

Phase Locking in high gamma during a speech task

**Master thesis by Lenny Ramsey
Neuroscience and Cognition, Utrecht University**

May 28, 2010

**Research project supervised by: Eric Leuthardt and
Zachery Freudenberg**

Credits: 7.5 ECTS (5 weeks)

Abstract

A large topic of research within cognitive neuroscience is about how brain areas communicate and how the brain integrates different sensory signals into a unitary experience. High gamma frequencies in EEG and ECoG are thought to play a large role in ensemble formation and neuronal communication. High gamma up till now is treated as one large band, it is not yet clear if this band is composed of multiple smaller bands. Coherence is a relatively new solution to the binding problem, neuronal activity between different areas synchronizes to integrate different aspects of a stimulus. This has not yet been investigated in the high gamma frequency range. In this project five subjects that underwent surgical resection of an epileptic source in the brain due to intractable epilepsy, temporarily had an electrode grid implanted (for clinical purposes). These subjects participated in a language task. For each subject the phase locking value and phase locking statistics were used to find significant connections between electrodes for nine different frequency bands of which five in the high gamma range (between 80 and 385 Hz). A significant difference in number of connections between the speech and rest condition was found for the lower frequency bands, but not for the high gamma bands. This finding might be due to noise in the results above approximately 150 Hz. Because of this issue the high gamma bands could not reliably be compared. More research is needed to explore high gamma and the significance of phase locking in neuronal communication.

Introduction

To investigate how mental processes are represented in the brain, brain activity in humans and animals can be measured in many different ways and on many different scales. A widely used method in research as well as clinical practice is electroencephalography (EEG), in which electrodes are placed on the scalp to measure brain waves (see box 2). In mammals different frequency bands have been specified in these brain waves based on different functional areas and properties. Most commonly used are delta (1.5-4), theta (4-7 Hz), alpha (8-12 Hz), beta (12-30 Hz) and low gamma (30-60 Hz, but typically around 40 Hz). According to Buzsaki and others (Buzsaki & Draguhn, 2004) the rhythms in the mammalian cortex range from 0.5 to 500 Hz. Everything above low gamma is now specified as high gamma, grouping it together as one band. It is however not clear yet if this is accurate, as high gamma may consist of many different bands which still need to be separated based on function and location.

Based on measurements of brain signals in animals and humans, from the single-unit to EEG scale, gamma activity has been associated with many different functions, among others maintenance in working memory, encoding and recall of long term memory, directed attention (Jensen, Kaiser, & Lachaux, 2007) and visual feature binding (Tallon-Baudry, Bertrand, Delpuech, & Permier, 1997). Besides these functions found in gamma, high gamma has been linked to additional modalities (Ray, Niebur, Hsiao, Sinai, & Crone, 2008), for example motor (Crone, Miglioretti, Gordon, & Lesser, 1998; Crone, Sinai, & Korzeniewska, 2006; Darvas et al., 2010), auditory (Crone et al., 2001; Edwards, Soltani, Deouell, Berger, & Knight, 2005), visual (Lachaux et al., 2005), language (Crone et al., 2001) and attentional processing (Ray, Niebur et al., 2008). Overall high gamma is thought to play a large role in ensemble formation and neural communication (Edwards et al., 2005).

The question of how brain areas communicate and how the brain integrates different sensory signals into a unitary experience is called the binding problem (Treisman, 1996). This is a large area of research within cognitive neuroscience. A relatively new solution to this problem was formed by Lopes da Silva (Lopes da Silva, 1991), who suggested that coherence of neuronal activity between different areas might occur to integrate different aspects of a stimulus (for more background information see box 1). If this coherence measures connectivity we can have a look at separate frequency bands to see if there is variation, for example between frequencies in the high gamma range. Different bands in high gamma might then reflect communication between different brain areas or different levels of processing information.

Coherence is influenced by changes in amplitude and phase. Changes in amplitude are produced by the local (de)synchronization of neural ensembles in response to a stimulus, which is not necessarily communication between separate brain areas. In this project we only want to look at phase relationship between two signals, without the influence of amplitude, this is called phase locking (Lachaux, Rodriguez, Martinerie, & Varela, 1999). When two electrodes are phase locked at a certain frequency the phase difference between them stays constant over trials.

Coherence and phase locking have mostly been researched in animals and the research that has been done in humans was mostly done with EEG. EEG directly measures local field potentials (LFPs) from the scalp and thus has a high temporal

resolution (sub-millisecond, limited by the sample frequency of recording (Lachaux, Rudrauf, & Kahane, 2003)), but the spatial resolution is poor due to the low conductivity of the skull and dura mater, which blurs the signal and filters out the higher frequencies. Moreover the signal is very susceptible to contamination of artifacts from for example muscles, eye movements and blinks. This makes it difficult to look at high gamma frequencies, which might be very important due to their role in neuronal communication. A different method is magnetoencephalography (MEG). This measures magnetic fields produced by the electric currents generated by neurons. It has a higher spatial resolution than EEG because the magnetic fields it measures are affected much less by the dura, skull and scalp (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). The magnetic field has a smaller range, so only superficial activity can be measured reliably.

