Spatial extent of coherent sensory-evoked cortical activity

Z-L. Lü and S.J. Williamson

Neuromagnetism Laboratory, Departments of Physics and Psychology, and Center for Neural Science, New York University, New York City, NY 10003, USA

Summary. Analysis of published values for the depth profile of evoked potentials in primary sensory cortex of cat and monkey provide a consistent estimate for the net current dipole moment per unit area of cortical surface. Comparison with values of the total current dipole moment obtained from neuromagnetic studies on human subjects indicates that coherent neuronal activity giving rise to long-latency sensory evoked components recorded in the human electroencephalogram or magnetoencephalogram extends over a cortical area that is typically ~ 40–400 mm^2.

Key words: Cerebral cortex – Current source-density – Sensory response – Extent of neuronal activity – Current dipole moment – Cat – Monkey

Introduction

Rapid progress has been made in the past decade to exploit magnetic and electric techniques for the purpose of providing quantitative information on sensory-related activity of the human cortex. For instance, it is possible by present neuromagnetic techniques to locate the center of auditory-evoked long-latency activity in cerebral cortex with a consistent accuracy of 3 mm (Yamamoto et al. 1988). Comparison with mathematical representations of stimulus-related functional sequences, such as the tonotopic (Romani et al. 1982) and amplitopic (Pantev et al. 1988) loci across auditory cortex, suggest that the precision is somewhat better. It is also possible to establish a quantitative measure for the strength of neuronal activity, by using a suitable model for the source. The simplest model is a current dipole whose magnetic field (or potential) pattern across the scalp best matches the measured pattern. The orientation of the model dipole when representing evoked activity of auditory, somatosensory,

or visual areas is generally perpendicular to the cortical surface, implying that the current it represents likely arises from currents of pyramidal cells.

However, at noise levels encountered in typical magnetic measurements, it is not possible to differentiate between magnetic field patterns generated by cortical sources of different spatial extent of activity unless the spread of activity is at least comparable to the distance to the nearest sensor – typically several centimeters (Okada 1985). The extent of cortical involvement is an important issue when considering possible models for neural networks that would account for observed signals. Consider that the just-noticeable difference for pitch in human auditory studies corresponds to a shift of the center of activity by ~ 10 μm along the tonotopic axis, and the just-noticeable difference for loudness to a shift of ~ 100 μm along the (approximately orthogonal) amplitopic axis. Then if cortical response strengths were determined experimentally to correspond to an active cortical area on the order of 1 cm^2, it would be unrealistic to interpret the psychophysical measures as reflecting a columnar organization, with activity limited to the column of best frequency and amplitude. Instead, neuronal populations responding to distinguishable frequencies or intensities must be largely overlapping across cortex.

As a first step toward determining the spatial extent of evoked cortical activity, we have utilized data on current source-density analyses in the somatosensory cortex of macaque monkey to determine the corresponding current-dipole moment that characterizes the activity underlying 1 mm^2 of cortical surface during moments of peak activity. A similar analysis was carried out with published data on visual cortex of the cat. The close correspondence in results prompts us to report these values as a first step toward establishing a quantitative relationship in higher mammals between physiological activity of sensory cortex and macroscopic measures provided by the electroencephalogram (EEG) and magnetoencephalogram (MEG). We also suggest that this measure of cortical activity may well characterize human sensory functions as well.

Method

We have analyzed electric potential data obtained by other researchers who employed arrays of microelectrodes extending through the depth of sensory cortex of two animal species – the cat and macaque monkey. For latencies of peak response we compute the net current-dipole moment per square millimeter of cortical surface area. Comparing this with observed values for the total current-dipole moment obtained from neuromagnetic studies of human subjects, we estimate the corresponding area of human cortex that overlies the observed coherent neuronal responses. An earlier study by Okada (Okada 1989) of the neuromagnetic field evoked by electrical stimulation of cells in a slice of turtle cerebellum in vitro provides an example where excellent quantitative agreement with only 20% discrepancy is obtained between intracortical potential measurements and the external magnetic field strength on the basis of present theory.

