

Rapid discrimination of visual and multisensory memories revealed by electrical neuroimaging

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Though commonly held that multisensory experiences enrich our memories and that memories influence ongoing sensory processes, their neural mechanisms remain unresolved. Here, electrical neuroimaging shows that auditory–visual multisensory experiences alter subsequent processing of unisensory visual stimuli during the same block of trials at early stages poststimulus onset and within visual object recognition areas. We show this with a stepwise analysis of scalp-recorded event-related potentials (ERPs) that statistically tested (1) ERP morphology and amplitude, (2) global electric field power, (3) topographic stability of and changes in the electric field configuration, and (4) intracranial distributed linear source estimations. Subjects performed a continuous recognition task, discriminating repeated vs. initial image presentations. Corresponding, but task-irrelevant, sounds accompanied half of the initial presentations during a given block of trials. On repeated presentations within a block of trials, only images appeared, yielding two situations—the image’s prior presentation was only visual or with a sound. Image repetitions that had been accompanied by sounds yielded improved memory performance accuracy (old or new discrimination) and were differentiated as early as ~60–136 ms from images that had not been accompanied by sounds through generator changes in areas of the right lateral–occipital complex (LOC). It thus appears that unisensory percepts trigger multisensory representations associated with them. The collective data support the hypothesis that perceptual or memory traces for multisensory auditory–visual events involve a distinct cortical network that is rapidly activated by subsequent repetition of just the unisensory visual component.

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Introduction

Neurophysiological investigation of when and where in the brain one’s memories or past experiences first affect responses to

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incoming stimuli has predominantly focused on the influence of unisensory memories; that is, stimulation of one sensory modality later influencing the responses to stimuli within the same modality. For example, studies of repetition priming have shown that behavior and brain responses change with repeated exposure to the same or similar stimuli (e.g., Doniger et al., 2001; Wiggs and Martin, 1998 for a recent review). More recently, investigations have begun examining how experiences in one or multiple senses alter later processing of stimuli of another sensory modality. These studies provide evidence that brain regions involved in an experience’s encoding are also involved during its subsequent active retrieval (e.g., James et al., 2002; Nyberg et al., 2000; Wheeler et al., 2000). Subjects learned auditory–visual or visual–visual associations during a study session and later classified visual stimuli according to the sensory modality with which it initially appeared (Nyberg et al., 2000; Wheeler et al., 2000). That auditory regions were active in response to visual stimuli that were first presented with sounds was taken as support for the theory of ‘redintegration’ (Hamilton, 1859), wherein a component part is sufficient to (re)activate the whole experience’s consolidated representation. Intracranial microelectrode recordings in monkeys provide similar evidence by demonstrating selective delay activity during a delayed match-to-sample task with visual–visual, somatosensory–visual, and auditory–visual paired associates (e.g., Colombo and Gross, 1994; Gibson and Maunsell, 1997; Haenny et al., 1988; Maunsell et al., 1991). In these studies, responses were elicited in cortical areas involved in visual object recognition (i.e., areas V4 and IT) by nonvisual stimuli and were selective for specific associations among the learned set. One implication of these collective data is that prior multisensory experiences can influence and be part of memory functions such that when an association is formed between stimuli of different modalities, presentation of one stimulus can alter the activity in regions typically implicated in the processing of the modality of the other stimulus. That is, responses to an incoming stimulus may vary, either in terms of their pattern within a region or overall activated network, according to whether it is part of a multisensory or unisensory memory. However, it is not clear where or when (either in terms of time poststimulus or in terms of levels of processing) such effects first occur. These previous studies either lacked adequate temporal resolution or had limited spatial sampling to

provide such information. Identification of the earliest effects can be used to place critical limits on the mechanisms of multisensory memory retrieval. It is similarly unclear whether such effects depend either on extensive training with the stimulus associations or on active classification of stimuli according to past experiences.

The aim of the present study was to determine the time course and initial locus of incidental effects of past multisensory experiences on current unisensory processes when subjects neither studied (through prolonged or repeated exposure) multisensory image–sound pairs nor later classified images according to the sense(s) initially stimulated. We applied high-density electrical neuroimaging techniques to this aim. We show that visual stimuli are rapidly differentiated according to their multisensory or unisensory association as early as ~60–136 ms poststimulus onset in regions of the right lateral–occipital complex (LOC), a system of areas of the ventral visual cortical pathway involved in object recognition (e.g., Malach et al., 1995; Murray et al., 2002). This observation indicates that multisensory memories first alter visual sensory responses at early processing stages and provides evidence of the functional efficacy of prior multisensory experiences.

Materials and methods

Subjects

Eleven (three female) paid volunteers aged 18–28 years (mean \pm SD = 23.6 \pm 3.4 years) provided written, informed consent to participate in the experiment, the procedures of which were approved by the Ethical Committee of the University Hospital of Geneva. All subjects were right-handed (Edinburgh questionnaire; Oldfield, 1971), had no neurological or psychiatric illnesses, had normal or corrected-to-normal vision, and reported normal hearing.

Stimuli and procedure

Subjects performed a continuous recognition task comprised of equal numbers of initial and repeated presentations of line drawings (Fig. 1). This task had subjects indicate whether each visual stimulus was appearing for the first time or had appeared previously. Visual stimuli were comprised of 268 line drawings of common objects selected from either a standardized set (Snodgrass and Vanderwart, 1980)¹ or obtained from an online library (<http://dgl.microsoft.com>) and modified to stylistically resemble those from the standardized set. Images appeared black on a white background and were centrally presented for 500 ms on a computer monitor (Sony Trinitron Multiscan model no. GDM-20SE1VT) located 150 cm from the subject. Images subtended an average of approximately 4.5° (\pm 1.2°) in both the vertical and horizontal planes. On initial presentations, visual stimuli could either be presented with or without a corresponding, but task-irrelevant, sound with equal likelihood. That is, the image set was equally divided into two groups: those that upon initial presentation appeared only visually and those that appeared with a corre-

