RESEARCH ARTICLE

From nodes to networks: How methods for defining nodes influence inferences regarding network interactions

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Abstract

Functional connectivity (FC) analysis of fMRI data typically rests on prior identification of network nodes from activation profiles. We compared Activation Likelihood Estimate (ALE) and the Experimentally Derived Estimate (EDE) approaches to network node identification and functional inference for both verbal and visual forms of working memory. ALE arrives at canonical activation maxima that are assumed to reliably represent peaks of brain activity underlying a psychological process (e.g., working memory). By comparison, EDEs of activation maxima are typically derived from individual participant data, and are thus sensitive to individual participant activation profiles. Here, nodes were localized by both ALE and EDE methods for each participant, and subsequently extracted time series were compared using connectivity analysis. Two sets of significance tests were performed: (1) correlations computed between nodal time series of each method were compared, and (2) correlations computed between network edges (functional connections) of each network node pair were compared. Large proportions of edge correlations significantly differed between methods. ALE effectively summarizes working memory network node locations across studies and subjects, but the sensitivity to individual functional loci suggest that EDE methods provide individualized estimates of network connectivity. We suggest that a hybrid method incorporating both ALE and EDE is optimal for network inference.

KEYWORDS

activation likelihood estimates, individual differences, functional connectivity, node identification

1 | INTRODUCTION

Networks are mathematical descriptions of interacting elements within a “real world complex system” (Rubinov & Sporns, 2010). In the case of brain networks, quantifying functional relationships between the elements that constitute a network commonly depends on the identification of network nodes. Network nodes summarize the functional neuroanatomy of the brain (Park & Friston, 2013), and their identification permits tractable investigation and estimation of network connectivity from fMRI data based on different model classes (Silverstein, Bressler, & Diwadkar, 2016). For instance, functional connectivity (FC) is usually computed as the correlation between time series from spatially dispersed, but interdependent, constituent regions and sub-regions of the brain (Rykhlevskaia, Gratton, & Fabiani, 2008; Van den Heuvel & Hulshoff Pol, 2010). In deriving estimates of FC from fMRI data, nodes are usually defined at fixed loci

representing local maxima of functional responses. Time series extracted from these nodes are then used for FC analysis (Bressler & Menon, 2010). It follows that, in this process, the *initial* choice of network nodes may affect inferences about functional interactions in the network (Butts, 2009; Sohn et al., 2015).

Small- and large-scale analyses of fMRI data have benefitted immensely from methods that permit analysis of such data in stereotactic space (Ashburner & Friston, 2005). Although gross variations and individual differences in neuroanatomy are imperfectly expressed when brain volumes are standardized (Amunts & Zilles, 2001; Eickhoff et al., 2005), almost all analyses of fMRI data are now undertaken in such space. Yet, there is no canonical approach for deciding the spatial coordinates of nodes to be used in network analysis. Here, we used undirected functional connectivity (uFC) analysis (Silverstein et al., 2016) to examine the interactions between the nodes of brain networks at play during both verbal and visual working memory task

performance (Diwadkar et al., 2011; Owen, McMillan, Laird, & Bullmore, 2005). Our goal was to compare two distinct methods of network node identification: (a) the widely-used Activation Likelihood Estimates (ALE), an established and powerful tool for discovering task-related activation maxima through data aggregation (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012); and (b) Experimentally Derived Estimates (henceforth called EDE) of activation peaks in individual-subject data recorded in verbal or visual working memory experiments. Working memory, or the ability to temporarily maintain and update information about stimuli to perform a task (Baddeley, 1992) provides a useful domain for these methodological investigations because multiple fMRI studies have converged on a reasonable understanding of its functional neuroanatomy (Cabeza & Nyberg, 2000; Diwadkar et al., 2013; Owen et al., 2005).

1.1 | Overview of ALE and EDE approaches

ALE is a well-established and widely employed meta-analytic methodology to determine aggregated task-related fMRI activation loci from multiple studies of the same cognitive function (Bzdok et al., 2013; Cortese, Castellanos, & Eickhoff, 2013; Wager, Lindquist, & Kaplan, 2007). The method provides spatial likelihood estimates of activation clusters from fMRI data collected by different groups in repeated neuroimaging studies of a specific cognitive domain (Laird et al., 2009). The key idea behind ALE is to treat common activation loci as centers for three-dimensional Gaussian probability distributions that capture the spatial uncertainty associated with each locus reported to be activated in the cognitive function. This uncertainty is determined from empirically reported activation data, aggregated across many different studies. The ALE algorithm weights the between-subject variance by the sample size of the studies entering the analyses. Studies with larger sample size are assumed to provide more reliable approximations of activation effects, and are therefore modeled by narrower Gaussian distributions (Eickhoff et al., 2012).

Though ALE treats individual differences in activation loci within a probabilistic framework, the method, by its very nature, does not explicitly utilize individual differences in activation loci for network analyses. This feature limits analysis because it excludes brain network interactions that are highly flexible and individualized (Bassett et al., 2011; Stevens, Tappin, Garg, & Fair, 2012). For example, FC in resting-state (rs) networks that include heteromodal association cortices is known to be highly variable across subjects (Mueller et al., 2013). We infer that such inter-subject variability is very likely also present in task-related processing (Hermundstad et al., 2013; Park & Friston, 2013).

