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BRIEF COMMUNICATION

Stereo-EEG–based ictal functional connectivity in patients with periventricular nodular heterotopia–related epilepsy

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Abstract

Nodular heterotopia (NH)–related drug-resistant epilepsy is challenging due to the deep location of the NH and the complexity of the underlying epileptogenic network. Using ictal stereo-electroencephalography (SEEG) and functional connectivity (FC) analyses in 14 patients with NH-related drug-resistant epilepsy, we aimed to determine the leading structure during seizures. For this purpose, we compared node IN and OUT strength between bipolar channels inside the heterotopia and inside gray matter, at the group level and at the individual level. At seizure onset, the channels within NH belonging to the epileptogenic and/or propagation network showed higher node OUT-strength than the channels within the gray matter ($p = .03$), with higher node OUT-strength than node IN-strength ($p = .03$). These results are in favor of a “leading” role of NH during seizure onset when involved in the epileptogenic- or propagation-zone network (50% of patients). However, when looking at the individual level, no significant difference between NH and gray matter was found, except for one patient (in two of three seizures). This result confirms the heterogeneity and the complexity of the epileptogenic network organization in NH and the need for SEEG exploration to characterize more precisely patient-specific epileptogenic network organization.

KEYWORDS

h^2 , IN-strength, OUT-strength, thermocoagulation

Member of the ERN EpiCARE Network: Elodie Garnier, Aude Jegou, Stanislas Lagarde, Julia Makhalova, Samuel Medina, Christian-G. Bénar, Fabrice Bartolomei, and Francesca Pizzo.

Fabrice Bartolomei and Francesca Pizzo are co-last authors.

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1 | INTRODUCTION

Nodular heterotopia (NH) is among the most common malformation of cortical development¹ and is frequently associated with drug-resistant epilepsy.² The treatment of NH-related epilepsy is challenging due to the deep NH localization and to the complex interactions of NH with adjacent cortex.^{3,4} Stereo-electroencephalography (SEEG) has been used to investigate and better characterizing the implication of NH in patients with drug-resistant epilepsy, and to perform radiofrequency thermocoagulation (RF-TC) on select channels.^{4,5}

The role of NH, as well as of the surrounding and remote neocortex, in the generation of seizures remains a matter of debate.^{6,7} Despite the use of intracranial SEEG recordings, identifying network leaders remains challenging.³ Functional connectivity (FC) analysis describes how different brain areas synchronize their activities through mathematical estimates of the inter-dependency between EEG, SEEG, and blood oxygen level-dependent (BOLD) signals, and allows for the determination of which structure takes the lead in the network, thanks to graph measures.

This study aims to characterize the mutual relation between NH and the cortex using ictal SEEG FC analysis, by estimating a “leading” role of one structure onto the other.

2 | METHODS

An observational retrospective cohort study was conducted at our center between January 2001 and January 2021. Inclusion criteria were: (1) the presence of at least one NH on magnetic resonance imaging (MRI) sampled by SEEG electrode and (2) available pre-operative MRI and postoperative computerized tomography (CT). Exclusion criteria were: (1) absence of spontaneous seizure on SEEG and (2) seizure lasting less than 64s (not allowing for sufficient data to apply FC analysis over three different ictal periods – see paragraph 2.2). The institutional review board approved this study (C3BHV2), and written patient consent was obtained both for the implantation of the electrodes for SEEG and for the subsequent RF-TC procedures.

2.1 | SEEG/MRI procedure and recordings

SEEG procedure and recordings were described previously.³ Signals were recorded on a 256-channel Natus system (Deltamed) with a .16 Hz high-pass filter. The sampling rate was at minimum 256 Hz. Patients’ epilepsy-related

characteristics, including classification of the NH on a three-dimensional (3D), T1-weighted sequence, were collected.⁸ The NHs were segmented semi-automatically using 3D, gadolinium-enhanced, axial T1-weighted images on preoperative MRI with the open-source ITK-SNAP software (Figure 1A; available at www.itksnap.org). Then, preoperative MRI studies were registered to a 1.0-mm isotropic brain atlas (Montreal Neurological Institute [MNI] 152) using open-source software (Statistical Parametric Mapping (SPM) 12, 2014; <https://www.fil.ion.ucl.ac.uk/spm/>) running on MATLAB (R2018a The MathWorks Inc.; 2018.). The regions of interest corresponding to the NH were normalized in the MNI space using the SPM transformation matrix. We then color-coded the frequency for visualization using open-source MRICroGL software (<https://www.mccauslandcenter.sc.edu/mricrogl/>).

