



## Multisensory interactions in early evoked brain activity follow the principle of inverse effectiveness

Daniel Senkowski<sup>a,b,c,\*</sup>, Dave Saint-Amour<sup>d,e,1</sup>, Marion Höfle<sup>b</sup>, John J. Foxe<sup>a,f,\*\*</sup>

<sup>a</sup> The Cognitive Neurophysiology Laboratory, Nathan S. Kline Institute for Psychiatric Research Program in Cognitive Neuroscience and Schizophrenia, 140 Old Orangeburg Road Orangeburg, N.Y. 10962, USA

<sup>b</sup> Department of Neurophysiology and Pathophysiology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany

<sup>c</sup> Department of Psychiatry and Psychotherapy Charité, University Medicine Berlin St. Hedwig Hospital, Große Hamburger Str. 5-11 10115 Berlin, Germany

<sup>d</sup> Centre de Recherche, CHU Sainte-Justine, 3175, Côte-Sainte-Catherine Montreal, H3T 1C5, Canada

<sup>e</sup> Département de Psychologie, Université du Québec à Montréal, C.P. 8888, Montreal, H3C 3P8, Canada

<sup>f</sup> The Cognitive Neurophysiology Laboratory, Children's Evaluation and Rehabilitation Center (CERC) Departments of Pediatrics and Neuroscience, Albert Einstein College of Medicine Van Etten Building, Wing 1C, 1225 Morris Park Avenue, Bronx, NY 10461, USA

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### ABSTRACT

A major determinant of multisensory integration, derived from single-neuron studies in animals, is the principle of *inverse effectiveness* (IE), which describes the phenomenon whereby maximal multisensory response enhancements occur when the constituent unisensory stimuli are minimally effective in evoking responses. Human behavioral studies, which have shown that multisensory interactions are strongest when stimuli are low in intensity are in agreement with the IE principle, but the neurophysiologic basis for this finding is unknown. In this high-density electroencephalography (EEG) study, we examined effects of stimulus intensity on multisensory audiovisual processing in event-related potentials (ERPs) and response time (RT) facilitation in the bisensory redundant target effect (RTE). The RTE describes that RTs are faster for bisensory redundant targets than for the respective unisensory targets. Participants were presented with semantically meaningless unisensory auditory, unisensory visual and bisensory audiovisual stimuli of low, middle and high intensity, while they were instructed to make a speeded button response when a stimulus in either modality was presented. Behavioral data showed that the RTE exceeded predictions on the basis of probability summations of unisensory RTs, indicative of integrative multisensory processing, but only for low intensity stimuli. Paralleling this finding, multisensory interactions in short latency (40–60 ms) ERPs with a left posterior and right anterior topography were found particularly for stimuli with low intensity. Our findings demonstrate that the IE principle is applicable to early multisensory processing in humans.

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### Introduction

Multisensory stimuli in our environment are often processed faster than the constituent unisensory inputs when presented alone. An example of such a processing advantage is the sensory redundant target effect (RTE), which describes that reaction times (RTs) to sensory stimuli are faster than those to the constituent unisensory targets. The RTE for bisensory stimuli often exceeds predictions on the basis of probability summations of unisensory stimuli, which is taken to indicate

integrative multisensory processing (Cappe et al., 2009; Diederich and Colonius, 2004; Teder-Salejarvi et al., 2005). Moreover, behavioral studies have demonstrated that the magnitude of the RTE is inversely related to stimulus intensity. The presentation of bisensory stimuli with low intensities leads to more robust behavioral facilitation than the presentation of bisensory stimuli with high intensities (Corneil et al., 2002; Diederich and Colonius, 2004; Rach et al., 2011). These findings are in line with the principle of *inverse effectiveness* (IE), first described in single-neuron studies in animals (Stein and Meredith, 1993), where the maximal multisensory response enhancements occur under conditions where the constituent unisensory stimuli are minimally effective in evoking responses. The neurophysiologic basis for the inverse relationship between stimulus intensity and the magnitude of the bisensory RTE in humans is to date unknown.

The study of crossmodal interactions in ERPs has revealed important insights about when (i.e., latency) and where (i.e., topography) multisensory interactions take place in the human brain (Foxe et al., 2000; Giard and Peronnet, 1999; Molholm et al., 2002; Murray et al.,

\* Correspondence to: D. Senkowski, Department of Neurophysiology and Pathophysiology, University Medical Center Hamburg-Eppendorf, Martinistr. 52 20246, Hamburg, Germany. Fax: +49 40 42803 7752.

\*\* Correspondence to: J. Foxe, Departments of Pediatrics and Neuroscience, Albert Einstein College of Medicine Van Etten Building, Wing 1C, 1225 Morris Park Avenue, Bronx, NY 10461, USA.

E-mail addresses: [dsenkows@uke.uni-hamburg.de](mailto:dsenkows@uke.uni-hamburg.de) (D. Senkowski), [john.foxe@einstein.yu.edu](mailto:john.foxe@einstein.yu.edu) (J. Foxe).

<sup>1</sup> These authors contributed equally to the manuscript.

2005). A frequently applied approach to assay multisensory interactions in the ERP is to compare the neuronal responses to multisensory stimuli with the linearly combined responses to the respective unisensory stimuli. Using this “additive approach”, a pioneering ERP study revealed multisensory interactions between auditory and visual inputs starting as early as 40 ms after stimulus presentation (Giard and Peronnet, 1999). Subsequent studies focusing on multisensory processing between auditory and visual stimuli (Fort et al., 2002; Molholm et al., 2002; Talsma et al., 2007), as well as on the crossmodal integration between other sensory modalities, like auditory and somatosensory stimuli (Foxy et al., 2000; Murray et al., 2005), confirmed the presence of early multisensory interactions around 50 ms. Invasive recordings in non-human primates showed similar early multisensory convergence (e.g., Schroeder & Foxe, 2002). Interestingly, recent studies have revealed the behavioral relevance of these early multisensory processes (Sperdin et al., 2009; Sperdin et al., 2010). However, some studies have failed to obtain short latency multisensory interactions (Gondan et al., 2005; Gondan and Roder, 2006). Notably in these studies, participants were presented with stimuli of relatively high intensities.

