Increase trend of correlation and phase synchrony of microwire iEEG before macroseizure onset

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Abstract Micro/macrowire intracranial EEG (iEEG) signals recorded from implanted micro/macroelectrodes in epileptic patients have received great attention and are considered to include much information of neuron activities in seizure transition compared to scalp EEG from cortical electrodes. Microelectrode is contacted more close to neurons than macroelectrode and it is more sensitive to neuron activity changes than macroelectrode. Microwire iEEG recordings are inevitably advantageous over macrowire iEEG recordings to reveal neuronal mechanisms contributing to the generation of seizures. In this study, we investigate the seizure generation from microwire iEEG recordings and discuss synchronization of microwire iEEGs in four frequency bands: alpha (1–30 Hz), gamma (30–80 Hz), ripple (80–250 Hz), and fast ripple (>250 Hz) via two measures: correlation and phase synchrony. We find that an increase trend of correlation or phase synchrony exists before the macroseizure onset mostly in gamma and ripple bands where the duration of the preictal states varied in different seizures ranging up to a few seconds (minutes). This finding is contrast to the well-known result that a decrease of synchronization in macro domains exists before the macroseizure onset. The finding demonstrates that it is

only when the seizure has recruited enough surrounding brain tissue does the signal become strong enough to be observed on the clinical macroelectrode and as a result support the hypothesis of progressive coalescence of microseizure domains. The potential ramifications of such an early detection of microscale seizure activity may open a new window on treatment by making possible disruption of seizure activity before it becomes fully established.

Keywords Synchronization · Correlation · Phase synchrony · Independent components · Epilepsy · Microwire intracranial EEG

Introduction

Micro/macrowire intracranial EEG (iEEG) signals, especially micro/macrowire intracranial EEG signals recorded from deeply implanted micro/macroelectrodes in epileptic patients, have been widely used by clinicians and researchers investigating physiologic and pathologic brain function. Recently, the use of EEG in the studies of synchronization has received wide attention (Aarabi 2008; Arthur and Boahen 2007; Dimitriadis et al. 2012; Dominguez et al. 2005; Guevara et al. 2005; Hong and Tong 2012; Knyazeva et al. 2013; Le Van Quyen et al. 2001; Lopes da Silva et al. 2003; Molinaro et al. 2013; Ozaki et al. 2012; Palva et al. 2005; Vialatte et al. 2009). Synchronization of neuronal activity, often associated with network oscillations, is considered to provide a mean for integrating anatomically distributed processing in the brain. There are some works to discuss synchronization changes during interictal, preictal, ictal and postictal states of epilepsy patients. For example, a decrease of phase synchrony prior to seizure onset between different regions of the brain

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using macrowire iEEG recordings of patients with temporal lobe epilepsy was reported (Feldt et al. 2007; Mormann et al. 2003a, b, 2007), where the duration of the preictal states was also estimated mostly of the order of several tens of minutes for partial epilepsy and they applied the decrease phenomena to predict upcoming seizures. A similar result was also shown in a work (Aarabi et al. 2008) for scalp EEG recordings recorded prior and during typical absence seizures by using linear and nonlinear measures where the duration of the preictal states varied in different seizures ranging up to a few seconds. These results were given without any specific frequency band filter on EEG signals.

Recent findings have shown that microwire iEEG and macrowire iEEG signals have a broad distribution of high-frequency oscillations (HFO) compared with scalp EEGs recorded from cortical electrodes. For example, ripples (80–250 Hz) and/or fast ripples (250–500 Hz) have been reported in human epilepsy patients (Blanco et al. 2010; Bragin et al. 2002; Donos et al. 2011; Fujiwara et al. 2012; Grenier et al. 2001; Jacobs et al. 2012; Jirsch et al. 2006; Nariai et al. 2011; Schevon et al. 2009; Staba et al. 2002, 2007; Telenczuk et al. 2011; Urrestarazu et al. 2006, 2007; Usui et al. 2011; Zijlmans et al. 2011). Ripple frequency oscillations were found in microwire iEEGs from the hippocampus of freely behaving rats to play an important physiological role in memory consolidation (Behrens et al. 2005; Buzsaki et al. 1992; Clemens et al. 2007) and in the genesis of seizures (Timofeev and Steriade 2004). In human brain study, our findings (Worrell et al. 2008) have revealed that the distribution of HFO frequencies recorded from the macroelectrodes was concentrated in the ripple frequency range and the average frequency of ripple HFO recorded from the macroelectrodes was lower than that recorded from the microelectrodes. One important reason for that is the location and size of the macroelectrodes and microelectrodes: macrowire iEEG reflects potentials beneath the macroelectrode which actually consist of sum of potentials of numerous surrounding neurons within a larger area because of the larger area of the macroelectrode, and the microwire iEEG reflects potentials surrounding the microelectrode which actually consist of sum of potentials of small number of neurons within a smaller area because of the smaller area of the microelectrode. More importantly, microelectrode is contacted more close to neurons than macroelectrode and microelectrode reflects activity of neurons more directly than macroelectrode. As a result, microwire iEEG recordings are more sensitive to neural activity changes than macrowire iEEG recordings and microwire iEEGs are inevitably advantageous over macrowire iEEGs to reveal neuronal mechanisms contributing to the generation of seizures. Hence, microwire iEEG may include more detailed signature in the generation of

epileptic seizures. It is noted that, due to the fact that microelectrode focuses on smaller local area, microwire iEEG has limitation on spatial restriction compared to clinic macrowire iEEG.