Alternatively, EDEs of coordinates are based on the activation maxima of *individual participants* within an experiment. The EDE approach locates network nodes at the activation maxima of *each* individual participant, rather than at single maxima for *all* participants.

Our goal here was to compare ALE and EDE methods of network node identification for subsequent use in network analysis. Notably, both ALE and EDE approaches are conducted after translation to stereotactic space, and neither can suitably account for individual differences in *structural* neuroanatomy. Therefore, our focus was not on how individual differences in structural variation are expressed in

fMRI activation. More specifically, we were trying to account for differences between methods that, in stereotactic space, define nodes based on fixed loci (ALE) or on individual differences in *activation* loci (EDE). In assessing this question for networks underlying working memory tasks (both verbal and visual), our analysis expands beyond previous explorations, which, to our knowledge, have been primarily directed at the analysis of *resting-state* fMRI data (Sohn et al., 2015).

2 | METHODS

2.1 | Participants

Data from two unique datasets were submitted to analyses: (a) Verbal n-back: Twenty-eight healthy individuals provided informed consent, or written assent, to participate in the study (Mean age: 19.25 years; Age range: 17–23 years; 14 males). All participants were recruited through community-based advertisements, and all experimental procedures were approved by the Human Investigative Committee at the Wayne State University School of Medicine. (b) Visual n-back data from the Human Connectome Project (HCP) database: Due to the limited statistical power of our first (verbal working memory) experiment and its relatively low participant count, task-based fMRI scans from the visual working memory task of HCP database were submitted to our analysis pipeline to validate our primary findings. The use of the HCP database and its working memory fMRI scans was motivated by the fact that the HCP database uses an n-back working memory task, though it is visual, as opposed to a verbal n-back, and the sample size in the HCP dataset is significantly larger, permitting us to explore replications of the primary analyses. As a criterion for inclusion in our analyses, participants from the HCP dataset were required to (i) have been considered to be behavioral proficient on the task, (ii) have been in an age range as close to the primary study (17–23 years) as possible. The resultant age range used (22–25), and the additional criterion, yielded 182 participants from the HCP dataset. Raw HCP fMRI data were downloaded and submitted to the same processing pipeline shown in Figure 1.

2.2 | fMRI data

(a) Verbal n-back data: Functional MRI (fMRI) BOLD-contrast time series data collection was performed by gradient echo planar imaging (EPI) on a 3 T Siemens Verio system using a 12-channel volume head coil (TR: 2.6 s, TE: 29 ms, FOV: $256 \times 256 \text{ mm}^2$, acquisition matrix: 128×128 , 36 axial slices, voxel dimensions: $2 \times 2 \times 3 \text{ mm}^3$). In addition, a 3D T1-weighted anatomical MRI image was acquired for each participant (TR: 2200 ms, TI: 778 ms, TE: 3 ms, flip angle = 13° , FOV: $256 \times 256 \text{ mm}^2$, 256 axial slices of thickness = 1.0 mm, matrix = 256×256). A neuroradiologist reviewed all scans to rule out clinically significant abnormalities. (b) Visual n-back (HCP) data: fMRI BOLD-contrast time series data collection by done by gradient echo EPI on a 3 T Siemens "Connectome Skyra" with a 32 channel head coil (TR: 720 ms, TE: 33.1 ms, FOV: $208 \times 180 \text{ mm}^2$, acquisition matrix: 104×90 , 72 axial slices, voxel dimensions: $2 \times 2 \times 2 \text{ mm}^3$). A 3D T1-weighted anatomical MRI image was also acquired for each

FIGURE 1 The flowchart provides a bird's eye view of the processing steps used in the implementation of each of the ALE (represented in red) and EDE (represented in yellow) methods for node identification and subsequent network analyses. The chart depicts the sequential steps that culminate in the two techniques of direct comparison between methodologies used to assess differences in network functionality. The blue portion of the flowchart highlights the steps where the two methods were contrasted through statistical computations [Color figure can be viewed at wileyonlinelibrary.com]

participant (TR: 2,400 ms, TI: 1,000 ms, TE: 2.14 ms, flip angle: 8°, FOV: 224 × 224 mm²).

2.3 | Task and data preprocessing

(a) The verbal n-back fMRI data were acquired while participants engaged in an n-back working memory task (Bakshi et al., 2011; Diwadkar, Asemi, Burgess, Chowdury, & Bressler, 2017). Letter stimuli were projected in sequence (Presentation Time: 500 ms; ISI: 2,500 ms) with subjects signaling by button press if the letter was a target letter (0-Back condition), or identical to the one shown two letters previously in the sequence (2-Back condition). A block design was employed with three experimental conditions: 0-back (30 s/epoch; 5 epochs), 2-Back (30 s/epoch; 5 epochs), and rest (20 s/epoch; 10 epochs). Extended rest epochs were also included to reduce fatigue. (b) Visual n-back fMRI data were obtained with all participants viewing the same series of visual stimulus (nonmutilated body parts with no nudity, faces, tools and places). Each scan had two runs of eight task blocks (10 trials, 25 s per block) split evenly between the 2-back and 0-back conditions, and four resting blocks (15 s). A more detailed explanation of the task, as well as visualization of the actual stimuli, can be found on the HCP website (WU-Minn Consortium Human Connectome Project, 2018).

