Functional identification of language-responsive channels in individual participants in MEG investigations

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Abstract

Making meaningful inferences about the functional architecture of the language system requires the ability to refer to the same neural units across individuals and studies. Traditional brain imaging approaches align and average brains together in a common space. However, lateral frontal and temporal cortex, where the language system resides, is characterized by high structural and functional inter-individual variability. This variability reduces the sensitivity and functional resolution of group-averaging analyses. This problem is compounded by the fact that language areas often lay in close proximity to regions of other large-scale networks with different functional profiles. A solution inspired by other fields of cognitive neuroscience (e.g., vision) is to identify language areas functionally in each individual brain using a 'localizer' task (e.g., a language comprehension task). This approach has proven productive in fMRI, yielding a number of discoveries about the language system, and has been successfully extended to intracranial recording investigations. Here, we apply this approach to MEG. Across two experiments (one in Dutch speakers, n=19; one in English speakers, n=23), we examined neural responses to the processing of sentences and a control condition (nonword sequences). We demonstrated that the neural response to language is spatially consistent at the individual level. The language-responsive sensors of interest were, as expected, less responsive to the nonwords condition. Clear inter-individual differences were present in the topography of the neural response to language, leading to greater sensitivity when the data were analyzed at the individual level compared to the group level. Thus, as in fMRI, functional localization yields benefits in MEG and thus opens the door to probing fine-grained distinctions in space and time in future MEG investigations of language processing.

1 Introduction

The functional architecture of the human language network is broadly consistent across individuals (e.g. Lipkin et al. (2022)). However, the precise topography of this network varies substantially even within homogenous groups of neurotypical adults (Fedorenko et al., 2010). Developing research methods that take these inter-individual differences into account by identifying functional areas in individual participants—an approach known as 'functional localization'—has proven vital in cognitive neuroscience across domains and has been shown to increase sensitivity, functional resolution, accurate effect size estimation, and interpretability (Saxe et al., 2006; Nieto-Castañón and Fedorenko, 2012; Fedorenko, 2021). So far, functional localizer paradigms have been predominantly used in fMRI research (Kanwisher et al., 1997; Saxe and Kanwisher, 2003; Fedorenko et al., 2010; Baldauf and Desimone, 2014), although a handful of studies had applied a similar approach in other recording modalities, including electrocorticography (ECoG) (Cogan et al., 2014; Fedorenko et al., 2016; Regev et al., 2022) and functional near-infrared spectroscopy (fNIRS) (Powell et al., 2018). With respect to magnetoencephalography (MEG), functional localization has only been applied in studies of visual processing so far (Liu et al., 2002; de Vries and Baldauf, 2019) to the best of our knowledge. Here, we extend this approach to MEG investigations of language processing.

Numerous studies over the last decade have provided evidence that the language network can be delineated in a robust and replicable way at the individual-subject level using a contrast between language comprehension and a perceptually matched control condition in fMRI (Fedorenko et al., 2010; Mahowald and Fedorenko, 2016; Braga et al., 2020)(see Lipkin et al. (2022) for data in > 800 individuals). Importantly, the language localizer contrast (language > perceptually matched control condition) has been shown to be robust to input modality (written, spoken, or signed)(Fedorenko et al., 2010; Scott et al., 2017; Richardson et al., 2020), stimulus content (hand-crafted sentences, sentences extracted from a corpus, or connected passages (Scott et al., 2017)), language (Malik-Moraleda, Ayyash et al., 2022), and the presence or absence of an active task (Fedorenko et al., 2010; Diachek et al., 2020; Ivanova et al., 2020). Furthermore, this network has been shown to be strongly selective for linguistic input (Fedorenko et al., 2011)(see Fedorenko and Blank (2020) for a review). The language network

likely stores linguistic knowledge and uses this knowledge to interpret linguistic information. This broad generalization across paradigm variations and selectivity for language processing jointly suggest that contrasts between language comprehension and perceptually matched control conditions identify a network that responds to linguistic stimulus features rather than some task-related demands or features that language may share with other domains.

Although fMRI investigations of the language network have yielded important findings, fMRI's poor temporal resolution limits its use for research questions where timing information is critical. Intracranial recordings provide an incredible opportunity to obtain high-spatial and high-temporal resolution data with high signal-to-noise ratio, but the approach is inherently limited with respect to both the population and the coverage. In contrast, magnetoencephalography (MEG) enables whole-brain non-invasive measurements of neural activity in typical brains at a millisecond-level resolution. Here, using data from two independent datasets (across two languages: English and Dutch), we establish the feasibility of identifying language-responsive sensors at the individual level in MEG investigations, and provide evidence that this approach is more sensitive than the standard brain-averaging approach.

2 Methods

2.1 Participants

We recruited 42 healthy young volunteers: 19 native Dutch speakers (18 female, between 19 and 29 years old, mean 23.4 years old) and 23 native English speakers (between 19 and 53 years old, mean 26.7 years old). The study was approved by the local Ethics Committees. All participants provided written informed consent in accordance with the Declaration of Helsinki.

2.2 Experimental design

In localizing the language network, we use a design that has been extensively validated in fMRI (first used in Fedorenko et al. (2010)), namely, a sentence reading task. Using fMRI, the sentences>nonwords sequences contrast has been shown to robustly and reliably identify the language-selective network (Lipkin et al., 2022; Malik-Moraleda, Ayyash et al., 2022). Participants performed the experiment in their native language. Materials can be downloaded from https://osf.io/vc2bw/. For the sentence condition, 80 12-word-long sentences were constructed in English using a variety of syntactic structures and covering a wide range of topics. The sentences were translated into Dutch, with minimal changes to obtain 12-word-long sentences. For the nonwords condition, care was taken to minimize low-level differences in the phonological make-up of the stimuli compared to the sentence condition. In English, the content words (noun, verb, adjective, adverb) of the sentence condition were syllabified to create a set of syllables that could be re-combined in new ways to create pronounceable nonwords. For syllables that formed real words of English, a single phoneme was replaced (respecting the phonotactic constraints of English) to turn the syllable into a nonword. The syllables were then recombined to create nonwords matched for length (in syllables) with sentence condition (Fedorenko et al., 2010). In Dutch, nonwords were derived from the content words in the sentence condition by means of the pseudoword generator Wuggy (http://crr.ugent.be/programs-data/wuggy). This program generates nonwords that match the original word in subsyllabic structure and respects the transition frequencies specific to Dutch (Keuleers and Brysbaert, 2010).

