

The role of auditory cortices in the retrieval of single-trial auditory–visual object memories

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Abstract

Single-trial encounters with multisensory stimuli affect both memory performance and early-latency brain responses to visual stimuli. Whether and how auditory cortices support memory processes based on single-trial multisensory learning is unknown and may differ qualitatively and quantitatively from comparable processes within visual cortices due to purported differences in memory capacities across the senses. We recorded event-related potentials (ERPs) as healthy adults ($n = 18$) performed a continuous recognition task in the auditory modality, discriminating initial (new) from repeated (old) sounds of environmental objects. Initial presentations were either unisensory or multisensory; the latter entailed synchronous presentation of a semantically congruent or a meaningless image. Repeated presentations were exclusively auditory, thus differing only according to the context in which the sound was initially encountered. Discrimination abilities (indexed by d') were increased for repeated sounds that were initially encountered with a semantically congruent image versus sounds initially encountered with either a meaningless or no image. Analyses of ERPs within an electrical neuroimaging framework revealed that early stages of auditory processing of repeated sounds were affected by prior single-trial multisensory contexts. These effects followed from significantly reduced activity within a distributed network, including the right superior temporal cortex, suggesting an inverse relationship between brain activity and behavioural outcome on this task. The present findings demonstrate how auditory cortices contribute to long-term effects of multisensory experiences on auditory object discrimination. We propose a new framework for the efficacy of multisensory processes to impact both current multisensory stimulus processing and unisensory discrimination abilities later in time.

Introduction

Perception is inherently multisensory. Multisensory processes impact the initial stages of stimulus processing and continue onwards (e.g. Murray & Wallace, 2011; Stein, 2012; van Atteveldt *et al.*, 2014). They affect, among other things, object detection and discrimination (Murray *et al.*, 2012; Stein, 2012) as well as attentional selection (Matusz & Eimer, 2011, 2013; Matusz *et al.*, 2015). Recent data demonstrated that multisensory processes occurring at one point in time also impact subsequent unisensory processes (Thelen & Murray, 2013; see also Gibson & Maunsell, 1997; Nyberg *et al.*, 2000; Wheeler *et al.*, 2000; von Kriegstein & Giraud, 2006). While most studies have focused on the effects of

multisensory context and learning on later visual processes, auditory processes are likewise affected. Discrimination of both images and sounds is improved for items originally encountered in a semantically congruent multisensory context, despite the multisensory information being task-irrelevant and only experienced in a single-trial setting (Thelen & Murray, 2013). Detriments or null effects on discrimination abilities can moreover be observed if the initial multisensory context had been either semantically incongruent or entailed a meaningless stimulus (Thelen *et al.*, 2012; Moran *et al.*, 2013; Thelen *et al.*, 2014). Overall, the behavioural effects of multisensory processing on auditory discrimination seem similar to those observed on visual discrimination.

Neuroimaging investigations elucidating brain mechanisms that underlie multisensory processing affecting unisensory perception have largely focused on the effects of multisensory contexts on later unisensory visual processing. Object-sensitive visual cortices show differential responses during the first 100 ms post-stimulus to visual stimuli that had been previously presented in an auditory–visual

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context (Murray *et al.*, 2004; Thelen *et al.*, 2012), with no evidence for parallel effects within auditory cortices (e.g. Murray *et al.*, 2005). The effects of prior multisensory experiences within visual cortices are not limited to tasks requiring visual discrimination. Voices and meaningless sounds both result in activations within visual cortices when previously studied in a multisensory context (fusiform face area: von Kriegstein & Giraud, 2006; medial occipital areas: Zangenehpour & Zatorre, 2010; Butler & James, 2011). It is unclear to what extent auditory cortices contribute to these effects.

We addressed the role of auditory cortices in the discrimination of unisensory auditory objects based on prior multisensory versus unisensory experiences. Resolving this issue will provide much needed insights into the locus of the presumed multisensory object representation formed during the initial object encounter and the spatio-temporal neural substrates of its later access. One possibility is that auditory cortices do contribute to these processes, given the rapid cortical responses to sounds (Musacchia & Schroeder, 2009) and their semantic attributes (Murray & Spierer, 2009; Bizley & Cohen, 2013). Alternatively, multisensory representations may be predominantly located within visual cortices or rely on their co-activation with auditory regions, given the predominance of vision in object memories (Yuval-Greenberg & Deouell, 2007, 2009; Cohen *et al.*, 2009). We differentiated between these possibilities via electrical neuroimaging of auditory event-related potentials (ERPs) recorded from adults performing a continuous old/new discrimination task involving sounds of environmental objects whose initial presentations entailed multisensory versus unisensory contexts.

Materials and methods

Participants

Twenty-two healthy adult volunteers (eight men) aged between 18 and 36 years old (mean \pm SEM = 25 \pm 1 years) participated in the experiment. All subjects provided written, informed consent for their participation. Experimental procedures were approved by the Ethics Committee of the Vaudois University Hospital Centre and the University of Lausanne and conformed to the World Medical Association Declaration of Helsinki [JAMA (2013), 310: 2191–2194]. Data from four of these participants were excluded from analyses due to artefact contamination and/or a low number of accepted electroencephalogram (EEG) epochs. The analyses presented here are based on the remaining 18 participants (seven men; age range 22–36 years, mean age 25.9 years; one left-handed and one ambidextrous). All participants reported normal or corrected-to-normal vision and hearing and had no neurological or psychiatric illnesses. Data from a subset of these participants as well as a subset of experimental conditions that are distinct from those analysed here were presented as a follow-up experiment in Thelen *et al.* (2014).

Stimuli and procedure

Participants performed a continuous recognition task involving the discrimination of initial versus repeated presentations of complex, meaningful sounds of environmental objects. This comprised a two-alternative forced choice between old and new sounds. They were instructed to complete the task as fast and as accurately as possible by a right-hand button press. When heard for the first time, sounds could be presented alone (A) or paired with either a semantically congruent image (AVc) or a meaningless image (AVm). Repeated sound presentations were always unisensory (auditory-only), and throughout the paper our nomenclature is according to their initial

presentation context: previously presented alone (A–) or previously paired with a congruent (A+c) or meaningless image (A+m) (see Fig. 1A). For the analyses, this led to six experimental conditions in total, although for task requirements there were only two conditions: initial and repeated presentations of sounds.

