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ABSTRACT

BACKGROUND AND PURPOSE: Dysphagia is a common deficit after a stroke and is associated with serious complications. It is not yet fully clear which brain regions are directly related to swallowing. Previous lesion symptom mapping studies may have overlooked structural disconnections that could be responsible for poststroke dysphagia. Here, we aimed to predict and explain the relationship between poststroke dysphagia and the topologic distribution of structural disconnection via a multivariate predictive framework.

MATERIALS AND METHODS: We enrolled first-ever ischemic stroke patients classified as full per-oral nutrition (71 patients) and nonoral nutrition necessary (43 patients). After propensity score matching, 43 patients for each group were enrolled (full per-oral nutrition group with 17 women, 68 ± 15 years; nonoral nutrition necessary group with 13 women, 75 ± 11 years). The structural disconnectome was estimated by using the lesion segmented from acute phase diffusion-weighted images. The prediction of poststroke dysphagia by using the structural disconnectome and demographics was performed in a leave-one-out manner.

RESULTS: Using both direct and indirect disconnection matrices of the motor network, the disconnectome-based prediction model could predict poststroke dysphagia above the level of chance (accuracy = 68.6%, permutation $P = .001$). When combined with demographic data, the classification accuracy reached 72.1%. The edges connecting the right insula and left motor strip were the most informative in prediction.

CONCLUSIONS: Poststroke dysphagia could be predicted by using the structural disconnectome derived from acute phase diffusion-weighted images. Specifically, the direct and indirect disconnection within the motor network was the most informative in predicting poststroke dysphagia.

ABBREVIATIONS: CPM = connectome-based predictive modeling; DOSS = Dysphagia Outcome and Severity Scale; FA = fractional anisotropy; HCP = Human Connectome Project; LOOCV = leave-one subject-out cross-validation; MNI = Montreal Neurological Institute; SSPL = shortest structural path length; SVM = support vector machine; VFSS = videofluoroscopic swallowing study

Oropharyngeal dysphagia is a frequent symptom in stroke patients. More than 50% of patients with stroke have had swallowing difficulty.[1] Poststroke dysphagia is associated with complications, such as malnutrition, dehydration, or aspiration pneumonia. In particular, aspiration pneumonia can cause longer hospitalization, higher disability, or even death,[2] making early diagnosis of poststroke dysphagia critical to prevent these worse outcomes.

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From the Department of Physical and Rehabilitation Medicine (K.J.Y., C.-H.P.), Medical Research Institute (K.J.Y., C.-H.P.), and Department of Radiology (M.-H.R., M.K.), Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea.

K.J. Yoon and C.-H. Park contributed equally to this work.

Please address correspondence to Minchul Kim, MD, PhD, Department of Radiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea, 03181; e-mail: minchulusa@gmail.com

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Poststroke dysphagia is diagnosed with various instrumental methods, such as videofluoroscopic swallowing study (VFSS) or fiberoptic endoscopic evaluation of swallowing.[3] However, these tests can be performed only for patients who have sitting balance or good cooperation, which makes it difficult to effect early detection of poststroke dysphagia. The bedside swallowing test can be applied for those who cannot comply with VFSS for fiberoptic endoscopic evaluation of swallowing but still have the risk of aspiration pneumonia. Very early detection of poststroke dysphagia to avoid complications is essential and beneficial for the management of acute stroke since dysphagia improves significantly during the early days; after 2 weeks, most patients swallow safely.[3] However, recent guidelines for dysphagia screening strategies for acute ischemic stroke have not yet provided reliable evidence,[4] with one recent study reporting several patient characteristics predictive of poststroke dysphagia.[5] In addition, the current body of evidence does not allow an exact relationship between acute focal brain lesions and related poststroke dysphagia, with some

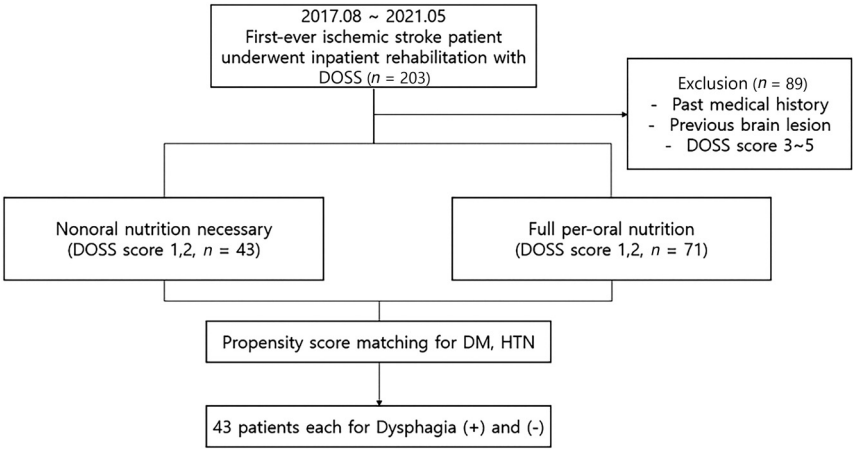

FIG 1. Flow chart of participants with poststroke dysphagia recruited for disconnectome analysis.