To help participants stay engaged, we used a memory probe version of the language localizer task in the Dutch version, where participants are asked to decide (by pressing one of two buttons) whether a word or nonword, presented at the end of each sentence or nonword list, was in the preceding trial. Probes were restricted to content words in the sentence condition and nonwords in the nonwords condition. Half of the trials required a positive response. In the English version, a button-press icon was presented at the end of each sentence or nonword list where participants are asked to press a button. This difference between the Dutch and English was introduced to reduce the duration of the English experiment by several minutes, in order to combine the paradigm with other, unrelated studies. As noted above,

previous fMRI work demonstrated that the sentences>nonwords localizer contrast is robust to different tasks including passive viewing (Fedorenko et al., 2010; Diachek, Blank, Siegelman et al., 2020).

The words/nonwords were presented one at a time in a rapid serial visual presentation paradigm at a fixed rate per word/nonword (385 ms per (non)word in Dutch, 400 ms in English). Each word/nonword was presented in the center of the screen in capital letters without punctuation. Then, the memory probe or button-press icon was presented, followed by a variable interval, between 0.5s and 2.25s. Participants could respond any time after the probe or button-press icon appeared and until the next trial started. The experiment lasted ~20 minutes. Five participants in the English dataset were scanned using a similar paradigm but with a different set of materials (8-word-long sentences and 8-nonword-long sequences). Previous fMRI work has shown that the sentences>nonwords localizer contrast is robust to such variation (Fedorenko et al., 2010).

2.3 MEG Data Acquisition

Continuous MEG data were recorded using a whole-head 306 channel (102 magnetometers, 204 planar gradiometers) Triux system (Elekta Neuromag, Helsinki, Finland) either at the CUB Hôpital Erasme (Brussels, Belgium) or at the Martinos Imaging Center (McGovern Institute for Brain Research at MIT, Cambridge, MA, USA). Participants were tested in a seated position. Four head-position indicator (HPI) coils were used to record the head position within the MEG helmet every 200 ms. The participant's head shape was digitally recorded by means of a 3D digitizer (Fastrak Polhemus, Inc., Colchester, VA, USA) along with the position of the HPI coils and fiducial points (nasion, left and right periauricular). MEG signals were recorded at a sampling rate of 1000 Hz.

2.4 MEG Data Preprocessing

Initial preprocessing of the raw data used MaxFilter version 2.2 (Elekta-Neuromag Oy, Helsinki, Finland): temporal signal space separation (Taulu et al., 2004) was applied to remove noise from

external sources and from HPI coils for continuous head-motion correction (correlation threshold: 0.98, 10 s sliding window), and to virtually transform data to a common head position. The latter facilitates comparison across experiments. MaxFilter was used to automatically detect and virtually reconstruct noisy channels. Further preprocessing was performed using Brainstorm (Tadel et al., 2011). Preprocessing consisted of high-pass filtering at 0.1 Hz, low-pass filtering at 300 Hz and notch filtering (Bruffaerts et al., 2019b). Denoising was performed by removing ICA components consistent with eye blinks and cardiac artefacts upon visual inspection (60 components derived by ICA, independently performed on data from magnetometers and planar gradiometers). Data were downsampled to 500 Hz and epoched (400ms before (non)word onset until 1 sec after (non)word onset). Visual inspection of all epochs was performed and epochs with clear artefacts were marked as bad and excluded from further analysis.

2.5 Statistical analysis

The "sentence condition" epochs selected for analysis consisted of the MEG signal elicited by each word except the first 4 words of each sentence trial (n=640), and the "nonwords condition" epochs consisted of all nonword epochs except the first 4 nonwords of each nonword trial (n=640). We omitted the first 4 (non)words in each trial from the analysis in order to focus on the part of the trial where the between-condition differences might be most pronounced (given what is known about the processes related to sentence meaning construction; e.g., Pallier et al., 2011; Fedorenko et al., 2016), although this choice proved not to impact the results in the end (see discussion). For all epochs, we grouped each pair of planar gradiometers into a single effective gradiometer derived as their Euclidean norm (hence measuring the amplitude of the field's tangential gradient, independently of orientation) (Chetail et al., 2018). A quantitative marker of noise was derived per participant by calculating the standard deviation across the baseline intervals of all trials averaged over all sensors (baseline defined as the interval of 200 ms prior to trial onset). Participants with markers of noise greater than two standard deviations from the average noise marker across participants scanned in the same MEG device were removed from further analysis. This procedure led to the removal of 1 participant from the English dataset. Two

additional participants were removed from the English dataset: one due to excessive motion and one due to the presence of high-amplitude "mu rhythm" apparent upon visual inspection. To facilitate between-participant comparisons, we calculated the percent signal change in the sentence and nonword conditions between 0 and 350 ms for every epoch compared to the baseline interval for that trial. Finally, we averaged the percent signal change values across all included word/nonword positions (i.e., the 5th word/nonword and all subsequent ones) within a condition to derive a single value per channel per participant.

To test whether MEG allows for a robust identification of language-responsive sensors at the individual participant level, we first evaluated the stability of the language responses within individuals across time (i.e., between the odd- vs. even-numbered trials). To do so, we performed three analyses. First, we examined the Spearman correlation in the size of the sentence effect (percent signal change for the sentence condition relative to the baseline) across all channels within each participant across odd- and even-numbered trials compared to the correlations between different participants (Wilcoxon rank sum test). Spearman instead of Pearson correlation was used because it is more robust to potential outliers (Rousselet and Pernet, 2012). This analysis asks: if a sensor shows a strong response to sentences in one half of the data, does it also show a strong response to sentences in the other half of the data in the same participant compared to another participant? Second, we used the data from the odd-numbered trials to define sensors of interest (SOIs) in each participant. SOIs were defined as the 10% sensors with the highest increase in percentage signal change in the sentence condition relative to the baseline. We then examined the effect size for the sentence condition in the even-numbered trials in these SOIs relative to the baseline and to the effect size for the nonword condition using a signed rank test. Finally, we defined SOIs (in the same way) using the data from the even-numbered trials and computed a Dice coefficient to examine overlap in SOI selection between the two halves of the data within and between individuals (significance calculated using random permutation labeling with 10^6 permutations).