All fMRI BOLD data (verbal and visual n-back) were processed employing established methods for temporal preprocessing (slice timing correction), followed by spatial preprocessing in SPM8. In spatial preprocessing, the echo planar images were manually oriented to the AC-PC line with the reorientation vector applied across the echo planar image set, realigned to a reference image to correct for head movement, and co-registered to the anatomical high resolution T₁ image. This high-resolution T₁ image was normalized to the Montreal Neurological Institute (MNI) template, with resultant deformations subsequently applied to the co-registered EPI images for normalization. Low-frequency components were removed using a low-pass filter (128 s) and images were spatially smoothed using a Gaussian filter

(8 mm full-width half-maximum [FWHM]). Subjects' head motion for all analyses was within accepted limits (<4 mm) and in all first-level models, the effects of motion were modeled including the six motion parameters as covariates of no interest.

2.4 | Coordinate identification

(a) Verbal n-back: Initial coordinate locations for the ALE network were compiled from a previously published meta-analysis of 24 unique *verbal n-back* working memory studies (Owen et al., 2005). The loci therein were compared with those in the BrainMap database (Eickhoff et al., 2012) for verification, given that BrainMap is considered a canonical repository for activation peaks. Using the Sleuth (Laird et al., 2009) and GingerALE programs in BrainMap (Eickhoff et al., 2012), the following search criteria were established to isolate relevant studies: (a) working memory (domain), (b) n-back (behavioral task), and (c) letters (visual stimuli). This comparative search identified a total of 66 unique studies. However, 51 of these studies also included (or were from) diseased cohorts, and therefore violated our criteria for inclusion.

Using the parameters from Owen et al. ($p_{FDR} < 0.01$, cluster extent >200 mm³), ALE identified five voxel clusters; four of these (left inferior Parietal Lobule, BA39; left dorsal Anterior Cingulate Cortex, BA32; left and right lateral Premotor Cortex, BA6) were also reported by Owen et al. (2005). These preliminary investigations indicated that the Owen et al. (2005) meta-analysis subsumed the investigations within BrainMap, producing a comprehensive set of coordinates. Therefore, the results from Owen et al. (2005) were retained for subsequent exploration and analyses.

The ALE meta-analytic coordinate locations from Owen et al. (2005) were translated into MNI space (Papademetris et al., 2017), where they yielded 17 unique cortical, thalamic, and cerebellar loci (see Table 1). Although 17 activation loci were reported in the meta-analysis of Owen et al. (2005), only 13 could be used here. Four regions [right medial Cerebellum, medial Cerebellum, left lateral Cerebellum, and left ventrolateral Prefrontal Cortex (PFC) (BA6)] had to be

TABLE 1 The list of activated ROIs reported by Owen et al. (2005)

1.1 verbal n-back				
ROIs	BA	MNI X	MNI Y	MNI Z
Right thalamus	N/A	9	-13	1
Right lateral cerebellum	N/A	34	-55	-33
Medial lateral cerebellum	N/A	24	-57	-55
Left lateral cerebellum	N/A	-27	-62	-61
Frontal pole	Left BA 10	-39	45	21
Frontal pole	Right BA 10	37	47	18
Lateral premotor cortex	Right BA 6	27	-4	56
Lateral premotor cortex	Left BA 6	-26	-1	57
Dorsal anterior cingulate cortex	Left BA 32	-3	10	46
Dorsolateral PFC	Right BA 9	43	31	30
Ventrolateral PFC	Left BA 44	-52	15	6
Ventrolateral PFC	Left BA 6	-65	2	13
Medial posterior parietal	Right BA 7	12	-68	54
Inferior parietal lobule [1]	Right BA 39	29	-62	46
Inferior parietal lobule [2]	Right BA 39	37	-49	40
Inferior parietal lobule	Left BA 39	-34	-51	40
1.2 visual n-back				
ROIs	BA	MNI X	MNI Y	MNI Z
Left frontal pole	BA 10	-28	66	-4
Left frontal mid	N/A	-33	44	10
Left inferior frontal triangularis	N/A	-41	27	25
Right inferior frontal triangularis	N/A	43	30	23
Left precentral	BA 9	-46	4	34
Left superior middle frontal	N/A	-1	25	39
Left inferior parietal	BA 40	-30	-57	43
Right inferior parietal	BA 40	58	-40	47
Right frontal mid	N/A	38	17	53

The ROIs housed the nodes for each of the two methods used in this study. Each node's spatial coordinates, from the Montreal neurological institute (MNI), are listed in the last three columns, and the respective Brodmann area (BA) in which the node resides, for the neocortex, is shown in the second column. 1.1 represents ROIs found with verbal stimuli while 1.2 represents ROIs found with visual stimuli.

excluded because their corresponding EDE location of maximal activation was already paired with another ALE location, because in mapping ALE coordinates to anatomical regions (a pre-requisite for the EDE approach), we restricted ourselves to a single maximum in an anatomical region (considering the single maxima as representative of the region). These 13 coordinates gave the locations of ALE-defined nodes, that were subsequently used to assess network functional connectivity, and also provided constraints for coordinate identification in the EDE method. This constraint was applied as follows: Using the Automated Anatomical Labeling (AAL), a regional label, reflecting a region of interest (ROI), was assigned to each ALE location (Maldjian, Laurienti, Kraft, & Burdette, 2003). Then, these ROIs were used as the spatial regions from within which EDE coordinates were located at individual-subject activation maxima. As a result, an EDE coordinate for each participant was assigned within the same ROI as the ALE-identified activation peak.

