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Frequency analysis of the visual steady-state response measured with the fast optical signal in younger and older adults

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Abstract

Relatively high frequency activity (>4 Hz) carries important information about the state of the brain or its response to high frequency events. The electroencephalogram (EEG) is commonly used to study these changes because it possesses high temporal resolution and a good signal-to-noise ratio. However, it provides limited spatial information. Non-invasive fast optical signals (FOS) have been proposed as a neuroimaging tool combining spatial and temporal resolution. Yet, this technique has not been applied to study high frequency brain oscillations because of its relatively low signal-to-noise ratio. Here we investigate the sensitivity of FOS to relatively high-frequency brain oscillations. We measured the steady-state optical response elicited in medial and lateral occipital cortex by checkerboard reversals occurring at 4, 6, and 8 Hz in younger and older adults. Stimulus-dependent oscillations were observed at the predicted stimulation frequency. In addition, in the younger adults the FOS steady-state response was smaller in lateral than medial areas, whereas in the older adults it was reversed in these two cortical regions. This may reflect diminished top-down inhibitory control in the older adults. The results indicate that FOS can be used to study the modulation of relatively high-frequency brain oscillations in adjacent cortical regions.

Keywords

aging; visual steady state response; frequency analysis; the event-related optical signal (EROS); fast optical signal (FOS)

Introduction

This paper reports the application of frequency-domain analysis methods to fast optical signals (FOS). FOS measure changes in the optical properties of the brain associated with neuronal activity (Gratton, Corballis, Cho, Fabiani, & Hood, 1995; Gratton & Fabiani, 2007). These changes are attributed to local variations in light scattering, associated with neuronal depolarization and hyperpolarization (Rector, Carter, Volegov, & George, 2005). Because of their direct association with neuronal membrane phenomena, FOS provide, at least in principle, the possibility of attaining millisecond-level temporal resolution (e.g.,

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Maclin, Low, Sable, Fabiani, & Gratton, 2004) combined with sub-centimeter spatial resolution (e.g., Gratton & Fabiani, 2003).

The fast nature of these optical responses distinguishes them from the more commonly known slow optical signals related to hemodynamic changes that are examined with near infrared spectroscopy (NIRS) (Villringer & Chance, 1997). NIRS uses multiple wavelengths to exploit differences in the absorption spectra of oxy- and deoxy-hemoglobin to derive estimates of the concentration of these substances. Unlike FOS, NIRS provides second-level temporal resolution because of the relatively slow nature of hemodynamic phenomena that are being measured.

Most studies using FOS have focused on event-related time-domain analyses, hence the term event-related optical signal (EROS) (Gratton, Corballis, et al., 1995; Gratton & Fabiani, 2007). EROS refers to the average of the fast optical signals *time-locked* to the onset of stimuli or behavioral responses. Using this approach EROS has been applied to the measurement of brain responses in the visual (Gratton, et al., 2006; Gratton, Corballis, et al., 1995), auditory (Fabiani, Low, Wee, Sable, & Gratton, 2006; Sable, et al., 2007), and somatosensory modalities (Maclin, et al., 2004). It has also been applied to the study of the brain activity associated with sensory and working memory (Fabiani, et al., 2006; Gratton, Fabiani, Goodman-Wood, & Desoto, 1998; Low, Leaver, Kramer, Fabiani, & Gratton, 2006; Medvedev, Kainerstorfer, Borisov, Barbour, & VanMeter, 2008), preattentive change detection (Rinne, et al., 1999; Tse & Penney, 2007, 2008; Tse, Tien, & Penney, 2006), executive function (Gratton, Rykhlevskaia, Wee, Leaver, & Fabiani, 2009) and language processing (Tse, et al., 2007).

This time-domain event-related approach, however, does not exhaust all types of fast neuronal activities of interest to cognitive neuroscientists. Studies of the electrocorticogram (ECoG; Canolty, et al., 2006; Ray, Crone, Niebur, Franaszczuk, & Hsiao, 2008), electroencephalogram (EEG) and magnetoencephalogram (MEG; see Kaiser & Lutzenberger, 2003 for reviews) utilize not only event-related signals, but also high-frequency (>4 Hz) oscillations. Both methods of analysis can reveal different properties of neuronal activity in information processing.

Although time- and frequency-domain analyses are related to each other, they do differ substantially in one basic feature: time-domain signal averaging is based on the assumption that the activity of interest is time-locked to a specific eliciting event (across trials and/or across subjects), whereas activity that is not time-locked is considered to be noise. This assumption is important because it allows for the use of signal averaging for reducing the noise level, in a manner proportional to the square root of the number of trials. This is done, however, at the cost of losing information when there is trial-to-trial or subject-to-subject variability in the phase of the brain activity with respect to the eliciting stimulus. The practical consequence is that latency jitter may reduce or even cancel brain responses, with this problem being particularly pronounced for high frequencies (compared to low frequencies). Because high frequencies (here defined as frequencies of 4 Hz or above) are of great interest in cognitive neuroscience, this poses some limitations to the use of time-domain signal averaging in brain imaging.

The phase-locking assumption is not made when data are first transformed into the frequency domain, and then the amplitude spectra are averaged across trials and/or subjects. Thus, frequency analysis (and the related time-frequency analysis) may be of great utility to study activity varying in latency across subjects and/or conditions. Here we intend to show that this type of analysis can be applied to FOS.