The most accurate measure for brain waves in humans is Electrocorticography (ECoG), which combines the high temporal resolution of EEG with a high spatial resolution. ECoG is an invasive method, in which the electrodes that measure the signal are placed under the dura, directly on top of the cortex. It has a higher signal to noise ratio than EEG because of a larger signal amplitude and less interference of artifacts. This makes ECoG more accurate and synchronized activity of neural ensembles of approximately 0.04 cm^2 (i.e. the surface of each electrode) can be recorded and the high frequencies can be measured.

In epilepsy patients ECoG can be used as a diagnostic method for intractable/pharmaco-resistant epilepsy to accurately localize the epileptogenic area and for mapping of brain-functional topography when EEG and functional and structural imaging are not sufficient. ECoG can be conducted during brain surgery, but to have more time for accurate mapping, in these patients the electrodes remain implanted for a few days up to two weeks after placement before the grids are removed and resection of the epileptogenic focus takes place. During the days in which the grids are implanted these patients can be asked to participate in research.

The phase locking between two electrodes is quantified using the Phase Locking Value. Since high gamma has not yet been explored with this method we will try to determine if there are different bands within the high gamma frequency range and if these high gamma bands play a role in communication between brain areas in a speech task. We postulate that phase locking measures communication between areas, which leads to more connections between areas during speech than during rest. We also think the high gamma frequency range consists of multiple bands which respond differently to the speech task, because they control communication between different brain areas and for different levels of language processing.

Methods

Subjects

Five subjects, all female, mean age 48.6 years (std 5.9), underwent surgical resection of an epileptic source in the brain due to intractable epilepsy at Washington University in St. Louis. They first had ECoG grids implanted for 3 to 11 days. The grids were placed over the left frontal, left frontal-parietal, left temporal, left frontal-parietal-temporal and right frontal-parietal-temporal areas of the cortex. All patients signed an informed consent form before participating. This study was approved by Human Research Protection Office at Washington University in St. Louis.

Data acquisition

Grids of 48 or 64 channels were implanted in each of the patients. The electrodes were referenced to an intracranial electrode facing up against skull. The signal from the electrodes was split before the clinical EEG amplifiers and lead to a computer with BCI2000 software. The signal was amplified and digitized at 1200 Hz. For more details on the recording system and electrode location mapping see the article of Wu and others (Wu et al., 2010).

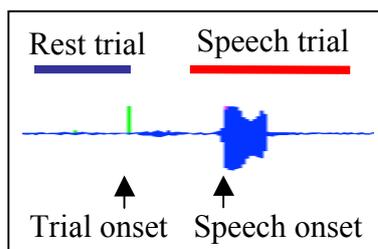
Task

The subjects performed a speech task during which the subjects heard a word through headphones which they were then asked to repeat in a microphone. The words were presented using BCI2000 (Schalk et al., 2004). The presented words were one phoneme words, divided into four categories by their phoneme: EE, E, A and OO. For this project we looked at speech in general, so we did not use the phoneme division. The words were randomized and presented in blocks of 36 trials, with an inter-stimulus interval of four seconds. Subjects were presented with 3 to 6 blocks depending on their willingness to participate.

Preprocessing

The data was then band- pass filtered from 0.15 to 500 Hz. Noisy channels were detected by visual inspection and were removed from the analysis. The data was filtered using a 3rd order Butterworth high pass filter at 1Hz and a Butterworth notch filter, set from 55 to 65 Hz.

To examine connectivity during speech, markers were placed based on the microphone signal of the speech of the subjects. This was done by creating a spectrum of the microphone signal, summing this signal, then averaging and finding the standard deviation of this summed signal. Subsequently the locations in the ECoG timeseries where the signal differed more than one standard deviation of the averaged signal were classified as speech. At the start of this speech period a marker was



placed. For each stimulus a window of 200 samples before the marker to 1800 samples after (167 to 1500 ms) was extracted from the ECoG data for analysis. As a baseline control condition, windows of 1200 samples (1000 ms) before stimulus presentation up to stimulus presentation were extracted. During this period it is most likely the participant is not exposed to, or responding to, any stimuli.

Nine target frequencies were chosen for each subject, determined separately for each subject by looking at an initial graph of averaged Phase Locking values (see below)

for each frequency to avoid the noise bands (at noise bands there is a very high overall PLV). The noise bands were found in each subject around 60 Hz and all of its harmonics (120, 180, 240, 300 Hz). The width of the bands and the frequency at which this noise was at its lowest slightly differed between subjects. The bands chosen were a theta (4 or 5 Hz), an alpha (between 9 and 12 Hz), a beta (between 18 and 24 Hz), a low gamma (40 Hz) and 5 high gamma bands (67-80 Hz, 150 Hz, 200-207 Hz, 267-274 Hz and 370-385 Hz).

Phase locking value

Within a frequency band the phase was calculated for each time point using a gabor wavelet centered at the center frequency f . This results in a complex value, of which the angle produces the phase value at a certain point in time. To decrease the size of the resulting datasets, phase output of the signal was down sampled to each 10th time point, bringing sampling rate down to 120 Hz.

The phase difference between pairs of electrodes was then calculated by comparing the phase values at the corresponding time points for each pair. The phase values were averaged over epochs and the absolute value was taken, resulting in a matrix with a phase locking value for each frequency, for each tenth time point and for each pair of electrodes.

