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Neural correlates of human echolocation of path direction during walking

[1]Katja Fiehler[*], [1]Immo Schütz[*], [1]Tina Meller, & [2]Lore Thaler

[1]Department of Psychology, Justus-Liebig-University Giessen, Germany
[2]Department of Psychology, Durham University, Durham, United Kingdom

[*]These authors equally contributed to the work

Corresponding authors:
Katja Fiehler
Justus-Liebig-University Giessen
Department of Psychology
Experimental Psychology
Otto-Behaghel-Str. 10F
35394 Giessen
Germany
Email: katja.fiehler@psychol.uni-giessen.de

Lore Thaler
Durham University
Department of Psychology
South Road
Science Site
Durham DH1 3LE
United Kingdom
Email: lore.thaler@durham.ac.uk

Abstract

Echolocation can be used by blind and sighted humans to navigate their environment. The current study investigated the neural activity underlying processing of path direction during walking. Brain activity was measured with fMRI in 3 blind echolocation experts, and 3 blind and 3 sighted novices. During scanning, participants listened to binaural recordings that had been made prior to scanning while echolocation experts had echolocated during walking along a corridor which could continue to the left, right, or straight ahead. Participants also listened to control sounds that contained ambient sounds and clicks, but no echoes. The task was to decide if the corridor in the recording continued to the left, right, or straight ahead, or if they were listening to a control sound. All participants successfully dissociated echo from no-echo sounds, however, echolocation experts were superior at direction detection. We found brain activations associated with processing of path direction (contrast: echo vs. no-echo) in superior parietal lobe (SPL) and inferior frontal cortex in each group. In sighted novices, additional activation occurred in the inferior parietal lobe (IPL) and middle and superior frontal areas. Within the framework of the dorso-dorsal and ventro-dorsal pathway proposed by Rizzolatti & Matelli (2003), our results suggest that blind participants may automatically assign directional meaning to the echos, while sighted participants may apply more conscious, high-level spatial processes. High similarity of SPL and IFC activations across all three groups, in combination with previous research, also suggest that all participants recruited a multimodal spatial processing system for action (here: locomotion).

Keywords: blindness, vision, audition, space perception, navigation, PPC, fMRI

1 Introduction

Echolocation is the ability to sense the environment through reflection of sound (Griffin, 1944). It is probably best known from bats and marine mammals (Thomas et al., 2004), but it is by now well established that humans are able to use echolocation as well (Kolarik et al., 2014; Schenkman & Nilsson, 2010; Stoffregen & Pittenger, 1995), and that echolocation can be learned by both blind (e.g. Worchel & Mauney, 1951) and sighted people (e.g. Ammons et al., 1953; Teng & Whitney, 2011). In fact, some blind humans who echolocate using mouth-clicks can echolocate with an accuracy approaching that of some bat species (Teng et al., 2012). Skilled echolocators can reliably determine the distance and direction to objects (Rice & Feinstein, 1965; Rice et al., 1965; Rosenblum et al., 2000; Schoernich et al., 2013), as well as their azimuth (Thaler et al., 2011; Wallmeier et al., 2013). They can also use echolocation to determine the shape of sound reflecting surfaces in 3D (Arnott et al., 2013; Thaler et al., 2011) and 2D (Milne et al., 2014a), as well as what materials a sound reflecting surface is made of (Arnott et al., 2013; Hausfeld et al., 1982; Milne et al., 2014b).

Only recently have scientists started to investigate brain areas involved in human echolocation. It has been reported that echolocation of objects and scenes recruits calcarine cortex (i.e. primary visual cortex) in skilled blind echolocators (Thaler et al., 2011). Following up on this initial finding, subsequent studies investigated the neural representation of specific echolocation features, such as movement (Thaler et al., 2011, 2014), shape (Arnott et al., 2013), or surface material (Milne et al., 2014b). From research to date it appears that there may be a feature specific organization. For example, echolocation

of moving surfaces leads to an increase in activation in temporal-occipital brain areas, potentially encroaching on visual motion area MT+ (Thaler et al., 2011, 2014). Furthermore, shape processing through echolocation is associated with activation in LOC (Arnott et al., 2013), and processing of surface materials is associated with an increase in activity in parahippocampal cortex (Milne et al., 2014a). It has also been shown that echolocation of surfaces positioned at one side can lead to a relative increase in brain activity in contralateral calcarine cortex (Thaler et al., 2011), or (for moving surfaces) in contralateral temporal-occipital brain areas (Thaler et al., 2014). There is also evidence suggesting that surfaces located more towards the periphery lead to more rostral activation in calcarine cortex, whereas more centrally located surfaces lead to a relative increase of activation at the occipital pole (Arnott et al., 2013). In sum, evidence gathered in blind echolocation experts to date suggests that neural processing for echolocation may be organized in a feature specific way and that it might include pathways typically associated with vision in sighted people.

One of the primary uses of echolocation is that it can provide information about the spatial environment useful for navigation. For example, bats use echolocation to avoid obstacles, locate passageways or to detect prey (Grunwald et al., 2004; Schnitzler et al., 2003; Weissenbacher & Wiegrebe, 2003). Blind echolocation experts also comment on the fact that a primary benefit of echolocation is to provide information beyond reachable space which improves their mobility and orientation. Accordingly, blind people who echolocate report having significantly better mobility in unfamilar places as compared to blind people who do not echolocate (Thaler, 2013). Also

consistent with this, behavioral studies have shown that echolocation can be used to detect doorways (e.g. Carlson-Smith & Wiener, 1996) and obstacles (e.g. Cotzin & Dallenbach, 1950; Supa et al., 1944) during walking. It is not known, however, which brain areas are involved when echolocation is used to orient oneself in the environment, despite studies investigating how spatial locations per se are represented in the echolocating brain (e.g. Arnott et al. 2013; Thaler et al. 2011, 2014).

In sighted humans, visual information from the calcarine cortex onwards is processed along two pathways: a ventral pathway projecting from the primary visual cortex to the infero-temporal cortex, and a dorsal pathway projecting from the primary visual cortex to posterior parietal cortex (PPC), respectively. Based on lesion studies in monkeys and humans, the dorsal pathway has been associated with visual spatial localization and goal-directed action, whereas the ventral pathway has been associated with object identification and conscious visual perception (Goodale & Milner, 1992; Ungerleider & Mishkin, 1982). For example, patients with lesions in the superior parietal lobe (SPL) are often impaired in reaching to visual targets in the periphery, a deficit termed Optic Ataxia (Pisella et al., 2009). Patients with damage to the inferior parietal lobule (IPL) commonly suffer from an inability to detect, orient toward or respond to left (contralesional) stimuli, known as Neglect (Heilman et al., 2000; Karnath & Perenin, 2005; Vallar & Perani, 1986). In contrast, patients with lesions to the ventral stream, e.g. the LOC, suffer from Visual Form Agnosia and are unable to identify objects, whilst still being able to grasp them (Goodale et al., 1991; Westwood et al., 2002). A division of labor between dorsal and ventral pathways has also been suggested within the auditory system

(Kaas & Hackett, 1999; Rauschecker, 2011; Rauschecker & Tian, 2000). Thus, both for audition and vision, the PPC in the sighted brain has been implicated in processing of spatial information with particular relevance for action and spatial orientation.

Less is known about the neural underpinnings of spatial processing for action and orientation in blind humans. Loss of vision is typically associated with loss in mobility and orientation skills (Brabyn, 1982; Brown and Brabyn, 1987; Deiaune, 1992; Long, 1990; Long et al., 1990; Roentgen et al., 2009; Salive et al., 1994). This highlights just how much people rely on vision for orienting themselves. Without vision, spatial information about the distal environment has to be received through other sensory modalities, in particular audition (note that touch, temperature and smell/taste apply to the proximal rather than distal environment). Another alternative to sense the distal environment are sensory substitution devices, that transform information about the distal environment obtained via artificial sensors into auditory or tactile information (Bach-y-Rita & Kercel, 2003; Brabyn, 1982; Roentgen et al., 2009).

In regard to spatial hearing on the behavioral level, blind people, in particular those who are early blind, as compared to sighted people are better at discriminating azimuth of peripheral sound sources (Voss et al., 2004), mono-aural sound localization (Lessard et al., 1998), and they also show better spatial tuning in the periphery (Röder et al., 1999; Voss et al., 2004). Most notably, both early and late blind people are also better than sighted people at discriminating distances of sound sources (Voss et al., 2004). However, some investigations have also reported deficits in auditory-spatial tasks; for example people who are

congenitally blind are impaired relative to sighted controls in detecting the elevation of an auditory target (Zwiers et al., 2001) or when spatially bisecting an auditory target array (Gori et. al, 2013). Interestingly, Vercillo et al. (2015) showed that the performance of congenitally blind echolocators in an auditory spatial bisection task was similar or even better, compared to the performance of sighted and non-echolocating blind participants, respectively. This suggests that echolocation experience may compensate for the lack of visual calibration of auditory spatial maps in congentially blind people.

Blindness is not only associated with complex changes on the behavioral level, but also on the neural level (for reviews see e.g. Bavelier & Neville, 2002; Burton 2003; Merabet & Pascual-Leone, 2010; Noppeney, 2007; Röder & Rösler 2004). In regard to spatial auditory processing, improved auditory performance in early and congenitally blind humans has been linked to the recruitment of occipital brain areas (Collignon et al., 2009; Gougoux et al., 2005), and parts of the PPC associated with spatial processing of visually perceived objects in sighted people (Collignon et al., 2009; 2011; Lingnau et al., 2014). Also for tactile processing it has been shown repeatedly that blind people as compared to sighted people have superior ability to read Braille and (possibly related to this) better tactile acuity (Goldreich & Kanics, 2003; Grant et al., 2000; Van Boven et al., 2000; Wong et al., 2011). In terms of brain activity, processing of tactile input, and in particular Braille reading, has also been linked to activity in striate and extra-striate visual areas (Büchel, 1998; Cohen et al., 1997; Sadato et al., 1996).