(b) Visual n-back: Assessment of the Owen et al. meta-analysis was re-evaluated using their published nine nonverbal clusters. Using the BrainMap database and its associated programs (Sleuth and GingerALE) the following search criteria were utilized in order to identify the list of studies from which to conduct the ALE: (i) working memory (domain), (ii) n-back (task), (iii) any stimulus from the HCP list or within the Owen et al. nonverbal category. Of the resulting 37 articles, 27 were discarded as they used atypical cohorts. Using the same parameters as described in the verbal n-back description, ALE found no clusters. Therefore, the nine clusters described from Owen et al. were used as the ALE nodes for the visual n-back portion of the current investigation.

As described in the verbal n-back portion of the investigation, the coordinates of the ALE-defined nodes constrained the mapping to the regions of interest (based on the AAL labeling scheme) to obtain the EDE-defined node. The entire procedure is depicted in Figure 1.

2.5 | Node localization

Network nodes were localized at coordinates identified by the two methods, resulting in networks having nodes in the same ROIs. Each node was defined as a sphere with a radius of 3 mm. Both networks were from the 2-back condition, allowing us to test hypotheses about the relation of network time series metrics to active working memory states. Time series representing the first eigenvariate from the effects of interest contrast ($p < .05$) were extracted from each node for each participant to represent activity across modeled conditions in the experiment. These were submitted for subsequent uFC analysis. If the ALE-identified coordinate did not reveal a significant activation for any participant, the most proximate supra-threshold peak within a search radius of 10 mm was used instead. If no activation peak was found within 10 mm, time series for the ALE node were not reported for that participant.

2.6 | Time series analysis

Both the verbal and visual n-back time series analyses compared working memory networks created by the two methods, with the aim of determining significant differences in network characteristics between them. Thus, time series analysis tested whether or not ALE and EDE network nodes were identical.

Time series analysis was applied in two different ways. In the first approach, the Pearson zero-lag correlation between nodal time series from the two methods was computed. If the correlation coefficients were found to be significant, it would suggest that estimates of functional dynamics were similar regardless of method. Correlations were taken from the 169-element correlation matrix (for the verbal n-back task) or 81-element correlation matrix (for the visual n-back task) representing all possible ALE-EDE node pairs. Diagonal values within the matrix were used to compare time series created by the two methodologies from nodes in the same anatomically bounded areas. The Fisher Z transformation was applied to each correlation coefficient prior to statistical analysis.

In addition, we assessed whether the *Euclidean* distance between the ALE and the corresponding EDE-defined node predicted the strength of the Pearson correlation coefficient between the time

series from corresponding nodes derived from the two methodologies. Euclidean distance is a simple estimate of the distance between node locations in three-dimensional stereotactic coordinate space and has been viably used to calculate the distance between subject's local maxima in previous studies (Eickhoff et al., 2009). Thus, these analyses were designed to address whether a simple distance metric might account for putative differences in estimates of time series correlations between corresponding nodes. This would constitute evidence that time series estimates are predicted by a simple spatial distance metric. Effect size (Cohen's d) was used to estimate the strength of the correlation, as it is a useful heuristic for assessing the magnitude of a Pearson correlation coefficient (Cohen, 1988) and quantifying the strength of an effect (see Supporting Information Figure S1 for results).

In the second approach to time series analysis, Pearson zero-lag correlations were computed for network edges from each of the two methods. The null hypothesis (that each network edge would *not* be different) would be rejected if network edges were significantly different across methodologies. The similarity (difference) test was executed by independently computing the Pearson correlation for all 78 network edges (all pairwise combinations of 13 nodes in the verbal n-back task) or all 36 network edges (all pairwise combinations of 9 nodes in the visual n-back task) of the ALE and EDE networks. Paired t -tests ($p_{FDR} < .05$ for verbal n-back and $p_{BONFERRONI} < .05$ for visual n-back task) across subjects were computed between edge correlation coefficients (between nodes) from the two methods, to identify significantly different edges between the networks of the two methods. In an additional analysis, designed to verify the veridical t -tests, we randomized the ALE and EDE 3D matrices by randomly assigning the subject name and the two node names to each Pearson correlation when constructing the 3D matrix. This newly constructed, randomly assigned, input was then put through the same statistical computations and the randomized results were compared with the veridical results.