Recent findings using macroelectrode recordings have shown the presence of ictal discharges starting locally and rapidly spreading in premotor or premotor/prefrontal or prefrontal/premotor/precentral/parietal areas (for a review see Hirsch et al. 2006), which supports that a focal seizure is generated and observed only in a small area of the brain at initial stage, then the neural activity spreads out to other brain areas as it becomes more strong. It is only when the seizure has recruited enough surrounding brain tissue does the signal become strong enough to be observed on the clinical macroelectrode. As the seizure starts to recruit surrounding brain tissue/neurons, microelectrodes may be able to detect the changes and macroelectrodes cannot. For example, as shown in this study, in some cases, visual inspection may reveal clear changes in the amplitude and frequency of microwire iEEG background activity or even microseizure can be found (Stead et al. 2010) up to several seconds to minutes before the macroseizure onset. The occurrence of these changes before the onset of macroseizures may highlight the presence of preictal state defined as a functional condition of the epileptic brain that inevitably evolves into a seizure. To the best of our knowledge, synchronization of microwire iEEGs from human epilepsy patients have never been studied. In this study, we investigate synchronization of microwire iEEGs from human epilepsy patients by using two measures: correlation (linear cross correlation at zero delay) and phase synchrony (mean phase coherence) and demonstrate the hypothesis of progressive coalescence of microseizure domains.

Methods

A. Patients Eight patients (male and female) ranged in age from 16–60 undergoing evaluation for epilepsy surgery with intracranial micro/macroelectrodes were investigated where all these patients had suspected mesial temporal lobe epilepsy and were hospitalized for 7–30 days for continuous video-EEG monitoring. Patients were selected consecutively from a database of patients whose clinical and neurophysiological information were stored for analysis from the EEG database at Epilepsy center of Mayo Clinic at Rochester, USA. The intracranial macroelectrodes consisted of either right and left temporal depth electrodes (RTD and LTD) composed of 8 Platinum–Iridium alloy contacts spaced at 10 mm intervals (e.g., for patients 1 and 2), or a subdural grid of electrodes covering the left anterior temporal neocortex (e.g., for

patients 3). The depth electrodes were placed via a posterior burr hole and implanted along the long axes of the hippocampi, with contact 1 targeted at the amygdalae. The grid consisted of a silastic sheet embedded with 32 Platinum–Iridium alloy electrodes, 2.3 mm diameter and separated by 10 mm in a 4×8 array. Microwire electrodes were incorporated into standard clinical macroelectrodes in a hybrid arrangement (see Stead et al. 2010).

The data were acquired on Neuralynx system which digitizes each channel at 1,000 Hz with predigitization analog high-pass filtering at 0.01 Hz. 24 seizures were collected and analyzed where all clinic seizure onsets were determined by neurologists in Mayo Clinic at Rochester, USA. For all these seizures, we calculated correlation and phase synchrony between microchannels based on four frequency bands: alpha (1–30 Hz), gamma (30–80 Hz), ripple (80–250 Hz), and fast ripple (250–500 Hz).

- B. Microwire channels were selected according to the following strategy: (1) remove all bad channels (i.e., channels without working normally, with too much artifacts or line noise); (2) after (1), if there are too many channels left, we only choose less than 20 channels to reduce computation time (since one needs to compute a large number of channel pairs for the bivariate metric correlation or phase synchrony used in this paper as the number of channels chosen increases) where these channels are close to the microwire channel of the macroseizure onset.
- C. Microwire iEEG data were prefiltered with BUTTER filter of the order of 2 to four frequency bands: alpha (1–30 Hz), gamma (30–80 Hz), ripple (80–250 Hz), and fast ripple (250–500 Hz). We selected 1 s as sliding window size (i.e., the number of data points $N = 1,000$ in each window since the sampling rate is 1,000 Hz), calculated linear cross-correlation at zero delay, for two normalized electrode pair data (where normalization was done on each analyzed data segment which only involves one clinic seizure and has interictal stage with enough length, preictal stage, and ictal stage) $x(t)$ and $y(t)$ as

$$C(0) = \left| \frac{1}{N} \sum_{t=1}^N x(t)y(t) \right|,$$

and calculated phase synchrony or mean phase coherence (Mormann et al. 2007)

$$R = \left| \frac{1}{N} \sum_{j=1}^N e^{i[\phi_x(t_j) - \phi_y(t_j)]} \right|$$

where $\phi_x(t)$ and $\phi_y(t)$ denote the phase variables of two data $x(t)$ and $y(t)$ determined by using Hilbert transform.

For each metric, window was slid by one sample point (this process involves huge computations). And then average value of 100 points of each metric was calculated by using another sliding window technology without overlap.

