A systematic review of neuroimaging approaches to single-subject studies of language processing

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Abstract

Task-based functional magnetic resonance imaging (fMRI) has become the method of choice for studying localized function in the human brain. Functional MRI studies often rely on group-level results to derive conclusions about the neurobiology of language. However, doing so without accounting for the complexities of individual brains may reduce the validity of the findings. Furthermore, understanding brain organization in individuals is critically important for both basic science and clinical application. To assess the state of single-subject language localization in the functional neuroimaging literature, we carried out a systematic review of studies published through April 2020. Out of 977 papers identified through our search, 121 met our inclusion criteria for reporting single-subject fMRI results. Of these, 20 papers reported using a single-subject test-retest analysis to assess reliability. Specific metrics included overlap measures (like the Dice coefficient), correlation measures (like Intraclass Correlation Coefficient), Euclidean Distance between peak activation/center of mass, and Sensitivity/Specificity. These papers varied substantially in their experimental paradigms and stimuli, making more detailed comparisons impossible. In the absence of quantified reproducibility, results from paradigms used for single-subject language localization may need to be treated with caution. Incorporating reliability and validity measures in language mapping paradigms increases the likelihood that task-based activations are reproducible. Our search found that a relatively modest number of papers reporting single-subject results quantified single-subject reliability. Future endeavors to optimize the localization of language networks in individuals will benefit from the broader reporting of reliability metrics for different tasks and acquisition parameters.

Introduction

Historically, much of our understanding of the neurobiology of language has come from lesion studies and the differing profiles of patients with acquired aphasia. Subsequent advances in functional neuroimaging methods have, helpfully, broadened our view of brain regions involved in language processing. Many of these endeavors rely on the conclusions drawn on a group level, even though language networks might vary from person to person. Thus, group results may suggest an organization that does not accurately represent any individual's language map (Fedorenko et al. 2010; Mahowald & Fedorenko 2016). Individual and group-level analyses are therefore complementary approaches that inform different aspects of how we understand language capabilities.

Characterizing language processing in individuals is not just a theoretical concern: Numerous clinical studies have shown evidence for atypical language organization due to various conditions, including epilepsy (Baciu et al. 2003; Gould et al. 2016; Lee et al. 2008), aphasia (Khateb et al. 2004), vascular malformations (Hakyemez et al. 2006; Pouratian et al. 2002), brain injury and long-standing tumors (Avramescu-Murphy et al. 2017; Kośla et al. 2015; Partovi et al. 2012; Ruff et al. 2008), and sensory deficits caused by congenital blindness (Röder et al. 2002; Roland et al. 2013). Non-clinical conditions such as left-handedness have been associated with an increased incidence of atypical language dominance (Acioly et al. 2014). Additionally, language processing differs for primary and secondary languages (Dehaene et al. 1997; Polczynska et al. 2016; Polczynska et al. 2017; Tomasino et al. 2014). Multilingual individuals also often demonstrate the recruitment of additional brain areas for language switching (Sierpowska et al. 2013; Tomasino et al. 2014). Given the complex nature of language representation in the brain, failure to map language regions effectively in preoperative mapping could mean a tradeoff between losing language function altogether versus capability in only one language.

A related and long-standing concern in cognitive neuroscience has been the degree to which fMRI-based activations, generally, are reliable (Bennett & Miller 2010; Elliott et al. 2020; Gorgolewski et al. 2013; McGonigle 2012; McGonigle et al. 2000; Noble et al. 2019; Smith et al. 2005). As with many areas of science, there is an increasing interest in measuring and improving reliability and reproducibility of neuroimaging research (Botvinik-Nezer et al. 2020; Button et al. 2013; Nosek & Lakens 2014; Poldrack et al. 2017; Simmons et al. 2011). Relatedly, there has been a recent re-emergence of interest in individual variability in brain organization (Gordon et al. 2017; Laumann et al. 2015; Poldrack et al. 2015)— which assumes (implicitly, if not explicitly) that differences in brain maps across individuals reflect true neural differences and not measurement error. Thus, accurate single-subject language mapping is essential in two contexts. First, it tells us about individual brain organization; and second, because measurement accuracy in single subjects affects the accuracy of group-level analyses. However, the degree to which neuroimaging studies of language localization have assessed the reliability of experimental paradigms is unclear.

