Clinical Imaging 55 (2019) 181–187

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag

Neuroradiology

Combined task activation display as an effective method to teach introductory fMRI users☆

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ARTICLE INFO

Keywords:
BOLD
Conjunction analysis
Epilepsy
Brain mapping

ABSTRACT

Rationale and objectives: Interpreting functional magnetic resonance imaging (fMRI) can be an overwhelming and challenging task for trainees, particularly when post processing, synthesizing and interpreting data from multiple language paradigms. Currently, there is no established best method for teaching fMRI interpretation to new trainees. The purpose of our study is to compare the use of combined task activation display (CTAD) and conventional display of fMRI language paradigms as an effective method to teach fMRI to the introductory learner.

Materials and methods: Following IRB approval, 43 unique cases (with 10 repeat cases to assess intra-reader variability) were identified based on the inclusion/exclusion criteria. Eight radiology trainees, without prior exposure to fMRI, were asked to determine language lateralization based on activation of Wernicke's area, Broca's area, and the pre-supplementary motor area. Prior to trainee interpretation, a 15-minute training session was conducted to describe the expected anatomic locations of the language centers. Trainees were asked to determine language dominance using either the CTAD or conventional methods. Following a 6-week washout period, the same eight trainees were asked to interpret the cases using the opposite interpretation approach.

Results: Interpreting fMRI with the CTAD method significantly increased trainee accuracy (85.4% vs 70.9% $p < 0.001$) and trainee confidence (4.3 vs 3.6 $p < 0.001$), while decreasing time to interpretation (mean difference of 29 min), and intra-reader variability when compared to the conventional approach.

Conclusion: Combined task activation display is an effective method to teach fMRI to introductory learners.

1. Introduction

Blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) is a powerful noninvasive technique that is frequently employed for pre-surgical language mapping in patients with epilepsy [1–4]. Preoperative assessment of language laterality is a useful predictor of possible post-operative aphasia and unintended verbal memory deficits [4,5]. Historically, the intra-carotid amobarbital (Wada) test has been used as a gold standard to identify language dominance; however, its implementation has many disadvantages [6–9]. The Wada test is an invasive angiographic procedure with up to a 3% complication rate. Its validity relies on symmetric arterial supply to the cerebral hemispheres, and it is not standardized among different institutions [10,11]. Furthermore, the Wada test provides information about lateralization, but does not localize language or cognitive function centers that may guide surgical approach. Many studies have identified fMRI as an excellent noninvasive alternative to determining language dominance and have shown to have a strong correlation with both Wada results and direct cortical stimulation when functional paradigms were combined [2,12,13].

Interpretation of BOLD fMRI can be a challenging task for the novice, particularly for trainees with little prior exposure. Different fMRI

Abbreviations: BOLD, blood oxygen level dependent; CTAD, combined task activation display; EHI, Edinburgh Handedness Inventory; fMRI, functional magnetic resonance imaging; LI, laterality index

☆ This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abstract previously presented at: 11th Annual Meeting of the American Society of Functional Neuroradiology, October 9–11, 2017; Portland, Oregon.

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https://doi.org/10.1016/j.clinimag.2019.03.015
Received 4 November 2018; Received in revised form 6 March 2019; Accepted 28 March 2019

