Lesion Location Predicts Transient and Extended Risk of Aspiration After Supratentorial Ischemic Stroke

Marian Galovic, MD*; Natascha Leisi, MSc*; Marlise Müller, BA; Johannes Weber, MD; Eugenio Abela, MD; Georg Kägi, MD; Bruno Weder, MD

Background and Purpose—To assess the association of lesion location and risk of aspiration and to establish predictors of transient versus extended risk of aspiration after supratentorial ischemic stroke.

Methods—Atlas-based localization analysis was performed in consecutive patients with MRI-proven first-time acute supratentorial ischemic stroke. Standardized swallowing assessment was carried out within 8±18 hours and 7.8±1.2 days after admission.

Results—In a prospective, longitudinal analysis, 34 of 94 patients (36%) were classified as having acute risk of aspiration, which was extended (≥7 days) or transient (<7 days) in 17 cases. There were no between-group differences in age, sex, cause of stroke, risk factors, prestroke disability, lesion side, or the degree of age-related white-matter changes. Correcting for stroke volume and National Institutes of Health Stroke Scale with a multiple logistic regression model, significant adjusted odds ratios in favor of acute risk of aspiration were demonstrated for the internal capsule (adjusted odds ratio, 6.2; P<0.002) and the insular cortex (adjusted odds ratio, 4.8; P<0.003). In a multivariate model of extended versus transient risk of aspiration, combined lesions of the frontal operculum and insular cortex was the only significant independent predictor of poor recovery (adjusted odds ratio, 33.8; P<0.008).

Conclusions—Lesions of the insular cortex and the internal capsule are significantly associated with acute risk of aspiration after stroke. Combined ischemic infarctions of the frontal operculum and the insular cortex are likely to cause extended risk of aspiration in stroke patients, whereas risk of aspiration tends to be transient in subcortical stroke. (Stroke. 2013;44:2760-2767.)

Key Words: deglutition disorders ■ magnetic resonance imaging ■ stroke

Swallowing difficulties are common sequelae of ischemic stroke occurring in ≥50% of cases and may be associated with poor outcome and increased mortality. Traditionally, risk of aspiration after stroke has been related to brain stem lesions, whereas the association of cortical stroke location and aspiration or dysphagia has not been confirmed by lesion studies yet. Some authors found a correlation merely on a lobar level, whereas others did not find an association at all. Thus, a recent systematic review could not provide enough neuroanatomical evidence for emerging dysphagia after supratentorial ischemic stroke.

Approximately half of dysphagic patients fail to recover swallowing function within 1 week and are subject to an increasing risk of aspiration-related complications. Recovery of swallowing continues beyond 7 days, which is why at 6 months only 8% are dysphagic and 13% fail to return to prestroke diet. According to guidelines, patients with insufficient oral intake for ≥7 days qualify for enteral tube feeding, however, nasogastric tube feeding should be preferred to percutaneous endoscopic gastrostomy feeding in the early phase. Enteral nutrition should be administered early (ie, beginning within 72 hours after stroke), emphasizing the need for an early and accurate prediction of patients at risk of persisting aspiration for ≥1 week. Nevertheless, little knowledge exists on reliable neuroanatomical predictors of recovery of swallowing disorders.

Consequently, the aims of our lesion-behavior mapping study were (1) to assess the association of lesion location and risk of aspiration and (2) to establish MRI-based predictors of transient versus extended risk of aspiration after supratentorial ischemic stroke.

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Patients and Methods

Study Population
We performed a prospective, longitudinal cohort study between January 2011 and February 2012, and screened 320 consecutive patients for eligibility. Excluded were patients with recurrent stroke (n=69), infratentorial stroke (n=54), transient ischemic attack or lack of evidence of stroke on MRI (n=19), diagnosis other than ischemic stroke (n=32), no MRI performed (n=19), and late patient arrival (n=15). Some patients did not complete follow-up because of death or early referral to a peripheral hospital (n=8), did not give consent (n=1), had pre-existing dysphagia (n=1), or a severe disorder of consciousness hindering swallowing evaluation (n=8). Eventually, we included 94 patients in our final analysis. The study was approved by the local ethics committee, and subjects gave informed consent.