All analyses were conducted in R (RStudio, 2016) using individualized scripts. The scripts used the `sqlf` package to import data into R, and the `psych` package for statistical analysis. The first script performed the first analysis (comparison of time series created by the two methods at network nodes). It first created 169 Pearson correlations for both the ALE and EDE methods (all 13×13 possible ALE–EDE interactions) for the verbal n-back task and 81 Pearson correlations (all 9×9 possible ALE–EDE interactions) for the visual n-back task. The values of r representing the correlations were then stored as a 3D matrix. The on-diagonal elements of this matrix, representing the correlations of a single node obtained from the two methods, were transformed to Z -values, and then subjected to statistical analysis. The second script performed the second analysis (comparison of network edges, Pearson correlations between time series of node pairs, created by the two methods). ALE and EDE 3D matrices, with each cell value representing the Pearson correlation corresponding to a pairwise combination of nodes, were subjected to paired t -tests to compare the network edges. As noted earlier, the resulting p -values were corrected by the False-Detection Rate method (Benjamini & Hochberg, 1995) for the verbal n-back task and corrected by the Bonferroni method for the visual n-back task.

2.7 | Behavioral proficiency and network metrics for ALE and EDE-derived networks for the verbal n-back

Finally, we explored the relationships between global network measures for ALE and EDE networks, and behavioral proficiency for the verbal n-back. The goal of these exploratory analyses was to discover whether one class of methods for network identification was more closely predictive of behavioral proficiency than the other. Behavioral profiles for the verbal n-back were summarized using d' (Macmillan & Creelman, 2005), a measure of discrimination sensitivity frequently used in detection tasks (such as the verbal n-back). Independently, for each of the ALE and EDE derived networks, we computed their cluster coefficients, measuring segregation of the network as a metric that characterizes global network organization (Rubinov & Sporns, 2010). For all 28 participants performing the verbal n-back task, we conducted two separate regression analyses to estimate the effect size relating the cluster coefficient for each of the ALE and EDE derived networks, with d' . Notably the EDE- d' analyses resulted in a larger effect size ($r = .32$) than the ALE- d' analyses ($r = -.19$). The difference in correlation coefficients was marginally significant ($p < .05$, one-tailed; see Supporting Information Figure S2).

3 | RESULTS

3.1 | Brain activations during working memory

Figure 2 shows averaged activation profiles from the primary (Figure 2a, verbal n-back task) and secondary analyses (Figure 2b, HCP, visual n-back task). In each, significant clusters are depicted on a montage of axial slices ($p_{FWE} < .01$). Superimposed on the activation profiles are ALE loci (shown as numbered blue circles) that were used in the analyses. As noted in the Methods, the precise ALE locations were derived from Owen et al. (2005).

Figure 3 depicts the identified EDE loci from *each* of the 28 participants (blue spheres) and in *each* of the ROIs (see Methods) for the verbal n-back data. The ROIs are shown as highlighted region of interest masks (in pink) overlaid on each view. They correspond to the anatomical mask (from AAL) to which the ALE coordinates were localized, establishing the space in which the EDE local activation maximum was localized for time series extraction. In effect, Figure 3 highlights the heterogeneity in the functional loci of activity for each of the ROIs in each of the participants.

3.2 | Comparison of ALE and EDE time series

In order to assess whether ALE and EDE nodal time series represented similar functional information in the working memory domain, intra-regional correlations between the two methods were assessed. For the verbal n-back data although 16 activation loci were reported in the meta-analysis of Owen et al. (2005), only 13 of them were used here: three regions [right medial Cerebellum, left lateral Cerebellum, and left ventrolateral Prefrontal Cortex (PFC) (BA6)] were excluded because they were not available in the EDE methodology as the EDE location of maximal activation was already paired with another ALE location. In the ALE based approach, multiple nodes may be mapped to the same anatomical

FIGURE 2 (a) Activation profiles of the verbal n-back task from the primary analyses ($n = 28$) are projected onto a montage of axial views ($p_{FWE} < .01$). Table 1 indicates the specific locations of the 13 regions of interest (ROIs). (b) Activation profiles of the visual n-back from the HCP dataset ($n = 182$) are projected onto a montage of axial views ($p_{FWE} < .01$). Table 1 Indicates the specific locations of the nine regions of interest (ROIs) in both montages, the precise ALE loci derived from Owen et al.'s meta-analysis (2005) from the nonverbal (a) and visual (b) n-back tasks are overlaid [Color figure can be viewed at wileyonlinelibrary.com]

region (ROI). However, in the EDE approach, we identified only a single maximum in an anatomical region. The heat map in Figure 4a displays the correlations between ALE and EDE nodes residing within the same ROI averaged across the subjects. All the 13 on-diagonal locations of the 169-element correlation matrix had large effect sizes according to the Cohen standard (>0.8). Figure 4b provides a dimensional depiction of the data in 4A, where the height of the cell locations reflects the Pearson correlation coefficients obtained from that specific ALE–EDE interaction. Figure 4c represents the on-diagonal values organized in terms of the 13 ROIs and their respective effect size. As detailed from the panel, all ALE–EDE interactions averaged across subjects and restricted to the same anatomical region had large effect sizes.

Figure 5 displays the same information as Figure 4 but for the 182 participants performing the visual working memory task, and included in the HCP database. Consistent with our primary analyses, for ALE–EDE node pairs restricted to the same anatomical space (on the diagonal of the heat map), all had large effect sizes (as noted in the figure caption).

