Effect of brain lesions on voluntary cough in patients with supratentorial stroke: an observational study

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Abstract

Background: Patients with stroke are known to manifest decreased cough force, which may increase the risk of aspiration. Specific brain lesions have been linked to impaired reflexive cough. However, only a few studies investigated whether specific stroke lesions are associated with impaired voluntary cough. The present study analyzed the effects of stroke lesion on voluntary cough using voxel-based lesion-symptom mapping (VLSM).

Methods: In this retrospective cross-sectional study, the peak cough flow was measured in patients who complained of weak cough (n = 39) after supratentorial lesions. Brain lesions were analyzed via magnetic resonance imaging (MRI) at the onset of stroke. These lesions were analyzed using VLSM.

Results: The VLSM method with non-parametric mapping revealed that lesions in the sub-gyral frontal lobe, superior longitudinal and posterior corona radiata were related to weak cough flow. Also, lesions in the inferior parietal and temporal lobes, and both superior and mid-temporal gyrus were also associated with weak peak cough flow during voluntary coughing.

Conclusions: The present study identified several brain lesions underlying impaired voluntary cough. The results may be useful in predicting those at risk of poor coughing function and may facilitate the prognosis of patients at increased risk of respiratory complications after stroke.

Background

Respiratory dysfunction and pneumonia are leading causes of post-stroke hospitalization and high mortality [1]. Many patients with respiratory complications may manifest impaired cough reflex and poor clearance of secretions, along with impairments in swallowing, which may increase the risk of aspiration. Although cough and swallow require coordinated but distinct oral, laryngeal and respiratory muscles [2], they both share similar nerves and muscles with a significant overlap in the control mechanisms. Despite these similarities, it is still difficult to predict patients at risk of impaired cough especially in those with swallowing disturbances. Early identification of those with impaired cough and thus, at risk of respiratory complications based on neuroimaging findings may be helpful. The motor act of cough is characterized by reorganization of the central breathing pattern to produce the three characteristic phases of a typical cough that include inspiration, compression with glottic
closure and expiration, which are known to originate in the cortex [2]. Cough may be produced either via reflexive or voluntary manner, though both types prevent aspiration and protect the airway. Reflexive cough (RC) is automatically generated by afferent activation, whereas voluntary cough (VC) is a conscious act and requires voluntary activation of the respiratory muscles, including the diaphragm, a major inspiratory muscle. Stroke patients are known to have reduced excursion of the diaphragm, and therefore generate poor peak cough flow during VC [3, 4].

While the cough center is located at the brainstem, previous transcranial magnetic stimulation studies have shown that excursion of the diaphragm, which is important in VC, is mediated by the cortico-respiratory projections across the cortex [5–7] suggesting supra-medullary control. Similarly, a recent study by Suntrup-Krueger et al. [8] demonstrated the role of specific cortical lesions with impaired RC in stroke patients. Although middle cerebral artery (MCA) [9, 10] and capsular infarctions [11] represent major risk factors contributing to a weak diaphragm, the localization of supratentorial regions associated with poor VC is still poorly understood [12]. The brain lesions associated with poor VC are still unknown.

Disturbances in cough can be life-threatening especially in post-stroke patients. Therefore, identifying those at risk of poor cough is crucial to prevent aspiration pneumonia. Thus, the aims of this study were to investigate the effects of stroke lesions on VC function using voxel-based lesion-symptom mapping (VLSM). We also aimed to identify the brain lesions that are associated with poor VC in post-stroke patients.

Methods

Patient selection

The present study was a retrospective cross-sectional study that included 39 right-handed patients with a confirmed ischemic stroke. Medical records of patients with a positive record of weak VC, based on the assessment of a physical therapist at the point of rehabilitation entry, were used for analysis [13]. After subjective diagnosis of weak cough, these findings were confirmed by objective analysis via a respiratory pressure meter.