The average PLV at time t is defined as:

$$PLV_t = \frac{1}{N} \left| \sum_{n=1}^N \exp(i\theta(t, n)) \right|$$

Where $\theta(t, n)$ is the phase difference between the two electrodes at time point t .

The resulting PLV defines the inter-trial variability. If there is little variability of the phase difference over trials the PLV is close to 1, if there is a lot of variability it is close to 0.

Statistics

To calculate a statistical threshold, we used a Phase Locking Statistic (PLS) based on the work of Lachaux and others (Lachaux et al., 1999). Because uniformity of the distribution is unknown, a non-parametric statistical approach is needed, which does not assume a particular distribution, in this case we used a permutation approach for exact statistics.

PLVs were calculated for the original rest data, after the trials of electrode 1 were made independent of the trials of electrode 2. Within each frequency, for each pair of electrodes, the phase locking values were calculated for the rest trials, but the rest trials in each second electrode were reordered by changing the order of the trials ($y'(n)=y(\text{shuffle}(n))$), removing any time-locked phase locking. The values were averaged across trials and the maximum phase locking value over the trial time was taken, leading to a value for each frequency, for each pair of electrodes. This was done 200 times providing a distribution of values from which the PLS was derived. This is related to a measure Friston and others (Friston, Stephan, & Frackowiak, 1997) describe for the analysis of MEG data.

The original phase locking value for a frequency and electrode pair is statistically significant if it lies beyond the PLS value corresponding to 95% of the area under the curve of the distribution.

Comparisons

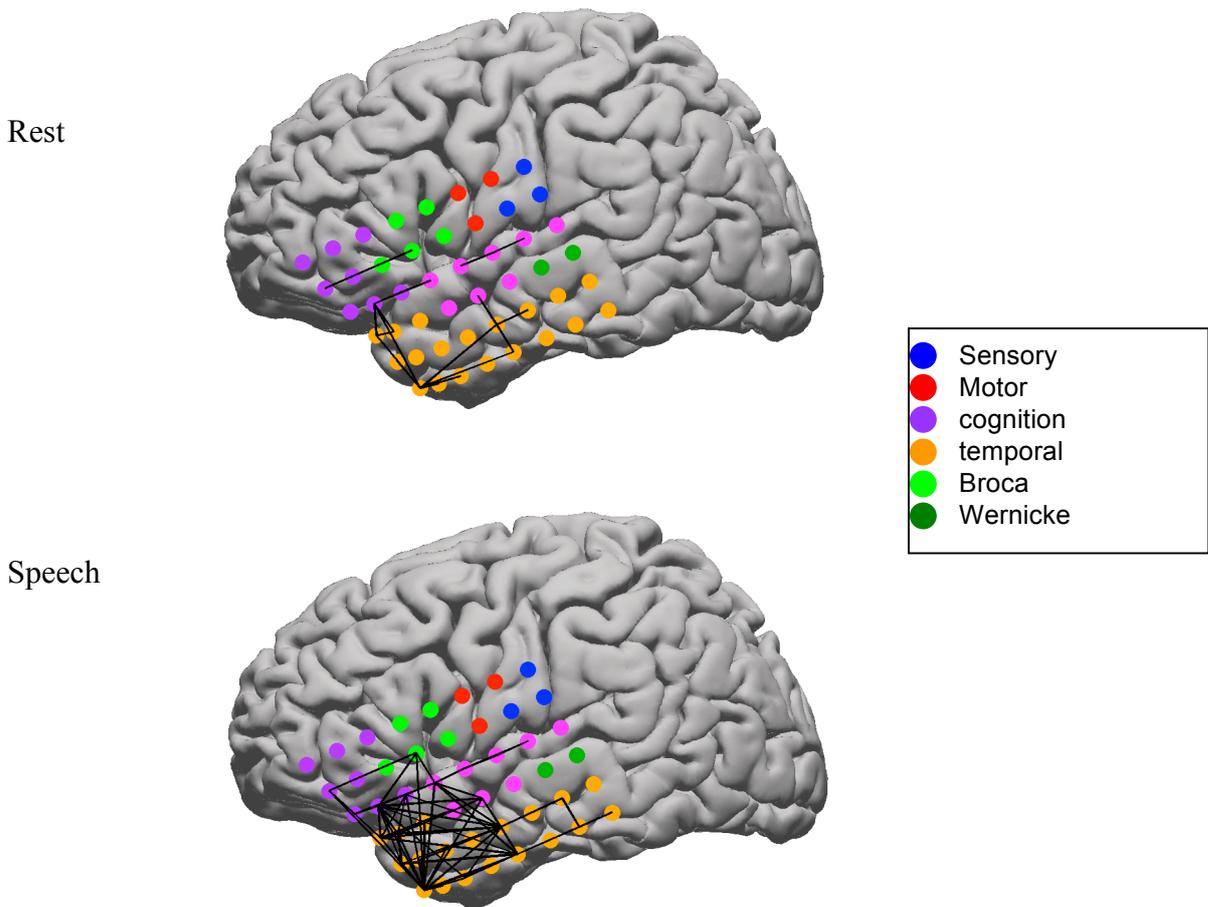
To look at the differences between speech and rest, brain plots were composed which show the significantly phase locked connections in a plot. This was done for average rest (averaged over the whole time period of the rest epochs) and average speech (averaged over the first 450 ms of the speech epochs). To determine if there was a significant difference the number of connections during rest and speech were compared.

