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RESEARCH ARTICLE

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Flow of activation from V1 to frontal cortex in humans

A framework for defining "early" visual processing

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Abstract This study provides a time frame for the initial trajectory of activation flow along the dorsal and ventral visual processing streams and for the initial activation of prefrontal cortex in the human. We provide evidence that this widespread system of sensory, parietal, and prefrontal areas is activated in less than 30 ms, which is considerably shorter than typically assumed in the human event-related potential (ERP) literature and is consistent with recent intracranial data from macaques. We find a mean onset latency of activity over occipital cortex ($C1_e$) at 56 ms, with dorsolateral frontal cortex subsequently active by just 80 ms. Given that activity in visual sensory areas typically continues for 100–400 ms prior to motor output, this rapid system-wide activation provides a time frame for the initiation of feedback processes onto sensory areas. There is clearly sufficient time for multiple iterations of interactive processing between sensory, parietal, and frontal areas during brief (e.g., 200 ms) periods of information processing preceding motor output. High-density electrical mapping also suggested activation in dorsal stream areas preceding ventral stream areas. Our data suggest that multiple visual generators are active in the latency range of the traditional C1 component of the ERP, which has often been taken to represent V1 activity alone. Based on the temporal pattern of activation shown in primate recordings and the evidence from these human recordings, we propose that only the initial portion of the C1 component (approximately the first 10–15 ms; $C1_e$) is likely to represent a response that is predominated by V1 activity. These data strongly suggest that activity represented in the "early" ERP components such as P1 and N1 (and possibly even C1) is likely to reflect relatively late processing, after the initial volley of sensory afference through the visual system and involving top-down influences from parietal and frontal regions.

Keywords High-density mapping · Event-related potential · C1 component · Visual cortex · Area V1 · Frontal cortex · Scalp current density · Human

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Introduction

The relatively recent capability to record from high-density electrode arrays in human subjects (128–256 channels) has provided substantially better spatial resolution for mapping information flow between the multiple cortical areas that subserve perception and cognition (Gevins et al. 1995; Junghofer et al. 1997; Potts et al. 1998). This improvement in our ability to dissect spatially overlapping activation topographies on the scalp affords us the opportunity to more thoroughly exploit the temporal resolution of the event-related potential (ERP) method. We can now explore the temporal structure of information flow and interareal interactions within the network of functional cortical areas by examining finer topographic transitions on the scalp surface, millisecond by millisecond. While the spatial accuracy of these methods remains at a gross level, it is now sufficient to differentiate cortical activations at a level relevant to many fundamental neuroscience issues. Potentially, we can observe the time course of sequential activations and dissociate the timing of information flow along both the

dorsal and the ventral visual streams (Ungerleider and Mishkin 1982; Ungerleider and Haxby 1994), as well as into prefrontal areas. Furthermore, we can address the relative timing of communication between functionally distinct areas such as the interaction between frontal and parietal areas during selective attention tasks.

The recent wealth of functional magnetic resonance imaging (fMRI) data has inspired revisiting the topic of timing of activity in brain areas in order to understand the functional role of activations within particular brain regions and networks of regions. Animal data have suggested a rapid spread of activity through visual systems and frontal cortex which speaks to issues of alerting systems, reentrant processing in sensory cortices, and top-down influences. The present data analysis was intended to examine the rapidity with which visual activation could proceed through the dorsal and ventral visual areas and into the frontal cortex with respect to latencies of well-known visual ERP components (i.e., C1, P1, N1). To this end, we analyzed ERP recordings from a portion of an earlier study, employing a high-density, 128-channel electrode montage, while 12 subjects participated in an intermodal attentional cuing paradigm. Anticipatory attention effects from the cuing phase of this study have been published elsewhere (Foxe et al. 1998). In particular, our aim was to examine the time frame of information-flow through the dorsal and ventral streams of the visual system into parietal and frontal regions. Detailing this temporal trajectory allows us to posit the time frame for stimulus-driven, top-down feedback onto sensory processing, in the context of the traditional ERP componentry. We propose a time frame that is significantly shorter than is usually assumed in the extant human electrophysiological literature. Traditionally, surface components of the ERP from 50 to 150 ms poststimulus onset have been considered "early" indices of information flow through a hierarchical visual system. In particular, the notion that the initial ERP component C1 (peaking between approximately 60 and 90 ms), represents V1 activation and that the ensuing P1 component (peaking between approximately 100 and 140 ms) represents subsequent extrastriate activation will be reexamined. We submit that the time frame of "early" signal transmission is likely to be significantly more condensed than this, consistent with evidence from monkey intracranial literature and human ERP studies.

Results from monkey intracranial recordings provide strong support for this position (Raiguel et al. 1989; Givre et al. 1994; Zipser et al. 1996, Nowak and Bullier 1997; Schmolesky et al. 1998; Schroeder et al. 1998, 2001,; Nowak et al. 1999). The timing pattern of early visual activations shown in these studies suggests that signal transmission through the human visual hierarchy is likely to occur within a time frame as brief as the duration of the initial component of the human ERP (C1, which lasts for some 40–60 ms). The inference is that this initial visual ERP component contains contributions from occipital/parietal areas other than just V1. Indeed, the latency of transmission from V1 to the highest level of the ventral visual stream (inferotemporal cortex, IT) is only ~23 ms in macaques (Schroeder et al. 1998, 2001). One important implication of these data for investigations of early human cortical processing, especially with neuroimaging methods, is that fine temporal resolution on the scale of milliseconds will be required to dissociate the largely overlapping temporal courses of activity across the anatomically neighboring early visual areas.

Further, intracranial investigations in macaque V1 have shown contextual modulation of V1 responses that do not conform to the classic receptive-field properties of V1 cells (Lamme 1995; Zipser et al. 1996; Lamme et al. 1998a; Lamme and Spekreijse 2000). Compellingly, these contextual effects occur as little as 30 ms after the initial afferent activation of V1, strongly suggesting corticocortical feedback modulation from "higher level" extrastriate visual areas. In fact, the entire temporal visual stream was activated before the appearance of the V1 contextual modulation in one study (Zipser et al. 1996). Also, both anesthesia (Lamme et al. 1998b) and extrastriate ablations (Lamme et al. 1998a) abolish contextual modulations in V1 without changing the classic receptive-field tuning properties, further supporting the role of cortical feedback mechanisms in these early effects. A similar time frame for corticocortical feedback onto the early visual areas is likely in the human. Note, for example, that under certain stimulus parameters, V5 can be activated before V1 and that the two can presumably interact within very early periods of activation (Ffytch et al. 1995; Buchner et al. 1997). Determining the amount of time that the initial trajectory of activations through the human visual system engages will allow us to predict a putative time frame for such feedback mechanisms in humans.

