Crossmodal integration improves sensory detection thresholds in the ferret

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Abstract

During the last decade ferrets (*Mustela putorius*) were established as a highly efficient animal model in different fields in neuroscience. Here we asked whether ferrets merge sensory information according to the same principles established for other species. Since there are only a few methods and protocols for behaving ferrets we developed a head-free, body-restrained approach allowing a standardized stimulation position and the utilization of the ferret's natural response behaviour. We established a behavioural paradigm to test audiovisual integration in the ferret. Animals had to detect a brief auditory and/or visual stimulus presented either left or right from their midline. We first determined detection thresholds for auditory amplitude and visual contrast. In a second step, we combined both modalities and compared psychometric fits and the reaction times between all conditions. We employed Maximum Likelihood Estimation (MLE) to model bimodal psychometric curves and to investigate whether ferrets integrate modalities in an optimal manner. Furthermore, to test for a redundant signal effect we pooled the reaction times of all animals to calculate a race model. We observed that bimodal detection thresholds were reduced and reaction times were faster in the bimodal compared to unimodal conditions. The race model and MLE modeling showed that ferrets integrate modalities in a statistically optimal fashion. Taken together, the data indicate that principles of multisensory integration previously demonstrated in other species also apply to crossmodal processing in the ferret.

Introduction

During the last decade ferrets (*Mustela putorius*) have become increasingly relevant as an animal model in different fields in neuroscience [1–21]. Ferrets provide advantages for developmental studies due to their immaturity at birth, allowing to investigate brain processes that occur prenatally in other species [9,10]. An additional advantage of the ferret is that its brain shows substantial homologies with those of other species and established animal models, such as the cat [14]. Taking this into account, extensive work has been performed to map cortical and subcortical regions of the ferret brain functionally and anatomically [8,12,15,17,18,20,21]. These mapping studies have shown that ferrets have highly complex sensory cortical systems, making them an interesting model for the study of sensory processing pathways, response properties and topographies of sensory neurons. Several studies have addressed multisensory response properties in anesthetized ferrets [6,11,13,16], but multisensory interactions have not yet been studied in a behavioural preparation in this species.

Substantial effort has been made to uncover principles of multisensory integration in a variety of species and paradigms [22–27]. Multisensory integration is crucial for animals and influences behaviour in synergistic or competitive ways. Sensory integration can lead to faster reaction times, better detection rates and higher accuracy values in multi- compare to unimodal conditions [25,28,29]. Specifically, sensory integration increases the reliability by reducing the variance in the sensory estimate [28,30,31]. The consistent estimate with the lowest mean squared error is the Maximum Likelihood Estimate (MLE) [32], which can be derived from the weighted sum of the individual sensory estimates, with weights being inversely proportional to the variance of the unisensory signals [28,31]. A substantial number of studies indicate that humans and animals indeed integrate information across sensory modalities in this way. For example, Ernst and Banks [28] used a MLE model to predict the results of a visual-haptic experiment and showed that humans integrate information in a statistically optimal fashion. Similar results were obtained by application of MLE in a human audio-visual study [29] and in a vestibular-visual study in macaque monkeys [33]. These studies demonstrate that the MLE is a robust statistical model to predict the crossmodal response and to test whether subjects integrate information in a statistically optimal fashion. As a results of the sensory integration process, the accumulation of information in multimodal compared to unimodal conditions is faster, which in turn leads to decreased reaction times (RT) [34–39].

In the present study, we investigated whether ferrets merge sensory signals according to the same principles established for humans [25,40] and non-human primates [33]. Previous studies in behaving ferrets have used either freely-moving [1,7,41] or head-restrained [42] animals. Here, we developed a head-free, body-restrained approach allowing

a standardized stimulation position and the utilization of the ferret's natural response behaviour. An additional demand was that the setup should be sufficiently flexible to allow combination of the behavioural protocol with electrophysiological recordings. We established a behavioural paradigm, requiring combination and integration in the auditory and/or visual modality, to describe features of uni- and multisensory integration in the ferret and compare it to data reported from other species. Ferrets were tested in a 2-alternative-choice task requiring them to detect lateralized auditory, visual, or combined audio-visual targets of varying intensity. We expected the ferrets to perform more accurate and faster in the bimodal cases, because congruent inputs from two modalities provide more reliable sensory evidence. We first determined unimodal thresholds for auditory amplitude and visual contrast detection. Subsequently, we combined both modalities and compared psychometric fits and the RTs between all conditions. We used MLE to model psychometric curves and to test whether ferrets integrate visual and auditory signals in an optimal manner. Furthermore, to test for a redundant signal effect (RSE) we pooled the RT of all animals to calculate a race model and investigate potential intensity- and modality-dependent effects [35,43,44].

Materials and Methods

Ferrets were trained in a spatial detection paradigm, which was used to perform two behavioural experiments. In the first experiment, the animals' auditory and visual unisensory detection thresholds were determined. In the second experiment, unimodal and bimodal thresholds were assessed in a combined approach, using the unimodal results from the first experiment to adjust the test parameters.

Animals

Four adult female ferrets (*Mustela putorius;* Euroferret, Dybbølsgade, Denmark), from two different litters were tested in the experiment. They were individually housed in a standard ferret cage with enriched environment under controlled ambient conditions (21°C, 12-h light/dark cycle, lights on at 8:00 a.m.). The animals had ad libidum access to food pellets. Access to tap water was restricted 8-h before the experiments. All behavioural testing was done during the light cycle between 10:00 a.m. and 2:00 p.m.

Ethics statement

All experiments were approved by the Hamburg state authority for animal welfare (BUG-Hamburg; Permit Number: 22/11) and performed in accordance with the guidelines of the German animal protection law. All sections of this report adhere to the ARRIVE Guidelines for reporting animal research [45]. A completed ARRIVE guidelines checklist is included in Checklist S1.

Experimental setup

The experiments were carried out in a dark sound attenuated chamber to ensure controlled conditions for sensory stimulation. Once per day each ferret performed the experimental task in a custom-build setup (Fig. 1A). We crafted a flat-bottomed tube to conveniently house the animal during the experiment. The body of the ferret was slightly restrained by fixation to three points in the tube via a harness, while the head remained freely movable outside the tube throughout the session. The semi-circular tube was fixed on an aluminium pedestal to level the animals' head at 20cm distance to the centre of the LED screen used for visual stimulation (BenQ XL2420T, Taipei, Taiwan). On the front ('head side'), two convex aluminium semicircles were mounted horizontally below and above the animals' head, respectively, at 150mm distance. They carried three light-barrier-fibers (FT-FM2), in the centre, left and right, respectively, connected to high-speed (sampling interval: 250µs) receivers (FX301, SUNX, Aichi, Japan). This allowed the detection of the animal head during the experiments. In addition, a waterspout was co-localized with each light-barrier source. On both sides of the LED screen a speaker (T1; Beyerdynamic, Heilbronn, Germany) was

placed with a 45° angle to the screen surface and at the height of the horizontal screen midline. A custom made 3-channel water-dispenser was installed outside the sound attenuated chamber to avoid acoustical interference during the experiments. It consisted of three valves from SMC Corporation (Tokyo, Japan), a Perfusor syringe (Melsungen, Germany) as water reservoir and Perfusor tubing to connect it with the waterspouts. The setup was controlled by custom-made routines using the Matlab environment (The Mathworks Inc.; MA, USA) on a MacPro. Behavioural control (light-barriers) and reward application (water-dispenser) were triggered through NI-PCI-cards (NI-6259 and NI-6251; National Instruments GmbH, Munich, Germany). The Psychtoolbox and the custom-written NI-mex-function referred to the same internal clock allowing the precise timing of behaviour and stimulation.

