# Early (N70m) Neuromagnetic Signal Topography and Striate and Extrastriate Generators Following Pattern Onset Quadrant Stimulation

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#### **INTRODUCTION**

The MEG signal generated by sinusoidal grating pattern onset at 1 and 3 cpd, presented randomly to the four quadrants, was analyzed in terms of gross signal properties and current dipole modeling and for a subset of subjects with magnetic field tomography (MFT). In all subjects a prominent wave was identified with a peak latency around 70 ms (N70m), modulated by spatial frequency and varying systematically with the stimulation quadrant. Sensors over occipital areas recorded stronger responses with lower field quadrants, while the signal for sensors a few centimeters more superior was stronger with upper quadrant stimuli. A strong signal in inferior occipitotemporal areas was less sensitive to upper and lower field stimulation and was stronger in the left hemisphere with contralateral (right) visual field stimulation. For lower visual field stimulation a good fit to the average data was obtained with a single dipole for 3 cpd, but was less consistent across run repetitions for 1 cpd. Neither the singledipole model nor the two-dipole model produced a good fit across runs with the upper field stimuli. MFT solutions identified overlapping activity in striate and extrastriate areas in all conditions. The MFT solutions in the V1/V2 at the N70m were highly reproducible across run repetitions for 1 and 3 cpd, and consistent with the cruciform model, even though they were often weaker than simultaneously activated extrastriate generators. Extrastriate generators in V5 and the human homologue of V6, which were variable across run repetitions at N70m, settled to highly reproducible activations between 100 and 200 ms. © 2001 Academic Press

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There is a long history of magnetoencephalography (MEG) and electroencephalography (EEG) studies focusing on the topography of the signal. The strongest signal is usually seen around 100 ms and as it has a positive sign in EEG it is known as the P100 component. Most studies attempt to explain its origin by referring to the cruciform model of retinotopic organization, either using EEG surface electrodes (Butler et al., 1987; Ikeda et al., 1998; Ossenblock and Spekreijse, 1991) or MEG acquisition (Nakamura et al., 1997; Ahlfors et al., 1992; Harding et al., 1994; Odaka et al., 1996; Brecelj et al., 1998; Aine et al., 1990, 1995, 1996). At least partial consistency with the above model is claimed by Butler et al. (1987), Harding et al. (1994), Ikeda et al. (1998), Nakamura et al. (1997), and Brecelj et al. (1998). Extrastriate generators have been suggested by Ossenblock and Spekreijse (1991). Aine et al. (1995) describe the asynchronous activation of multiple spatially separable sources around 110 ms. From their results, Aine et al. (1996) and Onofrj et al. (1996) conclude that there was a discrepancy from the classical cruciform model. Odaka et al. (1996) suggest that a single dipole is not sufficient to describe the activity of the central fovea and the areas close to the vertical meridian.

Considerable earlier visually evoked potential (VEP) research with humans has focused on the first 70-75 ms of the response (Bodis-Wollner et al., 1981). A negative deflection recorded at the end of this period (N70 peak) has been assumed to be the first peak generated in the visual cortex and to represent the initial response of the striate and/or extrastriate visual cortex. High-frequency oscillatory activity (Sannita et al., 1995; Tzelepi *et al.*, 2000) in the  $\gamma$  and  $\beta$  range has also been reported to peak around this latency. Furthermore, it is known from VEP studies (Bodis-Wollner *et* al., 1989; Previc, 1988) that the N70 peak exhibits spatial frequency tuning, which peaks around 4 cycles/ degree (cpd), similar to the human contrast sensitivity curve. These results and of course the relatively early latency suggest that the N70 peak is related to fewer



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synaptic stages than the stronger and more extensively studied P100. The P100 is still considered the most reliable index of normal visual function in clinical applications, despite the fact that its latency is influenced by gross lesions in either retina or retinocortical pathways. Understanding better how stimulus properties affect the generators should lead to better stimuli for robust N70 or N70m generation and lead to complementary and more refined clinical uses than the ones relying on the P100 alone.

The striate contribution to the surface pattern-reversal VEP was studied in awake monkeys, by examining laminar profiles of VEP, current source density, and concomitant multiunit activity in area 17 (Shroeder et al., 1991). The study concluded that the N50 simian response is the analogue of the human N70 and it is generated primarily by current sinks in lamina 4C of V1, while the simian P60 is the analogue of the human P100, which is generated primarily by large current sources in supragranular laminae of V1. More elaborate studies with recordings from striate and extrastriate areas from the same group (Shroeder et al., 1998) and others have revised this conclusion. The evidence clearly shows that within the first 60 ms not only V1 but also the entire visual pathway is activated. For a review see Nowak and Bullier (1997). Shroeder et al. (1998) conclude "The small latency differences across the system combined with the long response durations ... make it likely that multiple structures contribute to any surface ERP or MEG component. Early components not originating in V1 are most likely to arise from dorsal stream areas." Our study takes off from this point, exploring whether the generators of the early but robust responses elicited by well-defined stimuli can be reliably extracted from noninvasive MEG measurements.

We used stimuli designed to enhance the magnetic analogue of the N70 (N70m) in the normal human brain. We looked specifically for contributions to the MEG signal from V1 and nearby area(s) and tested how reliably the corresponding generators can be identified for individual subjects.

Our choice of stimuli and protocol was guided by the wish to obtain a clean reproducible MEG signal for the N70m. We avoided pattern reversal since it excites cells with different spatial frequency tuning and gives rise to movement sensations. We have used instead sinusoidal gratings in an on/off mode at two spatial frequencies, 1 and 3 cpd, presented randomly in each of the four quadrants of the visual field to avoid habituation and after-image responses. Of course, given that stimuli appear fairly rapidly at different parts of the visual field, the excitation of motion-like response cannot be completely avoided. We have tested stimuli of different sizes, identifying a signal-above-noise level each time. For small stimuli the reproducibility of the signal and its robustness at the N70 latencies was judged insufficient for the purpose of the study. We settled for the largest stimuli (quadrants) which in their classical V1 representation excite cortical sites whose electric equivalent dipoles summate in the magnetic signal. We used high luminance to generate large signals, so that we could check for reproducibility directly on the signal traces. In order to avoid interactions and contamination from different quadrants of the visual field, a central stripe along the vertical and horizontal meridian was not stimulated.

