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Normalized power variance change between pre-ictal and ictal phase of an epilepsy patient using NAT analysis: A case study

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Abstract— **Variance of state variables shifts due to phase-instability and may serve as an early-warning signal of phase transition of complex systems such as an epileptic seizure of brain cortical activity. Neuronal Activity Topology (NAT) analysis calculates a normalized-power-variance (NPV) of electroencephalogram (EEG) data in each frequency band to obtain relative values comparable among different power states.**

In this study, using NAT analysis, we investigated NPV changes between the pre-ictal and ictal phase in a patient with mesial frontal lobe epilepsy. We also investigated interictal cortical electrical activity in each frequency band using exact low resolution brain electromagnetic tomography (eLORETA) analysis.

NAT analysis demonstrated a NPV increase in beta frequency band at mesial frontal lobe in the pre-ictal period, and NPV decrease in beta frequency band at mesial frontal lobe in ictal period. In addition, eLORETA analysis localized a beta band cortical electrical activity at mesial frontal lobe in the interictal period.

These results indicate instability of cortical electrical activity at seizure onset zone in the pre-ictal phase and its stabilization by phase transition to ictal phase. Overall findings indicate that NAT analysis can sensitively detect instability of cortical electrical activity and may serve as an early-warning signal of phase transition of cortical electrical activity.

I. Introduction

Phase transition is a sudden change of a system state and it widely exists in complex systems. Examples include epileptic seizures in cortical neuronal populations, asthma attacks in somatic cell populations, cancer in gene populations and melting of ice in molecular populations. Thermal and statistical physics and real data analysis of progression of somatic diseases demonstrated that around the phase transition point, variance of state variables, autocorrelation and spatial correlation increase. Furthermore, thermal and statistical physics theoretically indicates that, as state approaches a phase transition point, variance diverges to infinity. Ergo, variance may sensitively indicate the oncoming phase transition prior to phase transition onset itself, thus serving as an early-warning signal of phase transition [1].

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Mesial frontal lobe epilepsy (mesial FLE) has a seizure onset zone at the mesial surface of the frontal lobe including the primary sensorimotor cortex, the supplementary motor area (SMA), the anterior cingulate cortex and the prefrontal cortex. The typical seizure of mesial FLE is a bilateral asymmetric tonic seizure without loss of consciousness, often preceded by a somatosensory aura [2]. Recent studies proposed that this somatosensory aura may arise from the sensory representation area within the SMA [3], [4]. The mesial FLE also exhibits interictal epileptiform discharges which has been reported to show midline (Fz, Cz) or in some cases frontal (F4, F3) spike foci [5], [6]. This may be explained as follows: mesial frontal seizure onset zones are nearest to midline electrodes but their tangential dipole direction to the scalp reduces spike amplitude in midline electrodes and in some cases, the spike doesn't appear in midline electrodes but in seizure propagation area, where dipole direction is vertical to the scalp.

In this study, we illustrate the case of a patient with mesial FLE whose seizure onset zone was suggested to be in the left SMA by ictal semiology, and demonstrate the NPV change between pre-ictal and ictal phases at the seizure onset zone for the first time.

II. Methodology

A. Subject

A 40-year-old, left-handed, male patient began to have seizures at the age of 3 after suffering from measles encephalitis. Thereafter, the patient experienced good seizure control on carbamazepine, even though a few periods of seizure exacerbation were reported. At the age of 19, the seizures recurred up to several times per year. Seizures were characterized by abrupt bilateral asymmetric tonic posturing of the arms (the right showing greater elevation than the left), typically accompanied by head deviation to the right, and often preceded by an aura of nonspecific sensation localized to the head. At the age of 35, 37 and 40 (years2007, 2009 and 2012), the patient was admitted to our hospital, in which cases gabapentin was added to carbamazepine therapy, lamotrigine was added, and levetiracetam substituted gabapentin, respectively. Thereafter the patient experienced transient improvement of seizure control.

B. EEG data acquisition and data analyses

Subject underwent EEG registration in a resting state, eyes closed condition for more than 10 min. Prior to each recording, subject was instructed to keep their eyes closed but to stay awake. Spontaneous electrical brain activity was recorded with a 19-channel EEG data acquisition system

(EEG-1000/EEG-1200, Nihon Kohden, Inc., Tokyo, Japan) with a frequency band of 0.53 to 120 Hz, sampled at 500 Hz.

EEG was recorded with the electrodes positioned according to the International 10-20 system (i.e., Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz) using a linked ears reference. Impedance was kept below 5kΩ.