As material we have chosen recent electrophysiological studies of sensory evoked activity of cerebral cortex that characterize with comparatively fine resolution the current source density (CSD) at various depths. The data are those of Mitzdorf (1987) for visual cortex of cat, Mitzdorf and Singer (1979) for visual cortex of macaque monkey, and Cauller and Kulics (1990) for somatosensory cortex of macaque monkey. We shall describe our method by reference to the data of Mitzdorf (1987) obtained in penetrations through visual areas 17 and 18 in cat, which are representative of many close inspections of several thousand CSD profiles. Several stimuli were employed. One was a double reversal of a grating with spatial frequency of 0.5 cycle/deg, presentation time of 100 ms, and

interstimulus interval of 1200 ms. Figure 1a illustrates the depth dependence of the observed field potentials at long latencies recorded at 150 µm intervals within area 17. The corresponding depth profile of the current source-density is shown in Figure 1b. These traces represent the density of current appearing in the extracellular space from the intracellular medium at the indicated depth, as given by the negative of the second derivative of the variation of extracellular potential with depth (Mitzdorf 1987). The methodology of current source-density analysis has been described elsewhere (e.g., Nicholson and Freeman 1975) and will not be reviewed here.

For simple geometries, the predominant source of extracranial magnetic field is the *intracellular* current, as evidenced by the relative polarities of sensory evoked potentials and magnetic fields (Hari et al. 1980) and studies of isolated nerve preparations (Wikswo et al. 1980, Swinney and Wikswo 1980, Plonsey 1981, Roth and Wikswo 1985). The intracellular current flows in the opposite direction to that of the extracellular current. Since the distribution of current source-density was nearly invarient parallel to the laminae, we computed the intracellular current per unit area of cortical surface flowing perpendicular to the laminae at each depth (illustrated in Fig. 1c) by reversing the sign of the current source density, integrating it from the most superficial electrode to the deepest electrode, and multiplying by the conductivity of the medium for translaminar current flow.[1] The net current-dipole moment-density, expressed as the current-dipole moment per square millimeter of