- D. The following five concepts play an important role in this study. (1) The last segment for each correlation or phase synchrony curve. It has the following properties: The ending time instant of the last segment of each curve is at the macroseizure onset; Time interval of the last segment is seizure-dependent (i.e., the length of the last segment may be different for different seizure even from the same patient) and varies from several seconds to several minutes; Time intervals of the last segments of all correlation and phase synchrony curves are same for one specific seizure. (2) The ratio ρ , i.e., the length of the early time period divided by the length of the last segment where the early time period means the time period before the beginning time instant of the last segment. In this paper, the early time period needs to satisfy the following requirements: (1) mean value of the last segment is greater than that of any segment of the same length in the early time period (in this way, the starting time instant of the last segment of each curve is generally such that the last segment is obviously different from any segment of the same length in the early time period, i.e., the last segment has larger mean value than any other early segment); (2) If the length of the last segment is greater than 100 s, then the ratio $\rho > 3$ is required. If the length of the last segment is in the range of several seconds or tens of seconds, then the ratio $\rho > 10$ is required. Such kind of requirement for the ratio ρ is reasonable based on our experiments. (3) A correlation or phase synchrony curve is said to have an increase trend if there is an early time period satisfying above requirements. (4) A given seizure is said to have an increase trend before the macroseizure onset for correlation or phase synchrony of microwire iEEGs if the ratio $\phi \geq 50\%$ where ϕ is the number of correlation or phase synchrony curves having increase trend divided by the number of all correlation or phase synchrony curves. (5) A channel is said to be an optimal channel if it yields the maximum number of correlation or phase synchrony curves which have an increase trend. Therefore, to determine whether a given seizure has an increase trend before the macroseizure onset for correlation or phase synchrony of microwire iEEGs, there are three key factors: The selection of time interval of the last segment, the ratio ρ , and the ratio ϕ based on the optimal channel. For example, in this study we selected $\phi > 50\%$. This is rather reasonable

because we cannot guarantee all curves have an increase trend in reality. But more than half of curves having the property is enough to draw the conclusion. However, if we raise more strict constraint on ϕ , e.g., $\phi > 70\%$, then some of seizures do not have an increase trend based on this strict constraint. It should be pointed out that the last segment of correlation or phase synchrony curve is only approximately defined; that is, there is no exact definition for the starting time instant and the ending time instant (clinic seizure onset) of the last segment, due to the complexity of seizures. The general rule for selecting the starting time instant is to make sure the last segment has an obvious larger mean value than other segments of the same length in the early time period. In this study, the optimal channel of the same patient is same for all possible macroseizures.

Now for more clearness we summarize the detailed process in D: (1) Define the last segment of correlation or phase synchrony curves; (2) check if there is an early time period satisfying the two requirements in D for all correlation or phase synchrony curves. If so for one correlation or phase synchrony curve, then this curve has an increase trend before the macroseizure onset. If the ratio $\phi \geq 50\%$ based on the optimal channel, then the seizure has an increase trend before the macroseizure onset for correlation or phase synchrony metric.

Results

In this section we present results for three representative epilepsy patients in detail and make a summary of correlations and phase synchronies of microwire iEEGs for 24 seizures from 8 epilepsy patients. All iEEG traces were created using EEGLAB (Delorme and Makeig 2004).

Patient 1

For one seizure of Patient 1 we report the detailed results including the description of the last segment. 50 s macro-wire iEEGs and 100 s micro iEEGs are presented in Fig. 1a, b respectively where the macroseizure onset is at 740 s of MacroMF3 and earlier microseizure activities can be observed on MicroMT09–11. Figure 1c presents 16 ICs by applying fastICA algorithm (Hyvarinen and Oja 2000) to 16 microwire iEEGs in Fig. 1b. Earlier microseizure activities on IC11 and IC15 are very clear. Correlations (phase synchronies are very similar to correlations and omitted here) between MacroPT3 with all other macrowire channels in ripple band are plotted in Fig. 1d from which one can find that all correlations decrease before the

Fig. 1 Patient 1: **a** A 50 s sample of macrowire iEEGs where the macroseizure onset is at 740 s of macroMF3. **b** A 100 s sample of microwire iEEGs where microMT9–11 have earlier microseizure activities. **c** ICA generates 16 independent components, IC1–16 from microwire iEEGs. **d** Correlations of macroPT3 with all other macrochannels in ripple band. Before the seizure onset at 740 one can see decrease trend which is a well-known result in macro domain. **e** Correlations of microMT02 with other 8 microchannels (microPF01–05, 07, 08, and 11) in ripple band. **f** phase synchronies of microMT02 with other microchannels (microPF01–05, 07, 08, and 11) in ripple band. It is clear that increase trend can be found before the seizure onset at 740 s for both correlation and phase synchrony which are similar. **g** Correlations between IC7 and IC15. One can see the obvious increase trend before the seizure onset, which demonstrates that these two ICs are two major sources causing increase trend. *ICA* independent component analysis

