

Audio-visual multisensory training enhances visual processing of motion stimuli in healthy participants: an electrophysiological study

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Abstract

Evidence from electrophysiological and imaging studies suggests that audio-visual (AV) stimuli presented in spatial coincidence enhance activity in the subcortical colliculo-dorsal extrastriate pathway. To test whether repetitive AV stimulation might specifically activate this neural circuit underlying multisensory integrative processes, electroencephalographic data were recorded before and after 2 h of AV training, during the execution of two lateralized visual tasks: a motion discrimination task, relying on activity in the colliculo-dorsal MT pathway, and an orientation discrimination task, relying on activity in the striate and early ventral extrastriate cortices. During training, participants were asked to detect and perform a saccade towards AV stimuli that were disproportionately allocated to one hemifield (the trained hemifield). Half of the participants underwent a training in which AV stimuli were presented in spatial coincidence, while the remaining half underwent a training in which AV stimuli were presented in spatial disparity (32°). Participants who received AV training with stimuli in spatial coincidence had a post-training enhancement of the anterior N1 component in the motion discrimination task, but only in response to stimuli presented in the trained hemifield. However, no effect was found in the orientation discrimination task. In contrast, participants who received AV training with stimuli in spatial disparity showed no effects on either task. The observed N1 enhancement might reflect enhanced discrimination for motion stimuli, probably due to increased activity in the colliculo-dorsal MT pathway induced by multisensory training.

Introduction

Multisensory integrative mechanisms can improve detection and localization of audio-visual (AV) stimuli concurrently presented in the same spatial position (for a review, see Alais *et al.*, 2010). In line with this behavioural evidence, electrophysiological studies (Stein & Meredith, 1993) have revealed enhanced neural responses in the multisensory neurons of the superior colliculus (SC) when auditory and visual stimuli are presented in spatial and temporal coincidence. In addition to the SC, dorsal posterior parietal cortices (Colby *et al.*, 1993; Dong *et al.*, 1994; Duhamel *et al.*, 1998; Schlack *et al.*, 2002) constitute a pivotal site of convergence for AV information (for a review, see Calvert, 2001).

Although the behavioural advantages of concurrent AV stimulation have been widely reported, it is unclear whether repetitive AV stimulation might induce a post-training enhancement of the neural circuit underlying the integration process, i.e. the colliculo-dorsal extrastriate pathway. To test whether exposure to AV stimulation might specifically enhance activity in the dorsal extrastriate pathway, participants

were tested before and after AV training with two tasks: a motion discrimination task, relying on activation of the dorsal MT pathway (Kolster *et al.*, 2010; Tootell *et al.*, 1995; Watson *et al.*, 1993; Zeki *et al.*, 1991), and an orientation discrimination task, relying on activation of the striate and early ventral extrastriate cortices (Boynton & Finney, 2003; Fang *et al.*, 2005; Kamitani & Tong, 2005; Murray *et al.*, 2006; Yacoub *et al.*, 2008; Swisher *et al.*, 2010).

Specifically, the motion discrimination task, in which participants discriminated the motion direction of random-dot kinematograms, was selected based on the idea that motion processing involves both the SC and dorsal extrastriate area MT (Kolster *et al.*, 2010), therefore suggesting a shared neural pathway with AV multisensory integration. In contrast, the orientation discrimination task, in which participants reported the tilt of Gabor patches, entails the activation of striate and early ventral extrastriate cortices (Fang *et al.*, 2005), and does not involve the neural structures mediating AV integration. During each task, electroencephalograms (EEGs) were recorded to measure electrophysiological correlates of motion and orientation discrimination.

In addition, to test the role of multisensory integrative processes in activating the colliculo-dorsal extrastriate pathway, one group of participants received training with concurrent AV stimuli presented

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in the same spatial position, i.e. following the multisensory integrative principles of spatial and temporal coincidence (Stein & Meredith, 1993), while a control group received training with AV stimuli presented at a spatial disparity of 32° , preventing optimal integration of the two sensory modalities. If AV integration relies on activity in the colliculo-dorsal extrastriate pathway, then systematic stimulation with spatially coincident AV stimuli should enhance activation of that pathway, resulting in a post-training increase in motion discrimination, which typically requires the activation of dorsal extrastriate cortices. Specifically, an increase in the amplitude of early visual-evoked potentials, reflecting the visual discrimination process (i.e. the N1 component), might be expected. In contrast, no effect would be expected after training with AV pairs presented in spatial disparity.

Materials and methods

Participants

Thirty-two healthy volunteers took part in the study (20 females; mean age: 23.5 years; range: 19–33 years). All subjects were right-handed, had normal or corrected-to-normal vision and had no history of neurological or psychiatric disorders. Participants were informed about the procedure and the purpose of the study, and gave written informed consent. The study was designed and performed in accordance with the ethical principles of the Declaration of Helsinki, and was approved by the Ethics Committee of the Psychology Department at the University of Bologna.

Experimental design

Each participant underwent two visual tasks: the motion discrimination task and the orientation discrimination task (see Motion discrimination task and Orientation discrimination task). EEGs were recorded during both tasks. Each task was performed before (pre-training session) and after (post-training session) AV training (Fig. 1). Experimental blocks of the motion discrimination and orientation discrimination tasks were interleaved, and the order of block presentation was counterbalanced between participants. Two experimental sessions were performed on two separate days. On the first day, participants performed the motion and orientation discrimination titration procedures (see Motion discrimination titration procedure and Orientation discrimination titration procedure). Then, on the same day, they completed the pre-training

session, in which EEGs were recorded during the motion discrimination and orientation discrimination tasks. On the second day of testing (2 or 3 days after the pre-training session), participants completed the AV training (see AV training) and the post-training session, in which EEG was again recorded during the motion discrimination and orientation discrimination tasks.

For the AV training, participants were randomly assigned to two different groups, each of which received a different type of training: the AV-SC group received multisensory training in which AV stimuli were presented in spatial coincidence, i.e. according to the principles of optimal multisensory integration (Stein & Meredith, 1993), while the AV-SD group received a control training procedure in which AV stimuli were presented in spatial disparity (see AV training).

Motion discrimination titration procedure

The titration procedure was performed to select the stimulus difficulty level (i.e. the coherence level) at which participants performed with a discrimination accuracy of about 60–65%, in order to avoid possible floor and ceiling effects during the subsequent motion discrimination task.

Participants were seated in a dimly lit and sound-controlled room in front of a 19" monitor (60 Hz refresh rate) at a distance of 57 cm. Stimuli consisted of modified random-dot kinematograms (Gummel *et al.*, 2012), i.e. small white dots moving within a circular frame (5° diameter), displayed on a black background (velocity $2.2^\circ/s$; lifetime: 8 frames; number: 150; density: 14.5 dots/deg^2). Stimuli were randomly presented 15° to the right or to the left of the centre of the screen. In each trial, dots moved in one of the four cardinal directions, and participants were asked to discriminate the direction of motion (vertical or horizontal) by pressing one of two vertically aligned response buttons on the keyboard. Response buttons were counterbalanced between subjects. During the task, participants kept their gaze at the centre of the screen, and were instructed to respond as quickly as possible using the index and middle fingers of their right hand.

