Title: Functional connectivity across the human subcortical auditory system using a Gaussian copula graphical model approach with partial correlations

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Abstract/Summary

The central auditory system is comprised of multiple subcortical brain structures that hierarchically process and refine incoming acoustic signals along the primary auditory pathway. Due to the technical limitations of imaging small structures deep inside the brain, most of our knowledge of the subcortical auditory system is based on research in animal models using invasive methodologies. Advances in ultra-high field functional magnetic resonance imaging (fMRI) acquisition have enabled novel non-invasive investigations of the human auditory subcortex, including fundamental features of auditory representation such as tonotopy and periodotopy. However, functional connectivity across subcortical networks is still underexplored, with ongoing development of functional connectivity methods. Traditionally, functional connectivity using fMRI data is estimated with simple correlation matrices. Partial correlations however reveal the connectivity between two regions after removing the effects of all other regions and hence are often more meaningful. Partial correlation analysis is

particularly promising in the subcortical auditory system, where sensory information is passed serially, in an obligatory manner, from nucleus to nucleus up the primary auditory pathway, providing redundant but also increasingly abstract representations of auditory stimuli (Chechik and Nelken, 2012). In this project, we adapted a Gaussian copula graphical model (GCGM) approach to estimate the partial correlations and thereby infer the functional connectivity patterns within the auditory system. Given the paucity of non-invasive methods for human subcortical investigations, we aim to provide novel insights regarding the hierarchy and direct connections throughout the human subcortical auditory system. Our results show strong positive partial correlations between contralateral structures throughout the auditory system, particularly in the auditory midbrain and thalamus. We also found positive partial correlations between successive structures in the auditory pathway on each side (left and right), including between auditory midbrain and thalamus, and between primary and associative auditory cortex. Further, we confirmed that these connectivity estimates were unique to the auditory system, as non-auditory regions included as controls—namely, visual cortex and superior frontal cortex—were strongly connected to their contralateral homologues but only minimally connected with auditory brain regions. Additionally, these results were highly stable when splitting the data in half according to the acquisition schemes and computing partial correlations separately for each half of the data, as well as across cross-validation folds. Overall, these results demonstrate that unique functional connectivity patterns along the auditory pathway are recoverable using novel connectivity approaches and that our connectivity methods are reliable across multiple acquisitions.

Keywords (6): resting state connectivity, functional MRI, partial correlation, subcortical auditory system, Gaussian copula graphical model

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1. Introduction

The mammalian auditory pathway conveys acoustic information between the inner ear—where sounds are mechanoelectrically transduced in the cochlea—and auditory cortex by way of multiple subcortical nuclei in the brainstem, midbrain, and thalamus. Much of our knowledge of the auditory system arises from anatomical and physiological research with non-human animal models (Popper and Fay, 1992; Webster *et al.*, 1992). This work has contributed tremendously to our understanding of the mammalian auditory system. However, due to methodological and ethical limitations, our ability to directly assess auditory function in the human nervous system is severely constrained (see (Moerel *et al.*, 2021) for further discussion).

This is particularly true when it comes to subcortical auditory structures. In mammals, the ascending central auditory system receives signals from the cochlear of the inner ear by way of the cochlear nerve, which principally innervates the cochlear nucleus in the brainstem. Auditory signals are then transmitted to the superior olivary complex, which is the first decussation point at which signals largely pass contralaterally from the left cochlear nucleus to the right superior olive (and similarly from right to left). From the superior olive, auditory signals are passed (via the lateral lemniscus) to the inferior colliculus in the midbrain. The last subcortical auditory structure is the medial geniculate nucleus of the thalamus, which then passes information to primary auditory cortex. However, due to the small size of the subcortical auditory structures—tightly packed in with other heterogeneous nuclei and white matter pathways—and their anatomical location deep within the cranium, the subcortical auditory structures have received limited attention in non-invasive human research.

Constraints in human subcortical auditory research have translational consequences beyond basic science. For instance, while cochlear implants have been widely successful at providing sensory information to individuals with sensorineural hearing impairments with an intact cochlear nerve (Kral *et al.*, 2019; Reiss, 2020), auditory prostheses in the central auditory system have been less successful (Lim *et al.*, 2009; Shetty *et al.*, 2021), due in no small part to our limited understanding of the complexity of sound representation in the ascending auditory pathway.

Magnetic resonance imaging (MRI) methods such as functional MRI (fMRI) are one such group of non-invasive methods that have only scarcely been used to investigate the subcortical auditory system. Previous task fMRI research has functionally localized the subcortical auditory structures (Sitek *et al.*, 2019), identified the tonotopic frequency mappings within the auditory midbrain and thalamus (De Martino *et al.*, 2013; Moerel *et al.*, 2015; Ress and Chandrasekaran, 2013), separated top-down and bottom-up speech-selective subregions of auditory thalamus (Mihai *et al.*, 2019; Tabas *et al.*, 2021), and recorded level-dependent BOLD signals throughout the auditory pathway (Hawley *et al.*, 2005; Sigalovsky and Melcher, 2006).

In contrast to task-related BOLD activity, fMRI connectivity methods (often utilizing resting state or passive movie watching fMRI paradigms) are commonly used to assay cortical brain networks (Biswal *et al.*, 1995; Gordon *et al.*, 2017; Power *et al.*, 2011; Smith, Beckmann, *et al.*, 2013), including the cortical auditory system (Abrams *et al.*, 2020; Cha *et al.*, 2016; Chen *et al.*, 2020; Eckert *et al.*, 2008; Maudoux *et al.*, 2012; Ren *et al.*, 2021). However, fMRI connectivity methods have limited history in human subcortical research, especially in the auditory system, where they have—to our knowledge—only been utilized a handful of times to assess connectivity differences between individuals with and without tinnitus percepts (Berlot *et al.*, 2020; Hofmeier *et al.*, 2018; Leaver *et al.*, 2016; Zhang *et al.*, 2015).

Given the anatomical and methodological constraints with subcortical fMRI, such limited fMRI connectivity literature isn't too surprising. First, the deep location of the subcortical structures places them far from MRI transmit and receive coils, limiting the signal-to-noise ratio from these regions (Miletić *et al.*, 2020). Additionally, because the brainstem is relatively centrally located relative to the multiple receiver coils, accelerated acquisition techniques that are based on phase differences between receiver coils are less effective (Preibisch *et al.*, 2015). Second, subcortical nuclei can be quite small, requiring higher resolution imaging protocols (which unfortunately trade off SNR in order to achieve greater spatial resolution). Third, subcortical nuclei are densely organized adjacent to nuclei with heterogeneous functions, so voxels immediately next to those containing core auditory structures could contain visual, motor, or sensory nuclei, white matter, CSF, or a combination of any of these. Ultimately, each of these constraints limits the SNR from subcortical auditory nuclei.

Recent advances in MRI acquisition have facilitated subcortical auditory investigations. Perhaps the largest advance is the wider adoption of 7 Tesla (7T) MRI for human cognitive neuroscience research. With a stronger standing magnetic field, 7T MR scanners are capable of higher SNR than the more common 3 Tesla (3T) scanners, which can be used to push resolution higher for more anatomical specificity. Indeed, one of the previous functional connectivity investigations of the subcortical auditory system was conducted at 7T.

