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Functional heterogeneity within Broca's area during verbal working memory

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Abstract

In previous fMRI research, we found that two subregions of the left inferior frontal cortex showed distinct patterns of activity during a verbal working memory task. Specifically, a more dorsal region tracked with performance, while a more ventral region was sensitive to lexical status. To test the veracity of this finding, we developed a new method for meta-analysis of neuroimaging results. In this method, Gaussian probability distributions are formed around stereotaxic coordinates obtained from published neuroimaging studies. These probability distributions are then combined to identify regions of convergence across studies. When this method was applied to prior studies of working memory, the results largely paralleled those from earlier reviews of the literature on working memory, but also confirmed our empirical findings showing distinct foci within Broca's area. Further application of this meta-analytic technique substantiated the dissociation in these regions for performance and sublexical processing. These results help to validate a novel approach for meta-analysis of neuroimaging findings that avoids many of the subjective assumptions involved in alternative approaches.

Keywords: Working memory; Language; Inferior frontal gyrus; Broca's area; Neuroimaging; Meta-review; Lexicality effects; Nonwords; Memory load; Memory performance

1. Introduction

Working memory is a cognitive mechanism, or system, through which limited amounts of information can be maintained and operated upon over brief intervals of time [1]. Because working memory is central to both basic and higher cognitive functioning, it has been the topic of extensive cognitive behavioral research, and has also emerged as a hotly investigated field of study for cognitive neuroscientists. In one recent study [2], we asked subjects to perform a delayed serial recall task. For each trial, subjects attempted to maintain a set of five verbal items across a 20-s delay, and then tried to recall them aloud in the correct serial order. Subjects performed the task under four different stimulus conditions that were motivated by prior behavioral findings: one-syllable phonological distinct words, one-syllable phonologically similar words, three-syllable phonologically distinct words, and one-syllable phonologically distinct pronounceable nonwords. Our study revealed differences in the activity pattern exhibited by two regions in the left inferior frontal gyrus (broadly referred to as Broca's area). In this paper, we use a new approach for reviewing the scientific literature on neuroimaging to determine whether our findings can be supported by data that have been overlooked in past studies.

Most previous interpretations of the role of the left inferior frontal gyrus in verbal working memory have treated this region as functionally homogenous, but we found [2] that two spatially distinct regions within the left inferior frontal gyrus were active during the delayed serial recall task. More importantly, these two subregions behaved differently. A dorsal and slightly posterior region (centered in the superior pars opercularis (BA 44), near the border

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with the precentral gyrus) exhibited activation that tracked inversely with the recall success associated with each of the four different stimulus conditions (e.g., performance was better and activation was lower when the items were one-syllable words, as compared to three-syllable words). Activity in this region also showed a significant decline over the delay interval. In contrast, a more ventral region (centered in the pars triangularis, BA 45), exhibited significant activation for all of the conditions, but was additionally sensitive to the nonword condition. Unlike the more dorsal region, this ventral region showed sustained activation throughout the delay interval. This dissociation is an indication that verbal working memory relies on multiple processes mediated by distinct subregions of Broca's area. We speculated that the more dorsal region contributes to the organization and automation of a sequence of verbal items that are rehearsed across a delay interval, whereas the ventral region is sensitive to sublexical phonological processes.

Previous reviews of neuroimaging studies of working memory (e.g., Refs. [3–6]) have not identified separate regions of activation within Broca's area. However, in these reviews, areas of common activation were determined from subjective identification of foci clusters (e.g., through visual inspection), or by setting a priori boundaries that could obscure subpopulations within a broader region (e.g., all foci that fall within BA 44/45 were grouped together). We therefore set out to devise a meta-analytic approach that could provide a quantitative and objective assessment of the areas of convergence across studies. We will refer to the method we have developed as the aggregated Gaussian-estimated sources (AGES) approach to meta-analysis.

2. Methods

The AGES approach to meta-analysis relies upon the same data used in traditional reviews of neuroimaging findings: three-dimensional coordinates reported in the space of the Talairach and Tournoux brain atlas [7]. Unlike traditional approaches, it capitalizes on basic image-processing steps, such as image filtering and thresholding, to obtain a quantified metric of convergence at each voxel in the stereotaxic space. Rather than modeling each coordinate as a singular point, we treat each source coordinate as a Gaussian-estimated distribution (three-dimensional), having its center at the point in space associated with the coordinates (Fig. 1A and B). For the next step, the images containing the Gaussian-estimated source coordinates from the set of studies included in the analysis are added together (Fig. 1C). By aggregating the Gaussian sources taken from multiple studies, a probability map (meta-image) representing the degree of convergence at each voxel in stereotaxic space is obtained. As a final step in the basic meta-analysis path, an intensity threshold can be applied to the image obtained in the prior step. The application of this intensity