In all of the aforementioned ERP studies, the effect of stimulus intensity was not explicitly examined, which could account for the discrepancies regarding the time course and magnitude of early multisensory interactions. In the present high-density electroencephalography (EEG) study, we tested the hypothesis that the inverse relationship between stimulus intensity and the magnitude of multisensory response facilitation in the RTE is reflected maximally in multisensory interactions in early evoked brain activity. To this end, multisensory interactions in behavioral data and ERPs were investigated for bisensory audiovisual stimuli of low, middle, and high intensity.

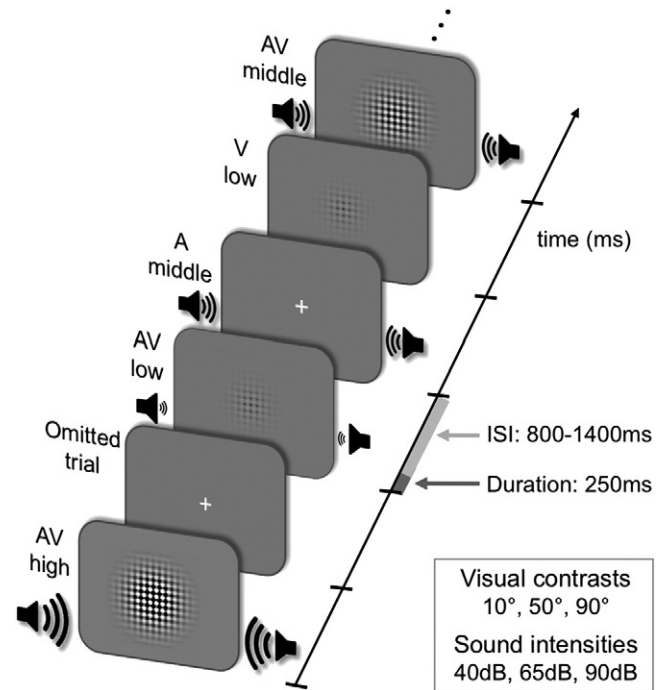
## Material and methods

### Participants

Twelve neurologically normal paid volunteers participated in the study. One participant was excluded from the analysis due to extensive eye movement artifacts in the EEG. The remaining 11 participants (all right-handed, age range 23–48 years, four females), reported normal hearing and had normal or corrected-to-normal vision. The institutional review board of the Nathan Kline Institute for Psychiatric Research approved the experimental procedures, and each participant provided written informed consent.

### Procedure and stimuli

Participants were presented with a randomized stream of unisensory auditory (A), unisensory visual (V) and bisensory AV stimuli at low, middle and high intensities (Fig. 1). They were instructed to maintain central fixation and to make a speeded button response with their right index finger when a stimulus (either sensory modality (unisensory or bisensory) was detected. “No-stimulus” events were intermixed at a presentation rate of 29.4% (about 1500 trials) into the continuous stream of unisensory A, unisensory V and bisensory AV stimuli. No-stimulus events are “blank” trials containing no stimulation, randomly distributed in the trial sequence as if they were real stimulus events. The duration of no-stimulus events was 250 ms. It has been previously shown that no-stimulus events do not elicit physiological responses by themselves when presented at rates of about 30% (Busse and Woldorff, 2003). Importantly, however, the selective average of no-stimulus events represents the average overlap of adjacent trials and/or anticipatory activity, which are contaminating factors when unisensory responses are summed and compared with multisensory stimuli (Teder-Salejarvi et al., 2002). Removing the averages of these responses from the event-related activity to unisensory and bisensory stimuli is one approach to effectively control for these contaminating factors (Talsma and Woldorff, 2005).



**Fig. 1.** Experimental setup. Participants were presented with a continuous stream of low, middle, and high intensity unisensory auditory (A), unisensory visual (V) and bisensory AV stimuli. The participant's task was to make a speeded button response when a stimulus (unisensory or bisensory) was presented. Low, middle, and high intensity bisensory stimuli comprised of the combination of the respective unisensory inputs (e.g., low intensity bisensory AV stimuli comprised of low intensity A and low intensity V inputs).

The visual stimuli comprised of centrally presented Gabor patches with vertical gratings (spatial frequency = 1 cycle/degree; Gaussian standard deviation = 1.5). To manipulate the stimulus intensity levels of the Gabor patches, the contrast was changed while keeping the mean luminance constant at a level of 20 cd/m<sup>2</sup>. Michelson contrast  $((\text{luminance maximal} - \text{luminance minimal}) / (\text{luminance maximal} + \text{luminance minimal})) * 100$  of the low, middle, and high intensity stimuli was 10%, 50% and 90%, respectively. All visual stimuli (V-only and bisensory AV trials) were presented for 250 ms. The auditory stimuli comprised of 1000 Hz sinusoidal tones, which were presented for 250 ms (10 ms rise and fall times) through two speakers placed to the left and to the right of the monitor. Low, middle, and high intensity stimuli had sound-pressure levels (SPL) of 40, 65, and 90 dB, respectively. The selection of these intensities was motivated by previous studies examining the effects of stimulus intensities on visual (Ellemberg et al., 2001) and auditory (Jaskowski et al., 1994; Michalewski et al. 2009) evoked potentials. Low, middle, and high intensity bisensory stimuli comprised of corresponding combined unisensory inputs (e.g., low intensity A and low intensity V stimuli constituted low intensity bisensory AV trials, etc.). Bisensory stimuli were presented at three intensity levels: AV-low, AV-middle, and AV-high. Auditory and visual inputs had the same onset in bisensory trials. For each of the nine stimulus types (A-low, A-middle, A-high, V-low, V-middle, V-high, AV-low, AV-middle, AV-high) about 400 stimuli were presented. All stimuli, including no-stimulus events, were presented with a randomly varying inter-stimulus interval (ISI; measured from the offset of one trial to the onset of the next) between 800 and 1400 ms (mean = 1100 ms). During the ISI and during the no-stimulus and unisensory auditory events, a fixation cross was centrally presented. On average, 25 blocks with a duration of about 4 minutes each were presented. Stimulus presentation was controlled using Presentation software (Neurobehavioral Systems, Albany, CA).

