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Functionally specific oscillatory activity correlates between visual and auditory cortex in the blind

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Many studies have shown that the visual cortex of blind humans is activated in non-visual tasks. However, the electrophysiological signals underlying this cross-modal plasticity are largely unknown. Here, we characterize the neuronal population activity in the visual and auditory cortex of congenitally blind humans and sighted controls in a complex cognitive task. We recorded magnetoencephalographic responses from participants performing semantic categorization of meaningful sounds that followed the presentation of a semantically related or unrelated haptic object. Source analysis of the spectrally resolved magnetoencephalography data revealed that: (i) neuronal responses to sounds were stronger and longer lasting in the auditory cortex of blind subjects; (ii) auditory stimulation elicited strong oscillatory responses in the visual cortex of blind subjects that closely resembled responses to visual stimulation in sighted humans; (iii) the signal in the gamma frequency range was modulated by semantic congruency between the sounds and the preceding haptic objects; and (iv) signal power in the gamma range was correlated on a trial-by-trial basis between auditory and visual cortex in blind subjects, and the strength of this correlation was modulated by semantic congruency. Our results suggest that specifically oscillatory activity in the gamma range reflects non-visual processing in the visual cortex of blind individuals. Moreover, our results provide evidence that the deprived visual cortex is functionally integrated into a larger network that serves non-visual functions.

Keywords: congenital blindness; visual cortex; cross-modal plasticity; gamma oscillations; magnetoencephalography

Introduction

Congenital blindness provides a unique opportunity to study cross-modal plasticity in the human brain (Bavelier and Neville, 2002; Merabet and Pascual-Leone, 2010). The sensory-deprived visual cortex of the blind is characterized by profound anatomical and metabolic differences compared with the sighted. In particular, grey matter volume and cortical surface have been found to

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be reduced (Noppeney *et al*., 2005; Jiang *et al*., 2009; Park *et al*., 2009; Lepore *et al*., 2010), the geniculocortical white matter tracts to be atrophic (Shimony *et al*., 2006) and metabolic baseline activity to be increased (Veraart *et al*., 1990). In contrast, many studies have reported task-related modulations of occipital cortical activity in the blind. Functional MRI and PET studies have found strong modulations of haemodynamic and metabolic signals in the primary and secondary visual cortex during various tasks such as Braille reading (Sadato *et al*., 1996; Büchel *et al*., 1998), sound localization (Gougoux *et al*., 2005; Collignon *et al*., 2011), speech perception (Röder *et al*., 2002; Bedny *et al*., 2011) and verbal memory (Amedi *et al*., 2003). In line with these findings, event-related EEG studies have revealed posteriorly shifted scalp topographies in blind participants compared with sighted controls (Rösler *et al*., 1993; Röder *et al*., 1999; Collignon *et al*., 2009). Moreover, transcranial magnetic stimulation over the occipital cortex can disrupt the performance in non-visual tasks in blind subjects (Cohen *et al*., 1997; Amedi *et al*., 2004), suggesting a functional significance of visual cortex activity in blind humans. Thus, although some studies provide evidence that the visual cortex of the blind exhibits profound atrophic changes, it may be functional and serve non-visual processing. However, the nature of occipital cortical function and its underlying physiological mechanisms in blind humans remain largely unknown (Bavelier and Neville, 2002; Pavani and Röder, in press).

In the visual cortex of sighted humans, sensory stimulation gives rise to responses with a characteristic spectral signature. Signal power in the alpha and beta range decreases, while signal power in the gamma range increases relative to pre-stimulus baseline (Hoogenboom *et al*., 2006; Hipp *et al*., 2011). The decrease of power in the alpha and beta frequency range is spatially broad and rather unspecific, while the oscillatory signal in the gamma range reflects specific visual stimulus features and is thought to reflect local cortical processing (Hasenstaub *et al*., 2005; Cardin *et al*., 2009; Donner and Siegel, 2011). Moreover, oscillatory neuronal activity may be critical for the integration of local populations into larger processing networks (Engel *et al*., 2001; Hipp *et al*., 2011). Thus, the spectral characteristics of neuronal activity in the visual cortex of blind humans, that have not been studied, may provide new insights into the function of the visual cortex following visual deprivation. In particular, the investigation of neuronal activity in the visual cortex and the interaction with signals in other cortical areas such as the auditory cortex may provide new experimental support for the hypothesis that the visual cortex of the blind is integrated into new functional networks to serve non-visual functions.

We used magnetoencephalography in combination with source analysis to characterize oscillatory neuronal population activity in the visual cortex of congenitally blind individuals and matched sighted controls in response to environmental sounds. We systematically manipulated the semantic congruency to a preceding haptic object. This allowed us to analyse the electrophysiological signals in the visual cortex of blind subjects and their correlation to those signals arising in auditory areas during both auditory processing and higher semantic functions. Our results reveal fundamental aspects of the electrophysiological signals underlying adaptive plasticity.

Subjects and methods

Participants

Eleven congenitally blind participants (six females; age 35.5 ± 9.5 years, mean ± SD, range 23–48 years; handedness: eight right, two ambidextrous, one left) and 11 control participants matched in age, gender, handedness and education (age 34.3 ± 10.4 years, mean ± SD; deviation in age between blind and control participants: SD 1.7 years, maximal difference 5 years; one of the ambidextrous blind participants was matched to a right-handed control, the other to a left-handed control participant) took part in this study and received monetary compensation for their participation. The causes of blindness included retinopathy of prematurity ($n = 6$), genetic defects ($n = 2$), oxygen deficiency at birth ($n = 1$), a distorted optic nerve ($n = 1$) and retinoblastoma ($n = 1$). Four of the congenitally blind participants had very weak residual light perception. All participants had normal hearing and had no history of neurological or psychiatric illness. Approval of the local ethics committee for this study was obtained and the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants prior to the recordings.

Stimulation and behavioural task

The stimulus set consisted of 22 objects for haptic exploration (Supplementary Fig. 1). Half of the objects belonged to the category 'leisure' and half to 'household' (Supplementary Fig. 1A and B). Each object was associated with a semantically congruent sound of ~400 ms duration (65 dB). For example, a table tennis ball was associated with the sound of a bouncing table tennis ball. Additionally, there were 10 objects referred to as 'control objects' that were not associated with a sound and neither related to 'leisure' nor 'household'.

All participants were blindfolded during the entire experiment. First, we trained the participants to name and categorize the stimuli. In two separate blocks, participants learned the stimuli based on haptic exploration with the right hand (including the control objects) and based on listening to the sounds. The stimuli were presented in a randomized order. Once a stimulus had been named and categorized correctly, it was removed from the set until all objects had been correctly identified. When participants encountered a control object they had to categorize it as such. This procedure was carried out twice.

After the participants were familiarized with the stimulus set, they performed the magnetoencephalography experiment (Fig. 1). An experimental trial started with an auditory cue (50-ms beep) indicating the start of the haptic exploration phase. During the haptic exploration phase, pink noise was presented via the headphones to ensure that participants did not hear any object-related sounds. After 2 s, a second cue signalled the end of the haptic exploration and instructed the participants to indicate via button press whether the object was a control object (10% of trials). This task ensured active processing of the haptic stimulus. Trials containing control objects did not enter the analysis. The auditory target stimulus was presented 2–2.4 s after the end of the exploration phase. The auditory stimulus could either be semantically congruent or semantically incongruent to the haptic stimulus (45% of trials, respectively). The participants' task was to identify the category of the auditory stimulus as either 'household' or 'leisure'. One second after the auditory stimulus offset, a third cue was presented to trigger the response of the participant. This enforced response delay ensured a large analysis window that was not confounded by the motor response. In total, we presented nine

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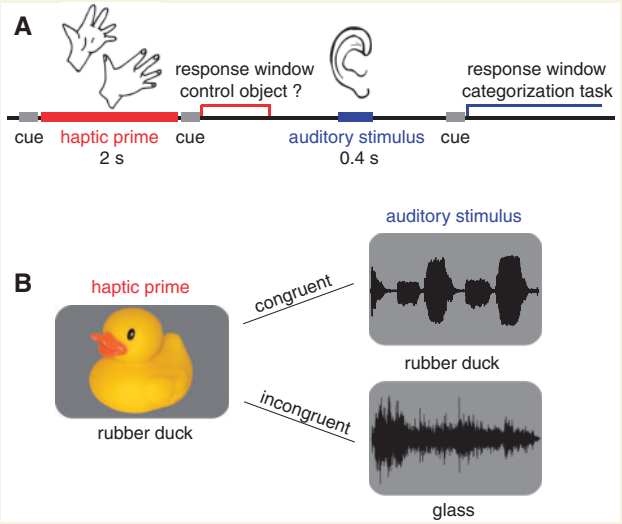

Figure 1 Behavioural task. (**A**) Timeline of an experimental trial. (**B**) Examples of congruency and incongruency between haptic prime and auditory stimulus.

practice and 294 experimental trials. For three participants, the experiment was divided into three blocks and for the remaining 19 participants, the experiment consisted of six blocks. All participants explored the objects with their right hand. The assignment of the response buttons for 'leisure' and 'household' to the left and right hand was randomized across participants.