Each trial (Fig. 2A) started with a blank screen with a central fixation cross (1000 ms), and then a blank screen of random duration ranging from 150 ms to 300 ms. This was followed by presentation of the motion stimulus (530 ms), and then another blank screen, during which participants' responses were recorded (maximum duration 2000 ms).

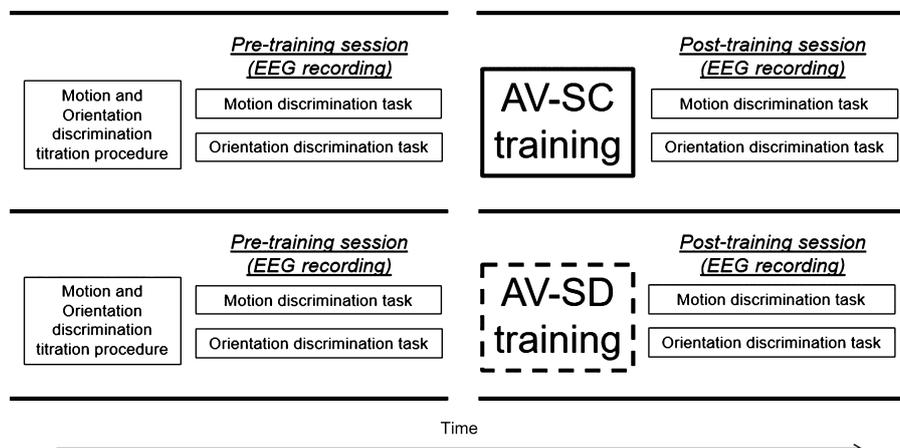


FIG. 1. Schematic representation of the experimental design.

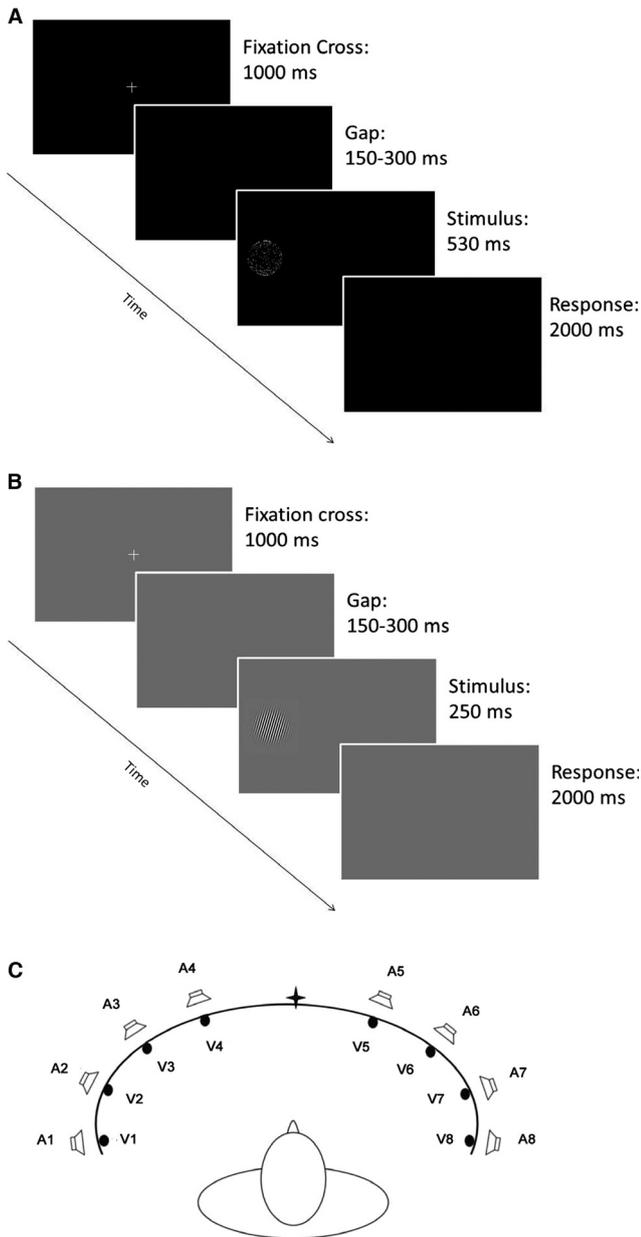


FIG. 2. Experimental tasks and audio-visual (AV) training. (A) Motion discrimination task. (B) Orientation discrimination task. (C) A schematic bird's-eye view of the apparatus used for multisensory training, depicting the locations of visual (V1–V8) and auditory (A1–A8) stimuli. Stimuli were positioned at 8, 24, 40 and 56 visual degrees of eccentricity into both the left and right visual fields, on an elliptical apparatus.

The titration procedure consisted of 13 experimental blocks, each one composed of 80 trials. In 40 trials, the stimulus was presented in the right visual field, and in the remaining 40 trials the stimulus was presented in the left visual field. In each block, motion stimuli were presented at a different level of coherence in order to test participants' motion perception performance. The 13 blocks corresponded to 13 consecutive levels of coherence. Starting from 100% coherence in the first block, the number of coherently moving dots was decreased at a rate of 20.6% in each subsequent block by substituting a percentage of the coherent dots with noise dots moving in a Brownian manner. Starting from the first block, in which all the dots moved coherently in a specific direction (100% coherence), the number of coherently moving dots decreased until reaching 6.3% coherence in block 13.

The titration procedure was administered twice before the pre-training session, in order to minimize learning effects. Performance during the second titration procedure was used to select the coherence level to be used in the motion discrimination task.

Orientation discrimination titration procedure

The titration procedure was performed to select the stimulus difficulty level (i.e. the tilt orientation) at which participants performed with a discrimination accuracy of about 60–65%, in order to avoid possible floor and ceiling effects during the subsequent orientation discrimination task.

The setup was similar to the one used in the motion discrimination titration procedure. Stimuli consisted of circular, equiluminant Gabor patches (7°), displayed on a grey background. The Gabor patches were composed of a 2D sinusoidal luminance grating with a spatial frequency of 3.5 cycles per degree. They were randomly presented 15° to the right or to the left of the centre of the screen. Participants were asked to discriminate the tilt orientation from the vertical axis of the Gabor patch (clockwise or anti-clockwise) by pressing one of two vertically aligned response buttons on the keyboard. Response buttons were counterbalanced between subjects. During the task, participants kept their gaze at the centre of the screen, and were instructed to respond as quickly as possible using the index and middle fingers of their right hand.

Each trial (Fig. 2B) started with a blank screen with a central fixation cross (1000 ms), and then a blank screen of random duration ranging from 150 ms to 300 ms. This was followed by presentation of the Gabor patch (250 ms), and then another blank screen, during which participants' responses were recorded (maximum duration 2000 ms).

