Behavioral/Systems/Cognitive

Ultra-Rapid Sensory Responses in the Human Frontal Eye Field Region

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Most of what we know about the human frontal eye field (FEF) is extrapolated from studies in animals. There is ample evidence that this region is crucial for eye movements. However, evidence is accumulating that this region also plays a role in sensory processing and that it belongs to a "fast brain" system. We set out to investigate these issues in humans, using intracerebral recordings in patients with drug-refractory epilepsy. Event-related potential recordings were obtained from 11 epileptic patients from within the FEF region while they passed a series of visual and auditory perceptual tests. No eye movement was required. Ultra-rapid responses were observed, with mean onset latencies at 24 ms after stimulus to auditory stimuli and 45 ms to visual stimuli. Such early responses were compatible with cortical routes as assessed with simultaneous recordings in primary auditory and visual cortices. Components were modulated very early by the sensory characteristics of the stimuli, in the 30–60 ms period for auditory stimuli and in the 45–60 ms period for visual stimuli. Although the frontal lobes in humans are generally viewed as being involved in high-level cognitive processes, these results indicate that the human FEF is a remarkably quickly activated multimodal region that belongs to a network of low-level neocortical sensory areas.

Introduction

Ever since Ferrier's pioneering experiments in 1873, evidence has accumulated in favor of the view that the frontal eye fields (FEFs) play a key role in the initiation of eye movements (Ferrier, 1873). In particular, Bullier (2001) has argued that the structure may be thought of as part of a "fast brain" system for generating rapid behavioral responses to visual stimulation. Single-unit recordings in macaque monkeys have shown that the FEFs contain two different groups of neurons. The first group contains movement neurons that do not respond directly to visual stimulation, but are active before and during saccades. They thus respond in the opposite way to fixation neurons (Bruce and Goldberg, 1985). The second group includes visually and aurally responsive neurons that are active during target discrimination independently of saccade programming (Mohler et al., 1973; Russo and Bruce, 1994).

It has generally been thought that FEF is not involved in sensory processing per se, because in monkeys, contrast sensitivity is not impaired by FEF lesions (Schiller and Chou, 2000), and simple visual detections are not impaired after FEF reversible inactivation (Wardak et al., 2006). However, recent studies have revealed that FEF neurons can have visual responses that are selective to stimulus shape (Peng et al., 2008), and monkeys can detect microstimulation of the FEF at intensities well below the levels needed to trigger saccades (Murphey and Maunsell, 2008). Both these results suggest that FEF may be closer to sensory analysis than previously believed.

Analysis of onset latencies in different cortical areas of macaque monkeys indicates that visually responsive FEF cells have onset latencies that can be almost as short as low-level cortical areas such as V1 and MT (Nowak and Bullier, 1997). This observation led to the idea that FEF may be lower in the visual hierarchy than previously thought (Petroni et al., 2001). Furthermore, FEF cells receive very-short-latency inputs through the superior colliculus (SC)–mediodorsal thalamus–FEF ascending pathway (Sommer and Wurtz, 2000). It thus appears that the FEF could take part in a highly optimized network of visual scene analysis for ultra-rapid saccadic responses.

Evidence that the FEF could belong to this fast brain network is much scarcer in humans. The kind of representations processed at such short latencies is also unclear. Given the absence of precise data on the latencies and characteristics of the early electrophysiological responses of the human FEF, we set out to investigate the precise temporal sequence of sensory processing using intracerebral recordings in human epileptic patients.

Materials and Methods

Stimuli and tasks. Visual stimuli were presented using E-Prime version 1.1 (Psychology Software Tools). Temporal precision between the onset of visual stimulation and the EEG recordings was controlled using a photodiode on the screen used for stimulus presentation (cathode ray tube monitor, 17 inches, Dell Trinitron UltraScan P991 with a refresh rate of 100 Hz). The screen was adjusted to be ~80 cm from the patients'

Received March 13, 2009; accepted April 5, 2009.

We thank Prof. P. Chauvel, Prof. F. Bartolomei, Dr. M. Gavaret, Dr. M. Guye, Dr. A. Trébuchon, and Dr. A. McGonigal (Department of Clinical Neurophysiology, Assistance Publique Hôpitaux de Marseille, Hôpital de la Timone) for providing access to patients and clinical data. We also thank Patrick Marquis for dedicated help in data acquisition and Dr. Nathalie Vayssière for help with figures.

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DOI:10.1523/JNEUROSCI.1233-09.2009

 0270-6474/09/297599-08$15.00/0

Table 1. Demographic and epileptic status of the patients retained for further analysis in this study