Neuroworkbench software was used for visual inspection of the EEG recordings and manual selection of samples. For NAT analysis, 10 consecutive 3-s segments before ictal onset whenever possible and one ictal 3-s segment at seizure onset that was spike and wave discharges with shorter (300—600ms) and almost same interspike intervals and with no tonic electromyogram and for LORETA analysis, 120-s interictal segments were selected. We also avoided selecting particular epochs containing ocular movements, muscle or cardiac contamination and drowsiness signs so that reliable estimates of brain function in the pre-ictal, ictal and interictal state under awake resting condition could be obtained.

NAT analysis

In NAT (Neuronal Activity Topology) analysis, all electrodes were re-referenced to an average reference (i.e., a mean value of the 19 recorded potentials). Then, the power (the energy of the EEG signal) was calculated by the square of the amplitude of the EEG signal. Finally, a normalized power variance (NPV) was calculated for the first 2.56-s of each 3-s segment on each of 19 recorded EEG signals, where NPV was defined as a power variance divided by a squared mean power to obtain relative values comparable among different power states. The output of the NAT analysis program was a z-score which indicates a deviation of an observed NPV value from the average NPV values of healthy controls in unit of its standard deviation and color mapped on a standard brain surface [7]. The number of healthy control subjects included in the NAT analysis program was 52 (71.5 ±8.4 years old, 27 men, 25 women) with normal results in Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and magnetic resonance imaging (MRI), and no history of neurological or psychiatric disorders.

eLORETA analysis

We used eLORETA (exact low resolution brain electromagnetic tomography) to compute the cortical electrical current density from the surface EEG data. The eLORETA method is a discrete, three-dimensional distributed, linear, weighted minimum norm inverse solution. This particular weight which assumes spatial smoothness was tested by trial point sources and it became clear the property of exact localization even with 19 EEG channels. In addition, eLORETA with 19 EEG channels was validated with real human EEG during diverse sensory stimulations, yielding the correct localization of activity in sensory cortices. A further property of eLORETA is that it has no localization bias even in the presence of structured noise [8]. In this sense, eLORETA is an improvement over previously related tomographies LORETA [9] and the standardized version sLORETA [10].

The current eLORETA implementation employs a three-shell spherical head model including scalp, skull and brain and EEG electrode coordinates derived from cross-registrations between spherical and realistic Talairach head geometry. The head model and the electrode coordinates were registered to the Montreal Neurologic Institute average MRI brain (MNI152) [11]. The solution space was restricted to the cortical gray matter, corresponding to 6239 voxels at 5x5x5 mm spatial resolution. Validation for the eLORETA tomography rests upon the abundantly published validation for the previous LORETA and sLORETA methods using fMRI [12], [13], structural MRI [14], PET [15], and intracranial EEG recordings [16]. The healthy control subjects used in eLORETA analysis were 11 in their 30's and 40's (39.6 ±5.1 years old, 7 men, 4 women) with no history of neurological and psychiatric disorders.

These analyses were performed for five frequency bands: delta (2—4 Hz), theta (4—8 Hz), alpha (8—13 Hz), beta (13—30 Hz), and gamma (30 — 40 Hz).

Statistical analysis

For each eLORETA result, the difference from 11 healthy controls in each frequency band was assessed by the independent t-test and Talairach coordinates of the most prominent cortical electrical activity were indicated. Next, the group difference of all eLORETA results from 11 healthy controls in each frequency band was assessed by the independent t-test, with the level of significance set at $P < 0.05$. For NAT analysis results, the group differences between NPVs of before-pre-ictal (i.e., one segment before pre-ictal segment), pre-ictal (i.e., one segment before ictal segment) and ictal segments were assessed by one-way ANOVA (analysis of variance) with Bonferroni test, using SPSS Statistics, with the level of significance set at $P < 0.05$.

III. Results

We obtained five sets of about 10 consecutive 3-s segments before ictal onset and one ictal 3-s segment for NAT analysis and four sets of 120-s interictal segments for eLORETA analysis from EEG recordings in June 2007, December 2009, October 2012 and January 2013. By visual inspection of the ictal EEG segment, we detected the electrode with the maximum amplitude spike and identified the mesial frontal (Fz or Cz) electrode as the seizure onset electrode.

Then, NAT analysis demonstrated a NPV increase in beta frequency band in pre-ictal segment (p=0.014), and a NPV decrease in beta frequency band in ictal segment at seizure onset electrode (p=0.021) (Fig. 1—5, Table 1). Other significant NPV changes in other frequency bands we also listed in Table 1.

eLORETA analysis of interictal EEG also revealed that the most prominent beta band cortical electrical activity was localized at the left mesial frontal lobe compared with healthy controls in their 30's and 40's [(X = -10, Y = -15, Z = 55; SMA) for EEGs in June 2007, December 2009 and October 2010 and (X = -10, Y = -15, Z = 60; SMA) for EEG in January 2013]. Group analysis of these four results compared with healthy controls also revealed that the most significant beta band activity was localized at mesial frontal lobule (X = -10, Y = -15, Z = 55; SMA | t = 1.6, p = 0.01) (Fig. 6). In other frequency bands, no constant activities among the four EEGs were obseved.

