Chronometry of Visual Responses in Frontal Eye Field, Supplementary Eye Field, and Anterior Cingulate Cortex

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Pouget, Pierre, Erik E. Emeric, Veit Stuphorn, Kate Reis, and Jeffrey D. Schall. Chronometry of visual responses in frontal eye field, supplementary eye field, and anterior cingulate cortex. *J Neurophysiol* 94: 2086–2092, 2005. First published June 8, 2005; doi:10.1152/jn.01097.2004. The latency and variability of latency of single-unit responses to identical visual stimulation were measured in the frontal eye field (FEF), supplementary eye field (SEF), and anterior cingulate cortex (ACC) of macaque monkeys performing visually guided saccades. The mean visual response latency was significantly shorter in FEF (64 ms) than in SEF (81 ms) or ACC (100 ms), and latency values determined by four methods agreed. The latency variability of the visual response was respectively less in FEF (21 ms) than in SEF (37 ms) or ACC (41 ms). Latency, variability of latency, and magnitude of the visual responses were correlated within FEF and SEF but not ACC. These characteristics of the visual response are consistent with the degree of convergence of visual afferents to these areas and constrain hypotheses about visual processing in the frontal lobe.

INTRODUCTION

The frontal eye field (FEF), supplementary eye field (SEF), and anterior cingulate cortex (ACC) are innervated by extrastriate visual cortical areas (Huerta and Kaas 1990; Schall 1997; Stanton et al. 1995; Tehovnik et al. 2000; Van Hoesen et al. 1993). The purpose of this study was to characterize and compare the latency and latency variability of the visual responses in FEF, SEF, and ACC of macaque monkeys with identical stimulus conditions and analytical procedures. At the cortical level, visual processing begins in area V1 and is hypothesized to proceed through different streams that have been described as an anatomic hierarchy routed from the occipital through the parietal and temporal lobes (Felleman and Van Essen 1991; Hilgetag et al. 1996; but see Petroni et al. 2001). Visual processing in this hierarchy can be characterized by the time required for the transfer of information from one stage of processing to the next. Visual response latencies have been measured in a number of cortical areas across the visual system (Kawano et al. 1994; Maunsell and Van Essen 1987; Nowak et al. 1995; Raiguel et al. 1989; Schmolesky et al. 1998). The data indicate that visual responses occur earliest in V1 followed by concurrent activation in extrastriate areas associated with the dorsal stream and successive activation of areas in the temporal lobe. Studies describing the visual latency of FEF (Schmolesky et al. 1998) demonstrate that the majority of FEF visual neurons respond to stimuli at the same time or before visual areas in the occipital, parietal, and temporal lobes. Less is known about the visual response latencies of neurons in SEF (but see Schall 1991a) and, to date, none have been reported for ACC.

METHODS

Subjects and surgery

Data were collected from five male macaque monkeys (*Macaca mulatta, M. radiata*) 3–11 yr old and weighing 7–9 kg. The animals were cared for in accordance with the National Institute of Health's Guide for the Care and Use of Laboratory Animals and the guidelines of the Vanderbilt Animal Care Committee. Detailed descriptions of the surgical procedures and behavioral training have appeared previously (Hanes et al. 1998).

Data collection

Data were obtained from monkeys performing a saccade countermanding task (Hanes et al. 1998). Monkeys were seated in an enclosed chair within a magnetic field to monitor eye position via a scleral search coil. Stimuli were presented on a video monitor (48 × 48°) using computer-controlled raster graphics (Peritek VCH-Q, 512 × 512 resolution). The fixation spot subtended 0.3° of visual angle and the target stimuli subtended from 0.3 to 3° of visual angle, depending on their eccentricity and had a luminance of 10 or 30 cd/m^2 on a 1-cd/m^2 background. Identical fixation and target stimuli were used for all behavioral tasks.

A PDP 11/83 presented stimuli, recorded eye movements, spikes, and other events, and delivered juice reward. In two monkeys (*A* and *C*), action potentials were discriminated with a time-amplitude window discriminator (BAK) and sampled at 1 kHz. Single units were admitted to the database if the amplitude of the action potential was sufficiently above background to reliably trigger the time-amplitude window discriminator, the action potential wave shape was invariant throughout recording, and the isolation could be sustained for a sufficient period. For the other three monkeys (*F, H,* and *N*) all waveforms that passed a threshold were saved digitally (Plexon). One or more action potentials were discriminated from the electrode on-line using two-dimensional (2-D) principal-component analysis and template matching (RASPUTIN, Plexon). The identification and isolation of individual spikes was reevaluated and corrected off-line using 3-D principal-component analysis and visual inspection of selected waveforms (Off-line Sort Program, Plexon).