In monkey, dorsal stream areas receive their inputs faster than ventral areas at the same anatomical hierarchical level. This is most likely to be due to the predomination of magnocellular inputs to the dorsal stream (see Merrigan and Maunsell 1993). Recordings in the macaque suggest that initial inputs to high-level ventral areas such as V4 and IT are likely to be lateral corticocortical inputs from the dorsal stream rather than direct ascending afferent input along the ventral stream (Schroeder et al. 1998). High-density electrophysiological mapping allows for simultaneous recording of both the dorsal and temporal stream activation trajectories and will allow us to assess directly this uneven timing between the two streams in humans.

Evidence from human ERPs also gives cause to expect that "early" processing occurs considerably quicker than is commonly thought. Thorpe et al. (1996) have used some 4,000 unique photographs, half of which contained an animal of some sort as target in a go/no-go task. They found a robust frontal negativity in the no-go trials which onset at just 150 ms. They contended that this represented a point in time before which the visual processing needed to achieve the complex neural computations required by their stimuli had taken place. This provided a time frame within which the human visual

system must be able to process complex natural images, a task that most likely requires multiple computational routines involving feedback and feedforward loops (see Lee et al. 1998).

In the current study, we investigated the spatial topography of the initial activations along the visual processing streams by the use of high-density ERP recordings (128 scalp electrodes) and scalp current density (SCD) mapping (Perrin et al. 1989). It has been demonstrated that spatial sampling of this order (more than 100 channels; Junghofer et al. 1997) is necessary for accurate calculation of the SCD map and that conclusions about underlying brain sources based on lower density montages (e.g., 32 channels) should be interpreted cautiously (also Soong et al. 1993; Fletcher et al. 1996). Our aim in this study was to make use of the fine spatial detail afforded by high-density recordings to address the time frame of signal transmission through the human visual system. Of particular interest was determining the temporal relationship of dorsal versus ventral activation and the earliest time point at which frontal cortical areas became active. Our data highlight the limitations of purely serial hierarchical conceptions of visual processing and the "component" approach to the evoked electrical activity on the scalp.

Materials and methods

Subjects

Twelve (four women, eight men) right-handed (except one man) neurologically normal, paid volunteers, aged 20–34 years (mean ± SD 26±4.9 years) participated. All subjects provided written informed consent, and the procedures were approved by the Institutional Review Board of the Albert Einstein College of Medicine, where the experiments were conducted, and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All subjects had normal or corrected-to-normal vision.

Stimuli

Visual stimuli were bilateral red discs, 3.75° in diameter, centered 4.2° to the left and right of a central fixation cross on the horizontal meridian. They were presented on a computer monitor (NEC 6FGx; NEC, Tokyo, Japan), 160 cm from the subject, with a duration of 280 ms.

These stimuli were presented to subjects in the context of an intermodal selective-attention paradigm, where subjects were engaged in a demanding attention task. The bilateral disc stimuli (S2) were preceded on every trial by a centrally presented word cue (S1), which instructed subjects to attend to upcoming stimulation in either the auditory or visual sensory modality (S2). On each "Cue-S2" trial, subjects saw the following words as cues: "BEEP," which denoted an attend-auditory trial, or "FLASH," which denoted an attend-visual trial. Response averages used for the current analysis reflect only visual disc stimuli (S2s) that were seen on attend-visual trials. Stimulus-onset asynchrony between the cue word (S1) and disc stimuli (S2) was 1,085 ms, and the intertrial interval (S2–S1) was 1,915 ms. Please note that results related to the Cue-S2 period from this data set have been previously published (see Foxe et al. 1998); more detail regarding the stimulus paradigm can also be found in this report.

Measurements

High-density ERPs were acquired from 128 scalp electrodes referenced to the nose (band-filtered from DC to 100 Hz; digitized at 1,000 Hz; impedances less than 5 kΩ, interelectrode spacing ~2.4 cm). Trials were epoched for the period from –100 to 600 ms around stimulation and any trials with eye movements were rejected offline on the basis of horizontal and vertical DC electro-oculogram. An artifact criterion of ±60 μV was used at all other electrode sites to reject trials with excessive EMG or other noise transients.

Scalp current density analysis

The topographic display of scalp potential has a number of significant drawbacks that serve to obscure the relationship of the surface map to the putative underlying neural generators. First, the distribution of the scalp potential is dependent on the reference electrode, being a measure of the difference between the voltage recorded at a given site and any activity that is recorded at the reference electrode. Thus, the position of the reference electrode can severely affect the distribution of the scalp potential topography. Second, the volume conductive properties of the brain and its coverings (especially the low-conductivity skull) result in a high degree of spatial smearing/superposition of the electrical fields generated by multiple intracortical sources, severely reducing spatial resolution.

The surface Laplacian transformation is one method by which these limitations can be ameliorated (Hjorth 1975; Perrin et al. 1989; Babiloni et al. 1995, 1998; Murray et al. 2001; Saron et al. 2001) and has been widely applied to high-density ERP data sets in recent years. The advantage of the Laplacian or SCD technique is that it emphasizes local contributions to the surface map, providing for better visualization of approximate locations of intracranial generators. The Laplacian estimator eliminates the influence of the electrical reference and mathematically eliminates the voltage gradients due to tangential current flows within the scalp. In the present study, SCDs (second spatial derivative of the potential) were computed from the spherical spline interpolation of the surface voltage recordings (according to the methods of Perrin et al. 1989) as implemented in EEG-FOCUS V2.0 software (MEGIS Corporation, Munich, Germany). EEG-FOCUS uses a fourth-order spherical spline to interpolate the potential distribution over a spherical head model, optimally fit to the electrode cloud. The constraint that the spherical spline passes through the exact instantaneous values of each electrode in the array can lead to erroneous values due to noise in the EEG data or to the behavior of single electrodes (Perrin et al. 1989). To counter this possibility, the constraint is relaxed by applying a spline-smoothing coefficient, which is termed lambda (λ; see Wahba 1990 for a detailed treatment of the subject). In the current study, λ was set to 1×10^{-6}, an optimal value for an electrode montage of this size based on simulation studies (see Babiloni et al. 1995, 1998). The use of a sufficiently dense sensor array (see also Law et al. 1993; Yvert et al. 1997), in conjunction with spline interpolation and application of λ smoothing, reduces the potential influence of noise on the surface maps.