To test whether identification of language-responsive sensors at the individual level is superior to identifying language-responsive sensors at the group level, we compared the results of the second analysis above to a version of the analysis where we performed the same calculation using group-

averaged maps (where the responses are averaged across participants from either the English or Dutch dataset in each sensor). In particular, we used the data from the odd-numbered trials to create a group map and defined SOIs as the 10% of sensors with the highest increases in percent signal change in the sentence condition relative to the baseline. We then examined the effect size for the sentence condition in the even-numbered trials in these SOIs for each participant. Critically, unlike in the individual-level analyses, the SOIs in the group analysis are the same for all participants. To compare the effect sizes in SOIs defined individually vs. based on a group-level map, we used a signed rank test.

3 Results

In the English dataset, the average correlation in the size of the sentence effect across all channels within each participant across odd- and even-numbered trials was 0.51 (s.d. 0.21). The mean correlation between pairs of participants was significantly lower (mean rho: 0.14, s.d. 0.24, $P < 0.001$, **Figure 1A**). Visual inspection confirmed the similarity between the topographies of the signal changes during the sentence condition in the odd- and even-numbered trials (**Figure 2A**).

The effect size for the sentence condition in the individually defined SOIs (based on the odd-numbered trials) was 5.4% signal increase compared to baseline in the even-numbered trials ($P<0.001$, **Figure 3A**) and was reliably greater than the effect size for the nonwords condition ($P = 0.017$). At the level of individual participants, 16 of the 20 showed a sentence > nonwords effect (**Figure 4A**).

The SOIs that were selected within individual participants as sentence-responsive based on the odd-numbered trials vs. based on the even-numbered trials exhibited moderate overlap (mean Dice coefficient = 0.37, $P = 0.017$).

When assessing the topography of the language-responsive SOIs that were selected in different participants, inter-individual differences were notable (**Figure 2AC**): although some channels were consistently selected in a substantial fraction of participants (up to 45%, or 9 of the 20 participants, **Figure 5A**), other channels were only selected in a small fraction of individuals. This inter-individual

variability, combined with the intra-individual topographic stability, results in the superiority of the individual-level analyses. In particular, the traditional group-level analysis is less sensitive compared to the individual-level analysis: when defining the SOIs based on the group-level map for the odd-numbered trials, the effect size for the sentence condition was significantly smaller compared to the analyses that take inter-individual differences into account ($P < 0.001$, **Figure 3A**). At the level of individual participants, 17 of the 20 participants showed a larger effect size in the individually defined SOIs compared to the group-level SOIs (**Figure 4A**).

In the Dutch dataset, the results were highly similar. The average correlation in the size of the sentence effect across all channels within each participant across odd- and even-numbered trials was 0.59 (s.d. 0.19). The mean correlation between pairs of participants was significantly lower (mean rho: 0.20, s.d. 0.24, $P < 0.001$, **Figure 1B**). The topographies of the signal changes during the sentence condition in the odd- and even-numbered trials were visually similar (**Figure 2B**). The effect size for the sentence condition in the individually defined SOIs was 7.3% signal increase compared to baseline in the even-numbered trials ($P<0.001$, **Figure 3B**) and was reliably greater than the effect size for the nonwords condition ($P < 0.001$). At the level of individual participants, 18 of the 19 showed a sentence > nonwords effect (**Figure 4B**). The SOIs that were selected within individual participants as language-responsive based on the odd-numbered trials vs. based on the even-numbered trials exhibited moderate overlap (mean dice coefficient = 0.43, $P = 0.002$). When assessing the topography of the language-responsive SOIs that were selected in different participants, inter-individual differences were notable (**Figure 2BD**): some channels were consistently selected in a substantial fraction of participants (up to 47%, or 9 of the 19 participants, **Figure 5B**).

Again, the group-level analysis was less sensitive compared to the individual-level analysis: when defining the SOIs based on the group-level map for the odd-numbered trials, the effect size for the sentence condition was significantly smaller compared to the analyses that take inter-individual differences into account ($P < 0.001$, **Figure 3B**). At the level of individual participants, 15 of the 19 participants showed a larger effect size in the individually defined SOIs compared to the group-level SOIs (**Figure 4B**).

