

Human auditory primary and association cortex have differing lifetimes for activation traces

Zhong-Lin Lü, Samuel J. Williamson and Lloyd Kaufman

Neuromagnetism Laboratory, Departments of Physics and Psychology and Center for Neural Science, New York University, New York, NY 10003 (U.S.A.)

(Accepted 22 October 1991)

Key words: Cortical activation trace; Event-related field; Event-related potential; Habituation; Interstimulus interval; Magnetic source image

The magnetic field pattern over the temporal area of the scalp 100 ms following the onset of a tone burst stimulus provides evidence for neuronal activity in auditory primary and association cortices that overlap in time. Habituation studies indicate that onset and offset features of a tone produce activation traces in primary cortex that are at least partially common, but only the onset produces an appreciable trace in association cortex. The characteristic time constant for the decay of the latter's activation trace is several seconds longer than for the former.

Psychophysical studies of recognition memory for tone pitch provide evidence for a short-term component having a duration of about 2–5 s^{5,24}. Behavioral⁴ and electrophysiological investigations²² of auditory memory functions in animals provide evidence that similar short-term memory functions are served by sensory areas of cerebral cortex. We have exploited advantages of magnetic source imaging (MSI) to investigate the retention of stimulus-related information within areas of the primary and association auditory cortex. By measuring the accompanying magnetic field just outside the scalp it is possible to locate active populations of neuronal activity within the human brain². Such studies of sensory areas have provided evidence for functional organizations that are similar to those observed in electrophysiological studies of animal models, such as a tonotopic sequence across primary auditory cortex¹⁹. We report studies of the 100-ms component of the event-related field for tone-burst stimuli that reveal contributions from primary and association auditory cortex that habituate to different physical aspects of the stimuli. The two areas have different characteristic time constant, which vary considerably across individual subjects. The duration of the activation trace for these components may well reflect the period of time over which an event remains available for processing by working (short-term) memory, although the neural residue of the event need not actually be processed.

Four right-handed adult volunteers served as subjects

after providing informed consent. All of the studies were carried out within a magnetically shielded room with the subject comfortably reclined on his side. Bursts of a 1 kHz tone were presented by earphones with a constant interstimulus interval (ISI). They were generated by an Amiga 1000 computer and presented contralaterally via Etymotic Research type ER3-5A earphone, which produced no detectible magnetic artifact. The stimulus duration was 500 ms with a ramp of 12 ms for the onset and offset to enhance spectral purity. The intensity was estimated as 75 db SPL. The magnetic field associated with the response was measured by standard techniques³¹ with a neuromagnetometer probe consisting of an array of 5 sensors²⁹. With the probe placed at a measurement position over the scalp, the subject was presented with 200 epochs having a short ISI of 1.2 s and then 100 epochs involving a long ISI of 6 s. This was repeated in sequence with the probe moved to new locations until the field had been measured at 100–120 different positions over the lateral area of the scalp. The output signal of each sensor is bandpass filtered (0.1–100 Hz) and recorded by a computer. The average auditory evoked field time-locked to the stimulus onset was determined for each run, within a bandwidth of 0.5–20 Hz.

Isofield contours were computed to characterize the field pattern over the lateral scalp at a latency of 100 ms for two subjects, for both a short ISI condition of 1.2 s and long ISI condition of 6 s. Coordinates are specified in the PPN system²⁷. The origin is midway between the

periauricular points; the x -axis passes from the origin through the nasion; the z -axis is perpendicular to both x -axis and line between the periauricular points and passes from the origin dorsally to emerge near the vertex; and the y -axis is perpendicular to both x - and z -axes and passes from the origin outward through the left hemisphere near the ear canal.

In the short ISI condition (Fig. 1A), field extrema of opposite polarity were identified at the anterior temporal and parietal ends of the lateral sulcus, for all subjects. The field emerges from the scalp in the posterior region and enters in the anterior region, to encircle the neuronal source lying midway between. We denote this component as N100m, the 'm' indicating it is observed magnetically, and identify it with the classic 100-ms component of primary auditory cortex originating from neuronal activity on the superior temporal plane^{1,8,16}. The location and other parameters of the current dipole source best accounting for its field pattern for three representative subjects are listed in Table I.