With respect to navigation and/or spatial orientation specifically, it has been shown that blind people who have been trained to navigate in an environment using a sensory substitution device that transforms visual information into eletroctactile stimulation on the tongue perform superior to equally trained sighted blindfolded controls (Kupers et al., 2010). Furthermore, in the same study Kupers et al. (2010) also showed that brain activation during route recognition in blind people coincided with locations of activations in sighted people performing the task based on visual information, and that the largest cluster of activation was in the PPC, in particular SPL, with other common activations in superior occipital cortex, cuneus and parahippocampus. This suggests that the 'visual' navigation system may be usurped by navigation through other modalities.

In this study we investigated which brain areas are involved during echolocation of path direction during walking in a naturalistic setting inside and outside a building. To this end, we compared brain activations as measured with fMRI in three skilled blind echolocators to those measured in three blind and three sighted control subjects who had rarely or never used echolocation before. During fMRI scanning, participants listened to pre-recorded echolocation clicks and echoes that had been recorded when walking through a corridor inside and outside a building. After sound presentation they had to decide whether the walkway within the corridor continued to the left, straight ahead or to the right. Participants also listened to control recordings that contained clicks but not echoes.

2 Materials and Methods

2.1 Participants

Three early blind, male echolocation experts (BE1, BE2, BE3) participated in this study. All reported using tongue click-echolocation on a daily basis. Both BE1 (age 41) and BE2 (age 42) were enucleated in infancy due to retinoblastoma (BE1 at 18 months (left eye) and 30 months (right eye); BE2 at 12 months (both eyes)) and used echolocation since childhood, starting at age 8-10 years and 4 years, respectively. BE3 (age 16) completely lost his sight due to congenital amaurosis with 36 months and started to use echolocation at 3.5 years of age. All echolocation experts were right-handed measured with the Edinburgh Handedness Inventory (EHI; Oldfield 1971) and reported no residual vision and normal hearing. We tested 6 male control participants who reported being unfamiliar with echolocation prior to the study. They were matched by gender, age, handedness and education to the 3 echolocation experts (Table 1). The 3 blind novices (BN1-3, aged 33, 37, 22 years) also lost sight shortly after birth. BN1 and BN2 reported diffuse brightness detection, whereas BN3 lacked any light perception since he was enucleated in the first months after birth. Sighted participants (SN 1-3, aged 36, 38, 20 years) had normal or corrected to normal vision. The experiment was conducted in accordance with the Declaration of Helsinki (2008) and approved by the local ethics committees. All participants gave written informed consent.

Please insert Table 1 here

2.2 Apparatus and Stimuli

2.2.1 Recording procedure and setup

Stimuli were created by recording echolocation clicks and echos from each echolocation expert in different spatial scenarios. Binaural recordings were made both in an indoor and outdoor environment while each expert walked through a corridor, which was constructed from four poster-boards and made of wood fibers and attached to metal stands. Corridors were 185cm long and 110cm wide and opened to the left, the right or continued straight ahead (see Figure 1 for exact dimensions), resulting in 6 different scenarios (left-indoor/outdoor, straight-indoor/outdoor and right-indoor/outdoor). Start and end points of the corridor were marked haptically to assure the same walking distance of approx. 150cm for each participant in every trial. In the indoor environment, the corridor was set up in the entrance hall of the university building. Outdoors, the corridor was placed on grass next to the building. In both environments, the echolocation experts walked along the corridor without shoes in order to minimize additional acoustic information. For the same reason, the ground was covered with fleece blankets in the outdoor environment, which were also used to cover surrounding objects (e.g., picture frames) in the indoor setting. Consistent with previous studies (e.g. Thaler et al. 2011, 2014), in-ear omni-directional microphones (Sound Professionals-TFB-2; flat frequency range 20–20.000Hz) were placed at the opening of the participant's auditory canals and attached to a portable Edirol R-09

digital wave recorder (24-bit, stereo, 96 kHz sampling rate). The experts were instructed to slowly walk through the setup facing straight ahead, while clicking loudly with their usual frequency and pausing for a short moment at the critical point where they recognized a change in the direction of the corridor, if present. For each echolocation expert, recordings were created when participants were walking and clicking, and whilst walking without making clicks. Participants were timed during walking to make sure that the start and end of the walking path would be traversed within 10 seconds at a steady pace. Recordings were made separately for BE1, BE2 and BE3 with 6 to 8 recordings per expert and scenario. Only the blind experts traversed the corridor in the recording phase; the BN and SN groups never physically traversed the corridor.

Please insert Figure 1 and Table 2 here

2.2.2 Stimulus processing and selection

Sounds were processed in Audacity (2.0.2, 2012). Prior testing had revealed a slight imbalance between right and left microphone channels. Thus, prior to any further processing the left channel of sounds was amplified by 0.44 dB. Because of specifications of the software used to present sound stimuli (Presentation 16.1, Neurobehavioral Systems) sounds were downsampled to 44.1 kHz. For each scenario and echolocation expert, two recordings were selected based on objective (absence of interference sounds like a crossing car) and subjective (identifiability of the directions as rated by the experts)

criteria. Control stimuli which did not contain the click echos were created as follows. First, we cut samples from recordings during which participants had walked without clicking to a length of 10 seconds. Then, for matching conditions in echolocation conditions (i.e. walking whilst clicking) we isolated the left channel, and selected the clicks within that channel, whilst taking care to truncate the main part of the echo (based on visual criteria). This truncation served to remove monaural information contained in click-echos. Subsequently, each truncated click was inserted into an empty (i.e. silent) track so that the onset of each truncated click matched the onset of its 'partner' click in the echolocation stimulus. Subsequently, the empty + click track (which at to this point was left channel only) was duplicated to create a stereo-track. We chose to duplicate the left-truncated click instead of truncating and copying both the left and right track from the original, in order to avoid binaural information that could have possibly still been present in the truncated clicks. Then these stereo empty-click trains were merged with the 10-second track from when participants had walked without clicking. Using this procedure, we created a control clip for each echolocation clip. Importantly, control clips were matched to echolocation clips both in terms of background and ambient sounds, as well as in regard to the spectro-temporal features of clicks, whilst truncation and channel-doubling essentially removed mono- and binaural echo information.

This resulted in 72 different stimuli, i.e. 2 per direction (3), environment (2) and expert (3) both with and without echos (2 x 3 x 2 x 3 x 2 = 72). During behavioral training and fMRI scanning, each expert was presented with his own clicks and clicks from another expert. The sighted and blind novices heard the clicks from two different experts

(BN1, SN1: BE1 and BE2; BN2, SN2: BE1 and BE3; BN3, SN3: BE2 and BE3). This resulted in 48 stimuli for each participant, i.e. 2 per direction (3), environment (2) and expert (2) for both with and without echos (2 x (3 x 2 x 2 x 2) = 48). Table 2 lists average acoustic energy and clicking frequencies for each echolocation expert and condition. As an additional control, a silent baseline condition was introduced during the fMRI scanning.

2.3 Task and Procedure

2.3.1 Training

To become familiar with the task and stimuli, each novice participant received a circa 60-minute training session before the scanning, which took place in a quiet room at the University of either Gießen or Marburg. Participants were comfortably seated in front of a laptop equipped with MRI compatible stereo in-ear headphones (Sensimetrics, Model S14, Malden, MA, USA), which were also used during the scanning task. The headphones are surrounded by cone shaped foam for noise attenuation and were adjusted in size and shape to fit each participant. In each run, 48 stimuli (see above) were presented in random order via Presentation (16.1, Neurobehavioral Systems) software. Participants were instructed to press the appropriate key as soon as they identified the direction of the corridor as “echo left”, “echo straight ahead”, “echo right” or “no echo” (control). After each trial, acoustic feedback was given indicating the correct stimulus. After 3 to 4 runs, all participants reached the criteria of 100% correct discrimination of echo versus no-echo (irrespective of corridor direction) and at least 65% correct identifications of the corridor

direction with echos. This was followed by 1 to 2 runs without feedback to prepare for the task procedure during scanning.

2.3.2 Functional paradigm

Before the scanning session, participants performed one training run outside the scanner. After the training, they were instructed and prepared for the scanning by adjusting earphone position and volume to a comfortable level. In order to enable them to discriminate subtle auditory differences in the MR environment, the circulatory fan was turned off and participants were equipped with additional headphones for noise protection. Participants were allowed to try the four-button response box to which the four responses ("echo left", "echo straight ahead", "echo right" and "no echo") were assigned from left to right, equivalent to the layout on the laptop keyboard used in the training. They performed the task in the dark inside the scanner while keeping their eyes closed and wearing a blindfold. All participants were instructed to close their eyes during scanning. The functional paradigm consisted of six runs (each lasting about 10 min) with 36 active and 10 silent baseline trials each. The four conditions, Echo_Source1, noEcho_Source1, Echo_Source2, and noEcho_Source2, were counterbalanced (latin square design) across four different clusters. Each cluster contained four trials (one of each condition) and combined them in a different order. Per functional run, nine clusters were presented with one silent baseline trial preceding and following each cluster, as illustrated in Figure 2. Recording environment (indoor/outdoor) and direction (left, straight, right) categories were distributed equally across and within stimulus conditions. The sparse-sampling design resulted in a 2s scan, followed by a 10s scanning

pause in which, after a 0.5s pause, the stimulus was presented for 9s. The onset of the next scan after another 0.5s pause cued the participant to provide their response via button-press. Training, experimental setup and scanning took about 120min.