The sounds were of 60 common objects used in prior work (Marcell *et al.*, 2000; Murray *et al.*, 2006). These stimuli were modified with Adobe Audition to be of equal loudness (root mean square) and duration (500 ms, including 10 ms rise/fall to prevent clicks; 16 bit stereo, 44.1 kHz digitisation). Sounds were presented through stereo loud speakers (Speaker System Z370; Logitech, Lausanne, Switzerland) placed on each side of the monitor. The sound volume was adjusted to a comfortable level (53.3 \pm 0.2 dB). We have previously used these sounds in studies of environmental object recognition and have controlled their familiarity to listeners (Murray *et al.*, 2006). Nonetheless, to further ensure that the current participants understood to which object each sound referred, we presented each sound with its corresponding image twice during the course of a single block of trials preceding the main experiment. No responses were required from the participants.

For the AVc condition, visual stimuli were line drawings of common objects that were obtained either from a standardised set (Snodgrass & Vanderwart, 1980) or an online library (dgl.microsoft.com). For the AVm condition, images were either abstract drawings (consisting of lines and circles, prepared by a professional artist) or scrambled versions of the line drawings (achieved using an in-house MATLAB script that divided the images into 5 \times 5 square matrices and randomised the arrangement of the pixels within each square). Visual stimuli were presented on a computer monitor (model HP LP2065; refresh rate of 60 Hz) at a viewing distance of 120 cm.

Stimuli were presented for 500 ms followed by a variable inter-stimulus interval of 1500–2500 ms (mean = 2000 ms with a uniform distribution). The experiment was divided into six blocks of 120 trials each. All six conditions were presented with the same likelihood over the 120 trials within an experimental block. Sounds were presented in initial encounter contexts in a counterbalanced way, such that over the six blocks each sound was presented twice in each initial encounter context and was repeated once per block. There was an average of 9 \pm 4 trials between initial and repeated presentations. The order of blocks was randomised between subjects. All stimuli were delivered and controlled by E-PRIME 2.0, and responses were recorded with a serial response box (Psychology Software Tools, Pittsburgh, PA, USA).

EEG acquisition and pre-processing

Continuous EEG was recorded at 500 Hz from 64 scalp electrodes (EasyCap, BrainProducts, Gilching, Germany), positioned according to the international 10–20 system, using an electrode on the tip of the nose as the online reference. An additional electrooculogram electrode was placed below the right eye. The mean impedances over all electrodes for all subjects were kept below 4.5 k Ω . Continuous EEG was segmented into peri-stimulus epochs from 100 ms pre-stimulus to 500 ms post-stimulus onset. Only trials with correct responses were included in the analyses. Additionally, data quality was controlled with a semi-automated artefact rejection criterion of \pm 80 μ V at each channel as well as visual inspection to exclude transient noise and eye movements. To obtain ERPs, the remaining epochs were averaged for all subjects for each of the three repetition conditions (A–, A+c, A+m). The percentage of accepted epochs (out of a total of 120) per participant per condition was 71.6 \pm 2.9% for

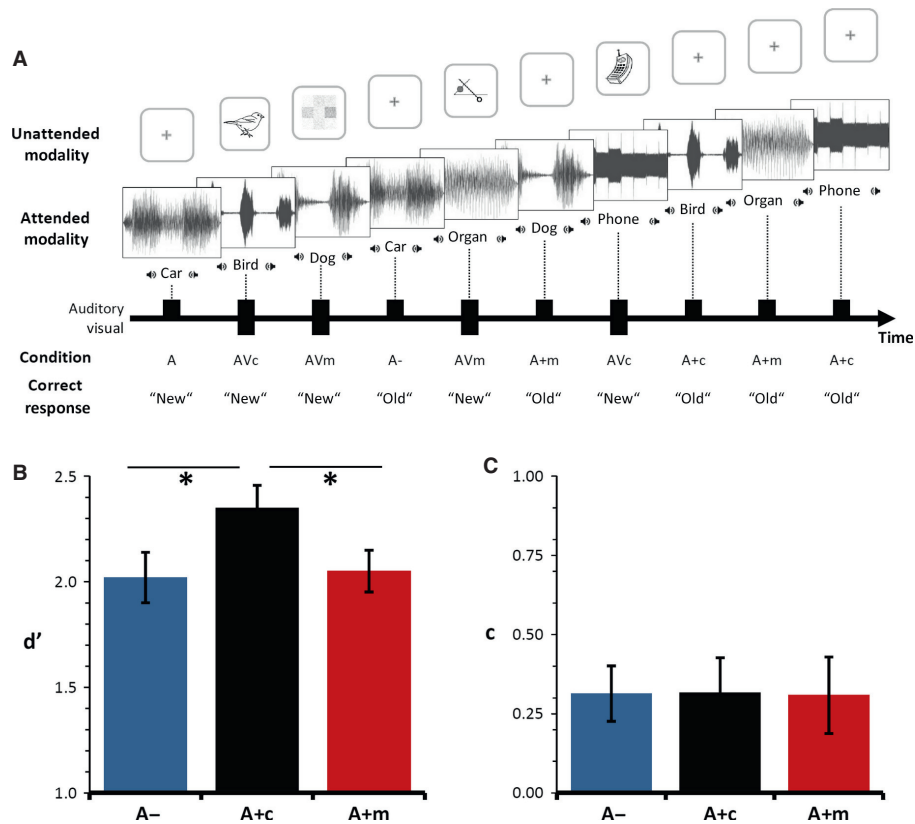


FIG. 1. (A) Illustration of the paradigm used to investigate the effects of multisensory learning on auditory object discrimination. (B,C) Group-averaged sensitivity, d' , and response criterion, c , for the three experimental conditions: repeated presentations of auditory stimuli initially encountered in a purely auditory context (A-), semantically congruent multisensory context (A+c) and a meaningless multisensory context (A+m). Error bars indicate SEM. Significant post-hoc effects ($P < 0.05$) are marked with an asterisk.