A problem with averaging in the frequency domain is that, once the phase-locking assumption is eliminated, the noise cannot be suppressed in the data simply on the basis of the time-locking criterion. For this reason, dealing with noise in the frequency-domain signal averaging is more difficult than in the time-domain signal averaging, and the signal-to-noise ratio (S/N) is expected to be much lower. This is particularly a problem with FOS, because fast optical data typically have lower S/N than other techniques, such as EEG. The purpose of this paper is to show that the application of frequency-domain signal averaging to FOS can provide interpretable data, capable of distinguishing signal from noise. Importantly, this demonstration needs to be done within a frequency range that is meaningful for future applications of FOS to the study of brain rhythmic activity (i.e., >4 Hz).

Up to now there is only one published report of frequency domain analysis of FOS (Gratton, Fabiani, et al., 1995; see also Zhao, Valle-Inclan, & Hackley, 2006), and that study involved the analysis of relatively slow oscillations in brain activity (0.8 Hz) associated with movement preparation. In the current study, we examined the FOS steady-state response (SSR) in visual cortex using a paradigm similar to those employed in electrophysiological studies (Di Russo, et al., 2007; Galambos, Makeig, & Talmachoff, 1981), in which stimuli presented at a fast rate (> 4 Hz) evoke an oscillatory EEG response at the frequency of stimulus presentation (Regan, 1966). The SSR has been reported in both the visual and auditory domains (Galambos, et al., 1981), when the stimulation frequency is at or above 4 Hz, reaching its largest amplitude when the stimulation frequency is 15 Hz (Herrmann, 2001; Pastor, Artieda, Arbizu, Valencia, & Masdeu, 2003). A number of studies (Di Russo, et al., 2007; Di Russo, et al., 2005; Fawcett, Barnes, Hillebrand, & Singh, 2004; Hillyard, et al., 1997; Krolak-Salmon, et al., 2003; Pastor, et al., 2003) have been conducted to identify the cortical regions responsible for the generation of the visual SSR. Pastor and colleagues (2003) obtained positron emission tomography (PET) data concurrently with steady-state visual evoked potentials (SS-VEP) and showed an increase in regional cerebral blood flow in primary and association visual cortex for stimulation frequencies from 5 to 60 Hz. Furthermore, significant correlations between the PET and EEG responses were found in primary visual cortex. Hillyard and colleagues (1997) carried out a study using functional magnetic resonance imaging (fMRI) and EEG (in this case measured separately) and found that the amplitude of SS-VEP was enhanced by attention in extrastriate cortex (Brodmann areas 18–19). Combined dipole-modeling and fMRI studies (Di Russo, et al., 2007; Di Russo, et al., 2005) suggest that visual cortex may be one of the generators of the SS-VEP response. Results consistent with a visual cortex origin of the SS-VEP have also been found with MEG (Fawcett, et al., 2004) and ECoG (Krolak-Salmon, et al., 2003).

Based on the results of these studies, we predicted that frequency analysis of FOS would show a selective increase in activity at the stimulation frequency in visual cortex. Specifically, we presented subjects with checkerboards reversing at different frequencies (approximately 4, 6 and 8 Hz). We expected that at each of these frequencies the FOS would be dominated by the corresponding oscillation frequency. In other words, increases in the amplitudes of 4, 6 and 8 Hz FOS oscillations should be expected in the 4, 6 and 8 Hz reversal frequency conditions respectively. Moreover, the peak frequency response should be located in a region of interest (ROI) within primary visual cortex.

A further aim of the current study was to examine age differences in FOS in the frequency domain. Both EEG (Fiorentini, Porciatti, Morrone, & Burr, 1996; Porciatti, Burr, Morrone, & Fiorentini, 1992; Tomoda, Celesia, Brigell, & Toleikis, 1991) and fMRI (Buckner, Snyder, Sanders, Raichle, & Morris, 2000; Ross, et al., 1997) studies show differences between younger and older adults in the visual cortex response to stimulation. For instance, Porciatti and colleagues (1992) reported an age-related reduction of VEP amplitude at low

temporal reversal frequencies (below 6 Hz), but not at high reversal frequencies (above 9 Hz). In addition to amplitude differences, Fiorentini and colleagues (1996) found an increased latency in the VEP of older adults. A reduction in the hemodynamic signal was also found in older adults in striate and extrastriate visual cortex (Buckner, et al., 2000; Ross, et al., 1997). Therefore, based on these studies, we can expect a global reduction of the FOS SSR in older adults (as we are using stimulation frequencies lower than 9 Hz) at all occipital locations.

In addition to the diffused effects of age on the FOS SSR, we were also interested in investigating more localized effects. In our previous work using event-related brain potentials (ERPs) and EROS, we found that older adults show reduced adaptation to repeated stimulation in the auditory domain (Fabiani, et al., 2006). We attributed this phenomenon to a loss of inhibitory processing in aging (Hasher, Lustig, & Zacks, 2008; Hasher & Zacks, 1988; see also Gazzaley et al., 2007) for similar findings in the visual domain). In other words, this phenomenon was viewed as an “attentional” effect, leading to the top-down suppression of processing of uninformative/repeated stimuli in younger adults, but not in older adults. As shown by Hillyard and colleagues (1997; see also Martinez, et al., 1999), attention effects on the SSR should be more prominent in lateral than medial occipital areas (Gratton, 1997). Thus, we were also interested in determining whether younger adults would show a greater suppression of the FOS-SSR in lateral occipital cortex (relative to medial occipital cortex) than older adults.