## Data analysis

### Behavioral data

To investigate whether the factor stimulus intensity had a general influence on RTs, a two-factorial repeated measures analyses of variance (ANOVA) using the factors of stimulus intensity (low, middle, high) and stimulus type (unisensory A, unisensory V, bisensory AV) was conducted. If this ANOVA revealed a significant interaction of stimulus intensity  $\times$  stimulus type, subsequent repeated measures ANOVAs with the factor stimulus type were conducted separately for each of the three stimulus intensity levels. Finally, pair wise follow-up comparisons were computed if these ANOVAs revealed a significant effect of stimulus type.

In the next step of the analysis, the “race model” inequality was tested (Miller, 1982) to examine whether the RTs for bisensory stimuli exceeded the facilitation predicted by the probability summation of unisensory stimuli. The race model places an upper limit on the cumulative probability (CP) of RT at a given latency for unisensory stimulus pairs. For any latency  $t$ , the race model holds when this CP value is less than or equal to the sum of the CP from each of the single unisensory stimuli (e.g., A and V) minus an expression of their joint probability ( $CP(t)_{AV} < ((CP(t)_A + CP(t)_V) - (CP(t)_A * CP(t)_V))$ ). For each subject the RT probability distribution within the valid RTs (in accordance with Molholm et al. (2002), responses falling between 100 and 800 ms post stimulus onset were considered valid) was calculated over the three stimulus conditions (unisensory A, unisensory V, and bisensory AV) and divided into quintiles from the first to the hundredth percentile in 5% increments (1–5%, 5–10%, ..., 90–95%, 95–100%). Due to type 1 error accumulation that occurs during the computation of multiple  $t$ -tests in the race model, Kiesel et al. (2007), who conducted simulation analyses, suggested to focus the analysis on a restricted range of percentiles ranging up to 25% and to reject the race model only if significant differences are found at multiple percentiles. In the present study,  $t$ -tests comparing the RTs to bisensory stimuli and the predicted facilitation of RTs based on the respective unisensory stimuli (i.e.,  $CP(t \text{ quintile interval})_{AV}$  vs.  $((CP(t \text{ quintile interval})_A + CP(t \text{ quintile interval})_V) - (CP(t \text{ quintile interval})_A * CP(t \text{ quintile interval})_V))$ ) were performed across subjects for five quintiles ranging from 1% to 25%. Furthermore, we determined that the majority of the applied  $t$ -tests had to reach a significance threshold of 5% (i.e., in the present study at least three of the five  $t$ -tests should reveal  $p < 0.05$ ). For all quintiles, the Miller inequality, which represents the difference between the actual bisensory and the predicted probabilities, was plotted. Any violation of the race model would indicate that the reaction time facilitation was at least partially due to interactions between the auditory and visual inputs. The race model was computed separately for low, middle, and high intensity stimuli.

### EEG data acquisition and analysis of event-related potentials

High-density EEG recordings were acquired using a BioSemi Active-Two electrode system with 4 EOG and 164 scalp channels. Data were band-pass filtered from 0.05 to 100 Hz during recording at a sample rate of 512 Hz and off-line re-referenced to average reference, which is a standard reference for high-density EEG recordings (Murray et al., 2008). In addition, a 55 Hz low-pass filter was applied prior to the data analysis. The data were epoched from  $-400$  ms before to  $700$  ms after stimulus onsets. Baselines were computed from a  $-50$  to  $0$  ms time interval prior to the onset of the stimuli and subtracted from each trial. For artifact rejection, trials were automatically excluded from averaging if the standard deviation within a moving 200 ms time window exceeded  $30 \mu V$  in any one of the channels in an epoch from  $-200$  ms to  $500$  ms. Channels with extremely high and/or low frequency artifacts throughout the entire topography at the unit sphere surface based on all non-artifactual channels (Perrin et al., 1989).

Multisensory interactions to low, middle, and high intensity stimuli were assessed by comparing the ERPs to multisensory stimuli with the linear summation of the responses to the respective unisensory constituents (e.g., ERP AV-low vs. (ERP A-low + ERP V-low)). Prior to this analysis, the 20 Hz low-pass filtered time locked average of the no-stimulus events (see above) was subtracted from the ERPs of V-only, A-only and bisensory AV trials for each subject individually in order to eliminate overlapping activity from adjacent trials and/or anticipatory activity. In line with previous reports of early audiovisual interactions around 50 ms (Fort et al., 2002; Giard and Peronnet, 1999; Molholm et al., 2002; Talsma et al., 2007), the focus of the statistical analysis of multisensory interactions in the present study was on the interval between 40 and 60 ms (i.e., mean ERP amplitudes). This time interval comprises the auditory P1 and the visual C1 components. The statistical analysis was carried out on integrated potential measurements averaged across electrodes within each of five regions of interest (ROI). In line with a previous study (Senkowski et al., 2007), we examined multisensory interactions at two bilateral ROIs over posterior scalp regions and one medial-central ROI. Moreover, since early multisensory interactions have also been observed over anterior scalp (Molholm et al., 2002), two bilateral anterior ROIs were included in the statistical analysis. Each ROI comprised six electrodes (Fig. 2).

To establish the presence of multisensory interactions, two levels of analysis were applied. The first level was conducted to render a full description of the spatio-temporal properties of the AV interactions for low, middle, and high intensity stimuli. The ERPs to multisensory stimuli were compared with the linear summation of the ERPs to the respective unisensory constituents using point-wise running  $t$ -tests (two-tailed) for each scalp electrode. An AV interaction was defined as at least seven consecutive data points meeting a 0.05 alpha criterion (7 data points = 14 ms at a 512 Hz digitization rate) (for details on the use of running  $t$ -tests, see e.g., Guthrie and Buchwald, 1991). In the second level of analysis, repeated measures ANOVAs were performed for the three stimulus intensities for the time interval between 40 and 60 ms. The ANOVA comprised the within-subject factors of stimulus type (AV and A + V), and ROI (left anterior, right anterior, medial-central, left posterior, right posterior). Since three ANOVAs were computed, the significance threshold in this analysis was adjusted to a Bonferroni corrected significance threshold of  $p < 0.0166$  (i.e.,  $0.05/3$ ). If the ANOVA revealed a significant interaction between stimulus type  $\times$  ROI, then planned comparisons using the factor stimulus type (AV and A + V) were performed separately for each of the five ROIs.

