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Supporting Information for

Regional variability in intracerebral properties of NREM to REM sleep transitions in humans

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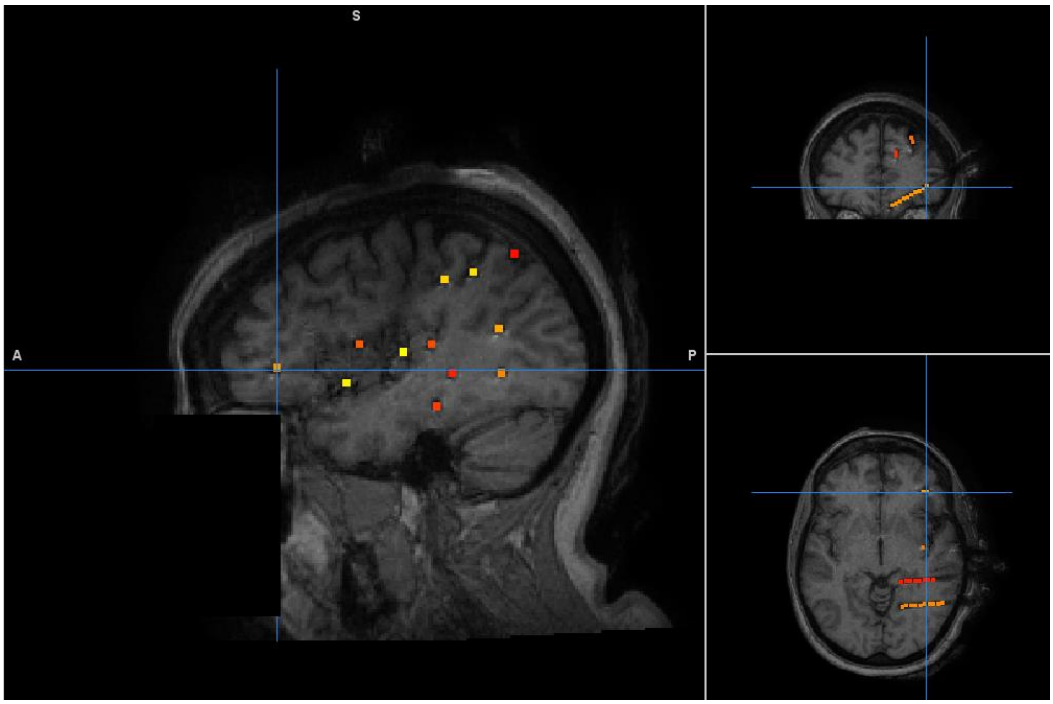
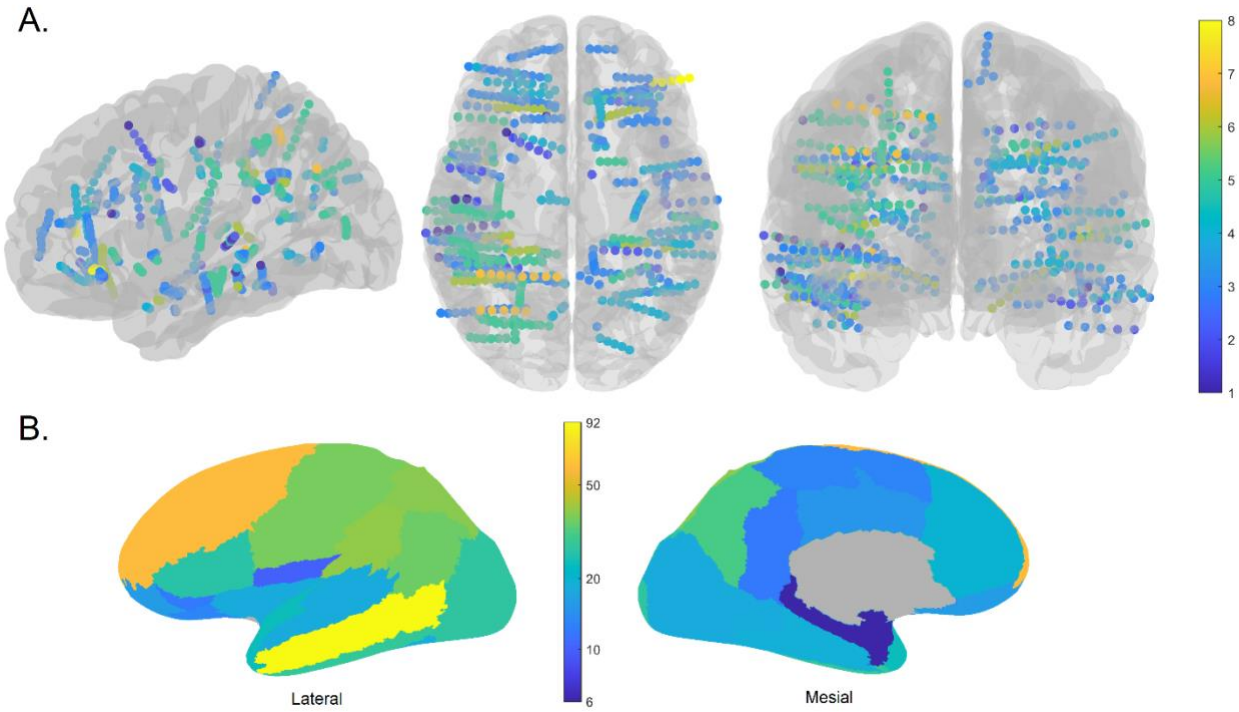
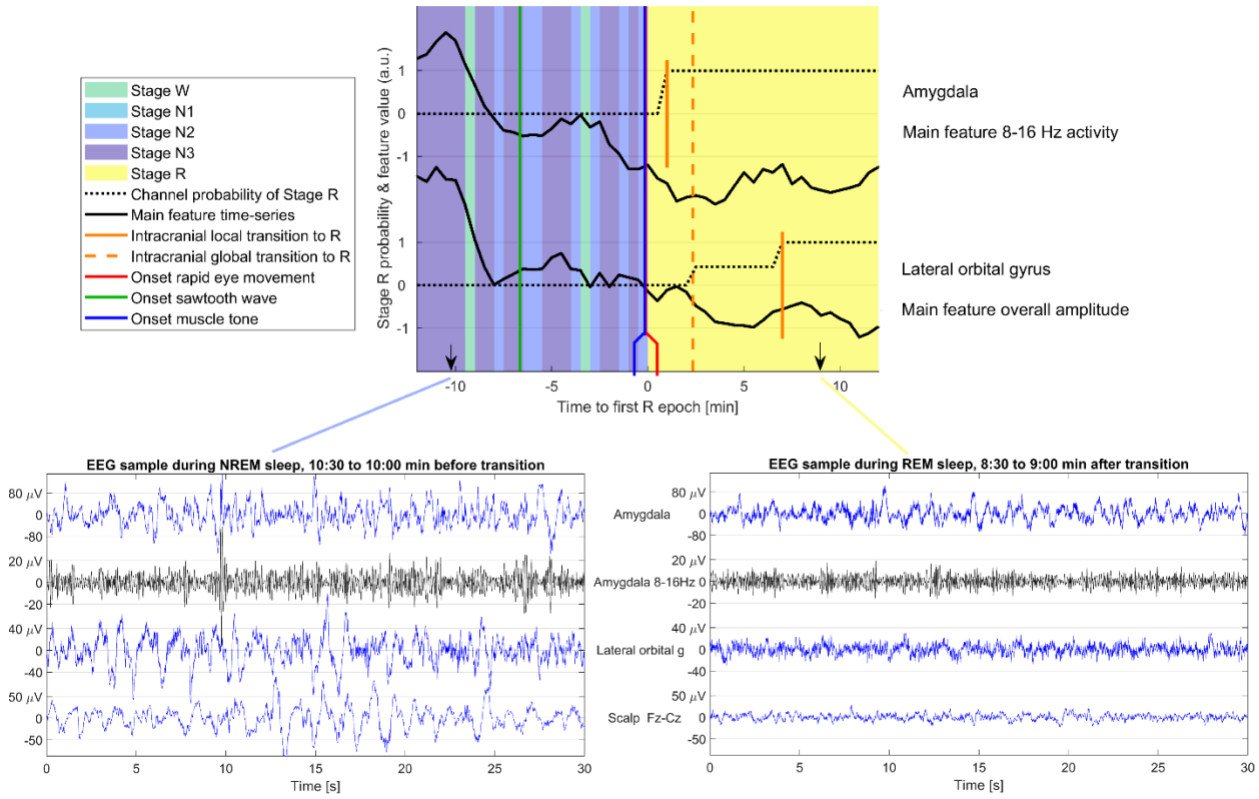


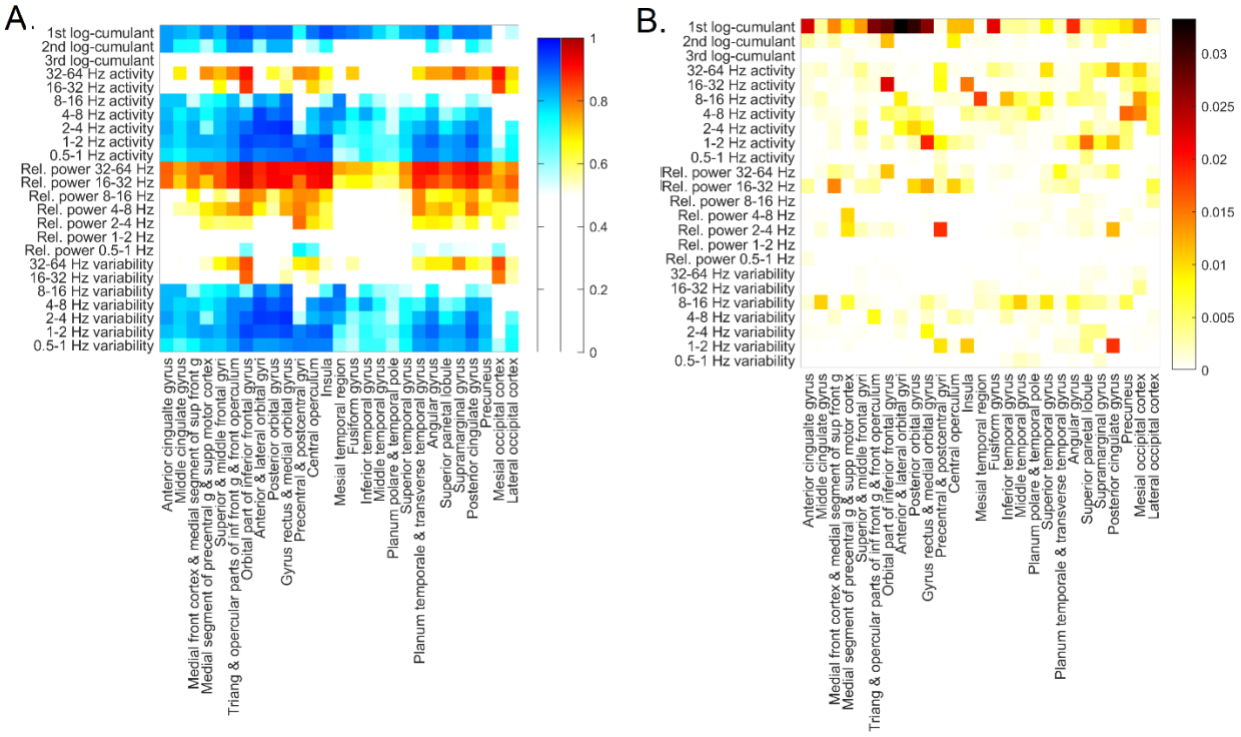
SI Appendix Figure S1. Example of MRI slices of patient with implanted electrodes. The position of the depth-electrode contacts is indicated by dots in colors. Only bipolar channels showing physiologic activity were included in the study.



