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Functional Connectivity between Brain Areas Estimated by Analysis of Gamma Waves

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Abstract

The goal of this study is to investigate functional connectivity between different brain regions by analyzing the temporal relationship of the maxima of gamma waves recorded in multiple brain areas. Local field potentials were recorded from motor cortex, hippocampus, entorhinal cortex and piriform cortex of rats. Gamma activity was filtered and separated into two bands; high (65–90Hz) and low (30–55Hz) gamma. Maxima for gamma activity waves were detected and functional connectivity between different brain regions was determined using Shannon entropy for perievent histograms for each pair channels. Significant Shannon entropy values were reported as connectivity factors. We defined a connectivity matrix based the connectivity factors between different regions.

We found that maxima of low and high frequency gamma occur in strong temporal relationship between some brain areas, indicating the existence of functional connections between these areas. The spatial pattern of functional connections between brain areas was different for slow wave sleep and waking states. However for each behavioral state in the same animal the pattern of functional connections was stable over time within 30 minutes of continuous analysis and over a 5 day period. With the same electrode montage the pattern of functional connectivity varied from one subject to another.

Analysis of the temporal relationship of maxima of gamma waves between various brain areas could be a useful tool for investigation of functional connections between these brain areas. This approach could be applied for analysis of functional alterations occurring in these connections during different behavioral tasks and during processes related to learning and memory. The specificity in the connectivity pattern from one subject to another can be explained by the existence of unique functional networks for each subject.

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Disclosure.

None of the authors has any conflicts of interests to disclosure. 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.

Keywords

functional connections; gamma waves; perievent histograms; Shannon entropy; connectivity value

Introduction

Identification of interrelated regions reveals **pathways that the brain uses to process** information both normally and abnormally. Two kinds of connectivity between different brain regions have been explored by neuroscientists: structural and functional (Bullmore and Sporns, 2009). Structural connectivity (SC) can be determined by histology and imaging techniques, and it can elucidate how different brain regions intertwine through direct contacts. Functional connections (FC) between different regions of brain are the results of complex interactions by electrical activity of neuronal elements. These connections can be revealed by mathematical techniques performed on the electrical or imaging signals recorded from diverse brain regions and help us to understand how the brain processes the information from sensory inputs and performs its mental activity (Bressler, 1995; Mesulam, 1998; McIntosh, 2000; Buzsáki, 2006).

Among EEG methods used to investigate FC between brain areas the most popular are: correlation, covariance, coherence and phase locking between the signals recorded from the regions of interest and some of these were proposed in previous publications (Jalili and Knyazeva, 2011; Blinowska, 2011; de Haan, 2009; Chu et al., 2012).

In this study we wished to investigate whether **FC** between different brain areas could be revealed by detecting amplitude maxima of gamma activity recorded in these areas and evaluated by measuring the Shannon entropy of the perievent histograms. Then, we applied statistical methods to examine whether the FC patterns varied from one state to another state and to check consistency in the FC during gamma activity over time within each state. Finally, statistical analysis was used to compare the functional networks among different animals using the same electrode montage.

Methods

All procedures described in this study were approved by the University of California at Los Angeles Institutional Animal Care and Use Committee. Experiments were performed on adult male (200–250 g) Wistar rats.

Microelectrode implantation

Animals (n=7) were anesthetized with a mixture of ketamine (100 mg/kg), xylazine (5.2 mg/kg), and acepromazine (1.0 mg/kg, administered i.m.). A pair of tungsten micro-wires (50 μ m OD) with 1mm distance between tips were implanted bilaterally into the following brain areas: 1) CA3 area of posterior hippocampus (coordinates: **anterior-posterior** (AP)=−5.6, **medial-lateral** (ML)=3.5 **dorsal-ventral** (DV)=5.0), 2) DG of the anterior hippocampal complex (coordinates (AP)=−3.5, ML=2.0, DV=4.5), 3) entorhinal cortex (EC) (coordinates AP=−8.0, ML=5.0, DV=7.0), 4) piriform cortex (Pir) (coordinates (AP)=1.0, ML=4.5, DV=7.5). **Two stainless steel watch screws driven into the bone above the cerebellum served as indifferent and ground electrodes.**