Data acquisition and analysis

Magnetoencephalography was recorded continuously using a 275-channel whole-head system (Omega 2000, CTF Systems Inc.) in a magnetically shielded room. The electro-oculogram was recorded simultaneously for off-line artefact rejection. The head position relative to the magnetoencephalography sensors was measured before and after each recording session. The head displacement across a magnetoencephalography recording session was on average ± SD (7.3 mm ± 4.2 mm).

Magnetoencephalography signals were low-pass filtered online (cut-off: 300 Hz) and recorded with a sampling rate of 1200 Hz. Offline, the data were band-pass filtered (0.5–250 Hz, Butterworth filter; low pass filter order 4; high pass filter order 3) and line-noise was removed by subtracting the 50, 100, 150 and 200 Hz Fourier components. Then the continuous data were epoched from −1 to 1.2 s around the auditory stimulus onset. The mean signal was subtracted and the sampling rate was reduced to 600 Hz. Trials containing eye blinks, eye movements, muscle artefacts or signal jumps were manually detected and rejected from further analysis. Notably, saccadic spike artefacts have been localized far from the auditory and visual regions of interest we analysed here (Carl *et al*., 2011). Consequently, our results should not be affected by such signals.

T_1-weighted structural MRIs were obtained for all participants except one blind and one sighted. The MRIs were used to build individual head models for source analysis (see below). For the two participants without individual MRIs, the standard MNI brain was used.

The behavioural data were analysed with SPSS Statistics 15 (http://www.spss.com). All other data analyses were performed in Matlab (MathWorks) using custom scripts and the open source Matlab-toolboxes Fieldtrip (http://www.ru.nl/fcdonders/fieldtrip; Oostenveld *et al*., 2011) and SPM2 (http://www.fil.ion.ucl.ac.uk/spm).

Analysis of event-related fields

For the analysis of event-related fields (i.e. phase-locked activity) on the sensor level, the magnetoencephalography data were interpolated towards standard gradiometer positions (average positions across all subjects). The alignment was done by computing a minimum norm estimate using a large number of dipoles that are placed in the upper layer of the brain surface. We used individual head models for this procedure. Then a forward computation towards the standard gradiometer positions was applied. After the realignment, the planar gradients were calculated using a nearest-neighbour method. Signals were approximated by estimating the horizontal and vertical gradients of the recorded signal from the axial gradiometers. The data were baseline corrected with a baseline from −200 to 0 ms with respect to the auditory onset, before statistical testing was performed.

To compare event-related fields between blind subjects and sighted groups and between experimental conditions (congruent, incongruent), we applied cluster-based non-parametric randomization tests (Maris and Oostenveld, 2007). These tests control the type I error rate in experimental designs involving multiple comparisons by clustering adjacent sensor-time points exhibiting the same effect. For the group statistics, independent sample *t*-tests were calculated between the blind and sighted groups. For the statistics on condition effects within a group, dependent sample *t*-tests were calculated. The analyses were performed for a time window from 80 to 180 ms (cluster-$\alpha = 0.05$, 5000 randomizations). This time window broadly comprises the temporal window of the auditory N1 component (Näätänen and Picton, 1987).

Analysis of spectrally resolved signal power

All spectral estimates were performed using the multi-taper method based on discrete prolate spheroidal (Slepian) sequences (Mitra and Pesaran, 1999; Thomson, 1982). We computed spectral estimates across logarithmically scaled frequencies f from 4 to 181 Hz (0.25 octave steps) and across 23 points in time t from −0.5 to 1.05 s (0.05 s steps). We adjusted the temporal ($\Delta t = t_{max} - t_{min}$) and spectral smoothing ($\Delta f = f_{max} - f_{min}$; $f = \sqrt{f_{max} \cdot f_{min}}$; $f_{min} = f \cdot 2^{-o/2}$; $f_{max} = f \cdot 2^{+o/2}$) using the multi-taper method to match ∼200 ms and 3/4 octave [$o = \log_2(f_{max}/f_{min})$], respectively. For frequencies >18 Hz, we used temporal windows of 200 ms and adjusted the number of Slepian tapers N to approximate a spectral smoothing of 3/4 octave [$N = \text{round}(\Delta t \Delta f - 1)$]. For frequencies <16 Hz, we adjusted the time window to yield a frequency smoothing of 3/4 octaves with a single taper ($\Delta t = 2/\Delta f$). To estimate signal power, we multiplied the complex spectrum with its complex conjugate and averaged this across trials and tapers. We characterized the power response relative to the pre-stimulus baseline. The baseline window was selected to end at $t = 0$ s with a duration of ∼200 ms for frequencies >18 Hz and of up to 950 ms for frequencies <16 Hz (see details on spectral analysis above). This ensured that the baseline estimate was not affected by the auditory stimulation, but at the same time the baseline was as close as possible to the signal interval of interest.

To analyse the evolution of gamma power (90 Hz) at high temporal resolution, we performed additional analyses using just a single taper (Figs 2D, E and 3D). For the same spectral smoothing (3/4 octave),

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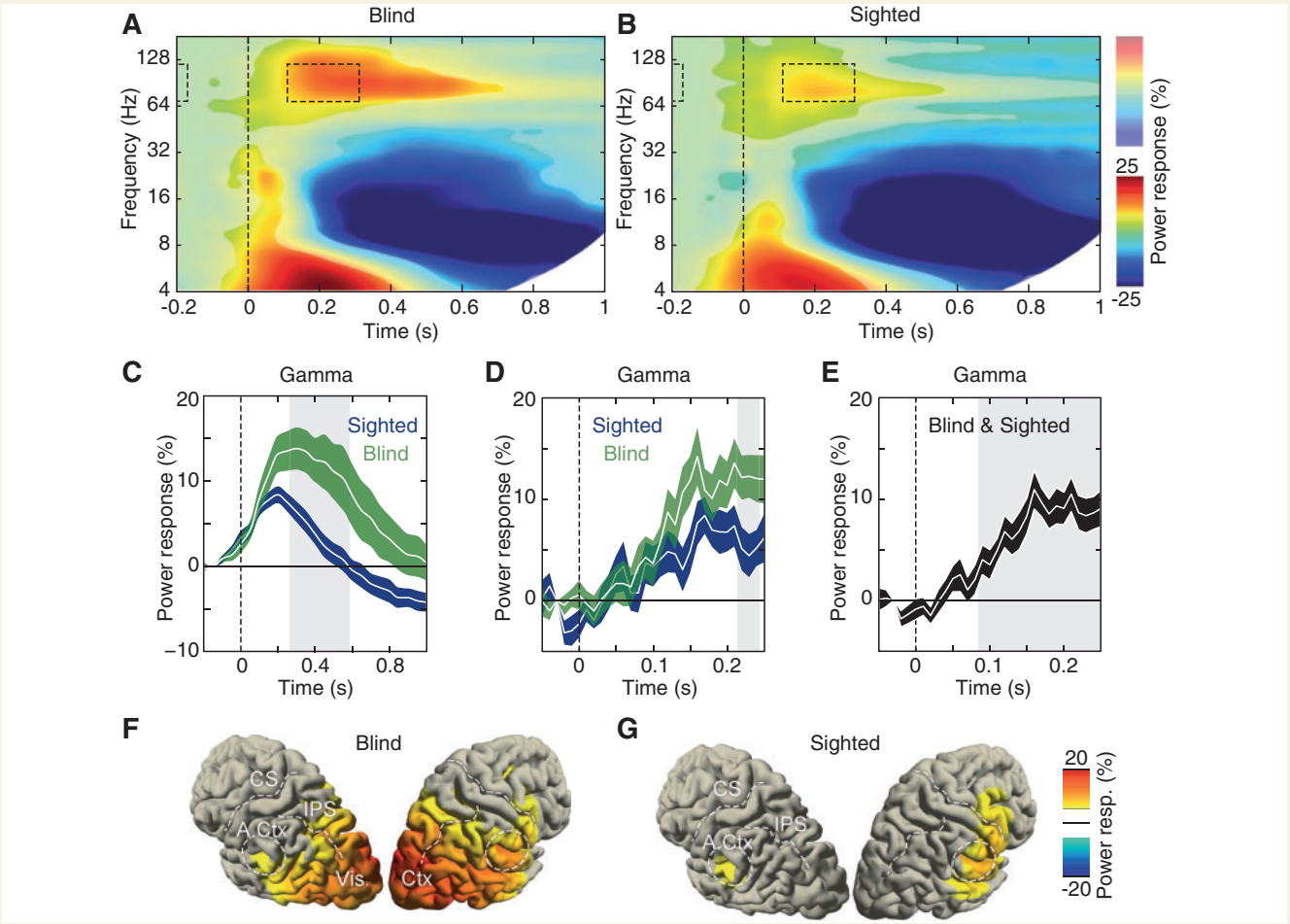

Figure 2 Neuronal response to auditory stimulation in the auditory cortex. (**A** and **B**) Change of neuronal activity in the early auditory cortex (BA 41, see the 'Subjects and methods' section) relative to pre-stimulus baseline for the blind (**A**) and the sighted controls (**B**). Time-point zero indicates sound onset. Data at long latencies for low frequencies is unavailable as a consequence of larger analysis windows for low frequencies. Dashed boxes indicate the time–frequency ranges used for the analysis illustrated in the other panels. (**C**) Temporal evolution of gamma range (75–110 Hz) activity in the auditory cortex. Colour bands represent the standard error of the mean. The grey shade indicates statistically significant differences between the blind and sighted controls (*t*-test, $P < 0.05$, false discovery rate corrected). (**D** and **E**) Temporal evolution of the response onset at high temporal resolution (centre frequency: 90.5 Hz; 45 ms analysis window) for the blind, the sighted (**D**) and all (blind and sighted, **E**) participants. Grey shades indicate significance (*t*-test, $P < 0.05$ for at least two successive time steps). (**F** and **G**) Spatial distribution of gamma range activity relative to pre-stimulus baseline for the blind (**F**) and the sighted controls (**G**) (75–110 Hz, 100–300 ms; statistical mask: *t*-test, false discovery rate corrected $P < 0.05$). A. Ctx = auditory cortex; Vis. Ctx = visual cortex; CS = central sulcus; IPS = intraparietal sulcus.

this results in a time window of 42 ms. We estimated the spectral power in 0.01 s steps ranging from −0.1 to 0.3 s and used the 42 ms before time 0 as baseline.