To characterize the current state of the field with respect to single-subject language localization, we performed a systematic review of fMRI studies reporting single-subject results. Our goals were to document approaches used for assessing the reliability of single-subject results, place language studies in a broader context of fMRI reliability, and, if possible, identify potential design choices associated with improved single-subject reliability.

Materials and Methods

The information gathered in this systematic review was structured by following the PRISMA statement (Liberati et al. 2009), summarized in **Figure 1**. Supplemental materials, including data and analysis scripts, are available from https://osf.io/x692b/. We used SunburstR package in R to create the figures (Bostock et al. 2020; Team 2013).

Search Methods Statement

We searched published literature using strategies (Search Strategy in Supplemental materials) designed by a medical librarian for the concepts of functional magnetic resonance imaging (fMRI), speech or language mapping, and brain mapping. These strategies were established using a combination of controlled vocabulary terms and keywords and were executed in Ovid-Medline, Embase, Scopus, Cochrane Register of Controlled Trials (CENTRAL), and Clinicaltrials.gov. We verified the effectiveness of the search strategies based on how well a set of predefined benchmark papers were captured by the search. All searches were performed on April 8th, 2020. Results were exported to EndNote, and duplicate citations were removed, leaving 970 unique citations for analysis. Database-supplied limits for English were used.

Additional literature

The initial search did not capture seven previously identified benchmark papers due to missing keywords in the title or abstract. These were added to the final list of papers, which resulted in a total of 977 papers.

Eligibility Criteria

We selected all published papers before April 8th, 2020, that met the following criteria:

- Used fMRI as an independent modality or in conjunction with other modalities
- Primary research literature in adults
- Language task used in the experimental design
- Performed single-subject level analysis
- Reported task-based single-subject maps or quantification of single-subject results

Specific search terms are available in supplemental materials. The resulting papers from the database search then underwent abstract screening and full-text screening using the procedure discussed below.

Abstract Screening

We screened abstracts obtained after the literature search to exclude conference abstracts, reviews, technical notes, clinical trials, and other non-primary literature. Articles that were unavailable after a Google Scholar search, duplicate entries, incorrect citations, empty results for abstract contents, studies conducted on children, and abstracts that did not mention fMRI use were also excluded. The extent to which fMRI was used as an imaging modality was not always clear from the abstract alone. Therefore, papers with abstracts that mentioned task-based fMRI, or cited fMRI results, passed the abstract screening step. A group of individuals with an academic background in neuroscience assisted with the abstract level screening. After an initial categorization, abstract eligibility was verified by the first author. All the abstracts were reviewed by at least one person and checked by the first author.

Full-text screening

We then screened the contents of the articles that passed abstract screening. Papers were excluded from the final list if they did not contain quantified single subject task-based fMRI results and only reported group-level results. The finalized papers were screened and categorized based on imaging modalities, reliability metrics, language tasks used, and clinical condition of research participants. To the extent possible, we categorized the tasks using labels from the Cognitive Atlas (Poldrack et al. 2011).