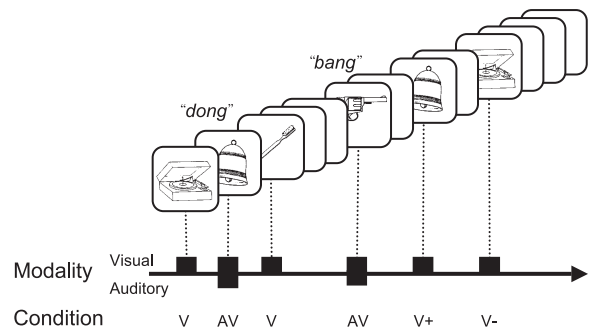


Fig. 1. Stimulus paradigm. The continuous recognition task was comprised of initial and repeated image presentations. Half of the initial presentations were simultaneously paired with corresponding, but task-irrelevant, sounds (e.g., an image of a bell was paired with a “dong” sound). This was the AV condition. The other half of initial presentations only contained images—the V condition. While all repeated presentations only contained images, they were subdivided for analysis purposes into two conditions—those that on their initial presentation had been presented with sounds (V+ condition) and those that had only been presented visually (V– condition). See Materials and methods for full details.

sponding sound as a simultaneous auditory–visual multisensory pair (hereafter ‘V’ and ‘AV’ conditions, respectively). To minimize the possibility that observed effects were a result of categorical perception rather than the sensory modalities stimulated at the time of initial exposure, each group included approximately the same number of different categories of objects (e.g., animals, tools, musical instruments, vehicles, and miscellaneous household items, etc.). Likewise, upon interviewing after the experiment, no subject reported noticing any difference in terms of object categories between the V and AV conditions.

Auditory stimuli were complex, meaningful sounds (16 bit stereo, 44,100 Hz digitization, 500 ms duration), each of which corresponded to one of the visual stimuli in the AV group (e.g., a “dong” sound with the image of a bell; see Fig. 1). Sounds were obtained from an online library (<http://dgl.microsoft.com>), modified using audio editing software (Cool Edit Pro version 1.0) so as to be 500 ms in duration, and were delivered through stereo speakers located on each side of the computer monitor. The volume was adjusted to a comfortable and comprehensible level for each subject, such that sounds were not disturbing during the task.

On repeated presentations, only the visual stimuli from the initial presentations were displayed. The subjects’ task was to indicate as quickly and as accurately as possible, via a right-hand button press, whether the image was being presented for the initial or repeated time (i.e., if the image was new or had been seen before). Thus, there were two classes of repeated presentations: (1) those having initially been presented as visual alone and (2) those having initially been presented with sounds (hereafter, ‘V–’ and ‘V+’ conditions, respectively). These conditions differed only in whether or not the initial presentation of the image was paired with a sound—that is, whether or not there was an auditory–visual multisensory memory associated with the image. Subjects were not asked to make this distinction and performed the same task with both V+ and V– conditions. As such, the context (i.e., whether a sound had been simultaneously presented on the image’s initial encounter) was completely incidental rather than integral to the task. The subjects’ naivety about this V– and V+ subdivision was

¹ The images in this set were standardized for name agreement, image agreement, familiarity, and visual complexity, and are described in detail in Snodgrass and Vanderwart (1980).

confirmed in interviews with each subject after the completion of the experiment, indicating that subjects were strongly engaged in the visual task.

Stimuli were blocked into a series of 136 trials (except for the 4th and 8th blocks that each had 132 trials), with equal likelihood of initial and repeated presentations as well as V, AV, V–, and V+ conditions. During a block of trials, each image was repeated once, independently of how the image was initially presented. The average number of trials between the initial and repeated presentation of any given stimulus was 13 (± 3) images. The timing of trials was such that stimuli were presented for 500 ms, followed by a 1200–1500-ms period of randomized stimulus onset asynchrony (SOA). Each subject completed eight blocks of trials.

EEG acquisition and preprocessing

Continuous EEG was acquired with a Geodesics Netamps system (Electrical Geodesics, Inc., USA) from 123 scalp electrodes (impedances < 50 k Ω ; vertex reference; 500 Hz digitization; bandpass filtered 0.1–200 Hz). Epochs of EEG from 50 ms prestimulus to 500 ms poststimulus onset were averaged for each of the four stimulus conditions and from each subject to calculate the event-related potential (ERP). Only trials leading to correct responses were included. In addition to the application of an automated artifact criterion of ± 80 μ V, the data were visually inspected to reject epochs with blinks, eye movements, or other sources of transient noise. The average EEG epoch acceptance rate was 83.7% ($\pm 10.9\%$). Baseline was defined as the 50 ms prestimulus period. For each subject's ERPs, data at artifact electrodes were interpolated (Perrin et al., 1987) and the ERP was further down-sampled to a 111-channel montage used in the estimation of the inverse solution (see below). ERPs were bandpass filtered (1–40 Hz), recalculated against the average reference, and normalized to their mean global field power (GFP; see below as well as Lehmann and Skrandies, 1980) before group averaging. Additionally, the ERPs of each subject and condition were aligned such that the GFP peak of the P1 component was at 100 ms poststimulus onset (see e.g., Goffaux et al., 2003; Morand et al., 2000; Picton et al., 2000 for similar approaches). The average alignment shift for the V+ condition was $+0.64 \pm 5.4$ data points (1.2 ms at 500 Hz digitization) and that for the V– condition was $+0.27 \pm 6.1$ data points (0.54 ms at 500 Hz digitization), where positive values indicate a shift from a value less than 100 ms. Moreover, a paired t test indicated that this alignment procedure did not produce a systematic difference between ERPs of each subject ($t_{(10)} = 0.21$; $P = 0.84$).