The use of a custom-designed electrode cap (see Fig. 1) allowed for even sampling of the scalp potential and constrained the relative positions of the electrodes with respect to each other. Precise determination of the interelectrode distances is critical, as miscalculation of this spacing can produce artifacts in the SCD estimation. The positioning of electrodes in this study was confirmed by 3D digitization of each subject's electrode montage on the day of recording. Subjects were placed in a bite-bar apparatus to stabilize their head and registration of the 3D locations of their electrode positions with reference to a set of anatomic fiduciary markers was obtained with a sonic digitizer (Science Accessories, Columbia, Md.). The methods are described in more detail by Simpson et al. (1995a).

Note that units of current source density are given as voltage per unit distance per unit distance (microvolts per square centime-

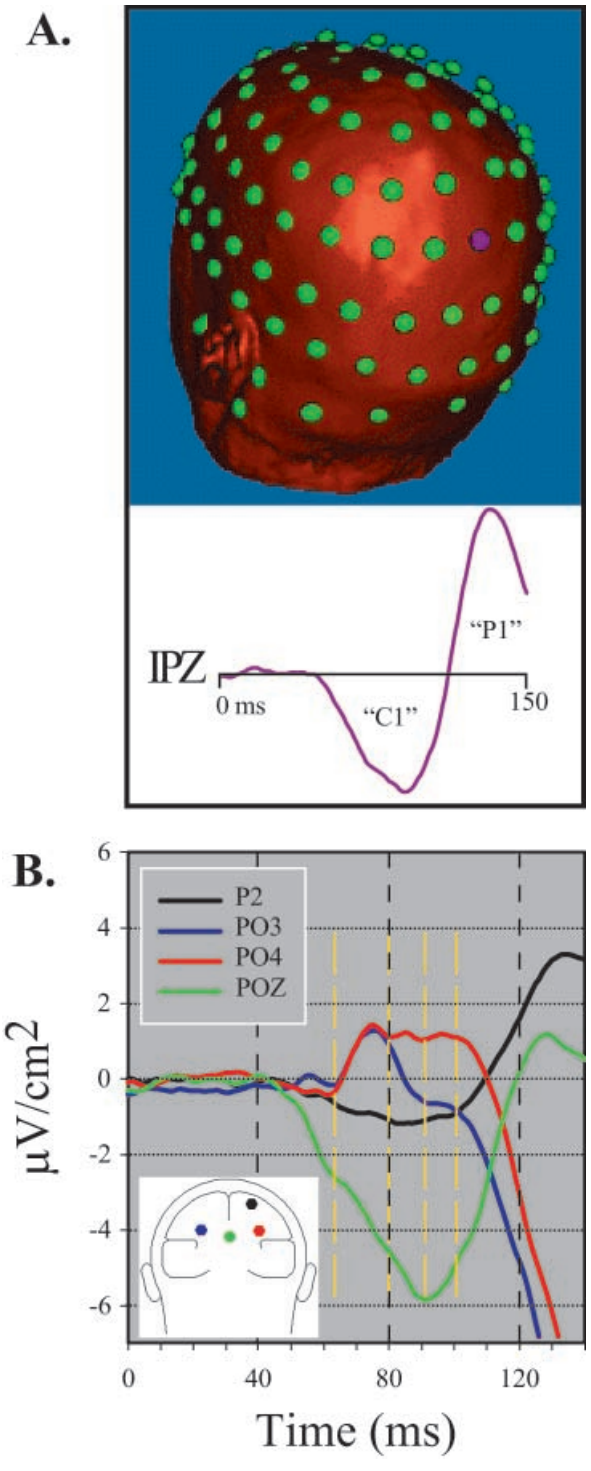


Fig. 1 **a** The 128-channel electrode montage (*green discs*) with the classic C1/P1 component complex of the visual evoked potential (group-averaged scalp current density, SCD, waveform; *n*=12) at inferior-parietal scalp site IPZ (*purple disc*). **b** SCD waveforms from four scalp sites (indicated in *inset* by *colored dots*), reveal an elaborate subcomponent structure to the C1. *Dashed yellow lines* delimit temporal transition points at which the relative contributions to the waveforms undergo sharp changes

ter) rather than in units of current per unit area (milliamps per square centimeter). This measure is directly proportional to the current density (microamps per cubic centimeter), where the constant of proportionality is dependent upon the dimensions and conductivity properties of the head. While much important work is being done on the use of realistic head models for the computation of the SCD (Babiloni et al. 1996; He et al. 2001; see Babiloni et al. 2001), these conductivity properties are not yet well defined and have yet to be widely applied.

Laplacian waveforms were derived from the surface spline-interpolated SCD data at standard "International extended 10–20 system" scalp sites (American EEG Society 1991). All analyses were conducted on these derived Laplacian waveforms rather than on the recorded potential waveforms (see Urbano et al. 1996; Murray et al. 2001; Saron et al. 2001 for similar approaches). All waveforms plotted in this paper are these Laplacian waveforms rather than voltage waveforms.

Lastly, one obvious constraint of the printed page is that only a limited number of discrete maps can be shown to represent a given topographic distribution, and such static maps fail to depict the full spatiotemporal dimensionality of the data. This can make it particularly difficult for the reader to assess the extent of contribution to the maps of background noise. In determining the display gain to be used for the maps in the current study, we followed the topography over its entire time course for each subject (through observing animated time series). Observation of these maps in the baseline period (from –100 ms up to the onset of significant activity at about 50 ms) allowed us to determine the relative contribution of noise to the SCD topographic maps. The gain was then set so that background noise during this baseline period only accounts for one or two topographic lines of current density in a given subject's maps.

Results

In the ERP literature, the C1 is considered an early component of short duration with a singular generator configuration. Figure 1a displays the digitized electrode montage superimposed on a 3D reconstruction of the head of one subject (S.A.) from anatomic MRI (see Simpson et al. 1995a for methodological details), with a typical recording of the C1/P1 complex of the human ERP (group-averaged SCD waveform; *N*=12) at inferior-parietal scalp site IPZ. The apparently simple pattern for the negativity that comprises the classical C1 component is examined in more detail in Fig. 1b. SCD waveform derivations from just four scalp sites over the posterior region are plotted for the latency range 0–140 ms in order to illustrate the underlying complexity. We identify an early C1 phase (hereafter termed $C1_e$), seen from approximately 50–62 ms as a negativity at scalp site POZ. During this period, no obvious change in current density is occurring at the other three scalp sites. This is in contrast to the next phase of the C1 (~62–80 ms),where positive current density is evident at both PO3 and PO4 scalp sites. At ~80 ms, the current density at site PO3 begins a negative deflection, whereas PO4 remains positive, dissociating this third period from the previous two. Further changes in the relative contributions to the waveforms at these sites are again evidenced at ~90 ms and ~100 ms. Multiple generators are necessarily active to give this pattern of waveform deflections.

