NeuroImage: Clinical 35 (2022) 103103

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Neural correlates in the development of and recovery from dysphagia after supratentorial stroke: A prospective tractography study

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ARTICLE INFO

Keywords:
Corticobulbar tract
Diffusion tensor imaging
Dysphagia
Deglutition
Stroke
Predict

ABSTRACT

Background: Swallowing impairment after stroke may be related to the state of the corticobulbar tract (CBT), which is the motor projection fiber responsible for deglutition, but evidence is still lacking regarding which parameter could relate to poststroke swallowing recovery as measured by videofluroscope findings. This prospective study evaluated diffusion tensor imaging (DTI) parameters among dysphagic stroke patients compared with those of nondysphagia stroke patients and age-matched healthy subjects and followed swallowing recovery in dysphagic patients as assessed with the Modified Barium Swallow Impairment Profile (MBSImP©).

Methods: Diffusion tractography was performed in 69 subjects, consisting of 27 S patients with dysphagia, 18 healthy subjects and 24 S patients with no evidence of dysphagia. DTI was performed within 14 days of stroke onset. Follow-up DTI was performed in the dysphagic group at three months. The tract volume (TV) of the CBT and frontal operculum as determined by fractional anisotropy (FA) was compared among the 3 groups. Correlations of these parameters with initial dysphagia severity and swallowing parameters at baseline and 3 months postonset were assessed.

Results: All stroke patients showed lower CBT TV on the affected and unaffected sides than those in the control group, even in those who showed no evidence of clinical dysphagia. The dysphagia group showed a greater reduction in CBT TV on the affected side ($P < 0.001$). Receiver operating characteristic analysis showed that cutoff values of 4.1 cm^3 for TV and 0.24 for FA from the affected side could classify dysphagia with good accuracy (AUC = 0.77, 0.75, respectively) and specificity levels. FA values in the unaffected frontal operculum showed a significant correlation (rho = −0.40, $P = 0.02$) with swallowing outcome as observed by the total scores of MBSImP©. In addition, these values proved to be significant variables to predict swallowing outcome in multiple regression analysis ($R^2 = 0.6317$, $adjR^2 = 0.5815$, $F = 12.58$, $p < 0.001$, AIC = 203.65).

Conclusions: Even when clinical dysphagia is not apparent, individuals with a supratentorial stroke may show reduced CBT parameters compared to healthy controls. Supratentorial stroke may manifest with dysphagia if a certain extent of CBT volume and white matter tract integrity is involved, with a greater degree of CBT injury in the affected sides determining poststroke dysphagia severity. In contrast, recovery was independent of the affected parameters, and an initial lower FA value in the unaffected frontal operculum was indicative of a poorer 3-month dysphagia outcome. DTI parameters obtained within two weeks of stroke onset may help classify those with dysphagia, predict recovery and help plain therapeutic strategies to maintain the adaptive role of the white matter tract, which is crucial in swallowing recovery.

Abbreviations: CBT, corticobulbar tract; MBSImP©, Modified barium swallow impairment profile©; VFSS, videofluoroscopic swallowing study; DTI, diffusion tensor imaging; GUSS, Gugging Swallowing Screen; FOIS, Functional Oral Intake Scale; MASA, Mann Assessment of Swallowing Ability; PAS, Penetration-Aspiration Scale; MBI, modified Barthel Index; ROIs, Regions of interest; FA, fractional anisotropy.

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https://doi.org/10.1016/j.nicl.2022.103103
Received 31 January 2022; Received in revised form 20 June 2022; Accepted 24 June 2022
Available online 27 June 2022

1. Introduction

Approximately 50% of all patients with stroke experience dysphagia (Daniels et al., 1998). Dysphagia is associated with increased stroke mortality (Arnold et al., 2016) and medical complications such as malnutrition, dehydration (Crary et al., 2013) and aspiration pneumonia (Martino et al., 2005). Long-term recovery of functional swallowing is independently associated with poor outcomes after stroke (Galovic et al., 2019). Therefore, in addition to quickly and accurately detecting dysphagia, it is imperative to identify patients manifesting poor swallowing recovery after stroke.

Stroke lesions involving the frontal operculum, the posterior limb of the internal capsule, and bilateral hemispheres have been associated with the occurrence and prognosis of poststroke dysphagia.(Galovic et al., 2013; Galovic et al., 2019; Lee et al., 2020) Past research has focused on the lesion location causing dysphagia. However, strokes show highly variable lesion locations, lesion extents, and degrees of neural tract injury. Recently, the importance of analyzing neural pathways and their integrity related to swallowing has been highlighted (Im et al., 2020; Jang et al., 2020; Jang et al., 2021).

The corticobulbar tract has been shown to be a potent neural pathway involved in swallowing, and any lesions disrupting this pathway can lead to dysphagia.(Galovic et al., 2017) Fibers from the caudal part of the premotor and primary motor cortex pass through the corona radiata, internal capsule, and pons and finally project bilaterally to the motor neurons of cranial nerve nuclei V, VII, IX, X, XI, and XII.(Afifi and Bergman, 2005) Swallowing musculatures receive innervation from corticobulbar projections from both hemispheres, while at the same time, one hemisphere can control the bilateral swallowing nuclei of the brainstem.

Diffusion tensor imaging (DTI) can provide an assessment of the whole structural integrity of the corticobulbar tract (Jang and Seo, 2015). A recent study has shown that the tract integrity of the unaffected corticobulbar tract may indicate the severity of poststroke dysphagia (Im et al., 2020). However, the retrospective study primarily compared tractography findings between patients with dysphagic stroke and age-matched healthy subjects, without direct comparison with nondysphagic stroke patients. Most DTI studies on the corticobulbar tract (CBT) made comparisons between healthy controls and lacked a detailed comparison to stroke patients who do not manifest any evidence of dysphagia. Not all stroke patients manifest swallowing disturbances, and little is known about how CBT involvement in patients with dysphagia differs from its involvement in those who show no dysphagia after a supratentorial brain lesion. Likewise, little is known about how these DTI parameters relate to the degree of swallowing recovery.

In addition, past studies have reported the primary outcome of recovery based on the level of tube feeding. Instrumental swallowing tests, such as the videofluoroscopic swallowing study (VFSS), are gold standards for the comprehensive assessment of dysphagia and allow global rating to a scoring system. However, neuroanatomical correlations from DTI to recovery as assessed by standardized instrumental tests are still lacking. Research elucidating the precise relationship between neuroimaging analysis and instrumental swallowing tests is needed to apply these parameters to predicting dysphagia development and swallowing recovery after a supratentorial stroke.

In this prospective study, we compared DTI-derived parameters among 1) age-matched healthy subjects 2) stroke patients with dysphagia and 3) stroke patients without dysphagia to elucidate the role of the bilateral corticobulbar tracts on poststroke swallowing function and outcome. In those with dysphagia, swallowing parameters, including the modified barium swallow impairment profile (MBSImP©) based on the VFSS, were obtained within two weeks of stroke onset and at the 3-month follow-up. We aimed to determine which DTI parameters best reflect dysphagia development after supratentorial stroke and explore which parameters relate to swallowing recovery at 3 months poststroke.

2. Methods

2.1. Subjects

The participants were first-ever stroke patients who were admitted to the stroke center between March 2017 and February 2018. The inclusion criteria were as follows: (i) de novo ischemic stroke; (ii) infarction restricted to the supratentorial territory; and (iii) brain DTI performed within the first 2 weeks of stroke onset. The exclusion criteria were as follows: (i) history of prior ischemic or hemorrhagic stroke, (ii) bihemispheric stroke, and (iii) additional disorders that may cause swallowing impairment other than stroke, such as Parkinson's disease, Alzheimer's disease, Guillain–Barre syndrome, and myasthenia gravis.

This study was performed at a university affiliated hospital, where stroke patients are assessed for dysphagia presence upon admission. Stroke patients are referred for a VFSS or FEES if oral feeding is deemed unsafe and requires tube feeding or modification of diet or liquid consistency after testing the Gugging Swallowing Screen (GUSS). Patients with stroke manifesting dysphagia were investigated after validation with a VFSS performed within the first 2 weeks, which required dietary modification or tube feeding and availability for follow-up assessment at 3 months after stroke onset. Stroke patients who showed no evidence of dysphagia requiring dietary modification or treatment at the initial stroke onset were defined as the nondysphagia stroke group. They were required to have an initial GUSS of 20 assessed upon admission to the stroke unit. Stroke patients were enrolled by voluntary participation. They were included in the study if they fully consented to the study protocols and were available for all required assessments at baseline and at follow-up.