The nature of the generators was explored in three stages: we considered first the robust and model independent distribution of MEG signals over the occipital pole and adjacent parietal and inferior temporal areas. We then fitted the single- and double-dipole model to the 70 most occipital sensors to derive point source solutions for all subjects and conditions. Finally we applied magnetic field tomography (MFT) (Ioannides et al., 1990; Ioannides, 1994) to extract from the MEG signal of all sensors a complete description of generators throughout the head without any assumption about their number location and nature (e.g., point-like or distributed). Although we anticipated that MFT would produce the most reliable solutions, we emphasized the less demanding current dipole analysis. Since many earlier MEG studies have used this model, repeating the exercise was the only way to relate to a large volume of earlier work.

#### **MATERIAL AND METHODS**

#### **Subjects**

Six right-handed subjects (four males), ages between 24 and 36 years (mean value 28.7, SD 4.9), with normal visual acuity were tested. All subjects gave their informed consent to participate in the experiment. The data from one female subject were excluded from the analysis because the MEG signal for the 1-cpd runs was too noisy.

#### Stimuli

Stimuli consisted of vertical gratings with a sinusoidal luminance profile presented in an "on" and "off" mode (Fig. 1A). The on and off periods lasted for 400 and 300 ms, respectively (Fig. 1B). A pretrigger interval of 100 ms was used for baseline estimation. The repetition frequency was 1.4 Hz. When the pattern was off the screen had the mean luminance of the pattern. The subject was comfortably seated inside a semidarkened shielded room, about 70 cm from the screen, which subtended a visual angle of  $30^{\circ} \times 21^{\circ}$ .

The stimuli were projected from the back using an LCD projector driven by a PC under commercial Neuroscan's STIM software. Sinusoidal gratings in the two spatial frequencies, 1 and 3 cpd, appeared randomly on

A



**FIG. 1.** (A) Stimuli consisted of a sinusoidal grating pattern (1 or 3 cpd), presented randomly in each of the four quadrants of the visual field in an on/off mode. The time course of presentation is shown. (B) The contour plot at the peak latency is displayed for subjects S3 (top) and S1 (bottom). Note that 1-cpd produces weaker and less well defined foci than 3-cpd stimulation. (C) The time course of occipital MEG channels (identified in the head model figurines) for the same subjects and cases. Each trace corresponds to the averaged response across three identical runs. For each subject the MEG signal is displayed separately for upper left, upper right, lower left, and lower right quadrant stimulation, as indicated by the dark portion of the rectangle above each set of averaged responses, and separately for 1 cpd (top traces) and 3 cpd (bottom traces). Note the modulation of the N70m amplitude with spatial frequency. The dashed vertical line marks the peak for the 3-cpd case and is drawn on all displays (the slightly earlier peak latency for 1-cpd stimulation is not obvious at this time scale).

each of the four quadrants of the visual field (Fig. 1A). Throughout the paper, each stimulus is identified by a triple binary label: the first two characters identify the location of the quadrant, upper (U) or lower (L) for the first and left (L) or right (R) for the second, and the third part of the label is either 1 or 3 denoting either 1 or 3 cpd. For example UL1 represents a 1-cpd sinusoidal grating presented in the upper left quadrant of the visual field. In order to avoid contamination from adjacent quadrants, stripes subtending 50" of arc across the vertical and horizontal meridian were not stimulated. The pattern alternated between on and off without change of the average luminance. The mean luminance of the screen was 360 cd/m<sup>2</sup> and the contrast of the pattern was 92%. The subject viewed the screen binocularly, fixating on a small cross on the center of



FIG. 1-Continued

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the screen. The subject was instructed to avoid blinking unless it was too uncomfortable to do so.

# **MEG Hardware**

Visually evoked fields were measured using the whole-head Omega biomagnetometer (CTF Systems, Inc., Vancouver, BC, Canada). The helmet-shaped, liguid helium-filled dewar of Omega is placed inside a 3 imes $4 \times 2.4$ -m shielded room (NKK, Japan). The helmet itself houses 151 primary channels uniformly distributed in the inner lower surface of the dewar and 28 reference sensors. Each primary channel is a firstorder axial gradiometer with the two 1-cm-radius coils separated by 5 cm (baseline). The proximal sensor coils are on average a little over 3 cm from the room-temperature (outside) wall of the helmet. The distance between a proximal sensor coil and the brain surface varies from 5 to 8 cm depending on the shape and actual position of the subject's head inside the dewar. The reference channels are a collection of magnetometers and gradiometers placed about 30 cm above the uppermost gradiometer inside the dewar away from the subject's head. The signal from a subset of the reference channels is used to construct in the software a synthetic higher order signal which behaves like a gradiometer with a long baseline and is therefore very effective in eliminating noise components from distant sources. In addition to the MEG channels the EOG and ECG were acquired at the same time for offline noise elimination. The signal was collected in epoch mode with each mode triggered by the signal from a photocell attached on the opaque edge on the projection (back) side of the viewing screen. In this way the delay from the triggering of acquisition to the onset of the stimuli was not more than 2-3 ms.

#### Recordings

Responses were recorded with a 200-Hz low-pass filter at a sampling rate of 1250 Hz. Data were originally recorded with no balancing of the MEG sensors. After recording, each run was digitally low-pass filtered at 140 Hz and the mean amplitude of the pretrigger period was subtracted to compensate for DC offset. In our current dipole analysis we have used about 70 sensors over the occipital area with synthetic third-order gradient form for the MEG signal to improve noise cancellation. For MFT we used all sensors and first gradient MEG signal.

