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How single-trial electrical neuroimaging contributes to multisensory research

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Abstract This study details a method to statistically determine, on a millisecond scale and for individual subjects, those brain areas whose activity differs between experimental conditions, using single-trial scalp-recorded EEG data. To do this, we non-invasively estimated local field potentials (LFPs) using the ELECTRA distributed inverse solution and applied non-parametric statistical tests at each brain voxel and for each time point. This yields a spatio-temporal activation pattern of differential brain responses. The method is illustrated here in the analysis of auditory-somatosensory (AS) multisensory interactions in four subjects. Differential multisensory responses were temporally and spatially consistent across individuals, with onset at ~50 ms and superposition within areas of the posterior superior temporal cortex that have traditionally been considered auditory in their function. The close agreement of these results with previous investigations of AS multisensory interactions suggests that the present approach constitutes a reliable method for studying multisensory processing with the temporal and spatial resolution required to elucidate several existing questions in this field. In particular, the present analyses permit a more direct comparison between human and animal studies of multisensory interactions and can be extended to

examine correlation between electrophysiological phenomena and behavior.

Keywords Multisensory · Electrical neuroimaging · Single-trial EEG · Inverse solution · ELECTRA · Auditory · Somatosensory · ERP · LFP

Introduction

In order to understand how the human brain processes and conjoins responses to stimulation of the different sensory modalities, high spatio-temporal imaging of brain activity is required (e.g. Calvert 2001; Schroeder et al. 2004). This is a challenge for most existing neuroimaging methods that lack sufficient temporal (hemodynamic methods) or spatial (electromagnetic methods) resolution. Overcoming these limitations is critical both for facilitating the extrapolation of results from animal intracranial microelectrode recordings to those obtained from non-invasive neuroimaging in humans, and by extension for deriving a clearer understanding of the neurophysiological mechanisms of multisensory interactions and their behavioral consequences. The goal of this study is to demonstrate the use in multisensory research of a method capable of estimating local field potentials (LFPs) within the brain from scalp-recorded EEG of individual subjects (see also Grave de Peralta Menendez et al. 2000, 2004). In so doing, this method retains the high temporal resolution of electrophysiological data as well as its direct relation to neural activity, while also adding spatial information concerning the active areas of the brain.

The estimation of LFPs is accomplished with a neurophysiologically driven solution to the bioelectromagnetic inverse problem. Although this problem is known to lack a unique solution, it can be solved by incorporating a priori information about the generators of scalp recorded fields combined with details about the spatial relationships existing between local field potentials as

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dictated by electromagnetic laws in biophysical media (see Grave de Peralta Menendez et al. 2004 for discussion). Instead of relying on mathematical constraints (as is the case in the majority of inverse solution algorithms), the solution strategy and the source model applied here emulate the properties of brain activity's actual generators (see Michel et al. 2004 for recent review of different inverse solution approaches). Critically, this added information is independent of both the recorded data and head model and suffices for obtaining a unique solution compatible with and aimed at analyzing experimental data.

We illustrate the application of this method in the comparison of combined auditory-somatosensory (AS) multisensory stimulation versus their separate unisensory counterparts. This comparison has been a focus of recent research across human and non-human primates. In macaques, Schroeder and colleagues (Schroeder et al. 2001, 2003, 2004; Schroeder and Foxe 2002; Fu et al. 2003) have shown that a belt region of auditory cortex located adjacent and caudomedial to primary auditory cortex, termed CM, responds both to auditory and somatosensory stimuli. In addition, the laminar profile of each type of response is consistent with feedforward inputs. We have observed highly similar findings in humans, wherein supra-additive non-linear response interactions were observed just 50 ms post-stimulus onset (Foxe et al. 2000; Murray et al. 2004a). Such supra-additive interactions were also obtained with fMRI measures (Foxe et al. 2002). Lastly, both fMRI and ERP source estimations (Murray et al. 2004a) localized these interactions to auditory area LA (Rivier and Clarke 1997), which lies posterior to primary auditory cortex on the superior temporal cortex. Collectively, these data support the hypothesis that AS interactions identified in humans are homologous with those observed in macaques (Schroeder et al. 2004). At present, however, the results from different techniques and species are not amenable for direct comparison. Although scalp-recorded ERPs have the same temporal resolution as intracranial recordings, they have no localization value, i.e. they lack information about the specific brain regions active or their temporal responses. Instead, the researcher is currently limited to statements regarding specific electrodes, global field power, or scalp topography. By contrast, fMRI has relatively high spatial precision, but poor temporal resolution. Consequently, its measures can be regarded as a temporal integral,