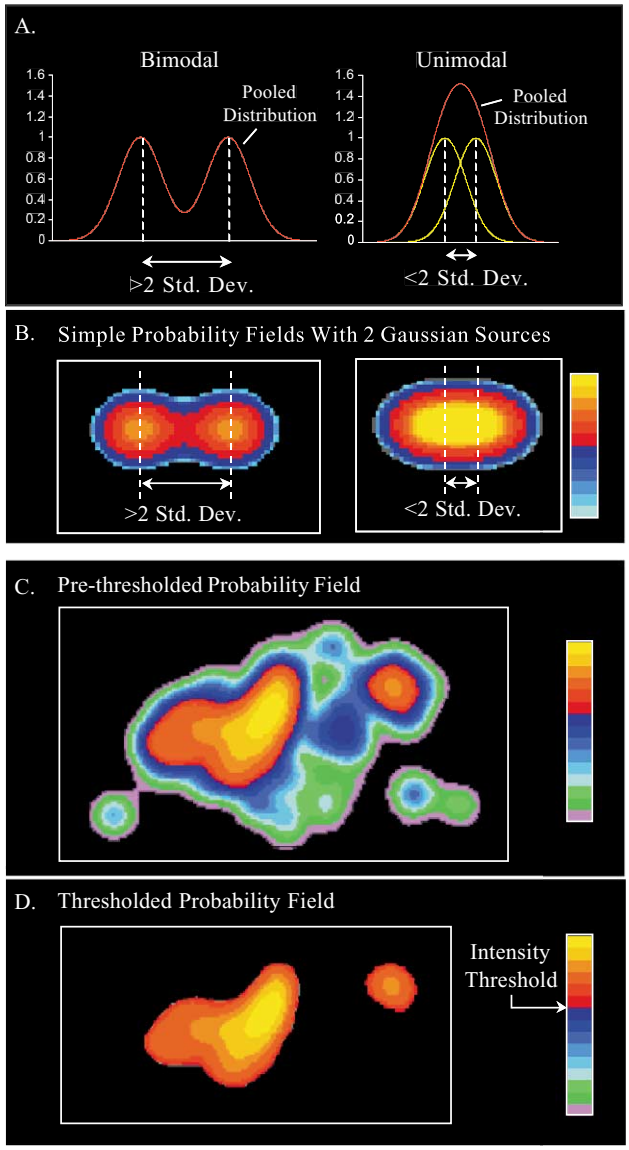

Fig. 1. Illustration of the logic underlying the AGES meta-analysis. (A) A simple example of the additivity exhibited by two equal variance (i.e., having the same FWHM), one-dimensional Gaussian distributions. When the means are separated by more than 2 S.D. (left), a bimodal pooled distribution is observed. When the means are separated by less than 2 S.D. (right), a unimodal pooled distribution is observed. (B) An extension of the example given in (A), when two three-dimensional Gaussian distributions are added. The resulting probability field for the pooled distribution is shown in the plane passing through the peak region(s) of additivity for bimodal (left) and unimodal (right) cases. Coordinates in close proximity to each other (within 2 S.D. or 85% of the FWHM of the Gaussian sphere) will yield a single convergence, whereas coordinates that are further apart will yield multiple foci of convergence. (C) A demonstration of the complex probability field that can result from the combination of many neighboring three-dimensional Gaussian spheres, each with a unique center. The field is shown before a threshold is applied, in the plane passing through the peak region of convergence. (D) The "meta-image" probability field that results from applying an intensity threshold to the field shown in Panel C. Regions surviving the intensity threshold represent the areas of highest convergence.

threshold yields a final image in which only the most highly convergent areas remain visible (Fig. 1D).

We applied our image-based method for meta-analysis to a set of 30 prior studies that had used neuroimaging to investigate brain activity during performance of a verbal working memory task. These 30 studies represented PET and fMRI investigations in which the focus was on verbal working memory in unimpaired human populations, a statistical contrast to a nonmnemonic baseline was available, and group-averaged results were presented in standard stereotaxic [7] coordinates. The tasks used in these studies spanned a variety of working memory paradigms, including delayed recognition, delayed recall and N-back type tasks. All reported activation foci reported in these studies were submitted to the analysis. We had two principal objectives: (1) to validate the method by demonstrating convergence with empirical findings and more traditional approaches to meta-analysis and (2) to determine whether our observation of two functionally distinct regions of activation within Broca's area could be supported by previously observed findings in the literature that have gone unrecognized.