Three identical runs were recorded for each subject to enable us to test the reproducibility of responses. In each run, stimuli from each of the eight conditions were randomly blocked (e.g., LL3 cpd, UR1 cpd), populating equally the 200 trials. Responses were also recorded when the screen was "blank" with the mean luminance of the grating pattern, called from now on "noise." After acquisition, the 25 trials for each of the eight conditions were separated offline. The EOG signal for each single trial was visually inspected and any trial containing an eye artifact was completely removed from the set. On average 13–14 trials were removed from each run. Averaging of the remaining clean trials produced three sets of averaged signal for each of the eight conditions. The use of three runs limited the time the subject had to stay motionless (in one run) and provided valuable repetition runs. The reproducibility of the responses across the three runs was quantified by computing their signal-to-noise ratio over short windows sliding across the latency range. The noise runs were processed in exactly the same way, providing together with the prestimulus period two measures of baseline for the subject noise level.

#### **Coregistration of MRI and MEG**

MRI images were acquired for each subject with either a 1.5-T Siemens Magneton Symphony or Varian Unity Inova 4T system. In both cases 256 slices were collected with 256  $\times$  256, 1  $\times$  1-mm square pixels in each slice. Three probe coils were attached to the scalp, one close to the nasion and two close to the preauricular points. The coil positions and subject's head shape (a few thousand points) were digitized with a threedimensional digitizer (Polhemus, 3Space/Fastrak, U.S.A.). The digitized points were then matched to the surface of the scalp using dedicated software developed for this purpose. Before and after each run the probe coils were activated and their positions identified by the CTF software. This defines the exact position of the sensors relative to the coils and hence with respect to the head of the subject and its MRI representation. The procedure yields an accurate superimposition of the estimated sources on the corresponding MRI slice. This allows solutions to be compared on the same anatomical background from runs of the same experiment or even across different experiments on the same subject performed days, months, or years apart, provided that a new digitization and coregistration are performed for each session.

#### **Source Analysis**

# Dipole Localization

The standard software provided with the system was used for dipole estimation. This software is based on least-squares minimization of the difference between the forward problem and the acquired signals. A separate independent fit was done for each time point in the selected window. The uniform conducting sphere model was used. The sphere center was estimated from a least-square fit to a spherical shell of the skull outline extracted from the MRI of each subject. For the dipole analysis we used 70 sensors at the back of the head. We analyzed the data for all subjects from 58 to 85 ms. Dipole fits were accepted when the error of the fit to the actual data in a least-squares sense was less than 10-15%, This range depended on the observed residual field. If the residual didn't approximate a dipole-like field distribution, then fits with error up to 15% were accepted.

#### Magnetic Field Tomography

All sets of average signals for two subjects were analyzed using MFT for the entire period  $(-100 \text{ to } 600 \text{ to$ ms, at steps of 1.6 ms). The MFT analysis was performed in the by now standardized fashion. Four separate MFT computations were used with separate source spaces covering the left and right hemisphere and the back and top of the head. For each source space the 90 channels providing the best coverage were used with the lead fields computed for a conducting sphere with center defined from the local curvature of the inner surface of the skull around the source space. The a priori probability weight was independently determined for each combination of source space and its subset of channels from computer-generated data with current dipoles spread over the entire source space (Ioannides et al., 1990; Taylor et al., 1999). In MFT the two free parameters (regularization and a priori probability weight) are fixed before the real data are processed time slice by time slice (Ioannides, 1994). The four separate solutions cover the entire brain, with most of the points represented in at least two source spaces; exceptions were points very close to the front of the head or in the cerebellum and brain stem, which were represented in just one source space. The solutions from the four source spaces were brought into one source space, which covered the entire brain. The value of the current density in the combined source space was determined by the current density of the neighboring points in the four original source spaces, weighted by lead field combinations determined by the local standard error in source variance. The combination of the four source space solutions into one was performed separately and independently for each subject condition and time slice. At the end of this process the information from all sensors was used to compute the current density throughout the brain.

# RESULTS

#### **Signal Distribution**

The MEG signal was highly reproducible for the same condition, in all three runs for each subject. In the average response to pattern onset, all subjects showed a prominent wave around 70 ms (N70m). This early peak was consistent among different runs and among different subjects and was the sharpest of the whole response, starting approximately at 50 ms and

ending at 80 ms. The range of N70m peak latency varied between 64 and 75 ms among subjects. There was no systematic difference in N70m latency related to stimulated quadrant of the visual field. N70m was followed by a wave of opposite polarity (P100m) peaking between 112 and 120 ms, which was rather variable across the different subjects. After 500 ms the offset response could be identified in almost all cases. The results reported in this study will concentrate on the N70m peak.

Lower quadrant stimulation always resulted in robust, high-amplitude N70m with clear and distinct morphology dominating over the following P100m. In four of six subjects, N70m with 3 cpd and lower quadrant stimulation was the largest peak in the whole response. With upper visual field stimulation, N70m was less pronounced and sometimes overlapped with the beginning of the next component. N70m varied systematically and consistently in size and polarity according to the quadrant being stimulated. Upper and lower field responses were of opposite polarity at the peak latency of N70m. Lower field stimulation resulted in stronger responses in the occipital area than upper field stimulation.