Methods

Participants

Thirteen younger adults (5 females, age 21–26, mean age 22.2) and twelve older adults (9 females, age 66–80, mean age 72.6) participated in this study after giving informed consent. All of the participants had normal or corrected to normal vision, had no history of neurological disorders or head trauma, and did not take any medications known to affect the central nervous system. The procedures used in this experiment were approved by the Institutional Review Board of University of Illinois at Urbana-Champaign. Time-domain analyses of FOS data (EROS analyses) for a sample of young adults that includes those in this study have been presented elsewhere (Gratton, et al., 2006).

Stimuli and procedures

Visual stimuli were presented on a computer monitor centered at eye-level at a distance of about 80 cm from the participants. Participants were instructed to fixate at the center of the monitor throughout the experiment. Each experimental block consisted of a 20 s rest period followed by a 19.2 s stimulation period. A fixation cross was displayed at the center of the screen during the rest period. During the stimulation period, a black and white checkerboard was presented and the color of each cell reversed at one of the following frequencies¹: 1.0417 Hz (“1-Hz” condition), 2.0833 Hz (“2-Hz” condition), 4.1667 Hz (“4-Hz” condition), 6.2500 Hz (“6-Hz” condition), and 8.3333 Hz (“8-Hz” condition). These reversal frequencies (with the exception of the highest frequency) were chosen to be factors of the sampling frequency (62.5 Hz), so that an integer number of points occurred between stimuli. The 1-Hz and 2-Hz conditions are not relevant to the purposes of this paper since they do not generate SSRs. The checkerboard spanned 15 degrees horizontally and 17 degrees vertically across the visual field and had a spatial frequency of 0.4 cycles/degree. It should be noted that the checkerboard and its reversals were isoluminant, so that during the

¹Each cell returns to its original state (black or white) after 2 reversals (1 cycle).

stimulation period there was no change in the intensity of the light emitted by the computer screen.

A total of 120 stimulation blocks (60 blocks for each of two sessions) were presented to the participants. Because there are inherently more checkerboard reversals in the higher than in the lower frequency conditions, the number of blocks for the lower frequency conditions was increased to make the number of reversals more comparable. The reversal frequency conditions were presented in the following order: 1-Hz, 2-Hz, 4-Hz, 6-Hz, 8-Hz, 1-Hz, 2-Hz, 4-Hz, 2-Hz, 1-Hz, 8-Hz, 6-Hz, 4-Hz, 2-Hz, 1-Hz; and this sequence was repeated four times to produce the 60 blocks for each session.

EROS recording and analysis

A frequency-domain oxymeter (Imagent, ISS Inc., Champaign, Illinois, USA) was used to record the fast optical data. Frequency-modulated (110 MHz) near-infrared light (690 nm for half of the channels and 830 nm for the other half)² was channeled to the participant's scalp by plastic-clad silica optic fibers (400 μ m-diameter core). Some of this light was collected by fiber-optic detector bundles (3 mm diameter) also placed on the participant's scalp and carried to photo-multiplier tubes (PMTs). The PMTs were modulated at 110.00625 MHz, thereby generating a 6.25 kHz heterodyning (i.e., cross-correlation) frequency. The analog-to-digital sampling rate was 50 kHz. DC (average) intensity, AC (amplitude) intensity, and relative phase delay of the output current were obtained by Fast Fourier Transform (FFT) of periods of 1.6 ms for each channel (source-detector combination). The analyses presented in this paper focused on phase delay data only. Each of 8 detectors received light from 10 time-multiplexed sources, with a total of 80 channels per session. The effective sampling of the data was 62.5 Hz (i.e. it took 16 ms to cycle through the 10 light sources). Two different recording montages (i.e. source-detector pair configurations; see figure 1 in Gratton, et al., 2006) were used in the two recording sessions, yielding a total of 160 channels. The recording montages covered the occipital cortex (160 channels over a space of approximately 100 cm², with a density of 1.6 channels/cm²). The order of the recording montages was counterbalanced across participants. A modified motorcycle helmet was used to hold the source and detector fibers on the participant's head.

For each participant, all source and detector locations, and three fiducial points (i.e., the nasion and pre-auricular locations) were digitized in 3D space (Polhemus Fastrak 3Space®, Colchester, Vermont, USA) thereby permitting subsequent co-registration of the functional optical data to T-1 weighted anatomical MR images previously obtained for each participant using an MPRAGE sequence on a 3T Siemens Magnetom Allegra scanner (for additional details on co-registration procedures see Whalen, Maclin, Fabiani, & Gratton, 2008). Fiducial points had also been marked on the MR images with vitamin E pills. The individually co-registered source and detector locations were then Talairach-transformed (Talairach & Tournoux, 1988) for surface plotting purposes. The steps used for the analysis of FOS are summarized in Figure 1. Briefly, for each block, the phase delay optical data were corrected for phase wrapping, normalized by subtracting the phase mean, and corrected for the effects of vascular pulsation (Gratton & Corballis, 1995; Gratton & Fabiani, 2007). In this procedure, the time of each pulse is first identified in each channel, the average pulse waveform is computed, each pulse is regressed with the average pulse and the estimated single-trial pulse is subtracted from the original data. This approach, described in Gratton

²The brain's scattering and absorption coefficients for 830 and 690nm light are slightly different. The 830nm light is absorbed less and penetrates deeper into brain tissue than the 690nm light. Both wavelengths were used in this experiment because this study was also designed to examine hemodynamic changes, which require having both wavelengths. In fact, we compared FOS obtained using these two wavelengths in our previous report (Gratton, et al., 2006), and found substantially similar effects (as expected if FOS are due to scattering changes). Therefore we combined these two sets of data in the current report to increase statistical power.

and Corballis (1995), has been employed by other labs (e.g., Steinbrink, Kempf, Villringer, & Obrig, 2005), and shown to greatly reduce the impact of pulse artifacts. In any case, the experimental paradigm, based on the prediction that *specific* frequencies should be present in the optical data depending on the stimulation frequency, effectively rules out the possibility that any observed effects could be due to the pulse or any of its harmonics.

