PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/175222

Please be advised that this information was generated on 2019-04-21 and may be subject to change.
Frequency-specific directed interactions in the human brain network for language

Jan-Mathijs Schoffelen¹,²,³, Annika Hultén¹,², Nietzsche Lam¹,², André F. Marquand⁴, Julia Uddén¹,²,³, and Peter Hagoort¹,²,⁴

¹Radboud University Nijmegen, Donders Institute for Brain, Cognition, and Behaviour, 6500 HB Nijmegen, The Netherlands; and ²Max Planck Institute for Psycholinguistics, 6525 XD Nijmegen, The Netherlands

The brain’s remarkable capacity for language requires bidirectional interactions between functionally specialized brain regions. We used magnetoencephalography to investigate interregional interactions in the brain network for language while 102 participants were reading sentences. Using Granger causality analysis, we identified inferior frontal cortex and anterior temporal regions to receive widespread input and middle temporal regions to send widespread output. This fits well with the notion that these regions play a central role in language processing. Characterization of the functional topology of this network, using data-driven matrix factorization, which allowed for partitioning into a set of subnetworks, revealed directed connections at distinct frequencies of interaction. Connections originating from temporal regions peaked at alpha frequency, whereas connections originating from frontal and parietal regions peaked at beta frequency. These findings indicate that the information flow between language-relevant brain areas, which is required for linguistic processing, may depend on the contributions of distinct brain rhythms.

Significance

The brain’s remarkable capacity for language requires bidirectional interactions between functionally specialized brain regions. Although the functional role of individual regions in the brain network for language has been well studied, as of yet little is known about the mechanisms that facilitate the information exchange between these brain regions. In this paper we show that communication between language-relevant areas in the brain is supported by rhythmic neuronal synchronization and that different rhythms reflect the direction of information flow. These findings likely reflect a generic mechanism that allows for dynamic routing of information in a network of task-relevant brain regions during cognitive processing.

Author contributions: A.H., J.U., and P.H. designed research; J.-M.S., A.H., N.L., and J.U. performed research; J.-M.S. contributed new reagents/analytic tools; J.-M.S. and A.F.M. analyzed data; J.-M.S. and P.H. wrote the paper; and A.H., N.L., and A.F.M. helped with part of the analysis.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission. B.G. is a guest editor invited by the Editorial Board.

¹To whom correspondence may be addressed. Email: jschoffelen@donders.ru.nl or p.hagoort@donders.ru.nl.
²Present address: Department of Neuroscience and Biomedical Engineering, Aalto University, FI-00076 Helsinki, Finland.
³Present address: Department of Linguistics and Stockholm University Brain Imaging Centre, University of Stockholm, SE-106 91 Stockholm, Sweden.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1703155114/-/DCSupplemental.

www.pnas.org/cgi/doi/10.1073/pnas.1703155114

PNAS | July 25, 2017 | vol. 114 | no. 30 | 8083–8088
connections, projecting to ipsilateral anterior middle and superior temporal cortex [Brodmann areas (BA) 21/22/38], to contralateral middle and superior temporal cortex (BA 21/22), and to frontal cortex (BA 6/9/44/45/47) (P < 0.05, Bonferroni corrected randomization test). Left and right inferior frontal regions (BA 47), however, were observed to receive Granger causal input from ipsilateral frontal cortex (BA 44/45/46), ipsilateral superior temporal cortex (BA 22), ipsilateral angular gyrus (BA 39), and ipsilateral extrastriate visual cortex (BA 19, area 17/18 present in the right hemisphere only) (P < 0.05, Bonferroni corrected randomization test). Additionally, regions receiving substantial inflow were located bilaterally in the anterior temporal pole (receiving input from superior and middle temporal regions, as well as from inferior frontal cortex), in the occipital pole (receiving input from extrastriate regions as well as from inferior temporal and occipito-temporal cortex), and in the right anterior temporal cortex.