Finally, similar to Sperdin et al. (2008), if significant multisensory interactions were found in behavioral data and ERPs, the association between the response times of multisensory stimuli and early evoked brain activity was tested. To this end, trials were sorted into two bins comprising the 50% of trials with the shortest RTs (i.e., fast trials) and the 50% of trials with the longest RTs (i.e., slow trials) within each condition and subject. ERPs were computed separately for short and

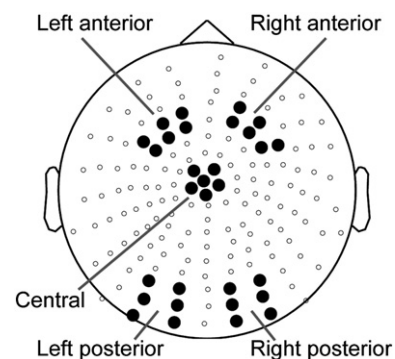


Fig. 2. Definition of ROIs for the statistical analysis of evoked brain potentials. Two anterior, two posterior, and one medial-central ROI were analyzed.

long RT trials. The ANOVA included the factors of intensity (low, middle, and high), reaction times (fast and slow), and ROI (left anterior, right anterior, medial-central, left posterior, right posterior). To further test the relationship between multisensory interactions in early ERPs and RTs across participants, non-parametric Spearman's Rho correlation coefficients were computed between the ERP difference to AV minus A + V trials and the RT difference to AV versus combined A-only and V-only trials for the ROIs and conditions for which significant effects were found in the first two levels of the analysis. To estimate the predicted mean RTs of combined A-only and V-only trials within each participant, one A-only and one V-only trial was randomly picked from each of the two RT distributions. The trial with the shorter RT was selected for the calculation of the predicted mean RT for combined A-only and V-only trials. This procedure was repeated 1000 times, resulting in 1000 combined A-only and V-only trial RTs for which the average was computed. Within each participant, this average was subtracted from the average RT to bimodal AV-trials (i.e., AV minus combined A-only and V-only trials).

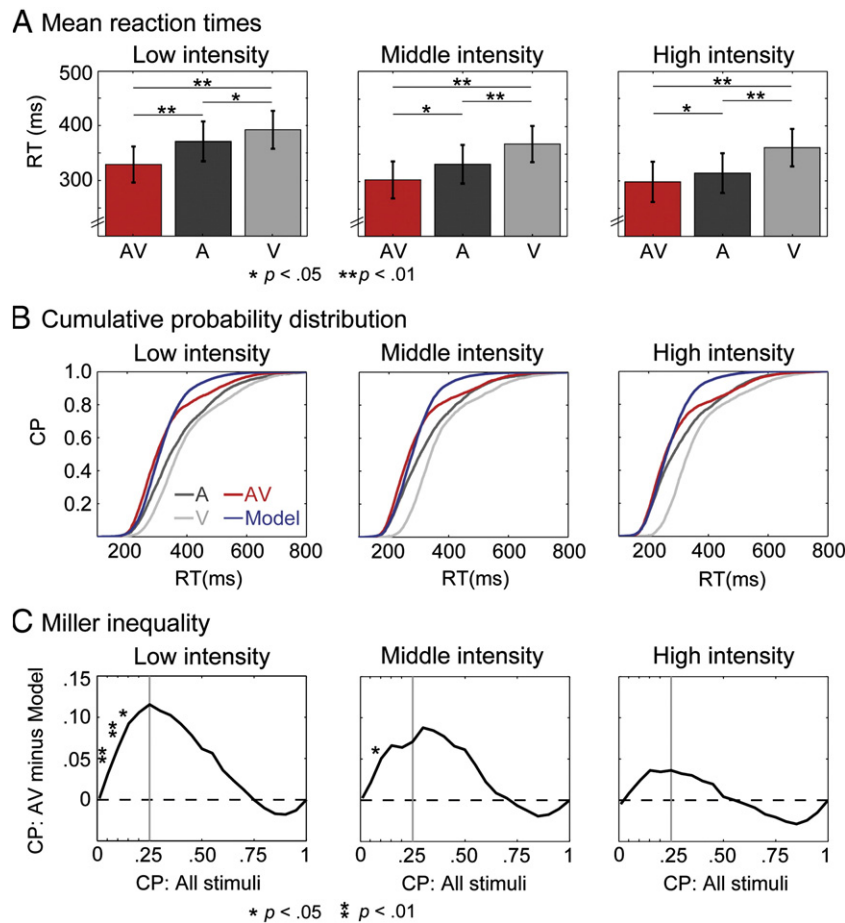
**Results**

*Behavioral data*

Fig. 3 illustrates the RTs for low, middle, and high intensity unisensory and bisensory stimuli. Across the three intensity levels, the RTs declined with increasing stimulus intensity, as reflected by a significant main effect of stimulus intensity in the two-factorial

ANOVA ( $F(2,20) = 39.99, p < 0.001$ ). An additional main effect of stimulus type ( $F(2,20) = 39.46, p < 0.001$ ) and an interaction between stimulus type and stimulus intensity were found ( $F(4,40) = 8.80, p < 0.002$ ). Follow-up ANOVAs, which were conducted for the three intensity levels separately, revealed significant main effects of stimulus type for all intensities (low intensity:  $F(2,20) = 30.46, p < 0.001$ ; middle intensity:  $F(2,20) = 32.75, p < 0.001$ ; high intensity:  $F(2,20) = 52.25, p < 0.001$ ). Pair wise comparisons between the different stimulus types revealed faster RTs for bisensory AV compared to unisensory A and unisensory V trials (Fig. 2A). Moreover, RTs were faster for unisensory A than for unisensory V trials (i.e., RTs:  $AV < A < V$ ).