FEF and SEF were the regions where saccades could be evoked with thresholds of <50 µA (Bruce et al. 1985; Schlag and Schlag-Rey 1987). For ACC, well-isolated neurons were recorded on entry into

the gray matter, concentrated in the dorsal bank and the fundus of the cingulate sulcus (Ito et al. 2003).

Data analysis

A spike-density function was produced by convolving the spike train from each trial with a function resembling a postsynaptic potential specified by τ_g, the time constant for the growth phase, and τ_d, the time constant for the decay phase as $R(t) = (1 - \exp(-t/\tau_d)) * \exp(-t/\tau_g)$. Based on physiological data from excitatory synapses τ_g was set to 1 ms and τ_d to 20 ms (Sayer et al. 1990). The magnitude of the visual response was determined for each cell as the maximum value of the spike-density function during the time interval between the onset and the end of visual response.

Many distinct algorithms have been used to determine times of neural modulation in response to stimulus presentation (Azzopardi et al. 2003; Bair et al. 2001–2003; Maunsell and Gibson 1992), but results of multiple methods have not been compared. Therefore we contrast the visual response latencies of FEF, SEF, and ACC neurons using the following four methods.

POISSON SPIKE TRAIN ANALYSIS. The principle of this algorithm is to search for intervals in single trials in which the number of spikes exceeds what would be expected by chance from a Poisson process with a mean rate given by the total number of spikes in the trial (Hanes et al. 1995; Legendy and Salcman 1985). The beginning and end of each interval were measured. The latency of the response was defined as the earliest mode of the beginning of activation across trials (Thompson et al. 1996); the mode provided a less biased measure than the mean or median because it is less sensitive to outliers. Because this analysis obtains a value for each trial, a measure of the variability of the latency of the visual response could be defined as the SD of the beginning of the activation across trials. This method has been applied usefully for FEF data (Hanes et al. 1995; Schmolesky et al. 1998; Thompson et al. 1996) as well as to other neural systems (Dicke et al. 2004; Everling et al. 1999; Kovacs et al. 2003; McPeek and Keller 2002; Salinas and Romo 1998; Tanabe et al. 2004; Thier et al. 2000).

DEVIATION FROM POISSON SPONTANEOUS RATE. The principle of this algorithm is to search for the time at which a peristimulus time histogram (PSTH) smoothed with a Gaussian filter ($\sigma = 5$ ms) first exceeds the mean spontaneous rate by 2.33 Poisson SDs estimated from the unfiltered histograms from the moment the stimulus was presented (Azzopardi et al. 2003).

PROPORTION OF MAXIMUM RESPONSE. The principle of this algorithm is to identify the latest time at which a Gaussian-filtered ($\sigma = 2$ ms) PSTH from which the average prestimulus discharge rate was subtracted reaches a specified fraction (usually 5%) of its peak (Bair et al. 2001–2003).

POISSON FIT THRESHOLD. The principle of this algorithm is to measure the time of the first of three consecutive 2-ms PSTH bins containing a number of spikes equal to or greater than the 99th percentile of the Poisson distribution derived from the spike count in the 100 ms preceding stimulus presentation (Bisley et al. 2004; Maunsell and Gibson 1992).

RESULTS

Only correct trials with no stop signal in which the visual stimulus was presented within or contralateral to the most sensitive location of the receptive field were analyzed for neurons recorded in FEF ($n = 36$ of 152 neurons, sampled in 2 monkeys, A and C), SEF ($n = 74$ of 407 neurons, sampled in 4 monkeys, A, F, H, and N), and ACC ($n = 29$ of 371 neurons, sampled in 2 monkeys, H and N). Mean saccadic reaction times were 264 ± 39 (SD) ms for FEF data, 330 ± 87 ms for SEF

data, and 311 ± 85 ms for ACC data. Representative neurons from each area are shown in Fig. 1. The percentage of trials in which a significant activation was found for these three cells is representative of all the recorded neurons 71, 48, and 22% for FEF, SEF, and ACC, respectively.