Data Acquisition

Experiments were carried out under freely moving conditions. Beginning one week after surgery rats were plugged in for 6 hours a day for one week to a MOSFET input operational

amplifiers mounted in the cable connector to reduce cable movement artifacts. Brain electrical activity was recorded **with referential montage** in the frequency-band 0.1 Hz to 3.0 kHz. and sampled at 10.0 kHz/channel with 12 bit precision on Run Technologies (Mission Viejo, CA) DataPac software. After completion of experiments animals were anesthetized with an overdose of Nembutal (50 mg/kg). Fifteen minutes after cessation of breathing and heart beat, animals were plugged in to the cable and activity was recorded for five minutes. Then animals were perfused with physiological solution followed by 4% paraformaldehyde. After 3 days of postfixation the brains were sliced in 60 μ m sections for visualization of microelectrode location after staining with cresyl violet.

Data Analysis

To obtain data under comparable conditions, we selected file durations of 3 to 5 minutes from two behavioral states in each animal: 1) slow-wave sleep (SWS), periods of sleep with high amplitude slow wave activity, and 2) during exploratory activity, which is characterized by EEG theta activity (TA). These states were verified by video recording and identified on the basis of amplitude of EEG and dominance of slow waves (<1Hz) and TA respectively, on the power spectrograms.

Theory and Calculation

Functional connectivity during gamma activity was estimated based on the temporal relationship of its amplitude maxima between different brain areas. The first step in this process was to filter the recorded signal. Data were down sampled up to 1.0 kHz, gamma frequency was divided into two parts; low gamma (LG) 30–55 Hz and high gamma (HG) 65–90 Hz (Belluscio et al. 2012). The frequency band 55 to 65 Hz was excluded to avoid the false connectivity detection during 60 Hz produced by electrical devices. The data recorded from dead subject were considered to be the system noise. This noise was canceled from the signal using Wiener filter. After noise cancellation, we detected local maxima for each recording microelectrode in the filtered signals using Matlab software an FIR bandpass filter was applied to extract the gamma frequency and then the local maxima were detected using the local detection algorithm existing in matlab toolbox. The detected peaks were called “the events” (Figure 1. A).

To evaluate the relationship of detected events, we used peri-event histograms which visualize the rate and timing of events in relation to each other. For each event in one channel, (channel A) we looked at T seconds before and after to that event and counted the number of events in each time bin in the other channel (channel B). We repeated these for all N detected events in channel A and draw the time histogram in the range of $-T$ to $+T$. The details of the algorithm can be found in Davey et al., 1986, Bretschneider and De Weille, 2006 and Palm et al. (1988). (Figure 1. B,C). Based on the Nyquist rate the highest detectable frequency of events should be half the sampling rate ($1000\text{Hz}/2=500\text{ Hz}$). Two events can be separated from each other by the time resolution of 2 ms ($1/500\text{ Hz}$). Therefore, we chose 2ms as a bin size. The time window (L) during which a related event could occur was chosen as $1/f_{\text{min}}$ (f_{min} is the minimum frequency in each frequency range). For LG, f_{min} is 30 Hz, thus L is $1/30\text{Hz}\approx 34\text{ ms}$ and for HG, f_{min} is 65 Hz, thus L is $1/65\text{Hz}\approx 16\text{ ms}$. According to a rule of thumb used by statisticians, to produce a valid histogram we need at least 30 data points for each bin interval. Therefore, we needed $1020(=34\text{ bins}\times 30\text{ events})$ events for LG and $480(=16\text{ bins}\times 30\text{ events})$ events for HG. Based on the mid-frequency for each gamma band widths; $((30\text{ Hz}+55\text{ Hz})/2)=42.5\text{ Hz}$ and $((65\text{ Hz}+90\text{ Hz})/2)=77.5\text{ Hz}$, we needed minimum file duration 24 seconds ($\approx 1020\text{ events}/42.5\text{ Hz}$) for LG and 8 seconds ($\approx 480\text{ events}/77.5\text{ Hz}$) for HG.

The two channels from the histogram can be considered functionally connected when there is a significant peak in the peri-event histogram. Shannon entropy measures the strength of the peak in the histogram. For the histogram with N bins, the p_i was the probability of an event belonging to the i^{th} bin. S defined as:

$$S = - \sum_{i=1}^N p_i \ln(p_i)$$

The lower the S is, the more certainty in the data (stronger connectivity between the two channels involved in the histogram). Maximum S indicates uniform distribution. In uniform distribution, all events have the same likelihood of occurrence ($p_i = 1/N$). Therefore S_{max} is:

$$S_{max} = - \sum_{i=1}^N \frac{1}{N} \ln\left(\frac{1}{N}\right) = \ln(N).$$

To examine the authenticity of measured connectivity, we applied bootstrapping (Manly, 2007).