Topographic SCD mapping of activity in the second phase of the C1 confirms the contribution of multiple

generators. Figure 2a shows the scalp current distribution for the initial phase of the $C1_e$ negativity (60 ms; group data) and the next phase at 75 ms. The $C1_e$ at 60 ms has a simple central negativity with a scalp location consistent with lower bank striate activity bilaterally. By 75 ms, the generator configuration contributing to this negativity has become considerably more complex, as evidenced by the buildup of multiple neighboring foci and the dorsal shift in distribution of the central C1 negativity from that of the $C1_e$ negative focus. If the $C1_e$ reflects the initial activation in area V1, then the very next phase of this negativity (~63–80 ms) contains contributions from multiple generators, probably striate, and the neighboring extrastriate areas as activity spreads up the visual system. Figure 2b shows the same basic pattern for three individual subjects. An important aspect to note, however, is the intersubject variation in topography for the initial $C1_e$ negative focus and for the subsequent spreading activity into neighboring extrastriate areas. This is consistent with known cortical geometric variability between subjects and between hemispheres within subjects (Brindley 1972; Stensaas et al. 1974; DeYoe et al. 1996). Group-averaged data disguise the informative topographic shifts that the C1 negativity makes during the initial visual activation period, as witnessed in the individual subject maps.

Variability in $C1_e$ onset latency was also observed by inspecting individual subject waveforms. We tested for the latency of $C1_e$ onset in each subject in the following manner. The topography of the initial phase of the $C1_e$ negativity was established for each subject from his or her SCD maps (see Fig. 5a). We then chose the scalp site nearest the center of this focus on an individual basis for each subject and derived the SCD waveform from that site. A measure of background noise was then computed for each subject by determining the standard deviation of the mean amplitude over the time window from –60 ms prestimulus presentation to 20 ms poststimulus presentation. We then searched forward in time from 20 ms to find the point at which a negative deflection became greater then 2.5 times this standard deviation in each subject. If 11 subsequent time points also met this criterion, the first point was then established as "$C1_e$ onset". This strategy ensured that high-frequency noise would not be accepted as significant activation, but that only a process that lasted for longer than 10 ms would be accepted as a real physiological activation (see Rugg et al. 1995; Doniger et al. 2001 for similar strategies). This strategy was successful for 11 of the 12 subjects; the 12th subject's waveform was extremely noisy and so the 11-point criterion proved too strict. We excluded this subject from this particular time analysis. We found a mean significant onset latency of 56.2 ms (±4.8), with a range from 50 to 63 ms. In close agreement with the previous strategy, a follow-up running *t*-test analysis (one-tailed, one sample) for significant differences from the zero baseline across the 12 subjects established onset at 57 ms. The criterion of 11 consecutive time-points was also met for this analysis. It is important to note that both of these statistical strategies detail the point at which activation reaches significance. These conservative methods will tend to overestimate onset latencies. Visual inspection of the group waveform at IPZ suggests that onset is likely to be on the order of 3–5 ms earlier.

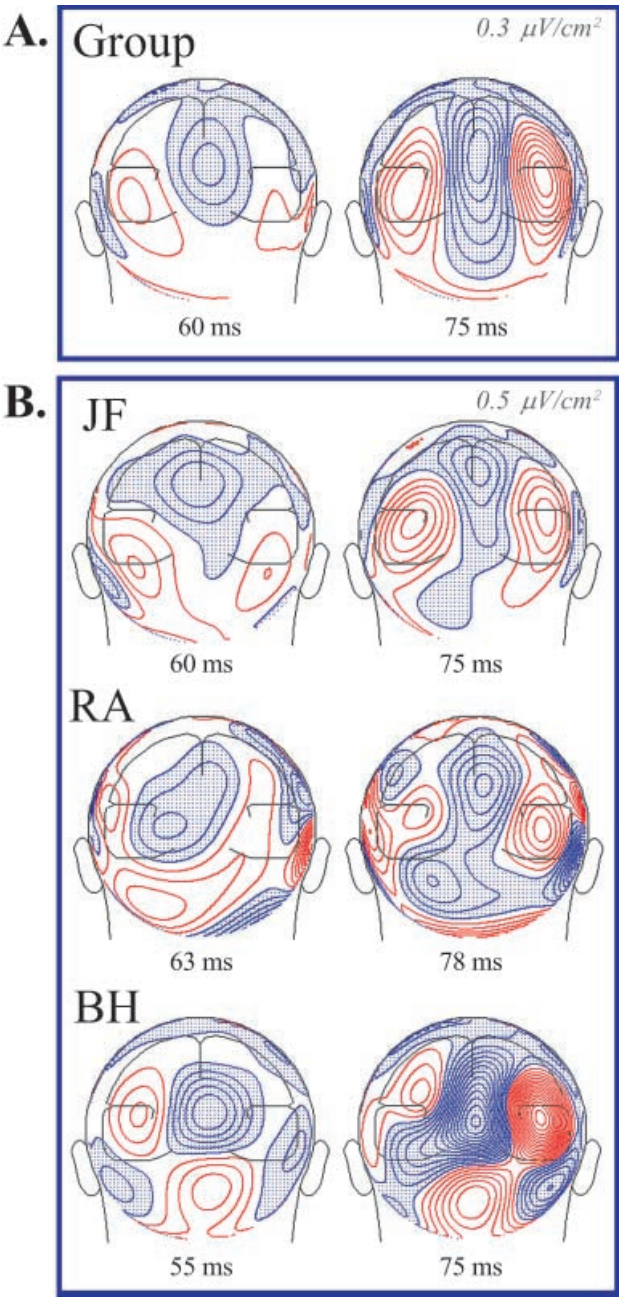


Fig. 2 **a** SCD maps of the group-averaged data (occipital view). *Red isocontour lines* indicate positive values and *blue*, negative. The early phase of the C1 negativity ($C1_e$) is seen as a negative focus over parieto-occipital cortex (60 ms; *left map*). By 75 ms, bilateral extrastriate activations are evidenced by the addition of two positive foci and are accompanied by a change in the topography of the central negativity. **b** SCD maps for three individual subjects showing the early phase ($C1_e$) and later extrastriate spread of activity illustrate the topographic variability across subjects