recent studies suggesting that white matter tract rather than focal cortical lesion involvement is crucial.[6,7]

Previous voxel-based lesion symptom mapping studies reported poststroke dysphagia to be caused by distributed lesions in the swallowing network comprising the primary sensorimotor cortex, frontal operculum, insula, and associated white matter tracts.[8,9] Recent data indicate that white matter disconnection might be a better predictor of brain dysfunction and recovery than the location of the lesion itself.[10] Thus, we hypothesized that, rather than a focal lesion, a group of brain areas that is interconnected by the structural brain network is conjointly responsible for poststroke dysphagia. To investigate this possibility, we adapted a multivariate connectome-based symptom mapping approach combined with indirect estimation of structural disconnection to detect brain networks supporting swallowing.[11,12] Multivariate predictive modeling aims to develop brain models that are tightly coupled with target outcomes by using pattern recognition techniques (or "machine learning").[13] In contrast to the mass-univariate approach, which focuses on permitting the inference that disconnection C is responsible, conditional on symptom S (ie, poststroke dysphagia), and assesses the probability P(C|S), a new trend of predictive modeling has recently emerged to address the reverse inference that symptom S must have occurred given disconnection C being related to P(S|C).[13] Further, the indirect estimation of structural disconnection is a recently developed method that combines a patient's structural lesion information and normative connectome data to estimate lesion-induced structural disconnection. This method involves embedding the patient's lesion mask into normative connectome data obtained from healthy individuals to model the expected impact of a lesion on the typical white matter connectome, namely, the disconnectome (ie, the disruption of the network architecture of the brain) after a brain lesion.[14]

In this study, we aimed to achieve 2 objectives: 1) to develop an early prediction model of dysphagia in patients with ischemic stroke with clinically plausible acute phase diffusion-weighted brain MRI; and 2) to disclose the pattern of network disconnections responsible for poststroke dysphagia, thereby deepening our understanding of pathophysiology.

MATERIALS AND METHODS

Patient Selection

We retrospectively reviewed the medical records of patients with ischemic stroke who underwent inpatient rehabilitation between August 2017 and May 2021. The inclusion criteria were 1) first-ever stroke confirmed by DWI within 7 days of symptom onset (because apparent diffusion coefficient maps may depict persistent darkening for ~7–10 days)[15] and 2) Dysphagia Outcome and Severity Scale (DOSS) evaluation by using VFSS performed within 1 month after stroke onset. The exclusion criteria were as follows: 1) prior imaging evidence of stroke and 2) other neurologic disorders causing oropharyngeal dysphagia, such as parkinsonism and dementia. The Institutional Review Board of Kangbuk Samsung Hospital approved the study protocols, which were in accordance with the Declaration of Helsinki, and informed consent was waived for retrospective study based on medical records. Among 180 patients with stroke with available DOSS scores, we enrolled those that received full per-oral nutrition (71 patients with DOSS scores 6 and 7) and others that received nonoral nutrition (43 patients with DOSS scores 1 and 2), based on DOSS scores.[16]

Because diabetes mellitus and hypertension were reported to be associated with dysphagia in ischemic patients,[17] we used propensity score matching analysis to minimize the effects of these confounding factors.[18] Propensity scores were matched by selecting the cases in the 2 groups, and the variables listed above were used as matching parameters by using the MatchIt R package (R Core Team, R Foundation for Statistical Computing).[19,20] Figure 1 shows a flowchart of the participants included.

Image Acquisition

MRI data were acquired by using 1.5T and 3T scanners from Philips Healthcare (Intera, Ingenia, and Achieva), each with a standard head coil. The acute stroke MRI protocol for each patient included 6-direction DWI and FLAIR sequences. Fractional anisotropy (FA) and ADC maps were automatically created from DWI scans by using built-in software. DWI was acquired with a single-shot spin–echo echo-planar imaging sequence in alignment with the horizontal plane with the following parameters: diffusion-sensitizing gradients applied along 6 noncolinear directions with a b-value of 1000 seconds/mm^2, together with acquisition without diffusion weighting ($b = 0$ s/mm^2); section thickness, 4 mm with no gap; repetition time, 5300 ms; echo time, 74 ms; number of averages, 2; flip angle, 90°; matrix size, 128 × 128.

Lesion Segmentation and Normalization

A schematic diagram of the procedure for lesion segmentation and normalization is shown in Figure 2*A*. The infarct cores were automatically segmented by using ADC maps and DWI by