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[1] We used the value $0.5\,\Omega^{-1}m^{-1}$ for the conductivity, which is established with an uncertainty or about ±15% as reported by Hoeltzell and Dykes (1979)
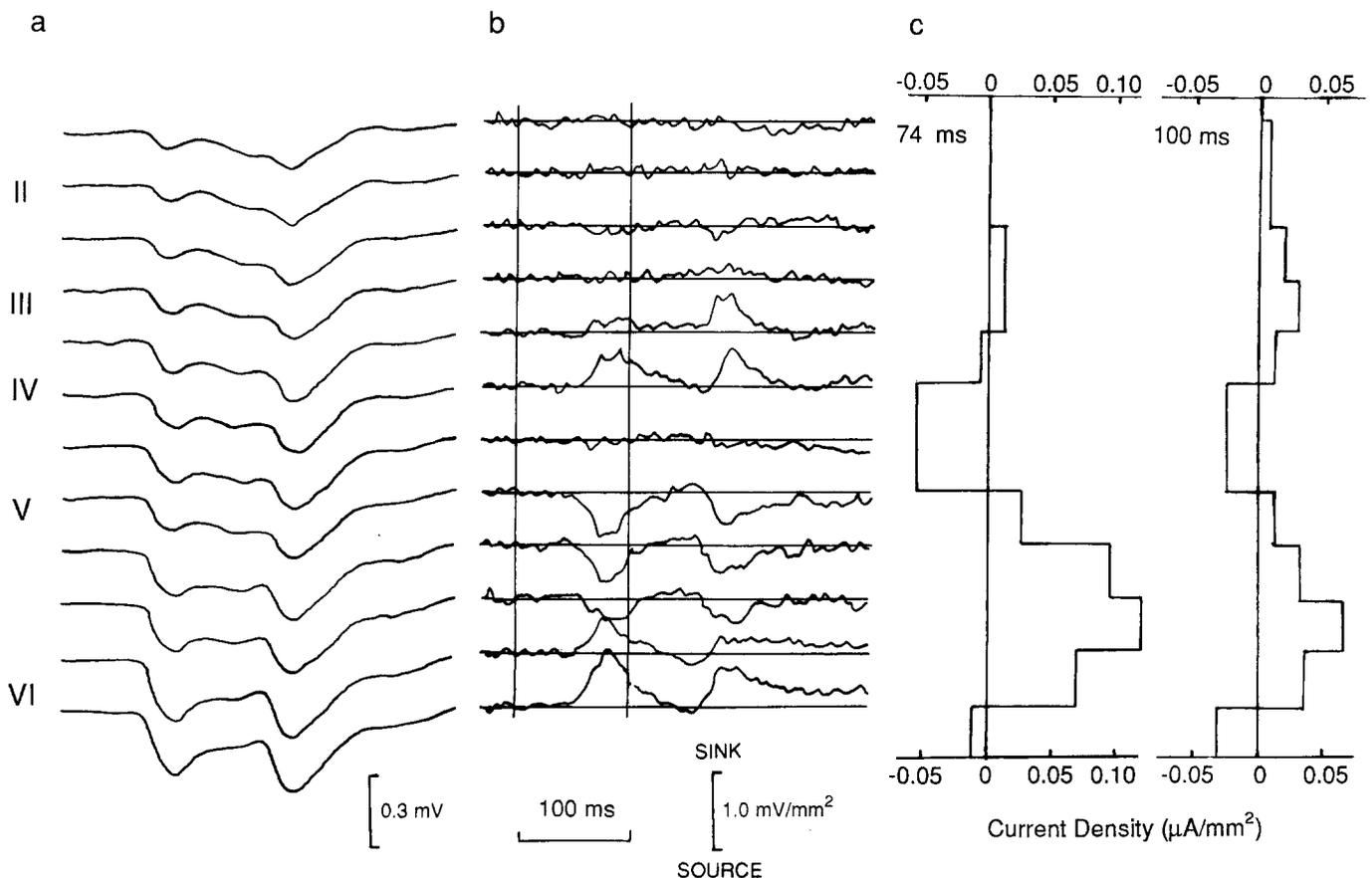

Fig. 1. a Field potential measurements shown for 150 µm depth intervals in visual area 17 of cat in a cortical area responding to a double reversal of a grating, with receptive field within the central 3 deg, and **b** computed current source density profiles in the *extracellular* medium where sinks are indicated by upward deflection, with times of pattern reversal denoted by the two vertical lines (adapted from Mitzdorf 1987). **c** Computed profile for the translaminar *intracellular* current density, averaged over 150 µm depth intervals for responses at 74 and 100 ms. Integration of current source-density was from surface of cortex to depth, with positive sign indicating current directed toward the surface

cortical surface area, was obtained by integrating this intracellular current density over the same path. As a measure of control, we computed the total current entering the intracellular space and compared it with the total current that leaves, both per unit area of cortical surface. With ideal data and accurate analysis, the two should be equal. The ratio of their difference to the average of the two values is called the "current imbalance", and this value when expressed as a percentage serves as a measure of error in the procedure. Table 1 lists representative values in the third column. The effect of current imbalance on the deduced current-dipole moment-density is obtained by comparing the results of computing the values of the latter in two ways: integrating into the depth of cortex and by integrating from the bottom to the superficial layer. These respective values are shown in the fourth column.[2]

The effects of boundaries separating media of differing electrical conductivity may also contribute to the magnetic field outside the scalp. One such "secondary source" is where the pattern of extracellular current of a neuron is perturbed near the outer surface of its membrane. This has the effect of enhancing the field produced by the intracellular current and has been considered by Okada (1989) in studies of a slice of turtle cerebellum in vitro. As this effect appears to provide only a $\sim 10\%$ contribution to the observed field, it will be neglected in our future considerations. Another secondary source is the pial membrane covering the cortical surface. Because the electrical conductivity of cortex is less than that of cerebrospinal fluid outside the membrane, there is a net secondary current source distribution along the membrane pointing in the same direction as the cortical dipole moment. This effect may indeed be very large and produce a field that is comparable to that of intracellular currents, as evidenced by their studies of cerebellar tissue in a bath of physiological saline. However, for cortical sources in sulci and fissures this contribution will be cancelled by an oppositely directed secondary source in the facing sulcal wall (Huang et al. 1990) and therefore need not be considered further.