Fig. 1B shows the contour map obtained at the moment of peak activity evoked by stimuli with the long ISI. Two features in this plot should be emphasized. (i) The pattern extends to the lower region of the plot near the ear canal where there is no evidence of the classic N100m component and where the latency at the moment of peak field is about 10 ms shorter than that of N100m. (ii) The amplitude of the posterior extremum in the long ISI condition is much greater than that displayed at the

anterior extremum. The field pattern can be explained if we assume that one field extremum of a second neuronal source overlaps that of N100m in the posterior region, and the other extremum lies near the ear. For convenience we shall refer to the contribution of this second source, which becomes significant only for long latencies with this paradigm, as the *latent* component and denote it by L100m. This terminology is based on the definition of latent as 'not apparent but capable of being expressed'.

Standard procedures were followed to locate the neuronal sources²⁸. The head was modeled by a sphere of uniform conductivity, placed at the center of curvature that describes the inner surface of the skull extending over an area of 5 cm diameter overlying the source, as determined from MRIs¹². With the position and orientation of the N100m dipole fixed, a subsequent 2-dipole fitting program was employed to deduce the L100m dipole. We assumed the N100m dipole's position and orientation remained unchanged and allowed the program to adjust only its strength and all 5 parameters of the L100m dipole. To obtain a second estimate for the parameters of both sources, the parameter values provided by the first fit were used as an initial estimate for the sources in a two-dipole fitting program, which adjusted the 10 parameters determining the positions and the orientations of both dipoles. The quality of the fit was gauged by computing the square of the correlation between the measured field at each position and the field predicted by the best fitting dipoles. The two procedures yielded results

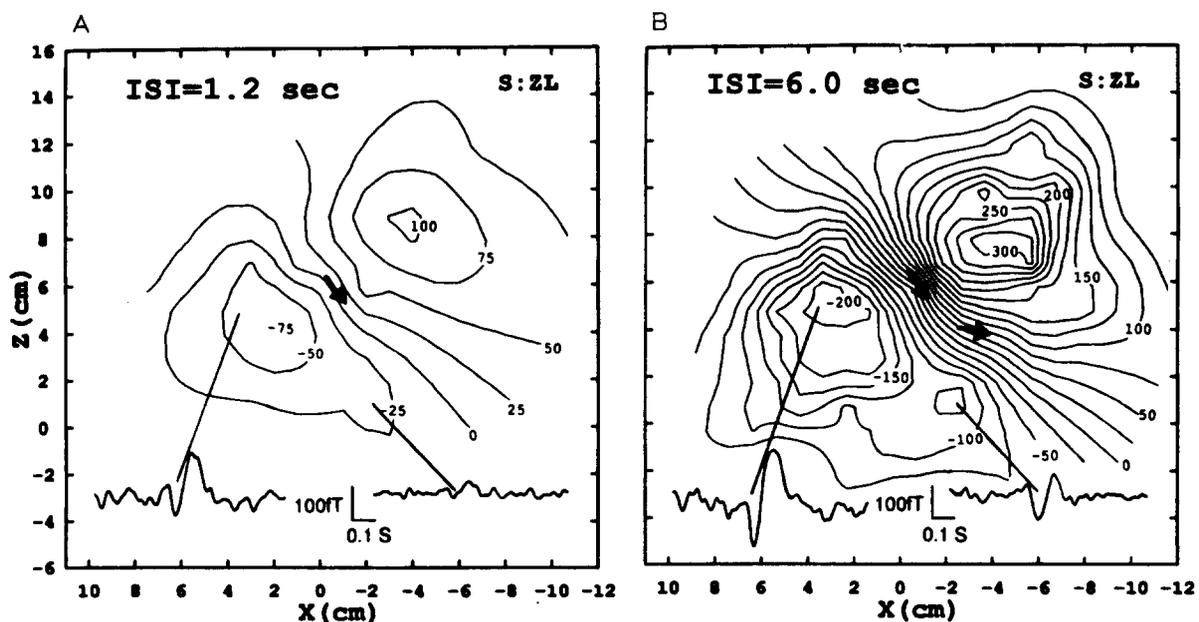


Fig. 1. Isofield contours for subject ZL characterizing the measured field pattern over the left hemisphere 100 ms following the onset of a tone burst stimulus. Arrows denote the direction of current dipole sources that account for each pattern, with their bases placed at the dipole's surface location. In the right panels, the upper arrow is the N100m source and the lower arrow is the L100m source. Insets illustrate response waveforms obtained at the indicated positions. Both waveforms also exhibit a 200 ms component.

that differ in placement of each source by only 4 mm.