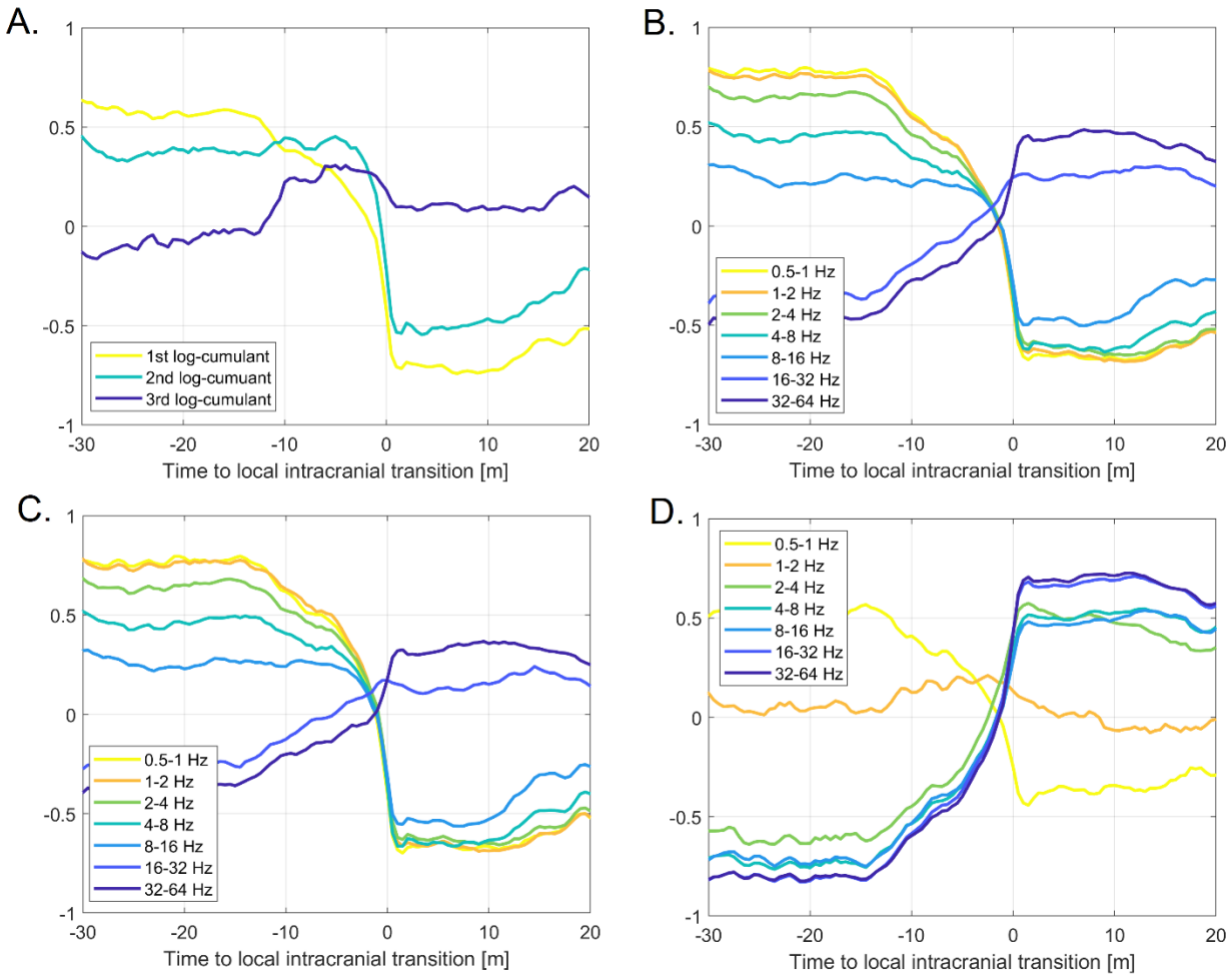
SI Appendix Figure S2. Location of intracranial EEG channels
Figure 2A. Location of intracranial EEG channels with no ictal or interictal epileptic activity, co-registered to a brain template. The total number of channels is 718 obtained from 29 patients. The color of each dot indicates the number of studied transitions for each channel.
Figure 2B. Number of intracranial EEG channels per brain region, grouping left and right hemisphere channels together. Each of the 27 brain regions has channels from at least four different patients, and all regions have at least ten channels, except for the mesio-temporal region with 6 channels. The color scale indicates the number of electrodes.