Spatial frequency modulated the latency and amplitude of the N70 peak: the mean latency of N70m was computed for each subject by averaging separately the N70m latency over the three runs for 1 and 3 cpd. The mean latency for 1 cpd was always earlier for all subjects. The minimum and maximum differences found were 3 and 6 ms, respectively. Figure 1B shows the contour plots for the MEG signal distribution at the N70m peak for subjects S3 and S1 and demonstrates that the patterns are similar for the two spatial frequencies but weaker with the lower spatial frequency. Figure 1C illustrates the signal distribution, time evolution, and spatial frequency modulation. In accordance with the previously reported electrophysiological studies (Bodis-Wollner et al., 1989; Previc, 1988) the figure shows smaller N70m amplitude for 1 cpd stimuli than for 3 cpd in all four quadrants.

The grand average (across subjects and left and right quadrant runs) of the power of averaged responses at the peak time of N70m is displayed in Fig. 2 separately for each spatial frequency and upper and lower visual fields. The signal power was computed as the square of the signal value relative to the prestimulus baseline. The occipital activation is considerably higher for lower than for upper quadrants (paired *t* test: P < 0.05). In contrast the MEG signal at slightly more superior sensors is significantly enhanced during upper field stimulation (paired *t* test: P < 0.05). The MEG signal over inferior temporal areas has a trend to be stronger during lower field stimulation. This difference increases with 1-cpd stimulation. However, neither of the two conditions (1 or 3 cpd) reaches a level of significance.



**FIG. 2.** (A) Mean signal power at the peak time of N70m with upper and lower visual field over occipital, inferior temporal, and parietal sensors for 1 and 3 cpd. Note the high occipital activity for lower field stimulation and the enhancement of parietal activity for upper field stimulation. (B) The area covered by each selection of sensors from a top view of the MEG array.

#### **Dipole Estimation**

#### Lower vs Upper Quadrant Stimulation with 3 cpd

Lower quadrant responses with 3 cpd were always lateralized to the contralateral side of the visual field being stimulated. The equivalent dipoles were located on the contralateral operculum. In most runs, the dipole was estimated on the upper part of the calcarine sulcus, with occasional estimates on or below the calcarine sulcus. This was not always easy to ascertain because of the irregular nature of the operculum part of V1. The locations were nevertheless consistent among different runs and among different subjects as shown in Fig. 3. The mean fit error varied from 5 to 8% at the peak time of N70m. Dipoles were active and stable for a time period of about 20–24 ms and their moments peaked at the peak time of N70m. They showed an upward oblique direction and they were symmetrical, with left and right lower quadrant stimulation.

Upper visual field responses with 3 cpd showed high variability among different subjects, with location spread from medial brain regions to lower occipital and parietal areas. The estimated dipoles even when consistent among different runs were stable only for a limited period up to 5 ms during the peak amplitude of N70m, where they often showed a downward oblique direction. The mean fit error varied between 11 and 21% at peak time of N70m. Because the single-dipole model was clearly inadequate, we continued the analysis using two dipoles. At the peak latency the twodipole model improved the fit to the signal with resid-



**FIG. 3.** Single-dipole solutions at the peak of N70m, to lower quadrant stimulation, with 3-cpd spatial frequency, superimposed on the corresponding MRI for subjects S3 (left) and S1 (right). Red and yellow dipoles represent the response to lower left and lower right quadrant stimulation, respectively, as indicated with the same colors on the rectangle above the MRIs.

ual error between 5 and 12%. At this latency the location for the first dipole was on the contralateral lower occipital areas for two subjects, but still very lateral for the others. The second dipole was less consistent in its location, but for each subject good fits were obtained at some latency with this second dipole in the general parietal occipital area superior to V1.

# Low (1 cpd) vs High (3 cpd) Spatial Frequency Stimulation

The dipole fit was performed for the different spatial frequencies. In general the fits for 1 cpd were less accurate (as measured by the residual error) and more variable across runs and subjects. For upper quadrants the signal is too weak to allow any conclusions to be drawn from either the single- or the double-dipole fits. For the lower visual field quadrants, the runs with good single-dipole fits tend to produce deeper and more eccentric locations for lower spatial frequency, but this trend is not significant.

# Magnetic Field Tomography: Regions of Interest (ROI) and Activation Curves

We have applied MFT to all sets of average data from two subjects, which produced tomographic estimates for the current density distribution. Three estimates (one for each repetition run) of the current density were thus obtained for each time slice (at intervals of 1.6 ms) for each condition. The loci of strong activity were first identified throughout the brain volume and then reduced to the ones with current density consistent and stable over at least 10 ms across the three averages of at least one of the eight stimuli. For this study we restricted this set further to the six foci which were consistently and/or strongly activated during the N70m; an ROI of radius 1 cm was defined around each such focus. The main direction was defined as the vector along the maximum current density at the time of the N70m, if this activity was consistent across the three repetitions; this was the case for the four striate ROIs. For the two extrastriate ROIs the main direction was defined about 50 ms later when the overall maximum had a consistent direction across the three repetitions. Different conditions could lead to different main directions for the same extrastriate ROI. For each ROI the activity of the current density vector along the main direction was computed for all points within the ROI to provide at each time slice the instantaneous estimate of activity for each stimulus and run. Having defined the ROIs in functional terms, we used their centers to compute the Talairach coordinates (Talairach and Tournoux, 1988) and superimposed each ROI on the individual MRIs of each subject. The ROIs in striate cortex were named using a two-label prefix to V1 which specifies the location with respect to the dorsal/ventral and left/right aspect in the tracing of the calcarine of each subject, e.g., dR-V1 for the dorsal right part of V1. We will refer to one of the extrastriate ROIs as V5 because it was located within 1 cm of the V5 center identified in an independent fMRI experiment The other extrastriate ROI was in the parietooccipital sulcus, which has been proposed to be the human V6 homologue in an earlier MEG study (Portin et al., 1999). For ease of reference we will label this area as V6 here too, but we emphasize that this is very much a putative and provisional assignment.

