Aus der Klinik für Neurologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

„High frequency oscillations in the basal ganglia and their functiononal role in motor processing“

zur Erlangung des akademischen Grades
Medical Doctor – Doctor of Philosophy in Medical Neurosciences
(MD/PhD in Medical Neurosciences)

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von

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1. Introduction

1.1. Abstract:

What is the function of the basal ganglia in human behaviour? It is known that alterations of basal ganglia function can lead to motor symptoms like bradykinesia, tremor or dystonia. Yet, direct physiological data from human basal ganglia are limited.

Recent advances in functional neurosurgery using deep brain stimulation for the treatment of severe movement disorders allow for direct recordings of local field potentials (LFP) from the human basal ganglia. We used this approach in our studies to investigate basal ganglia function and the role of oscillatory activities during rest, sleep and motor tasks. Changes of oscillatory activity in different frequency bands were analysed in relation to the recording condition. We could demonstrate the presence of lateralized movement-related increase in high frequency (~60-80 Hz, gamma) activity in the basal ganglia of patients with dystonia and a positive correlation of this gamma activity with movement speed and amplitude. Gamma band activity was independent of movement direction and did not occur during passive movements. The stepwise increase of gamma activity with movement amplitude and speed suggests a role of neuronal synchronization in this frequency range in the basal ganglia in order to control the scaling of ongoing movements. In a second study we could show that 13 out of 24 patents with four different pathologies had a narrow band activity centred at ~70 Hz in spectra of thalamic LFP recordings. This activity was modulated by movement and varied over the sleep–wake cycle, being suppressed during slow wave sleep and re-emergent during rapid eye movement sleep, which physiologically bears strong similarities with the waking state. Furthermore, there was sharply tuned coherence between thalamic and pallidal LFP activity at 70 Hz in eight out of the 11 patients in whom globus pallidus and thalamus were simultaneously implanted.

Our results support a functional role of gamma activity in small and large scale (between basal ganglia nuclei and thalamus binding), as a possible way of communication between brain areas. More specifically, in the motor system subcortical oscillatory activity at ~70 Hz may be involved in the control of the scaling of ongoing movements and arousal.

1.2. Background:

First oscillating potentials were recorded from the cortex of animals by Richard Canton (Canton, 1875) and by the physiologist Adolf Beck in 1890. In the early 20th century Hans Berger studied the electrical activity of the human brain recorded from the surface of the head and found two main rhythms in the signals. The large amplitude ~10Hz rhythm named alpha rhythm and the faster rhythm with a lower amplitude, which was named beta. The finding, that a non-periodic normal behaviour like opening and closing the eyes could lead to a change of alpha rhythm power picked up in the occipital region of the skull and that epileptic seizures could lead to an abnormality in the recorded waves, paved the way for many subsequent studies looking into the functional significance of oscillatory brain activity (Berger, 1929). Since then we have seen an immense accumulation of knowledge about brain rhythms during behaviour and disease. Technical advances like multichannel electroencephalogram (EEG), magnetoencephalogram (MEG), electrocorticogram (ECoG, recordings in epileptic patients) and recording local field potentials (LFP) provide measurements with a higher spatiotemporal resolution and good signal-to-noise ratio. The increase of computational power, the development of new analytic algorithms and computational models has helped in better understanding and conceptualizing the experimental data. These new possibilities lead to a re-emerging interest in systems neurophysiology and disease specific neuronal patterns in the last twenty years (overview in Uhlhaas and Singer, 2006). Especially neuronal synchronisation in the gamma (>35Hz) frequency range has been found in different brain regions and has been related to specific functions, such as object binding in vision, somatosensory processing, memory encoding and motor preparation. Coherent oscillations may play a role in coordination and communication between neural populations (Singer and Gray, 1995; Buzsáki, 2006; Wang, 2010), which are considered relevant for feature “binding“ through integration of neuronal activity at different brain areas (so called *binding* theory), as described first in the visual system (Engel et al. 1991). Movement-related induced gamma band activity can be recorded in the electrocorticogram from the motor cortex of patients with epilepsy contralateral to the side of the movement (Crone et al., 1998; Pfurtscheller et al., 2003) and has been localized to the contralateral human motor cortex in healthy subjects using magnetoencephalography (MEG) (Cheyne et al., 2008). Movement-related gamma synchronisation has been found to carry information about movement direction in primate studies (Pesaran et al., 2002; Rickert et al., 2005). While the functional role of synchronization in cortical areas is increasingly appreciated, gamma band activity in the

human basal ganglia (BG) has only recently been found in patients undergoing deep brain stimulation (DBS) for severe movement disorders. In patients with Parkinson's disease, increased 60 – 80 Hz activity has been considered prokinetic (Brown, 2003) since it occurs in the subthalamic nucleus (STN) and globus pallidus internus (GPi) at rest after intake of dopaminergic medication in parallel with improvement of motor symptoms (Brown et al., 2001; Cassidy et al., 2002; Silberstein et al., 2003) and was associated with dyskinesia (Fogelson et al., 2005).