Stroke lesions were confirmed by neurological symptoms and initial brain imaging studies such as
magnetic resonance imaging (MRI) or CT scan. All data were obtained from patients recruited from a single stroke center from August 2015 to July 2017. Only those with ischemic stroke confined to the supratentorial area and who met the following inclusion criteria were included for the analysis: 1) age from 20 to 80 years, 2) first-ever unilateral stroke, 3) ability to follow verbal instructions, and 4) full records of swallowing and respiratory pressure measurements including voluntary peak cough flow (PCF).

The exclusion criteria were as follows: 1) a history of spinal cord injury affecting the respiratory muscles, 2) stroke related to infratentorial lesions, 3) a history of chronic obstructive pulmonary disease, asthma or other lung disorders that may affect respiratory pressure parameters, 4) Parkinson’s disease, myopathy, head and neck cancer lesions, dementia, or other disorders that affect respiratory function and 5) poor conscious state or inability to follow commands to initiate a cough. Demographic and brain MRI data were collected from all subjects to evaluate swallowing and respiratory pressure parameters. Brain lesions were evaluated using a high-resolution 3-T anatomical MRI system with a 5-mm slice thickness within 14 days of stroke.

The study protocol was reviewed and approved by the Institutional Review Board of our institution (Registry No. BC000000).

Clinical assessment

Basic patient demographics and medical diagnosis along with the National Institutes of Health Stroke Scale (NIHSS) [14], stroke classification according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria [15] were recorded. Functional assessments including the modified Barthel index (MBI) [16], Mini Mental State Examination (MMSE) were retrieved from the medical charts.

Lesion analysis

Lesions were mapped using the MRICron software (http://www.mricro.com/mricron) and were drawn manually on individual T2 scans of patient by a trained image analyst, and confirmed by an experienced clinical psychiatrist, who was blinded to all clinical data except for the side with hemiparesis. For more accurate analyses, the origin of each image (coordinates: 0 × 0 × 0 mm) was reoriented such that it was located close to the anterior commissure. To increase the statistical power
for identification of the lesion pattern, which showed a significant contribution to PCF independent of hemispheric lateralization, the volume-of-interest (VOI) images were transformed to the right hemisphere. To analyze the mutual lesion maps, segmentation and normalization were employed[17]. We used MR segment-normalize function of a plugin toolbox (www.mricro.com/clinical-toolbox/) to map the stereotaxic space using the normalization algorithm provided by the SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) software. T2 images were co-registered with each participant’s T1 MRI. The T1 and lesion maps were normalized to the Montreal Neurologic Institute space using statistical parametric mapping. A unified segmentation-normalization was performed on the anatomical scan. A VLSM procedure was developed to analyze the relationship between tissue damage and behavior on a voxel-by-voxel basis. VLSM was usually performed using binary data (with/without a deficit) with a cutoff value. However, information reflecting varying degrees of capacity may be lost under such approach [18]. To avoid this potential issue, a direct statistical comparison of lesions was performed according to the degree of PCF using a VLSM method implemented in non-parametric mapping (NPM) software included in the MRIcron software [19]. Only voxels that exhibited lesions in at least 10% (n = 4) of all patients were included in the final analysis. Non-parametric Brunner–Munzel tests for continuous data were used [19] because of continuous clinical deficit. In the NPM analyses, a lower value refers to a poorer performance; thus, subjects with a score of 40 were severe compared with those scoring 80. Colored VLSM maps representing the z statistics were generated and overlaid onto the automated anatomical labeling and Johns Hopkins University white matter templates provided with MRIcron software [19]. Additionally, to identify relevant anatomic structures implicated in the analyses, Talairach Daemon (http://www.talairach.org/) was used [20]. P-values < 0.05 were considered to indicate statistical significance.

