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Gamma-band synchronisation in a frontotemporal auditory information processing network

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Gamma-band synchronisation in a frontotemporal auditory information processing network

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ABSTRACT

Neural oscillations are fundamental mechanisms of the human brain that enable coordinated activity of different brain regions during perceptual and cognitive processes. A frontotemporal network generated by means of gamma oscillations and comprising the auditory cortex (AC) and the anterior cingulate cortex (ACC) has been shown to be involved in the cognitively demanding auditory information processing. This study aims to reveal patterns of functional and effective connectivity within this network in healthy subjects by means of simultaneously recorded electroencephalography (EEG) and functional magnetic resonance imaging (fMRI).

We simultaneously recorded EEG and fMRI in 28 healthy subjects during the performance of a cognitively demanding auditory choice reaction task. Connectivity between the ACC and AC was analysed employing EEG and fMRI connectivity measures.

We found a significant BOLD signal correlation between the ACC and AC, a significant task-dependant increase of fMRI connectivity (gPPI) and a significant increase in functional coupling in the gamma frequency range between these regions (LPS), which was increased in top-down direction (granger analysis). EEG and fMRI connectivity measures were positively correlated.

The results of these study point to a role of a top-down influence of the ACC on the AC executed by means of gamma synchronisation. The replication of fMRI connectivity patterns in simultaneously recorded EEG data and the correlation between connectivity measures from both domains found in our study show, that brain connectivity based on the synchronisation of gamma oscillations is mirrored in fMRI connectivity patterns.

1. Introduction

Neural oscillations are fundamental mechanisms of the human brain that enable coordinated activity of different brain regions during perceptual and cognitive processes. Thus, detailed questions about how information is processed by the brain and how brain regions cooperate can only be answered adequately, if these temporal dynamics of brain activity are considered (Engel et al., 2001). The synchronisation of high frequency oscillatory activity within the gamma frequency range is known to be a fundamental operation mode of activated cortical networks (Fries, 2009) being critically involved in the integration of parallel neuronal activity (Singer, 1999). The 'communication through coherence' theory proposes that the between-region synchronization of gamma oscillations facilitates interregional communication, increases under attention-demanding conditions and enhances sensory processing (Fries, 2015). For instance, gamma oscillations have been suggested to be a correlate of the binding of sensory and high-order cortical areas (Başar et al., 2001; Richter et al., 2017). Interareal gamma-band synchronisation has been shown to mediate bottom-up stimulus processing during attentional task performance in the visual (Michalareas et al., 2016; Richter et al., 2017; van Kerkoerle et al., 2014) and auditory cortex (Fontolan et al., 2014). There is also evidence suggesting that gamma oscillations might be involved in top-down processing of sensory information (Citherlet et al., 2019; Debener et al., 2003; Jensen et al., 2007; Mulert et al., 2010, 2007; Polomac et al., 2015; Schadow et al., 2009). The processing of sensory information has been shown to involve an

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interaction between bottom-up information coming from primary sensory areas of the brain and top-down feedback connections accounting for influences of e.g. attention or expectation coming from higher-order cortical areas (Gilbert and Sigman, 2007).

Evoked gamma-activity, which typically appears in the early stages of sensory information processing and is phase-locked to the stimulus onset, is suggested to play a crucial role in the context of tasks demanding attentional control over sensory information processing (Fell et al., 2003; Gurtubay et al., 2004; Mulert et al., 2007; Senkowski et al., 2007; Tallon-Baudry et al., 2005). One example for this is the auditory evoked 40 Hz gamma-band response (aeGBR), which is usually found between 25 and 100 ms after stimulus presentation (Leicht et al., 2011). Not only sensory, but also attentional processing has been suggested to contribute to the aeGBR (Leicht et al., 2010; Mulert et al., 2007; Tiitinen et al., 1993). Indeed, its close relationship to selective attention has been reported for the 40 Hz aeGBR (Gurtubay et al., 2004; Senkowski et al., 2007; Tiitinen et al., 1997, 1993). Modulation of the aeGBR has been suggested to reflect top-down attentional processing of auditory stimuli (Debener et al., 2003; Schadow et al., 2009). Accordingly, besides generators in the auditory cortex (AC) (Edwards et al., 2005; Pantev et al., 1991; Steinschneider et al., 2008), the aeGBR has been shown to additionally originate from the dorsal anterior cingulate cortex (ACC) by means of EEG source localisation (Ahveninen et al., 2000; Mulert et al., 2007; Schadow et al., 2009) and simultaneous recordings of EEG and fMRI (Mulert et al., 2010) during effortful and cognitively demanding auditory tasks. A study using magnetencephalography (MEG) showed an increase of gamma synchronisation between ACC and AC to be associated with higher cognitive demands of an auditory task (Polomac et al., 2015). In other words, the observation of a relationship between attentional processes and gamma oscillations observed early during processing of sensory information has recently been supplemented by findings of generators of this gamma activity within frontal brain regions and a gamma-mediated interaction between frontal brain regions and sensory areas.

However, it is still unclear whether the aeGBR is involved in bottom-up or top-down processes or a combination of both whilst forming this frontotemporal network engaged in the cognitively demanding auditory information processing. This study aims to find out whether the ACC is (1) interacting with the AC and (2) is influencing the AC or is influenced by the AC or both via synchronisation of gamma oscillations during the aeGBR timeframe of auditory information processing under cognitive demands. We have investigated the connectivity between the ACC and bilateral ACs by using functional and effective connectivity measures in simultaneously recorded EEG and fMRI data in order to cross-validate findings from both modalities. As it is still unclear how synchronisation of oscillatory activity as a measure of interaction between brain regions is reflected in fMRI connectivity patterns, this study also aimed to investigate the relationship between fMRI and EEG gamma connectivity measures. We hypothesized that an increase of EEG gamma synchronisation between the ACC and the AC during the performance of a cognitively demanding auditory task will be accompanied by an increase of fMRI connectivity between those regions. Moreover, we assumed that effective connectivity measures from both modalities will show an ACC top-down modulation of ACs and that EEG and fMRI connectivity values will be correlated in our group of healthy subjects.

2. Materials and methods

2.1. Participants

This study relies on a data sample from 24 healthy adults ($n = 11$ males and $n = 13$ females, mean age 23.0 (SD 3.7), all right-handed), which has been acquired as a control group in a recently published study comparing a gamma-band specific brain network involved in the auditory information processing between healthy controls and individuals at high risk for psychosis (Leicht et al., 2016). Exclusion criteria for the healthy participants were substance abuse of any kind, a psychiatric or neurological disorder or treatment as well as any family history of psychiatric disorders. All subjects could perceive tones above 30 db at a pitch level of 1000 Hz as assessed by means of a hearing test prior to the MRI recording. One subject had to be excluded from the analysis due to excessive noise in EEG and fMRI data. Written informed consent was obtained from all participants prior to any study procedures. The study was approved by the Ethics committee of the Hamburg Medical Association and was carried out in accordance with the latest version of the Declaration of Helsinki.

2.2. Paradigm

We used an auditory reaction task, which has previously been shown to increase both the aeGBR amplitude as well as the aeGBR-specific BOLD response within the auditory cortices and the dorsal ACC depending on the level of attentional demand (Leicht et al., 2010; C. Mulert et al., 2010; Christoph Mulert et al., 2007). In this paradigm 300 tones of 3 different pitches (33% at 700 Hz, 33% at 1000 Hz, 33% at 1300 Hz) were presented for 200 ms using the Presentation software version 17 installed on a personal computer outside the shielded MR room. Stimuli were presented in pseudo-randomized inter-stimulus-intervals (ISI: 2.5–7.5 s, mean 3.8 s.) using MRI-compatible electrostatic headphones. Tones of 700 Hz and 1300 Hz were defined as target stimuli and participants were instructed to respond to those tones as fast and accurately as possible using their left and right index fingers, respectively. Reaction times and error rates (number of incorrect responses or missing responses within 2 s of target stimulus presentation) were registered.

2.3. fMRI: data acquisition and preprocessing

The MRI data was acquired by means of a 3 Tesla MRI scanner (Siemens Magnetom Trio) equipped with a 12-channel head coil using a standard gradient echo-planar imaging T2* sensitive sequence designed for functional BOLD imaging. 24 slices covering the whole brain (456 vol, TR = 2.5 s; TA = 1.4 s, TE = 30 ms; FOV = 216/216 mm; matrix = 72 × 72; interleaved slice acquisition, slice thickness = 4 mm; interslice gap = 1 mm; resulting pixel size = 3 × 3 mm) were acquired in the same position as a 3-dimensional MPRAGE data set (T1 weighted). MR-acquisition free periods of 1.1 s were used for interleaved EEG acquisition in a sparse sampling design in order to avoid disturbances of gradient artefacts in our EEG signal of interest or disturbances in the delivery of auditory stimuli due to scanner noise. During the acquisition of fMRI data the vacuum pump of the MRI scanner was switched off in order to avoid EEG artefacts within the gamma frequency range of interest.