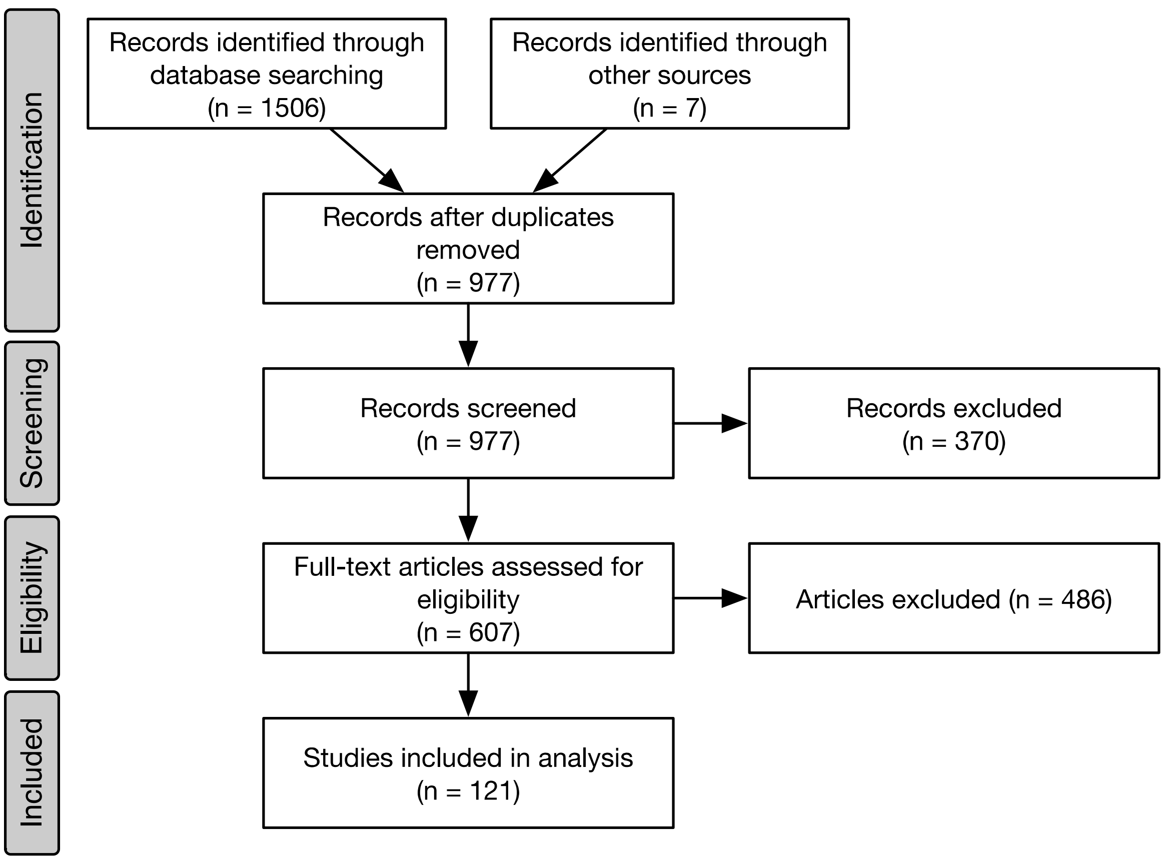

Figure 1: PRISMA diagram summarizing the literature search.

Reliability measures

A common way of quantifying a neuroimaging study's reliability is to assess the test-retest reproducibility. Assuming brain networks have remained stable, performing the same task should result in a similar pattern of brain activity, with differences attributable to measurement error. A concern with these metrics is the amount of data available to carry out analyses or the technical considerations of repeating an experiment. Nevertheless, including measures for reproducibility may increase confidence in the findings or establish precedence towards good research practice. The following are the most common measures used by the papers included in this review.

- **Lateralization Index (LI)** is used as a comparative measure of language-related activations between the hemispheres of the brain. Although not a reliability measure on its own, a considerable number of papers rely on the reproducibility of LI as a reliability metric (Agarwal et al. 2018; Benjamin et al. 2017; Fernandez et al. 2003; Knecht et al. 2003; Nettekoven et al. 2018; Otzenberger et al. 2005; Voyvodic 2012; Wilson et al. 2018). A score of 1 indicates fully left-lateralized activation, a score of -1 indicates fully right-lateralized activation, and a score of 0 refers to bilateral (i.e., non-lateralized) activation.

  LI is a metric of interest in reliability because of the typical dominance of language in the left hemisphere. Lateralization of function may differ in relation to the complexity of the stimulus used in the task design (Peelle 2012). A task involving hearing tones might only activate the bilateral auditory cortex whereas stimuli with more complex language requirements might have activations localized to the left hemisphere. Hence, LI can be an effective way to communicate stimulus-based differences in brain activations.