**Respiratory pressure parameters**

To assess the voluntary PCF the patient was asked to perform a quick forceful cough. The clinician educated the patient regarding how to cough on the portable spirometer. Both voluntary and respiratory pressure parameters were measured by therapists not involved in the imaging analysis of the cases.
The voluntary PCF, the maximal inspiratory pressure (MIP), and the maximal expiratory pressure (MEP) were measured using the same methods following the guidelines recommended by the Society/European Respiratory Society [21]. For VC, the PCF values were presented as the mean of the three highest values of five attempts. The MIP and the MEP were measured using a respiratory pressure meter (Micro-Plus Spirometer; Carefusion, Corp., San Diego, CA, USA). The highest recorded values after three attempts were used for analysis. Patients with PCF values lower than <80 L/min were considered at risk of aspiration. The cut-off values were based on past reports as valid references to predict respiratory complications [22]. Aspiration pneumonia within the first month after stroke onset was identified. Aspiration pneumonia was defined by respiratory symptoms with a temperature exceeding 38°C, leukocytosis, and infiltration confirmed by chest radiography warranting the use of antibiotics.

**Swallowing assessment**

Swallowing assessment was performed first via a screening test; the Gugging Swallowing Screen (GUSS) test [23, 24] at admission, followed by formal assessment using the Mann Assessment of Swallowing Ability (MASA) scales [25], the Functional Oral Intake Scale (FOIS) [26] and Penetration-Aspiration Scale (PAS) [27] scores obtained during the initial videofluoroscopy studies.

**Statistical analysis**

Intergroup differences between those with PCF <80 versus > 80 L/min were assessed using t-test and chi-squared test as appropriate based on the data expressed as either the mean or median values for continuous variables and frequencies and percentages for normal variables. If Kolmogorov–Smirnov test and the Shapiro–Wilk test failed to show normal distribution, Mann-Whitney U test was performed.

Correlation analysis of the variables between the PCF and swallowing parameters was performed, followed by analysis between the volume lesion and functional parameters. The rho values ranging between 0.9 and 1.0 were considered to show with very high positive correlation, 0.7-0.9 with high positive correlation; 0.3-0.5 with low positive and 0.0-0.3 with negligible correlation. All tests with \(P\)-values of <0.05 were considered significant. Statistical analyses were performed using R 2.15.3.
package software (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Clinical assessment**

A total of 39 cases that fulfilled the inclusion criterion and had full assessment of the respiratory pressure meter were identified. The basic demographic and clinical features of the patients are presented (Table 1).

**Lesion analysis**

A lesion overlay of all the subjects is presented in Fig 1. Based on the results of VLSM with NPM, lesions of the subgyral parietal and frontal lobe, superior longitudinal fasciculus (SLF), posterior corona radiata, temporal lobe, the posterior limb of internal capsule, and superior temporal gyrus (STG) of the temporal lobes were associated with decreased coughing function post-stroke (Fig 2, Table 2).

**Respiratory pressure parameters**

All assessments were made at 9.4 ± 6.8 days after stroke onset. The mean value of the PCF was 98.4 ± 58.4 L/min. Those with low cough values (n = 19) with increased risk of aspiration showed significant differences in stroke severity and functional disabilities.

Twelve of the 39 patients (30.7%) carried a positive history of aspiration pneumonia during the first month of stroke onset. Among these patients, a higher proportion of those with PCF < 80 L/min (52.6% versus 10%, p = 0.004) developed aspiration pneumonia within the first month post onset.

**Swallowing parameters**

Overall, most patients had some evidence of dysphagia but those with PCF < 80 L/min showed more increased severity of dysphagia. By the time of the assessments, their median FOIS value was “1” which denoted nil per mouth status. However, no intergroup differences were observed in the PAS.

**Correlation analysis of PCF**

The PCF showed a statistically significant (P < .0001) positive correlation with the swallowing parameters that included the FOIS (r = 0.695), MASA (r = 0.714) and GUSS (r = 0.733) scores, confirming that weak cough correlates with increased severity of swallowing disturbance (Fig 3).
However, no significant correlation was observed with the PAS (r = -0.221). Modest degree correlations were also between the PCF and other functional parameters (i.e. NIHSS, Berg, MMSE, MBI) (absolute rho values = 0.38-0.58).