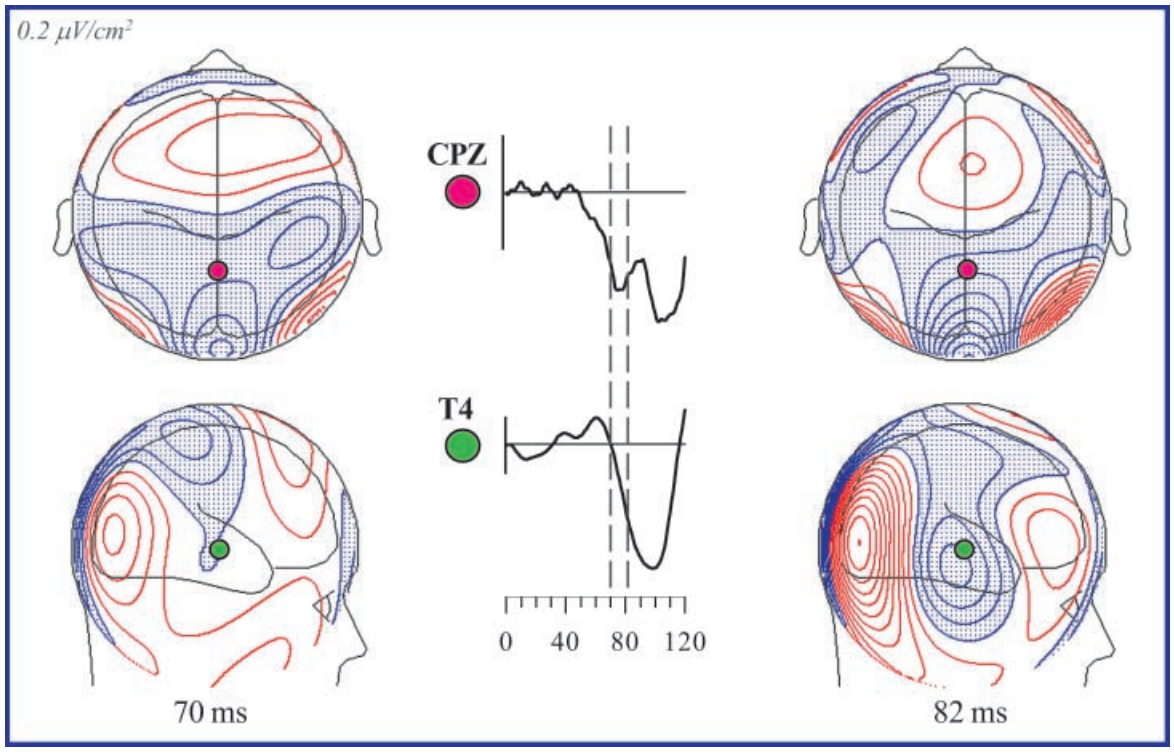


Fig. 3 Dorsal visual stream areas become active earlier than temporal stream areas. At 70 ms, SCD maps from a top view (*upper left map*) and right-side view (*lower left map*) show a spread of activation up over parietal visual areas in the absence of activity over the occipitotemporal scalp. By 82 ms, both dorsal activity and now occipitotemporal activity can be seen (*right maps*). This latency difference can also be seen in SCD waveforms from scalp site CPZ (*red disc*) and T4 (*green disc*)

Activation spreads dorsally over the parietal scalp before it spreads ventrally over the occipitotemporal scalp. Figure 3 illustrates this difference in timing of activation. At 70 ms, the SCD map shows negativity over parietal cortex, whereas no obvious activity is seen over the occipitotemporal cortex. SCD waveforms illustrate this timing disparity; a negative deflection onsets at central-parietal scalp site CPZ ~10 ms earlier than the negative deflection at temporal site T4. At 70 ms, a negative deflection occurs at site CPZ, whereas a similar negativity at T4 has not yet begun. At 82 ms, the negativity at T4 is well established and is accompanied by a distinct negative focus over the inferior occipitotemporal region that can be dissociated from the focus over the parietal scalp. Thus, both parietal and occipitotemporal areas are now active, as seen in the maps on the right of this figure. By as little as 80 ms poststimulus (less than 30 ms post-V1 activation), temporal stream structures are activated by these attended visual stimuli. The point of significant onset (running *t*-test method; 11-point criterion) was established as 70 ms at CPZ and 80 ms at site T4.

By just 85 ms, a consistent, if small, activation peak is seen over left dorsolateral frontal areas (Fig. 4). A dipolar field can be seen over left dorsolateral frontal cortex and SCD waveforms are plotted to show the time course of this activation. The point of significant onset (running *t*-test method; 11-point criterion) was established as 80 ms at scalp site F3. Thus, given an onset for $C1_e$ of ~56 ms and an onset of activation over dorsolateral frontal cortex at ~80 ms, a crude time frame for activation of the entire visual-processing hierarchy (at least for these stimuli in this paradigm) could be established as less than 30 ms.