To estimate neuronal activity at the source level, we first derived individual physical forward models. To this end, we defined a regular grid (1 cm spacing) in MNI space (Collins *et al*., 1994), affine transformed this into individual head space using the participants' individual MRI (see above), and aligned the magnetoencephalography sensors to the head geometry based on three fiducial points (nasion, left and right ear, defined in the magnetoencephalography by three head localization coils). To derive the physical relationship between sources and sensors, we employed a single shell model (Nolte, 2003).

We used adaptive linear spatial filtering ('beamforming'; Van Veen *et al*., 1997; Gross *et al*., 2001) to estimate the spectral amplitude and phase of neuronal population signals at the cortical source level. The implementation details of the beamformer were as follows: for each time *t*, the frequency *f*, and the source location *r*, three orthogonal filters [$\hat{A} = (A_x, A_y, A_z)$; one for each spatial dimension] were computed that pass activity from the location *r* with unit gain, while maximally suppressing activity from all other sources:

$$\hat{A}(r,t,f) = [L^T(r)C_{real}(t,f)^{-1}L(r)]^{-1}L^T(r)C_{real}(t,f)^{-1} \quad (1)$$

where $L(r)$ is a matrix whose columns are the lead-fields of three orthogonal dipoles at the source location *r*, C_{real} denotes the real part of the complex cross-spectral density matrix for the data at frequency *f* and time *t*, and ^{T} indicates the transpose. To estimate power in source space, we applied the three spatial filters, took the

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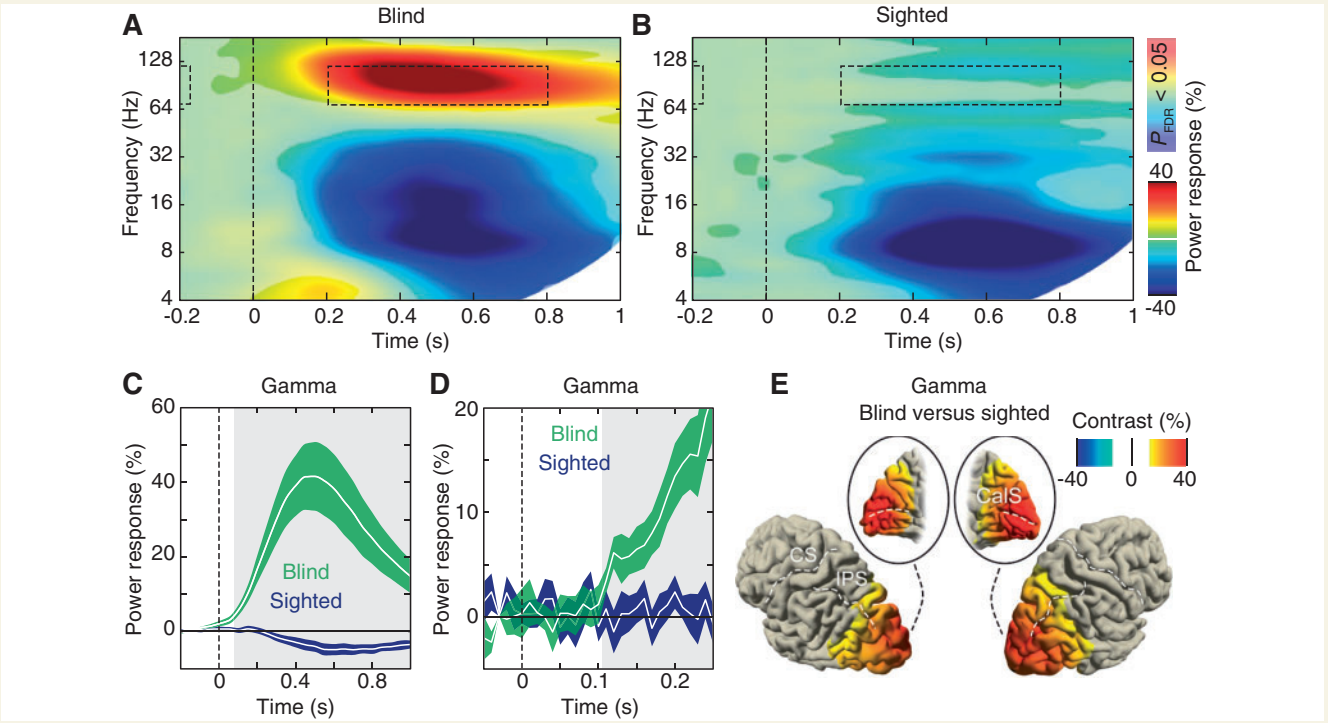

Figure 3 Neuronal response to auditory stimulation in the visual cortex. (**A** and **B**) Change of neuronal activity in the early visual cortex (BA 17, see the 'Subjects and methods' section) relative to pre-stimulus baseline for the blind (**A**) and the sighted controls (**B**). Dashed boxes indicate the time–frequency ranges used for the analysis illustrated in the other panels. (**C**) Temporal evolution of gamma range (75–110 Hz) activity in the visual cortex. Colour bands represent the standard error of the mean. The grey shade indicates statistically significant differences between the blind and sighted controls (*t*-test, $P < 0.05$). (**D**) Temporal evolution at high temporal resolution (centre frequency: 90.5 Hz; 45 ms analysis window). (**E**) Spatial distribution of difference in gamma range activity between the blind and the sighted (75–110 Hz, 200–800 ms; statistical mask: *t*-test, false discovery rate corrected $P < 0.05$). CalS = calcarine sulcus; CS = central sulcus; IPS = intraparietal sulcus.

square of the absolute values, summed over the three estimates and optionally averaged across all trials and tapers.

To illustrate estimated cortical source activity, we projected the statistically masked (see below for details in the 'Statistical analysis' section) sources onto the segmented surface of the 'colin27' MRI T_1 average (Holmes *et al*., 1998).

We investigated neuronal activity in predefined cortical regions (early visual cortex, auditory cortex). The auditory volume of interest was defined as the set of all sources in the regular MNI space grid (see above) that, transformed into Talairach space (Talairach and Tournoux, 1988; using mni2tal.m, http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach), are labelled as Brodmann Area (BA) 41. For the visual volume of interest, we used BA 17 accordingly. Source power was estimated at all locations in a volume of interest individually and was then averaged.

For statistical testing of differences in spectral power (activation versus baseline intervals; blind versus sighted participants; congruent versus incongruent trials), we first log transformed the power values to render the distributions more normal and then computed *t*-tests between conditions (Figs 2 and 3; Supplementary Figs 3 and 4). Although each blind participant had a matched sighted control, we took a conservative approach and based all group comparisons on unpaired statistical tests. Where necessary, we controlled for multiple comparisons using false discovery rate correction (Benjamini and Hochberg, 1995; Genovese *et al*., 2002) with $q = 0.05$ and the assumption of positive dependence. For experimental contrasts with a natural reference (baseline for the baseline versus activation interval; sighted for the blind versus sighted contrast), we report per cent change relative to this reference. For the contrast between congruent and incongruent trials where none of the two conditions qualifies as the reference, we report the contrast (difference divided by the sum; Fig. 4).

To investigate if the prominent gamma activity in the visual (75–110 Hz, 200–800 ms) and auditory cortex (75–110 Hz, 100–300 ms) during auditory stimulation in blind subjects were functionally related, we computed power–power correlations (Bruns *et al*., 2000). To this end, we extracted single trial power estimates from the volumes of interest (or for all locations in the regular grid, see above), applied a log transform to render the distribution more normal and computed Pearson's correlation coefficients. The correlation between gamma activity in auditory (75–110 Hz, 100–300 ms) and visual (75–110 Hz) cortex was computed in a sliding window of 200 ms length.