Please insert Figure 2

2.3.3 Imaging Parameters

Imaging was performed at the Bender Institute of Neuroimaging (BION) at Gießen University on a 1.5 Tesla scanner (Symphony Quantum; Siemens, Erlangen, Germany) with a quantum gradient system and a standard single-channel head coil. A gradient-echo field map was measured before the functional run to allow later correction for inhomogeneities in the static magnetic field. Functional imaging was conducted using a T2*-weighted gradient-echo-planar (EPI) imaging sequence in combination with a sparse-sampling design (Hall et al., 1999) with a repetition time (TR) of 12s (10s silent gap + 2s image acquisition) and an echo time (TE) of 43ms (matrix size: 64 x 64 mm; field of view: 192 mm^2, flip angle: 90°). In descending order, 24 contiguous axial 5mm-slices of the whole brain were measured with a resolution of 3 x 3 x 5mm^3. We acquired 47 functional volumes for each run. Anatomical images were acquired at a resolution of 1x1x1.4 mm^3 using T1-weighted magnetization-prepared, rapid-acquisition gradient echo (MPRAGE) sequence (matrix size: 256 x 180 mm; field of view: 250 mm; TE: 4.18 ms; TR: 1990 ms; voxel size: 1.4 x 1.0 x 1.0 mm). Scanning time in total was approximately 75 minutes.

2.3.4 Preprocessing

Functional MRI data were preprocessed and analyzed using the FMRIB Software Library (FSL version 5; Jenkinson et al. 2012, www.fmrib.ox.ac.uk/fsl). Only runs with more than 50% correct responses were included in the MRI analysis, leading to the exclusion of two sessions (BE1 run 5, SN2 run 5). The first volume of each run was always a silent baseline trial and removed from further analysis. EPI volumes were corrected for B0 field inhomogenities using individual field maps recorded in each run. Motion correction was performed using FSL's MCFLIRT with the middle volume as reference volume (Jenkinson et al., 2002). Additionally, we used a custom-made FSL tool to check for motion-related outlier volumes by calculating the mean squared difference to the respective adjacent volumes. No participant had to be excluded due to motion artifacts. EPI volumes were corrected for differences in slice acquisition time, and a high-pass filter cutoff of 360 s was applied to remove slow linear trends from the data. Functional images were then coregistered onto the high-resolution anatomical scan through boundary-based registration (BBR; Greve & Fischl 2009) using the FSL FLIRT tool. Subsequently, all images were coregistered onto the MNI152 standard space template image at 2mm resolution using linear (12 degrees of freedom) and additional non-linear transformations (FSL FNIRT). Finally, spatial smoothing was applied using a 7mm full width at half maximum (FWHM) Gaussian kernel.

2.4 Statistical Analysis

2.4.1 Behavioral Data

Behavioral response data were analyzed by calculating the percentage of correct responses for participants' judgements about whether an echo was present or not present (regardless of direction), as well as for judgements about direction within the stimuli that contained echos. Due to technical problems, participant BE1's key press responses were not correctly recorded and had to be excluded from behavioral data analyses. Trials without any response were also dropped from further analyses (average: 4.3%; blind experts: 2.5%, blind novices: 4.0%, sighted novices: 5.9%). The percentage of correct responses was then compared to chance performance (echo detection: 50%, direction discrimination: 33%) using Binomial tests.

2.4.2 MRI Data

Statistical fMRI analysis of each separate run was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL version 5.0 (Jenkinson et al., 2012). Analyses were based on a least-square estimate using a General Linear Model (GLM) for each run. Four regressors of interest were specified for the conditions Echo_Source1, noEcho_Source1, Echo_Source2, and noEcho_Source2. Silent baseline (SB) trials were not explictly modelled, thus serving as implicit model baseline. Due to the sparse sampling design, regressors were not convolved with a template HRF, but rather defined as a Boxcar function spanning the whole 2s volume acquired after each stimulus. The six motion parameters from MCFLIRT 6 DoF motion correction were added to the GLM as regressors of no interest.

In a second level analysis, functional data from all six runs of each participant were coregistered and normalized to MNI standard space at 2mm resolution using FLIRT. Single-participant activations across all runs were calculated by fitting a random-effects (RFX) GLM using FSL FLAME1. Additionally, an overall RFX GLM was fit to all recorded functional runs across participants, allowing for the detection of activations common to all participants. For the RFX analysis across all 9 participants, data within each participant was treated as a fixed effects model. Contrasts were defined for the effect of *sound source* (own > foreign click sounds, and vice versa), of *spatial echos* by comparing sounds that included echos to control sounds without echos (echo > no echo) and *of all sounds*, contrasting sound trials against the silent baseline (sounds > baseline). RFX fMRI results were corrected for multiple comparisons by applying Gaussian Random Field Theory at the cluster level using $z > 2.3$ ($z > 3.7$ for the global analysis) and a cluster probability threshold of $p < 0.05$ ($p < 0.01$ for the global analysis). To define common areas for echo-related activation in each group (BE, BN, SN), we took RFX activation maps resulting from the echo > no echo contrast in each participant and used these to calculate logical overlapping regions across all three participants in each group. For these calculations we adopted a clustersize threshold of 100 contiguous voxels (instead of a cluster probability threshold of $p < .05$) for all participants.

Labeling of activated areas was done using the Jülich Histological Cyto-Architectonic Atlas (Eickhoff et al., 2007) if possible, otherwise the Harvard-Oxford Subcortical Structural Atlas was used to assign labels to structures (Desikan et al., 2006).

3 Results

3.1 Behavioral Data

Figure 3A displays the percentage of correct responses for echo detection (regardless of direction). All participants successfully judged stimuli with echo as echo sounds, as well as those without echos as control sounds (overall mean: 96.8% ± 5.5% correct responses). Thus, participants were able to discriminate echo from control stimuli. Binomial tests indicated all participants' responses to be significantly above the 50% chance level, regardless of whether echoes were present or absent (all $p < 0.001$).

Please insert Figure 3 here

When participants discriminated path directions in trials which contained echoes, performance was lower than for simple detection of echoes as illustrated in Figure 3B. On average, directions were judged correctly in 36.8 ± 14.6% of all trials, with comparable mean performance for blind experts (40.1%) and blind novices (39.2%) but lower performance for the sighted novices (34.2%). Binomial tests showed significant above-chance performance in one blind expert (BE2: 41.1%, $p=0.048$) and a trend in the other (BE3: 40.0%, $p = 0.079$). When we excluded the first run of each expert, BE3's performance was also significantly better than chance (BE3: 43.7%, $p = 0.024$) indicating a possible effect of training or familiarization. Such an improvement was not present in one of the novices. Surprisingly,

one of the blind novices also performed significantly better than chance (BN3: 50.0%, < 0.001). All other participants were not different from chance level (BN1: 32.1%, p = 0.616; BN2: 35.7%, p = 0.318; SN1: 30.8%, p = 0.711; SN2: 39.3%, p = 0.103; SN3: 32.7%, p = 0.562).

3.2 Functional Imaging Data

3.2.1. Sound vs. Silence

We first tested whether the processing of sound stimuli depended on the person who produced the click-sounds. The sound-source contrasts which compared between the two different sound sources for each participant (own vs. foreign clicks for BE, sound source 1 vs. 2 for BN and SN) did not show any differential activation between the two sources. The respective trials were therefore pooled for further analyses and all reported activations are based on both sound sources.

Please insert Figure 4 here

Activations resulting from both types of echolocation stimuli (clicks with echos present and clicks with echos removed) compared to silent baseline trials (sounds vs. baseline contrast) as assessed using RFX GLM across all 9 participants are shown in Figure 4. It is evident that the global GLM analysis based on all participants revealed activation in right and left primary auditory cortices (for more details see supplementary Table S1). A breakdown for each group and participant separately is shown in Figure 5. Consistent with the global

GLM result, for this contrast we found bilateral activations in primary auditory cortex in all nine participants.

Please insert Figure 5

3.2.2. Echo vs. Control

In order to determine activations associated specifically with processing of path direction, we examined the echo vs. no-echo contrast, which compared BOLD activity during listening to echolocation stimuli with clicks and echoes to BOLD activity during listening to control stimuli where echoes were absent. Please note that even though participants were not very accurate judging path direction (compare Figure 3B), they were nearly perfect judging when an echo had been present or not (compare Figure 3A). Importantly, the response whether an echo was present or not was always tied to a direction judgment ("echo left", "echo straight ahead", "echo right"). Thus, participants engaged in path direction judgments in echo conditions; in contrast to the control condition where no-echo responses were not tied to a direction judgment ("no echo"). In fact, upon questioning after scanning participants said that they had tried to determine the direction of the path when they had listened to what they felt were echo-stimuli, but that they had found the task difficult. Global GLM RFX analysis showed activation in all participants in right Premotor Cortex (PMC, BA6), right IFC (BA44) and right PPC (i.e. SPL and IPL) (Figure 6). Just as for the contrast sound vs. silence, the contrast echo vs. no-echo also revealed bilateral activations in auditory cortices. However, for the

contrast echo vs. no-echo these activations are more superior/posterior, and also comprise the planum temporale (for more details see supplementary Table S2). Since individual participant analyses revealed that activations were more consistent within than between groups, we below present results separately for each group.

Please insert Figure 6 here

Figure 7 displays BOLD activations for the echo vs. no-echo contrast for each participant according to the experimental groups. Detailed cluster-level results of each participant are shown in Table 3. In the blind expert echolocators, the most prominent activation was found in the SPL. All three experts showed right-hemispheric SPL activity, BE1 and BE2 additionally activated the left SPL. All three experts also showed activation in right PMC/IFC. BE1 and BE3 displayed activation in right primary visual cortex (BA 17/18), and BE1 and BE2 additional bilateral IPL activations. We observed a similar activation pattern in the blind novice group. BN1 and BN2 showed activation in right V1. All three blind novice participants showed activation in right SPL, comparable to the blind experts. Parietal activations in the BN group extended further into the IPL/IPS as compared to the BE group. Furthermore, we observed right ventral PMC/IFC activations in all blind novices. The sighted novice participants also showed activation in right ventral PMC/IFC. In contrast to the blind participants, even though they did show activations in right SPL, their parietal activation was more bilateral and as a whole located more inferior extending into IPL and adjacent aIPS.

Additionally, activation of the left ventral IFC (BA 44 and 45 / Broca's area) was found in all sighted participants, which was absent in the blind expert and blind novice groups.

