

Working memory training integrates visual cortex into beta-band networks in congenitally blind individuals



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ABSTRACT

Congenitally blind individuals have been shown to activate the visual cortex during non-visual tasks. The neuronal mechanisms of such cross-modal activation are not fully understood. Here, we used an auditory working memory training paradigm in congenitally blind and in sighted adults. We hypothesized that the visual cortex gets integrated into auditory working memory networks, after these networks have been challenged by training. The spectral profile of functional networks was investigated which mediate cross-modal reorganization following visual deprivation. A training induced integration of visual cortex into task-related networks in congenitally blind individuals was expected to result in changes in long-range functional connectivity in the theta-, beta- and gamma band (imaginary coherency) between visual cortex and working memory networks. Magnetoencephalographic data were recorded in congenitally blind and sighted individuals during resting state as well as during a voice-based working memory task; the task was performed before and after working memory training with either auditory or tactile stimuli, or a control condition. Auditory working memory training strengthened theta-band (2.5–5 Hz) connectivity in the sighted and beta-band (17.5–22.5 Hz) connectivity in the blind. In sighted participants, theta-band connectivity increased between brain areas typically involved in auditory working memory (inferior frontal, superior temporal, insular cortex). In blind participants, beta-band networks largely emerged during the training, and connectivity increased between brain areas involved in auditory working memory and as predicted, the visual cortex. Our findings highlight long-range connectivity as a key mechanism of functional reorganization following congenital blindness, and provide new insights into the spectral characteristics of functional network connectivity.

1. Introduction

The ability to flexibly adapt to a steadily changing environment is a crucial prerequisite for human survival and has been related to the brain's capacity for structural rewiring and functional reorganization (Buonomano and Merzenich, 1998; Pascual-Leone et al., 2005; Röder, 2012). In the case of sensory deprivation, such as in congenital blindness, adaptation is required, as individuals have to cope with the lack of information from one of the sensory organs. Congenital blindness results in severe handicaps in everyday tasks, such as auditory spatial learning or sound localization (Voss et al., 2010), due to the lack of visual augmentation of the preserved senses. Nevertheless, in numerous non-visual tasks blind individuals show higher performance compared to

the sighted (Amedi et al., 2003; Collignon et al., 2009; Gougoux et al., 2005; Röder et al., 1996). Behavioral improvements have been attributed to intramodal changes, that is, changes within the intact sensory systems (Elbert et al., 2002; Röder et al., 1996) and to cross-modal changes, that is, an increased recruitment of the visual cortex for non-visual tasks (Collignon et al., 2009; Pascual-Leone et al., 2005; Pavani and Röder, 2012; Ricciardi and Pietrini, 2011). The functional relevance of cross-modal plasticity is still debated: TMS studies have demonstrated impaired non-visual processing in congenitally blind individuals when activity within the visual cortex was temporarily disturbed (Amedi et al., 2004, 2003; Collignon et al., 2009; Ptito et al., 2008; for review, see Pascual-Leone and Hamilton, 2001; Ricciardi and Pietrini, 2011). Other functional magnetic resonance imaging (fMRI) studies have shown distinct occipital regions to be activated depending on the task,

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Abbreviations	
CRR	correct rejection rate
Cs	cross-spectra
FDR	False discovery rate
FFA	fusiform face area
FG	fusiform gyrus
fMRI	functional magnetic resonance imaging
MT	medial temporal lobe, occipital-temporal-parietal junction (human correlate of macaque middle temporal visual area)
HR	hit rate
IFG	inferior frontal gyrus
HSWBS	Habituelle Subjektive Wohlbefindens Skala
IPC	inferior parietal cortex
IPG	inferior parietal gyrus
IPL	inferior parietal lobe
ITI	inter-trial interval
ITL	inferior temporal lobe
LFP	local field potential
MEG	magnetoencephalography
MFG	middle frontal gyrus
MNI	Montreal Neurological Institute
MTG	middle temporal gyrus
Pow	power
PSQ-20	Perceived Stress Questionnaire
ROI	regions of interest
SD	standard deviation
STG	right superior temporal gyrus
STS	anterior superior temporal sulcus
VLMT	Verbaler Lern-und Merkfähigkeitstest

suggesting a task-specific involvement of the visual cortex (Amedi et al., 2010, 2007; Collignon et al., 2013; Hölig et al., 2014; Pietrini et al., 2004; Röder and Neville, 2003; Watkins et al., 2013). Despite the reliable activation of visual cortex by non-visual tasks, it is yet controversial how visual cortex is integrated in auditory, somatosensory or cognitive processing in the congenitally blind (Bedny, 2017; Pascual-Leone and Hamilton, 2001; Renier et al., 2014).

The present study addressed the neuronal mechanisms underlying the recruitment of the visual cortex for non-visual tasks in congenitally blind participants. In the following, we discuss possible mechanisms for cross-modal reorganization. According to a current view, the connections between brain areas strongly determine their functional specification (Friederici and Singer, 2015; Hannagan et al., 2015). Local connectivity supposedly affects the function of a brain area (i.e., the computation that is performed) (Passingham et al., 2002). In contrast, long-range connections affect the networks a brain area communicates with (Passingham et al., 2002; Varela et al., 2001). Thus, in the blind, long-range connections might be relevant for re-routing of non-visual information to the visual cortex and altered functional connectivity might constitute an important mechanism of cross-modal reorganization. In the present study we, therefore, expected an integration of the deprived visual cortex into task-related networks, which should be reflected in an alteration of the dynamics of long-range functional connectivity. In line with this assumption, studies on changes in structural connectivity following congenital blindness report atrophy of the geniculocortical tracts, while cortico-cortical connections of the visual cortex are largely preserved, suggesting that information from non-visual areas reaches the visual cortex through cortico-cortical connections (Shimony et al., 2006). Although structural connectivity affects the functional specification of brain areas, direct conclusions about the networks involved in cognitive functions can only be drawn from functional connectivity measured during the performance of a specific task. Some evidence for altered task-related networks in congenitally blind individuals comes from fMRI research (Klinge et al., 2010; Liu et al., 2007; Püto et al., 2012; for review: Lazzouni and Lepore, 2014). In line with the assumption that information during non-visual tasks reaches the visual cortex through cortico-cortical connections, an fMRI study found increased effective connectivity between A1 and V1 in congenitally blind compared to sighted individuals during the performance of several auditory tasks (Klinge et al., 2010). These functional connectivity measures, however, might be affected by pre-existing differences between the blind and sighted groups that are unrelated to task-specific network activity.

Here, we used a working memory training approach that benefits from an intra-subject setting by investigating changes across pre-post training sessions. The intra-subject normalization isolates task-related functional connectivity from pre-existing differences between groups.

We used working memory training to experimentally induce changes in task-related networks in congenitally blind and sighted individuals to access the underlying neural mechanisms of cross-modal plasticity. If cross-modal plasticity alters the long-range connectivity of visual cortex, this should increase the capability to integrate visual cortex into functional networks of newly learned non-visual tasks. We analyzed changes in functional networks involved in auditory working memory processing resulting from the training intervention in the congenitally blind and compared those to changes in matched sighted participants. Working memory training provides a suitable approach to alter neuronal networks, as it has been shown to increase working memory capacity (for review: Jaeggi et al., 2008; Klingberg, 2010; von Bastian and Oberauer, 2013) and alter the interaction within neuronal networks (Aster et al., 2015; Langer et al., 2013). Working memory denotes the ability to temporarily maintain and manipulate information to make it accessible to current cognitive processes (Baddeley, 2012; Baddeley and Hitch, 1974; Cowan, 1995; D'Esposito and Postle, 2015).

Several brain areas have been previously shown to be activated during auditory working memory processing and constitute auditory working memory networks that involve ventrolateral prefrontal cortex (Plakke et al., 2015; Cohen et al., 2014; Plakke and Romanski, 2014), inferior parietal cortex (IPC) (Jonides et al., 1998; Owen et al., 2005), the insula (Huang et al., 2013; Koelsch et al., 2009), as well as auditory sensory processing areas (Bancroft et al., 2014; Cohen et al., 2014) (for review: Curtis and D'Esposito, 2003; Owen et al., 2005; Plakke and Romanski, 2014). In the present study, we selected the regions of interest (ROIs) accordingly. As previous fMRI studies showed activation of fronto-parietal brain areas during working memory processing in congenitally blind individuals, similarly to that observed in sighted, plus additional activation of the visual cortex (Amedi et al., 2003; Deen et al., 2015; Park et al., 2011), we furthermore chose a visual cortex ROI. A working memory task was used where participants had to maintain voice identity information. Previous studies in congenitally blind individuals have shown an activation of regions in the ventral visual stream, particularly the fusiform gyrus, during voice identity processing (Hölig et al., 2014). Thus, the ventral visual stream (partly located in the temporal lobe) was included in the visual ROI.