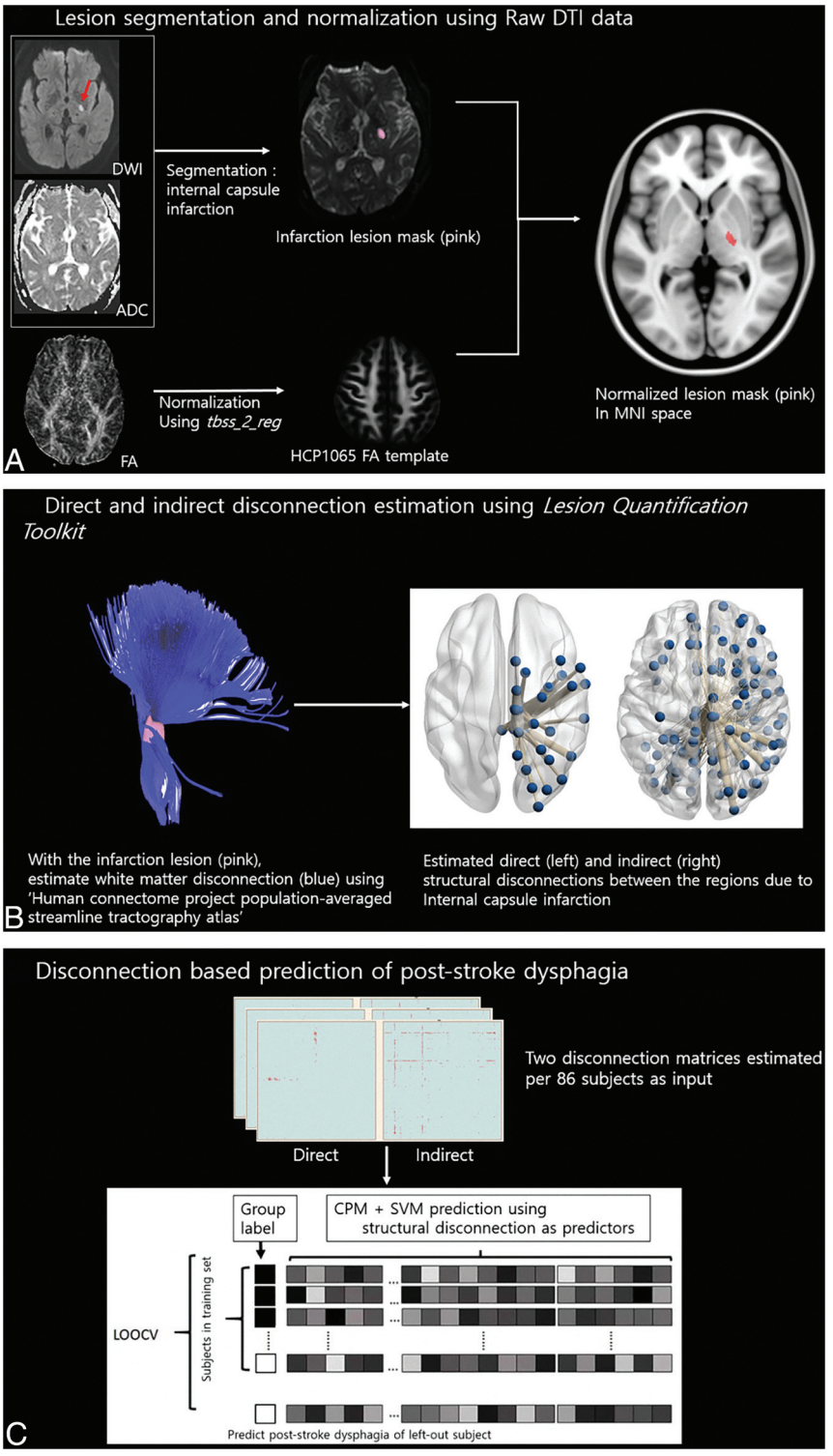

FIG 2. Schematic of using a CPM-SVM to predict poststroke dysphagia from the structural disconnectome. *A*, Processing scheme of a patient with internal capsule posterior limb infarction (*red arrow*). We segmented the infarct core using ADC maps and DWI. To normalize the lesion mask to the MNI space, we used warping results derived from the patient's FA map normalized to the FA template. In the end, we get the segmented lesion normalized in MNI space (pink in the image on the right). *B*, The lesion Quantification Toolkit uses the lesion segmentation in *A* to estimate the structural disconnection using the HCP-842 population-averaged streamline tractography atlas. The blue tractography on the left is the tracts disconnected by the internal capsule posterior limb infarction, and the brain plotted on the right shows the distribution of direct and indirect disconnection due to infarction. The patient had poststroke dysphagia probably owing to disruption in the motor network. *C*, Using the disconnection derived from *B* as prediction features, we adopted the CPM-SVM model and LOOCV to predict poststroke dysphagia.

applying normalized absolute thresholding[21] and minimally corrected by a board-certified neuroradiologist (M.K., code available at https://github.com/HyunnaLee/StrokeOnset/tree/master/1_InfarctSegmentation). We defined the infarct core as a lesion because the infarct core is considered irreversible tissue damage that cannot be recovered with treatment.[22] Three patients had short-term follow-up imaging due to hyperacute infarction, and we used the image with a larger extent of infarct core.