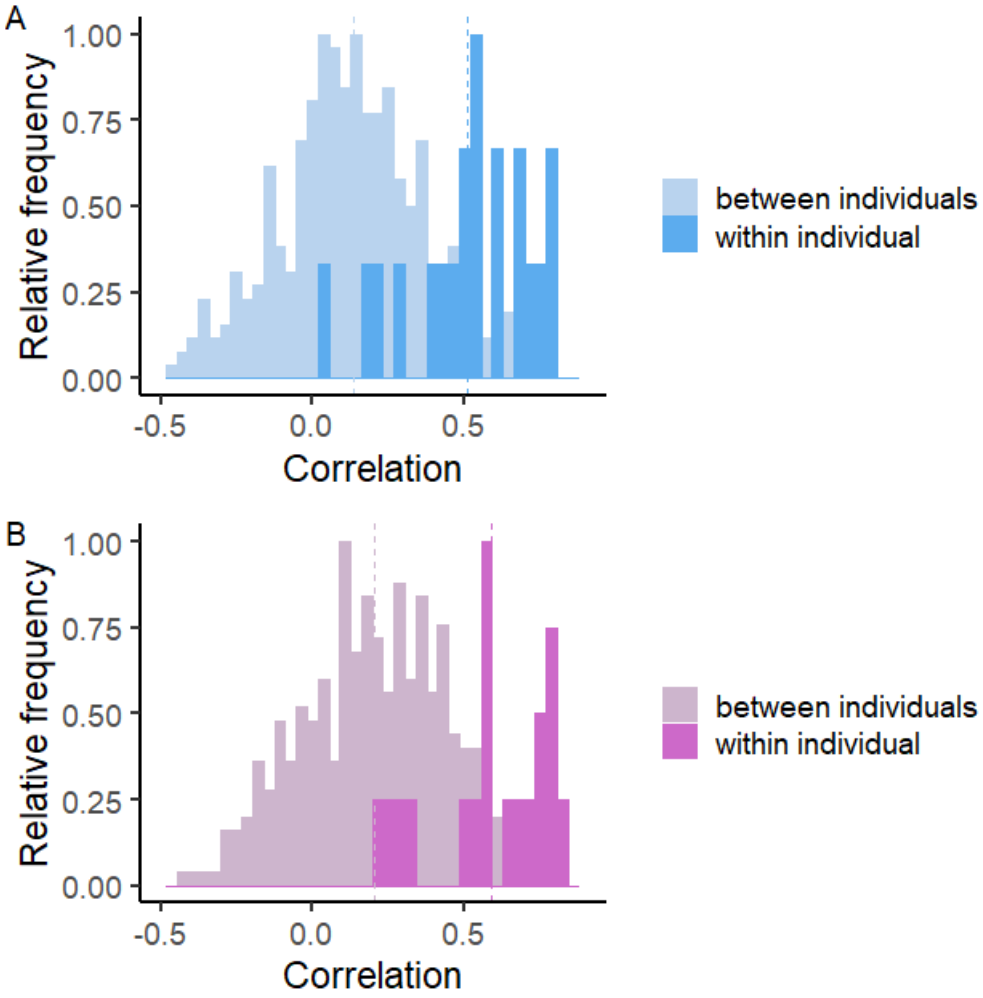

Figure 1: Distribution of the correlation (Spearman) values for the size of the sentence>baseline effect across channels within individuals across odd- and even-numbered trials (darker shades) and between data halves taken from different individuals (lighter shades) in the in the A) English and B) Dutch datasets. Relative frequency counts were plotted because of the different numbers of possible combinations between vs within individuals. Vertical striped lines indicate the mean of each distribution.

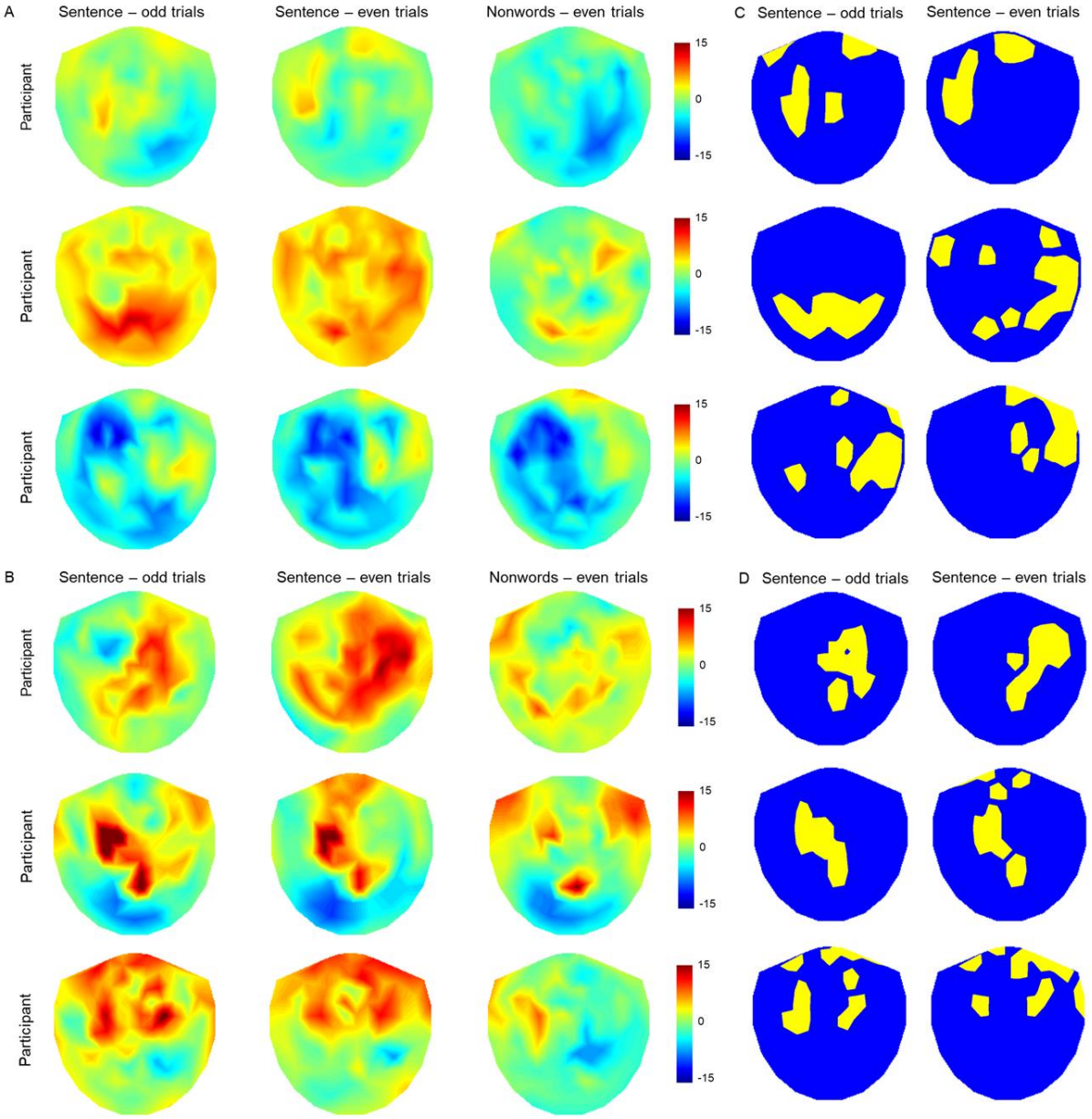

Figure 2: Topographies and selected sensors in sample participants. Topographies of the effect sizes (percentage signal change) during the sentence condition in the odd- and even-numbered trials and the nonwords condition in three participants from the A) English and B) Dutch datasets. SOIs (yellow) derived from the sentence condition in the odd- and even-numbered trials in the same participants from the C) English and D) Dutch datasets.