**Correlation analysis of lesion volume**

The lesion volume of patients with “weak” versus “strong” cough showed no statistical differences (P = 0.766). Correlation analysis of lesion volumes and PCF failed to show any significance (rho = -0.25, P = 0.13). Though lesion volume showed some significant correlations with MEP (P = 0.016) and MIP (P = 0.022), the rho values indicated only moderate negative association (rho= -0.38, -0.36). In addition, lesion volume showed significant correlations to other functional parameters such as MBI (rho = -0.357, P = 0.025) and initial NHISS scores (rho = 0.53936, P = 0.00039). (Fig 4)

**Discussion**

The results of this study suggest that specific supratentorial lesions are associated with decreased VC function in patients diagnosed with stroke, confirming previous studies [6, 7, 10] implicating both cortical and subcortical regions in the control of VC. Our findings establish the role of supratentorial lesions in the frontal sub-gyral area, STG, some parts of the parietal lobes, and superior corona radiata. In addition, the SLF showed significant association. Knowledge of these brain sites involved in poor VC may facilitate early identification of patients with poor coughing function.

Due to disruption of the cortical and medullary area associated with cough generation [28] both the RC and VC may be affected after stroke [9]. These two types of cough share common features, including a 3-phase inspiration pattern compressed with glottic adduction followed by expulsion via contraction of the respiratory muscles [29]. They also share the same afferents and efferents. In line with these similarities, a few lesions from our study overlapped with those known to be involved in poor RC [8]. The overlapping lesions include the temporal lobe and STG areas, which are also crucial components in the swallowing mechanism. The supramarginal gyrus and temporal area represent sensorimotor regions are known to associated with impaired swallowing and also with impaired motor reaction in RC [8]. The similarities of the muscle activation and output between RC and VC suggest a possible role of the temporal, STG and suprmarginal gyrus lesions in the motor components of cough,
and their potential crucial roles in airway protection during swallowing.

Despite these similarities, the underlying musculoskeletal mechanisms and motor patterns of these two coughs differ considerably [29] with different stroke sites resulting in distinct cough impairment. Specific brain lesions that were exclusively investigated in this study; include the frontal lobe, the posterior corona radiate, and the sub-gyral area, which consist of the descending cortico-respiratory projections located within the pyramidal tract [11]. These cortico-respiratory projections are frequently affected in patients with hemiparesis due to stroke [6, 7]. These regions have not been strongly implicated in RC impairment in previous studies [8]. Our findings support the clinical role of these regions in the diminished ability to generate a VC due to direct involvement of the cortico-respiratory tract.

The frontal subgyral region and the frontal cortex may correspond closely to the cortical “hotspot” sites identified by electrophysiological studies using the transcranial magnetic stimulation [5, 6, 11]. Furthermore, the cortical representation of the inspiratory muscles is known to lie close to the vertex [30]. The corona radiata is part of the descending cortico-respiratory projection located within the pyramidal tract [11], and is also associated with increased risk of aspiration [31]. Although swallowing has been related to the superior or anterior portion of the corona radiata, our results indicate the involvement of the posterior part. The corona radiata is somatotopically arranged and while the anterior part involves the corticobulbar tract, the posterior portion controls the truncal muscles [31]. Since the role of the truncal and abdominal muscles is related not only to truncal control, but also to the control of the respiratory pump muscles and ventilation [32], it is plausible that the posterior portion of the corona radiata may reflect the involvement of respiratory muscles in VC. Thus, though not directly part of the corticobulbar tract involved in the act of swallowing, our results further suggest that these posterior corona radiata regions are crucial regions in airway protection.