The present analysis will not distinguish between different cell populations in cortex that contribute to the dipole moment, for instance pyramidal cells of overlapping dendritic trees whose call bodies lie in different cortical layers. In the following analysis we shall consider only the total intracellular current at each depth of cortex. However, we should note that comparisons of extracranial magnetic fields with current source-density profiles during direct electrical stimulation of cortex of rat provide a means of identifying separate contributions (Barth and Sutherling 1988).

Results

Three sets of current source-density measurements were analyzed. The first to be described are the data of Mitzdorf (1987) for visual areas 17 and 18 of cat. Data for visual area 17 shown in Fig. la display three strong components with latencies of about 76, 152, and 228 msec. The most likely reason for obtaining large non-zero values of current imbalance for two of these components, as well as for several other components given in Table 1, is that the array of electrode positions did not properly sample all neuronal sources or sinks, particularly in superficial layers. In addition, typical length constants describing the variation of intracellular current along dendritic branches into the depth of cortex are

[2] A simpler procedure to determine the current-dipole moment-density from the depth dependence of the field potential is to compute the difference in potential between depth and surface and multiply it by the translaminar conductivity. However, this method does not provide a measure of the effect or inaccuracies, unlike the present procedure

about 100 μm, which implies that electrode spacings greater than this will miss details in the transcortical potential profile. This problem is accentuated when the current source-density is computed by taking the second spatial derivative of the profile. Other complications may arise from the influence of efferent and afferent fibres on the local conductivity, but there is no gauge as yet for the magnitude of this effect.

Numerical values for the computed current-dipole moment-density are summarized in the right-hand column of Table 1 for a variety of responses of cat to visual grating stimuli. The units for current-dipole moment-density are expressed as picoampere-meter per square millimeter of cortical surface $(pA \cdot m/mm^2)$.

It is noteworthy that markedly greater current-dipole moment-densities may be obtained for direct electrical stimulation. We have analyzed data of Mitzdorf and Singer (1979) on the macaque monkey where electrical stimulation was applied to the optic chiasm. Table 2 shows that the corresponding current-dipole moment-

Table 1. Visually evoked responses in the visual cortex of cat. In the right-hand column, the first value for the current-dipole moment-density is obtained by integrating the deduced intracellular current from the most superficial electrode to the deepest and the second value by integrating in the opposite direction. Positive values indicate moment directed toward cortical surface. Analysis of data of Mitzdorf (1987)

Stimulus	Latency (ms)	Current imbalance (%)	Dipole moment per unit area $(pA \cdot m/mm^2)$	
			Down ward	Upward
Movement	76	15	96	67
of grating[a]	152	32	− 104	− 48
(Area 17)	228	42	118	24
Movement	141	21	72	37
of grating[b]	193	24	57	38
(Area 17)	259	14	76	49
Double	74	9	35	17
reversal of	100	28	− 44	− 12
grating[c]	183	50	51	− 51
(Area 17)				
Appearance	80	16	34	74
of grating[d]	100	− 30	113	47
(Area 18)	160	17	75	26
	200	0	25	25
Appearance	100	− 10	81	54
of grating[e]	500	25	140	62
(Area 18)	560	2	25	31

[a] Receptive field within the central 3 deg for movement (at 13 deg/s) of a rectangular grating (40 × 50 deg) with spatial frequency of 0.2 cycle/deg
[b] As in (a) but for a circular grating of 12 deg diameter
[c] Receptive field within the central 3 deg for double reversal, with 100 ms interval, of a grating with spatial frequency of 0.5 cycle/deg
[d] Receptive field 12 deg eccentric to appearance of a large-area grating (72 deg) of spatial frequency 0.1 cycle/deg at constant average luminance
[e] As in (d) but sparing a region of 22 deg in diameter around the receptive field

Table 2. Electrically evoked responses in visual cortex of monkey. Positive values indicate moment directed toward cortical surface. Analysis of data of Mitzdorf and Singer (1979)

Stimulus	Latency (ms)	Dipole moment per unit area $(pA \cdot m/mm^2)$
Electrical stimulation	10	400
	12	-140
	14	390

density for a short-latency response is typically about 10 times greater than those for natural stimuli characterized in Table 1. How much of this difference may be attributed to differences between short-latency and long-latency characteristics remains to be determined.