Clinical Assessment
Swallowing was evaluated in all patients using a comprehensive assessment by a speech-language pathologist within 48 hours (mean, 8±18 hours) of admission in all but 5 cases, in whom a detailed scoring for study inclusion could not be performed due to time because of a severely lowered general state. In these 5 patients acute risk of aspiration was later confirmed by a swallowing assessment within 3 to 4 days after admission; hence, they were still included in the final analysis. All patients who were classified as being at risk of aspiration during the first assessment were re-evaluated by the same comprehensive swallowing assessment within 7 to 9 days (mean, 7.8±1.2 days) after admission. The rationale for choosing this time period was the need for enteral nutrition if oral intake was inadequate for a period of ≥7 days because of persisting swallowing difficulties. Furthermore, we anticipated the highest rate of functional recovery of swallowing within the first week after stroke. The speech-language pathologists were not aware of specific lesion location in the delineated regions of interest (ROIs; see below). In between both assessments standard therapeutic interventions were performed.

The oral motor assessment consisted of the examination of oral musculature strength, agility and symmetry, as well as the examination of protective reflexes, sensation, and testing of water swallowing. To classify the risk of aspiration we used a standardized clinical assessment tool (2 out of 6 scale) consisting of 6 features (dysphonia, dysarthria, abnormal gag reflex, abnormal volitional cough, cough after swallowing, and voice change after swallowing) which was established and validated by Daniels et al. The presence of ≥2 features provides an objective indicator of an elevated risk of aspiration, whereas <2 features indicate no risk of aspiration (sensitivity 92%; specificity 67%; as referenced to a study on video-fluoroscopic swallowing, in the online-only Data Supplement). Demographic variables, stroke risk factors, National Institutes of Health Stroke Scale (NIHSS), and the prestroke disability assessed with the modified Rankin Scale were noted by the treating physician at admission. Cause of stroke according to the Trial of Org 10172 in Acute Stroke Treatment classification was defined at discharge based on a comprehensive standard workup.

Classification of Subgroups
The classification of patients relied on the 2 out of 6 scale scores of the 2 assessments. During the first swallowing assessment, scheduled whenever applicable within 48 hours after admission, patients were classified as (1) controls (no risk of aspiration) with a score of 0 to 1 or as (2) having acute risk of aspiration with a score of 2 to 6. Patients with acute risk of aspiration were further subclassified during a follow-up examination scheduled 7 to 9 days after admission as having (1) transient risk of aspiration or if they had meanwhile recovered toward a score of 0 to 1 or as (2) extended risk of aspiration in the early subacute phase if they failed to recover and had a score of 2 to 6.

Definition of ROIs
On the basis of a literature review of swallowing function, we explored the individual MRIs according to ROIs, which were mentioned in a list of previous research articles. Eleven nonoverlapping ROIs (Figure 1; for details and references see online-only Data Supplement) were identified in studies of functional brain imaging (number of studies, n=22) and cortical stimulation (n=7) in healthy individuals or lesion-based studies in dysphagia patients (n=9). Brodmann areas (BAs) were additionally assigned to the corresponding cortical ROIs to increase the reproducibility of results. Furthermore, the caudal sensorimotor and premotor cortices were described as portions of the BAs 1 to 4 and 6 lying caudal of the uppermost parts of the lateral ventricles.

Image Analysis
Brain scans were retrospectively analyzed by a neurologist (M.G.) who was blind to the results of the swallowing assessment at the time of image analysis. Diffusion-weighted imaging sequences were used for lesion definition because of superior contrast for the delineation of ischemic lesions. For detailed information on the parameters used for image acquisition see online-only Data Supplement. To compare and describe brain structures while accounting for individual differences in size and overall shape of the brain we performed a semiautomatic atlas-based image analysis. We relied on the MIPAV software (http://mipav.cit.nih.gov) for transformation to the Talairach coordinate system and proceeded as follows: In the first step, spatial normalization of diffusion-weighted imaging data sets was performed via landmark-driven realignment of the anterior/posterior commissural and the mid sagittal planes. Second, the brain was rescaled in a piece-wise nonlinear transformation to match its boundaries within the Talairach space. Finally Brodmann area labels were superimposed on the realigned brain MRI, and the visual presence or absence of lesions in the predefined ROIs was noted on a binomial scale (ie, 1=presence of lesion in ROI; 0=no lesion in ROI).