Figure 1. Experimental setup and behavioural task.

(A) Schematic of the components of the experimental setup in a top view: the LED-screen (a) with a speaker (b) on each side, the aluminium pedestal (d), and the three light-barrier-waterspout combinations (c). The semi-circular acrylic tube with a ferret (e) inside is placed on the pedestal. (B) Successive phases in the detection task: The intertrial window (I), the trial initialization window (II), the event window (III) and the response window (IV). The three circles below each frame represent the light-barriers (white = unbroken, red = broken). The center of the screen displays a static visual random noise pattern. (C) Schematic of trial timing. When the ferret broke the central light-barrier (II) for 500ms a trial was initialized and the event window started (III), indicated by a decrease in contrast of the static random noise pattern. At a random time between 0-1000ms during the event window the auditory and/or visual stimulus appeared for 100ms either left or right from the center. After stimulus offset the ferret had a response time window between +100-700ms (IV) to pan its head from the central position to the light-barrier on the side of the stimulation. Subsequently, the intertrial screen (I) appeared again. During the whole session the screen's global luminance remained unchanged.

Sensory stimulation

Auditory and visual stimuli were created using the Psychtoolbox (V3) [46] in a Matlab environment (The Mathworks Inc.; MA, USA). A white noise auditory stimulus (100ms) up to 50dB amplitude was used for auditory stimulation. It was generated digitally at 96kHz sample rate on a high-end PCI-audio card (HDSPe AES, RME-Audio, Germany) and delivered through two 'T1' Beyerdynamic speakers (Heilbronn, Germany). Visual stimuli consisted of concentric moving circular gratings (22.5°, 0.2cycles/°, 5Hz) up to 0.38 Michelson contrast (Cm) shown for 100ms (6 frames @ 60 Hz monitor-refresh rate). The background was set to

half-maximum luminance to avoid global luminance changes at stimulus onset. In the center of the screen, a static random noise pattern was displayed (7°, Cm between 1-0). During 'bimodal' trials, both visual and auditory stimuli were presented synchronously as described below.

Detection task

The ferrets were trained to solve a spatial detection task, as shown in Figure 1B and C. To initialize a trial the ferret had to maintain a central head position by breaking the central light-barrier for 500ms. This caused the random noise pattern in the center of the screen to decrease contrast and indicate the animal that the stimulus-window (up to 1000ms) had started. During this interval the animal had to further maintain a central head position. A stimulus was presented for 100ms on the left or on the right side, respectively, starting at a random time in this window. The stimulus could be a unimodal visual (circular grating), unimodal audio (white noise burst) or temporally congruent bimodal stimulus (further details see below). After stimulus offset, the animal had to respond within 600ms by panning its head to the respective side. If the response was correct the animal received a water reward (~80µl) on that position and could immediately start the next trial. If the response was too early (before stimulus onset or within 100ms after stimulus onset), incorrect (wrong side) or omitted (no response), the trial was immediately terminated, followed by a 2000ms interval during which no new trial start was allowed.

General procedure

Following the habituation to the harness, tube and setup all ferrets learned to detect unimodal stimuli. Two of the animals were trained in the auditory task first and then the visual; the other two were trained in reverse order. After completion of the training and reaching of sufficient performance, we presented stimuli of both modalities during the same sessions and determined the individual detection threshold. Twenty different stimulus amplitudes (0-50dB; 0-0.38Cm) were chosen in a 1down/3up staircase procedure [47], i.e., if the animal solved the trial correctly (hits) the stimulus amplitude decreased by one step for the next trial, down to the minimum, whereas false responses (misses, or omitted responses) led to a 3 step increase. No change occurred for responses that were issued too early (rash trials). In each trial either the auditory or the visual stimulus was presented in a pseudo-randomized fashion with individual staircases. To avoid a side- or modality-bias, each modality-side-combination was titrated to an equal number of hits within each session. Due to the huge combinatorics of conditions, each ferret had to complete 10-15 sessions to accumulate a sufficient number of trials per amplitude level. The data was pooled and treated as one sample, i.e., session information was discounted during further analysis. We

interpolated the data by fitting a Weibull Cumulative Distribution Function (CDF) to determine the 75% threshold for each ferret individually.

In a subsequent set of measurements, we combined simultaneous stimulus presentation in both modalities. To this end, we fixed the stimulus in one modality at the amplitude where the tested animal had an accuracy of 75% during the unimodal testing and varied the amplitude in the other modality according to the staircase procedure described above. In these bimodal sessions we again included the unimodal conditions, such that we obtained four different stimulation classes: unimodal auditory (A), unimodal visual (V), auditory supported by visual (Av), visual supported by auditory (Va). These four stimulation conditions were presented in a pseudo-randomized fashion and separate staircases during the sessions. All ferrets completed 10-12 sessions and the threshold was determined for each ferret by fitting a Weibull CDF to the data.

Data Analysis

All offline data analysis was performed using custom written scripts in Matlab (The Mathworks Inc., MA, USA).

Psychometrics

We evaluated the accuracy values (P) for all N stimulus amplitude classes (a) with at least 6 hit-trials in total on both sides using equation (1).

$$P_a = \frac{N_{a,h}}{(N_{a,o} - N_{a,r})} \tag{1}$$

Here, *a* denotes the intensity of the stimulus, $N_{a,h}$ (*hit trials*) was defined as the number of correct response trials for stimulus amplitude a, $N_{a,o}$ (*onset trials*) was the number of trials for stimulus amplitude a where the animal reached stimulus onset time, and $N_{a,r}$ (*rash trials*) as the number of trials for stimulus amplitude a were the animal gave a response before the response-window had started (up to 100ms after stimulus onset), assuming the animal was guessing and not responding based on sufficiently collected sensory evidence. We estimated the detection threshold by fitting a Weibull CDF function to P_a,

$$F_a = 1 - \exp^{-(\lambda a)^k} \tag{2}$$

here *k* signifies the form-parameter and λ represents the scale-parameter. The number of trials were used as weights during the fitting procedure. Due to the fact that every animal had different thresholds in the respective modalities, we calculated the standard deviation of each fit by using a delete-d jackknife method, were d = 20% corresponds to the number of sessions excluded per run, i.e. 2 or 3, respectively.