An unexpected finding was the SLF, which is not part of the cortico-respiratory projections, to show positive association with VC. The SLF, which consists of longitudinal fibers that connect the dorsolateral frontal and parietal cortices [33], mediates the spatial coordination of the trunk and limbs and contributes to the preparatory sages of movement planning [34]. Therefore, the SLF may
contribute to the preparatory truncal function related to the respiratory muscles, such as the abdomen and respiratory muscles required for cough. The SLF also plays an important role in swallowing and its temporal part has been implicated in impaired RC [8]. In addition to these past findings, our results demonstrate that the lesions in the SLF may also interfere with airway protection by limiting VC.

Though swallowing and coughing are independent behaviors, both these two actions are strongly coordinated structural movements that require reconfiguration of the ventilatory breathing pattern [2]. Apparently, a few brain lesions already known to be involved in swallowing such as the STG [8] and the SLF [31] overlap with lesions that were associated with weak cough in this study. Therefore, it is not surprising that the PCF values showed strong correlations with swallowing parameters, suggesting that swallowing and coughing are closely linked. Coordination of these two behaviors is vital to protect the airway from aspiration. Therefore, further studies are needed to understand coughing and swallowing as both independent and as a coordinated response to aspiration events [35].

Post-stroke patients are known to carry impaired contralateral corticodiaphragmatic pathways and may manifest abnormal motion of the diaphragm. Patients diagnosed with dysphagia after stroke are known to exhibit a greater degree of diaphragm weakness than those without swallowing disturbance [3]. Accordingly, patients with stroke-related dysphagia are known to produce low PCF during VC compared to stroke patients without dysphagia and healthy controls [36]. In accordance, our results showed that those with PCF below 80 L/min showed increased severity of dysphagia and more respiratory infections. These results indicate that weakness of cough strength based on the measurement of cough flow can be used as an indicator of pneumonia risk and in acute stroke [37]. Increased lesion volume has been linked to severe dysphagia in previous studies [31]. In contrast, our results failed to show significant association between brain volume and PCF, obviating the need for adjustment of stroke lesion volume in our analysis. Though the functional parameters were affected by the total stroke volume, PCF was more specific to the lesion location rather than the total volume per se.
The study limitations are as follows. First, it was a retrospective study and many subjects who were either too ill to undergo spirometry may not have been included. Second, the PCF and PAS scores were poorly correlated. Nevertheless, patients with a lower PCF showed an increased incidence of respiratory complications, which was consistent with the results of multiple regression analysis reported by Sohn et al. [22], suggesting that PAS per se was not a predictor of respiratory complications. Third, no laterality was considered in this study with all the lesions flipped to one side. Past studies have shown that the majority of patients with left MCA [13] show weak or absent VC and suggested laterality in VC with the left cerebral hemisphere playing a dominant role in the voluntary control of cough. However, other studies failed to associate RC with a specific hemisphere [8, 38]. Indeed, right supratentorial stroke patients were also identified in our study. The discrepancies of our findings to those that suggested left laterality may be attributed to varying number of cases and different assessment methods for defining weak cough, where subjective classification of cough as either weak or absent, was used in the previous report [13]. All our cases were first screened by the physiotherapist to have a weak cough based on the same subjective classification as above, and then had undergone full objective measurements of the PCF. The mean PCF in our study, are lower than those reported from post-stroke patients with no coughing dysfunction(mean195 ± 67.1 L/min) or from healthy participants (253.2 ± 90.8 L/min)[3], confirming that all those in our analysis had impairment in VC. In addition, one has to consider that the diaphragm and voluntary respiratory movement are under the control of both hemispheres of the brain with no dominance [39]. Finally, it should be investigated whether the proposed lesions were specific to coughing alone given the overlap of patients with both dysphagia and cough dysfunction. However, our results did not reveal obvious lesions that are hallmarks of dysphagia, such as the insula or thalamus. Instead the lesions in our study closely correspond to the cortico-respiratory pathways [5, 11, 40].