Please insert Figure 7

Please insert Table 3

In order to better qualify which activations were consistent within the groups, we overlaid z-statistic maps of all three participants in each group, and identified all clusters that were above threshold. Data used for participant's individual maps are essentially those on which Figure 5 is based, with the exception that instead of using a cluster probability threshold of $p<.05$, we adopted a minimum cluster size threshold of 100 contiguous voxels for individual participants' maps (compare also section 2.4.2. "Statistical analysis of MRI data").

The overlapping clusters in each experimental group are reported in Table 4, sorted by the number of overlapping voxels. In both blind expert and blind novice participants, the only brain areas where activation overlapped across all three participants were right IFC/PMC and right SPL. Most notably, activation also overlapped in the same area in the sighted group. Furthermore, the sighted group also showed activation overlap in right IFC, showing the largest cluster there and in the IPL and IPS. The left-hemispheric IFC activation and additional frontal activations in middle frontal gyrus which were unique to the sighted novice group spatially overlapped in all three SN participants.

Please insert Table 4

In sum, the analysis investigating groups separately highlights the involvement of right IFC/PMC and right SPL for BE, BN and SN. For BE and BN it also highlights involvement of right V1 (four out of six BE and BN participants), and for SN participants the involvement of a more bilateral SPL/IPL network, left IFC/PMC and additional frontal areas. Overall, this pattern of results is consistent with results from the global GLM RFX analysis for this contrast, but pinpoints areas of activation in parietal cortex and PMC more precisely.

4 Discussion

We investigated the neural correlates of blind human echolocation experts as well as blind and sighted novices in a spatial path direction detection task based on click-echoes recorded in a naturalistic setting. Participants heard click-echo stimuli from one of two expert echolocators and had to determine the direction in which a path continued (left, straight ahead, right). On the behavioral level we found that all three groups were very good at detecting echoes, but only the blind experts and one of the blind novices were better than chance at deciding in which direction the path went. In regard to brain activity as measured with fMRI we found that all participants showed higher activation in the right IFC/PMC (BA 6, 44 and 45) when listening to echoes as compared to control sounds without echoes. In addition, there was an increase of activity in the right SPL in each participant. While in the blind experts and blind novices this activation was

primarily located in SPL, in sighted participants, this activation widely spread into the IPS and IPL of both hemispheres. Moreover, additional activations in the left IFC (BA 44 and 45) and superior and middle frontal areas were found only in sighted participants.

4.1. Behavioral Performance

All participants, blind and sighted alike, were able to decide between echo and control sounds with very high accuracy. This is in line with previous studies showing that sighted people can easily learn to dissociate between click sounds with and without echo (e.g., Thaler et al., 2011). It is important to note that blind and sighted novices received training in the echo detection and direction detection task before participating in the fMRI experiment, while the blind expert echolocators received no such training. The higher performance of the BE group without much familiarization with the sounds is therefore indicative for their experienced use of click-echo sounds. However, one of the blind experts (BE2) showed comparably low performance in the echo detection task, but only when classifying control sounds without echoes (Figure 3A). To further investigate this finding, we looked at his performance across scanning sessions and found that he responded at chance for control sounds in the very first run and then consistently improved in performance up to above 90% in the last run. The discrepancy between echo and control sounds for BE2 might be due to the artificial nature of the control stimuli. Therefore, even blind echolocation experts may need training or familiarization with unfamiliar sounds before reaching optimal discrimination performance. However, none of the nine subjects showed any trend in performance across scanning sessions when discriminating path directions,

indicating that a possible familiarization effect not necessarily influences further spatial processing of auditory stimuli.

While participants were very good at dissociating echo-sounds from control sounds, the task of detecting path directions from echo-stimuli proved to be hard. As expected, the blind echolocation experts achieved above-chance classification performance in the MRI experiment; however, also one blind novice performed better than chance. In general, direction detection accuracy was surprisingly low in the blind experts, although they were able to tell path direction with a high success rate, and generally found the task easy when they had walked through the corridor setup while recording the stimuli, and whilst screening stimuli via headphones (compare section 2.2.2. "Stimulus processing and selection"). The low performance in the direction detection task during scanning was possibly caused by the echo sounds overlaid with additional sound information from the environment due to recordings in real-world settings, or the unfamiliar MR environment which might have distracted from the task.

Nonetheless, the marked difference in judgments between echo and no-echo conditions clearly shows that all participants engaged in the task during scanning. Specifically, the response wether an echo was present or not was always tied to a direction judgment ("echo left", "echo straight ahead", "echo right"). Thus, even though participants were not accurate at judging path direction, they nevertheless engaged in path direction judgments in echo conditions. Upon questioning after scanning participants also said that they had tried to determine the direction of the path when they had listened to what they felt were echo-stimuli. In contrast, since no-echo responses were not tied to a

direction judgment ("no echo"), participants did not engage in direction judgments in control conditions. Thus, the high accuracy in "echo left", "echo right" and "echo straight ahead" vs. "no echo" judgments behaviorally validates our comparison of brain activity between echo and no-echo conditions, even though accuracy of "echo left", "echo right" and "echo straight ahead" answers when evaluated by direction was low.

4.2. Interpretation of Activations in Parietal Cortex

We found that all nine subjects showed an increase in activation in right SPL while they performed the path direction detection task as compared to the control condition. Similar activations have been reported in a study where blind and blindfolded sighted subjects navigated a 2D virtual pathway using an electrotactile Tongue Display Unit suggesting that the SPL is part of a navigation and/or route-recognition network (Kupers et al., 2010). Importantly, in that study SPL was not only active during tactile route navigation but also when sighted control subjects executed the same task with full vision suggesting that parietal brain areas involved in navigation using vision can be recruited by other modalities in the blind. Our findings support and extend the results by Kupers et al. (2010) showing that the SPL is also involved in spatial navigation based on echo sounds in blind and sighted people highlighting its function in multisensory spatial navigation.

Within the PPC, the blind experts and blind novices mainly activated the bilateral SPL (overlapping only in the right hemisphere) while activation in the sighted novices was more widespread and centered in the bilateral IPS and IPL extending into the SPL. In the

well-known visual pathway model by Goodale and Milner (1992), the PPC is seen as a structure of the dorsal visual pathway which is involved in visual spatial localization for the guidance of action. These functions, however, are explicitely assigned to the SPL leaving the role of the IPL widely unclear. The authors speculate that the IPL may subserve perceptual awareness by transforming information from both the dorsal and the ventral pathway (Milner & Goodale, 1995). A later model by Rizzolatti & Matelli (2003) extended the dorsal pathway and proposed two sub-streams, a dorso-dorsal (d-d) stream projecting to the SPL and a ventro-dorsal (v-d) stream projecting to the IPL including the anterior IPS, respectively. The d-d stream is supposed to have the basic characteristics of the dorsal pathway of Goodale and Milner (1992), i.e. a system for online action control, and causes Optic Ataxia after damage. The v-d stream is suggested to play a crucial role in both perception and action and engages in high-level spatial and motor functions. In contrast to the SPL those functions seem to be equally distributed across both hemispheres, the IPL shows a clear hemispheric difference: the right IPL is involved in space perception and action and the left IPL engages in action organization, necessary for object manipulation, grasping and tool use, and even in cognitive tasks, such as action recognition from preceding motor knowledge. Thus, lesions to the right v-d stream lead to Neglect while lesions to the left v-d stream cause Limb Apraxia. Our results show that the blind participants mainly activated the d-d stream bilaterally while the sighted participants relied also on the bilateral v-d stream. In the context of this model, this may imply different task strategies depending on vision. Blind subjects, in particular blind expert echolocators, may have accessed on-line mechanisms of action control to ‘automatically’

assign directional meaning to the echos, without having to consciously process the click-echos. Sighted participants, on the other hand, may have applied more conscious, high-level spatial processes as they were untrained and thus unable to automatically decode complex echo information, such as spatial directions. The observed activation in the IPL is suggestive of the idea that sighted participants engaged a more cognitive route, possibly by retrieving memories of sounds presented during training and their associated directions and comparing them to the current stimulus. In support of this asssumption, the right IPL has been previously found to mediate auditory working memory for monitoring and updating sound locations independent of motor acts (Claude et al., 2008).

As mentioned in the introduction, not only visual processing is split along dorsal and ventral routes, but parietal coretx has also been implicated within a dual-stream model of auditory processing. According to this model, there is a dorsal 'where' and a ventral 'what' stream within the auditory system, with stronger focus on spatial processing for action/sensorimotor control along the dorsal pathway which has its nodal point in the IPL, with a right-hemispheric preference, and further projections to the IFC (Kaas & Hackett, 1999; Rauschecker, 2011; Rauschecker & Tian, 2000). Since we did not include visual or regular 'source' hearing conditions in our study, we are unable to determine to what degree parietal areas we identified for processing of path direction with echolocation map onto visual or auditory dorsal pathways. Future research is needed to address this issue.

4.3. Interpretation of Activations in Prefrontal Cortex

Sighted participants showed additional activations in superior frontal and middle frontal brain areas which were absent in both blind groups. Together with the activations we found in the left IPL and IPS in the sighted, these areas form a parietofrontal circuit processing conceptual knowledge and the pragmatics of action, also known as 'acting with' system (Johnson & Grafton, 2002). This is consistent with our suggestion that sighted people relied stronger on high-level spatial functions and recognition of spatial memories. Similar findings have been revealed in a study in which early blind and sighted people learned to determine distance based on an ultrasound-based sensory substitution device, and where sighted people showed stronger frontal activations (Chan et al., 2012). Moreover, Kupers et al. (2010) demonstrated in the above mentioned electrotactile navigation study more activations in frontal areas in sighted participants not seen in the blind and argued for the use of cognitive strategies, such as decision making, in the sighted. Since the parietofrontal circuit has also been associated with spatial working memory (Silk et al., 2010), this may underline the possibility that our sighted subjects reactivated and maintained memory representations acquired during the training. However, the lack of hippocampal and parahippocampal activations in our study would make the involvement of spatial memory unlikely (see also next paragraph). In sum, our results suggest that sighted participants used a different strategy to resolve the direction detection task based on click-echoes compared to the blind echolocation experts and blind novices.