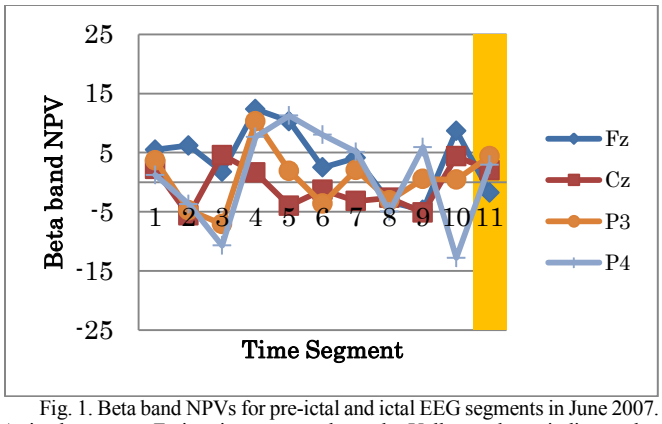

Fig. 1. Beta band NPVs for pre-ictal and ictal EEG segments in June 2007. At ictal segment, Fz is seizure onset electorde. Yellow column indicates the ictal segment.

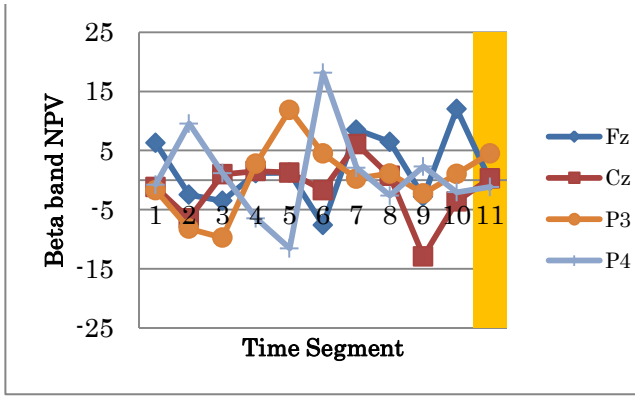

Fig. 2. Beta band NPVs for pre-ictal and ictal EEG segments in December 2009. At ictal segment, Fz is seizure onset electorde. Yellow column indicates the ictal segment.

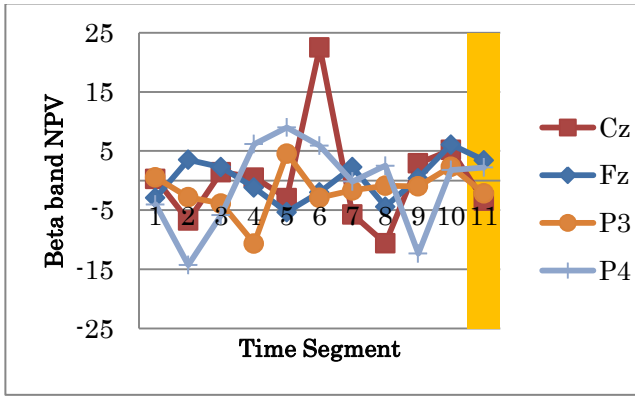

Fig. 3. Beta band NPVs for pre-ictal and ictal EEG segments in October 2012. At ictal segment, Fz is seizure onset electorde. Yellow column indicates the ictal segment.

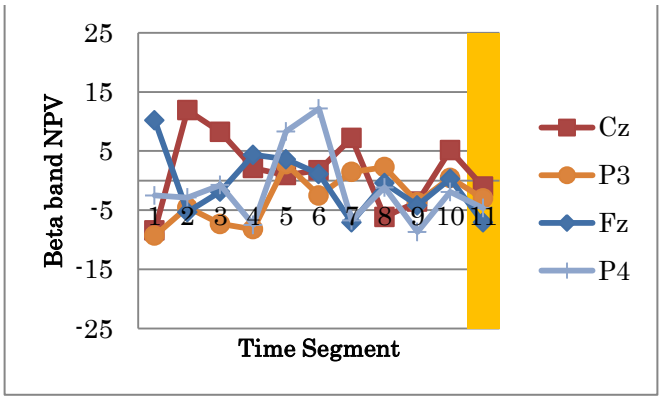

Fig. 4. Beta band NPVs for pre-ictal and ictal EEG segments in January 2013. At ictal segment, Cz, Fz is seizure onset electorde. Yellow column indicates the ictal segment.