Latency of visual responses

The Poisson spike train analysis provided measures of the latency, variability of latency, and duration of the visual responses. The distributions of latencies measured with the Poisson spike train analysis in each area are shown in Fig. 2. Visual latency in FEF ranged from 29 to 118 ms [64 ± 19 (SD) ms]. One half of the FEF neurons exhibited latencies <61 ms, and 20% exhibited latencies <50 ms with only a 14-ms difference between the first and third quartile of the distribution.

The visual latency of SEF neurons ranged from 21 to 163 ms (81 ± 29 ms). One half of SEF neurons exhibited latencies <80 ms, and only 14% exhibited latencies <50 ms with 35 ms separating the first and third quartile of the distribution.

The latency of ACC neurons ranged from 36 to 198 ms (100 ± 41 ms). One half of ACC neurons exhibited latencies <96 ms, and 7% exhibited latencies <50 ms with 36 ms separating the first and third quartiles of the distribution.

Significant variation in latency across the areas was confirmed by a Kruskal-Wallis one-way ANOVA on ranks [$H(2,139) = 21.03$, $P < 0.001$]. According to a multiple Mann-Whitney two-way rank sum comparisons corrected by the Bonferroni method ($P = 0.017$), FEF responded significantly earlier than SEF [$U(36,74) = 790$, $P < 0.001$], which responded significantly earlier than ACC [$U(74, 29) = 806$, $P = 0.05$]. An examination of the distribution of response latencies and magnitudes as a function of receptive field eccentricity revealed no systematic variation.

Reliability of latency measurement

The distributions of response latencies of FEF visual neurons estimated using four methods are compared in Fig. 3. The FEF visual response latency measured using the deviation from a Poisson spontaneous rate ranged from 3 to 152 ms (73 ± 33 ms). According to a multiple Mann-Whitney two-way rank sum comparisons corrected by the Bonferroni method ($P = 0.017$), this distribution was not significantly different from the Poisson spike train analysis values [$U(36,33) = 506.5$, $P = 0.29$]. The FEF neurons visual latencies to 5% of the maximum response ranged from 20 to 97 ms (58 ± 19 ms). This distribution also was not significantly different from the Poisson spike train analysis values [$U(36,31) = 462.5$, $P = 0.23$]. The FEF visual latency measured from the Poisson fit threshold ranged from 8 to 120 ms (64 ± 22 ms). This distribution was not significantly different from the Poisson spike train analysis values [$U(36,36) = 624.5$, $P = 0.79$]. The results of the four methods produced FEF visual responses that were not significantly different.