To gain more detailed insight into the spatial and spectral structure of this brain wide network we applied nonnegative matrix factorization (NMF) to the group-level connectivity data (8). Specifically, we modeled the connectivity data as a mixture of a limited number of spatially static network components, each with a subject-specific spectral profile. The decomposition algorithm did not incorporate any specific constraints with respect to the spatial or spectral structure of the underlying components. In particular, no assumptions were made about the spatial clustering of edges (i.e., the decomposition algorithm did not favor sets of connections to end up in the same component when the cortical parcels on each end of the directed connection were spatially clustered). However, the majority of extracted network components were physiologically interpretable, judging from the spatial clustering of the cortical parcels participating in component-specific directed interactions. Fig. 2 shows the network components with predominant connections between language-relevant cortical areas (components with predominant connections between visual cortical areas and components with more spatially diffuse connections are shown in Fig. S1). The components' cortical locations for outflow and inflow are depicted in blue and orange/yellow, respectively, in the leftmost panel for each quadruplet of columns. For some of the components, the subject-averaged spectral profiles were band-limited to a certain frequency range, which moreover showed a consistent peak frequency across subjects (Fig. 2 B–H, middle panels for each quadruplet of columns). This suggests that these components represent frequency-specific rhythmic directed interactions between key regions in this large-scale network. We categorized the extracted components based on the dominant region for outflow. The majority of the components reflected predominantly intrahemispheric connections (Fig. 2 B–H, right panel for each quadruplet of columns). We identified left and right hemispheric directed rhythmic interactions from posterior and midtemporal cortical regions to ipsilateral frontal cortex (mainly inferior frontal), with a median peak frequency at 12 Hz [interquartile range (IQR) 11–13 Hz] (Fig. 2F). A somewhat spatially more diffuse component with predominantly left intrahemispheric connections led from midtemporal areas to inferior and superior frontal areas (Fig. 2C). Connections from posterior and midtemporal regions to ipsilateral anterior temporal cortex had a slightly higher median peak frequency of 14 Hz (with an IQR of 12–15 Hz and 13–15 Hz for the left and right hemispheric components), compared with the tempo-frontal connections (Fig. 2D). Next, there was a set of components predominantly interconnecting temporal cortical regions that showed somewhat more variability in their spectral profile across subjects (Fig. 2E). These components reflected connections from superior and middle temporal cortex (along the whole anterior–posterior axis) to mid and anterior inferior temporal cortex, and connections from midmiddle and superior anterior temporal cortex to the temporal pole.

In contrast to the network components with the outflow regions in temporal cortex, the rhythmic interactions with predominant

---

Fig. 1. Topology of the brain network for language as quantified with GC. (A) Overview of the left hemispheric anatomical parcels used for source reconstruction and serving as network nodes, displayed on the inflated cortical surface. Lateral and medial surfaces are shown on the Left and Right, respectively. Right hemispheric homologous parcels were also considered for network estimation, yet not displayed here. (B) Left Node degree for inflow (i.e., the number of nodes from which each of the nodes receives significant Granger causal input) (P < 0.05, nonparametric permutation test, Bonferroni corrected) and outflow (i.e., the number of nodes to which each of the nodes sends significant Granger causal output). (B, Right) Uncorrected P values associated with the statistical comparison (nonparametric permutation) of the topology observed in the left panels, and randomly connected networks, keeping the overall degree distribution constant. Orangelyellow parcels survive Bonferroni correction for multiple comparisons (the number of edges) and reflect hubs in the network. (C) Topology of the connections for each of the highly connected hubs identified in B, and the other cortical areas, for inflow hubs (blue parcels in B) and outflow hubs (red parcels in B), with the hubs displayed in yellow, and the Granger causal strength to sending/receiving areas in red.
Network components obtained with NMF show frequency, regional, and direction-specific interactions. (A) Location of the cortical nodes, displayed on an inflated cortical sheet (Left) with color coding and labeling convention (Right), as used in B–H. Circular grouping was according to anatomical location, using BA labeling for the parcels outside temporal cortex, and using their relative location along the anterior/posterior and superior/inferior axis for temporal parcels. (B–H) Components reflecting connections between language-relevant cortical areas. Leftmost panels show the location of the parcels involved. Dark/light blue colors: regions for outflow (the lighter the color of the parcel, the stronger the relative contribution of the parcel to the component). Orange/yellow/white colors: regions for inflow. The histograms show for each of the components the distribution of the subject-specific peak frequency. The spectra show the median peak frequency of the rhythmic interactions between components with predominant connections from the anterior/posterior and superior/inferior regions for temporal and frontal cortex, respectively. We statistically evaluated the peak frequency of the rhythmic interactions between components with predominant connections between parietal, frontal, and temporal brain areas (Fig. 3A). Overall, the component-specific median peak frequencies ranged from the upper end of the alpha range (12 Hz) to the upper end of the beta range (30 Hz). Moreover, components with rhythmic Granger causal outflow predominantly from temporal areas had a consistently lower peak frequency.
frequency than components with Granger causal outflow from parietal or frontal areas (P < 0.05, nonparametric permutation test, multiple comparison corrected). Notably, in the NMF we could distinguish temporo-frontal interactions, with a peak frequency of 12 Hz (Figs. 2A and B and 3B and C, connection in dark red), from fronto-temporal interactions, with a peak frequency of 27 Hz (Figs. 2F and 3B and C, connection in dark blue). Fig. 3B shows a schematic summary of the dominant rhythmic interactions, with the corresponding spectral profile in Fig. 3C.