Channels with amplitude deviations greater than 240 ps and/or source-detector distances outside a 15–75 mm range were excluded from further analysis (Gratton, et al., 2006). Discrete Fourier transforms were performed on a moving window of 60 data points (i.e. 960 ms) to obtain amplitude spectra, which were then averaged for each trial, channel and condition. To account for different amounts of noise in the data in different channels and subjects (which would shift the entire spectrum up or down), the average amplitude frequencies of 4, 6, and 8-Hz was subtracted from each frequency amplitude value.

The resulting baseline-corrected average frequency spectra for each channel were reconstructed into the voxel space and analyzed by an in-house computer program, Opt-3D, (Gratton, 2000) using a back-projection algorithm. The spectrum for a given pixel was reconstructed by averaging the spectra of channels that overlapped at that particular pixel (Wolf, et al., 2000). In order to reduce the effects of background noise, the frequency spectrum obtained during the rest period was subtracted from each stimulation condition. *T*-statistics were computed at the group level for each pixel and converted into *Z*-scores. Statistical maps of the spectrum for each voxel were generated by projecting the *Z*-score onto the posterior surface of a template brain in Talairach space, with an 8 mm spatial filter, according to the location information from the co-registration procedure. The Talairach coordinates reported here comprise only the *x* (left-right) and *z* (dorsal-ventral) dimensions because the statistical maps were surface-projected onto a back-view of a template brain. A 3 cm × 3 cm (width × height) region of interest (ROI) covering Brodmann areas 17 (MV in figure 2) and two 3 cm × 3 cm ROIs covering left and right Brodmann areas 18 (LLV and RLV in figure 2) was used in the analyses to select the areas of visual cortex commonly associated with SS-VEP (Di Russo, et al., 2007; Di Russo, et al., 2005; Pastor, et al., 2003). Corrections for multiple comparisons were carried out using the methods described in (Friston, et al., 1994).

Results

Statistical maps of the frequency spectra were examined separately for younger and older adults to demonstrate that the FOS exhibited a significant response (i.e., increased activity during the stimulation period compared to fixation) at the appropriate checkerboard reversal frequency compared to other frequencies. To reduce the problem of multiple comparisons, statistical analyses were based only on the activity recorded at the three frequencies used for deriving the SSR (4, 6, and 8 Hz). Two sets of contrasts were set up. The first contrast was an “omnibus” contrast, comparing the average activity at the predicted frequency (i.e., pooling together the 4, 6, and 8 Hz conditions when the stimulation occurred at the corresponding frequencies) with the activity at these same frequencies when they were not predicted (i.e., when different stimulation conditions were used: 6 and 8 Hz activity for the 4 Hz stimulation condition, 4 and 8 Hz activity for the 6 Hz stimulation condition, and 4 and 6 Hz activity for the 8 Hz stimulation condition). This contrast was used to reduce the number of comparisons to one and thus maintain maximum statistical power. The second contrast involved a comparison of each checkerboard reversal frequency condition against the other two frequencies (i.e., the 4-Hz frequency bin against 6 and 8-Hz; the 6-Hz frequency bin against 4 and 8-Hz; and the 8-Hz frequency bin against 4 and 6-Hz).

Statistical maps of the frequency spectra of the first set of contrasts are shown in figure 3, separately for younger (upper panel) and older adults (lower panel). The first contrast was an overall test for the presence of FOS activity at the expected frequency (i.e., the frequency corresponding to the reversal frequency) against all other stimulus-response frequency combinations (which served as controls). They showed significant peaks within the medial occipital (MV) ROI ($p < .05$, corrected for multiple comparisons), corresponding to increased FOS activity at the predicted frequency compared to the unpredicted ones for *both* younger adults (peak Z score = 2.53, critical Z = 2.22, at $x = -1$, $z = -16$), and older adults (peak Z score = 2.35, critical Z = 2.20, at $x = 7$, $z = -21$). In addition, significant peaks within the right lateral occipital (RLV) ROI were found in the older adults (peak Z score = 3.14, critical Z = 2.17, at $x = 34$, $z = -6$), but did not reach significance (when adjusted for multiple comparisons) in the left lateral occipital (LLV) ROI (peak Z score = 2.26, critical Z = 2.35). In younger adults, no significant peaks were found for either of the lateral ROIs (RLV peak Z score = 2.07, critical Z = 2.44; LLV peak Z score = 1.86, critical Z = 2.39). To ensure that these results were not influenced by violations of the normal distribution assumption (which may be generated by the discrete FT), we also ran bootstrap analyses for each set of contrasts. These analyses yielded results that were very similar to those reported above. Further, given the apparent asymmetry between the RLV and LLV peaks in older adults, we extracted the peak activities from each ROI separately and tested their difference. Paired *t*-tests showed that the peak activation of the left and right lateral ROIs were not statistically different from each other (mean amplitude LLV = .4403 $SE = .1962$; RLV = .6815 $SE = .2435$, $t(7) = 1.171$, n.s.).

