Interactive Processing of Sensory Input and Motor Output in the Human Hippocampus

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Abstract

■ Recent studies of visuomotor integration suggest that the motor system may be intimately involved in the detection of salient features of the sensory scene. The final stages of sensory processing occur in hippocampal structures. We measured human neuromagnetic responses during motor reaction to an auditory cue embedded in high-speed multimodal stimulation. Our results demonstrate that large-scale cognitive networks may recruit additional resources from the hippocampus during sensorimotor integration. Hippocampal activity from 300 msec before to 200 msec after cued movements was enhanced significantly over that observed during self-paced movements. The dominant hippocampal activity appeared equally synchronized to both sensory input and motor output, consistent with timing by an intrinsic mechanism, possibly provided by ongoing theta oscillations. ■

INTRODUCTION

A widely held view of brain organization is that the motor system is activated only after the immediate sensory scene is fully elaborated in sensory networks. However, recent studies of visuomotor integration suggest that the motor system may be intimately involved in the detection of relevant features of the sensory scene (cf. Churchland, Ramachandran, & Sejnowski, 1994). The final stages of sensory processing involved in memory encoding (Mesulam, 1990; Squire & Zola-Morgan, 1991) and novelty detection (Knight, 1996) occur in hippocampal structures. We suggest that large-scale cognitive networks also may recruit additional resources from the hippocampus during sensorimotor integration in humans.

Hippocampus and cortico-hippocampal networks have been traditionally associated with memory encoding (Scoville & Milner, 1957; Mishkin, 1978; Zola-Morgan, Squire, Amaral, & Suzuki, 1989; Squire, 1992). The foremost function of reciprocal cortico-hippocampal connections is believed to be the rapid and accurate exchange of information between sensory cortical areas and hippocampal structures for the encoding of memory traces (Rolls, 1989; Squire, 1992; Vinogradova, 1975) and possibly for the immediate comparison of novel input with stored traces (Knight, 1996). Hippocampal structures thus participate in the selection of pertinent information that needs to be held "on line" during the temporal interval required for a decision or for the performance of an operation, that is, to working memory (Baddeley, 1992; Goldman-Rakic, 1989). In everyday life, these functions are exercised during, and often form an inseparable part of, goal-directed motor activity.

The timing of the attentional enhancement of hippocampal neuronal population responses has been evaluated in humans by depth electrode recordings performed on neurological patients (Halgren, Squires, & Wilson, 1980; McCarthy, Wood, Williamson, & Spencer, 1989) and by magnetoencephalographic (MEG) studies performed on normal subjects (Okada, Kaufman, & Williamson, 1983; Nishitani, Nagamine, Fujiwara, Yazawa, & Shibasaki, 1998; Tesche, Karhu, & Tissari, 1996). Event-related potentials (ERPs) and fields (ERFs) have been observed in the medial temporal lobe to attended infrequent deviants embedded in trains of standard stimuli. Results include task-dependent ERPs and ERFs at peak latencies of 300 to 600 msec following auditory, visual, and somatosensory oddballs. However, the dynamic interactions between motor networks and hippocampal structures are poorly known.

RESULTS

We monitored sensory and movement-related MEG responses in normal adults to determine the extent of on-line hippocampal participation in a demanding goal-directed task. Subjects were presented with infrequent

auditory and visual deviants embedded in trains of rapidly presented standard stimuli. They performed either a self-paced or an oddball-cued motor action following instruction given at the beginning of the stimulus block. The cued movements required sustained attention to the stimuli, a task that is known to activate hippocampal areas (Pardo, Fox, & Raichle, 1991).

Figures 1 and 2 show examples of MEG evoked-response data recorded during movement cued by the auditory oddball stimuli. Responses recorded during a single stimulus block were averaged on-line time-locked to the oddball cue (cf. Figure 1) and to the motor response by the right hand (cf. Figure 2). The magnetic field pattern at the scalp receives contributions both from "primary" current flow, generated predominantly by postsynaptic activity in dendritic processes, and also from subsequent passive, or "secondary," current flow within the conducting volume of the brain (for a review, cf. Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). Synchronization of activity is essential: Population responses involving tens of thousands of neurons are believed to be required to generate typical cortical-evoked magnetic responses (Hämäläinen et al., 1993).

A planar-gradiometer detector in our MEG array is quite sensitive to primary neuronal current that flows in the fissural cortex directly beneath the sensor. Responses at 100 to 200 msec following the auditory oddball cues are most prominent in sensors clustered over the sylvian fissure (cf. Figure 1B and F). Responses synchronized with the movement, including both pre- and postmovement deflections, are largest in waveforms recorded by detectors located over the rolandic fissure (cf. Figure 2C). However, each sensor in the MEG array records a weighted sum of magnetic signals that are produced by all primary generators within both cortical and subcortical areas and by the corresponding secondary currents. The activation of multiple neuronal populations with varying time courses is reflected in the remarkable complexity of the MEG waveforms recorded by individual sensors in our whole-scalp array.