While spectral characteristic of neural activity have been previously investigated (Engel and Fries, 2010; Fries, 2015; Roux and Uhlhaas, 2014; Watrous et al., 2015; Weiss and Mueller, 2012) the neural mechanisms of long-range coupling of visual and other cortical regions following blindness are not yet understood (Gudi-Mindermann et al., 2018; Hawellek et al., 2013). The spectral characteristics of functional networks can be investigated by analyzing changes in synchronization of oscillatory brain activity (e.g., using electroencephalography, EEG or magnetoencephalography, MEG), which has been proposed to provide a

mechanism for the formation of functional networks (Engel et al., 2001, 1992; Engel and Singer, 2001; Jutras and Buffalo, 2010; Watrous et al., 2015). In sighted individuals, neuronal oscillatory activity in the theta- (Roux and Uhlhaas, 2014), beta- (Engel and Fries, 2010; Kopell et al., 2011; Spitzer and Haegens, 2017; Weiss and Mueller, 2012), and gamma-band (Pesaran et al., 2002; Roux et al., 2012) has been associated with working memory maintenance, and theta- and beta-band neural networks have been shown to be modulated by working memory training (Astle et al., 2015; Langer et al., 2013). The alpha-band seems to be more indirectly involved in working memory processing, indicating inhibition of irrelevant information rather than working memory maintenance per se (Roux and Uhlhaas, 2014). Furthermore, typically a reduction of alpha-band power is observed in congenitally blind individuals (Birbaumer, 1970; Hawellek et al., 2013; Kriegseis et al., 2006; Noebels et al., 1978). Thus, the theta-, beta, and gamma-bands, but not the alpha-band, were analyzed in the present study.

In contrast to the sighted, little is known about the neural coupling mechanisms involved in working memory processing in the blind. Coupling mechanisms might be altered in congenitally blind compared to sighted individuals due to deprivation related changes in the structural and functional architecture of visual areas (Gudi-Mindermann et al., 2018; Hawellek et al., 2013; Lazzouni and Lepore, 2014; Leclerc et al., 2005; Schmiedt et al., 2014). For example, in a recent MEG study, coupling between visual cortex and other cortex regions during typical resting state activity of visual cortex have been shown to be altered in congenitally blind individuals (Hawellek et al., 2013). Interestingly, changes in the structural connectivity of the visual system can affect the spectro-temporal profile of the visual cortex activity, as has been shown in macaque monkey research, using local field potentials (LFPs) (Bastos et al., 2015; Schmiedt et al., 2014). Specifically, resecting a portion of V1 in macaque monkey increased beta-band activity during visual stimulation by disabling feedforward connections between V1 and V4, while gamma-band activity (>30 Hz) was reduced (Schmiedt et al., 2014). In summary, previous research suggests that neuroplasticity might be mediated by changes of the spectral characteristics of neuronal networks.

In the present MEG study, we investigated the neuronal mechanisms of the visual cortex recruitment into functional networks in congenitally blind individuals. Functional networks were challenged by a working memory training to reveal the neuronal mechanisms of the visual deprivation related reorganization in congenitally blind individuals. A phase-based connectivity measure (imaginary coherency; Nolte et al., 2004) was used to analyze the effects of working memory training with voices on the synchronization of neural activity between different brain areas. An advantage of using imaginary coherency as connectivity measure is that it is insensitive to spurious brain connectivity that can result from volume conduction (Nolte et al., 2004). Connectivity was analyzed in the theta, beta-, and gamma-band between brain areas associated with auditory working memory (fronto-parietal, insular and auditory cortex ROI) and visual processing (occipito-temporal cortex ROI) in congenitally blind and sighted individuals. We hypothesized that training results in an integration of regions of the visual cortex into auditory working memory networks in the congenitally blind, as indicated by increased long-range connectivity of the visual cortex with auditory working memory networks.

We provide neurophysiological evidence that in sighted participants working memory training results in a strengthening of theta-band connectivity across brain areas associated with auditory working memory. In contrast, beta-band connectivity increased between brain areas associated with auditory working memory and the visual cortex in the blind group. By showing group-specific training induced changes in long-range functional connectivity, our results suggest an integration of the visual cortex into working memory networks in the blind and demonstrate that the spectral characteristics of networks associated with working memory training differ in blind and sighted individuals.

2. Materials and Methods

2.1. Experimental paradigm

The experiment was part of a larger working memory training study (insert [Supplementary Table S1](#) here) (the remaining data is reported elsewhere, see [Gudi-Mindermann et al., 2018](#)).

2.1.1. Pre- and post-training sessions: 2-back task

The MEG data were recorded in two sessions: a pre-training session preceding and a post-training session following extensive working memory training. In an auditory 2-back task participants were instructed to continuously indicate whether the current speaker (10 different speakers) of a pseudo-word matched the speaker of the next-to-last stimulus ([Fig. 1 A](#)). Congenitally blind and sighted participants were assigned to three training conditions: (1) working memory training with voices; (2) working memory training with tactile motion stimuli; (3) an active training-control task. Here, we report the MEG data recorded during the auditory 2-back task in the pre- and post-training sessions. Additionally, we here report data that were recorded during resting state (~3.5 min) prior to the 2-back task in the pre-training session.

Throughout the MEG recording, participants were seated in a comfortable chair. All participants were blindfolded. Instructions were provided orally to each participant in the beginning of the experiment. Throughout the experiment instructions and auditory stimuli were presented through insert ear-plugs (E-A-RTONE Gold 3A Insert Earphones, Ulrich Keller Medizin-Technik, Weinheim, Germany) at normal conversational level (~75 dB SPL). Prior to the experiment all participants performed several blocks of the working memory task to ensure task comprehension (an error sound provided direct feedback). An extended version of the “Verbaler Lern- und Merkfähigkeitstest” (VLMT; German version of the Auditory Verbal Learning Test) was conducted after the pre- and post-training recording session. The VLMT was extended by instructing participants to remember the items in the correct order if possible, and additionally analyzing scores for absolute (counting correct responses up to the first error) and relative (counting all responses where a correct sequence of minimum two items was reported) temporal order memory (see [Supplementary Methods](#) for an analysis and correlation with the behavioral and neuronal data). Following ([Jaeggi et al., 2007](#)), we accessed participants working memory strategies using an inventory that was conducted after the last experimental session. Participants

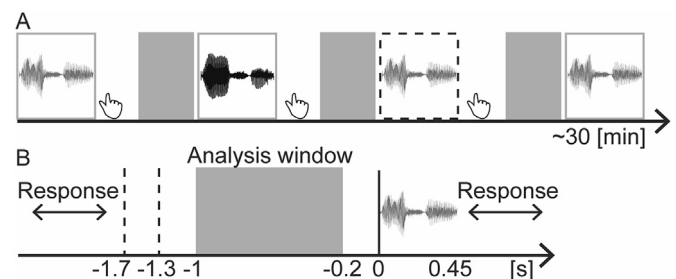


Fig. 1. Schematic of the Voice Recognition Task (A) In an auditory 2-back task the pseudo-word “befa” (waveform) pronounced by 10 different speakers (speaker identity in gray shades) was presented. Participants had to indicate by button press whether the current speaker matches the speaker presented two stimuli ago. A target (dashed frame) required a “yes” response, while a non-target (gray frame) required a “no” response. The duration of the experiment depended on the response times (~30 min). **(B)** MEG activity was analyzed in the analysis window (-1 to -0.2 pre-stimulus) during the delay period. During the delay period (A, B: gray boxes) participants were maintaining items in memory. Each response was followed by an inter-trial interval (ITI) that was randomly jittered between 1300–1700 ms. The minimum ITI lasted from -1300 ms to stimulus onset (0 ms) in all participants. To avoid overlap with response- and stimulus-related processing the first 300–700 ms and last 200 ms of this ITI were discarded for the analyses.

indicated whether they used any of the following strategies: verbal memorization, internal rehearsal, internal sequencing, storytelling, visual imaging, spatial imaging, episodic memorizing, whether they performed the task intuitively, or whether they had no strategy (cf. Supplementary Material).