The titration procedure consisted of 13 experimental blocks, each one composed of 80 trials. In 40 trials, the stimulus was presented in the right visual field, and in the remaining 40 trials the stimulus was presented in the left visual field. In each block, the Gabor patches were presented at a different tilt orientation from the vertical axis, in order to test participants' orientation discrimination performance. The 13 blocks corresponded to 13 different degrees of tilt, in which tilt orientation decreased at a rate of 29.3% of the previous level. Tilt orientation from the vertical axis reduced from 16° in block 1 to 0.25° in block 13. The titration procedure was administered twice, in order to minimize learning effects. Performance during the second titration procedure was used to select the degree of tilt to be used in the orientation discrimination task.

Motion discrimination task

The motion discrimination task was performed both before (pre-training session) and after (post-training session) the AV training, and EEGs were recorded in both sessions. Stimuli consisted of the same modified random-dot kinematograms (Gummel *et al.*, 2012) used in the motion discrimination titration procedure. In each trial, dots moved in one of the four cardinal directions, and participants were asked to discriminate the direction of motion (vertical or horizontal) by pressing one of two vertically aligned response buttons on the keyboard. Response buttons were counterbalanced between subjects. During the task, participants kept their gaze at the centre of the screen, and were instructed to respond as quickly as possible using the index and middle fingers of their right hand.

For each participant, the kinematograms were set at the coherence rate corresponding to 60–65% accuracy in the motion discrimination titration procedure (see above; mean coherence rate: 15.8%). Stimuli were randomly presented 15° to the right or to the left of the centre of the screen.

Each trial (Fig. 2A) started with a blank screen with a central fixation cross (1000 ms), and then a blank screen of random duration ranging from 150 ms to 300 ms. This was followed by presentation of the motion stimulus (530 ms), and then another blank screen, during which participants' responses were recorded (maximum duration 2000 ms).

Participants completed six blocks, consisting of 80 trials per block, i.e. 40 trials with stimuli presented in the right visual field and 40 trials with stimuli presented in the left visual field. In total, participants underwent 480 trials (240 trials per side of presentation). Behavioural performance was measured by computing inverse efficiency scores (IES = mean reaction times/proportion of correct responses).

Orientation discrimination task

The orientation discrimination task was performed both before (pre-training session) and after (post-training session) AV training, and EEGs were recorded in both sessions. Stimuli consisted of the same circular, equiluminant Gabor patches used in the orientation discrimination titration procedure. In each trial, a Gabor patch was presented with either a clockwise or anti-clockwise tilt from the vertical axis, and participants were asked to discriminate the tilt orientation by pressing one of two vertically aligned response buttons on the keyboard. Response buttons were counterbalanced between subjects. During the task, participants kept their gaze at the centre of the screen, and were instructed to respond as quickly as possible using the index and middle fingers of their right hand. For each participant, the tilt was set at the orientation corresponding to 60–65% accuracy in the orientation discrimination titration procedure (see above; mean tilt orientation: 1°). Stimuli were randomly presented 15° to the right or to the left of the centre of the screen.

Each trial (Fig. 2B) started with a blank screen with a central fixation cross (1000 ms), and then a blank screen of random duration ranging from 150 ms to 300 ms. This was followed by presentation of the Gabor patch (250 ms), and then another blank screen, during which participants' responses were recorded (maximum duration 2000 ms). Participants completed six blocks, consisting of 80 trials per block, i.e. 40 trials with stimuli presented in the right visual field and 40 trials with stimuli presented in the left visual field. In total, participants underwent 480 trials (240 trials per side of presentation). Behavioural performance was measured by computing IESs (IES = mean reaction times/proportion of correct responses).

AV training

Participants sat on a comfortable chair with their head placed on a chin rest positioned at the centre of the training apparatus. The apparatus consisted of a concave ellipse, 200 cm wide × 30 cm high, placed on a table. Visual and auditory stimuli were delivered at eight positions along the median line at 8°, 24°, 40° and 56° of eccentricity to the right and to the left of the centre (Fig. 2C). Auditory stimuli consisted of 100 ms bursts of white noise at 80 dB, emitted by hidden piezoelectric loudspeakers (A1–A8 in Fig. 2C). Visual stimuli consisted of 100 ms flashes of red LED light (luminance at 90 cd/m²; V1–V8 in Fig. 2C). Three different kinds of sensory stimulation were administered: (i) unisensory visual stimulation, in which only visual stimuli were presented at the 24°, 40° and 56° positions on the apparatus; (ii) unisensory auditory stimulation, in which only auditory stimuli were presented at the 24°, 40° and 56° positions on the apparatus; (iii) multisensory AV stimulation, in which auditory and visual stimuli were coupled.

Participants were asked to press a response button when they detected a visual stimulus and to perform eye movements towards the position of the visual stimulus. Trials with unisensory auditory stimuli could be considered catch trials, as no response was required. In contrast, participants had to respond to the visual stimuli on both unisensory visual and multisensory AV trials. Whereas multisensory AV stimuli were used to increase the activity of the SC-dorsal MT pathway, the role of the unisensory visual trials was to make the task less predictable and to increase participants' attentional engagement.

Half of the participants received multisensory training with AV pairs of stimuli presented in spatial coincidence, i.e. auditory and visual stimuli were presented in the same spatial position at 24°, 40° or 56° on the apparatus (AV-SC group). The remaining half received multisensory training with AV pairs, in which the visual stimulus was presented at the 24°, 40° or 56° position on the apparatus, and the auditory stimulus was presented at a spatial disparity of 32° within the same hemifield (AV-SD group).

AV stimulus pairs were disproportionately allocated to one side of the visual field, i.e. participants received 75% of the AV pairs in either the left or the right visual field (trained hemifield), while the remaining 25% were delivered on the other side (untrained hemifield). Unisensory visual and auditory stimuli were equally distributed on both sides. The side in which participants received 75% of the AV pairs (i.e. the trained hemifield) was counterbalanced between participants.

Participants performed 38 blocks of trials. Each block consisted of 12 unisensory visual stimuli (six in the left and six in the right visual field; i.e. two per spatial position), 12 unisensory auditory stimuli (six in the left and six in the right visual field; i.e. two per spatial position) and 24 multisensory AV stimuli (18 in the trained hemifield, i.e. six per spatial position; six in the untrained hemifield, i.e. two per spatial position).

EEG recording and event-related potential (ERP) analysis

EEG was recorded during the motion discrimination and orientation discrimination tasks with Ag/AgCl electrodes (Fast 'n Easy Electrodes, Easycap, Herrsching, Germany) from 27 electrode sites on the scalp (Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, O1, O2) and one on the right mastoid. The electrode on the left mastoid was used as the reference, while the ground electrode was placed on the right cheek. Impedances were kept below 10 kΩ. All electrodes were off-line re-referenced to the average of both mastoids. Vertical and horizontal electrooculogram data (EOG) were recorded from above and below the left eye, and from the outer canthi of both eyes. EEG and EOG were recorded with a band-pass of 0.01–100 Hz and amplified by a BrainAmp DC amplifier (Brain Products, Gilching, Germany). The amplified signals were digitized at a sampling rate of 500 Hz and off-line filtered with a 40-Hz low-pass filter.