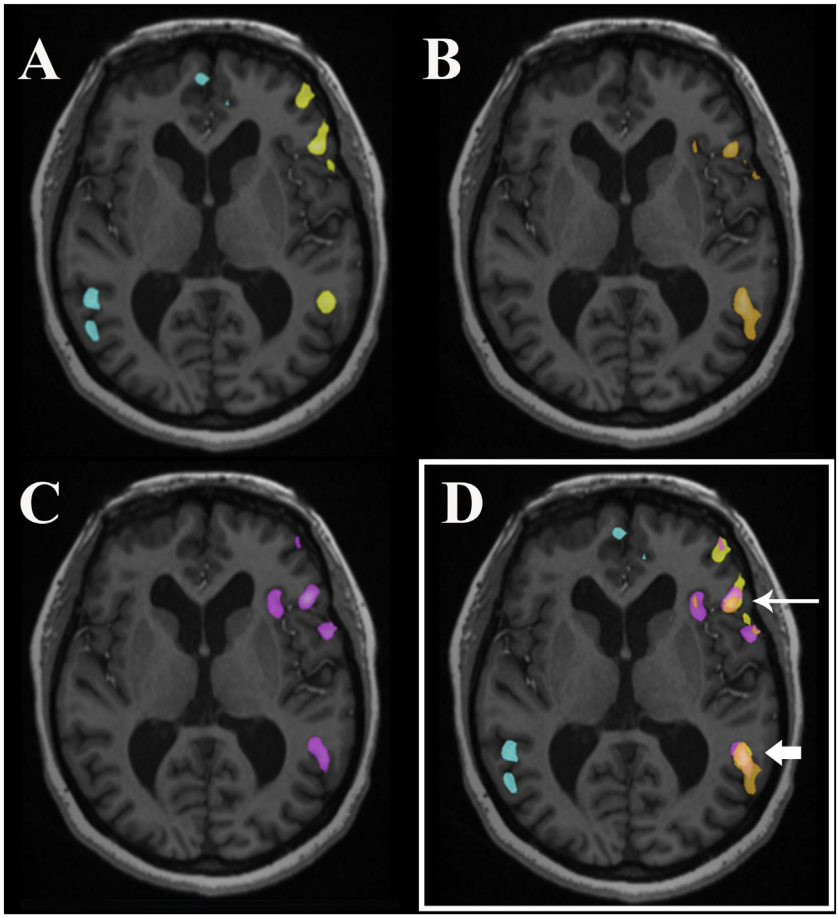

Fig. 1. Left language dominant. A–C: Conventional method of interpretation. A: Sentence completion (yellow is positive signal, turquoise is negative signal). B: Word generation (orange is positive signal). C: Verb generation (purple is positive signal). D: Combined task activation with overlay of the above paradigms demonstrating overlap of paradigms in the left Broca's area (thin arrow), and left Wernicke's area (thick arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

analysis methods have been proposed to help assess language laterality. Binder et al. describe the laterality index (LI) to determine statistical cutoff values for language dominance by quantitating the number of activated voxels in the lateral two thirds of each cerebral hemisphere [2]. Although the computed laterality indices were shown to have comparable results compared to intra-carotid amobarbital testing, a fixed statistical threshold may not fully capture differences between the cerebral hemispheres since this approach does not consider signal intensity [14]. Furthermore, negative values may further contribute to misinterpretation of LI. Conjunction display of multiple related paradigms emphasizes common areas of overlapping activation and improves laterality assessment for language task based fMRI [15,16]. However, post processing conjunction data can be time consuming and requires specific software that may not be readily available outside of large academic centers with research support staff. Some studies have suggested that language dominance varies with the degree of handedness based on the Edinburgh Handedness Inventory (EHI) [17]. Studies have demonstrated that left-handedness increases the likelihood of right hemisphere language dominance, but is not a precondition or a necessary consequence of right dominance [18].

Combined task activation display (CTAD) is a method of displaying several related BOLD tasks (in this case language) onto a structural series rather than the conventional manner of a single task at a time [19]. CTAD can highlight common areas of overlapping language activation to better differentiate “essential” activation from noise. This can be accomplished by easily manipulating various post-processing software (usually on a separate workstation) to display all similar paradigms simultaneously on a single structural MRI series. Regions of overlapping signal will therefore help to localize true activation (e.g. if sentence completion, object naming, and word generation paradigms all overlap in the left inferior frontal gyrus, this would increase confidence in localizing left sided Broca's area). Conventionally, it can be overwhelming for the novice fMRI user to synthesize and interpret data from many language paradigms in addition to the complexity of both structural and functional data and adjustable statistical thresholds during post processing. There is not an established best method in the literature that shows how to teach fMRI interpretation for the new trainee. The purpose of our study is to compare the use of CTAD and conventional display of fMRI language paradigms as an effective method to teach fMRI to the introductory learner. We propose that CTAD will facilitate more accurate interpretation of fMRI, increase trainee confidence, and decrease interpretation time, making CTAD a superior method.