The current dipole parameters describing the individual N100m and L100m neuronal sources are listed in Table I. Typically, the L100m dipole was found to lie about 2 cm inferior to that of the N100m dipole, as illustrated in the magnetic source image of Fig. 2. While dipole orientations and positions differ between hemispheres, their positions relative to cortical topography are similar. The location of N100m lies within primary auditory cortex, with intracellular current oriented perpendicular to the surface, as expected for postsynaptic responses of pyramidal cells. To our knowledge, neuronal activity giving rise to the L100m component has not previously been localized. Of the six candidate sources that may contribute to N100¹⁴, the closest to the L100m source is Tb of Wolpaw and Penry³⁰. However, this was thought to be radially oriented, whereas the L100m clearly has a strong tangential component.

The more inferior location of L100m places it within the auditory association cortex¹⁵, with activity extending into the supratemporal sulcus. Using 50 pA·m/mm² as an estimation for the current dipole moment per unit area of cortical surface¹³, we deduce the areas of cortical involvement producing N100m and L100m as about 200 mm² and 100 mm², respectively. If L100m has a strong radial component of intracellular current (not detected magnetically) its total area of activity will exceed this estimate.

The field patterns for individual dipoles revealed a lo-

cation on the scalp where the field has an appreciable contribution from only the N100m source (near the '-200' notation in Fig. 1B) and another location where it was produced by only the L100m source ('-100' in Fig. 1B). By placing the probe at one or the other location, the activity of an individual neuronal source could be monitored. In this way the ISI dependence of the strengths of N100m and L100m responses could be independently measured for the range of ISIs between 0.8 and 16 s for each subject.

It has long been known that the classic N100 of the event-related potential (ERP) measured at the vertex exhibits refractory properties, so that amplitudes diminish if stimuli are presented sufficiently soon after an identical preceding one^{8a,17}. However, these studies did not take account of the presence of L100m and so did not identify the separate contributions of responses having different habituation features. As illustrated in Fig. 3 for both hemispheres of 2 subjects, the amplitude of L100m reaches its asymptotic value at a much longer ISI than that of N100m. To obtain these data, several trials of from 50 to 200 stimuli each were presented with representative ISIs before each main recording session began, since animals studies^{6,7,25} revealed that habituation

TABLE I

Parameters describing the location x , y , z , orientation ψ , and strength Q of the current dipole best accounting for the field pattern of the indicated response component

Subject	Condition	x (cm)	y (cm)	z (cm)	ψ (degrees)	Q (nA·m)
ZL (Left)	N100m'	-0.9	6.3	6.2	-140	3.3
	N100m	-0.4	6.5	6.4	-143	9.8
	L100m	-2.50	6.6	4.4	-111	2.8
ZL (Right)	N100m'	-0.3	-6.7	6.0	145	4.4
	N100m	-0.2	-7.2	6.2	151	7.3
	L100m	1.0	-6.0	4.2	114	9.1
SW (left)	N100m'	0.8	4.3	5.4	-134	11.4
	N100m	1.2	5.2	5.9	-122	11.4
	L100m	-1.9	6.7	4.2	-94	2.3
WS (left)	N100m'	0.4	6.9	5.9	-168	2.3
	N100m	-0.4	6.6	6.0	-170	6.8
	L100m	-1.8	5.4	4.5	-175	5.3



Fig. 2. Deduced locations for neuronal sources that are responsible for N100m (upper arrow) and L100m (lower arrow), on sagittal MRIs of the left hemispheres of subject SW. Coordinates are expressed in the PPN system, with a distance of 1 cm between adjacent ticks on the axes. The base of each arrow indicates the respective positions, with the ellipse indicating the estimated range of uncertainty (95% confidence level), and the direction of each arrow specifies the flow of intracellular current. The N100m source lies within the lateral sulcus, and L100m source lies within 1 cm of the superior temporal sulcus.