ERP data were analysed using custom routines in Matlab 7.12.0.635 (R2011a; The Mathworks, Natic, MA, USA) and EEGLAB v10.2.5.8b (Delorme & Makeig, 2004; <http://www.scn.ucsd.edu/eeGLab>). Segments of 200 ms before and 900 ms after stimulus onset were extracted from the continuous EEG. The baseline window ran from –100 to 0 ms relative to stimulus onset. Epochs with incorrect responses were rejected (motion discrimination task: pre-training 38%, post-training 36%; orientation discrimination task: pre-training 38%, post-training 35%). In addition, epochs contaminated with large artefacts were identified using the following methods from the EEGLAB toolbox (Delorme *et al.*,

2007): (i) an epoch was excluded whenever the voltage on a channel exceeded an individually adjusted threshold (motion discrimination task: pre-training 280 μV , post-training 275 μV ; orientation discrimination task: pre-training 281 μV , post-training 280 μV) to remove epochs with large voltage peaks (mean excluded epochs: motion discrimination task, pre-training 3.3%, post-training 2.3%; orientation discrimination task, pre-training 3.1%, post-training 3.4%); (ii) an epoch was excluded whenever the joint probability of a trial exceeded five standard deviations to remove epochs with improbable data (mean excluded epochs: motion discrimination task, pre-training 1.7%, post-training 2%; orientation discrimination task, pre-training 1.5%, post-training 1.7%). Remaining vertical EOG artefacts were corrected using a multiple adaptive regression method (Automatic Artifact Removal Toolbox Version 1.3; <http://kasku.org/projects/eeg/aar.htm>; Gratton *et al.*, 1983), based on the least mean squares algorithm. Finally, epochs were discarded from the analysis when saccadic movements ($> 30 \mu\text{V}$ in the horizontal EOG channels) were registered in a time window between 0 and 530 ms following stimulus onset in the motion discrimination task (mean excluded epochs: pre-training 2.1%, post-training 3.3%), and between 0 and 250 ms following stimulus onset in the orientation discrimination task (mean excluded epochs: pre-training 1.2%, post-training 1.8%). The remaining epochs (mean epochs: motion discrimination task, pre-training 54.9%, post-training 57.4%; orientation discrimination task, pre-training 56.2%, post-training 58.1%) were averaged separately for each participant, each session and each hemifield of stimulus presentation.

ERP channels were swapped cross-hemispherically for participants in which the trained hemifield was the right visual field. In this way, the entire participant sample was analysed as if the trained hemifield was the left side.

The N1 component was quantified as the mean amplitude in a time window of 140–180 ms post-stimulus presentation (Figs 3C–F and 4C–F). Scalp topographies for the N1 component were also calculated as the mean amplitude in a time window of 140–180 ms post-stimulus presentation. Scalp topographies of the mean N1 amplitude in the pre-training session (Figs 3A and 4A) and the post-training session (Figs 3B and 4B), both in the motion and orientation discrimination tasks, showed a maximal negative deflection over electrodes FC1, FC2 and Cz; data from these electrodes were used for statistical analysis.

Mean N1 amplitudes were analysed with $2 \times 2 \times 3 \times 2$ ANOVAs with Time (pre-training, post-training), Hemifield (trained hemifield, untrained hemifield) and Electrode (FC1, FC2, Cz) as within-subjects variables, and with Group (AV-SC group, AV-SD group) as a between-subjects variable. The ANOVAs were performed separately for each experimental task (motion discrimination task, orientation discrimination task). To compensate for violations of sphericity, Greenhouse–Geisser corrections were applied whenever appropriate (Greenhouse & Geisser, 1959), and corrected P -values (but uncorrected degrees of freedom) are reported. *Post hoc* comparisons were performed using the Newman–Keuls test.

Results

Behavioural results

IESs in the motion discrimination and orientation discrimination tasks were analysed with two separate $2 \times 2 \times 2$ ANOVAs with Time (pre-training, post-training) and Hemifield (trained hemifield, untrained hemifield) as within-subjects factors, and Group (AV-SC group, AV-SD group) as a between-subjects factor.

The analysis on IES in the motion discrimination task revealed a main effect of Time ($F_{1,30} = 9.38$, $P = 0.004$; $\eta_p^2 = 0.24$), showing a significant improvement in performance in the post-training session (1336 ms) compared with the pre-training session (1423 ms). No other main effects (all P -values > 0.118) or interactions (all P -values > 0.223) were significant.

In contrast, the analysis on IES in the orientation discrimination task revealed no significant main effects (all P -values > 0.097) or interactions (all P -values > 0.181).

Electrophysiological results

The ANOVA on mean N1 amplitudes elicited in the motion discrimination task (Fig. 3) revealed a significant Hemifield \times Electrode interaction ($F_{2,60} = 25.17$, $P < 0.001$, $\eta_p^2 = 0.46$). For stimuli presented in the trained hemifield, the contralateral FC2 electrode showed a significantly greater N1 amplitude ($-2.29 \mu\text{V}$) compared with both ipsilateral FC1 ($-2.01 \mu\text{V}$, $P = 0.002$) and central Cz ($-2.13 \mu\text{V}$, $P = 0.030$). For stimuli presented in the untrained hemifield, the contralateral FC1 electrode showed a significantly greater N1 amplitude ($-2.31 \mu\text{V}$) compared with both ipsilateral FC2 ($-1.85 \mu\text{V}$, $P < 0.001$) and central Cz ($-2.11 \mu\text{V}$, $P = 0.003$).

More importantly, the Time \times Hemifield \times Group interaction was significant ($F_{1,30} = 4.80$, $P = 0.036$, $\eta_p^2 = 0.13$). *Post hoc* comparisons revealed that, in the group who received coincident AV training, a significantly greater N1 amplitude was observed in response to stimuli presented in the trained hemifield in the post-training session ($-3.02 \mu\text{V}$) compared with the pre-training session ($-1.96 \mu\text{V}$, $P = 0.003$; Fig. 3C and G). In contrast, in the same group of participants, no significant difference between the pre-training session ($-1.93 \mu\text{V}$) and the post-training session ($-2.19 \mu\text{V}$, $P = 0.747$) was found in response to stimuli presented in the untrained hemifield (Fig. 3D and G). Notably, in the group who received spatially disparate AV training, no significant differences in N1 amplitude were found between the pre-training session and the post-training session, either in response to stimuli presented in the trained hemifield (pre-training: $-1.84 \mu\text{V}$; post-training: $-1.74 \mu\text{V}$, $P = 0.702$; Fig. 3E and H), or in response to stimuli presented in the untrained hemifield (pre-training: $-2.00 \mu\text{V}$; post-training: $-2.23 \mu\text{V}$, $P = 0.644$; Fig. 3F and H). No other main effects (all P -values > 0.163) or interactions (all P -values > 0.090) were significant.