ERP analyses

Waveform modulations

To determine the timing of differences in ERP responses to V+ and V– stimuli, we calculated pointwise paired t tests between ERP responses using the across subjects variance. By this method, we identified the onset of differential responses between the V+ and V– stimulus conditions. For each electrode, the first time point where the t test exceeded the 0.05 alpha criterion for at least 10 consecutive data points (> 20 ms at a 500 Hz digitization rate) was labeled as onset of an ERP modulation (see e.g., Fort et al., 2002a,b; Guthrie and Buchwald, 1991; Molholm et al., 2002; Murray et al., 2002 for similar approaches). The results of the

pointwise t tests from the 111-electrode montage are displayed as an intensity plot (Fig. 2B).

We include the results of these tests for several reasons. First, this analysis provides an estimate of the onset and offset of ERP effects and maintains the temporal resolution of the EEG methodology. Second, the entire data set can be concisely summarized without the observer-dependent assumption of picking electrode locations for statistical tests. Third, in addition to providing temporal information, the results of these t tests can assist in the interpretation of scalp topographic analyses (see below) by indicating which electrode site(s) demonstrates a statistically significant differential response at any given time point. It is important to note that there is, at present, no established statistical means of addressing the questions of either the spatial (i.e., over how many electrodes) or temporal (i.e., over how much time) extent a difference must be observed to be considered statistically robust. Nor is there an accounting for the added statistical power provided by high-density EEG recordings. As such, and perhaps most importantly, this analysis serves as a fundamentally important hypothesis generation tool.

Field strength modulations

Changes in electric field strength were identified by calculating the global field power (GFP; Lehmann and Skrandies, 1980) for each subject and stimulus condition. GFP is equivalent to the spatial standard deviation of the scalp electric field, yields larger values for stronger electric fields, and is calculated as the square root of the mean of the squared value recorded at each electrode (vs. the average reference). As with the ERP waveform data, the GFP data underwent a pointwise paired t test using the variance across subjects as well as the same 10-point temporal criterion. It is important to note that the observation of a GFP modulation does not exclude the possibility of a contemporaneous change in the electric field topography. Nor does it rule out the possibility of topographic modulations that nonetheless yield statistically indistinguishable GFP values. However, the observation of a GFP modulation in the absence of a topographic modulation (see below for details) would be indicative of amplitude modulation of statistically indistinguishable generators across experimental conditions.

Topographic modulations

To statistically identify periods of topographic modulation, we calculated the global dissimilarity (Lehmann and Skrandies, 1980) between V+ and V– responses for each time point of each subject's data. Global dissimilarity is an index of configuration differences between two electric fields, independent of their strength. This parameter equals the square root of the mean of the squared differences between the potentials measured at each electrode (vs. the average reference), each of which is first scaled to unitary strength by dividing by the instantaneous GFP. Dissimilarity can range from 0 to 2, where 0 indicates topographic homogeneity and 2 indicates topographic inversion. We applied a Monte Carlo MANOVA (Manly, 1991) to test for statistical differences in the dissimilarity between V+ and V– conditions. This is a nonparametric bootstrapping procedure, wherein the each subject's data from each time point was permuted such that they could "belong" to either stimulus condition. The dissimilarity was then calculated for each of the 5000 such permutations for each time