After lesion segmentation, we performed FA map normalization to the Montreal Neurological Institute (MNI) template brain image by using the tract-based spatial statistics commands ('tbss_1_preproc' and 'tbss_2_reg') in the FMRIB Software Library toolbox (http://www.fmrib.ox.ac.uk/fsl), involving an established, carefully tuned nonlinear registration of FA maps.[23] Then, the infarct core masks in the DWI space were transformed to the MNI space by using the 'applywarp' command, which is also a part of the FMRIB Software Library toolbox.[24]

Estimating the Structural Disconnectome Using the Lesion Quantification Toolkit

A schematic diagram of the procedure for acquiring the disconnectome is shown in Figure 2*B*. The Lesion Quantification Toolkit, a publicly available MATLAB software package for quantifying the structural impacts of focal brain lesions implemented in MATLAB 2020b (MathWorks), was used to estimate the white matter disconnections.[25] In brief, the toolkit uses atlas-based approaches to estimate parcel-wise disconnection matrices. To estimate the degree of disconnection by using the Lesion Quantification Toolkit, 2 inputs are needed: 1) a binary lesion segmentation that is registered to the MNI template (ie, the infarction core in our case); and 2) a regional gray matter parcellation (ie, atlas) that is also registered to the MNI brain template space. We used the Shen 268-node atlas (available at https://www.nitrc.org/frs/?group_id=51), which has 8 specific functional networks (for details, see Online Supplemental Data), to test the hypothesis that certain brain

Clinical characteristics of the study population

	Full Per-Oral Nutrition (n = 43, 17 Women)	Nonoral Nutrition Necessary (n = 43, 13 Women)	P Value
Age (yr)	68.83 ± 15.69	75.09 ± 11.38	$t = 2.264$, $P = .029$[a]
HTN	35	34	$\chi^2 = 0.073$, $P = .786$
DM	15	19	$\chi^2 = 0.778$, $P = .377$
Onset to VFSS interval (days)	11.67 ± 7.50	12.24 ± 7.64	$t = 0.327$, $P = .745$
MRI scanner	Intera = 35 Ingenia = 5 Achieva = 3	Intera = 37 Ingenia = 4 Achieva = 2	$\chi^2 = 0.367$, $P = .832$

Note:—DM indicates diabetes mellitus; HTN, hypertension.
[a] $P < .05$.

networks contribute more to poststroke dysphagia than others.[26] The toolkit outputs several estimations based on the provided lesion and parcellation, including parcel-wise disconnection matrices and parcel-wise increases in shortest structural path length (SSPL) matrices (Fig 2*B*, brain images on the right). Parcel-wise disconnection matrices are estimated by using the Human Connectome Project (HCP)-842 population-averaged streamline tractography atlas.[27,28] First, an atlas structural connectivity matrix is created by using the HCP-842 streamline tractography atlas and the provided Shen atlas. The structural connections between a parcel pair are defined as the number of atlas streamlines that bilaterally terminate within both parcels. Then, the lesion is embedded into the HCP-842 streamline tractography atlas, and the atlas is filtered to retain only the subset of streamlines whose trajectories intersect the volume occupied by the lesion (ie, disconnected streamlines, Fig 2*B*, tract image on the left) and terminate bilaterally within a parcel pair, creating a disconnection matrix. Finally, this raw disconnection matrix is converted to a "percent disconnection severity matrix" relative to the atlas structural connectivity matrix. The values for each cell (ie, parcel pair) in the final percent disconnection severity matrix correspond to the estimated disconnection severities for each pair of parcels.[25] Parcel-wise SSPL increases are also computed according to the same procedure used in a previous study.[28] The rationale for obtaining the matrix is that the white matter disconnections caused by focal brain lesions can disrupt communication between brain regions that are "indirectly" connected via a series of intermediary regions.[29]

Disconnectome-Based Predictive Modeling

A schematic diagram of the procedure for predictive modeling is shown in Figure 2*C*. The code and data for replicating the predictive model are available at https://osf.io/u4m5j/. To predict poststroke dysphagia by using structural disconnection, we used connectome-based predictive modeling (CPM), a data-driven protocol for developing predictive models of brain-behavior relationships.[12] We modified the CPM approach by replacing its core learning algorithm with a support vector machine (SVM).[30]

First, we separated the subjects into the 85-person training set and 1 test set in each iteration, implementing a leave-one-subject-out cross-validation (LOOCV) process. LOOCV was performed to protect against overfitting.[12] Then, across all subjects in the training set, each edge in the disconnection matrices and SSPL increase matrices was correlated to the subjects' group label (ie, whether 1 subject had poststroke dysphagia or not) as behavioral data by using the Spearman correlation.[30] Those edges that significantly correlated (below the threshold value of 0.05, which means severe disconnection in patients with severe dysphagia) were selected. Next, for each subject, the selected edges were summed into 2 predictive variables (ie, disconnection matrix and SSPL increase matrix), and 3 SVM models (see Models 1–3 below) were trained and tested[31]:

- Model 1, Predicted group label = disconnection matrix
- Model 2, Predicted group label = SSPL increase matrix
- Model 3, Predicted group label = disconnection matrix + SSPL increase matrix

From the perspective of functional integration and segregation, whole-brain and 8 functional system analyses were conducted separately. Model performance (ie, correspondence between predicted and actual values) was assessed mainly by using classification accuracy, and we performed a permutation test to examine the significance of our model. For interpretation purposes, we identified those edges that appeared in every iteration of the leave-one-out process to yield "consensus edges" (edges appearing in 100% of the LOOCV iterations across all subjects).[32]

In addition, for exploratory purposes, we calculated the diagnostic performance of the combined model incorporating the disconnection and demographic variables (age, sex, and lesion volume).