The ANOVA on mean N1 amplitudes elicited in the orientation discrimination task (Fig. 4) revealed only a significant Hemifield \times Electrode interaction ($F_{2,60} = 16.42$, $P < 0.001$, $\eta_p^2 = 0.35$). For stimuli presented in the trained hemifield, the contralateral FC2 electrode showed a significantly greater N1 amplitude ($-0.91 \mu\text{V}$) compared with ipsilateral FC1 ($-0.61 \mu\text{V}$, $P = 0.011$). For stimuli presented in the untrained hemifield, the contralateral FC1 electrode showed a significantly greater N1 amplitude ($-0.86 \mu\text{V}$) compared with ipsilateral FC2 ($-0.45 \mu\text{V}$, $P < 0.001$). In contrast with the results of the motion discrimination task, the Time \times Hemifield \times Group interaction was not significant ($F_{1,30} = 0.003$, $P = 0.961$, $\eta_p^2 = 0.00008$). In addition, no other significant main effects (all P -values > 0.713) or interactions (all P -values > 0.266) were found.

To ascertain whether there were any differences in N1 enhancement during motion discrimination between participants who received AV training in the left visual hemifield and those who received training in the right visual hemifield (Corral & Escera, 2008; Sosa *et al.*, 2010, 2011), a $2 \times 2 \times 3 \times 2 \times 2$ ANOVA was performed with Time (pre-training, post-training), Hemifield (trained

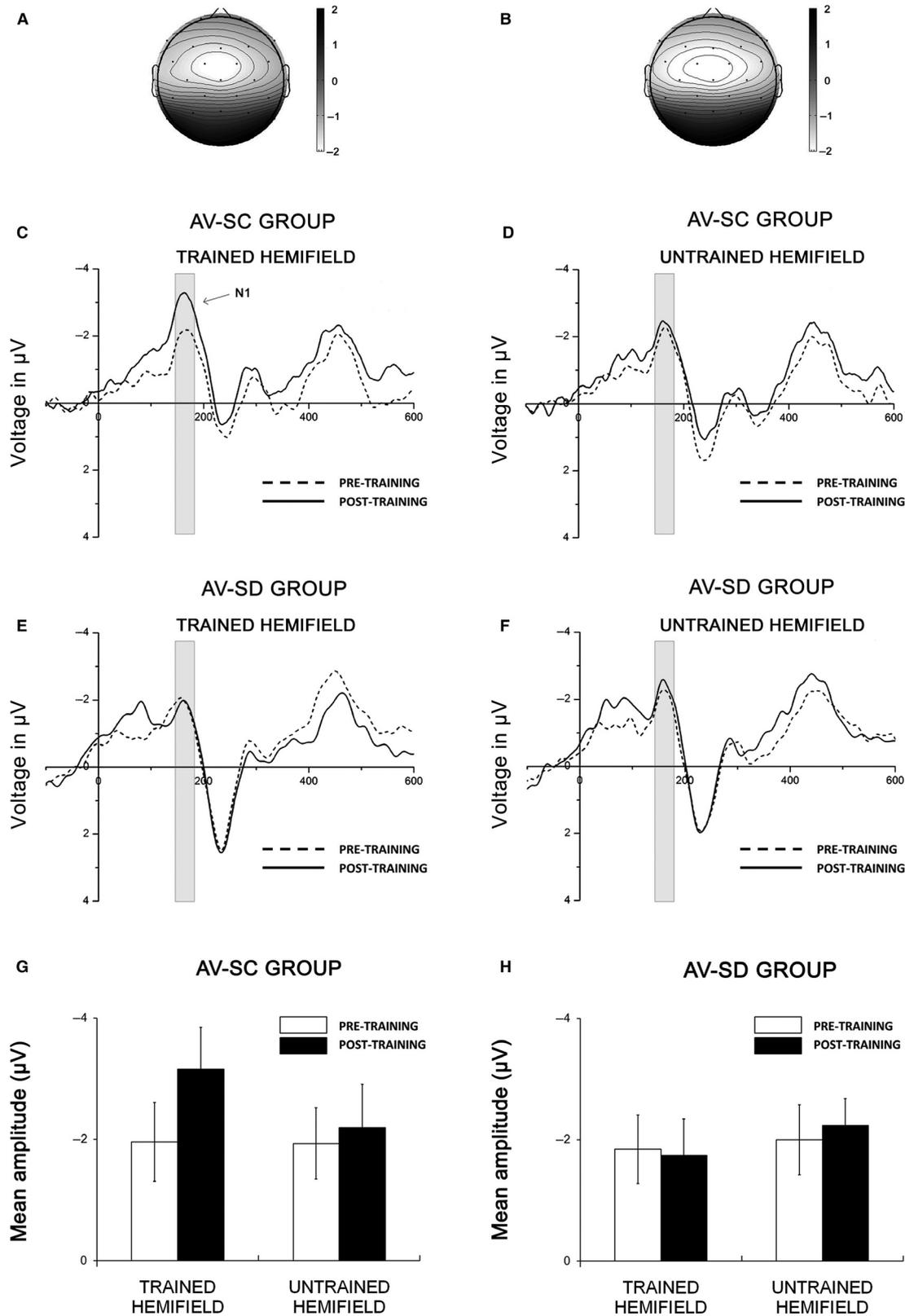


FIG. 3. Motion discrimination task. (A and B) Scalp topographies of the mean N1 amplitude in a time window between 140 and 180 ms, averaged over stimuli presented in the trained hemifield and the untrained hemifield, in the pre-training session (A) and the post-training session (B) for both the audio-visual (AV)-spatial coincidence (SC) (AV training with stimuli in spatial coincidence) and the AV-spatial disparity (SD) (AV training with stimuli in spatial disparity) groups. Grand-average event-related potentials (ERPs) averaged across electrodes FC1, FC2 and Cz, elicited by motion stimuli in the pre-training session and the post-training session, in the trained (C) and untrained (D) hemifields in the AV-SC group, and in the trained (E) and untrained (F) hemifields in the AV-SD group. Mean N1 amplitudes elicited by motion stimuli in the pre-training and post-training sessions, presented in the trained and untrained hemifields in the AV-SC group (G) and the AV-SD group (H), averaged across electrodes FC1, FC2 and Cz in a time window between 140 and 180 ms.