We proceeded to test whether the strength of the rhythmic interactions was modulated by the functional requirements imposed by the perceptual input. To this end, we divided the stimulus material into four conditions, based on whether the subjects were reading a well-structured sentence or a pseudorandom sequence of words (sentences and word lists), and based on the ordinal position of the words (early and late words). Importantly, we stratified the data for lexical frequency and overall signal variance, to avoid as much as possible interpretational confounds for the estimated connectivity (12, 14) due to differences in univariate signal and stimulus properties (8). Subsequently, we computed the Granger causal interactions for each subject and condition for the most prominent functional connections, which were extracted from the NMF results by means of spatial clustering. We constrained the analysis to band-limited estimates of GC, averaging across frequencies and edges. The connection-specific frequency bands were obtained from the components’ peak frequencies and IQRs.

Contrasting sentences with sequences, we observed the strength of the interactions to be modulated from left middle temporal regions to the left temporal pole, where sequences elicited stronger interactions than sentences, and from right striate to extrastriate visual regions (Fig. 4A, P < 0.05, nonparametric permutation test, Holm–Bonferroni correction for multiple comparisons). Comparing early words with late words in the sentence condition showed several significantly modulated connections, with rhythmic interactions being stronger early in the sentence (Fig. 4B). These connections were bilateral from temporal to frontal regions, and from middle temporal regions to the temporal pole. In addition, in the right hemisphere we identified significantly modulated connections from frontal regions to temporal regions, and from the superior temporal gyrus to the middle temporal gyrus (P < 0.05, nonparametric permutation test, Holm–Bonferroni correction for multiple comparisons). Moreover, we identified two right hemispheric connections that showed a significant interaction effect between early vs. late words and sentences vs. sequences (Fig. 4B and Fig. S2).

Discussion

We have provided evidence for directed interactions between cortical regions in the human brain network for language during sentence reading. Topological analysis of the overall network revealed a high degree of Granger causal inflow into anterior inferior frontal cortical regions, right anterior temporal cortex, and the temporal pole bilaterally. This is in line with these regions’ being “high-order” regions, involved in the processing of more abstract features of the linguistic input, which requires integration of converging information. Frontal regions are engaged in unification operations (15), integrating lexical units into the larger context. Anterior temporal cortex is associated with conceptual object representations (16, 17).

Middle temporal cortical regions, however, displayed a high degree of Granger causal outflow. This is in agreement with the middle temporal gyrus’ crucial role in language comprehension at the level of single words (18, 19). Its functional connections to more anterior temporal areas, as well as to inferior frontal cortex, reflect the necessity to propagate information about individual lexical items to areas that subserve integration operations. Notably, we did not observe a clear lateralization in the pattern of connections, which lends support to the evolving notion that both cerebral hemispheres are involved in the processing of linguistic stimuli (20).

Data-driven decomposition of the overall network into smaller subnetworks revealed several spatially constrained components, corresponding with local and long-range directed interactions. The clear frequency-resolved profile displayed by some of these components displayed is indicative of the interactions’ being mediated by rhythmic interareal synchronization. Connections originating from temporal cortical areas showed a consistently lower peak frequency (alpha and low beta) than connections originating from parietal or
Materials and Methods

Experimental Procedure and MEG Data Acquisition. Native Dutch speakers (n = 102, 51 males), with an age range of 18–33 y, participated in the experiment. All participants were right-handed, had normal or corrected-to-normal vision, and reported no history of neurological, developmental, or language deficits. The study was approved by the local ethics committee (CMO, the local "Committee on Research Involving Human Participants" in the Arnhem-Nijmegen region) and followed the guidelines of the Helsinki declaration. All participants gave written informed consent before participation. The participants read sequences and lists of words (total number of 240, with 9–15 words per sequence), presented sequentially on a back-projection screen, placed in front of them. MEG data were collected with a sampling frequency of 1,200 Hz. Throughout the measurement the head position was continuously monitored using custom software (26).