Postoperative CT and preoperative 3D T1-weighted sequences were co-registered using the in-house GARDEL software (<https://meg.univ-amu.fr/wiki/GARDEL:presentation>). The SEEG channels were classified into two groups according to anatomic location: (1) contacts within the NH and (2) contacts outside of the NH but within the gray matter (GM). A SEEG bipolar montage was created including the NH and all gray matter channels having an exploitable signal.

2.2 | Functional connectivity and epileptogenic index analysis

FC analyses were done using the in-house Anywave software (<https://meg.univ-amu.fr/wiki/AnyWave:Download>).⁹ For each patient, we selected four time periods lasting 16s in each SEEG seizure (Figure 1C): (1) Background (BG), which finished 10s before seizure onset; (2) onset of seizure (OS), representing the first 16s of the seizure; (3) middle of seizure (MS), placed just after the end of OS period; and (4) end of seizure (ES), corresponding to the last 16-s period of the seizure. Seizure onset was positioned at the beginning of ictal discharges (first neurophysiological change from background activity in at least one bipolar channel) and end of seizure, just before the end of ictal discharge in all sampled channels. For each patient, one to three spontaneous seizures were analyzed. Interdependencies between bipolar SEEG signals were estimated by pairwise nonlinear regression analysis based on the h^2 coefficient.¹⁰ The h^2 was computed on broadband signals with a frequency ranging from 2 to 45 Hz, a sliding window of 3s, and an overlap of 1.5s. Because h^2 values are asymmetric, we created a directed connectivity matrix using the h^2 value between two bipolar channels (channel1 > channel2 and channel2 > channel1). We calculated for each channel the mean of the h^2