The preprocessing of the MRI signal was performed in SPM 12 while using the CONN-toolbox in MATLAB (Whitfield-Gabrieli and Nieto-Castanon, 2012). Functional images were slice time corrected and realigned in order to correct for motion artefacts. Anatomical images were coregistered to the mean of functional images. After coregistration of functional volumes, the imaging data were resliced to 3 mm^3. Functional images were then normalized to the Montreal neurologic Institute (MNI) template (Evans et al., 1993). In order to remove confounding effects from the BOLD time series, the aCompCor strategy was used (Behzadi et al., 2007). This method identifies and associates principal components associated with white matter and cerebrospinal fluid for each subject individually in an automated manner. This has the advantage of not affecting intrinsic functional connectivity during noise reduction without cancelling out the global signal, which could lead to false negative correlations in the processed data (Chai et al., 2012). The time courses of the top five principle components associated with white matter and cerebrospinal fluid were omitted as confounds (Behzadi et al., 2007; Chai et al., 2012). Functional images were smoothed with an

$8 mm^3$ isotropic gaussian kernel. During denoising, 12 motion regressors (comprised of 6 realignment parameters and their respective first derivatives) were included to control for correlations due to subject movement in the scanner. Furthermore, the main effects of the choice reaction task were included as confounders in the denoising step and a high-pass filter of 0.008 Hz was applied to the data (Friston et al., 1997).

2.4. fMRI: regions of interest

The selection of regions of interest (ROIs) was based on procedures from previous EEG- (Leicht et al., 2010; Mulert et al., 2007), MEG- (Polomac et al., 2015) and simultaneous EEG-fMRI (Mulert et al., 2010) studies on the involvement of the ACC and its interaction with the auditory cortices (Polomac et al., 2015) in performing a cognitively demanding auditory task, which was used in the present study. A previously conducted conventional fMRI BOLD analysis of the present dataset revealed task-related activity within the auditory cortices and the ACC (Leicht et al., 2016). Accordingly and in view of our hypothesis, we anatomically defined an ACC ROI and bilateral auditory cortex ROIs using the FSL Harvard-Oxford maximum likelihood cortical atlas (Desikan et al., 2006). This atlas contains 34 cortical regions in each hemisphere and allows the selection of anatomical ROIs in MNI normalized data. The ACC ROI comprised all voxels within the anterior cingulate gyrus according to this atlas (centre of mass: $x = 0$; $y = 18$; $z = 24$, extension: X [−12 to 15], Y [−17 to 46], Z [−9 to 47]). The bilateral auditory cortex ROIs included all voxels within the posterior superior temporal gyrus (pSTG; centre of mass: right [$x = 61$; $y = -24$; $z = 2$], left [$x = -62$; $y = -29$; $z = 4$]; extension right: X [45 to 71], Y [−35 to −9], Z [−14 to 16]; extension left: X [−69 to −49], Y [−42 to −13], Z [−7 to 16]).

2.5. fMRI: analysis of connectivity

In order to test for an increase of fMRI functional connectivity between ACC and auditory cortex during target stimuli trials on group level, a seed-to-whole-brain approach with the ACC ROI as the seed was used. Therefore, the Pearson correlation between the BOLD signal of the ACC ROI and the BOLD signal of every single brain voxel was calculated. The connectivity between single voxels and the ACC ROI was considered to be significant, if the correlation analysis revealed a $p < 0.0001$ (FDR [false discovery rate] corrected).

In order to extract functional connectivity values between ROIs on the single subject level, we calculated bivariate ROI-to-ROI correlations between all possible pairs of the three ROIs. The threshold for significance was set at $p < 0.01$ (FDR corrected). Connectivity values for each subject and connection were extracted for comparison with EEG connectivity measures. Correlation values were Fisher-transformed in order to achieve normal distribution.

As a second measure of functional connectivity in the fMRI domain, we used the generalized psychophysiological interaction (gPPI) analysis (McLaren et al., 2012). The gPPI models an interaction between the time course of a seed region and a general linear model describing the task condition and compares this computed time course with the observed time courses of target voxels, thereby measuring correlation with the constructed interaction model. This is done using a bivariate regression model (Friston, 2002). The result of the comparison between observed and computed time courses is an asymmetric connectivity matrix. A change in condition modulates the degree to which the activity in the target region can be predicted by the activity of the seed region. The change in the seed region's modulation of the activity in the target region, which can be assigned to experimental manipulation, is defined as a psychophysiological interaction (Friston, 2002; Friston et al., 1997). This can be interpreted in two different ways: The experimental factor can either directly modulate the contribution of one area to another or it can modulate the responsiveness of the target area to the psychological factor by modulating its condition-specific response (Friston et al., 1997).

We performed gPPI analyses in order to identify the brain regions showing a significant task-dependant increase in functional connectivity by comparing target to non-target stimuli trials. Therefore, trials in which target stimuli were presented were assigned a weight of 1, whereas trials in which the non-target stimuli were presented, were assigned a weight of 0 in order to model a baseline condition. The resulting time course was convoluted with a canonical hemodynamic response function (HRF) in order to create the psychological regressor for the gPPI analysis. The threshold for significance was defined as $p < 0.05$ (FDR corrected). In order to extract gPPI connectivity values for the comparison with EEG effective connectivity measures, we extracted ROI-to-ROI gPPI connectivity values (one connectivity value per directed connection per subject) between the ACC and auditory cortex ROIs.

2.6. EEG: acquisition and preprocessing

EEG recordings were obtained within the MRI scanner interleaved with the acquisition of fMRI data. Subjects were lying on their back and were asked to keep their eyes open and look at a fixation cross projected to a mirror mounted onto the head coil. For EEG data recordings two EEG amplifiers were used, which were developed specifically for the operation in the MRI scanner environment in order to avoid saturation through magnetic activity (BrainAmp MR plus, Brain products). EEG recordings were performed in alternating current mode with 64 active EEG electrodes mounted on an elastic cap (BrainCapMR 64, Brain Products) using the BrainVision Recorder software (Version 1.10, Brain Products). Electrodes were arranged according to a modified 10/10 system, using FCz as reference electrode and AFz as ground. The electrode skin impedance was kept below 10 kΩ. Data were collected at a sampling rate of 5000 Hz with an analogous band-pass filter (0.1–250 Hz). The amplitude resolution was set to 0.1 microVolt in order to accurately measure low amplitude gamma oscillations.

The EEG data preprocessing was carried out using Brain Vision analyzer (BVA) Version 2.0 (Brain Products) as described in detail in (Leicht et al., 2016). The continuous EEG data were segmented into gradient artefact free epochs (MR-acquisition-free periods of 1.1 s) including the aeGBR to the stimuli, filtered using a band-pass (30–100 Hz, Butterworth Zero Phase Filter, slope 48 db/oct) and a notch filter (50 Hz), resampled to a sampling rate of 1000 Hz and re-referenced to common average reference. Next, we identified the subjects' individual peak frequencies of the aeGBR (method described in (Leicht et al., 2016)). This information was used in an independent component analysis (ICA) based approach in order to identify the aeGBR power information on a single trial level. ICA (Algorithm: Infomax [Gradient] extended biased, calculating components corresponding to an eigenvalue >0.05) was performed on appended single trial epochs with a length of 500 ms starting 250 ms prior to the target stimuli (number of calculated components 61.3 [SD: 1.3]). After baseline correction (baseline: 250 ms prior to the stimulus) and averaging of the resulting components over trials for every subject, a continuous wavelet transformation with a complex Morlet wavelet (real values [μV2], 10 frequency layers distributed on a logarithmic scale, Morlet parameter $c = 5$, Gabor Normalization) for the frequency range from 30 to 50 Hz was performed on every ICA component. Next, components including the aeGBR information were identified by showing a threefold gamma power peak value within the timeframe of 30–120 ms after stimulus presentation compared to the gamma power peak value within a baseline of 100 ms before stimulus presentation in the subjects' individual peak frequency layer. Only the components carrying the aeGBR information were projected back to the sensor space (number of aeGBR carrying components: 10.2 [SD: 4.4]) followed by a baseline correction (baseline: 100 ms prior to the stimulus). This resulted in gamma frequency oscillatory activity data for each of the single trials and recording electrodes of each subject (sensor level single trial gamma activity). These data were forwarded to EEG source localisation and connectivity analyses.

2.7. EEG: source localisation and regions of interest

In order to identify sources of the gamma activity recorded at electrodes on the scalp, we transformed the preprocessed single-trial sensor level data into the source space using the linearly constrained minimum variance (lcmv) beamformer approach. The lcmv beamformer method has commonly been used in the analysis of EEG and MEG data (Gross et al., 2001; Knyazev et al., 2016; Mill et al., 2017; Safar et al., 2018; Schoffelen and Gross, 2009; Sekihara et al., 2001; Van Veen et al., 1997; Vrba and Robinson, 2001). In simulations with MEG data, it is better suited for point-sources rather than other solutions such as Minimum Norm estimates (Hincapié et al., 2017). Mathematically, this approach includes the minimizing of the output of a linear filter under the constraint that its gain is unity at the location of interest (Darvas et al., 2004). It can be interpreted as a “virtual depth electrode”, which extracts the contribution of the desired dipole source while at the same time minimizing the overall output power. This results in a maximal suppression of contributions from all regions other than the desired dipole.