SI Appendix Figure S3. Example of a transition between NREM and REM sleep, and typical intracranial EEG in NREM and REM. (Top) Transition between NREM and REM sleep in patient 19, showing 2 channels in different brain regions. The background color indicates the sleep stage as scored by human experts. The black curves show the variation in time of the most important feature for determining the transition time in the corresponding brain region. The dotted black lines show the probability of NREM for each of the channels as a function of time. The first epoch with stage R in each intracerebral channel is indicated with a short vertical orange line, while the broken vertical orange line indicates the global transition time as derived from all the intracerebral channels used in this patient. The vertical green line indicates the onset of the first sawtooth waves, the vertical blue line the onset of muscle tone decrease, and the vertical red line the onset of the first rapid eye movements, all marked by human experts. In this example the transition in the amygdala is a clear transition (high clarity), and the transition in the lateral orbital gyrus is late compared to other regions, six and a half minutes after the scalp transition. (Bottom) Examples of the scalp EEG (Fz-Cz) and SEEG signals in one sleep epoch before and after the transition are shown on the bottom left and right respectively. The same channels as in the top panel are shown. The blue traces correspond to the broadband signals, and the black trace to the particular band associated with the most important feature in each brain region (8-16 Hz activity in the amygdala, 1st log-cumulant of the multifractal spectrum in the posterior orbital gyrus, which in practice is highly correlated to the overall amplitude; thus in the latter case, the main feature corresponds to the raw blue signal).). The amplitude scale is different to better show the signals in different channels, but it is the same in the NREM and REM epochs, to facilitate the comparison.



SI Appendix Figure S4. Features according to brain regions and sleep stages
Figure 4A. Separation of stable NREM and REM sleep based on individual features in different brain regions. The color indicates the maximum achievable separation of epochs in stable NREM and REM sleep based on each feature. Ranging from 0 (identical distribution) to 1 (perfect separation). The color indicated the degree of separation, and whether the feature values are higher in REM sleep (red) or in NREM sleep (blue). Thus, a dark blue color indicates that the corresponding feature is always higher in the corresponding brain region during stable REM sleep compared to stable NREM sleep. In other words, darker color (blue or red) indicates that the feature could be useful for classification.
Figure 4B. Average importance in the identification of stage R for different features and brain-regions. The different features are correlated, and this is the reason why not all of them are used for classification. After including the first feature, only features that provide extra uncorrelated information are used by the classification algorithm. There is a certain degree of subjectivity in the importance values, associated to the construction of the classifier. To interpret the differences between NREM and REM sleep it is better to focus on the feature value separation shown in panel A. The first log-cumulant is of high importance in many brain regions. It corresponds to the average slope of the spectrum in the 1-64 Hz frequency band. In practice, it is highly correlated with the overall amplitude of the iEEG.



SI Appendix Figure S5. Average value of normalized features as a function of time, with respect to the local transitions. The features are normalized to zero mean and unit variance throughout the night. The average of all 2837 local transitions is shown, in 30 s epochs. A. Features related to non-oscillatory activity showing the first three log-cumulants of the multifractal spectrum. The 3rd log-cumulant of the multifractal spectrum quantifies the skewness of the distribution of the average exponent of the 1/f model in the 1-64 Hz band, and the higher its absolute value, the more complex the model. Higher values in the 10 minutes preceding the transition are likely related to the dynamic changes during this period, including arousals, and thus may reflect NREM sleep instability during the pre-REM period. B. Average activity in different frequency bands. C. Variability of the activity in the different frequency bands. C. Proportion of power in each frequency band.