Healthy subjects were recruited prospectively for DTI after informed consent was obtained. They were excluded if they had (i) a history of psychopathology or neurological disorders ascertained via a health questionnaire and medical examination, (ii) structural abnormalities on their scan, or (iii) a prior history of swallowing defects. The institutional review board approved the study protocols, which were in accordance with the Declaration of Helsinki (HC17OESI0033).

2.2. Assessment of swallowing and functional outcomes

All baseline swallowing assessments, including the VFSS, from the dysphagia stroke patients were evaluated within two days, ideally on the same day, of performing DTI. Swallowing function was evaluated using screening tools, including the GUSS (Warnecke et al., 2017) and the Mann Assessment of Swallowing Ability (MASA) (Oh, 2014). The Penetration-Aspiration Scale (PAS) (Rosenbek et al., 1996) and Modified Barium Swallow Impairment Profile (MBSImP©) (Martin-Harris et al., 2008) were assessed via VFSS performed by a certified specialist with more than 10 years of experience. VFSS was performed via digitalized fluoroscopy (AXIOM LUMINOS DRF; SIEMENS, Germany) on continuous setting with image capture settings of 30 frames per second. Thin/thick fluid consisting of 35% v/v low/70% v/v high concentration liquid containing 300 mL of normal saline mixed with 140 g/100 mL of barium sulfate (Baritop HD; Kaigen Pharm, Osaka, Japan) (Son et al., 2015) was used along with semisolid and solid boluses according to standard protocols. We used a modified version of the MBSImP© protocols (Martin-Harris et al., 2008). Patients were presented with one 5-ml teaspoon of nectar-thick liquid barium and one 5-ml teaspoon of pudding-thick barium. If patients were tolerable, larger volumes of thin liquid barium (two trials of 5-ml cup sip, followed by sequential swallows), nectar-thick liquid barium, honey-thick and pudding thick barium were presented. If allowed, rice or cookies coated with thick barium followed were presented.

While the Penetration-Aspiration Scale indicated the presence and severity of penetration or aspiration, the MBSImP© is a standardized and validated tool used to rate 17 different swallowing components that are scored in terms of 11 different swallowing tasks (such as teaspoon thin, sequential nectar and solid) during the VFSS (Martin-Harris et al., 2008; Hazelwood et al., 2017). The MBSImP© quantifies physiological swallow impairments, while the Functional Oral Intake Scale (FOIS) (Crary et al., 2005) describes the level of oral intake of liquid and food. If multiple swallows occurred, scoring was based on the initial swallow. The sum of the oral components was used as the oral total sum score (min 0, max 22), and the sum of the pharyngeal components was used as the pharyngeal total sum score (min 0, max 29) (Martin-Harris et al., 2008).

Baseline stroke severity was evaluated using the National Institutes of Health Stroke Severity Scale (Goldstein and Samsa, 1997). The Mini-mental State Exam (Park and Kwon, 1990) and Berg balance scale (Berg et al., 1989) scores at baseline were assessed to evaluate baseline cognitive and balance impairment. The modified Rankin scale (Burn, 1992) and modified Barthel index (MBI) (Shah et al., 1989) were assessed at baseline to evaluate the participants' mobility and ability to perform the activities of daily living.

2.3. Diffusion tensor imaging and tractography

The patient underwent MRI by using a 3 T Philips MRI scanner (Phillips Health care, Best, The Netherlands) with a 32-channel head coil. Data were acquired in the form of single-shot spin-echo echo-planar images, with axial slices covering the whole brain across 75 interleaved slices of 2.0 mm thickness [no gap; repetition time/echo time = 1000/75 ms; field of view = 230.4 × 230.4 mm^2; matrix = 144 × 144; voxel size = 2 × 2 × 2 mm^3 (isotropic), number of excitations = 1]. Diffusion-sensitizing gradients were applied in 32 noncollinear directions with a b-value of 1,000 ms/mm^2. The b = 0 images were scanned before acquisition of the diffusion-weighted images, with 33 volumes acquired in total.

2.4. Image processing

The images were processed using the FMRIB Software Library (FSL; ver. 5.0.9; https://www.fmrib.ox.ac.uk/fsl). Source data were corrected for eddy currents and head motion by registration to the first b = 0 image using an affine transformation. Probability distributions in two fiber directions were modeled at each voxel for probabilistic tractography using the BEDPOSTX program, which is based on a multifiber diffusion model. The fractional anisotropy (FA) maps were prepared using the DTIFIT program.

Probabilistic tractography was performed using the FSL ProbtrackX program to reconstruct the corticobulbar tract. The fiber-tracking parameters were as follows: number of samples 5000; curvature threshold 0.1 (cosine 84.3°); and step length 0.5 mm (Jo et al., 2017). A two-region of interest (ROI) approach was used to reconstruct the corticobulbar tract. The seed ROI was set on the frontal operculum and the caudal part of the premotor and primary motor cortex (Hazzaa et al., 2019; Im et al., 2020; Jang et al., 2021). The way ROI was placed at the mid-pontine level, where the corticobulbar/corticospinal tract is represented by the blue fibers of the anterior pons on the color fractional anisotropy (FA) map. (Supplementary Fig. 1). The FA and tract volume (TV) of the corticobulbar tract in each hemisphere were determined (Jang and Seo, 2015; Jenabi et al., 2015). FA values were measured on the seed ROIs from the frontal operculum (Im et al., 2020). The TV values of the corticobulbar tract were calculated by multiplying the voxel volume by the number of traced voxels during fiber tracking performed based on a robust minimum intensity threshold of 1 (Im et al., 2020). The DTI of all participants was analyzed by an expert with 5 years of experience in tractography analysis, who was blinded to swallowing assessments. We overlaid the participants' lesion map with a probabilistic tract derived from diffusion tensor images of the patients.

2.5. Statistical analysis

All statistical analyses were performed using R Statistical Software (version 2.15.3; R Foundation for Statistical Computing, Vienna, Austria). The Shapiro–Wilk test for normality was used to evaluate the distribution of the continuous variables. Between-group analyses were conducted using the Kruskal–Wallis test, followed by a post hoc Dunn test. P values were adjusted with Bonferroni correction. Spearman correlation analysis was used to assess the association between tractography parameters and swallowing. Within the dysphagia stroke group, a paired *t* test or Wilcoxon signed-rank sum test was conducted to determine significant differences in swallowing parameters obtained at baseline and at 3 months of follow-up. Finally multiple linear regression analysis was used to predict initial and follow-up swallowing function including the covariates of lesion size, affected and unaffected FA values, MMSE and initial NIHSS. Only variables with a p value <0.2 on simple analysis were included. The significance level was determined as $P < 0.05$. Continuous variables are expressed as the mean and standard deviation or median with interquartile range, and categorical variables are expressed as percentages. Optimal cutoff values were computed from the receiver operating characteristic (ROC) curve for CBT TV and FA values obtained with data regarding the presence of dysphagia.

3. Results

3.1. Participants

A total of 79 participants were enrolled in the study. Fig. 1 shows a flowchart of the participants included (Fig. 1). The baseline characteristics of the 3 groups along with the clinical characteristics of the two stroke groups showed that the dysphagia group showed greater neurological severity, as reflected by their initial National Institutes of Health Stroke Severity Scale and modified Rankin Scale scores (Table 1). The dysphagia group showed a larger mean (±SD) total lesion volume of 21.7 (3.3) cm^3 than the nondysphagia stroke group (7.4 (1.2) cm^3), although statistical analysis tests failed to identify statistical significance ($P = 0.067$). Both groups showed similar degrees of deep white matter lesions as assessed by the Fazekas scale. The enrolled participants in the dysphagia group showed severe dysphagia, with the majority on tube feeding.

3.2. Comparison of the DTI-derived parameters among the three groups with threshold values

DTIs were acquired at a mean of 10.5 (SD = 4.25) days after stroke. All three groups showed significant differences ($P < 0.001$) in the TV of the affected corticobulbar tract, with the dysphagia stroke group showing the greatest reduction (Fig. 2). In contrast, on the unaffected side, the two stroke groups showed a smaller TV than the healthy control TV (<0.001), but no intergroup differences were observed between the two stroke groups ($P = 0.224$) (Fig. 3).

ROC curve analysis showed that the CBT TV cutoff value of 4.10 cm^3 (area under the receiver operating characteristic curve (AUC) = 0.77; sensitivity 61.5%; specificity 86.0%) was associated with dysphagia.

When FAs were obtained from the affected frontal operculum, the dysphagia stroke group showed the greatest reduction among the three groups ($P < 0.001$). Additionally, the dysphagic stroke groups showed greater FA reductions from the unaffected frontal operculum than those of the healthy control group ($P = 0.005$). However, no significant differences in the FA values were observed between the two stroke groups (Fig. 4).