RESULTS

Demographics

The characteristics of the study samples are displayed in the Table. Contingency χ^2 tests and paired t-tests were used to examine group differences in demographics across the 2 groups. The statistical analyses were conducted in MATLAB 2020b. Using propensity matching, the incidence of diabetes mellitus and hypertension between the groups showed no significant difference ($\chi^2 = 0.073$, $P = .786$ and $\chi^2 = 0.778$, $P = .377$, respectively), though the full per-oral nutrition group showed a younger age ($P = .029$). There was no significant difference between the MRI scanners used between the 2 groups ($\chi^2 = 0.367$, $P = .832$).

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Figure 3*A* summarizes the model performance of individual classification from whole-brain and network-based analyses. Notably, the best prediction model was the one that took the disconnection matrix and SSPL increase matrix of the motor

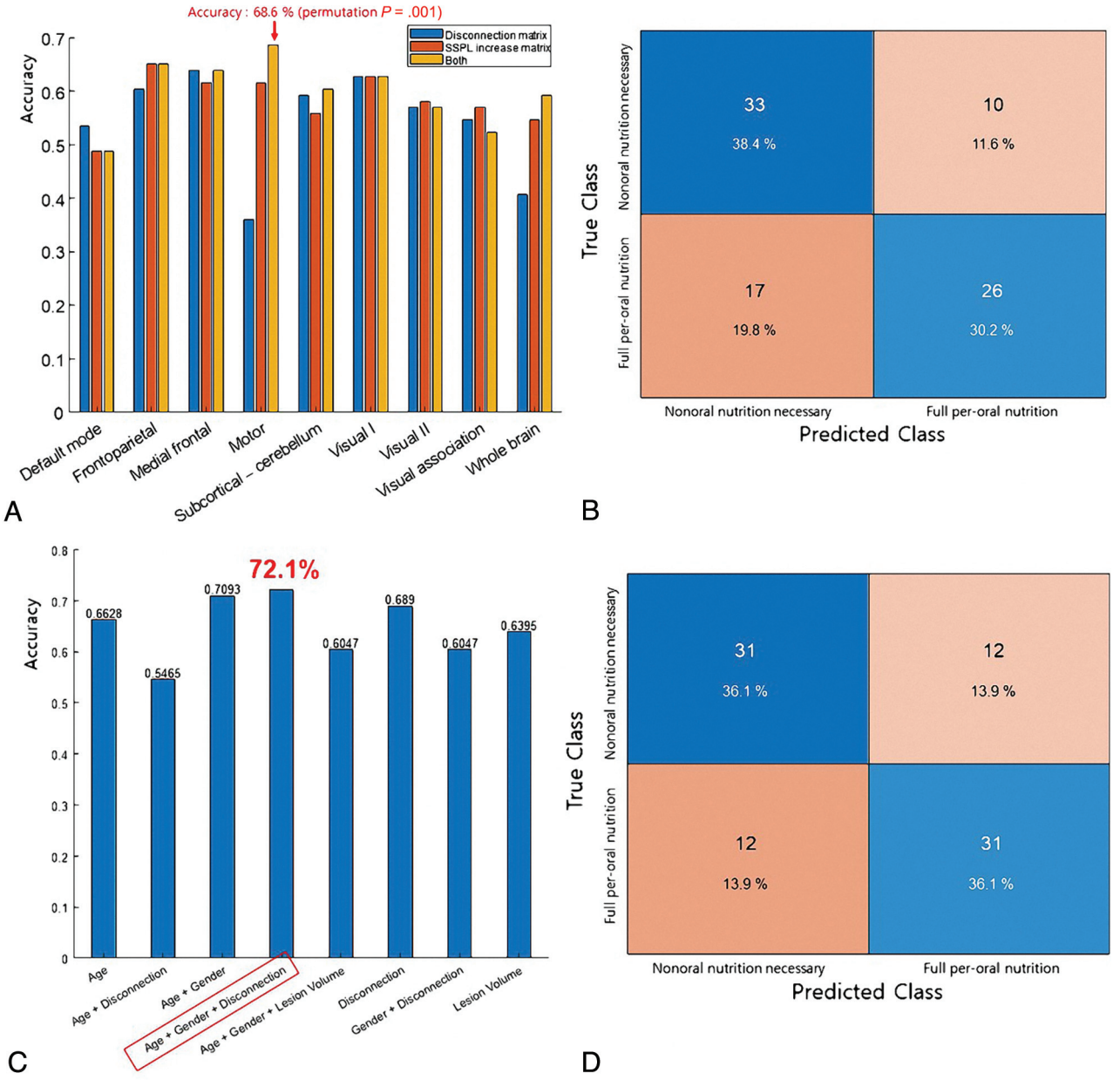

FIG 3. Leave-one-out classification result. *A*, Classification results in which, by using both the disconnection and SSPL, increased matrix of the motor network (*red arrow*) presented the highest accuracy. *B*, Confusion matrix of the motor network–based model, where the vertical axis is the true label of all patients. Blue boxes represent individuals correctly identified by the model. Orange boxes represent incorrect identification. Percentages in each box correspond to the proportions of subjects in the subgroup relative to the total subjects. *C* and *D*, Classification result when combined with demographic variables, indicating that the model, by using both disconnection and demographic features, shows the best prediction accuracy of 72.1%.

