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Gamma band directional interactions between basal forebrain and visual cortex during wake and sleep states

Jayakrishnan Nair [a], Arndt-Lukas Klaassen [a,b], Jordan Poirot [a], Alexei Vyssotski [c], Björn Rasch [b], Gregor Rainer [a,*]

[a] Visual Cognition Laboratory, Department of Medicine, University of Fribourg, Chemin du Musée 5, 1700 Fribourg, Switzerland
[b] Department of Psychology, University of Fribourg, Rue P.A. de Faucigny 2, 1700 Fribourg, Switzerland
[c] Institute of Neuroinformatics, University of Zürich/ETHZ, Winterthurerstrasse 190, 8057 Zürich, Switzerland

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ABSTRACT

The basal forebrain (BF) is an important regulator of cortical excitability and responsivity to sensory stimuli, and plays a major role in wake-sleep regulation. While the impact of BF on cortical EEG or LFP signals has been extensively documented, surprisingly little is known about LFP activity within BF. Based on bilateral recordings from rats in their home cage, we describe endogenous LFP oscillations in the BF during quiet wakefulness, rapid eye movement (REM) and slow wave sleep (SWS) states. Using coherence and Granger causality methods, we characterize directional influences between BF and visual cortex (VC) during each of these states. We observed pronounced BF gamma activity particularly during wakefulness, as well as to a lesser extent during SWS and REM. During wakefulness, this BF gamma activity exerted a directional influence on VC that was associated with cortical excitation. During SWS but not REM, there was also a robust directional gamma band influence of BF on VC. In all three states, directional influence in the gamma band was only present in BF to VC direction and tended to be regulated specifically within each brain hemisphere. Locality of gamma band LFPs to the BF was confirmed by demonstration of phase locking of local spiking activity to the gamma cycle. We report novel aspects of endogenous BF LFP oscillations and their relationship to cortical LFP signals during sleep and wakefulness. We link our findings to known aspects of GABAergic BF networks that likely underlie gamma band LFP activations, and show that the Granger causality analyses can faithfully recapitulate many known attributes of these networks.

1. Introduction

The BF is an important regulator of cortical activity (Semba, 2000; Jones, 2003; Zaborszky and Duque, 2003; Lin et al., 2015). Thus, lesions of the BF result in abnormalities of cortical EEG or LFP signals. Increases of delta (1–4 Hz) activity (Buzsaki et al., 1988; Kaur et al., 2008; Fuller et al., 2011) as well as reductions in gamma (30–90 Hz) activity (Berntson et al., 2002) have been reported following BF lesions. Since the cholinergic neurons of the BF are the major source of Acetylcholine to neocortex, much work has focused on the functional role of this projection system. However, BF contains cholinergic, glutamatergic and GABAergic corticopetal projection systems, and considerable effort has been made in attempting to link these specific projection systems to modulations of the cortical EEG. Evidence from lesion studies suggests that selective immunotoxic lesions of the cholinergic projection system are insufficient for causing changes in cortical EEG (Kaur et al., 2008; Fuller et al., 2011). However, more extensive lesions that affect also the GABAergic corticopetal systems have been linked to enhanced delta band EEG activity and very extensive lesions induce a coma-like state with almost exclusive delta wave EEG (Fuller et al., 2011). Consistent with these findings, increased delta band EEG has also been observed following the infusion of agents that inhibit cholinergic (Cape and Jones, 1998; Toth et al., 2005; Tóth et al., 2007) or GABAergic BF neurons (Anaclet et al., 2015). These studies suggest that BF cholinergic and non-cholinergic, in particular the GABAergic neurons, operate in an ensemble manner in order to influence cortical activity.

Activation of BF has opposite effects of BF lesions on the cortical EEG. Using BF electrical microstimulation, which is thought to cause non-specific activation regardless of cell type, many studies have demonstrated suppression of delta activity and an enhance-

* Corresponding author at: Department of Medicine, University of Fribourg, Chemin du Musée 5, CH-1700 Fribourg, Switzerland.
E-mail address: gregor.rainer@unifr.ch (G. Rainer).

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ment of higher frequency and in particular gamma oscillations (Metherate et al., 1992; McLin et al., 2002; Bhattacharyya et al., 2013). Similar excitatory effects on cortical EEG can be elicited by pharmacological activation of BF neurons, as has been demonstrated using infusion of nonspecific glutamate receptor agonists (Cape and Jones, 2000) or substances that target BF cholinergic neurons such as Neurotensin (Cape et al., 2000) or Noradrenalin (Cape and Jones, 1998). Recent findings have emphasized the importance of the GABAergic corticopetal system for initiating and sustaining EEG gamma oscillations. Accordingly, chemogenetic (Anaclet et al., 2015) or optogenetic (Kim et al., 2015) activation of GABAergic BF neurons has been shown to evoke robust cortical gamma oscillations, an effect that persists even when cholinergic BF neurons are destroyed using immunotoxic lesions (Kim et al., 2015). Indeed, previous studies demonstrating enhanced responsivity and sensitivity of visual cortical neurons following BF stimulation have already suggested a prominent role for the GABAergic corticopetal system based on the observation that the effect of BF stimulation on VC cannot be accounted for by cholinergic mechanisms alone (Bhattacharyya et al., 2012, 2013). Taken together, manipulations of BF activity have been linked to cortical EEG modulations, particularly relating to the delta and gamma frequency bands. These effects are mediated mainly by GABAergic and also by cholinergic corticopetal systems.