To resolve if there are indeed meaningful differences between frequency bands within the high gamma frequency range the differences in Phase Locking between different bands can be studied by assessing the locations of significantly connected electrodes and by assessing the differences in the number of connections between the frequency bands and between functionally different areas.

Results

Phase locking value plots were made for speech and for rest. For one of the subjects the significant connections for the beta band are shown below in figure 1. To make it easier to orient where on the brain the grid is placed the electrodes are colored based on the approximate functional area in which they are located. This is done based on the coordinates and Brodmann areas (Brodmann, 1909). The most important groups are the somatosensory areas BA 1-3, 5 and 40, motor areas BA 4 and 6, cognition areas including the dorsolateral prefrontal cortex (DLPFC) BA 9 and 46, Wernicke a part of BA 22 and Broca BA 44 and 45.

Figure 1. The significant connections for one of the subjects for 150 Hz for rest and for speech.



Rest versus speech

When looking at the difference in phase locking between rest and speech trials there are different patterns visible in all subjects. How these patterns differ is not consistent across subjects. In the total number of connections over all of the nine frequency bands (divided by the total number of electrodes) all five subjects have more significant connections during the speech condition (see table 1), this difference (using a paired t-test) however is not significant. Subject 1 is an outlier in the number of connections. Without this subject the difference in the number of connections between the rest and speech condition is significant ($P < 0.05$). This is most apparent

for the lower four bands ($P < 0.05$), especially alpha, but not for the high gamma frequencies ($P = 0.66$).

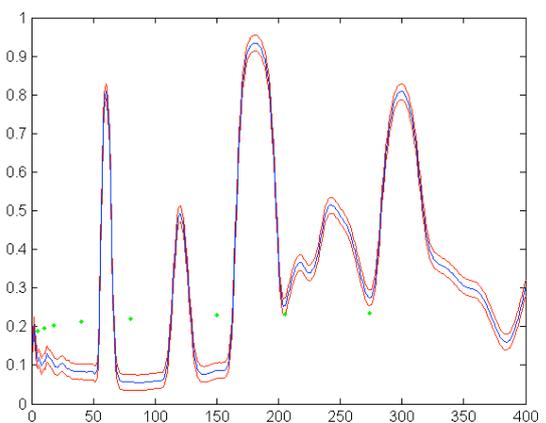
Table 1. The total number of connections for the lower four and higher five bands and all of them together, divided by the total number of electrodes, for each subject, to compare the rest and speech condition.

subject	delta, alpha, beta, gamma		high gamma		all	
	rest	speech	rest	Speech	rest	speech
1	0.47	0.78	1.36	1.27	1.83	2.05
2	21.81	31.46	48.10	48.00	69.92	79.48
3	16.33	24.46	17.63	21.17	33.96	45.63
4	13.27	19.04	21.71	20.71	34.98	39.75
5	16.75	19.69	13.80	13.36	30.55	33.05

High gamma

In four of the subjects a large number of connections was found for the highest frequency bands. To verify our results the phase locking values in 10000 random points of the signal were calculated for all frequencies and then averaged. These values were then compared with the average PLS for the frequency bands chosen for each subject (figure 2). There was a large difference between the PLVs of the random time points and the mean PLSs up to approximately 150 Hz, which means that any significant connections found here are well above any noise in the signal. For the higher frequencies this is not the case, in that some of the mean PLS values are even below the average PLV of the random time-points. This would lead to still finding connections that are noise instead of connections due to brain activity. To solve this problem we also computed an extra, more conservative, threshold. The phase locking value for each frequency for the 10000 random points in the signal, averaged over the time-points, for each of the different frequencies and for all connections was calculated. The value of two standard deviations above the mean of these PLV values can then be taken (corresponding to 2.3%). If this value is higher than the PLS this value was used instead of the PLS value. This however creates a problem when wanting to compare the different frequency bands since different thresholds are used. This noise issue also raises the question of how much information we can gather from these higher frequencies. The part of the signal consisting of noise might be larger than the signal we actually want to measure, which would lead to only measuring signal reliably up to 150 Hz.

Figure 2. In this figure the phase locking values of 10000 random time points in the signal was calculated for each frequency. This clearly shows where the noise is found in the data. Based on this the frequency bands were chosen (separately) for each subject to avoid these noise bands. The green dots specify the mean phase locking statistics for the chosen bands. In the lower frequencies these points are above any noise, but this is not the case for some of the high gamma bands.



Discussion

We analyzed ECoG data obtained from 5 patients performing a language task to see if the high gamma frequency range consists of multiple smaller bands and if phase locking is a useful measure of communication between brain areas.

Connections based on phase locking were found in the rest as well as speech condition. The patterns for both conditions differ between subjects and over different frequency bands. There were more connections in the speech than in the rest condition, but this was not significant for the whole group. When one outlier was removed the difference was significant for the four lower frequency bands, but not for the high gamma bands. The connections in the high gamma bands might (partly) be noise, which would make the task related difference in number of connections between speech and rest smaller and thus harder to detect. More connections during the speech condition is as we expected, just as Rodriguez and others (Rodriguez et al., 1999) and Haig and others (Haig, Gordon, Wright, Meares, & Bahramali, 2000) who show more connections during the performance of a task and presentation of task relevant stimuli. If our phase locking connections are functionally relevant to speech, however, still has to be determined in further research.