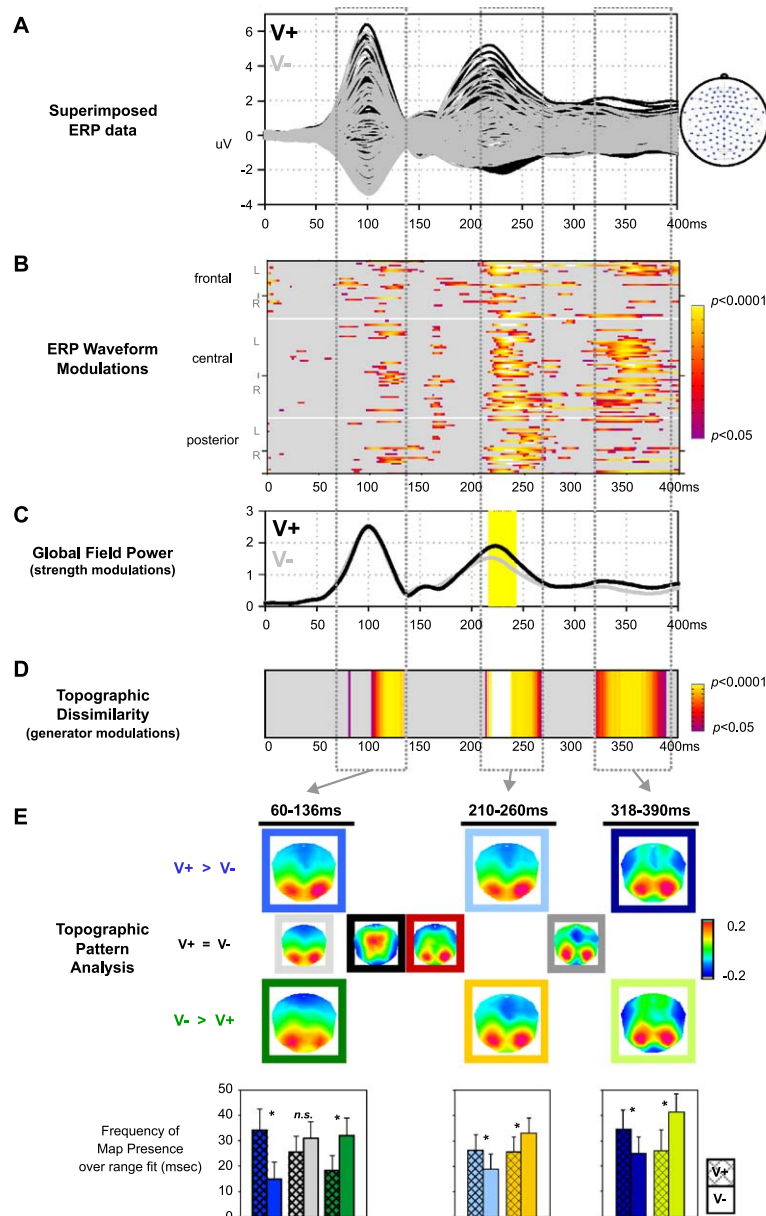


Fig. 2. Event-related potential (ERP) data and results of the stepwise analyses. (A) Group-averaged ($N = 11$) ERP waveforms are shown superimposed across all electrodes and both V+ and V- conditions (black and gray traces, respectively, with the electrode montage shown in the inset). (B) ERP waveform modulations were assessed with pointwise paired t tests for each electrode and time point using the variance across subjects. Time is plotted along the x -axis, scalp electrode location along the y -axis, and the P value of these t tests as a color value (see Materials and methods for details). These tests indicate several phases of response modulation that are highlighted by dotted outline boxes. The earliest phase covered the ~ 60 –136-ms period, with subsequent phases at 210–260 and 318–390 ms. (C) Field strength modulations across time were assessed from each subject's global field power (GFP) from each condition. This analysis revealed a single, late phase of modulation over the 218–244-ms period (indicated by the yellow bar). (D) Global dissimilarity tested topographic homogeneity between the V+ and V- conditions at each time point. Several phases where the scalp topography significantly differed across conditions were observed—the earliest of which included the ~ 60 –136-ms period. (E) A topographic pattern analysis ascertained how many generator configuration changes or alternatively whether latency differences between conditions underlie changes in topographic homogeneity between conditions. The top portion displays the obtained template maps. Those framed in shades of blue dominated in the V+ condition, whereas those framed in green or yellow dominated the V- condition. All others were common to both conditions. The pattern observed in the group-averaged data was tested at the individual subject level. The results of these tests are shown in the bar graphs, showing the frequency within specific time ranges that each template map was observed. Asterisks indicate significant differences ($P < 0.05$) between conditions for a given template map's observation.

point and was used to generate a distribution of values against which the observed data could be compared. From such, we determined the probability of obtaining a dissimilarity value from the permutations that exceeded the actual measured value. Since

electric field changes are indicative of changes in the underlying generator configuration (e.g., Fender, 1987; Lehmann, 1987), this test provides a statistical means of determining if and when the brain network activated by the V+ and V- conditions differ.

Topographic pattern analysis

A pattern analysis of the ERP scalp topography across both time and experimental conditions was performed to determine whether topographic differences observed above were explainable by a single or multiple configuration changes, or alternatively by a latency shift across conditions. The spatio-temporal analysis approach applied here has been used in several previous event-related potential studies, both from our laboratory (e.g., Ducommun et al., 2002; Pegna et al., 2002; Schneider et al., 2002; as well as Michel et al., 1999, 2001 for reviews) as well as from those of others (e.g., Brandies and Lehmann, 1989; Koenig and Lehmann, 1996; Lavric et al., 2001; Pizzagalli et al., 2000, 2002; Vitacco et al., 2002). The method applied here consisted of the following steps.

First, a spatial cluster analysis (Pascual-Marqui et al., 1995) identified the most dominant scalp topographies appearing in the group-averaged ERPs from each condition over time. This approach is based on the observation that scalp topographies do not change randomly, but rather remain for a period of time in a certain configuration and then switch to a new stable configuration (e.g., Lehmann, 1987; Michel et al., 1999). We further applied the constraint that a given scalp topography must be observed for at least 10 consecutive data points (>20 ms at a 500 Hz digitization rate) in the group-averaged data. This criterion is effectively similar to that frequently applied in the analysis of ERP waveform modulations, as discussed above. From such pattern analysis, it is possible to summarize ERP data by a limited number of scalp configurations, which we refer to here as “template maps”. Each such template map is thought to represent a given “functional microstate” of the brain or a given computational step during information processing (Lehmann, 1987, Michel et al., 1999). This method is independent of the reference electrode and is insensitive to amplitude modulation of the same scalp configuration across conditions, because topographies of normalized maps are compared (Lehmann, 1987). The optimal number of template maps that explains the whole data set (i.e., the group-averaged ERPs from both V+ and V– conditions collectively) is determined by a modified cross validation criterion (Pascual-Marqui et al., 1995).

Second, the appearance of template maps identified in the group-averaged data was statistically verified in the ERPs of the individual subjects. To do this, each template map was compared with the moment-by-moment scalp topography of the individual subjects’ ERPs from each condition by strength-independent spatial correlation (e.g., Michel et al., 1999, 2001 for review). That is, for each time point of the individual subject’s ERP (note that the 10 data point/20 ms criterion was not applied to the individual subject data), the scalp topography was compared to all template maps and was labeled according to the one with which it best correlated. It is important to note that this labeling procedure is not exclusive, such that a given period of the ERP for a given subject and stimulus condition is often labeled with multiple template maps. Nonetheless, the results of the labeling reveal if a given ERP is more often described by one template map vs. another. That is, from this fitting procedure, we determined the total amount of time a given topography was observed for a given condition across subjects. These values were then subjected to a repeated measures ANOVA using stimulus condition (V+ and V–) and template map as within-subject factors. In addition to the above timing information (including onset and offset of a given topography), this fitting procedure also yields information about when a given template map was best fit to the data. However, in contrast to the test of dissimilarity, this labeling procedure does not