Investigating source–space relationships between neuronal signals from magnetoencephalography data is difficult. The limited spatial resolution of magnetoencephalography translates into a dominant spatial correlation pattern that drops slowly from any reference location and masks potentially meaningful interaction patterns even at large distances (Schoffelen and Gross, 2009; Hipp *et al*., 2011). This problem is illustrated in Supplementary Fig. 5, which shows the spatial profile of gamma range power–power correlations (75–110 Hz, 100–300 ms) between the auditory volume of interest and activity from locations on a straight line connecting the auditory and visual cortex. The correlation drops slowly from the auditory cortex and does

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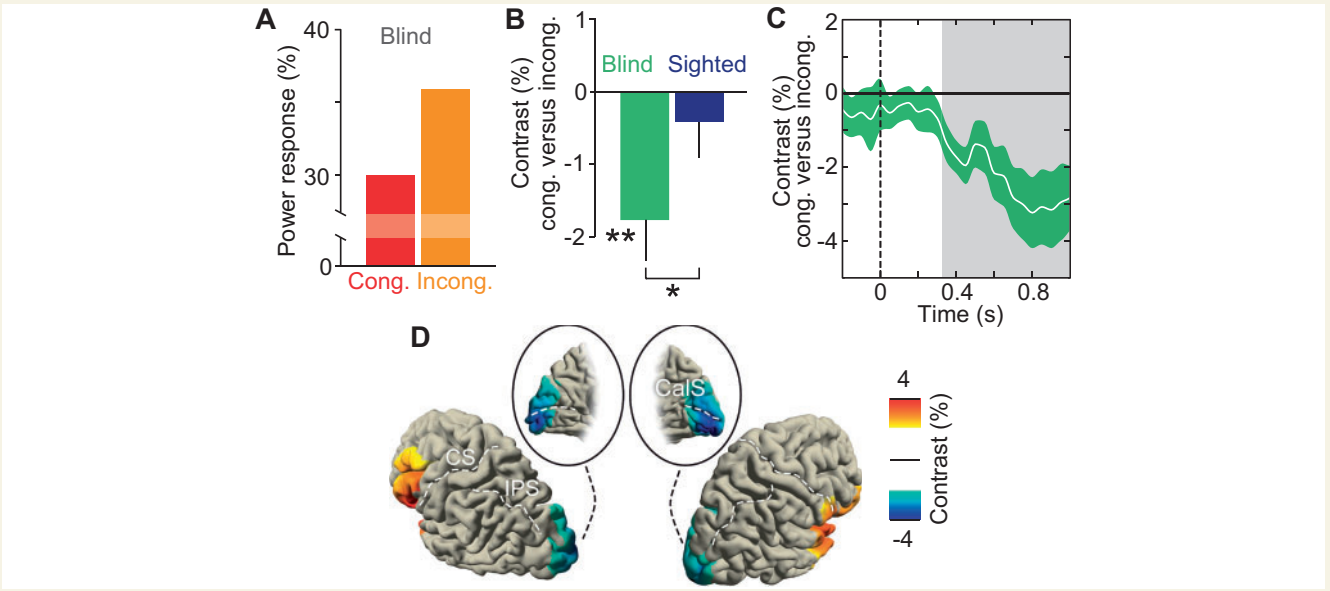

Figure 4 Congruency of haptic and auditory stimuli is reflected in gamma range activity in the visual cortex of the blind. (**A**) Average gamma range activity in the visual cortex of the blind relative to pre-stimulus baseline for congruent and incongruent trials. (**B**) Contrast (difference divided by sum) of gamma range activity (75–110 Hz, 200–800 ms) in the visual cortex for congruent and incongruent trials (asterisks indicate significant effects, *t*-test: $*P < 0.05$, $**P < 0.01$). (**C**) Temporal evolution of the gamma range activity contrast (75–110 Hz) in the visual cortex of the blind. Green bands represent the standard error of the mean. The grey shade indicates significant differences between congruent and incongruent trials (*t*-test, $P < 0.05$). (**D**) Spatial distribution of gamma range contrast (75–110 Hz, 400–1000 ms) between congruent and incongruent trials in the blind (statistical mask: *t*-test, $P < 0.05$). CaIS = calcarine sulcus; CS = central sulcus; IPS = intraparietal sulcus).

not vanish even at a distance of several centimetres and is highly similar for both groups. Consequently, the direct correlation between the signal power in auditory and visual areas (blind: $r = 0.25$, $P = 0.00004$; sighted: $r = 0.15$, $P = 0.0004$) cannot be interpreted. To remove the artefactual fraction of the correlation resulting from limited spatial resolution, we computed 'differences' between correlations (Δr) for blind subjects and the sighted controls instead of analysing 'raw' correlations. In other words, we used the correlation pattern in the sighted as a bias estimate or baseline for the blind.

For statistical testing of the correlations, we applied Fisher's *z*-transform and computed an unpaired *t*-test between blind subjects and sighted controls or for the double difference congruent versus incongruent between blind subjects and sighted controls.

Results

Behavioural task and performance

To investigate the processing of complex auditory stimuli and the effects of priming on auditory stimulus processing in blind and sighted humans, we presented our participants with an auditory task involving semantic categorization of meaningful sounds, which followed the presentation of a haptic object (Fig. 1). The congruency between the auditory stimulus and the preceding haptic object was experimentally manipulated, i.e. both stimuli were either semantically congruent or incongruent.

We analysed the behavioural performance (reaction times and accuracy) using repeated measures analyses of variance (ANOVA) with Congruency (congruent, incongruent) as a within-subject factor and Group as a between-subject factor. Overall, participants showed a higher accuracy in the categorization task on the auditory stimulus when the preceding haptic object was semantically congruent compared with trials in which it was incongruent [$F(1,20) = 10.46$, $P = 0.004$; congruent: mean ± SD (95.04 ± 3.62%), incongruent: 91.98 ± 6.44%]. Additionally, blind subjects showed a higher accuracy on the task than the sighted [$F(1,20) = 15.39$, $P = 0.001$; blind: mean ± SD (96.52 ± 2.22%), sighted: 90.50 ± 4.59%]. No interaction was found between the factors congruency and group for the task accuracy ($F = 2.92$, $P = 0.103$).

Similarly categorization was faster on congruent than on incongruent trials [$F(1,20) = 7.79$, $P = 0.011$; congruent: mean of the medians ± SD (467.80 ± 148.92 ms), incongruent: (391.25 ± 171.11 ms)] and blind subjects showed overall much faster reaction times than the sighted [$F(1,20) = 25.47$, $P < 0.001$; blind: mean of the medians ± SD (262.96 ± 101.08 ms), sighted: (494.09 ± 114.98 ms)]. Additionally, we found an interaction between the factors congruency and group on the reaction times [$F(1,20) = 8.12$, $P = 0.010$]. Despite the introduction of a delay between the complex sounds and the time to respond, the sighted responded faster in the congruent than in the incongruent condition [paired *t*-test, $t(10) = -3.03$, $P = 0.013$; sighted congruent: 471.91 ± 106.16 ms, sighted incongruent: 519.32 ± 126.21 ms]. We did not find an effect of congruency on reaction times for the blind [$t(10) = 0.08$, $P = 0.937$].

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In summary, the analysis of two behavioural parameters revealed that congruency between the haptic prime and the auditory stimulus led to a behavioural benefit for both blind subjects and the sighted controls. Thus, the haptic prime modulated the processing of the auditory stimulus.

We proceeded to analyse the concurrent changes in neuronal population activity following the presentation of the auditory stimulus. While the focus of this study was on oscillatory activity without a strict temporal relationship with the auditory stimulus onset, we also found changes in phase-locked signals. In particular, the event-related field was increased at left temporal and left occipital sensors during the time of the auditory N1 component (110–140 ms) in blind subjects compared with the sighted (cluster randomization test, $P = 0.005$). For more details and additional analyses of phase-locked signals see Supplementary Fig. 2.

Neuronal activity in the auditory cortex

Sound presentation induced frequency-specific changes of oscillatory activity in the auditory cortex. We employed source analysis ('beamforming') to estimate local neuronal population activity bilaterally in the early auditory cortex (BA 41) as a function of time and frequency. We quantified the change in neuronal activity in response to auditory stimulation relative to the pre-stimulus baseline for blind subjects and sighted controls (Fig. 2A and B). The modulation of neuronal activity was qualitatively similar for both groups. Following the stimulus onset, activity increased at low frequencies (<8 Hz) and in the gamma range (~64–128 Hz). In contrast, with a latency of 200 ms activity decreased at intermediate frequencies (alpha and beta range; ~8–32 Hz) (for all effects: *t*-test, $P < 0.05$, false discovery rate corrected). The modulation at low frequencies mainly reflects signals phase-locked to the onset of the stimulus presentation (i.e. auditory-evoked fields; Supplementary Fig. 3B).

The stimulus-related gamma frequency modulation in the auditory cortex was more pronounced and longer lasting in blind subjects compared with sighted controls. We compared the temporal evolution of neuronal activity in the identified time–frequency ranges for blind subjects and sighted controls. Neuronal activity in the gamma range was stronger for blind subjects than for the sighted between 300 and 600 ms after the stimulus onset (Fig. 2C; *t*-test, $P < 0.05$, false discovery rate corrected). To investigate the onset of this response, we performed an analysis with increased temporal resolution (centre frequency: 90.5 Hz; 45 ms analysis window). Oscillatory activity differed significantly from baseline from 90 ms onwards (Fig. 2E) but was indistinguishable between blind subjects and sighted controls up to 200 ms post-stimulus (Fig. 2D). No other frequency range revealed significant differences between groups (Supplementary Fig. 3D and F). Thus, the neuronal response in the auditory cortex had an overall qualitatively similar pattern for blind subjects and sighted controls but differed in the strength and the duration of the gamma range power.