Parallel findings

We did not only find significant connections in the speech condition, but also in the rest condition, some of these are evident in both. This implies that there is constant communication between certain areas, also when no functional response is expected or that there is a third area which is not covered by the electrodes which regulates both these areas. In this case the areas are correlated, but they are not causally related to one another.

Speech

To investigate task related connectivity it is not good enough to look at the electrodes located in speech related areas like Broca and Wernicke. The models of speech have changed in the past decades, stating that language consists of multiple compartments working parallel to each other for different aspects of language (see Box 3). In addition there is a lot of variation between people in the location of the language necessary areas. Ojemann and others (G. Ojemann, Ojemann, Lettich, & Berger, 1989) used electrical stimulation in 117 patients and found a large variability in all language related areas, also the most well known areas. The variability between subjects was so large that at any zone stimulated within the classical Wernicke area language naming errors only occurred in a maximum of 40 percent of the patients and there were patients in which the classical Broca area was not found to be involved in language at all.

The best way to locate the electrodes over the brain areas necessary for speech in each subject would be to use pre-operative fMRI or electro-stimulation through the implanted electrodes. This last method is the most accurate and would not be influenced by motor and auditory brain activity due to pronouncing and hearing a word. When the appropriate electrodes, corresponding to the language areas, are determined, the connections between them and other areas can be counted and divided by the number of electrodes. These numbers can be compared to see if there are significant differences between conditions and frequency bands.

Restrictions

Even though ECoG is one of the most accurate techniques to record brain signal in terms of the high spatial and temporal resolution, it is an invasive method. This restricts it to measuring in patients who need it for clinical purposes. The patients that participated in this study all have brain malformations causing (and possibly due to) years of epileptic seizures and they have been taking anti-epileptic drugs.

Furthermore, at the time of recording they just underwent surgery to implant the electrodes. Because of this their brain deviates from the normal brain and the results might not be comparable to healthy people. To decrease this difference between the patients' brain signals and those of a healthy subject, recordings during and around seizure activity were discarded.

Besides the population one of the major constraints of ECoG is that only a small portion of the brain is covered (electrodes are spaced about 1 cm apart and usually between 48 and 128 electrodes are placed). The location of these electrodes and the duration of the implantation are determined based on the clinical needs of the patients. The locations of the grids and the results vary strongly between subjects, which makes it very difficult to group these results. To be able to combine the results and formalize better specified conclusions a larger group is needed.

Future research

Because the field of phase locking in ECoG/EEG is relatively new and unexplored a standard statistical method still needs to be determined. In this study we used statistics based on those described by Lachaux (Lachaux et al., 1999) since for now this seems to be the best substantiated and documented method of quantification for the phase locking value. More research and analysis needs to be done to be able to resolve issues due to noise in the high gamma frequency bands above 150 Hz. This might enable us to learn more about the significance of the high gamma signals, the possibility to divide this range into separate bands and its role in communication. This project was focused on the high gamma frequencies. It might be interesting to investigate the lower frequencies for functional connections during different conditions. We found significant differences in the number of connections between the speech and rest condition and there is already a lot known about the amplitude responses of the delta, alpha, beta and low gamma bands during the performance of many tasks.

The importance of phase locking in general in the communication between the different brain areas in the high gamma frequency range can not be determined by these results, more research will need to be done to resolve this and to be able to say something about phase locking in language.

Conclusion

How brain areas communicate is a large topic of research in neuroscience. A relatively new theory that tries to solve this issue is neuronal coherence or synchrony in which brain areas are thought to synchronize their firing to connect. To measure this synchrony phase locking can be used. This method measures how much the brain waves measured with EEG or ECoG in a certain frequency stay at a constant phase difference in response to a stimulus.

The focus of this project was to look at phase synchrony in the high gamma frequency range, measured with ECoG. The high gamma frequency range is thought to play a large role in ensemble formation and neuronal communication. But up till now this has been seen as one large band, which might not be the case. It might consist of multiple bands which then play different roles in the areas that communicate or the depth of processing. We used the phase locking value and phase locking statistic to find significant connections between temporarily implanted electrodes in five patients. The patients performed a speech task in which they repeated words. The goal was to compare different high gamma frequency bands and the rest and speech condition using phase locking.

More connections were found in the speech condition than in the rest condition, this difference was significant for the lower frequency bands, not for high gamma. Due to a lot of noise in the higher frequencies it was not possible to compare the high gamma bands. Besides this more information is needed about the exact location of the language necessary brain areas for each subject to investigate the functional role of the connections during the speech condition.

In the end more research needs to be done with a larger group of subjects and new and improved analysis methods to see if the noise can be reduced or removed and to be able to make solid conclusions about the high gamma frequencies, phase locking connections in speech and the role of phase locking in communication.