Recording neural activity in BF has also provided insights into how BF projections modulate the cortical EEG. Such studies have almost exclusively focused on recording the activity of single neurons, often labelled according to cell type, and linking their firing patterns to the cortical EEG (Duque et al., 2000; Manns et al., 2000a, 2000b; Hassani et al., 2009), wake/sleep regulation (Szymusiak et al., 2000; Lee et al., 2004, 2005), aspects of sensory stimulation (Lin and Nicolelis, 2008; Nguyen and Lin, 2014), and behavioral task performance (Thomson et al., 2014; Tingley et al., 2014, 2015). Convergent evidence (Zaborszky et al., 1999; Yang et al., 2014; Xu et al., 2015) indicates that BF contains multiple interconnected and heterogeneous networks, which operate as an ensemble to modulate cortical state and play distinct roles during sleep and wakefulness. It is thus quite surprising that very little is known about BF ensemble activity, as estimated by the LFP; but see (Quinn et al., 2010; Whitmore and Lin, 2016). The LFP might provide a useful window into the aggregate activation state of BF corticopetal and local networks that might be linked to specific activation patterns of these networks during REM and slow-wave sleep as well as wakefulness. In addition, simultaneous LFP recordings in BF and cortex could yield insights into the functional interactions between these regions. Methods that can reveal directionality of interactions between BF and cortex based on LFP signals might be particularly useful in this context. This can be achieved for example using autoregressive modelling or Granger causality analyses (Bressler and Seth, 2011; Seth et al., 2015), which have been used to obtain insights into local processing within brain regions (Chen et al., 2014; Plomp et al., 2014), as well as distant interactions between brain regions (Brovelli et al., 2004; Wilson et al., 2010; Kang et al., 2015) based on LFP or EEG signals.

Here we recorded bilateral LFPs from rat BF and VC, in order to comprehensively characterize BF LFPs and study functional interactions between the two brain regions. We found strong dependence of BF LFP signals on brain state. We describe spectral differences between wakefulness, REM and SWS, with gamma oscillations occurring during all states but being particularly pronounced during wakefulness. Based on coherence and Granger causality analyses, we present evidence for directional BF-cortex interactions in the gamma band during wakefulness and SWS, consistent with corticopetal modulations originating from a BF source.

2. Methods

Animals and surgery: Adult male Long Evans rats (80–120 days old, $n = 8$) were used in this study with free access to food and water. General anaesthesia was induced using a mixture of ketamine and xylazine (i.p.) and maintained using isoflurane (3.0–4.5%) in pure O_2 inhalation. We used tungsten microelectrodes of 200 μm diameter for implantation in both VC (target coordinates: 1 mm anterior and 1.5 mm ventral from lambda and 3.5 mm lateral from the midline corresponding approximately to the primary visual cortex) and BF (target coordinates Nucleus Basalis: 0.8 mm posterior from bregma, 2.8 mm lateral and 8.2 mm ventral) bilaterally. We verified based on histology for all available animals ($n = 6$) that BF recording sites were located within a 500 μm radius of the target coordinates. For VC, histological reconstruction was not possible due to the electrode track artefact, but we consider the recordings to originate from the infra-granular layers based on implantation depth during surgery. Additionally, one screw electrode placed on the midline over the cerebellum, served as both reference and ground electrode (target coordinates: 3 mm posterior from lambda). Each electrode was connected to flexible wires that were in turn connected to a 7-pin connector that was suitable for connection to a custom-made miniature neural recording device. The connector and leads were fixed and stabilized with dental cement to the animal's skull and the animals were allowed at least two weeks to recover after surgery. All experimental procedures were in compliance with European and applicable Swiss regulations.

Neural recordings: Animals were housed in 12-h dark/12-h light cycle (light on between 7:00 and 19:00). All the recording sessions were performed between 12:00 and 18:00. Recordings were performed by using a miniaturized data logger (Neurologger 2A) which has four channels for LFP recordings. Movements of the animal were registered by the Neurologger in a separate three channels through a 3-D accelerometer, providing sensitive signals related to locomotion that we used in lieu of EMG activity. The signals were recorded at a sampling rate of 1600 Hz and data were downloaded to a PC at the end of the recording session for analysis. Movement signals did not differ during SWS and REM sleep, but we did observe transient movement sensor activity around and preceding state transitions between sleep states or sleep and wakefulness. For tethered recordings, we connected the implanted electrodes to a Tucker-Davis RZ5 system using a motorized commutator, and digitized the waveforms at 22 kHz. This allowed clustering of neural spiking activity, which we used to confirm locality of gamma band LFPs in the basal forebrain in 4 animals.

Behavioral analysis: We used the cortical LFP, movement sensor data, and videographic records to manually define epochs of wakefulness, REM and SWS. Specifically we first segregated the WAKE state from the two sleep states based on the 3-D accelerometer data. Next SWS and REM sleep stages were determined by the theta (5–10 Hz)/delta (1–5 Hz) ratio extracted from the power spectrum of the LFP from VC, according to generally accepted practice (Grosmark et al., 2012; de Lavilléon et al., 2015).

Pre-processing and Spectral analysis of LFPs: The LFP data were down-sampled to 200 Hz and partitioned into 15 s epochs for further analysis. Epochs containing artefacts were rejected by generating a histogram of peak-to-peak amplitude for each epoch and rejecting epochs for which this value exceeded the median plus 1 s.d.; between 4% and 8% of epochs were generally rejected using this conservative criterion. Artefact free LFPs were used for all further analysis. Power spectra were calculated for each epoch by FFT and occasional 50 Hz line noise was removed by multitaper filtering. The oscillations are grouped into bands based on their center frequencies: delta (1–5 Hz), theta (5–10 Hz), beta (20–30 Hz) and