  Studies using the Wada procedure as the primary language mapping tool often rely on the reproducibility of LI as their only reliability measure. However, this will be of limited use since the information conveyed by LI is not enough to fully direct surgical decisions as it ignores localization. Moreover, the robustness and strength of different language tasks might also contribute to the variability (Bradshaw et al. 2017b). Thus, LI is best used in conjunction with other metrics.

$$LI = \frac{\sum left\ activations - \sum right\ activations}{\sum left\ activations + \sum right\ activations}$$

- **Overlap measures** such as Dice Coefficient measures the overlap of the number of active voxels across scan sessions separated by time. The Dice coefficient for any two sessions, as calculated by the following equation, ranges from 0 to 1, with 0 indicating no overlap and 1 indicating complete overlap (Crum et al. 2006). Several studies included in this review have implemented the Dice (or related overlap measure). An example of a related measure is the Reproducibility Index, as mentioned in Maldjian et al. (2002). Here, the metric is obtained by calculating the pairwise ratio of the probability-weighted intersection volume divided by the union volume of surviving activation clusters. Overlap metrics such as Dice are some of the most intuitive methods of accounting for reproducibility. However, factors such as absolute and relative voxel-wise thresholds, cluster sizes, and focus on a priori language regions could affect this measure (Wilson et al. 2017).

$$Dice\ coefficient = 2\ \frac{Number\ of\ overlapping\ voxels}{Voxels\ in\ first\ session + Voxels\ in\ second\ session}$$

- **Intra-class Correlation Coefficient (ICC)** is calculated by dividing the difference between and within-subjects mean sum of squares by their sum (Fernandez et al. 2003). ICC ranges from -1 to 1, with ICC < 0 indicating no agreement and ICC of 1 indicating perfect agreement (Nettekoven et al. 2018). It can be used to measure test-retest reliability at a voxel or an ROI for a chosen level of activation. This metric provides a measure of the contribution of individual-level differences in a group result. However, it is vital to treat this measure with caution since it combines information from between-subject and between-sessions variances (i.e., the same ICC value can result from different activation patterns resulting from inadequate models) (Gorgolewski et al. 2013).

$$ICC = \frac{Between\ subject\ variance - Within\ subject\ variance}{Between\ subject\ variance + (k-1)\ Within\ subject\ variance},$$

where k is the number of test sessions.

- **Euclidean Distance (ED)** is commonly used to quantify the distance between peak activation across sessions or different task types (Agarwal et al. 2018; Nettekoven et al. 2018; Voyvodic 2012). Localization accuracy can be determined based on how close the activation peaks are for subsequent sessions. This metric can be highly susceptible to shifts in activation patterns due to subject motion across sessions.

$$ED = \sqrt{(x_1 - x_2)^2 + (y_1 - y_2)^2 + (z_1 - z_2)^2},$$

where, $x_{1,2}, y_{1,2}, z_{1,2}$ represent coordinates in 3D space.

Results

Our literature search resulted in 977 unique papers, of which 121 met our inclusion criteria of using single-subject level fMRI to study language processing. Thirty-eight out of the 121 studies used more than one modality to carry out language mapping. The distribution of the modalities used by the papers is presented in **Figure 2A**. Language localization studies in a clinical setting are sometimes conducted in the context of pre-surgical planning. Most of the clinical studies that met our inclusion criteria used fMRI as a preliminary method for language localization but relied on the results of invasive mapping methods (such as electrical stimulation) to carry out surgical planning. Additionally, the feasibility of using fMRI in conjunction with electrical stimulation to predict language dominance has also been tested in post-surgical cases (Peck et al. 2009). Several publications in our literature search have also compared various modalities under the same experimental paradigm to demonstrate the relative effectiveness of the individual approaches. Studies with Electrocorticography (ECoG), fMRI, and electrical stimulation reported that ECoG and fMRI results were better than electrical stimulation (Genetti et al. 2015; Tie et al. 2009). Similarly, since electrical stimulation is the current gold-standard in brain mapping, studies have used it as a metric to optimize and standardize fMRI protocols (Rutten et al. 2002; Wilson et al. 2018). Moreover, numerous studies have used multimodal approaches to demonstrate the benefits of combining the strengths of the individual modalities such as fMRI and Magnetoencephalography (MEG), Transcranial Magnetic Stimulation (TMS) and fMRI (Kononen et al. 2015), simultaneous Electroencephalography (EEG) and ultra-high field MRI (Grouiller et al. 2016) and, fMRI and Diffusion Weighted Imaging (DWI) (Tomasino et al. 2014).