2. Materials and methods

Following IRB approval, a retrospective review identified approximately 61 patients who underwent fMRI for pre-surgical evaluation of epilepsy from July 2017 to March 2018. The inclusion criteria included individuals with epilepsy who underwent diagnostic fMRI within this time period, had representation of at least three language paradigms (e.g. verb generation, word generation, sentence completion, object naming), and received clinical testing for handedness. Individuals with prior intracranial surgery, intracranial mass lesions, examinations with two or fewer language paradigms, and non-diagnostic examinations were excluded from the study. A total of 43 unique cases were identified based on the inclusion and exclusion criteria. All fMRI cases were acquired via one of two 3.0-Tesla scanners (Magnetom Skyra and TIM Trio, Siemens Healthineers, Erlangen, Germany) for evaluation of language lateralization in pre-surgical epilepsy patients. Functional MRI post processing was performed using DynaSuite (Invivo, Gainesville, FL) with a statistical threshold of $p < 0.001$ for all language

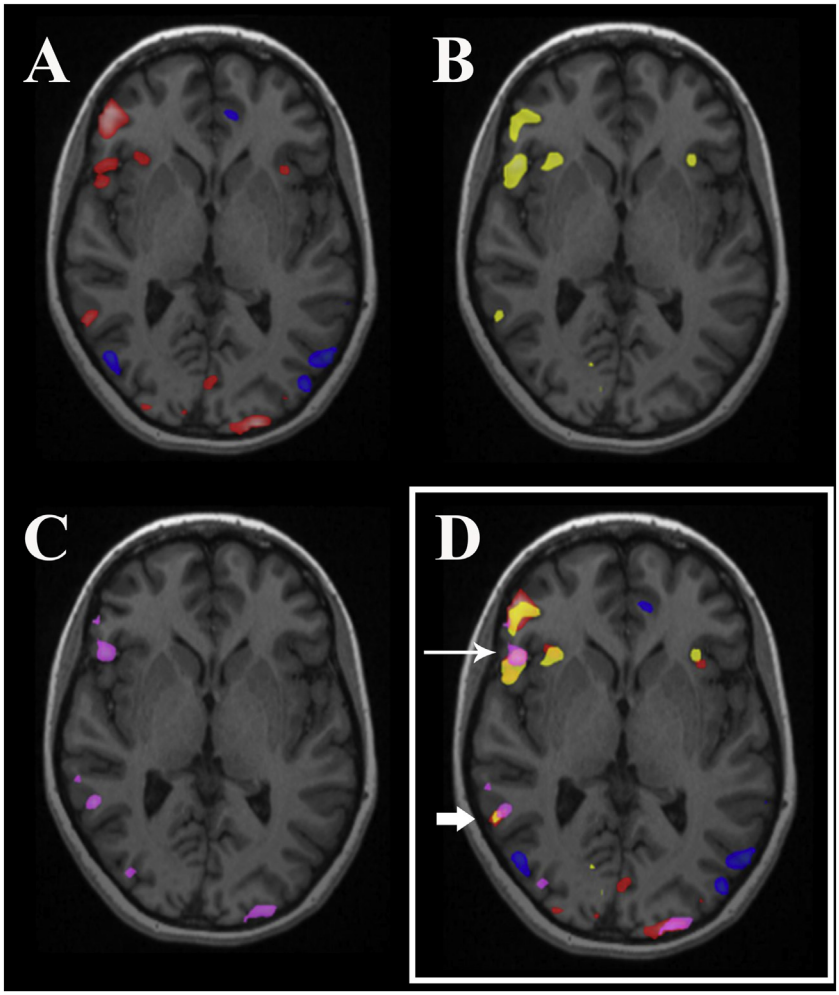

Fig. 2. Right language dominant. A–C: Conventional method of interpretation. A: Sentence completion (red is positive signal, blue is negative signal). B: Word generation (yellow is positive signal). C: Verb generation (purple is positive signal). D: Combined task activation with overlay of the above paradigms demonstrating overlap of paradigms in the right Broca's area (thin arrow), and right Wernicke's area (thick arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

paradigms. As there is no concrete agreement in the literature on the best method to determine this statistical threshold, the value above is based on the best representative threshold for our study between the activation starting point and plateau for the laterality index function [14].