Auditory stimuli consisted of a pseudo-word (“befa”), with a stimulus length of 450 ms, spoken by 10 different speakers (5 female). All stimuli were peak normalized. We used pseudo-words to avoid effects related to speech semantics, such as semantic associations, or word familiarity, which might affect the processing of voice identity differently in the blind and sighted participants. Participants were instructed to prioritize response accuracy over speed. Each response was followed by an inter-trial interval that was randomly jittered between 1300 and 1700 ms. The 2-back task comprised 15 blocks in the pre-training session, and 12 blocks in the post-training session with 32 (30 + n) stimuli per block. For each block, stimulus sequences were quasi-randomly designed using Matlab: (1) positions of targets (30%) and non-targets were randomized; (2) stimuli were quasi-randomly assigned as targets or non-targets; (3) 19% catch trials (i.e., 1-back and 3-back stimulus pairs) were randomly inserted.

2.1.2. Training and training-control sessions: n-back task

Congenitally blind and sighted participants of the different training conditions were matched with respect to age, gender, and handedness (Table 1). The training comprised four sessions (~2–3 h duration each). During the working memory training with voices participants performed an adaptive auditory n-back task and during the working memory training with tactile motion stimuli an adaptive tactile n-back task (30 blocks of 30 + n stimuli). In the auditory n-back task, participants had to indicate whether the current speaker matches the n-to-last speaker. In the tactile n-back task, participants had to indicate whether the current motion direction and stimulated finger match those of the n-to-last stimulus. A programmable mechanical Braille stimulator (QuaeroSys Medical Devices, Schotten, Germany) with 5 stimulator units (2 × 4 pin matrix) was used to generate an up- or a down movement at each of the five fingers of one hand (the stimulated hand was matched between groups and conditions). This resulted in 10 tactile apparent motion stimuli. The first training session started with a 2-back block. The HR and correct rejection rate (CRR) were used to adapt the task demands to the individual performance: $HR = \frac{\text{hits}}{n_{\text{targets}}}$; $CRR = \frac{\text{correct rejections}}{n_{\text{non-targets}}}$. When participants showed high performance in a block, the n was increased ($HR \geq 70\%$ and $CRR \geq 75\%$). The n was decreased after low performance ($HR < 60\%$ or $CRR < 60\%$). Otherwise the n did not change. Participants in the training-control condition conducted a 1-back task with low cognitive demand in both modalities. The stimuli for the 1-back task

Table 1
Sample demographics.

Group	n	Training	Age (mean, sd)	Gender (f)	Education (\geq A-levels)
Sighted	9	Auditory	39 (10)	4	7
	9	Tactile	32 (10)	5	7
	9	Control	40 (11)	4	9
Blind	9	Auditory	41 (9)	4	6
	9	Tactile	33 (9)	5	7
	9	Control	40 (11)	4	7

The number of participants n, the mean age (SD, displayed in brackets), the gender of participants (number of female participants) and participants education (number of participants with A-levels or a higher degree) are displayed for the sighted and congenitally blind participants in each training condition (auditory working memory training; tactile working memory training; training-control condition). There were no differences between sighted and blind participants in the distribution of educational degree (Fishers exact test, 2-tailed, Bonferroni corrected $\alpha = 0.0167$; auditory training, $p = 1$; tactile training, $p = 1$; training-control, $p = .47$), and the distribution of age (independent-samples Kolmogorov-Smirnov test; Bonferroni corrected $\alpha = 0.0167$; auditory training, $p = .98$; tactile training, $p = .7$; training-control, $p = 1$).

were the same as used in the auditory and tactile n-back task, respectively. Participants indicated whether the current stimulus matched the last stimulus. The auditory and tactile 1-back task were performed on alternating training days, while we balanced which modality was tested first (overall 40 blocks á 30 + n stimuli; note that more blocks were required for the easy 1-back compared to the n-back task to achieve the same total training duration of approximately 8 h per participant. Note that the training duration in one single modality was reduced in the training-control compared to the training conditions.). The active control condition was chosen to differentiate working memory training effects from more general effects, such as repetition or intervention effects. Note that we investigated the elaboration of brain networks as a consequence of training. Auditory and tactile working memory tasks were selected that allowed for improvements in all individuals. By analyzing the neural correlates of individual training effects, we controlled for possible differences in pre-training skills in auditory and tactile processing.

2.2. Subjects

Congenitally blind (n = 27) and sighted (n = 27) matched control participants took part in the study. All participants were healthy with normal hearing (self-report) and no history of psychiatric or neurological disorders. One blind participant reported a history of depressive mood disorder, however, with no current symptoms or need for treatment. Sighted participants had normal or corrected to normal vision (self-report). Due to loss of vision, following (pre)natal anomalies in the peripheral visual system (retinopathy of prematurity: n = 9; genetic defect, n = 5; congenital optic atrophy: n = 3; Leber's congenital amaurosis: n = 2; congenital cataracts, glaucoma: n = 2; congenital retinitis: n = 2; binocular anophthalmia: n = 2; retinitis pigmentosa: n = 1; congenital degeneration of the retina, n = 1), congenitally blind participants were totally blind since birth with minimal residual light perception in 18 participants. During the training sessions all participants underwent additional psychological tests, including the German version of the PSQ-20 (Perceived Stress Questionnaire, (Levenstein et al., 1993); German modified version, (Fliege et al., 2005); 2); the HSWBS (German Habituelle Subjektive Wohlbefindens Skala; (Dalbert, 1992) to measure wellbeing; and the MWT-B (German Mehrfachwahl-Wortschatz-Test, (Lehrl, 2005) to assess verbal intelligence. The blind and sighted participants did not differ in any of the assessed psychological variables (PSQ-R20: $t(45.06) = 0.38$, $p = .704$; HSWBS: $t(46.55) = 0.46$, $p = .647$; MWT-B: $t(48.14) = 0.67$, $p = .507$).

The study was approved by the German Psychological Association (DGPs). All participants gave written informed consent prior to the experiments and received monetary compensation for participation.

2.3. Behavioral data analysis

For the behavioral data analysis all responses within a response window (2–6 s) were analyzed. The first two trials of each block were removed (participants were informed that a “non-target response” was correct for these initial trials). The hit rate (HR) was calculated separately for each participant and session (pre, post). Analyses of Variance (ANOVAs) were used to test training-related differences in working memory performance increases across sessions (post minus pre HR) with the between-subject factors training condition (auditory, tactile, control) and group (blind, sighted) (Shapiro-Wilk-Test of normality performed separately for groups and conditions, $ps > .322$).

2.4. MRI and MEG data acquisition

T1-weighted structural MRI scans were obtained for each participant except for those who did not meet the MRI scan criteria (sighted: n = 3). The MRI recording was performed on a 3 T scanner (Siemens Magnetom Trio, Siemens, Erlangen, Germany). The MEG data were recorded in a magnetically shielded room using a 275-channel whole-head system

(Omega, 2000, CTF Systems Inc.). The electrooculogram and electrocardiogram were derived for offline artifact rejection. Prior to and after each experiment the head position was measured relative to the MEG sensors. The head position was tracked during the recording and head displacement was corrected in the breaks using the fieldtrip toolbox (<http://fieldtrip.fcdonders.nl>; (Stolk et al., 2013)). The data were recorded with a sampling rate of 1200 Hz and low pass filtered online (cut-off: 300 Hz).

2.5. MRI data analysis

The FieldTrip toolbox (<http://fieldtrip.fcdonders.nl>; (Oostenfeld et al., 2011)) and other customized Matlab toolboxes were used for data analyses. Anatomical landmarks (nasion, left and right pre-auricular points) were manually identified in the individual MRIs. Individual MRIs of all participants were then analyzed by, first, obtaining probabilistic tissue maps (including cerebrospinal fluid white and gray matter) from the anatomical MRI. The standard Montreal Neurological Institute (MNI) brain was used for cases without an individual MRI. Second, a single shell volume conduction model (Nolte, 2003) was used to estimate the physical relation between sensors and sources. A source model was generated using a regular 3-D grid (0.8 cm spacing). The grid was used to generate a warped MNI grid to project individual MRIs on the standard MNI brain. Finally, based on the warped MNI grid and the probabilistic tissue map a leadfield (forward model) was calculated that was used for source reconstruction.