The SEF visual response latencies from the different methods are compared in Fig. 4. The resulting distributions were compared by using a Kruskal-Wallis one-way ANOVA on ranks. The latencies estimated using the deviation from a Poisson spontaneous rate ranged from 35 to 158 ms (86 ± 28
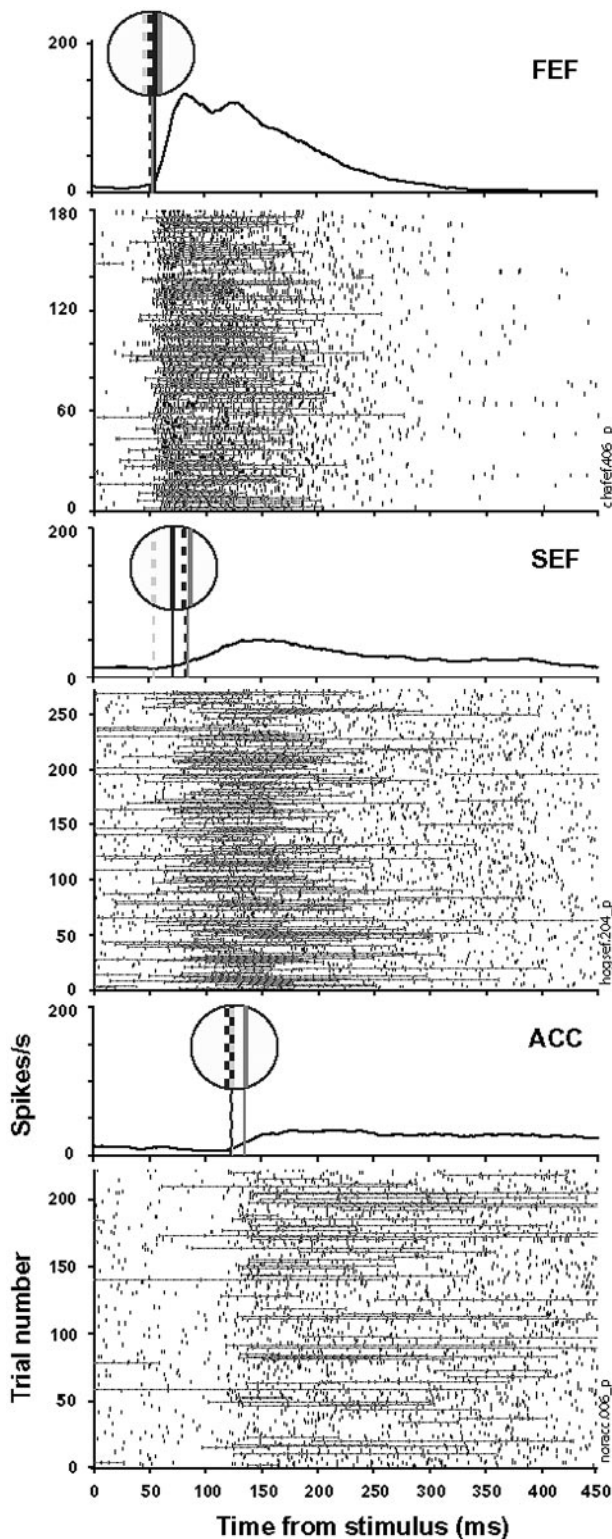
FIG. 1. Visual responses of representative neurons in frontal eye field (FEF), supplementary eye field (SEF), and anterior cingulate cortex (ACC). Spike times are shown in raster plots; lines over rasters show periods of activation determined in each trial by the Poisson spike train analysis. Periods of significant activation were measured in 71% of trials for the FEF neuron, 48% for the SEF neuron, and 22% for the ACC neuron. Average spike density function is plotted with visual latency across trials measured by the Poisson spike train analysis (solid black), proportion of maximum response (solid gray), deviation from Poisson spontaneous rate (dashed gray) and Poisson fit threshold (dashed black). The circle magnifies the plots for clarity.
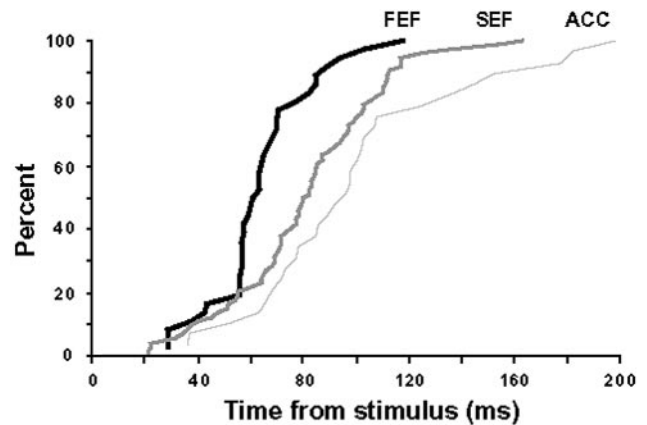

FIG. 2. Cumulative distributions of visual response latencies in FEF (dark), SEF (intermediate), and ACC (lightest) measured by the Poisson spike train analysis.

ms), which were not significantly different from the Poisson spike train analysis values [$U(74,73) = 2587.5$, $P = 0.66$]. Latencies obtained using the Poisson fit threshold ranged from 18 to 176 ms (89 ± 33 ms), which were not significantly different from that obtained using the Poisson spike train analysis [$U(74,47) = 1,568.5$, $P = 0.37$]. Visual latencies to 5% of the maximum response ranged from 17 to 146 ms (72 ± 25 ms), which were significantly different (−9 ms) from the visual latency estimated using the Poisson spike train analysis [$U(74,56) = 1573$, $P = 0.02$]. This difference was due to the low criterion, for the latency to 50% of the maximum response ranged from 55 to 163 ms (95 ± 26 ms); although these values were also significantly different (+14 ms) from the Poisson spike train analysis values [$U(74,56) = 1,574.5$, $P = 0.02$]. These results demonstrated that for this particular pool of neurons the visual latency estimated using the proportion of a maximum response was sensitive to the value of the criterion.