ROC curve analysis revealed that the optimal cutoff value of FA of the affected side to classify dysphagia was 0.241 with modest accuracy levels but high specificity levels. (Sensitivity: 61.5%, specificity: 86.0%, AUC = 0.75 [0.63–0.87]) (Fig. 5). Analysis of laterality showed no differences between the right and left lesions, although a tendency of

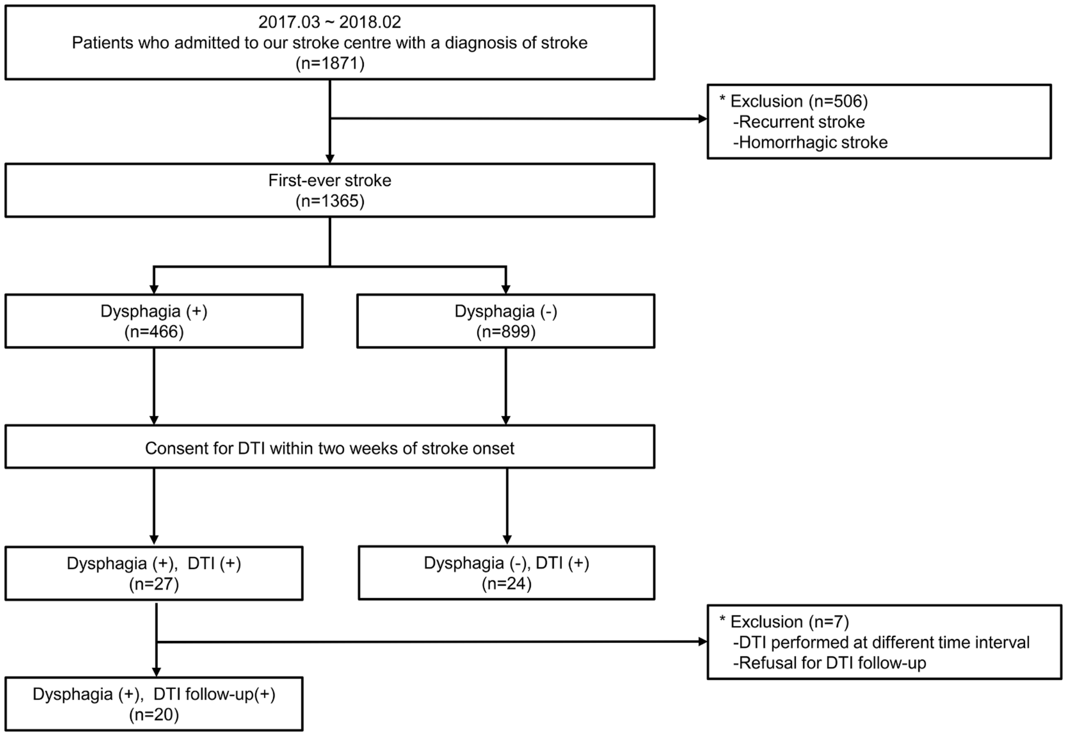

Fig. 1. Flow chart of participants with supratentorial stroke recruited for diffusion tractrography image analysis. Abbreviation: DTI, diffusion tensor imaging.

Table 1
Baseline demographics of enrolled participants.

	Normal	Stroke dysphagia (−)	Stroke dysphagia (+)	p-value
Age (y)	64.9 ± 7.6	63.7 ± 11.4	68.6 ± 11.2	0.253
Male n, (%)	8 (44.4%)	9 (36.0%)	14 (53.8%)	0.440
Lesion laterality				
Right	–	14 (56.0%)	1 (53.8%)	1.00
Lesion Etiology				
Large-artery atherosclerosis	–	9 (36.0%)	11 (42.3%)	0.518
Cardioembolism	–	16 (64.0%)	14 (53.8%)	
Stroke or other undetermined etiology	–	0 (0.0%)	1 (3.8%)	
MBI	–	56.6 ± 19.7	30.8 ± 31.2	0.001
NIHSS	–	4.3 ± 3.2	11.7 ± 6.5	< 0.001
MMSE	–	25.7 ± 5.5	14.1 ± 10.2	< 0.001
BBS	–	22.2 ± 23.6	27.2 ± 20.2	0.420
mRS	–	2.2 ± 0.9	3.7 ± 1.3	< 0.001
Deep white matter Fazeka scale				
0	–	8 (36%)	7 (23.1%)	0.632
1	–	6 (40%)	8 (38.5%)	
2	–	5 (20%)	11 (34.6%)	
3	–	1 (4%)	1 (3.8%)	

Values are presented as mean ± standard deviation, number (%), or median (quarter range).
Abbreviations: MBI, Modified Barthel Index; NIHSS, National Institutes of Health Stroke Severity Scale; MMSE, Mini-mental state exam BBS, Berg balance scale; mRS, modified Rankin scale.
$P < 0.05$ intergroup differences between the good versus poor outcome group by *t*-test or Manny-Whitney *U* test for non-parametric analysis.

intragroup differences between the affected and nonaffected CBT volume was shown, although it did not reach statistical significance (Supplementary Table 1).

3.3. Correlation with swallowing parameters with outcome prediction at 3 months

At baseline, a large proportion of patients in the dysphagia stroke group (65.4%, n = 17) were at near tube feeding status (FOIS level 1,2), with only 34.6% (n = 9) showing partial oral feeding ability. Significant improvement was found at follow-up, with 84.6% (n = 22) of patients on some form of oral feeding showing improvement in all swallowing parameters, including aspiration severity.

Total stroke volume was correlated with the initial total MASA scores (rho = −0.57, P = 0.002) and aspiration severity (rho = 0.49, P = 0.012).

The TV of the corticobulbar tract failed to show any significant correlation with any swallowing parameters assessed at the 3-month follow-up. The FA values of the affected frontal operculum showed a significant correlation with the initial swallowing level as reflected by the FOIS scores (rho = 0.49, p = 0.011) but not the follow-up parameters. In contrast, the initial FA values of the unaffected frontal region correlated with the total MBSImP© values (rho = −0.40, P = 0.02) at 3 months and with the oral and pharyngeal MBSImP© subscores (Supplementary Table 2).

3.4. Multiple regression analysis

Variables of the affected FA from the frontal operculum, stroke lesion, NIHSS and MMSE accounted for 62.38% of the total variation of the initial FOIS level. Affected FA values (p = 0.045) and MMSE (p = 0.002) were significant predictors in this model after controlling lesion size and NIHSS ($R^2 = 0.6238$, adj$R^2 = 0.5521$, $F = 8.7$, $p < 0.001$).

Variables of the unaffected FA from the frontal operculum and initial NIHSS accounted for 58.09% of the total variation in the FOIS level at 3 months. A final model showed that the nonaffected FA values (p = 0.043) and NIHSS (p < 0 0.001) were significant predictors, after controlling for lesion size and MMSE ($R^2 = 0.5809$, ${}_{adj}R^2 = 0.5444$, $F = 15.94$, $p < 0.001$, AIC = 91.51) (Table 2).

Additional multiple regression analysis was performed for the MASA,

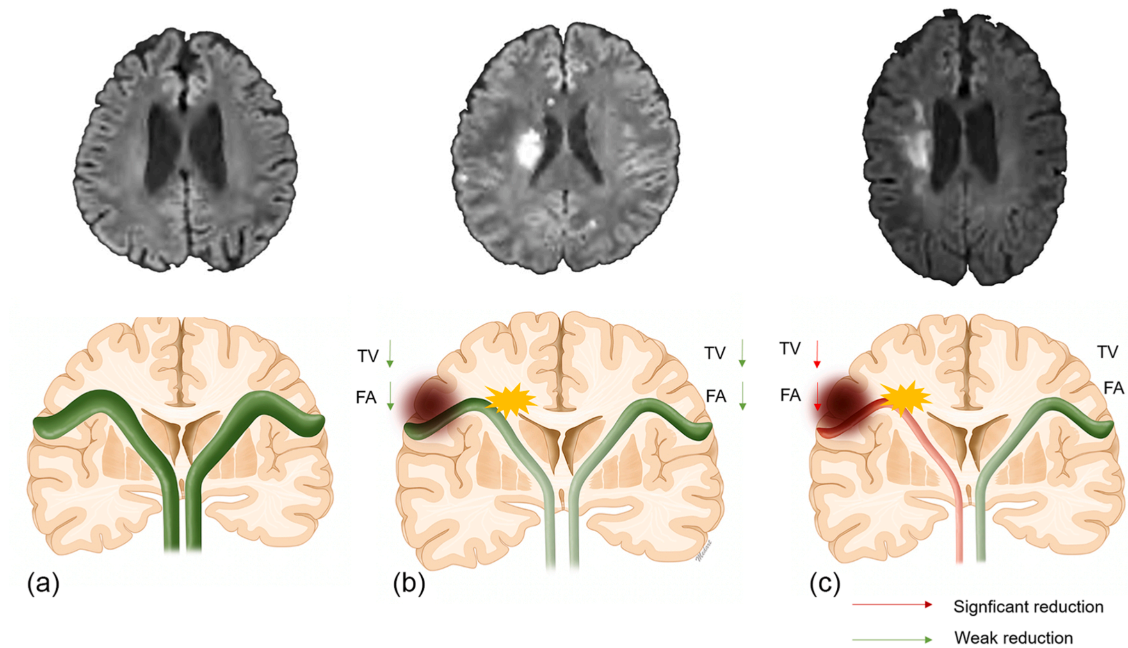

Fig. 2. Graphical illustration of the corticobulbar tract involvement in a.healthy control, supratentorial stroke b. without dysphagia and c.with dysphagia. Abbreviations: FA, fractional anisotropy; TV, tract volume.