LI was calculated for all cases using the verb generation task on a DynaSuite workstation. Regions of interest were manually drawn within the bilateral cerebral hemispheres on an overlay of volumetric T1-weighted images. The regions of interest were drawn to include the inferior frontal gyrus, temporoparietal cortex and superior temporal gyrus similar to previously published works [20–23]. The number of active voxels within each region of interest was calculated using the equation: $LI = [V_L - V_R]/[V_L + V_R] \times 100$; where V_L and V_R indicate the number of active voxels in the left and right cerebral hemispheres, respectively. The laterality index ranged from +100 (completely lateralized to the left) to −100 (completely lateralized to be right). Atypical language dominance was considered to range from a laterality index of −20 to +20 [24].

Eight (four PGY-3, one PGY-4, and three PGY-6) trainees, without prior exposure to fMRI, were asked to evaluate language lateralization based on activation of Wernicke's area (WA), Broca's area (BA), and the pre-supplementary motor area (pre-SMA). All trainees had prior exposure to brain MRI, but not functional MRI. Prior to trainee interpretation of cases, a 15-minute training session was conducted in which a single case was used an example to describe the expected anatomic locations of BA (operculum of the inferior frontal gyrus), WA (posterior superior temporal gyrus), and the pre-SMA (posterior superior frontal gyrus). Four trainees were randomly chosen to interpret images using the conventional approach (analyzing each language paradigm separately) and the other four were chosen to interpret images using CTAD (overlaying the multiple language paradigms within a single series). Following a 6-week washout period, the same eight trainees underwent another 15-minute training session and were asked to interpret the cases using the opposite interpretation approach. Ten repeat cases were randomly included for evaluation of internal consistency, hence, a total of 53 cases were interpreted by the trainees for each display method. Trainees were blinded to all clinical and patient data, including radiology reports.

Trainees were asked to determine language laterality as being either left dominant (Fig. 1), right dominant (Fig. 2), bilateral left > right (Fig. 3), or bilateral right > left. Trainee confidence in assessing language dominance was graded on a Likert scale (1 to 5 with 5 being very confident) for each case using the different interpretation approaches. The Wilcoxon signed rank test was used to assess the mean differences between nonparametric matched samples. The McNemar's chi-square test was used to assess statistical significance between paired nominal data. A p-value < 0.05 was deemed statistically significant. A short post-interpretation survey was also conducted (Supplemental Table 1).