In conclusion, this study provides novel insight into the cortical and subcortical dimensions of VC. The lesions defined in this study may facilitate stratification of patients at risk of impaired VC and respiratory complications, and thus identify candidates for respiratory training [41] along with conventional rehabilitation therapy after stroke.
Conclusions
Control of cough and the involved respiratory muscles may be under different control than the limbs. In post-stroke patients, specific regions were associated with impaired VC. The information provided in this study may facilitate early identification of patients with deficits in generating a proper VC, and thus have limited airway protective function.

Abbreviations
RC: Reflexive cough; VC: voluntary cough; MCA: middle cerebral artery; VLSM: voxel-based lesion-symptom mapping; PCF: peak cough flow; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; GUSS: Gugging Swallowing Screen; MASA: Mann Assessment of Swallowing Ability Scales; FOIS: Functional Oral Intake Scale; PAS: Penetration-Aspiration Scale
SLF: superior longitudinal fasciculus; STG: superior temporal gyrus; MBI: modified Barthel index
MMSE: Mini Mental State Examination; TOAST: Trial of ORG 10172 in Acute Stroke Treatment Classification; NIHSS: National Institutes of Health Stroke Severity Scale; NPM: non-parametric mapping

Declarations
Acknowledgements
None.

Authors’ contributions
KBL performed statistical and VLSM analysis
SHL was involved in the conceptual and design of the manuscript
GYP was involved in the collection of information
SI performed statistical analysis, wrote the manuscript and was responsible for the data collection
All authors read and approved the final manuscript

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Availability of data and materials
Not available
Ethics and consent approval

Consent was waived due to retrospective nature of the study

The institutional review boards approved the protocols of this study (HC17RESI0080)

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Tables

Table 1 Basic demographic and clinical features
| Variables                                      | Total (n=39) | Cough <80 L/min (n = 19) |
|------------------------------------------------|--------------|--------------------------|
| **Basic demographics**                         |              |                          |
| Age                                            | 72.6 ± 12.5  | 76.6 ± 10.3              |
| Gender                                         |              |                          |
| Male                                           | 25 (64.1)    | 13 (68.4)                |
| Female                                         | 14 (35.9)    | 6 (31.6)                 |
| Body mass index                                | 22.9 ± 2.9   | 23.4 ± 2.6               |
| **Brain lesion classification**                |              |                          |
| Total lesion volume (voxels)                   | 55985.1 ± 91883.6 | 60558.8 ± 92950.9     |
| Laterality                                     |              |                          |
| Right                                          | 24 (61.5)    | 11 (57.9)                |
| Left                                           | 15 (38.5)    | 8 (42.1)                 |
| **TOAST**                                      |              |                          |
| Large artery atherosclerosis                    | 18 (46.1)    | 8 (42.1)                 |
| Cardioembolism                                 | 9 (23.1)     | 6 (31.6)                 |
| Small-vessel occlusion                         | 12 (30.8)    | 5 (26.3)                 |
| **Medical Comorbidities**                      |              |                          |
| Diabetes mellitus                              | 12 (30.8)    | 7 (36.8)                 |
| Hypertension                                   | 24 (61.5)    | 15 (78.9)                |
| Atrial fibrillation                            | 9 (23.1)     | 6 (31.6)                 |
| Hyperlipidemia                                 | 1 (2.6)      | 0 (0.0)                  |
| **Neurological function**                      |              |                          |
| NIHSS                                          | 6.4 ± 4.2    | 7.6 ± 4.2                |
| MBI                                            | 38.7 ± 27.7  | 26.5 ± 25.5              |
| MMSE                                           | 19.6 ± 6.4   | 17.3 ± 6.6               |
| Berg                                           | 17.7 ± 20.6  | 9.7 ± 14.7               |
| **Respiratory pressure measurements**          |              |                          |
| Peak cough flow (L/min)                        | 98.4 ± 58.4  | 53.0 ± 20.6              |
| MIP (cmH$_2$O)                                 | 26.6 ± 25.4  | 14.5 ± 8.8               |
| MEP (cmH$_2$O)                                 | 40.2 ± 32.4  | 23.2 ± 16.6              |
| **Swallowing parameters**                      |              |                          |
| FOIS                                           | 2 (1-4)      | 1 (1-2)                  |
| K-MASA                                         | 155.1 ± 17.1 | 142.9 ± 14.9             |
| GUSS                                           | 7.6 ± 4.3    | 4.7 ± 2.6                |
| PAS                                            | 8 (7-8)      | 8 (7.5-8)                |