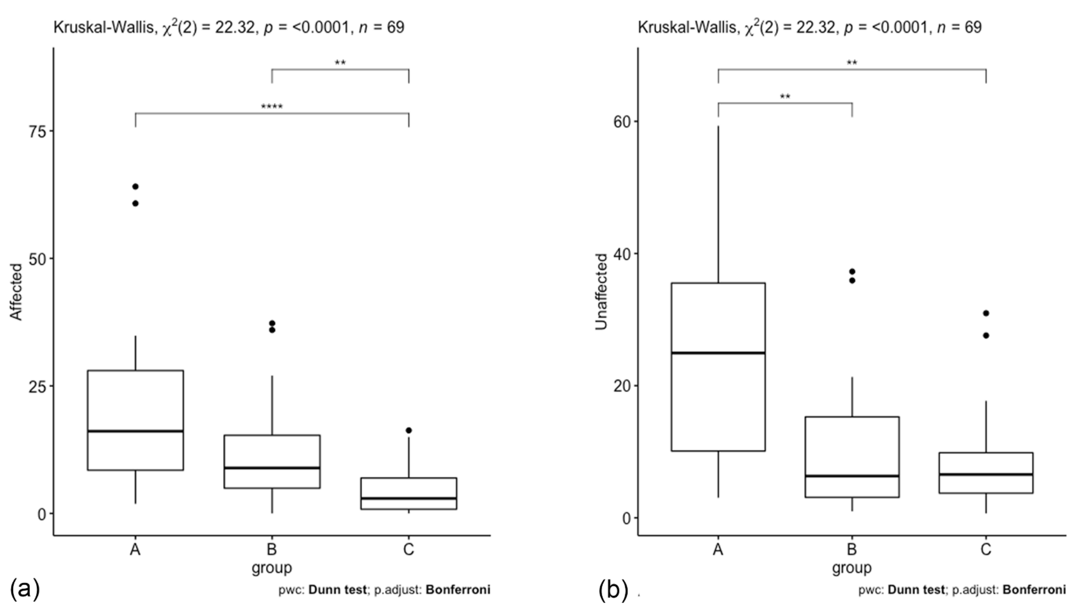

Fig. 3. Bar plot comparison of the corticobulbar tract volume among the three groups of the affected and non-affected sides showing that supratentorial stroke influences corticobulbar tract in group B and C but greatest involvement observed in group C. Abbreviations: A. healthy control, B. supratentorial stroke without dysphagia and C supratentorial stroke with dysphagia. ** P value < 0.01 ***P value < 0.001.

PAS and MBSImP©. Although the unaffected FA from the frontal operculum failed (Supplementary Table 3) to be significant predictors in the MASA, PAS and MBSImP© at 3 months, a final model that included the unaffected FA(p = 0.006) accounted for 63.1% of the total variation for predicting the degree of improvement as reflected in the degree of MASA score changes between baseline and follow-up ($R^2 = 0.6317$, ${}_{adj}R^2 = 0.5815$, F = 12.58, p < 0.001, AIC = 203.65).

3.5. Follow-up DTI parameters and correlation with outcome

For the three-month follow-up analysis, only data obtained from 74% of the dysphagic stroke patients (n = 20), who completed the second DTI on the same week the VFSS was performed, were used for analysis. The DTI parameters from baseline to follow-up were compared, but no significant differences were observed, although there was a tendency for the affected CBT volume to increase and the unaffected FA values to decrease (Supplementary Table 4). Unlike the initial FA values, the absolute FA values at the 3-month follow-up did not show any meaningful association with the follow-up swallowing outcomes (results not shown). However, a greater degree of FA value changes across follow-up showed a significant correlation with PAS (rho = −0.46, P = 0.041) and oral component score of the MBSImP© (rho = 0.47, P = 0.035), indicating that greater reduction of the unaffected FA across the three months could lead to poor outcome.

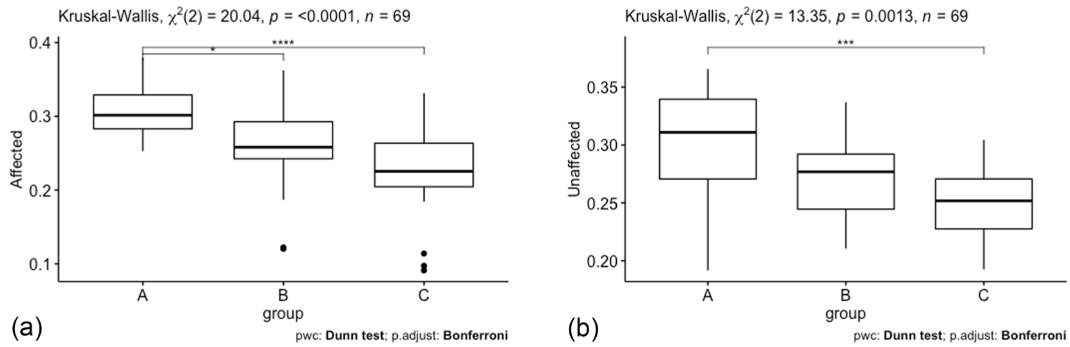

Fig. 4. Bar plot comparison of the corticobulbar fractional anisotropy among the three groups of the affected and non-affected sides showing that supratentorial stroke influences corticobulbar tract in group B and C but greatest involvement observed in group C. Abbreviations: A. healthy control, B. supratentorial stroke without dysphagia and C supratentorial stroke with dysphagia. * P value < 0.05 ***P value < 0.0001.

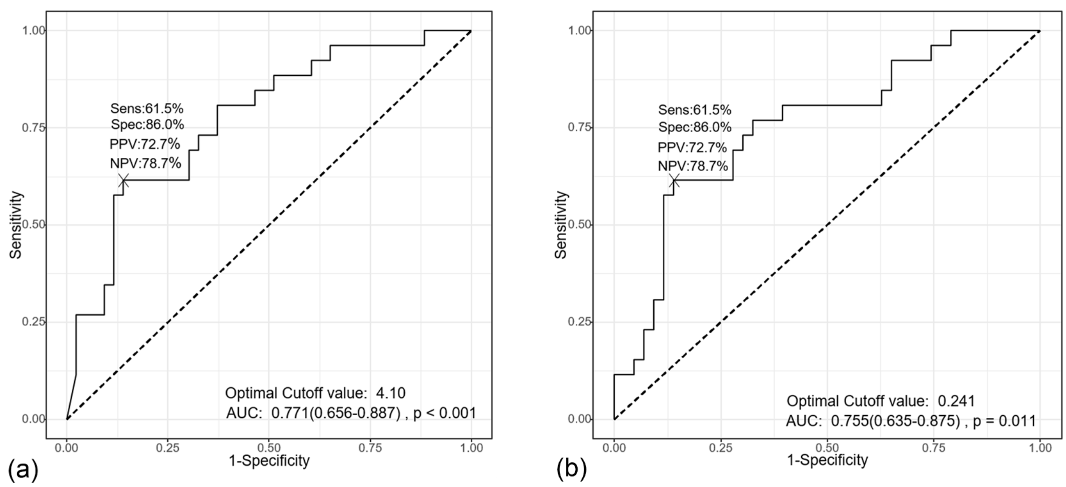

Fig. 5. ROC analysis show that cut-off values of the (a) corticobulbar tract volume and (b) fractional anistropy of the affected side that classifies dysphagia with good accuracy levels.

Table 2
Multiple regression model to predict FOIS and MASA score changes.