The latencies of ACC visual responses for each of the algorithms are compared in Fig. 5. The latencies from the deviation from a Poisson spontaneous rate ranged from 34 to 199 ms (105 ± 41 ms), which was not significantly different from the Poisson spike train analysis values [$U(29,26) = 359.5$, $P = 0.77$]. The latencies to 5% of the maximum response ranged from 47 to 196 ms (109 ± 39 ms,) which was
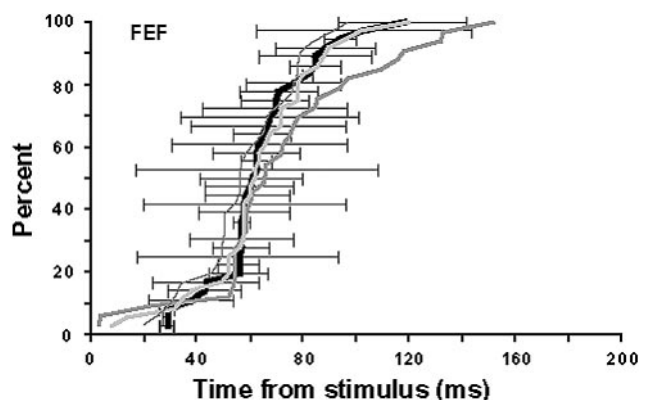

FIG. 3. Cumulative distributions of visual latencies of FEF neurons measured by the Poisson spike train analysis (black) with ±0.5 SD of the latency for each neuron, deviation from Poisson spontaneous rate (darkest gray), proportion of maximum response (lighter gray), and Poisson fit threshold (thin gray).
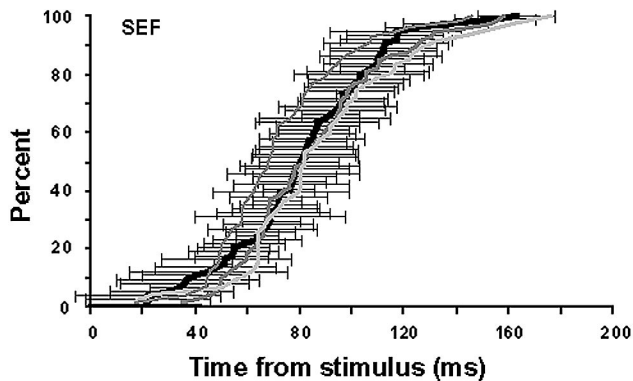
FIG. 4. Cumulative distributions of visual latencies of SEF neurons measured by each method. Conventions as in Fig. 3.

not significantly different from the Poisson spike train analysis distribution [U (29,19) = 235.5, P = 0.40]. The latencies from the Poisson fit threshold ranged from 54 to 196 ms (112 ± 39 ms) which was not significantly different from the Poisson spike train analysis values [U(29,20) = 239.5, P = 0.30].

The latencies measured by the three additional methods for FEF, SEF, and ACC were compared using multiple Mann-Whitney two-way rank sum comparisons. Based on the latencies of the deviation from a Poisson spontaneous rate, FEF responded earlier than SEF [U(33,73) = 894.5, P = 0.03], which responded earlier than ACC [U(73,26) = 683.5, P = 0.035], and FEF responded significantly earlier than ACC [U(33,26) = 220.5, P = 0.001]. According to the latencies to 5% of the maximum response FEF responded earlier than SEF [U(31,56) = 620.5, P = 0.03], which responded earlier than ACC [U(56, 19), P < 0.001], and FEF responded earlier than ACC [U(31,19) = 69, P < 0.001]. Finally, for the Poisson fit threshold, FEF responded earlier than SEF [U(36,47) = 410.5, P < 0.001], which responded earlier than ACC [U(47, 20) = 311.5, P = 0.03], and FEF responded earlier than ACC [U(36,20) = 110.5, P < 0.001].