raising the possibility that effects of opposite polarity are cancelled out.

In order to bolster this specific claim regarding homology in AS interactions, as well as the general issue of devising reliable methods for directly relating data from different species, we have analyzed the single-trial EEG data of four healthy subjects from an earlier surface event-related potential study (Murray et al. 2004a), who had performed a simple reaction time paradigm with auditory, somatosensory, or combined auditory-somatosensory multisensory stimuli.

The use of a single-trial analysis method constitutes an important advancement from the event-related potential analysis of our previous study. For one, the present analysis allows us to rule out the existence of early multisensory effects at brain areas that would have otherwise been obfuscated by the limitations of the original analysis employed. That is, when a linear inverse solution is applied to an instantaneous scalp map, as we did in Murray et al. (2004a), the results can be affected by the known limitations of this type of inverse solution. Of particular relevance is the uncertainty in the estimation of amplitude of the sources, which depends upon: (1) the distance between the source and the sensors and (2) the specific location of active sources. Because of these dependencies, superficial sources tend to dominate the instantaneous inverse map, obscuring deep sources that could also be candidates for early multisensory effects. In contrast, the single-trial procedure used here can detect voxels differing between conditions, independently of their positions or their distance to the sensors. Even if the estimated LFP amplitude for a voxel has been underestimated with respect the amplitude at more cortical sources, the differences in amplitude between conditions that appear systematically over single trials will nonetheless yield a significant result. Consequently, the statistical significance map obtained by this analysis leads to a robust picture of the brain areas and timing of multisensory processes that is less influenced by limitations of linear inverse solutions.

Materials and methods

Subjects

Four healthy volunteers (see Table 1) were paid for their participation. Three were right-handed (Oldfield 1971).

Table 1 Demographic and reaction time data from each subject

Subject	Age, sex, and handedness	Mean reaction time (\pm SEM)		
		Multisensory AS stimulus	Auditory stimulus	Somatosensory stimulus
MM	26 years, ♂, L	361 (\pm 5)	372 (\pm 6)	425 (\pm 6)
MR	27 years, ♂, R	268 (\pm 4)	310 (\pm 6)	324 (\pm 5)
MY	30 years, ♀, R	280 (\pm 4)	305 (\pm 5)	315 (\pm 3)
RS	23 years, ♂, R	473 (\pm 9)	512 (\pm 9)	528 (\pm 8)

All reported normal hearing and no neurological or psychiatric illnesses, as well as provided written, informed consent to the experimental procedures that were approved by the Institutional Review Board of the Nathan Kline Institute.

Stimuli and task

The data of these subjects have been previously presented in a group analysis of surface event-related potentials (Murray et al. 2004a). In this study, subjects were presented with eight different stimulus conditions that included unisensory auditory and somatosensory stimuli, as well as simultaneous multisensory stimuli. The conditions varied in their spatial location and alignment (see Murray et al. 2004a for full details). Here, we have restricted our analyses to three conditions: (a) auditory stimulation to the left-sided speaker alone, (b) somatosensory stimulation of the left hand alone, and (c) simultaneous auditory-somatosensory stimulation of the left hand and left-sided speaker (A, S, and AS, respectively). While examination of all of the spatial combinations described in our previous work with the current methods would be of interest, it falls beyond the methodological aim of the present study. Thus, and in order to minimize the possibility of confusing the reader, we have opted to analyze one example of multisensory interactions.