Modeling cross-modal interaction

In order to quantify the cross-modal interaction, we used the MLE approach. Therefore we utilized the audio and visual accuracy from the multimodal experiment for all existing stimulus intensities. Assuming a model of a hidden Gaussian representation of the sensory input in the brain we estimated the variance (σ) for all points based on the F_a values form the Weibull CDF:

$$\sigma = \frac{\sigma_0}{inv.erf.(F_a)} \tag{3}$$

here '*inv.erf.*' equates to the inverse error function and σ_0 an unknown scale factor. As in the following calculation of σ_{bi} it drops out we can set it arbitrarily to a value of 1. The next step was to combining both unimodal variances to get the bimodal (σ_{bi}) according to

$$\sigma_{bi} = \frac{\sigma_{\mathrm{mod}} \cdot \sigma_{fix}}{\sqrt{\sigma^2_{\mathrm{mod}} + \sigma^2_{fix}}} \tag{4}$$

represents the variance for the modality which intensity were modulated and σ_{fix} for the modality that was fixed at 75% threshold. Subsequently, we used the inverse value of the bimodal variance in an error function (*erf.*) to determine the bimodal accuracy (5).

$$accuracy_{bi} = erf.(\frac{1}{\sigma_{bi}}) \tag{5}$$

Reaction time

The RT was defined as the time difference between stimulus-onset and the time point when the animal panned its head out of the central light-barrier. Only intensity classes with at least 6 successful responses (hits) were included in the RT analyses. To quantify the RT between the corresponding intensities from uni- and bimodal stimulation we computed the Multisensory Response Enhancement (MRE) [35] as follows:

$$MRE = \frac{\min(\overline{RT_A}, \overline{RT_V}) - \overline{RT_{AV}}}{\min(\overline{RT_A}, \overline{RT_V})} \tag{6}$$

with $\overline{RT_A}$ and $\overline{RT_V}$ referring to the observed mean RT of the audio and visual stimuli, respectively. $\overline{RT_{AV}}$ is the mean RT of the corresponding bimodal stimulus. We calculated a race model [43] to evaluate potential RSE. In our study, accuracy varied across subjects and sensory conditions. In order to compare reaction times across subjects and compute the race

model for all related modality combinations we introduced ‘subjective intensity classes’ (SIC) as determined by the accuracy fit in different unimodal conditions (0-74%, 75-89% and 90-100% indicating low, medium and high performance accuracy, respectively). This ensured a sufficient number of trials per SIC and additionally normalized for subjective stimulus intensities. Intensity and modality effects on the RT were tested applying the same grouping mechanism and computing a two-way ANOVA.

Results

Four ferrets were trained in a lateralized audio/visual spatial detection task until they accomplished to solve the detection task in both modalities at high supra-threshold amplitudes (audio = 50dB, visual = 0.38Cm). The training was discontinued, once they showed a stable baseline performance (>90%) across 5 consecutive days with high accuracy levels (audio = 92±1%, visual = 92±1%; mean±SEM). All animals achieved high performance levels demonstrating the suitability of the training paradigm.

In the two experiments for the determination of audio(-visual) thresholds we pooled results from both stimulation sides to calculate the accuracy values for all amplitudes. Testing for a stimulus-side bias by comparing hit performance on both sides with a paired *t*-test revealed no significant bias (unimodal experiment: all animals = p >0.05; bimodal experiment: all animals = p >0.05).

Determination of unimodal thresholds

In the first experiment we determined the 75% accuracy threshold for both unimodal modalities for each individual ferret (Fig. 2), with an individual range for each animal. Ferrets performed on average 12 (±2) sessions (104±26 trials±SEM/session) in the unimodal condition. Before pooling the sessions, we tested each ferret for non-stationarity effects across sessions by comparing the variance of the first three sessions at 84% accuracy threshold against the one of the last three sessions. We used three sessions, because three sessions were needed to ensured a sufficient number of trials for a proper Weibull function fit. No animal showed a non-stationarity in any modality (p >0.05 Two-sample t-test, 2-sided). The pooled data could well be described by a Weibull function (r^2 = 0.56 - 0.92, Fig. 2).

Figure 2. Detection task performance of the unimodal experiment.

(A) Data for performance in the unimodal auditory detection task. (B) Data for the unimodal visual detection task. Each row represents one animal (1-4). Each dot represents the average performance of N trials (diameter) for the tested auditory amplitudes (dB) or visual contrasts (Cm). The data is fitted by a Weibull function. The values within the plot are the amplitude values corresponding to the 75% and 84% thresholds. The blue shaded area around the fit indicates the standard deviation. Note different scaling of the X-axes.

Determination of uni- and bimodal thresholds

In the second experiment, the two crossmodal stimulation conditions were added to the sessions. One modality's intensity was fixed at 75% threshold, as determined from the unimodal experiment (Fig. 2) while the other modality varied intensity according to the

staircase procedure. All ferrets participated in 12 (±1) multimodal sessions (111±37 trials±SEM/session). Like for the unimodal sessions, we again tested for non-stationarity effects across the first and the last sessions by comparing the 84% accuracy threshold variance as determined by the Weibull fit. Since the introduction of bimodal classes reduced the relative number of unimodal stimulus presentations during each session, we had to pool minimum across the first and last 5 sessions, respectively, to generate a proper Weibull fit. No animal showed non-stationarity across the bimodal sessions (2-sided two-sample *t*-test; $p > 0.05$). Subsequently, we calculated the accuracy for each amplitude where at least 6 trials were done and the psychometric curves were fit using a Weibull CDF (Fig. 3). The pooled data could well be described by a Weibull function ($r^2 = 0.39 - 0.90$, Fig. 3).

Figure 3. Detection task performance of the bimodal experiment.
(A) Data for the stimulus conditions auditory-only (A) and auditory supported by visual stimulus (Av). (B) Data for the for the stimulus conditions visual-only (V) and visual supported by auditory stimulus (Va). Each row represents one ferret (1-4). Each dot represents the average performance of N trials (diameter) at a given audio amplitude (dB) or visual contrast (Cm). The data is fitted by a Weibull function. The uni- and bimodal fit is represented by the blue and red line, respectively. The shaded area around the fit indicates the standard deviation. Δ_{84} displays the relative amount of threshold shift of the bimodal compared to the unimodal psychometric function at a performance of 84%, a positive shift indicates a threshold decrease. The black curve represents the Maximum Likelihood Estimation model. Note the individual values on the X-axis.

The comparison of the unimodal 75% thresholds between both experiments revealed a slight increase from the uni- to the multimodal experiment, except in animal 2 which showed a decrease (left side, Table 1). However, the differences are smaller than one of the amplitude steps in the staircase procedure. Furthermore, two of the animals (1 and 4) did not reach a performance above 90±5% in the highest intensities in one modality (audio and visual, respectively). These findings indicate that the bimodal experiments were slightly more demanding, presumably because four stimulation classes were presented compared to the unimodal experiment with only two stimulation classes.

	Amplitude values @ 75%		Amplitude values @ 84%		
	unimodal Exp.	bimodal Exp.	unimodal Exp.	bimodal Exp.	
	A	A	A	A	Av

1	39	40	42	45	41
2	27	30	29	32	26
3	25	28	27	33	31
4	31	31	33	34	25
	V	V	V	V	Va
1	0.08	0.08	0.10	0.10	0.09
2	0.09	0.08	0.11	0.09	0.09
3	0.07	0.10	0.09	0.18	0.12
4	0.15	0.19	0.19	0.25	0.10

Table 1. Comparison of threshold values for uni- and bimodal experiments.
The amplitude values at the 75% and 84% thresholds in the unimodal and bimodal experiments (columns) for all animals (rows).

Because we used different assumptions for the point of intersection at X_0 during uni- (50%) and crossmodal (75%) fitting, we employed the 84% threshold for comparisons between uni- and crossmodal settings. All fits to the bimodal psychometric functions showed a left shift compared to their unimodal complements, except animal 2 in the V-Va comparison (amplitude decrease±SEM: A-Av = 5.3±1.5; V-Va = 0.06±0.03; for absolute values see Table 1). This demonstrates a decrease in detection thresholds in all ferrets, except animal 2 in the Va comparison where the auditory support had no effect. For quantification we calculated the relative shifts at the 84% performance-level between the uni- and bimodal psychometric fit (Δ_{84} in Fig. 3). A positive number indicates a lower threshold as determined by the bimodal fit, i.e., an increase in bimodal detection performance. On average, there was a shift (±SEM) of 15±5%, indicating an effective bimodal integration.

