2014): The chronnectome: Time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron 84:262–274.
11. Zamani Esfahlani F, Jo Y, Faskowitz J, Byrge L, Kennedy DP, Sporns O, Betzel RF (2020): High-amplitude cofluctuations in cortical activity drive functional connectivity. Proc Natl Acad Sci 117:28393–28401.

12. Bassett DS, Sporns O (2017): Network neuroscience. Nat Neurosci 20:353–364.
13. Krohn S, von Schwanenflug N, Waschke L, Romanello A, Gell M, Garrett DD, Finke C (2023): A spatiotemporal complexity architecture of human brain activity. Sci Adv 9:eabq3851.
14. Preti MG, Bolton TA, Van De Ville D (2017): The dynamic functional connectome: State-of-the-art and perspectives. NeuroImage 160:41–54.
15. Lohmann G, Margulies DS, Horstmann A, Pleger B, Lepsien J, Goldhahn D, *et al.* (2010): Eigenvector centrality mapping for analyzing connectivity patterns in fMRI data of the human brain. PLoS One 5: e10232.
16. Wink AM, de Munck JC, van der Werf YD, van den Heuvel OA, Barkhof F (2012): Fast eigenvector centrality mapping of voxel-wise connectivity in functional magnetic resonance imaging: Implementation, validation, and interpretation. Brain Connect 2:265–274.
17. von Schwanenflug N, Krohn S, Heine J, Paul F, Prüss H, Finke C (2022): State-dependent signatures of anti-*N*-methyl-d-aspartate receptor encephalitis. Brain Commun 4:fcab298.
18. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, *et al.* (2016): A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 15:391–404.
19. Von Schwanenflug N, Ramirez-Mahaluf JP, Krohn S, Romanello A, Heine J, Prüss H, *et al.* (2023): Reduced resilience of brain state transitions in anti-*N*-methyl-D-aspartate receptor encephalitis. Eur J Neurosci 57:568–579.
20. Parkes L, Fulcher B, Yücel M, Fornito A (2018): An evaluation of the efficacy, reliability, and sensitivity of motion correction strategies for resting-state functional MRI. NeuroImage 171:415–436.
21. Eijlers AJC, Meijer KA, Wassenaar TM, Steenwijk MD, Uitdehaag BMJ, Barkhof F, *et al.* (2017): Increased default-mode network centrality in cognitively impaired multiple sclerosis patients. Neurology 88:952–960.
22. Wink AM (2019): Eigenvector centrality dynamics from resting-state fMRI: Gender and age differences in healthy subjects. Front Neurosci 13:648.
23. Eijlers AJC, Wink AM, Meijer KA, Douw L, Geurts JJG, Schoonheim MM (2019): Reduced network dynamics on functional MRI signals cognitive impairment in multiple sclerosis. Radiology 292:449–457.
24. Fuchs TA, Schoonheim MM, Broeders TAA, Hulst HE, Weinstock-Guttman B, Jakimovski D, *et al.* (2022): Functional network dynamics and decreased conscientiousness in multiple sclerosis. J Neurol 269:2696–2706.
25. Schoonheim MM, Geurts JJG, Wiebenga OT, De Munck JC, Polman CH, Stam CJ, *et al.* (2014): Changes in functional network centrality underlie cognitive dysfunction and physical disability in multiple sclerosis. Mult Scler J 20:1058–1065.
26. Binnewijzend MAA, Adriaanse SM, Van der Flier WM, Teunissen CE, de Munck JC, Stam CJ, *et al.* (2014): Brain network alterations in Alzheimer's disease measured by Eigenvector centrality in fMRI are related to cognition and CSF biomarkers: Brain Network changes in AD Measured by EC in fMRI. Hum Brain Mapp 35:2383–2393.
27. Wink AM, Tijms BM, ten Kate M, Raspor E, de Munck JC, Altena E, *et al.* (2018): Functional brain network centrality is related to APOE genotype in cognitively normal elderly. Brain Behav 8:e01080.
28. Chen Z, Zhou J, Wu D, Ji C, Luo B, Wang K (2022): Altered executive control network connectivity in anti-NMDA receptor encephalitis. Ann Clin Transl Neurol 9:30–40.
29. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, *et al.* (2011): The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 106:1125–1165.
30. Kuchling J, Jurek B, Kents M, Kreye J, Geis C, Wickel J, *et al.* (2024): Impaired functional connectivity of the hippocampus in translational murine models of NMDA-receptor antibody associated neuropsychiatric pathology. Mol Psychiatry 29:85–96.
31. Preston AR, Eichenbaum H (2013): Interplay of hippocampus and prefrontal cortex in memory. Curr Biol 23:R764–R773.
32. Hansen JY, Shafiei G, Markello RD, Smart K, Cox SML, Nørgaard M, *et al.* (2022): Mapping neurotransmitter systems to the structural and functional organization of the human neocortex. Nat Neurosci 25:1569–1581.
33. Scherzer CR, Landwehrmeyer GB, Kerner JA, Counihan TJ, Kosinski CM, Standaert DG, *et al.* (1998): Expression of N-methyl-D-aspartate receptor subunit mRNAs in the human brain: Hippocampus and cortex. J Comp Neurol 390:75–90.
34. Petracca M, Cordano C, Cellerino M, Button J, Krieger S, Vancea R, *et al.* (2017): Retinal degeneration in primary-progressive multiple sclerosis: A role for cortical lesions? Mult Scler J 23:43–50.
35. Brandt AU, Oberwahrenbrock T, Mikolajczak J, Zimmermann H, Prüss H, Paul F, Finke C (2016): Visual dysfunction, but not retinal thinning, following anti-NMDA receptor encephalitis. Neurol Neuroimmunol Neuroinflamm 3:e198.
36. Peer M, Nitzan M, Bick AS, Levin N, Arzy S (2017): Evidence for functional networks within the human brain's white matter. J Neurosci 37:6394–6407.
37. Phillips OR, Joshi SH, Narr KL, Shattuck DW, Singh M, Di Paola M, *et al.* (2018): Superficial white matter damage in anti-NMDA receptor encephalitis. J Neurol Neurosurg Psychiatry 89:518–525.
38. Hartung TJ, Cooper G, Jünger V, Komnenić D, Ryan L, Heine J, *et al.* (2024): The T1-weighted/T2-weighted ratio as a biomarker of anti-NMDA receptor encephalitis. J Neurol Neurosurg Psychiatry 95:366–373.