We have also analyzed current source-density studies for the monkey obtained in somatosensory studies by Cauller and Kulics (1990). Measurements were reported for 200 µm intervals into the depth of cortex at the crown of the postcentral gyrus of two awake monkeys, with special care to ensure that the penetrations were perpendicular to the pial surface (to within 13°). This location corresponds to the projection of hand representations in somatosensory areas 1 and 2. Responses to separate mechanical and electrical stimulation of the receptive field center of the palm or finger were recorded. Figure 2a, b illustrates responses to mechanical stimulation of finger IV. Using these data we computed the percentage current imbalance as described previously for cat, by comparing the difference between the total source and total sink of intracellular current with the average of their absolute values. These imbalances are shown as a percentage in Table 3. Similarly we computed the translaminar intracellular current per unit area of cortical surface, as illustrated in Fig. 3c. Integrating through cortex downward and then upward provides two measures for the
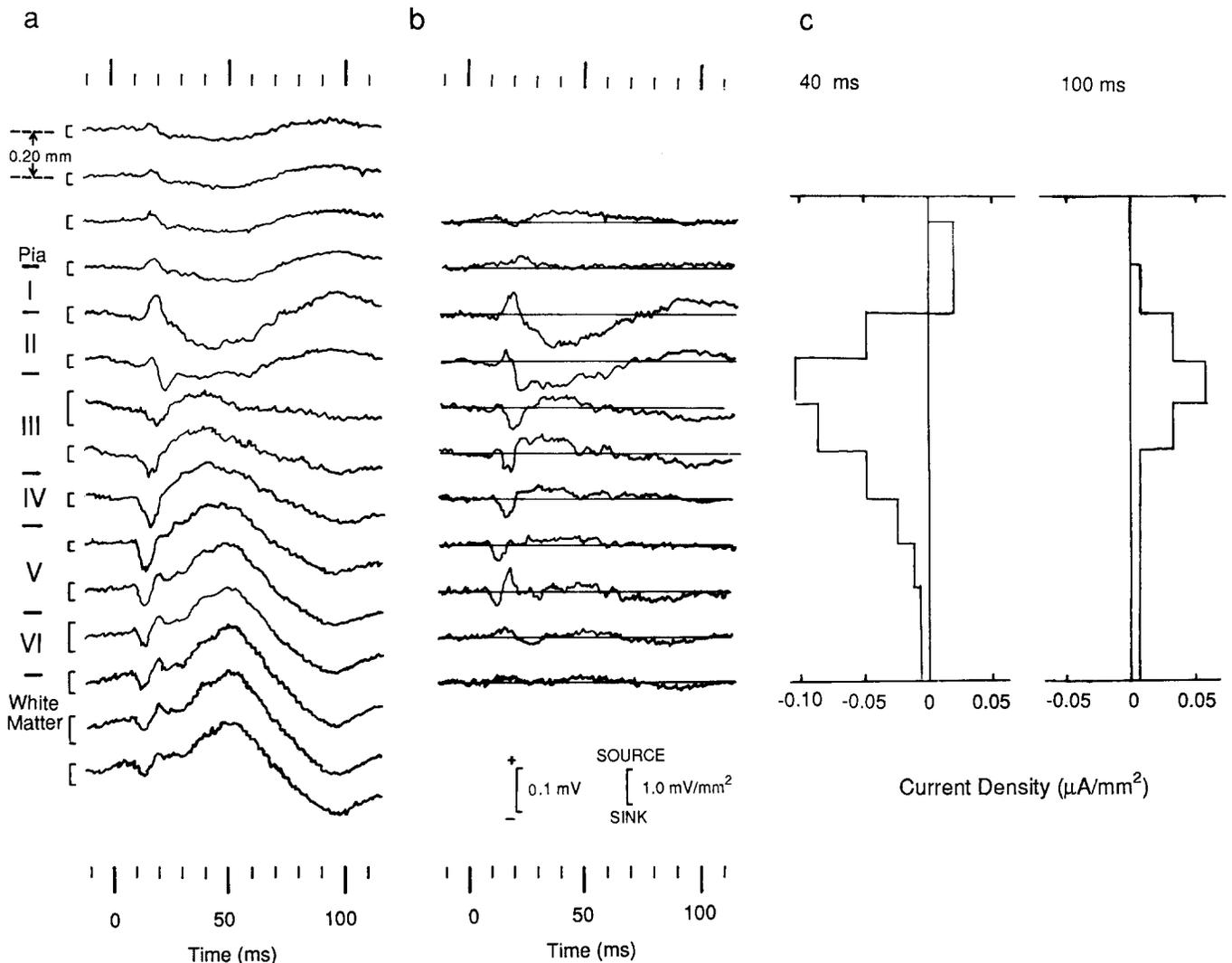