Somatosensory stimuli were driven by DC pulses (+5 V; ~685 Hz; 15-ms duration) through Oticon-A 100 Ω bone conduction vibrators (Oticon Inc., Somerset, N.J., USA) with 1.6×2.4 cm surfaces held between the thumb and index finger and away from the knuckles to prevent bone conduction of sound. To further ensure that somatosensory stimuli were inaudible, the hands of these subjects were wrapped in sound-attenuating foam. Auditory stimuli were 30 ms white noise bursts (70 dB; 2.5 ms rise/fall time) delivered through a stereo receiver (Kenwood, model no. VR205) and speakers (JBL, model no. CM42) located next to the subjects' hand. Each of the original eight stimulus configurations was randomly presented with equal frequency in blocks of 96 trials. The inter-stimulus interval varied randomly (range 1.5–4 s). Subjects were instructed to press a pedal located under the right foot in response to stimulus detection, while maintaining central fixation. They were asked to emphasize speed, but to refrain from anticipating.

EEG acquisition and analyses

Continuous EEG was recorded with Neuroscan Synamps (Neurosoft Inc.) from 128 scalp electrodes (inter-electrode distance ~2.4 cm; nose reference; 0.05–100 Hz band-pass filter; 500 Hz digitization; impedances <5 k Ω). Peri-stimulus epochs were selected from –100 ms pre-stimulus to 300 ms post-stimulus, without the application of an artifact rejection criterion nor any

interpolation. Each subject contributed a minimum of 276 trials to the data for each condition.

The goal of our analysis was to determine the brain areas where and the timing when the responses to combined auditory-somatosensory stimulation differed from the responses to both unisensory conditions (i.e. multisensory = auditory + somatosensory). To accomplish this goal, we estimated for each single trial of each of the three experimental conditions, the intracranial local field potentials (LFPs) using the ELECTRA source model combined with the biophysically driven regularization strategy described in Grave de Peralta Menendez et al. (2004). This regularization strategy is based on local auto-regressive averages (LAURA). The specific LAURA parameters applied here are based on our previous work with spontaneous (i.e. non-averaged) EEG data from epileptic patients, in whom independent confirmation about the sources of electrical activity could be obtained (see Michel et al. 2004 for recent review). The spatial precision obtained with these parameters in the case of epileptic patients therefore justifies their current application to single-trial, experimental EEG data. More specifically, this distributed source localization procedure selects a unique solution to the bioelectromagnetic inverse problem on the basis of physical laws governing propagation of potential fields in biological media (see, e.g. Grave de Peralta Menendez et al. 2004). ELECTRA provides estimates of the 3D distribution of LFPs within 4024 nodes homogeneously distributed within the inner compartment of a realistic head model derived from the Montreal Neurological Institute average brain used by the Human Brain Mapping Consortium. The voxels were restricted to the gray matter of this inner compartment and formed a regular grid with 6 mm spacing. Based on this information, the lead field matrix relating intracranial activity with externally measured data was computed. We would emphasize that the ELECTRA source model yields (intracranial) local field potentials, rather than the customary current source density presented in our previous work (e.g. Murray et al. 2004a, b, c).

In order to obtain statistics for each individual subject, we compared the single-trial LFP estimates in response to simultaneous auditory-somatosensory multisensory stimuli with the pooled trials (i.e. the union) of the constituent unisensory auditory and somatosensory stimuli within each of the 4024 gray matter voxels. This analysis is distinct from the prototypical approach of statistically comparing the response to the multisensory “whole” to the summed responses from the unisensory ‘parts’ (AS versus A + S, as in Foxe et al. 2000; Murray et al. 2004a; see also, e.g. Giard and Perronet 1999; Murray et al. 2001; Fort et al. 2002; Molholm et al. 2002, 2004), wherein variance is calculated across subjects. Here, however, there is no justification for calculating the algebraic sum of any two individual trials. Consequently, a Wilcoxon rank-sum test was conducted on the estimated LFPs at each voxel and time point, which is a non-parametric equivalent of