While this analysis showed that RTs were faster for bisensory compared to unisensory trials across all stimulus intensities, the tests of the race model inequality revealed that significant response facilitation for RTs to bisensory compared to predicted RTs occurred primarily for low intensity trials (Fig. 3B and C). For low intensity stimuli, three consecutive RT quintiles (2nd to 4th quintile of combined unisensory and multisensory trials) differed significantly between the bisensory and the predicted RTs ( $p = 0.004, p = 0.001, p = 0.020$ , respectively). No significant RT facilitation effects were observed for high intensity stimuli and only one significant quintile (2nd quintile,  $p = 0.01$ ) for middle intensity stimuli. However, the criterion of at least three significant quintiles was not fulfilled for these stimuli (see above). Thus, the only robust violations of the race model, indicative of integrative processes, were observed for bisensory stimuli with low intensity.



**Fig. 3.** Effects of stimulus intensity on multisensory interactions in reaction times. (A) RTs declined with increasing stimulus intensity. Moreover, the comparison between unisensory and bisensory stimuli showed faster RTs for bisensory stimuli compared to unisensory trials and faster RTs for unisensory A compared to unisensory V trials. (B) Cumulative probability (CP) distributions of RTs for bisensory (red traces), unisensory A (dark gray traces), and unisensory V (light gray traces) stimuli and predicted (blue traces) CPs in relation to RTs. (C) Testing the Miller inequality, robust response facilitations occurred only for low intensity trials, in which violations of the race model were found in three of five tested quintiles.

### Evoked brain activity to unisensory stimuli

The amplitudes of the ERP components changed with stimulus intensity (Figs. 4 and 5). Fig. 4 shows the ERP traces to unisensory A and unisensory V stimuli at right anterior, medial-central, and the left posterior ROIs. The amplitude of the early auditory evoked P1 component (around 50 ms) was pronounced for stimuli with middle and high intensities, whereas it was small for low intensity stimuli. A similar pattern emerged for the visual evoked C1 and P1 components. In line with previous reports (Hegerl et al., 1994; Senkowski et al., 2003), the auditory evoked N1 component (around 100 ms) increased almost linearly with increasing stimulus intensities. Fig. 5 illustrates the topography of the short latency ERPs to unisensory A and unisensory V stimuli. Longer latency (around 150–200 ms) deflections primarily were comprised of the auditory P2 and the visual N1 components.

### Multisensory interactions in the evoked brain activity: Point wise running *t*-tests

Fig. 6 shows the results of the point wise running *t*-tests (AV vs. A + V) for low, middle and high intensity stimuli. Gray shades highlight the short latency, i.e., 40–60 ms, time interval that was selected for the ROI analysis. For the low intensity stimuli, a clear pattern of integration effects is visible at a short latency of around 50 ms. Moreover, the figure shows longer latency integration effects for low intensity stimuli, which were not the focus of the present study. Although few electrodes indicate signatures of early multisensory interactions in the middle intensity condition, no systematic integration effects were found when considering the topographic clustering of electrodes. Thus, the point wise running *t*-tests did not reveal robust patterns of integration effects for the middle and high intensity stimuli.

### Topography of multisensory interactions in the early evoked brain activity

The ANOVA for ERPs to low intensity stimuli using the factors of stimulus type (AV and A + V) and ROI (left anterior, right anterior, medial-central, left posterior, right posterior) revealed a significant interaction between the two factors ( $F(4,40) = 3.45$ ,  $p = 0.0163$ ). Follow up ANOVAs were conducted separately for the different ROIs using the factor stimulus type. These ANOVAs revealed significant main effects of stimulus type at the right anterior and left posterior ROIs ( $F(1,10) = 5.58$ ,  $p = 0.0397$  and  $F(1,10) = 5.62$ ,  $p = 0.0392$ , respectively). The amplitudes of the right anterior ROI were more positive in the bisensory (0.47  $\mu\text{V}$ ) compared to the combined unisensory condition (−0.25  $\mu\text{V}$ ), whereas at the left posterior ROI they were more negative in the bisensory (−0.56  $\mu\text{V}$ ) than in the combined unisensory condition (0.17  $\mu\text{V}$ ). Figs. 7 and 8 illustrate this effect, which we refer to as superadditive interaction (i.e.,  $AV > A + V$ ), since both the anterior and the posterior amplitudes (independent of their polarity) were larger in the bisensory than in the combined unisensory ERPs. In contrast to low intensity stimuli, the ANOVAs for middle and high intensity stimuli did not reveal any significant effects.

### Comparing early evoked brain activity and reaction times

The ANOVA using the factors of reaction times (50% fastest and 50% slowest trials), intensity (low, middle, and high), and ROI (left anterior, right anterior, medial-central, left posterior, right posterior) did not reveal any significant main effects or interactions. In the first two levels of the ERP analysis, multisensory interactions were found in the right anterior and left posterior ROIs but only in the low intensity condition. Therefore, Spearman's Rho correlation coefficients between the multisensory interactions in ERPs at these two ROIs and the RTs across participants were computed only for

low intensity stimuli. This analysis revealed no effect for the right anterior ROI ( $\rho = -0.35$ ,  $p < 0.30$ ) but a trend towards a significant correlation for the left posterior ROI ( $\rho = 0.55$ ,  $p < 0.09$ ). Participants with stronger negative left posterior ERP amplitudes in the AV vs. A + V comparison tended to show larger response time facilitation in behavior.

### Discussion

Our study showed that stimulus intensity affects both response facilitation during the bisensory redundant target effect and early integrative multisensory processing in evoked brain activity. While bisensory stimuli with middle and high intensity levels did not reveal robust multisensory interactions, low intensity multisensory stimuli showed a response time facilitation that was paralleled by an early (40–60 ms) superadditive interaction in the evoked brain activity.