Unmasking Internally Synchronized Responses

We exploit random stimulus presentation to unmask internally synchronized responses from those time-locked predominantly with either stimulus presentation or motor response. Both the order of presentation and the interstimulus intervals of the auditory and visual
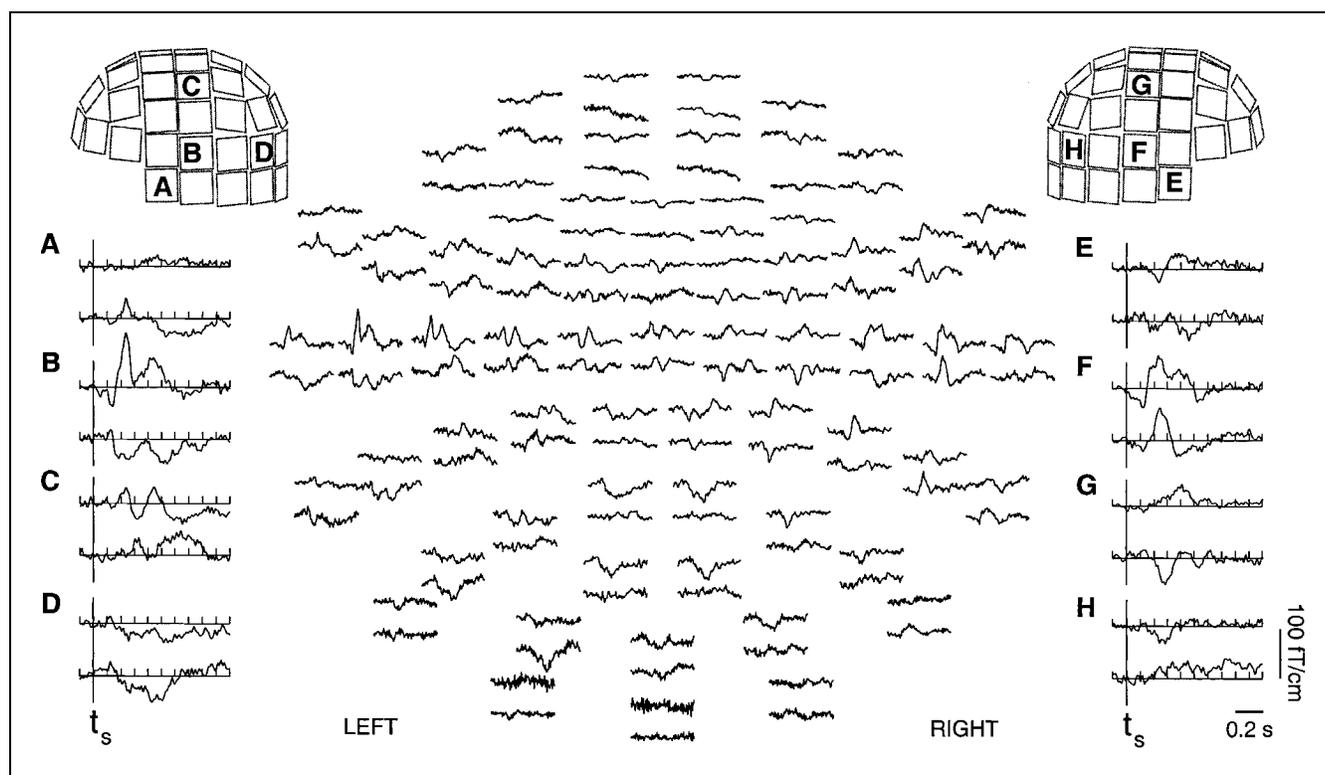
Figure 1. Magnetic evoked responses to auditory oddballs averaged time-locked to the presentation of the auditory oddball stimuli at time t_s. The subject (S4) was instructed to lift the right index finger upon detection of an auditory oddball. The location of each pair of sensors is indicated by a square on the helmet-shaped array. Waveforms for all sensors are shown in a flattened projection with the frontal, left, and right sensors located on the top, left, and right of the figure, respectively. The upper trace of each pair corresponds to the time-dependent magnetic field gradient $(\partial B_z/\partial x)$ and the lower trace to $(\partial B_z/\partial y)$. The z direction is along the outward pointing normal to the x-y plane containing each pair of MEG detectors, with x direction tangent to the bottom of the array. Selected waveforms are shown on the left and right of the figure for locations indicated on the helmet-shaped array from 0.1 sec prior to 1 sec following the auditory oddball cues.
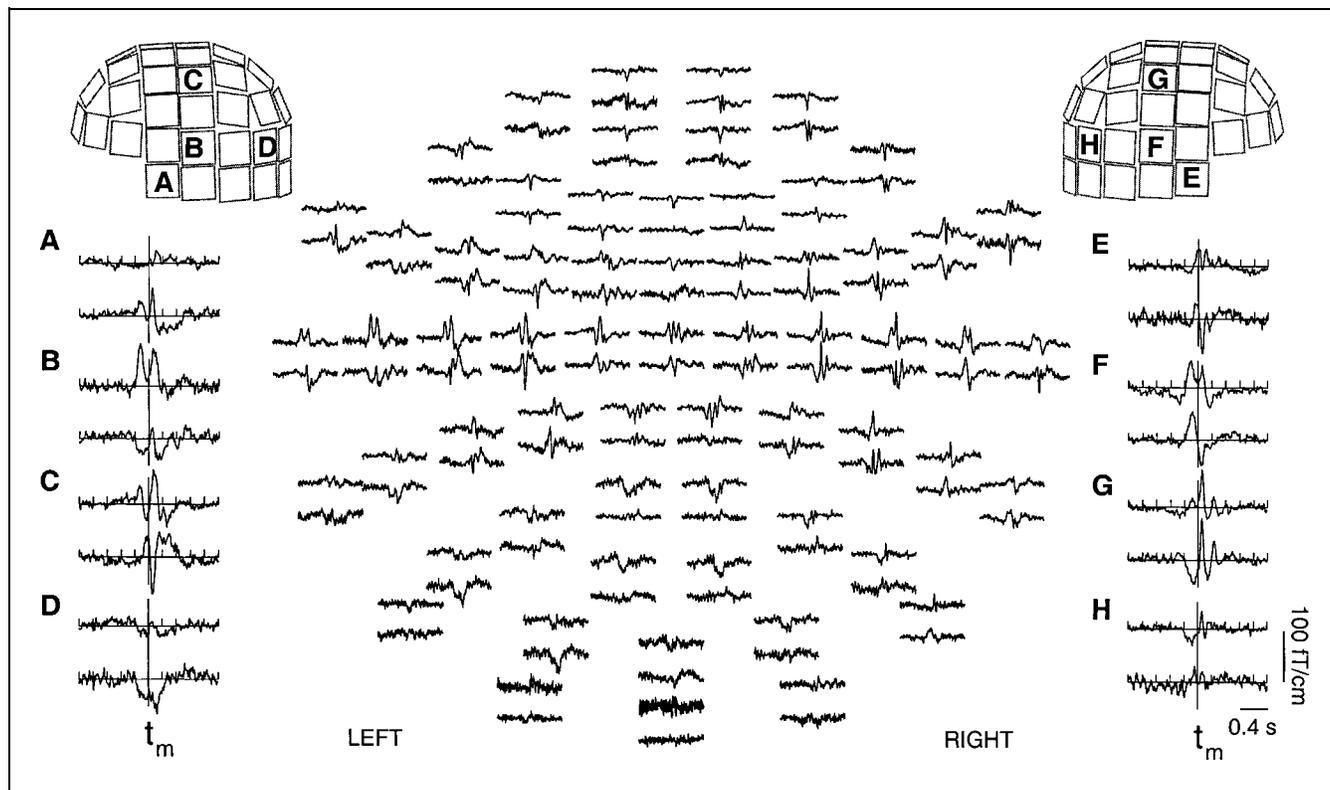
Figure 2. Magnetic evoked responses to auditory oddballs averaged time-locked to the motor responses (onsets at t_m). The subject, task, and set of trials are identical to those described for Figure 1. Waveforms are shown from 1 sec prior to 1 sec following the motor responses.

stimuli were randomized. Thus, events that were synchronized with either the oddball cues or motor responses can be disentangled from each other, even if there is some temporal overlap due to the rapid presentation of the stimuli. Figure 3 demonstrates this effect on the averaged traces of the pulses generated by the software to trigger the presentation of the auditory and visual oddball stimuli. The trace of the auditory oddball triggering pulses averaged time-locked to the auditory stimulus presentations at time t_a is identical to that of the individual triggering pulses. However, subsequent auditory oddballs are random with respect to the first. These pulses are strongly suppressed in the average (cf. Figure 3a). Visual stimuli were randomly interleaved with respect to the auditory stimuli. Any event that was synchronized with respect to the visual stimuli will appear smeared out in averages time-locked to the auditory oddballs. The traces of the visual oddball triggering pulses averaged time-locked to the auditory oddballs show a reduction in amplitude of approximately a factor of 10 (cf. Figure 3d).