Patient	Sex	Age (years)	Hand laterality	Implantation	Epileptic focus	Talairach coordinates of the contact in the FEF			Eye deviation on stimulation	Visual tasks	Auditory tasks
						x	*y*	*z*			
1	F	27	L	Right frontal	Prerolandic	42.0	2.5	43.0	Yes	Yes	Yes
2	F	33	R	Right frontal	Frontopolar	30.2	−4.2	43.5	n/e	Yes	No
3	F	49	R	Right frontal	Prefrontal	40.5	10.0	36.0	No	Yes	No
4	M	25	R	Right temporofrontal	Perisylvian	35.5	1.2	52.0	n/e	Yes	Yes
5	F	26	R	Left parietofrontal	Mesioparietal	−32.0	2.1	48.5	Yes	Yes	Yes
6	F	26	R	Left temporo-parieto-frontal	Lateral occipital	−27.2	−3.2	52.7	Yes	Yes	Yes
7	M	25	A	Right temporofrontal	Temporal lobe, temporo-occipital junction, and frontal operculum	45.4	7.8	43.2	Yes	Yes	Yes
8	F	41	R	Right occipito-parieto-frontal	Mesio-occipital	51.5	5.2	41.0	No	Yes	Yes
9	M	32	R	Left temporofrontal	Temporopolar	−46.7	2.5	35.5	Yes	Yes	No
10	F	17	R	Bilateral occipito-temporo-frontal	Bilateral occipitotemporal	37.8	9.1	54.4	No	Yes	Yes
11	F	48	A	Right frontal	Premotor	35.0	0.0	48.0	Yes	Yes	Yes
12 (added for ERPs in V1)	F	25	R	Bilateral occipito-parieto-temporal	Bilateral mesial occipito-temporal	None in the FEF	None in the FEF	None in the FEF	n/e	Yes	No

F, Female; M, male; R, right handed; L, left handed; A, ambidextrous; n/e, not evaluated.

eyes at the beginning of each experiment. Auditory stimuli were presented through closed dynamic headphones (Sennheiser HD 25-1, 70 Ω) by use of a custom interface running under MatLab (The MathWorks) and a National Instruments card. All patients had normal hearing as assessed by audiograms. The sounds were presented at an intensity of 80 dB sound pressure level (SPL). All stimuli were presented in a dimly lit, quiet room while patients remained comfortably reclined.

Pure tones were 50 ms long (0.3 ms rise and decay time) and presented in stereo. Each frequency was presented pseudorandomly (no two identical pure tones could be presented one after the other) with an interstimulus interval (ISI) of 1000–1300 ms. "BA"/"PA" (voiced/voiceless) syllables (383/216 ms) were presented randomly with an ISI of 1030–1230 ms. The checkerboard (eight columns, six rows, size 23° × 18°) was presented centrally using the entire screen with a small yellow fixation rectangle in the middle. The checkerboard was alternated every 1700 ms. In the visual oddball task, each stimulus was presented during 400 ms, with a fixation cross between trials lasting 600–1000 ms. All five stimuli were equalized in luminance and presented on a gray background, size 5° × 5°, 330 × 330 pixels. Tasks using natural scene stimuli used the same parameters.

Patients and recordings. Patients had drug-refractory epilepsy and were undergoing evaluation for possible surgical intervention. The choice of the location of intracranial electrodes was based on clinical and video-EEG recordings and was therefore independent of the present study. This study did not add any invasive procedure to the depth EEG recordings. Event-related potential (ERP) recordings were part of the functional mapping procedure that aims at characterizing electrophysiological indices to identify healthy from lesional tissues (latencies, morphologies, and amplitudes of responses). This study was approved by the Institutional Review Board of the French Institute of Health (agreement nos. IRB0000388, FWA00005831). All patients signed informed consent before participation.

Characteristics of the patients are provided in Table 1. From 6 to 10 intracerebral electrodes were implanted stereotaxically orthogonal to the midline vertical plane. Each electrode was from 33.5 to 51 mm long, had a diameter of 0.8 mm, and contained from 10 to 15 contacts, each 2 mm long and separated from each other by 1.5 mm (Alcis).

Anticonvulsant therapy was reduced or withdrawn during the EEG exploration to facilitate seizures. However, no subject had seizures in the 12 h before ERP recordings. Signals were acquired using SynAmps amplifiers and NeuroScan software (Compumedics). The sampling frequency of EEG depth recordings was 1000 Hz with an acquisition band-pass filter of between 0.15 and 200 Hz. The reference was a surface electrode at location Fz.

ERP processing. ERPs were computed off-line using BrainVision version 1.05 (Brain Products) from 0 to 500 ms after stimulus with a prestimulus baseline of 100 ms. Automatic artifact rejection procedures as well as visual inspection of single trials were used to reject periods with interictal activities. Eye movements were monitored using electrodes placed laterally to the eyes. Periods with eye movements were also rejected.

Group and individual analyses. Not all subjects underwent the same tasks because their availability varied depending on clinical factors. Therefore, analyses were performed with different subgroups of patients who had undergone the same tasks. When comparisons were performed across tasks, patients who had undergone the same tasks were selected. Despite different subgroups having been selected, the same characteristic ERP response was identified in the FEF region (aN30–aN50 and vN50–vN80; see Results), suggesting good overall reproducibility.

Individual analyses are also reported. No subgroup could be constituted for the comparison of ERPs recorded in the FEF and in primary cortices because this combination of implanted electrodes is rare. However, in this case, latencies matched those reported in the literature (see Discussion). Within-subjects analyses were also performed for auditory evoked responses because the group averages cancelled out an effect that may be important. In this case, detailed within-subjects statistics were reported (Table 2).

Statistical analyses. Statistical analysis was performed using SPSS version 14.0. Group onset latencies were identified as the first millisecond significantly different from 0 using a one-sample *t* test performed every millisecond starting at the onset of the epoch, and remaining significant for >5 ms. Onset latencies of single-subject ERPs (i.e., for FEF and primary cortex comparisons) were identified by eye and were complemented by peak analyses. Group within- and across-tasks comparisons were performed using matched-paired two-tailed signed-rank Wilcoxon tests every millisecond starting at 30 ms after stimulus onset. Within-subject comparisons (i.e., for auditory evoked responses) were performed using two-tailed matched-paired *t* tests on single trials every millisecond starting at 30 ms after stimulus onset. Only periods significant for at least 5 ms consecutively were considered in all analyses. The level of significance was set to $p = 0.05$ and was subjected to Bonferroni correction for multiple comparisons when appropriate.