Analogous to the fMRI ROI selection and in accordance with our hypothesis, we anatomically defined ROIs within the ACC (Brodmann area 24) and the bilateral auditory cortex (Brodmann area 22) for the purpose of EEG connectivity analyses. The localization of the ROIs was based on experimental evidence from EEG-, MEG- and EEG-informed fMRI studies investigating the localisation of aeGBR sources (Busch et al., 2004; Leicht et al., 2010, 2016; Mulert et al., 2010, 2007; Polomac et al., 2015). The definition of the ROIs was done using a three-shell spherical head model registered to a standardized stereotactic space (Talairach and Tournoux, 1988). In order to extract the ROI gamma activity time series data, the signal of the centroid of each ROI was extracted. The centroid is an excellent representative of source-space activity in the surrounding area (Canuet et al., 2011).

2.8. EEG: analysis of connectivity

EEG connectivity analyses were conducted in Matlab (MathWorks) using the Fieldtrip-toolbox (Oostenveld et al., 2011). As a measure of EEG functional connectivity we used the lagged phase synchronization (LPS) analysis. This is a measure of dependence between two signals that reflects the similarity between these two signals in the frequency domain based on normalized Fourier transforms. It excludes the instantaneous zero-lag contribution, which is useful in EEG signals due to the influence of field spread and volume conduction artefacts in the zero-lag domain (Pascual-Marqui et al., 2011).

We calculated LPS values between each pair of ROIs using the single trial gamma activity time series extracted from each of the ROIs. Connectivity values calculated for the aeGBR timeframe from stimulus onset to 50 ms poststimulus were compared with baseline values calculated for a timeframe of 50 ms prior to the stimulus onset. A statistical comparison was conducted using a repeated-measures ANOVA with post-hoc t-tests.

A granger causality analysis was used in order to assess the effective connectivity in the EEG domain. Granger causality is a statistical tool that uses lagged-vector autoregressive models to determine, if one signal time-course predicts the future behaviour of another when given full knowledge of all signals in a system that could potentially have a causal impact (Granger, 1969). One granger signal causes another, if the error term increases significantly when excluding the first signal from the model. Here, granger causality was calculated in the frequency domain in order to achieve a spectral representation of connectivity (Ding et al., 2006).

Analyses were conducted using the network ROIs described above and a time period from 0 - 250 ms after stimulus onset in order to allow for the frequency decomposition. In order to calculate granger connectivity values in the frequency domain, a multitaper-frequency transformation was applied to the data using a Hanning-Taper. Afterwards, the data was fourier-transformed in order to calculate the coherence spectra as well as granger causality through non-parametric spectral matrix factorization (Dhamala, Rangarajan, & Ding, 2008). This non-parametric approach to granger causality calculation has the advantage of not requiring the estimation of an autoregressive model order. Connectivity values were then tested for significance using a simple *t*-test against the Null-hypothesis of zero connectivity. The threshold for significance was set at $p < 0.001$ (FDR corrected). Using the frequency-dependant granger connectivity matrix, an individual ACC – auditory cortex connectivity value was extracted for each individual subject using the local maximum value between 30 Hz and 70 Hz in the corresponding granger causality chart.

2.9. Statistical analysis

In order to test for significant interactions between ROIs we used a repeated measurements ANOVA. In the case of a significant Mauchly-test the Greenhouse-Geisser correction was used followed by post hoc paired sample t-tests. In order to investigate the relationship between connectivity measures derived from the different domains (EEG and fMRI), individual connectivity values were only forwarded to the correlation analysis, if both the EEG and the fMRI connectivity analyses for a certain connection (ACC – left AC, ACC – right AC or left AC – right AC) and direction had revealed a significant result. Correlation analyses between EEG and fMRI domain results were conducted using the Pearson correlation coefficient. All statistical analyses were performed using the SPSS software package (23.0) as well as the robust correlation toolbox in MATLAB (Pernet, Wilcox, & Rousselet, 2013).

3. Results

The mean reaction time between onset of the auditory stimuli and button press was 625 ms (SD 97 ms), the mean error rate was 6.5%. The fMRI analysis for target stimuli revealed bilateral activations of the auditory cortex, the medial frontal lobe and the ACC, the DLPFC and the thalamus. Moreover, the presentation of target stimuli evoked an oscillatory response in the gamma frequency range of the EEG (around a centre frequency of 40 Hz) about 50 ms after stimulus onset. For a full description of fMRI and EEG results please see the results of (Leicht et al., 2016) on healthy subjects.

With respect to the analysis of brain connectivity in the fMRI domain, our seed-to-whole-brain approach using the ACC as seed region revealed a functional coupling of the ACC with other parts of the cingulum, the bilateral auditory cortex as well as the bilateral insulae and thalami (see Fig. 1 and Table 1). The ROI analysis showed significant ROI BOLD signal correlations for all pairs of ROIs (ACC – left AC, ACC – right AC and left AC – right AC; see Fig. 1).

Using a gPPI analysis of connectivity in the fMRI domain, we found a significant task-dependant increase of connectivity between ACC and right AC for target stimuli compared to non-target stimuli using either the ACC ($F[3,25] = 4.69$, $p[FDR] = 0.02$) or the right AC ($F[3,25] = 4.65$, $p[FDR] = 0.04$) as the seed. There were no significant results for both directions of the connections between ACC and left AC and between the bilateral ACs (see Fig. 2).

Regarding functional connectivity in the EEG domain, a repeated-measures ANOVA revealed a significant main effect of the factor “connection” (ACC – left AC, ACC – right AC and left AC – right AC) on the oscillatory synchrony between ROIs in the frequency range of 30 - 70 Hz as measured by means of LPS ($F[2,48] = 4.44$, $p = 0.017$). There was no significant main effect of the factor “timeframe” (prior to vs following the stimulus presentation) and no significant interaction effect (connection x timeframe). Post-hoc t-tests revealed a significant increase in functional coupling between the ACC and the left auditory cortex ($t = 2.55$, $p = 0.018$), when comparing post- versus pre-stimulus time windows. The comparison of gamma LPS values between post- versus pre-stimulus time windows for both ACC – right AC and left AC – right AC connections, did not reach significance (see Fig. 3).

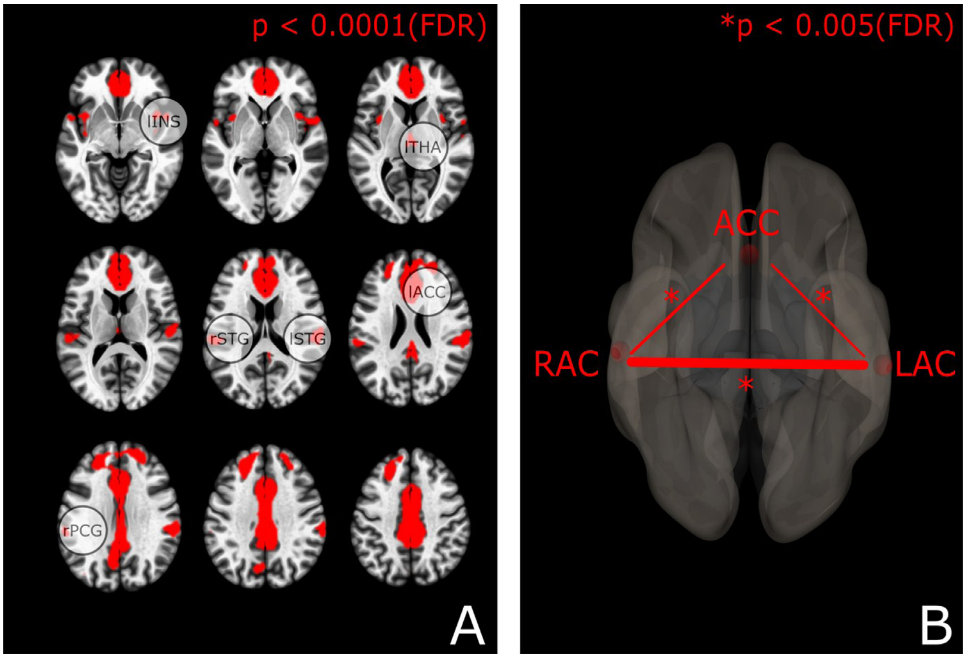

Fig. 1. fMRI functional connectivity analysis (correlation). (A) A Pearson correlation analysis between the BOLD signal of the ACC ROI and the BOLD signal of every single brain voxel reveals significantly increased functional coupling between the ACC and other parts of the cingulum, the bilateral auditory cortex as well as the bilateral insulae and thalami. INS = insula, THA = thalamus, ACC = anterior cingulate cortex, STG = superior temporal gyrus, PCG = postcentral gyrus, *l* = left, *r* = right. (B) The ROI analysis shows significant ROI BOLD signal correlations for all pairs of ROIs. The thickness of bars represents absolute connectivity values.

Table 1

FMRI functional connectivity. Brain regions with significant BOLD signal correlation with the ACC ROI seed (seed-to-whole-brain analysis, P 〈 0.0001, FDR corrected, only cluster 〉 10 voxels reported).