A-, 73.9 \pm 3.2% for A+c and 72.0 \pm 3% for A+m. Data from artefact-contaminated or broken electrodes were interpolated using three-dimensional splines (Perrin *et al.*, 1987). On average, fewer than one electrode was interpolated per participant (range 0–3). ERPs were filtered with Butterworth second-order filters with –12 dB/octave roll-off that were computed linearly with both forward and backward passes to eliminate any phase-shift (low-pass = 40 Hz; high-pass = 0.1 MHz; notch = 50 Hz) and recalculated against the average reference.

Behavioural data analyses

Performance data were analysed using median reaction time (mRT) as well as according to signal detection theory, using perceptual sensitivity and response bias (Macmillan & Creelman, 2004). Perceptual sensitivity (d') was calculated using the hit rate (HIT = correct answer; e.g. labelling A+c as A+c) and the false alarm rate (FA = wrong discrimination; e.g. labelling AVc as A+c), according to the formula $d' = [z(\text{HIT}) - z(\text{FA})]$. Response bias (c) was calculated according to the formula $c = [0.5 * (z(\text{HIT}) + z(\text{FA}))]$. More generally, we would note the following regarding signal detection theory. Sensitivity (d') is a quantification of the distance between two (estimated) distributions: that of the signal and that of the noise. As such, it provides a measure of how easily a target signal is discriminated from the background noise. Response criterion (measured by c) is a measure of how conservatively or liberally a participant makes a decision. These two measures have been widely characterised as reflecting perceptual vs.

post-perceptual (i.e. decisional) stages (Macmillan & Creelman, 2004). Statistical analyses were conducted exclusively for the repeated sound presentations using a one-way analysis of variance (ANOVA) for the within-subject factor of condition (A-, A+c and A+m). Post-hoc t -tests were performed and P -values were corrected for multiple comparisons with the Holm–Bonferroni method (Holm, 1979). Throughout, we report mean \pm standard error of the mean (SEM). Analyses were performed using the spss software version 21 (IBM, Armonk, NY, USA).

ERP data analyses

Event-related potential data were analysed within an electrical neuroimaging framework that focuses on reference-independent measures of the electric field at the scalp and uses multivariate analyses (Michel & Murray, 2012; Koenig *et al.*, 2014). We also performed univariate analyses of each scalp electrode as a function of time (one-way ANOVA for the within-subject factor of condition). For this analysis we used an average reference as well as both a temporal criterion (>10 ms contiguously; Guthrie & Buchwald, 1991) and a spatial criterion (>5% of the electrode montage at a given latency) for the detection of statistically significant effects (see also Thelen *et al.*, 2012; for a similar approach). This analysis is included to provide readers with a sense of the general waveform shape and the prototypical ERP components at the latency of our observed effects, although we emphasise that analyses of voltage waveforms are reference-dependent (Murray *et al.*, 2008).

The electrical neuroimaging analyses entailed the following. As these methods have been described in several recent reviews (Murray *et al.*, 2008; Michel & Murray, 2012; Tzovara *et al.*, 2012; Koenig *et al.*, 2014) and have been used extensively in ERP studies of sensation and perception (Berchio *et al.*, 2014; Chouiter *et al.*, 2014; Hardmeier *et al.*, 2014; Hauthal *et al.*, 2014; Skrandies, 2014; Altieri *et al.*, 2015), we provide only the essential details here.

First, ERP strength was quantified using global field power (GFP), which is reference-free and equals the root mean square across the electrode montage (Lehmann & Skrandies, 1980). GFP was analysed as a function of time using a one-way ANOVA for the within-subject factor of condition (the same temporal criterion as above was applied).

Second, ERP topographic differences were quantified using global dissimilarity (DISS), which is reference-free and equals the root mean square of the difference between two GFP-normalised vectors (here the 64-channel ERP; Lehmann & Skrandies, 1980). DISS ranges in value from 0 to 2, with 0 indicating no topographic differences and 2 indicating topographic inversion. DISS was analysed using the Randomisation Graphical User interface (RAGU; Koenig *et al.*, 2011). Briefly, RAGU performs a non-parametric randomisation test on the DISS values, comparing the observed value to an empirical distribution based on permutations of the data from all participants/conditions. Topographic differences between conditions indicate that there is a difference in the configuration of the underlying neural generators (Lehmann, 1987). Note that GFP and DISS are orthogonal measures of ERP, which means that these two features (strength and topography) can be analysed independently.

Third, the collective post-stimulus group-average ERPs were subjected to a topographic analysis based on a hierarchical clustering algorithm (Murray *et al.*, 2008). This clustering identifies stable electric field topographies (hereafter 'template maps'). The clustering is exclusively sensitive to topographic modulations, because the data are first normalised by their instantaneous GFP. The optimal number of temporally stable ERP clusters (i.e. the minimal number of maps that accounts for the greatest variance of the dataset) was determined using a modified Krzanowski–Lai criterion (Murray *et al.*, 2008). The clustering makes no assumption regarding the orthogonality of the derived template maps (Pourtois *et al.*, 2008; De Lucia *et al.*, 2010a; Koenig *et al.*, 2014). Template maps identified in the group-average ERPs were then submitted to a fitting procedure, wherein each time point of each single-subject ERP is labelled according to the template map with which it best correlated spatially (Murray *et al.*, 2008). An ANOVA with within-subject factors of map and condition statistically tested the relative presence (in milliseconds) of each template map in the moment-by-moment scalp topography of the ERP and the differences in such across conditions.

