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Connecting occipital alpha band peak frequency, visual temporal resolution, and occipital GABA levels in healthy participants and hepatic encephalopathy patients

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ABSTRACT

Recent studies have proposed a connection between the individual alpha band peak frequency and the temporal resolution of visual perception in healthy human participants. This connection rests on animal studies describing oscillations in the alpha band as a mode of phasic thalamocortical information transfer for low-level visual stimuli, which critically relies on GABAergic interneurons.

Here, we investigated the interplay of these parameters by measuring occipital alpha band peak frequency by means of magnetoencephalography, visual temporal resolution by means of behavioral testing, and occipital GABA levels by means of magnetic resonance spectroscopy. Importantly, we investigated a sample of healthy participants and patients with varying grades of hepatic encephalopathy, which are known to exhibit decreases in the investigated parameters, thus providing an increased parameter space.

We found that occipital alpha band peak frequency and visual temporal resolution were positively correlated, i.e., higher occipital alpha band peak frequencies were on average related to a higher temporal resolution. Likewise, occipital alpha band peak frequency correlated positively with occipital GABA levels. However, correlations were significant only when both healthy participants and patients were included in the analysis, thereby indicating a connection of the measures on group level (instead of the individual level). These findings provide new insights into neurophysiological and neurochemical underpinnings of visual perception.

1. Introduction

Neuronal oscillatory activity has received increasing attention within the neuroscientific community during the last two decades (Buzsáki and Draguhn, 2004). Neuronal oscillations presumably represent a dynamic functional link for neuronal communication. In this role, neuronal oscillations are centered between the relatively invariant dimension of anatomical connections on the one side and the highly flexible dimension of behavioral output on the other side (Buzsáki and Watson, 2012; Singer and Lazar, 2016). Historically, the brain was interpreted as operating in a passive stimulus-driven mode substantially focused on bottom-up serial processing of stimulus properties (e.g., Hubel and Wiesel, 1965; Thorpe et al., 1996). In contrast, current theories emphasize the role of dynamic internal brain states which affect stimulus processing in a largely stimulus-independent top-down direction. In this context, neuronal oscillations are considered to be

Abbreviations: CFF, Critical flicker frequency; CSD, Cross-spectral density; EC, Eyes-closed; ECG, Electro-cardiogram; EO, Eyes-open; EOG, Electro-oculogram; GABA, γ-aminobutyric acid; GABA+/Cr, GABA-to creatine -ratio; HE, Hepatic encephalopathy; HE1, Clinically manifest HE grade 1; HPI, Head position indication; ICA, Independent component analysis; MEG, Magnetoencephalography; mHE, Minimal HE; MNI, Montreal Neurological Institute; MRS, Magnetic resonance spectroscopy

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critical for the implementation of top-down processes (Engel et al., 2001; Hipp et al., 2011).

The functional impact of neuronal oscillations is specifically well documented for the alpha band (~7–14 Hz, Haegens et al., 2014). Alpha band oscillations are most prominent in parieto-occipital cortex areas (Hari et al., 1997) and are both predictive (Hanslmayr et al., 2007; van Dijk et al., 2008) and causally relevant (Romei et al., 2010) for neuronal processing and perception of visual stimuli. Mechanistically, the connection between cortical alpha band oscillations and visual stimulus perception rests on the synchronization of alpha band oscillations to periodic activity in thalamic relay neurons (Lőrincz et al., 2009). Thus, alpha band oscillations likely reflect a mode of phasic information transfer within a thalamocortical network (Bollimunta et al., 2011; Vijayan and Kopell, 2012). This phasic pattern relies heavily on pulsed inhibition mediated by GABAergic interneurons (Lőrincz et al., 2009). Both the phasic patterns of information transfer as well as the alpha cycle length predetermine alpha band activity to shape the temporal structure of perception (Busch et al., 2009; Mathewson et al., 2009).

This temporal dimension of perception is closely linked to the concept of perceptual cycles (Varela et al., 1981; Vanrullen and Koch, 2003; Vanrullen, 2016; Baumgarten et al., 2015; Baumgarten et al., 2017). Perceptual cycles constitute discrete temporal windows for neuronal stimulus processing, which temporally sample incoming stimuli. While experimental evidence for this concept and its connection to oscillatory alpha band activity has been first provided by a seminal study of Varela et al. (1981), multiple attempts to replicate this finding have remained unsuccessful (see Vanrullen and Koch, 2003; Vanrullen et al., 2014). Nonetheless, recent findings demonstrate that perceptual sampling of visual stimuli is primarily determined by the frequency of individual alpha band activity (Dugué et al., 2011; Chakravarthi and Vanrullen, 2012; Cecere et al., 2015; Samaha and Postle, 2015). Some studies aimed to connect individual markers of alpha band activity to individual perceptual performance levels. Such approaches targeting individual oscillatory parameters mostly focus on the peak frequency of a specific predetermined frequency band. Here, peak frequency is defined as the specific frequency within a predefined band exhibiting the highest spectral power (i.e., the power-dominant frequency). Recent studies reported correlations between the individual alpha band peak frequency and the speed of temporal sampling in the visual (Samaha and Postle, 2015) and audio-visual domain (Cecere et al., 2015). The theory of perceptual cycles and the abovementioned findings provide the hypothesis of a positive linear correlation between alpha band peak frequency and visual temporal resolution. Individuals with a low alpha band peak frequency should exhibit a low visual temporal resolution. However, testing this hypothesis is hindered because, in healthy subjects, alpha band peak frequencies are distributed only across a limited range (Haegens et al., 2014). Therefore, it can be beneficial to include groups showing systematic shifts of alpha band activity, which consequently increases alpha band frequency ranges measurable in the overall study sample.