# Contributions to the N70m from Generators in the Striate Area

The stimuli of each quadrant produced activations on the contralateral quadrant bank of the calcarine with almost identical positions and with almost identical shapes for all six runs (three repetitions each, for 1 and 3 cpd). The location and direction of the current density vector *was* in agreement with the prediction of the cruciform model. The maximum current density for the 1-cpd stimuli was about half that for the 3 cpd. The MFT solution was remarkably stable with the striate activation in the same location and with current density along the same direction for 20-40 ms, beginning around 50 ms. In each run this activation was occasionally masked by activity in other striate and/or extrastriate areas. The ECD solution was reasonably close to the MFT maximum when no other activity was present. When other sources became strong, the MFT solution maintained its form for much of the time while the current dipole shifted widely, especially for 1-cpd stimuli.

Figure 4 shows coronal and sagittal views for the results for subject S1 for the six runs with stimulation in the lower left quadrant, together with the ECD solution. The MFT solution is confined to the dR-V1. The result for right lower quadrant stimulation is an almost mirror image of the activation across the vertical meridian confined to the dL-V1. Very similar results were obtained for lower quadrant stimulation for subject S2 in terms of reproducibility across runs and the location and direction of the current density activations.

For upper visual field, stimulation activity in both the upper and the lower banks of the calcarine was evident. Figure 5 shows the activations for subject S3 for upper left stimulation. In this figure a mask is used to eliminate activity in extrastriate areas which would otherwise dominate the display for some of the images. The activation in the upper bank was in most cases confined to the left hemisphere; it was variable in strength across repetitions and on many occasions, especially for the first run, it was the strongest striate activity, masking the weaker activity in the lower contralateral corner of the calcarine. When not dominated by other striate activity the activation below the calcarine had the expected properties of contralateral localization and oblique inferior direction.

# Extrastriate Activations

Extrastriate activations as strong or stronger than the striate activations were identified in many areas at the time of the N70m. Focal activations in inferior occipitotemporal areas and in superficial and deep parts of the parieto-occipital sulcus, at or close to the "V5" and "V6" areas, respectively, were consistently observed. While the V1 activations were highly reproducible across run repetitions around the N70m peak, the V5 and V6 activations varied considerably in terms of latency and peak value from run to run. These labile V5 and V6 activations at the N70m were observed again 100 ms after stimulus onset but this time as focal and highly reproducible activations across run repetitions in terms of latency, location, and current density direction. Figure 6 shows this later V5 activation in the left inferior occipitotemporal area for the first and third run of subject S1 for each right quadrant activation (upper/lower, 1 and 3 cpd). Around 130 ms, for both subjects, the V5 activations were stronger on the left hemisphere for contralateral (right) hemisphere stimuli and were typically twice as strong for 3-cpd as for 1-cpd stimuli, with the current density direction distinguishing between upper and lower field stimulation. In contrast, at N70m, the direction of the current density maximum at V5 varied considerably across run repetitions with the same stimuli. During the first 100 ms after stimulus onset activations were encountered in deep and superficial parts of the parieto-occipital sulcus in each hemisphere, but few of these show high reproducibility across repetitions of identical stimuli. The right medial side of the posterior, dorsal bank of the parieto-occipital sulcus was the most consistent activation especially for subject S2. This V6 activation was variable in strength and latency at the N70m. The current density direction was, however, very stable during both early (N70m) and late activations. The V6 activation was identified for both upper and lower visual field stimulation runs but it was stronger for upper field, with no clear ipsilateral or contralateral bias or spatial frequency dependence. Figure 7 shows the activation in V6 at 127 ms for subject S2 for the first and third runs for stimuli in the upper quadrants.

# Stereotactic Coordinates and Reproducibility

Figures 4 and 5 have demonstrated the reproducibility of the striate N70m activations in the presence of strong but variable extrastriate activity. Figures 6 and 7 illustrate how these labile extrastriate activations become robust and reproducible some 50–60 ms after the N70m peak latency. Table 1 gives the Talairach coordinates of the four striate and two extrastriate areas that have been reliably and consistently identified across the three runs. A seventh ROI on the right V5 is also included; this was seen as a weak activation with some left visual field stimuli but not as consistently as the left V5. The table also gives the Talairach coordinates for V5 obtained in an independent fMRI investigation of the two subjects.

The reproducibility of the striate activations at the N70m is not confined to the peak latency; it is good across repetitions despite the small number of trials in each average. Figure 8 shows the time courses of striate and extrastriate generators for subject S1. Each activation curve shows the current density along the main direction averaged over the volume of each ROI. Each graph shows together activation curves for one ROI for the three runs with the signal-to-noise ratio (SNR) computed from a 6-ms window sliding across latencies for the same three curves. To aid comparisons



**FIG. 4.** MFT solutions for lower left visual field stimulation for subject S1 at 66 ms after the onset of stimuli. The calcarine fissure is traced in green on each display. In this and the following figures the color shaded contour delineates the area and shape of high current density modulus. The main direction at the points of highest activity is indicated by the thin yellow arrow. A thick red arrow marks the single-current dipole solution if it lies within 0.5 cm of the displayed slice. Notice the wide fluctuation of the current dipole solution especially for 1-cpd stimuli. The instantaneous current density distribution is displayed for each of the six runs. (A) Three runs for 1 cpd and (B) three runs for 3 cpd are shown. The current density within each image is normalized separately from its own maximum, but for ease of comparison the ratio of the maximum in each image to the overall current density maximum (run 1 in B, LL3) is displayed.

the same scale was used throughout the figure, with arbitrary units chosen so that unity is the maximum of the strongest activation (L-V5 ROI with UR3 stimulus). The lower field runs show excellent reproducibility for both 1 and 3 cpd. The activity for the 20 ms on either side of the N70m is two to three times higher for the 3 cpd, but the SNR is similar in the two cases; only the activations for the weaker stimulus, 1 cpd, are shown as the activations for 3 cpd would dominate all other activation curves. The other graphs show the ventral V1 activations in the second row and the extrastriate activations in the last row, with the best 3-cpd stimuli in each case. We have also computed the activation curves for the noise runs (blank screen) after



**FIG. 5.** MFT solutions for upper left visual field stimulation for subject S2. The instantaneous current density distribution is displayed for the first and last (third) run of the 1- and 3-cpd stimuli. Details and conventions are as in Fig. 4. In only one case the current dipole solution is captured within 0.5 cm of the displayed slice (sagittal view for run 3 of UL3). In contrast to the wandering ECD solution the MFT solution is in the same location with maximum current density direction in the same direction for each run.

processing the data in exactly the same way as for the live runs. The activations from the noise runs were small, at about the same level as the activations in the live runs for the prestimulus period. They are not shown in Fig. 8 as they would clutter the display without adding any extra information.