Individual motor responses to the auditory oddball stimuli displayed considerable variability in response times (span for all subjects: 185 to 500 msec following oddball cue). Moreover, the peak response times showed considerable differences between subjects (mean 308 msec, range 225 to 360 msec). Thus neuronal events that were synchronized with the presentation of the stimuli

should show significant smearing of the corresponding MEG waveforms when averaged time-locked to motor responses. We illustrate this effect using the individual motor responses of subject S4 to auditory oddball stimuli to generate back-averages of the auditory stimulus triggering pulses. The averaged auditory oddball triggering pulse is reduced by approximately a factor of 2 (cf. Figure 3b). The visual oddball triggering pulses are more strongly suppressed, again by about a factor of 10 (cf. Figure 3e). Interestingly, if the movement-triggered average of the visual triggering pulses is shifted by the subject's peak response time t_m, the two waveforms nearly coincide (cf. Figure 3f). This overlap of the waveforms is a fingerprint for events (i.e., the presentation of the visual oddballs) that are random with respect to both the auditory oddballs and the motor responses. Most importantly, the same fingerprint would occur for neuronal events that are synchronized by an internal timing mechanism that is independent of stimulus presentation and motor response.

Synchronization of MEG Waveforms

The effects of the random stimulus presentation times are apparent in the averaged waveforms recorded by individual MEG sensors in the array. Figures 3A to D shows the superposition of averages time-locked to the auditory and visual oddballs and to the motor responses.

Figure 3. Waveforms derived from recordings of the trigger pulses of 80-msec duration with pulse onsets coincident with (a, b, c) the onsets of the auditory oddball stimuli and (d, e, f) the onsets of the visual oddball stimuli. (a, d) Results for averages of the trigger pulses time-locked with the auditory oddball stimuli. (b, e) Results for averages of the trigger pulses time-locked to the motor responses of subject S4 when cued by auditory oddballs. The averages time-locked to the movements are shifted by the subject's peak reaction time of 360 msec. A–D Examples of a superposition of averaged magnetic evoked response data recorded by the array. The subject, task, and set of trials are identical to those described for Figure 1. The averages time-locked to the movements are shifted by 360 msec.
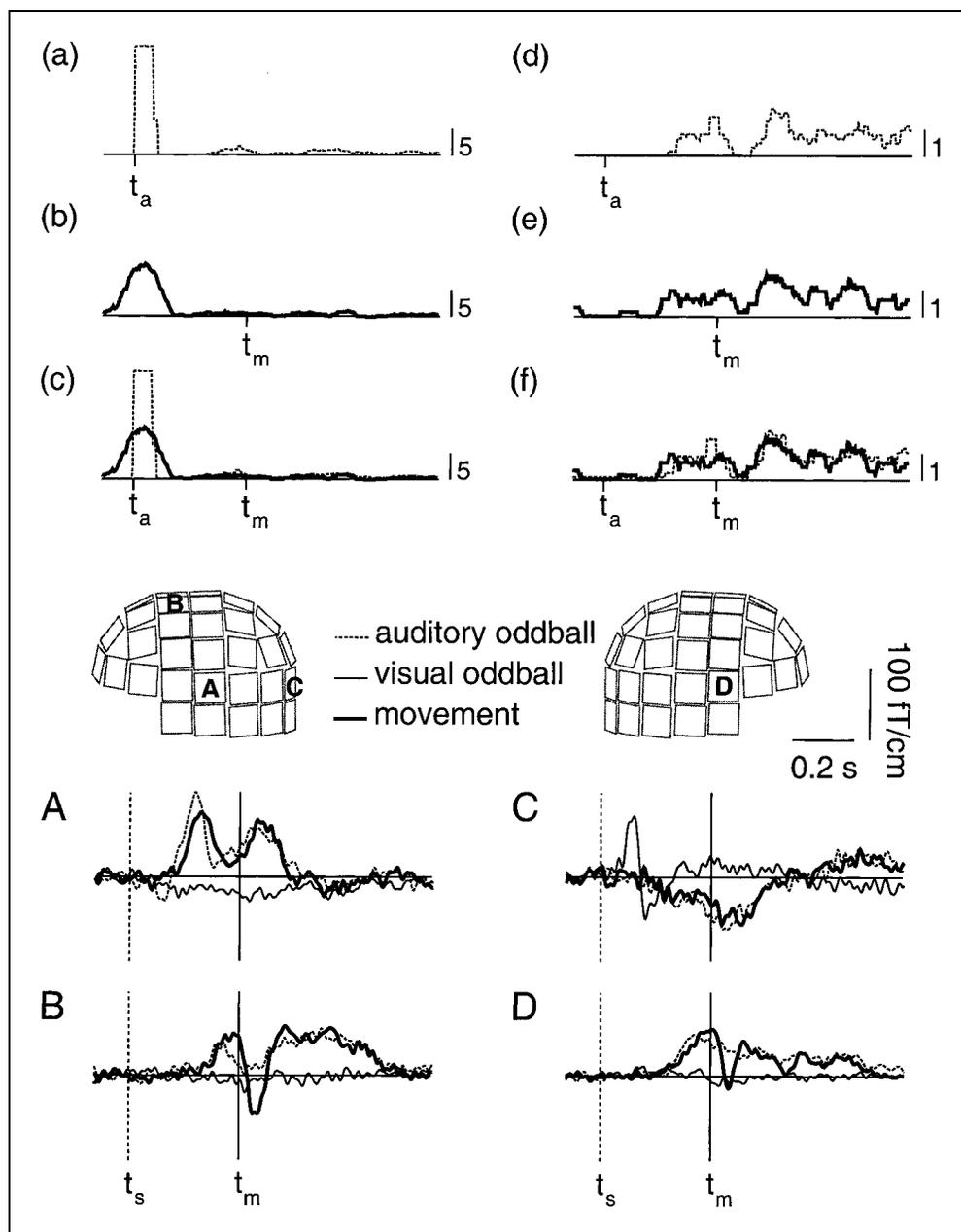
The movement-triggered average waveforms are shifted by the subject's peak response time to facilitate the comparison. Some prominent features in the oddball-triggered waveforms appear smeared out in traces time-locked to the movements. The early occipital response at 110 msec following the visual oddballs (cf. Figure 3C) is almost completely suppressed in averages time-locked to the auditory oddballs and motor responses. Similarly, the earliest responses over the left temporal area (cf. Figure 3A) are reduced, although less at 240 msec than at 130 msec. Conversely, responses occurring within 100 msec of the peak reaction time for a detector located over contralateral sensorimotor cortex appear significantly reduced in the oddball-triggered averages (cf. Figure 3B).