Variability of visual response latency

The Poisson spike train analysis provides a measure of the variability of the visual response latency across all trials in which significant activation was detected. The SDs of the beginning of the activation of FEF, SEF, and ACC are shown in Fig. 6. The SD of visual response latencies of neurons in
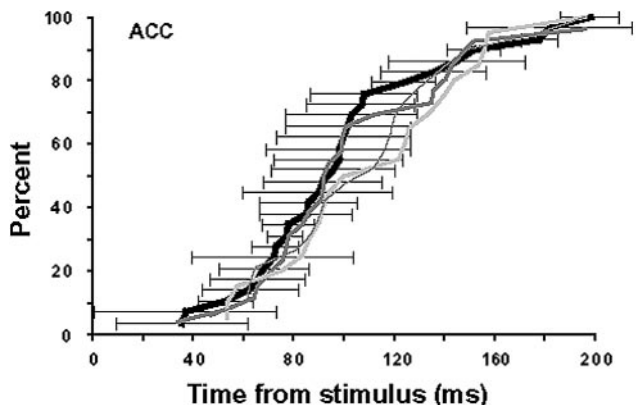

FIG. 5. Cumulative distributions of visual latencies of ACC neurons measured by each method. Conventions as in Fig. 3.
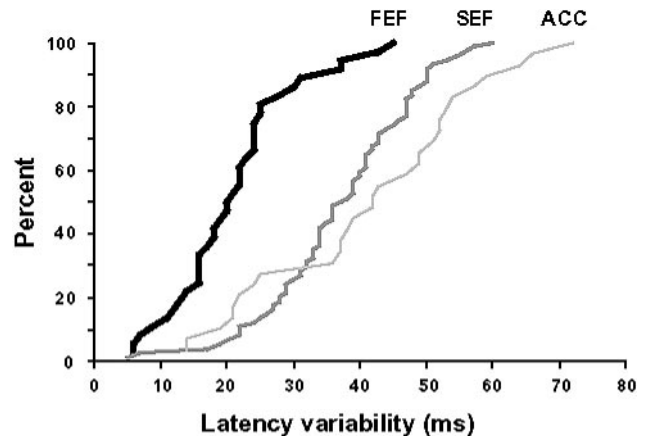

FIG. 6. Cumulative distributions of visual latency variability of FEF, SEF, and ACC neurons. Conventions as in Fig. 2.

FEF ranged from 6 to 45 ms (21 ± 9 ms). 50% of the neurons in FEF had a latency variability <20 ms, and only 5% of FEF neurons had a latency variability >40 ms.

The distribution of the latency variability among SEF neurons ranged from 5 to 60 ms (37 ms ± 11 ms) with 50% having a latency variability <37 ms and 42% showing latency variability >40 ms.

The variability of visual latency of ACC neurons ranged from 14 to 72 ms (41 ms ± 16 ms) with 50% <42ms and 55% of ACC neurons showing latency variability >40 ms.

The variability of latency varied significantly across areas [Kruskal-Wallis 1-way ANOVA on ranks H(2, 139) = 41.80, P < 0.001]. According to multiple Mann-Whitney two-way rank sum comparisons, the latency variability in FEF was less than that in SEF [U(36,74) = 359.5, P < 0. 001], which was not significantly less than that in ACC [U(74,29) = 871, P = 0.14].

Magnitude of the visual responses

The magnitude of the visual response was determined for each neuron as the maximum value of the spike-density function during the interval between the onset and the end of visual response. The distributions of magnitudes of the visual responses in FEF, SEF, and ACC are compared in Fig. 7. Visual response magnitude varied significantly across areas [H(2,139) = 72.82, P < 0.001], being higher in FEF (121 ± 38 spikes/s) than in SEF [48 ± 41 spikes/s; U(36,74) = 180.5, P < 0.001]), which exceeded that in ACC [26 ± 24 spikes/s; U(74,29) = 521, P < 0.001]. Visual response magnitude in FEF was significantly higher than that in ACC [U(36,29) = 26.5, P < 0. 001].

Relationship among latency, variability of latency, and magnitude of the visual response

Table 1 presents results of a Pearson correlation analysis among the latency, variability of latency, and the magnitude of visual responses of neurons in FEF, SEF, and ACC.