		Beta	lwr	upr	SE	std. Beta	lwr	upr	SE	t value	p
Multiple regression model for initial FOIS	(Intercept)	−1.15	−4.54	2.24	1.63	−0.00	−0.27	0.27	0.13	−0.706	0.488
	Affected_F_FA	11.20	0.29	22.12	5.25	0.38	0.01	0.75	0.18	2.135	0.045*
	Lesion size	0.00	−0.00	0.00	0.00	0.37	−0.04	0.78	0.20	1.889	0.073
	NIHSS	−0.09	−0.18	0.00	0.04	−0.31	−0.63	0.02	0.16	−1.981	0.061
	MMSE	0.10	0.04	0.16	0.03	0.59	0.24	0.93	0.17	3.505	0.002*
	$R^2 = 0.6238$, ${}_{adj}R^2 = 0.5521$, F = 8.7, $p < 0.001$, AIC = 89.55										
Multiple regression model for follow-up FOIS	(Intercept)	2.00	−2.88	6.88	2.36	0.00	−0.27	0.27	0.13	0.849	0.405
	Nonaffected_F_FA	18.54	0.60	36.49	8.67	0.31	0.01	0.60	0.14	2.138	0.043*
	NIHSS	−0.18	−0.27	−0.09	0.04	−0.61	−0.90	−0.31	0.14	−4.234	< 0.001*
	$R^2 = 0.5809$, ${}_{adj}R^2 = 0.5444$, F = 15.94, p < 0.001, AIC = 91.51										
Multiple regression model for MASA score changes	(Intercept)	−17.06	−56.67	22.54	19.10	0.00	−0.26	0.26	0.13	−0.893	0.381
	Affected_F_FA	−73.50	−176.33	29.33	49.58	−0.27	−0.64	0.11	0.18	−1.482	0.152
	Nonaffected _F_FA	224.54	72.09	377.00	73.51	0.42	0.13	0.70	0.14	3.055	0.006*
	Lesion_size	0.00	0.00	0.00	0.00	0.56	0.20	0.92	0.17	3.246	0.004*
	$R^2 = 0.6317$, ${}_{adj}R^2 = 0.5815$, F = 12.58, $p < 0.001$, AIC = 203.65										

Abbreviations: F, Frontal; FA, fractional anisotropy; FOIS, Functional Oral Intake Scale; MASA, Mann assessment of swallowing ability; NIHSS, National Institutes of Health Stroke Severity Scale; MMSE, Mini-mental state exam; AIC, Akaike Information Criterion.
* p-value < 0.05.

3.6. Stroke lesion overlap with CBT

An overlapping density map of the stroke lesion and reconstructed corticobulbar tract is shown (Fig. 6). The two stroke groups showed similar overlap of stroke lesions and CBT.

4. Discussion

We analyzed the DTI-derived parameters of the bilateral corticobulbar tracts assessed within two weeks of stroke onset and explored whether these parameters were related to swallowing function in the

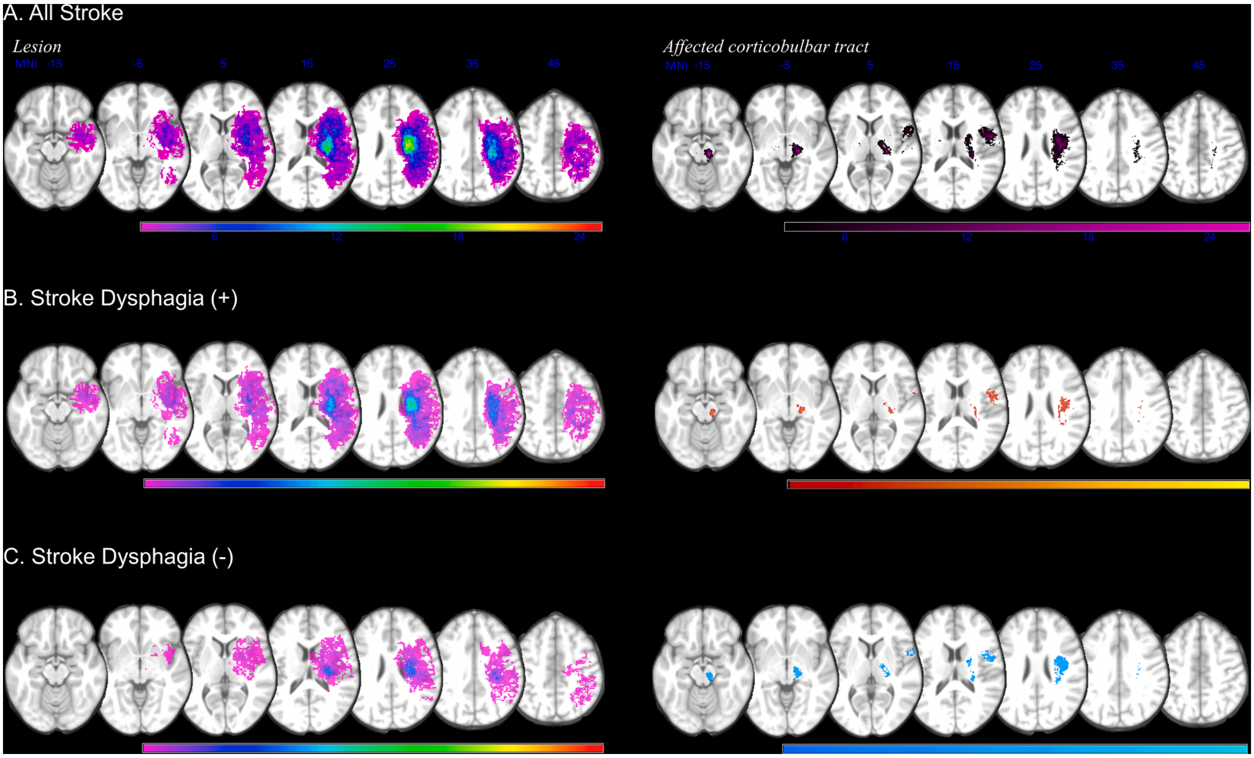

Fig. 6. Overlapping density map of the stroke lesion and reconstructed corticobulbar tract. Left hemispheric lesions were flipped to the right side. z-coordinates from –15 to + 45 in Montreal Neurological Institute space of (a) all stroke participants (b) dysphagic stroke group and (c) nondysphagic stroke group.

acute phase of stroke and to recovery at three months. Supratentorial infarctions affected CBT of both the affected and unaffected sides in all stroke patients, but the optimal cutoff value of CBT TV values associated with dysphagia was 4.10 cm^3. Similarly, the FA reduction of the affected frontal operculum was associated with dysphagia presence and severity, with cutoff values of 0.24 associated with dysphagia. These two cutoff values showed good specificity levels. In contrast, the lower FA value of the unaffected frontal operculum was indicative of a poorer 3-month dysphagia outcome. Our results suggest that initial dysphagia presence depends on the involvement of the affected CBT TV. However, long-term swallowing recovery may depend on the integrity of the unaffected FA which showed early changes within two weeks of stroke onset. The greater involvement of the unaffected white matter integrity at three months predicted the degree of dysphagia recovery even after controlling for other confounding factors.

The fact that the degree of CBT involvement and total stroke lesion volume determined the initial severity of dysphagia as manifested by the MASA scores and the aspiration severity as manifested by the PAS scores corresponds well with the results of past studies (Alberts et al., 1992; Galovic et al., 2013) that indicated larger stroke volume to be associated with dysphagia and aspiration severity. These data are in line with recently published studies investigating those lesions that disrupt the CBT structural integrity as the primary mechanisms for impaired swallowing after stroke (Daniels et al., 1998; Mosier and Bereznaya, 2001). However, because supratentorial stroke by itself may cause CBT TV reduction, without any evidence of dysphagia, precaution is warranted in interpreting any reduction in CBT TV compared to healthy controls as indicative of dysphagia. According to our results, a CBT TV higher than the cutoff value of 4.10 cm^3 could classify those without dysphagia with high specificity.

Interestingly, the FA of the unaffected side of the frontal operculum showed a positive correlation with a 3-month dysphagia outcome, suggesting the compensatory role of the contralesional corticobulbar tract in swallowing recovery after unilateral hemispheric stroke. Recent studies have also suggested the role of the unaffected hemisphere in poststroke swallowing recovery in patients with intracerebral hemorrhage and medullary infarctions. Jang et al. have shown that injuries to the corticobulbar tract in both hemispheres prevented removal of the nasogastric tube until six months after hemorrhagic stroke and lateral medullary infarction (Jang et al., 2020; Jang et al., 2021). Similar results have been reported after middle cerebral artery infarction by Im et al., who reported that a lower corticobulbar tract volume in the unaffected hemisphere was indicative of worse swallowing function (Im et al., 2020). Our findings are in line with the idea that swallowing function was dependent on a network connecting both cortical and subcortical lesions from both hemispheres with asymmetrical connectivity (Mihai et al., 2016) and that the cortical reorganization of the nondominant hemisphere plays a crucial role in the recovery of swallowing function (Hamdy et al., 1998).