Based on the AGES approach, we modeled each point source as a Gaussian distribution with a width of 15 mm at half of its maximum value (FWHM = 15 mm = ~ 6.14 S.D.). The 15-mm FWHM used for each Gaussian distribution accommodates the variability associated with reporting of stereotaxic coordinates (based on our own assessment and on reports of variability available in the literature), allows for a reasonable degree of convergence when coordinates are near neighbors (based on random simulations), and also conforms to conceptual notions regarding the size of a typical functional region. We used random simulations to determine an intensity threshold associated with a 0.05% false probability rate, and then applied this threshold to identify convergence foci in our meta-image. For the random simulations, we assumed all of the tissue within stereotaxic space was sampled, we modeled 400 sources (approximately the number of sources sampled from the 30 verbal working memory studies), and we implemented a Gaussian spread of 15 mm.

To further substantiate the pattern of dissociation obtained in our empirical study, we conducted two further meta-analyses. These additional meta-analyses were intended to determine whether the sensitivity to level of performance (difficulty) exhibited by our dorsal subregion, and the sensitivity to lexical status exhibited by our ventral subregion, were consistent with the broader literature. Accordingly, we compiled one set of neuroimaging studies in which performance level or level of difficulty was manipulated in the context of a verbal working memory task. A second set of neuroimaging studies contrasting activity associated with word processing to that associated with pseudoword processing was also compiled. Independently for each of these two sets of studies, coordinates reported in the left inferior frontal gyrus were then submitted to the image-processing based meta-analysis, using a threshold (based on random simulations) that was suitable to the number of coordinates included in each set.

3. Results

The set of convergence foci obtained from the AGES meta-image of 30 previous studies of verbal working memory are listed in Table 1. When compared to the set of foci identified empirically in our fMRI study of delayed serial recall task performance, there is a readily apparent correspondence: 11 of the 13 foci identified with the meta-analysis fell within 15 mm of a foci of activation identified in our empirical study (Table 1). Furthermore, the meta-analytically derived regions are consistent with those found in prior reviews/meta-analyses of the verbal working memory literature [3,4,6]. The consistency of the AGES approach with prior findings lends substance to this meta-analytic technique.

Perhaps, the more remarkable aspect of the meta-analysis findings, and the most relevant to our hypothesis regarding Broca's area, was that two distinct foci of convergence were present within the left inferior frontal region (Fig. 2A). As with the subregions of Broca's area we had dissociated empirically, one meta-analytically derived left inferior frontal gyrus focus was centered in the dorsal and posterior aspect of the inferior frontal gyrus ($x = -43$, $y = 7$, $z = 26$ mm), while another was centered more ventrally in the inferior frontal gyrus ($x = -49$, $y = 14$, $z = 7$ mm). Taken together, the empirical and meta-analytic data provide strong convergent evidence that verbal working memory draws on multiple spatially and functionally distinct subregions of the left inferior frontal gyrus.

Table 1
Stereotaxic coordinates for brain areas identified empirically and meta-analytically

Anatomical region	BA	Empirical	Meta-analysis
		x, *y*, *z*	*x*, *y*, *z*
Medial frontal g.	6	0, 5, 49	0, 7, 48
Anterior cingulate g.	24, 32	0, 10, 31	–
L. precentral g.	6	−41, −9, 44	−31, −1, 50
R. precentral g.	6	47, 10, 27	42, 4, 31
L. middle frontal g.	46, 10	–	−36, 39, 21
R. middle frontal g.	46	36, 33, 13	35, 32, 27
L. inferior frontal g.	44	−39, 7, 25	−43, 7, 26
L. inferior frontal g.	45	−47, 15, 2	−49, 14, 7
R. inferior frontal g.	45	45, 19, 2	29, 19, 3
L. anterior insula	45	−28, 22, 9	−29, 16, 5
R. IFG/ant. insula	45	34, 17, 20	29, 15, 7
L. inferior parietal	40, 7	−27, −58, 43	−29, −57, 40
R. inferior parietal	40, 7	–	39, −48, 39
R. caudate nucleus		19, −11, 24	–
L. thalamus		6, −11, 16	–
L. lateral cerebellum		−27, −58, −24	–
R. lateral cerebellum		41, −62, −23	31, −58, −25

Coordinates for the empirical study reflect the average coordinate for regions that activated across encoding, maintenance, and retrieval phases. Regions in early sensory and motor processing areas, which are normally subtracted out in WM studies, have not been included.