The distribution of the clinical conditions represented in the papers is summarized in **Figure 2B**. Out of the 121 studies reporting single-subject fMRI results, 58 included clinical populations, most of which were multimodal studies. These studies included a wide variety of clinical conditions, epilepsy and tumor being the most common. The study population's distribution highlights the importance of reliable single-subject language mapping methods for both clinical and basic research.

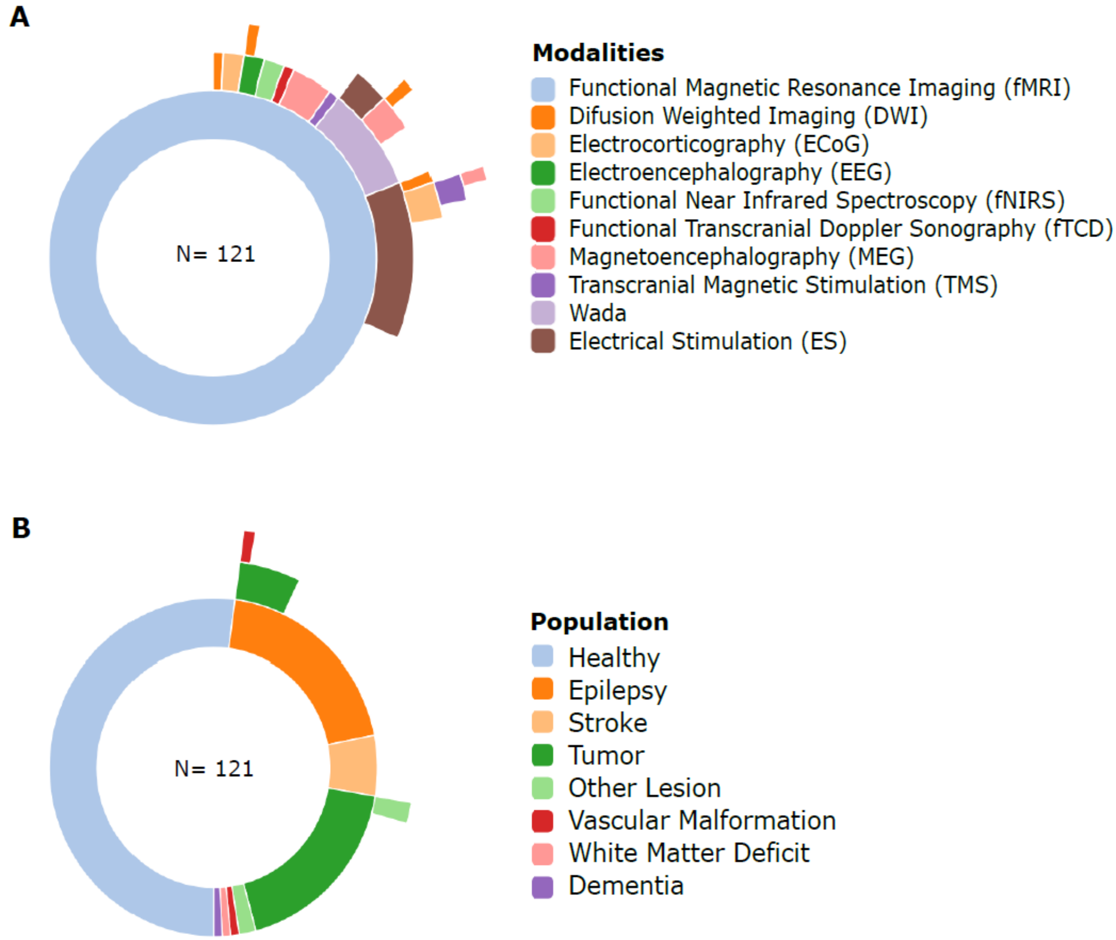

Figure 2: Each circle or part of a circle in the Sunburst plot indicates the proportion of studies that belong to the subgroup represented in the legend. **A.** The full inner circle shows the number of studies that used fMRI as one of the imaging modalities. Each subsequent layer represents the proportions of studies with each added modality. **B.** The proportions represent the distribution of population subtypes in the papers. Subsequent layers indicate studies that investigated individuals from more than one population. Details on the number of papers for each category is presented in the supplemental information.