Of note, the unaffected FA values were also reduced in the nondysphagic stroke group compared to the healthy control group. Some have suggested abnormal FA values of the contralateral stroke lesion to reflect generalized aberrant connectivity, diffuse dysregulation of neural dynamics or possible compensatory changes in response to the primary deficit (Alba-Ferrara and Erausquin, 2013). Such bilateral hemispheric reorganization can be observed as early as 12 days poststroke onset (Saur et al., 2006). Therefore, the reduced FA values of the contralesional side in all the stroke participants were expected. Based on our results, these early adaptive changes in the unaffected white matter integrity within two weeks of stroke seem crucial in dysphagia outcome. Additionally, more significant FA reductions of the unaffected frontal operculum, indicating poorer white matter integrity, were associated with poorer swallowing recovery, even after controlling for multiple confounding factors that may affect recovery. Therefore, the unaffected parameters are helpful as early biomarkers in predicting dysphagia outcome. More critically, they may help to guide strategies to maintain the adaptative role of the contralesional white matter, which would prove essential in enhancing swallowing recovery.

Unlike the corticospinal tract, a strong biomarker of motor recovery, which is characterized by competitive interhemispheric connections, bilateral corticobulbar tracts may act noncompetitively. Swallowing is unique from other motor activities in that it is a midline function with bilateral cortical representation (Hamdy et al., 1996) that is mediated by a complex bilateral neural network(Gonzalez-Fernandez et al., 2008). Teismann et al. (Teismann et al., 2009) reported that cortical activation in the unaffected hemisphere during swallowing was a predictor of dysphagia in the subacute phase of stroke. Similarly, a functional MRI study showed that following unilateral hemispheric stroke, the region of the motor cortex involved in swallowing showed reorganization with a compensatory shift in the area activated during swallowing in the unaffected hemisphere (Li et al., 2009). Based on these findings, studies on the target location for repetitive transcranial magnetic stimulation revealed that facilitatory high-frequency stimulation on the bilateral or unaffected hemisphere showed positive therapeutic effects (Park et al., 2017). Our results are a natural extension of recent studies indicating that the unaffected hemisphere plays a role in swallowing modulation and neural plasticity and that swallowing recovery depends on an extended swallowing network (Mosier and Bereznaya, 2001) involving bilateral cortices and subcortical connections.

Our results also support the role of the affected FA from the fontal operculum in predicting poststroke dysphagia, which showed a significant correlation with the initial level of functional swallowing. The importance of the microstructural organization of the frontal operculum is strongly supported by recent emerging evidence that indicates that this stroke location influences swallowing function (Wilmskoetter et al., 2019). The frontal and insular lobes were most commonly affected in patients with dysphagia persisting for 2 weeks (Broadley et al., 2005), with the frontal operculum being the only ROI significantly associated with an extended risk of aspiration in the univariate analysis (Galovic et al., 2013). The insula plays a singular role in swallowing by contributing to the processing of food taste and texture (Rolls, 2016) and controlling the timing and synchronization of swallowing motor events by integrating sensorimotor information (Mosier and Bereznaya, 2001). The frontal operculum is known to play a role in peri-infarct tissue recruitment after insular stroke, and parts of it in the zone of transition to the insular cortex may exhibit swallowing features similar to those of lesions in the insula (Daniels and Foundas, 1997).

An important characteristic of this study is that stroke patients with/without dysphagia were enrolled consecutively. For the former, full serial VFSS based on MBSImP© scores with DTI metrics were collected. VFSS allows bolus flow visualization in relation to structural movement throughout the upper aerodigestive tract in real time (Martin-Harris et al., 2008). Past CBT DTI studies have used the presence of tube feeding as the primary outcome parameter for swallowing recovery (Jang et al., 2020; Jang et al., 2021). However, successful tube removal after a stroke may depend on other clinical factors, such as age, nutritional status, or frailty, and may not fully reflect the degree of swallowing recovery. Thus, the outcome parameter used to determine swallowing recovery should be based on a parameter that is less ambiguous, more modality specific, standardized and validated to assess swallowing. The changes reported in our study are clinically relevant since the MBSImP© is a standardized semiobjective measure for evaluating oral and pharyngeal swallowing physiology. Although some studies have used this scoring system with lesion localization in poststroke dysphagia (Wilmskoetter et al., 2019), our study is the one of the few studies to monitor score changes and demonstrate positive associations with neuroanatomical correlates. In addition, our study provides longitudinal DTI follow-up data that were obtained in a prospective manner and indicates the positive association of swallowing recovery with the degree of white matter changes of the unaffected sides at three months postonset.

The study has a few limitations. First, the DTIs were obtained within two weeks of acute ischemic stroke, during which FA may be subject to confounding effects of tissue edema and acute injury and require additional time to reflect Wallerian degeneration (Feng et al., 2015). According to the literature, Wallerian degeneration can be detected histopathologically within the first week, (McCaman and Robins, 1959) and DTI can detect these early changes within the first two weeks even before they can be visualized in T2-weighted MRI (Thomalla et al., 2004; Venkatasubramanian et al., 2013). Therefore, we feel that the two-week time frame was adequate to reflect the early changes. Additionally, the reliability of using the DTI parameters after a stroke has been supported by previous studies (Doughty et al., 2016; Zolkefley et al., 2021). Second, although a similar proportion of right or left lesions was observed in the two stroke groups, lateralization was not considered in this study. Lateralization involving left-side hemispheres has been shown to be associated with oral stage dysfunction, lateralization involving the right side has been shown to be associated with pharyngeal stages and aspiration (Robbins and Levin, 1988), and lateralization involving the right hemisphere stroke lesions has been shown to be associated with a higher rate of dysphagia (Suntrup et al., 2015). However, the role of lateralization is still disputed and inconclusive (Galovic et al., 2013), and although our study showed no significant differences in all the parameters between the right and left side lesions, a tendency for right side dominancy was suggested. Third, although a previous study conducted voxel-based lesion mapping with each MBSImP© element separately (Wilmskoetter et al., 2019), our results presented the oral and pharyngeal subscores. Since the main objective of this study was to demonstrate overall improvement of swallowing rather than track changes in specific types of impairment, these subscores were selected for analysis. Fourth, the CBT TV of the affected side failed to show any association with the swallowing parameters at baseline. This finding may be related to the fact that all patients were already classified with severe dysphagia. Fifth, factors other than swallowing recovery may be influenced by clinical features such as age, degree of brain atrophy (Flowers et al., 2017), genetic polymorphism (Oh et al., 2021), sex, or type of therapy. Our findings are limited to brain lesions and structural integrity of the CBT and cannot be generalized to all clinical scenarios involving supratentorial infarction. Nevertheless, the results from the multiple regression analysis showed that even after controlling for NIHSS, stroke lesion size and MMSE; factors known to affect the degree of swallowing recovery; the non-affected FA helped predict swallowing recovery. Additionally, the reconstructed TV may be influenced by the angle threshold or b-values, and anatomical differences may lead to high intersubject variability (Maffei et al., 2019); therefore, the cutoff values provided in this study should be interpreted with caution. Further studies investigating the optimal TV under different threshold b values that best reflect clinical swallowing are warranted. The interaction of other clinical factors with tractography findings in swallowing recovery is a topic that requires further exploration in future studies. Finally, the sample size of the dysphagia stroke group may have been limited to reflect the influence of all the independent variables on the follow-up swallowing outcome parameters. Further validation of this imaging biomarker in another cohort with a large sample size is needed.

Despite the initial severity of dysphagia, most patients recover well within the first three months, but 15% of patients may have persistent dysphagia and increased mortality (Crary et al., 2013). Conventional CT or MRI results have a limited role in predicting poor swallowing recovery (Daniels et al., 2019). Our findings highlight that the microstructural organization of the unaffected CBT within the two weeks of stroke onset may help predict dysphagia outcomes. After supratentorial stroke, the degree of the TV of the affected CBT could classify those with dysphagia, but the FA values of the unaffected sides were associated with swallowing recovery. These parameters could be potentially relevant to developing neuroimaging biomarkers that predict those that may benefit from neuromodulation techniques that enhance neuroplasticity.

In summary, this prospective study demonstrates that, a supratentorial stroke may lead to changes in DTI parameters regardless of the presence of dysphagia. Our study indicates that patients may exhibit dysphagia when CBT parameters are involved past a certain cutoff value. However, despite severe CBT injury after a supratentorial stroke, the bihemispheric organization of the tract is crucial in swallowing recovery.