## DISCUSSION

# Limitations of the Study

Before discussing the results of our study we comment on two aspects of our design which are a little different from those employed in most other studies and add a cautionary remark regarding the stereotactic coordinates we have extracted from our measurements. First, we have used a shorter interstimulus interval and fewer trials in our averages than are commonly used. This was of course forced upon us by the conflicting requirements of covering all quadrants at the two grading densities in one go, while keeping each run short. It could therefore be argued that the extrastriate activity simply reflects the noisy nature of the signal. This is unlikely because the baseline activity computed either from the prestimulus period or from the separate noise runs is much smaller than the activity during the N70m. The striate activity during the N70m is highly reproducible across the three repetitions and the SNR for the activation curves for both

the striate and the extrastriate generators is high. Nevertheless, it will be useful to do a new experiment using longer ISI and more trials in block design. The second criticism that might be raised concerns the rather high luminance (360 cd/m<sup>2</sup>) of our stimuli, which may have decreased the latency of the observed N70m. The N70m latencies we have identified were between 65 and 80 ms after stimulus onset, which is well within the expected range, as the name N70 implies. Slightly longer latencies have been reported with checkerboard pattern stimuli. For example, Portin et al. (1999) used luminance of 60 cd/m<sup>2</sup> (for white checks) and a check size of 32' (~2 cpd) and identified the maximum around 80 ms. Ikeda et al. (1998), again using checkerboard pattern, but, in contrast to Portin et al., using an even higher luminance (540 cd/m<sup>2</sup> for white checks) than the one we used and a check size of 30' (~2 cpd), describe an initial reliable deflection around 82.5 ms. We acknowledge that differences in stimulus properties, used in different experiments, often do affect the latency and other properties of the early responses, but we argue that this is not likely to change qualitatively our findings. Finally a warning: the Talairach coordinates of the identified foci of activity in both striate and extrastriate visual cortex are included so our results can be compared with results from other relevant studies, especially those using PET and/or fMRI. Although the Talairach coordinates are



**FIG. 6.** MFT solutions on the left occipitotemporal region for right quadrant stimuli at the latency of its peak activity (133 ms) for subject S1. The instantaneous current density distribution is displayed for the first and last (third) run of the 1- and 3-cpd stimuli for upper and lower right quadrant stimulation. The same sagittal MRI slice is used in all displays. The same area is identified in all cases; the upper and lower visual quadrants distinguished by the current density main direction (thin yellow arrows) irrespective of the spatial frequency of the stimulus. The maximum for each image is printed after normalization to the overall maximum of the set (run 1 of LR1).

very reasonable, we wish to stress that they should be used only as indicators for functional plausibility, given the known intersubject variability and the approximate positions of cytoarchitectonic areas in this atlas (Amunts *et al.*, 2000). The comparison between fMRI and MEG activations in identical, or at least similar, protocols for the same subject (like our V5 determination) is much more meaningful.

## **General Overview**

In this study we stimulated the four quadrants of the visual field with sinusoidal gratings of two spatial frequencies and we acquired the neuromagnetic signals from 151 MEG sensors. We analyzed the data in three stages. In the first stage we used the MEG signal itself and first identified the N70m peak, which was modulated as expected by spatial frequency. In terms of signal morphology the N70m reproducibility within a subject was excellent, especially for the 3-cpd stimuli, and very consistent across subjects. The signal distribution over the occipital and parietal sensors showed a systematic dependence on stimulus properties. Lower field stimulation yielded stronger MEG signals than upper field in the occipital area. In contrast, the signal over the midparietal area was stronger for upper than for lower field stimulation. An activation over the inferior occipitoparietal sensors was evident in all stimulus conditions, similar in strength for upper and lower field stimuli.

In the second stage the data for latencies around the N70m (58 to 85 ms after stimulus onset) were analyzed for all stimuli and subjects using single- and doublecurrent dipole models. For lower field stimulation, a single dipole provided a reasonable description of the activity elicited with 3-cpd stimuli. The dipole location was estimated on the contralateral part of calcarine sulcus. Although the dipole position was reproducible among the three runs, its exact location in relation to the calcarine sulcus was not always consistent with V1 retinotopy. The single-dipole model fit to the data de-



**FIG. 7.** MFT instantaneous estimates for parieto-occipital (V6) at the latency of its peak activity (127 ms) for subject S2. The first and last (third) run of the 1- and 3-cpd stimuli are displayed for left and right upper quadrant stimulation. The same area is identified in all cases and it is shown on the same coronal MRI slice in all displays. The same area is activated together with the striate area at the N70m peak. The maximum for each image is printed after normalization to the overall maximum of the set (run 1 of UL3).

teriorates for 1-cpd and upper field stimuli. The use of the two-dipole model improved the fit but still failed to produce a consistent description of the data for all subjects. The first two stages of our analysis have produced results which are broadly consistent with earlier

#### TABLE 1

Talairach Coordinates (Talairach and Tournoux, 1988) for the Bilateral Foci of Strong Activity for Two Subjects (S2, Top, and S1, Bottom)