Artifact Rejection and Subtraction of Single-Trial Activity. All analyses were done with custom-written MATLAB scripts and FieldTrip (27). Data were epoched from −100 to 600 ms relative to word onset, and segments contaminated by artifacts were discarded before further analysis. We subtracted the result in signal cancellation effects upon averaging, due to sign ambiguity of the resulting cardinal dipole orientations, which might result from signal cancellations effects upon averaging, due to sign ambiguity of the resulting cardinal dipole orientations.

Preselection of the Connections Between Language-Relevant Areas. We constrained ourselves a priori to a subset of connections between parcel pairs, using known “long-range” macroanatomical fiber pathways between parcels comprised of core language regions and the visual system as described in the literature (9–11). In addition, we showed a priori that feedback connections between neighboring nodes, based on the characteristics of cortico-cortical connections (e.g., refs. 24 and 33). We included intrahemispheric connections from both hemispheres and also included interhemispheric connections between homologous areas. Fig. 2A shows how the individual nodes were labeled. Connections between directly adjacent parcels were excluded for further analysis to reduce spurious estimates of connectivity due to spatial leakage of source-reconstructed activity. The selection scheme resulted in 4,350 connections between pairs of parcels, which notably consisted of a sparse subset of all possible pairwise connections between the 156 parcels used for the GC analysis.

GC Computation and Statistical Evaluation of Overall Network Topology. We computed the spectral representation of the signals at the sensor level and projected this into source space, using the parcel-specific spatial filters. The spectral representation of the signals was obtained using the fast Fourier transform (FFT) as a combination of ongoing activity and event-related components (31) and subtracted the modeled single-trial evoked responses from the data (Fig. S3).

Source Reconstruction and Parcellation of Source-Reconstructed Activity. We performed source reconstruction using a linearly constrained minimum variance beamformer (LCMV) (32), estimating a spatial filter at 8,196 locations of the subject-specific reconstructed midcortical surface. Next, we applied an atlas-based parcellation scheme to reduce the dimensionality of the data. We used a refined version the Conte69 atlas, resulting in a parcellation scheme consisting of 191 parcels per hemisphere. Spatial filters were concatenated across vertices comprising a parcel, and we obtained a set of time courses of the event-related field at each parcel and selected for each parcel the first two spatial components explaining most of the variance in the signal. We opted for this method, rather than averaging, because we used rank-reduced forward solutions (excluding the most noise-sensitive dipole orientations), which might result in signal cancellation effects upon averaging, due to sign ambiguity of the resulting cardinal dipole orientations.
between GC and reverse GC was statistically significant (across subjects) at a P value <0.05, corrected for multiple comparisons (one-sided t test, with Bonferroni correction). This illustrates the number of connections that were used for subsequent analysis from 4,350 to 713.

NMF and Network Visualization.} We explored the network topology by performing NMF with sparsity constraints (38) on the resulting GC spectra. The purpose of this analysis is to describe the reconstructed connectivity data as a low-dimensional mixture of network components, each of which with a subject-specific spectral profile. This technique has successfully been applied to sensor-level MEG-signals before (39). We opted for sparse NMF, because the nonnegativity constraint facilitates the interpretation of the components, as opposed to, for example, a statistical independence constraint as applied in independent component analysis. This is because GC is strictly nonnegative. The outcome of NMF is dependent on the number of components. We explored a range of “number of components” but settled on the number 20 for the reconstruction procedure on the outcome to extract the underlying structure of the data, irrespective of the random initializations of the NMF algorithm.

Condition-Specific Statistical Evaluation. We estimated condition-specific GC in the dominant connections extracted from the identified network components. The individual conditions were defined according to whether the words were presented in a well-formed sentence context (or were part of a word list) and according to whether the words were presented early in the sentence/word list (words two to four) or late in the sentence/word list (n – 3 until n – 1, with n the number of words in the sentence/word list). To account for potential intertemporal confounds of the resulting GC estimates we used a stratification procedure to ensure that the marginal distributions of the epochwise signal variances as well as the words’ lexical frequencies were equalized across conditions. As a consequence only a subset of epochs is used for the GC estimation, where the parcel-pair specific number of epochs varies across parcel pairs. On average 50% of the epochs were retained (range: 20–75%), corresponding to 147 (range: 45–235) epochs. We defined dominant connections as spatially clustered sets of edges. We computed subject- and condition-specific GC and performed a nonparametric permutation test to evaluate (i) sentence – word list words, (ii) for the sentence condition: early – late words, and (iii) an interaction effect: (early-late words sentences) – (early-late words sequences).

ACKNOWLEDGMENTS. This work was supported by a Dutch Organization for Scientific Research (NWO) gravitation grant and Spinoza award (to P.H.) and an NWO VIDI grant (to J.-M.S.).