2.6. MEG data analysis

For preprocessing, the data were band-pass filtered off-line (1–160 Hz, Butterworth filter; filter order 4) and line-noise was removed using bandstop filters (49.5–50.5, 99.5–100.5, 149.5–150.5 Hz, two-pass; filter order 4). Only correct responses and, matched with the behavioral data analyses, only trials where participants responded within a 2–6 s window were analyzed, while the first two trials of each block were removed. In a common semi-automatic artifact detection procedure (i.e. the output of the automatic detection was monitored) (Gross et al., 2013; also see <http://www.fieldtriptoolbox.org/>), the signal was filtered in a frequency range that typically contains muscular artifacts (band-pass: 110–140 Hz) or jump artifacts (median filter) and z-normalized per time point and sensor. To accumulate evidence for artifacts that typically occur in more than one sensor, the z-scores were averaged over sensors. We excluded trials exceeding a predefined z-value (muscular artifacts, $z = 20$; jumps, $z = 100$). Slow artifacts were removed by rejecting trials where the range (min-max difference) in any channels exceeded a threshold (threshold = $0.75e-11$). The continuous data were epoched with respect to stimulus onset (–2 to 2 s) and down sampled to 500 Hz. Independent component analysis (infomax algorithm; Makeig et al., 1996) was used to remove eye-blink, eye-movement and heartbeat-related artifacts (components were first reduced to 64 components using principal component analysis; note that dimension reduction with PCA is controversial, and might reduce our effects; Artoni et al., 2018). In the Components were removed only when the conjunction of component topography, time course and variance across trials was clearly conclusive (overall removed components, Table S2; insert Supplementary Table S2 here). For eye-blink and eye-movements the EOG was inspected in case the other indicators were not distinct. The number of trials was matched across pre- and post-training sessions for each participant by randomly removing trials from the larger set (Gross et al., 2013). This resulted in the following amount of trials in each session (pre, post) for the sighted participants: Auditory training, mean = 319 (sd = 15), tactile training, mean = 307 (sd = 26), training-control, mean = 292 (sd = 61); and for the blind participants: auditory training, mean = 286 (sd = 33), tactile training, mean = 297 (sd = 26), training-control, mean = 293 (sd = 34); overall sighted participants, mean = 306 (sd = 40); overall blind participants, mean = 291.8

(sd = 30). Data in the delay window (–1 to –0.2 s pre-stimulus; 0.8 s segments) were further analyzed. The data recorded during resting state were processed similarly. The continuous data were epoched into 0.8 s segments to match the auditory 2-back data. The number of trials was matched between the pre-training auditory 2-back data and the resting state data separately for each participant: Sighted participants, mean = 298 (sd = 41); congenitally blind participants, mean = 293 (sd = 37).

2.7. Source power and connectivity analysis

Discrete Fourier transform was performed at 2.5–100 Hz, separately for each participant and session (pre, post, resting state) (segment length: 0.4 s; segment shift: 0.05 s; frequency resolution: 2.5 Hz). The cross-spectrum was retrieved by calculating the cross-covariance function of the Fourier transformed data (Nolte et al., 2004). Given that $x_i(f)$ and $x_j(f)$ are the Fourier transforms of the time series $x_i(t)$ and $x_j(t)$ of sensor i and j the cross-spectrum (cs) was calculated as:

$$cs_{ij}(f) = \langle x_i(f)x_j^*(f) \rangle$$

Exact Low-Resolution Brain Electromagnetic Tomography (eLoreta) was used to calculate a spatial filter based on the individual leadfield (2982 inside brain voxel, 3 dipole directions) (Pascual-Marqui, 2007).

2.7.1. Source connectivity analysis

Based on previous literature the automated anatomical labeling (AAL) procedure (Tzourio-Mazoyer et al., 2002) was used to select four ROIs involved in auditory working memory: frontal, parietal, insula, and temporal; and a ventral visual stream ROI: occipito-temporal. Additionally, to distinguish which parts of the visual cortex were activated, ROIs in the left and right V1 and the extra striate cortex (ESC) were selected based on the AAL, and the Brede database was used to select coordinates of the left and right fusiform gyrus (FG) and medial temporal areas (MT) (insert Supplementary Table S3 here).

The cross-spectrum was averaged across frequencies for three frequency bands: theta (2.5–5 Hz), beta (17.5–22.5 Hz) and gamma (40–60 Hz) (Frequency bands were selected based on previous literature, while an overlap with the alpha-band was avoided and the selection of frequency bands was constrained by our frequency resolution. Note that the delta- and theta-band cannot be clearly distinguished.). For each frequency and each pair of signals imaginary coherency was calculated as the complex cross-spectrum normalized by the square root of the product of powers. For each pair of voxels dipole directions were estimated by maximizing imaginary coherency values (Ewald et al., 2012). Fischer's z-transformation was used for variance stabilization (inverse hyperbolic tangent). In order to estimate imaginary coherency between each voxel and a ROI, we averaged the connectivity between that voxel and all voxels of an AAL brain region (Table S3), first, per hemisphere and, second, across hemispheres and across all AAL regions of a ROI. The imaginary coherency during resting state, and the differences between sessions (auditory 2-back post-minus-pre; auditory 2-back pre-minus-resting state) were further analyzed. The (maximized) imaginary coherency values range between 0 and 1, with 1 indicating maximally synchronous time series.

2.7.2. Source power analysis

For each voxel, source power (pow) was calculated based on the individual $N \times 3$ spatial filter (A), for N channels and 3 dipole directions, and cross-spectra (cs) at each frequency (3–100 Hz) separately (Pascual-Marqui, 2007).

$$pow_f = \lambda_{max}(A^* cs_f^* A)$$

where λ_{max} denotes the maximum eigenvalue. Source power was averaged for each participant and each session and averaged across fre-

quencies of each frequency band (theta: 2.5–5 Hz, beta: 17.5–22.5 Hz, gamma: 40–60 Hz). Source power (resting state) and source power contrasts between sessions were further analyzed: $\frac{pow_{post} - pow_{pre}}{pow_{post} + pow_{pre}}$ and $\frac{pow_{pre} - pow_{resting\ state}}{pow_{pre} + pow_{resting\ state}}$.

2.8. Permutation statistics

Independent-sample random permutation statistics (Nichols and Holmes, 2002) were performed to test connectivity and power changes in the auditory 2-back task separately for the three frequency bands (theta, beta, gamma). In all analyses, false discovery rate (FDR; Benjamini and Hochberg, 1995) with Q values equal 0.2 (Genovese et al., 2002) was used to control for multiple comparisons of voxels, ROIs and frequency bands, if not stated otherwise. The Q values indicate that the average proportion of false discoveries for repeated experiments does not exceed this value. FDR computes a p-value threshold (corrected p-value): p-values of the multiple comparisons are put in ascending order such that $p(k) \leq p(k+1)$ for $k = 1, \dots, N-1$ for N observations. The threshold is the largest p-value for which $p(k) \leq Q \cdot k/N$. Each p-value of each of the multiple comparisons that is below this threshold is considered significant. Larger p-value thresholds indicate that there were more observations with p-values lesser-than the threshold within the multiple comparisons compared to smaller p-value thresholds. To account for false positives that can result in physiologically implausible effects, a minimum of 100 observations were required to meet the threshold.

First, we tested differences in training-related connectivity and power changes between the blind and sighted participants. Training-related changes (i.e., differences in connectivity or power changes across sessions, using the individual post-minus-pre difference for connectivity and the contrast for power, between the working memory training with voices and the training-control condition) in the blind were tested against training-related changes in the sighted participants. Differences were tested by randomly permuting participants' group affiliation (blind, sighted) (10,000 permutations) separately for the auditory training and training-control condition. Training-related changes were then calculated, (1), separately for participants of each group and, (2) for the randomly permuted groups. Finally, we tested the observed group difference (blind minus sighted) against the differences of the randomly permuted groups.

Second, effects of working memory training on connectivity and power changes across sessions (using the individual post-minus-pre difference for connectivity and the contrast for power) during the auditory 2-back task were tested separately for the blind and sighted participants. We tested differences in changes across sessions between the training conditions by randomly permuting participants' training condition affiliation (10,000 permutations) and comparing the observed condition difference against the difference of the randomly permuted conditions.

The resting state data of one participant had to be discarded due to file distortion resulting in the analysis of data from 26 congenitally blind and 27 sighted participants for the analysis of the pre-training data. In an exploratory analysis, where we only controlled for multiple comparisons of voxels, we tested whether differences in the working memory networks of blind and sighted participants already existed prior to the training. Independent-sample permutation statistics were performed to test differences between blind and sighted participants during the auditory 2-back task and during resting state prior to the training. The analyses were performed on the difference of the connectivity data recorded during the pre-training auditory 2-back task and resting state, as well as on the contrast of the power data recorded during the pre-training auditory 2-back task and resting state. Participants' group affiliations (blind, sighted) were randomly permuted (10,000 permutations). The observed group differences were tested against the differences of the randomly permuted groups. Furthermore, we similarly analyzed the pre-training connectivity and power data recorded during the resting state to access baseline differences in power and connectivity between blind and

sighted participants.