1.3. Aim of the studies:

The aim of the studies was to characterize the oscillatory neuronal activity of the basal ganglia (BG) in patients with movement disorders to extend our understanding of the functional role of the motor basal ganglia circuits in humans during voluntary movements. By studying patients with DBS-electrodes implanted in different BG nuclei for various movement disorders, we investigated whether local gamma band synchronisation is important for goal-directed motor plan execution and evaluated gamma activity as a signature of movement parametrization in the human BG. These findings will deepen our understanding of how task-dependent motor control is communicated in the BG and how abnormal synchronisation may lead to movement disorders.

The ultimate hope is that a better understanding of the physiological basis of motor behaviour will help to develop new treatment strategies for movement disorders such as new DBS targets or second-generation deep brain stimulators with, for example, demand-control stimulation to reduce side effects. Moreover, a movement signature recorded from the BG may help to develop new strategies for brain-computer interfaces in the future.

1.4. Methods:

Local field potentials (LFP) were recorded from thalamus (Kempf et al. 2009) or the internal part of the globus pallidus (GPi) (Brücke et al. 2008; Brücke et al. 2012) from patients undergoing implantation of electrodes for treatment with deep brain stimulation. Overall, 33 patients suffering from dystonia (31 primary dystonia, 2 secondary dystonia), and 24 patients undergoing thalamic DBS for various disorders were included in the studies. 13 out of 24 patients with thalamic DBS showed gamma activities at rest and were analysed further during task specific trials (Kempf et al., 2009). Patients took part with informed consent and the permission of the local ethics committee of the Charité – University Medicine Berlin, the University Hospital Mannheim (Germany), the Oxford Radcliffe Infirmary (United

Kingdom), Albert-Ludwigs-Universität Freiburg (Germany) and University “La Sapienza”, Rome (Italy). The studies were performed in accordance with the standards set by the Declaration of Helsinki.

LFP recordings were made postoperatively before chronic stimulation was commenced. LFPs were recorded bipolarly from the four adjacent contacts of each DBS electrode (contact pairs 01, 12, 23). Signals were amplified (x50,000) and recorded onto a computer. Signals were sampled at 625 Hz or 1 kHz and monitored online. EMG activity was recorded from upper limb muscles during arm movements using Ag–AgCl surface electrodes, filtered at 10–250 Hz and amplified (x1000) and recorded as described above. EEG recordings were obviated by surgical wound dressing in our patients.

Patients were recorded alert and at rest, during sleep, during simple self-paced arm movements (Kempf et al. 2009) and during the performance of a GO/noGO reaction time paradigm (Brücke et al. 2008). In this task patients were asked to press a button with the right or left hand as fast as possible. A warning cue informed the patients about the laterality indicating the hand to be activated following imperative GO cues. In 20% of trials noGO imperative signal instructed the subjects to withhold any pre-prepared button press. In the last study, patients performed a choice-reaction-time task, where they had to perform forearm pronation-supination movements with differing amplitude and speed (Brücke et al. 2012). In all three studies time evolving power spectra of LFPs were calculated using a discrete Fourier transform and spectral power in different frequency bands analysed in relation to motor performance of patients using Spike2 and Matlab software. Statistical significance of effects was tested using parametric tests (repeated-measures ANOVA and Student's t-test) or non-parametric tests (Friedman test and Wilcoxon signed-rank test) when values were not normally distributed.

1.5. Results:

Results will be discussed separately for the three studies:

1.) *Kempf et al. 2009*: The main results of this study was the occurrence of sharply tuned gamma activity centred at ~70Hz (range 58–90Hz) in spectra of thalamic local field potential (LFP) recordings at rest in thirteen patients with four different pathologies. An increase of this gamma activity was found with startle reaction, during REM-sleep and movement. Sleep recordings in two patients showed that continuous gamma activity seen in the awake state was absent during non-REM sleep. In REM sleep the gamma activity re-emerged. The occurrence of rapid eye movements during REM sleep was associated with periods of increased activity

at ~70 Hz. An additional finding was that fast thalamic oscillations were lost in untreated parkinsonian patients, paralleling the behaviour of this activity in the subthalamic nucleus (Brown et al. 2003). Finally gamma synchronization occurred with self-paced arm movements together with coherence between thalamic and pallidal LFP activity at ~70 Hz in eight out of the 11 patients in whom globus pallidus and thalamus were simultaneously implanted.