Fig. 2. a Field potential measurements at 200 µm depth intervals in somatosensory area SI of monkey, in response to mechanical stimulation of the receptive field center of finger IV, and **b** computed current source density profiles in the *extracellular* medium with sinks indicated by downward deflection (adapted from Cauller and Kulics 1990). **c** Computed profile for trans-laminar *intracellular* current density, for 40 and 100 ms latencies. Integration of current source-density was from surface of cortex to the depth, with positive sign indicating current directed toward the surface

Table 3. Somatosensory evoked responses in SI cortex of awake monkey. The first value for the dipole moment per unit area is obtained by integrating the deduced intracellular current from the most superficial electrode to the deepest and the second value by integrating in the opposite direction. Positive values indicate moment directed toward cortical surface. Analysis of data of Cauller and Kulics (1990)

Stimulus	Latency (ms)	Current imbalance (%)	Dipole moment per unit area $(pA \cdot m/mm^2)$	
			Down ward	Upward
Electrocutaneous	40	33	−36	−100
stimulation of thenar	50	12	−63	−108
eminence	100	17	30	91
Mechanical stimulation	40	17	−76	−121
of receptive fild center:	50	28	−74	−120
finger IV	100	10	36	22
Electrocutaneous	40	−8	−90	−74
stimulation of receptive	80	−40	20	45
field center:	100	40	−28	−54
tip of thumb				

current-dipole moment-density as summarized in the right-hand column of Table 3.

Discussion

The purpose of this analysis is to determine whether there is sufficient uniformity in the strength of sensory evoked, spatially coherent cortical activity in mammals to establish an estimate for a "typical" level of activity. Although the conclusions we shall draw are based on this limited set of data, the agreement we obtain across the two species and sensory modalities for long latency responses is sufficiently strong to suggest a more general applicability. A useful measure for activity is the current-dipole moment-density representing the integral of intracellular current through the thickness of cortex, per unit surface area. Variability in this measure may be expected, because the number of participating neurons could depend on the task required and also because response strength in sensory cortex, as measured by the total current dipole moment, is influenced by many factors such as attention (Curtis et al. 1988) and adaptation (Yamamoto et al. 1988).

Nevertheless, it is remarkable that despite these considerations, the limitations in the accuracy of our analysis, and the fact that data from different species and sensory modalities were included, all of the estimates in Tables 1 and 2 lie within a factor of ~ 2 of the value $50 \, pA \cdot m/mm^2$. We obtain a more reliable gauge if we restrict attention to those values that are established with highest confidence, viz. to those where the current imbalance is less than 25%. Confining attention to these in Table 1, we take for each condition and latency the average of values computed by integrating upward and downward through cortex. Then the average of the magnitudes across conditions and latencies is 53 $pA \cdot m/mm^2$

(S.D. = 28). This is remarkably close to the average obtained in the same way for the values in Table 3: 66 $pA \cdot m/mm^2$ (S.D. = 33). We conclude that a representative value for natural stimuli at suprathreshold levels could be taken as 50 $pA \cdot m/mm^2$ with an uncertainty of a factor of 2 above and below that value. Enhancement in strength by an order of magnitude is shown in Table 2 for short-latency responses to a stimulus that is not normally experienced, viz. electrical stimulation of white matter in the visual system of monkey.