Peak MNI coordinates (x,y,z)			Location of peak voxel	Cluster size (number of voxels)	Maximum t-value
−4	20	28	left anterior cingulate gyrus	12,918	38.70
60	−24	22	right postcentral gyrus	1065	20.33
−38	12	−10	left insula	806	18.11
58	4	0	right superior temporal gyrus	632	18.06
−60	−30	15	left superior temporal gyrus	538	16.22
−2	−20	8	left thalamus	193	16.21

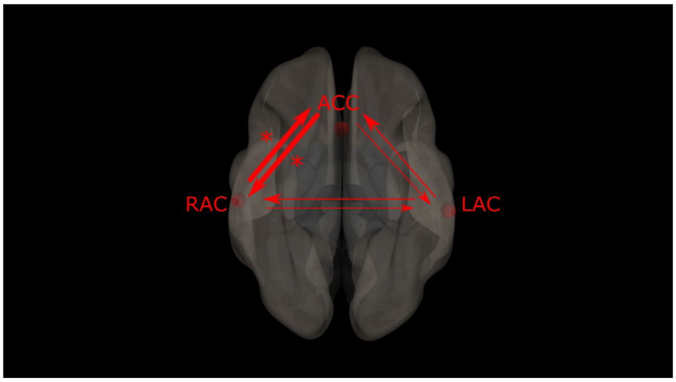

Fig. 2. fMRI functional connectivity analysis (gPPI). A gPPI analysis considering all possible connections between ROIs reveals a significant task-dependant increase of connectivity between the ACC and the right AC for target stimuli compared to non-target stimuli using either the ACC or the right AC as the seed. The thickness of arrows represents absolute connectivity values.

Fig. 4 and 5.

EEG effective connectivity analyses revealed a significant main effect of the factor direction (F[1,27] = 9.50, $p = 0.005$). This finding was qualified by significantly higher granger connectivity values for top-down directions between ACC and left AC ($t = 2.31$, $p = 0.028$) as well as ACC and right AC ($t = 2.23$, $p = 0.034$) as compared to the bottom-up direction. There was no significant difference between the two directions of the connection between left and right AC. Moreover, there was no significant main effect of connection (ACC – left AC, ACC – right AC and left AC – right AC) and no significant connection x direction interaction.

Thus, only the top-down connection between ACC and right AC showed significant results for both EEG and fMRI connectivity measures and was forwarded to the correlation analysis, which revealed a significant correlation between EEG granger connectivity and fMRI gPPI values for the ACC – right AC connection in top-down direction ($r = 0,4$, $p = 0,03$).

4. Discussion

In order to investigate the connectivity within a frontotemporal auditory information processing network involving the synchronisation of gamma oscillatory activity (Leicht et al., 2010; Mulert et al., 2010, 2007; Polomac et al., 2015), we have re-analysed simultaneously recorded EEG and fMRI data of healthy participants from a previously published study (Leicht et al., 2016). In a multimodal neuroimaging approach we have conducted various connectivity analyses on both EEG and fMRI data. Moreover, we hypothesised a correlation between EEG and fMRI connectivity measures showing significant task-related changes for particular connections between brain regions in both domains. We used an iterative approach verifying the presence of a relevant signal whenever possible before proceeding to a more advanced analysis (e.g. fMRI seed-to-voxel analysis before extracting fMRI ROI-to-ROI connectivity data).

In line with previous studies using EEG (Leicht et al., 2010; Mulert et al., 2007) and MEG (Polomac et al., 2015) source localisation as well as EEG-informed fMRI (Mulert et al., 2010), the cognitively demanding auditory information processing during performance of our auditory choice reaction task involved task-related activity in the audi-

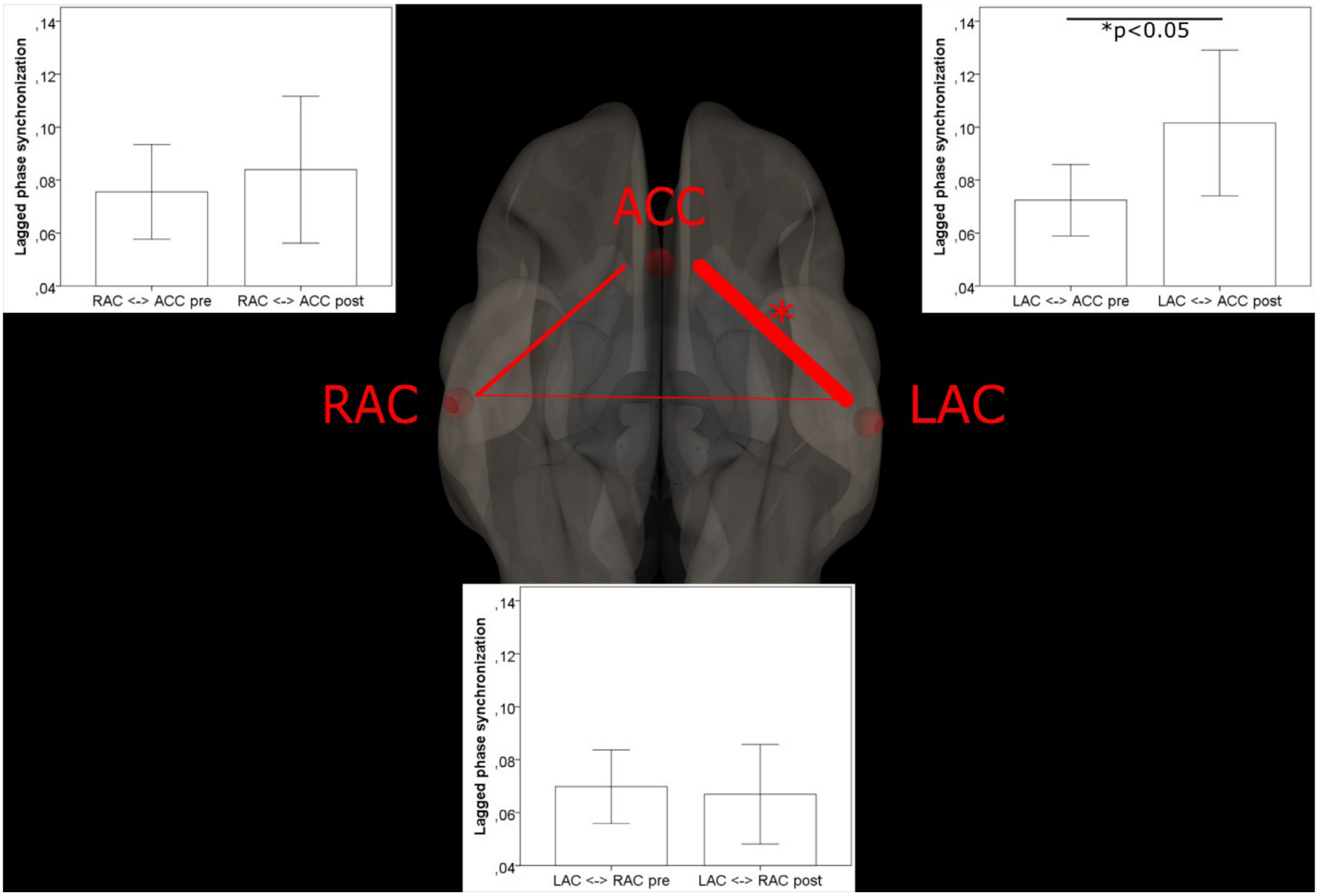

Fig. 3. EEG functional connectivity analysis. LPS values as a measure of functional connectivity in the gamma frequency range are significantly increased for the connection between the ACC and the left auditory cortex, when comparing post- versus pre-stimulus time windows. The thickness of bars represents absolute connectivity values.

tory cortices, the medial frontal lope and the ACC, the DLPFC and the thalamus as revealed in the previously conducted fMRI BOLD analysis of the dataset re-analysed here. Moreover, we observed an oscillatory gamma response to auditory target stimuli (Leicht et al., 2016). The current analysis focused on the connectivity between anatomically defined regions of interest within the ACC and the bilateral auditory cortex based on these previous findings. For instance, a gamma-band specific network comprising these regions has been shown in EEG-informed fMRI studies (Leicht et al., 2016; Mulert et al., 2010) and a MEG work from Polomac et al. reported an increase of functional connectivity in the gamma frequency range between auditory cortices and the ACC during the performance of the task.

Here, we report a functional coupling of the ACC with the bilateral auditory cortex in a fMRI seed-to-whole-brain analysis using the ACC as seed region and significant BOLD signal correlations between the ACC and the ACs. Our fMRI gPPI analysis revealed a significant task-dependant increase of connectivity between the ACC and right AC for target stimuli compared to non-target stimuli. This difference regarding the connectivity within the left and right hemisphere might be related to earlier findings of a stronger aeGBR within the right AC using the same paradigm (Polomac et al., 2015). It has been suggested that evoked gamma-band activity is sensitive to high-level stimulus properties and that non-speech sounds as used in our study produce larger aeGBR amplitudes in the right hemisphere (Palva et al., 2002).