Within the field of functional connectivity analysis, moving beyond the traditional full correlation analysis should enable greater specificity in assessing functional connectivity patterns (Marrelec *et al.*, 2006; Smith, 2012). In particular, by identifying unique shared covariance between specific nodes in a network (and not other nodes in the network), partial correlation methods hold great promise for estimating direct functional connectivity within a network—in comparison to full correlations, which represent both direct and indirect connections (Smith, Beckmann, *et al.*, 2013). However, we are unaware of the application of such methods to assess functional connectivity within subcortical networks, particularly within the human auditory system.

In this article, we build on the prior Bayesian precision factor (PF) analysis model in Chandra et al. (2021) and develop a novel and highly robust Gaussian copula graphical model (GCGM) to assess functional connectivity within the human auditory subcortical network. Using matrix-factorization based dimension-reduction techniques, the existing PF model can handle very high-dimensional problems far beyond the current state-of-the-art Bayesian methods in the literature of graphical models. However, it has the crucial assumption that each of the variables are marginally Gaussian distributed. Several studies in the literature have this assumption (Yu *et al.*, 2022; Zhang *et al.*, 2014). The Gaussian assumption has the useful implication that a zero partial correlation between two variables also means independence between them after removing the effects of other variables. However, in many applications—including ours—data are often not Gaussian distributed. The GCGM extends the PF model to the case where the univariate marginals can come from different distribution families. The association between the variables are modeled using a Gaussian copula that also implies conditional independence for zero partial correlation allowing easy interpretability of the conditional dependence graph.

However, existing applications of GCGM to human neuroscience (e.g., (Gao *et al.*, 2019)) have lacked principled uncertainty quantification in reporting the significant edges.

Here, we use our novel GCGM approach to investigate functional connectivity between specific nodes across the human auditory system. We used publicly available 7T resting state fMRI from over one hundred participants to examine auditory connectivity. In particular, we used the minimally preprocessed Human Connectome Project Young Adult 7T dataset with linear detrending to fit statistical assumptions about the data. To probe connectivity within the auditory system, we included auditory cortical regions of interest as well as subcortical auditory regions derived from human histology (Sitek *et al.*, 2019). As the auditory pathway comprises a chain of multiple subcortical structures, and due to the largely lateralized organization of the auditory system, we hypothesized that partial correlations would be greatest between adjacent nodes in the same hemisphere, over and above the contributions from other auditory (and non-auditory) regions of interest. In particular, because of the critical position of auditory midbrain and thalamus as obligatory nodes involving bottom-up and top-down information transfer (Mihai *et al.*, 2019; Tabas *et al.*, 2021), we hypothesized strong partial correlations between inferior colliculus and medial geniculate. We further assessed reliability across acquisitions by separately analyzing data with anterior–posterior and posterior–anterior phase-encoding directions, as well as leave-10%-out cross-validation. Overall, our findings demonstrate the methodological reliability of our GCGM approach as well as the neurobiological organization of auditory structures in the human auditory system.

2. Materials and methods

2.1 Magnetic resonance imaging acquisition and processing

We used resting state fMRI from 106 participants in the 7T Human Connectome Project (Elam *et al.*, 2021; Van Essen *et al.*, 2012). Specifically, we utilized the minimally preprocessed volumetric data in common space (Glasser *et al.*, 2013). BOLD fMRI data were acquired with 1.6 mm isotropic voxel size across four runs of a resting state paradigm (repetition time [TR] = 1 s, 900 TRs per run). Two runs were acquired with anterior–posterior (AP) phase encoding, and two were acquired with posterior–anterior (PA) phase encoding.

For each individual and each run, we extracted mean timeseries from predefined regions of interest (ROIs). Subcortical auditory ROIs were defined using the Sitek–Gulban atlas (Sitek *et al.*, 2019). Cortical ROIs were defined using FreeSurfer's implementation of the DKT atlas (Dale *et al.*, 1999; Klein and Tourville, 2012). For this study we used transverse temporal gyrus (TTG) and superior temporal gyrus (STG) as auditory ROIs, as well as pericalcarine cortex (Calc) and superior frontal gyrus (SFG) as non-auditory control ROIs. Pericalcarine cortex is the anatomical location of primary visual cortex, while superior frontal gyrus was selected due to its lack of association with auditory processing in Neurosynth (https://neurosynth.org/analyses/terms/auditory/). Each of these control regions is associated with cortical networks that are distinct from networks involved in auditory processing (Yeo *et al.*, 2011). Mean timeseries were extracted for each ROI using nilearn's [Masker] function. Subject and run-specific timeseries were then concatenated across subjects for each run (1–4).

2.2 Removing scanner drift

Strong temporal trends were observed in each ROI, a low-frequency artifact caused by minor instability of the fMRI scanner commonly known as scanner drift (Bianciardi *et al.*, 2009). Let $\mathrm{Y}_{\mathrm{i,j}}^{(\mathrm{t})}$ be the fMRI timeseries corresponding to the i-th individual's j-th ROI at the t-th timepoint. We average over the timeseries across the subjects (i.e., average the $\mathrm{Y}_{\mathrm{i,j}}^{(\mathrm{t})}$ over i) and plot the

mean timeseries separately for each ROI and runs in Figure 1. A strong decreasing trend can be observed uniformly across all scenarios.