macroseizure onset 740 s. The decrease trend for phase synchrony before seizure onset in macro domain widely exist (Mormann et al. 2003a, b). Correlations and phase synchronies of MicroMT02 with other 8 microwire channels (MicroPF01–05, 07, 08, and 11) are presented in Fig. 1e, f, respectively. All these curves satisfy the strict criteria, that is, mean value of the defined last segment (see Fig. 2a) covering 587–740 s (i.e., 153 s) for each curve is greater than that of previous any segment of the length of 153 s (>100 s) in the interval $[0, 587]$ which is the early time period (the ratio $\rho = 587/153 = 3.84 > 3$, so the early time period satisfies the requirements in D of Methods section and as a result, all these curves have an increase trend). All other curves are not included in Fig. 1e, f because they do not satisfy the strict criteria. Comparing Fig. 1e, f, both of correlation and phase synchrony are very similar and the only difference is that phase synchrony is smoother than correlation. All these curves in Fig. 1e, f have an increase trend before the macroseizure onset time at 740 s. Since 8 curves among total 15 curves (so, the ratio $\phi = 8/15 > 50\%$) have an increase trend before the seizure onset time at 740 s, we can conclude that both of correlation and phase synchrony have an increase trend before the macroseizure onset time at 740 s in micro domain. This finding of increase trend for correlation or phase synchrony before the macroseizure onset is totally different from the above result in macro domain. Figure 1g presents correlation between IC7 and IC15 which follows the same pattern as Fig. 1e. It shows that these two ICs are two major sources causing the increase trend. So, the increase trend demonstrates the progressive coalescence (or spread process) from source IC15 to source IC7. It is only when the seizure has recruited enough surrounding brain tissue does the signal become strong enough to be observed on the clinical macroelectrode. For this patient, it is noted that microseizure activities start at 587 s on Micro09–11 (omitted here) and cause that correlation or phase synchrony starts to increase from 587 s.

Fig. 1 continued

Recently surrogate data is widely used to decide whether a given value of a nonlinear measure reflects an underlying nonlinear dynamics by testing a specified null hypothesis in the nonlinear dynamic systems (Andrzejak et al. 2003; Lachaux et al. 1999). Correlation between two original data (MicroMT2 and MicroPF1) in ripple band and correlation between their surrogate data in ripple band are shown in Fig. 2a where surrogate data keep the same linear cross correlation and autocorrelation as the original data and the last segment of each curve covers 587–740 s (i.e., 153 s) (Andrzejak et al. 2003). Phase synchrony between two original data (MicroMT2 and MicroPF1) in ripple band and phase synchrony between original MicroMT2 and surrogate (MicroPF1) in ripple band are plotted in Fig. 2d where the surrogate data was obtained by randomly exchanging phases of the original MicroPF1 (Lachaux et al. 1999) and the last segment of each curve covers 587–740 s (i.e., 153 s). In the following, we suggest the

Fig. 2 Patient 1 (continued): **a** Correlations of MicroMT2 with MicroPF1 and MicroMT2 (surrogate) with MicroPF1 (surrogate) where surrogate data keep the same linear cross correlation and autocorrelation as original data. **b** Histogram of sample for the *dashed line* in **a** where sample points include one point, which is mean value of the last segment covering 587–740 s (i.e., 153 s), and all other points, which are mean values of segments of the fixed window size (i.e., 153 s as the length of the last segment) in the interval [0, 587]. **c** Histogram of sample for the *solid line* in **a**. **d** Phase synchronies of MicroMT2 with MicroPF1 and MicroMT2 with MicroPF1 (surrogate) where surrogate data is obtained by randomly exchanging phases of the original MicroPF1. **e** Histogram of sample for the *dashed line* in **d**. **f** Histogram of sample for the *solid line* in **d**. The samples in **c**, **e** and **f** are defined as in **b** similarly. The *dashed lines* in **a** and **d** prove the hypothesis that the last segment of correlation or phase synchrony curve is significantly different from any previous segments. The hypothesis is also proved by the fact that the mean value of the last segment (MVLS) for correlation or phase synchrony of raw data (see the marked “MVLS” in **b** or **e**) is outside the main distribution of mean values of segments. Moreover, the hypothesis is further proved by the fact that the mean value of the last segment for correlation or phase synchrony of surrogate data falls into the main distribution of mean values of segments based on **c** and **f**

null hypothesis that the last segment is not significantly ($p < 0.001$) different from any previous segment in the interval $[0, 587]$. Histograms of sample for the dashed line in Fig. 2a, d are described in Fig. 2b, e where sample points include one point, which is mean value of the last segment, and all other points, which are mean values of all

segments of the fixed window size (i.e., 153 s as the length of the last segment) in the interval $[0, 587]$. One can see that the mean value of the last segment for correlation or phase synchrony of the original data (see the marked “MVLS” in Fig. 2b or e) is outside the main distribution of mean values of segments. This fact proves that the last

segment is significantly different from any previous segment in the interval $[0, 587]$ and demonstrates that there is a significant increase trend before the macroseizure onset in micro domain. Histograms of sample for the solid line in Fig. 2a, d are presented in Fig. 2c, f where sample points are calculated in a similar way as those sample points in Fig. 2b. And the mean value of the last segment for correlation or phase synchrony of surrogate data falls into the main distribution of mean values of segments. That means the above hypothesis holds for the surrogate data. We generated 100 surrogate data to test the above hypothesis for correlation and phase synchrony and found that the above hypothesis holds by 100 times for correlation and phase synchrony. As such, for correlation and phase synchrony of surrogate data the last segment is not significantly ($p < 0.001$) different from any previous segment in the interval $[0, 587]$ at all. Therefore, for correlation and phase synchrony between real microwire iEEG MicroMT2 and MicroPF1 the above hypothesis should be rejected with full confidence. This conclusion is still true for all other curves in Fig. 1e, f when we did analysis in above similar way. Due to the ratio $\phi = 8/15 > 50\%$ where 8 is the number of curves having increase trend and 15 is the number of total available microwire channels, we can make a conclusion that an increase trend for correlation or phase synchrony of microwire channels in ripple band well exists before the macroseizure onset of Patient 1.