2.) *Brücke at al. 2008*: In this study we evaluated the movement related changes in LFP activity during the performance of a GO/noGO task in 11 patients with dystonia. We found a perimovement increase in 60–80 Hz activity in the LFP, which was predominant in GPi contralateral to the moved side. In contrast, low-frequency LFP activity decreased symmetrically starting just before movement onset in the 6–11 Hz and 18–25 Hz range. This was followed by an increase in oscillatory activity in the 18–25 Hz band after completion of movement that was more pronounced on the contralateral side. No significant gamma power increase occurred in the contralateral GPi during the noGO trials. In 9 of the 22 GPi hemispheres we observed a contralateral decrease in gamma power during noGO trials, which did not reach statistical significance level.

3.) *Brücke et al. 2012*: Here we aimed to better characterize the lateralized gamma synchronization seen in the GPi. Pallidal local field potentials were recorded in 22 patients during performance of a choice-reaction-time task. Movement amplitude of the forearm pronation-supination movements was parametrically modulated with an angular degree of 30°, 60°, and 90°. Replicating the results of the previous study (Brücke et al. 2008) a contralateral gamma band (35–105 Hz) ERS centred at ~70 Hz occurred at movement onset. The maximum of the gamma ERS was reached during the peak movement speed and the pallidal oscillatory activity correlated with movement parameters: the larger and faster the arm movement, the stronger was the synchronization in the gamma band. In contrast, the event-related decrease in beta band activity was similar for all movements. Movement direction did not show a significant effect on the gamma band synchronization. During passive arm movements no significant increase of gamma activity occurred.

1.6. Discussion:

We have demonstrated a strong contralateral, frequency specific increase in gamma band LFP activity in the GPi during voluntary movement that is correlated with movement amplitude and velocity (Brücke et al., 2008; Brücke et al., 2012). Moreover, we have shown that gamma

activity is not confined to the motor output nucleus of the basal ganglia but can also be found in the human thalamus. Here, the sharply tuned oscillatory LFP activity centred ~70Hz occurs at rest and is also modulated by voluntary movement and during sleep (Kempf et al., 2009).

Movement-related gamma band synchronization as a feature of basal ganglia activity has been described in different movement disorders. Gamma band synchronization has been recorded from GPi in both generalized and focal dystonia (Brücke et al., 2008; Liu et al., 2008, Brücke et al., 2012), from the subthalamic nucleus in Parkinson's disease patients, and in patients with non-parkinsonian tremor (Androulidakis et al., 2007; Kempf et al., 2007). The movement-related gamma increase appears lateralized in patients with dystonia, and lateralization was enhanced by dopaminergic treatment in Parkinson's disease (Androulidakis et al., 2007). Here, our data provide further support to the idea that movement-related lateralized gamma band synchronization could be a feature of physiological basal ganglia activity encoding information about movement kinematics.

These observations from deep brain recordings are paralleled by activity at the cortical level as measured in ECoG (electrocorticography) in patients with epilepsy (Crone et al., 1998; Crone et al., 2006; Mehring et al., 2004) and in normal subjects using MEG and EEG (Cheyne et al., 2008; Waldert et al., 2008; Ball et al., 2008; Huo et al., 2010) that have demonstrated the occurrence of gamma oscillations in a similar frequency range (60–150 Hz) in the primary motor cortex during movement onset contralateral to the moved limb. More recently, Muthukumaraswamy (2010) has revealed that motor cortical gamma synchronization is greater with larger movements, not sustained during isometric contraction, and absent during passive movements. These results are strikingly similar to our observations from deep brain recordings, strongly indicating that local gamma synchronization at cortical and basal ganglia levels reflects a concerted motor processing during ongoing movement. Since the strongest synchronization was seen during the ongoing movement, it seems to reflect a relatively late stage of motor control as a possible form of "online control".

Motor slowing and reduced amplitude of movements has been observed in patients treated with bilateral high-frequency stimulation of the GPi for Huntington's disease (Moro et al., 2004), dystonia (Ostrem et al., 2007), or Tourette's syndrome (Diederich et al., 2005). A possible mechanism of this bradykinesia could be an interference of high-frequency DBS with physiological pallidal motor output coding the movement velocity as indexed by the gamma band synchronization.

We have further shown that GPi synchronization is related to the motor output and is not a result of proprioceptive feedback, since increase in pallidal LFP activity during passive

movements was significantly smaller compared with active movement. This is in line with results of a previous study of different sensorimotor conditions that revealed gamma synchronization with voluntary but not passive movements in patients with dystonia (Liu et al., 2008).