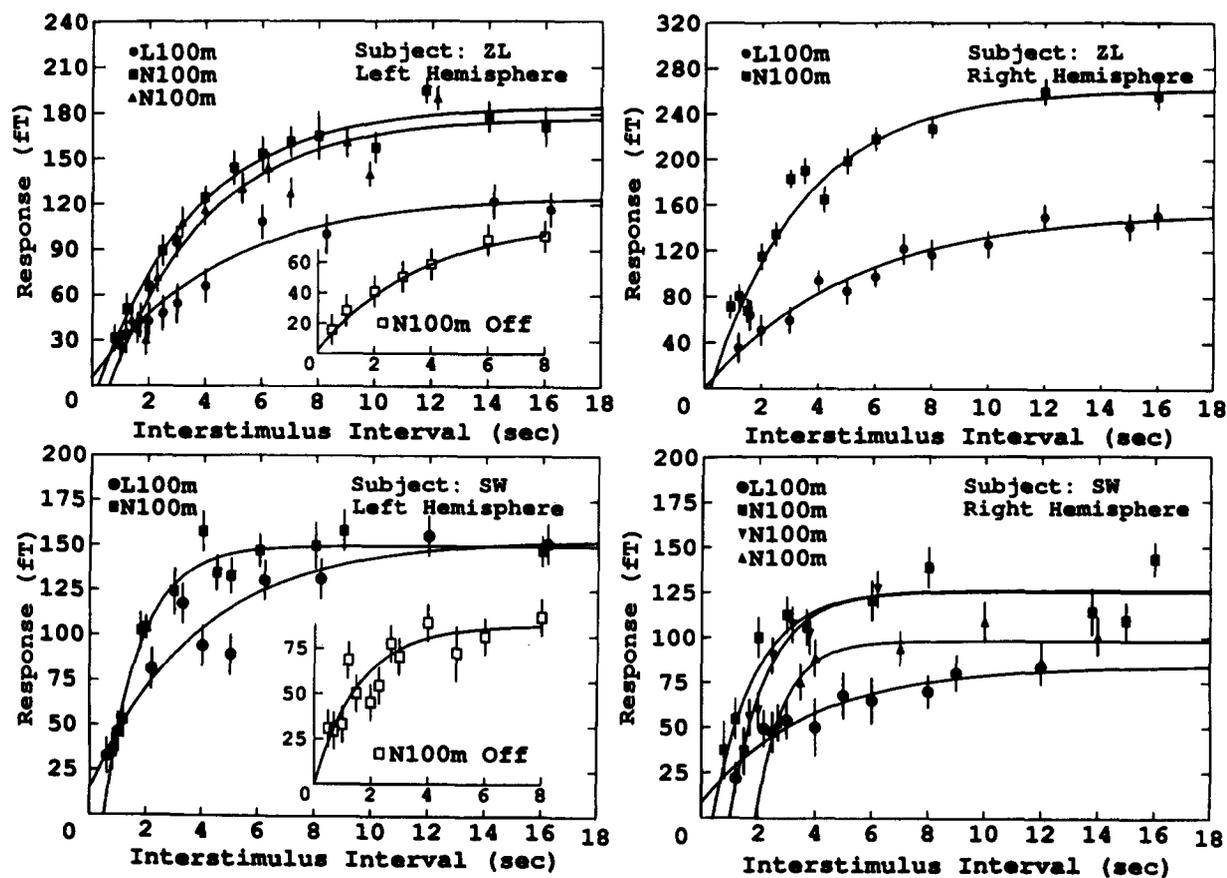


Fig. 3. Response amplitudes vs ISI over left and right hemispheres for 2 subjects, for tones of 0.5 s duration (N100m = squares; L100m = circles), 1.2 s (N100m = triangles), and 2 s (N100m = inverted triangles). Insets illustrate the dependence for the N100m offset response for tones of different duration indicated by the horizontal axis.

can extend for many minutes or even hours. With this preparation of the subject, stable results could be obtained consistently, both within a session and across sessions on different days.

Weak responses obtained with short ISIs is a characteristic of habituation. This has been demonstrated in studies of animal models where electrodes were placed directly on the auditory cortex^{3,10,20,26}. Subcortical as

TABLE II

Parameters for the expression $A(1 - e^{-(t-t_0)/\tau})$ that best fit the ISI dependence for the indicated onset response components and tone duration dependence for the offset component

Brackets indicate the durations, and parentheses indicate standard deviations.