BOX 1. Background information

The binding problem in cognitive neuroscience attempts to find an explanation on how the brain integrates different sensory signals into a unitary experience (Treisman, 1996). The most common model for neuronal communication at this moment is that it is modulated by firing rate. This model was formed based on the findings that firing rate often correlates with stimulus presentation. A problem with this model is however that changes in firing rate for communication with other neurons would interfere with the firing rates that code for different stimulus properties (Fell, Fernandez, Klaver, Elger, & Fries, 2003).

The idea of neural synchrony was called the temporal binding theory by Malsburg (von der Malsburg, 1995) and later the temporal correlation hypothesis by Singer (Singer & Gray, 1995). This theory states that for binding of information between different cortical areas the neurons should exhibit synchronous firing on a millisecond time scale. The advantage would be that different ensembles can be formed at any moment, in any configuration without the need of any additional structural requirements. Besides this neural synchrony can either be long lasting, but also dynamic and short-lived (Engel & Singer, 2001).

Synchrony is already known to be present locally between neurons within an area (see Box 4). For synchronized firing to be used as a valid way of communication between separate brain areas single neurons need to be able to change their firing patterns to change their correlation with other neurons and form functional groups without changing their firing rate. Vaadia and others (Vaadia et al., 1995) demonstrated in monkeys that this was indeed possible.

Essential for the synchronous firing hypothesis to work is that the time between sending and receiving a spike between different area's needs to be predictable and reliable (Fries, 2005). To support this theory Salami and others (Salami, Itami, Tsumoto, & Kimura, 2003) found that irrespective of the length of an axon, the response time from a thalamical neuron to the cortex is constant. This difference in conduction velocity is mediated by the length of the myelinated parts, in which the velocity is up to 10 times higher than in unmyelinated parts of the axon.

Synchrony between brain areas was first seen in intracranial recordings in the cat visual cortex and was evident when presenting a stimulus to neuronal groups that had non-overlapping receptive fields, but had a preference for the same feature (Gray, Konig, Engel, & Singer, 1989). Gray suggested that the synchronization of remote areas was mediated by tangential intracortical connections or reciprocal connections from other cortical areas. Later Roelfsema and others (Roelfsema, Engel, Konig, & Singer, 1997) also found synchronization between the visual and parietal and parietal and motor cortex in awake cats, especially between areas that relate to common functions. The importance of synchronization was later demonstrated in honey bees. Stopfer and others (Stopfer, Bhagavan, Smith, & Laurent, 1997) administered Picrotoxin to the bees, a GABA receptor antagonist which prevents synchronization but does not alter firing rate. After administration the bees were not able to distinguish odors they previously could.

In humans synchrony has been investigated using EEG. Rodriguez and others (Rodriguez et al., 1999) show long distance gamma phase synchrony when viewing faces and Haig and others (Haig, Gordon, Wright, Meares, & Bahramali, 2000) found that the scale of this synchronization can go from local to long distance connections, they show synchrony between many areas over both hemispheres around the 40Hz band for task relevant auditory stimuli in contrast to task irrelevant stimuli.

BOX 2. The biological basis of waves

EEG and ECoG measure brain waves coming from the brain in a wide range of frequencies. Up till the low gamma frequency (~60Hz) the measured local field potentials (LFPs) are thought to reflect the synchronized excitatory and inhibitory post synaptic potentials (EPSPs and IPSPs) of neural ensembles (Edwards et al., 2005). The potentials are primarily recorded from the pyramidal neurons, of which the apical dendrites are oriented perpendicular to the skull surface, creating measurable dipoles when groups fire synchronously. The rhythmic firing is most likely caused by thalamocortical circuits, which are influenced by attention, cognition and behavioral processes (Sterman, 1996).

High Gamma is thought to reflect the summation of the action potentials of groups of spiking pyramidal neurons. Ray and others found a strong correlation between firing rates and high gamma power in the somatosensory cortex of a macaque after tactile stimulation (Ray, Crone, Niebur, Franaszczuk, & Hsiao, 2008). In contrast to low gamma frequencies in which the power increased before the firing rate, the changes in high gamma firing rate came before the changes in power. This supports the idea that low gamma reflects synchronized input (post synaptic potentials) to the cortex and that high gamma reflects synchronized output (action potentials). According to Mukamel and others (Mukamel et al., 2005) this high gamma output signal correlates with the BOLD signal measured with fMRI.

BOX 3. Language/Speech

Language is predominantly found in the left hemisphere of the brain. The most widely accepted model mainly involves Wernicke's and Broca's area. Broca's area (Brodmann areas 44 and 45) is associated with speech production and articulation and is located in the frontal lobe, besides the areas of the motor cortex that control the facial and articulation movements. Wernicke's area (the posterior part of Brodmann area 22), associated with comprehension and fluent speech, is located in the posterior superior temporal cortex, besides the primary auditory cortex.

For speech, Geschwind's model (1972) states that information is processed serially. When responding to a visual cue the information goes from the visual areas of the brain through the angular gyrus to Wernicke's area. From there the information is transferred through the arcuate fasciculus (the main pathway between Wernicke's and Broca's area) to Broca's area. The message is then transmitted to the motor areas to be translated into motor commands to actually articulate the word or sentence.

The last twenty years new evidence has, however, changed this view. Producing and understanding language does not solely rely on the activation of these brain regions. Language as a whole is based on the dynamic interaction between areas that are relevant, but not necessarily essential or language specific areas (Weiss & Mueller, 2003).