3. Results

3.1. Working memory training with voices increases performance

Participants' high pre-training performance (HR sighted: auditory training, mean = 0.87, sd = 0.09; tactile training, mean = 0.91, sd = 0.06; training-control, mean = 0.87; sd = 0.08; HR blind: auditory training, mean = 0.77, sd = 0.13; tactile training, mean = 0.89, sd = 0.09; training-control, mean = 0.91; sd = 0.05) shows that participants were able to perform the task. As expected, working memory training with voices resulted in a HR increase in the 2-back task with voices (Fig. S1; main effect of condition, $F(2,48) = 4.96$, $p < .0500$, $\eta^2_p = .17$). Participants who performed the working memory training with voices showed a higher HR increase across sessions compared to those in the training-control condition (post-hoc independent-sample Student's t-tests; $p = .0123$; Bonferroni corrected α : 0.0167) and to those who underwent tactile working memory training ($p = .0161$). In contrast, working memory training with tactile stimuli did not improve performance compared to the training-control condition ($p = .5939$) indicating a modality-specific training effect. No differences in working memory training effects were observed between blind and sighted participants (no main effect of group; $p = .5453$; and no interaction of group and condition; $p = .7174$). As an adaptive working memory training with voices, but not with tactile motion stimuli, compared to a training-control condition resulted in a performance increase in the auditory 2-back task, for the analyses of the neurophysiological data the effects of the adaptive working memory training with voices on working memory networks were compared to those of the training-control condition (for data on the tactile training condition: Fig. S5 B).

3.2. Training integrates visual cortex into a beta-band network in the blind

To test effects of working memory training on visual cortex integration into working memory networks, we analyzed connectivity and power during the delay period where participants were maintaining items in memory during the 2-back task with voices (Fig. 1B). Differences in training-related connectivity and power changes between participants with working memory training with voices and those in the training-control condition were analyzed in the theta-, beta- and gamma-bands and compared between blind and sighted participants. Connectivity was analyzed for ROIs related to auditory working memory (frontal, parietal, insula, temporal) and visual processing (occipito-temporal; Table S3).

The blind participants showed a stronger training-related increase in beta-band connectivity compared to the sighted between the visual cortex and brain areas associated with auditory working memory (Fig. 2A and Fig. S5 A; $Q = 0.2$; FDR corrected p-value = .0079; p-values < .0079). Connectivity particularly increased between the frontal, insula and temporal ROIs and occipito-temporal brain areas (including V2, the right fusiform gyrus, and the right inferior temporal lobe, ITL); between the frontal ROI and right inferior parietal gyrus (IPG); and between the occipito-temporal ROI and the inferior frontal gyrus (IFG), the middle frontal gyrus (MFG), the right superior temporal gyrus (STG), the anterior superior temporal sulcus (STS), and the right insula.

An analysis of theta-, beta- and gamma-band connectivity, where we controlled for multiple comparisons of voxels, ROIs and frequency-bands, in the congenitally blind revealed no training-related connectivity changes across sessions. However, in order to further explore the training-related connectivity differences between the sighted and the blind, we performed an exploratory analysis of the theta- and beta-band with a more liberal control for multiple-comparison (multiple comparisons of voxels at each ROI while not for the amount of ROIs and frequency bands). We confirmed that the observed differences between sighted and blind participants in the beta-band originated from training-

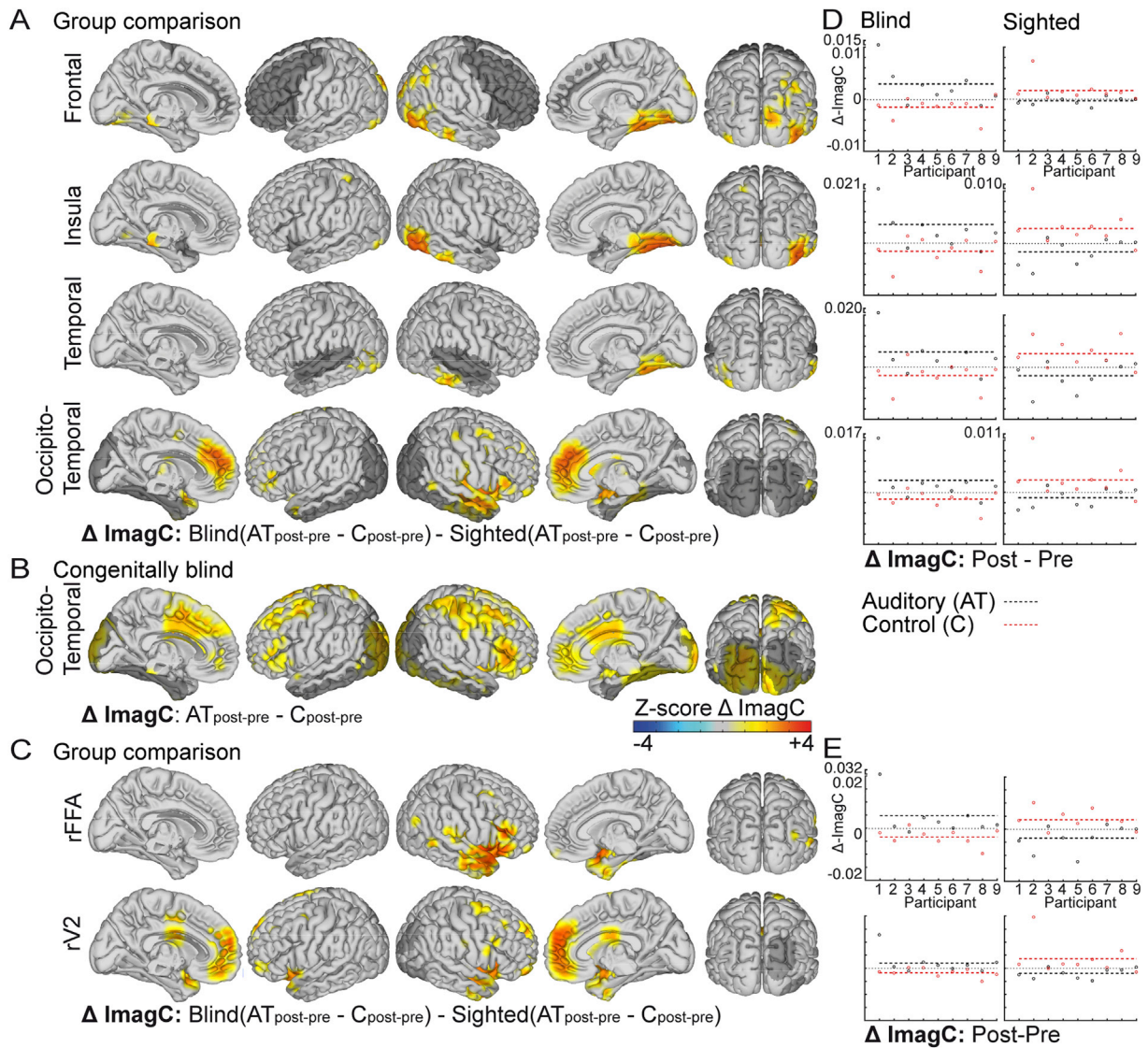


Fig. 2. Increased Beta-Band Connectivity in the Congenitally Blind (A) Congenitally blind participants showed training-related (AT, auditory training; C, control condition) increases in connectivity in the beta-band compared to the sighted between the frontal, insula, temporal and occipito-temporal regions of interest (ROIs; displayed in dark transparent gray) and the voxels displayed in color. Each row shows effects for the ROI labeled on the left. Higher connectivity values in the blind compared to the sighted participants are displayed in warm colors. (B) In blind participants working memory training with voices increased connectivity across sessions in the beta-band between the occipito-temporal ROI (displayed in dark transparent gray) and the voxels displayed in color compared to the training-control condition. Higher connectivity increases in the working memory training with voices compared to the training-control condition are displayed in warm colors. (C) Congenitally blind participants showed increased training-related connectivity in the beta-band compared to the sighted between the right fusiform gyrus (FG) ROI (displayed in dark transparent gray) and the voxels displayed in color. Higher connectivity values in the blind compared to the sighted participants are displayed in warm colors. In (A–C) connectivity differences are displayed as z-scores (connectivity differences divided by the SD of the permutations). The distribution of participants' connectivity values is plotted on the right for the main comparison (D) and the comparison with specific ROIs in the ventral and dorsal visual stream (E). The post-minus-pre difference in connectivity (imagC) at each ROI, averaged across voxels with significant effects, is plotted separately for the auditory training condition (black circles) and the control condition (red circles), for the sighted and blind participants respectively. The mean connectivity difference of each training condition is displayed as dashed line. Note that several data points are plotted offset with the value displayed at the y-axis.