Localization of the electrode contacts. Contact location has been described in detail previously (Barbeau et al., 2005). The anatomical location of each contact could be obtained by combining information about the location of the contacts obtained from a postoperative CT scan with information about the trace of the electrode determined using a postimplantation magnetic resonance imaging (MRI) scan.

Table 2. Single-subjects analyses

Patient	Min–max epochs	250–750 Hz	250–2000 Hz	250–4000 Hz	750–2000 Hz	750–4000 Hz	2000–4000 Hz
P1	45–62		58–68 ms, min $p = 0.001$*	29–35 ms, min $p = 0.022$	54–58 ms, min $p = 0.028$		50–62 ms, min $p = 0.004$*
P4	79–103	30–57 ms, min $p = 0.002$*			30–42 ms, min $p = 0.001$*	27–38 and 43–53 ms, min $p = 0.001$*	45–50 ms, min $p = 0.003$*
P5	39–67	29–42 ms, min $p < 0.001$*	33–40 and 44–53 ms, min $p < 0.001$*	34–39 and 43–54 ms, min $p < 0.001$*	42–48 and 58–64 ms, min $p = 0.002$*	39–48 and 53–85 ms, min $p = 0.001$*	
P6	59–63		41–47 ms, min $p = 0.01$	41–53 ms, min $p = 0.001$*		47–54 ms, min $p = 0.009$	
P8	63–82	41–63 ms, min $p = 0.002$*					
P10	57–80						
P11	103–111		52–58 ms, min $p = 0.009$	53–60 ms, min $p = 0.009$		56–73 ms, min $p = 0.002$*	

Periods of significant difference between pure tones in an analysis limited to the 30–60 ms period (tested each millisecond, with at least five consecutive bins with $p < 0.05$). The table gives the minimum (min) and maximum (max) epochs used for ERP averaging. *The difference survives Bonferroni correction for multiple comparisons ($p \leq 0.0083$) during at least some periods. The minimum p values reached during the period (min p) are therefore also provided.

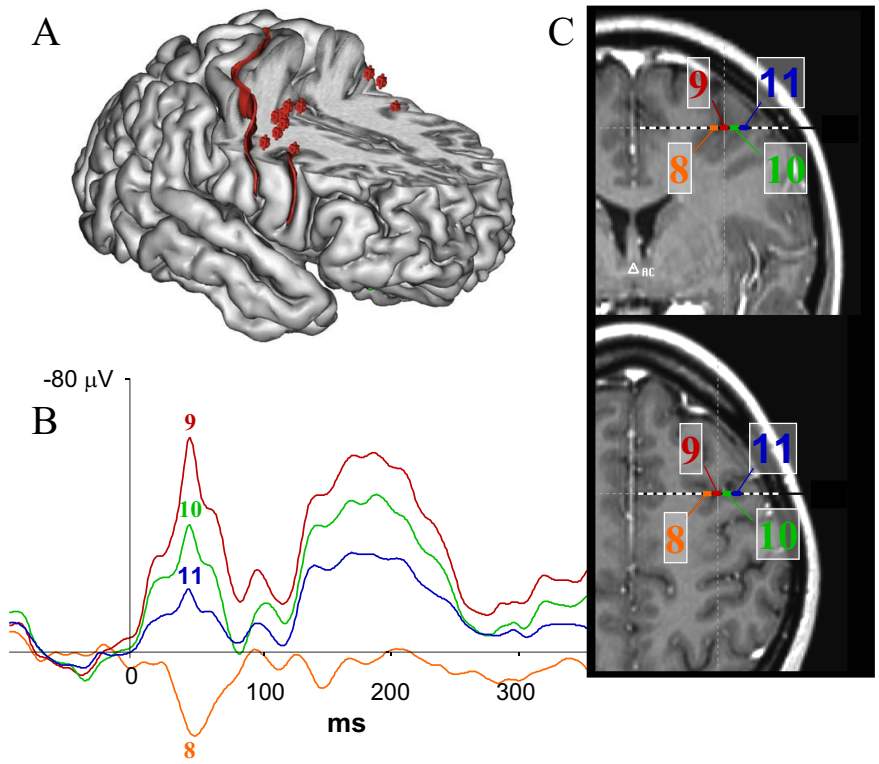

Figure 1. ***A***, Location in a template brain using Talairach coordinates of the contacts of each patient retained for analysis. The central sulcus and part of the precentral sulcus are highlighted in red to facilitate localization. ***B***, Example of polarity inversion between adjacent contacts 8 and 9 in patient P5. Potentials were evoked by 750 Hz pure tones heard passively. Colored numbers correspond to the contact position along the electrode, as reported in ***C***. ***C***, Electrode reconstruction in the coronal and axial planes of the MRI of patient P5. The small white rectangles correspond to the different contacts. Note that contacts 8–11 were all located in the same cortical region but that response amplitude was clearly focal on contact 9, indicating that the neuronal population responding to the stimulus is highly localized.