Figure 1. Regions of interest (ROIs) involved in swallowing. Illustration of the 11 studied ROIs in the stereotaxic Talairach space. See online-only Data Supplement for detailed description of ROIs. *Insular Brodmann areas (BA) corresponding to those described in nonhuman primates.
Lesion size was calculated with the ImageJ software (http://rsbweb.nih.gov/ij/). We used a previously described method\(^2\) of manually outlining the lesion pattern on each slice and multiplying the obtained area by the slice thickness to calculate the volume. Age-related white-matter changes were classified according to a rating scale proposed by Wahlund et al.\(^23\) The analysis of vascular territories was based on previously published atlas data.\(^24\) A lesion overlap map of the frontal operculum (BA 44) was finally generated for the subgroup of patients with extended risk of aspiration (see online-only Data Supplement for detailed description).

**Statistical Methods**

Individual lesions were introduced into the statistical analysis as categorical variables describing their overlap with an ROI, if they projected on an ROI or they did not. Patients with acute risk of aspiration versus controls and those with transient versus extended risk of aspiration were analyzed separately, because different pathogenetic mechanisms were assumed in the development of acute risk of aspiration, as compared with recovery of swallowing function.

Using the Kolmogorov–Smirnov test the assumption of a normal distribution was rejected in all continuous variables, hence, nonparametric testing was performed using median, interquartile range, and the Mann–Whitney \(U\) test or the Kruskal–Wallis test. Categorical variables were consistently analyzed with Fisher exact test because of small sample sizes in several subgroups. A 2-tailed \(P\) value of <0.05 was considered significant, corrected with the Holm–Bonferroni method for multiple comparisons.

Multiple logistic regression models with a stepwise backward elimination method (removal if \(P > 0.1\)) were fitted for variables, whose value considered significant. Goodness of fit was measured with overall model accuracy, specificity, and sensitivity, Nagelkerke \(R^2\), and Model \(\chi^2\). The Wald test was used to calculate variable significance. To test the robustness of the regression method and to verify that all relevant ROIs were included in the obtained models, we fitted separate multivariate models for every ROI including 3 variables per model (because of possible limitations of sample size).\(^25\) All calculations were done with the SPSS 20.0 software.

**Results**

Of 94 included patients 34 (36\%) were classified as having acute risk of aspiration at assessment 1 (mean, 8±18 hours after admission). Of these patients, 17 (50\%) had either transient or extended risk of aspiration in the early subacute phase at assessment 2 (mean, 7.8±1.2 days after admission). Patients with transient or extended risk of aspiration performed worse on several swallowing measures (50 mL water swallowing test, functional oral intake measured by Bogenhausener dysphagia score-2\(^{27}\); see online-only Data Supplement for additional information on Bogenhausener dysphagia score-2). Patients with extended risk of aspiration were significantly more likely to suffer from chest infection or failed return to pre-stroke diet during hospitalization, had longer hospital stay and higher institutionalization rate, and received enteral tube feeding more frequently (Table 1).

**Assessment 1: Acute Versus No Risk of Aspiration**

There were no between-group differences in age, sex, cause of stroke, risk factors, pre-stroke disability according to the

<table>
<thead>
<tr>
<th>Table 1. Outcome and Swallowing Characteristics of Patient Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Risk of Aspiration (n=60)</strong></td>
</tr>
<tr>
<td>Results of swallowing assessments, 2 of 6 scale(^17)</td>
</tr>
<tr>
<td>Assessment 1†</td>
</tr>
<tr>
<td>Assessment 2†</td>
</tr>
<tr>
<td>Abnormal 50 mL water swallow</td>
</tr>
<tr>
<td>Assessment 1‡</td>
</tr>
<tr>
<td>Assessment 2‡</td>
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<tr>
<td>Functional oral intake (BODS-2)(^27)</td>
</tr>
<tr>
<td>Assessment 1‡</td>
</tr>
<tr>
<td>Assessment 2‡</td>
</tr>
<tr>
<td>Time between assessment 1 to MRI, days†</td>
</tr>
<tr>
<td>Outcome during hospital stay</td>
</tr>
<tr>
<td>No return to pre-stroke diet at discharge‡</td>
</tr>
<tr>
<td>Chest infection‡</td>
</tr>
<tr>
<td>Nasogastric tube feeding‡</td>
</tr>
<tr>
<td>PEG feeding‡</td>
</tr>
<tr>
<td>Duration of hospital stay, days†</td>
</tr>
<tr>
<td>Institutionalization‡</td>
</tr>
</tbody>
</table>