3.3 | Comparison of ALE and EDE network edges

Between-method differences of the initial experiment (verbal n-back) in the estimated network edge values (uFCs) were compared by computing the paired t -test between network edges generated by the two

methods (across participants). Figure 6 shows the 15 network edges that were significantly different between methodologies with a line between network nodes denoting significance. These 15 edges represent 19% of the total of 78 edges within the network model. Six of the fifteen edges converged on the left inferior Parietal Lobule (BA39), four on the right Thalamus, three each on the right dorsal inferior Parietal Lobule (BA39), left ventrolateral PFC (BA44), and right dorsolateral PFC (BA9), two each on the right medial posterior Parietal Cortex (BA7), right ventral inferior Parietal Lobule (BA39), left lateral Premotor Cortex (BA6), right lateral Premotor Cortex (BA6) and right Frontal Pole (BA10), and one on the left dorsal anterior Cingulate Cortex (BA32). The left Frontal Pole (BA10) and right lateral Cerebellum were the only nodes having no edges that significantly differed between the two methodologies. Randomization of the assignments of r values from the ALE and EDE methods was performed for comparison with the veridical results. An across-subject, between-methodology paired t -test on the randomization results showed that, with 100 iterations, only 2 edges on average were significantly different by chance, a number well below the 15 edges that differed in the veridical results.

After identifying network edges that significantly differed between the ALE and EDE methods, we next sought to identify the regional sources of those differences. To do this, each network was first categorized into the following sets of sub-regions: left and right hemisphere, anterior and posterior regions, and cortical and sub-

FIGURE 3 The spatial distribution of network nodes derived from EDE from the primary analyses (verbal n-back) is depicted. In a series of lateral views, we depict the individual loci derived for each of the 28 participants in each region of interest (ROI). The anatomical regions are shaded and each depicted sphere (blue) represents a single participant. The red sphere within each ROI (not always visible) represents the corresponding ALE coordinate. As seen (and expected), individual maxima are spatially dispersed within any ROI, evidence of variation across subjects in the location of activation peaks within each ROI during working memory. A corresponding figure for the visual n-back is not tractable because of the substantially larger sample size [Color figure can be viewed at wileyonlinelibrary.com]

cortical regions. A Welch two-sample t -tests was performed between the divisions so as to investigate whether the networks differed at the sub-region level. No significant differences were found between any of the sub-regions created (p 's > .05) suggesting that any differences in methodologies were not mediated by general regional assignments.

These results were replicated with the data obtained from the HCP database (visual stimuli). Figure 6b shows the 28 edges, 77% of the total number of edges that were significantly different between methodologies. The lines between network nodes denote significant difference in ALE–EDE correlations. The left Frontal Mid and left Frontal Pole, regions of particular relevance during working memory, both had eight significantly different edges (100% of their edges) across methodologies. The left precentral node had the lowest number of significantly different edges across methodologies with five edges.

4 | DISCUSSION

This study was conducted with the aim of comparing differences regarding network interactions between nodes, wherein nodes were

identified based on ALE or experimentally derived estimates (EDE). On balance, if differences in how nodes are identified *do not* exert effects on inferences regarding network interactions between them, we would expect similar profiles of working memory networks identified using ALE and EDE methods. Specifically, we would expect time series to be strongly correlated, particularly as the distance between the ALE and corresponding EDE defined nodes decreases.

In this section, we first list the principal results of our analyses. Following this, we argue that ALE approaches can guide the search space for network node identification in individual data sets, and that identification of nodes in this space can be subsequently “tuned” by being sensitive to individual activation loci. Figure 1 outlines how this approach might be viable.

Our principal observation was that, as seen in Figure 2, the activation maxima from a group-level, random-effects analysis based on EDE analysis were distinct from those maxima obtained based on ALE analysis. This result was obtained both for verbal working memory ($n = 28$) and visual working memory ($n = 182$). Furthermore, as seen in Figure 3, *individual* activation loci were (as expected) spatially dispersed within the anatomical region of interest to which the ALE loci

FIGURE 4 Assessing time series correlations between network nodes of ALE and EDE networks for the verbal n-back task. (a) The correlation matrix between time series of respective nodes derived from the ALE (rows) and EDE (columns) methods is depicted in the heat map. The index to the right denotes the 13 regions of interest (ROIs) listed in the same order as in the rows and columns of the matrix. (b) The same correlations between ALE and EDE derived networks are further elucidated in a 3D histogram. The strength of the Pearson correlation coefficient (r) between ALE and EDE node time series is color coded. As is evident, a range of correlation strengths is revealed. (c) To parse these sub-networks we detail the effect size for the time series restricted to the same anatomical ROI, that is, the diagonal. That is, when ALE and EDE time series are restricted to the same ROI, the ALE–EDE nodal correlations have large effect sizes. The mean Euclidean distance (across subjects) between network nodes is overlaid for each ROI [Color figure can be viewed at wileyonlinelibrary.com]

were mapped (see the methods followed in the flowchart of Figure 1). These effects reinforce the idea that *individual* functional profiles have uncertain spatial correspondences in anatomical space (Brett et al., 2003). An ANOVA, and subsequent post-hoc tests, of the mean distances of the three effect sizes only showed that the mean distance of the large effect size group was statistically different from the other two. It was noted that corresponding nodes whose profiles were highly correlated (i.e., had a Large effect size) were often as distant in space as corresponding nodes whose profiles were poorly correlated (i.e., had a Small effect size).