Results

Each patient was implanted with macroelectrodes perpendicular to the brain midline, each containing 10–15 contacts (Fig. 1*C*). The data we report here are intracerebral ERPs recorded in the FEF region in response to visual and auditory stimulation. The location of the human FEF region was determined based on Talairach coordinates and related literature (Paus, 1996; Blanke et al., 2000; Lobel et al., 2001; Lachaux et al., 2006). To identify ERPs generated focally in this region, criteria were polarity reversal between adjacent contacts (Fig. 1) and/or steep voltage gradients and high voltage fluctuations between adjacent contacts (Fernandez et al., 1999; Barbeau et al., 2008). ERPs in this region had a specific morphology at similar latencies (Fig. 2), facilitating identification. Furthermore, contacts in this region when stimulated with low currents evoked saccadic deviation of the eyes in 75% of the patients. Stimulations were performed on a clinical basis independently from this study and may have been negative in some cases because of variations in the cortical excitability threshold. Comparisons of the ERPs of the patients with and without eye deviation did not reveal any obvious differences. All reported evoked potentials were recorded from the contact for which the response had the highest amplitude. Seventeen patients passed a series of passive and active perceptual tests. No saccadic response was required and eye movements were recorded and monitored throughout all the tasks. An evoked response in the FEF region could be clearly determined in a subgroup of 11 patients who were thus included in this study (Table 1). The remaining six patients did not show ERPs either because the contacts were not in the FEF or because of their neurological condition.

Ultra-rapid evoked responses to visual and auditory stimulation

In a series of different tasks, participants passively viewed an alternating checkerboard or listened to pure tones presented via headphones. The auditory response started and peaked earlier than the visual response. Both visual and auditory stimuli elicited similar complex series of characteristic evoked responses composed of two early negativities peaking between 30 and 80 ms after stimulus onset (aN30 and aN50 for auditory stimuli and vN50 and vN80 for visual stimuli). They were followed by a large positivity at ~100–120 ms and a large negativity at ~200 ms. In this study, we focus on the early responses (i.e., before 100 ms). The onset of the electrophysiological activity in the FEF was remarkably fast: 24 ms after stimulus onset for the average of four pure tones ($p < 0.05$, $n = 7$) (Fig. 2*B*) and 45 ms for the checkerboard ($n = 9$).

Figure 2*A* shows these responses averaged across four patients who underwent both tasks. A further important feature of these results is that in many patients (e.g., the four patients presented in Fig. 2*A*), both visual and auditory responses were recorded from the same contact. These results indicate that this region is not specialized solely for vision but is clearly multimodal. It thus appears that the human FEF has both visual and auditory inputs that are processed very rapidly after stimulus onset.

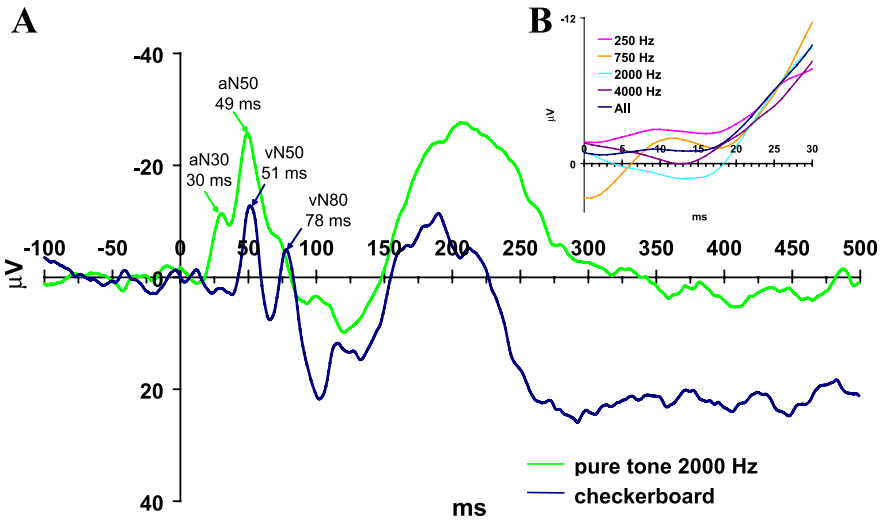

Figure 2. ***A***, Visual and auditory evoked responses in the human FEF. Evoked responses were averaged across the same four patients who had undergone both passive viewing of a checkerboard and passive listening to a pure 2000 Hz tone. ***B***, Onset of the ERP to four different pure tones across seven patients. All, Average of all pure tones.