SI Supplementary Table S1. Demographic, neuroimaging, and electrophysiological data of the investigated patients

ID	Age	Sex	Epilepsy diagnosis	Seizure Onset Zone (S-EEG)	MR Imaging	ASM	Total number of electrodes	Selected channels for transitions analyses
1	37	M	Bilateral TLE	L temporal neocorticex + R mesial temporal	PNH	CBZ (1400), LEV (3000), CLO (10)	10	LOF5-10; RCa9-14
2	37	M	L temporo-insular epilepsy	L temporal mesial and neocortical + posterior insula	Normal	CLO (30), CBZ (600), TPM (200)	12	LIs4-8; LIp4-8; LOF4-9; LCa1-9; LCm1-9; LPH1-9; RH5-7; RHp5-7
3	57	F	R insular epilepsy	R Insula	surgery bed (normal before)	LTG (200), CLO (20)	7	RCa6-9: RCp5-9; RLi7-9; ROF 5-9
4	62	F	Bilateral mesial TLE	L and R hippocampus	Bilateral mesial temporal sclerosis	CBZ (800), CLO (15), LAC (400)	8	RA4-9; RH4-9; RHp5-9
5	41	M	Bilateral mesial TLE	L and R hippocampus + amygdala + parahippocampus	R mesial temporal sclerosis	CBZ (1400), CLO (10)	10	RCar1-9; Ria6-9
6	34	F	L temporo-occipital epilepsy	L basal temporo-occipital cortex	Normal	CBZ (1200), CLO (20), LTG (200)	8	LA4-7; LCp6-15; LFu7-10; LHp1-5
7	36	M	Bilateral neocortical TLE	L + R temporal neocortex	L hippocampus atrophy	OXC(1200), LEV (3000), LTG (400)	8	LFu1-4 ; RFu1-4
8	38	M	L temporo-occipital epilepsy	L posterior hippocampus, lingual gyrus and cuneus	L posterior temporal atrophy and gliosis	PHE (350), CLO (30), LEV (1000)	9	LCp1-8; LIa4-8; LOF1-9
9	39	M	Bilateral TLE	L+R temporal mesial and neocortical	R hippocampus atrophy	CLO (30), LEV (3000)	12	LCa1-7; LCs1-6; RCs1-3
10	27	F	L occipital lobe epilepsy	L lateral temporo-occipital cortex	L lateral occipital FCD	LTG (300), CBZ (400)	7	LCi1-9; LH1-5; LOs4-9 ; LPc1-9
11	30	M	L FLE	L orbitofrontal (mesial) neocortex	possible mesial orbitofrontal FCD	LEV (1000), CLO (20)	9	LHa6-10; LHp6-10
12	29	M	L mesial TLE	L hippocampus + amygdala	L left mesial temporal sclerosis + hemispheric atrophy	CBZ (1200), CLO (20)	8	LCa1-8; LFP1-10
13	27	F	L insular lobe epilepsy	L posterior insula	Posterior Insula / Heschl gyrus FCD + surgical	CBZ (1400), LTG (100), CLO (40)	13	LCa1-2; LCp5-8; LM1-5; LS 1-4; LSMA1-7

					bed (temporal neocortex)			
14	24	M	Bilateral temporal mesial epilepsy	L and R hippocampus + amygdala	R hippocampus atrophy and L hippocampus malformation	CLO (15)	10	LCp4-8; LOF1-10; RCp5-9; RHp7-10; ROF1-10
15	47	M	R temporo-parietal epilepsy	R posterior temporal and parietal neocortex	R postsurgical defect (anterior temporal resection) + R ischemic frontal lesion	LEV (4000), LTG (200), CLO (20), ZNZ (200)	12	RCm1-3 ; RFu1-4
16	20	M	R temporo-occipital epilepsy	R fusiform gyrus and R heterotopia	PNH	BRV (100), CLO (20), OXC (750)	14	LPNHa4-10, RT1p4-10
17	32	M	L fronto-temporo-insular epilepsy	L insula + temporal +/- frontal	L parieto-temporal encephalomalacia	LEV (1500), LAC (200), CLO (30)	10	LCm1-5; LCp1-6; LPO1-4 ; LPO8-10; LSMA1-3