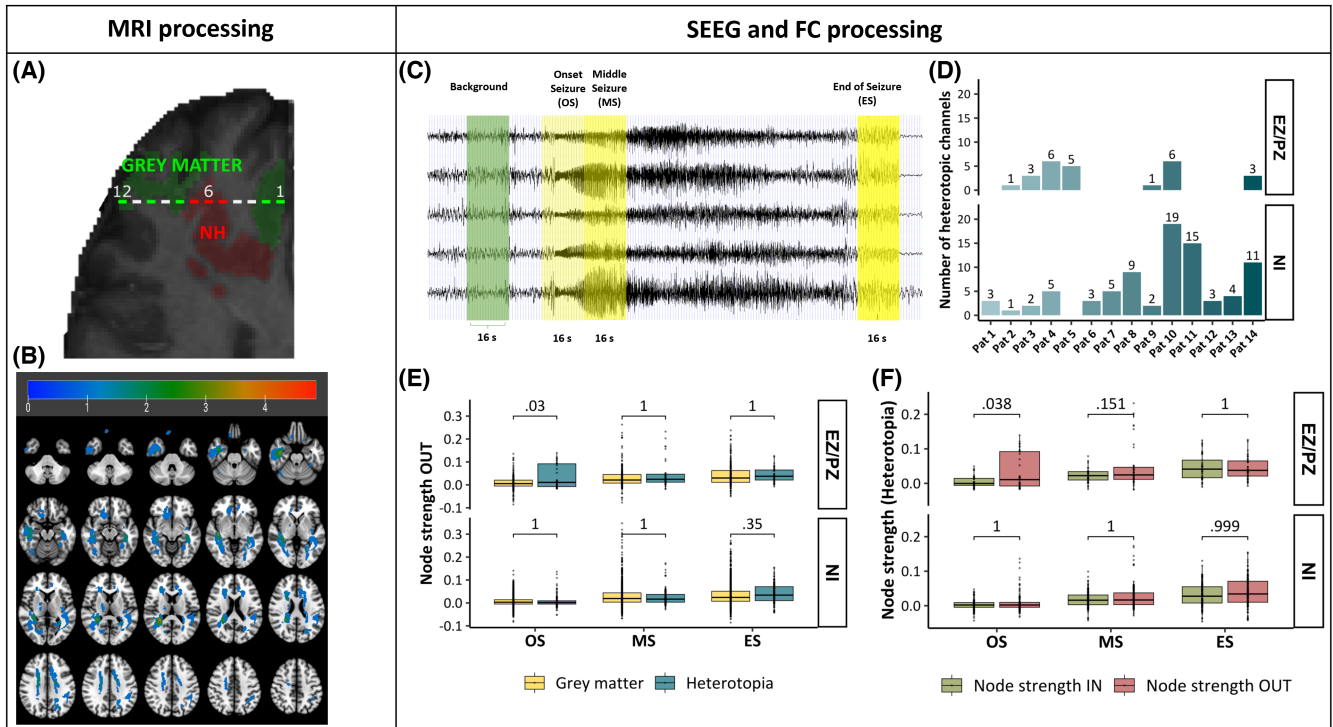


FIGURE 1 Methods and results synthesis. (A) Manual segmentation of the nodular heterotopia (NH) and gray matter (GM) on the preoperative magnetic resonance imaging (MRI) using ITK-SNAP software with overlay of a stereo-electroencephalography (SEEG) electrode. (B) Location and prevalence of NH in our cohort. Color frequency map illustrates the number of patients with NH in a certain location. (C) Illustration of the different periods of the seizure selected for functional connectivity (FC) analysis. (D) Distribution of number of bipolar channels in heterotopia per patient with involvement in the epileptogenic network (EZ/PZ, belonging to the epileptogenic/propagation zones; NI, belonging to the non-involved zone). (E) Node OUT-strength of channels within GM or NH according to the different seizure period (onset of seizure [OS], middle of seizure [MS], end of seizure [ES]) and the epileptogenic network (EZ/PZ and NI). Note that channels within heterotopia and belonging to the EZ/PZ had higher node strength-OUT values during the seizure onset (OS) than channels within the GM. (F) Comparison of node OUT- and IN-strengths for channels inside heterotopia: at OS the node OUT-strengths were higher than node IN-strengths only for channels belonging to the EZ/PZ.

values of (1) all ingoing links (node IN-strength), (2) all outgoing links (node OUT-strength), (3) the sum of the node IN- and OUT-strength (node total strength = TOT-strength) divided by the number of channels per patient, as described previously.¹¹ The mean node strength of BG was subtracted from the other periods (OS, MS, and ES) to better estimate the changes in FC due to seizures activity.

The epileptogenicity index (EI, estimating the propensity of a brain region to generate fast discharge early during the seizure course, maximum = 1) was calculated to determine the epileptogenic zone (EZ, $EI > .4$), the propagation zone (PZ, EI between .2 and .4), and the non-involved zone (NI, $EI < .2$).⁹

2.3 | Statistical analysis

The objective of statistical analyses was to determine if channels within NH or GM were leading the other during the seizure. We used two approaches to determine

this. First, we considered NH as “leader” if the node OUT-strength was significantly higher than the node IN-strength. To answer this question, node-strength changes in heterotopic channels were assessed in a linear mixed model with periods (OS vs MS vs ES), directionality (IN vs OUT-strength), and involvement in the epileptogenic network (EZ/PZ vs NI) as fixed effects and patient as random effect. Second, we compared the node OUT-strength between channels within NH and GM to establish which structure was more “sender,” reinforcing its role as a “leader.” To evaluate changes in node OUT-strength only, a second linear mixed model was then computed, with periods, structures (NH vs GM), and involvement in the epileptogenic network as fixed effects and patient as random effect. For both analyses, interaction between factors was included in the model. A stepwise regression using Akaike information criterion was used to optimize the models. Post hoc analyses (pairwise comparisons) were performed on significant factors using least-squares mean with Tukey correction for multiple comparisons. Finally,

node strength was also assessed at the individual level for each seizure using Wilcoxon test with Bonferroni correction. The differences in node strength were investigated as a function of the NH volume, between periods (OS, MS, and ES), between different EI classifications (EZ/PZ and NI), and anatomic classifications (NH or GM).

A *p*-value of less than .0 after correction was considered statistically significant. All analyses were conducted with R Statistical Software (Version 4.0.4.).