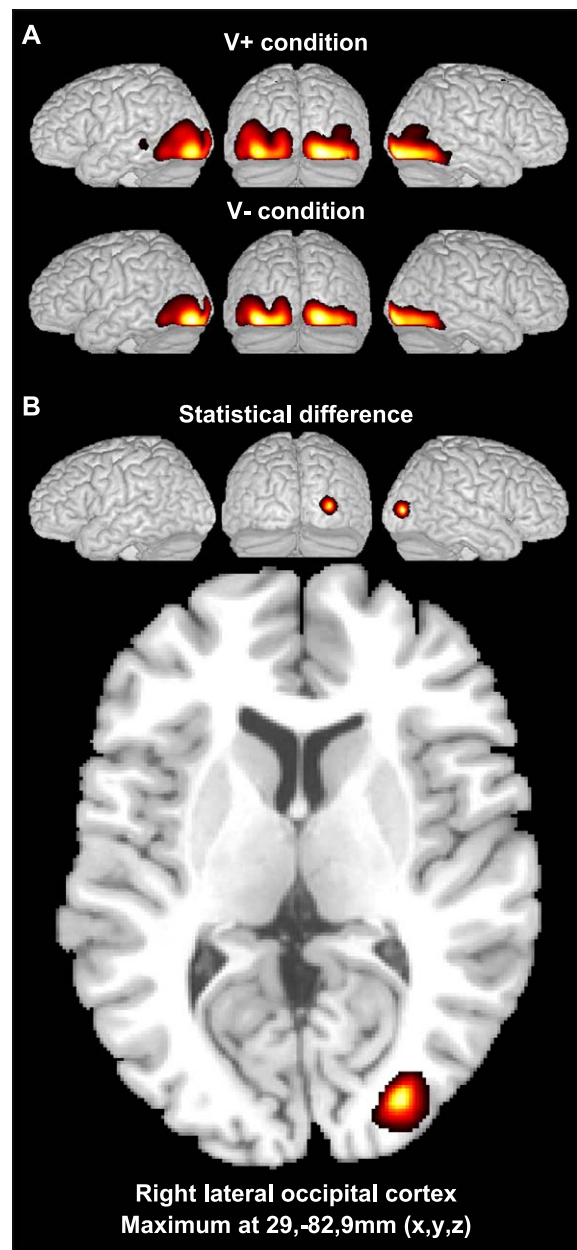


Fig. 3. Source estimation and analysis. LAURA distributed linear inverse solution estimations and statistical analysis were conducted for the 60–136-ms period after averaging the ERP from this period for each subject’s ERP. Source estimations are rendered on a brain supplied by MRICRO (Rorden and Brett, 2000). (A) Group-averaged ($N = 11$) source estimations for the V+ condition (top) and V– condition (bottom) shown from left-sided, posterior, and right-sided views. The color scale indicates current density strength. (B) Results of the statistical comparison of the source estimations for the V+ and V– conditions (paired t test for each voxel; thresholded at $t_{(10)} > 5.12$; $P < 0.00045$ to correct for the number of independent measurements). This revealed a right lateral–occipital complex source (Talairach and Tournoux, 1988 coordinates indicated) that was stronger in response to the V+ than to V– condition. This source is shown for the same views as in A, as well as for an axial slice at level of maximal statistical difference ($z = 9$ mm) with the right hemisphere shown on the side.

statistically test whether time periods that are fit with different maps indeed have statistically different scalp topographies.

Source estimation analysis and statistics (SEAS)

The intracranial generators for each condition were estimated using a distributed linear inverse solution based on a Local Auto-Regressive Average (LAURA) model of the unknown current density in the brain (Grave de Peralta et al., 2001). LAURA uses a realistic head model with a solution space of 4024 nodes, selected from a $6 \times 6 \times 6$ mm grid equally distributed within the gray matter of the Montreal Neurological Institute's (MNI's) average brain. Like other inverse solutions of this family, LAURA is capable of dealing with multiple simultaneously active sources of a priori unknown location and makes no assumptions regarding the number or location of active sources. This linear distributed inverse solution selects the source configuration that better mimics the biophysical behavior of electric vector fields and produces a unique estimator of the current source density vector inside the brain. That is, the estimated activity at one point depends on the activity at neighboring points as described by electromagnetic laws (see Grave de Peralta and Gonzalez Andino, 2002 for details). For the analysis presented here, we used the cubic power of the inverse distance. The LAURA method increases up to 32% (vs. the 20% reported for other inverse solution approaches) the number of sources with zero localization error and decreases the maximum error while keeping the average error lower than 1 for almost any eccentricity within the solution space (see Grave de Peralta and Gonzalez Andino, 2002 for details).

Statistical analysis of the LAURA source estimations was executed in the following manner. First, the above analyses of the scalp ERP data were used to define a time period not only where stable topographies were observed within each condition, but also where these topographies significantly differed between conditions. Next, this period's ERP data were averaged across time to generate a single time point of data for each subject and condition. The LAURA inverse solution for these data (11 subjects \times 2 conditions) was estimated for each of the 4024 nodes in the solution space. Paired *t* tests were then calculated for each node in the inverse solution space using across-subjects variance. Since the maximum number of independent sources that can be identified is limited by the number of recording electrodes minus the reference electrode, which in this study is 110 electrodes (i.e., the number of independent measurements), only nodes with *P* values < 0.00045 ($t_{(10)} > 5.12$) were considered significant, representing a Bonferroni type of correction for multiple tests. The results of these source estimations are rendered on a brain supplied by MRIcro (Rorden and Brett, 2000) with the coordinates (Talairach and Tournoux, 1988) of the largest statistical difference indicated.

Results

We restricted our analyses to responses to the repeated presentations (i.e., the V+ and V− conditions), reasoning that differences between responses to these stimuli reveal brain mechanisms of incidental multisensory memory discrimination. Subjects readily discriminated between initial and repeated presentations of images (overall accuracy across all four conditions = $91 \pm 1\%$). More precisely, the subjects' accuracy was significantly higher for stimuli from the V+ than the V− condition (88.5% vs. 86.1% correct; $t_{(10)} = 3.18$; $P < 0.01$). Such improvement for indicating

V+ image repetitions was observed in 10 of the 11 subjects (the 11th showed equal accuracy for both conditions). Reaction times from these conditions did not significantly differ ($V+ = 636.1$ ms vs. $V- = 635.6$ ms; $t_{(10)} = 0.18$; $P = 0.86$). The improved accuracy for the V+ condition provides a first indication that visual stimuli are incidentally and differentially processed according to the multisensory memories associated with them.