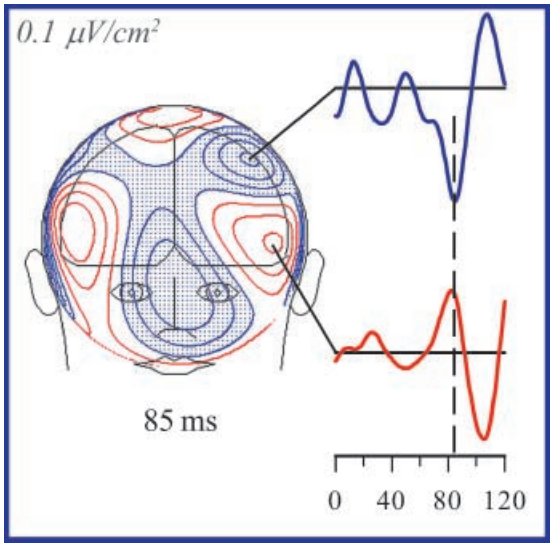
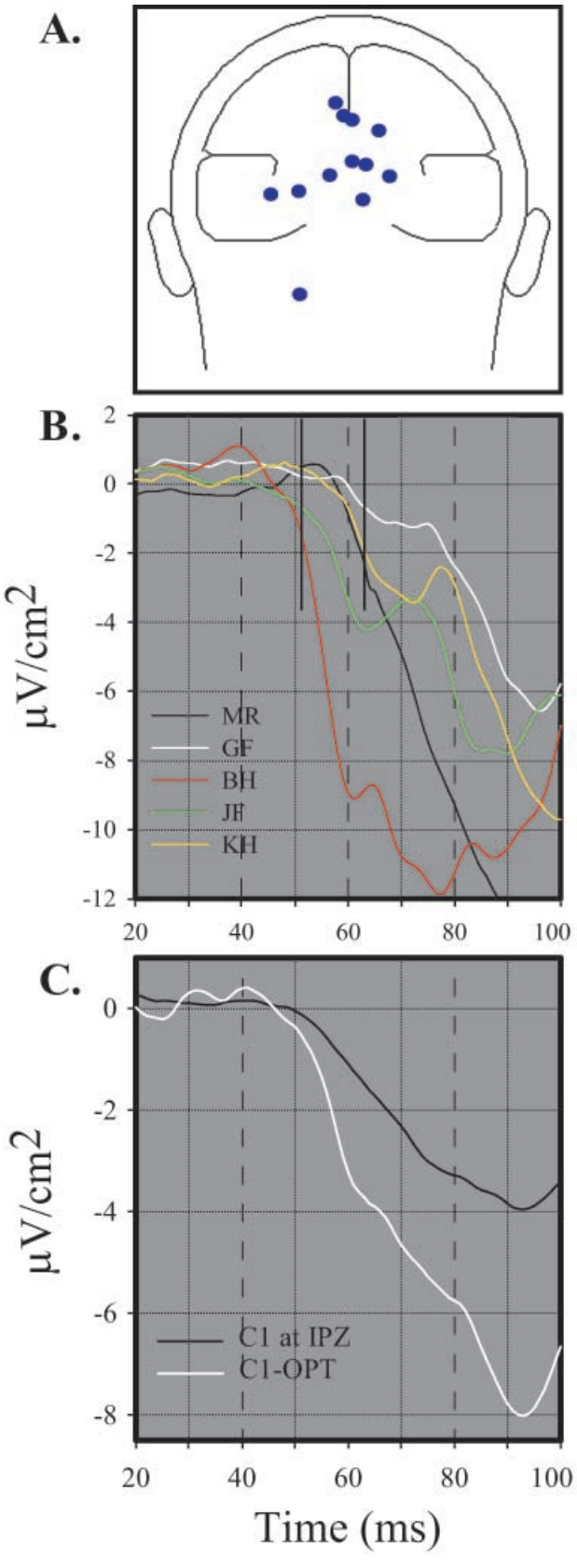


Fig. 4 Dorsolateral frontal cortex is active by 85 ms. An SCD map (front view) shows paired negative (*blue isocontours*) and positive (*red*) foci over the left prefrontal cortex. SCD waveforms from scalp sites F3 (*blue trace*) and F7 (*red trace*) are depicted



To illustrate the topographic variability of the $C1_e$ across subjects, we inspected the SCD maps for each subject and marked the center of the focus during the earliest phase of the C1 negativity for each (Fig. 5a). Thus, while the spatial focus of this earliest activity is fairly circumscribed within individuals, group-averaged data will result in a spatially blurred representation, thereby diminishing the ability to localize underlying brain generators. Also, onset latency of the $C1_e$ is variable across subjects, with a range of some 13 ms between the fastest and slowest subjects (Fig. 5b). Group averaging will tend to particularly effect this earliest portion of the negativity given its short duration (~10 ms) and range for onset latency (more than 10 ms). The effect of spatial blurring on the amplitude of the $C1_e$ caused by group averaging is illustrated in Fig. 5c. The scalp site nearest the center of each subject's $C1_e$ focus was localized from the topographic maps. The SCD waveforms from these optimal scalp sites were then averaged. This spatially optimized waveform resulted in considerably greater (2.3 times) $C1_e$ amplitude compared with the traditional group mean.

Discussion

This study provides a time frame for the initial trajectory of information flow along the dorsal and ventral visual processing streams and on into prefrontal cortex of the human. We provide evidence that this signal transmission occurs over approximately 30 ms; considerably shorter than is typically assumed in the human ERP literature. With the current stimulus configuration and in the context of an attention cuing paradigm, we find a mean onset latency of activity over occipital cortex ($C1_e$) at 56 ms, with dorsolateral frontal cortex subsequently active by just 80 ms. High-density electrical mapping also revealed a timing advantage for dorsal visual areas over ventral areas, with activation in dorsal areas preceding activation of ventral areas. The rapid flow of activation through the visual system to parietal and prefrontal cortices (less than 30 ms) provides a context for appreciating the 100–400 ms commonly needed for information processing prior to response output in humans. It demonstrates that there is ample time for multiple cortical interactions at all levels of the system during this relatively long processing period. Thus, our findings support models of information processing that involve extensive interactions between cortical systems. Our data do not directly examine whether there are top-down functional in-

Fig. 5a–c Topographic and temporal variability of the $C1_e$ across subjects. **a** *Blue dots* indicate the center of the early $C1_e$ focus for each subject. **b** For five representative subjects, SCD waveforms derived from the scalp site at the center of the $C1_e$ focus illustrate the variability in onset latencies. *Solid black lines* at 51 ms and 63 ms indicate the range within which all 12 subjects showed $C1_e$ onset. **c** The group mean C1 at IPZ (*black trace*) is here compared with a spatially optimized C1 (*white trace*; *C1-OPT*)

teractions between frontal and sensory areas. However, they indicate that frontal activation can occur early enough (with respect to sensory cortical activation) to be involved in initial alerting functions and subsequent, more fine-tuned top-down influences on sensory processing.

Further, given this condensed time frame of just 30 ms for signal transmission, we propose that current approaches to the early visual ERP in humans need to be refined. We provide mapping data showing multiple visual generators active in the latency range of the traditional C1 component of the ERP, which has previously been taken to represent V1 activity alone (Hillyard and Anllo-Vento 1998; Martinez et al. 1999). We show that the early C1 displays a high degree of topographic variability across subjects, consistent with known cortical geometric variability in the early visual areas (Brindley 1972; Stensaas et al. 1974; DeYoe et al. 1996). Based on the temporal pattern of activation shown in primate recordings and the evidence from these human recordings, we propose that only the initial portion of the C1 component (approximately the first 10–15 ms; $C1_e$) is likely to represent a response predominated by V1 activity. Shortly after the onset of the $C1_e$, multiple visual areas begin to contribute substantially to the surface potential and C1 begins to reflect contributions from a number of visual areas other than, but is likely also to include V1. The following sections will expand upon these issues.