network into account (Model 3). The model accurately and relatively evenly identified individuals with dysphagia after stroke (accuracy = 68.6%, permutation testing, 1000 times, $P = .001$; sensitivity = 76.7%, specificity = 60.4%; Fig 3*B*). It is notable that disruption in the motor network contributes to the prediction of developing poststroke dysphagia. When we included the patient's demographic variables of age and sex in the prediction model, the prediction accuracy rose to 72.1% (sensitivity = 72.1%, specificity = 72.1%; Fig 3*C*-, *D*), while the demographics could substantially predict poststroke dysphagia (eg, combination of "age + sex" achieved 70.9%).

The "consensus edges" of the disconnection matrix included 40 edges in which the highest-degree node (ie, the node with the most connections) was located in the left parietal lobe. The "consensus edges" in an SSPL increase matrix included 241 edges, and the highest-degree node in the SSPL increase matrix was located in the right insula, with the left motor strip being the location of the next highest (Fig 4).

DISCUSSION

In this study, we used a multivariate CPM to predict poststroke dysphagia and identify disconnections that are predictive of

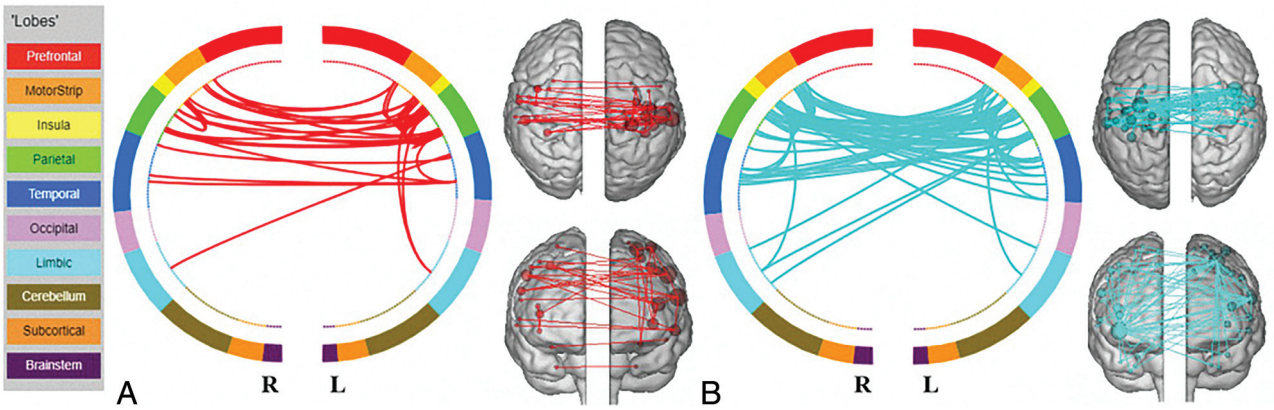

FIG 4. Spatial network anatomy of the motor network-based model. *A*, Spatial extent of the "consensus edges" from the disconnection network. In the circular plot, regions are organized according to their anatomic locations, with more anterior regions at the top and more ventral and posterior regions displayed toward the bottom. Node size in the brain represents the degree of the node (ie, the number of connections with the node). *B*, Summarization of "consensus edges" from the disconnection network. The nodes were filtered to have at least 20 edges for visualization purposes.

the disease. Across classification analyses, the motor network combining the information from both direct and indirect disconnections emerged as being the most informative in prediction.

There are 2 main advantages in our findings that we want to emphasize. First, we showed the potential of predicting poststroke dysphagia based only on clinically plausible acute-phase diffusion-weighted brain MRI. This is an advantage because no other advanced sequences, such as diffusion tractography, are needed. In addition, we conducted our study based on publicly available toolboxes, and we make our data and analysis code available to increase transparency and allow future researchers to replicate our findings (https://osf.io/u4m5j/). Clinically, our results can be utilized to predict whether a patient with stroke is at high risk of poststroke dysphagia at the time of symptom onset. If one is predicted to have a high risk of dysphagia, clinicians can postpone oral nutrition without any swallowing test, thus lowering the chance of aspiration in the acute phase.