Fig. 2 compares ERP responses to V+ and V− conditions and displays the results of our stepwise spatio-temporal analysis. It shows several phases of differential responses—the earliest occurring over the ~ 60 –136-ms period. To statistically define these phases of response modulation between V+ and V− conditions, we first conducted a series of *t* tests for each time point (2 ms at 500 Hz sampling rate) and scalp electrode using across subjects variance (see Materials and methods for details). The results of this waveform analysis are displayed as a statistical cluster plot (Fig. 2B), which shows that the earliest ERP modulation onset at approximately 60 ms, continuing until ~ 140 ms at several electrodes. Two subsequent periods of response modulation followed, covering the ~ 210 –260- and 320–390-ms periods. The presence of ERP modulations across several time periods thus indicates that the nature of past experiences (multisensory vs. unisensory) alters brain responses at both early, presumably sensory, as well as later, higher-level processing stages.

In addition to determining the time course of ERP response modulations, we were interested in statistically determining their likely underlying neurophysiological mechanisms. To do this, a further series of independent analyses were conducted utilizing global measures of the scalp electric field. The first of these tested for modulations in electric field strength as measured by the instantaneous global field power (GFP; Lehmann and Skrandies, 1980). These values were submitted to an identical point-wise paired *t* test as was conducted with each electrode described above. This analysis provided no evidence for GFP modulations over the 60–140 ms period. Rather, only a single, later phase of modulation over the 218–244-ms period was observed (Fig. 2C). As such, this analysis suggests that the earliest modulation between responses to V+ and V− stimuli at ~ 60 –140 ms is not explained by a simple modulation of the global strength of the electric field.

We therefore directly tested whether these early ERP modulations were due to topographic modulations, which would indicate changes in the underlying generator configuration. To do this, we calculated the global dissimilarity (Lehmann and Skrandies, 1980) between the two conditions for each time point of each subject's data. A Monte Carlo bootstrapping approach revealed three phases where the scalp topography significantly differed across conditions—the earliest of which included the ~ 60 –136-ms period (Fig. 2D). Subsequent topographic modulations were also observed over the ~ 210 –260- and 318–390-ms periods. From this topographic profile analysis, we thus conclude that the ERP waveform modulations shown in Figs. 2A,B are due to differences in the active brain sources at the same moments in time. However, thus far, the comparisons between the ERPs and the V+ and V− conditions were performed on a millisecond-by-millisecond basis. Such analyses run into difficulties if the speed of processing differs between conditions (i.e., if the same processes were active, but with latency shifts between conditions).

To test for such an explanation for the observed ERP modulations, we performed a pattern analysis of the ERP scalp topography across both time and experimental conditions (see Materials

and methods for details). This first identified the most dominant scalp topographies appearing in the group-averaged ERPs from each condition over time, independent of their strength, which we refer to as template maps. It has been repeatedly shown that a limited number of such template maps can be used to describe ERP time series, with each predominating for a certain amount of time. Periods of stable scalp topography are interpreted as reflecting distinct ‘functional microstates’ during cerebral processing, comparable to the definition of ERP components offered by Donchin et al., 1978. The identification and analysis of these template maps allowed us to ascertain whether the same functional microstates appear in both conditions, but with shifted latencies, or whether different functional microstates occur in each condition. In the group-averaged data, we indeed found that some of these template maps appeared in one condition but not the other and vice versa. Moreover, the latencies at which this occurred overlapped with the time periods of response modulation identified in the preceding analyses (Fig. 2E). Those template maps framed in shades of blue dominated in the V+ condition, whereas those framed in green or yellow dominated the V– condition.

The appearance of these template maps was then statistically verified in the ERPs of the individual subjects using a strength-independent spatial correlation fitting procedure, wherein each time point of each subject’s ERP was labeled with the template map with which it best correlated (see Materials and methods for details). From this fitting procedure we determined both when and also the total amount of time a given topography was observed in a given condition across subjects (Fig. 2E, bottom). These latter values were subjected to a repeated measures ANOVA using stimulus condition (V+ and V–) and template map as within-subject factors for specific time periods. Over the 60–136-ms period, three template maps were identified in the group-averaged ERPs from both conditions. The ANOVA after the fitting procedure revealed a significant interaction between the factors of condition and template map ($F_{(2,20)} = 4.21$; $P < 0.03$), indicating that different template maps were more often observed for each stimulus condition, respectively. Follow-up planned comparisons (paired *t* tests) confirmed the observations in the group-averaged data, where one map was more often observed for the V+ condition (that framed in blue in Fig. 2E, bottom) and a different map was more often observed for the V– condition (that framed in green in Fig. 2E, bottom). Similar interactions between condition and template map were likewise observed for the 210–260- ($F_{(1,10)} = 6.70$; $P < 0.03$) and 318–390-ms ($F_{(1,10)} = 9.74$; $P < 0.01$) periods.

While these multiple independent analyses of the ERP data indicate several periods where different generator configurations described responses to the V+ and V– conditions, we were particularly interested in identifying the active sources during the earliest of these periods (60–136 ms). For one, the early latency of this effect would suggest that responses to visual stimuli are altered by the nature of their past experiences at sensory processing stages. Likewise, this timing raises the question of whether this response modulation is indeed first occurring within visual sensory areas, although the multisensory memory representation itself is likely widely distributed throughout brain regions. As such, identifying the earliest differentially activated sources provides an indication of and limitation on the spatio-temporal mechanism of incidental multisensory memory discrimination. We estimated the sources that were active during the 60–136-ms period for both the V+ and V– conditions using a distributed linear inverse solution (LAURA; Grave de Peralta et al., 2001). These were calculated by first

averaging the surface ERP over the 60–136-ms period for each subject and condition. Next, the inverse solution for each subject and condition was estimated. These estimations were then group-averaged. Fig. 3A shows the group-averaged LAURA source estimations for each condition. Both conditions included active sources within the occipital and lateral–occipital cortices, bilaterally. Visual inspection of these inverse solution estimations also indicated generator differences between the conditions. Statistical tests of LAURA inverse solutions allowed us to determine the pixels significantly differing between the V+ and V– conditions. This was accomplished by submitting the inverse solution estimations to a paired *t* test using across-subjects variance at each of the 4024 lead field nodes. Fig. 3B shows the results of this analysis, which have been adjusted for multiple tests, such that only voxels where $t_{(10)} > 5.12$; $P < 0.00045$ are considered significant. This analysis reveals that this earliest ERP difference between conditions was explained by a right lateral–occipital complex (LOC) source (coordinates $x, y, z = 29, 82, 9$ mm; Talairach and Tournoux, 1988) that was stronger in response to the V+ than to the V– condition.