related connectivity increases in the blind (Fig. 2B; Fig. 3). Blind participants with working memory training showed stronger beta-band connectivity increases across sessions compared to those in the control condition at the occipito-temporal ROI ($Q = 0.2$; FDR corrected p -value = .0531; p -values < .0531; Fig. 2B). Connectivity increased between the occipito-temporal ROI and the IFG, the MFG, the pre- and post-central gyrus, and parts of occipital cortex. Working memory training did not affect connectivity in blind participants at the beta-band at any other ROI ($Q = 0.2$; at all other ROIs FDR corrected p -value = .0001; auditory: p -values $\geq .0011$; frontal, insula, parietal: p -values $\geq .0004$), or the theta-band (at all ROIs FDR corrected p -value = .0001; auditory: p -

values $\geq .0012$; occipito-temporal: p -values $\geq .0106$; frontal: p -values $\geq .0110$; insula, parietal: p -values $\geq .0051$).

In sum, working memory training with voices resulted in differences between congenitally blind and sighted participants in the beta-band. Further analyses showed working memory training increased beta-band connectivity between visual areas and an auditory working memory network in the blind.

3.3. Beta-band connectivity of the fusiform gyrus increases in the blind

In previous brain imaging studies, congenitally blind individuals

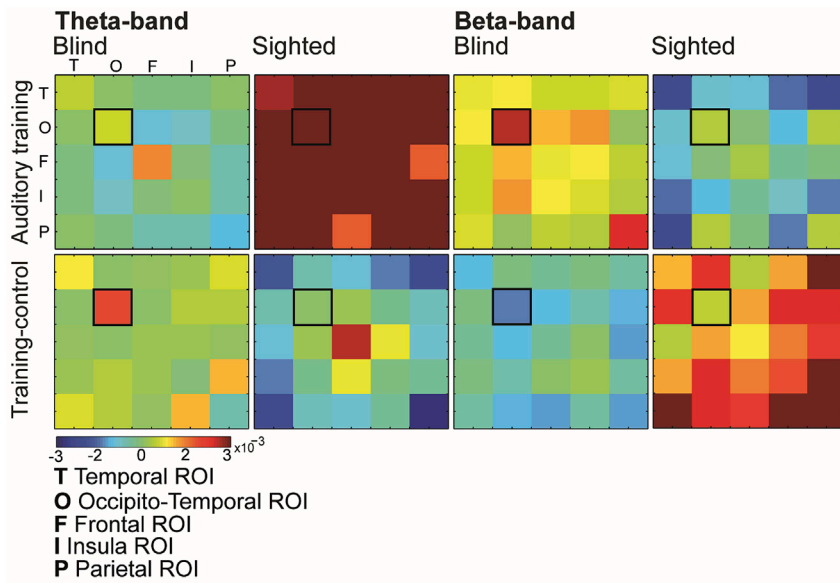


Fig. 3. Connectivity Matrix The difference in connectivity (imaginary coherency) across sessions (post-minus-pre) between all ROIs (temporal, occipito-temporal, frontal, insula, parietal) is displayed separately for the sighted and congenitally blind participants, the auditory working memory training and training-control condition and the theta and beta frequency band. Connectivity was averaged separately for each participant, for each voxel between that voxel and all voxels of each ROI, as described in the Materials and Methods section. This resulted in connectivity measures between each ROI and all voxels. For the purpose of illustration ROI-ROI connectivity pairs were computed, by additionally averaging connectivity for each ROI between that ROI and all voxels of each of the five ROIs. The figure illustrates the connectivity patterns in the different groups and training conditions, particularly, the increase in theta-band connectivity in the sighted participants with auditory training, and in beta-band connectivity in the blind participants with auditory training. Connectivity within occipito-temporal ROIs is highlighted (black box). Interestingly an antagonism between theta- and beta-band networks can be observed, such that when working memory training resulted in an increased connectivity in one frequency band, it rather decreased in the control group while connectivity in the other frequency band showed the opposite pattern across training groups (cf. discussion section). Note the figure does not refer directly to the statistical analyses.

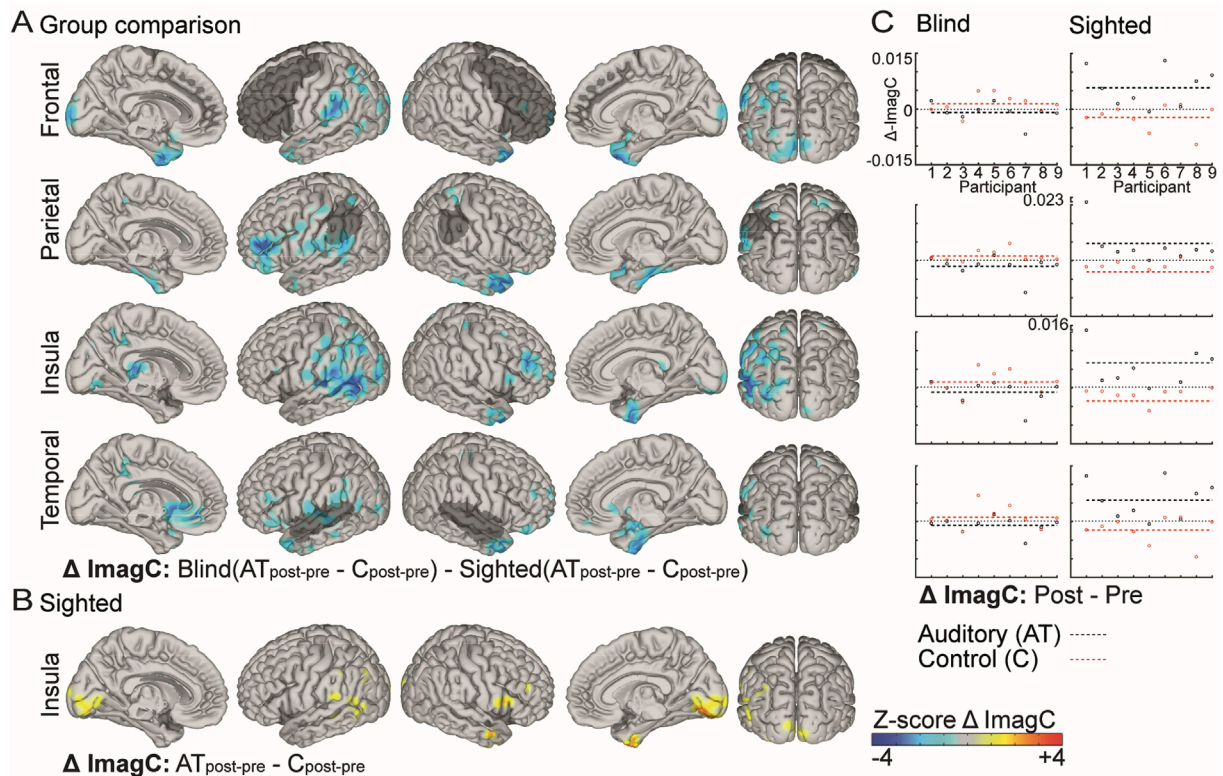


Fig. 4. Increased Theta-Band Connectivity in the Sighted (A) Sighted participants showed increased training-related connectivity (AT, auditory training; C, control condition) in the theta-band compared to the congenitally blind between the frontal, parietal, insula, and temporal ROIs (displayed in dark transparent gray) and the voxels displayed in color. Each row shows effects for the ROI labeled on the left. Note that cold colors highlight connectivity increases in the sighted compared to the congenitally blind. (B) In sighted participants working memory training with voices increased connectivity across sessions in the theta-band between the insula ROI (displayed in dark transparent gray; labeled on the left) and the voxels displayed in color compared to the training-control condition. Higher connectivity increases in the working memory training with voices compared to the training-control condition are displayed in red. In (A-B) connectivity differences are displayed as z-scores. (C) The distribution of participants connectivity values is plotted on the right. The post-minus-pre difference in connectivity (imagC) is plotted separately for the auditory training condition (black circles) and the control condition (red circles), for the sighted and blind participants respectively. The mean connectivity difference of each training condition is displayed as dashed line. Note that several data points are plotted offset with the value displayed at the y-axis.

showed activation of the right fusiform face area (FFA), part of the ventral visual stream, during voice identity processing (e.g., Hölig et al., 2014). Here, we performed an analysis of the beta- and theta-band effects using more specific visual cortex ROIs to test whether the ventral visual stream was recruited in congenitally blind individuals. In the present study, blind participants showed a stronger training-related increase in beta-band connectivity across sessions compared to the sighted between the right FG ROI and the right IFG, STG and insula (Fig. 2C; $Q = 0.2$; FDR corrected p -value = .0031; all p -values < .0031), and between the right ESC ROI and the insula, the right STS/STG and frontal brain areas. There were no effects at the left FG ROI, the dorsal visual stream ROIs (left and right MT), and the left and right V1 ROIs (p -values > .0031). There were no effects in the theta-band (p -values > .0031). The findings suggest that training in a non-visual n-back task with voices results in the extension of auditory working memory networks in the congenitally blind compared to the sighted, by integrating parts of the ventral visual stream.