Values are presented as mean ± standard deviation (SD), number (%), and median (range of interquartile).

TOAST: Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Classification; NIHSS: National Institutes of Health Stroke Severity Scale; MBI: Modified Barthel Index; MMSE: Mini-Mental State Examination; MIP: Maximal inspiratory pressure; MEP: Maximal expiratory pressure; FOIS: Functional Oral Intake Scale; MASA: Mann Assessment of Swallowing Ability; GUSS: Gugging Swallowing screen; PAS: Penetration Aspiration Scale.

*Estimated by a t-test for continuous variables or Mann-Whitney U test between Cough force < 80 L/min versus > 80 L/min groups.
### Table 2 Stroke lesions related to voluntary cough impairment

| MNI coordinates (X, Y, Z) | BM Z max | n Voxels | Anatomical brain lesion |
|---------------------------|-----------|----------|------------------------|
| 34, -38, 35               | 2.90267   | 114      | Parietal lobe, Sub-Gyral |
| 29, -26, 32               | 3.38958   | 111      | Frontal lobe, Superior longitudinal |
| 29, 13, 28                | 2.85527   | 116      | Frontal lobe, Sub-Gyral |
| 29, -27, 30               | 3.17468   | 114      | Posterior corona radiata |
| 38, -35, 15               | 2.65207   | 106      | Temporal lobe, STG      |
| 42, -41, -7               | 2.55235   | 115      | Temporal lobe, MTG      |

The Montreal Neurological Institute (MNI) coordinates represents the voxels which is tested significant based on Brunner-Munzel (BM) Z score and the number (n) of clustering voxels that survived the threshold of $Z < 0.05$, false discovery rate corrected. Anatomical region is identified using Talairach daemon tool, the automated anatomical labeling and the Johns Hopkins University white matter templates. STG: superior temporal gyrus, MTG: middle temporal gyrus.

### Figures

#### Figure 1

Overlay of lesions for stroke patients included in this study (n = 39). Maps are overlaid on a T1-template in Montreal Neurologic Institute space $1 \times 1 \times 1$ mm.
Figure 2

Statistical voxel-based lesion-symptom mapping. The nonparametric Brunner–Munzel statistical analysis was used for the continuous peak cough flow. Color scale indicates Brunner–Munzel rank order z-statistics. Only voxels significant at $P < 0.05$ are shown. Colored bar represents the z statistics. We set the maximum range of the Z score as 4, which are shown with the maximum brightness.
Heat map of correlation coefficients (Spearman) between the peak cough flow (L/min) and degree of dysphagia and aspiration, are displayed in different colors. The color scale indicates the degree of correlation (blue, strong positive correlation; white, weak correlation; red, strong negative correlation). PCF: peak cough flow; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; FOIS: Functional Oral Intake Scale; MASA: Mann Assessment of Swallowing Ability; GUSS: Gugging Swallowing Screen
Figure 4

Heat map of correlation coefficients (Spearman) between the lesion volume and functional parameters displayed in different colors. The color scale indicates the degree of correlation (blue, strong positive correlation; white, weak correlation; red, strong negative correlation).

PCF: peak cough flow; NIHSS: National Institutes of Health Stroke Severity Scale; MMSE: Mini-Mental State Examination; MBI: Modified Barthel Index