4.4. Absence of Activation in Hippocampus or Parahippocampus

The hippocampus has been implicated in spatial memory, for example relevant for navigation and route finding (Hartley et al., 2014), and the parahippocampus has been linked to related aspects of cognition, such as scene and route recognition (Aminoff et al., 2013). Kupers et al. (2010) found that a navigation and route-recognition task completed with an eletrotactile sensory substitution device led to an increase in activity not only in SPL, but also in parahippocampal cortex in blind people. They also found that this activity overlapped with activity observed in sighted people performing the task visually. They suggested that the parahippocampal activation can be understood considering that participants were presented with two routes on each trial and had to decide which route had been presented previously. Thus, the task had a scene recognition component, likely mediated through parahippocampus. In our current study, we did not find an increase in activation in parahippocampus (or hippocampus) during path direction detection as compared to control conditions. This could be understood considering that our task did not contain a scene or route recognition component like the task used by Kupers et al. (2010). Specifically, our task required online processing of spatial information mediated by echo information, but there was no requirement to match any path or route to a path or route traversed previously. Another possible explanation for the lack of increase in activation in parahippocampus (or hippocampus) in our study as compared to Kupers et al (2010) might also be that subjects in Kupers et al.'s study performed at much higher levels than our subjects and thus were perceiving a spatial scene more successfully on average.

4.5. Activations in Primary Auditory Cortex and Planum Temporale

As expected, the contrast *all sound vs. baseline* revealed an increase in activation in primary auditory cortex. Unexpectedly, however, we also observed an increase in activity in primary auditory cortex/planum temporale for the contrast echo vs. no-echo (compare Figure 6 and supplementary Table S2). The activity in primary auditory cortex for this contrast was unexpected because we had constructed stimuli such as to minimize differences in acoustic properties of stimuli between the two conditions, i.e. acoustic properties known to drive A1, such as frequency or sound pressure level. Furthermore, previous research using stimuli constructed in a similar way did not find an increase in activity in primary auditory cortex for the comparison echo vs. no-echo (Milne et al., 2014b; Thaler et al., 2011). Nevertheless, in our study the absence of echoes in the control stimuli led to a slight drop in sound pressure level in control stimuli as compared to echo stimuli (compare Table 2), and it is possible that this is responsible for the activity difference we observed in A1. The echo-related activity in planum temporale can be understood considering that the planum temporale is involved in binaural perception of sound location and movement (Arnott et al. 2004; Deouell et al. 2007; Griffiths & Warren, 2002; Krumbholz et al., 2005). Thus, binaural spatial properties in our echo stimuli are likely to have driven the relative increase in activity in the planum temporale for the echo vs. no-echo contrast. This is consistent with previous findings showing that echo information can drive activity in the planum temporale (Thaler et al., 2014).

4.6. Occipital vs. Parietal Activations - Comparison to previous Echolocation Studies

Past research comparing activations between conditions that required processing of an echo and echo-less control condition have suggested that in particular occipital brain areas are involved in echo processing in blind echo experts (Arnott et al., 2013; Thaler et al., 2011, 2014). The current study suggests that two out of three BE and two out of three BN showed increased activation in right BA17/18 for processing echo as compared to control sounds. Nevertheless, the difference in activation between echo and control sounds is mainly evident in parietal, not occipital areas. The main difference between the current and previous studies investigating spatial echo processing is that previous studies focused on how spatial locations per se are represented in the blind brain, with a focus on the perceptual appraisal of the stimulus (Arnott et al., 2013; Thaler at al., 2011; 2014), whereas the current study required people to engage in spatial processing as relevant for an action, i.e. locomotion, associated with activation of the SPL.

5 Acknowledgments

This project was supported by the IRTG 1901 „The Brain in Action“ and the DFG grant Fi1567/3-1.

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Figure 1: Schematic representation of the stimulus recording setup for "left", "straight ahead" and "right" corridor conditions. Dark grey bars denote building walls, light grey bars indicaty the felt start and end positions of the walking paths and black bars the positions of mobile poster boards used to create a corridor. Blind experts (BE) slowly walked from the start position to the end position while producing click sounds.

Figure 2: Exemplary overview of a single run during the experiment. Each participant performed 6 runs. Each run was split into 9 clusters separated by silent baseline trials. Each cluster contained combinations of echo vs. no echo trials and source (i.e. the expert with whom the recording had been made). Path directions and indoor/outdoor environments were presented in pseudo-random order within each run. Note that the displayed example only shows a subset of all possible stimulus conditions.

Figure 3: *A*: Percentage of correct responses for stimuli with echos (black bars) and without echos (grey bars) in terms of echo detection regardless of direction. The dotted line illustrates chance level of 50%. *B*: Percentage of correct responses when considering participants' judgments of direction from those stimuli which contained echos. The dotted line indicates chance level of 33%. Stars mark results which were significantly above chance level, while (*) marks a trend of $p = 0.079$. Error bars show ± 1 standard error in both plots.

Figure 4: Global RFX GLM activations for the contrast sounds vs. silent baseline, overlaid on the MNI-Colin27 brain template (data shown in neurological convention, i.e. Right-is-Right). Shown activations are significant using a cluster-level threshold of $z > 3.7$ and a cluster probability threshold of $p < 0.01$.

Figure 5: Activations for all three participants in each group for the contrast sounds vs. silent baseline, overlaid on the MNI-Colin27 brain template (data shown in neurological convention, i.e. Right-is-Right). Shown activations are significant using a cluster-level threshold of $z > 2.3$ (except for participant BN2 where $z > 2.3$, but no cluster-level correction was applied due to generally low activations) and a cluster probability threshold of $p < 0.05$

Figure 6: Global RFX GLM activations for the contrast echo vs. no echo, overlaid on the MNI-Colin27 brain template (data shown in neurological convention, i.e. Right-is-Right). Shown activations are significant using a cluster-level threshold of $z > 3.7$ and a cluster probability threshold of $p < 0.01$.

Figure 7: Activations for all three participants in each group for the contrast echo vs. no-echo overlaid on the MNI-Colin27 brain template (data shown in neurological convention, i.e. Right-is-Right). Displayed activations are significant using a cluster-level threshold of $z > 2.3$ and cluster probability threshold of $p < 0.05$.

Table 1 - Sample description of echolocation experts (BE), blind novices (BN) and sighted novices (SN). The handedness score was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971; right-handed: maximum score +100, left-handed: maximum score -100).

Subject	Gender	Age	EHI	Education	Blindness since	Cause of blindness	Degree of blindness
BE1	Male	41	64	A-level	12 months both eyes	enucleation due to retinoblastoma	total, no light detection
BE2	Male	42	91	A-level	18 months first eye, 30 months second eye	enucleation due to retinoblastoma	total, no light detection
BE3	Male	16	91	Highschool	36 months	congenital amaurosis	total, no light detection
BN1	Male	33	82	A-level	birth	genetic defect	detection of bright light
BN2	Male	37	100	A-level	birth	congenital amaurosis	detection of bright light
BN3	Male	22	82	A-level	both eyes first month	enucleation due to retinoblastoma	total, no light detection
SN1	Male	36	92	A-level	-	-	-
SN2	Male	38	100	A-level	-	-	-
SN3	Male	20	100	A-level	-	-	-

Table 2 - Average acoustic energy of echolocation and control sounds broken down by participants (HM, WF, DJ) and condition (indoor vs. outdoor). Numbers in parentheses are standard deviations. *The comparably large difference in average sound level between echo and control conditions for 'HM – outdoors' (and comparably large SD) is due to variation in background sounds that we could not match perfectly across echo and control conditions for this participant. Note that for all other stimuli differences in sound intensity between echo and control conditions were below threshold for human listeners (Raab & Taub, 1969).

	Control	Echo	
	Average (dB RMS)	Average (dB RMS)	Clicking speed (Hz)
HM - indoor	-38.8 (0.2)	-38.7 (1.4)	2.4
HM - outdoor	-35.1 (4.8)*	-31.8 (4.8)*	2.2
WF - indoor	-36.8 (0.1)	-35.6 (0.4)	3
WF - outdoor	-35.4 (1.5)	-34.4 (1.8)	2.4
DJ - indoor	-40.5 (0.2)	-40.2 (1.3)	3.8
DJ - outdoor	-37.2 (1.1)	-36.4 (2.8)	3.5

Table 3 - Activations found in all individual subjects for the echo>no echo contrast. Results are cluster-level corrected at z > 2.3 with a cluster probability threshold of p < 0.05. Z-values reference peak activations within each cluster, corresponding peak coordinates are reported in MNI space (mm). * - even though peak voxels are located in one hemisphere, clusters also extend into the other hemisphere.