Significant ALE–EDE differences persisted in the secondary analysis ($n = 182$ subjects, HCP) where 77% of network edges in secondary analyses were significantly different. Correlating the network measure (defined as a subject's clustering coefficient) with the behavioral performance of the verbal n-back (defined as the subject's d -prime), indicated that the EDE methodology was more predictive of behavioral proficiency.

These results are the first to offer an assessment of differences between node identification methods in task-based fMRI data, and are consistent with Sohn et al. (2015) resting-state investigation. That investigation showed that subject-specific, resting-state FC networks have higher correlations and lower variance than networks created

using canonical coordinates from meta-analyses found in the literature. Like our study, Sohn et al. demonstrated that the method used to determine node location (group-based vs. subject-specific) affects subsequent functional connectivity analysis. In their study, this difference affected understanding of how aging impacts resting connectivity.

4.1 | Data aggregation, individual variation, and network profiles

As our results imply, node identification for FC analysis based on data aggregation methods such as ALE produces FC results that are substantively and systematically different from node identification methods that are responsive to individual differences. Different *parcellation* strategies have previously been shown to impact brain networks in steps *following* FC analysis (Wang et al., 2009), but the present investigation shows that the method of node location *prior* to FC analysis can also significantly impact assessment of brain network interactions. The results present a challenge, because (a) data aggregation methods like ALE are of fundamental importance in providing statistically stable summaries of activation profiles across large study samples, but (b) *individual* activation loci encode individual “functional neuroanatomy.” Notably, EDE is not the only method which can account for

FIGURE 5 The effects presented in Figure 4 are replicated for the visual working memory task (HCP). (a) The correlation matrix between time series of respective nodes derived from the ALE (rows) and EDE (columns) methods is depicted in the heat map. The index to the right denotes the nine regions of interest (ROIs) listed in the same order as in the rows and columns of the matrix. (b) The same correlations between ALE and EDE derived networks are further elucidated in a 3D histogram. (c) To illustrate the differences between ALE and EDE network nodes, we show that the effect size of the correlations when the nodes are restricted to the same anatomical ROI, that is, as seen on the diagonal of the correlation matrix. In other words, when ALE and EDE time series are restricted to the same ROI, the ALE–EDE nodal correlations are large and have large effect sizes. The mean Euclidean distance (across subjects) between network nodes identified from each of the two methods is overlaid for each ROI [Color figure can be viewed at wileyonlinelibrary.com]

inter-subject variability and the presence of functional heterogeneity across individuals. Methodologies which localize nodes through a voxel–voxel analysis can also account for individual differences within functional networks. Stanley et al. (2013), specifically due to the lack of ROI functional homogeneity, advocated a voxel-wise approach that uses the least amount of a priori information to create a given network, rather than constructing networks from anatomical atlases (Stanley et al., 2013). Machine Learning techniques have also been used to construct brain networks and provide a rapid whole-brain analysis with little a priori information required (Hacker et al., 2013).

As Figure 1 implies, “hybrid” approaches to this question may be valuable and may help in reconciling the different assumptions of the two methods. In effect, the pipeline implicitly advocates such a method. In this framework, methods such as ALE could be used to map robust activation loci in a task-related domain to anatomical ROIs. In the current investigation, these ROIs were defined based on the AAL scheme (though other deterministic and probabilistic schemes exist) (Eickhoff et al., 2005). The ROI then effectively serves as a search space within which *individualized* activation maxima can be localized. This hierarchical approach uses the strength of data aggregation to narrow the spatial window of activation but retains the element of individual variation in identifying precise loci.

4.2 | Network divergence exists at critical nodes

An interesting element of the results observed in Figure 6 was the presence of the parietal lobe as a common node in networks that differed in FC between ALE and EDE approaches. Several studies have noted the influence exerted by the posterior parietal cortex in the context of working memory, specifically in its role in information retrieval (Olson & Berryhill, 2009). The superior longitudinal fasciculus III connects portions of the inferior parietal lobule to areas of the premotor and prefrontal cortex (BA 6, 8, 9, 46) (Schmahmann & Pandya, 2006). Olson and Beryhill (2009) reviewed hypotheses for the role of the posterior parietal cortex, including the superior parietal lobule (BA 5, 7) and inferior parietal lobule (BA 39, 40), in working memory: the PPC either manipulates information (along with PFC connections) or maintains information aggregation. Within our study, the left inferior parietal lobule node had the greatest number of significantly different edges between the two methodologies, and the left ventrolateral PFC, right dorsolateral PFC, and right inferior Parietal Lobule (1) all had over 20% of their edges significantly differ between the ALE and EDE networks, while the right medial Posterior parietal and right inferior Parietal Lobule (2) had over 15%. Additionally, as seen in Figure 6, edges between the left inferior Parietal Lobule and both PFC nodes (left ventrolateral and right dorsolateral) were