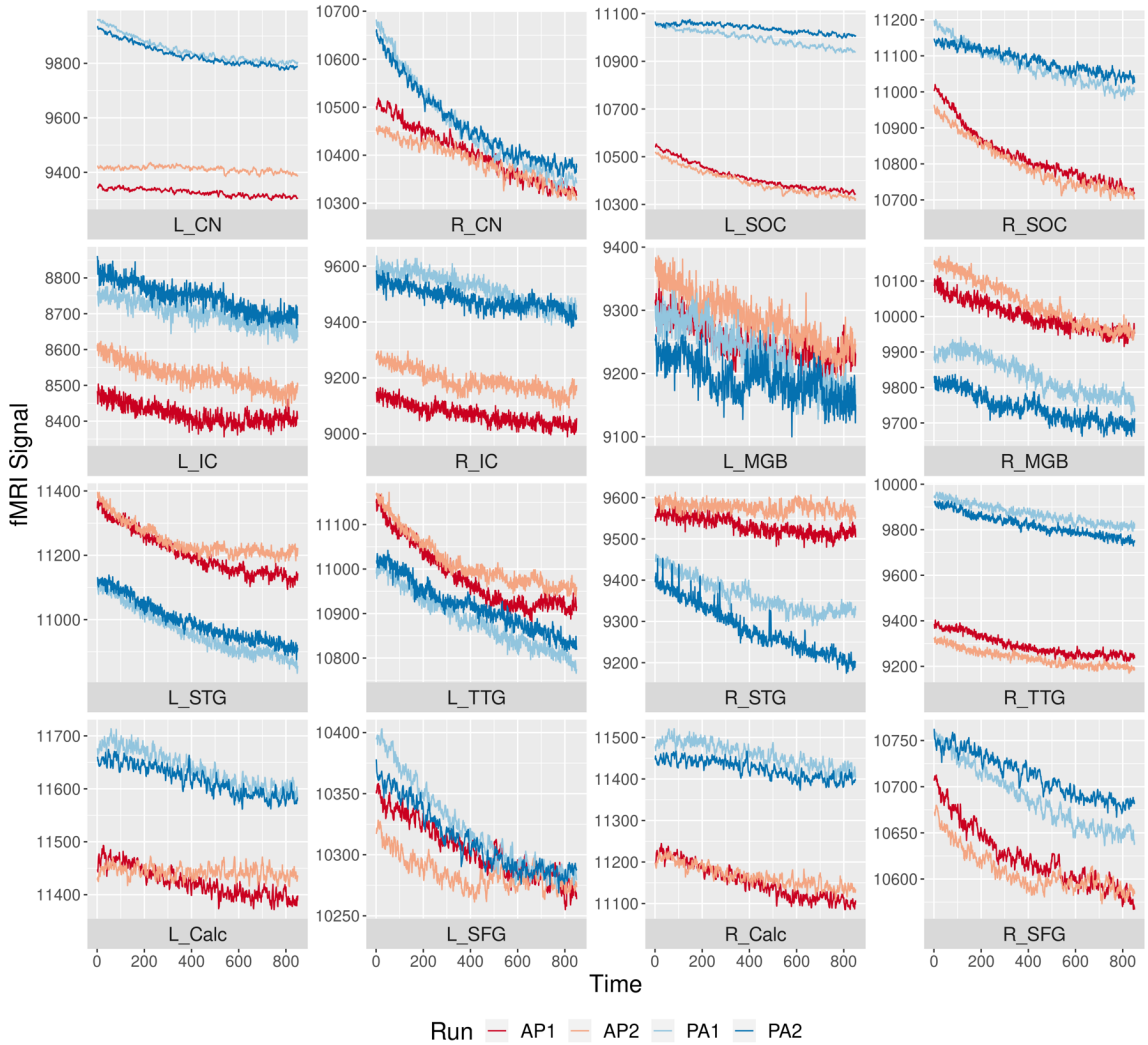

Figure 1 Scanner drift in different acquisition schemes: A strong decreasing trend can be observed when the timeserieses are averaged across the subjects for each acquisition scheme.

To remove this artifactual effect, we fit linear trend models on each of the mean timeseries separately for different ROIs and runs. Then we subtract the estimated linear trend from each individual's timeseries. In Figure 2 we illustrate the trend-removal pipeline with an example. We see that the decreasing trend induced by the scanner drift almost disappears from the individual timeseries after the trend-removal step.

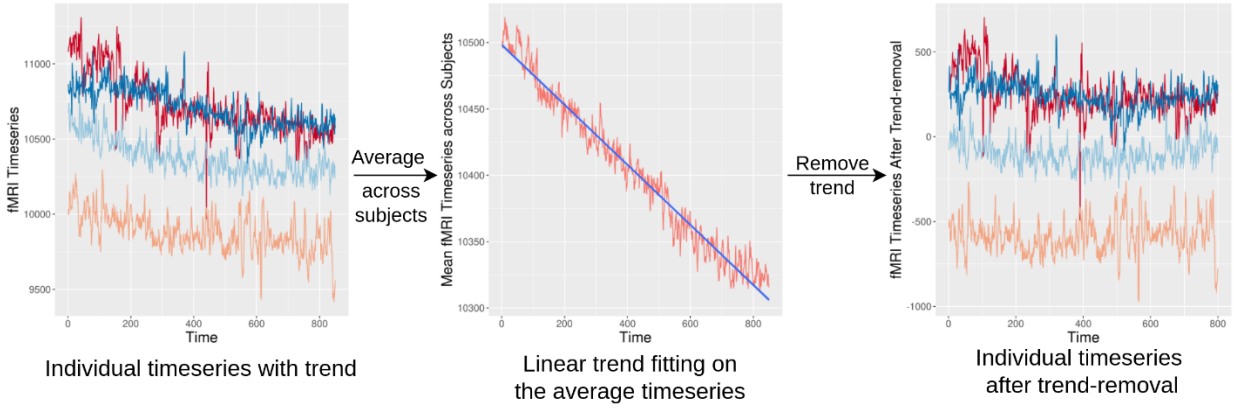

Figure 2 Linear trend removal pipeline: On the leftmost panel, timeserieses of some selected individuals have been plotted where a decresing trend can be observed uniformly across the subjects. On the middle panel, we plot the mean timeseries and fit a linear trend model to it. We subtract the fitted linear trend from the original timeserieses and again plot those in the rightmost panel. We can see that after the trend-removal procedure, the decresing trend almost disappears from the individual timeserieses.

2.3 Data partitioning and cross-validation

BOLD fMRI is prone to geometric distortions in the phase-encoding direction which can be largely corrected using a variety of methods (Esteban *et al.*, 2021; Jezzard and Balaban, 1995). Adjacent to motion-sensitive cerebrospinal fluid (CSF), the brainstem is particularly susceptible to such geometric distortions. Although the HCP minimal preprocessing pipeline corrects for phase-encoding distortions (Glasser *et al.*, 2013), to isolate the potential residual contribution of phase encoding direction on functional connectivity estimates, we conducted separate analyses on data collected with an anterior–posterior (AP) phase encoding direction (runs 1 and 3) and posterior–anterior (PA) phase encoding direction (runs 2 and 4). As opposed to within-subject analyses (Smith, Vidaurre, *et al.*, 2013), but similar to approaches used in group independent component analysis (Calhoun *et al.*, 2001) and cohort-level brain mapping (Varoquaux *et al.*, 2013), we concatenated the fMRI timeseries across subjects for each phase-encoding direction and performed partial correlation analysis on the merged dataset. This approach to reveals connectivity between auditory regions that could not have been identified due to variability inherent in individual-specific analyzes.

We further interrogated our results using a leave-10%-out cross-validation (CV) approach. We assessed the stability of the connectivity estimates by checking the correlation between the results obtained from each acquisition scheme.

2.4 Gaussian copula graphical models

The precision factor model, developed recently in (Chandra *et al.*, 2021), provided a novel computationally efficient robust technique for estimating sparse precision matrices. Since partial correlations can be readily obtained from the precision matrix, the approach allowed straightforward estimation of the underlying connectivity graphs. Their model however assumed the joint distribution of the data to be a zero mean multivariate Gaussian which implied that the univariate marginal distributions were also all Gaussians. The trend-removal makes the data mean centered but their marginal distributions still substantially deviate from the Gaussian distribution assumption of Chandra et al. (2021). In this paper, we therefore extend their model to accommodate non-Gaussian marginals as well.

Suppose we have d ROIs and Y_j be the observation corresponding to the j-th ROI with (unknown) marginal distribution f_j and corresponding cumulative distribution function (CDF) F_j. Copulas provide a broadly applicable class of tools that allow the joint distribution of $Y_1, \dots, Y_d$ to be flexibly characterized by first modeling the univariate marginals f_j's and then separately modeling their joint dependencies by mapping the $F_1(Y_1), \dots, F_d(Y_d)$ to a joint probability space. For Gaussian copulas, this is done by setting $Z_j = \Phi^{-1}\{F_j(Y_j)\}$, where $\Phi(\cdot)$ is the CDF of a standard Gaussian distribution. This implies marginally $Z_j \sim \mathrm{N}(0,1)$ for all $j = 1, \dots, d$, where $\mathrm{N}(\mu, \sigma^2)$ denotes a univariate Gaussian distribution with mean μ and variance σ^2. For their joint, we further assume

$$(Z_1, \dots, Z_d) \sim \mathrm{N}_d(0, R),$$

where R is a $d \times d$ order <u>correlation matrix</u>. Let $\Omega = \left(\left(\omega_{j,j'}\right)\right)$ be the corresponding precision matrix of $Z_1, \dots, Z_d$, that is, $R = \Psi^{-1/2}\Omega^{-1}\Psi^{-1/2}$ with $\Psi = \mathrm{diag}(\Omega^{-1})$. Then, by properties of copula and the simple multivariate Gaussian distribution, it can be shown that, irrespective of

the form of the marginal f_j's, the ROIs Y_j and $Y_{j'}$ will be conditionally dependent on (and hence functionally connected with) each other given the rest if and only if $\omega_{j,j'} \neq 0$. This way, the precision matrix Ω characterizes the functional connectivity between the different Y_j's.