In the EEG domain, an analysis of lagged phase synchronisation revealed a significant increase in functional coupling in the gamma frequency range between the ACC and left auditory cortex compared to baseline conditions. Gamma-band synchronisation is a cortical mechanism which reflects sensory (including auditory (Moinnereau et al., 2020)) stimulus features and is modulated by selective attention (Bosman et al., 2012). It has been proposed to reflect communication between neuronal groups (Fries, 2005). Central to this mechanism is that high frequency rhythmic brain activity in the gamma frequency range has been related to alternating levels of inhibition in neuronal networks modulating the degree of the neurons' receptiveness for input (Ni et al., 2017). The effective communication between brain regions requires the alignment of receptive periods of weak inhibition by synchronisation (Besserve et al., 2015). Regarding fMRI investigations, EEG can add such important information of specific neuronal oscillatory modes involved in the functional relationships between brain regions (Mulert, 2013; Scheeringa and Fries, 2019). This is especially true for EEG high frequency oscillations, which are known to be involved in both local and large-scale neuronal synchronization (Engel et al., 2001; Fries, 2005). Moreover, correlations between oscillatory EEG power and BOLD signals are especially high in the gamma-band frequency range (Logothetis et al., 2001; Mukamel et al., 2005; Niessing et al., 2005). In our study the EEG granger connectivity values for the ACC – right AC connection in top-down direction were positively correlated with the respective fMRI gPPI values. The replication of fMRI connectivity patterns in simultaneously recorded EEG data and the correlation between connectivity measures from both domains found in our study show, that brain connectivity based on the synchronisation of gamma oscillations is reflected in fMRI connectivity patterns.

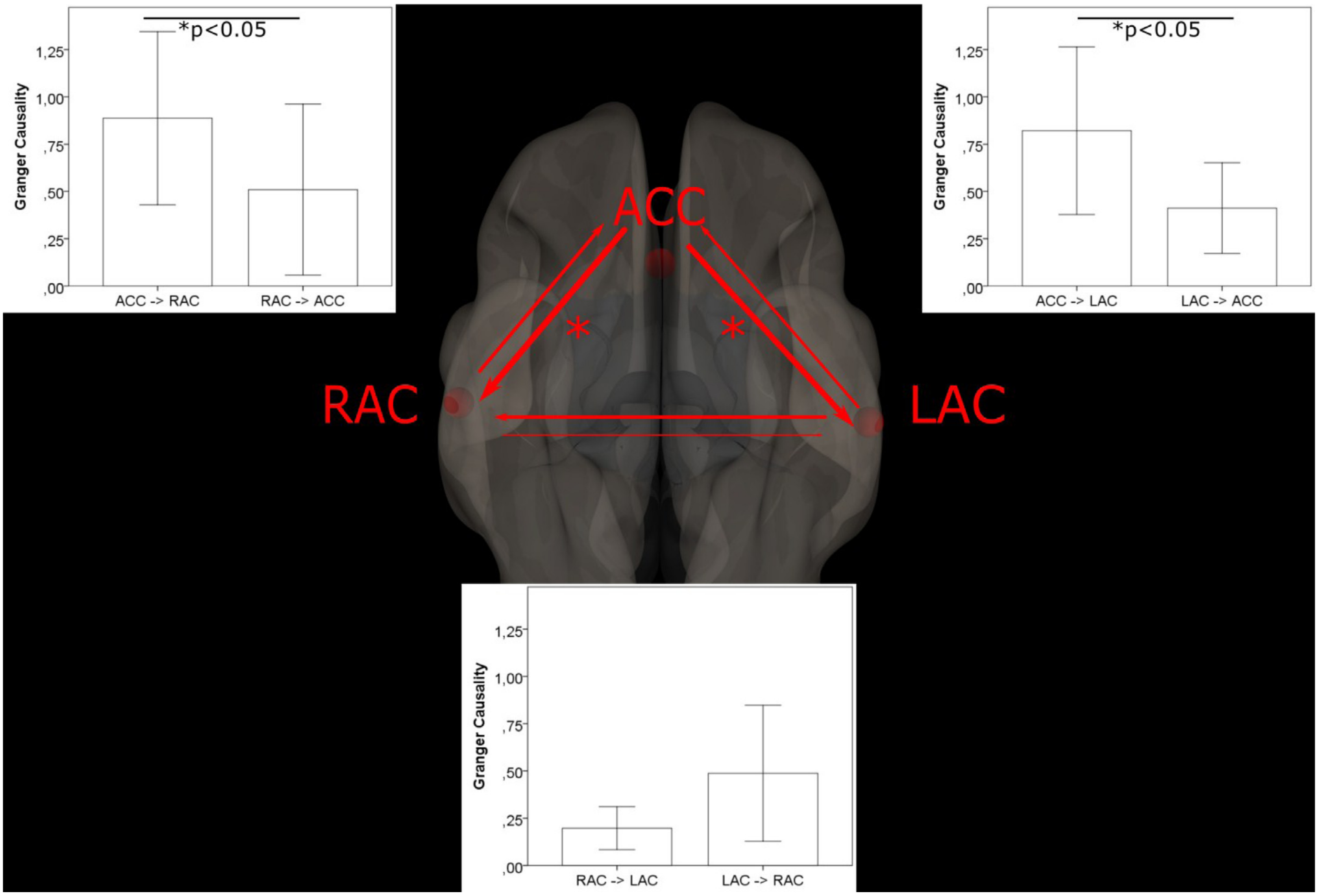

Fig. 4. EEG effective connectivity analysis. A granger causality analysis reveals a significantly higher connectivity in top-down directions between the ACC and both ACs as compared to the bottom-up direction. The thickness of arrows represents absolute granger connectivity values.

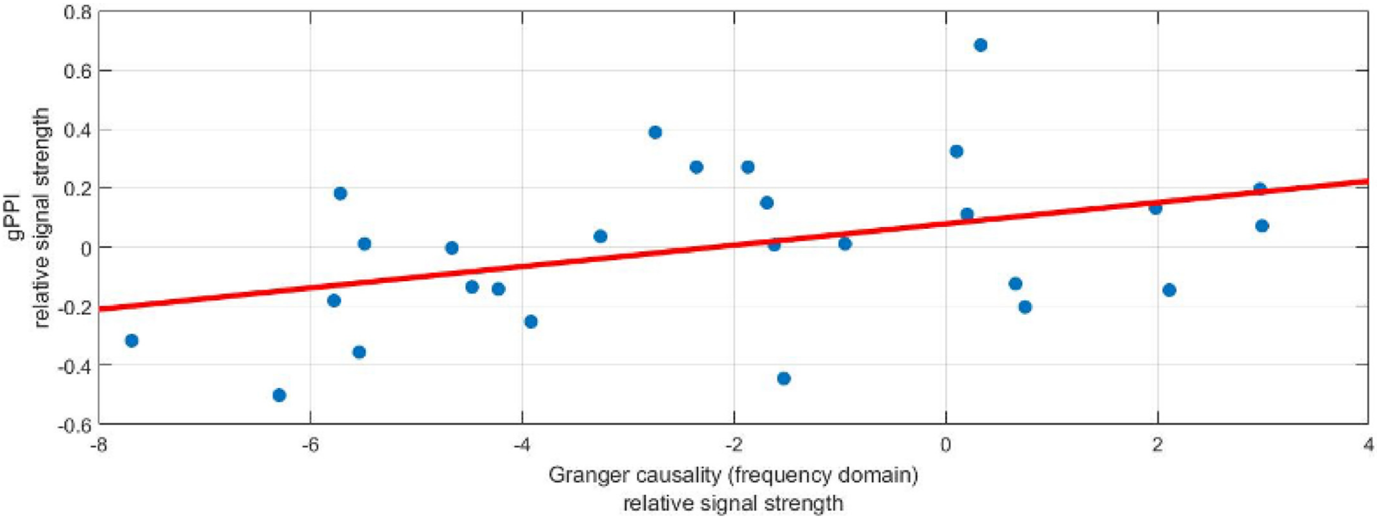

Fig. 5. Correlation between fMRI and EEG connectivity measures. Significant correlation between EEG granger connectivity and fMRI gPPI values for the ACC – right AC connection in top-down direction.

Gamma oscillation phenomena such as the auditory evoked gamma-band response and the synchronisation of gamma oscillations have been related to cognitive processes (Gurtubay et al., 2004; Senkowski and Herrmann, 2002; Tiitinen et al., 1993) as well as cognitive disturbances e.g. in schizophrenia (Andreou et al., 2015; Leicht et al., 2015). Accordingly, besides main generators of the aeGBR in the ACs, an additional ACC involvement has been shown in cognitively demanding auditory tasks (Mulert et al., 2010). In order to interpret our findings of the interplay between the ACC and the auditory cortices, it is important to mention evidence from non-human primates suggesting the existence of anatomical connections between the two areas. The dorsal ACC receives sensory auditory input from the anterior medial claustrum and from the superior temporal area 22 (Mega and Cummings, 1997; Vogt and Pandya, 1987). The dorsal ACC also projects back to the area 22 (Pandya et al., 1981). Single trial coupling of the aeGBR and the corresponding BOLD signal revealed the thalamus to be involved in a gamma-band-specific network including the ACC and the auditory cortex (Mulert et al., 2010), which might be a correlate of thalamo-cortical interactions (Barth and MacDonald, 1996). However, the cortex is able to generate gamma oscillations independently from subcortical input (Whittington et al., 1995) and cortico-cortical gamma band interactions have been found to be crucial in auditory information processing (Bhattacharya et al., 2001; Steinmann et al., 2014).