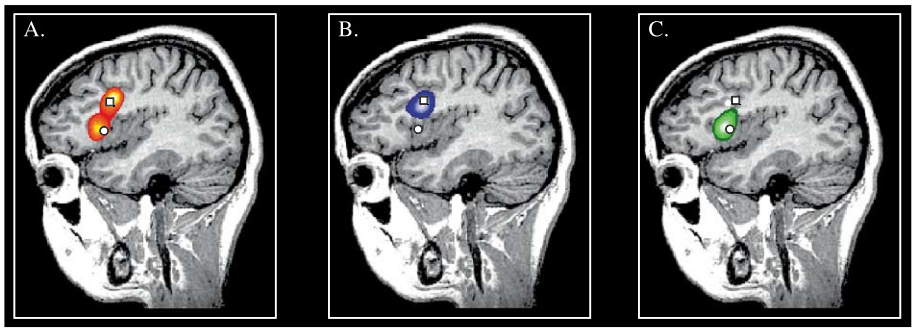

Fig. 2. Left inferior frontal foci revealed in three AGES meta-images. The results are shown in sagittal sections 40 mm left of the midline. The projected peak coordinates from the dorsal (square) and ventral (circle) left inferior frontal regions found in our prior empirical study [2] are shown for reference. (A) The meta-image from 30 studies of verbal working memory, revealing two distinct left inferior frontal foci. (B) A single, dorsally located, focus found in the meta-image of prior verbal working memory studies in which the level of difficulty/performance was manipulated. (C) A single, ventrally located, focus found in the meta-image of studies that contrasted word and pseudoword processing.

The foci observed in the AGES meta-images of performance and lexicality effects are shown in Fig. 2 (B and C). The results further substantiate the dissociations observed in our prior neuroimaging study [2]. The AGES meta-image of performance manipulations in working memory yielded a single convergence in dorsal inferior frontal gyrus ($x=-44$, $y=7$, $z=26$ mm); this focus is centered very close to our empirically derived dorsal Broca's subregion ($x=-37$, $y=13$, $z=24$ mm), in which we found that activation tracked with performance. In contrast, the studies manipulating lexical status yielded a single convergence in ventral inferior frontal gyrus ($x=-41$, $y=13$, $z=7$ mm); this focus is spatially consistent with our empirically derived ventral Broca's subregion ($x=-42$, $y=14$, $z=5$ mm), in which we found greater activation for the short-term maintenance of nonwords as compared to words.

4. Discussion

As the neuroimaging literature grows, there is increased pressure to synthesize previous findings. The AGES approach offers the strengths of other meta-analytical techniques in supporting such synthesis, while also promoting the discovery of novel structure–function relationships by not imposing subjective assumptions about spatial clustering. Still, there are a number of caveats that must be mentioned. As with other methods, the AGES approach requires that inclusion criteria be used to filter which studies, experiments, and foci are added into the analysis. Although our method obviates subjectivity regarding spatial clustering judgments, it also introduces two new sources of subjectivity. Specifically, both the spread (variance) attributed to the Gaussian distributions modeled about each point, and the intensity threshold employed to highlight areas of convergence, are unconstrained parameters that remain subject to the user's preference. Methods to establish settings for these parameters objectively, and a priori, are the topics of continuing work in our lab. Empirical bases for choosing particular parameter settings, such as choosing a spread based on empirically derived estimates of intra- and intersubject functional anatomical variability are one approach (cf. Ref. [8]). We have also explored the use of random (Monte Carlo) simulations. By determining false probability rates for randomly selected coordinates, when modeled with various degrees of spread and at various intensity thresholds, a statistical justification for different parameter values can be achieved.

When the AGES approach was applied to prior studies of verbal working memory, the results confirmed our empirical findings showing functionally distinct foci within Broca's area. Other neuroimaging studies that have compared different tasks using within-subject designs provide additional evidence for functional heterogeneity within Broca's area. For example, several studies have contrasted a semantic task, such as making a synonym judgment, with a phonological task of roughly comparable difficulty, such as making a rhyme judgment [9–12]. In general, activation associated with semantic tasks is found more ventrally and anteriorly than the activation associated with phonological tasks. More recently, two studies contrasting syntactic and semantic processing [13,14] have supported the localization of semantically related activation to the anterior-ventral inferior frontal gyrus and have distinguished it from more dorsal and posterior syntactically related activation.

Thus, while neuroimaging and neuropsychological studies have implicated Broca's area in a diverse set of linguistically relevant operations (e.g., phonological [11,15], semantic [16], and syntactic [17] processing), this should not be interpreted as a failure to arrive at a unitary theory of inferior frontal function. Rather, these diverse findings may be a reflection of multiple processes mediated by distinct subregions within a relatively restricted, though neuroanatomically diverse [18], patch of cortex. Empirical studies that make use of within-subject designs to contrast different types of processing, and meta-analytic techniques (such as AGES) that avoid a priori and subjective spatial clustering, will be instrumental in further delineating the functional topography of this region.

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Note in press

Since the preparation of this manuscript, a nearly identical approach to meta-analysis was reported independently by Turkeltaub and colleagues [19], and applied to the domain of single-word reading. We believe that both the similarity of the two approaches, and the methodological advancements provided by these authors, support the general validity and utility of this meta-analytic technique.

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