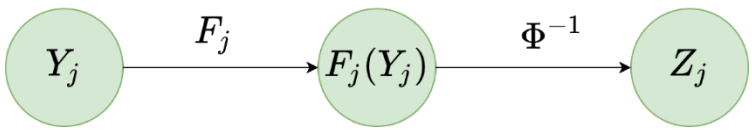

Figure 3 Copula model.

We model the unknown univariate marginal distributions of the f_j's using location-scale mixtures of Gaussians. Such mixtures can flexibly estimate a very large class of unknown densities (Ghosal *et al.*, 1999). Specifically, we let

$$f_j = \sum_{h=1}^{K} \pi_{j,h} \mathrm{N}\left(\mu_{j,h}, \sigma_{j,h}^2\right), (1)$$

where $\pi_{j,h}$ is the weight attached to the jth mixture component where $\sum_{h=1}^{K} \pi_{j,h} = 1$ with K being a suitably chosen, moderately large, fixed integer.

To estimate the precision matrix Ω, we consider the framework of Chandra et al. (2021). Recall that $R = \Psi^{-1/2}\Omega^{-1}\Psi^{-1/2}$ with $\Psi = \mathrm{diag}(\Omega^{-1})$. We next assume Ω to admit a lower-rank plus diagonal (LRD) decomposition $\Omega = \Lambda\Lambda^T + \Delta$ where Λ is a $d \times q$ order matrix and a diagonal matrix $\Delta = \mathrm{diag}(\delta_1^2, \ldots, \delta_d^2)$ with positive δ_j^2's. All positive definite matrices admit such a representation, in practice often sufficing to produce excellent approximations.

We take a Bayesian route to estimation and inference where we assign priors on the parameters of the proposed model and inference is based on samples drawn from the posterior using a Markov chain Monte Carlo (MCMC) algorithm discussed in detail in the supplementary materials. As was shown in Chandra et al. (2021), the LRD representation makes the MCMC very straightforward via a latent variable augmentation scheme. In the supplements, we also discuss a multiple hypothesis testing-based edge discovery procedure that utilizes the posterior uncertainty of the parameters and controls the false discovery rate (FDR) at 10% level in a principled manner.

2.5 Priors on the parameters

For the parameters of the mixture models specifying the marginals in equation (1), we consider the following priors

$$\left(\pi_{j,1}, \dots, \pi_{j,K}\right) \sim \mathrm{Dir}\left(\frac{\alpha_\pi}{K}, \dots, \frac{\alpha_\pi}{K}\right), \left(\mu_{j,h}, \sigma_{j,h}^2\right) \overset{iid}{\sim} \mathrm{NIG}(\mu_0, \nu_0, a_0, b_0),$$

where $(\mu, \sigma^2) \sim \mathrm{NIG}(\mu_0, \nu_0, a_0, b_0)$, implying that $\mu|\sigma^2 \sim \mathrm{N}(\mu_0, \nu_0^{-1}\sigma^2)$ and $\sigma^{-2} \sim \mathrm{Ga}(a_0, b_0)$, and $\mathrm{Ga}(a_0, b_0)$ is a gamma distribution with mean a_0/b_0 and variance a_0/b_0^2.

We assign a two-parameter generalization of the Dirichlet-Laplace (DL) prior from Bhattacharya et al. (Bhattacharya *et al.*, 2015) that allows more flexible tail behavior on the elements of Λ. On a d-dimensional vector θ, our DL prior with parameters a and b, denoted by $\mathrm{DL}(a, b)$, can be specified in the following hierarchical manner

$$\theta_j \mid \psi, \phi, \tau \overset{ind}{\sim} \mathrm{N}\left(0, \psi_j \phi_j^2 \tau^2\right), \psi_j \overset{iid}{\sim} \mathrm{Exp}(1/2), \phi \sim \mathrm{Dir}(a, \dots, a), \tau \sim \mathrm{Ga}(da, b),$$

where θ_j is the j-th element of θ, ϕ and ψ are vectors of same length as θ, $\mathrm{Exp}(a)$ is an exponential distribution with mean $1/a$, $\mathrm{Dir}(a_1, \dots, a_d)$ is a d-dimensional Dirichlet distribution. The original DL prior is a special case with $b = 1/2$. We let $\mathrm{vec}(\Lambda) \sim \mathrm{DL}(a, b)$.

The d distinct δ_j^2 's may result in over-parametrization. To reduce the effective number of parameters in an adaptive manner, we use a Dirichlet process (DP) prior (Ferguson, 1973) on the δ_j^2's as $\delta_j^2|G \overset{iid}{\sim} G, G|\alpha \sim \mathrm{DP}(\alpha, G_0)$ with $G_0 = \mathrm{Ga}(a_\delta, b_\delta), \alpha \sim \mathrm{Ga}(a_\alpha, b_\alpha)$,where α is the concentration parameter and G_0 is the base measure. The DP model allows clustering the δ_j^2's allowing for additional data-adaptive parameter reduction. We discussed a Markov chain monte Carlo (MCMC) based implementation strategy of our model in the supplementary materials.

3. Results

3.1 Partial correlations between regions of interest

Using our copula graphical model approach, we first estimated the precision matrix Ω and subsequently computed the partial correlations. We reported the significant edges subject to

controlling the posterior false discovery rate (Sarkar *et al.*, 2008) at the 10% level. We found that the strongest auditory connectivity was between adjacent structures in the same hemisphere, particularly between the auditory midbrain (inferior colliculus, or IC) and thalamus (medial geniculate body, or MGB) and between core and associative auditory cortex (TTG and STG). We also saw strong connectivity between homologous control regions (i.e., between left and right calcarine cortex, and between left and right SFG). Weaker (but still present) connectivity was observed between homologous auditory structures, particularly in midbrain and thalamus. Weak connectivity was present between adjacent brainstem auditory structures (cochlear nucleus [CN] and superior olivary complex [SOC]) on the left (but not right). Interestingly, despite the SOC being the primary (and earliest) decussation point in the ascending auditory pathway, we did not observe partial correlations between contralateral CN and SOC. (See the Discussion section for potential explanations.)