In order to investigate the directionality of the connections in the brain network we used an EEG granger causality analysis, which revealed higher connectivity in top-down direction between the ACC and both ACs as compared to the bottom-up direction. There is evidence that bottom-up and top-down signalling is subserved by interareal synchronisation in different frequencies (Fries, 2015). Contrary to our results of a gamma-mediated top-down influence of the ACC on the right auditory cortex, numerous studies on the visual processing pathway have gained evidence for bottom-up gamma oscillations driving top-down beta oscillations in the hierarchy of the processing pathway (Bastos et al., 2015; van Kerkoerle et al., 2014; Wang, 2010). For instance, gamma-band synchronisation has been shown to mediate bottom-up stimulus processing during the performance of an attentional task in the visual (Michalareas et al., 2016; Richter et al., 2017) and auditory cortex (Fontolan et al., 2014).

On the other hand, gamma oscillations have also been reported to be involved in top-down processing of sensory information (Citherlet et al., 2019; Debener et al., 2003; Jensen et al., 2007), which is in line with our results. A high-frequency top-down information flow has been shown when observing cross-frequency coupling signatures in evoked field potentials during auditory processing in the macaque cortex (Márton et al., 2018). Another study suggests that the early auditory gamma band response might reflect anticipation by mediating information processing at the earliest stages of auditory information processing (Schadow et al., 2009). In line with this, the aeGBR is known to be modulated by attention (Mulert et al., 2007) and a frontal generator of the aeGBR within the dorsal ACC has been reported (Mulert et al., 2010). A disturbed theta and gamma driven top-down effect of the ACC on the auditory cortex has been reported to underlie a top-down subtype of tinnitus reflecting a deficient top-down noise-cancelling system (De Ridder et al., 2011; Vanneste et al., 2018).

Electrophysiological studies using local field potentials and ECoG have also proposed fluctuations of granger causality in the gamma frequency range that only sequentially merge into a dominant direction, thus proposing the role of gamma oscillations as a bidirectional medium of information exchange (Fontolan et al., 2014). It has also been suggested that early gamma band responses might be involved in matching bottom-up and top-down information (Herrmann et al., 2004). Müsch et al. reported evidence for gamma oscillations to be involved in both feedforward and feedback processing during the evaluating of facial expressions (Müsch et al., 2017).

In summary, before the background of strong evidence on a crucial role of gamma oscillations in bottom-up processing of sensory information we interpret our results as a hint to an involvement of gamma oscillations in both feedforward and feedback processing or even in matching bottom-up and top-down information.

The gPPI is a robust model for the investigation of seed-based network interactions (Friston, 2011; Horwitz and Horovitz, 2012). It is model-driven and requires prior assumptions and knowledge of the network. As the gPPI is a relatively simplistic pairwise model of network interactions in the brain, which makes it difficult to exclude complex network interactions (Friston et al., 2013). We are quite confident, that this issue did not limit our results, because we were specifically interested in the connectivity between two specific brain regions, namely the ACC and the AC, which is based on prior knowledge as outlined above. The gPPI assesses task-specific changes in correlation strength between two areas which cannot be explained simply by a shared external driving force (O'Reilly et al., 2012). Thus, due to its pairwise nature and accuracy for task-related effects, gPPI was well suited for our analysis.

Granger causality analyses have been used earlier to investigate effective connectivity in EEG and MEG data. Some studies have raised the issue of source mixing in granger connectivity. In general, sensor space data are not suitable for granger causality analysis (Van de Steen et al., 2016). In this study, we used the lcmv beamformer approach in order to facilitate the granger connectivity analysis in the source space. Various studies have combined lcmv beamformer with granger causality analyses (Hassan and Wendling, 2018; Lou et al., 2011; Schlee et al., 2009). When looking at source-level connectivity data, it is important to remember that a large number of dipoles might cause spurious correlations (Schoffelen and Gross, 2009). This should not be the case in our analysis, because we were able to restrict it to a ROI-to-ROI connectivity approach using three previously validated network ROIs.

Conclusion: Auditory information processing during performance of a cognitively demanding task involves a functional coupling of the ACC with the bilateral auditory cortex as shown here by means of different EEG and fMRI connectivity measures. Our results suggest a top-down interaction. The replication of fMRI connectivity patterns in the simultaneously recorded EEG data and the correlation between connectivity measures from both domains found in our study, show that brain connectivity based on the synchronisation of gamma oscillations is reflected in fMRI connectivity patterns.

Author contributions

GL Conceptualization, Funding acquisition, Methodology, Supervision, Writing - original draft, review & editing **JB** Data curation, Formal analysis, Methodology, Visualization, Writing - original draft, review & editing **SV** Data curation, Formal analysis, Methodology, Project administration **MM** Data curation, Formal analysis, Project administration **MH** Validation, Visualization, Writing - review & editing **SS** Formal analysis, Validation, Writing - review & editing **JR** Methodology, Project administration, Validation, Writing - review & editing **CM** Conceptualization, Funding acquisition, Supervision, Writing - review & editing

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Declaration of Competing Interest

None

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Data availability statement

Data will be made available via the Open Science Framework platform.

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Darstellung der Publikation mit Literaturverzeichnis

Das Gehirn verfügt über unterschiedliche Mechanismen, um Informationen und Sinneseindrücke aus verschiedenen Arealen zu verarbeiten.
Neben der anatomisch-strukturellen Sichtweise, nach der bestimmte Hirnfunktionen einzelnen Regionen zugeschrieben werden, basiert ein aktuelles Verständnis der Interaktion verschiedener Hirnregionen auf der Betrachtung kombinierter Aktivität und Interaktion zwischen verschiedenen Arealen und Neuronengruppen (McIntosh, 2000).

Der Begriff Konnektivität beinhaltet hierbei verschiedene Konzepte, welche die Organisationsstruktur des Gehirns beschreiben (Horwitz, 2003).

Die Basis für plausible Hypothesen über die Konnektivität zwischen verschiedenen Regionen bietet dabei die anatomische (strukturelle) Konnektivität. Diese beschreibt wie verschiedene Hirnareale anatomisch miteinander verbunden sind, um Kommunikation zu ermöglichen. Diese Verbindungen bilden die Basis für detailliertere Hypothesen über Konnektivität in neuronalen Netzwerken, wobei die genaue Interaktion zwischen strukturellen Bahnen und funktioneller Kopplung von Hirnarealen komplex ist (Damoiseaux & Greicius, 2009).

Funktionelle Konnektivität bezeichnet zeitabhängige statistische Zusammenhänge wie Korrelationen zwischen räumlich segregierten neurophysiologischen Ereignissen (K. Friston, 2002). Bei der Interpretation funktioneller Konnektivitätsdaten ist zu beachten, dass keine Aussage über die Direktionalität der neuronalen Beziehung getroffen werden kann. Zudem kann ohne eine differenziertere Modellierung plausibler Verbindungen nicht ausgeschlossen werden, dass die Korrelation wie beschrieben aufgrund eines gemeinsamen Eingangssignals einer dritten, nicht a priori beobachteten Region im Rahmen eines gemeinsamen Input-Signals basiert (Lebedev et al., 2016).

Darüberhinausgehend bezeichnet effektive Konnektivität einen kausalen Einfluss, den eine neuronale Einheit auf eine andere ausübt (K. Friston, 2002; K. J. Friston et al., 1997). Innerhalb des Modells kann hier also eine Aussage über Direktionalität getroffen werden (Park & Friston, 2013). Effektive Konnektivität kann als die einfachste zeit- und experimentabhängige mögliche Beziehung zwischen verschiedenen Regionen verstanden werden, welches es erlaubt, die beobachteten zeitlichen Beziehungen zwischen den beobachteten Neuronen zu erklären (Colombo & Weinberger, 2017).

Neben der örtlichen Lokalisation neuronaler Aktivität mittels bildgebender Verfahren spielt auch die zeitliche Dynamik und Synchronisation neuronaler Aktivitätsmuster eine große Rolle, um lokale und globale Phänomene der neuronalen Verarbeitung und Sinneswahrnehmung zu verstehen. Dies wird durch das Konzept von Segregation und Integration beschrieben (Tononi et al., 1994). Während Segregation die Lokalisation verschiedener spezifischer Hirnfunktionen zu bestimmten Arealen beschreibt, umfasst Integration die Koordination neuronaler Aktivität zwischen verschiedenen Arealen und ist daher essentiell für das Verständnis des komplexen Einflusses verschiedener kognitiver Prozesse im Zusammenspiel von Regionen und neuronalen Netzwerken (Bullmore & Sporns, 2009; Sporns et al., 2005).