Note that each curve in Fig. 1e, f satisfies the strict criteria and as a result, mean value of the last segment is outside the main distribution of mean values of segments (i.e., $p < 0.001$). If we loose the criteria and use $p < 0.05$, we can collect more curves showing increase trend before the macroseizure onset and/or extend the interval $[0, 587]$ to a longer interval (e.g., $[-100, 587]$) so that the last segment is significantly ($p < 0.05$) different from any previous segment in the longer interval (e.g., $[-100, 587]$).

Patient 2

We present correlations (similar results for phase synchrony are omitted) of one microwire channel with all other available microwire channels in four frequency bands (i.e., alpha, gamma, ripple and fast ripple) in Patient 2 and show the difference before the macroseizure onset. A 200 s sample of iEEGs is plotted in Fig. 3a where we collected 8 microwire channels (Micro1–8) and the microseizure onset at 800 s is the same as the macroseizure onset. One can see the obvious different neural oscillations of higher amplitudes during $[760, 800]$ compared to previous time period. This phenomenon further confirms that it is only when the seizure has

Fig. 3 Patient 2: Correlations of MDMicro7 with all other microwire channels in four frequency bands. **a** A 200 s sample of iEEGs where the macroseizure onset is at 800 s. One can see the obvious different neural activity during $[760, 800]$ compared to previous time period. **b** Correlation in alpha band. **c** Correlation in gamma band. **d** Correlation in ripple band. **e** Correlation in fast ripple band. If we set the last segment covering from 760 to 800 for each curve in **b–e**, then, base on the strict criteria increase trend for correlation can be found in alpha, gamma and ripple bands before seizure onset (e.g., among 7 curves in each subfigure, 4 curves (MDMicro7–1, MDMicro7–2, MDMicro7–3, MDMicro7–8) in **b**, 6 curves (MDMicro7 ~ 1, ..., MDMicro7 ~ 6) in **c**, and 4 curves (MDMicro7–1, MDMicro7–3, MDMicro7–4, MDMicro7–6) in **d** are found to have increase trend in the interval $[0, 800]$). This kind of increase trends are caused by the obvious changing neural activity during $[760, 800]$. No increase trend can be found for any curve in **e**

recruited enough surrounding brain tissue does the signal become strong enough to be observed on the clinical macroelectrode. Correlations of Micro7 with other microwire channels in alpha, gamma, ripple and fast ripple bands are plotted in Fig. 3b, e, respectively. Now define the last segment covering from 760 to 800 for each curve in Fig. 3b, e. Base on the strict criteria, that is, mean value of the last segment for each curve is greater than that of previous any segment of the length of 40 s in the interval $[0, 760]$, an increase trend for correlation can be found in alpha, gamma and ripple bands before the macroseizure onset (e.g., among 7 curves in each subfigure, 4 curves (MDMicro7–1, MDMicro7–2, MDMicro7–3, MDMicro7–8) in Fig. 3b, 6 curves (MDMicro7 ~ 1, ..., MDMicro7 ~ 6) in Fig. 3c, and 4 curves (MDMicro7–1, MDMicro7–3, MDMicro7–4, MDMicro7–6) in Fig. 3d are found to have an increase trend in the interval $[0, 800]$). The increase trend is caused by the obvious changing neural activity during $[760, 800]$. No increase trend can be found for any curve in Fig. 3e.

Patient 3

Four consecutive seizures with total 14,895 s (i.e., 4 h, 8 min, and 15 s) are presented in Fig. 3 where a sample of 100 s iEEGs of the first seizure with the macroseizure onset at 4,075 s of RATstrip, a sample of 100 s iEEGs of the second seizure with the macroseizure onset at 9,022 s of RATstrip1, a sample of 100 s iEEGs of the third seizure with the macroseizure onset at 10,423 s of RATstrip1, a sample of 150 s iEEGs of the fourth seizure with the macroseizure onset at 14,263 s of RATstrip1, are shown in Fig. 4a, d, respectively. One can see that the second and fourth seizures have larger amplitudes and longer time period than the first and third ones. The fourth seizure has larger amplitudes and longer time period than the second one. Moreover, for each seizure the onset took place simultaneously for both microseizure and macroseizure.