To separately examine the visual cortex response at different frequencies for each stimulation frequency condition, the locations of the peak FOS-SSR within each ROI were identified in the omnibus test. For these peak locations, frequency spectra were derived. Figure 4 shows the relative amplitude of the peak response for MV (left column) and RLV (right column) for each stimulation condition (4, 6, and 8 Hz) for younger (upper row) and older adults (lower row)³. These results suggest that, for younger adults, the spectrum was dominated by the predicted frequency in the MV but not in the RLV; however, for older adults, the spectrum was dominated by the predicted frequency in the RLV but reached significance only for the 4 Hz condition in the MV.

Statistical maps of the frequency spectra of the second set of contrasts (i.e., checkerboard reversal frequency minus the other two frequencies) are shown in figure 5. Results for the younger and older adults are shown in the upper and lower panels, respectively. In the 3 by 3 matrices, each column represents a contrast of each FOS frequency bin (4, 6, and 8-Hz, respectively) minus the other 2 frequencies (6 and 8, 4 and 8, 4 and 6-Hz, respectively), and each row represents a checkerboard reversal frequency condition. As suggested by the omnibus test in the first contrast, significant increases in the amplitude of the frequency spectrum ($p < .05$, corrected for multiple comparisons, one-tailed) were found consistently within the MV ROI for younger adults and within the RLV ROI for older adults in the corresponding checkerboard reversal frequency condition (i.e. along the diagonal of the 3×3 matrix). Specifically, in the younger adults, significant peaks were found consistently in the MV ROI for the predicted frequency, that is in the 4-Hz bin for the 4-Hz reversal frequency condition (peak Z score = 3.35, critical Z = 2.39, at $x = -8$, $z = -18$), in the 6-Hz bin for the 6-Hz reversal frequency condition (peak Z score = 3.57, critical Z = 2.42, at $x = 2$, $z = -26$), and in the 8-Hz bins for 8-Hz reversal frequency condition (peak Z score = 3.24, critical Z = 2.43, at $x = 9$, $z = -18$). All of the off-diagonal entries did not show statistically significant values within the MV ROI. For the older adults, significant peaks were found consistently in

³The data from LLV are not shown because the omnibus analysis did not reach significance for this ROI.

the RLV ROI in the predicted frequency, that is in the 4-Hz bins for the 4-Hz reversal frequency condition (peak Z score = 2.58, critical Z = 2.49, at x = 27, z = -11), in the 6-Hz bins for the 6-Hz reversal frequency condition (peak Z score = 2.99, critical Z = 2.22, at x = 34, z = -3), and in the 8-Hz bins for the 8-Hz reversal frequency condition (peak Z score = 2.56, critical Z = 2.22, at x = 34, z = -6). Again, no significant value was observed in the off-diagonal entries.

The results of the contrasts suggest a possible difference between younger and older adults in the location of the peak FOS-SSR. Specifically, the peak FOS response appeared localized to medial occipital areas in younger adults, but involving also lateral occipital areas in older adults. To evaluate the differential relationship between medial and lateral areas in younger and older adults, we ran a series of analyses comparing activity in medial and lateral occipital regions in younger and older adults. For each individual participant, we identified the location of the peak predicted FOS-SSR of the second contrast within each ROI.

The mean amplitudes for each ROI and age group⁴ are presented in Table 1, showing a differential relationship between medial and lateral areas in younger and older adults. A mixed-design, repeated-measure ANOVA (with ROI and age group as factors) showed non-significant main effects of both ROI ($F(1,20) = 0.80$, $p > .05$) and age group ($F(1,20) = 1.81$, $p > .05$), but a significant interaction effect ($F(1,20) = 5.45$, $p < .05$). Analyses of simple effects demonstrated a significant difference between MV and LV in younger adults ($t(9) = 2.32$, $p < .05$) showing a *decrement* in response in the lateral areas compared to the medial area. Conversely, in the older adults, there was a significant *increment* in response in the lateral areas compared to the medial area ($t(11) = 10.34$, $p < .05$). We also examined the 3-way interaction between stimulation frequency, ROI and age group with a mixed-design ANOVA (stimulation frequency $\times$ ROIs $\times$ age group) on the peak amplitude of the expected frequency response. Consistent with the results of the analysis conducted on the omnibus contrast, only a significant interaction of location and age was found ($F(1,20) = 1.81$, $p > .05$). However, no significant main effect or interaction involving stimulation frequency was found (all F 's < 1).

For illustration purposes, frequency spectra of FOS from the peak locations (averaged across medial and lateral regions and younger and older subjects) are presented in Figure 6. These spectra indicate that the peak of the FOS activity is obtained at the stimulation frequency for each of the three stimulation frequency conditions. Figure 7 reports the time course of the optical response (the event-related optical signal, or EROS). The EROS response was obtained by averaging the data from all points in the medial ROI, and pooling together the three stimulation frequencies. To demonstrate the reliability of the EROS time course, subjects were sorted in three groups (each including 5 younger and 4 older subjects) on the bases of their ordinal number (subject 1, 4, 7 etc., in the first group, subject 2, 5, 8, etc. in the second group, and subject 3, 6, 9, etc. in the third group). The results indicate that the time course of EROS is very similar in each of the three groups, indicating a very stable response across subjects. Also shown in the figure is the grand average across all groups.