Lesion studies as well as intraoperative electrical stimulation show results directing towards a parallel processing system which consists of various modules (G. A. Ojemann, 1991). These modules can be separate for example for different languages (Fabbro, 2001), reading, writing, speech (Beauvois & Dérouesné, 1979) and for different word categories (Hillis & Caramazza, 1991).

BOX 4. Local synchrony

To be able to measure signal with EEG or ECoG a group of neurons need to fire in synchrony. A neuron receives input from multiple neurons, which result in post synaptic potentials (PSPs). These potentials are relatively slow to allow summation. A single excitatory PSP has duration of approximately 10 -100 milliseconds (Buzsaki, 2006), and shows a gradual decline. The closer these incoming action potentials coincide, the higher the summation and thus the better the integration in the post synaptic neuron. This spatial summation in the receiving neuron is maximized when neurons within a network fire in synchrony. Fries and others (Fries, Nikolic, & Singer, 2007) suggest that this is realized by the gamma cycle in which, as was first found in the hippocampus (Bartos, Vida, & Jonas, 2007), the GABA-ergic (inhibitory) interneurons play a significant role by interacting with the excitatory pyramidal neurons. After an excitatory input the interneurons generate inhibitory activity which temporarily inhibits the local network. The excitatory pyramidal neurons can then only fire when this inhibitory phase starts to end, but because these pyramidal neurons are the main excitatory input for the inhibitory interneurons this then, with a small delay, causes another inhibitory wave. The stronger the excitatory drive of a pyramidal neuron, the earlier it will be able to overcome the inhibitory input of the interneurons and vice versa, which might cause for a weakly driven pyramidal neuron not to be able to fire at all within a cycle. This mechanism turns amplitude into a phase value, and can contribute to a better signal to noise ratio. The higher the frequency of the oscillations, the tighter the synchronization needs to be, this will cause communication to be more efficient (Jensen et al., 2007). The largest effect is thus reached when a group of neurons receives input synchronized to the frequency of the local network and because of this it has been proposed that long distance communication is mediated by phase synchronization (Jensen et al., 2007).

References

- Bartos, M., Vida, I., & Jonas, P. (2007). Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nature Reviews Neuroscience*, 8(1), 45-56.
- Beauvois, M. F., & Dérouesné, J. (1979). Phonological alexia: Three dissociations. *Journal of Neurology, Neurosurgery & Psychiatry*, 42(12), 1115-1124.
- Brodmann, K. (1909). *Vergleichende lokalisationslehre der grosshirnrinde in ihren prinzipien dargestellt auf grund des zellenbaues von dr. K. brodmann,...* Leipzig: J. A. Barth.
- Buzsaki, G. (2006). *Rhythms of the brain*. Oxford University Press.
- Buzsaki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science (New York, N.Y.)*, 304(5679), 1926-1929.
- Crone, N. E., Hao, L., Hart, J., Jr, Boatman, D., Lesser, R. P., Irizarry, R., et al. (2001). Electrocorticographic gamma activity during word production in spoken and sign language. *Neurology*, 57(11), 2045-2053.
- Crone, N. E., Miglioretti, D. L., Gordon, B., & Lesser, R. P. (1998). Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. event-related synchronization in the gamma band. *Brain : A Journal of Neurology*, 121 (Pt 12)(Pt 12), 2301-2315.

- Crone, N. E., Sinai, A., & Korzeniewska, A. (2006). High-frequency gamma oscillations and human brain mapping with electrocorticography. *Progress in Brain Research, 159*, 275-295.
- Darvas, F., Scherer, R., Ojemann, J. G., Rao, R. P., Miller, K. J., & Sorensen, L. B. (2010). High gamma mapping using EEG. *NeuroImage, 49*(1), 930-938.
- Edwards, E., Soltani, M., Deouell, L. Y., Berger, M. S., & Knight, R. T. (2005). High gamma activity in response to deviant auditory stimuli recorded directly from human cortex. *Journal of Neurophysiology, 94*(6), 4269-4280.
- Engel, A. K., & Singer, W. (2001). Temporal binding and the neural correlates of sensory awareness. *Trends in Cognitive Sciences, 5*(1), 16-25.
- Fabbro, F. (2001). The bilingual brain: Bilingual aphasia. *Brain and Language, 79*(2), 201-210.
- Fell, J., Fernandez, G., Klaver, P., Elger, C. E., & Fries, P. (2003). Is synchronized neuronal gamma activity relevant for selective attention? *Brain Research. Brain Research Reviews, 42*(3), 265-272.
- Fries, P. (2005). A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends in Cognitive Sciences, 9*(10), 474-480.
- Fries, P., Nikolic, D., & Singer, W. (2007). The gamma cycle. *Trends in Neurosciences, 30*(7), 309-316.