Maximum likelihood estimates

To investigate if ferrets integrate modalities in a statistically optimal fashion, we computed a MLE model and compared the r^2-difference between the empirical fit (Fig. 3, red) and model (Fig. 3, black) fit to the measured bimodal accuracies. The range of $\Delta_{bimodal-MLE}$ was -1 to 49% (mean-difference±SEM 14±6). In four cases the MLE line matched the bimodal curve and the difference of the explained variance between the empirical fit (Fig. 3) and the MLE was 10% or less (A1: Δ_{Va-MLE} = 8%; A2: Δ_{Va-MLE} = 2%; A3: Δ_{Av-MLE} = 1% and Δ_{Va-MLE} = -1%). For one condition (animal 1: Δ_{Av-MLE} = 11%) the MLE underestimated the empirical fit at the highest stimulus amplitudes (Fig. 3A). This may be caused by the low unimodal performance at high stimulus amplitudes, since the MLE model depends on the unimodal performance. This argument also holds true for the Va case (Δ_{Va-MLE} = 15%) of animal 4 (Fig. 3B, bottom

panel). If the animal had shown a unimodal performance comparable to that previously measured in the unimodal experiment, the MLE model would be similar to the empirical bimodal fit. In the other two cases the MLE underestimated the empirical fit in the intermediate amplitude ranges (animal 2: Δ_{Av-MLE} = 25% and animal 4: = 49%, Fig.3). Overall, the MLE modeling results support the conclusions drawn from the uni- and bimodal 84% threshold comparison. The results indicate that ferrets integrated the two modalities as good or even better than predicted by the MLE estimator (Fig. 3).

Reaction time analysis

One of the most important benefits of multisensory integration is the reduction of RTs for bimodal stimuli compared to unimodal stimulation. The measured RT varied during the multisensory experiment with target amplitude in all modality types. In all stimulus conditions and all animals, RT showed a significant negative correlation with stimulus amplitude (range A: r = -0.17 to -0.41; V: r = -0.25 to -0.45; Av: r = -0.17 to -0.41; Va: r = -0.34 to -0.46; all correlations: $p < 0.01$; e.g. animal 4 in Fig. 4). RT significantly increased with decreasing intensity (ANOVA $p < 0.05$) in all but one condition (animal 1: audio-alone, ANOVA $p > 0.05$). This is an expected finding, because the signal-to-noise ratio (SNR) decreases with decreasing stimulus amplitude and the internal signal processing is faster for high SNR.

Figure 4. Example of reaction time data from the bimodal experiment.
Representative example data taken from animal 4. (A) Data for the stimulus conditions auditory-only (A) and auditory supported by visual stimulus (Av). (B) Data for the stimulus conditions visual-only (V) and visual supported by auditory stimulus (Va). The top panels show the Multisensory Response Enhancement (MRE) for each pair of uni- and bimodal RTs. Bottom panels RT ± SEM as a function of stimulus amplitude (red = bimodal, blue = unimodal). Each data point represents the RT average for the corresponding stimulus intensity, estimated by all hit reaction times measured at that amplitude (*t*-test: * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$). Pearson correlation coefficient and regression line for both data sets are shown. The two vertical lines mark the borders between the subject intensity classes (left of first line: 0-74%, between the lines 75-89%; right of the second line 90-100% performance).

To reduce the dimensionality and compare reaction times across subjects we used ‘subjective intensity classes’ (SIC) (see Material and Methods). To quantify the percentage of RT gain for potential multimodal enhancement effects, we calculated a MRE between existing uni- and bimodal pairs and summed these according to the SICs. The average MRE

of both modalities is positive (A = 3.93%; V = 0.06%). The visual MRE average is only very slightly positive because of the high negative values of animal 2 and 3 in the lower SIC. However, the comparison of uni- and bimodal RT pairs revealed that about one-third of the cases (7 out of 24, Table 2) showed a negative MRE. Data from animal 2 are shown as an example in Fig. 4. A negative MRE occurs if the average unimodal RT is faster than the average RT of the bimodal condition. Therefore it seems that the variable modality has a competitive effect on the RT at medium and low intensities, because the negative MRE occur in these SICs. Overall, the MRE results suggest a multimodal enhancement effect in the high and medium and a competitive effect in the lower SIC.

	0-74%	75-89%	90-100%	0-74%	75-89%	90-100%
	A vs. Av			V vs. Va		
1	-6,00	4,33	8,00	1,00	-0,67	2,22
2	5,50	6,33	4,83	-20,50	-19,00	4,40
3	-9,40	-3,00	6,88	-18,75	3,00	8,50
4	15,00	5,50	9,20	10,00	12,50	18,00

Table 2. Reaction time: average MRE.

Multisensory Response Enhancement (MRE) computed for the reaction times from all animals (rows) and stimulus conditions (A: audio, V: visual, Av: audio supported by visual, Va: visual supported by audio) of the bimodal experiment. The MRE's were sorted by the subjective intensity classes (SIC; columns from left to right).

To investigate a potential RSE we calculated a race model on the pooled RTs according to the SIC. The race model assumes that during multimodal stimulation no modality integration happens, instead both signals of either modality are processed independently. Whichever of the two leads to a result first, triggers and determines the response, i.e. the head movement to the corresponding side. Therefore the bimodal CDF of the RT can be modelled by sampling from the unimodal RT CDFs. Afterwards the modelled bimodal RT CDF can be compared with the empirical bimodal RT CDF (see Fig. 5). If the empirical RT CDF is faster in 20-50% of the percentiles compare to the modelled RT CDF the race model can be rejected and modality integration is suggested [48]. For a detailed explanation of the race model see Ulrich et al. [43].

Figure 5. Race model example.

Visual high SIC CDFs for each modality (A75%: audio@75% (green), V: visual (blue), Av: audio supported by visual (red)) and combination of both unimodal CDFs (V+A75% (black)) from animal 4. In this case the race model gets rejected, because the empirical bimodal CDF (red) is 'faster' than the modelled CDF (black).

We computed the relative (%) deviation from the linear unimodal combination for all stimulus conditions (Fig. 6) for each SIC. If this difference for the empirical bimodal CDF is in 20-50% of the cases negative the race model can be rejected (Miller and Ulrich, 2003). The biggest effect of the supportive value occurred in the highest intensity group, because there the change was negative compare to the combined unisensory CDF in the lower percentiles (upper row, Fig. 6). In the 75-89% SIC no percentile of the crossmodal combinations was negative (middle row Fig. 6) and in the lowest intensity-group the bimodal and the supportive value RTs were similar (bottom row Fig. 6), i.e., the benefit of the redundant signal seems to diminish with decreasing intensity group. However, in the medium and high performance classes the bimodal RT seemed to be closer to the combined CDF than each of the unimodal distributions. Nevertheless, we cannot reject the race model on a descriptive level in any of the six cases. Overall, this indicates that multisensory integration processes are not reflected in RT gains beyond what can be predicted from the fastest unimodal responses.

Figure 6. Reaction time: race model results.