the unpaired *t*-test. This statistic compares the median value of the multisensory response with the median value from the pooled unisensory responses to test the hypothesis that two independent samples have come from the same population. Because it is non-parametric, this test makes limited assumptions about the distribution of the data. For any single time point, the significance criterion was set at $P < 0.05$ after correction for multiple comparisons based on the number of independent samples, which in our case is the number of electrodes (see Grave de Peralta Menendez et al. 2004; Michel et al. 2004; Murray et al. 2004b for applications of this correction approach). Likewise, in order to account for temporal auto-correlation in the data, only temporally sustained differences were considered reliable. We used a criterion of at least 11 consecutive time points [> 20 ms at 500 Hz frequency sampling; see, e.g. Guthrie and Buchwald (1991)]. This yields a spatio-temporal activation pattern of voxels with differential responses to AS multisensory stimuli.

Results

Behavioral results

Behavioral results for each subject are summarized in Table 1 and displayed in Fig. 1. Each subject showed significantly faster reaction times to the multisensory versus either unisensory condition, indicative of a redundant signals effect (one-way ANOVA and follow-up comparisons; all $P < 0.01$). Moreover, the magnitude of this effect exceeded that predicted by probability summation over the fastest portion of the reaction time distribution, as assessed using Miller's inequality (Miller 1982). This inequality places an upper limit on the cumulative probability (CP) of a reaction time at a given latency for a multisensory stimulus pair. For any latency, *t*, probability summation suffices when this value is less than or equal to the sum of the CP from each of the constituent unisensory stimuli minus an expression of their joint probability [i.e. when $CP_{(t)\text{multisensory}} < (CP_{(t)\text{auditory}} + CP_{(t)\text{somatosensory}} - (CP_{(t)\text{auditory}} \times CP_{(t)\text{somatosensory}}))$]. That probability summation did not sufficiently account for the redundant signals effect is suggestive of neural response interactions between auditory and somatosensory inputs. Additional details of the behavioral analysis and results are described elsewhere (Murray et al. 2004a).

Electrophysiological results

All subjects demonstrated early, temporally sustained differences between the multisensory and the pooled unisensory conditions. Figure 2a depicts the percentage of voxels yielding significant differences ($P < 0.05$, corrected; see Materials and methods) as a function of time. Several periods of temporally sustained (i.e. longer than