### The bisensory redundant target effect and stimulus intensity

As expected, the RTs for multisensory and unisensory stimuli decreased with increasing stimulus intensity. Furthermore, for all stimulus intensities we observed significantly faster RTs for bisensory compared to unisensory stimuli. More importantly, robust violations of the race model occurred primarily in the low intensity stimuli. The Miller inequality, furthermore, suggests a continuous reduction in multisensory response facilitation with increasing stimulus intensity (Fig. 3c). This observation fits with previous studies, which demonstrated an inverse relationship between the magnitude of the RTE for bisensory inputs and stimulus intensity (Corneil et al., 2002; Diederich and Colonius, 2004; Rach et al. 2011). Interestingly, an inverse association between the magnitude of the RTE and the intensity of multisensory stimuli has been recently found also in monkeys (Cappe et al., 2010a). This observation, in addition to the present data, suggests that stimulus intensity influences integrative

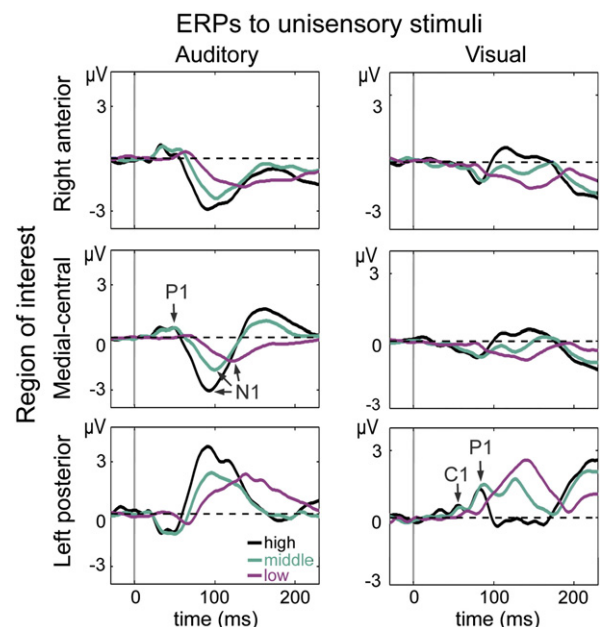
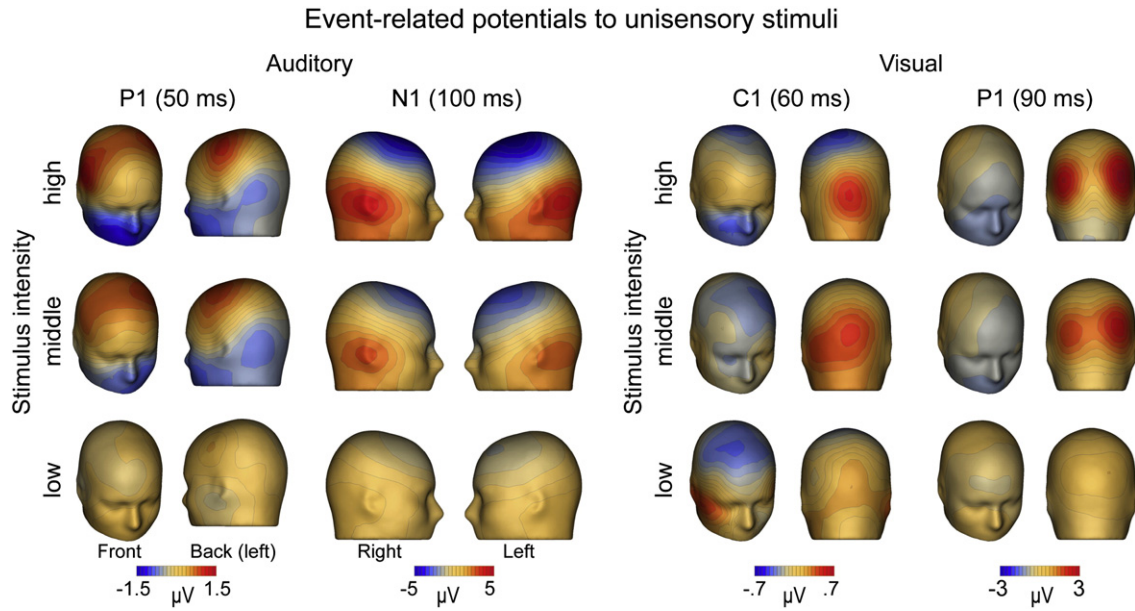


Fig. 4. Traces of event-related potentials to unisensory stimuli (no-stimulus event responses were subtracted prior to the ERP analysis). ERPs to unisensory A (left panel) and unisensory V (right panel) stimuli are plotted for a right anterior (upper panel), medial-central (middle panel) and left posterior (lower panel) region of interest. The majority of the early (<100 ms) evoked potentials showed an increase with increasing stimulus intensity. Notice the dipolar pattern (i.e., the reversed amplitudes) between left posterior and medial-central ROIs for the auditory P1 and N1 components.



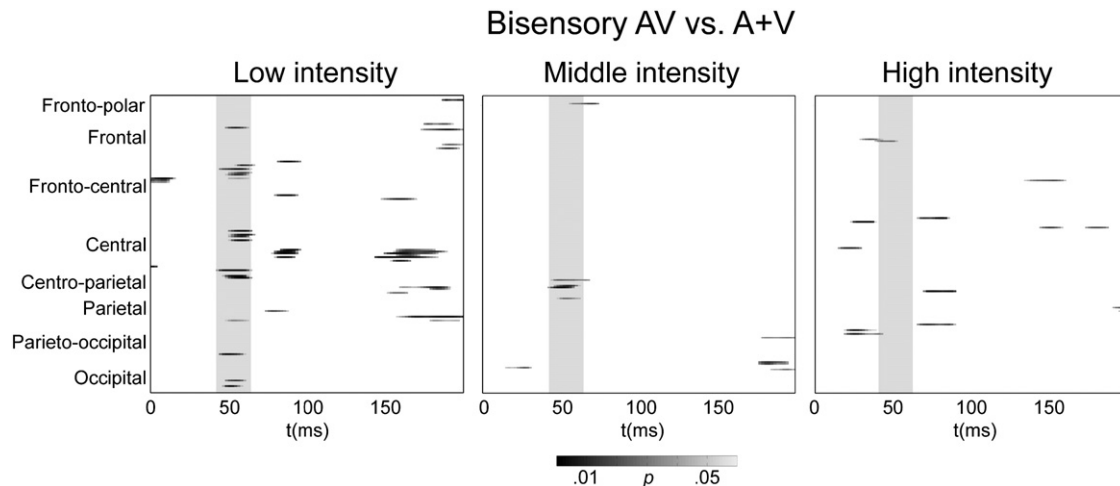
**Fig. 5.** Topographic maps of early event-related potentials to unisensory stimuli. Both the auditory P1 and the N1 components showed dipolar response patterns between lateral posterior and medial-central scalp regions. The main activity patterns of the visual C1 and P1 components were found over posterior scalp regions.

multisensory processing such that the RT facilitation effect to bisensory redundant targets is strongest when stimuli are low in intensity.