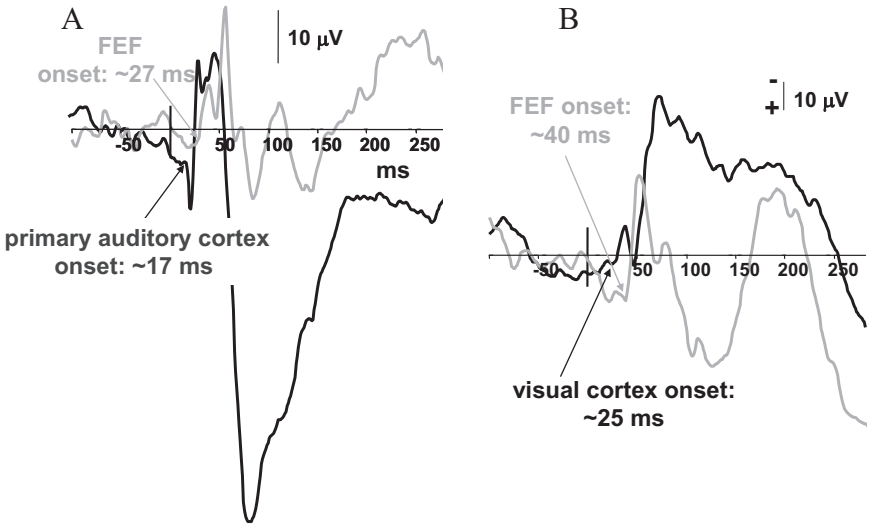

Figure 3. ***A***, ERP onset to a 4000 Hz tone in the primary auditory cortex and the FEF recorded simultaneously in both regions of patient P4. ***B***, ERP onset to an alternating checkerboard recorded simultaneously in the visual cortex and in the FEF of patient P6. The FEF onset in this patient occurred slightly earlier than for the group average (~40 vs 45 ms). The vertical line indicates stimulus onset.

Early activity in related areas

It is noteworthy that the morphology of the ERPs recorded in the FEF region were not observed in any other brain areas, such as the parietal, temporal, and frontal lobes, and are thus characteristic of this region. As information to the FEF could potentially arrive via a retinotectal pathway and/or follow a cortical route, recording of the activity of primary sensory cortices could inform about afferent pathways to FEF. In three of the patients, other electrodes were implanted in the primary visual or auditory cortices, as assessed through electrode reconstruction in patients' MRIs and the presence of steep voltage gradients and high voltage fluctuations between adjacent contacts. No group analysis could be performed because such implantations are rare. In patient P4, the onset of the auditory evoked response to pure tones in the auditory cortex occurred ~10 ms earlier than the equivalent evoked response recorded simultaneously in the FEF (Fig. 3*A*). Because ERP onsets were determined visually, the latencies of the first peak of each ERP were also compared [first negative peak latency in the auditory cortex: 30 ms (an earlier positive component peaked at 22 ms); in the FEF: 39 ms]. In patient P6, a first visual response was recorded in the visual cortex (the contact was located in the cuneus above the calcarine sulcus) with an onset that was ~12 ms earlier than the visually evoked potential recorded simultaneously in the FEF to an alternating checkerboard (Fig. 3*B*). The first component peaked at 37 ms in the visual primary cortex and at 52 ms in the FEF region. To corroborate this latter result, we compared the evoked potentials recorded from V1 in a patient belonging to another study (P12 in Table 1) to the averaged visually evoked response in the FEF. We found that the evoked potential started ~20 ms earlier in V1 (25 ms after stimulus onset; first peak at 30 ms) than the averaged response in the FEF.

Therefore, although the activity starts very early in the FEF, these results are consistent with the information arriving via cortical pathways.

Off responses

It has often been reported that the responses of some neurons in the primary cortices can be time locked to either stimulus onset ("on" response) or offset ("off" responses). Surprisingly, off responses could be recorded in the FEF region ($n = 7$) (Fig. 4) at 100 ms, corresponding to the length of the pure tones (50 ms) added to the peak of the aN50. In the visual modality, the mere presentation of a gray screen with a small fixation cross (0.2° × 0.2°) after the stimulus was enough to elicit small responses [see Figs. 6 ($n = 5$) and 7 ($n = 4$, scenes, ~450 ms)]. Together with the finding that early activities are compatible with a very fast cortical route, these results indicate that the human FEF belongs to a multimodal cortical network of low-level sensory areas.

Auditory evoked responses in the FEF

Figure 4 displays the overlay of AEPs in response to different tonal frequencies. Group comparison of the auditory potentials evoked by four pure tones revealed significant differences between tones starting at 64 ms after stimulus onset ($n = 7$, $p <$

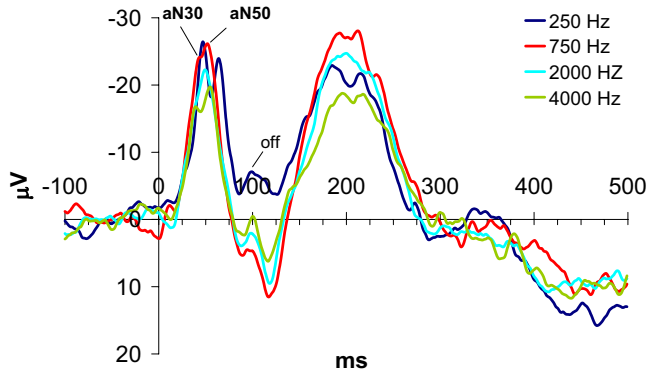

Figure 4. Grand average ($n = 7$) of auditory potentials evoked by pure tones in the human FEF. off, Off response.

0.05) because of the delayed negativity (N50) recorded to 250 Hz. No differences were noted during the aN30.

The group analysis failed to find any evidence for a tonotopic organization. However, single-subject analyses suggested that some tonotopic organization could exist. Specifically, robust differences in the 30–60 ms period were regularly observed between different pairs of tones, even after Bonferroni correction for multiple comparisons (Table 2). In many instances, there appeared to be one or two tonal frequencies that elicited amplitude peaks earlier or higher than the others. The group analysis failed to identify these because these "best-frequency" tones could differ between subjects and were lost through averaging. Figure 5, *A* and *B*, shows examples from patients P2 and P4. Interestingly, the aN30 component in patient P2 was largest for the 4000 Hz tone. Given that at the same physical intensity (80 dB SPL), high frequencies are perceived as less loud than low frequencies, the above results suggest that early auditory responses in FEF are not simply a function of the perceived intensity of the stimuli (Fletcher and Munson, 1933).