Finally, we estimated the localisation of the electrical activity in the brain using a distributed linear inverse solution (minimum norm) combined with the LAURA (local autoregressive average) regularisation approach comprising biophysical laws as constraints (Grave de Peralta Menendez *et al.*, 2001, 2004; see also Michel *et al.*, 2004, for a review). LAURA selects the source configuration that better mimics the biophysical behaviour of electric vector fields (i.e. activity at one point depends on the activity at neighbouring points according to electromagnetic laws). In our study, homogeneous regression coefficients in all directions and within the whole solution space were used. LAURA uses a realistic head model, and the solution space included 4024 nodes, selected from a $6 \times 6 \times 6$ mm grid equally distributed within the grey matter of the Montreal Neurological Institute's average brain (courtesy of R.

Grave de Peralta Menendez and S. Gonzalez Andino; <http://www.electrical-neuroimaging.ch/>). Prior basic and clinical research from members of our group and others has documented and discussed in detail the spatial accuracy of the inverse solution model used here (e.g. Grave de Peralta Menendez *et al.*, 2004; Michel *et al.*, 2004; Gonzalez Andino *et al.*, 2005; Martuzzi *et al.*, 2009). In general, the localisation accuracy is considered to approximately follow the matrix grid size (here 6 mm). The results of the above topographic pattern analysis defined time periods for which intracranial sources were estimated and statistically compared across conditions. Prior to calculation of the inverse solution, the ERP data were down-sampled and affine-transformed to a 61-channel montage. Statistical analyses of source estimations were performed by first identifying the peak of the ERP over the time period demonstrating statistically reliably topographic differences (here, 32–84 ms as detailed below). The inverse solution was then estimated for this peak latency for each of the 4024 nodes prior to conducting an ANOVA for the within-subjects factor of condition. Only solution points meeting the $P \leq 0.05$ statistical criterion were considered significant. Additionally, we applied a spatial extent criterion of at least 10 contiguous significant nodes (see also Toepel *et al.*, 2009; Cappe *et al.*, 2010, 2012; De Lucia *et al.*, 2010b; Knebel *et al.*, 2011; Knebel & Murray, 2012; for a similar spatial criterion). This spatial criterion was determined using the ALPHASIM program (available at <http://afni.nimh.nih.gov>) and assuming a spatial smoothing of 2-mm full-width half maximum and cluster connection radius of 8.5 mm. This criterion indicates that there is a 3.41% probability of a cluster of at least 10 contiguous nodes, which gives an equivalent node-level P -value of $P \leq 0.00009$. The results of the source estimations were rendered on the Montreal Neurologic Institute's average brain.

Results

Behavioural data

The overall mean accuracy on the task was $74.3 \pm 2.3\%$. To assess the impact of multisensory memories on the later recognition of environmental sounds, mRTs, d' and c were analysed for the repeated sound presentations. Participants performed the task equally fast in all conditions ($F_{2,34} < 1$; 965 ± 27 , 965 ± 29 and 966 ± 29 ms for the A-, A+c and A+m conditions, respectively). The ANOVA on the d' values revealed statistically reliable differences in participants' memory performance as a function of the initial context ($F_{2,16} = 13.47$, $P = 0.001$, $\eta_p^2 = 0.63$). Post-hoc comparisons via paired t -tests revealed significantly better memory performance in the A+c condition (2.4 ± 0.1) than either the A- (2.0 ± 0.1 , $t_{17} = 3.69$, $P = 0.0018$, two-tailed) or the A+m condition (2.1 ± 0.1 , $t_{17} = 5.31$, $P = 0.000058$, two-tailed), the latter two of which did not significantly differ ($t_{17} < 1$, two-tailed; see Fig. 1B). This pattern indicates that the discrimination of repeated sounds was higher in situations where past contexts were multisensory and semantically congruent. Importantly and by contrast, participants showed no differences in response bias across the three conditions ($F_{2,16} < 1$; Fig. 1C), with values of 0.31 ± 0.09 , 0.32 ± 0.11 and 0.31 ± 0.12 for the A-, A+c and A+m conditions, respectively.

ERP data

As above, the ERP analyses focused on determining the effects of multisensory context on repeated sound discrimination. Figure 2

displays group-averaged ERPs from A-, A+c and A+m conditions from an exemplar frontal midline electrode (Fz; Fig. 2A) as well as the univariate ANOVA results across the electrode montage, displayed as the number of electrodes exhibiting a significant main effect of context as a function of time peri-stimulus and including a threshold of 10% of the electrode montage (Fig. 2B). There were multiple time intervals exhibiting a main effect, the earliest of which was observed over the 30–52 ms post-stimulus interval. Subsequent main effects were found over the time periods 136–168, 224–274, 312–368 and 446–468 ms. While this analysis provides a general sense of the timing of ERP modulations, we focus the remainder of the Results section on the findings using an electrical neuroimaging framework (detailed in Materials and methods).

The ANOVA on the GFP time series failed to document significant GFP differences at any latency during the –100 to 500 ms post-stimulus period (data not shown). These results thus provided no evidence for differences in response strength as a function of past multisensory vs. unisensory experience. A set of topographic analyses were therefore conducted (see Methods for details). We would remind the reader that biophysical laws dictate that topographic differences forcibly follow from changes in the underlying configuration of active brain sources. First, the randomisation-based analysis of ERP topography (Koenig *et al.*, 2011) identified significant differences across the three conditions over the 32–50, 236–270 and 336–368 ms post-stimulus periods. Second, topographic differences were likewise tested using a topographic cluster analysis of the full 500-ms post-stimulus period. Eight clusters, involving 19 distinct template maps, accounted for 94.6% of the variance in the cumulative group-average ERPs. In general, the same pattern of template maps characterised the ERP in each condition, with the exception of the 32–84 and 142–272 ms post-stimulus periods (Fig. 2C). Note that a template map refers to a stable ERP topography observed in the group-averaged data that is then used for spatial correlation analyses at the single-subject level across all experimental conditions.