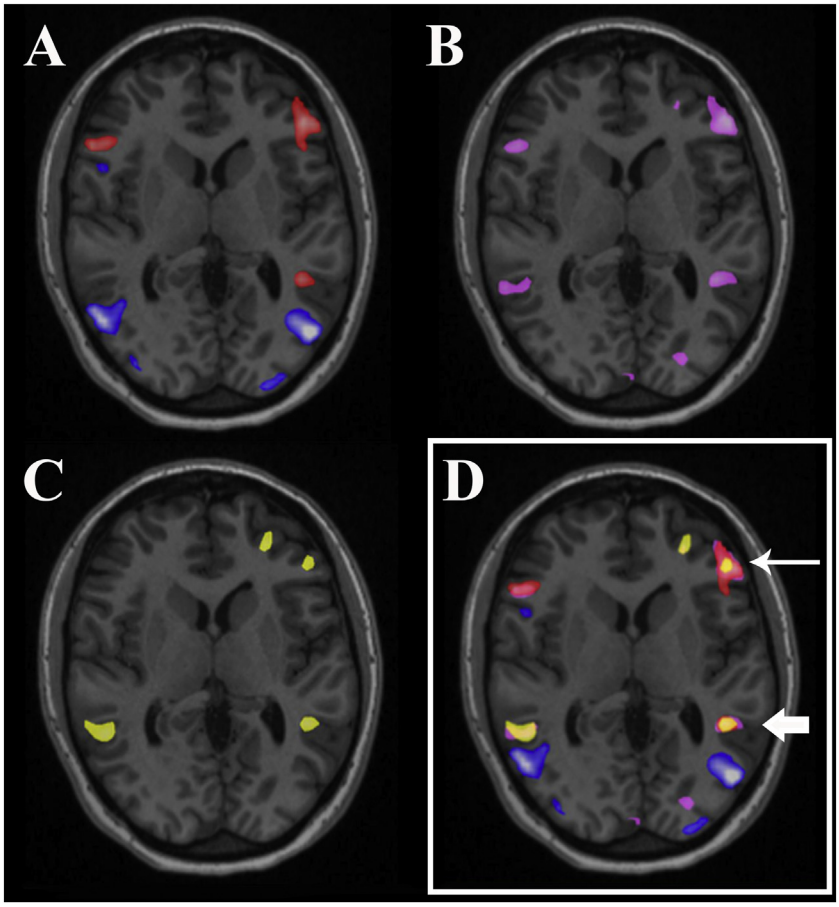

Fig. 3. Bilateral left > right language. A–C: Conventional method of interpretation. A: Sentence completion (red is positive signal, blue is negative signal). B: Word generation (purple is positive signal). C: Verb generation (yellow is positive signal). D: Combined task activation with overlay of the above paradigms demonstrating overlap of paradigms in the left > right Broca's area (thin arrow), and left > right Wernicke's area (thick arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Patient demographics. Language dominance was determined by a combination of EHI, LI, and consensus read among 2 neuroradiologists.

N	Sex	Age	Handedness	Edinburgh Handedness Index	Laterality index	Language dominance
43 cases + (10 repeat cases)	34 F	36.2 ± 11.2	29 Right	Mean: +73.8	Mean: +39.2	29 Left
	9 M		3 Ambidextrous	Min: −68	Min: −100	5 Left > right
			11 Left	Max: +100	Max: +100	7 Right
						2 Right > left

Gold standard language lateralization was determined by the consensus read of two fMRI-trained CAQ certified neuroradiologists, using the conventional and combined task activation methods, each with 4 years of fMRI experience. The calculated LI and EHI scores were used as supplemental references. Correlation with WADA testing was not performed, as this test is not routinely done at our institution and was only done in 2 of our subjects.

3. Results

A total of 53 fMRI cases were interpreted by eight trainees for each the conventional and CTAD methods. A summary of their demographic data can be found in Table 1. Cases included 43 unique patients and 10 repeat cases that were implemented for assessment of intra-reader variability. The attending consensus read identified 29 left language dominant, 7 right language dominant, 5 bilateral left > right, and 2 bilateral right > left patients. The EHI score yielded 29 right-handed patients, 11 left-handed patients, and 3 ambidextrous patients with a mean EHI of +73.8. The LI was calculated for all patients yielding a mean index of +39.2 (min: −100 to max: +100). The laterality index correlated well with the attending consensus read with only six discrepancies out of 43 cases.

Interpretation accuracy was assessed for the conventional vs CTAD methods, respectively (Fig. 4): mean accuracy: 70.9% vs 85.4%, $p < 0.01$, trainee A: 83.7% vs 88.4%, $p = 0.53$; trainee B: 58.1% vs 79.1%, $p = 0.04$; trainee C: 81.4% vs 88.4%, $p = 0.37$; trainee D: 72.1% vs 88.4%, $p = 0.02$; trainee E: 51.2% vs 76.7%, $p = 0.01$; trainee F: 72.1% vs 90.7%, $p = 0.01$; trainee G: 79.1% vs 86.0%, $p = 0.26$; trainee H: 69.8% vs 86.0%, $p = 0.02$). Increased confidence was seen with the CTAD method (Table 2: trainee A: 3.3 vs 4.3, $p < 0.001$; trainee B: 3.5 vs 4.3, $p < 0.001$; trainee C: 4.0 vs 4.5, $p = 0.022$; trainee D: 3.2 vs 3.9, $p < 0.001$; trainee E: 3.6 vs 4.1, $p = 0.019$; trainee F: 3.9 vs 4.5, $p < 0.001$; trainee G: 4.0 vs 4.4, $p = 0.022$; trainee H: 3.4 vs 4.6, $p < 0.001$). When using the CTAD method, trainees demonstrated a statistically significant increased confidence of determining language dominance with a mean confidence of 4.3 vs 3.6 in the conventional approach, $p < 0.001$. The mean accuracy was also assessed for trainees who interpreted fMRI language dominance using the CTAD first (Group 1: $p = 0.06$) to those who interpreted language dominance using the conventional method first