3.4. Training strengthens a theta-band network in the sighted

The sighted participants showed a stronger training-related increase in theta-band connectivity compared to the blind between brain areas associated with auditory working memory. The training-related increase in connectivity in the sighted compared to the blind was observed at the frontal, parietal, insula and temporal ROIs (Fig. 4A and Fig. S5 A; $Q = 0.2$; FDR corrected p -value = .0079; p -values < .0079). Connectivity differences were most pronounced between the frontal ROI and the right insula, the left STG, the left inferior parietal lobe (IPL), the anterior middle temporal gyrus (MTG), and parts of left V1; between the parietal ROI and the left IFG and MFG, and the anterior MTG; between the insula ROI and right MTL, the left IPG the left posterior STG and STS, and left V1; and between the temporal ROI and IFG, and anterior MTG. There were no effects at the occipito-temporal ROI (p -values \geq .0081).

In an analysis of theta-, beta- and gamma-band connectivity in the sighted we confirmed that the observed changes were due to training-related connectivity increases across sessions in the sighted participants. The sighted participants with working memory training with voices showed a stronger increase in theta-band connectivity across sessions compared to participants in the training-control condition (Fig. 4B; $Q = 0.2$; FDR corrected p -value = .0018; all p -values < .0018; Fig. 3) between the insula ROI and the right anterior MTG, the right IFG, the left STG, and parts of the visual cortex. In the sighted participants, there were no significant differences at any other ROI (frontal: p -values \geq .0019; parietal: p -values \geq .0019; temporal: p -values \geq .0019; occipito-temporal: p -values \geq .0019), or in beta- and gamma-band (beta-band: frontal: p -values \geq .0020; insula: p -values \geq .0020; parietal: p -values \geq .0022; temporal: p -values \geq .0025; occipito-temporal: p -values \geq .0020; gamma-band: frontal: p -values \geq .0787; insula: p -values \geq .0403; parietal: p -values \geq .0343; temporal: p -values \geq .0532; occipito-temporal: p -values \geq .1669) connectivity across sessions between participants of the auditory working memory training vs. control condition.

In sum, working memory training with voices strengthened a theta-band auditory working memory network in the sighted.

3.5. Local activity was not affected by working memory training

Besides large-scale connectivity, working memory training with voices might impact local activity within areas relevant for working memory processing differently in blind and sighted participants. However, we did not find working memory training-related power differences between the congenitally blind and sighted at any frequency band ($Q = 0.2$; all frequency bands FDR corrected p -value = .0001; theta-band: all p -values \geq .0012; beta-band: all p -values \geq .0061; gamma-band: all p -values \geq .0002), and no working memory training effects on power in any group ($Q = 0.2$) (for a ROI specific analysis: Fig. S4 A, Fig. S4 B). Note that visual inspection of the overall power-spectrum (averaged across

voxels, pre and post training sessions and training conditions), in line with previous literature (Hawellek et al., 2013; Kriegseis et al., 2006; Noebels et al., 1978), shows reduced alpha-band power in the congenitally blind compared to the sighted participants (Fig. S2 A).

3.6. Working memory network differences prior to the training

In our study, we used a working memory training paradigm to induce neuroplasticity and test differences in the formation of new networks in congenitally blind and sighted individuals. However, differences in working memory networks between the groups might have existed prior to the training due to plasticity following early visual deprivation, and the training might have enhanced these differences. We tested this in an analysis where differences in theta-, beta- and gamma-band connectivity and power between blind and sighted participants in the pre-training 2-back session (contrasted with resting state data recorded at the beginning of the first MEG session) were compared. The analyses showed no significant effects, using the rigorous control for multiple comparisons. As these analyses were thought of as follow-up exploratory analyses, however, we performed another set of tests with a more liberal control for multiple-comparison of voxels at each ROI. The blind participants showed reduced theta-band connectivity compared to the sighted between the insula ROI and the IFG, the STG and pre- and post-central areas ($Q = 0.2$; FDR corrected p -value = .0298; p -values < .0298; Fig. S3 A). There were no differences at any other ROI ($Q = 0.2$; frontal: FDR corrected p -value = .0057; p -values > .0057; auditory: FDR corrected p -value = .0023; p -values > .0023; occipito-temporal and parietal: FDR corrected p -value = .0001; p -values > .0086) or frequency-band (beta-band: $Q = 0.2$; FDR corrected p -value = .0001; frontal: p -values \geq .0065; insula: p -values \geq .0003; parietal: p -values \geq .0004; temporal and occipito-temporal: p -values > .0001; gamma-band: $Q = 0.2$; FDR corrected p -value = .0001; frontal: p -values > .0001; insula: p -values \geq .0026; parietal: p -values \geq .0014; temporal: p -values \geq .0037; occipito-temporal: p -values \geq .0101) and no differences in power (beta- and gamma-band: $Q = 0.2$; FDR corrected p -value = .0001; beta-band: p -values \geq .0007; gamma-band: p -values > .0001) (for between group differences in the resting state data: Fig. S3 B, C).

These findings suggest that differences in theta-band working memory networks between congenitally blind and sighted participants were partly present prior to the training, while differences in beta-band networks were largely established during the training.

4. Discussion

The goal of this study was to extend previous reports on visual cortex activation during non-visual tasks in congenitally blind individuals in order to provide insights into the neuronal mechanisms underlying cross-modal reorganization, particularly the role of altered long-range functional connectivity (i.e., as indicated by phase-synchronization between brain areas). Importantly, our paradigm benefits from a within-subject normalization (analyses of changes across pre-post training sessions), which reduces the impact of task-unrelated anatomical differences between the blind and the sighted. Our study revealed, first, that working memory training altered long-range functional connectivity of visual cortex in the congenitally blind individuals, suggesting an integration of the visual cortex into working memory networks (Fig. 5). Second, working memory training altered spectro-temporal characteristics of the networks differently in the blind (beta-band) and the sighted (theta-band), supposedly indicating different coupling regimes. Crucially, our findings suggest that visual deprivation results in an increased capability of visual cortex to connect to networks involved in non-visual tasks, possibly (in line with previous proposals: Pelland et al., 2017) because cross-modal reorganization of visual cortex strengthened the coupling of visual cortex with other cortical brain areas which facilitates the integration of the visual cortex into different functional networks.

In both, blind and sighted participants, working memory training

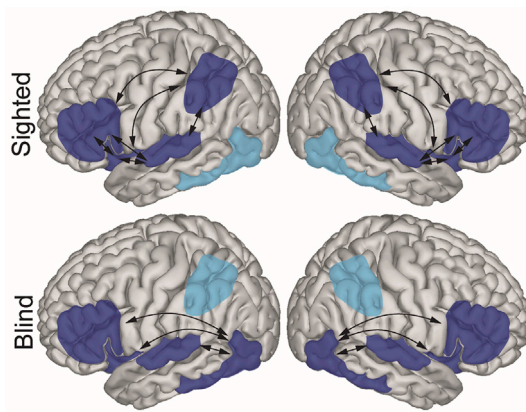


Fig. 5. Schematic of the Networks Affected by Working Memory Training Connectivity increases due to working memory training were observed in the theta-band for sighted and in the beta-band for congenitally blind participants. All regions of interest (ROIs) that showed significant changes in connectivity to other brain areas (indicated by arrows) in the analysis of training-related differences between congenitally blind and sighted participants are displayed in dark blue. ROIs that did not show effects are shown in light blue.

with voices affected brain areas typically associated with auditory working memory processing, such as the ventrolateral prefrontal cortex (Plakke et al., 2015; Cohen et al., 2014; Plakke and Romanski, 2014), the inferior parietal cortex (Jonides et al., 1998; Owen et al., 2005), the insula (Huang et al., 2013; Koelsch et al., 2009) and the auditory cortex (Bancroft et al., 2014). Furthermore, these findings are in line with earlier studies on voice identity processing, as the inferior frontal gyrus, the superior temporal sulcus and the insular cortex have been previously shown to interact during voice identity processing (McGettigan et al., 2013). In sighted participants, working memory training with voices increased connectivity between these brain areas, possibly indicating a strengthening of processing efficiency within the task-relevant auditory working memory network (Kelly and Garavan, 2005) (for a correlation with the behavioral performance see Table S5; insert Supplementary Table S5 here).