As noted above, we were particularly interested in how many papers reported reliability measures. Of the 121 papers reporting single subject results, 20 reported test-retest sessions and discussed reliability measures as summarized in **Table 1**. The duration between test and retest sessions in these papers ranged from as close as a few minutes (consecutive test and retest on the same day) to a few years. Following Wilson et.al (2017), we make a distinction between validity (effectiveness of tasks to activate known language regions) and reliability (test-retest reproducibility of data). Most common validity measures were hemispheric lateralization (16/20), volume of activation (4/20), and sensitivity/specificity calculations (3/20). Meanwhile, most common reliability measures were overlap metrics (e.g., Dice) (16/20), correlation measures (e.g., Intraclass Correlation Coefficient) (7/20), and comparison of the distance between peak activations (5/20).

Paper	Lateralization variability	Activation volume	Sensitivity/ Specificity	Overlap metric	Correlation metric	Activation Distance
Binder et.al (1995)	X					
Maldjian et.al (2002)	X			X		
Rutten et.al (2002)	X	X		X		
Fernández et.al (2003)	X			X	X	
Knecht et.al (2003)	X			X		
Otzenberger et.al (2005)	X			X		
Harrington et.al (2006)	X			X		
Jansen et.al (2006)	X			X	X	
Chen et.al (2007)			X			
Rau et.al (2007)				X		
Voyvodic (2012)	X			X		X
Gorgolewski et.al (2013)				X	X	X
Mahowald & Fedorenko (2016)	X	X			X	
Benjamin et.al (2017)	X			X		
Wilson et.al (2017)	X		X	X		
Agarwal et.al (2018)	X					X
Nettekoven et.al (2018)	X			X	X	X
Wilson et.al (2018)	X	X		X	X	X
Paek et.al (2019)				X	X	
Yen et.al (2019)	X	X	X	X		

Table 1: Summary of validity and reliability measures used in the papers that reported test-retest sessions.

A quantitative comparison of the studies is not possible due to the variability in tasks, study population, duration between scans, and thresholding measures (detailed in **Supplementary Table 1**). There was a wide range of expressive and receptive tasks used in a multi-task setting (Acioly et al. 2014; Arora et al. 2009; Seghier et al. 2004; Tailby et al. 2017). The most common tasks among these studies were verbal fluency tasks (such as naming and word generation), while less common tasks involved connected speech. The 20 papers that discussed test-retest reliability used block design for their experiments but differed in the technical execution.

Overlap measures were used in 16 of the 20 papers, with 8 using Dice. The 8 Dice papers reported values ranging from 0.34–0.66.

Discussion

Accurate measurements of regional brain activation in individual participants are essential for clinical research and basic science. In the context of group studies, individual variability in task-based responses has been noted in several domains (Van Horn et al. 2008). The focus of our current review was on studies reporting fMRI-based language localization in single subjects. Given the diverse range of language research that spans the clinical and basic science domains, the search results that we have presented might not have captured all the relevant literature. However, the need for reproducible and robust results is essential in any research outcome. The metrics discussed in this paper can also serve as a primer for the most common ways in which reliability metrics can be used while reporting neuroimaging results, and we hope to encourage wider adoption of such analyses.

Although test-retest reproducibility is not the only measure of accuracy, it is widely used and directly addresses within-subject replicability. Of the papers identified in our search, approximately 1/6 included some measure of test-retest reliability. However, this represents a modest number of studies (20) that vary considerably in the specific language paradigm, participant population, and amount of data collected. Moreover, the choice of metric used to establish reliability was not the same across these studies. Thus, it may prove challenging to generalize existing findings of test-retest reliability to new paradigms or populations. Obtaining an agreement on a standardized approach of quantifying reliability in neuroimaging results would enhance the credibility of research findings. Given that most conclusions are drawn from thresholded statistical maps, the Dice overlap measure is an appealing candidate.