For FEF, the visual response latency was correlated significantly and positively with the visual response latency variability (FEF r_p = 0.36, P = 0.03). For FEF, but not SEF and ACC, longer increases of latency responses are correlated with larger increases of the responses variability. For SEF, but not FEF or
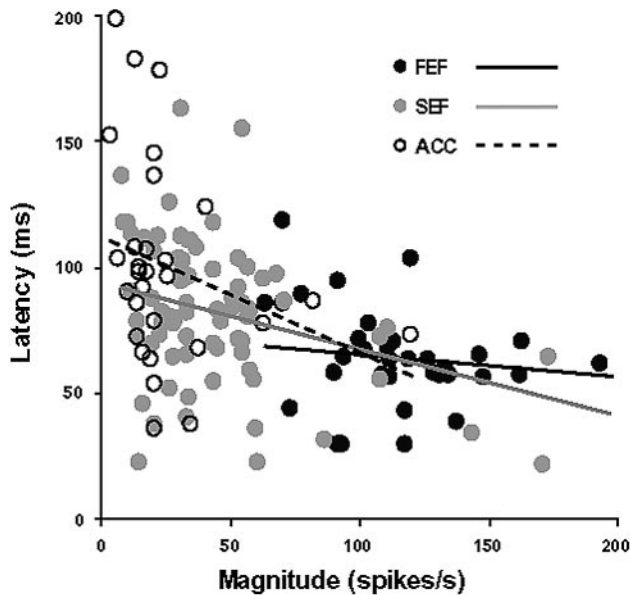
FIG. 7. Visual latencies of FEF (dark disk), SEF (gray disk), and ACC (white disk) neurons as a function of the magnitude of the responses. Regression line for each area is plotted for FEF (dark line), SEF (gray line), and ACC (dashed black).

ACC, response magnitude correlated significantly and negatively with visual response latency (SEF $r_p = -0.37$, $P = 0.001$). For SEF, but not FEF and ACC, larger increases in the magnitude of the responses tended to have shorter increases of latencies.

Suppressed visual responses in FEF

Twenty-two percent of the visual neurons in FEF (8/36) exhibited an apparent reduction in discharge rate when the stimulus was presented contralateral to the receptive field, in the ipsilateral hemifield (Fig. 8). The beginning of the suppression was determined by adapting the Poisson spike train analysis to detect the beginning and end of significantly fewer spikes than expected by chance for each trial.

According to the Poisson spike train analysis, four neurons in FEF exhibited significant suppression with latencies ranging from 60 to 85 ms (58 ± 27 ms). Compared with the latency of the visual on response when the stimulus appeared in the receptive field, the suppression response was delayed (24 ± 19

TABLE 1. *Relationship between latency, variability, and magnitude of visual response*

	Latency	Magnitude
FEF		
Latency		−.17
Variability	.36*	−.20
SEF		
Latency		−.36**
Variability	−.14	−.52**
ACC		
Latency		−.27
Variability	−.16	−.33

FEF and SEF, frontal and supplementary eye field, respectively; ACC, anterior cingulate cortex. *correlation is significant at 0.05. ** correlation is significant at 0.01.
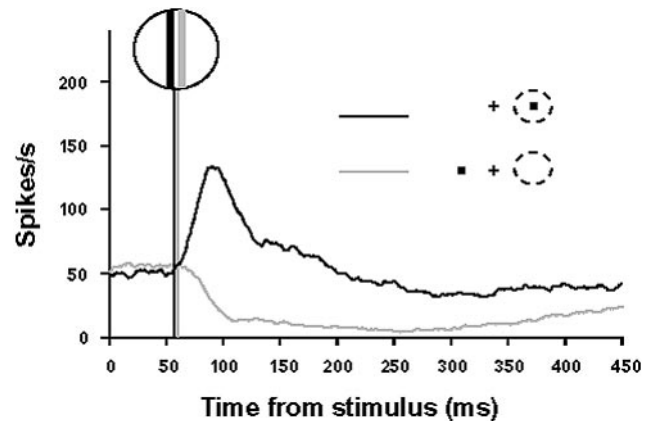

FIG. 8. Average spike density functions for a neurons in FEF with excitatory response to stimulus in receptive field (black) and suppressed response to stimulus in ipsilateral hemifield (gray). The latency of each response is also shown.

ms). No decrease of activity was observed in the sample of SEF or ACC neurons. Previous studies have reported a suppression of visual activity in FEF of monkeys performing visual search (Schall and Hanes 1993; Schall et al. 2004). Because this suppression was observed during a visual search task, the reduced activity was interpreted in terms of a visual selection process. In the stop signal task, only a single stimulus is presented. The relation of our present results and the suppression observed previously during a visual search task is not clear and further investigation is needed.