Crucially, our first main finding is that congenitally blind participants compared to the sighted showed a stronger training-related increase in connectivity between brain areas previously related to auditory working memory processing and the regions of visual cortex, particularly parts of the fusiform gyrus (see Table S5). Our findings are in line with previous fMRI studies that described activation of fronto-parietal brain areas during working memory processing in congenitally blind and sighted individuals, while the visual cortex was additionally activated in the blind (Amedi et al., 2003; Deen et al., 2015; Park et al., 2011). We extend these findings (and previous MEG findings of enhanced occipito-temporal connectivity in early blind individuals during speech comprehension; Van Ackeren et al., 2018) by showing training-induced changes in long-range neuronal network connectivity of visual cortex. Note, although the spatial resolution of source reconstruction in MEG is limited, our source space findings are in line with previous fMRI research. fMRI studies on voice recognition in congenitally blind individuals found increased activation of the right fusiform face area (Hölig et al., 2014), an area particularly involved in the visual processing of faces (Kanwisher et al., 1997), as well as increased activation of the left STS and bilateral fusiform gyrus (Gougoux et al., 2009). Cross-modal face-voice priming studies have shown that healthy sighted individuals are able to combine identity information from faces and voices (Ellis et al., 1997), possibly involving multisensory audiovisual integration areas, or direct connections between unisensory face- (fusiform face area) and voice-selective areas (along anterior STS; Belin et al., 2004, 2000) in cases where faces and voices are associated (Campanella and Belin, 2007; von Kriegstein et al., 2005). Thus, our finding of training-related connectivity increases between auditory and visual areas in the congenitally

blind might indicate unmasking or strengthening of cross-modal connections, due to congenital visual deprivation, that are only used under certain conditions in sighted humans (Pascual-Leone et al., 2005).

Activation of the ventral visual stream in congenitally blind individuals during voice identification has been previously interpreted as support of the notion of a preserved functional organization (i.e., ventral and dorsal stream; Goodale and Milner, 1992) as observed in sighted individuals for visual processing (Hölig et al., 2014; Renier et al., 2014). Thereby, the ventral visual stream would be involved in auditory object processing (e.g. voice processing; for an analysis of acoustic processing in visual cortex see Fig. S6; Supplementary Material). Recently, another hypothesis has been suggested to account for these findings (Bedny, 2017): visual deprivation paves the way for recruitment of visual cortex into higher cognitive processing, i.e., the activation does not depend on the intrinsic functional organization of visual cortex but, rather, on connectivity with higher-level processing areas and the information received from these areas. Thus, the ventral visual stream activation in our study, alternatively, might result from the use of a cognitive task, that is working memory processing.

Our second main finding revealed that working memory training effects had different spectro-temporal profiles in congenitally blind (beta-band) and sighted (theta-band) participants, suggesting different dynamics of network communication in the two groups. Both theta- and beta-band oscillations, supposedly, play a role in long-range cortical connectivity (Varela et al., 2001), and thus might be crucial for the interaction within widely distributed working memory networks. The finding of increased theta-band connectivity in the sighted is in line with the role of theta-band oscillations in the maintenance of multiple sequential items in working memory (Roux and Uhlhaas, 2014), suggesting that training strengthened maintenance-relevant communication within the working memory networks. Similarly, theta-band connectivity recorded during resting state EEG has been shown to be altered by working memory training (Langer et al., 2013), specifically connectivity (degree centrality) decreased anteriorly (prefrontal, premotor, right entorhinal cortex) and increased posteriorly (parietal, right superior temporal gyrus, left inferior frontal gyrus, insular cortex). Our findings of increased beta-band connectivity, in the congenitally blind, are in line with the previous literature. Beta-band oscillations have been suggested to have a particular role in maintaining the current sensorimotor or cognitive state (Engel and Fries, 2010), and thus might be relevant for memory maintenance processes (Kopell et al., 2011; Weiss and Mueller, 2012; Spitzer and Haegens, 2017). Furthermore, fronto-parietal beta-band connectivity has been shown to be altered by working memory training (Aster et al., 2015).

There are several possible interpretations of the differences in spectro-temporal profiles between the congenitally blind and sighted individuals. One possibility could be that these differences might relate to group differences in performance. However, no behavioral advantage was observed in the congenitally blind compared to the sighted in the 2-back task, presumably because participants were trained up to their performance limit in the adaptive n-back training task. Therefore, it seems unlikely that the differences in the spectro-temporal profile of the working memory networks in congenitally blind and sighted participants relate to working memory performance differences or learning progress in the 2-back task. Another possible explanation for these findings would be that congenitally blind individuals apply different working memory strategies, resulting in the different spectro-temporal profile of the networks. Crucially, in the present study, we found no differences in the reported strategies (insert Supplementary Table S4 here; Supplementary Material). We, thus, propose that the different spectral profiles observed in sighted and blind individuals arose from changes in the functional architecture of working memory networks in the congenitally blind, due to the alteration of long-range connectivity by integrating the visual cortex into existing networks. One possibility is that the changes in spectral profile reflect changes in the functional architecture that are directly related to structural changes; for instance, additional

connections might exist in the congenitally blind due to reduced pruning (Jiang et al., 2009). Yet another possibility is that the different spectro-temporal profile in the blind and the sighted reflect differences in the relative contribution of neural feedforward and feedback communication within the working memory networks. Feedforward connections are directed from primary to higher sensory areas (Bastos et al., 2015). They originate in supragranular layers and target the granular layers in higher areas (Felleman and Van Essen, 1991). Feedback connections take the inverse direction and originate in infragranular layers. LFP recordings in macaque monkey suggest that frequency-bands carry distinct information within neuronal networks (Bastos et al., 2015; Schmiedt et al., 2014). Beta-band (12–20 Hz) activity seems to indicate feedback connectivity from V4 to V1, while theta- (2–6 Hz) and gamma-band (>30 Hz) activity was involved in feedforward communication from V1 to V4 (Bastos et al., 2015) (for similar findings in human auditory cortex: Fontolan et al., 2014). Crucially, the spectral characteristics of the neuronal activity in V4 were altered when the feedforward connections from V1 were removed (Schmiedt et al., 2014). Beta-band activity increased, as the inhibition by feedforward processes was reduced. Based on these findings, it might be speculated that deprivation-related atrophy in the thalamo-cortical connections to V1 in congenitally blind individuals (Ptitto et al., 2008) could increase beta-band connectivity in the visual cortex due to reduced feedforward input. Our findings suggest that such rather local changes in spectro-temporal characteristics might be at play at large-scale brain interactions too. Nevertheless, whether and how local changes in spectro-temporal characteristics are reflected in the communication within larger working memory networks requires further research.

Furthermore, in the present study, visual inspection suggests an antagonism between theta- and beta-band networks (Fig. 3), such that when working memory training resulted in increased connectivity in one frequency band, it rather decreased in the control group while connectivity in the other frequency band showed the opposite pattern across training groups. This dissociation suggests that working memory training resulted at the same time in enhancement and suppression of distinct (theta- and beta-band) networks. Further research, however, is required to better understand this effect.

In the present study, working memory training overall had more pronounced effects on connectivity compared to local activations reflected in oscillatory power. Overall, data from an exceptionally high number of congenitally blind individuals was included in this study ($n = 27$), however, note, although common for this type of investigation, a rather small number of participants was included in each condition ($n = 9$), possibly reducing the statistical power of our analyses, and contributing to the lack of findings on local activations.

In conclusion, our study provides novel evidence that congenital visual deprivation alters long-range interactions of visual cortex, resulting in an increased capability of visual cortex to be integrated into working memory related neural networks in a newly learned task. Different spectral characteristics of networks in congenitally blind compared to sighted adults might indicate different neural coupling mechanisms due to the integration of the visual cortex into task-related auditory working memory networks in the blind.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroimage.2019.03.003>.

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