3 | RESULTS

3.1 | Patient population

Table 1 summarizes the patients' characteristics and Figure 1B presents the frequency location map of the NHs. Fourteen adult patients were included (10 female, mean age at SEEG: 32.8 ± 11.7 years). The mean duration of epilepsy before SEEG was 16.6 ± 13.1 years (range, 3–46 years). The mean volume of NH was 8.7 ± 8.9 cm³ (range, 1.3–25.4 cm³). NHs were located primarily in the right hemisphere, specifically near the atrium of the right lateral ventricle (Figure 1B). The mean number of SEEG electrodes was 13.6 ± 3.7 (range, 8–19 electrodes), corresponding to 176.6 ± 46.3 contacts (range 100–245). The management comprised SEEG-guided thermocoagulation in nine patients, neuromodulation (vagus nerve stimulation/deep brain stimulation) in four, disconnection in one, and tailored cortectomy in one patient (Table 1). Sustained Engel class I outcome was obtained in six patients and Engel class II in two patients; six patients were in Engel class II/IV and one patient refused surgery (Table 1). Concerning the FC analysis, 25 seizures were analyzed (mean number of seizures by patient: $1.8 \pm .8$; range, 1–3). The mean number of bipolar channels included in the final analysis was 64.4 ± 16.4 (range, 33–99).

3.2 | Connectivity at the group level

NH was involved in the EZ/PZ in 7 of 14 cases (Figure 1D). The node TOT-strength increased during the seizure. The mean node TOT-strength was significantly higher during the MS period than during the OS period and was also higher during the ES period than in the OS and MS periods (*p* < .001 in all cases). This increase existed in both the GM and the NH nodes. Notably, the node TOT-strength was unrelated to NH volume (*p* = .63).

Concerning the nodes belonging to the EZ/PZ, we found a higher node OUT-strength in the NH than in the GM only during the OS (Figure 1E; *p* = .03). There was no significant difference for other periods or nodes belonging

to the NIZ. The nodes within NH and belonging to the EZ/PZ also showed significantly higher node OUT-strength than IN-strength (Figure 1F). This difference was not found for contacts within the GM.

3.3 | Connectivity at the individual level

Although a statistically significant difference between NH and GM was shown in only two seizures of one patient, some considerations can be drawn by looking at single case results: in some seizures, the NH showed only a minor connection with the epileptogenic network (Figure 2: Patient 3), whereas in other seizures, the NH was strongly connected to the GM and had a leading role (Figure 2: Patient 4). In most of cases, the differences between NH and GM were not very pronounced (Figure 2: Patient 10). This heterogeneity was observed inter-individually as well as between different seizures of the same patient.

4 | DISCUSSION

We report the variation of SEEG FC during seizure in a series of patients presenting NH-related drug-resistant epilepsy. This study showed that (1) NH, but not GM, if involved in seizure generation/propagation, acted as the seizure “leader,” with a high OUT-strength FC at the seizure onset; and (2) there was a great heterogeneity of the FC patterns at the individual level.

At the group level in the present series, NH was likely to lead the epileptogenic network, despite some intra- and inter-individual variability observed at the individual level. In comparison with our previous study on NH epileptogenicity (based on time-frequency analysis at seizure onset), the actual findings argue that NH can play a pivotal/“leading” role in the ictal modification of FC (node strength), even when it is involved in the propagation network, and not only in the EZ (referred to as the “heterotopic seizures” in our previous study).³

Node strength increased during all seizure periods, and this result was in line with previous publications.¹¹ Despite this global result, there was a great heterogeneity in the FC patterns between patients and even between the different seizures of the same patient. This could be due to the heterogeneity in patients with NH-related drug-resistant epilepsy, with significant variability in the location, the number of NHs, the epilepsy duration before SEEG, and the type of seizures. Also, notable, some genetic factors can contribute to the observed heterogeneity: apart from animal model data, filamin 1 gene or *NRAS* mutation have been associated with NH.^{12–14} A recent study has focused on morphological aspects of

TABLE 1 Patient, epilepsy, and imaging characteristics.