DISCUSSION

We characterized the temporal attributes of visual neurons in FEF, SEF, and ACC. Using four algorithms to measure latency, we found that although there is overlap in the distributions of latencies, on average, FEF responds before SEF, which responds before ACC. The latencies derived from each method were in good agreement. A trial-by-trial Poisson spike train analysis also measured variability of latency of visual responses. The variability of the latency of visual responses was less in FEF than in SEF or ACC. Only in SEF, and not in FEF and ACC, are the magnitude and the response latency correlated.

Relation to previous studies

The visual latencies measured in FEF are comparable to those reported previously (Bruce and Goldberg 1985; Goldberg and Bushnell 1981; Mohler et al. 1973; Pigarev et al. 1979; Schall 1991b; Thompson et al. 1996). The mean visual latency in FEF measured in this analysis was 64 ms was shorter than that reported in an earlier study of this laboratory [Schall (1991b) reported a latency for sensory neurons of 77 ms, 65 ms for transient visual-movement units, and 98 ms for sustained visual-movement neurons]. The longer latencies reported by Schall (1991b) are probably due to the fact that the stimuli in that study were light-emitting diodes (LEDs) at one of just four locations that may not have been positioned to evoke an optimal response. The mean visual latency in FEF measured in this analysis also was significantly shorter than that reported in anesthetized monkey (Schmolesky et al. 1998) [$U(36,26) =$

264, $P = 0.004$] possibly an effect of anesthesia or the use of weaker stimuli. In contrast, the visual latency reported here was not significantly different from that obtained during a visual search task with identical stimuli and analyzed using the Poisson spike train analysis (Thompson et al. 1996) [$U(36,66) = 1159$, $P = 0.84$]. The visual latencies measured in SEF were less than those observed by Schall (1991a) (sensory neuron, 92 ms; set neuron, 106 ms; sensory move, 116 ms) probably because the earlier study used LEDs at fixed locations. Finally, although visual responses have been reported in ACC (Isomura et al. 2003; Nishijo et al. 1997; Shima et al. 1991), latency, latency variability and duration have not been measured.

Comparison across areas

In agreement with previous studies, visual response characteristics distinguished FEF and SEF (Schall 1991a,b). Relative to FEF, visual responses in SEF and ACC had longer and more variable latencies and lower magnitudes. Relative to SEF, visual responses in ACC had slightly longer latency but longer duration and lower magnitude.

Anatomical differences in the extent of convergence of afferents can account for these differences. FEF is uniquely strongly interconnected with nearly all extrastriate visual areas (Jouve et al. 1998; Schall et al. 1995; Stanton et al. 1995). All of FEF is innervated by LIP, MSTl, FST, IPa and PGa. Whereas lateral FEF that produces shorter saccades receives more inputs from the central field representation of areas MT and V4 as well as TEO and caudal TE, medial FEF, which produces longer saccades, is more strongly innervated by the peripheral field representation of areas MT and V4 and MSTd, area PO and area 23 in posterior cingulate cortex. Within the frontal lobe FEF is reciprocally connected most densely with SEF, area 46 and area 12. The early, brief, strong visual response in FEF most likely arrives in afferents from areas MT and MST.

Compared with FEF, SEF receives many fewer cortical afferents, being innervated only by MST, the superior temporal polysensory area, and LIP and also FEF, premotor cortex and ACC in the frontal lobe (Huerta and Kaas 1990). Compared with FEF and SEF, ACC receives even fewer visual afferents, being connected with area PO, area 7a in the inferior parietal lobule, and inferotemporal area TG (Van Hoesen et al. 1993). Within the frontal lobe, ACC is reciprocally connected with SEF (Huerta and Kaas 1990; Luppino et al. 1990) and much less densely with FEF (Huerta et al. 1987; Stanton et al. 1993; Wang et al. 2004).

Thus neurons in FEF sum more visual inputs than do neurons in SEF or ACC. This difference in convergence of visual afferents can account for the difference in latency, reliability, and magnitude of visual responses across the areas because neurons that receive more visual afferents are more likely to respond earlier and stronger to a given stimulus. Whereas visual signals occur in FEF early enough to contribute to visual processing, we hypothesize that visual signals in SEF and ACC signal only the context of a stimulus in relation to production of saccades or other actions.

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