Subject	Hemisphere	Condition	A (fT)	t_0 (s)	τ (s)
ZL	Left	L100m [0.5 s]	126 (0.9)	-0.2 (0.4)	5.0 (0.9)
		N100m [0.5 s]	185 (1.0)	0.2 (0.2)	3.5 (0.4)
		N100m [1.0 s]	178 (0.4)	0.6 (0.2)	3.5 (0.4)
ZL	Right	L100m [0.5 s]	155 (0.7)	0.0 (0.1)	5.2 (0.7)
		N100m [0.5 s]	262 (0.4)	0.0 (0.2)	3.3 (0.3)
SW	Left	L100m [0.5 s]	154 (0.5)	-0.4 (0.3)	3.9 (0.5)
		N100m [0.5 s]	150 (0.8)	0.5 (0.1)	1.3 (0.2)
SW	Right	L100m [0.5 s]	85 (1)	-0.4 (0.7)	3.8 (0.8)
		N100m [0.5 s]	126 (0.4)	0.4 (0.2)	1.5 (0.3)
		N100m [1.0 s]	126 (0.7)	1.0 (0.1)	1.3 (0.2)
		N100m [2.0 s]	98 (0.8)	1.9 (0.2)	1.0 (0.2)

well as cortical processes play important roles in habituation, as recently summarized by Weinberger²¹ although receptors do not^{11,23}. Such a decrement in response for repeated stimulation is but one of four characteristics of habituation. The other three are increments in response to: presentation of a different stimulus to demonstrate that the response to standards is not a result of a change in the subject's general state (called here 'elevated probe response'); presentation of the same stimulus following a period in which stimuli are withheld (spontaneous recovery); and presentation of the same stimulus following an inserted stimulus of a different type (dis-habituation). Therefore, responses were recorded and separately averaged for a probe stimulus one octave higher, when inserted between every 5th standard stimulus presented with a 1 s ISI. The probe stimuli evoked significantly higher averaged N100m and L100m responses than the preceding standards (elevated probe response). Moreover, the following standard evoked a stronger response than if the probe had not been present (dis-habituation). If trains of tones presented with 1.0 s ISI are separated by 5 s of silence, the averaged responses to the first stimulus of each train is significantly higher than for the others (spontaneous recovery). Therefore, the weak responses characterized in Fig. 3 meet the traditional criteria to be classified as examples of habituation.

We find in all cases that the effect of ISI on response amplitudes can be described adequately by the expression $A(1 - e^{-(t-t_0)/\tau})$, where the amplitude A , time constant τ , and time origin t_0 are fitting parameters. We emphasize that the *shape* of the curve in each case is determined by a single parameter τ . Table II summarizes the corresponding values of the time constants. Each subject's left and right hemisphere responses for a given component have essentially the same respective values. For a given subject, τ is significantly shorter for N100m than L100m. However, τ varies considerably across subjects, indicating marked inter-subject differences in habituation characteristics.

Another important feature of the fitted curves shown in Fig. 3 is the difference in time origins t_0 for N100m and L100m responses. The curves for L100m intersect the horizontal axis near the origin, which corresponds to the onset of the previous tone (the data are consistent with $t_0 = 0$ being the intercept). By contrast, the curves for N100m have their intercepts at the offset of the previous tone. Fig. 3 shows that t_0 is nearly equal to the tone duration. This difference in intercepts provides clear evidence that the N100m is primarily habituated by the offset of the preceding tone and L100m by the onset.

That the offset habituates the N100m onset to the following tone suggests there may be a reciprocal relationship, viz. that the onset of a tone habituates the offset response to the same tone. In support of this, Fig. 3 insets show how the offset amplitude increases with tone duration (with a fixed silent period of 500 ms separating tones). The dependence is identical to the increase in amplitude of the onset N100m with increasing ISI, for tones of short duration. The time constants differ by less than 0.3 s for each subject.