- Friston, K. J., Stephan, K. M., & Frackowiak, R. S. J. (1997). Transient phase-locking and dynamic correlations: Are they the same thing? *Human Brain Mapping, 5*(1), 48-57.
- Gray, C. M., Konig, P., Engel, A. K., & Singer, W. (1989). Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature, 338*(6213), 334-337.
- Haig, A. R., Gordon, E., Wright, J. J., Meares, R. A., & Bahramali, H. (2000). Synchronous cortical gamma-band activity in task-relevant cognition. *Neuroreport, 11*(4), 669-675.
- Hämäläinen, M., Hari, R., Ilmoniemi, R. J., Knuutila, J., & Lounasmaa, O. V. (1993). Magnetoencephalography—theory, instrumentation, and applications to noninvasive studies of the working human brain. *Reviews of Modern Physics, 65*(2), 413.
- Hillis, A. E., & Caramazza, A. (1991). Category-specific naming and comprehension impairment: a double dissociation. *Brain, 114*(5), 2081-2094.
- Jensen, O., Kaiser, J., & Lachaux, J. P. (2007). Human gamma-frequency oscillations associated with attention and memory. *Trends in Neurosciences, 30*(7), 317-324.
- Lachaux, J. P., George, N., Tallon-Baudry, C., Martinerie, J., Hugueville, L., Minotti, L., et al. (2005). The many faces of the gamma band response to complex visual stimuli. *NeuroImage, 25*(2), 491-501.
- Lachaux, J. P., Rodriguez, E., Martinerie, J., & Varela, F. J. (1999). Measuring phase synchrony in brain signals. *Human Brain Mapping, 8*(4), 194-208.

- Lachaux, J. P., Rudrauf, D., & Kahane, P. (2003). Intracranial EEG and human brain mapping. *Journal of Physiology, Paris*, 97(4-6), 613-628.
- Lopes da Silva, F. (1991). Neural mechanisms underlying brain waves: From neural membranes to networks. *Electroencephalography and Clinical Neurophysiology*, 79(2), 81-93.
- Mukamel, R., Gelbard, H., Arieli, A., Hasson, U., Fried, I., & Malach, R. (2005). Coupling between neuronal firing, field potentials, and fMRI in human auditory cortex. *Science (New York, N.Y.)*, 309(5736), 951-954.
- Ojemann, G., Ojemann, J., Lettich, E., & Berger, M. (1989). Cortical language localization in left, dominant hemisphere. an electrical stimulation mapping investigation in 117 patients. *Journal of Neurosurgery*, 71(3), 316-326.
- Ojemann, G. A. (1991). Cortical organization of language. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 11(8), 2281-2287.
- Ray, S., Crone, N. E., Niebur, E., Franaszczuk, P. J., & Hsiao, S. S. (2008). Neural correlates of high-gamma oscillations (60-200 hz) in macaque local field potentials and their potential implications in electrocorticography. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 28(45), 11526-11536.
- Ray, S., Niebur, E., Hsiao, S. S., Sinai, A., & Crone, N. E. (2008). High-frequency gamma activity (80-150Hz) is increased in human cortex during selective

attention. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, 119(1), 116-133.

Rodriguez, E., George, N., Lachaux, J. P., Martinerie, J., Renault, B., & Varela, F. J. (1999). Perception's shadow: Long-distance synchronization of human brain activity. *Nature*, 397(6718), 430-433.

Roelfsema, P. R., Engel, A. K., Konig, P., & Singer, W. (1997). Visuomotor integration is associated with zero time-lag synchronization among cortical areas. *Nature*, 385(6612), 157-161.

Salami, M., Itami, C., Tsumoto, T., & Kimura, F. (2003). Change of conduction velocity by regional myelination yields constant latency irrespective of distance between thalamus and cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 100(10), 6174-6179.

Schalk, G., McFarland, D. J., Hinterberger, T., Birbaumer, N., Pfurtscheller, G., & Wolpaw, J. R. (2004). BCI2000: A general-purpose brain-computer interface (BCI) system. *IEEE Transactions on Biomedical Engineering*, 51(6), 1034-1043.

Singer, W., & Gray, C. M. (1995). Visual feature integration and the temporal correlation hypothesis. *Annual Review of Neuroscience*, 18, 555-586.

Sterman, M. B. (1996). Physiological origins and functional correlates of EEG rhythmic activities: Implications for self-regulation. *Biofeedback and Self-Regulation*, 21(1), 3-33.

- Stopfer, M., Bhagavan, S., Smith, B. H., & Laurent, G. (1997). Impaired odour discrimination on desynchronization of odour-encoding neural assemblies. *Nature*, 390(6655), 70-74.
- Tallon-Baudry, C., Bertrand, O., Delpuech, C., & Permier, J. (1997). Oscillatory gamma-band (30-70 hz) activity induced by a visual search task in humans. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 17(2), 722-734.
- Treisman, A. (1996). The binding problem. *Current Opinion in Neurobiology*, 6(2), 171-178.
- Vaadia, E., Haalman, I., Abeles, M., Bergman, H., Prut, Y., Slovin, H., et al. (1995). Dynamics of neuronal interactions in monkey cortex in relation to behavioural events. *Nature*, 373(6514), 515-518.
- von der Malsburg, C. (1995). Binding in models of perception and brain function. *Current Opinion in Neurobiology*, 5(4), 520-526.
- Weiss, S., & Mueller, H. M. (2003). The contribution of EEG coherence to the investigation of language. *Brain and Language*, 85(2), 325-343.
- Wu, M., Wisneski, K., Schalk, G., Sharma, M., Roland, J., Breshears, J., et al. (2010). Electrographic frequency alteration mapping for extraoperative localization of speech cortex. *Neurosurgery*, 66(2)