Over the 32–84 ms post-stimulus period, the ERP in the A+c condition was dominated by one template map, whereas the ERPs in the A- and A+m conditions were both characterised by the same pair of template maps. This pattern observed in the group-averaged ERPs was statistically assessed in the single-subject data using a spatial-correlation fitting procedure. There was a significant condition \times map interaction ($F_{2,16} = 5.16$, $P = 0.019$, $\eta_p^2 = 0.39$), which was further confirmed by post-hoc comparisons likewise showing that one template map predominated ERPs elicited in the A+c condition versus either the A- or the A+m condition (see Fig. 2D).

Over the 142–272 ms post-stimulus period, the ERP in the A+c condition was characterised by two template maps, whereas the ERPs in the A- and A+m conditions were both characterised by the same single template map. This pattern observed in the group-averaged ERPs was statistically assessed in the single-subject data using a spatial-correlation fitting procedure, as above. There was a non-significant trend for a condition \times map interaction ($F_{2,16} = 2.85$, $P = 0.087$, $\eta_p^2 = 0.26$). The robustness of this topographic difference will need confirmation in future studies. Finally, over the 322–448 ms post-stimulus period, the two template maps were observed across all conditions in the group-averaged ERPs, albeit with the appearance of differing relative durations. Statistical analysis based on spatial-correlation fitting did not yield a significant interaction between condition and map ($F_{2,16} < 1$). Given the statistical reliability of the effects over the 32–84 ms post-stimulus period across analyses of voltage waveforms and electric field

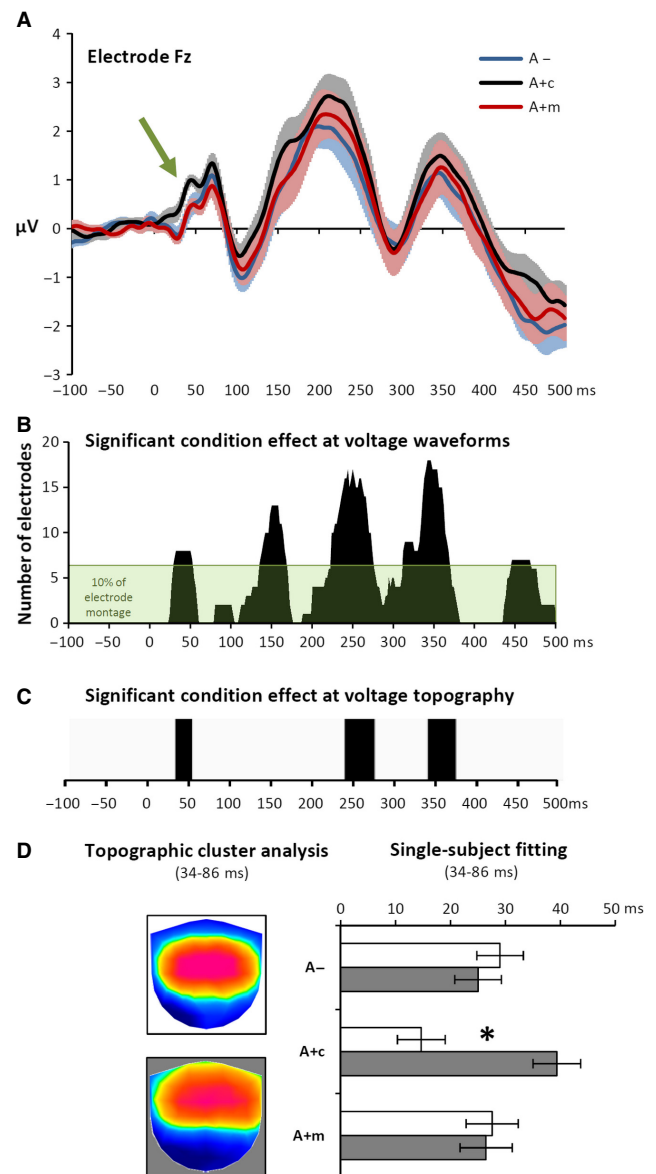


FIG. 2. (A) Group-averaged (SEM indicated) auditory evoked potentials at an exemplar frontal midline electrode shown separately for the three repeated sound presentation conditions. (B) The results of the millisecond-by-millisecond one-way ANOVA across the electrode montage displaying the number of electrodes showing a main effect of condition and meeting the $P < 0.05$ criterion for over 10 ms contiguously and across at least 10% of the electrode montage (shaded region). (C) The results of the millisecond-by-millisecond one-way ANOVA on the strength-normalised electric field topography showing a main effect of condition and meeting the $P < 0.05$ criterion for over 10 ms contiguously. (D) The results of the topographic cluster analysis identified two template maps over the 34–86 ms post-stimulus interval that were then used for the single-subject fitting procedure. Note that both template maps are characterised by a fronto-central positivity and that the intensity of these template maps is arbitrary given that this analysis entailed strength-normalised data to isolate topographic differences. The single-subject fitting results show the group-average duration each template map was ascribed to each condition (SEM indicated). The 2×3 ANOVA on these duration values revealed an interaction between template map and condition. The post-hoc comparisons showed this interaction was due to the predominance of one template map in the A+c condition. This was not observed for either the A- or the A+m conditions.

topography as quantified both using global dissimilarity as well as clustering, we focused our source estimations on this early time period.

Source estimations

Source estimations from the 32–84 ms time period were statistically analysed to identify the likely brain regions contributing to these differential effects. The statistical contrast of these source estimations identified four clusters exhibiting a significant main effect of condition (Fig. 3A). These clusters were located within the right posterior superior temporal cortex, the right inferior occipital cortex, the right inferior parietal cortex and the left frontal cortex. Overall, responses were significantly weaker for the A+c and A+m conditions than for the A– condition. In addition, responses were reliably weaker for the A+c than A+m condition within portions of the right posterior superior temporal cortex as well as right inferior parietal cortex. This pattern can be seen in Fig. 3B, displaying the mean scalar values at the node within each cluster exhibiting the largest F -value, as well as in Fig. 3C, which shows axial slices with the results of the

post-hoc contrasts for pairs of conditions. Activity within the regions reported here essentially mirrors the pattern observed in behaviour as well as ERP analyses at the scalp surface; namely, responses to the A+c condition are distinct from those to either the A– or the A+m conditions.

