Interictal anomalies in patients with migraine without aura: absence of hemodynamic refractory effects

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Introduction

Hemodynamic refractory effects have been subject to investigation for many years. In 2000, Huettel et al. described the phenomenon in human visual cortex using fMRI [1]: for very short interstimulus intervals an attenuated amplitude and a delay in time-to-peak is observed at the group level. Quantification of this effect is essential when differences between healthy controls and patient groups are under investigation. Therefore, raw data points should be fitted to determine all parameters involved in characterizing refractory effects in individual hemodynamic responses (e.g. amplitude, time-to-peak, peak width,…).
In this study, hemodynamic refractory effects in the fusiform face area (FFA) are quantified in a control group and compared with migraine patient data.

Methods & Materials

51 healthy volunteers (mean age 29.5 ± 10.7 years) and 21 patients (33.1 ± 12.1) participated in this study. Patients with migraine without aura (ICHD-II criteria) experienced 2 to 8 attacks per month, did not receive any prophylactic treatment and were attack-free for at least 48 hours. Data were acquired at 3 Tesla (Siemens Trio Tim) using a slow event-related design with male faces as visual stimulus. The scan protocol comprised one functional localizer for the FFA and 4 conditions in the main task: a single event as reference condition and 3 conditions to provoke hemodynamic refractory effects (onset-to-onset interstimulus intervals of 1, 2 and 6 seconds).
All processing was performed at single subject level. Data points were extracted from the FFA as region of interest and averaged over all events for every single condition. Net responses were obtained by subtracting the reference condition from these overall responses. Curve fitting of these net responses was necessary for quantification of the hemodynamic refractory effects. Therefore three inverse logit functions (IL) were combined. Software was offered by Martin Lindquist [2] and adapted to get the desired parameters: amplitude, latency (time-to-peak), peak width of the response (FWHM) and latency of the rising edge measured at FWHM. Validation of the fitting was obtained by calculating the R^2 for each fitted curve. All parameters, including absolute and relative differences with respect to the reference condition, were statistically compared between the patient group and healthy controls.

Results

There was no difference in the amount of voxels included in the ROI for both groups, nor in the maximum t-values in this ROI.
Data from 72 subjects were analyzed, providing 288 net responses to be fitted. For the patient and control group 81,0% and 79,4% of the curves could be fitted, with a mean R^2 of 0.9544 ($\pm$ 0.0055) and 0.9749 (0.0019) respectively.
In the control group, the amplitude for the response to the 1s interstimulus interval is significantly decreased compared to the reference condition. This amplitude decrease is not present in the patient group ($p < 0.05$)(fig. 1). Visual inspection of the curves shows a slight increase in latency seen in the control group, not in the patient group. This could not be confirmed statistically, however, with $p = 0.07$ the difference in time-to-peak for the "1s" condition between both groups is showing a trend towards significance.
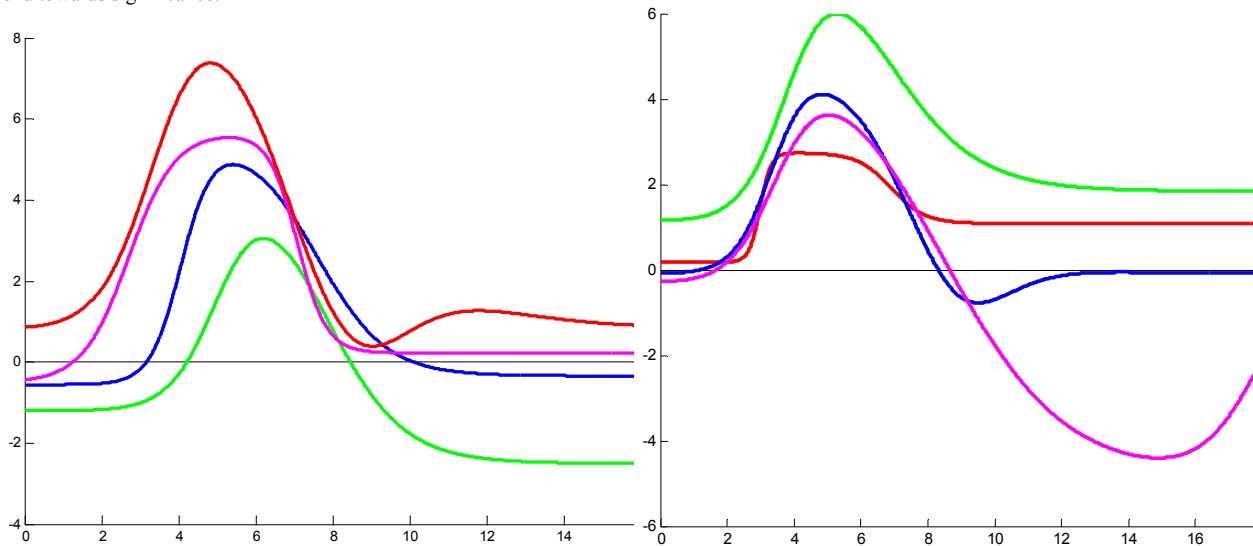

Figure 1: fitted hemodynamic responses for two representative subjects: one healthy control (left) and one migraine patient (right). Red curves are the averaged responses to a single stimulus. Green, blue and pink curves are averaged responses to stimuli after a 1, 2 and 6 s interval, respectively.

Discussion & Conclusion

Particularly for quantifying hemodynamic refractory effects, inverse logit functions are preferred, since they offer enough flexibility. Gamma functions are often used for fitting, but have too many constraints and force a fit e.g. at a certain time-to-peak, which is inappropriate for this purpose.
In the control group, hemodynamic refractory effects are measurable at single-subject level, cfr. the group results of Huettel et al. These effects are distorted in the patient group. Our results are in good agreement with findings by Schoenen et al. [3]: they demonstrated a lack of habituation in patients with migraine using VEP-measurements. Our findings may be interpreted as the neurovascular correlate of this electrical dishabituation. However, exact relationships remain to be investigated.

References

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