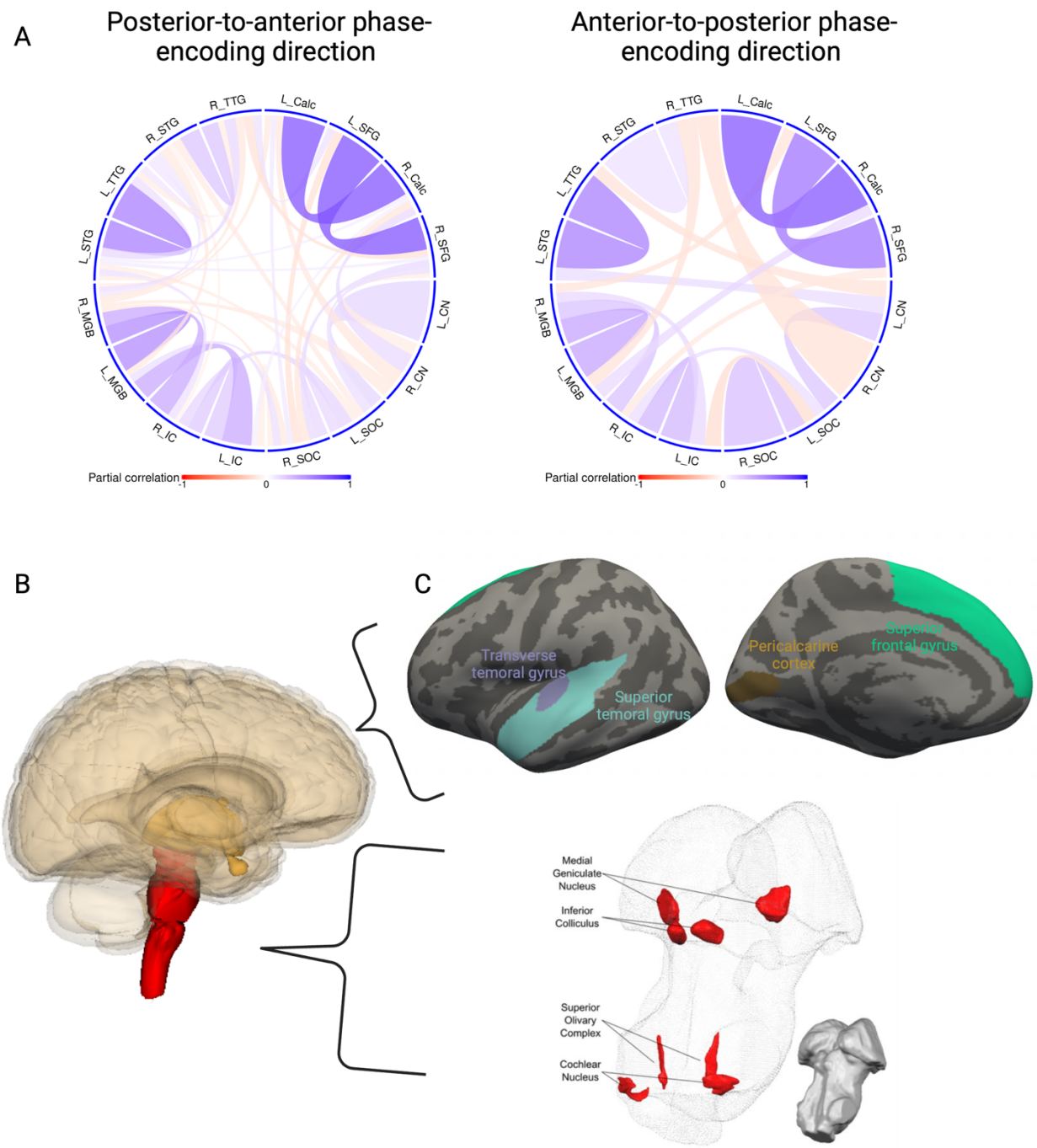

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Figure 4. A: Partial correlation connectivity in data acquired with posterior-to-anterior (PA; left) and anterior-to-posterior (AP; right) phase-encoding directions. B: 3-dimensional view of the human brain with the brainstem highlighted in red. C: regions of interest from which functional timeseries were extracted. Top: cortical regions from FreeSurfer's DKT atlas. Bottom: subcortical auditory regions (Sitek et al., 2019).

3.2 Effect of phase encoding scheme on subcortical connectivity

Due to the anatomical location of the subcortical auditory structures—in dense, heterogeneous subcortical regions and largely adjacent to CSF—we conducted connectivity analyses separately on AP- and PA-acquired fMRI runs. We then compared the connectivity results from the two acquisition schemes. Overall connectivity patterns were highly similar between the two phase-encoding schemes (Figure 4; Pearson's $r = 0.805$, $p < 0.001$). Subcortical connectivity was quite robust between the brainstem auditory regions (except for left and right CN), as was cortical connectivity (with the exception of right TTG and right STG).

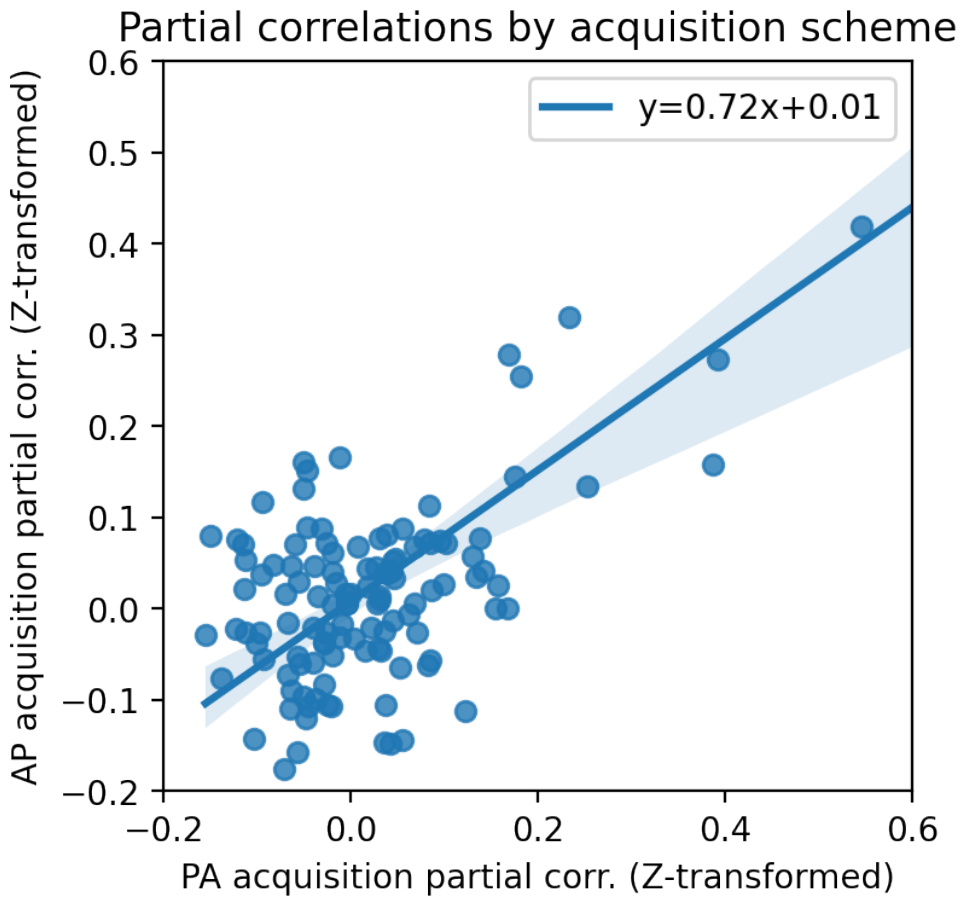


Figure 5. Pearson correlation of partial correlation values between posterior-to-anterior and anterior-to-posterior phase-encoding acquisition schemes across all edges in the graph (region-to-region connections).