Across a variety of paradigms, we found that average Dice coefficients ranged from 0.34–0.66. This range is roughly comparable to that reported by Bennett and Miller (2010), who across a large number of tasks (most not language tasks), report a range of average Dice coefficients from 0.23–0.79. As Bennett and Miller highlight, many factors contribute to reliability of fMRI studies, including differences in acquisition, analysis, paradigm, and participants. The number of potential permutations among these factors typically make controlled comparisons impossible. That is, although an individual study may ask "among these four paradigms, which provides the strongest reliability?", it is far more difficult to answer, "among all the tasks, analysis pipelines, and acquisition parameters available, which provides the strongest reliability?" (which we would all like to know!). However, the variability in reliability measures (such as Dice) suggest that some approaches are more reliable than others. As suggested above, one approach would be to more widely adopt reporting of reliability measures to facilitate optimizing these protocols. More simply, labs might internally use such metrics during task development, to steer them away from tasks that have poor reliability.

In the context of modest test-retest reliability, it is important to note that the issue of single-subject reliability also extends to group-level studies. If the outcome of interest is a group-level univariate map with a relatively large number of participants, inaccuracies in individual participants may have little effect on the result. However, researchers interested in explaining individual differences in brain activation patterns—for example, due to age, language status, hearing loss, etc.—rely on the accuracy of both neural and non-neural estimates of data at an individual level. At a minimum, inaccuracies in measuring brain activity in individual participants will hurt the ability of researchers to detect these effects of interest, and more worryingly, they may lead to spurious findings. A related concern applies to multivariate analyses. Even when these analyses are not explicitly designed to localize activity in individual participants, multivariate tests are typically conducted in single subjects. Error in measuring responses that account for individual differences will likely decrease the accuracy of these analyses.

The high spatial resolution and noninvasiveness of fMRI enable it to complement other language localization approaches to target potentially more subtle or complex functions than standard clinical practices (Austermuehle et al. 2017; Baciu et al. 2003; Bizzi et al. 2008). However, using fMRI as an independent tool for localizing language for clinical purposes is still in its early stages. Patient and methodological challenges need to be addressed to do so (Beisteiner et al. 2019; Bradshaw et al. 2017a; Bradshaw et al. 2017b; Seghier 2008). An improvement in the reliability of language localization with fMRI might not replace invasive procedures entirely but can help identify subjects that can be assisted without invasive procedures. For those that do undergo invasive procedures, fMRI-based language localization can also assist in monitoring post-surgical recovery.

An important point is that all the studies identified by our search that discussed test-retest reliability carried out univariate analyses. Multivariate analyses are increasingly used to study individual differences (Woo et al. 2017), and may well provide reliability that exceeds traditional univariate approaches (Kragel et al. 2021). With respect to localization, multivariate approaches can vary in their spatial specificity, but searchlight approaches (Etzel et al. 2013; Kriegeskorte et al. 2006) provide an approach for conducting multivariate analyses throughout the brain. Multivariate approaches may therefore prove to be a valuable approach for improving reliability of language localization.

Finally, another avenue that facilitates assessing reliability is to make data freely available. Sharing original data sets would enable researchers to conduct their own measures of reliability across studies. Increasing awareness of data sharing benefits is occurring across scientific disciplines (Poldrack & Gorgolewski 2014), and publicly available infrastructure for sharing neuroimaging datasets continues to improve (Poldrack et al. 2013). As illustrated in our findings, a wide variety of tasks, populations, and metrics currently exist, making qualitative and quantitative comparisons across studies challenging.

In conclusion, we found that a relatively small number of papers investigating the neurobiology of language—all of which used univariate analysis methods—have assessed the test-retest reliability of single-subject fMRI paradigms. Increased attention to this issue can improve the accuracy and replicability of findings in multiple domains. Some concrete steps towards addressing these concerns could be making reliability metrics such as the Dice coefficient a standard part of analyses, reporting both single-subject and group level results to allow transparency, and making data freely available so that researchers can reproduce results or conduct their own reliability analyses.

Supplementary Materials

1. Database search strategies
2. Database search results
3. Table with detailed summary of metrics
4. PRISMA checklist
5. Code to generate figures

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