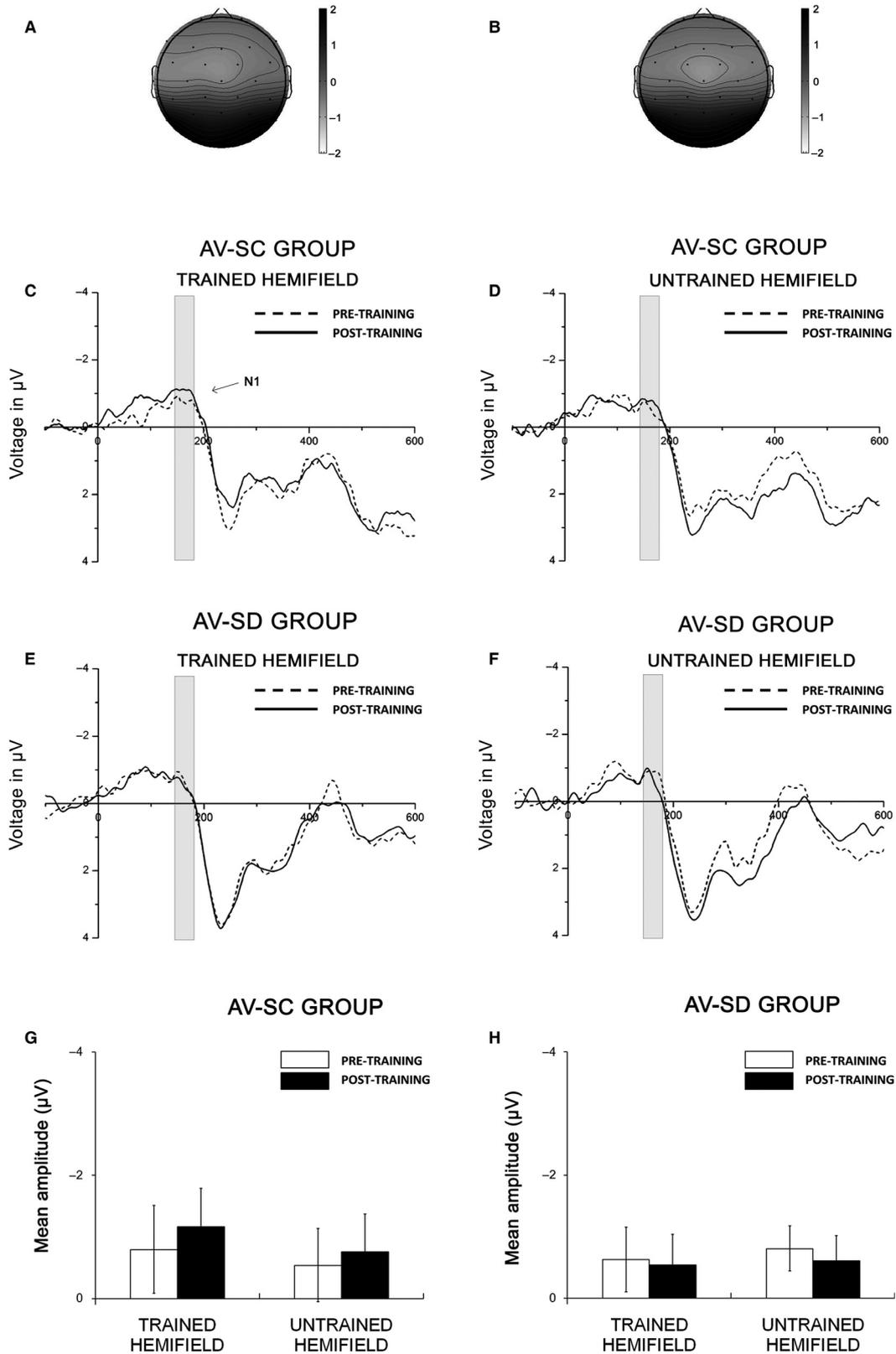


FIG. 4. Orientation discrimination task. (A and B) Scalp topographies of the mean N1 amplitude in a time window between 140 and 180 ms, averaged over stimuli presented in the trained hemifield and the untrained hemifield in the pre-training session and the post-training session for both the audio-visual (AV)-spatial coincidence (SC) (AV training with stimuli in spatial coincidence) and the AV-spatial disparity (SD) (AV training with stimuli in spatial disparity) groups. Grand-average event-related potentials (ERPs) averaged across electrodes FC1, FC2 and Cz, elicited by orientation stimuli in the pre-training session and the post-training session, in the trained (C) and untrained (D) hemifields in the AV-SC group, and in the trained (E) and untrained (F) hemifields in the AV-SD group. Mean N1 amplitudes elicited by orientation stimuli in the pre-training and post-training sessions, presented in the trained and untrained hemifields in the AV-SC group (G) and the AV-SD group (H), averaged across electrodes FC1, FC2 and Cz in a time window between 140 and 180 ms.

hemifield, untrained hemifield) and Electrode (FC1, FC2, Cz) as within-subjects variables, and Group (AV-SC group, AV-SD group) and Trained side (left, right) as between-subjects variables. Again, the Time \times Hemifield \times Group interaction was significant ($F_{1,28} = 5.07$, $P = 0.032$, $\eta_p^2 = 0.15$), confirming a significant post-training increase in N1 amplitude in response to stimuli presented in the trained hemifield in the group who received coincident AV training (pre-training: $-1.96 \mu\text{V}$; post-training: $-3.02 \mu\text{V}$; $P = 0.002$). No significant difference was found in response to stimuli presented in the untrained hemifield (pre-training: $-1.93 \mu\text{V}$; post-training: $-2.19 \mu\text{V}$; $P = 0.730$). Moreover, no significant differences were found in the group who received spatially disparate AV training (all P -values > 0.469). Importantly, the Time \times Hemifield \times Group \times Trained side interaction was not significant ($F_{1,28} = 1.70$, $P = 0.203$, $\eta_p^2 = 0.06$), suggesting a similar post-training N1 enhancement in participants who received training in the left hemifield and the right hemifield.

In addition, to control for possible hemispheric differences in N1 enhancement during motion discrimination, mean N1 amplitudes recorded from the lateralized electrodes FC1 (in the hemisphere ipsilateral to the trained hemifield) and FC2 (in the hemisphere contralateral to the trained hemifield) were analysed with a $2 \times 2 \times 2 \times 2$ ANOVA with Time (pre-training, post-training), Hemifield (trained hemifield, untrained hemifield) and Hemisphere (ipsilateral, contralateral) as within-subjects variables, and with Group (AV-SC group, AV-SD group) as a between-subjects variable. Similar to the previous analyses, the Time \times Hemifield \times Group interaction was significant ($F_{1,30} = 5.42$, $P = 0.027$, $\eta_p^2 = 0.15$), and *post hoc* comparisons confirmed a significant post-training increase in N1 amplitude in response to stimuli presented in the trained hemifield in the group who received coincident AV training (pre-training: $-2.00 \mu\text{V}$; post-training: $-3.06 \mu\text{V}$; $P = 0.002$). No significant difference was found in response to stimuli presented in the untrained hemifield (pre-training: $-2.01 \mu\text{V}$; post-training: $-2.25 \mu\text{V}$; $P = 0.624$). In addition, no significant differences were found in the group who received spatially disparate AV training (all P -values > 0.526). Neither the main effect of Hemisphere ($F_{1,30} = 1.23$, $P = 0.276$, $\eta_p^2 = 0.04$) nor the Time \times Hemifield \times Hemisphere \times Group interaction ($F_{1,30} = 0.09$, $P = 0.759$, $\eta_p^2 = 0.003$) was significant, suggesting no hemispheric differences in the observed N1 enhancement.

An additional control analysis was performed to ascertain that the N1 increase after spatially coincident AV training was not influenced by the preceding C1 component. Two separate $2 \times 2 \times 3 \times 2$ ANOVAs for each experimental task were performed on C1 amplitudes, quantified as the most negative peak in a time window of 70–130 ms post-stimulus onset, with Time (pre-training, post-training), Hemifield (trained hemifield, untrained hemifield) and Electrode (FC1, FC2, Cz) as within-subjects variables, and with Group (AV-SC group, AV-SD group) as a between-subjects variable.