Subject	Voxels	p	z_{max}	X	Y	Z	L/R	Area(s)
BE1	6259	7.09e-26	3.30	2	-76	40	R*	Superior Parietal Lobule Visual Cortex V1, BA17; V2, BA18 Inferior Parietal Lobule
	2578	1.31e-13	3.52	54	18	26	R	Inferior Frontal Gyrus Premotor Cortex
	1860	1.24e-10	3.32	50	-72	14	R	Inferior Parietal Lobule Visual Cortex V4
	1607	1.69e-09	3.29	-32	24	-4	L	Premotor Cortex Inferior Frontal Gyrus Orbito-Frontal Cortex
	558	0.0007	3.51	0	8	50	R	Superior Frontal Cortex Premotor Cortex
	529	0.00109	2.88	32	-56	44	R	Superior Parietal Lobule Anterior Intra-Parietal Sulcus hIP1, hIP2, hIP3
	517	0.00131	3.36	38	18	2	R	Inferior Frontal Gyrus Insular Cortex
	501	0.00168	2.84	4	-76	-18	R	Cerebellum
	418	0.00637	2.89	-30	-68	-22	L	Cerebellum
	359	0.0173	2.91	-52	-24	10	L	Primary Auditory Cortex Insular Cortex
BE2	1838	1.12e-10	3.33	14	-72	54	R*	Superior Parietal Lobule Inferior Parietal Lobule
	1183	1.5e-07	3.06	60	-30	28	R	Inferior Parietal Lobule Superior Parietal Lobule
	770	2.86e-05	3.41	-56	-16	2	L	Primary Auditory Cortex Inferior Parietal Lobule
	514	0.0012	3.24	54	-2	48	R	Premotor Cortex
	464	0.00267	3.26	24	-6	62	R	Premotor Cortex
	343	0.0208	3.15	-36	-2	56	L	Premotor Cortex
	300	0.0451	3.08	-58	-64	8	L	Lateral Occipital Cortex
BE3	1664	8.63e-08	3.21	32	-78	18	R	Superior Parietal Lobule Visual Cortex V2, BA18, V1 BA17
	761	0.000495	3.22	56	20	30	R	Inferior Frontal Gyrus
	485	0.0131	3.44	54	-42	14	R	Primary Auditory Cortex
	387	0.0475	3.46	54	8	48	R	Inferior Frontal Gyrus
BN1	7063	1.30e-24	3.55	10	-96	18	R*	Visual Cortex V1 BA17, V2 BA18, V4 Superior Parietal Lobule

								Inferior Parietal Lobule Anterior Intra-Parietal Sulcus hIP1
	2378	3.95e-11	3.60	58	18	30	R	Inferior Frontal Gyrus Premotor Cortex
	1909	2.08e-09	3.22	-34	-64	54	L	Superior Parietal Lobule Inferior Parietal Lobule
	561	0.00259	3.41	68	-34	14	R	Inferior Parietal Lobule
	429	0.0159	2.97	-34	-72	-16	L	Visual Cortex V4
BN2	941	0.000237	3.31	46	-48	60	R	Inferior Parietal Lobule Anterior Intra-Parietal Sulcus hIP1, hIP3 Superior Parietal Lobule
	559	0.0111	3.32	52	6	42	R	Premotor Cortex
	463	0.0329	3.09	16	-80	16	R	Visual Cortex V1 BA17, V2 BA18
	449	0.0387	2.99	14	-74	54	R	Superior Parietal Lobule
BN3	8370	5.15e-29	3.87	30	-46	44	R	Superior Parietal Lobule Inferior Parietal Lobule Anterior Intra-Parietal Sulcus hIP3 Premotor Cortex Inferior Frontal Gyrus
	1312	1.8e-09	3.54	-36	-46	38	L	Superior Parietal Lobule Anterior Intra-Parietal Sulcus hIP1
	433	0.0107	3.29	36	-86	16	R	Visual Cortex BA19 Inferior Parietal Lobule
SN1	2291	1.15e-13	3.33	52	12	44	R	Premotor Cortex Inferior Frontal Gyrus Middle Frontal Gyrus
	1485	7.9e-10	3.40	-42	54	-6	L	Frontal Pole
	895	1.5e-06	3.23	-44	6	24	L	Inferior Frontal Gyrus
	818	4.48e-06	3.14	38	-50	48	R	Superior Parietal Lobule Anterior Intra-Parietal Sulcus hIP3 Inferior Parietal Lobule
	817	4.55e-06	3.34	-36	-58	44	L	Superior Parietal Lobule Anterior Intra-Parietal Sulcus hIP1,3
	668	4.2e-05	3.22	16	-70	58	R	Superior Parietal Lobule
	644	6.1e-05	3.34	-6	-82	-24	L	Cerebellum
	583	0.000161	3.33	40	58	-2	R	Frontal Pole
	533	0.000365	3.41	0	34	44	R	Superior Frontal Gyrus
	394	0.00413	3.03	64	-38	10	R	Inferior Parietal Lobule Superior Temporal Gyrus
	304	0.023	3.30	40	28	-4	R	Orbito-Frontal Cortex
	286	0.033	2.91	-58	-28	12	L	Planum Temporale

SN2	5008	5.42e-19	3.65	44	34	30	R	Inferior Frontal Gyrus Premotor Cortex
	2198	2.38e-10	3.56	24	-76	54	R	Superior Parietal Lobule Anterior Intra-Parietal Sulcus hIP1,3 Inferior Parietal Lobule
	1875	3.69e-09	3.42	-34	-44	40	L	Anterior Intra-Parietal Sulcus hIP1, hIP2 Primary Somatosensory Cortex Inferior Parietal Lobule
	1382	3.35e-07	3.31	-36	40	30	L	Inferior Frontal Gyrus
	671	0.000699	3.48	-48	40	-14	L	Frontal Pole
	589	0.00195	3.37	-56	-14	6	L	Primary Auditory Cortex
	553	0.00311	2.98	32	-44	46	R	Superior Parietal Lobule Anterior Intra-Parietal Sulcus hIP3 Primary Somatosensory Cortex
	471	0.00934	3.41	68	-20	0	R	Superior Temporal Gyrus
	467	0.00986	3.28	30	0	56	R	Middle Frontal Gyrus
	447	0.013	3.18	-12	-70	64	L	Superior Parietal Lobule
SN3	3306	3.7e-14	3.68	56	6	42	R	Premotor Cortex
	2531	1.31e-11	3.64	34	-40	40	R	Anterior intra-parietal sulcus hIP2,3 Inferior Parietal Lobule Superior Parietal Lobule
	1448	1.52e-07	3.53	-30	-52	42	L	Anterior intra-parietal sulcus hIP2,3 Inferior Parietal Lobule Primary Somatosensory Cortex
	1118	4.08e-06	3.79	-44	0	36	L	Premotor Cortex Inferior Frontal Gyrus
	937	2.84e-06	3.37	64	8	8	R	Inferior Frontal Gyrus
	783	0.000164	3.62	8	20	36	R	Premotor Cortex
	514	0.00474	3.43	68	-28	18	R	Primary Auditory Cortex

Table 4 - Areas of overlapping activations within each group, reported as contiguous clusters of > 100 voxels. Coordinates are MNI coordinates in mm for the center of gravity (COG) of each cluster.

Group	Voxels	X	Y	Z	L/R	BA	Area(s)
BE	1448	51	5	47	R	44/6	Premotor Cortex / Inferior Frontal Cortex
	138	13	-78	52	R	7	Superior Parietal Lobule
	104	9	-83	45	R	7	Superior Parietal Lobule
BN	1272	15	-74	45	R	7	Superior Parietal Lobule
	972	36	-48	52	R	7/40	Superior Parietal Lobule / Anterior intra-parietal sulcus
	206	49	11	39	R	44/6	Inferior Frontal Cortex / Premotor Cortex
SN	4428	46	23	32	R	45	Inferior Frontal Cortex
	2063	-36	-43	45	L	40	Anterior Intra-Parietal Sulcus / Inferior Parietal Lobule
	1069	-45	8	30	L	44	Inferior Frontal Cortex
	1019	38	-42	47	R	40	Anterior Intra-Parietal Sulcus / Inferior Parietal Lobule
	1010	40	-52	51	R	40	Anterior Intra-Parietal Sulcus / Inferior Parietal Lobule
	360	11	-72	53	R	7	Superior Parietal Lobule
	349	31	9	61	R	9	Middle Frontal Gyrus
	270	34	28	1	R	11	Orbito-Frontal Gyrus
	108	66	-29	14	R	40	Inferior Parietal Lobule Superior Temporal Gyrus

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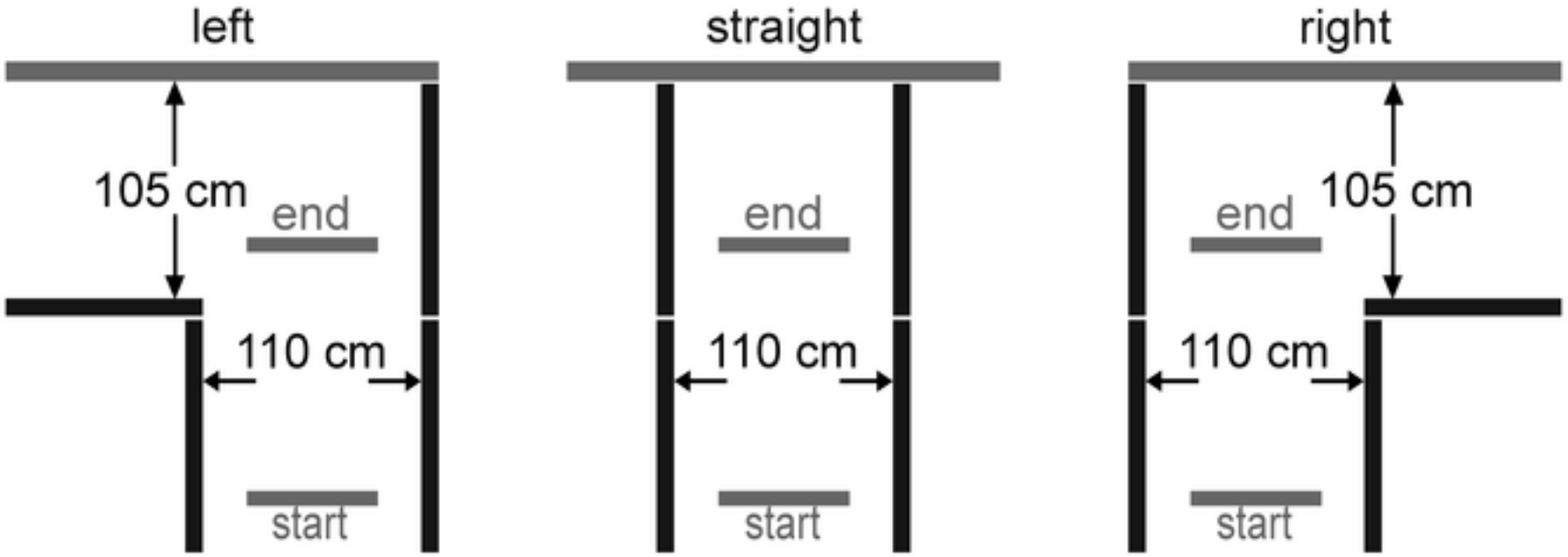