Interestingly, there are some exceptional intervals of coincidence in the averaged MEG waveforms. For example, the auditory oddball and movement triggered waveforms in Figure 3C are both of substantial amplitude and nearly identical from approximately 200 msec prior to 200 msec following the peak reaction time. This result cannot be generated by a random smearing of the 110-msec responses to visual stimuli, which are of approximately the same amplitude in visual-oddball triggered averages. Nearly coincident waveforms of substantial amplitude can be seen in data recorded by many other sensors. These intervals of coincidence suggest that subsets of the active neuronal population may be synchronized by intrinsic timing mechanisms that are independent of both the oddball cues and the motor

responses and that these synchronized populations may be fairly widespread in both cortical and possibly subcortical areas.

Cortical Components

Although population responses in the brain are the result of complex nonlinear interactions between various neuronal entities, magnetic signals detected at the scalp are a linear superposition of contributions generated by current flow in specific brain areas. As a result it is possible to decompose MEG (and/or EEG) signals into components utilizing a weighted average of results recorded by various detectors in the array. In this discussion, we have selected components corresponding to activation of the auditory and sensorimotor cortex and hippocampus. It is instructive also to investigate responses in the occipital cortex associated with the randomly interleaved visual stimuli. Waveforms for these components are identified in the text as signal-space (SSP) waveforms (Ilmoniemi & Williamson, 1987; Tesche et al., 1995; Uusitalo & Ilmoniemi, 1997).

SSP waveforms characterizing neuronal population activity in the auditory and somatosensory cortex show several typical features when data are averaged either time-locked to the oddball cue or to the oddball-cued movement (cf. Figure 4). The detection of a sound in the audiovisual input stream generates prominent bilateral responses within the temporal lobe at 30 to 120 msec (P50m and N100m) that are time-locked to the auditory cue. Sensorimotor responses reveal prominent activity within about 100 msec of the lift of the right finger that are time-locked to the movement, including both the preparatory premovement motor responses ("bereitschaftpotential," (Kornhuber & Deecke, 1964) that are known to involve the bilateral precentral cortex and postmovement (at 0 to 100 msec) responses in the contralateral sensorimotor cortex. The reduction of amplitude of these sensorimotor responses when averaged with respect to the auditory oddball cues and the reduction of early auditory responses when averaged with respect to the movements are consistent with substantial synchronization of sensorimotor responses with movement and auditory responses with auditory cues, respectively. In addition, the 130-msec occipital response to the visual oddballs is well defined in the visual oddball triggered average but strongly suppressed in both the auditory oddball and movement triggered averages, demonstrating synchronization of this population response with the randomized presentation of visual oddball stimuli.

Hippocampal Components

Figures 5 and 6 show examples of SSP waveforms for hippocampal components with current flow in the coronal plane (h_c) and with anterior orientation (h_a), respec-
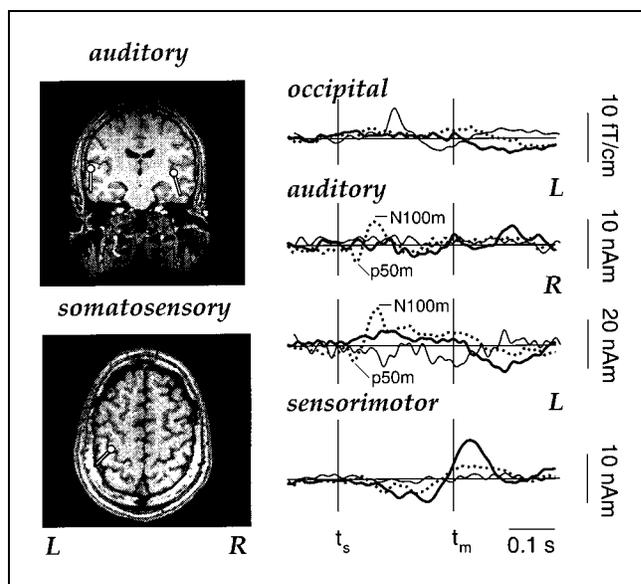
Figure 4. SSP waveforms characterizing averaged cortical neuronal population responses time-locked to the auditory (dashed lines) and visual (thin solid lines) oddballs at time t_s and to the motor responses (heavy solid lines) at time t_m (subject S1). The subject was instructed to lift the right index finger upon detection of an auditory oddball. Localized sources of current flow in the left (L) and right (R) auditory cortex and left (L) somatosensory cortex define the auditory and somatosensory components, respectively. The locations (dots) and orientations (tails) of these current sources are indicated on the individual's MR images. The waveforms are expressed in units of nAm. Waveforms for the occipital component are defined with respect to the averaged signals recorded in the array at 113 msec after the visual oddballs (not shown) and are expressed in units of magnetic field gradient. Averages time-locked to the movements are shifted by the subject's peak reaction time of 255 msec.

tively (cf. Tesche et al., 1996). Results are shown both for self-paced and auditory oddball-cued movement. In this subject, prominent task-dependent responses are roughly coincident with widespread MEG activity recorded 200 to 500 msec after the oddball cue. Moreover, the premovement hippocampal responses generated under the imperative to move that are time-locked with the movement are enhanced over those observed for self-paced movement, suggesting an increase in the number of activated neurons or in the coherence of the activated neuronal population.

