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Evidence for increased visual gamma responses in photosensitive epilepsy

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Summary
Background: A sustained gamma (30—70 Hz) oscillation induced in occipital cortex by high-contrast visual stimulation has been well characterised in animal local field potential recordings and in healthy human participants using magnetoencephalography (MEG). The spatial frequency of a static grating stimulus that gives maximal gamma is also that most likely to provoke seizures in photosensitive epilepsy.
Methods: We used MEG to study visual responses induced by grating stimuli of varying contrast and size in twelve patients with photosensitive epilepsy and two matched control groups, one with epilepsy but no photosensitivity, the other healthy controls. We used a beamformer approach to localise cortical responses and to characterise the time—frequency dynamics of evoked and induced oscillatory responses.
Results: A greater number of patients with photosensitivity had particularly amplitude gamma responses compared to controls. Formal statistical testing failed to find a group difference. One photosensitive patient, tested before and after sodium valproate, had a peak gamma amplitude when drug naive over four times larger than the group mean for controls; this high amplitude was substantially decreased after treatment with sodium valproate. We found no difference in the frequency of the sustained gamma response between the three groups.
Discussion: Altered power, but not frequency, in induced cortical responses to a static grating stimulus may be a characteristic of photosensitive epilepsy. Our failure to find a group difference

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on statistical testing may have been due to a wide intersubject variability and heterogeneity of the photosensitive group. A high amplitude response would be in keeping with previous evidence of altered contrast gain and increased spatial recruitment in photosensitive epilepsy.

Introduction

Between 1 and 3% of people with epilepsy demonstrate photosensitivity, where epileptic seizures are provoked by visual stimuli and a photoparoxysmal response (PPR) is seen on EEG testing (Guerrini and Genton, 2004). High intensity visual flicker, alternating patterns and high contrast achromatic gratings are most likely to induce seizures or a PPR (Binnie et al., 1985; Wilkins et al., 1979b). Several lines of evidence from MEG (Parra et al., 2003), EEG (Porciatti et al., 2000), fMRI (Chiappa et al., 1999), transcranial magnetic stimulation (Siniatchkin et al., 2007), and psychophysical measures (Shepherd and Siniatchkin, 2009), point to the abnormal recruitment of large assemblies of synchronously firing neurons in photosensitive epilepsy (PSE), suggesting underlying neural network abnormalities.

The induced response to visual stimulation includes an emergent gamma oscillation (30—70 Hz) that has been well characterised with intracranial local field potential (LFP) recordings in animals (Gray et al., 1989; Kayser et al., 2003; Ray and Maunsell, 2010), and non-invasively using magnetoencephalography (MEG) in humans (Adjamian et al., 2004; Hall et al., 2005). Notably, the stimulus properties that produce the greatest visual gamma response, namely a high contrast achromatic grating, with spatial frequency of 3 cycles per degree (Adjamian et al., 2004) are also those most likely to induce a PPR in those individuals with photosensitive epilepsy (Wilkins et al., 1979a). Furthermore, a correlation exists between the oscillatory frequency of visually induced gamma and the concentration of GABA in occipital cortex (Muthukumaraswamy et al., 2009) as predicted by modelling of coupled excitatory and inhibitory networks (Brunel and Wang, 2003).

In this study, we used MEG to characterise evoked and induced visual cortical responses to static luminance-defined visual gratings in three groups: epilepsy patients with, and without, photosensitivity and in non-epilepsy controls. We hypothesised that the induced gamma frequency would differ in patients with photosensitive epilepsy and controls. Our further objective was to examine in detail the time—frequency dynamics of evoked and induced responses in the three groups.

Materials and methods

Participants

We tested the following groups: (1) photosensitive group: 12 patients (8 female, aged 13—30, mean age 22) with a diagnosis of idiopathic generalised epilepsy, and recent clinical EEG showing a PPR (type 3/4 Waltz classification) to photic stimulation, without a change in medication since the PPR was recorded, all but 2 patients had a history of clinical seizures induced by visual stimulation; (2) epilepsy control group: 9 epilepsy control patients (7 female, mean age: 24 years, range: 12—31 years) with a diagnosis of idiopathic generalised epilepsy (IGE) but no history of visually induced seizures and no evidence of PPR on any previous clinical EEG (see Table 1 for electro-clinical details of participants); and (3) 12 non-epilepsy controls (8 female, mean age: 23 years, range: 12—29 years) with no known neurological condition and no first-degree relatives with epilepsy. Our sample size calculation was based on data showing that the standard deviation of the induced gamma frequency is around 6 Hz (Muthukumaraswamy et al., 2010). For the current study, this is a likely upper-bound as it has also been demonstrated that age contributes around 30% of this inter-subject variance (Gaetz et al., 2012), and the experimental groups used here were age matched. However, assuming a 6 Hz standard deviation, the 12 subjects per group we proposed for the current study would allow us to detect a group difference in peak gamma frequency of around 7 Hz (with $p < 0.05$ and a statistical power of 80%).

All participants had normal or corrected-to-normal vision (based on self-report). Written informed consent to take part in the study was given by all participants (or a parent/guardian for those <16). The study was approved by the South East Wales NHS Research Ethics Committee.

Visual stimulation

Participants underwent two 18-minute MEG recordings with visually presented gratings at three levels of contrast: 40%, 60% and 100% (responses to the 60% contrast grating were not successfully collected from one participant and so data from that condition was not included in the analysis for that participant). All stimuli were stationary, black/white, square-wave vertical gratings with a spatial frequency of 3 c.p.d presented at maximum contrast on a grey background. Stimuli were masked by a square window that was 4° in size in one session and 8° in the other session. Displays were generated by Matlab (The Mathworks, Inc.: Natick, MA) using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997), and presented on a Mitsubishi Diamond Pro 2070 monitor (1024 × 768 pixel resolution, 100 Hz refresh rate).

Stimuli were presented to the lower left visual field with a small red fixation square (~0.2° in width) located at the top right-hand edge of the stimulus. We used the lower left (rather that full field) visual stimulation to (1) ensure a low level stimulus with minimal risk of provoking photosensitive seizures and (2) avoid theoretical concerns of field cancellation due to opposing dipoles occurring on opposite banks of the calcarine sulcus or on opposite sides of the interhemispheric fissure.