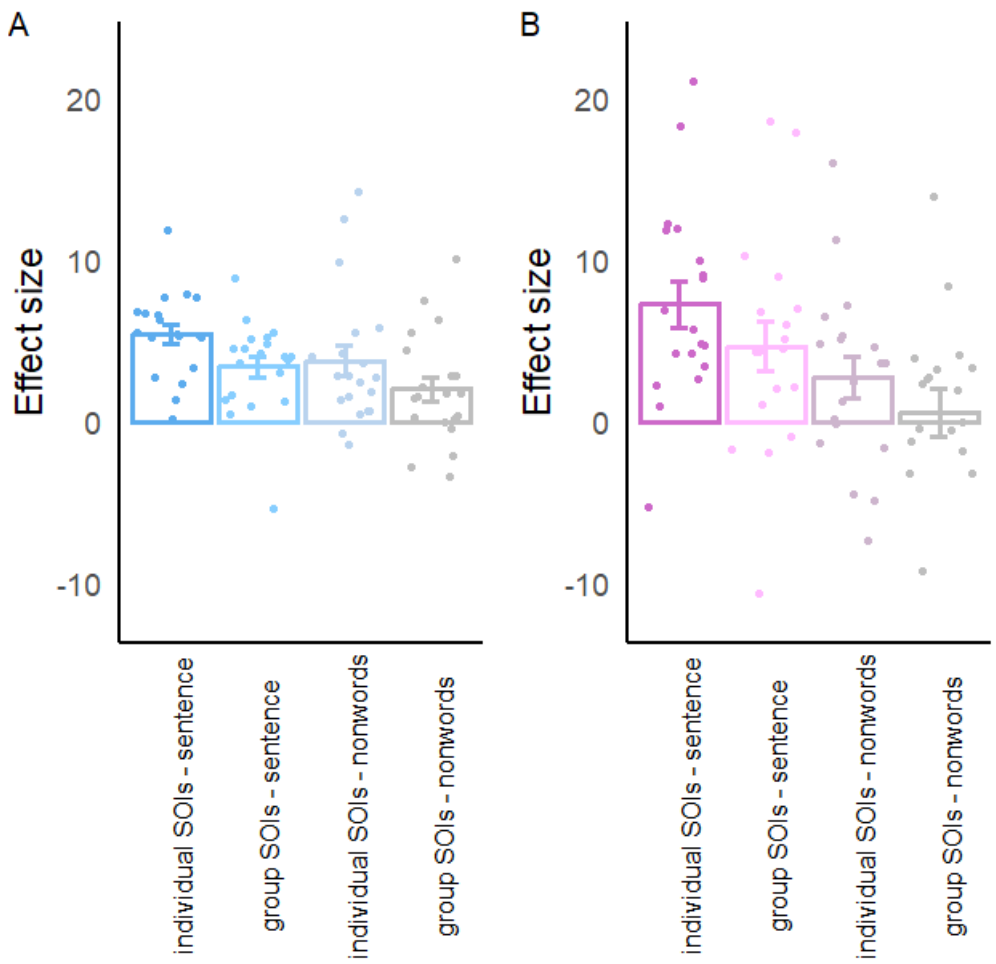

Figure 3: Mean effect sizes (percent signal change) for the sentence and nonwords conditions when the language-responsive sensors of interest (SOIs) are defined at the individual level vs. at the group level in the A) English and B) Dutch datasets. In both cases, the SOIs are defined using one half of the data (odd-numbered trials) and the response magnitudes are examined in the other half of the data (even-numbered trials).

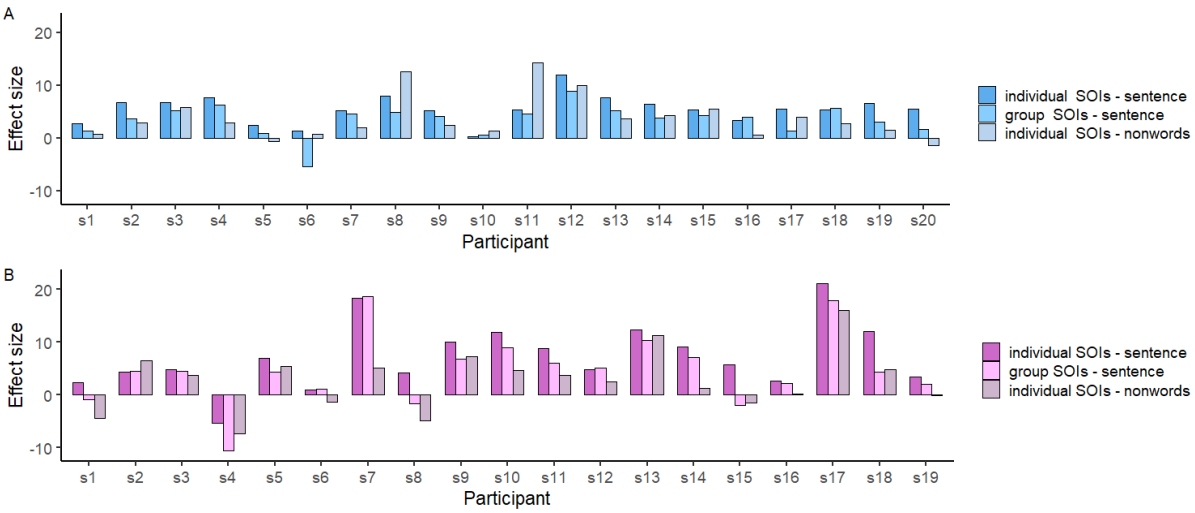

Figure 4: Effect sizes (percent signal change) in each participant for the sentence and nonwords conditions when the language-responsive sensors of interest (SOIs) are defined at the individual level and for the sentence condition when the SOIs are defined at the group level in the A) English and B) Dutch datasets. The SOIs are defined using one half of the data (odd-numbered trials) and the response magnitudes are examined in the other half of the data (even-numbered trials).