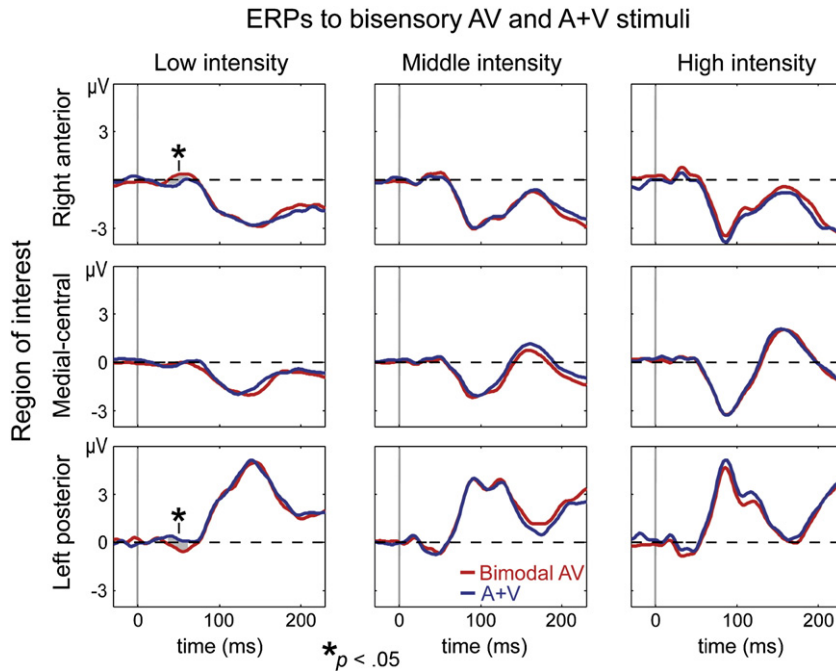
*Multisensory interactions in early evoked brain activity and stimulus intensity*

The finding of multisensory interactions at a short latency of 40–60 ms in the present study is in agreement with previous reports on multisensory audiovisual processing of redundant targets (Fort et al., 2002; Giard and Peronnet, 1999; Molholm et al., 2002; Talsma et al., 2007). However, our results extend those of previous ERP studies by demonstrating that early multisensory interactions occur most robustly when the presented stimuli are low in intensity. A closer inspection of previous studies reveals that in the majority of experiments that reported early interactions at least one of the presented inputs was relatively low in intensity. For instance, Giard and Peronnet (1999), as well as Fort et al. (2002), presented their

participants with low intensity auditory inputs of 50 dB HL, while the visual stimuli comprised centrally presented circles that deformed into horizontal or vertical ellipses. Molholm et al. (2002) presented low intensity visual stimuli that were comprised of laterally presented small discs and auditory stimuli of 75 dB SPL. Furthermore, Talsma et al. (2007) used relatively low intensity visual stimuli consisting of horizontal square wave gratings, which were presented below a central fixation cross. The auditory stimuli in this study were at a middle intensity level of 65 dB SPL. Thus, our findings and the results from aforementioned studies suggest that early multisensory interactions occur primarily when stimuli in at least one modality are low in intensity. However, our study does not allow us to draw conclusions about possible multisensory interactions in early evoked brain responses to stimuli with different intensity levels across modalities (e.g. a low intensity auditory stimulus paired with a high intensity visual stimulus). Further studies are needed to address the question of how differences in stimulus intensity levels across modalities affect early multisensory processing.



**Fig. 6.** Point wise running *t*-tests for bisensory AV vs. A + V responses. Robust interactions in the time interval of interest, i.e., 40–60 ms (highlighted in gray shades), were only found in the low intensity trials.



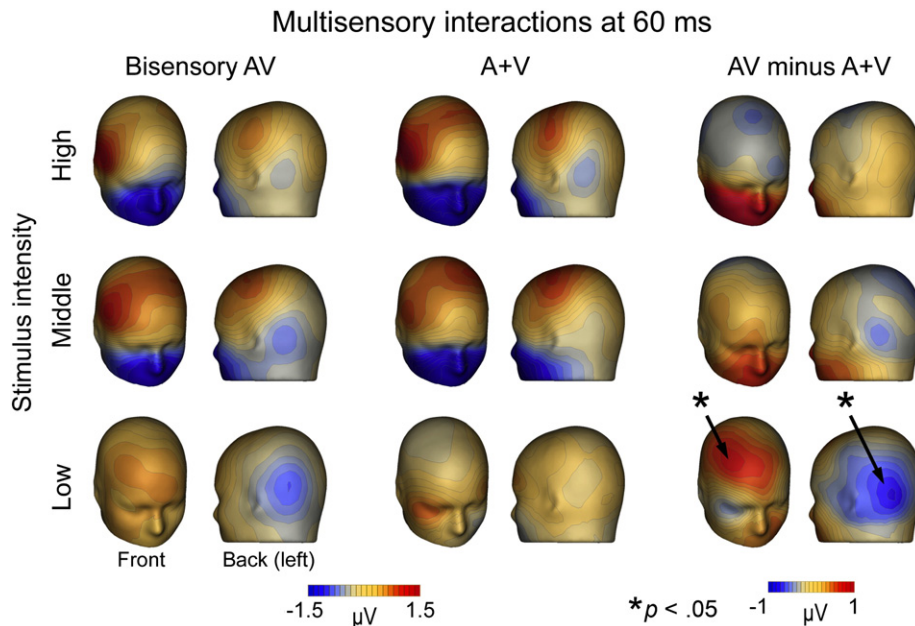
**Fig. 7.** Traces of event-related potentials for bisensory AV and combined A + V trials. The statistical analysis revealed significant effects for the low intensity stimuli at right anterior and left posterior ROIs in the time interval between 40 and 60 ms. No significant effects were observed for middle and high intensity trials.