Discussion

The present study examined the time course and initial locus of incidental effects of past multisensory experiences on current unisensory responses when subjects neither explicitly studied multisensory associations nor later classified stimuli according to these associations. Both the behavioral and electrophysiological data provided evidence for such effects. Image repetitions during a continuous recognition task were more accurately discriminated if they had initially been presented with a sound than when presented only visually, providing one indication of the functional efficacy of incidental multisensory memories or perceptual traces on later sensory functions. That is, visual stimuli with specific auditory–visual multisensory pasts during this experiment yielded improved memory performance vis à vis image repetition discrimination. In addition, the electrical neuroimaging data and stepwise statistical analysis thereof provided insights into the likely neurophysiological mechanisms of such multisensory memories’ incidental impact on sensory–cognitive processing. They reveal that responses to repeated visual stimuli were rapidly differentiated, first over the 60–136 ms poststimulus period, according to past multisensory vs. unisensory experiences. Furthermore, this effect resulted from an alteration in the underlying generator configuration of active brain sources within visual object recognition areas. In what follows, we discuss the implications of these findings on our understanding of multisensory interactions and memory representations.

Our primary finding was that responses to repeated unisensory visual stimuli were incidentally affected at early latencies by whether or not these stimuli had been previously presented with a sound. This suggests that brain responses to unisensory stimuli have access to multisensory memory representations early on in sensory–cognitive processing. Furthermore, the LAURA inverse solution analysis indicates that this access initially manifests within visual object recognition areas of the right LOC. We propose that this early modulation reflects the rapid reactivation of distinct multisensory and unisensory perceptual traces established during initial stimulus presentation within the LOC (see e.g., Doniger et al., 2001 for a similar model in the case of repetition priming following perceptual learning). This proposal, however, relies on

(at least) three prerequisites: (1) that the LOC indeed demonstrates auditory–visual convergence, (2) that multisensory memory representations are both localized and distinguishable from their unisensory counterparts within the LOC, and (3) that sensory responses can propagate to and differ within the LOC within the latency of the present effects.

Regarding the first prerequisite, hemodynamic and electrical neuroimaging studies of humans provide evidence of both auditory–visual (Calvert et al., 1999, 2000, 2001; Fort et al., 2002a,b; Giard and Peronnet, 1999; MacSweeney et al., 2002; Molholm et al., 2002; Raji et al., 2000) and tactile–visual (Amedi et al., 2001, 2002; Deibert et al., 1999; James et al., 2002; Stoesz et al., 2003; Zangaladze et al., 1999) multisensory convergence in the LOC and other nearby visual cortices. Additional support for the role of higher-tier object recognition areas in multisensory interactions is found in microelectrode recordings from monkey infero-temporal (IT) cortex, for which the LOC is considered to be the human homologue, as well as visual area V4. In these studies, selective delay-period responses on a delayed match-to-sample task were observed for specific multisensory and unisensory paired associates (e.g., Colombo and Gross, 1994; Gibson and Maunsell, 1997; Haenny et al., 1988; Maunsell et al., 1991; see also Goulet and Murray, 2001). The selectivity of these responses indicates that neurons within these regions distinguish unisensory stimuli according to their learned association with another stimulus of the same or different sensory modality. Moreover, neurons showing selective responses for multisensory associations did not show selective responses to other unisensory associations (Gibson and Maunsell, 1997). The suggestion is that there are distinct neural responses to and perhaps also distinct representations of unisensory and multisensory associations within the IT cortex, which would satisfy the second prerequisite described above. Additional evidence speaks to the rapid time course of visual discrimination capabilities. During active discrimination, responses likely originating within object recognition areas modulate to specific classes of visual stimuli within the initial approximately 100 ms poststimulus onset (e.g., Braeutigam et al., 2001; Debruille et al., 1998; George et al., 1997; Halgren et al., 2000; Landis et al., 1984; Mouchetant-Rostaing et al., 2000a,b; Murray et al., 2002; Seeck et al., 1997), thereby supporting the third prerequisite described above.

Given the satisfaction of these prerequisites, the present data demonstrate the functional efficacy of multisensory interactions on sensory–cognitive processes. Although there is a growing body of evidence detailing the anatomical and physiological underpinnings of multisensory interactions, there is substantially less evidence detailing their role in sensory–cognitive functions. At an anatomical level, studies using tracer injections have revealed direct projections to visual areas V1 and V2 from both primary as well as association areas of auditory cortex (Falchier et al., 2002; Rockland and Ojima, 2003). Others not only have observed similar patterns of projections from somatosensory and visual cortices that terminate in belt and parabelt auditory association areas, but also describe the laminar activation profile of multisensory convergence in these auditory regions as consistent with feedforward inputs (see Schroeder and Foxe, 2002; Schroeder et al., 2003 for recent reviews). The implication of these studies in nonhuman primates is that the initial stages of sensory processing already have access to information from other sensory modalities. In strong agreement are the repeated observations in humans of nonlinear neural response interactions to multisensory stimulus pairs at early (<100 ms) latencies (e.g.,

Fort et al., 2002a,b; Foxe et al., 2000; Giard and Peronnet, 1999; Lutkenhoner et al., 2002; Molholm et al., 2002) and within traditionally unisensory cortices (e.g., Amedi et al., 2001, 2002; Calvert et al., 1999, 2000, 2001; Foxe et al., 2002; Macaluso et al., 2000, 2002; Stoesz et al., 2003). For example, auditory–visual neural response interactions were observed at just approximately 45 ms poststimulus onset, effectively simultaneous with the onset of the response to unisensory visual stimuli, and with a scalp topography focused over the right posterior scalp (e.g., Molholm et al., 2002).