Discussion

The present study demonstrates that the neural recruitment of brain areas during early, sensory–perceptual stages of auditory object processing is strongly influenced by the sensory context in which a given auditory object was perceived initially. As predicted, discrimination of object sounds that had previously been encountered in a semantically congruent multisensory context was facilitated compared with sounds presented either alone or together with a meaningless image.

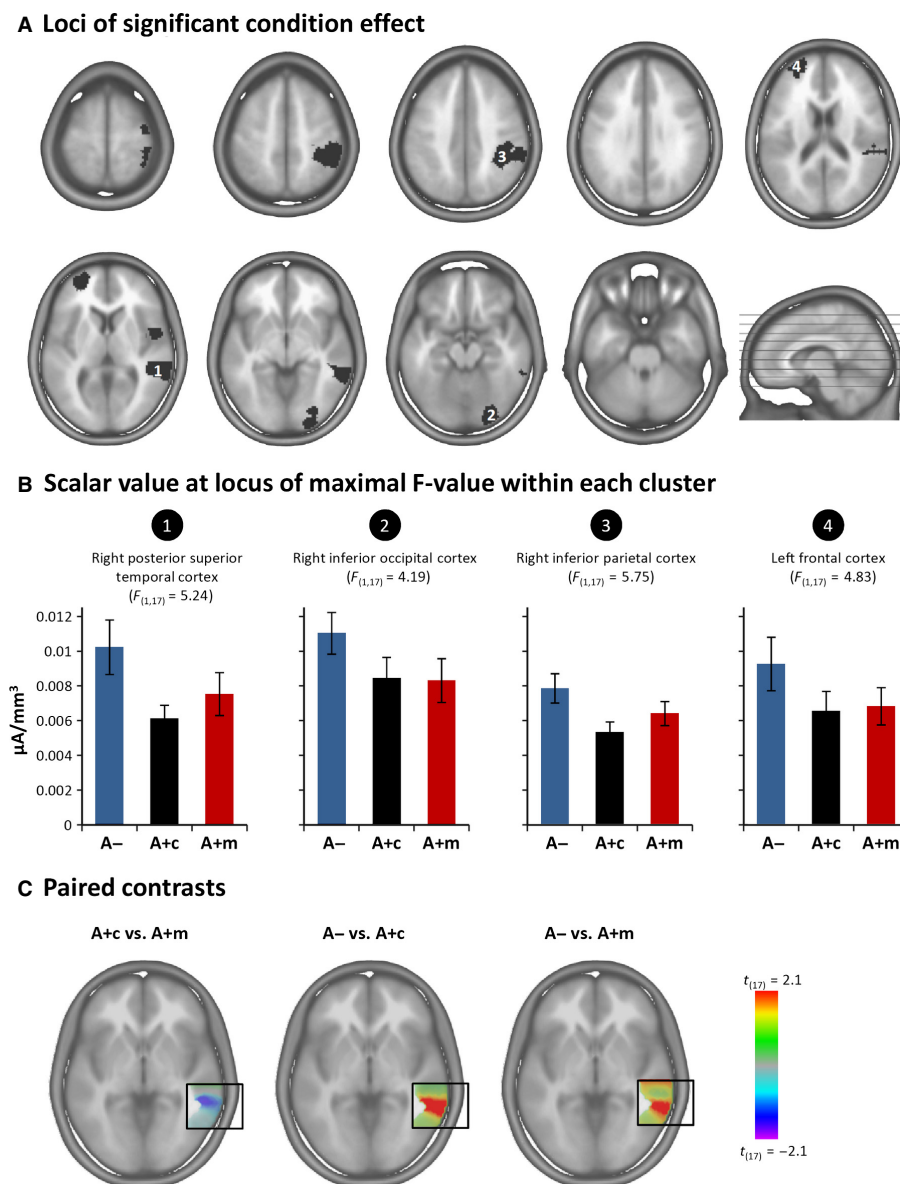


FIG. 3. (A) The results of the one-way ANOVA on source estimations calculated over the 34–86 ms post-stimulus interval showed a significant main effect of condition within a distributed set of brain regions, indicated by numbers. Data are shown on axial slices with the left hemisphere on the left and the nasion upwards. (B) Within each region depicted in A are shown the mean current source density values at the locus of maximal F -value for each condition (SEM indicated). (C) Post-hoc comparisons show t -values specifically for nodes within the right posterior superior temporal cortex.

Electrical neuroimaging analyses of ERPs elicited by the repeated sounds revealed that this facilitatory effect of past incidental encounters was accompanied by differential processing of the repeated sounds starting as early as ~30 ms post-stimulus onset, which followed from changes in the topography of the electric field map at the scalp. Source estimations localised these effects to right-hemisphere brain regions, most notably the superior temporal cortex (STC), as well as the inferior parietal cortex (IPC). Overall, source activity was weaker for conditions where memory performance was improved. This suggests an inverse relationship between the responsiveness of auditory cortices and the behavioural outcome in the 'old/new' task. The current findings are discussed in terms of the importance of auditory cortices in mediating supporting facilitated discrimination of auditory objects based on incidental single-trial multisensory learning.