We defined a “**connectivity factor**” as the strength of connectivity between two recording channels, which varies from ‘0’ to ‘1’ (‘1’ means fully connected and ‘0’ means fully disconnected). A “connectivity factor” (h_{ij}) between two recorded channels (i and j) was calculated by subtracting the Shannon entropy calculated for the peri-event histogram between those channels (s_{ij}), from its maximum (S_{max}):

$$h_{ij} = \frac{S_{max} - s_{ij}}{S_{max}}$$

For calculation of the **significance** of the connectivity factor in each network two channels were selected randomly and a bootstrapping algorithm was used to find the significance level. An example of such a calculation is presented in Figure 1.C. The original connectivity matrix is shown in Figure 1.D. As seen, the connectivity value between channels 3 and 4 had the largest value (0.1088). Two channels were selected randomly (here 5 and 10) and the histogram of the connectivity values for 1000 trials was illustrated in Figure 1.C. The 950th highest connectivity value was 0.0098. Every functional connection that had higher than 95% significance level was considered as non random.

All the connectivity factors were combined into a matrix, the “**connectivity matrix**” (Figure 1.D). The components of the connectivity matrix reflect the connectivity factors between different recording sites, i.e. the i^{th} row j^{th} column component shows the connectivity factor between channels i and j. The connectivity matrix must be symmetrical since the connectivity factor between channels i and j is equal to the connectivity factor between channels j and i. We built an $M \times M$ “connectivity matrix” for M recording channels. The component of i^{th} row and j^{th} column was h_{ij} , which reflected the strength of connectivity between two recording channels (i and j) (Figure 1.D and E).

To compute the resemblance between two matrices with the same rank, we used the Mantel test (Mantel 1967). In the Mantel test method, to compare matrices A and B, we need to calculate the sum of the inner products of the components in each matrix, excluding the diagonal values:

$$z_m = \sum_{i=1}^{n-1} \sum_{j=i+1}^n a_{ij} b_{ij},$$

where a_{ij} and b_{ij} are the i^{th} row and j^{th} column components of the two matrices A and B respectively. However, z_m can be normalized and more easily interpreted as the numbers between -1 and 1 (Legendre P. and Legendre L., 1998). Normalized z_m is called r_M

$$r_M = \frac{1}{d-1} \sum_{i=1}^{n-1} \sum_{j=i+1}^n \left(\frac{a_{ij} - \bar{a}}{\sigma_a} \right) \left(\frac{b_{ij} - \bar{b}}{\sigma_b} \right),$$

where d is the number of components in the upper triangular part of each matrix, σ_a and σ_b are the standard deviations and $\bar{a}$ and $\bar{b}$ are the mean of a_{ij} 's and b_{ij} 's. Later on, by applying Monte Carlo randomization techniques, the p-value is estimated by permutation tests (Manly, 2007). The Mantel test gives two values, first the p-value which indicates the significance of the calculated similarity factor, and second the similarity factor. *If the similarity factor is not significant, it means the two matrices are different from each other.* Two matrices are being considered similar, if not only their similarity value is significant but also if the value is higher than threshold. This threshold can be determined heuristically based on the analyzed data.

Bootstrapping was applied to identify the locations of differences between two networks (Manly, 2007). For m files recorded during TA and n files during SWS, we formed m and n connectivity matrices. These two groups of matrices were compared by the bootstrapping method.

Results

Information values of different types of analysis

Perievent histogram analysis is used to investigate the temporal relation between two selected channels (Figure 1.A, B). The matrix of color coded perievent histograms (Figure 1.C) shows the functional connectivity of the selected channel with each individual channel within a network of electrodes implanted in a brain. The connectivity matrix (Figure 1.E) depicts the functional connections of the entire network at a given time in an individual animal. In addition, this matrix estimates functional connections of each recording site in each individual animal. For example color perievent histograms show that channel 1 has stronger functional connections to channels 2, 5 and 9 than to other channels (Figure 1.C arrows). This temporal relation can be seen in the connectivity matrix depicted in Figure 1.E, (see arrows). Graphical presentation of some functional connections from this connectivity matrix (Figure 1.F) shows that there are strong functional connections between pairs of electrodes 1–2, 3–4, 5–6, and 15–16. In addition the recorded site 1 has long connections with channels 5 and 9, while recorded site 12 has broad functional connections with recording sites 2, 3, 4, 9, 15, 16.