Correlations (or phase synchronies) of microRAT3 with microRAT1, 2, 4 in gamma band are plotted in Fig. 4e for the interval [0, 9,270] and Fig. 4f for the interval [9,270,14,895] (or, Fig. 4g, h). It is noted that phase

synchrony is similar to the corresponding correlation except for a little difference that phase synchrony is smoother than correlation. We use the downside arrow to mark each seizure onset in Fig. 4e, h. Increase trend can be

Fig. 4 continued

clearly seen in some interval before each seizure onset in Fig. 4e, h except for decrease trend of the dashed line before the fourth seizure onset in Fig. 4f or h. It is also observed that the increase trend before the fourth seizure

onset is the strongest than the increase trends before other three seizure onsets. So, the stronger increase trend leads to the fourth seizure with larger amplitude and longer time period compared with other three seizures. This once again

◀ **Fig. 4** Patient 3: Four consecutive seizures with total 14,895 s (i.e., 4 h, 8 min, and 15 s). **a** A sample of 100 s of iEEGs with macroseizure onset at 4,075 s of RATstrip1. **b** A sample of 100 s of iEEGs with macroseizure onset at 9,022 s of RATstrip1. **c** A sample of 100 s of iEEGs with macroseizure onset at 10,423 s of RATstrip1. **d** A sample of 150 s of iEEGs with macroseizure onset at 14,263 s of RATstrip1. Comparing with four seizures, the fourth seizure in **d** has larger amplitudes and longer time period. Moreover, for each seizure the microseizure onset is the same as the macroseizure onset. **e** and **f** Correlations of microRAT1 with microRAT2, 3, 4 in gamma band (30–80 Hz) during the interval [0, 9,269] and [9270, 14,895], respectively. **g, h** Phase synchronies of microRAT1 with microRAT2, 3, 4 in gamma band during the interval [0, 9,269] and [9270, 14,895], respectively. The *downside arrows* in **e–h** mark four seizure onsets. One can see that there is a clear increase trend before each seizure onset for both metrics of correlation and phase synchrony except for the *dashed line* in **f** and **h** before the fourth seizure onset

provide more evidence to support the hypothesis of progressive coalescence of microseizure domains.

For patient 3 we analyzed correlation (or phase synchrony) for more than 4 h microwire channel iEEGs. Although we find that there is an increase trend before each seizure onset, we cannot guarantee that macroseizure must follow once we find an increase trend before some time instant for correlation or phase synchrony. For example, no seizure exists around 11,270 s in Fig. 4f or h even if we find the peaks at 11,270 s for two solid lines.

Summary of correlation or phase synchrony of microwire iEEGs for 24 seizures

In this study, we conducted analysis of correlations and phase synchronies of microwire iEEGs for 24 seizures from 8 epilepsy patients in four different frequency bands: alpha, gamma, ripple, and fast ripple. The results are summarized in Table 1 where Seizures 1–4 are from Patient 3, Seizures 5–8 are from Patient 1, Seizures 9–10 are from Patient 2, Seizures 11–14 are from Patient 4, Seizures 15–17 are from Patient 5, Seizures 18–19 are from Patient 6, Seizures 20–21 are from Patient 7, Seizures 22–24 are from Patient 8. From Table 1, we highlight the following points: (1) increase trend of correlation or phase synchrony before macroseizure onset can always be found in one or more frequency bands for all 24 seizures (e.g., all four bands for Seizure 8 and only one band for Seizure 3); (2) Time interval of the last segment, which is seizure-dependent, varies from several seconds to several hundreds of seconds; (3) The strict criteria, that is, mean value of the last segment is greater than mean value of any previous segment of the same length as that of the last segment in the early time period, plays a key role in determining whether an increase trend exists before macroseizure onset. Due to this criteria, sometimes correlation increases, but phase synchrony may not increase in some frequency band (e.g., Seizure 11) or vice versa (e.g., Seizure 6); (4) based on the last row of the

table, correlation or phase synchrony increases before macroseizure onset mainly in gamma and ripple bands.

Discussions and conclusions

Micro/macrowire intracranial EEG signals recorded from deeply implanted micro/macroelectrodes in epileptic patients have been widely used because they include much information in seizure transition compared to that from cortical electrodes. The difference between macrowire iEEG and microwire iEEG is that macrowire iEEG reflects potentials beneath the macroelectrode which actually consist of sum of potentials of numerous surrounding neurons within a larger area because of the larger area of the macroelectrode, and microwire iEEG reflects potentials surrounding the microelectrode which actually consist of sum of potentials of small number of neurons within a smaller area because of the smaller area of the microelectrode. Moreover, microelectrode is contacted more close to neurons than macroelectrode and microelectrode reflects activity of neurons more directly than macroelectrode. Due to this different structure, microwire iEEG includes much more neural activity information than macrowire iEEG. As such, in some cases, much earlier microseizure activities can be clearly seen in microwire iEEGs from some microelectrodes before the macroseizure onset, but no any macroseizure activities can be observed in macrowire iEEGs before the macroseizure onset (see, e.g., Fig. 1a, b). The possible reason for no observation of macroseizure lies in the fact that many other potentials from surrounding normal tissue/neurons dominate potentials reflected on the macroelectrode so that microseizure signals are rather weak and can not be observed on the macroelectrode. Later on, after microseizure signals become more strong and cause more surrounding tissue/neurons generating microseizure signals so that microseizure signals dominate potentials reflected on the macroelectrode, then macroseizure can be observed on the macroelectrode. The above evidence actually supports the following idea that a focal seizure is generated and observed only in a small area of the brain at initial stage, then the neural activity spreads out to other brain areas as it becomes more strong. It is only when the seizure has recruited enough surrounding brain tissue does the signal become strong enough to be observed on the clinical macroelectrode. Therefore, it seems that the signal from microelectrode is becoming more and more strong before the macroseizure onset.