5. Conclusion

Prolonged dysphagia may lead to increased poststroke mortality. Delineating potential biomarkers that allow early identification of those with severe dysphagia and protracted swallowing recovery is clinically relevant to prevent respiratory complications and prolonged morbidity. Analysis of CBT via tractography within the first two weeks may be considered a viable method for predicting poststroke swallowing recovery to tailor treatment to the individual patient.

CRediT authorship contribution statement

Youngkook Kim: Visualization, Writing – review & editing, Methodology, Software. **Yeon-Jae Han:** Software, Validation. **Hae-Yeon Park:** Methodology, Formal analysis. **Geun-Young Park:** Resources, Supervision. **Moa Jung:** Writing – review & editing. **Soohwan Lee:** Writing – review & editing. **Sun Im:** Data curation, Writing – original draft, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors wish to acknowledge the financial support of the Catholic Medical Center Research Foundation made in the program year of 2017. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) 2017R1C1B501792.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103103.

References

Afifi, A.K., Bergman, R.A., 2005. Functional Neuroanatomy: Text and Atlas, 2nd ed. McGraw Hill, Health Professional Division, New York.
Alba-Ferrara, L.M., Erausquin, G.A.d., 2013. What does anisotropy measure? Insights from increased and decreased anisotropy in selective fiber tracts in schizophrenia. Front. Integr. Neurosci. 7, 9. https://doi.org/10.3389/fnint.2013.00009.
Alberts, M.J., Horner, J., Gray, L., Brazer, S.R., 1992. Aspiration after stroke: Lesion analysis by brain MRI. Dysphagia 7, 170–173. https://doi.org/10.1007/bf02493452.
Arnold, M., Liesirova, K., Broeg-Morvay, A., Meisterernst, J., Schlager, M., Mono, M.L., El-Koussy, M., Kagi, G., Jung, S., Sarikaya, H., 2016. Dysphagia in acute stroke: incidence, burden and impact on clinical outcome. PLoS One 11. https://doi.org/10.1371/journal.pone.0148424.
Berg, K., Wood-Dauphine, S., Williams, J., Gayton, D.J.P.C., 1989. Measuring balance in the elderly: preliminary development of an instrument. Physiother. Can. 41, 304–311.
Broadley, S., Cheek, A., Salonikis, S., Whitham, E., Chong, V., Cardone, D., Alexander, B., Taylor, J., Thompson, P., 2005. Predicting prolonged dysphagia in acute stroke: the Royal Adelaide Prognostic Index for Dysphagic Stroke (RAPIDS). Dysphagia 20, 303–310. https://doi.org/10.1007/s00455-005-0032-y.
Burn, J.P., 1992. Reliability of the modified Rankin Scale. Stroke 23, 438.
Crary, M.A., Humphrey, J.L., Carnaby-Mann, G., Sambandam, R., Miller, L., Silliman, S., 2013. Dysphagia, nutrition, and hydration in ischemic stroke patients at admission and discharge from acute care. Dysphagia 28, 69–76. https://doi.org/10.1007/s00455-012-9414-0.
Crary, M.A., Mann, G.D., Groher, M.E., 2005. Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. Arch. Phys. Med. Rehabil. 86, 1516–1520. https://doi.org/10.1016/j.apmr.2004.11.049.
Daniels, S.K., Brailey, K., Priestly, D.H., Herrington, L.R., Weisberg, L.A., Foundas, A.L., 1998. Aspiration in patients with acute stroke. Arch. Phys. Med. Rehabil. 79, 14–19. https://doi.org/10.1016/s0003-9993(98)90200-3.
Daniels, S.K., Foundas, A.L., 1997. The role of the insular cortex in dysphagia. Dysphagia 12, 146–156. https://doi.org/10.1007/PL00009529.
Daniels, S.K., Huckabee, M.L., Gozdzikowska, K., 2019. Dysphagia following stroke, 3rd ed. Plural Publishing, San Diego, CA.
Doughty, C., Wang, J., Feng, W., Hackney, D., Pani, E., Schlaug, G., 2016. Detection and Predictive Value of Fractional Anisotropy Changes of the Corticospinal Tract in the Acute Phase of a Stroke. Stroke 47, 1520–1526. https://doi.org/10.1161/STROKEAHA.115.012088.
Feng, W., Wang, J., Chhatbar, P.Y., Doughty, C., Landsittel, D., Lioutas, V.A., Kautz, S.A., Schlaug, G., 2015. Corticospinal tract lesion load: An imaging biomarker for stroke motor outcomes. Ann. Neurol. 78, 860–870. https://doi.org/10.1002/ana.24510.
Flowers, H.L., AlHarbi, M.A., Mikulis, D., Silver, F.L., Rochon, E., Streiner, D., Martino, R., 2017. MRI-based neuroanatomical predictors of dysphagia, dysarthria, and aphasia in patients with first acute ischemic stroke. Cerebrovasc. Dis. Extra 7, 21–34. https://doi.org/10.1159/000457810.
Galovic, M., Leisi, N., Muller, M., Weber, J., Abela, E., Kagi, G., Weder, B., 2013. Lesion location predicts transient and extended risk of aspiration after supratentorial ischemic stroke. Stroke 44, 2760–2767. https://doi.org/10.1161/STROKEAHA.113.001690.
Galovic, M., Leisi, N., Pastore-Wapp, M., Zbinden, M., Vos, S.B., Mueller, M., Weber, J., Brugger, F., Kagi, G., Weder, B.J., 2017. Diverging lesion and connectivity patterns influence early and late swallowing recovery after hemispheric stroke. Hum. Brain Mapp. 38, 2165–2176. https://doi.org/10.1002/hbm.23511.
Galovic, M., Stauber, A.J., Leisi, N., Krammer, W., Brugger, F., Vehoff, J., Balcerak, P., Muller, A., Muller, M., Rosenfeld, J., Polymeris, A., Thilemann, S., De Marchis, G.M., Niemann, T., Leifke, M., Lyrer, P., Saladin, P., Kahles, T., Nedeltchev, K., Sarikaya, H., Jung, S., Fischer, U., Manno, C., Cereda, C.W., Sander, J.W., Tettenborn, B., Weder, B.J., Stoeckli, S.J., Arnold, M., Kagi, G., 2019. Development and validation of a prognostic model of swallowing recovery and enteral tube feeding after ischemic stroke. JAMA Neurol. 76, 561–570. https://doi.org/10.1001/jamaneurol.2018.4858.
Goldstein, L.B., Samsa, G.P., 1997. Reliability of the national institutes of health stroke scale. extension to non-neurologists in the context of a clinical trial. Stroke 28 (2), 307–310.
Gonzalez-Fernandez, M., Kleinman, J.T., Ky, P.K., Palmer, J.B., Hillis, A.E., 2008. Supratentorial regions of acute ischemia associated with clinically important swallowing disorders: a pilot study. Stroke 39, 3022–3028. https://doi.org/10.1161/STROKEAHA.108.518969.
Hamdy, S., Aziz, Q., Rothwell, J.C., Power, M., Singh, K.D., Nicholson, D.A., Tallis, R.C., Thompson, D.G., 1998. Recovery of swallowing after dysphagic stroke relates to functional reorganization in the intact motor cortex. Gastroenterology 115, 1104–1112. https://doi.org/10.1016/s0016-5085(98)70081-2.
Hamdy, S., Aziz, Q., Rothwell, J.C., Singh, K.D., Barlow, J., Hughes, D.G., Tallis, R.C., Thompson, D.G., 1996. The cortical topography of human swallowing musculature in health and disease. Nat. Med. 2, 1217–1224. https://doi.org/10.1038/nm1196-1217.
Hazelwood, R.J., Armeson, K.E., Hill, E.G., Bonilha, H.S., Martin-Harris, B., 2017. Identification of swallowing tasks from a modified barium swallow study that optimize the detection of physiological impairment. J. Speech. Lang. Hear. Res. 60, 1855–1863. https://doi.org/10.1044/2017_JSLHR-S-16-0117.
Hazzaa, N.M., Mancini, L., Thornton, J., Yousry, T.A., 2019. Somatotopic organization of corticospinal/corticobulbar motor tracts in controls and patients with tumours: A combined fMRI-DTI study. Neuroimage Clin. 23, 101910. https://doi.org/10.1016/j.nicl.2019.101910.
Im, S., Han, Y.J., Kim, S.H., Yoon, M.J., Oh, J., Kim, Y., 2020. Role of bilateral corticobulbar tracts in dysphagia after middle cerebral artery stroke. Eur. J. Neurol. 27, 2158–2167. https://doi.org/10.1111/ene.14387.
Jang, S.H., Kwak, S.Y., Chang, C.H., Jung, Y.J., Kim, J., Kim, S.H., Kim, J.Y., 2020. Prognostic prediction of dysphagia by analyzing the corticobulbar tract in the early stage of intracerebral hemorrhage. Dysphagia 35, 985–992. https://doi.org/10.1007/s00455-020-10093-3.
Jang, S.H., Lee, J., Kim, M.S., 2021. Dysphagia prognosis prediction via corticobulbar tract assessment in lateral medullary infarction: a diffusion tensor tractography study. Dysphagia 36, 680–688. https://doi.org/10.1007/s00455-020-10182-3.
Jang, S.H., Seo, J.P., 2015. The anatomical location of the corticobulbar tract at the corona radiata in the human brain: diffusion tensor tractography study. Neurosci. Lett. 590, 80–83. https://doi.org/10.1016/j.neulet.2015.01.072.
Jenabi, M., Peck, K.K., Young, R.J., Brennan, N., Holodny, A.I., 2015. Identification of the corticobulbar tracts of the tongue and face using deterministic and probabilistic DTI fiber tracking in patients with brain tumor. AJNR Am. J. Neuroradiol. 36, 2036–2041. https://doi.org/10.3174/ajnr.A4430.
Jo, K.W., Kim, Y., Park, G.Y., Park, I.S., Jang, Y., Gyun, S.D., Im, S., 2017. Oropharyngeal dysphagia in secondary normal pressure hydrocephalus due to corticobulbar tract compression: cases series and review of literature. Acta Neurochir. (Wien.) 159, 1005–1011. https://doi.org/10.1007/s00701-017-3157-5.
Lee, W.H., Lim, M.H., Seo, H.G., Seong, M.Y., Oh, B.M., Kim, S., 2020. Development of a Novel Prognostic Model to Predict 6-Month Swallowing Recovery After Ischemic Stroke. Stroke 51, 440–448. https://doi.org/10.1161/STROKEAHA.119.027439.
Li, S., Luo, C., Yu, B., Yan, B., Gong, Q., He, C., He, L., Huang, X., Yao, D., Lui, S., Tang, H., Chen, Q., Zeng, Y., Zhou, D., 2009. Functional magnetic resonance imaging study on dysphagia after unilateral hemispheric stroke: a preliminary study. J. Neurol. Neurosurg. Psychiatry 80, 1320–1329. https://doi.org/10.1136/jnnp.2009.176214.
Maffei, C., Sarubbo, S., Jovicich, J., 2019. Diffusion-based tractography atlas of the human acoustic radiation. Sci. Rep. 9, 4046. https://doi.org/10.1038/s41598-019-40666-8.