The RTs were sorted by the 'subjective intensity classes' (rows) and both modalities (A: audio, B: visual) pooled across all animals. The X-axis displays the cumulative reaction time differences to the race model for each modality (± SEM). A value of 0 at the X-axis corresponds to the prediction from the combination of both unimodal CDF's. The blue curve displays the unimodal condition, the green curve the RTs at the supportive value and the red curve the bimodal class, respectively.

To investigate intensity, modality and interaction effects on a more global scale we pooled the RT of all animals according to subjective intensity classes and calculated a two-way ANOVA, with modality and intensity as main factors (Fig. 7). This revealed main effects in both factors (Modality: $F(3, 4632) = 18.84$ ($p < 0.001$); Intensity: $F(2, 4633) = 310.65$ ($p < 0.001$)) and an interaction effect (Modality*Intensity: $F(6, 4624) = 3.93$ ($p < 0.01$)). A post hoc *t*-test (Holm-Bonferroni corrected) revealed significant differences between and within performance classes (Fig. 7), respectively. The post hoc *t*-tests between the intensity groups and modalities were all highly significant ($p < 0.001$). This result suggests that the ferrets'

RTs increase as the intensity of the stimulus gets weaker and significantly decrease in the multimodal compared to the unimodal classes.

Figure 7. Reaction time: two-way ANOVA results.

The reaction times (RT) pooled by subjective intensity classes (0-74%, 75-89%, 90-100%). The X-axis displays the three performance classes and the Y-axis shows the RT in milliseconds ± SEM. The solid lines represent the unimodal, the dashed lines the bimodal, red indicates the audio and blue the visual modalities (*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; Holm-Bonferroni corrected). +++, significant differences between performance classes within each modality (Holm-Bonferroni corrected); red and blue asterisks, significant differences between uni- and bimodal conditions in one performance class (Holm-Bonferroni corrected); green asterisk, significant difference between the two unimodal conditions.

Discussion

How information from different modalities is integrated has been a subject of intense research for many years. Here we asked if ferrets merge senses according to the same principles established for other species [23,25,27–31,33,49,50]. We expected the ferrets to perform more accurately and with lower RTs in the bimodal cases, because congruent inputs from two modalities provide more reliable sensory evidence [49,51–53]. As predicted, bimodal detection thresholds were reduced and RTs were faster in the bimodal compared to unimodal conditions, demonstrating multimodal integration effects. Furthermore our results on MLE modeling suggest that ferrets integrate modalities in a statistically optimal fashion.

Methodological considerations

Previous studies in behaving ferrets have used either freely-moving [1,4,7,41] or head-restrained [42] animals. Here, we developed a head-free, body-restrained approach allowing a standardized stimulation position and the utilization of the ferret's natural response behaviour. The setup is especially suited for psychometric investigations because the distance between animal and the stimulus sources remains constant across trials. The high inter-trial-consistency and the fixed animal position allow the combination of behavioural protocols with neurophysiological recordings comparable to head-restrained approaches [42]. An additional advantage is the usage of a screen instead of a single light-source for the visual stimulation [4,23], this enables a wide rage of visual stimuli. Similar to other ferret studies [1,41], one disadvantage of this model is low number of trials collected per session. We therefore had to pool data from different sessions to obtain a sufficient number of trials for the fitting procedure. Merging of sessions was justified by the absence of non-stationarity effects and the low variance of the fits. This also indicates for a low day-to-day-variability of perceptual thresholds. Our results complement that of an earlier study in ferrets demonstrating that measured thresholds were not affected by trial-to-trial fluctuations in the animals' decision criterion [4]. Overall, these findings suggest that the experimental design presented in this study is well suited for psychophysical investigations.

Establishing links across species, our behavioural paradigm was inspired by previous human psychophysical studies which showed that temporally congruent crossmodal stimuli enhance detection [49,51–53]. Frassinetti et al. [49] adopted an animal approach [37] to humans and received similar results in terms of multisensory enhancement effects. Another study form Lippert and colleagues [51] showed that informative congruent sounds improve detection rates, but this gain disappears when subjects are not aware of the fact that the additional sound offers information about the visual stimulus. They concluded that cross-modal influences in simple detection tasks are not exclusively reflecting hard-wired sensory

integration mechanisms but, rather, point to a prominent role for attention-like effects. This contrasts with more classical views suggesting that information form different sensory modalities may be integrated preattentively and substantially rely on automatic bottom-up processing [27]. Our observation of the inter-experiment threshold increase might suggest a divided attention effect [54], because the animals had to divide their attention between two modalities in half of the trials in the second experiment compared to the first one, were only one modality was presented. A possibility is that in our study the ferrets preferred solving the bimodal over the unimodal trials because detection in the bimodal conditions was easier for them. This could also explain why the performance in the unimodal tests in the multimodal experiment did not reach 95-100% accuracy in the highest intensities, unlike in the unimodal experiment.

Taken together, our study demonstrates that the implemented behavioural paradigm is suitable to determine uni- and bimodal thresholds and to operationalize multisensory integration processes. Possible contextual and attention-like effects seem hard to elucidate by pure psychometrics, but simultaneous electrophysiological recordings could provide valuable insights into the underlying brain processes during the task.

Optimal modality integration

This is the first study on behaving ferrets to quantify multimodal enhancement effects and to test for optimal modality integration. Our results of the multimodal experiment show clear multisensory enhancement effects. The left-shift and the variance reduction, derived at 84% accuracy, is caused by increased detection rates and reliability for lower test-intensities in the bimodal stimulation classes, indicating that the ferrets indeed integrate information across modalities as shown for other species [23,27,29,33,40,50–52]. MLE modeling is typically used in multisensory integration to test the hypothesis that the integrative process is statistically optimal by fitting the parameters of the model to unisensory response distributions and then compare the multimodal prediction of the model to the empirical data. Studies on humans have shown that different modalities get integrated in a statistical optimal fashion. For example, Battaglia et al. [29] found that human subjects integrate audio and visual modalities as an optimal observer. The same is true for visual and haptic integration [28], and integration of stereo and texture information [31,55]. Furthermore, Alais and Burr [30] could show that the ventriloquist effect is based on a near-optimal sensory integration. Rowland and colleagues showed statistical optimal integration in the cat for audio-visual perception [50] and Gu et al. [33] could demonstrate the same principle in macaques for visual and vestibular sensory integration. Similar to the abovementioned studies, our results on MLE modeling suggest that ferrets integrate modalities in a statistically optimal fashion. Surprisingly, in two of our cases the MLE underestimates the empirical fit, which is

counterintuitive because the MLE provides already the maximum estimate. A potential explanation might be that multisensory benefit is larger for some modalities compared to others, as suggested by the modality precision hypothesis by Welch and Warren [56]. These hypotheses states that discrepancies are always resolved in favour of the more precise modality, i.e. the modality with the highest SNR gets weighted higher in the final sensory estimate. Battaglia and coworkers [29] showed that humans have a bias towards the visual modality in a multisensory spatial detection task. Finally, it could be caused by a low unimodal performance in the intermediate intensities since the MLE model depends on the unimodal performance. In summary, the MLE model provides evidence that ferrets merge modalities in a near-optimal fashion, similar to other species [28–30,33,55].