The pattern of connectivity matrix in different behavioral states

To examine how the pattern of FC changes from one state to another, we compared the components of connectivity matrices during LG-SWS to the same components of connectivity matrices during LG-TA in the same subject. Each component represented the connectivity between two recording channels out of 16 channels recorded from

hippocampus, entorhinal cortex and piriform cortex. For each connection, we compared 17 to 49 values using bootstrapping to determine the statistical significance. Figure 2.A shows an example of peri-event histograms between RAH and RPir during LG-TA (top) and LG-SWS (bottom). During TA a significant number of events in these areas occurred within time window 0–10ms indicating the existence of functional connectivity. During SWS functional connectivity was absent and gamma events in RAH and RPir occurred independently.

There were one hundred twenty connections in total; each channel was compared with fifteen other channels during SWS and TA states. ($16 \times 15/2$, division by two performed to cancel the repetition, there was no difference between connections among channel i and j or j and i). Analysis of the connectivity pattern between all channels revealed that during SWS strong connections (p-value <0.05) were depicted between RAH-RPH and CA3-REC (Figure 2.B **top**). The connectivity values of fifty-seven out of 120 connections were significantly different between SWS and TA states. They were significantly broader between different brain areas during the TA state (Figure 2.B **bottom**). All connections that changed significantly between the two states are summarized in the matrix shown in Figure 2.C (**red**).

A similar analysis was performed for the HG. One hundred and fifty two files during SWS were compared to fifty six files during TA. There were twenty connections out of 120 that changed significantly between the two states. One of those twenty connections was significantly stronger during SWS (LAH-RPH) and the rest were significantly stronger during TA with p-value <0.05 (not shown).

Consistency of the connectivity matrix over different time periods

Over a single behavioral state period—Record durations of 3–5 minutes from all 7 animals obtained during SWS and TA were divided on 24 second consecutive files for LG and 8 second files for HG. These files were compared with each other to see whether the connectivity varied over time. Normalized similarity factors were calculated based on the Mantel test (see the Methods Section). An example of this analysis for one subject is shown in Figure 3. There were 5 files during LG and 16 files during HG. As seen in this figure, there was consistency in the brain network FC over this time period in the same subject during the same behavioral state. Based on the analysis the connectivity matrices of these files were similar to each other with a p-value of <0.001.

Over different days—One or 2 files recorded during SWS and TA in one day were compared during four different days in the same animal. The connectivity matrix for each day was the average of the connectivity matrices of the continuous recorded files on that day. The validity of this approach was proven in the previous section, when we demonstrated that the connectivity matrix did not change within a single SWS or TA state. Six files were averaged during LG and nineteen files during HG (p-value<0.0001) (Figure 4.A). The same procedure was applied to investigate FC consistency during the TA state for four days (Figure 4.B) and p-values for similarity of all files were less than 0.0001.

Consistency of the connectivity matrix between different subjects—Similar to previous analysis the Mantel test was used to check similarity and p-values of connectivity matrices in different animals for the LG frequency band. If the p-value was less than 0.05, the calculated similarity factor was considered to be significant. As seen in Figure 5. A, B during SWS the pattern of FC was different between animals 2 and 3, as well as between 3 and 7 (p>0.05) and between all other animals it was similar (p<0.05). During TA in the same group of animals the pattern of FC was different in animals 3 and 4 (p-value<0.05). In

five animals the pattern of FC was similar (Figure 5. C,D). These data illustrate that functional networks during gamma activity could vary from one animal to another in both states; SWS and TA.

Discussion

Functional connectivity between brain areas has many “faces”. It is detected by different methods, such as EEG, MEG and fMRI and each approach has its own advantages and limitations. fMRI analysis provides good whole brain spatial and poor temporal resolution, while EEG and MEG provide good temporal and poor whole brain spatial resolution. Combinations of these MRI and electrographic approaches may bring significant progress in investigation of properties of functional connectivity in normal and pathological conditions. In this study, we investigated the functional connectivity between brain regions by analyzing temporal relations of peaks of gamma waves recorded in different brain areas. One of the reasons we choose this frequency band is because is less likely to be volume conducted due to its low amplitude. We used the peri-event time histogram for an initial analysis which provides a mean of correlating between series of simultaneously recorded events. It also could be applied for analysis of other electrographic events like sharp waves, interictal spikes or high frequency oscillations.