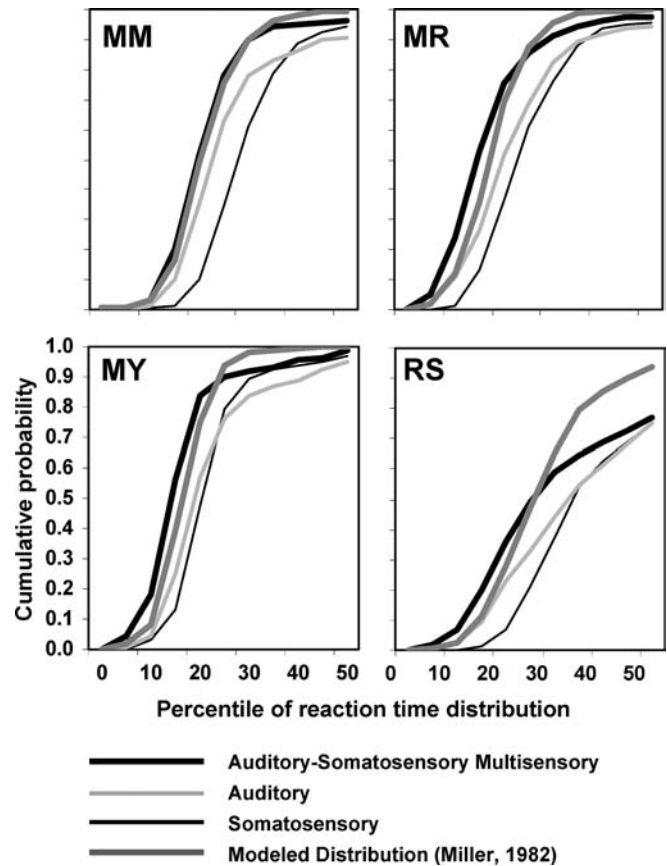
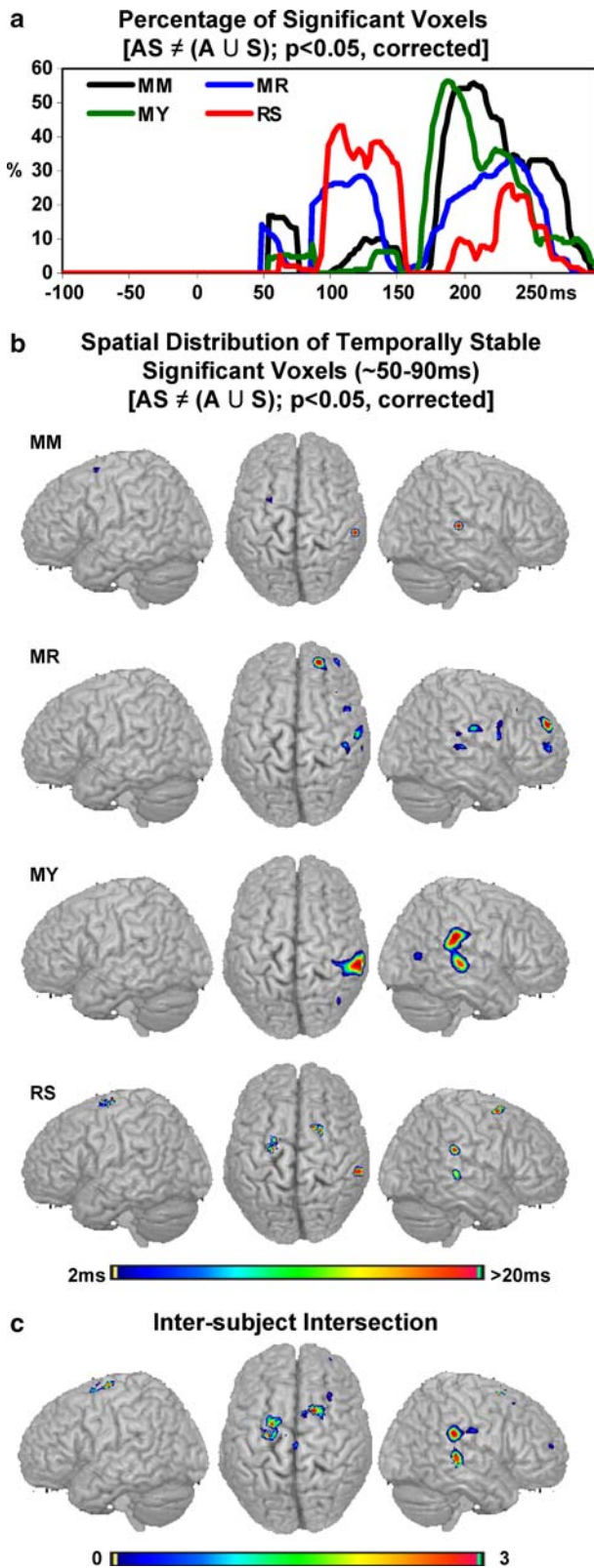


Fig. 1 Cumulative probability distributions of the reaction times for each subject in the three experimental conditions, as well as the modeled values based on application of Miller's (1982) inequality. This inequality tests the observed reaction time distribution against that predicted by simple probability summation. Distributions are shown as a percentage of the entire reaction time range for each subject