The perceptual nature of single-trial multisensory learning

Before treating in more depth our electrical neuroimaging results, the present behavioural findings warrant qualification. Previous work from our lab (A. Thelen, D. Talsma & M.M. Murray, under review) provided some of the first evidence for the sensitivity of auditory object perception to single-trial multisensory memories: sounds that had been initially presented together with a congruent image were discriminated more accurately, as shown by higher sensitivity (d'), but responded to equally quickly compared with sounds presented alone (or sounds presented with either a semantically incongruent or a meaningless, abstract image). More accurate discrimination of sounds that had been encountered in a multisensory (semantically congruent) vs. unisensory context was likewise recently demonstrated by Moran *et al.* (2013). However, despite a very similar paradigm, they found that sounds previously encountered in the multisensory context elicit slower responses. This contrasts with the typical finding of null effects on response times involving visual and auditory object recognition alike (for a review, see Thelen & Murray, 2013). The pattern observed by Moran *et al.* (2013) may thus follow from a speed-accuracy trade-off, raising doubts as to the mechanism that led to the observed increased performance accuracy. Here, we used analyses based on signal detection theory (Macmillan & Creelman, 2004) and demonstrated that facilitation of processing of semantically congruent multisensory pairings relative to sounds with unisensory past can take place without any effect on the response criterion. As in our prior studies, we failed to observe response time differences. Although we hesitate to over-interpret a null result, similarly to (A. Thelen, D. Talsma & M.M. Murray, under review), we also found that sounds encountered initially without an image and those presented together with a meaningless image were discriminated with similar accuracy. Thus, the current behavioural results showing an effect on d' provide important support for the involvement of perceptual, rather than later, decisional processes in single-trial multisensory learning and for the importance of this type of learning for auditory (and probably also visual) object processing. It is noteworthy that other forms of learning involving stimuli in multiple modalities (studied jointly or separately) typically require conscious effort and extensive periods of exposure/training (in the range of hours; e.g. von Kriegstein & Giraud, 2006; Zangenehpour & Zatorre, 2010), which further underlines that the effects studied in our continuous discrimination paradigm are engendered by a distinctive form of multisensory learning that is more implicit in nature.

The brain dynamics of semantic discrimination of sounds

The timing of our electrical neuroimaging effects speaks to the perceptual nature of multisensory learning and memory at play in our

task as well as, more generally, to the understudied role of auditory cortices in semantic processing. The fact that our effects were observed over the 30–85 ms post-stimulus period could be misconstrued as these effects occurring too early for any semantic analysis. However, it is critical to situate their latency alongside current knowledge concerning signal propagation throughout the human auditory system, which is often extrapolated from the timing data from studies with non-human primates (using a 3:5 ratio; Musacchia & Schroeder, 2009). Response onset in the primary fields is in the order of 10–15 ms (e.g. Steinschneider *et al.*, 1992; reviewed by Musacchia & Schroeder, 2009). Intracranial recordings in humans indicate there is a synaptic delay of 2–3 ms from primary to lateral superior temporal cortices (Howard *et al.*, 2000; Brugge *et al.*, 2003). Thus, there would be in principle another 15–75 ms of cortical processing occurring prior to the effects at the latency observed in our study. This time would allow ample opportunity for recursive processing between superior temporal cortices and more or less remote loci, including frontal as well as medial temporal cortices, which are 1–2 synapses away (e.g. Romanski *et al.*, 1999; Kaas & Hackett, 2000). What is more, complex sound discrimination that is semantic in nature manifests itself at latencies of ~30–100 ms, as recorded intracranially in non-human primates within the STCs (Russ *et al.*, 2008; see also Schnupp *et al.*, 2006 for data from ferrets), the temporal pole (Ng *et al.*, 2014), as well as the prefrontal cortices (e.g. Romanski & Goldman-Rakic, *et al.*, 2002). In humans, EEG studies from our laboratory have likewise demonstrated semantic discrimination within the initial 70–100 ms post-stimulus onset that was located within the superior and middle temporal cortices (e.g. Murray *et al.*, 2006; De Lucia *et al.*, 2010b). The timing and localisation of the present results are thus in strong agreement with the existing literature on the effects of semantic processing of sounds, while providing novel evidence that the semantic analysis of incoming auditory information can be influenced by its prior incidental and single-trial presentation in multisensory contexts.

Response suppression as a marker of efficient object discrimination

Differential responses in the present study were characterised by significantly weaker activity for sounds that had been initially encountered in a multisensory rather than unisensory context. Moreover and within some regions showing this general multisensory context effect, activity was further reduced in response to sounds that had been initially encountered in a context involving a semantically congruent rather than a meaningless, abstract image. This type of response suppression is reminiscent of repetition suppression phenomena (Desimone, 1996; Gibson & Maunsell, 1997; Murray *et al.*, 2008; De Lucia *et al.*, 2010c). It has been argued that response suppression may reflect more efficient processing of a stimulus, involving activation of fewer and/or more selective units or populations (Grill-Spector *et al.*, 2006). In agreement with this account, in a study using the classic delayed match-to-sample task, Ng *et al.* (2014) provided evidence suggesting that response suppression may in fact be a characteristic signature of recognition memory within the auditory system. That the currently observed suppression effects transpired during early post-stimulus stages (i.e. within 100 ms post-stimulus onset), and the strongest response suppression was observed for sounds that were discriminated most successfully, is consistent with the notion that suppressed neural responses may reflect particularly efficient discrimination (e.g. Buchsbaum & D'Esposito, 2009; Rong *et al.*, 2010). While a causal relationship between the specific patterns of neural activity and memory

performance remains to be firmly established, to the extent that response suppression is an established proxy for behavioural outcomes would provide strong evidence for the efficacy of multisensory processes in memory functions, in audition as well as more generally. This notion is further supported by recent work from our group showing that the extent of multisensory processing during the initial encounter context is predictive of later memory performance under unisensory conditions (Thelen *et al.*, 2014). Moreover, the present ERP results demonstrate that the mechanism of response suppression extends to a discrimination task involving more implicit memory processing, and, more importantly, to situations where memory performance varies according to the nature of the context of the initial encounter (multisensory vs. unisensory; semantically congruent vs. arbitrary, 'episodic' multisensory context; see also Thelen *et al.*, 2012).