In order to reveal dependencies between brain areas, we defined the connectivity matrix. This approach is similar to the association matrix presented by Stephen et al., 2000, where they put a threshold on this matrix and came up with a binary adjacency matrix. However, we used the connectivity matrix in which the connectivity between nodes was not binary and since we calculated the connectivity by statistical analysis, these data were presented in the strength format. For statistical differences between connectivity matrixes we used Mantel test, however other approaches could be used (see Seba 2003, Osorio and Lai, 2011)

The calculated connectivity pattern was consistent over time within each behavioral state; SWS and TA. However, the pattern of functional connections could vary between different states. There was high similarity between the brain network patterns between LG and HG (higher than 0.7) and it seems reasonable in a future to merge these two bandwidths. We compared the FC between different animals with the same montage during SWS and TA. Functional connectivity between different subjects was not similar which indicate the existence of a unique signature of functional connectivity detected by electrical activity in each animal.

Chu et al., 2012 studied the human brain and used two measures of functional connectivity, both are linear coupling: cross correlation and coherence. With this approach stable network “templates” emerged within approximately 100 seconds. In our experiments we were able to get a stable pattern of functional connectivity within 8–24 seconds, which indicates that this approach is more sensitive for establishing of functional connections than cross correlation.

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Hlghlites

- Functional connections between brain areas were calculated on the basis of analysis of gamma activity
- Temporal relationships between maxima of gamma waves was estimated by applying the Shannon entropy to the values of perievent histograms
- The pattern of functional connections was different during slow wave sleep and exploratory activity.

Figure 1.

Information value of different steps in analysis of functional connectivity. A – An example of raw data (black) with band pass 30–55Hz filtering (red) and indication of the detection of the peak of gamma events (blue) B - The peri-event histogram between the two channels presented in the part A. C - the color coded peri-event histograms between channel 1 and all other channels within a recorded electrodes montage placed next to each other. D - The histogram of the connectivity values between channels 5 and 10 (selected randomly), one was shuffled 1000 times and the other one was kept. The 950th largest value was 0.0098. E - connectivity matrix formed based on the peri-event histograms or all channels. F –

Graphical model illustrating functional connectivity between recording electrodes presented in the matrix (E). Color indicates relative strength of connections.

Figure 2.

Functional connections during slow wave sleep and theta state. A - the peri-event histogram between RAH and RPIr during TA (top) and SWS (bottom) in a file during LG-SWS. As seen, during TA, there was more connection between these two channels. B - An average of FC for group of animals ($n=7$) that their connectivity values were significantly different for LG between two states were depicted. If the connectivity values were higher during SWS, the connections were illustrated in the top part and those were higher during TA, were shown in bottom part. C - the significant different connections between two states; SWS and TA, were shown in a matrix (p -value <0.5). Red indicated that the connections between the

two channels crossing at the red spot were significantly (p-value <0.05) different from each other among two states; SWS and TA.

Figure 3.

Consistency of connectivity matrix during a 130-second period of recording. A file from one subject was divided into 5, 24-second files for LG and 16, 8-second files for HG: A - similarity factor based on Mantel test between 5 files during LG, SWS and B - 16 files during HG, SWS in one subject. C - similarity factor based on Mantel test between 5 files during LG, TA and D - 16 files during HG, TA, in one subject. In all cases the p-values were less than 0.001. Color scale indicates similarity factor on the basis of Mantel test.

Figure 4.

Consistency of connectivity factors during SWS (A) and TA (B) within four consecutive days. The connectivity matrix for each day was the average of the connectivity matrices of six files during LG and nineteen files during HG. These estimations were acceptable, since we have already shown that the connectivity matrix would not change over consecutive time periods. The p-values for all similarity values were less than 0.0001. Color scale indicate similarity factor on the basis of Mantel test.

Figure 5. Similarity factor based on Mantel test for seven different animals during LG-SWS (A) and LG-TA (C) and their significance (B,D). Blue indicates no significant differences between patterns of connectivity matrices and red means that patterns of connectivity matrixes are different (p-value < 0.05). Color scale indicate similarity factor on the basis of Mantel test.