One natural interpretation of the present results is to consider the difference between the maximum response at very long ISI and the observed response at any shorter ISI as a measure for the existing level of the neuronal activation trace that was established by responses to previous stimuli and need not be further reactivated¹⁸. Our data indicate that an adequate empirical description of this difference has the form of a decaying exponential $Ae^{-(t-t_0)/\tau}$, where $(t - t_0)$ is the elapsed time since the last activation and the parameter τ is the lifetime. When these notions are applied to the habituation characterized by our data, we may infer the decay of the cortical activation trace for L100m commences near the onset of the tone stimulus. This suggests that information processing in the corresponding region of association cortex emphasizes the initial features of the stimulus. By contrast, decay of the activation trace for N100m commences after the onset and again after the offset. This suggests that the activation trace associated with the offset N100m is similar to that for the onset N100m, and both are related to activity in primary cortex. Indeed, Hari et al.⁹ have shown that both onset and offset N100m responses detected magnetically are in primary cortex, although the center of neuronal activity for the offset on the average is about 7 mm anterior to the onset.

The present study provides evidence that decay of the activation trace in each cortical area can be characterized empirically by a single lifetime for the class of stimuli employed. This is undoubtedly an oversimplification for describing the details of the relevant physiological processes, for τ characterizes only the rate-limiting step. Moreover, it is reasonable to expect that the lifetime may well depend on certain physical aspects of a sound.

This research was supported in part by Grants F49620-88-K-0004 and AFOSR-90-0221 from the Air Force Office of Scientific Research and by support from Silicon Graphics, Incorporated. We thank N. Chase for support in the MR studies, J. Stephenson for assistance in recording them, D. Karron for contributions in developing computer analyses of MR images, J.-Z. Wang for help with computer systems, E. Vitale for assistance with the experiments, and A. Fregly for helpful encouragement.