Another important result is that the motor network emerged as being the most informative in predicting poststroke dysphagia. Figure 5 shows a representative case of infarction in the middle cerebellar peduncle without disconnection in the motor network, and the patient did not have poststroke dysphagia. This is in line with previous reports, which revealed that dysphagia secondary to stroke is associated with disruptive functional and structural integrity in the large-scale brain networks involved in motor control.[33] Specifically, the connection between the motor cortex and bulbar areas (corticobulbar tract) has been shown to be a potent neural pathway involved in swallowing, and any lesions disrupting this pathway can lead to dysphagia.[9] Several recent studies utilizing advanced neuroimaging techniques support this by emphasizing the role of motor cortex connections to the bulbar area.[34,35] In addition, our study is the first to point out that not only direct but also indirect disconnection (ie, SSPL increase) in the motor network is responsible for poststroke dysphagia. The increase in the shortest path length results in a decrease in network efficiency. It has also been reported that structural disconnections along the shortest structural paths linking indirectly connected regions represent a general mechanism of stroke-induced functional connectivity disruptions.[28] On the contrary, some other networks, such as frontoparietal, reached similar prediction accuracy (65.1%), and the direct disconnection of the motor network had poor prediction (36.0%). This result implies networks other than the motor have a role in poststroke dysphagia. Together, we suggest that not only direct disconnection within the motor but also insufficient, including decreased, functional connectivity, may underlie the occurrence of poststroke dysphagia. In addition, our exploratory analysis by using the demographic variable as an additional predictor showed increased prediction accuracy with a decreased number of false-positives (17 → 12 in Fig 3*B*, *D*), giving the potential of a prediction model by using both brain-based and clinical features, and may be promising (Fig 6).

Although the prediction accuracy (Fig 3, 72.1%) we reported may seem modest, we suggest several reasons. To our knowledge, there is one paper investigated to predict acute stage poststroke dysphagia by using only clinical variables and can be a benchmark.[5] The reported area under the receiver operating characteristic curve value was 0.86; however, this is a simple logistic regression result without cross-validation and thus cannot be directly compared with our LOOCV prediction accuracy, which provides a more conservative estimate.[12] It should also be mentioned that the combination of several demographic variables could substantially predict poststroke dysphagia. For example, "age + sex" alone had higher accuracy than the disconnection-based model (68.9%), and adding the disconnection to the "age + sex," the accuracy only increased by 1.9%. It makes the disconnection seem somewhat trivial and the disconnection-model only was not very helpful. Interestingly, age and sex are included in our result and the prediction model of Zhang et al.[5] As our study discovered that structural disconnection in the motor network has predictive information about poststroke dysphagia, future research could benefit from integrating larger demographic data.

Our study has a prominent limitation that the age was significantly younger in the full per-oral nutrition group, which may be a confounder. To see how much of the results were explained by