Chest infection during hospital stay was defined as ≥3 of the following: fever >38°C; productive cough; abnormal respiratory examination (tachypnoea >22 bpm, tachycardia, inspiratory crackles, bronchial breathing); culture of relevant pathogen; positive chest radiograph; and elevated CRP in a patient with suspected chest infection. BODS-2 indicates Bogenhausener dysphagia score\(^{27}\); see online-only Data Supplement for additional information on Bogenhausener dysphagia score-2.

\(*P\) value considered significant after Holm–Bonferroni correction for multiple comparisons.

Data presented either as median (interquartile range) or as \(\%\) and analyzed using Fisher exact test and analyzed using Kruskal–Wallis test or Mann–Whitney \(U\) test for independent samples.
Table 2. Group Characteristics of Patients in a Univariate Analysis

<table>
<thead>
<tr>
<th></th>
<th>Acute vs No Risk of Aspiration</th>
<th>Extended vs Transient Risk of Aspiration in the Early Subacute Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=34)</td>
<td>(n=17)</td>
</tr>
<tr>
<td></td>
<td>Acute Risk of Aspiration</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>No Risk of Aspiration</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (41)</td>
<td>0.5 (0.2–1.3)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (59)</td>
<td></td>
</tr>
<tr>
<td>Age, y†</td>
<td>74 (19)</td>
<td></td>
</tr>
<tr>
<td>Cause of stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microangiopathy</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Macroangiopathy</td>
<td>12 (36)</td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>14 (41)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>5 (15)</td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (94)</td>
<td>3.2 (0.7–15.6)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>28 (82)</td>
<td>0.8 (0.3–2.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (35)</td>
<td>1.5 (0.6–3.7)</td>
</tr>
<tr>
<td>Smoking (active)</td>
<td>9 (26)</td>
<td>2.3 (0.8–6.8)</td>
</tr>
<tr>
<td>Smoking (stopped)</td>
<td>5 (15)</td>
<td>0.8 (0.2–2.4)</td>
</tr>
<tr>
<td>Positive family history</td>
<td>3 (9)</td>
<td>0.5 (0.1–1.9)</td>
</tr>
<tr>
<td>Obesity</td>
<td>10 (29)</td>
<td>1.3 (0.5–3.5)</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>20 (59)</td>
<td>1.6 (0.7–3.8)</td>
</tr>
<tr>
<td>mRS premorbid†</td>
<td>0 (0)</td>
<td>0.95</td>
</tr>
<tr>
<td>NIHSS at admission†</td>
<td>7.5 (11)</td>
<td>0.008</td>
</tr>
<tr>
<td>ARWMC†</td>
<td>2 (1)</td>
<td>0.96</td>
</tr>
<tr>
<td>Lesion side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>17 (5)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Right</td>
<td>13 (38)</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>4 (12)</td>
<td></td>
</tr>
<tr>
<td>Lesion size, mL†</td>
<td>21 (59)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Arterial territory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>34 (100)</td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>3 (9)</td>
<td></td>
</tr>
<tr>
<td>PCA</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Regions of interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudal sensorimotor and</td>
<td>19 (56)</td>
<td></td>
</tr>
<tr>
<td>premotor area (BA 1–4, 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior parietal cortex</td>
<td>13 (38)</td>
<td></td>
</tr>
<tr>
<td>Frontal operculum (BA 44,47)</td>
<td>19 (56)</td>
<td></td>
</tr>
<tr>
<td>Insular cortex (BA 13, 14, 16)</td>
<td>24 (71)</td>
<td></td>
</tr>
<tr>
<td>Superior temporal cortex</td>
<td>19 (56)</td>
<td></td>
</tr>
<tr>
<td>Parieto-occipital cortex</td>
<td>10 (29)</td>
<td></td>
</tr>
<tr>
<td>Anterior cingulum (BA 24,32)</td>
<td>3 (9)</td>
<td></td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>20 (59)</td>
<td></td>
</tr>
<tr>
<td>Internal capsule</td>
<td>17 (50)</td>
<td></td>
</tr>
<tr>
<td>Perventricular white matter</td>
<td>25 (74)</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>3 (9)</td>
<td></td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; ARWMC, age-related white-matter changes; BA, Brodmann area; CI, confidence interval; MCA, medial cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and PCA, posterior cerebral artery.