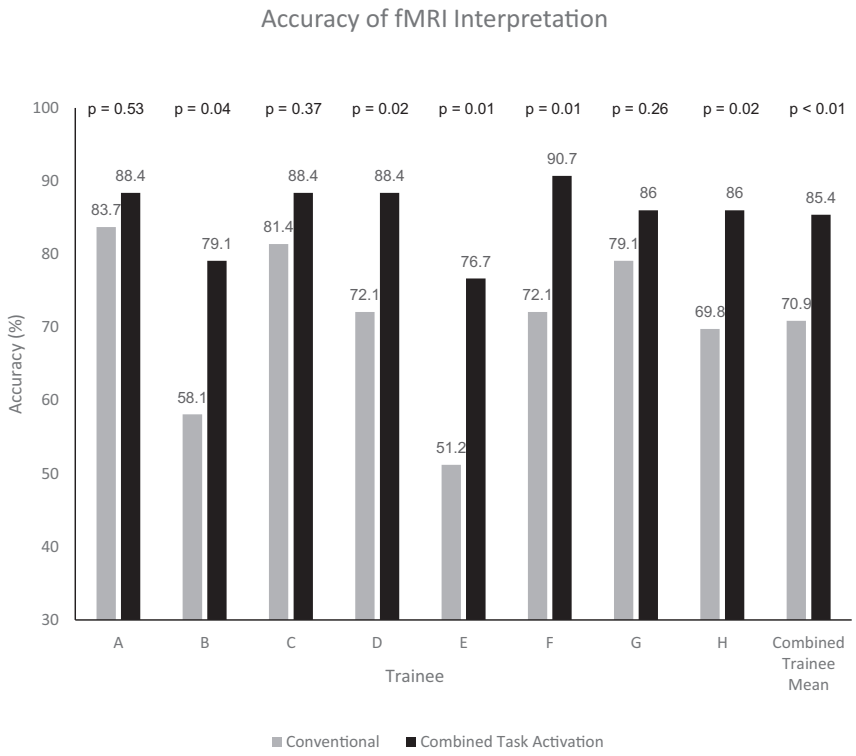

Fig. 4. Trainee interpretation accuracy of conventional versus combined task activation methods. p-Values compare difference between both methods and $p < 0.05$ are statistically significant. The combined task activation method was superior for all trainees.

Table 2
Statistically increased trainee confidence when interpreting language dominance via the combined task activation display method ($p < 0.05$ is statistically significant).

	Conventional (Mean confidence)	Combined task activation (Mean confidence)	p-Value
Trainee A	3.3	4.3	< 0.001
Trainee B	3.5	4.3	< 0.001
Trainee C	4.0	4.5	0.022
Trainee D	3.2	3.9	< 0.001
Trainee E	3.6	4.1	0.019
Trainee F	3.9	4.5	< 0.001
Trainee G	4.0	4.4	0.022
Trainee H	3.4	4.6	< 0.001
Combined trainee mean	3.6	4.3	< 0.001

(Group 2: $p < 0.01$; Fig. 5).

Six out of eight trainees demonstrated less intra-reader variability using the combined task activation display (Supplemental Table 2). Trainees C and F demonstrated a similar degree of variability with both methods (kappa scores, trainee A: 0.836 vs 1.00; trainee B: 0.697 vs 1.00; trainee C: 0.836 vs 0.836; trainee D: 0.836 vs 1.00; trainee E: 0.697 vs 0.836; trainee F: 1.00 vs 1.00; trainee G: 0.836 vs 1.00; trainee H: 0.836 vs 1.00). All trainees demonstrated a more rapid time of interpretation using the combined task activation display with a time difference of 33 min for trainee A; 20 min for trainee B; 15 min for trainee C; 41 min for trainee D; 41 min for trainee E; 20 min for trainee F; 25 min for trainee G; and 35 min for trainee H (Table 3). Overall, an average of 29 min was saved interpreting language dominance with the CTAD method.