Multisensory response enhancement

In a second analysis approach we compared modality specific and SIC pooled RTs of the corresponding stimulation classes and computed a race model to test a RSE. Our main results are in line with findings from other species. Previous work in humans revealed that subjects respond faster to bimodal compared to unimodal stimuli [35,51]. Miller [39] showed that this RT gain is a result of a modality integration effect and not only a product of the fastest processed modality. Gleiss and Kayser [23] demonstrated that additional non-informative white noise decreases RT in a visual detection task in rats. The effect size of the RT gain increased when the light intensity decreased. In our study the influence of amplitude on RT is directly related to the SNR, i.e. the internal signal processing is faster for high SNR. For high intensities of the varying modality (>75% unimodal performance), the SNR should be higher compared to the fixed supporting modality. Decreasing the intensity of the variable modality leads to a continuous decrease of its SNR (until 0), such that for low intensities the RT is completely determined by the supporting-value. Interestingly, some MRE's have negative values in the lower and intermediate SICs. This is due to the fact that the MRE model uses the fastest unimodal RT for calculation and the RT of the supporting values is faster than the average bimodal RT. The variable modality seems to have a competitive effect on the RT at low intensities, because the average bimodal RT is slower than the RT of the supportive value. Alternatively, the race model compares RT in a more sophisticated way, by comparing a modelled bimodal RT CDF with the empirical bimodal RT CDF. The benefit of the redundant signal increases from low to high SIC. Ferrets reached the criterion to reject the race model only in the high SIC. In the intermediate and low SIC the linear unimodal combination is faster compared to the empirical bimodal group. Nevertheless, in the intermediate SIC the bimodal percentiles are closer to the linear combination than the unimodal groups, indicating a minor gain of the supportive value and therefore a multisensory enhancement effect. In contrast, in the low SIC the bimodal group matches the

supporting value group, implying that the supportive value is the driving modality in the sensory process [44,48].

Conclusions

In conclusion, our data demonstrate that basic principles of multisensory integration, such as congruence related enhancement effects on detection rates, precision and RT apply to crossmodal processing in the ferret brain. The race model and MLE modeling provides evidence that ferrets integrate modalities in a statistically optimal fashion. To quantify this in more detail an advanced behavioural paradigm is required, where the stimulus onset of both stimulus types jitters and a broader range of supportive values is covered. The setup we have developed to test ferrets in multimodal tasks is similar to human and non-human primate tasks, and can be combined for future research with methods for study of the underlying neural substrate. The approach would allow investigations on top-down influences on sensory processing as well as large-scale communication across distinct sensory regions during different behavioural paradigms. Altogether, our results describe a highly multifunctional experimental approach which may further enhance the viability and suitability of the ferret model.

Acknowledgements

We would like to thank Dorrit Bystron for assistance during data acquisition and Guido Nolte for advice in data modeling. This research was supported by a Grand from the DFG (SFB 936/A2; A.K.E.; http://www.dfg.de). The funders had no role in study design, data collection and analysis, decision to publish, or preparation oft the manuscript.

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Supporting Information

S1 ARRIVE Guidelines. Completed “The ARRIVE Guidelines Checklist” for reporting animal data in this manuscript

S2 Dataset. Raw data of the unimodal detection task for all animals.

S3 Dataset. Raw data of the multimodal detection task for all animals.

Figure 1

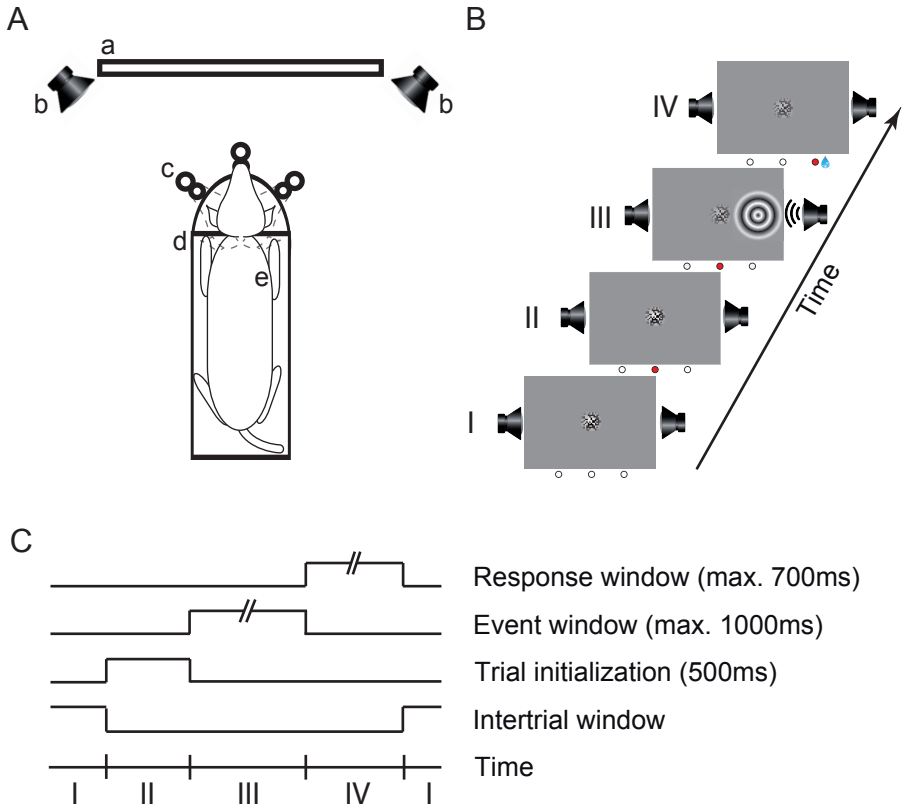

A
a
b
b
c
d
e
B
IV
III
II
I
Time
C
Response window (max. 700ms)
Event window (max. 1000ms)
Trial initialization (500ms)
Intertrial window
Time
I
II
III
IV
I