Such frequency shifts have been repeatedly reported in patients with hepatic encephalopathy (HE). HE describes changes in neurological function as a consequence of liver dysfunction (Häussinger and Schliess, 2008). This patient group is known to exhibit a global slowing of oscillatory activity (Kullmann et al., 2001; Timmermann et al., 2005; Olesen et al., 2011; Butz et al., 2013), with especially prominent effects found for the alpha band peak frequency (Kullmann et al., 2001; Marchetti et al., 2011; Olesen et al., 2011; Götz et al., 2013). In addition to alpha band peak frequency decreases, topographical changes of peak frequency generators have been repeatedly shown in HE patient samples. Early electrophysiological studies mention topographical shifts in peak frequency sources from the occipito-parietal to parieto-central areas (Sagalés et al. (1990), Kullmann et al. (2001), Montagnese et al. (2007), Olesen et al. (2011)). Although most of these results remain on the descriptive level, this repeatedly published effect has been labeled "anteriorization" of peak frequency activity. A recent MEG study likewise addressed this topic and reported a spatial blurring of oscillatory sources in HE patients compared to healthy controls (Götz et al., 2013).

HE patients also demonstrate a variety of neuropsychological impairments, including deficits in visual perception (Häussinger et al., 2007; Götz et al., 2013). These visual perceptual impairments are reflected in a decreased critical flicker frequency (CFF). The CFF assesses the temporal resolution of the visual sensory system by presenting a red light with an initial frequency of 60 Hz, which is gradually and linearly decreasing in frequency. While initially being perceived as a steady and continuous light, subjects indicate the time point at which they perceive the light as a discontinuous flicker (Kircheis et al., 2002). The CFF can be used to differentiate subclinical disease stages from overt clinical HE manifestation (Romero-Gómez et al., 2007; Sharma et al., 2007; Torlot et al., 2013) and further correlates with the disease severity in HE patients (Kircheis et al., 2002).

Regarding neurotransmitter concentration levels, HE patients show disease-related changes in γ-aminobutyric acid (GABA) levels. However, so far results have been inconsistent. Whereas classical theories advocated a generally increased GABAergic tone in HE patients (Schafer and Jones, 1982), recent studies put forward a more complex picture of regionally specific changes in GABA levels (e.g., Cauli et al., 2009a; Cauli et al., 2009b; Llansola et al., 2015). Moreover, our group reported a significant decrease in the occipital GABA-to-creatine ratio (GABA+/Cr) for HE patients compared to healthy controls (Oeltzschner et al., 2015). Although first investigations of healthy subjects have not demonstrated a relationship between occipital alpha band peak frequency and occipital GABA levels (Baumgarten et al., 2016), connections remain unknown for HE patients. Given such a connection, occipital GABA levels could represent a critical parameter linking disease-related changes in oscillatory activity and disease-related sensory impairments in HE.

The present study investigated the relationship between individual electrophysiological (occipital alpha band peak frequency), perceptual (CFF), and neurochemical (occipital GABA+/Cr levels) parameters in patients with varying grades of HE (minimal HE / manifest HE) and healthy controls. With this approach, we aimed to assess if neuronal oscillatory activity acts as a connecting factor between the perceptual visual sampling rate and occipital GABA+/Cr levels. By specifically including a patient sample for which perceptual impairments and regionally specific decreases in GABA+/Cr levels were known, the present investigation goes beyond previous studies, which examined only healthy subjects and only single connections (i.e., only the connection between alpha band peak frequency and CFF or GABA+/Cr levels). This way, the hypothesized connections can be tested within an increased parameter space of the investigated metrics, as compared to the investigation of healthy subjects alone. In accordance with previous findings (e.g., Kullmann et al., 2001; Olesen et al., 2011; Götz et al., 2013), we hypothesized that HE subjects demonstrate decreased occipital alpha band peak frequency and that this decrease worsens with progressing disease state. Given the comparatively high spatial resolution provided by MEG measures of neural activity, we additionally investigated if the topographical distribution of alpha band peak frequency differs between HE patients and healthy controls. Here, the main aim was to specify effects of peak frequency anteriorization previously reported by electroencephalographic studies. Further, we hypothesized a positive connection between occipital alpha band peak frequency and temporal visual perception as measured by the CFF in accordance with current models of perceptual cycles. Finally, we hypothesized that occipital alpha band peak frequency is correlated positively with occipital GABA+/Cr ratios.