An important question remains as to how the underlying diseases may have influenced our results. We should not forget that results are obtained in patients with movement disorders, thus there is no certainty that findings are physiological in nature. However, to avoid major confounds induced by abnormal hand movements [shown to induce activity in generalized dystonia patients, see the study by Liu et al. (2008)], we have only included patients with normal hand motor function in our last study (Brücke et al. 2012). In line with this, subgroup analysis did not show significant difference in gamma synchronization between patients with generalized or focal dystonias without affected arm (Brücke et al. 2008). The narrow band gamma activity recorded in the thalamus was seen across four different disease entities with differing pathomechanisms, which suggests, that it represents a mainly physiological thalamic feature, although we cannot exclude its quantitative alteration in certain diseases. In this regard it is interesting to note that the narrow banded thalamic gamma activity can be seen in records made at rest and during movement, whereas the broader gamma band changes are only evident in averages time-locked to movement (Androulidakis et al., 2007; Kempf et al., 2007; Brücke et al., 2008; Brücke et al. 2012). The possible underlying difference between finely tuned gamma activity and broad band gamma event-related synchronization requires further investigation. It is possible that the thalamic narrow band gamma activity is a marker for the attentional state or arousal, since it is enhanced by startling stimuli and disappears when patients fall asleep. The broad band gamma is related to the movement itself where it could code the speed/amplitude variables or movement vigour. In a recent study it was suggested that basal ganglia may regulate motor control by scaling of the effort or motor energy invested in movements (Mazzoni et al., 2007). The results of the third study would also be in line with the assumption that basal ganglia control motor costs rather than specific motor parameters.

The parametric modulation of GPi LFP activity with movement parameters was frequency selective for gamma activity and occurred only contralateral to the moved hand and around movement onset, supporting a link between gamma oscillations and kinematics of ongoing movements in patients with dystonia with normal hand motor function. The implication is that the GPi as a major output station of the basal ganglia influences the scaling of ongoing movements, whereas a decrease in beta band activity might be a more general phenomenon

during motor preparation that is necessary to allow movement parametrization through other frequencies to occur (Brown, 2007).

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2. Anteilserklärung:

Hiermit wird folgender Anteil von Christof Brücke an den vorgelegten Publikationen bestätigt:

Publikation 1: *Brücke C, Kempf F, Kupsch A, Schneider GH, Krauss JK, Aziz T, Yarrow K, Pogosyan A, Brown P, Kühn AA, Movement-related synchronization of gamma activity is lateralized in patients with dystonia, Europen Journal of Neuroscience, 2008*
Antei: 70 Prozent
Beitrag im Einzelnen: Durchführung der Experimente, Auswertung der Ergebnisse, Schreiben des Manuskriptes

Publikation 2: *Kempf F, Brücke C, Salih F, Trottenberg T, Kupsch A, Schneider GH, Doyle Gaynor LM, Hoffmann KT, Vesper J, Wöhrle J, Altenmüller DM, Krauss JK, Mazzone P, Di Lazzaro V, Yelnik J, Kühn AA, Brown P, Gamma activity and reactivity in human thalamic local field potentials, European Journal of Neuroscience, 2009*
Anteil: 25 Prozent
Beitrag im Einzelnen: Durchführung der Experimente, kritische Revision des Manuskriptes

Publikation 3: *Brücke C, Huebl J, Schönecker T, Neumann WJ, Yarrow K, Kupsch A, Blahak C, Lütjens G, Brown P, Krauss JK, Schneider GH, Kühn AA, Scaling of movement is related to pallidal γ oscillations in patients with dystonia, Journal of Neuroscience, 2012*
Anteil: 70 Prozent
Beitrag im Einzelnen: Entwurf der Studie, Durchführung der Experimente, Auswertung der Ergebnisse, Schreiben des Manuskriptes

Christof Brücke Prof. A. Kühn

Publikationen:

Brücke C, Kempf F, Kupsch A, Schneider GH, Krauss JK, Aziz T, Yarrow K, Pogosyan A, Brown P, Kühn AA, Movement-related synchronization of gamma activity is lateralized in patients with dystonia, Europen Journal of Neuroscience, 2008

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DOI: 10.1523/JNEUROSCI.3860-11.2012

http://www.jneurosci.org/content/32/3/1008.long

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Liste der eigenen Publikationen in chronologischer Ordnung (Gesamt 14, Impact Punkte gesamt: 80,27)

Neumann WJ, Huebl J, **Brücke C**, Herrojo - Ruiz M, Kupsch A, Schneider G-H, Kühn AA *Enhanced low frequency oscillatory activity of the subthalamic nucleus in a patient with dystonia*. Mov Disord. 2012 (accepted) (Impact Punkte: 4,01)

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Erklärung

„Ich, Christof Brücke, erkläre, dass ich die vorgelegte Dissertation mit dem Thema: „High frequency oscillations in the basal ganglia and their functiononal role in motor processing“ selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.“

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