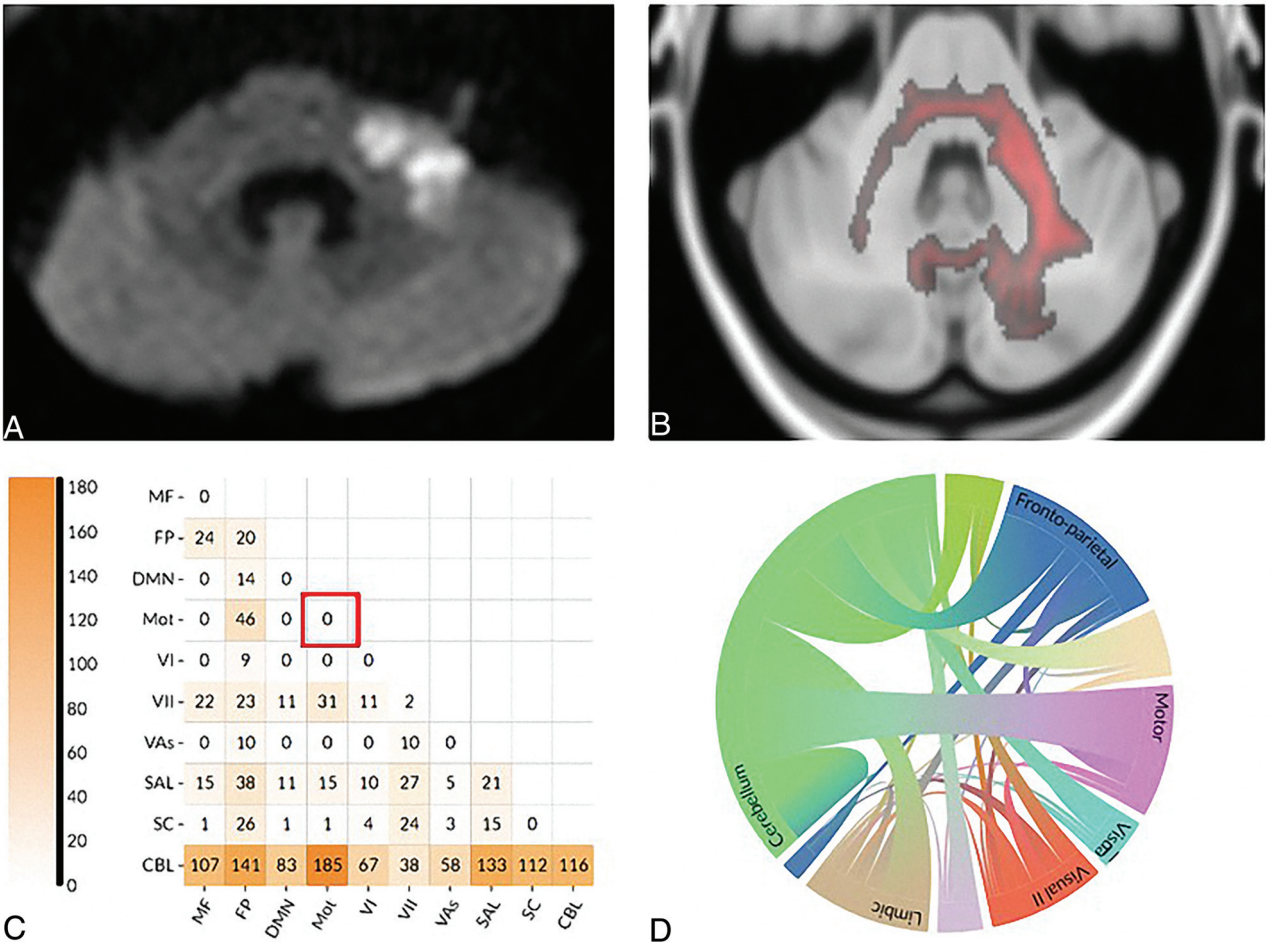

FIG 5. Representative case of a 62-year-old man with left middle cerebellar peduncle ischemic infarction. He did not have poststroke dysphagia, and the model also predicted negative results. *A*, Substantial infarction volume in DWI. *B*, Disconnected tract attenuation map (*red*) due to infarction. Nonetheless, the disconnection is mostly distributed in the cerebellar network, with no disconnection within the motor network (*C*, *red square*; *D*), which may be preventing the patient from poststroke dysphagia.

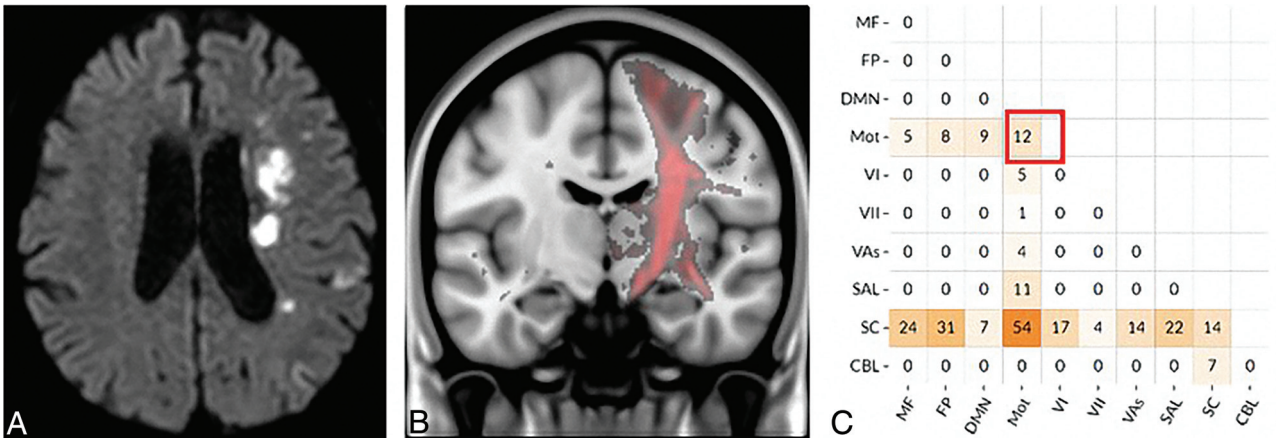

FIG 6. Representative case of a 39-year-old woman with left corona radiata ischemic infarction. The patient did not have poststroke dysphagia. She had disconnection in the motor network and not predicted correctly only by disconnection matrix (*C*, *red square*). However, the model incorporating both demographic variable and disconnection predicted correctly, maybe owing to the patient's relatively young age of 39. *A*, Left corona radiata infarction in DWI. *B*, Disconnected tract attenuation map (*red*) due to infarction. Substantial amount of the disconnection distributed in the motor network (*C*, *red square*); however, the prediction model incorporating both disconnection and age, sex could predict correctly.

age, we classified the groups only by using age and the result was 66.2% (Fig 3*C*). Age is indeed a protective factor for poststroke dysphagia as displayed in Figure 6.[5] In addition, we tried to add age as a matching variable in the propensity score matching, and the significant difference remained, regardless of our effort. However, we showed that disconnection has additional information in the prediction of poststroke dysphagia.

There are several other limitations in this study. First, 3 different MRI scanners were used in our data set, which may bias the estimation of lesions. Second, this is a single-center retrospective study, which may limit the generalizability of the results. To compensate, we made our processed data and code available to increase reproducibility. Third, we did not include the cortical lesion in the analysis procedure because we wanted to focus on structural disconnection and reduce redundancy. Fourth, 3 patients with hyperacute infarction had follow-up MRI, and this may affect the generalizability of the study. Last, we used 6-direction DWI data to estimate the FA map in the normalization process. Although there are clear advantages in acquiring higher angular resolution data, several studies showed that 6-direction data provide diffusion measures with comparable robustness.[36]

CONCLUSIONS

Although trivial, we show that structural disconnection as derived from acute phase stroke imaging is predictive of poststroke dysphagia. In addition, we suggest that not only direct but also indirect disconnection in the motor network is important in the prediction.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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