18	26	F	L mesial and basal TLE	L hippocampus + amygdala + fusiform gyrus	Normal	PER (8), LAC (250), LTG (275)	10	LCi11-14 ; LFu4-12; LHp4-11; LIa5-8; LIp3-8
19	26	F	R parieto-occipital epilepsy	R parietal dysplasia	R posterior cingulate FCD	BRV (100), CBZ (400), LTG (150)	15	RA1-8; RCa1-10; RC1-10; RCi1-10; RCp1-6; RDa8-13; RIa6-11; RIp1-6; RLia1-5; RLip5-10; RSMA1-5
20	18	F	R occipito-temporal epilepsy	R occipito-temporal cortex	normal	no treatment (CBZ and PER stopped)	15	RFu4-9; ROa1-10; ROp1-6
21	40	M	Hypothalamic hamartoma	Hypothalamic hamartoma	hypothalamic hamartoma	CLO (10), LEV (1500), OXC (300)	6	LHm 2-15
22	47	M	L temporo-insular epilepsy	L ant insula and anterior temporal neocortex	Normal	CBZ (1200)	9	LCa1-12; LOF1-6; LCp1-8; LFu1-8
23	53	M	R mesial temporal epilepsy	R mesial temporal and inferior isthmus	Normal	OXC (1800), LEV (1000)	8	RPc1-4; RCp1-8; ROs1-2; ROi1-4
24	31	F	L mesial and basal temporal epilepsy	L Hc and fusiform gyrus	L hippocampus atrophy	LTG (600), CBZ (800)	8	LCp4-9, LCi1-6, LOi1-9, LCa4-9

25	41	F	R mesial temporal epilepsy	R hippocampus and amygdala	Bilateral mesiotemporal sclerosis, R > L	CLO (20), CBZ (800)	9	LOF1-9; LHp3-8; LI1-9; LIm1-9; ROF1-8
26	30	F	Bilateral mesial temporal epilepsy	L + R hippocampus and amygdala	Normal	OXC (1800), PHE (150), CLO (20), TPM (25)	11	LH5-10; RCa1-6; RCm1-5; RCp1-5; RPc1-6
27	26	F	L mesial and basal TLE	L hippocampus	Normal	LTG (550), LAC (100), PER (8)	13	LT11-5; LPc2-13; LIp5-15; LLea1-8; LLep1-6; LLeb1-9; LCpa5-14; LCpp1-15; LCi1-14; LCu1-10; LOs1-9; LOi1-10
28	32	M	Bilateral mesial temporal	L + R hippocampus	L hippocampal lesion	LEV (500), CBZ (300)	14	LOF1-15; LIa1-10; LT1p1-15; LA4-10; LHa7-10; LHp5-15; LCi5-15; LTO1-15; LEc6-10; LFua1-10; LFum1-10; LFup1-9; RA 8-10; RH 6-10
29	43	F	R fronto-insular	R anterior insula and frontal operculum	Normal	OXC (2100), CLO (10)	15	RFP7-14, ROF7-10, RFi1-9, RIp1-15, RHG1-8, RPT5-15, RLi1-10, RSMA3-15

Abbreviations: A, amygdala; a, anterior; ASM, antiseizure medication; BRV, Briveracetam; CBZ, carbamazepine; C, cingulate gyrus; Ci, isthmus of the cingulate gyrus; CLB, clobazam;; E, epilepsy; Ec, entorhinal cortex; F, frontal; FCD, focal cortical dysplasia; Fu, fusiform gyrus; FP, frontal polar; H, hippocampus; Ha, anterior hippocampus; HG: Heschl gyrus; Hp, posterior hippocampus; I, insula; i, inferior; Ip, insula posterior; Is; superior insula; L, left; LAC, lacosamide; Le, lesion; LEV, levetiracetam; Li, lingual; LTG, lamotrigine; m, middle; M, motor cortex; MR, magnetic resonance; O, occipital; OXC, oxcarbazepine; OF, orbitofrontal; p, posterior; P, parietal; Pc, pre-cuneus; PER, perampanel; PHE, phenytoin; PH, parahippocampal gyrus; PNH, periventricular nodular heterotopia; R, right; S-EEG, stereo-electroencephalography; s, superior; SMA, supplementary Motor Area; SOZ, seizure onset zone; T, temporal; T1, superior temporal gyrus; TPM, topiramate; ZNZ, zonizamide.