Responses in the left h_c component to cued movement are particularly prominent from approximately 200 msec before to 60 msec after movement (cf. Figure 5). Interestingly, the averaged responses time-locked to the movement are very similar to the averaged responses time-locked to the auditory oddball cues. Are these waveforms smeared reflections of averaged evoked responses to an external event, that is, the presentation of the visual oddball stimuli, that generate evoked responses at about the same latency? This is highly unlikely. The visual evoked responses are both of insufficient amplitude to survive the random smearing and, more significantly, are
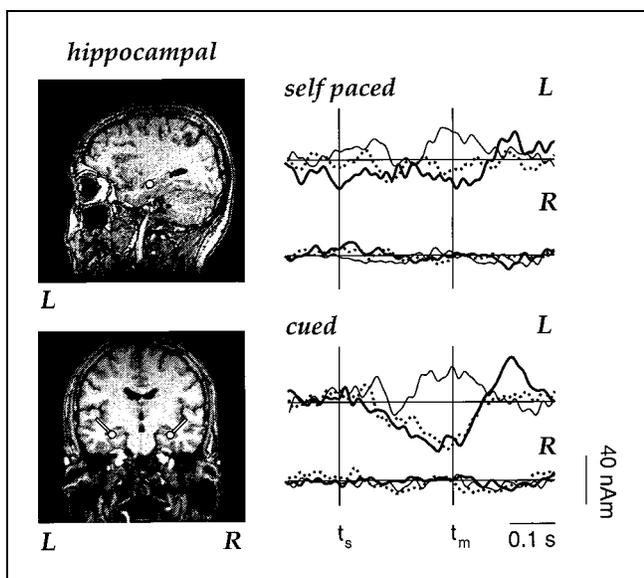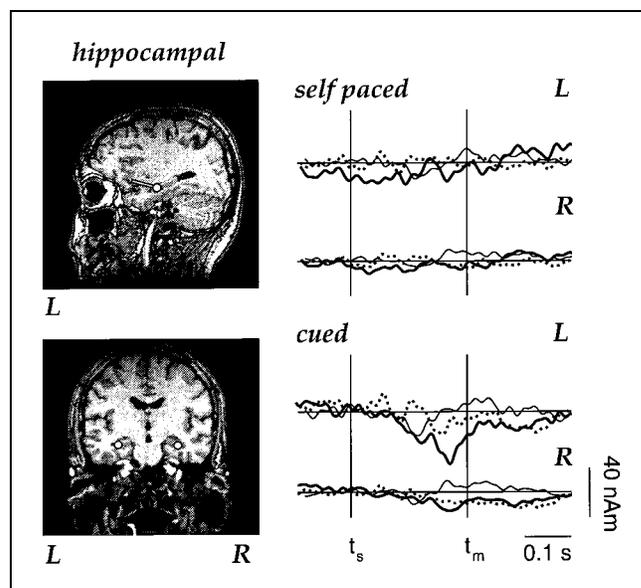
Figure 5. SSP waveforms characterizing averaged hippocampal neuronal population responses time-locked to the auditory (dashed lines) and visual (thin solid lines) oddballs at time t_s and to the motor responses (heavy solid lines) at time t_m. Sources for current flow in left (L) and right (R) anterior hippocampus with orientations in the coronal plane (component h_c) are indicated on the individual's MR images. The subject, task and set of trials are identical to those described in Figure 4.


Figure 6. SSP waveforms characterizing averaged hippocampal neuronal population responses time-locked to the auditory (dashed lines) and visual (thin solid lines) oddballs at time t_s and to the motor responses (heavy solid lines) at time t_m. Sources for current flow with anterior orientation (component h_a) in the left (L) and right (R) anterior hippocampus are indicated on the individual's MR images. The subject, task, and set of trials are identical to those described for Figure 4.

of opposite polarity. Thus the coincidence in the morphology of the left h_c waveforms suggests a synchronization of activity by a timing mechanism that is random both with respect to stimulus presentation and motor response in this subject.

The hippocampal responses averaged time-locked to the movement also show enhanced amplitude after the execution of the movement (cf. Figures 5 and 6). However, this activity is clearly distinct from the responses originating prior to the movement. The contralateral h_c component is again most prominent but of opposite polarity. This is significant because a shift in the polarity of a MEG response that is characterized by oriented current flow may indicate activation of a different neuronal population. Interestingly, this population response generates SSP waveforms that are no longer coincident with the corresponding auditory oddball triggered averages.

Comparison of Sensory- and Movement-Related Hippocampal Responses

The strengths of the hippocampal responses are estimated individually for all subjects from the time-averaged areas of the SSP waveforms for the before movement and after movement epochs (cf. Figure 7). Mean results across subjects for all hippocampal components are summarized in Table 1.

Before Movement

Bilateral activation of both coronal and antero-posterior hippocampal components appear in cue-triggered average evoked responses 100 to 500 msec after attended auditory oddballs. In contrast, comparison of responses time-locked to movement shows that cued movements generate significantly larger response than self-paced movement for the contralateral component h_c but not for the homologous ipsilateral component (cf. Table I). Moreover, the enhancement of the contralateral h_c component time-locked to the movement is almost identical in amplitude to that time-locked to the auditory oddballs. In contrast, there is no indication of any lateralization of the responses in the h_a component of the hippocampal current flow. Both ipsilateral and contralateral h_a components are slightly, but not significantly, enhanced for cued movements, with the largest responses occurring in averages time-locked to the stimuli.

Most remarkably, however, not only the amplitude but also the time course of the averaged contralateral h_c component preceding and time-locked to a cued movement appear very similar to the simultaneous hippocampal activation time-locked to and following the auditory oddball cue in all subjects. The onset of this hippocampal activity occurred on average 200 msec before the detected movement, with a relatively large intersubject range of 135 to 320 msec. Interestingly, shifting the auditory evoked waveforms backward in time by the individual's peak reaction time generated a near super-
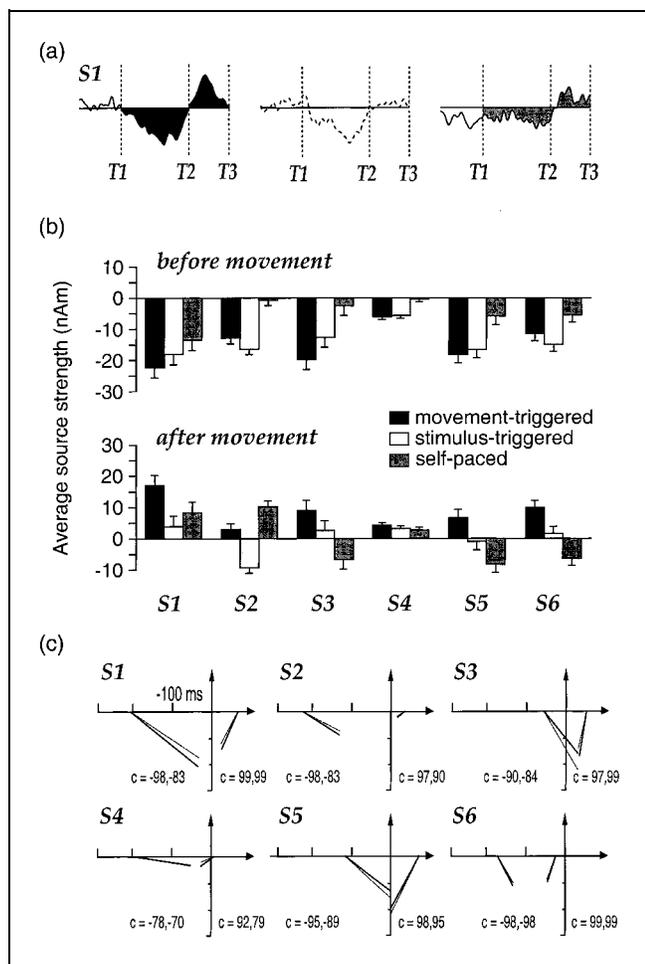
Figure 7. (a) Examples of SSP waveforms for the left h_c component (cf. Figure 5). The epochs T1 and T2 (before movement) and T2 and T3 (after movement) are defined by the baseline crossings of the movement-triggered waveform as indicated by the vertical dashed lines. The shaded areas show the source strengths during each epoch. (b) Time-averaged source strengths for left h_c component for all six subjects. (b, c) Movement-triggered averages for cued movement (black shading), stimulus-triggered averages for cued movement (light gray shading), and movement-triggered averages for self-paced movement (dark gray shading). (c) Approximation of the onset and offset of activity of the left coronal hippocampal component h_c for cued movement by linear fits to the data for each subject. The vertical arrows indicate the initiation of the movements. The cue-triggered average responses (dashed lines) and movement-triggered average responses (solid lines) are shown with x axis intercepts of the onset and offset linear approximates occurring at the baseline crossings of the movement-triggered responses. The accuracy of the linear fits is given by the linear correlation coefficients c, with the first value corresponding to the movement-triggered averages.