Data presented as n (%) and analyzed using Fisher exact test unless specified differently.

*P value considered significant after Holm–Bonferroni correction for multiple comparisons.
†Median (interquartile range), Mann–Whitney U test.
modified Rankin Scale, lesion side, degree of age-related white-matter changes, or frequency of thrombolysis (Table 2). Patients with acute risk of aspiration had a significantly larger lesion size (21 [range, 1.5–330] versus 6 mL [range, 0.1–166]; \( P < 0.002 \)), whereas the NIHSS (7.5 versus 4; \( P < 0.008, \) Holm–Bonferroni corrected significance threshold <0.002) did not differ significantly after correction for multiple comparisons. All patients at risk of aspiration had stroke in the territory of the medial cerebral artery (100% versus 88%; \( P = 0.05 \)).

In the univariate analysis 4 ROIs had significant odds ratios (ORs) for the risk of aspiration after Holm–Bonferroni correction: internal capsule (OR, 7.6; \( P < 0.001 \)), insular cortex (OR, 5.6; \( P < 0.001 \)), periventricular white matter (PVWM; OR, 4.8; \( P < 0.001 \)), and basal ganglia (OR, 4.3; \( P < 0.002 \)). The frontal operculum, caudal sensorimotor and premotor cortex, superior temporal cortex, superior parietal cortex, parieto-occipital cortex, and anterior cingulate cortex did not show significant ORs.

Apart from lesion location, stroke severity and ischemic volume were the best predictors of acute risk of aspiration in the univariate analysis. To correct for these confounding variables, we have fitted a multiple logistic regression model (Table 3) including the 4 significant ROIs and adjusted for NIHSS and lesion size. Significant adjusted odds ratios (aORs) for acute risk of aspiration were shown for the internal capsule (aOR, 6.2; \( P < 0.002 \)) and the insular cortex (aOR, 4.8; \( P < 0.003 \)), whereas the PVWM (aOR, 2.7; \( P < 0.06 \)) indicated a trend. Conversely, stroke severity and lesion volume did not retain statistical significance after adjustment for lesion location. Overall model accuracy was 76% (specificity 82%; sensitivity 65%; Nagelkerke \( R^2 \) 0.4; Model \( \chi^2 \) P<0.001), and no relevant collinearity was observed.

To test the robustness of our regression method, we have fitted separate multivariate models for every ROI (3 covariates per model: ROI, NIHSS, lesion size; forced-entry method). Adjusting for stroke severity and lesion size, significant aORs were demonstrated for: internal capsule (aOR, 5.3; \( P < 0.003 \)), insular cortex (aOR, 3.7; \( P < 0.01 \)), PVWM (aOR, 3.5; \( P < 0.01 \)), and basal ganglia (aOR, 3.0; \( P < 0.03 \)). All other ROIs as well as the NIHSS and lesion size failed yet again to attain significance. Finally, to account for a possible bias of neighboring ROIs we fitted a further multivariate model with the 3 subcortical ROIs as independent variables. Although the internal capsule and the PVWM retained their statistical significance, the basal ganglia were not shown to be of any significance, suggesting a confounding effect because of the proximity of the basal ganglia and the internal capsule.

### Assessment 2: Extended Versus Transient Risk of Aspiration

Similar to the results of assessment 1, there were no differences in age, sex, cause of stroke, risk factors, prestroke disability (modified Rankin Scale), lesion side, degree of age-related white-matter changes, or frequency of thrombolysis (Table 2). Likewise, patients with extended risk of aspiration had a significantly larger lesion size (62 [range, 8–330] versus 7 mL [range, 1.5–90]; \( P < 0.001 \)) and nonsignificantly higher NIHSS (12 versus 5; \( P < 0.009 \); Holm–Bonferroni corrected significance threshold <0.002).

The frontal operculum was the only ROI to be significantly associated with extended risk of aspiration in the univariate analysis (OR, 74.7; \( P < 0.001 \)) after Holm–Bonferroni correction. In the multivariate logistic regression model adjusted for NIHSS and lesion size (Table 4), ischemic infarction of the frontal operculum remained the single independent predictor of extended risk of aspiration (aOR, 33.8; \( P < 0.008 \)). Overall model accuracy was established at 88% (specificity 82%; sensitivity 94%; Nagelkerke \( R^2 \) 0.7; Model \( \chi^2 \) P<0.001).