- 1 Bak, C., Kofoed, B., Lebech, J., Saermark, K. and Elberling, C., Auditory evoked magnetic fields from the human brain. Source localization in a single-dipole approximation, *Phys. Lett.*, 82A (1981) 57–60.
- 2 Brenner, D., Lipton, J., Kaufman, L. and Williamson, S.J., Somatically evoked magnetic fields of the human brain, *Science*, 199 (1978) 81–83.
- 3 Buchwald, J.S. and Humphrey, G.L., An analysis of habituation in the specific sensory systems. In Stellar, E. and Sprague, J.M. (Eds.), *Progress in Physiological Psychology*, Academic Press, New York, 1973, pp. 1–75.
- 4 Colombo, M., D'Amato, M.R., Rodman, H.R. and Gross, C.G., Auditory association cortex lesions impair auditory short-term memory in monkeys, *Science*, 247 (1990) 336–338.
- 5 Crowder, R.G., *Principles of Learning and Memory*, Erlbaum, Hillsdale, 1976.
- 6 Gerken, G.M. and Neff, W.D., Experimental procedures affecting evoked responses recorded from auditory cortex, *Electroencephalogr. Clin. Neurophysiol.*, 15 (1963) 947–957.
- 7 Hall, R.D., Habituation of evoked potentials in the rat under conditions of behavioral control, *Electroencephalogr. Clin. Neurophysiol.*, 24 (1968) 155–165.
- 8 Hari, R., Aittoniemi, K., Järvinen, M.-L., Katila, T. and Varpula, T., Auditory evoked transient and sustained magnetic fields of the human brain: localization of neural generators, *Exp. Brain Res.*, 40 (1980) 237–240.
- 8a Hari, R., Kaila, K., Katila, T., Tuomisto, T. and Varpula, T., Interstimulus interval dependence of the auditory vertex response and its magnetic counterpart: implications for their neural generation, *Electroenceph. Clin. Neurophysiol.*, 54 (1982) 561–569.
- 9 Hari, R., Pelizzone, M., Mäkelä, J.P., Hällström, J., Leinonen, L. and Lounasmaa, O.V., Neuromagnetic responses of the human auditory cortex to on- and offsets of noise bursts, *Audiology*, 26 (1987) 31–43.
- 10 Horn, G., Physiological and psychological aspects of selective perception. In D.S. Lehrman et al. (Eds.), *Advances in the Study of Behavior*, Academic Press, New York, 1965, pp. 155–216.
- 11 Horvath, R.S., Variability of cortical auditory response, *J. Neurophysiol.*, 32 (1969) 1056–1063.
- 12 Karron, D., Lü, Z.-L. and Williamson, S.J., submitted.
- 13 Lü, Z.-L. and Williamson, S.J., Spatial extent of coherent sensory-evoked cortical activity, *Exp. Brain Res.*, 84 (1991) 411–416.
- 14 Näätänen, R. and Picton, T., The N1 wave of the human electric and magnetic response to sound, *Psychophysiology*, 24 (1987) 375–425.
- 15 Pandya, D.N. and Seltzer, B., Association areas of the cerebral cortex, *Trends Neurosci.*, (1982) 386–390.
- 16 Pantev, C., Hoke, M., Lehnertz, K., Lütkenhöner, B., Anogianakis, G. and Wittkowski, W., Tonotopic organization of the human auditory cortex revealed by transient auditory evoked magnetic fields, *Electroencephalogr. Clin. Neurophysiol.*, 69 (1988) 160–170.
- 17 Picton, T.W., Hillyard, S.A. and Galambos, R., Habituation and attention in the auditory system. In Keidel, W.D. and Neff, W.D. (Eds.), *Handbook of Sensory Physiology, Vol. 5. Auditory System. Clinical and Special Topics*, Springer-Verlag, Berlin, 1976, pp. 343–389.
- 18 Picton, T.W., Woods, D.L. and Proulx, G.B., Human auditory sustained potentials. I. The nature of the response, *Electroencephalogr. Clin. Neurophysiol.*, 45 (1978) 186–197.
- 19 Romani, G.L., Williamson, S.J., Kaufman, L. and Brenner, D., Characterization of the human auditory cortex by the neuromagnetic method, *Exp. Brain Res.*, 47 (1982) 381–393.
- 20 Thompson, R.F. and Spencer, W.A., Habituation: a model phenomenon for the study of neuronal substrates of behavior, *Psychol. Rev.*, 73 (1966) 16–43.
- 21 Weinberger, N.M., Ashe, J.H., Metherate, R., McKenna, T.M., Diamond, D.M. and Bakin, J., Retuning auditory cortex by learning: a preliminary model of receptive field plasticity, *Concepts Neurosci.*, 1 (1990) 91–132.
- 22 Weinberger, N.M. and Diamond, D.M., Physiological plasticity in auditory cortex: rapid induction by learning, *Prog. Neurobiol.*, 29 (1987) 1–55.
- 23 Westenberg, I.S., Paige, G., Golub, B. and Weinberger, N.M., Evoked potential decrements in auditory cortex. I. Discretized and continual stimulation, *Electroencephalogr. Clin. Neurophysiol.*, 40 (1976) 337–355.
- 24 Wickelgren, W.A., Associative strength theory of recognition memory for pitch, *J. Math. Psychol.*, 6 (1969) 13–61.
- 25 Wickelgren, W.A., Auditory or articulatory coding in verbal short-term memory, *Psychol. Rev.*, 76 (1969) 232–235.
- 26 Wickelgren, W.O., Effect of acoustic habituation on click-evoked responses in cats, *J. Neurophysiol.*, 31 (1968) 777–785.
- 27 Williamson, S.J. and Kaufman, L., Advances in neuromagnetic instrumentation and studies of spontaneous brain activity, *Brain Topography*, 2 (1989) 129–139.
- 28 Williamson, S.J. and Kaufman, L., Analysis of neuromagnetic signals. In Gevins, A.S. and Rémond, A. (Eds.), *Methods of Analysis of Brain Electrical and Magnetic Signals*, Elsevier, Amsterdam, 1987, pp. 405–448.
- 29 Williamson, S.J., Pelizzone, M., Okada, Y., Kaufman, L., Crum, D.B. and Marsden, J.R., Magnetoencephalography with an array of SQUID sensors. In Collan, H., Berglund, P. and Krusius, M. (Eds.), *ICEC10: Proc. Tenth International Cryogenic Engineering Conference*, Butterworth, Guildford, England, 1984, pp. 339–348.
- 30 Wolpaw, J.R. and Penry, J.K., A temporal component of the auditory evoked response, *Electroencephalogr. Clin. Neurophysiol.*, 39 (1975) 609–620.
- 31 Yamamoto, T., Williamson, S.J., Kaufman, L., Nicholson, C. and Llinás, R., Magnetic localization of neuronal activity in the human brain, *Proc. Natl. Acad. Sci. U.S.A.*, 85 (1988) 8732–8736.