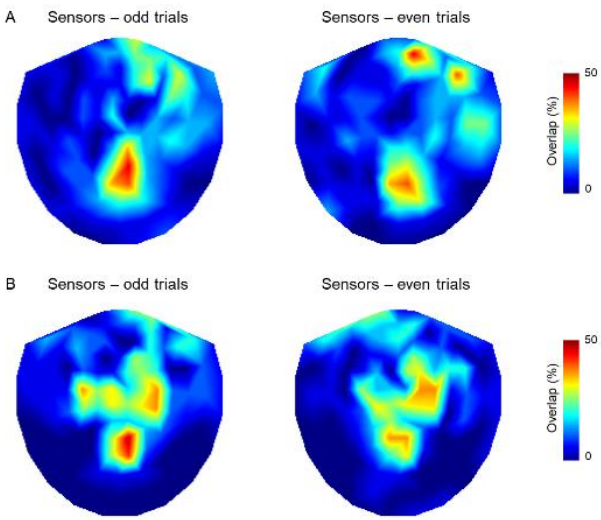

Figure 5: Topographies of selected sensors of interest (SOIs) across participants in the odd- and even-numbered trials of the A) English and B) Dutch datasets.

4 Discussion

In two independent datasets, MEG recordings allowed the identification of language-responsive sensors at the individual-participant level. During sentence reading, reproducible neural signal changes could be detected at the individual level in both English (Dataset 1) and Dutch (Dataset 2) native speakers. We showed that in both datasets, the response to language is spatially consistent (over time) within individuals: similar sensors show strong responses during language processing in two halves of the data. Importantly, the response to language is spatially variable across individuals due to differences in the functional neuroanatomy. The consequence is that analyses that take inter-individual variability into account have greater sensitivity that the traditional group-level analysis. Overall, the results suggest that the functional localization approach, where sensors of interest are defined in individual participants, can yield advantages in MEG, including greater sensitivity, functional resolution, and interpretability.

4.1 Individual-level localization of the language network

In line with prior results using the same language localizer task with fMRI (Lipkin et al., 2022) and intracranial recordings (Fedorenko et al., 2016), we observed that analyses that take into account inter-individual variability in the location of language-responsive cortex yield higher sensitivity: language responses are reliably higher when the channels are selected at the individual level, compared to the group level. When using a typical fMRI preprocessing and analysis pipeline, voxel-wise neural responses from each participant are warped from the subject space to a common space based on a brain template and functional correspondence is assumed in each voxel. This assumption has long been shown to be flawed, especially when examining cognitive functions supported by the association cortex (Nieto-Castañón and Fedorenko, 2012; Fedorenko and Blank, 2020). Analysis of resting-state MEG data demonstrated that functional connectivity patterns enable differentiation between different individuals

(da Silva Castanheira et al., 2021) and we here extend the individual-level neural characterization to the language network.

In brain recording approaches, like fNIRS and MEG, where a fixed number of sensors are used, a similar assumption is typically made when data are pooled across participants: that the same sensor is functionally equivalent across individuals. However, because of the inter-individual neuroanatomical differences in cortical thickness, gyrification, and total brain volume, and differences in the placement of the recording channels relative to the brain, the same sensor may capture different underlying sources of neural signals depending on the individual's anatomy. This variability in the sources captured by the same channels across participants introduces noise when signals are averaged across participants and complicates interpretation leading to incorrect conclusions (e.g., see Powell et al., 2018 for a discussion of this issue in fNIRS).

Source modelling allows to map neural signals from the sensors to an individual's structural brain scan for both fNIRS and MEG. However, group-level analysis after source modelling is associated with the same limitations as group-level analysis performed in a common space using fMRI: specifically, warping the neural signals across participants to a common space wrongly assumes functional equivalence of the same voxel or vertex across participants (Nieto-Castañón and Fedorenko, 2012; Fedorenko and Blank, 2020). Functional localization in individual participants provides a powerful alternative solution. This approach allows us to circumvent potential differences in the underlying anatomy and focus on the functional responses. Functional localization at the individual level can be performed in sensor space, as we have done here, or in source space. Logistically, a MEG source modelling approach requires additional data acquisition using MRI. Future research will investigate the use of source modelling combined with our functional localizer approach to localize the language-responsive vertices at the individual level.

We established the feasibility of individual-participant functional localization in MEG using an extensively validated language localizer paradigm. Previous work established the replicability of neural responses evoked by language processing using MEG within the same group of individuals (Roos and Piai, 2020). We demonstrated the topographic stability of the language-responsive channels within

individuals over time—the critical foundation of individual-level functional localization. The functional localization approach yields greater sensitivity and functional resolution. In particular, with respect to sensitivity: by grouping the selected SOIs, one statistical test can be performed across the ensemble of sensors, avoiding the need for multiple statistical comparisons (Nieto-Castañón and Fedorenko, 2012a). Further, effect sizes are more accurately estimated. This greater sensitivity can be helpful in examining subtle effects in some new, critical conditions and has the potential for application in patients with neurological disease, where neural responses may be overall weaker. With respect to functional resolution, this approach improves the ability to distinguish between some nearby functionally distinct areas, which is critical given that the language areas are abutted by multiple functionally distinct areas (Braga et al., 2020; Fedorenko and Blank, 2020).

These advantages in sensitivity and functional resolution are afforded by the application of the individual-subject analyses in any study regardless of whether a functional localizer task is included. However, if a validated localizer paradigm is used, the study will additionally benefit from greater interpretability. By using the same paradigm to identify the relevant functional subset of the brain across individuals, studies, imaging modalities, and species (in cases of shared cognitive capacities e.g., face processing), we can a) make stronger inferences about the origins of an effect (e.g., the ability to interpret some critical effect as arising within the language system), which cannot be done based on anatomy alone because of the inter-individual functional differences, and b) be generally more confident that we are referring to the same system which is critical for knowledge accumulation and for comparing findings across studies and labs. In this way, the functional localization approach aligns with the field's current focus on robust and replicable science (Lipkin et al., 2022). In addition to affording the ability to refer to the same system across studies, studies that rely on functional localization include an internal replication component because half of the data is used to identify the voxels/sensors of interest and the other half is used to quantify the response magnitudes, similar to what is commonly done in other modalities (Peelen and Downing, 2005; Nieto-Castañón and Fedorenko, 2012a; Powell et al., 2018). Thus, the use of a localizer task yields a replication of the effect in every new participant and study, thus reducing type I errors.