ROI	Left hemisphere			Right hemisphere		
	X	У	Z	X	У	Z
dV1/V2	-15	-85	12	-1	-85	10
vV1/V2	-10	-89	0	-1	-90	-1
V5	-50	-65	22	52	-65	22
V6				8	-58	43
V5 (fMRI)	-48	-58	11	35	-64	10
dV1/V2	-19	-83	1	1	-84	1
vV1/V2	-14	-86	-16	7	-85	-14
V5	-45	-70	2	44	-70	9
V6				7	-72	41
V5 (fMRI)	-40	-61	4	39	-62	13

*Note.* The left and right foci for dorsal (d) and ventral (v) part of V1/V2 are listed together with V5. The part of the putative V6 area consistently activated for each subject is also given. The last row for each subject gives the Talairach coordinates determined in a separate fMRI experiment performed specifically to identify V5.

studies, allowing for differences in protocol and stimuli. The stronger responses to lower visual field stimulation in the occipital area are consistent with results of most other researchers. Particularly relevant in this context are two recent MEG studies reporting early activation of the human occipital and parietal cortex with pattern and luminance hemifield stimuli (Portin *et al.*, 1998) and stronger occipital activation to lower than to upper visual field quadrant stimuli (Portin *et al.*, 1999).

The computationally demanding MFT analysis made up the third and more detailed stage of analysis. It was applied to all available data from two subjects. The MFT results provided more specific description of striate and extrastriate early activity in three aspects. First, activations outside V1 do not interfere unduly with the activity of interest within V1. Second, the distribution of activity is recovered within V1, showing in its shape and direction of current density vector the relative presence or absence of activity in the left and right, dorsal and ventral aspects of V1. Finally and as a result of the first two improvements, we can get reliable activations from fewer single trials and distinguish stable and labile activations across run repetitions. The MFT analysis shows that the N70m activity elicited by upper and lower visual field stimulation differs both in terms of its distribution within V1 and in terms of extrastriate generators. Within V1 the ac-



**FIG. 8.** The activation curves in the first 100 ms for the main ROIs identified by MFT analysis. The activations for the primary visual areas are displayed in the first two rows: dorsal V1 activations evoked by lower visual fields with the weaker 1-cpd stimuli are on the first row while ventral V1 activations evoked by upper visual field stimuli with the more effective 3-cpd stimuli are on the second row. The last row shows the activations in the two extrastriate areas V5 (with UR3) and V6 (with UL3). ROIs on the left (right) hemisphere are displayed in the left (right) column. In each graph the three lines correspond to the MFT estimate for the current density along the main direction,  $J_{md}$ , extracted from the average signal of one repetition run. The same scale is used for all graphs with  $J_{md}$  expressed in arbitrary units, such that the overall maximum (L-V5) is 1. A window of 6 ms is used around each latency to compute the signal-to-noise ratio (SNR) for the set of three curves which is shown by the thick black dashed line. The SNR scale is different across each graph so the maximum value of the SNR is printed next to the peak to aid comparison. The solid vertical line marks the 70-ms latency and is printed solely to aid comparisons across graphs. The two labels on the left side of each graph identify in turn the quadrant (upper/lower and left/right) and grading density (1 or 3 cpd), on the first line, and the ROI location on the second line.

tivation is weaker for upper field stimulation, but it is identified for both upper and lower visual fields in the "proper" location and with current density direction as predicted by the cruciform model. The much better accuracy of the MFT reconstructions compared to the "good" ECD solutions became evident only after the MFT solutions were superimposed on individually traced outlines of the calcarine (green outlines in Figs. 4 and 5). This is because of the rather irregular progress of the calcarine in our two subjects, which is all too common. The V1 activation for lower visual field stimulation is confined to the contralateral dorsal part with little interference from the remaining striate cortex. For upper field stimulation the "proper" contralateral ventral part is activated as expected, but in the presence of strong interference from the dorsal side of V1, which often dominates.

Two broad extrastriate areas show strong activations in our MFT solutions around the N70m, one from the left occipitotemporal area and the other superior to V1 around the parieto-occipital sulcus. The first area is consistent in location to the human "motion area" referred to as MT or V5. The second area is in and around the parieto-occipital sulcus, the putative V6 mentioned above and featuring prominently in earlier studies (Portin *et al.*, 1998, 1999). The V5 and V6 activations are highly reproducible around 130 ms as demonstrated by the examples in Figs. 6 and 7. For the V5 activation in Fig. 6, the direction is highly reproducible for all six repetitions for stimulation at either one of the two right quadrants, but different for upper and lower right visual field stimulation. This can be explained by two distinct neuronal populations in V5, which either overlap or are too close together to be disentangled by our analysis. These V5 and V6 activations are also seen earlier at the N70m together with a number of other extrastriate generators. The activations for V5 and V6 around the N70m are less reproducible across repetition runs than around 130 ms.

## **Overall Consistency of the Results**

The three stages of analysis provided a progressively more elaborate description of the generators and, when looked at together, a consistent one. This consistency is best seen between the first (signal properties) and the last (MFT) stages and the way the details of these results explain the failures of the second stage. The inability of the current dipole fits to provide a consistent description can be traced to the cases in which the extrastriate and striate generators produced similar contributions to the occipital sensors. This was the case when the V1 activation was weak and the V6 activation was strong. Figure 2 shows that the signal power over occipital areas is about three to four times stronger for 3 cpd compared to 1 cpd and nearly twice as strong for lower compared to upper quadrant stimulations. These signal properties are consistent with the weak activation in V1 for 1 cpd and especially for stimulation of the upper quadrants in agreement with the MFT results. Figure 2 also shows that stimuli in the upper visual field produce a stronger signal in the group of parietal sensors just above the occipital ones, in agreement with the stronger V6 activity for upper quadrant stimuli identified by MFT. The main direction for the MFT activation for V6 is upward (Fig. 7), almost opposite to the main direction on the ventral side of V1, as predicted by the cruciform model and seen in the MFT solutions (Fig. 5). The V5 activation interferes little with either the V1 or the V6 activation in our MFT solutions, although it can shift the location of the single- or double-dipole fits in a rather complicated way. From these considerations it is evident that the single-current dipole model is most likely to succeed for 3-cpd lower visual field stimuli, when its location will be determined primarily by the dominant V1 activation, with small but not negligible shift from the true activation center. The current dipole model is expected to fare worse for 1-cpd upper visual field stimuli, when three weak generators of similar strength can be simultaneously active, with one of them probably a lot stronger and with current density vector in a direction opposite to the current density in V1. Both predictions agree with the outcome of the current dipole computations, and hence our three levels of analysis provide a consistent description from the level of signal power distribution to the specific generator loci and the direction of the current density vector derived from MFT.