Last, real-world complex verbal sounds such as syllables "PA" or "BA" presented passively also elicited clear activity in the human FEF. The time course of evoked potentials also appeared modulated, depending on whether the syllables were voiced ("BA") or voiceless ("PA") (Fig. 5*C*), suggesting sensitivity to temporal features.

Visually evoked responses in the FEF

To further investigate the nature of these early sensory responses in the human FEF, we analyzed evoked potentials in different visual tasks. First, five participants performed an oddball task in which a red target was present on 20% of the trials, and the distractors were composed of the colors green and gray as well as vertical and oblique orientations. The visually evoked response contained the characteristic vN50 and vN80 components seen in the FEF (Fig. 6). Statistical analysis across patients revealed that responses to the vertical grating differed from both the red target and the gray stimulus starting from ~54–59 ms after stimulus onset (vs red target: 59–63 ms and 82–86 ms; vs gray: 54–61 ms; $p < 0.05$). Likewise, the oblique orientation differed from the red target during the peak of the vN50 (51–56 ms). These results indicate that contrast within the stimulus may enhance responses or alternatively that the FEF may be sensitive to lines.

Single-subject analyses did not reveal many differences between conditions in the 30–100 ms period, except between the vertical or oblique orientations and some of the other stimuli in three subjects, emphasizing again the special role of these stimuli.

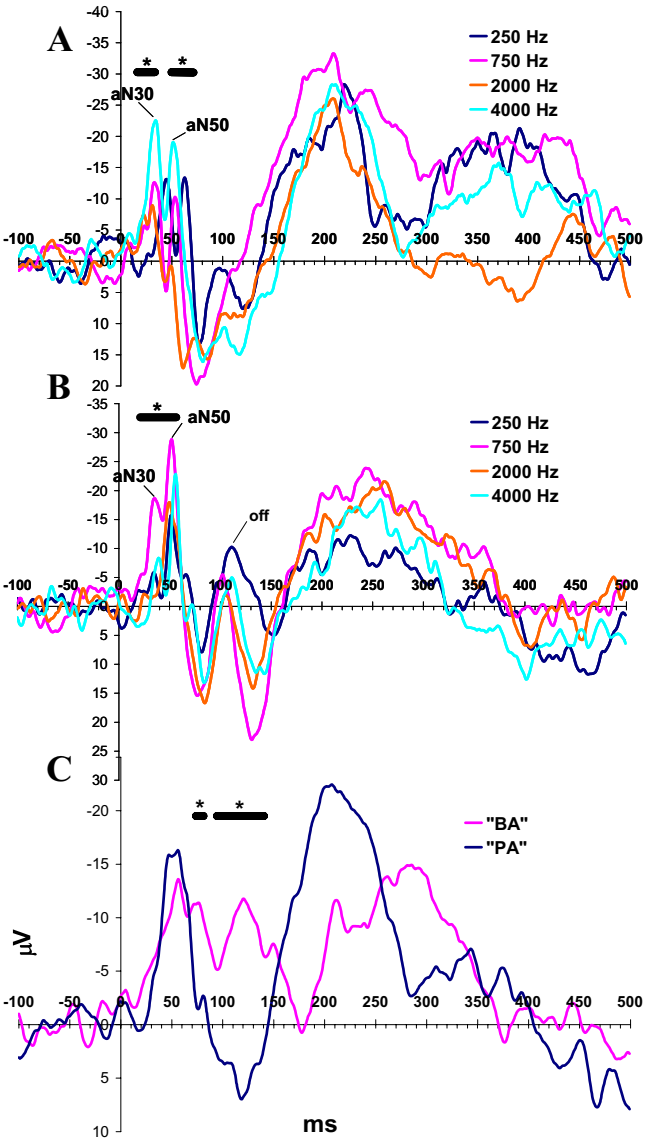

Figure 5. ***A***, Evoked potentials to pure sounds in patient P2. The best frequency (BF) was 4000 Hz. ***B***, Patient P4. The BF was at 750 Hz. off, Off response. ***C***, Grand average ($n = 7$) of the evoked potentials to real-world sounds (voiced and voiceless syllables "BA" and "PA"). Thick dark lines: periods of significant difference ($p < 0.05$).

Note, however, that the number of trials per condition (30–40 because of the length of the experiment) was about half the number of trials used in the auditory tasks (Table 2), which may explain why these differences were less robust. Alternatively, visual responses may be more variable.

In another experimental condition, a group of patients passively viewed a checkerboard. This condition was compared with the presentation of the horizontal orientation and red target described in the previous task in the same patients. The vN50 evoked by the checkerboard had an earlier onset than that seen for vertical orientation (both conditions were different during the 43–48 ms period, $p < 0.05$) and red target (42–48 ms, $p < 0.05$) and peaked 5 ms earlier (51 vs 56 ms) (Fig. 7). The size (the checkerboard was larger than the other stimuli; see Materials and Methods) and contrast of the visual stimulus may therefore play a crucial role even in the earliest visual evoked responses.

A different subset of four patients underwent a task in which they saw natural scenes containing faces. These stimuli elicited

the expected vN50 and vN80, implying that the FEF is involved in the processing of real-world complex visual stimuli and not only in the processing of simple or highly contrasted stimuli (Fig. 7). Overall, vN80 amplitude appeared to be more strongly influenced by the nature of stimuli than the earlier vN50.