Figure 2

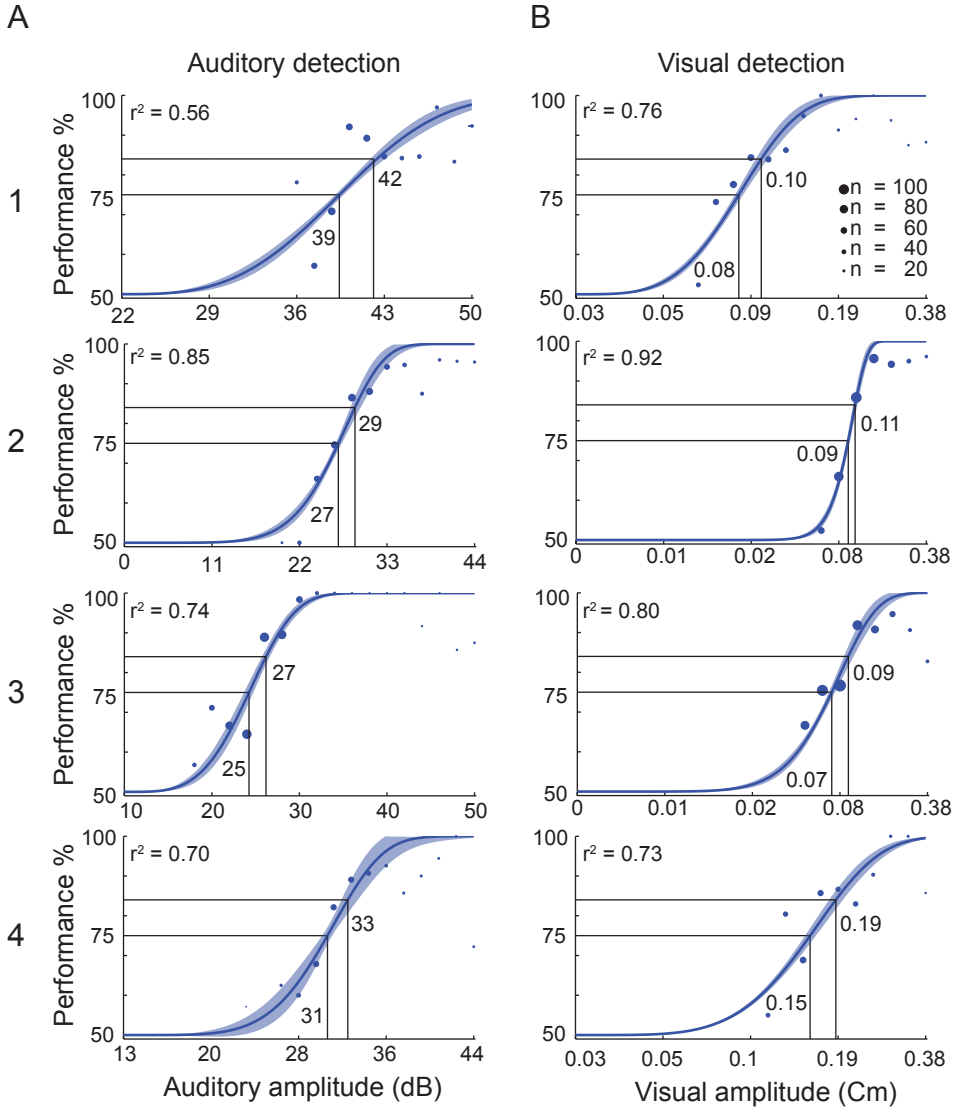

A
B
Auditory detection
Visual detection
1
2
3
4
Performance %
r² = 0.56
r² = 0.85
r² = 0.74
r² = 0.70
r² = 0.76
r² = 0.92
r² = 0.80
r² = 0.73
n = 100
n = 80
n = 60
n = 40
n = 20
Auditory amplitude (dB)
Visual amplitude (Cm)

Figure 3

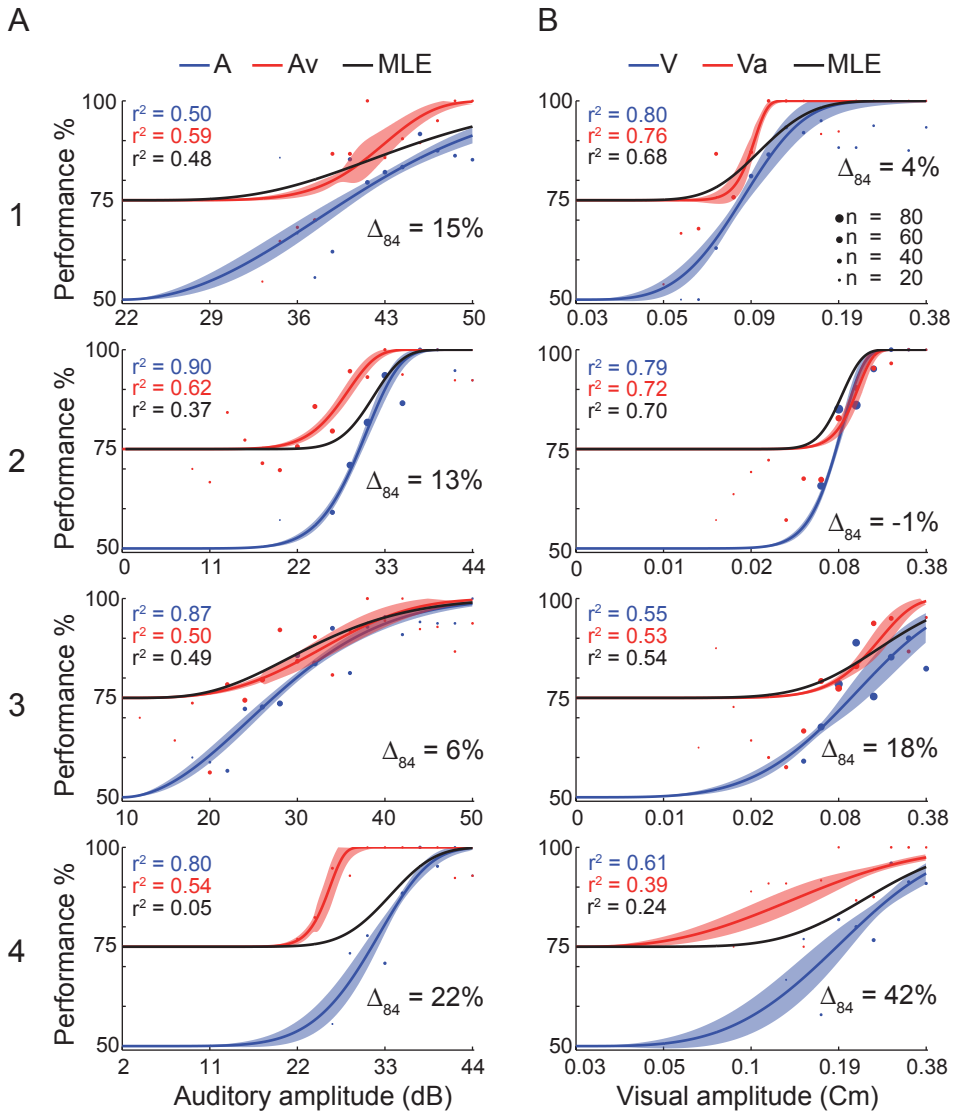

A
B
A
Av
MLE
V
Va
MLE
1
2
3
4
Performance %
r² = 0.50
r² = 0.59
r² = 0.48
Δ84 = 15%
r² = 0.80
r² = 0.76
r² = 0.68
Δ84 = 4%
n = 80
n = 60
n = 40
n = 20
r² = 0.90
r² = 0.62
r² = 0.37
Δ84 = 13%
r² = 0.79
r² = 0.72
r² = 0.70
Δ84 = -1%
r² = 0.87
r² = 0.50
r² = 0.49
Δ84 = 6%
r² = 0.55
r² = 0.53
r² = 0.54
Δ84 = 18%
r² = 0.80
r² = 0.54
r² = 0.05
Δ84 = 22%
r² = 0.61
r² = 0.39
r² = 0.24
Δ84 = 42%
Auditory amplitude (dB)
Visual amplitude (Cm)