3.3 Cross-validation of partial correlations

To assess the stability of our partial correlation results, we ran leave-10%-out cross-validation within each phase encoding scheme and computed (full) correlations across the 10 folds per scheme (for a total of 20 folds; see Figure 6). Across all folds (and both phase encoding schemes), the results were highly similar (intraclass correlation of edgewise partial correlations across cross-validation folds = 0.912).

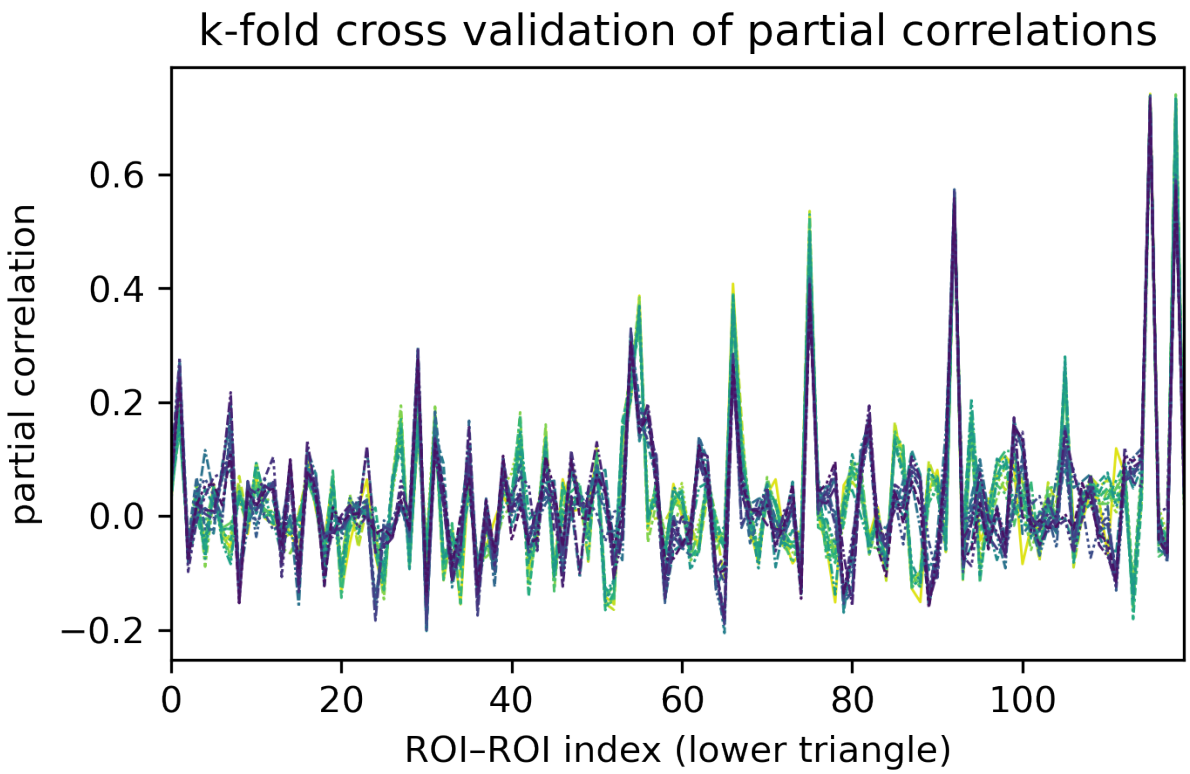


Figure 6. Partial correlations across cross-validation folds (10 folds for each of the two phase-encoding acquisition schemes).

3.4 Fit of the copula graphical model

We studied the goodness-of-fit of the copula graphical model. In Figure 7 we plotted the sample histogram and the corresponding fitted marginal densities for some selected ROIs. The sample histograms strongly indicated that distribution of the data substantially deviate from the Gaussian assumption. The following figure shows that our flexible location-scale mixture of Gaussians fit the data very well even though marginally the data are not Gaussian distributed.

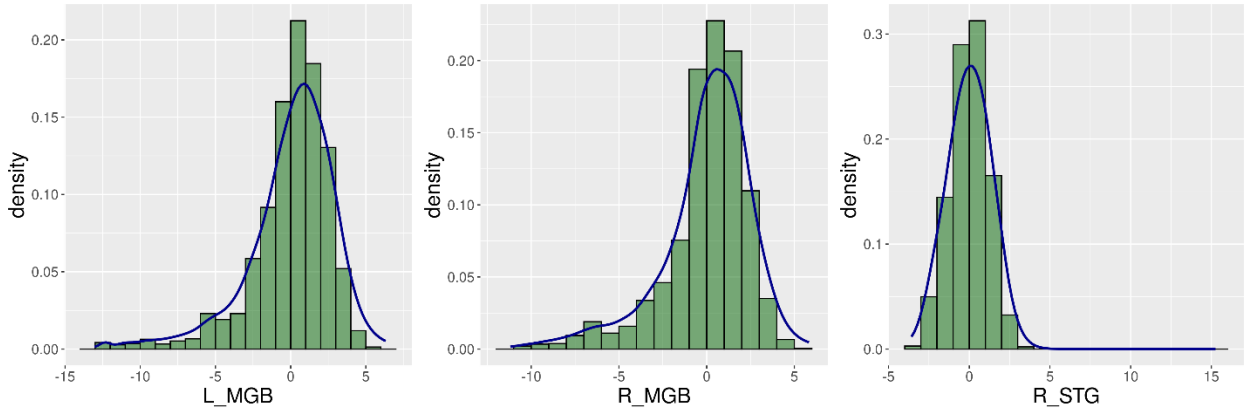
326 

Figure 7 Marginal fits for the location-scale mixture of Gaussian distributions: The sample histograms in green clearly showed that distribution of the ROIs substantially deviates from Gaussian assumption. The blue lines are the respective fitted densities corresponding to the mixture model in eqn (1). These figures indicate excellent goodness-of-fit.

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328 *3.5 Comparison with existing approaches*

329 We compared with two standard approaches in the literature: (1) analyzing the graphs for each
330 subject separately and then combining them (Smith, Vidaurre, *et al.*, 2013); and (2) the
331 precision factor model (Chandra *et al.*, 2021) that assumes Gaussian distribution on the BOLD
332 signals corresponding to each ROI. In both comparisons, we did separate analyzes for each of
333 the acquisition schemes.

334 For comparison (1) the results are provided in Figure 8. While the strongest edges in the
335 network can be recovered, we can see that the weak edges are mostly absent compared to
336 Figure 4 (for instance, between IC and MGB). Due to the low signal-to-noise ratio in fMRI
337 timeseries in small, deep subcortical structures, the weak edges may not be optimally
338 recovered from the individual-specific analyzes.