Discussion

The frontal lobes are generally viewed as mainly involved in high-level processes in humans, such as reasoning, working memory, or behavioral control. Here, we demonstrate that some sensory information can reach these lobes extremely fast, in <50 ms. Such fast processing is certainly necessary for saccade generation to complex stimuli (Kirchner and Thorpe, 2006) but may also be crucial for integration with current behavior independently of saccades (Fuster et al., 2000), a hypothesis that remains to be further tested. These responses were compatible with cortical routes despite their extremely short latencies and also displayed characteristics of low-level sensory areas (e.g., on–off responses). The human FEF region thus clearly belongs to a cortical network of low-level sensory areas, e.g., to the fast brain as proposed by Bullier (2001). This study also provides evidence that the human FEF region processes both visual and auditory information to similar extents, implying, contrary to a widely held belief, that this region is not specialized solely in visual information processing but is clearly multimodal (Bruce and Goldberg, 1985; Clarke et al., 1995). The amplitudes and latencies of these FEF responses were modulated very early by the sensory properties of the stimuli, which suggests that the area may do more than simply act as an "alerting system." Such findings fit with the observation that information can reach the FEF via fast cortical routes, implying that information has already been processed to some extent.

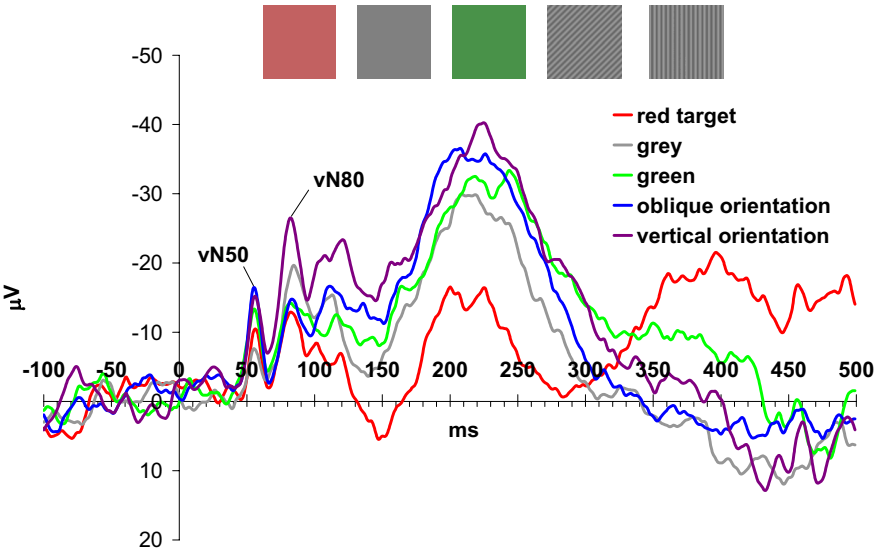

Figure 6. Grand average ($n = 5$) of visual evoked responses in the human FEF. Subjects had to press a button to the red target in a go/no-go paradigm. The different stimuli are depicted. Note the small response at ~450 ms corresponding to the presentation of the fixation cross after the stimulus has been removed.

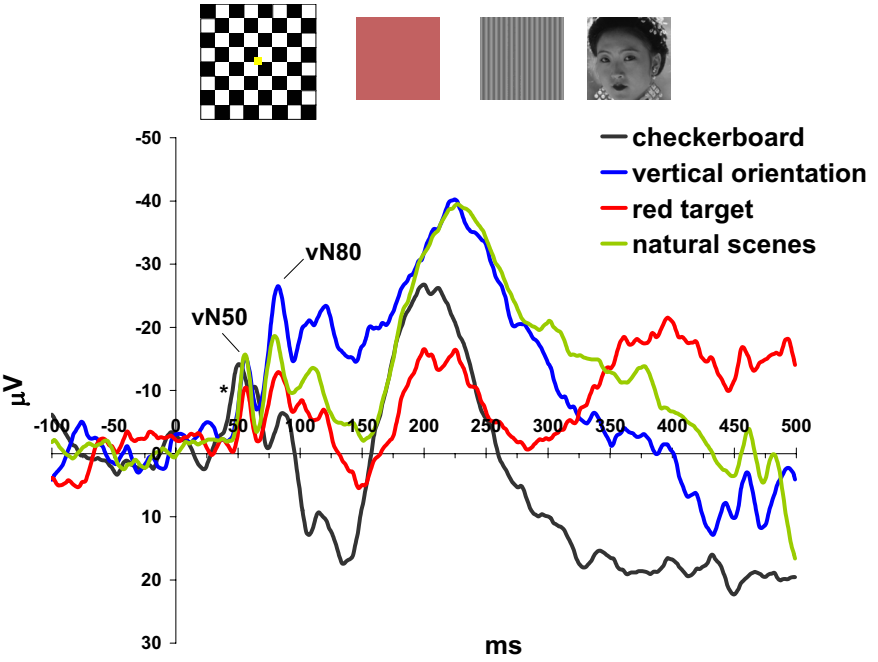

Figure 7. Visually evoked responses in the human FEF to different stimuli. The same patients ($n = 5$) viewed either a checkerboard (presented full screen) or other stimuli, as presented in Figure 6. A subset of patients ($n = 4$) viewed complex natural scenes containing faces. Note the small response to the fixation cross at ~450 ms, not present for the checkerboard, as it always alternated. *$p < 0.05$.