Discussion

The current study investigated the possibility of using FOS to identify rhythmic brain activity with frequencies exceeding 4 Hz. By adopting an SSR paradigm, we showed that

⁴We excluded 8 younger adults from this and the analyses involving contrasts between the medial and lateral regions because they were missing data from one of the lateral (LV) ROIs (i.e., the optode montage did not cover these regions appropriately for these individuals).

the peak amplitude of the FOS frequency spectrum was dominated by the corresponding checkerboard reversal frequency, at least up to a frequency of 8 Hz, and that this frequency response was observable in ROIs localized within visual cortex. This result is consistent with predictions from previous studies based on electrophysiological methods (Di Russo, et al., 2007; Di Russo, et al., 2005; Fawcett, et al., 2004; Hillyard, et al., 1997; Krolak-Salmon, et al., 2003; Pastor, et al., 2003), which are typically interpreted as indicating that the SS-VEPs are generated in primary and/or secondary visual cortex (Di Russo, et al., 2007)⁵. In our study, analyses using a single ROI encompassing both primary (BA17) and secondary (BA18 and BA19) visual areas showed correspondence between the peak of the FOS spectrum and the checkerboard reversal frequency both in younger and older adults. The FOS peak locations appear to vary slightly according to the stimulation frequency within each age group (see figure 5). In the younger adults (upper panel) these differences may reflect random variations in the relative contributions of the responses from the two hemispheres (as the surface projection of BA17 in each hemisphere is likely to fall onto the same – medial – ROI). In the older adults (lower panel) the peak location differences were smaller than the spatial resolution afforded by the recording montage. Further, it should be noted that in this group the largest responses were in right extrastriate areas, for which the homologous area in the left hemisphere is not likely to project onto the same ROI.

Further analyses using separate ROIs (MV and LV) showed differences in the amplitude of the SS-FOS activity at medial and lateral locations in younger and older adults. Specifically, older adults showed a reduced SS-FOS compared to younger adults, confirming similar results obtained with other methodologies; (Buckner, et al., 2000; Fiorentini, et al., 1996; Porciatti, et al., 1992; Ross, et al., 1997; Tomoda, et al., 1991). In addition, younger but not older adults showed a reduction in SS-FOS in lateral compared to medial areas. This may reflect the active inhibition of the brain response elicited by repeating stimuli, which may occur to a greater extent in younger than older adults in attention-sensitive regions of the brain (see Gazzaley, et al., 2007 and Fabiani, et al., 2006 for an analogous finding in the auditory domain). This phenomenon is usually attributed to a diminished top-down control of frontal regions onto sensory areas, which may result in enhanced distractibility at the behavioral level (for a review see Hasher, et al., 2008) and may manifest as increased and/or more diffused activity at the brain level in older compared to younger adults (e.g., Cabeza, 2002; Fabiani & Friedman, 1995; Reuter-Lorenz & Cappell, 2008; Schneider-Garces, et al., in press).

Most of the previous FOS studies have been confined to event-related or time-domain analyses. To our knowledge, only two studies (Gratton, Fabiani, et al., 1995; Zhao, et al., 2006) have investigated FOS in the frequency domain. The Gratton et al. (1995) study examined relatively low-frequency (0.8 Hz) activity in motor cortex associated with tapping. The Zhao's study demonstrated fast optical signals in prefrontal regions associated with the EEG delta wave during sleep in normal subjects, again investigating relatively low-frequency activity (< 4 Hz). Although these studies, together with several others (Fabiani, et al., 2006; Gratton, et al., 2006; Low, et al., 2006; Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000; Sable, et al., 2007; Tse, et al., 2007; Tse & Penney, 2008; Tse, et al., 2006), showed a correspondence between electrophysiological measures and fast optical signals, they did not provide direct evidence that FOS can be used to investigate oscillatory brain activity 4 Hz or higher. This is in part due to the fact that the event-related methodology used for analysis, coupled with the frequency filters applied to the data, did not allow for

⁵Previous research (Di Russo, et al., 2007) has suggested that V1 and V5 provide the two major contributing sources of the steady-state surface-recorded VEPs. In the current study we used an optical montage designed to study primarily V1 and V2. Therefore only a small proportion of participants had coverage V5/MT, which is not sufficient for a systematic examination. Further research is needed to examine the contribution of V5/MT to SS-FOS.

high frequencies to be represented in the averaged results. Thus, it is particularly important to demonstrate the actual temporal resolution of FOS (in contrast with its temporal localization power).⁶

Demonstration of the temporal simultaneity of electrical and optical activity is useful to indicate that FOS may be neuronal in origin. However, *per se*, it does not demonstrate that FOS can be used to independently investigate brain phenomena that occur sequentially at separations of less than a few hundred milliseconds from each other. For this, it is important to demonstrate that FOS can track relatively high-frequency (short-wavelength) oscillations in brain activity. In the current study we show that FOS can track brain oscillations with a frequency of up to 8 Hz. Importantly, the data show no sign of decline in the amplitude of brain activity at this frequency (compared to the 4 Hz condition), suggesting that this frequency is still not close to the temporal resolution limits of FOS.