position of the two curves (cf. Figure 5). We quantify this effect in Figure 7c by approximating the onsets and offsets of the before movement evoked responses by linear fits to the data for each subject. Remarkably good fits are obtained, with coefficients of linear correlation between 70 and 99 for all subjects and conditions. The slopes of these linear approximations provide a measure of the similarity of the waveforms that is relatively independent of the specific choice of peak reaction time for

the performance of the temporal offset. A comparison of the oddball-triggered and movement-triggered average evoked waveforms showed no significant difference of either the onset or offset slopes in the group of six subjects.

The intrasubject averaged time required for the onset from the baseline to maximum response and offset from maximum response to baseline value of the left contralateral h_c component is remarkably brief (mean onset time 106 msec, range 39 to 171 msec, mean offset time 34 msec, range 18 to 71 msec) compared to the span of the individual reaction times across trials (mean peak response time 308 msec, range 225 to 360 msec). The temporal interval between onset and offset is also interesting (mean 193 msec, range 107 to 257 msec), with values that are comparable to those associated with a single oscillation in the theta band (4 to 12 Hz corresponds to 83 to 250 msec).

After Movement

Both contra- and ipsilateral h_c components appear enhanced for cued movement when compared with self-paced lifting of the finger; however, only the contralateral component appeared significantly so. The polarities of these responses are also opposite to those of the before movement epochs, suggesting activation of separate neuronal populations. Interestingly, responses time-locked to the oddball cues are very strongly suppressed for both ipsilateral and contralateral h_c components. In contrast, both ipsilateral and contralateral h_a components show significant enhancement of responses time-locked to the auditory oddball cues over responses time-locked to either cued or self-paced movement.

DISCUSSION

Hippocampal activity during sensory detection involves activation of multiple hippocampal neuronal assemblies coincident with widespread cortical activity at 200 to 500 msec after oddball stimuli (Halgren et al., 1980; McCarthy et al., 1989; Tesche et al., 1996). Practically all cortical areas that project to the hippocampus via the entorhinal cortex are regarded as polysensory association cortex (Insausti, Amaral, & Cowan, 1987). Thus hippocampal activation at these latencies is consistent with polysynaptic neural transmission associated with the selecting of pertinent information from sensory flow for sustaining and updating of a model of the external environment (Donchin, Karis, Bashore, Coles, & Gratton, 1986; Tulving & Schachter, 1990). Although attention is known to enhance these sensory hippocampal responses (Halgren et al., 1980; McCarthy et al., 1989; Tesche et al., 1996), the impact of goal-directed movement on the detection and processing of salient sensory features in human hippocampal structures is not known.

In this study, we observed bilateral hippocampal

Table 1. Strength of hippocampal responses before and after movement (in nAm). The average strengths of responses were calculated from the individual response areas before and after the movement. Two orientations of hippocampal neuronal currents, coronal (h_c) and antero-posterior (h_a), were studied separately. Statistical significance of differences was evaluated by Friedman's test for comparison of the movement-triggered average responses during cued movement with movement-triggered average responses during self-paced movement and with cue-triggered average responses during cued movement. The level of significance was set at $p < 0.05$ and is depicted by an asterisk.

	Cued movement movement-triggered		Self-paced movement movement-triggered			Cued movement cue-triggered		
	Mean	S.E.M.	Mean	S.E.M.	p	Mean	S.E.M.	p
Before movement								
Left coronal (h_c)	−15.2	2.5	−3.5	2.4	*	−14.7	1.9	
Right coronal (h_c)	−4.6	0.9	0.7	2.6		−14.1	2.7	
Left antero-posterior (h_a)	−9.9	3.5	−6.0	1.8		−11.7	3.4	
Right antero-posterior (h_a)	−8.5	3.1	−4.9	1.2		−11.8	3.3	
After movement								
Left coronal (h_c)	8.3	2.1	0	3.4	*	0.2	2.0	*
Right coronal (h_c)	6.9	3.2	1.1	1.9		1.9	5.3	
Left antero-posterior (h_a)	−5.6	2.9	1.5	1.9		−13.9	3.6	*
Right antero-posterior (h_a)	−4.4	2.3	0.2	1.5		12.6	3.2	*

neuronal activity at 100 to 500 msec after attended auditory oddballs, with responses occurring during and subsequent to the cued movement. This observation is consistent with the known attentional enhancement of hippocampal responses to salient sensory input. In addition, we observed movement-related responses that were enhanced under a cued imperative to move as compared to a self-paced movement and to the sensory input per se. Two epochs were clearly distinguishable. Activity initiated prior to movement contained features indicative of integrated processing of sensory cues and motor responses. In contrast, responses following movement included components that were clearly synchronized with respect to the cued movement rather than with the presentation of the sensory cues.

Binaural, attended auditory stimuli evoked bilateral hippocampal activation of both the coronal h_c and antero-posterior h_a components. In contrast, responses following the same auditory oddball cues but time-locked to the cued finger movements were dominated by contralateral coronal h_c activity beginning 200 msec prior to movement. The increased lateralization of this response was specific for cued rather than for self-paced movement and indicates involvement of at least some hippocampal networks with motor networks responsible for the initiation of movement. Intracranial neurophysiological recordings of both the primary and supplementary (SMA) motor cortex imply that neuronal activity preceding finger movement by about 100 msec is strictly lateralized to the contralateral hemisphere (Ikeda, Lüders, Burgess, & Shibasaki, 1992). Hippocampal networks connected to frontal cortical areas are known to be involved in holding pertinent information on line during the temporal interval required for a decision or for the performance of an operation (Baddeley, 1992; Goldman-Rakic, 1989). Thus the active contralateral hippocampal neuronal assemblies identified here in normal human subjects may be recruited by and inform activated motor networks both for the identification and utilization of premovement cues and for immediate postmovement updating.