Figure 4

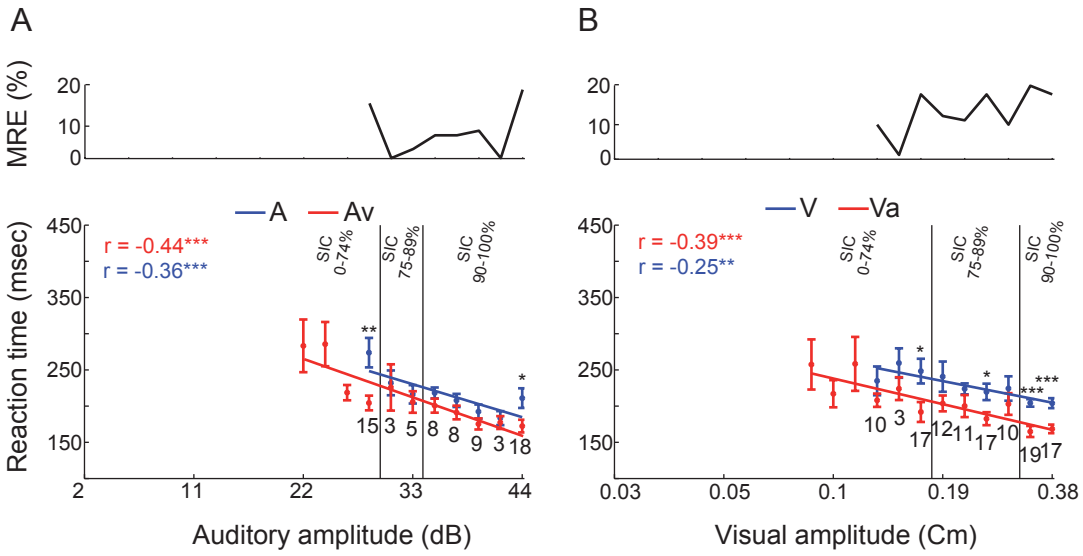

A
B
MRE (%)
20
10
0
Reaction time (msec)
450
350
250
150
A
Av
r = -0.44***
r = -0.36***
SIC 0-74%
SIC 75-89%
SIC 90-100%
**
*
15 3 5 8 8 9 3 18
2
11
22
33
44
Auditory amplitude (dB)
V
Va
r = -0.39***
r = -0.25**
*
*
***
***
10 3 17 12 11 17 10 19 17
0.03
0.05
0.1
0.19
0.38
Visual amplitude (Cm)

Figure 5

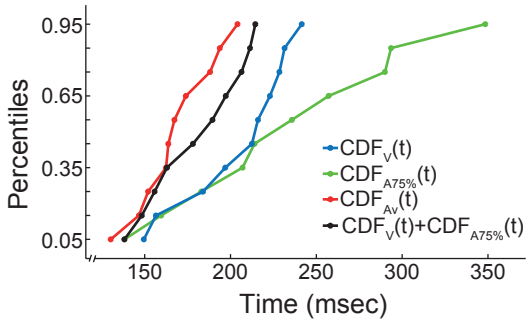

0.95
0.65
0.35
0.05
Percentiles
150
200
250
300
350
Time (msec)
CDF$_V$(t)
CDF$_{A75\%}$(t)
CDF$_{Av}$(t)
CDF$_V$(t)+CDF$_{A75\%}$(t)

Figure 6

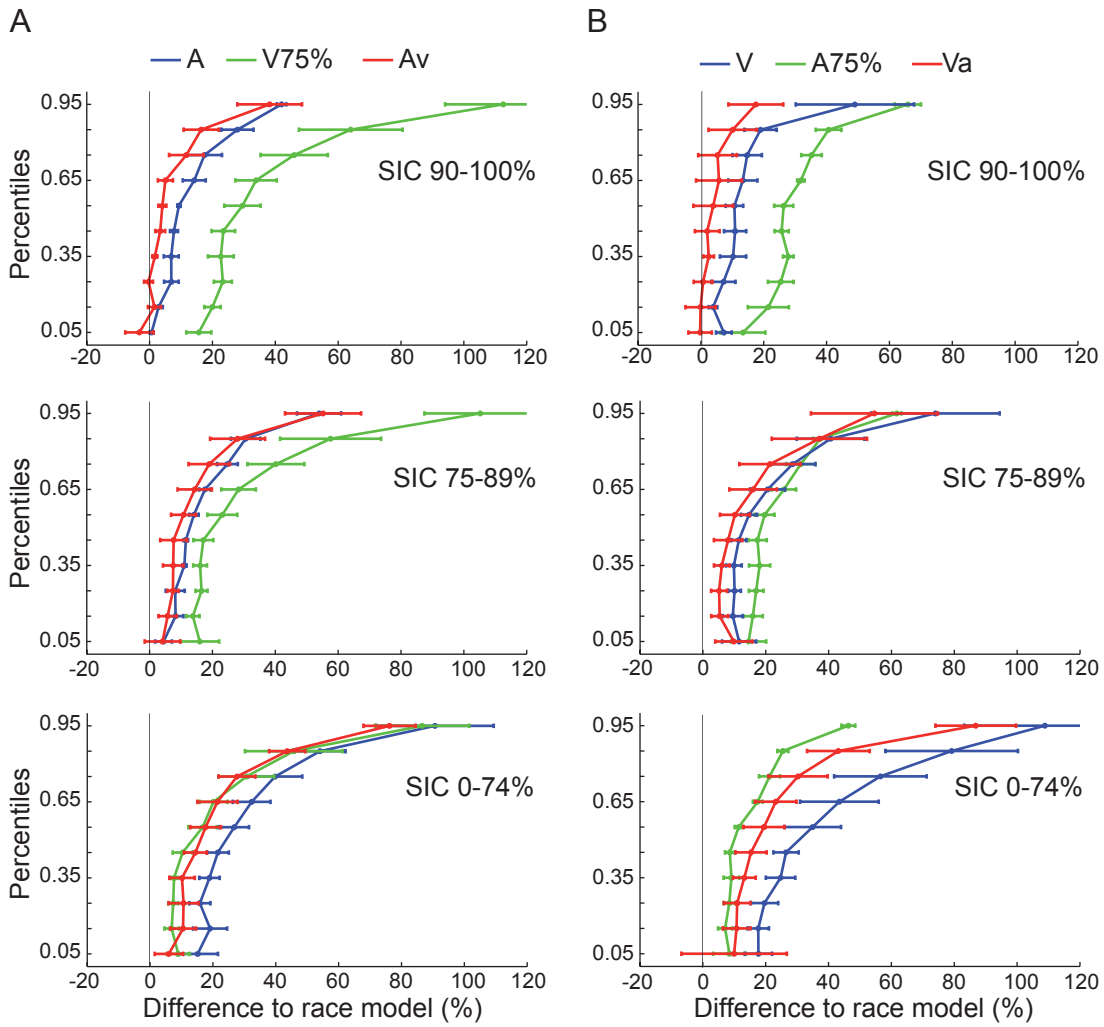
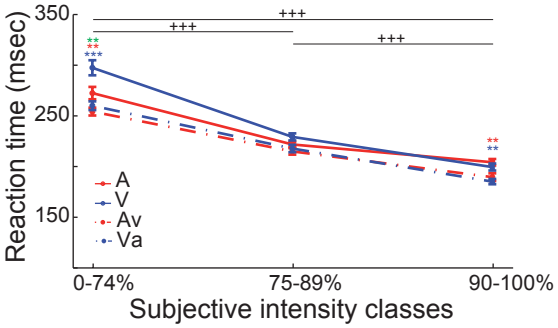

A
A
V75%
Av
B
V
A75%
Va
Percentiles
0.95
0.65
0.35
0.05
SIC 90-100%
SIC 75-89%
SIC 0-74%
-20
0
20
40
60
80
100
120
Difference to race model (%)

Figure 7


350
250
150
Reaction time (msec)
+++
+++
+++
A
V
Av
Va
0-74%
75-89%
90-100%
Subjective intensity classes