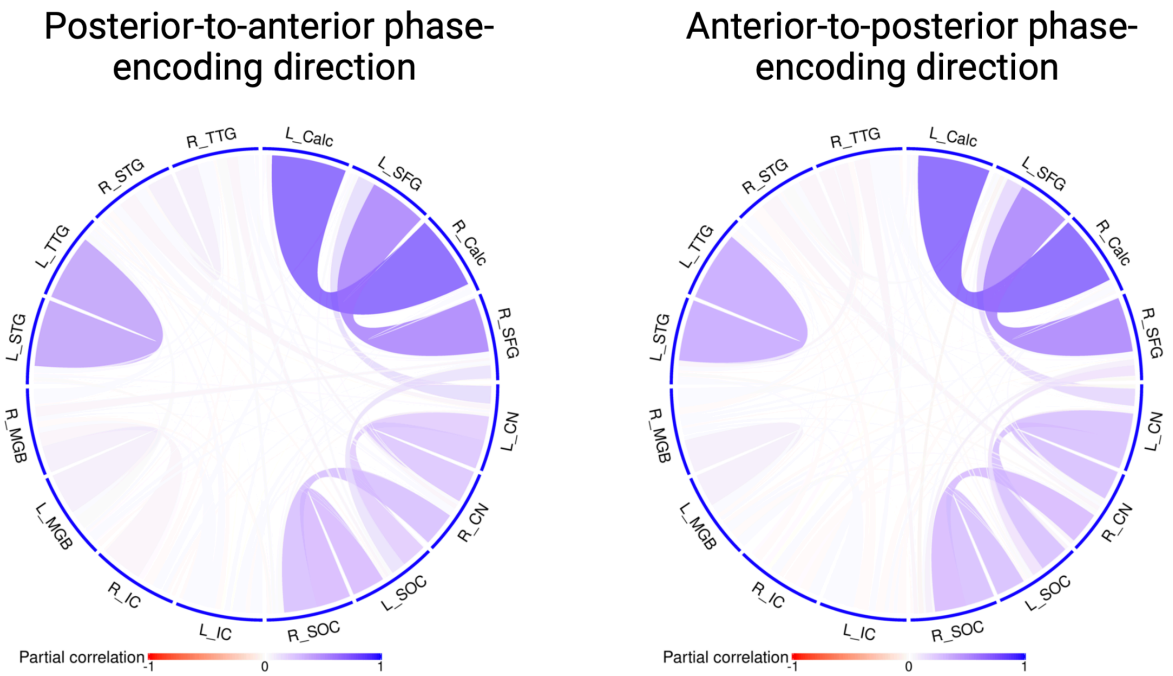

Figure 8 Conditional dependency graph for comparison (1): BOLD signals for each subject are analyzed separately and the average graphs are reported for each of the acquisition schemes.

Results corresponding to comparison (2) are provided in Figure 9. Graphs corresponding to the posterior-to-anterior phase encoding detection majorly differ between the Gaussian graphical model and the copula graphical model with the former being much denser. This is a common phenomenon for graphical models if the Gaussian assumption is made on non-Gaussian distributed data; see, e.g., Section 5, example 1(a) in (Guha *et al.*, 2020). In Figure 10 we plot the marginal Gaussian fits on the histograms of some BOLD signals. Clearly the simple Gaussian assumption does not hold here and more flexible model like the copula graphical model is required.

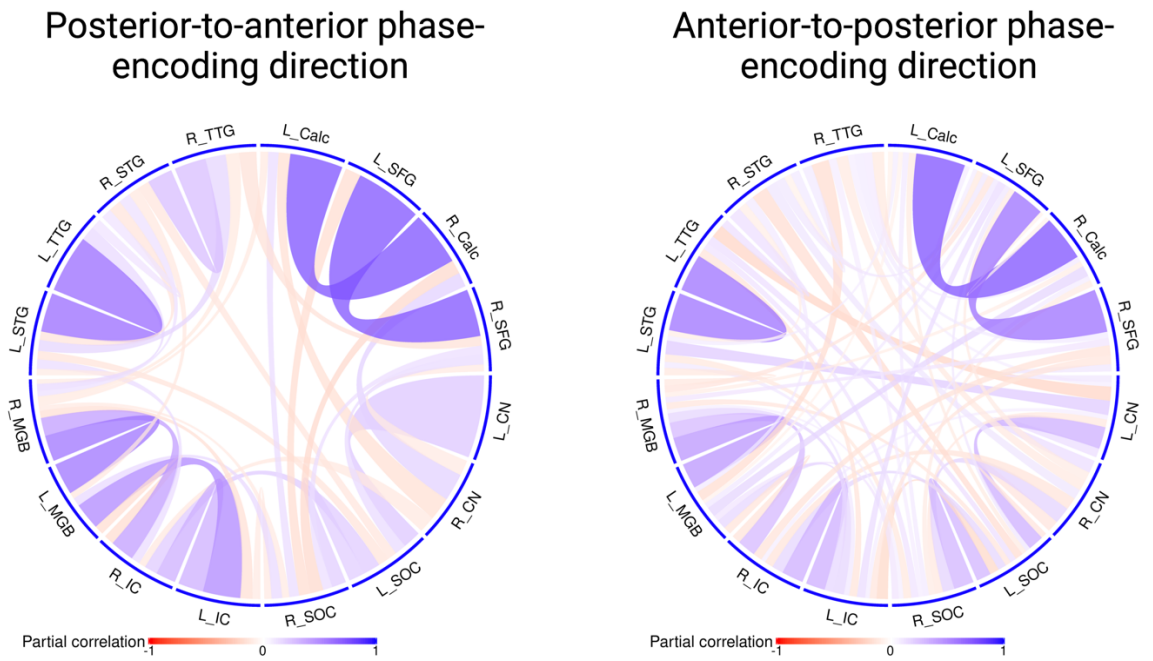

Figure 9 Conditional dependency graph for comparison (2): Instead of the proposed copula graphical model, the precision factor model in (Chandra *et al.*, 2021) *with Gaussian assumption on the marginal distribution of the BOLD signals corresponding to each ROI.*

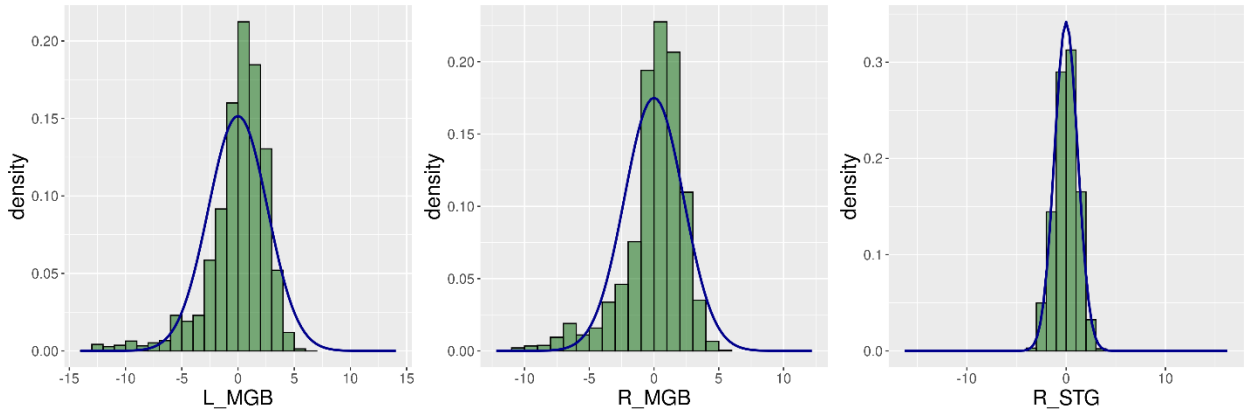

Figure 10 Marginal Gaussian fits (blue lines) on the BOLD signals (green histograms) for some selected ROIs. High skewness in the BOLD histograms suggests that the Gaussian assumption does not hold for these data.