The volume of interest analysis employed for the time–frequency analysis in the auditory cortex does not allow drawing conclusions on the spatial specificity of identified neuronal processes. To investigate the spatial extent and specificity of the gamma range effect, we imaged the changes in neuronal activity within the corresponding time–frequency window across the entire cortex (75–110 Hz, 100–300 ms; for other frequency ranges see Supplementary Fig. 3E and G). The neuronal response in sighted participants was centred bilaterally on the auditory cortex and extended with decreasing effect size into neighbouring areas (Fig. 2G). The spatial activation pattern in blind subjects was characterized by additional strong responses in the occipital and parietal cortex (Fig. 2F). To further characterize this prominent occipital activation in blind subjects, we next studied oscillatory activity in the visual cortex.

Neuronal activity in the visual cortex

The neuronal population response in the visual cortex differed profoundly between blind subjects and the sighted. We estimated the neuronal activity in the early visual cortex (BA 17) using the same volume of interest approach as for the auditory cortex. The neuronal response to auditory stimulation relative to the pre-stimulus baseline significantly differed between blind subjects and sighted controls (Fig. 3A and B; Supplementary Fig. 4A). The strongest effect was a sustained increase in gamma range power (~64–128 Hz) in blind subjects. This gamma range response peaked around 500 ms at ~40% above baseline and lasted to the end of the analysis window (1 s; Fig. 3C). This effect was completely absent in the sighted controls. An analysis with increased temporal resolution revealed that a significant elevation of gamma range activity above baseline started as early as 110 ms after stimulus onset (Fig. 3D). To investigate the spatial extent of this effect, we imaged differences in signal power between blind subjects and sighted controls in a broad time window in the gamma range (Fig. 3E; 75–110 Hz, 200–800 ms). In blind subjects, gamma frequency range activity strongly increased across the entire visual cortex.

Besides the increase in gamma range activity, we found differences in other frequency ranges (Fig. 3A and B; Supplementary Fig. 4A). The blind but not the sighted controls showed an increase in low-frequency power localized to visual areas (<8 Hz, 100–400 ms; unpaired *t*-test, $P < 0.05$, false discovery rate corrected; Supplementary Fig. 4B). Moreover, beta range activity decreased more in blind subjects compared with the sighted (16–32 Hz, 200–400 ms; unpaired *t*-test, $P < 0.05$, false discovery rate corrected, Supplementary Fig. 4C). Interestingly, the group difference in beta power was tightly constrained to the early visual cortex (mostly primary visual cortex, Supplementary Fig. 4C), while the beta range power decrease common to both groups spread across a large part of the occipital and parietal cortex (Supplementary Fig. 3G). In sum, our results demonstrate that auditory stimulation strongly modulated oscillatory activity in the visual cortex of blind subjects, the difference between groups being most pronounced in the gamma range.

Semantic congruency reflected in the visual cortex of blind subjects

The behavioural performance and, thus, processing of the auditory stimulus was modulated by the semantic congruency with the

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haptic prime (see above). We hypothesized that if a neuronal signal in the visual cortex of blind subjects reflected functionally relevant processing, it should be sensitive to experimental manipulations such as the stimulus congruency. Indeed, the neuronal response relative to the pre-stimulus baseline in the gamma range (75–110 Hz, 200–800 ms) was stronger for incongruent than for congruent trials (Fig. 4A; congruent, 29.9%; incongruent 35.9%). We confirmed the statistical significance of the congruency effect for blind subjects using the contrast of congruent versus incongruent trials (Fig. 4B, left; contrast: $-1.77 \pm 0.56\%$; *t*-test, $P = 0.0061$). This effect was robust also when tested against the sighted controls (*t*-test, $P = 0.044$; Fig. 4B). The congruency-related modulation of gamma range activity in blind subjects started at ~300 ms after the stimulus onset and peaked late at ~800 ms (Fig. 4C). To investigate the spatial extent of this effect, we imaged the congruency contrast across the entire brain of blind subjects (75–110 Hz, 400–1000 ms; Fig. 4D). The congruency effect was tightly localized to early visual areas (mostly primary visual cortex) in blind subjects. Notably, the functional map indicated a second congruency effect of opposite sign in blind subjects localized in the bilateral inferior frontal cortex [BA 47, Talairach coordinates of maximum (−45, 19, −9)]. This effect, however, did not reach significance when corrected for multiple comparisons (*t*-test $P > 0.05$, false discovery rate corrected). Note that when assessing the spatial extent of a known effect, no multiple comparison correction is necessary while it is required for explorative analyses.

Neuronal activity was not significantly modulated in the other frequency ranges in the visual cortex of blind subjects. We tested whether power in the lower frequencies was also modulated by semantic congruency. Neuronal signals in the visual cortex at lower frequencies were not modulated by stimulus congruency (low frequencies, <8 Hz, 100–400 ms, $P = 0.87$; beta range, 16–32 Hz, 200–400 ms; *t*-test, $P = 0.45$). However, we found a trend for a modulation of gamma range activity by stimulus congruency in the early auditory cortex (75–110 Hz, 100–300 ms; *t*-test, $P = 0.073$; contrast, 0.36%). Moreover, we performed all analyses reported in this section also for the sighted controls but did not find any significant effect ($P > 0.05$). In sum, gamma range activity in the visual cortex of blind subjects was cognitively modulated, suggesting a functional significance of these areas in blind subjects.

Correlation between auditory and visual cortex in blind subjects

If the visual cortex of the blind serves non-visual processing, it should interact with other areas involved in the respective tasks. We therefore investigated correlations of activity between visual and auditory cortex. Specifically, we derived single-trial gamma power estimates for the auditory (75–110 Hz, 100–300 ms) and the visual (75–110 Hz, 200–800 ms) cortex and computed correlations. To account for artefactual correlation due to the limited spatial resolution of magnetoencephalography, we computed differences of correlations (Δr) between blind subjects and the sighted controls instead of analysing raw correlations (Supplementary Fig. 5). Employing this strategy, we found a significant correlation between auditory and visual cortex ($\Delta r = 0.106$, $P = 0.032$; Fig. 5A). In a second step, we analysed the correlation between auditory and visual cortex in a time-resolved manner, correlating the auditory gamma range activity between 100 and 300 ms with visual gamma range activity in a sliding window (200 ms length). This correlation started at ~180 ms after the auditory stimulus onset and was significant between 180 and 400 ms and 600 and 800 ms (Fig. 5B; *t*-test, $P < 0.05$). To estimate the spatial specificity of the correlation with the visual cortex, we imaged the correlation between the gamma range activity in the auditory cortex and gamma range activity for the entire brain (auditory: 75–110 Hz, 100–300 ms; rest of the brain 75–110 Hz, 200–800 ms). The correlation with the auditory cortex as a seed area revealed a spatial pattern confined to early visual areas (Fig. 5C).

Stronger correlation on congruent trials

If the correlation between gamma power in auditory and visual areas in the blind reflected a functionally relevant interaction, it might be modulated by the semantic congruency of the auditory stimulus and the haptic prime. To test this possibility, we computed the inter-areal correlation separately for congruent and for incongruent trials (Fig. 5D). Indeed, the correlation was stronger in congruent trials compared with incongruent trials in blind subjects (congruent, $r = 0.29 \pm 0.04$; incongruent, $r = 0.21 \pm 0.04$; paired *t*-test difference, $P = 0.0060$) but not in the sighted (congruent, $r = 0.15 \pm 0.04$; incongruent, $r = 0.14 \pm 0.04$; paired *t*-test difference, $P = 0.78$). Importantly, the correlation for congruent and incongruent trials in blind subjects was larger than the baseline correlation in the sighted controls. Therefore, the difference between congruent and incongruent trials arose from auditory and visual areas exhibiting a higher correlation in congruent rather than a lower correlation in incongruent trials. Interestingly, this finding is in contrast with the local power change of gamma range activity in the visual cortex that was stronger for incongruent than for congruent trials (Fig. 4, see above). In summary, oscillatory activity in the gamma range was not only correlated between auditory and visual cortices of blind subjects, but the strength of this correlation varied with semantic congruency.

Discussion

Our study provides the first characterization of oscillatory neuronal signals in the visual and auditory cortex of blind humans and provides evidence that the deprived visual cortex is integrated into a larger network related to its new function.