FIGURE 6 (a) For the verbal n-back task, the orthoview shows the network edges where we observed significant differences in correlation between the ALE and EDE methods ($p_{FDR} < .05$). The accompanying legend denotes the identities of the 13 ROIs. Undirected functional connectivity analysis revealed 15 significantly different edges, that is 19% of the total (15/78). The left inferior parietal lobule had the greatest number of significantly different edges (6) while the left frontal pole and right lateral cerebellum had no significantly different edges. (b) For the visual n-back task, the orthoview shows the network edges where we observed significant differences in correlation between the ALE and EDE methods ($p_{Bonferroni} < 0.05$). The accompanying legend denotes the identities of the nine ROIs. Undirected functional connectivity analysis revealed 28 significantly different edges, that is 77% of the total (28/36) [Color figure can be viewed at wileyonlinelibrary.com]

significantly different between methodologies. Evidence for differences between the PFC and PPC connections were also noted in the secondary analyses (visual n-back, HCP) where 28 (out of a possible 36) edges of the PFC and PPC were significantly different. The significant difference of those edges implies that the ALE and EDE networks revealed different relationships between the PPC and PFC. Thus, since both these regions are vital to working memory (Olson & Berryhill, 2009), the methodology initially selected to localize nodes can affect subsequent conclusions about the network supporting this cognitive function.

Differences in nodal association between the ALE and EDE networks were also found for association cortices: the inter-methodology differences in association cortex node locations that we report are consistent with the resting-state findings of Mueller et al. (2013), who reported that multimodal areas, more than unimodal areas, have high inter-subject variability. In our study, nodes in the left inferior Parietal Lobule (BA39), left ventrolateral PFC (BA44), right ventral and dorsal inferior Parietal Lobule (BA39), right dorsolateral PFC (BA9), right Frontal Pole (BA10), right Thalamus, and right medial posterior Parietal Cortex (BA7) all had more than 20% of their edges significantly differ between the two methodologies. By contrast, nonassociation-cortex regions such as the left and right lateral Premotor Cortex (BA 6) only had two edges (15%) significantly differ between ALE and EDE working memory networks.

Since individuals exhibit unique topological network features (Gordon et al., 2017; Laumann et al., 2015), techniques used to identify spatial coordinates prior to network construction should parallel the network characteristics. The use of subject-specific methods could bridge systems neuroscience and clinical neuroscience by representing more accurate brain networks as they adapt to an individual

subject's functional profile. Figure 3, showing the spatial range of activation maxima found in this study for each of the ROIs, reveals high inter-subject variability in activation maxima. As argued by Zilles and Amunts (2013), characterizing variability across individuals is invaluable for understanding statistical maps in neuroimaging data, largely because these maps form functional "fingerprints" of the brain in action. In that sense, understanding individual differences in the brain's structural and functional neuroanatomy may inform questions of the brain's evolution and/or ontogeny (Mueller et al., 2013). Large inter-subject variability has likewise been found in the structure of the brain's Brodmann areas (Amunts et al., 1999; Eickhoff et al., 2005), even in the primary unimodal regions, such as BA17. By extension, we anticipate that individual differences in structure will only be amplified when brain regions are functionally primed for action.

Exploratory investigations relating network measures (ALE or EDE) during the verbal n-back to behavioral proficiency (estimated using d'), were suggestive of the superiority of EDE estimated networks. Across subjects ($n = 28$), the correlation coefficient between estimated cluster coefficients (a measure of functional network organization) for EDE derived networks was marginally greater than ALE measures (Supporting Information Figure S2). Our study was not optimized to address the relationship between network measures and behavior, but this effect motivates further investigation in future studies.

5 | CONCLUSIONS

Assessment of fMRI data now places increased emphasis on the discovery of network as opposed to regional function (Friston, 2011; Stephan & Roebroeck, 2012). As a result, drawing inferences about how the brain works is now an endeavor more consistent with general

systems theory and complex systems techniques (Stephan, 2004) than with “neo-phrenology.” Yet, with a surfeit of analytical choices that pre-empt the process of inference from fMRI data (Silverstein et al., 2016), like in all of network science in general (Butts, 2009), choices made in defining networks, and the use of models for the discovery of network function can exert significant impact on subsequent inference. Our investigation revealed that a higher than chance percentage of network edges were significantly different between methodologies, wherein one approach explicitly accommodated individual differences in node identity, whereas the other relied on data aggregation for defining nodes. Our investigations (in future iterations of which we will employ techniques for evaluating functional network organization including graph theoretic and topological assessment) suggest that network science in the service of uncovering human brain function will benefit from considering and accommodating the assumptions underlying different approaches to summarizing data prior to FC analyses. These issues become particularly pertinent in the study of disordered connectivity in clinical and neuropsychiatric syndromes such as schizophrenia. These syndromes are themselves characterized by a high degree of neurobiological heterogeneity (Brugger & Howes, 2017), which if unincorporated in network analyses, is likely to have unpredictable effects on the process of clinical inference.

Cognitive neuroscience relies on the “universality assumption” that there is little qualitative variation in the architecture of brain systems that perform in a cognitive domain (Caramazza & Coltheart, 2006). Yet, as we have noted, anatomical and functional variation are ubiquitous in the human brain. Methods like ALE provide a strong platform for operationalizing the meta-analytic search for nodes across scores of studies, and can be used to guide the search for individualized activation loci in structural neuroanatomy. Once this is accomplished, inferences regarding network interactions may be better served by the analyses of time series from individualized activation loci.

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