The ANOVA on mean C1 amplitudes elicited in the motion discrimination task revealed a significant effect of Time ($F_{1,30} = 17.6$, $P < 0.001$, $\eta_p^2 = 0.37$), showing a significant increase in C1 amplitude in the post-training session ($-1.55 \mu\text{V}$) compared with the pre-training session ($-1.01 \mu\text{V}$). Notably, the Time \times Hemifield \times Group interaction was not significant ($F_{1,30} = 0.45$, $P = 0.508$, $\eta_p^2 = 0.01$), suggesting that the observed C1 increase might reflect perceptual learning due to practice effects (Pourtois *et al.*, 2008; Bao *et al.*, 2010). In addition, the main effect of Electrode was significant ($F_{2,60} = 15.14$, $P < 0.001$, $\eta_p^2 = 0.33$), showing significantly greater C1 amplitudes over electrode Cz

($-1.45 \mu\text{V}$) compared with both FC1 ($-1.2 \mu\text{V}$, $P < 0.001$) and FC2 ($-1.18 \mu\text{V}$, $P < 0.001$). No other significant main effects (all P -values > 0.388) or interactions (all P -values > 0.260) were found.

In the orientation discrimination task, a significant main effect of Electrode ($F_{2,60} = 24.94$, $P < 0.001$, $\eta_p^2 = 0.45$) was found, revealing greater C1 amplitudes over electrode Cz ($-1.00 \mu\text{V}$) compared with both FC1 ($-0.66 \mu\text{V}$, $P < 0.001$) and FC2 (-0.69 , $P < 0.001$). No other significant main effects (all P -values > 0.907) or interactions (all P -values > 0.070) were found.

Finally, to test possible differences at a later time window post-stimulus onset, mean P2 component amplitudes were analysed with a $2 \times 2 \times 3 \times 2$ ANOVA for each experimental task, with Time (pre-training, post-training), Hemifield (trained hemifield, untrained hemifield) and Electrode (FC1, FC2, Cz) as within-subjects variables, and Group (AV-SC group, AV-SD group) as a between-subjects variable. The P2 component was quantified as the most positive peak in a time window between 220 and 260 ms post-stimulus onset. Overall, the P2 component was not significantly modulated by AV training. Indeed, the ANOVA on mean P2 amplitudes elicited in the motion discrimination task revealed no significant main effect of Time ($F_{1,30} = 1.04$, $P = 0.398$, $\eta_p^2 = 0.03$) or Group ($F_{1,30} = 0.93$, $P = 0.343$, $\eta_p^2 = 0.03$). In addition, no significant Time \times Hemifield \times Group interaction was found ($F_{1,30} = 0.009$, $P = 0.924$, $\eta_p^2 = 0.0003$).

Similarly, the ANOVA on mean P2 amplitudes elicited in the orientation discrimination task revealed no significant effect of Time ($F_{1,30} = 0.21$, $P = 0.650$, $\eta_p^2 = 0.007$) or Group ($F_{1,30} = 0.7$, $P = 0.408$, $\eta_p^2 = 0.023$). The Time \times Hemifield \times Group interaction was also non-significant ($F_{1,30} = 1.45$, $P = 0.237$, $\eta_p^2 = 0.046$).

Discussion

The results of the present study show an enhancement of the N1 component in a motion discrimination task extensively involving the dorsal MT pathway (Zeki *et al.*, 1991; Watson *et al.*, 1993; Tootell *et al.*, 1995; Kolster *et al.*, 2010) after training with spatially coincident AV stimuli. This effect was found in response to stimuli presented in the trained hemifield, while no effect was found in response to stimuli presented in the untrained hemifield. Notably, no effect was found in an orientation discrimination task involving the ventral extrastriate pathway. Furthermore, participants who received training with spatially disparate AV stimuli showed no effects in either task.

The observed N1 enhancement might reflect increased motion discrimination ability (Vogel & Luck, 2000) after the spatially coincident AV training. Indeed, the N1 component is an early visual-evoked potential, which has been associated with visual discrimination processes (Mangun & Hillyard, 1991; Martínez *et al.*, 1999; Vogel & Luck, 2000) and might be related to attentional preparation for discriminating task-relevant features (Chen *et al.*, 2006; Pinal *et al.*, 2014).

The enhanced processing of motion stimuli might reflect increased activity in the retino-colliculo-dorsal MT pathway due to the intensive 2 h training with spatially coincident AV stimuli. Indeed, a wide range of evidence suggests that both motion processing and AV integration share common neural circuits. On the one hand, primate studies suggest the existence of a functional pathway from the SC to cortical area MT (Berman & Wurtz, 2010, 2011; Lyon *et al.*, 2010), in which motion signals are processed (Zeki, 1974; Maunsell & Van Essen, 1983a,b; Albright, 1984). Similarly, evidence from humans suggests the involvement of the SC (Schneider & Kastner, 2005) and the dorsal extrastriate area MT in motion processing

(Zeki *et al.*, 1991; Watson *et al.*, 1993; Tootell *et al.*, 1995; Kolster *et al.*, 2010). On the other hand, converging evidence reveals the pivotal role of the human SC in integrating spatio-temporally coincident AV stimuli (Calvert, 2001; Bertini *et al.*, 2008; Leo *et al.*, 2008; Maravita *et al.*, 2008), and the relevance of the dorsal temporo-parietal and posterior parietal cortices in mediating orienting behaviour towards AV stimuli (Meienbrock *et al.*, 2007; Bertini *et al.*, 2010; Nardo *et al.*, 2014). Interestingly, a similar AV training administered to hemianopic cats induced a recovery of visual orienting behaviour towards the hemianopic field, co-occurring with the reinstatement of visual responsiveness in the SC (Jiang *et al.*, 2015), suggesting that coincident AV stimulation might induce plastic changes in the SC. The plasticity of the colliculo-dorsal pathway is also supported by the observation that repeated AV stimulation favours the development (Yu *et al.*, 2010; Xu *et al.*, 2012, 2014) and enhancement (Yu *et al.*, 2009, 2012, 2016) of multisensory integrative responses in the SC. Intriguingly, repeated exposure to multisensory pairs can also increase neuronal responses to stimuli in a single sensory modality (Yu *et al.*, 2009, 2012). This is in line with the current finding that the AV training affected responses to purely visual stimuli. Enhanced motion processing was observed only in response to the trained hemifield (i.e. the hemifield in which 75% of the coincident AV stimuli were presented), while no change was found in the untrained hemifield, in which participants received only 25% of AV stimuli. This seems to suggest a lateralized activation of the colliculo-dorsal MT pathway after the AV training, in line with previous evidence showing that the SC contains a representation of the contralateral auditory and visual space (for a review, see King, 2004). Interestingly, it can be speculated that the lack of any effect in the untrained hemifield might be due to an insufficient amount of multisensory stimulation presented in that hemifield. However, further studies are needed to investigate the exact quantity of stimulation needed to boost activity in the colliculo-dorsal MT pathway.