Superior task performance in blind subjects

We found superior task performance of blind subjects in terms of both accuracy and speed. This finding is in line with superior performance in a variety of other auditory tasks in blind subjects

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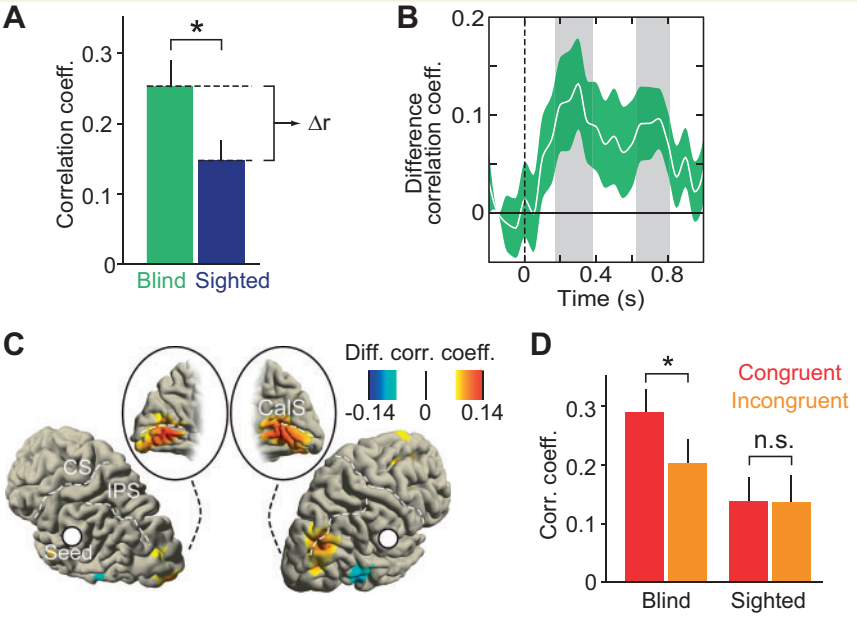

Figure 5 Correlation of gamma range activity in the auditory and visual cortex. (**A**) Correlation between gamma range activity in the auditory cortex (75–110 Hz, 100–300) and visual cortex (75–110 Hz, 200–800 ms) for the blind and sighted (asterisks indicate significant effects, *t*-test: $*P < 0.05$). (**B**) Temporal evolution of the difference in correlation between the blind and sighted controls. Correlation is computed between auditory gamma range activity (75–110 Hz, 100–300 ms) and visual gamma range activity (75–110 Hz) in a sliding window. Green bands represent the standard error of the mean. The grey shade indicates significant differences in correlation ($P < 0.05$). (**C**) Image of the differences in correlation between 'early' gamma range activity in the auditory cortex (75–110 Hz, 100–300 ms) and 'late' gamma range activity in the rest of the brain (75–110 Hz, 200–800 ms; statistical mask: *t*-test, $P < 0.05$). CalS = calcarine sulcus; CS = central sulcus; IPS = intraparietal sulcus. (**D**) Correlation for congruent and incongruent trials for blind subjects and sighted controls.

(Lessard *et al.*, 1998; Röder *et al.*, 1999; Gougoux *et al.*, 2004; Voss *et al.*, 2004). Superior tactile and auditory processing in blind subjects suggests that perceptual processing is accelerated (Röder *et al.*, 2003; Bhattacharjee *et al.*, 2010) and perceptual sensitivity is enhanced at least for some functions (Van Boven *et al.*, 2000; Gougoux *et al.*, 2004; Alary *et al.*, 2009; Wan *et al.*, 2010*a*; *b*; Norman and Bartholomew, 2011). Several electrophysiological processes in the auditory and visual cortex of blind subjects paralleled this increased behavioural performance.

Enhanced neuronal responses in the auditory cortex of blind subjects

Our results revealed that the spectro-temporal response signature to complex sounds in the auditory cortex is qualitatively similar in blind subjects and the sighted (increases in the gamma range and decreases in the alpha and beta range). This spectral signature is compatible with invasive electrocorticography recordings in the auditory cortex of neurosurgical patients (Crone *et al.*, 2001; Edwards *et al.*, 2005). Importantly, the neuronal response in the gamma range was stronger and longer lasting in blind subjects compared with sighted controls.

Furthermore, we found enhanced phase-locked signal amplitudes in blind subjects compared with the sighted. The amplitude at temporal sensors in the time range of the auditory N1 (110–140 ms) was increased for blind subjects. This finding is in line with a magnetoencephalography dipole modelling study, which suggested extended maps of tonotopic representation in blind subjects compared with the sighted (Elbert *et al.*, 2002). Moreover, it may relate to findings from a sensory substitution experiment in which blindfolded-sighted participants showed an enhanced N1 component (Pollok *et al.*, 2005).

Our results of increased electrophysiological activity in the auditory cortex of the blind extend functional MRI studies that report altered activity for blind subjects compared with the sighted (Gougoux *et al.*, 2009; Klinge *et al.*, 2010). The enhanced activity we report here may reflect intramodal plasticity in the blind, which has been suggested to be an important mechanism of behavioural compensation (Bavelier and Neville, 2002; Pavani and Röder, in press). Thus, the increased responses in the event-related field and the signal power may reflect enhanced processing in the auditory cortex of the congenitally blind underlying the superior behavioural performance.

Neuronal responses in the visual cortex of blind subjects to non-visual stimulation

Our results show that the neuronal response to auditory stimulation in the visual cortex of blind subjects closely resembles the spectro-temporal signature found for visual stimulation in

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the sighted (increases in the gamma range and decreases in the alpha and beta range; Hoogenboom *et al*., 2006; Hipp *et al*., 2011). This resemblance suggests that local neuronal activity in the deprived visual cortex has similar spectral characteristics as in non-deprived cortical areas even though the visual cortex of blind subjects undergoes major anatomical and metabolic changes (Veraart *et al*., 1990; Noppeney *et al*., 2005; Shimony *et al*., 2006; Jiang *et al*., 2009; Park *et al*., 2009; Lepore *et al*., 2010). In particular, oscillatory activity in the gamma frequency range (~64–128 Hz) was enhanced starting at ~110 ms. Oscillatory signals in the gamma range are thought to arise from local network activity (Hasenstaub *et al*., 2005; Cardin *et al*., 2009) and are modulated by the processing of specific stimulus features in the sighted visual cortex (Singer and Gray, 1995; Engel *et al*., 2001; Donner and Siegel, 2011). In other words, gamma band activity in the sighted visual cortex is an index of functionally relevant processing in local cortical circuits. Observing corresponding oscillatory signals in the deprived visual cortex strongly suggests intact processing in local cortical circuits. These findings substantiate changes in haemodynamic and metabolic activity, which were found during auditory and tactile tasks (Weeks *et al*., 2000; Burton *et al*., 2004; Renier *et al*., 2010). Thus, our results provide strong evidence that the activity in the visual cortex of blind subjects is involved in functionally relevant processing rather than being a mere co-activation (Röder *et al*., 2002).

Previous experiments in visually deprived animals reported altered single cell responses to auditory and somatosensory stimulation in the anterior ectosylvian cortex (a multimodal area; Korte and Rauschecker, 1993; Rauschecker, 1995) and in the visual cortex (Hyvärinen *et al*., 1981; Yaka *et al*., 1999; Izraeli *et al*., 2002; Kahn and Krubitzer, 2002). These experiments provide complementary evidence for cross-modal plastic changes in the deprived visual cortex on the microscopic level.

Neuronal responses in the visual cortex of blind subjects are modulated by semantic congruency

We found that activity in the visual cortex of blind subjects is modulated by the cognitive task: semantic congruency between the haptic prime and the auditory stimulus influenced the neuronal response in the gamma range. This finding agrees well with the idea that the deprived visual cortex is engaged in complex cognitive processing (Röder *et al*., 1996). Previous neuroimaging studies have found increased haemodynamic and metabolic activity in the visual cortex of the blind during tasks involving verbal memory (Amedi *et al*., 2003), episodic memory (Raz *et al*., 2005), Braille reading (Büchel *et al*., 1998; Sadato *et al*., 1998), language processing (Bedny *et al*., 2011) and semantic decisions (Noppeney *et al*., 2003). Moreover, transcranial magnetic stimulation over the occipital cortex interfered with verb generation and semantic mistakes were most frequent (Amedi *et al*., 2004). Noppeney *et al*. (2003) found that left visual cortex activation of blind subjects was increased compared with the sighted and stronger correlated with the left inferior frontal cortex during semantic processing. Furthermore, Bedny *et al*. (2011) linked increased haemodynamic signals in the visual cortex in blind subjects specifically to language processing, and functional connectivity of the visual cortex with the left inferior frontal cortex and the thalamus was increased relative to the sighted (Bedny *et al*., 2011). Importantly, in contrast with these studies, we used a direct measure of neuronal activity, which allowed us to assess the spectro-temporal characteristics of the modulation by semantic congruency. Specifically, oscillatory activity in the gamma frequency range (~64–128 Hz) was modulated from ~300 ms. Revealing this spectrally specific signature of the engaged visual cortex in blind subjects may help to understand cross-modal plasticity in the deprived cortex.

Notably, our study focused on the early auditory and visual cortex. However, other areas may be critically involved in cross-modal priming. Experiments on the effects of semantic congruency on multisensory processing have revealed temporal cortical areas (Hein *et al*., 2007; Doehrmann *et al*., 2010; Noppeney *et al*., 2010; Schneider *et al*., 2011), particularly the superior temporal sulcus, as well as prefrontal areas (Hein *et al*., 2007; Noppeney *et al*., 2008) to play a major role in cross-modal semantic processing.