Compared to EEG and ECoG, it still remains to be demonstrated that FOS are able to track brain activity occurring with very high frequencies (>20 Hz). So far a limitation to the tracking of such high frequencies is the presence of a trade-off, in the current recording apparatus, between the number of channels that can be recorded from without cross-talk and the attainable sampling rate. This is a practical rather than theoretical limit, which could be overcome with a more parallel instrumental design. In any case, the present experiment expands the realm of the observed FOS activities to frequencies higher than 4 Hz. In that respect the data reported here are novel and expand our current set of tools available for the assessment of brain activity in a non-invasive fashion.

FOS analysis of high-frequency brain responses provides a relatively good localization of the origin of the signal. In the present experiment this is demonstrated by the ability to differentiate steady-state activity occurring in medial and lateral occipital areas, which are located only a few cm from each other. In fact, the current study reports differential effects in medial and lateral occipital regions in younger and older adults, suggesting that FOS can be used to study the cortical distribution of high-frequency activity in visual and other cortical areas.

In principle, time-domain and frequency-domain analyses provide comparable information. However, due to the differences in filtering and time-locking that are inherent to these methods, they are sensitive to different aspect of FOS. For example, comparing the results of the frequency-domain analyses reported here with the time-domain analyses reported by Gratton, et al. (2006) for younger adults, it is apparent that event-related time-domain analyses (i.e. analyses of the EROS) are more sensitive to low-frequency signals, whereas frequency-domain analysis are more sensitive to high-frequency signals. This may be due to the fact that the fast optical data used for event-related time-domain analyses are usually heavily filtered, (e.g. using low-pass filters of 10Hz or below). As a consequence high-frequency signals may be removed or attenuated. Further, only phase-locked (both across trials and across subjects) activity is analyzed. Phase-locking may be easier to achieve for low-frequency than for high-frequency activity. Thus, time-domain event-related analyses are relatively insensitive to high-frequency signals. In contrast, frequency-domain analyses allow us to investigate high-frequency signals using unfiltered fast optical data.

Notwithstanding these advantages, there are also some limitations in the types of frequency analyses presented here. One problem is that it is difficult to distinguish between signal and

⁶Temporal localization is meant to indicate that the timing of an isolated event can be accurately identified. This differs from temporal resolution, which refers to the ability to provide independent measurements of two events occurring in rapid succession (Gratton, 2007).

noise, as the phase-locking criterion used for time-domain analyses is eliminated. Therefore frequency analysis data may have a higher chance of being contaminated by physiological responses, such as pulsation, hemodynamic signals and respiration. More specifically, pulsation and respiration, which are not time-locked or phase-locked to the event, can be eliminated by averaging in event-related designs. The impact of these sources of noise can be reduced by focusing on relatively high frequency activity (>4 Hz), at which these phenomena are not strongly represented. In addition, the pulse artifact was removed by applying the pulse correction procedure as described in the methods section (Gratton & Corballis, 1995). Finally, the observation that the SS-FOS is only observable at the stimulation frequency but not at the control frequencies demonstrates that the phenomenon is directly related to the stimulation conditions.

Although the earliest vascular changes associated with neuronal responses may start within a few hundred milliseconds from the eliciting event (e.g., Frostig, Lieke, Tso, & Grinvald, 1990; Kleinfeld, Mitra, Helmchen, & Denk, 1998; Sandman, Ohalloran, & Isenhardt, 1984), their duration (i.e., wavelength) is of several seconds (peaking at about 2–5s from the onset of the event) corresponding to a frequency well below 1 Hz. Thus, their frequency characteristics are completely different from those reported here, and are very unlikely to contaminate the results.

The frequency analyses used in the current study are based on a discrete Fourier Transform, which treats brain activity as the summation of sine waves. Because previous electrophysiological studies suggested that a stationary sine wave is a good model for steady-state responses (Di Russo, et al., 2007; Galambos, et al., 1981), Fourier Transforms were appropriate in the current study. However, other frequency-domain analysis methods, such as wavelet analysis, may be more suitable if transient and non-sine-wave-like responses are expected, as the stationarity assumption is not required by the latter methods.

Although SS-VEPs usually possess a relatively high S/N (Di Russo, et al., 2007), in the current study the S/N of the SS-FOS was much lower. This may reflect the generally lower S/N of FOS. A further contributing factor may be the use of a passive viewing paradigm. Hillyard et al. (1997) showed modulation of the amplitude of the SS-VEP by selective attention: The SS-VEP response was enhanced by more than 70% when attention was directed towards a flickering stimulus. Thus, a stronger fast optical response could be expected with an active viewing task.

The results of the current study do provide an additional replication of the possibility of obtaining fast optical signals in humans. However, two recent reports have cast some doubts on the feasibility of obtaining such data. The first of these studies (Steinbrink, et al., 2005), while reporting fast optical changes associated with median nerve stimulation, attributed them to movement artifacts, and implied that this explanation may be applied to *all other* fast signal reports. However, this explanation contrasts with a large number of studies, employing a number of different paradigms and experimental and control conditions, in which movements cannot possibly account for the observed effects (DeSoto, Fabiani, Geary, & Gratton, 2001; Fabiani, et al., 2006; Franceschini & Boas, 2004; Gratton, et al., 2006; Gratton, Corballis, et al., 1995; Gratton & Fabiani, 2003; Gratton, et al., 1997; Gratton, et al., 1998; Gratton, Sarno, Maclin, Corballis, & Fabiani, 2000; Low, et al., 2006; Maclin, et al., 2004; Medvedev, et al., 2008; Rinne, et al., 1999; Sable, et al., 2007; Tse, et al., 2007; Tse & Penney, 2007, 2008; Tse, et al., 2006; M. Wolf, et al., 2002; Zhao, et al., 2006). For example, in the current study, as well as in the (Tse & Penney, 2007, 2008; Tse, et al., 2006), no overt responses were required of the participants. In another recent study by Medvedev and colleagues (2008), the subject's response occurred *after* the observed FOS effects. Indeed, the Steinbrink et al. (Steinbrink, et al., 2005) paper does not report either any