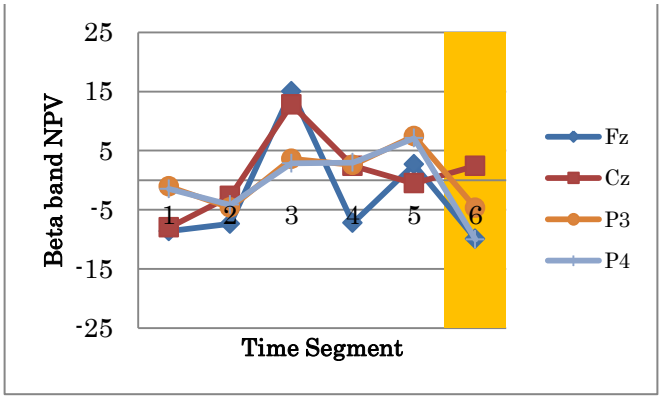

Fig. 5. Beta band NPVs for pre-ictal and ictal EEG segments in January 2013. At ictal segment, Fz is seizure onset electorde. Yellow column indicates the ictal segment.

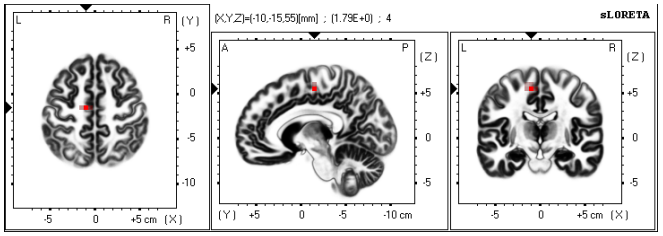

Fig. 6. Beta band cortical electrical activity at left mesial frontal lobe is most significant, comparing five interictal activities (June 2007, December 2009, October 2010 and January 2013) with 11 healthy controls. (X = -10, Y = -15, Z = 55; Supplementary motor area | t = 1.6, p = 0.01)

TABLE I.

Frequency band -electrode site	NPV changes between before-preictal, preictal and ictal segments			
	F-ratio	*P-value*	*Segment vs segment*	*Average difference*
Delta-P3	4.1	0.042	Ictal —before preictal	-14.9
Delta-T5	4.4	0.036	Preictal —before preictal	-11.0
Theta-P3	6.2	0.014	Ictal —preictal	+9.2
Theta-F7	6.3	0.013	Ictal —before preictal	+13.7
Beta-Fz	7.4	0.008	Preictal —before preictal	+9.6
			Ictal —preictal	-9.0

Frequency band -electrode site	NPV changes between before-preictal, preictal and ictal segments			
	F-ratio	*P-value*	*Segment vs segment*	*Average difference*
Gamma-Fz	5.1	0.025	Ictal —before preictal	+7.0
Gamma-Fp1	6.8	0.010	Ictal —before preictal	+7.2

NPV changes between before-preictal, preictal and ictal segments were assessed by one-way ANOVA with Bonferroni test

IV. Discussion and Conclusion

In the present study, we used eLORETA to reconstruct the cortical electrical activity and detected the prominent beta band activity at exactly the same cortical region among five EEGs.

The region indicated by our results was the left mesial frontal lobe, which is consistent with the features of seizure onset zone because the patient's somatosensory aura indicates the seizure onset zone may be within the SMA region [3], [4] and right dominance of the tonic seizure indicates the seizure onset zone is in the left hemisphere of the brain. In addition, the frequency band indicated by our results was beta, which is consistent with previous studies which reported that seizure onset zone in the frontal lobe tended to show beta and gamma band discharges during interictal and pre-ictal periods [17]. This evidence indicates that the mesial frontal beta band activity in this patient has a close relationship with epileptiform activity of the seizure onset zone.

NAT analysis also revealed that the beta band NPV at seizure onset electrode increases in pre-ictal period, and then decreases in ictal period, which is consistent with the theoretical expectation of variance increase at pre-ictal phase and decrease at ictal phase, due to phase-instability [1]. Therefore, these results indicate instability of seizure onset zone in pre-ictal phase and its stabilization by phase transition to ictal phase. A possible alternative explanation of this NPV increase at pre-ictal segment is the contamination of seizure activity, but in pre-ictal 3-s segments, only the first 2.56-s were used for NAT analysis, which was about 0.4-s apart from ictal segment. Furthermore, by visual inspection, we confirmed no contamination of spike and wave discharges or fibrillation prior to seizure onset in EEG. Moreover, other significant NPV changes in delta, theta and gamma band from ictal period may be due to emergence of fasts and slow EEG waves in ictal period and relative high p-values of other significant NPV changes make us consider the probability of type 1 errors of ANOVA as we repeated ANOVA for all frequency bands and electrode sites.

Overall findings indicate that NAT analysis can sensitively detect instability of cortical electric activity and may serve as an early-warning signal of phase transition of cortical electric activity.

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