Functional connectivity between visual and auditory cortex in blind subjects

In order to be recruited for new functions, deprived cortical areas need to exchange information with other areas involved in those functions in the non-deprived parts of the system. Our results provide evidence for such functional connectivity by showing that gamma range power was correlated on a trial-by-trial basis between auditory and visual cortex in the blind. Importantly, this functional connection was modulated by the semantic congruency between the haptic and the auditory stimulus. On semantically congruent trials, the correlation was found to be stronger than on incongruent trials suggesting a functional significance of the coupling between auditory and visual areas in blind subjects. Our findings extend and substantiate existing evidence from functional MRI experiments that suggest enhanced interaction between visual and non-visual areas in blind subjects (Liu *et al*., 2007; Fujii *et al*., 2009; Klinge *et al*., 2010). Our results expand these previous findings by characterizing the time course of the cortico-cortical correlation, demonstrating the spatial and spectral specificity of the coupling and showing that functional connectivity can be modulated by a cognitive task.

Several scenarios involving different brain structures and top–down as well as bottom–up signalling could explain the observed functional coupling. First, direct connections between early visual and early auditory cortex may underlie the covariation of signal power. This is supported by tracer studies in non-human primates (Falchier *et al*., 2002; Rockland and Ojima, 2003) and ferrets (Bizley and King, 2009) that found direct anatomical connections between sensory areas. A recent functional MRI study provides evidence for increased auditory to visual cortex connectivity in blind subjects compared with sighted controls in an auditory task (Klinge *et al*., 2010). Furthermore, multisensory interactions with very short latencies, as found in electrophysiological recordings, suggest that direct connections might also exist in humans

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(Giard and Peronnet, 1999; Molholm *et al.*, 2002). Secondly, alternatively or additionally to cortico-cortical connections, thalamo-cortical connections may underlie the covariation of activity in the auditory and the visual cortex. It has been proposed that broadly projecting thalamic nuclei such as the pulvinar serve as a relay for cortico-cortical connectivity (Sherman, 2007; Saalmann and Kastner, 2011). Thirdly, the correlation could reflect common top–down input to the auditory and visual cortex. In functional MRI studies, functional connectivity between the visual cortex and frontal language regions was increased in blind subjects (Noppeney *et al.*, 2003; Liu *et al.*, 2007; Bedny *et al.*, 2011). Thus, it is conceivable that frontal regions such as the inferior frontal cortex, which showed a trend for a congruency effect in our study, interact with the auditory and visual cortex in blind subjects leading to correlated activity between these areas. Such top–down connections from the prefrontal cortex might also explain the relatively late congruency effect starting ~300 ms. Fourthly, deprivation-related changes in thalamo-cortical bottom–up connectivity may underlie the correlation. Auditory stimulation may drive both the auditory and the visual cortex via altered thalamo-cortical pathways in blind subjects. Support for this hypothesis comes from animal studies (Asanuma and Stanfield, 1990; Karlen *et al.*, 2006), which have indicated altered thalamo-cortical connectivity due to visual deprivation. However, the relatively late congruency effect starting ~300 ms argues against this explanation. Importantly, these different scenarios are not mutually exclusive and may differ between early sensory and higher cognitive processing in the visual cortex of blind subjects.

In conclusion, we identified spectrally specific local and long-range neuronal signatures in the deprived visual cortex of blind subjects. Our findings provide novel electrophysiological evidence that the deprived visual cortex takes over new functions and is integrated dynamically into existing neuronal networks.

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Supplementary material

Supplementary material is available at *Brain* online.

References

Alary F, Duquette M, Goldstein R, Elaine Chapman C, Voss P, La Buissonniere-Ariza V, et al. Tactile acuity in the blind: a closer look reveals superiority over the sighted in some but not all cutaneous tasks. Neuropsychologia 2009; 47: 2037–43.

Amedi A, Floel A, Knecht S, Zohary E, Cohen LG. Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. Nat Neurosci 2004; 7: 1266–70.

Amedi A, Raz N, Pianka P, Malach R, Zohary E. Early 'visual' cortex activation correlates with superior verbal memory performance in the blind. Nat Neurosci 2003; 6: 758–66.

Asanuma C, Stanfield BB. Induction of somatic sensory inputs to the lateral geniculate nucleus in congenitally blind mice and in phenotypically normal mice. Neuroscience 1990; 39: 533–45.

Bavelier D, Neville HJ. Cross-modal plasticity: where and how? Nat Rev Neurosci 2002; 3: 443–52.

Bedny M, Pascual-Leone A, Dodell-Feder D, Fedorenko E, Saxe R. Language processing in the occipital cortex of congenitally blind adults. Proc Natl Acad Sci U S A 2011; 108: 4429–34.

Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B Methodol 1995; 57: 289–300.

Bhattacharjee A, Ye AJ, Lisak JA, Vargas MG, Goldreich D. Vibrotactile masking experiments reveal accelerated somatosensory processing in congenitally blind Braille readers. J Neurosci 2010; 30: 14288–98.

Bruns A, Eckhorn R, Jokeit H, Ebner A. Amplitude envelope correlation detects coupling among incoherent brain signals. Neuroreport 2000; 11: 1509–14.

Büchel C, Price C, Frackowiak RS, Friston K. Different activation patterns in the visual cortex of late and congenitally blind subjects. Brain 1998; 121: 409–19.

Burton H, Sinclair RJ, McLaren DG. Cortical activity to vibrotactile stimulation: an functional MRI study in blind and sighted individuals. Hum Brain Mapp 2004; 23: 210–28.

Cardin JA, Carlen M, Meletis K, Knoblich U, Zhang F, Deisseroth K, et al. Driving fast-spiking cells induces gamma rhythm and controls sensory responses. Nature 2009; 459: 663–67.

Carl C, Acik A, König P, Engel AK, Hipp JF. The saccadic spike artifact in MEG. Neuroimage 2012; 59: 1657–67.

Cohen LG, Celnik P, Pascual-Leone A, Corwell B, Falz L, Dambrosia J, et al. Functional relevance of cross-modal plasticity in blind humans. Nature 1997; 389: 180–3.

Collignon O, Vandewalle G, Voss P, Albouy G, Charbonneau G, Lassonde M, et al. Functional specialization for auditory-spatial processing in the occipital cortex of congenitally blind humans. Proc Natl Acad Sci USA 2011; 108: 4435–40.

Collignon O, Voss P, Lassonde M, Lepore F. Cross-modal plasticity for the spatial processing of sounds in visually deprived subjects. Exp Brain Res 2009; 192: 343–58.

Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J Comput Assist Tomogr 1994; 18: 192–205.

Crone NE, Boatman D, Gordon B, Hao L. Induced electrocorticographic gamma activity during auditory perception. Clin Neurophysiol 2001; 112: 565–82.

Doehrmann O, Weigelt S, Altmann CF, Kaiser J, Naumer MJ. Audiovisual functional magnetic resonance imaging adaptation reveals multisensory integration effects in object-related sensory cortices. J Neurosci 2010; 30: 3370–9.

Donner TH, Siegel M. A framework for local cortical oscillation patterns. Trends Cogn Sci 2011; 15: 191–9.

Edwards E, Soltani M, Deouell LY, Berger MS, Knight RT. High gamma activity in response to deviant auditory stimuli recorded directly from human cortex. J Neurophysiol 2005; 94: 4269–80.