We now argue that these values for long-latency responses may well be representative of sensory-evoked activity in human cerebral cortex, aside perhaps from the primary visual area. Our justification is the similarity of cell density for cat, macaque monkey, and human. Rockel et al. (1980) concluded that except for visual area 17 of primates there is a basic uniformity in cortical cell density across species. This conclusion was based on observations for a variety of species that about 110 neurons are found in a 30-μm-wide by 25-μm-length strip of cortex, from either motor, somatosensory, primary visual, frontal, parietal or temporal areas. About 75% of these cells are pyramidal cells. The only exception to the common neuron count of Rockel et al. occurred in the binocular region of area 17 in primates, where about 2.5 times more neurons were found than in other areas. The comparable level of evoked current-dipole moment-density that we deduce for macaque somatosensory cortex and cat visual areas 17 and 18 suggests further that the neuronal activity levels across these species are similar. We propose therefore that a typical value of 50 $pA \cdot m/mm^2$ is appropriate for the current-dipole moment-density of long latency components in human cortex as well. The actual value may well be $\sim 50\%$ greater than this estimate because of the greater thickness of human cortex. This comparative uniformity of cortical response across species may well be limited to stimuli well above threshold, where cortical response levels are insensitive to stimulus strength. When a stimulus is weakened, a level is reached where cortical response begins to decline, and the corresponding current-dipole moment-density may well be species and stimulus dependent. It is important to define these limits by future studies in other species, in primate visual areas where the cell density is higher, and in other sensory modalities. The prospect of establishing quantitative relationships between activity in animal preparations and non-invasive studies of humans should encourage continued development of current source-density techniques. In particular, attention must be devoted to solving the technical problems that appear in the present analysis as a large current imbalance between total intracellular sources and sinks for several temporal components.

Neuromagnetic studies of sensory evoked responses in human cortex reveal typical neuronal activity levels that correspond to a current-dipole moment in the range of 2–20 nA · m for middle and long-latency responses (for a recent conference proceedings, see Williamson et al. 1989). For the current-dipole moment-density just cited, these values correspond to cortical activation extending over a surface area in the range 40–400 mm². A reason-

able estimate for the smallest detectible area is ~10 mm², based on the weakest current dipole at a shallow depth that can be detected with the sensitivity of contemporary field sensors or electrodes. Since auditory, somatosensory, and visual cortical areas in human each comprise many square centimeters, MEG and EEG techniques are capable of monitoring comparatively confined cortical excitations.

However, even 10 mm² is a much larger area than certain length scales of organization in human cortex. One example is the 10 μm × 100 μm module that would be required to provide a columnar mosaic across the tonotopic and amplitopic surface of human auditory cortex, if the centers of contiguous columns are spaced by dimensions that are characteristic of just-noticeable differences in pitch and loudness. An important implication of this finding is that neuronal activity in human auditory cortex evoked by the onset of a tone burst is largely overlapping for these close-lying but distinguishable attributes of the stimulus.

It is of some interest to consider the prospect that activity could be observed in such a small region as a macrocolumn of visual cortex, with the dimension of about 800 μm × 800 μm (Mountcastle 1979). Unfortunately, such an area could produce a current dipole moment that is an order of magnitude too weak to be detected by present magnetic techniques. While the continuing development of magnetic sensors for human studies may ultimately provide this sensitivity, the first success is more likely to come in animal studies where the detection coil can be placed much closer to the neuronal source (Wikswo et al. 1989). A miniaturized sensing system with the detector only 1.5 mm from the exposed cortical surface is expected to provide this advantage (Buchanan et al. 1989).

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