All trainees were new to fMRI interpretation, and based on a free response posttest survey, the trainees reported preference for the CTAD method over conventional display. Trainees indicated the conventional approach required 1) interpreting more images to arrive at a conclusion, 2) was more difficult to interpret each language paradigm independently as this required constant comparison to other paradigms to arrive at the side of language dominance, 3) felt more time consuming, 4) was sometimes difficult to distinguish true signal from noise, and 5) sometimes left them insecure with the side of language dominance.

4. Discussion

For new learners, interpreting fMRI can be a challenging task, particularly when trying to determine language dominance. We found that using CTAD increased trainee confidence, overall accuracy, reduced time to interpretation and intra-reader variability. We noted that the four trainees who used the CTAD method as their initial session still had higher accuracy with CTAD than conventional display, and the difference in 3 out of the 4 trainees was smaller than the other four trainees who completed the sessions in the reverse order. Three out of the four trainees who used CTAD initially did not individually reach statistical significance. One possible explanation is that by beginning with the CTAD, trainees A, C, and G may have gained fMRI interpretation skills that translated to interpreting conventional display. The fact that the vice versa was not found hints at the value of using CTAD as a teaching tool.

The CTAD method was also determined to be a more efficient method of interpretation for new learners as time to interpretation was improved. Trainees completed interpreting 53 cases with a mean time of 90 min for the conventional method and 63 min with CTAD. These savings in time can be used to review relevant functional neuroanatomy and MRI physics at the workstation, promote discussion, or review additional cases. In addition, intra-reader variability was decreased for six out of eight trainees with CTAD and unchanged for two trainees. The majority of trainees were found to have incorrectly interpreted one particular case. Upon review of this case, it was noted that significant noise in both cerebral hemispheres probably lead to most trainees to indicate an atypical language dominance, when this patient had left

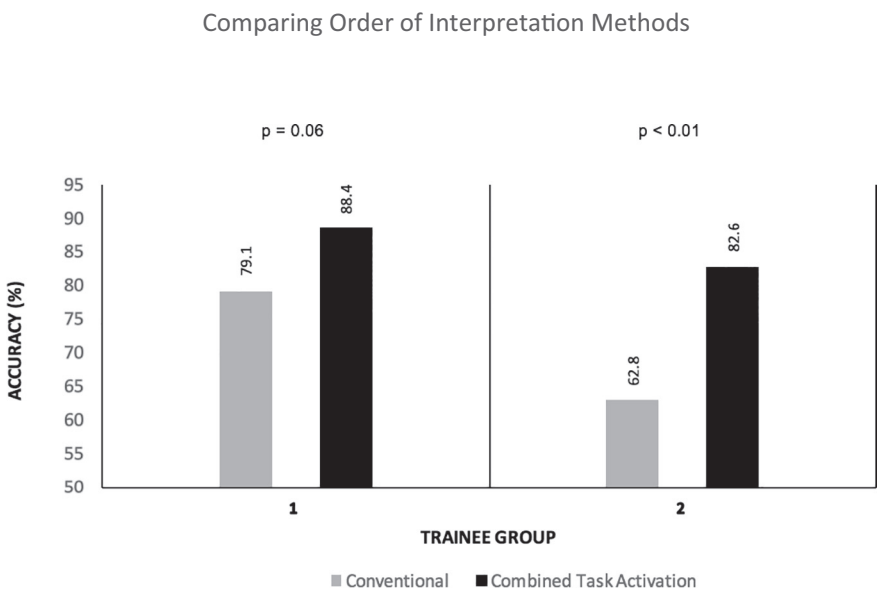

Fig. 5. Comparison of trainees who interpreted fMRI first using the CTAD method (Group 1) vs. trainees who interpreted fMRI first using the conventional method (Group 2). Mean confidence was also assessed (not shown above) with Group 1 demonstrating mean confidence of 3.8 vs. 4.4 (conventional vs CTAD) with $p = 0.01$. Group 2 demonstrated a mean confidence of 3.4 vs. 4.2 (conventional vs. CTAD) with $p = 0.02$. $p < 0.05$ are statistically significant.