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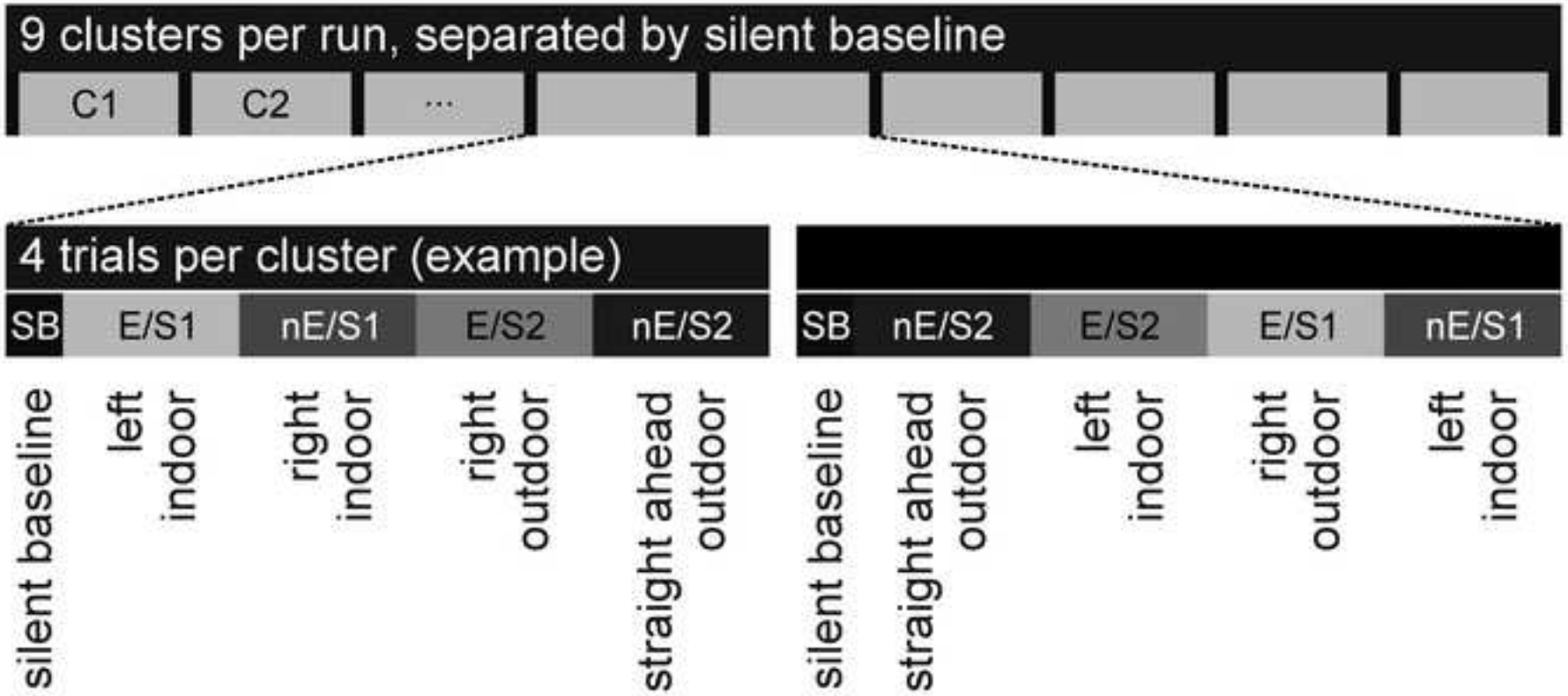

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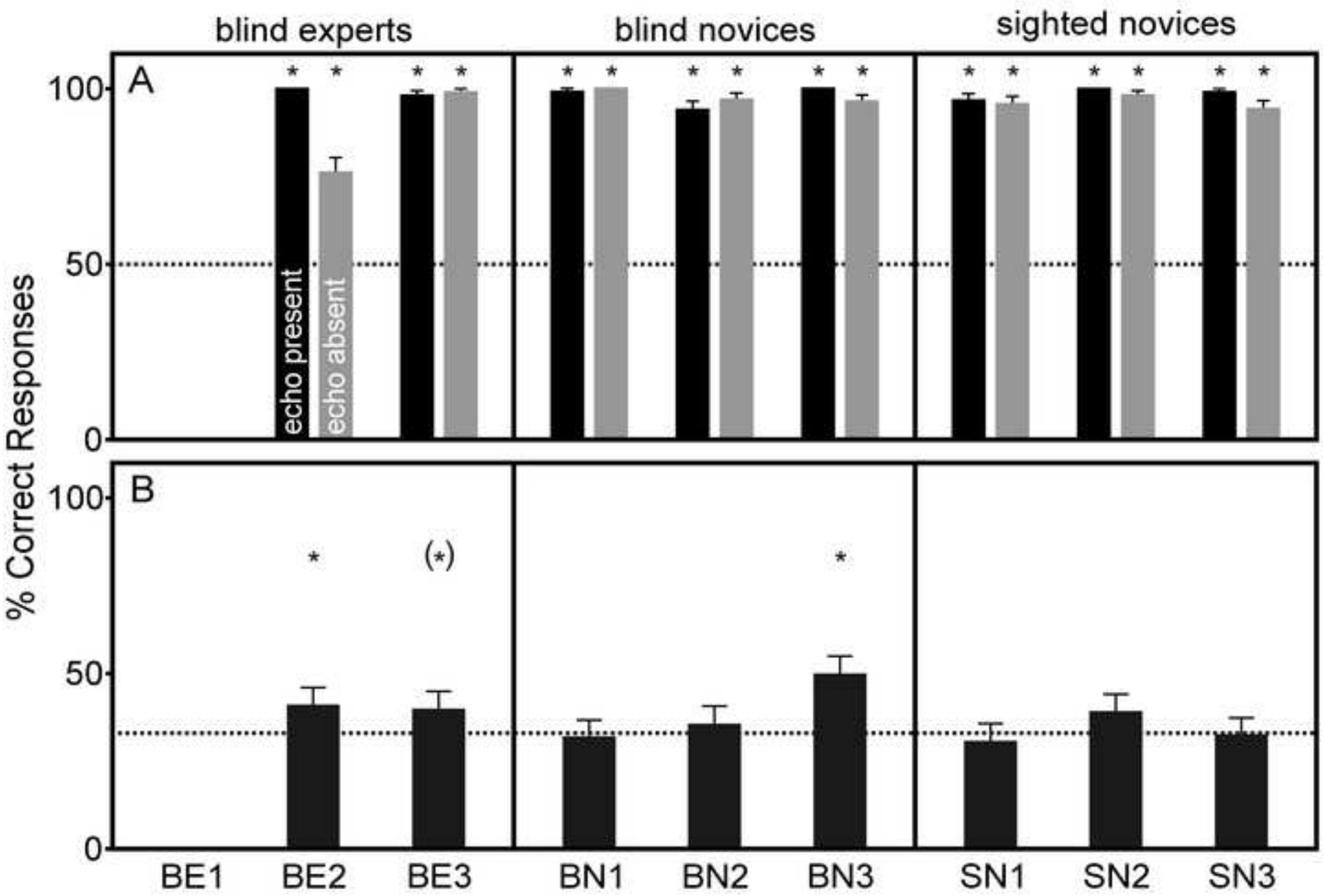

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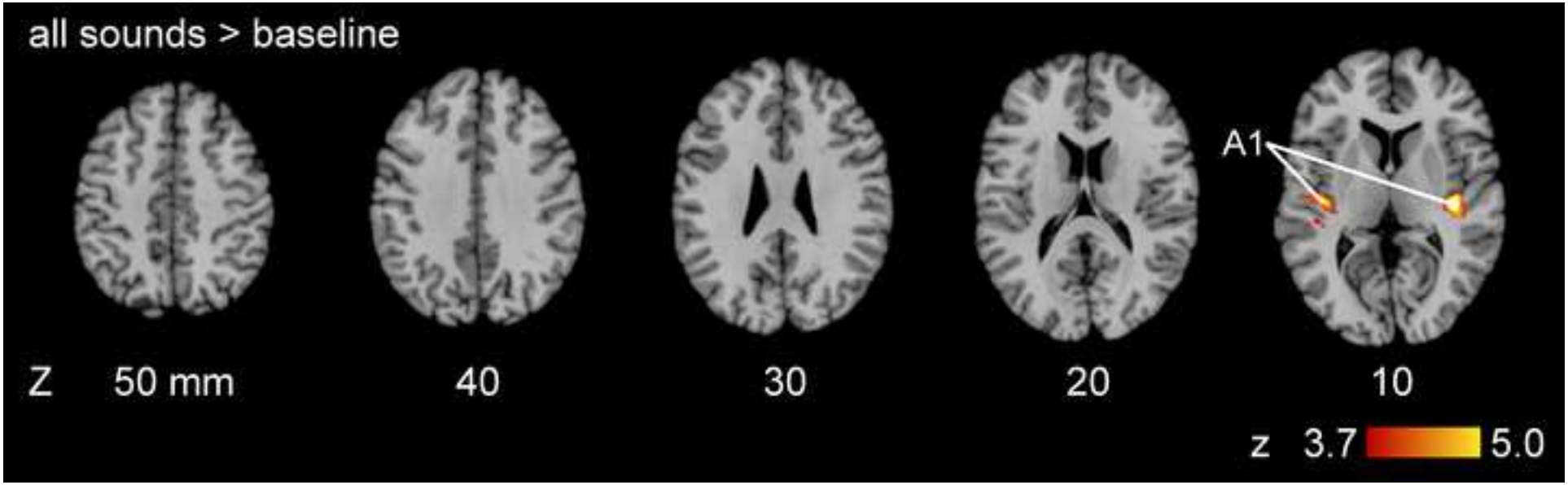