Parallels with monkey intracranial recordings

The 30-ms time frame established by these data for the initial trajectory of signal transmission is highly consistent with what would be expected from monkey intracranial recordings. Schroeder et al. (1998), using a multicontact linear-array electrode to record the laminar profiles of postsynaptic potentials, have charted the temporal activation pattern across the visual hierarchy in awake behaving macaques (stroboscopic flash stimuli). Their monkeys were involved in an intermodal attention task related to the one that the human subjects in this report were engaged in. They found mean onset latencies of 20.3 ms in area MT, 25.8 ms in IP, 26.3 ms in area V1, 27.4 ms in STP, 36.1 ms in V2, 32.3 ms in V4, and 49.2 ms in IT. Very similar latencies were seen in anesthetized macaques by single-unit recordings (Schmolesky et al. 1998). Activation of the most ventral visual structures of monkey IT lagged activation in V1 by only ~23 ms (Schroeder et al. 1998), consistent with the current human data set. Activation in dorsal stream structures such as the superior temporal sulcus (STSpv) preceded activation in V4 by ~10 ms, showing a similar dorsal over ventral speed advantage to that seen in the current data set. In fact, Schroeder and colleagues provide strong evidence that the initial activation of ventral areas such as V4 is provided by dorsal stream structures rather than direct input along the ventral stream through V1 and V2. That is, the initial activation of V4 and IT was seen in supragranular layers rather than layer IV, consistent with lateral corticocortical inputs rather than direct feedforward afferent input along the ventral pathway (see also Oram and Perrett 1996). Mean response latencies along dorsal stream areas (V3, MT, MST, and FEF) trail mean V1 latencies by less than 10 ms (Schmolesky et al. 1998). Note that FEF receives convergent inputs from both the dorsal stream and ventral stream (see Baizer et al. 1991; Schall et al. 1995). One implication of the dorsal speed advantage is that the faster information flow along the dorsal stream positions dorsal structures for modulation of ventral processing (e.g., form, shape, figure-ground segregation), perhaps including parietal spatial attention mechanisms. Models that predict attentional control of ventral processing by parietal areas have previously been proposed (van der Heiden 1991; LaBerge 1997; Foxe et al. 1998; Fu et al. 2001). Additionally, it has been shown that human V5/MT may be active before initial activation of V1 (Ffytche et al. 1995; Buchner et al. 1997), consistent with monkey intracranial findings (Schmolesky et al. 1998; Schroeder et al. 1998). The stationary (albeit rapid transition) stimuli in our experiment are likely to be suboptimal for eliciting V5 activation, which would be more robust to motion stimulation.

C1 contains contributions from more than just striate cortex

We found that the C1 component of the visual ERP consists of a brief early phase during which there is a largely simple topography over central occipital scalp, and we propose that this period most likely represents a response that is predominantly generated in V1. We term this early phase the $C1_e$. We show large variability across individuals in terms of the topography and onset latency of this $C1_e$. Additionally, 10–15 ms after $C1_e$ onset, extrastriate areas become active and begin to contribute to the C1 surface potential, as previously defined in the literature. The fact that the C1 contains contributions from multiple visual areas has important implications for component-based interpretations of visual ERP data at large.

Currently, the prevalent view is that the human C1 represents the initial activation of striate cortex (Hillyard and Anllo-Vento 1998; Martinez et al. 1999) by virtue of its lawful tracking of the retinotopic location of stimuli. That is, it reverses polarity as a result of upper or lower visual-field stimulation and is of greater amplitude over the hemisphere contralateral to the side of stimulation (Jeffreys and Axford 1972; Ahlfors et al. 1992; Mangun et al. 1993; Aine et al. 1996). Of course, areas V2 and V3 also conform to this organization (Sereno et al. 1995; DeYoe et al. 1996; Tootell et al. 1998). The C1 has a latency range of roughly 45–90 ms, and inverse dipole source estimation has repeatedly localized it to an occipitopolar position, apparently consistent with a striate cortical generator (Simpson et al. 1990, 1995a, 1995b; Gomez-Gonzalez et al. 1994; Clark et al. 1995; Clark

and Hillyard 1996; Ikeda et al. 1998; Shigeto et al. 1998). However, the extended latency range of the C1 is inconsistent with striate activation alone. While the C1 is likely to receive a substantial contribution from primary visual cortex, it has proven very difficult to isolate V1 from V2 activity with source localization techniques, particularly given their anatomic proximity (see Simpson et al. 1995b; Sereno 1998).

The current data set strongly suggests that C1 does not simply reflect the activation of striate cortex. In support, Clark et al. (1995) have shown previously the occurrence of extrastriate activity that overlapped in time with the latency of the human C1 component, suggesting that more is afoot during the C1 latency window. They found a positivity that they named the P75ot due to its occipitotemporal topography, which was concurrent with but dissociable from the C1, owing to its nonretinotopic behavior (also Clark and Hillyard 1996). Further support for the more complex series of activations that must underlie the very early VEP comes from results from large subdural electrode grids in epilepsy patients. Both the lingual gyrus and cuneus have been shown to produce negative potentials at about 70 ms (Arroyo et al. 1997). Additionally, activation in human frontal eye fields has been observed in the C1 latency range (Blanke et al. 1999).

Due to the relatively small amplitude generated by the initial activation of a single cortical region such as V1, it can be difficult to isolate this activity on the scalp. However, there are studies in which identification of initial V1 activity is important, as in ruling out or confirming early striate involvement in attention, for example. We propose the following method for optimizing identification of early V1 activity in such studies. A cohort of optimal $C1_e$ activators could be identified. Retinotopic probing (as in Clark et al. 1995) could be employed to identify the optimal visual spatial location for generating the largest $C1_e$ surface representation for each subject. Both spatial and feature attention paradigms could then be modified on an individual subject basis to particularly target these optimal stimulation locations. Measures of the $C1_e$ could then be taken from the optimal recording sites for each subject as defined by the initial high-density mapping study and adjusted temporally to account for individual differences in onset latency. By this method, sensitivity to the striate component of the VEP could be greatly enhanced and the power of observations aimed at determining the lack of effects in early V1 activity might be enhanced.