Linking performance and brain activity

Prior observations provided a conflicting picture of the link between the occurrence (and direction) of activity changes in sensory cortices and memory performance. A prevailing account explaining consequences of multisensory contexts on memory performance is based on redintegration (Hamilton, 1859; James, 1890), which refers to the idea that a component of a consolidated experience (e.g. the voice of a previously encountered person) is a sufficient cue to elicit responses within brain areas ordinarily activated by other components of that experience (e.g. the face of the same person). Neuroscientific investigations of this account have verified the importance of such reactivation of modality-specific brain regions and support a traditional view of how redintegration would manifest: activity increases in brain areas associated with the non-stimulated modality (Nyberg *et al.*, 2000; Wheeler *et al.*, 2000; von Kriegstein & Giraud, 2006; Butler & James, 2011; see also Fuster, 2010). Together with previous results from our laboratory (for a review, see Thelen & Murray, 2013) the present findings suggest a novel perspective on how redintegration processes may operate, highlighting the likely importance of both task demands (i.e. explicit vs. implicit processing) as well as behavioural outcome (i.e. benefits vs. impairments).

With regard to the role of auditory cortices in engendering performance benefits based on multisensory memories, it is noteworthy that both STC and IPC exhibited the weakest activity in response to sounds that had been initially encountered in a semantically congruent multisensory context versus either a purely auditory context or multisensory context involving a meaningless image. These loci have been previously implicated in the integration of object features into unified representations (Beauchamp *et al.*, 2004; Tanabe *et al.*, 2005; Werner & Noppeney, 2010; see also Thelen *et al.*, 2014). A contrasting viewpoint suggests that regions such as the superior temporal sulcus (STS) are not themselves the locus of the unified multisensory object representations, but rather that these regions, if anything, serve as a conduit for integrative processes elsewhere (Taylor *et al.*, 2006; Hocking & Price, 2008). In turn, others would suggest that multisensory representations of objects are predominantly localised to visual cortices, reflecting the presumed dominance of vision in object processes (e.g. Molholm *et al.*, 2004; Diaconescu *et al.*, 2013). However, in contrast to the latter two stances, even during a visual task auditory cortices were shown to be involved in discriminating between those images that had been previously encountered with vs. without sounds (Thelen *et al.*, 2012).

More generally, the present results provide an important interpretational framework for these activation results, which hitherto were

somewhat decoupled from behaviour. Several groups have shown differential responses in the STS or nearby auditory cortices to unisensory stimuli following multisensory learning or exposure. For example, both Nyberg *et al.* (2000) and Wheeler *et al.* (2000) reported increased activity within auditory cortices in response to words/labels studied together with versus without sounds. In the study by Wheeler *et al.* (2000), performance for all conditions was at ceiling levels, whereas in Nyberg *et al.* (2000), performance was *de facto* impaired by studying words with sounds, making it challenging to draw inferences on any direct links between brain responses and the efficacy of multisensory learning. Further adding to the confusion regarding the role of auditory cortices in multisensory learning and memory, von Kriegstein & Giraud (2006) failed altogether to observe any reliable differences within temporal cortices as a function of whether the studied voices had been learned with a face versus name (although such effects were observed in the fusiform gyrus). The discrepant pattern of brain activity and performance outcomes observed across these studies is only exacerbated by the diversity of paradigms they utilised. Moreover, results from these studies could in principle be driven by mental imagery, particularly in those studies that employed tasks requiring explicit recall. By contrast, studies from our lab consistently used one paradigm with systematic manipulations (i.e. semantic congruence and general meaningfulness of the multisensory contexts; the task-relevant modality) to study single-trial and implicit processes and their effects on multisensory learning and memory performance. Our current and prior (Thelen *et al.*, 2012) findings collectively show that there is an inverse relationship between the direction of responses within auditory cortices and memory performance. Specifically, the stronger the response of auditory cortices the worse is the observed memory performance. This suggestion is in strong correspondence with the notion of effective stimulus processing via suppressed activity discussed earlier.

The role of non-auditory cortices

It is noteworthy that response modulations within occipital and frontal cortices appeared to reflect sensitivity to the general multisensory vs. unisensory nature of the context of the initial exposure, rather than the nature of the multisensory context itself. That is, responses were significantly weaker to both the A+c and the A+m conditions vs. the A- condition, with no significant difference between the former. This pattern would suggest that occipital and frontal regions respond differently to sounds depending on their initial encounter context but independently of its semantic congruency, and despite the multisensory nature of this context being task-irrelevant and occurring only on a single trial. A similar set of regions was also identified using magnetoencephalography in response to successful discrimination of test stimuli during an auditory delayed match-to-sample task involving tones (Rong *et al.*, 2010).

While we can only speculate as to the root process(es) producing the effects in occipital and frontal cortices, one possibility would be that participants adopted a strategy of tagging incoming stimuli in a general manner as having been previously encountered in a multisensory context or not, irrespective of the nature of this context. However, this distinction would appear to occur in a fashion that does not directly affect memory performance; participants were able to benefit only from those multisensory contexts that were semantically congruent. To the extent this is the case, it is likewise noteworthy that response suppression was observed simultaneously across a wide network of brain regions (Fig. 3), but profiles in only a subset of these mirrored the behavioural effects. This concomitant

pattern suggests there are parallel and anatomically separable operations, some of which distinguish repeated stimuli according to their initial multisensory versus unisensory contexts, while others distinguish between semantically congruent and non-congruent multisensory contexts.

Conclusion

Single-trial and task-irrelevant visual information was sufficient to dramatically impact early stages of subsequent auditory object processing, thus providing compelling evidence for the effectiveness of multisensory learning contexts. Our findings are a direct demonstration of the crucial contribution of auditory cortices to these effects, which unfold during early stages of stimulus processing, exhibit an inverse relationship with behavioural outcome and transpire in a seemingly task-dependent manner (cf. Werner & Noppeney, 2010).

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Abbreviations

ANOVA, analysis of variance; DISS, global dissimilarity; EEG, electroencephalogram; ERPs, event-related potentials; GFP, global field power; IPC, inferior parietal cortex; LAURA, local autoregressive average; mRT, median reaction time; RAGU, Randomisation Graphical User interface; STC, superior temporal cortex; STS, superior temporal sulcus.

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