4. Discussion

The mammalian auditory pathway consists of a series of obligatory and interconnected subcortical and cortical brain structures. Assessing the connectivity of the human subcortical auditory structures has been limited due to methodological challenges of non-invasive imaging of the deep, small structures. Recent acquisition and analytical advances enable finer grained investigations of connectivity throughout the brain, including the brainstem. In this work, we developed a novel approach to estimating partial correlations using copula graphical models to a publicly available high-resolution resting state functional MRI dataset. We found highly consistent connectivity patterns between auditory brain regions that demonstrates the efficacy of our connectivity method as well as the potential for functional connectivity investigations of the subcortical auditory system.

Using partial correlations (as opposed to full correlations) allows us to identify specific relationships between nodes in a connectivity graph by removing shared variance across nodes as illustrated in the stylized example in the supplementary materials.

To model and learn the dependence structure between the regions of interest in this analysis, we implemented a Gaussian copula graphical model, which can be used for non-Gaussian distributed data as well, such as functional MRI data. In this study, we found strong partial correlations in resting state functional MRI data between cochlear nucleus (CN) and superior olivary complex (SOC) in the left hemisphere (but not in the right). These connectivity patterns between CN and SOC have not been previously observed in human auditory brainstem but follow our understanding of the mammalian auditory pathway based on research in animal models. Principally, auditory information that is transduced by the cochlea of each ear is transmitted via the cochlear nerve to the cochlear nucleus, the first stage of the central auditory pathway, on each side of the brainstem. From there, auditory signals are passed to both the ipsilateral and contralateral SOC for further auditory processing, including spatial localization (Moore, 2000). Interestingly, we only observed left CN–SOC connectivity (and in both data acquisition schemes). It is unclear why similar patterns were not observed between right CN and SOC or between contralateral structures (left CN to right SOC and right CN to left SOC). One contributor is the lower signal-to-noise ratio in MRI data from the lower brainstem.

383 Paired with the small size of each of the brainstem auditory nuclei, we may still be at the edge
384 of what is detectable using present functional connectivity methods. Additionally, this analysis
385 was conducted on “resting state” fMRI data, during which no auditory stimuli of interest were
386 presented or overt task was conducted. Resting state fMRI connectivity in the cochlear nucleus
387 and superior olivary complex has not been examined in the previous literature to our
388 knowledge; it is possible that sound-evoked connectivity methods would evoke greater
389 functional connectivity, particularly in these earliest stages of the auditory pathway. Further,
390 ipsilateral connections (e.g., between left CN and left SOC) may be stronger due to their close
391 physical proximity. Even with relatively high 1.05 mm spatial resolution 7T fMRI data, CN and
392 SOC on each side are only separated by a few voxels. These regions are thus at increased
393 likelihood of sharing temporal fluctuations due to partial volume effects, wide point-spread
394 functions, non-Gaussian spatial dependence, imperfect image registration, or other as-yet-
395 unsolved fMRI confounds that are particularly acute in the lower brainstem.

396 Moving up the primary auditory pathway, we found significant partial correlations between left
397 SOC and right inferior colliculus (IC) in each acquisition scheme. Due to crossing connections at
398 the level of the SOC, such contralateral connectivity is to be expected. The lack of right SOC to
399 left IC connectivity is challenging to reconcile, but when considered with the previous results—
400 an absence of right CN to right SOC connectivity—this suggests that right CN was particularly
401 affected by low MRI SNR in the brainstem. Further, both sets of data showed strong partial
402 correlations between left and right IC. Anatomically, IC contains a strong white matter bundle—
403 the commissure of IC—connecting left and right IC. Thus, the significant functional connectivity
404 between the two colliculi fits nicely with neuroanatomical features.

405 Passing information to the next level of the auditory pathway, we observed significant partial
406 correlations between left IC and left medial geniculate body (MGB) of the thalamus in the
407 posterior-to-anterior acquisition scheme and between right IC and right MGB in both phase-
408 encoding schemes. Interestingly, we found strong partial correlations between left and right
409 MGB in both datasets. Although not directly connected by large white matter bundles, left and
410 right MGB are expected to process auditory information from IC at similar levels of abstraction.

411 Thus, partial correlations may reflect indirect but shared neural mechanisms of auditory
412 processing in the thalamus.

413 Finally in auditory cortex, left transverse temporal gyrus (TTG)—the location of primary
414 auditory cortex—was strongly connected with left superior temporal gyrus (STG), which
415 contains secondary and associative auditory cortices. A homologous connectivity pattern was
416 found between right TTG and STG, but only in the posterior-to-anterior acquisition scheme.
417 These functional connectivity results align with a vast literature demonstrating information flow
418 between primary and non-primary auditory cortex (for review, see (Hackett, 2011).

419 In non-auditory cortical regions (superior frontal gyrus and calcarine cortex), we observed
420 strong partial correlations between contralateral homologues, as would be expected based on
421 prior literature of bilateral symmetry of functional connectivity patterns. These
422 contrahemispheric connections were missing from auditory cortex regions perhaps due to the
423 inclusion of multiple auditory cortical regions, as the partial correlation approach removes
424 variance that is shared across the network and leaves only the strongest region-to-region
425 connectivity. Complementarily, some literature suggests that left and right auditory cortex
426 process auditory information at distinct timescales and levels of abstraction (Güntürkün *et al.*,
427 2020; Hickok and Poeppel, 2007; Zatorre *et al.*, 2002), with left auditory cortex being uniquely
428 tuned to rapidly changing temporal information—such as the phonetics of speech sounds—
429 while right auditory cortex is more sensitive to slower changes in the spectral domain,
430 particularly for speech prosody as well as music.

431 Overall, the present study is one of the first investigations into functional MRI connectivity
432 across the entire human auditory system. To date, there have been only limited applications of
433 functional MRI methods to study subcortical auditory connectivity (Berlot *et al.*, 2020; Hofmeier
434 *et al.*, 2018). Due to the small size of the subcortical auditory structures, high spatial resolution
435 is highly beneficial for anatomical segmentation of the structures. However, increasing the
436 resolution of MRI scans results in decreased SNR in each voxel, requiring greater amounts of
437 MRI data to achieve reasonable fMRI contrast. In this study, we took advantage of the large
438 amounts of high-resolution data collected in the 7-Tesla Human Connectome Project (HCP; four

runs of 900 BOLD volumes with TR = 1 s at 1.6 mm isotropic spatial resolution) in order to identify connectivity patterns between auditory structures.

As the HCP data were collected in two phase-encoding acquisition schemes, we were able to investigate the potential influence of phase-encoding direction on subcortical auditory connectivity. Due to the location of subcortical auditory structures along the dorsal brainstem and midbrain—near or adjacent to ventricles that are known to conduct physiological motion—it was unknown whether correction for susceptibility distortion (as part of the HCP minimal preprocessing pipeline) was sufficient. In the present study, we found minimal differences between the two acquisition schemes after susceptibility distortion correction, reinforcing the efficacy of such methods for investigating subcortical (particularly brainstem) connectivity.

5. Conclusions

Using a Gaussian copula-based novel approach to partial correlation estimation, we identified functional connectivity in the human auditory system using resting state functional MRI. In particular, brainstem connectivity was highly consistent across acquisitions, demonstrating the utility and applicability of functional connectivity methods in deep brain structures. Future research will investigate global partial correlation connectivity using this Gaussian graphical model approach.

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