In this study, we investigated the seizure generation from microwire iEEGs and showed the hypothesis of progressive coalescence of microseizure domains as microwire iEEG signals become more strong before the

Table 1 Summary of correlations and phase synchronies of micro-wire iEEGs of 24 seizures from 8 patients in four frequency bands (A: alpha band (1–30 Hz), B: gamma band (30–80 Hz), C: ripple band (80–250 Hz), D: fast ripple band (>250Hz)) where Y represents

increase trend exists and N represents no increase trend exists for correlation or phase synchrony before the macroseizure onset which was checked and determined by Neurologists in Mayo Clinic at Rochester, USA

Seizures	Correlations				Phase synchronies				Time intervals of the last segments (s)
	A	B	C	D	A	B	C	D	
Seizure 1	N	Y	N	N	N	Y	N	N	109
Seizure 2	N	Y	Y	N	N	Y	Y	N	112
Seizure 3	N	Y	N	N	N	Y	N	N	345
Seizure 4	N	Y	Y	Y	N	Y	Y	Y	353
Seizure 5	N	Y	Y	N	N	Y	Y	N	153
Seizure 6	N	N	N	Y	N	Y	N	Y	160
Seizure 7	N	Y	Y	Y	N	Y	Y	Y	91
Seizure 8	Y	Y	Y	Y	Y	Y	Y	Y	423
Seizure 9	Y	Y	Y	N	N	N	N	N	40
Seizure 10	Y	Y	Y	Y	Y	Y	Y	Y	6
Seizure 11	Y	Y	Y	N	N	Y	N	N	16
Seizure 12	Y	N	Y	N	Y	N	N	N	10
Seizure 13	N	N	Y	N	N	N	N	N	6
Seizure 14	N	Y	Y	N	N	N	N	N	65
Seizure 15	Y	Y	N	Y	Y	Y	N	N	233
Seizure 16	N	Y	Y	Y	N	N	Y	Y	80
Seizure 17	N	Y	Y	Y	N	Y	Y	N	100
Seizure 18	N	Y	Y	Y	N	Y	N	Y	184
Seizure 19	N	Y	Y	N	N	Y	Y	N	45
Seizure 20	Y	Y	Y	N	N	Y	Y	N	129
Seizure 21	Y	N	Y	N	N	N	Y	N	130
Seizure 22	N	Y	N	N	N	Y	N	N	185
Seizure 23	Y	Y	Y	N	N	N	Y	N	24
Seizure 24	N	Y	N	N	N	N	N	N	69
Total no. of Ys	9	20	18	9	4	16	12	7	

macroseizure onset. To do so, we analyzed two metrics (correlation and phase synchrony) to show what is going on for both of correlation and phase synchrony before the macroseizure onset, and found that there is an increase trend of correlation and/or phase synchrony between microchannels before the macroseizure onset. A reason for the increase trend is that the microwire iEEGs are becoming more and more strong before the macroseizure onset (see, e.g., Fig. 3a) so that two microwire iEEGs are more and more correlated. This result is totally different from the well-known one in macro domain that decrease trend of phase synchrony of macro channel iEEGs before the macroseizure onset exists in common. A possible explanation for the decrease trend of phase synchrony in macro domain can be described as follows: When the seizure signal becomes strong enough so that it can be seen on the first macroelectrode, but meanwhile it is still in the process of spreading out and does not reach in time to

tissue beneath the second macroelectrode (especially when two macroelectrodes are placed at two different parts of the brain) before the macroseizure onset at the first macroelectrode. In this case, the signal recorded from the second macroelectrode is dominated by neural activity from normal tissue/neurons beneath the second macroelectrode. Hence, as the seizure signal at the first macroelectrode is becoming more strong, these two signals are becoming more uncorrelated and cause the decrease trend of phase synchrony before the macroseizure onset.

We studied correlations and phase synchronies of microwire iEEGs for 24 seizures from 8 epilepsy patients based on four different frequency bands: alpha (1–30 Hz), gamma (30–80 Hz), ripple (80–250 Hz), and fast ripple (250–500 Hz). First of all, one correlation or phase synchrony curve of microwire iEEGs is said to have an increase trend before the macroseizure onset of one seizure if mean value of the last segment is greater than mean