20 ms) differential multisensory responses are observed across subjects, the earliest of which begins at approximately 54 ms post-stimulus onset (MM = 54 ms, MR = 48 ms, MY = 54 ms, and RS = 62 ms). Two features of these differential responses are noteworthy. First, these periods are in phase across individuals, suggestive of inter-individual temporal stability in AS multisensory interactions. Second, there is a certain degree of inter-subject variability in the number of voxels with significantly different responses to multisensory stimuli during each of these time periods. Despite this variability, the use of a standard head model, as well as the lack of any application of a spatial smoothing kernel; there was, nonetheless, general superposition across individuals in the distribution of active voxels over the earliest time period (~54–90 ms). This lay within the posterior superior temporal cortex and temporo-parietal junction (Fig. 2b). This conclusion can also be gleaned from the intersection across subjects of those voxels yielding temporally stable response differences to AS multisensory stimuli (Fig. 2c). As a final step, we calculated the mean estimated LFP in the voxel of each



subject showing the earliest, temporally stable differential AS response. This location for each subject is shown in Fig. 3 (top), using the coordinate system of Talairach and Tournoux (1988). For each subject, this voxel was situated within the posterior superior temporal cortex

◀
Fig. 2 a Time course of differential responses to AS multisensory stimuli. Significant differences for each subject (see legend) were obtained by comparing the single-trial LFP estimations at each *gray matter* voxel over all single trials of the multisensory condition against the pooled trials of the auditory and somatosensory conditions. The *vertical axis* represents the percentage of the 4024 voxels, and the *horizontal axis* represents time in ms relative to stimulus onset. **b** Spatial distribution of temporally stable differential responses to AS multisensory stimuli for each subject. These distributions are rendered on the Montreal Neurological Institute's average brain from which the head model for the ELECTRA inverse solution was derived, using MRCRO software (Rorden and Brett 2000). *Color scale* indicates the temporal stability of differential activity at each differential voxel over the ~54–90-ms period. **c** Superposition of voxels differentially activated for the AS multisensory condition across subjects. *Color scale* indicates the number of subjects in whom a given voxel was differentially active in the AS multisensory condition for more than 20 ms over the ~54–90 ms period

(Brodmann's Area 22/42). In addition to this spatial information, the mean LFP in these voxels allowed us to determine the qualitative nature of the earliest AS multisensory interactions by comparing the group-averaged LFP estimate for the combined AS multisensory condition with that from the summed LFP estimates from each of the constituent unisensory conditions ("pair" and "sum", respectively; see Fig. 3, bottom). The response to the multisensory "pair" was enhanced relative to that of the "sum" of the constituent unisensory conditions over the ~54–90-ms period¹.

Discussion

This study illustrates how recently developed electrical neuroimaging techniques, based on the solution to the bioelectromagnetic inverse problem, can be combined with statistical analyses over single trials to examine multisensory interactions in humans to yield simultaneous high temporal and spatial resolutions. We demonstrate the feasibility of this approach in identifying spatio-temporal differences between responses to AS multisensory stimuli and the corresponding unisensory counterparts. Specifically, we observed significant AS multisensory interactions that began at ~50 ms and showed consistent temporal patterns as well as spatial distributions across individuals. In addition, the earliest differential multisensory responses were within regions of the posterior superior temporal cortex.

Both the timing and locus of these results are in strong agreement with those from our previous studies in humans (Foxe et al. 2000, 2002; Murray et al. 2004a). It is further worth noting the high degree of resemblance between the group-averaged mean LFPs from the voxel showing the earliest distinct multisensory response and

¹It is important to note that the summation of intracranial (estimated) LFPs is not subject to the same caveats as in the case of summing electric fields at the scalp (see, e.g. Molholm et al. 2002; Teder-Sälejärvi et al. 2002; Besle et al. 2004 for recent discussions)