Relative timing issues

An important observation from both human source localization studies (Simpson et al. 1990, 1995a, 1995b), and primate intracranial recordings (Schroeder et al. 1998) is the manner in which activity is sustained in early visual areas following the initial afferent volley. In fact, sustained V1 activity has been shown to contribute to both the P1 and later components of the human ERP (Simpson et al. 1990, 1995a, 1995b) and to the monkey equivalent of the surface P1 component (Givre et al. 1994). The use of the early human visual ERP as a tool for investigating human brain processing will be improved by incorporating our knowledge of the quick succession of initial activations across the early visual areas and the subsequent sustained nature of activity within these visual areas. Such sustained activity argues against treating scalp components as discrete indices of individual cortical areas, in which sequential components are considered to reflect discrete cortical generators becoming active in a serial manner. Rather, the surface componentry of the VEP generally reflects contributions from multiple areas across time and the extent of surface positivity or negativity simply reflects the fact that the relative contributions from different areas are changing over time. It may be more useful to think of the componentry of the human ERP as representing coordinated activity in a network of areas. These networks and the nature of the operations performed by them changes dynamically over time and is reflected in the temporal sequence of the surface components.

We would hold that sustained activation patterns within cortical areas are consistent with feedback modulation of "lower" visual areas by "higher" areas, as well as local intrinsic processing. Feedback modulation of earlier areas that conforms to the time frame detailed in this study has been shown in figure-ground segregation studies in monkeys (Lamme 1995; Zipser et al. 1996; Lamme et al. 1998b; Lee et al. 1998). The anatomy of visual cortical connectivity is relevant here (Felleman and Van Essen 1991). The fact that, in almost all cases where there is feedforward connectivity, there is reciprocal feedback connectivity has bearing on our conception of visual processing. Indeed, the largest projection to the lateral geniculate nucleus (LGN) of the thalamus comes from area V1 (Robson 1983; Murphy and Sillito 1996) and this projection is implicated in basic cortical processing (Sillito et al. 1994; Cudeiro and Sillito 1996). Sillito et al. have shown that synchronization of firing in LGN relay cells by the V1 corticofugal projections leads to a gain mechanism such that V1 representation of moving contours is enhanced. Similar feedback properties have been shown for the V2 backprojection to V1. Both reversible cooling of (Sandell and Schiller 1982) and GABA application to area V2 (Payne et al. 1996) cause changes to the receptive-field characteristics of V1 neurons. Payne et al. have suggested a "push-pull" mechanism, whereby feedback input from V2 increases the selectivity of neurons in V1. It seems reasonable to assume that corticocortical looping mechanisms such as "push-pull" will continue to operate at increasing levels of the visual hierarchy (Carpenter and Grossberg 1987; Mumford 1992; Pollen 1999).

Frontal activation

The rapid activation of prefrontal cortex following initial visual activation (within 30 ms) suggests that this input

is mediated through the faster dorsal visual stream. The requisite anatomical (Pandya and Kuypers 1969; Goldman-Rakic and Schwartz 1982; Andersen et al. 1985) and functional connectivity (Quintana et al. 1989; Chafee and Goldman-Rakic 1998) have been described. The "dorsal-before-ventral" timing advantage is likely to persist into prefrontal cortex and, therefore, may position frontal areas to feed back onto ventral visual stream areas. Again, the connectivity has been described (Pandya and Kuypers 1969; Chavis and Pandya 1976; Jacobson and Trojanowski 1977). Prefrontal cortex may play a role in integrating the dorsal "where" information with ventral "what" information, given these convergent inputs. Prefrontal areas showing both properties have been described (Kubota and Niki 1971; O'Scalaidhe et al. 1997; see Goldman-Rakic 1996) and some studies have shown convergence of both "where-and-what" activity in the same prefrontal neurons (Rao et al. 1997; Rainer et al. 1998). The current results support the arrival of dorsally mediated "where" information in prefrontal cortex before the arrival of the ventrally mediated "what" information, at least in the context of the current intermodal selective attention task. We find that prefrontal cortex becomes active ~10 ms later than dorsal sensory activation, but simultaneous with the onset of activation over temporal cortex. Modifying effects of prefrontal inputs to inferotemporal cortex of the monkey have been demonstrated previously (Fuster et al. 1985) and top-down prefrontal control of inferotemporal processing has been proposed (Chelazzi et al. 1993; Miller et al. 1996). An alternative interpretation of this initial input to frontal cortex might predict that this rapid input to frontal areas serves a simple alerting function, which prepares the neural circuitry for the subsequent slower and more detailed computations to be made. This would suggest that frontally mediated top-down processes come after this initial activation.

Since prefrontal activation precedes the majority of continued sensory processing (as represented by the classical P1 and N1 components), this positions feedback processes to impact the ongoing visual sensory processing that these components represent. This is in contrast to involvement of prefrontal executive mechanisms only subsequent to more extensive sensory processing. Future studies will address questions of when prefrontal activity influences sensory processing in humans. Since it is possible that some of the initial prefrontal activity is bottom-up stimulus-driven or preattentive activity, we will investigate when prefrontal activity differentiates between passive viewing and stimulus-dependent directives.

One important consideration regarding this early frontal activation concerns the possibility that it might reflect anticipatory responses that were generated in response to the cue stimulus, which preceded each attended visual stimulus, rather than a stimulus-driven response to the attended visual stimulus itself. Such anticipatory attentional responses have been described in many studies (Everling et al. 1997; Karayanidis and Michie 1997; Foxe et al. 1998; Hopf and Mangun 2000; Worden et al. 2000; Fu et al. 2001). While anticipatory potentials are also evident in the cue-S2 period in the current study (Foxe et al. 1998), we can rule them out as the source of the early frontal effect at ~80 ms. The cue-S2 interval was 1,085 ms, and anticipatory responses over an interval of this time frame are universally of the sustained slow-wave variety. The early frontal response seen here is a high-frequency component, characteristic of the exogenous components typically seen in the first 200 ms following stimulation. It appears highly unlikely that a component of such discrete duration could be generated some 1,200 ms following the presentation of a cue stimulus after an intervening period in which only slow-wave sustained potentials were seen to persist. However, it is quite probable that generation of this frontal component is a direct result of the attentional state of the subject, which is predicated on the cue instruction and evidenced by the anticipatory responses. That is, selectively preparing the brain for a visual task could well involve potentiation of the pathway from visual cortex to frontal regions such that the arrival of a to-be-attended visual stimulus activates the visual system more effectively than a passively viewed stimulus. Nonetheless, even passively viewed stimuli have been seen to result in early stimulus-driven activation of frontal cortex (Saron et al. 2001).

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