Patient no.	Sex	Age at SEEG (years)	Epilepsy onset (age, years)	Family history	Lesion type (NH /PNH)	NH localization	Posterior/anterior NH	Additional MRI abnormalities	SEEG contacts in NH	SEEG contacts in GM	Bipolar channels included in final analysis	Outcome (Engel class)			
												Surgery/thermocoagulation	6-12 Months	>12-18 Months	>18 Months
1	F	30	21	No	PNH	Bilateral	Post		5	101	70	Thermocoagulation	I	I	I
2	F	15	10	No	PNH	Left	Post		4	101	75	Thermocoagulation	I	I	I
3	M	48	19	No	NH	Right	Ant	Polymicrogyria	7	77	54	NA (Ref)			
4	M	44	20	No	NH	Right	Ant		14	88	69	VNS	IV	IV	IV
5	M	24	18	No	NH	Bilateral	Ant & Post		6	93	51	Right temporo-occipital disconnection	I	I	I
6	F	38	16	Yes (cousin and daughter)	PNH	Left	Ant		4	74	57	VNS & Bilateral DBS of ANT	IV	IV	IV
7	M	40	8		PNH & NH	Right	Ant	Polymicrogyria	5	49	33	VNS	IV	IV	IV
8	F	41	33	No	PNH & NH	Right	Post		16	97	72	Thermocoagulation	I	I	I
9	F	28	20	No	PNH	Left	Post		2	93	59	Thermocoagulation	IV		
10	F	51	5	No	PNH	Bilateral	Ant & Post	Schizencephaly & polymicrogyria	29	133	99	Thermocoagulation & VNS	IV	IV	IV
11	F	17	13	No	PNH	Bilateral	Ant & Post		23	117	76	Thermocoagulation	III	II	II
12	F	19	16	No	PNH	Right	Ant		7	63	43	Thermocoagulations x 2	I	I	I
13	F	38	20	Yes (maternal grandmother and grandfather)	PNH	Right	Post		5	116	68	Thermocoagulation & right temporal lobectomy	I	I	I
14	F	26	14	No (FLNA+)	PNH	Bilateral	Ant & Post		25	96	75	Thermocoagulation	I	II	II

Abbreviations: Ant, anterior; ANT, anterior nucleus of thalamus; DBS, deep brain stimulation; F, female; FLNA+, Filamin A alpha gene deficiency; M, male; NA, not applicable; NH, nodular heterotopia; PNH, periventricular nodular heterotopia; Post, posterior; Ref, patient refused surgery; VNS, vagus nerve stimulation.