Ein wesentlicher Mechanismus für die Integration von Aktivität verschiedener Hirnareale und Neuronengruppen sind neuronale Oszillationen (Engel et al., 2011; Fries, 2005; Herrmann et al., 2004). Synchrone Oszillationen im Gamma-Frequenzband spielen hierbei

für die Aktivierung kortikaler Netzwerke sowie für die Integration gleichzeitig stattfindender neuronaler Aktivität eine besondere Rolle (Fries, 2009; Singer, 1999).
Ein Mechanismus der Kommunikation ist die Synchronisation von Perioden der relativen Inhibition und Rezeptivität gegenüber Stimuli mittels Gamma-Oszillationen (Besserve et al., 2015).

Ein konkretes Beispiel hierfür ist die auditorische Gamma-Band-Anwort (aeGBR), welche 25ms – 100ms nach der Präsentation eines auditorischen Stimulus auftritt. In mittels Elektroenzephalografie (EEG) und Magnetoenzephalographie (MEG) konnten neben den auditorischen Kortizes auch frontale Areale wie der dorsale anteriore cinguläre Kortex (dACC) und der dorsolaterale präfrontale Kortex (DLPFC) als maßgeblich für die Entstehung der aeGBR identifiziert werden. In einer MEG-Studie aus unserer Gruppe konnte gezeigt werden, dass die funktionelle Konnektivität im Gamma-Frequenzbereich eine Rolle in der Interaktion beider Regionen zu spielen scheint (Polomac et al., 2015). Daten zur Direktionalität dieser Interaktion und bzgl. des Zusammenhangs zwischen Konnektivitätsmaßen aus verschiedenen Modalitäten (EEG und fMRT) hinsichtlich dieser Interaktion fehlen bisher.

Um die funktionale Rolle und Konnektivität innerhalb dieses Gamma-Band-Netzwerks weiter charakterisieren zu können, bietet sich eine kombinierte Auswertung von EEG und fMRT-Daten an. Durch die kombinierte Nutzung dieser beiden neurowissenschaftlichen Untersuchungsmethoden ergeben sich Möglichkeiten, die Vorteile der einzelnen Methoden (hohe zeitliche Auflösung beim EEG, hohe räumliche Auflösung bei der fMRT) zu kombinieren (Mayhew et al., 2018; Mulert, 2013; Mulert et al., 2008).
Besonders in Bezug auf Gamma-Oszillationen ist die Korrelation zwischen gemessenen EEG-Oszillationen und dem BOLD-Signal hoch (Lachaux et al., 2007; Logothetis et al., 2001).

Die vorliegende Arbeit hat hierbei zwei Ziele. Zum einen soll das zuvor bereits identifizierte Netzwerk speziell in Bezug auf direktionale Kommunikation und Konnektivität näher charakterisiert werden. Zum anderen soll exemplarisch an diesem Netzwerk der Zusammenhang zwischen verschiedenen auf Konnektivität fokussierten Untersuchungsmethoden evaluiert werden.

Methodik

In der Publikation wurden die Daten von 24 gesunden Erwachsenen ausgewertet, welche als Kontrolldatensatz in einer Vorstudie gewonnen wurden, die gesunde Kontrollpersonen mit Personen verglichen hat, die ein hohes Risiko für die Entwicklung einer Psychose haben (Leicht et al., 2016).
Nach einer ausführlichen Aufklärung und Prüfung von Ein- und Ausschlusskriterien wurde ein Hörtest durchgeführt, bevor die Patienten für eine simultane EEG-fMRT-Messung vorbereitet wurden. Als Paradigma kam eine Wahlreaktionsaufgabe mit auditorischen Stimuli zum Einsatz. Hierfür wurden den Patienten 300 individuelle Töne mit 3 verschiedenen Frequenzen für jeweils 200ms vorgespielt (700Hz, 1000 Hz, 1300 Hz). Teilnehmer wurden instruiert, Töne mit 700Hz und 1300 Hz jeweils mit dem rechten und linken Zeigefinger über einen Antwortknopf möglichst schnell und akkurat zu quittieren.

Während des Paradigmas wurde eine T2*-sensitive fMRT-Sequenz aufgenommen, um funktionelle BOLD-Daten zu erhalten. Zusätzlich wurde eine T1 MPRAGE-Sequenz in derselben Position zur anatomischen Korrelation aufgenommen. In einem 1,1 s langen

Zeitraum ohne fMRT-Gradientenschaltung wurden im MR-Scanner EEG-Daten aufgezeichnet.

Weitere Details zur Erfassung der Daten sowie zu vorbereitenden Analyseschritten finden sich in der Publikation.

Grundsätzlich wurde innerhalb jeder Domäne (fMRT und EEG) ein iterativer Ansatz verfolgt, in welchem zunächst in grundlegenden Analysen relevante Informationen ausgewertet wurden, bevor weitergehende Analysen zu funktioneller und effektiver Konnektivität vorgenommen wurden. Im letzten Schritt wurde dann die intermodale Korrelation der Konnektivitätsmarker berechnet, um den Grad der Konkordanz zwischen den beiden unterschiedlichen Modalitäten zu erfassen.

In den EEG-Daten wurde funktionelle Konnektivität mittels „Lagged Phase Synchronization (LPS)“ bestimmt. LPS beschreibt ein mathematisches Maß der Abhängigkeit zwischen zwei Zeitserien in der Frequenzdomäne in Abwesenheit des Signalanteils der Nullphase, welcher auf Messartefakten und elektrischen Störsignalen beruht (Pascual-Marqui, 2007). LPS kann daher als ein Maß für nichtlineare funktionelle Konnektivität betrachtet werden (Hata et al., 2016).

Um die effektive Konnektivität in den EEG-Daten zu analysieren, wurden Granger-Kausalitätsanalysen (GC) genutzt. GC identifiziert potentielle kausale Beziehungen zwischen zwei Signal-Zeitserien unter der Annahme, dass die beobachtete Zeitserie X eine andere Zeitserie Y kausal versursacht, wenn das zeitlich zurückliegende Signal von X eine Aussage über die zeitlich zukünftige Aktivität von Y erlaubt, welche über die Information hinausgeht, die in der vergangenen Aktivität der Zeitserie Y alleine beobachtet werden können (Barnett & Seth, 2014; Granger, 1969). Mathematisch betrachtet wird hierfür der Prädiktionsfehler für ein Modell berechnet, welches die Zeitserien X und Y einschließt, und dieses mit einem Modell verglichen, welches unter Ausschluss von X die Zeitserie Y vorherzusagen versucht. Wenn der Prädiktionsfehler für den zukünftigen Verlauf der Zeitserie Y durch zeitlich zurückliegende Informationen der Zeitserie X vorhersagt, wird ein Granger-kausaler Einfluss auf die Zeitserie Y postuliert.
Um GC berechnen zu können, ist die Berechnung eines Kohärenzspektrums aus den relevanten Signalen nötig. In der vorliegenden Arbeit wurde hierfür ein nichtparametrischer Ansatz zur Berechnung der Spektralmatrix genutzt, da dieser den Vorteil hat, im Gegensatz zu einem explizit berechneten autoregressiven Modell keine Spezifizierung der Modellordnung zu benötigen und auch mit komplexen Quelldaten ausreichend komplexe Spektralinhalte zu identifizieren (Dhamala et al., 2008).

Für die Auswertung der fMRT-Daten wurden ebenfalls zwei verschiedene Methoden zur Konnektivitätsanalyse genutzt. Um funktionelle Konnektivität mittels Pearson-Korrelation zu berechnen, wurde im ersten Schritt zur Plausibilisierung der Daten die Pearson-Korrelation zwischen ACC und allen anderen kortikalen Voxeln berechnet.
Im nächsten Schritt wurde die Korrelation zwischen dem ACC und den beiden auditorischen Kortizes für jede mögliche Verbindung dieses Netzwerks berechnet. Die individuellen Konnektivitätswerte dieser Analyse wurden für jeden Probanden berechnet und in der abschließenden vergleichenden Analyse zwischen EEG und fMRT-Konnektivitätswerten verwendet.

Als zweite Methode der fMRT-Konnektivitätsanalyse wurde die Konnektivitätsstärke mittels generalisierter psychophysiologischer Interaktion (gPPI) berechnet. Mit dieser Methode kann die Interaktion zwischen verschiedenen physiologischen Variablen innerhalb eines experimentellen (psychologischen) Settings evaluiert werden (K. J. Friston et al., 1997). Hierfür wird der Aufbau der experimentellen Aufgabe und die Aktivität in einer Seed-Region in einem linearen Modell genutzt, um das erwartete Signal in Zielregionen zu modellieren. Dieses modellierte Signal wird dann mit der tatsächlich beobachteten Zeitserie mittels bivariater Regression verglichen (K. Friston, 2002). Da die

Aktivität der Seed-Region mit in die Modellierung eingeht, ist die daraus resultierende gPPI-Konnektivitätsmatrix asymmetrisch.