# Links with Earlier Studies and Neurophysiological Implications

Our results confirm the presence of activity in the parieto-occipital sulcus, which Hari and Salmelin (1997) have suggested is the human homologue of the macaque V6 complex. Differences in the current dipole localization, especially for upper field stimuli, are not surprising. The stimuli used in our study and the two Portin studies differed in luminance levels, ISI interval, extent of visual field of quadrants, pattern and luminance type, and order of presentation. More importantly, the axial gradiometers used in our study are not as spatially selective as the planar gradiometer sensors used by Portin et al. (1998, 1999), which are primarily sensing nearby superficial sources. In both the Portin studies and ours the use of current dipole analysis suggested extrastriate activity in the parietal area, and in our study at least the current dipole location was widely spread across subjects and even within subjects across run repetitions. Portin et al. (1998) reported no difference between left and right visual field stimulation, and consistent with this we find no dependence on ipsilateral-to-contralateral bias in our V6 activations. A notable difference, however, is evident between the follow-up study and our clear demonstration of higher parieto-occipital activity for upper field quadrant stimulation. Portin et al. (1999) reported that the parieto-occipital responses were similar to lower and upper field stimuli.

The stronger occipital signals with lower visual field, in combination with the significant increase of amplitude over parietal areas, and the additional sources found in the occipital dorsal direction with upper visual field stimulation add to a number of neurophysiological findings about the vertical hemifields. It has been suggested that upper and lower visual field have different functional roles. The best-known functional difference comes from behavioral data on reaction time performance. Shorter reaction times to visual stimuli occur when stimuli are presented in the lower hemifield. Visual detection/discrimination tasks were better performed when presented in the lower than in the upper visual field (Skrandies, 1987). Recently, Rubin et al. (1996) showed a greater tendency to perceive illusory contours in the lower visual field.

## **Ecological and Evolutionary Plausibility**

Ecological and evolutionary interpretations of observed function rely necessarily on some speculation, but they can provide an alternative way of looking at the data. In any case it is at least of some theoretical interest to ponder why functional characteristics have survived in an organism. We recall here some evolutionary arguments voiced before and augment them a little in the light of our findings. Skrandies (1987) has conducted a series of experiments addressing the question of possible electrophysiological and functional differences in the processing of information in the human upper and lower visual field. His findings support a functional superiority in the lower visual field. Previc (1990), in his theoretical review, supports an increased functional specialization in the human upper and lower visual field: processing in the lower visual field developed according to task performance in peripersonal (near) visual space, while upper visual field developed according to task performance in extrapersonal (far) visual space. Both of these studies attribute the origin of the specialization to the adaptation of the human visual system to the environment in which we live.

In the spirit of these reports we also speculate on what new resources the extrastriate activations we have identified may add to the elementary visual processing already available in the striate region. In the upper visual field, falling objects or missiles, flying enemies, or a branch as one runs through the forest can appear suddenly in unpredictable locations. Many such encounters are threatening and demand fast evasive action at the expense of immediate detailed analysis of the visual input to extract form, texture, and object identity. The less rigid representation in V1, coupled to increased activations in V5, is consistent with this scenario. The parietal cortex and the visual "dorsal stream" add to the processing of spatial relationships and "where" information. The V6 activation may also relate to rapid allocation of attention to the general visual field suddenly activated by a moving object. The efficiency of the upper visual field for distant targets and visual search has been demonstrated in experiments using stimuli with crossed/uncrossed disparities (Breitmeyer et al., 1975) and saccadic eye movement (Heywood and Churcher, 1980). For the lower visual field saliency can be associated with both detail and motion. As a human walks or runs upright looking ahead, an object on the ground occupies a slowly changing and largely predictable position in the lower visual field as it is approached. Threatening objects like predators or valuable items like food can be distinguished only after elaborate recognition work before action is taken. The stronger occipital responses could serve this increased need and account for the lower field advantage in many visual functions, as described above. Very often precise inspection of a visual scene must be coupled with detection of sudden movement by a camouflaged enemy, e.g., when a serpent on the ground makes a movement. The coupling of precise retinotopy in dorsal V1 with movement detection in V5 may serve these two tasks.

#### **CONCLUSION**

In summary, using a simple well-defined set of stimuli we have succeeded in generating a robust and reproducible N70m. The analysis of the N70m signal identified early consistent activity in V1, around 70 ms, consistent with the cruciform model. Strong but labile activity in V5 and V6 was identified at the same early latencies, very much in agreement with the expectations derived from studies in the monkey (Shroeder et al., 1998): "Early components not originating in V1 are most likely to arise from dorsal stream areas." We have also identified activations in the fusiform and lingual gyrus, which with the stimuli used in our study were weaker than the activations in V5 and V6, at least in terms of their effect on the MEG signal and the way they interfere with the dipole localization. More studies with stimuli designed to excite preferentially the ventral stream are also needed to determine all extrastriate areas that are activated around the N70m.

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