We have so far focused on univariate analyses. However, the combined use of functional localization and multivariate analyses, like multivariate pattern analysis (MVPA), could powerfully enable investigations of fine-grained meaning and structure representations within the language network. For example, with respect to semantic knowledge, explicit quantitative models reflecting single-word and contextualized semantic knowledge can be used to test hypotheses about how the brain processes meanings extracted from linguistic input (Bruffaerts et al., 2019a). Focusing on language-responsive sensors can increase both the sensitivity of such an analysis but also help interpret the observed effects.

4.2 Using MEG to probe linguistic computations

We here advocate individual-level functional localization as an approach to achieving greater sensitivity and interpretability when investigating the language network using MEG. The present work introduces this approach using neural signals in sensor space. When dealing with well-characterized systems, like the language network or the face recognition system, for which certain localizer paradigms have been shown (in fMRI research) to reliably identify the relevant underlying functional neuroanatomy, obtaining the anatomical information from MEG becomes not critical: we already know where these signals are coming from based on dozens or even hundreds of fMRI studies, which are ideally suited for localizing functions. As a result, we argue for leveraging the advantages that MEG has over other recording modalities, the core one being the ability to study the detailed time-course of information processing. Specifically, the fine temporal resolution of MEG offers the potential to study the incremental construction of sentence structure and meaning in real time (e.g., (Heilbron et al., 2022; ten Oever et al., 2022). Previous MEG studies have suggested that the temporal dynamics of sentence processing entail both feed-forward as well as recurrent processing (Hultén et al., 2019), that different frequency bands may reflect distinct cognitive processes, such as lexical retrieval, semantic composition, and prediction of upcoming words (e.g., Lam et al., 2016), and that representations extracted from artificial neural network language models capture some aspects of neural signals recorded with MEG (Choi et al., 2021). The functional localization MEG approach presented here can

increase the sensitivity and interpretability of future investigations of the temporal dynamics of language processing, as needed to decipher the precise computations that enable language comprehension.

4.3 Limitations

Key choices in the functional localization approach have to do with how the SOIs are selected. As is typical with MEG, we used neural changes during sentence processing relative to the baseline to identify the SOIs rather than a contrast between two conditions. In the fMRI implementation of the language localizer, the cortical regions of interest are identified by the sentences > nonwords univariate contrast. It is known that the inverse contrast (nonwords > sentences) activates the multiple demand network (Duncan, 2010; Fedorenko et al., 2013), which is neuroanatomically in close proximity to the language network (Blank et al., 2014). The inherently lower spatial resolution of MEG may result in sources from the language and multiple demand networks being captured by the same SOIs. In visual neuroscience (e.g., Liu et al., 2002; de Vries and Baldauf, 2019), the use of a contrast with MEG has been implemented, but the variability in the MEG signals explained by visual stimulus features is several times larger compared to the variability explained by linguistic content (Bruffaerts et al., 2019b). Here, we opted to select SOIs based on the sentence condition and verified that the response to the nonwords condition was significantly lower from the sentence condition. The advantage of using the contrast of the sentence minus the nonwords condition is that non-language processing is subtracted out: in the case of the nonwords condition, this processing includes working memory and visual perceptual processing. As we did not use a contrast, some of the selected sensors may reflect sources in the occipital cortex reflecting lower-level visual processes (e.g., see Figure 5 for evidence that selection of occipital sensors occurs in some cases).

Second, we opted to include the top 10% of most responsive sensors in the sentence condition. A consequence of this choice it that the outlined language network has an equal extent in all participants. The advantage is that the sensors of interest enable the selection of a multivariate response pattern for each participant, suitable for MVPA. An alternative would be to preset a fixed threshold percent for

signal increase compared to baseline, but this may have an unpredictable effect on the extent of the language network if the method is applied to a non-neurotypical population.

Finally, we opted to average the percentage signal change from baseline between the fifth (non)word and the end of the trial to calculate the effect size. This choice did not critically impact the results: similar findings were observed when including signals across the whole trial. In the English dataset, the average correlation in the size of the sentence effect across all channels within each participant across odd- and even-numbered trials was 0.49 (s.d. 0.22) compared to 0.11 (s.d. 0.23) between participants ($P < 0.001$). Similar results were observed in the Dutch dataset (sentence effect size within participants: 0.57 (s.d. 0.22); between participants: 0.19 (s.d. 0.24); $P<0.001$).

5 Conclusion

Using an extensively validated language localizer task, based on sentence reading, we showed that the neural responses recorded with MEG are reproducible at the individual participant level and we generalized these findings across two datasets and two different languages (English and Dutch). We observed that language-responsive sensors are spatially variable across individuals, giving an individual-level approach an advantage over the traditional group-level analysis. This new MEG localization method has a wide range of applications—from the detailed characterization of the time-course of language processing to probing the language network in (small) non-neurotypical populations—and may generally encourage the use of MEG to study the functional neuroanatomy of human higher-order cognition.

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7 References

Baldauf D, Desimone R (2014) Neural Mechanisms of Object-Based Attention. Science 344:424–427.

Blank I, Kanwisher N, Fedorenko E (2014) A functional dissociation between language and multiple-demand systems revealed in patterns of BOLD signal fluctuations. J Neurophysiol 112:1105–1118.

Braga RM, DiNicola LM, Becker HC, Buckner RL (2020) Situating the left-lateralized language network in the broader organization of multiple specialized large-scale distributed networks. J Neurophysiol 124:1415–1448.

Bruffaerts R, De Deyne S, Meersmans K, Liuzzi AG, Storms G, Vandenberghe R (2019a) Redefining the resolution of semantic knowledge in the brain: advances made by the introduction of models of semantics in neuroimaging. Neurosci Biobehav Rev.

Bruffaerts R, Tyler LK, Shafto M, Tsvetanov KA, Clarke A (2019b) Perceptual and conceptual processing of visual objects across the adult lifespan. Sci Rep 9:1–13.