Most remarkably, however, the time course and amplitude of the left coronal h_c component preceding and time-locked to cued movements was very similar to the simultaneous hippocampal activation time-locked to and following the sensory cues. There was no significant difference between the strength of the movement-triggered and stimulus-triggered average activity. The similarity in time course was most striking at the sharp offset of the synchronized hippocampal activity. The mean time required for the offset from maximum response to baseline value was remarkably brief (34 msec) compared to the mean reaction times across subjects and trials (308 msec). Moreover, although the offset of this component was roughly coincident with or slightly later than the time of the actual movements, it is not possible that the offset was causally related with a fixed time delay to the individual motor responses.

The similarity of the waveforms of the robust stimulus- and movement-related hippocampal h_c responses is suggestive of a synchronizing action by an internal timing mechanism. The synchronization appears to occur on a

time scale of tens of milliseconds. This feature of the hippocampal h_c response is notably dissimilar to that observed in the early sensory- and movement-related responses in the auditory and sensorimotor cortex. We speculate that oscillatory field potentials in the theta band in the human hippocampus may be playing a role in the normal human hippocampus similar to that observed in rodents. A wealth of single cell and intracranial field potential recordings show oscillatory 4 to 12 Hz (theta) synchronization of input-output functions of hippocampus in rodents (for a review, see (Buzsáki, 1996). Afferentation seems to be crucially involved in the generation of theta, which is abolished by removal of entorhinal input (Ylinen et al., 1995). Synchronization of hippocampal theta during exploratory behavior in rats has been attributed both to attentional behavior and to direct interaction with cerebral motor control systems (Ranck, 1973; Vanderwolf, 1969). Interestingly, the frequency and amplitude of theta has been observed to increase linearly with running speed in both rats (McFarland, Teitelbaum, & Hedges, 1975) and guinea pigs (Rivas, Gaztelu, & Garcia-Austt, 1996). Theta oscillations may tune hippocampal networks close to the "resonant" properties of individual cells (Ylinen et al., 1995), enabling relatively few active entorhinal afferents to generate and sustain the activation of a large number of hippocampal pyramidal cells. Moreover, although theta is often remarkably prominent in the rat hippocampus, intracellular recordings may evidence theta-band variability of the firing of interneurons even when there is relatively poor representation of theta in the field potentials (for an example, see Freund & Buzsáki, 1996).

Although studies performed on highly trained animal models, as well as results recorded during various species-specific behaviors, may provide valuable insights into the function of the mammalian hippocampus, verification of functional specificity in humans can only be obtained from experiments conducted on this species. Action potentials recorded in the human hippocampus show firing of hippocampal units in relation to various movments, especially those requiring a high degree of effort (Halgren, 1991). However, there are only very sparse reports of theta detected with intracranial electrodes in patients (Arnolds, Lopes da Silva, Aitink, Kamp, & Boeijinga, 1980; Halgren, Babb, & Crandall, 1978; Isokawa-Akesson, Wilson, & Babb, 1987; Meador et al., 1991). In contrast to the abundance of data on theta in rats, there are no previous reports linking human theta with movement per se (cf. Halgren, 1991). Recently, observation of theta in the intact human hippocampus has been demonstrated with a whole-scalp MEG system system (Tesche, 1997). In this study, subjects performed a silent mental calculation by alternating addition and subtraction of integers determined from the location in alphabetical order of letters observed in a simple text. This task required both short-term retention of the results of the ongoing calculation and retrieval of information from long-term memory. No motor response was elicited from subjects beyond the self-paced scanning of the printed material. This first observation of spectral components in the theta band in recordings from normal human subjects suggests that theta may play a functional role also in human hippocampal formation.

Data presented here supports the notion that theta may be gating the sharp onset and offset of the contralateral h_c responses. The random stimulus presentation utilized here ensures that the phase of any ongoing activity will be uncorrelated both with the present and subsequent sensory input. Thus effects would be specific to a single stimulus-response event. The time-scale of a single cycle of activity may be reflected in the mean duration (193 msec) of the hippocampal h_c response during this demanding task. The difference between the onset and offset intervals of the internally synchronized premovement responses and the distinct character of the postmovement hippocampal activity may reflect modulation by reafferent input from the motor system.

Sensorimotor integration at the neuronal population level has been suggested from observations of synchronous activity in spatially distinct populations in the sensorimotor cortex (Murthy & Fetz, 1992). Zero time-lag synchronization of activity during visuomotor tasks has also been observed in cats (Roelfsema, Engel, Konig, & Singer, 1997). Similarly, the evidence for the initiation and subsequent dissolution of internal synchronization of activity in hippocampal formation presented here may evidence a mechanism for somatosensory interaction during the high-speed generation of motor responses to rapidly presented stimuli.

Sensorimotor integration at the neuronal population level has also been inferred from enhanced neuronal activity to combined input from sensory and motor systems. Results include MEG studies of the second somatosensory cortex (SII) (Huttunen et al., 1996) and PET studies of somatosensory integration in the posterior parietal cortex (Kertzman, Schwartz, Zeffiro, & Hallet, 1997). Our results demonstrate that large-scale cognitive networks recruit additional resources from the human hippocampus during interactive processing of an auditory input and the activation of a motor program that is cued by that input. The h_c component of hippocampal activity from 300 msec before to 200 msec after cued movements was enhanced significantly over that observed during self-paced movements. In a previous study using identical stimuli, we have shown enhancement of the h_c component in a task requiring cued motor responses over those observed during passive attention to the stimuli (Tesche et al., 1996).

Hippocampal structures are known to be associated with memory encoding and novelty detection. The present results provide evidence that large-scale cognitive networks also may recruit additional resources from the hippocampus during the generation of rapid motor responses to salient stimuli. However, a relationship be-

tween sensorimotor interaction and memory encoding in the human hippocampal formation remains to be elucidated.

EXPERIMENTAL METHODS

Subjects, Stimuli, and Tasks

Six healthy subjects (four males; age 25 to 50 years) were presented with auditory oddball targets in a flow of randomly presented auditory and visual stimuli. Binaural tone bursts of 50-msec duration (75% at 1 kHz and 25% at 2 kHz) and centrally presented (15°) colored squares of 50-msec duration (75% green and 25% red) were presented at random interstimulus intervals of 0.15 to 0.3 sec in blocks of 1000 to 3000 stimuli. The stimuli were presented to the subjects briefly before the recording session (elapsed time < 5 min). Subjects also received a verbal description of five different tasks. Task 1: Stimuli were to be observed passively. Task 2: Subjects were to listen to and view the stimuli while performing a self-paced lifting of the right index finger (mean frequency 0.27 Hz). Task 3: Subjects were to execute a right finger lift upon detection of the auditory oddball target. Task 4: Subjects were to execute a right finger lift upon detection of the visual oddball target. Task 5: Subjects were to execute a right finger lift upon detection of an oddball target, switching between auditory and visual modalities after each movement. Verbal instruction to perform a specific task was given during the measurement session at the beginning of each block of stimuli. Each task was performed twice during the measurement session. This research was approved by the ethical committee of the Helsinki University Hospital. Informed consent was obtained from all subjects.