Onset latencies of spikes to visual stimuli in the macaque FEF can be as short as 40–50 ms (Bruce and Goldberg, 1985; Schall, 1991; Thompson et al., 1996; Schmolesky et al., 1998; Pouget et al., 2005). In this study, we recorded evoked potentials that presumably reflect synchronized modifications of the polarization of large populations of pyramidal cell dendrites (i.e., postsynaptic potentials). Integration of this information in the cell soma may take a few milliseconds (Nielsen et al., 2006; Monosov et al., 2008). However, the latencies we found, ~45 ms for visual stimuli, were remarkably similar to those found in monkeys, despite the fact that latencies are usually delayed in humans compared with monkeys, for example in the medial temporal lobes (Mormann et al., 2008). Such short latencies fit with data from another study using subdural grids in humans (Blanke et al., 1999). This suggests that the human brain may have kept, through species evolution, a specialized system to process some aspects of sensory information very quickly. In contrast to the other systems in which processing takes longer in humans, the preservation of very-short-latency effects in FEF highlights the phylogenetic importance of these fast brain processes.

How can we explain such early responses? There are a number of possible anatomical pathways that could be involved, both cortical (Huerta et al., 1987) and subcortical (Huerta et al., 1986; Tian and Lynch, 1997). Given that the FEF takes part in the pro-

gramming of saccadic eye movements, it could be that the earliest FEF activities relate to an alerting system via the reticular activation system. For example, ascending activity could pass from the retina to the SC, thalamus (dorsomedial nucleus), and then to the FEF. The existence of such a pathway has been neatly demonstrated by retrograde tracing after injection of FEF, which resulted in first-order labeling in the thalamus and second-order labeling in intermediate layers of the colliculus (Lynch et al., 1994). However, Sommer and Wurtz (2004a,b) studied this pathway in the macaque and found that visual information arriving via this route arrived too late to contribute to short-latency responses in the FEF. They hypothesized that the pathway providing the short-latency responses probably involves extrastriate cortex.

Geniculocortical pathways are certainly an option because of the strong degree of interconnectivity between cortical visual areas. For example, an analysis of connectivity between cortical areas in the primate showed that, on average, only 1.7 synapses are required to get from a given cortical visual area to another (interarea steps) (Hilgetag et al., 2000). Specifically, in the case of the frontal eye fields, only one intermediate processing stage may be needed to get from V1 (Petroni et al., 2001). For example, FEF receives direct inputs from area MT (Stanton et al., 2005), which itself receives direct input from V1. Here, we demonstrated that the short latencies found in the FEF for both visual and auditory stimuli are compatible with cortical routes. Electrophysiological recordings in macaque monkeys show that FEF cells start to discharge just after the responses in primary visual cortex (Nowak and Bullier, 1997; Schmolesky et al., 1998). In this study, the earliest components in V1 and the visual cortex had onsets at ~25 ms. This latency is similar to other studies in humans [31 ms using spiking analyses in epileptic patients (Wilson et al., 1983); 27.5 ms using a magnetoencephalogram protocol (Inui and Kakigi, 2006)]. As mean onset latency was at ~45 ms in the FEF, this leaves ~20 ms during which information can travel from V1 to the FEF. Early inputs from striate and extrastriate visual areas could account for the early modulation of visual responses found in the FEF in the 40–80 ms range. Furthermore, O'Shea et al. (2004) found visual search to be disrupted by transcranial magnetic stimulations over human FEF as early as 40–80 ms after stimulus onset, latencies that match the latencies of the vN50 and vN80 visual components reported in this study. Regarding the auditory modality, direct connections have been observed in the macaque monkey between primary auditory cortex and FEF (Hackett et al., 1999). We found that ERPs in the primary auditory cortex start at ~17 ms, a latency that is also comparable with that of other studies [N13/P20/N30 complex (Liegeois-Chauvel et al., 1991)]. However, mean onset latency was at ~24 ms in the FEF, leaving ~10 ms for the information to travel from the auditory cortex to the FEF. Here again, early inputs from the auditory cortex could clearly account for the extremely early frequency response in the 30–60 ms range observed in the FEF. Interestingly, the FEF may display an organization similar to that of the auditory cortex, with modulation by both tonal and temporal properties of sound.

All the above experimental tasks involved central presentations of a simple visual cue or a sound presented binaurally via headphones (the sound is heard "in the head"). It thus appears that early activity in FEF occurs without the need for overt attentional processing because no spatialization of the stimulus was involved in the task. Furthermore, no saccade was required, and epochs with eye movements were rejected from the analyses. Overall, these results imply that the FEF is not activated solely when saccades are required. Ekstrom et al. (2008) recently provided evidence that the FEF could have a modulatory role (enhancement and suppression) on lower-order visual areas in monkeys, provided a visual stimulus was first presented. Our results from studies in humans fit well with this idea. This is all the more likely, as FEF cells have both afferent and feedforward connections with visual cortical areas such as V4 (Barone et al., 2000). The early activation observed in the FEF could reflect the early bottom-up flow of information triggered by the stimulus before top-down modulation. It will be interesting to assess whether similar mechanisms exist in the auditory modality.

We generally used the term "FEF region," rather than simply "FEF," throughout this study to account for the fact that not all stimulations elicited eye deviations. Further recordings in the human will allow characterizing responses in this region, and eventually in subregions, with more detail.

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