Some ERP studies investigating audiovisual multisensory interactions did not find early integration effects, while interactions at longer latencies were observed (Gondan et al., 2005; Gondan and Roder, 2006). Notably, none of the presented auditory or visual stimuli in these studies were low in intensity. Although our findings should be interpreted cautiously, they suggest that early crossmodal interactions in the ERP are obvious for low intensity stimuli, but weak or even vanish when stimuli are presented at a sufficiently high intensity.

An interesting question that has been recently addressed by Sperdin et al. (2009, 2010) is whether the early multisensory integration effect in ERPs is directly related to the behavioral facilitation in RTs. In line with a previous report (Sperdin et al.

2009), we did not find differences in the early evoked brain activity between multisensory stimuli with short and long RTs. However, across participants, the amplitude difference between early left posterior ERPs to bimodal versus combined unisensory stimuli tended to be positively associated with the facilitation effect in RTs. This indicates that early multisensory processes may be, at least in part, related to the behavioral facilitation of bimodal redundant targets.

When interpreting the present ERP results, some cautious assumptions about the underlying neuronal structures can be made. The early integration effect for low intensity stimuli had a left posterior and right anterior topography. It may be that a specific multisensory network, similar to the one recently found by Cappe et



**Fig. 8.** Topography of short latency multisensory interactions. The comparison of bisensory AV and combined A + V trials showed robust activity differences at right anterior and left posterior scalp sites for the low intensity trials. The figure illustrates that ERPs are more positive (at right anterior scalp) and more negative (at left posterior scalp) for bisensory compared to combined A + V trials. Thus, the multisensory integration effect observed for low intensity stimuli is superadditive (i.e., AV > A + V).

al. (2010b) for the processing of non-task relevant audiovisual stimuli in the 60–95 ms latency range, was involved. The multisensory integration effect in the study by Cappe et al., which had a posterior topography, was source localized to primary visual, primary auditory, and posterior superior temporal regions. In addition to the effects measured at posterior electrodes, we found multisensory interactions at right anterior electrodes, which may indicate an involvement of attention related processes (Talsma et al., 2007; Talsma et al., 2010). Future studies, possibly involving human intracranial recordings, will be necessary to uncover the neuronal generators underlying early multisensory interactions in more detail.

Overall, the inverse relationship between the magnitude of early multisensory interactions and RT facilitation for bisensory redundant targets is compatible with the IE principle (Meredith and Stein, 1986; Stein and Stanford, 2008; Wallace and Stein, 1997). While some concerns have been raised about the post-hoc sorting of data by the strength of the unisensory responses, like regression effects towards the mean (Holmes, 2009; but see Stein et al., 2009), the present study circumvents this issue by using ad-hoc selected discrete levels of stimulus intensities. In our study, stimuli with higher intensities also evoked larger ERPs (Figs. 4 and 5). Thus, our study provides evidence that, similar to what was found for single-neuron activity, the strength of early evoked responses in the human brain is inversely related to the magnitude of the multisensory integration effect. Interestingly, two recent functional magnetic resonance studies (fMRI) reported multisensory interactions in the superior temporal sulcus (STS) during the recognition of naturalistic audiovisual objects, which were presented at different degrees of degradation that are consistent with the IE principle (Stevenson and James, 2009; Werner and Noppeney, 2010). Another fMRI study examining integration effects between iconic gestures and auditory speech stimuli that were presented with varying amounts of noise, revealed multisensory interactions in the left STS and adjacent cortical regions that were stronger for degraded than for non-degraded stimuli (Holle et al 2010). Collectively, this suggests that multisensory interactions in the human brain follow, at least to some extent, the principle of *inverse effectiveness* (but see Ross et al., 2007).

The findings on multisensory processing of naturalistic audiovisual objects in recent fMRI studies (Holle et al 2010; Stevenson and James, 2009; Werner and Noppeney, 2010) raise the question of whether there is an inverse relationship between stimulus intensity and early multisensory processing of semantically meaningful stimuli. Three EEG studies have examined multisensory interactions in evoked brain activity using semantically meaningful stimuli, like picture drawings and sounds of objects (Molholm et al., 2004) or video clips with corresponding sounds (Senkowski et al., 2007; Stekelenburg and Vroomen, 2007). Although longer latency interactions (starting around 100–150 ms) were observed in all of these studies, no short latency multisensory interactions were found. Since the stimuli in these studies were salient (i.e., non-degraded) and of relatively high intensity, it remains to be investigated whether early multisensory interactions may be found when semantically meaningful stimuli are presented with lower signal strength (e.g., by masking or degrading the stimuli). Moreover, it would be interesting to address whether possible early multisensory interactions may be predictive of the previously reported recognition benefit of bisensory over unimodal semantically meaningful objects (Doehrmann and Naumer, 2008; Laurienti et al., 2004). In summary, the present study revealed an inverse relationship between stimulus intensity and the magnitude of integrative multisensory processing in behavior and early evoked brain activity for semantically meaningless but behaviorally relevant audiovisual stimuli.

## Conclusion

Our study suggests an important role of short latency multisensory interactions for the inverse relationship between stimulus intensity and behavioral facilitation in the RTE. The finding that multisensory

integration effects in RTs and early evoked brain activity occurred particularly for low intensity inputs, but not for stimuli with middle and high intensity, suggest that the principle of IE is applicable for integrative processing of basic multisensory stimuli in the human brain. Future studies wishing to emphasize on early multisensory integration processes in the human brain should therefore consider the use of low intensity stimuli.

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