direct demonstration that head movements did indeed occur in the study, or how such movements (if existing) could be capable of producing the reported fast effects, which were, as expected based on the known organization of somatosensory areas, larger on the side *contralateral* to stimulation than on the ipsilateral side. Thus the possibility that movement artifacts may in some cases mimic fast optical effects appears a mere suggestion rather than a factual conclusion.

The second paper (Radhakrishnan, et al., 2009) is based on optical recordings from the exposed visual cortex of two monkeys. In this study, no fast optical change was reported, apparently contradicting not only the results obtained non-invasively in humans, but also the many papers on fast optical signals reported with cortical recordings in rats and other animals (e.g., Rector, et al., 2005; Tsytsarev, Premachandra, Takeshita, & Bahar, 2008). It is important to note, however, that the recording methods used by Radakrishnan and colleagues, and in particular the source-detector distances used (exceeding 12 mm) appear inappropriate for recording from the surface of such a thin structure as the visual cortex of monkeys (< 2 mm thick; e.g., Bear, Connors, & Paradiso, 2006 which would require source-detector distances of 3–6 mm). Under these recording conditions, the photons' paths are likely to have largely overshoot the visual cortex, thus leading to small or no effects. Although the authors report the observation of slow (hemodynamic) signals under the same conditions, it is well known that hemodynamic effects, and specifically those due to increased blood flow reported in that study, are much more diffused than the neuronal phenomena associated with fast optical effects (e.g., Tsytsarev, et al., 2008).

Electrophysiological research has identified three forms of oscillatory activity that occur in the presence of stimulation: evoked, induced, and steady-state (see Galambos, 1992; Makeig, 1993; TallonBaudry, Bertrand, Delpuech, & Pernier, 1996). Similarly, oscillations in optical responses could also in principle be classified in the same fashion. In this case, the activity reported here is best described as “steady-state” in nature. However, there appear to be no reasons for which evoked and induced oscillatory activities could not be similarly explored using optical methods. This may be the target of future work.

In summary, the current study demonstrates the feasibility of using FOS to localize the brain regions associated with rhythmic brain activity with frequencies exceeding 4 Hz. As relatively high-frequency brain rhythms are considered of great significance for a number of areas in neurology, cognitive neuroscience and affective neuroscience, these findings pave the road for a number of possible new applications of fast optical imaging. Future research with this method may explore frequencies beyond 8 Hz, which are becoming increasingly more central to brain research.

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Figure 1.
Flow chart showing the steps used in the analysis of FOS.

Figure 2. Medial (MV; white), left and right lateral (LLV, RLV; black) occipital ROIs used to test the differences in the spatial distribution of steady-state FOS responses in younger and older adults.

Figure 3.

Z-score maps (computed across subjects) of the omnibus test results, showing significant increases in FOS activity at the stimulation frequency (compared to the control frequency conditions), projected on posterior coronal views of the visual cortex. Green boxes demarcate the ROIs. White crosses within the ROIs indicate the location of significant peak activity. The dark gray shading shows the area of cortex interrogated by the recording montage.

Figure 4.

Bar graphs of FOS amplitudes for the 4, 6, and 8 Hz stimulation conditions at the peak locations in the omnibus contrast, averaged across participants, separately for the MV and RLV ROIs. The error bars represent the standard error of mean. The stars indicate conditions that are significantly different from the controls ($p < .05$).

Figure 5. Z-score maps (calculated across subjects) of the results of the frequency analysis in occipital cortex. The data refer to the difference between the FOS activity of 4-Hz minus 6 and 8-Hz (left column), 6-Hz minus 4 and 8-Hz (middle column) and 8-Hz minus 4 and 6-Hz (right column) for younger adults (upper panel) and older adults (lower panel). Green boxes demarcate the ROIs. The size and position of the ROI relative to the whole brain is shown in the insert of the whole brain image. Yellow boxes indicate the cases in which the frequency of the FOS corresponds to the frequency of stimulation (diagonal). White crosses within the ROI indicate the location of peak activity.

Figure 6.

Amplitude frequency spectra (expressed as differences from a baseline averaged across conditions) for each frequency condition. The spectra are averaged across medial and lateral areas and across all subjects.

Figure 7.

Time course of the event-related optical signal (EROS) pooled across frequency conditions, and averaged across the entire medial ROI. Average HF is the average of all subjects for high frequencies (4, 6 and 8 Hz). The 3 groups represent independent and exhaustive sub-samples of the subjects ($N=9$ for each group), to demonstrate the reliability of the grand average waveform. The vertical bars indicate the standard error of the means.

Table 1

Mean amplitudes of FOS (in picoseconds) at the predicted frequencies for younger and older adults in the medial (MV) and right lateral (RLV) occipital cortex ROIs.

Younger Adults		
ROI	Mean	Standard Deviation
MV	1.671	0.859
RLV	1.414	0.993
Older Adults		
ROI	Mean	Standard Deviation
MV	0.772	0.751
RLV	1.348	1.102