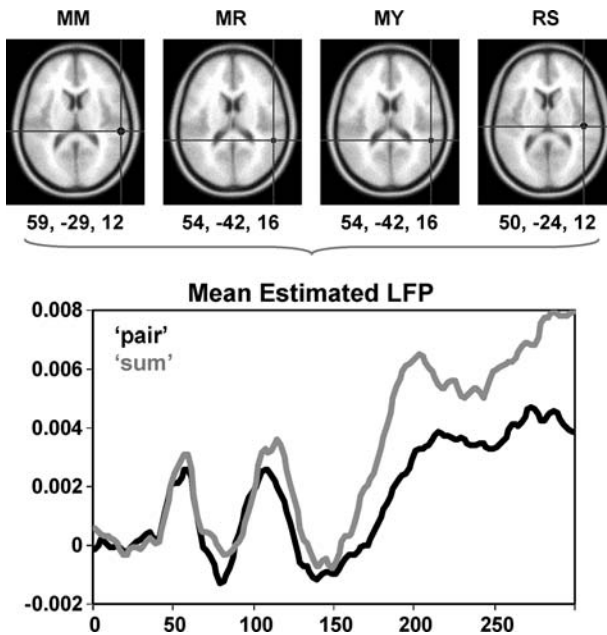


Fig. 3 *Top* axial slices indicating the location of the earliest, temporally sustained differential multisensory activity for each subject (Talairach and Tournoux (1988) coordinates indicated). *Bottom* group-averaged ($n=4$) estimated LFPs across those voxels shown above for the multisensory and summed unisensory conditions

our previously reported scalp ERPs (cf. Fig. 3 of Murray et al. 2004a). The high level of similarity between these measures supports the interpretation of early AS interactions being relatively focal, since surface recordings are subject to effects of volume conduct from “distant” sources.

While this is not the first attempt to use inverse solutions within the field of auditory-somatosensory multisensory research (e.g. Levänen et al. 1998; Foxe et al. 2000; Lütkenhöner et al. 2002; Gobbelé et al. 2003; Murray et al. 2004a, b), the analysis approach described here differs in several aspects. The first, and probably more important, difference is that this approach yields statistics on single subjects by considering as repetitions the estimated LFP for each trial and voxel. This is a key element to reduce uncertainties associated with the solution of the inverse problem (Grave de Peralta Mendez and Gonzalez Andino 1998). Consequently, the present procedure is likely to reveal cortical as well as subcortical structures (able to generate scalp EEG) as loci for early multisensory interactions. While for certain subjects, voxels at some deep structures (insula, basal ganglia, and colliculus) showed early significant differences between conditions, they were not consistently observed either in terms of temporal stability or across subjects during the ~50–90-ms period. It was only at voxels within regions of the posterior superior temporal cortex that consistent inter-subject activations were obtained. These present results obtained using a method more robust to inverse solution limitations are thus an independent validation to our previous study (Murray

et al. 2004a). A second difference with previous studies is that we estimate LFPs at each brain voxel instead of dipolar moments (e.g. Lütkenhöner et al. 2002) or the modulus of the current density vector (Murray et al. 2004a). These estimates of LFP are similar to those obtained using intracranial recordings in epileptic patients. While there are increasing numbers of intracranial investigations of multisensory processes in humans (Foxe et al. 2004; Matsushashi et al. 2004; Murray et al. 2004d), such patients are not readily available and the spatial sampling is often limited to locales near the putative epileptogenic site.

There are several future directions in which this method can be applied to multisensory research that are worth mentioning here. First, since LFPs are estimated for the whole gray matter volume, the relative timing of responses (including interactions) can be determined throughout the brain volume. As such, fundamental questions concerning the temporal flow of information can be addressed throughout the brain. As has recently been reviewed by Schroeder et al. (2004), temporal information can complement anatomical data in generating functional hierarchies of brain processes. Second, the analysis of single-trial data makes it possible to perform spectral or time-frequency analyses at each gray matter voxel. In terms of multisensory research, such analyses would facilitate the examination of the role of oscillatory activity in the binding of sensory information, as well as in attentional modulation between the senses (e.g. Fu et al. 2001; Sokolov et al. 2004). Similarly, behavioral measures such as reaction time can be correlated with oscillatory phenomena at specific brain sites as described in Gonzalez Andino et al. (2005). Finally, the present methods make it feasible to perform more direct comparisons of data obtained from human and non-human primates, with the promise of defining inter-species correspondence in functional anatomy and brain processes.

In conclusion, the present study illustrates the applicability of biophysically driven inverse solutions in offering a novel and reliable approach for studying multisensory processing in individual subjects with high temporal and spatial resolution.

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