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Elbert T, Sterr A, Rockstroh B, Pantev C, Muller MM, Taub E. Expansion of the tonotopic area in the auditory cortex of the blind. J Neurosci 2002; 22: 9941–4.
Engel AK, Fries P, Singer W. Dynamic predictions: oscillations and synchrony in top-down processing. Nat Rev Neurosci 2001; 2: 704–16.
Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 2002; 15: 870–8.
Gougoux F, Belin P, Voss P, Lepore F, Lassonde M, Zatorre RJ. Voice perception in blind persons: a functional magnetic resonance imaging study. Neuropsychologia 2009; 47: 2967–74.
Gougoux F, Lepore F, Lassonde M, Voss P, Zatorre RJ, Belin P. Neuropsychology: pitch discrimination in the early blind. Nature 2004; 430: 309.
Gougoux F, Zatorre RJ, Lassonde M, Voss P, Lepore F. A functional neuroimaging study of sound localization: visual cortex activity predicts performance in early-blind individuals. PLoS Biol 2005; 3: 324–33.
Gross J, Kujala J, Hamalainen M, Timmermann L, Schnitzler A, Salmelin R. Dynamic imaging of coherent sources: studying neural interactions in the human brain. Proc Natl Acad Sci USA 2001; 98: 694–9.
Hasenstaub A, Shu Y, Haider B, Kraushaar U, Duque A, McCormick DA. Inhibitory postsynaptic potentials carry synchronized frequency information in active cortical networks. Neuron 2005; 47: 423–35.
Hein G, Doehrmann O, Muller NG, Kaiser J, Muckli L, Naumer MJ. Object familiarity and semantic congruency modulate responses in cortical audiovisual integration areas. J Neurosci 2007; 27: 7881–7.
Hipp JF, Engel AK, Siegel M. Oscillatory Synchronization in large-scale cortical networks predicts perception. Neuron 2011; 69: 387–96.
Holmes CJ, Hoge R, Collins L, Woods R, Toga AW, Evans AC. Enhancement of MR images using registration for signal averaging. J Comput Assist Tomogr 1998; 22: 324–33.
Hoogenboom N, Schoffelen JM, Oostenveld R, Parkes LM, Fries P. Localizing human visual gamma-band activity in frequency, time and space. Neuroimage 2006; 29: 764–73.
Hyvärinen J, Carlson S, Hyvärinen L. Early visual deprivation alters modality of neuronal responses in area 19 of monkey cortex. Neuroscience Letters 1981; 26: 239–43.
Izraeli R, Koay G, Lamish M, Heicklen-Klein AJ, Heffner HE, Heffner RS, et al. Cross-modal neuroplasticity in neonatally enucleated hamsters: structure, electrophysiology and behaviour. Eur J Neurosci 2002; 15: 693–712.
Jiang J, Zhu W, Shi F, Liu Y, Li J, Qin W, et al. Thick visual cortex in the early blind. J Neurosci 2009; 29: 2205–11.
Kahn DM, Krubitzer L. Massive cross-modal cortical plasticity and the emergence of a new cortical area in developmentally blind mammals. Proc Natl Acad Sci USA 2002; 99: 11429–34.
Karlen SJ, Kahn DM, Krubitzer L. Early blindness results in abnormal corticocortical and thalamocortical connections. Neuroscience 2006; 142: 843–58.
Klinge C, Eippert F, Röder B, Büchel C. Corticocortical connections mediate primary visual cortex responses to auditory stimulation in the blind. J Neurosci 2010; 30: 12798–12805.
Korte M, Rauschecker JP. Auditory spatial tuning of cortical neurons is sharpened in cats with early blindness. J Neurophysiol 1993; 70: 1717–21.
Lepore N, Voss P, Lepore F, Chou YY, Fortin M, Gougoux F, et al. Brain structure changes visualized in early- and late-onset blind subjects. Neuroimage 2010; 49: 134–40.
Lessard N, Pare M, Lepore F, Lassonde M. Early-blind human subjects localize sound sources better than sighted subjects. Nature 1998; 395: 278–80.
Liu Y, Yu C, Liang M, Li J, Tian L, Zhou Y, et al. Whole brain functional connectivity in the early blind. Brain 2007; 130: 2085–96.
Merabet LB, Pascual-Leone A. Neural reorganization following sensory loss: the opportunity of change. Nat Rev Neurosci 2010; 11: 44–52.
Mitra PP, Pesaran B. Analysis of dynamic brain imaging data. Biophys J 1999; 76: 691–708.
Näätänen R, Picton T. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 1987; 24: 375–425.
Nolte G. The magnetic lead field theorem in the quasi-static approximation and its use for magnetoencephalography forward calculation in realistic volume conductors. Phys Med Biol 2003; 48: 3637–52.
Noppeney U, Friston KJ, Ashburner J, Frackowiak R, Price CJ. Early visual deprivation induces structural plasticity in gray and white matter. Curr Biol 2005; 15: 488–90.
Noppeney U, Friston KJ, Price CJ. Effects of visual deprivation on the organization of the semantic system. Brain 2003; 126: 1620–7.
Noppeney U, Josephs O, Hocking J, Price CJ, Friston KJ. The effect of prior visual information on recognition of speech and sounds. Cereb Cortex 2008; 18: 598–609.
Noppeney U, Ostwald D, Werner S. Perceptual decisions formed by accumulation of audiovisual evidence in prefrontal cortex. J Neurosci 2010; 30: 7434–46.
Norman JF, Bartholomew AN. Blindness enhances tactile acuity and haptic 3-D shape discrimination. Atten Percept Psychophys 2011; 73: 2323–31.
Oostenveld R, Fries P, Maris E, Schoffelen JM. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011; 2011: 1–9.
Park HJ, Lee JD, Kim EY, Park B, Oh MK, Lee S, et al. Morphological alterations in the congenital blind based on the analysis of cortical thickness and surface area. Neuroimage 2009; 47: 98–106.
Pavani F, Röder B. Crossmodal plasticity as a consequence of sensory loss: insights from blindness and deafness. In: Stein BE, editor. The new handbook of multisensory processes. MIT Press, 2012.
Pollok B, Schnitzler I, Stoerig P, Mierdorf T, Schnitzler A. Image-to-sound conversion: experience-induced plasticity in auditory cortex of blindfolded adults. Exp Brain Res 2005; 167: 287–91.
Rauschecker JP. Compensatory plasticity and sensory substitution in the cerebral cortex. Trends Neurosci 1995; 18: 36–43.
Raz N, Amedi A, Zohary E. V1 activation in congenitally blind humans is associated with episodic retrieval. Cereb Cortex 2005; 15: 1459–68.
Renier LA, Anurova I, De Volder AG, Carlson S, Vanmeter J, Rauschecker JP. Preserved functional specialization for spatial processing in the middle occipital gyrus of the early blind. Neuron 2010; 68: 138–48.
Röder B, Demuth L, Streb J, Rösler F. Semantic and morpho-syntactic priming in auditory word recognition in congenitally blind adults. Lang Cogn Processes 2003; 18: 1–20.
Röder B, Rösler F, Hennighausen E, Nacker F. Event-related potentials during auditory and somatosensory discrimination in sighted and blind human subjects. Brain Res Cogn Brain Res 1996; 4: 77–93.
Röder B, Stock O, Bien S, Neville H, Rösler F. Speech processing activates visual cortex in congenitally blind humans. Eur J Neurosci 2002; 16: 930–6.
Röder B, Teder-Salejarvi W, Sterr A, Rösler F, Hillyard SA, Neville HJ. Improved auditory spatial tuning in blind humans. Nature 1999; 400: 162–6.
Rösler F, Röder B, Heil M, Hennighausen E. Topographic differences of slow event-related brain potentials in blind and sighted adult human subjects during haptic mental rotation. Brain Res Cogn Brain Res 1993; 1: 145–59.
Saalmann YB, Kastner S. Cognitive and perceptual functions of the visual thalamus. Neuron 2011; 71: 209–23.
Sadato N, Pascual-Leone A, Grafman J, Deiber MP, Ibanez V, Hallett M. Neural networks for Braille reading by the blind. Brain 1998; 121 (Pt 7): 1213–29.
Sadato N, Pascual-Leone A, Grafman J, Ibanez V, Deiber MP, Dold G, et al. Activation of the primary visual cortex by Braille reading in blind subjects. Nature 1996; 380: 526–8.
Schneider TR, Lorenz S, Senkowski D, Engel AK. Gamma-band activity as a signature for cross-modal priming of auditory object recognition by active haptic exploration. J Neurosci 2011; 31: 2502–10.

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Schoffelen JM, Gross J. Source connectivity analysis with MEG and EEG. Hum Brain Mapp 2009; 30: 1857–65.

Sherman SM. The thalamus is more than just a relay. Curr Opin Neurobiol 2007; 17: 417–22.

Shimony JS, Burton H, Epstein AA, McLaren DG, Sun SW, Snyder AZ. Diffusion tensor imaging reveals white matter reorganization in early blind humans. Cereb Cortex 2006; 16: 1653–61.

Singer W, Gray CM. Visual feature integration and the temporal correlation hypothesis. Annu Rev Neurosci 1995; 18: 555–86.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain: 3-Dimensional proportional system—An approach to cerebral imaging. New York, NY: Thieme Medical Publishers; 1988.

Thomson DJ. Spectrum estimation and harmonic analysis. Proc IEEE 1982; 70: 1055–96.

Van Boven RW, Hamilton RH, Kauffman T, Keenan JP, Pascual-Leone A. Tactile spatial resolution in blind braille readers. Neurology 2000; 54: 2230–6.

Van Veen BD, van Drongelen W, Yuchtman M, Suzuki A. Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. IEEE Trans Biomed Eng 1997; 44: 867–80.

Veraart C, De Volder AG, Wanet-Defalque MC, Bol A, Michel C, Goffinet AM. Glucose utilization in human visual cortex is abnormally elevated in blindness of early onset but decreased in blindness of late onset. Brain Res 1990; 510: 115–21.

Voss P, Lassonde M, Gougoux F, Fortin M, Guillemot JP, Lepore F. Early- and late-onset blind individuals show supra-normal auditory abilities in far-space. Curr Biol 2004; 14: 1734–8.

Wan CY, Wood AG, Reutens DC, Wilson SJ. Congenital blindness leads to enhanced vibrotactile perception. Neuropsychologia 2010a; 48: 631–5.

Wan CY, Wood AG, Reutens DC, Wilson SJ. Early but not late-blindness leads to enhanced auditory perception. Neuropsychologia 2010b; 48: 344–8.

Weeks R, Horwitz B, Aziz-Sultan A, Tian B, Wessinger CM, Cohen LG, et al. A positron emission tomographic study of auditory localization in the congenitally blind. J Neurosci 2000; 20: 2664–72.

Yaka R, Yinon U, Wollberg Z. Auditory activation of cortical visual areas in cats after early visual deprivation. Eur J Neurosci 1999; 11: 1301–12.

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