Martin-Harris, B., Brodsky, M.B., Michel, Y., Castell, D.O., Schleicher, M., Sandidge, J., Maxwell, R., Blair, J., 2008. MBS measurement tool for swallow impairment–MBSImp: establishing a standard. Dysphagia 23, 392–405. https://doi.org/10.1007/s00455-008-9185-9.

Martino, R., Foley, N., Bhogal, S., Diamant, N., Speechley, M., Teasell, R., 2005. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. Stroke 36, 2756–2763. https://doi.org/10.1161/01.STR.0000190056.76543.eb.

McCaman, R.E., Robins, E., 1959. Quantitative Biochemical Studies of Wallerian Degeneration in the Peripheral and Central Nervous Systems—I. J. Neurochem. 5, 18–31. https://doi.org/10.1111/j.1471-4159.1959.tb13329.x.

Mihai, P.G., Otto, M., Domin, M., Platz, T., Hamdy, S., Lotze, M., 2016. Brain imaging correlates of recovered swallowing after dysphagic stroke: A fMRI and DWI study. Neuroimage Clin. 12, 1013–1021. https://doi.org/10.1016/j.nicl.2016.05.006.

Mosier, K., Bereznaya, I., 2001. Parallel cortical networks for volitional control of swallowing in humans. Exp. Brain Res. 140, 280–289. https://doi.org/10.1007/s002210100813.

Oh, H.M., Kim, T.W., Park, H.Y., Kim, Y., Park, G.Y., Im, S., 2021. Role of rs6265 BDNF polymorphisms and post-stroke dysphagia recovery-A prospective cohort study. Neurogastroenterol. Motil. 33, e13953.

Oh, J.-C., 2014. Reliability and validity of Korean Mann assessment of swallowing ability (K-MASA). Graduate School, Yonsei University, Seoul.

Park, E., Kim, M.S., Chang, W.H., Oh, S.M., Kim, Y.K., Lee, A., Kim, Y.H., 2017. Effects of bilateral repetitive transcranial magnetic stimulation on post-stroke dysphagia. Brain Stimul. 10, 75–82. https://doi.org/10.1016/j.brs.2016.08.005.

Park, J.-H., Kwon, Y.C., 1990. Modification of the mini-mental state examination for use in the elderly in a non-western society. Part 1. Development of korean version of mini-mental state examination. Int. J. Geriatr. Psychiatry 5, 381–387. https://doi.org/10.1002/gps.930050606.

Robbins, J., Levin, R.L., 1988. Swallowing after unilateral stroke of the cerebral cortex: preliminary experience. Dysphagia 3, 11–17. https://doi.org/10.1007/BF02406275.

Rolls, E.T., 2016. Functions of the anterior insula in taste, autonomic, and related functions. Brain Cogn. 110, 4–19. https://doi.org/10.1016/j.bandc.2015.07.002.

Rosenbek, J.C., Robbins, J.A., Roecker, E.B., Coyle, J.L., Wood, J.L., 1996. A penetration-aspiration scale. Dysphagia 11, 93–98. https://doi.org/10.1007/bf00417897.

Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., Weiller, C., 2006. Dynamics of language reorganization after stroke. Brain 129, 1371–1384. https://doi.org/10.1093/brain/awl090.

Shah, S., Vanclay, F., Cooper, B., 1989. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J. Clin. Epidemiol. 42, 703–709. https://doi.org/10.1016/0895-4356(89)90065-6.

Son, Y.R., Choi, K.H., Kim, T.G., 2015. Dysphagia in Tongue Cancer Patients. Ann. Rehab. Med. 39, 210–217. https://doi.org/10.5535/arm.2015.39.2.210.

Suntrup, S., Kemmling, A., Warnecke, T., Hamacher, C., Oelenberg, S., Niederstadt, T., Heindel, W., Wiendl, H., Dziewas, R., 2015. The impact of lesion location on dysphagia incidence, pattern and complications in acute stroke. Part 1: dysphagia incidence, severity and aspiration. Eur. J. Neurol. 22, 832–838. https://doi.org/10.1111/ene.12670.

Teismann, I.K., Dziewas, R., Steinstraeter, O., Pantev, C., 2009. Time-dependent hemispheric shift of the cortical control of volitional swallowing. Hum. Brain Mapp. 30, 92–100. https://doi.org/10.1002/hbm.20488.

Thomalla, G., Glauche, V., Koch, M.A., Beaulieu, C., Weiller, C., Röther, J., 2004. Diffusion tensor imaging detects early Wallerian degeneration of the pyramidal tract after ischemic stroke. Neuroimage 22, 1767–1774. https://doi.org/10.1016/j.neuroimage.2004.03.041.

Venkatasubramanian, C., Kleinman, J.T., Fischbein, N.J., Olivot, J.-M., Gean, A.D., Eyngorn, I., Snider, R.W., Mlynash, M., Wijman, C.A.C., 2013. Natural history and prognostic value of corticospinal tract Wallerian degeneration in intracerebral hemorrhage. J. Am. Heart Assoc. 2, e000090.

Warnecke, T., Im, S., Kaiser, C., Hamacher, C., Oelenberg, S., Dziewas, R., 2017. Aspiration and dysphagia screening in acute stroke - the Gugging Swallowing Screen revisited. Eur. J. Neurol. 24 (4), 594–601.

Wilmskoetter, J., Bonilha, L., Martin-Harris, B., Elm, J.J., Horn, J., Bonilha, H.S., 2019. Mapping acute lesion locations to physiological swallow impairments after stroke. Neuroimage Clin. 22, 101685. https://doi.org/10.1016/j.nicl.2019.101685.

Zolkefley, M.K.I., Firwana, Y.M.S., Hatta, H.Z.M., Rowbin, C., Nassir, C.M.N.C.M., Hanafi, M.H., Abdullah, M.S., Mustapha, M., 2021. An overview of fractional anisotropy as a reliable quantitative measurement for the corticospinal tract (CST) integrity in correlation with a Fugl-Meyer assessment in stroke rehabilitation. J. Phys. Ther. Sci. 33, 75–83. https://doi.org/10.1589/jpts.33.75.