The results of the present study extend upon such findings to suggest that the multisensory representations established within these visual regions involved in neural response interactions are later accessible during subsequent visual stimulation for rapid stimulus discrimination, even though such is unnecessary for task completion. While such does not exclude additional brain regions from either multisensory or memory functions, the present data would indicate that the earliest discrimination of stimuli according to past experiences is within locales associated with the initial multisensory neural response interactions themselves, rather than within other sensory cortices. As such, our data would contrast with two recent hemodynamic neuroimaging investigations of the spatial correspondence between memory encoding and retrieval (Nyberg et al., 2000; Wheeler et al., 2000). These authors observed auditory cortex activation in response to visual word stimuli originally studied or learned in either a purely visual context or as auditory–visual pairs and later discriminated according to the sensory modality or modalities stimulated during study, though we would note that the Nyberg et al. study limited their localization to regions defined by the statistical mask generated from the contrast between the auditory–visual and visual encoding conditions. Such results were interpreted to reflect reintegration processes (Hamilton, 1859), whereby visual stimuli could reactivate associated sound representations within auditory cortex because the visual–auditory associations had been consolidated in memory. However, the possibility that such responses in auditory cortex followed instead from the active discrimination of stimuli according to whether or not they been previously presented with sounds cannot be discounted. That is, the contrast in these studies may instead have measured a form of auditory “imagery”. Importantly, for the interpretation of the present results, neither extensive studying of the experimental auditory–visual associations nor active discrimination was part of the present experimental design. In addition, the block design and limited temporal resolution of these hemodynamic imaging studies precludes too direct a comparison. Such notwithstanding the present electrical neuroimaging results would suggest that reintegration processes might manifest without explicit consolidation of auditory–visual associations and first within regions involved in multisensory interactions. Even if one interprets these hemodynamic imaging results as evidence of reintegration processes, the present electrical neuroimaging results would provide a temporal constraint on such auditory cortex activity, because the earliest differentiation followed from generator changes within the LOC. As such, any subsequent auditory cortex activity would likely follow the reactivation of multisensory representations, rather than be a direct reactivation of the initial auditory sensory experience.

In addition to this early effect, we observed later periods of response modulation at approximately 210–260 and 318–390 ms that were each characterized by scalp topographic changes and, by extension, alterations in the underlying generator configuration.

The functional role of these later modulations is less clear. Given that the brain already distinguishes between stimuli having either unisensory or multisensory parts over the 60–136-ms period and that this distinction is task-irrelevant, these later periods of response modulation might reflect the brain's treatment of such incidental memory activations. Indeed, their timing is consistent with those found in many recent ERP investigations of object recognition and identification processes (e.g., Doniger et al., 2000, 2001; Murray et al., 2002; Ritter et al., 1982; Vanni et al., 1996), recognition memory (e.g., Rugg et al., 1998; Tsivilis et al., 2001), as well as the discrimination of memories that pertain to ongoing reality from those that do not (Schneider et al., 2002). We would speculate that the modulations observed in the present study might be serving similar functions. These uncertainties notwithstanding the present study unequivocally demonstrates the time course and initial locus of effects of past multisensory experiences on current unisensory processes.

Several alternative interpretations of these results are also worth a brief commentary. For example, it has recently been proposed that memory is enhanced for contextually novel items relative to less distinct experiences (e.g., Ranganath and Rainer, 2003). Under this conceptual framework, the AV condition would result in enhanced responses due to contextual novelty, rather than multisensory interactions per se. This enhanced response due to contextual novelty would then pervade subsequent responses to the V+ stimuli, which appeared some 13 ± 3 stimuli later. Even if one adopts such an account, the observed difference is nonetheless the consequence of one sensory modality influencing the responses of another sensory modality both at the time of initial image presentation as well as later when only the image was repeated. Thus, such an account would not dramatically differ from that which we have proposed. Whether or not the present effect needs to be elicited by task-irrelevant auditory–visual pairings on initial image presentation will require further investigation. However, we would note that previous research on the effects of context observed relatively late ERP effects (approximately 300 ms poststimulus onset; Tsivilis et al., 2001). A similar alternative, which again is in keeping with our own interpretation, would postulate that our observed effect reflects the brain's ability to detect current contextual novelty. That is, the V– condition would not be novel, because it is an exact replication of the initial exposure. In contrast, the V+ condition is a new context when compared with its initial exposure. The V+ vs. V– difference in brain response would therefore reflect the brain's ability to detect such context changes for individual stimuli, even when the context is task-irrelevant. Moreover, such discrimination would presumably rely on access to specific perceptual or memory traces of the variety we have proposed.

In summary, we present data demonstrating that past multisensory experiences can incidentally affect subsequent unisensory processes. It thus appears that unisensory percepts incidentally trigger multisensory memory representations associated with them. Effects were observed both behaviorally and electrophysiologically, with the latter occurring first over the approximately 60–136-ms period. We further introduce a stepwise analysis that provides a statistical basis for determining the neurophysiological mechanism of observed effects. These analyses revealed three periods of response modulation that all resulted from changes in the underlying generator configuration between conditions. Statistical analysis of the LAURA inverse solution estimation for the earliest of these effects revealed that multisensory memories first alter visual responses within the right LOC—a brain region

traditionally held to be unisensory in function. The collective data support the hypothesis that memory traces for multisensory auditory–visual events involve a distinct cortical network that is rapidly activated by subsequent repetition of just the unisensory visual component.

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