value of any previous segment of the same length as that of the last segment in the early time period. Then, this seizure is said to have an increase trend of correlation or phase synchrony of microwire iEEGs before the macroseizure onset if more than half of all correlation or phase synchrony curves have an increase trend before the macroseizure onset in one or more frequency bands. In this way, we found that increase trend exists for all 24 seizures before each macroseizure onset in one or more frequency bands. Moreover, increase trend mainly took place in gamma and ripple bands. The frequency range in gamma and ripple bands is consistent with the existing finding that an increase in high-frequency activity (60–100 Hz) in the 20 min prior to neocortical seizure onset was anticipated in most of seizures (Worrell et al. 2004) based on macro iEEGs. It should be noted that there are two key factors to determine whether a correlation or phase synchrony curve has an increase trend before the macroseizure onset: (i) Time interval of the last segment. We define the same time interval of the last segment for all correlation and phase synchrony curves of each seizure in all four frequency bands (see, e.g., Fig. 2a) where the last segment of each curve is ended at the macroseizure onset. Time interval of the last segment is seizure-dependent and varies from several seconds to several minute; (ii) The ratio ρ , i.e., the length of the early time period divided by the length of the last segment where the early time period means that before the beginning time instant of the last segment (e.g., the early time period in Fig. 2a covers [0, 587]) and mean value of the last segment is greater than that of any segment of the same length in the early time period. If the length of the last segment is greater than 100 seconds, then the ratio $\rho > 3$ is required. If the length of the last segment is in the range of several seconds or tens of seconds, then the ratio $\rho > 10$ is required. Such kind of requirement for the ratio ρ is reasonable based our experiments. In addition, we want to point out that due to the same constraint on ρ for correlation and phase synchrony, sometimes correlation has an increase trend, but phase synchrony may not have in some frequency band (e.g., Seizure 11) or vice versa (e.g., Seizure 6) in Table 1. Therefore, to determine whether a given seizure has an increase trend before the macroseizure onset for correlation or phase synchrony of microwire iEEGs, there are three key factors: The selection of time interval of the last segment, the ratio ρ , and the ratio ϕ where the ratio ϕ is the number of correlation or phase synchrony curves having increase trend over the number of all correlation or phase synchrony curves. For example, in this study we selected $\phi > 50\%$. This is rather reasonable because we cannot guarantee all curves have an increase trend in reality. But more than half of curves having the property is enough to draw the conclusion. Currently, many researchers calculate

one bivariate measure for all pair of possible channel pairs and then get average values to analyze EEG signals such as average phase synchrony and average maximum linear cross correlation (e.g., Mormann et al. 2003a, 2003b; Aarabi et al. 2008). However, if we calculate average values, we can not find increase trend in some case. For example, if we calculate average values of three correlation curves in Fig. 4f and get an average curve, we can find that this curve will decrease before the fourth macroseizure onset of this patient. Under the constraint of $\phi > 50\%$, we can get the result that all 24 seizures from 8 patients have an increase trend before their macroseizure onsets for correlation and phase synchrony of microwire iEEGs. However, if we raise more strict constraint on ϕ , e.g., $\phi > 70\%$, then some of seizures do not have an increase trend based on this strict constraint. In this study, the optimal channel is same for all possible macroseizures of the same patient.

To show the significant difference between the last segment and the early time period for each correlation or phase synchrony curve having increase trend before the macroseizure onset, we applied surrogate data to test the null hypothesis that the last segment is not significantly different from the early time period. The reason why we used surrogate data is that it makes no a priori assumptions on the nature of the experimental data. For correlation, we generated surrogate data to keep the same linear cross correlation and autocorrelation as original data (Andrzejak et al. 2003) (see the solid line in Fig. 2a). For phase synchrony, we kept one channel data unchanged and got surrogate data of the other channel data by randomly exchanging phases of this original channel data (Lachaux et al. 1999) (see the solid line in Fig. 2d). We obtained samples from correlation curve or phase synchrony curve of the original data and surrogate data where sample points include the mean value of the last segment and mean values of all segments of the same length as that of the last segment in the early time period, and plotted histogram of samples. We found that the point of mean value of the last segment is outside main distribution for correlation or phase synchrony of the original data (see Fig. 2b, e). However, mean value of the last segment falls inside main distribution for correlation or phase synchrony of surrogate data (see Fig. 2c, f). This fact proves that the last segment is significantly ($p < 0.001$) different from any previous segment in the early time period and demonstrates that there is a significantly increase trend before the macroseizure onset for real microwire iEEG. This conclusion does not hold for their surrogate data. We generated 100 surrogate data to test the null hypothesis that the last segment of correlation or phase synchrony curve is not significantly ($p < 0.001$) different from any early segment. We found the hypothesis holds for all 100 times for surrogate data.

Therefore, with full confidence the last segment is significantly ($p < 0.001$) different from any previous segment in the early time period for correlation or phase synchrony of real microwire iEEG before macroseizure onset, that is, there is a significantly increase trend for correlation or phase synchrony of real microwire iEEG before macroseizure onset.

We also conducted independent component analysis for microwire iEEGs and found that there are some components such that their correlations or phase synchronies have the similar pattern as that of raw data (see Fig. 1g), namely, the same increase trend before the macroseizure onset. This fact reveals that these ICs are major sources causing the increase trend. So, the increase trend further demonstrates the progressive coalescence (or spread process) from this source IC to other source ICs.

In this study, although we find that there is an increase trend for correlation or phase synchrony of microwire iEEGs before each macroseizure onset, we cannot guarantee that macroseizure must follow once we find an increase trend before some time instant. In the future, we will combine macrowire channels with a decrease trend of correlation or phase synchrony and microwire channels with an increase trend of correlation or phase synchrony together to propose a feasible algorithm to predict upcoming seizures.

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