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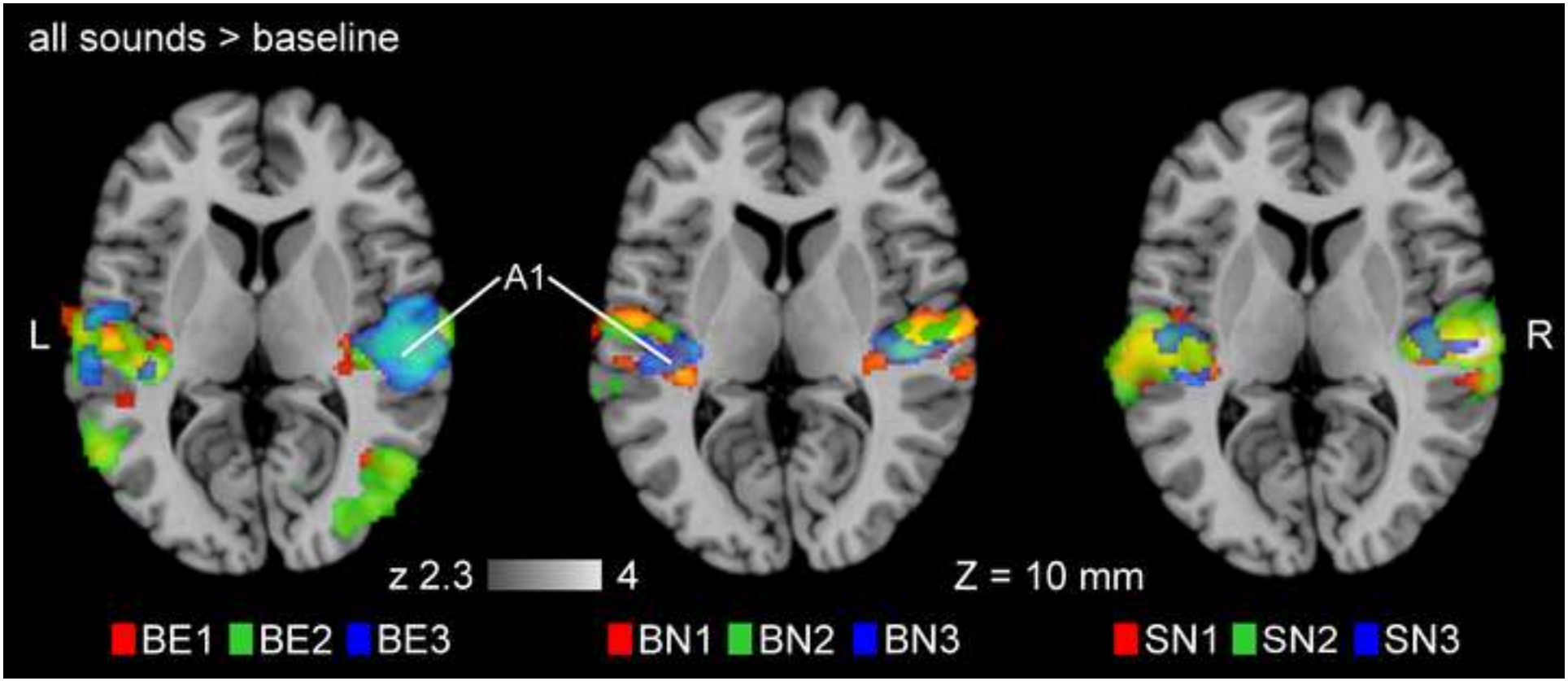

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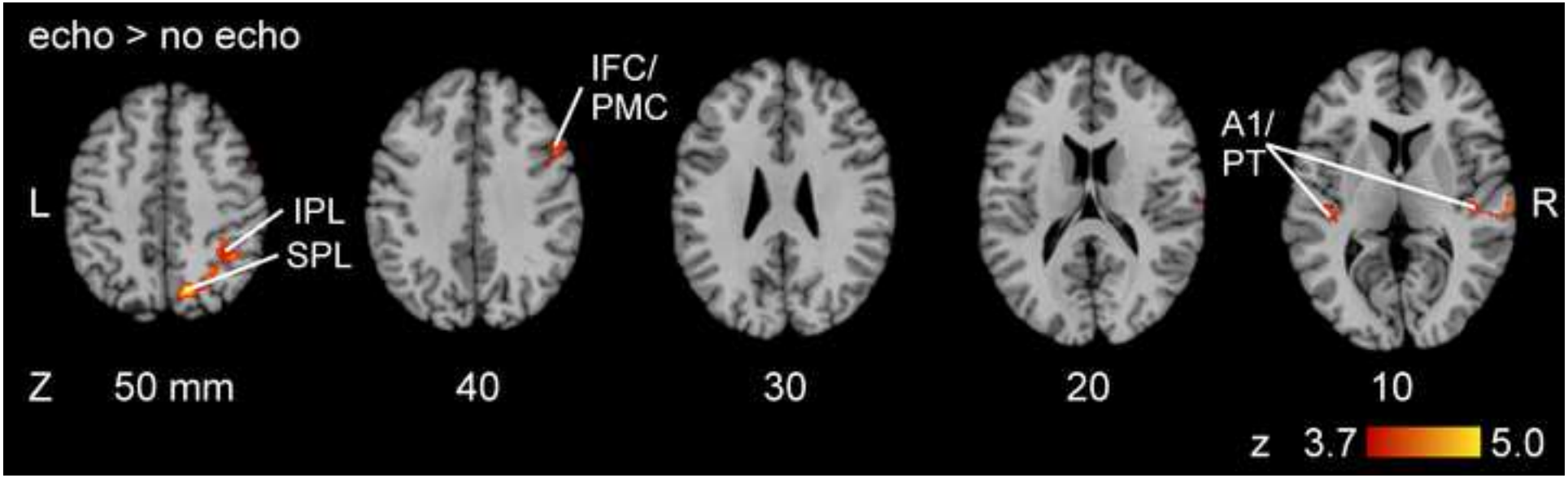

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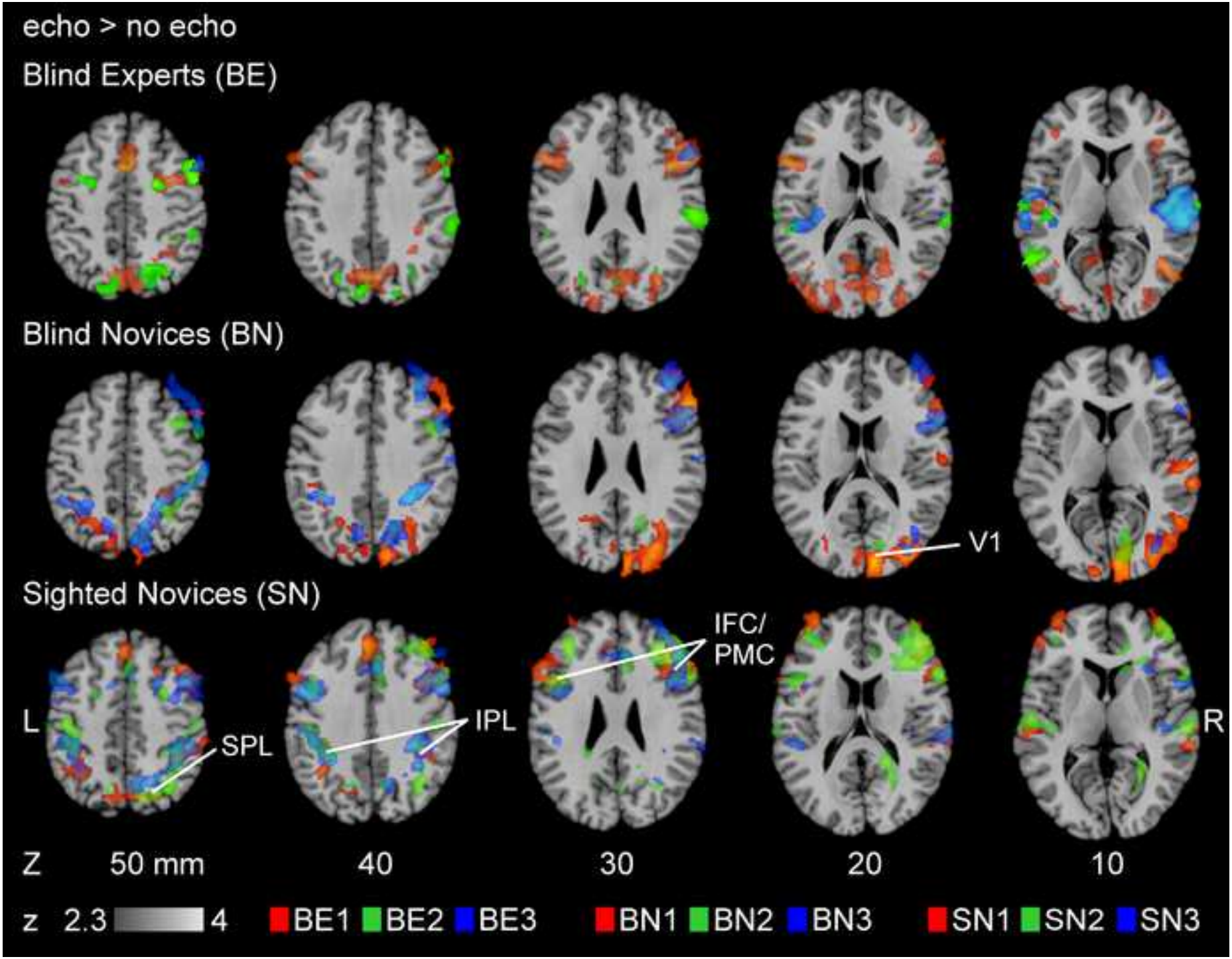

Supplement

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