Table 3
Decreased time of trainee interpretation with the combined task activation method.

	Conventional (min)	Combined task activation (min)	Time difference (min)
Trainee A	92	59	33
Trainee B	77	57	20
Trainee C	82	67	15
Trainee D	109	68	41
Trainee E	78	37	41
Trainee F	70	50	20
Trainee G	77	52	25
Trainee H	66	31	35
Combined trainee mean	81	53	29

language dominance. Nonetheless, two trainees correctly determined the left language dominance using the CTAD method.

Following fMRI interpretation, trainees were given a brief posttest questionnaire containing four free response questions (Supplemental Table 1). Trainees expressed strong preference for interpretation using the CTAD method over the conventional method. Trainees reported that determining language laterality using CTAD was subjectively easier given the overlay of multiple paradigms, and that it provided for a quicker, more confident interpretation. There was a consensus that the conventional method was more difficult to interpret, became tedious as trainees felt they were constantly trying to "overlay" the separate paradigms in their minds in order to arrive at a side of language dominance, resulting in uncertainty of language dominance. We believe that the perceived ease of using CTAD makes it a more approachable method to introduce fMRI interpretation to trainees. Early exposure to fMRI through this method may simplify a seemingly "advanced" and "complex" technique and promote increased participation and interest in functional neuroimaging. This is important as fMRI is increasingly becoming the standard of care for neurosurgical planning and there is growing demand for radiologists competent in fMRI interpretation.

CTAD is often confused with conjunctional analysis. Conjunction analysis is a similar method of interpretation that is focused on identifying common areas of neural activation of different tasks that share common neural processing [25]. By focusing on shared activation areas, conjunction analysis allows for identification of brain regions that are involved in more generic functions by excluding non-overlapping regions that are more task specific [25]. CTAD is a method for highlighting regions of brain that are co-activated in multiple tasks by displaying activation maps in combination. Although the concept of CTAD is similar to conjunction analysis, there are technical differences. Conjunction analysis models each task individually which is then contrasted to obtain the "main effect." In CTAD, only the "main effect" is constructed making analysis less sophisticated [15]. Moreover, in conjunction analysis, interaction effects are removed whereas CTAD relies on differential sensitivity for all tasks [15]. The higher order processing required for conjunction analysis might limit its availability in teaching centers without dedicated support staff. Ramsey et al. demonstrated that CTAD provides excellent detection of brain activity and better LI with less variability across different tasks compared to analysis of individual task [15]. It also appears to correlate well with intraoperative electro-cortical stimulation mapping [26].

We acknowledge several limitations with our study. As Wada testing is not routinely performed at our institution, determination of the gold-standard for language laterality was based on the consensus interpretation of language fMRI by two experienced neuroradiologists with supplementation of the LI and EHI score. However, we believe this is a reasonable approach given published literature supporting high correlation between fMRI and Wada, and that the specific focus of this work is on trainee education for fMRI interpretation and not on assessing the accuracy of language fMRI. Future studies correlating post-surgical outcomes to language lateralization determined by the CTAD method will be needed to address its diagnostic accuracy and clinical utility. Another limitation involves the absence of concordance data between neuroradiologists (Gold Standard) and calculating the LI for our subjects. A fixed statistical threshold was used across all studies for consistency, which may or may not be optimal for each individual case [27,28]. Furthermore, recall may affect our results given that each trainee interpreted the same cases using both methods. We tried to mitigate this by anonymizing the cases, using a 6-week washout period between sessions, and randomizing the order of the methods used. However, the effect of recall or learning curve may not be completely eliminated. Our fMRI educational trial was performed at a single academic institution. The results may be different if expanded to other academic radiology centers (since the basic neuroradiology training may be different) and may not be generalizable to other conditions for which fMRI is obtained.

5. Conclusion

Combined task activation display of BOLD fMRI language activation increased trainee accuracy, increased confidence, decreased interpretation time, and for most trainees, decreased intra-reader variability when determining language laterality. We believe CTAD is an effective method to teach fMRI to introductory trainees. We hope to implement such training approaches at our institution and aim to increase trainee interest in fMRI.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinimag.2019.03.015.

Financial disclosure

None.

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