Chetail F, Ranzini M, De Tiège X, Wens V, Content A (2018) The consonant/vowel pattern determines the structure of orthographic representations in the left fusiform gyrus. Cortex 101:73–86.

Choi HS, Marslen-Wilson WD, Lyu B, Randall B, Tyler LK (2021) Decoding the Real-Time Neurobiological Properties of Incremental Semantic Interpretation. Cereb Cortex N Y N 1991 31:233–247.

Cogan GB, Thesen T, Carlson C, Doyle W, Devinsky O, Pesaran B (2014) Sensory-motor transformations for speech occur bilaterally. Nature 507:94–98.

da Silva Castanheira J, Orozco Perez HD, Misic B, Baillet S (2021) Brief segments of neurophysiological activity enable individual differentiation. Nat Commun 12:5713.

de Vries E, Baldauf D (2019) Attentional Weighting in the Face Processing Network: A Magnetic Response Image-guided Magnetoencephalography Study Using Multiple Cyclic Entrainments. J Cogn Neurosci 31:1573–1588.

Diachek E, Blank I, Siegelman M, Affourtit J, Fedorenko E (2020) The Domain-General Multiple Demand (MD) Network Does Not Support Core Aspects of Language Comprehension: A Large-Scale fMRI Investigation. J Neurosci 40:4536–4550.

Fedorenko E (2021) The early origins and the growing popularity of the individual-subject analytic approach in human neuroscience. Curr Opin Behav Sci 40:105–112.

Fedorenko E, Behr MK, Kanwisher N (2011) Functional specificity for high-level linguistic processing in the human brain. Proc Natl Acad Sci 108:16428–16433.

Fedorenko E, Blank IA (2020) Broca's Area Is Not a Natural Kind. Trends Cogn Sci 24:270–284.

Fedorenko E, Hsieh P-J, Nieto-Castañón A, Whitfield-Gabrieli S, Kanwisher N (2010) New Method for fMRI Investigations of Language: Defining ROIs Functionally in Individual Subjects. J Neurophysiol 104:1177–1194.

Fedorenko E, Scott TL, Brunner P, Coon WG, Pritchett B, Schalk G, Kanwisher N (2016) Neural correlate of the construction of sentence meaning. Proc Natl Acad Sci 113:E6256–E6262.

Hultén A, Schoffelen J-M, Uddén J, Lam NHL, Hagoort P (2019) How the brain makes sense beyond the processing of single words – An MEG study. NeuroImage 186:586–594.

Ivanova A, Siegelman M, Chandler C, Pongos A, Kean H, Fedorenko E (2020) Effect of Task on Sentence Processing. Poster presentation at the Society for the Neurobiology of Language.

Kanwisher N, McDermott J, Chun MM (1997) The Fusiform Face Area: A Module in Human Extrastriate Cortex Specialized for Face Perception. J Neurosci 17:4302–4311.

Keuleers E, Brysbaert M (2010) Wuggy: A multilingual pseudoword generator. Behav Res Methods 42:627–633.

Lam NHL, Schoffelen J-M, Uddén J, Hultén A, Hagoort P (2016) Neural activity during sentence processing as reflected in theta, alpha, beta, and gamma oscillations. NeuroImage 142:43–54.

Lipkin B et al. (2022) Probabilistic atlas for the language network based on precision fMRI data from >800 individuals. Sci Data 9:529.

Liu J, Harris A, Kanwisher N (2002) Stages of processing in face perception: an MEG study. Nat Neurosci 5:910–916.

Mahowald K, Fedorenko E (2016) Reliable individual-level neural markers of high-level language processing: A necessary precursor for relating neural variability to behavioral and genetic variability. NeuroImage 139:74–93.

Malik-Moraleda S, Ayyash D, Gallée J, Affourtit J, Hoffmann M, Mineroff Z, Jouravlev O, Fedorenko E (2022) An investigation across 45 languages and 12 language families reveals a universal language network. Nat Neurosci 25:1014–1019.

Nieto-Castañón A, Fedorenko E (2012a) Subject-specific functional localizers increase sensitivity and functional resolution of multi-subject analyses. NeuroImage 63:1646–1669.

Nieto-Castañón A, Fedorenko E (2012b) Subject-specific functional localizers increase sensitivity and functional resolution of multi-subject analyses. NeuroImage 63:1646–1669.

Peelen MV, Downing PE (2005) Selectivity for the Human Body in the Fusiform Gyrus. J Neurophysiol 93:603–608.

Powell LJ, Deen B, Saxe R (2018) Using individual functional channels of interest to study cortical development with fNIRS. Dev Sci 21:e12595.

Regev TI, Casto C, Hosseini EA, Adamek M, Brunner P, Fedorenko E (2022) Intracranial recordings reveal three distinct neural response patterns in the language network. Neuroscience. Available at: http://biorxiv.org/lookup/doi/10.1101/2022.12.30.522216 [Accessed January 31, 2023].

Richardson H, Koster-Hale J, Caselli N, Magid R, Benedict R, Olson H, Pyers J, Saxe R (2020) Reduced neural selectivity for mental states in deaf children with delayed exposure to sign language. Nat Commun 11:3246.

Roos NM, Piai V (2020) Across-session consistency of context-driven language processing: A magnetoencephalography study. Eur J Neurosci 52:3457–3469.

Rousselet GA, Pernet CR (2012) Improving standards in brain-behavior correlation analyses. Front Hum Neurosci 6:119.

Saxe R, Brett M, Kanwisher N (2006) Divide and conquer: A defense of functional localizers. NeuroImage 30:1088–1096.

Saxe R, Kanwisher N (2003) People thinking about thinking peopleThe role of the temporo-parietal junction in “theory of mind.” NeuroImage 19:1835–1842.

Scott TL, Gallée J, Fedorenko E (2017) A new fun and robust version of an fMRI localizer for the frontotemporal language system. Cogn Neurosci 8:167–176.

Tadel F, Baillet S, Mosher JC, Pantazis D, Leahy RM (2011) Brainstorm: A User-Friendly Application for MEG/EEG Analysis. Comput Intell Neurosci 2011:1–13.

Taulu S, Kajola M, Simola J (2004) Suppression of interference and artifacts by the signal space separation method. Brain Topogr 16:269–275.