Um intermodale Konnektivitätswerte zwischen EEG und fMRT vergleichen zu können, wurden für jeden Probanden zwischen den ACs und dem ACC in alle Richtungen gPPI-Analysen durchgeführt und in die vergleichende Analyse gegeben.

Ergebnisse

In der initialen Auswertung der funktionalen Konnektivität im fMRT mittels Korrelationsanalyse zeigte sich eine signifikante Korrelation zwischen allen drei anatomisch festgelegten ROIs. Auch in der ACC zu Whole-Brain-Analyse, in welcher die Korrelation aller Voxel mit der ACC-ROI analysiert wurde, zeigte sich Aktivität in beiden auditorischen Kortizes sowie in anderen Teilen des Cingulums, der Insula und den Thalami.

Die fMRT gPPI-Analyse zeigte einen signifikanten Anstieg der Konnektivität zwischen ACC und rechtem auditorischen Kortex in beide Richtungen. Die übrigen ROI-zu-ROI-Verbindungen zeigten keinen signifikanten Anstieg der Konnektivität.

Die Auswertung der funktionellen Konnektivität in den EEG-Daten zeigte einen signifikanten Konnektivitätsanstieg zwischen ACC und linkem auditorischen Kortex nach Präsentation des Stimulus (LPS).

In der Auswertung der effektiven EEG-Konnektivität mittels Granger-Kausalitätsanalyse zeigten sich signifikant höhere Werte in der top-down-Richtung vom dACC zu beiden Hörkortizes als in der Gegenrichtung.

Diskussion

Die vorliegende Publikation nutzt verschiedene Methoden, um funktionelle Kopplung und Konnektivität im EEG und fMRT innerhalb eines auditorischen frontotemporalen Netzwerks zu evaluieren. Zwischen den drei beobachteten Arealen war lediglich die Verbindung zwischen rechtem auditorischen Kortex und ACC in allen vier methodischen Ansätzen signifikant. Für diese Verbindung konnte auch eine signifikante Korrelation zwischen Granger-Konnektivitätswerten und gPPI-Werten gezeigt werden.

Insgesamt deuten die Ergebnisse auf einen top-down-Einfluss über Synchronisation von Gamma-Oszillationen innerhalb des beschriebenen Netzwerks hin. Funktionell betrachtet könnte dies mit der zuvor beschriebenen Rolle hochfrequenter Gamma-Aktivität in der Synchronisierung von alternierenden Phasen relativer Inhibition und Rezeptivität verbunden sein (Besserve et al., 2015; Ni et al., 2017).
Entgegen der hier beobachteten Dynamik innerhalb des Netzwerks zeigen andere Studien die Rolle von Gamma-Oszillationen als bottom-up-Einfluss, welcher in einem zweiten Schritt die Entstehung von Beta-Oszillationen fördert (Bastos & Schoffelen, 2015; Van Kerkoerle et al., 2014; Wang, 2010)

Zusammengefasst betrachtet geben diese Beobachtungen Hinweise darauf, dass die auditorische evozierte Gammabandantwort (aeGBR) einen top-down Effekt von hierarchisch übergeordneten sensorischen Arealen wie dem dACC auf den auditorischen Kortex vermittelt, welcher der Beschleunigung der auditorischen Reizverarbeitung dient (Busch et al., 2006; Debener et al., 2003)

Neben der genaueren Charakterisierung der Interaktionen in diesem Netzwerk war ein zweites Ziel der vorliegenden Arbeit, verschiedene Methoden zur Berechnung von Konnektivität mittels EEG und fMRT-Daten zu vergleichen. Hierbei konnten wir eine Korrelation von signifikanten Ergebnissen der einzelnen Konnektivitätsanalysen über Berechnungsmethoden und Modalitäten hinweg beobachten. Die Integration solcher Ergebnisse über verschiedene Modalitäten, Methoden und zeitliche Auflösungen verschiedener Modalitäten ist ein vielversprechender Weg, die Organisation und Funktion verschiedener neuronaler Netzwerke besser zu verstehen (Sporns, 2014).

Mit Blick auf die Ergebnisse der vorliegenden Arbeit zeigt die Korrelation der Ergebnisse zwischen EEG und fMRT-Daten, dass fMRT-Konnektivitätsanalysen zumindest zum Teil Effekte aufzeigen, welche durch die Synchronisation von Gamma-Frequenzaktivität vermittelt werden.

Abkürzungsverzeichnis

aeGBR – auditory evoked gamma band response (auditorisch evozierte Gammabandantwort)
BOLD – blood oxygen level dependent imaging
dACC – dorsal anterior cingulate cortex
DLPFC – dorsolateral prefrontal cortex
EEG - Elektroenzephalogram
fMRT – funktionelle Magnetresonanztomographie
GC – Granger Causality
gPPI – generalized psychophysiological interaction
LPS – lagged phase synchronization
MEG – Magnetoenzephalographie

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Zusammenfassung

Deutsch

Das Gehirn verfügt über komplexe Mechanismen, um die Aktivität verschiedener Regionen für Wahrnehmungs- und kognitive Prozesse zu koordinieren.
Die vorliegende Arbeit analysiert Konnektivität in einem vorbeschriebenen Netzwerk im Gamma-Frequenzband, welches im Rahmen eines auditorischen Wahlreaktionsparadigmas aktiv wird. Ziel der Studie ist hierbei, die Beziehungen zwischen den auditorischen Kortizes sowie dem Cingulum (ACC) mittels verschiedener Konnektivitätsanalysen näher zu charakterisieren. Zudem wurden anhand dieses Netzwerks verschiedene Methoden der Konnektivitätsanalyse im EEG und fMRT-Bereich verglichen.
Analysiert wurden die simultan aufgezeichneten EEG- und fMRT-Daten von 28 gesunden Probanden. Hierbei konnten wir in den fMRT-Daten eine signifikante Korrelation zwischen den BOLD-Signalen im ACC und den auditorischen Kortizes sowie einen signifikanten Konnektivitätsanstieg zwischen diesen Regionen im Zusammenhang mit dem Paradigma feststellen. Bei der Analyse der EEG-Daten stellten wir ebenfalls einen signifikanten Anstieg der funktionellen Konnektivität sowie einen signifikant höheren top-down-Effekt im Bereich der effektiven Konnektivität fest.
Der Konnektivitätsanstieg vom ACC zum rechten auditorischen Kortex war hierbei in allen Domänen signifikant, zudem korrelierte die Stärke der Konnektivität zwischen den beiden Modalitäten (EEG und fMRT).
Zusammengefasst unterstützen die Ergebnisse die Hypothese eines top-down Einflusses vom ACC auf die hierarchisch niedrigeren Hörkortizes, welcher durch Gamma-Oszillationen vermittelt wird. Zudem zeigt die Korrelation zwischen EEG und fMRT-Konnektivitätswerten, dass die EEG-Konnektivitätsanstiege im Gamma-Frequenzband in fMRT-Konnektivitätsanalysen ebenfalls abgebildet werden können.

Englisch

The brain possesses a variety of complex mechanisms to coordinate the activity of different regions for perceptual and cognitive processes. This work analyzes connectivity in a previously described frontotemporal auditory processing network. The aim of this study is to further characterize connectivity and the relationships between areas of this network, including the auditory cortices and the cingulum. In addition, different methods to analyze connectivity in the EEG and fMRI domain are compared within the context of this network.
We analyzed simultaneously collected EEG and fMRI data from 28 healthy volunteers. In the fMRI data, we observed a significant correlation between the BOLD signals in the ACC and the auditory cortices as well as a significant increase in connectivity between these regions. Using the EEG data, we also found a significant increase in functional connectivity and a significant increase in top-down effective connectivity.
The increase in connectivity from the ACC to the right auditory cortex remained significant across domains and the strength of connectivity correlated across neuroimaging modalities.
To summarize, the results support the hypothesis of a top-down influence of the ACC on hierarchically lower regions involved in auditory processing which is mediated by gamma oscillations. Additionally, the correlation of connectivity values across domains suggests that increases in connectivity in the EEG domain within the gamma frequency domain can also be observed using fMRI connectivity analyses.

Erklärung des Eigenanteils

Die Erhebung der Rohdaten erfolge im Rahmen eines übergeordneten Forschungsprojektes des Sonderforschungsbereichs (SFB) durch verschiedene Mitarbeiter.

Die Konzeption des Studiendesigns erfolge durch PD Dr. Gregor Leicht und Prof. Dr. Christoph Mulert in Zusammenarbeit mit dem Doktoranden.

Die Vorbereitung der Daten für die Analyse, die genaue Auswahl der Vorbereitungs- und Analyseschritte sowie die Durchführung der Analysen erfolge durch den Doktoranden. Die Erstellung der finalen Analysen sowie Visualisierungen für die Publikation erfolge durch den Doktoranden.

Der erste Entwurf für die Publikation wurde durch den Doktoranden erstellt und durch die Ko-Autoren (Gregor Leicht, Marius Mussmann, Saskia Steinmann, Jonas Rauh, Christoph Mulert) korrekturgelesen und ergänzt.

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Lebenslauf

- Lebenslauf wurde aus datenschutzrechtlichen Gründen entfernt -

Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: ....