Notably, the post-training N1 enhancement that was observed in response to motion stimuli was detected over anterior fronto-central electrodes. Visual stimulus presentation is known to elicit a complex of temporally overlapping negative waves (the 'N1 complex') in the 135–200-ms time window, both with posterior occipito-parietal and anterior fronto-central scalp distributions (Mangun & Hillyard, 1991; Martínez *et al.*, 1999; Di Russo *et al.*, 2002, 2003, 2005, 2012). Interestingly, the neural sources of the anteriorly distributed N1 component have been shown to be located in the superior parietal cortex (Di Russo *et al.*, 2002, 2003, 2005), therefore corroborating the hypothesis that the observed N1 enhancement might reflect an increase in the activity of dorsal cortical areas. Indeed, a wide range of evidence suggests the existence of a network of cortical areas interconnected with the SC, including dorsal posterior parietal areas (Harting *et al.*, 1980; Robinson & Petersen, 1992; Krauzlis *et al.*, 2013).

Interestingly, no effect was found after training with AV stimuli presented at a spatial disparity of 32°, suggesting that the combination of auditory and visual stimuli per se is not sufficient to enhance motion processing. In order to activate the colliculo-dorsal MT pathway and enhance motion discrimination, AV pairs must be presented in spatial coincidence. Indeed, although spatial coincidence seems to play a marginal role in non-spatial tasks (Bertelson & Vroomen, 1994; Doyle & Snowden, 2001), spatial alignment has been widely demonstrated to be crucial for multisensory enhancement in tasks requiring an orienting response (either overt or covert; for a review, see Spence, 2013), as in the current AV training. In line with this idea, electrophysiological studies in animals report that

SC responses are enhanced only in the presence of spatially coincident AV stimuli (Stein & Meredith, 1993), while AV pairs presented in spatial disparity might depress SC responses (Kadunce *et al.*, 1997). Similarly, studies in humans have revealed enhanced activity in the SC (Calvert, 2001) and dorsal cortical areas with spatially coincident AV stimuli, compared with spatially disparate stimuli (Macaluso *et al.*, 2004; Meienbrock *et al.*, 2007; for a review, see Calvert, 2001; Stein & Stanford, 2008). The finding that the N1 was only enhanced after training with stimuli presented in spatial coincidence rules out a possible role of saccadic eye movements in mediating the post-training effect. Indeed, in order to obtain an orienting response during the training and, therefore, to enhance the spatial component of the task, participants were asked to perform eye movements towards the visual and AV stimuli. However, the saccadic response per se cannot account for the post-training N1 enhancement. Indeed, saccadic eye movements were also performed in the control training procedure with spatially disparate AV stimuli, after which no N1 enhancement was found.

Notably, the observed increase in the N1 component was not influenced by changes in the preceding C1 component. Indeed, the amplitude of the C1 component in the motion discrimination task was increased after training, irrespectively of the type of training (spatially coincident vs. spatially disparate) and the hemifield in which stimuli were presented (trained vs. untrained). This general increase in C1 amplitude is in line with the finding that behavioural performance on the motion discrimination task improved after training, regardless of the type of training and the side of stimulus presentation. Both these findings might reflect a practice effect in motion processing. In line with this hypothesis, it has been shown that increases in stimulus-evoked activity as early as the C1 might aid perceptual performance, resulting in perceptual learning (Pourtois *et al.*, 2008; Bao *et al.*, 2010; Rauss *et al.*, 2011). Indeed, a wide range of evidence has shown better performance on visual perception tasks, including motion discrimination (Saffell & Matthews, 2003; Lu *et al.*, 2004), after repeated exposure to visual (for a review, see Fahle, 2005) and AV stimuli (Kim *et al.*, 2008; Shams & Kim, 2012).

At a later stage of visual processing related to task relevance evaluations (i.e. the P2 component; Potts *et al.*, 1996; Potts & Tucker, 2001; Potts, 2004), no effects of AV training were found. This suggests that AV training specifically affects the early visual discrimination process, but has no effect on higher order cognitive processes. The specific activation of the colliculo-dorsal MT pathway after the coincident AV training is also suggested by the lack of any effects on orientation discrimination. Indeed, unlike with motion discrimination, both animal (Hubel & Wiesel, 1968; Hubel *et al.*, 1977; Vogels & Orban, 1994; De Weerd *et al.*, 1999) and human studies have revealed that grating orientation discrimination elicits activation in a visual pathway involving the striate cortex (Kamitani & Tong, 2005; Yacoub *et al.*, 2008; Swisher *et al.*, 2010) and early ventral extrastriate cortices (Boynton & Finney, 2003; Fang *et al.*, 2005; Murray *et al.*, 2006; Tong *et al.*, 2012).

Interestingly, in a single-case study, a patient with lesions in V1 and surrounding early visual cortices (for a complete clinical description, see Serino *et al.*, 2014) was not able to benefit from AV stimulation when discriminating the orientation of a line in his blind field (Cecere *et al.*, 2014). In contrast, his visual detection performance in the blind field was enhanced in the presence of auditory stimuli, in line with previous studies on patients with visual field defects (Bolognini *et al.*, 2005; Frassinetti *et al.*, 2005; Passamonti *et al.*, 2009). This suggests a role for the retino-colliculo-extrastriate pathway, bypassing the lesioned V1, in mediating the multisensory

improvement in visual detection performance. As a consequence, it seems reasonable that systematic, coincident AV training, activating the colliculo-dorsal pathway, would have effects on a motion discrimination task, which relies on the same pathway, but not on an orientation discrimination task, which relies on early ventral visual areas.

Overall, these results suggest that systematic AV stimulation with spatially coincident stimuli enhances post-training functionality of the colliculo-dorsal MT pathway. Even though the post-training effects were only observed at the electrophysiological level, it can be speculated that increasing the duration of training might also induce changes at the behavioural level. Although the present study did not systematically investigate the duration of this post-training enhancement, which was observed immediately after AV training (i.e. within 2 h), electrophysiological evidence from animals suggests that the effects of repetitive AV stimulation might outlast the exposure period and remain stable over a long period of time (i.e. more than 16 months after stimulation; Xu *et al.*, 2012). However, the duration of the effects of repetitive AV stimulation on humans needs further investigation. Moreover, the enhanced activity of this neural circuit may also be relevant to the rehabilitation of visual field defects. Indeed, patients with visual field defects due to lesions in the striate cortex might benefit from systematic training with coincident AV stimuli, activating the spared retino-colliculo-extrastriate pathway and, therefore, promoting improvements in oculomotor and orienting responses towards stimuli in the blind field (Bolognini *et al.*, 2005; Passamonti *et al.*, 2009; Dundon *et al.*, 2015).

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Abbreviations

AV, audio-visual; AV-SC, audio-visual spatial coincidence; AV-SD, audio-visual spatial disparity; EEG, electroencephalogram; EOG, electrooculogram; ERP, event-related potential; IES, inverse efficiency score; SC, superior colliculus.

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