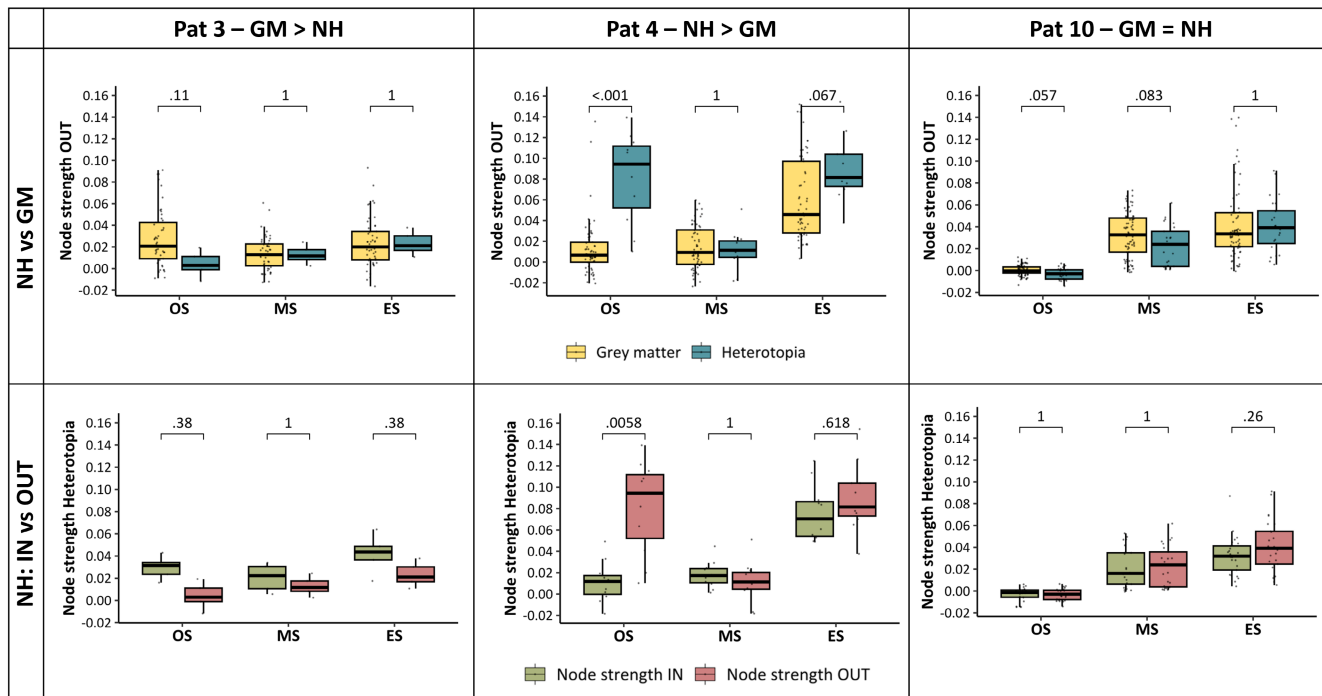


FIGURE 2 Illustrative cases of three patients showing different connectivity patterns. In the first line: difference in node OUT-strength of nodular heterotopia (NH) vs GM. In the second line: difference in node OUT vs IN-strength of channels within NH. Patient 3: gray matter leading heterotopia at onset of seizure (OS; not significant). Patient 4: Heterotopia leading GM at OS. Patient 10: no leader.

NH and associated cortical lesions using ultra-high field MRI.¹⁵ Of interest, in the present work, there was no statistical correlation between the NH FC values (node strength) and the NH volume.

Structural and functional MRI connectivity studies have shown aberrant connections of heterotopia with the overlying cortex.^{16,17} From a neurophysiological point of view, three main profiles of FC could be distinguished: NH poorly connected within the epileptogenic network; NH strongly connected and being the leader vs the GM; and no difference between NH and GM. The lack of significant differences between the GM and NH FC values at the individual level could be due to the complex network organization, without a “single leader” structure, or due to a limited statistical power of our analyses.

Results should be interpreted with caution due to the retrospective and monocentric nature of this study. By definition, SEEG is a personalized treatment; therefore the electrode implantations varied from one patient to another. The low spatial resolution of SEEG, combined with the fact that some trajectories were not possible due to anatomic constraints, limited the epileptic network investigation, possibly leading to sampling bias. Other limitations were the different numbers of seizures analyzed from the different patients in this series, bias lowered by the signal heterogeneity between seizures from the same patient.

Identifying seizure leader in cases of NH-related drug-resistant epilepsy is of particular importance. Indeed, several surgical approaches have been proposed: resective surgery, radiofrequency thermocoagulation (or RF-TC), laser interstitial thermal therapy, responsive neurostimulation, and deep brain stimulation, with various outcomes.^{18–24} NHs are deeply rooted, making resection surgery difficult. Good, albeit, inconsistent results with RF-TC have been reported.^{3,23} The high heterogeneity of this series called for personalized treatment strategies, and, given the good tolerance of SEEG, it seems reasonable to consider thermocoagulation following SEEG as a first surgical option.²⁵

To conclude, NH can be the leader structure in the epileptogenic network when data are analyzed at the group level, but each patient with NH showed an individual signature of the ictal FC pattern. This finding highlights the indication for the SEEG exploration^{4,26} to better understand the organization of epileptogenic networks in this peculiar population.^{6,10,25–27} Larger studies are needed to clarify the great heterogeneity in the NH patient population and to link network analysis and treatment outcomes.

AUTHOR CONTRIBUTIONS

M.Z., E.G., C.B., F.B., and F.P. contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript and the

drafting of the figures. A.J., S.M., and R.C. contributed to the analysis of the results and to the writing of the manuscript. S.L. and J.M. contributed to the design of the research and the writing of the manuscript. All authors discussed the results and commented on the manuscript.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, FP. The data are not publicly available due to restrictions (containing information that could compromise the privacy of research participants).

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