Magnetoencephalographic Recording

Scalp magnetic gradient field patterns were recorded with a whole-head magnetoencephalographic (MEG) array (Ahonen et al., 1993). The array was instrumented with 122 dc Superconducting Quantum Interference Devices (SQUIDs) (Tesche et al., 1985) coupled to individual planar gradiometer pick-up coils. Pairs of the orthogonally wound "figure eight" coils (area of each loop 2.6 cm^2, baseline 16.5 mm) were located on square substrates inside and parallel to the bottom of a helmet-shaped cryogenic dewar. A single planar-gradiometer detector in free space is most sensitive to a current element that is located directly beneath and tangent to the coils. More distant current elements are detected as weaker signals.

The subject was seated underneath the dewar, which was located inside a magnetically shielded room (Kelhä et al., 1982). The position of the head with respect to the MEG sensors was determined from measurements of the magnetic fields produced by three independently ener-

gized current loops, one attached tangent to the scalp behind the left and right ears, respectively, and the third in the center of the forehead. The locations of these coils with respect to the preauricular points and nasion were determined before the subject entered the shielded room with a 3–D digitizer (Isotrak 3S1002, Polhemus Navigation Sciences, Colchester, VT). This information was subsequently used to determine the locations of the MEG sensors with respect to the individual's magnetic resonance (MR) images (1-T Siemens Magnetom system: recorded at the Helsinki University Central Hospital, Helsinki, Finland).

Responses were bandpass filtered at 0.03 to 130 Hz, sampled at 400 Hz, and averaged on line. Three separate averages were performed for each block of data: time-locked to the auditory oddballs (600-msec epochs, 100 msec prestimulus) time-locked to the visual oddballs (600-msec epochs, 100 msec prestimulus), and time-locked to the cued or self-paced movement (1000-msec epochs, 500 msec prior to the movement in five subjects and 2000-msec epochs, 1000 msec prior to movement in one subject). The motor response (brisk lifting of the right index finger) was monitored with an optical switch. A vertical electrooculogram (threshold 150 mV) was used to reject data from the on-line averages that were contaminated by eye movements and blinks.

Data Analysis

The calculation of the location and orientation of current flow in the brain from magnetic signals observed at the scalp requires additional information beyond that available from MEG data. We utilized a routine MEG analysis technique, equivalent current dipole (ECD) modeling, for the identification of sources for early evoked responses in auditory and somatosensory cortex (cf. Hämäläinen et al., 1993). Magnetic field patterns recorded in a subset of 34 detectors located over the temporal or somatosensory cortex were used to determine a least-squares fit (goodness of fit > 90%) between the observed gradient field patterns and field patterns determined by simulation of a short flow of current (an ECD) with variable strength, location, and orientation. Modeling of magnetic field patterns for these cortical ECDs was performed utilizing a uniform conducting sphere whose surface approximated the local curvature of the brain (determined from MR images) directly underneath the subset of sensors.

Anatomical features were utilized to define source locations and orientations in hippocampal structures located utilizing the individual subject's MR images. Neuronal population activity in anterior hippocampus was approximated by short segments of current flow. The total current was divided into three orthogonal vector components: b_a oriented predominantly in the anterior direction, b_c oriented in the coronal plane at approximately 45° with respect to the vertical, and a third nearly

radial component orthogonal to both h_a and h_c (cf. Tesche, 1997; Tesche et al., 1996).

Current source distributions underlying early evoked responses in the occipital cortex were difficult to approximate with ECDs. Magnetic field patterns observed in data averaged time-locked to the visual standards at 100 to 150 msec after stimulation were characterized directly by the signals recorded in a subset of 32 sensors located over the occipital area. The set of sensor values at a specific latency was used to determine a unit vector in a subspace of a linear vector space identified as the signal-space for the 122-channel MEG array. Each axis in this 122-dimensional signal space corresponds to a single channel of information recorded by the array (Ilmoniemi & Williamson, 1987; Tesche et al., 1995; Uusitalo & Ilmoniemi, 1997).

ECDs determined for early auditory and somatosensory responses were characterized as unit vectors in the same signal space by simulating the signals recorded by the array for each ECD source using an individual spherical head model. Simulated magnetic field patterns were computed also for the hippocampal components for each location and direction of current flow. The geometry of the cranial volume for these deeper sources was approximated by a single-compartment boundary-element conductor model (Hämäläinen & Sarvas, 1989). Thus all desired components of the signal, auditory, somatosensory, occipital, and hippocampal were described in a compatible formulation as unit vectors in a common signal space.

SSP waveforms were determined simultaneously from a comparison of the signal-space unit vectors for all of the neocortical plus one of the hippocampal components with the data (Tesche et al., 1995). The effective noise of the MEG system for each component was determined from data recorded with no subject under the detector array. The same sampling rate, filter settings, and triggering conditions were used as in the actual experiment. Subsequently MEG system-noise waveforms were computed for each element of the set of components employed for the analysis of the individual subject's data. Although MEG system noise is uncorrelated with brain activity, ambient and detector-related sources often contribute a nonnegligible additive noise to evoked response waveforms. In contrast, prestimulus fluctuations in excess of system noise represent brain signals and were not used to characterize "noise" variance at this or any other latency (for a thorough explanation of this method with examples, see Tesche et al., 1996).

Time-averaged responses were determined separately for each subject (cf. Figure 7). Epochs were defined from examination of the SSP waveforms for the movement-triggered average evoked responses to the auditory oddballs. The before movement average source strength was defined by the normalized area between the waveform and the baseline for epoch (T1, T2), where T1 was defined by the crossing of the baseline of the h_c component at the onset of substantial activation (intrasubject mean T1: 206 msec before movement) and T2, by the subsequent crossing of the baseline following the negative peak response (intrasubject mean T2: 38 msec after movement). The after movement amplitudes were computed for the epoch (T2, T3), where T3 was defined by the return to the baseline of the h_c component following the positive peak response. Statistical significance of differences was evaluated by Friedman's test between the conditions. The level of significance was set at $p < 0.05$. The onset and offset slopes of the before movement responses were approximated by linear fits to the data between time T1 and the subsequent minimum response and time T2 and the preceding minimum response, respectively. The statistical significance of differences between the slopes was evaluated by a t test.

Acknowledgments

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