Fitting equivalent multivariate models for every other ROI did not reveal any significant effects. Nevertheless, testing for multicollinearity showed perfect correlation (1.00) of the insular cortex and the frontal operculum. Consequently, we calculated an equal aOR of prolonged dysphagia for a compound variable (simultaneous lesion of the insular cortex and the frontal operculum; aOR, 33.8; \( P < 0.008 \)) after adjusting for stroke severity and lesion size. Accordingly, in a post hoc inspection of our data, 16 of 17 patients (94%) with extended risk of aspiration had simultaneous lesions of the insular cortex and the frontal operculum. However, none of 14 patients with lesions of the insula but an intact frontal operculum suffered from extended risk of aspiration. Furthermore, none of 5 patients with a lesion of the frontal operculum but an undamaged insular cortex was at risk of aspiration. Additionally, we plotted the combined lesion pattern of the frontal operculum in patients with extended risk of aspiration (Figure 2). More than 75% of these lesions were localized in the perisylvian part of the frontal operculum at the transition zone to the insular cortex.

### Discussion

The new aspect of this comprehensive imaging study is the focus on the dynamics of aspiration risk during the first 2 weeks and an accordingly scheduled swallowing assessment.

**Table 3. Final Multivariate Model of Acute vs No Risk of Aspiration**

<table>
<thead>
<tr>
<th>ROI</th>
<th>Adjusted OR (95% CI)</th>
<th>( \beta ) (SE)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal capsule</td>
<td>6.2 (1.9–20.4)</td>
<td>1.8 (0.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Insular cortex (BA 13, 14, 16)</td>
<td>4.8 (1.7–13.7)</td>
<td>1.6 (0.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Periventricular white matter</td>
<td>2.7 (1.0–7.7)</td>
<td>1.0 (0.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>Eliminated in step 3 (( P = 0.75 ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion size</td>
<td>Eliminated in step 2 (( P = 0.87 ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>Eliminated in step 1 (( P = 0.97 ))</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data analyzed with multiple logistic regression, stepwise backward elimination method. BA indicates Brodmann area; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

**Table 4. Multivariate Model of Extended vs Transient Risk of Aspiration in the Early Subacute Phase**

<table>
<thead>
<tr>
<th>ROI</th>
<th>Adjusted OR (95% CI)</th>
<th>( \beta ) (SE)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal operculum (BA 44, 47)</td>
<td>33.8 (2.5–464)</td>
<td>3.5 (1.3)</td>
<td>0.008</td>
</tr>
<tr>
<td>Lesion size</td>
<td>1.01 (0.99–1.03)</td>
<td>0.01 (0.01)</td>
<td>0.37</td>
</tr>
<tr>
<td>NIHSS</td>
<td>1.1 (0.9–1.4)</td>
<td>0.1 (0.1)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Data analyzed with multiple logistic regression, forced-entry method. BA indicates Brodmann area; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.
in a tightly selected group of consecutive patients with supratentorial ischemic stroke. This provided us the opportunity for a comparative behavior-lesion mapping study to elucidate the underlying morphological principles of acute and extended risk of aspiration. Eleven supratentorial regions discussed repeatedly in the literature were evaluated using stereotaxic atlas-based MRI analysis.

Our study demonstrates 2 major findings in supratentorial ischemic stroke patients: (1) The insular cortex and the internal capsule seem to represent critical nodes of the supratentorial neuronal network underlying swallowing. Lesions of these regions are associated with significantly elevated odds for acute aspiration risk. (2) Ischemic infarctions of the frontal operculum associated with an additional lesion of the insular cortex are likely to cause extended risk of aspiration because of impaired recovery of swallowing function in the early subacute phase, whereas recovery tends to be fast in subcortical stroke.

Neuroanatomical Predictors of Acute Risk of Aspiration

We have confirmed the previously reported finding that the insular cortex is a main cortical area leading to aspiration after affliction by a supratentorial ischemic stroke. A recent intracortical microstimulation study found that stimulation of the anterior sector of the dorsal insula triggered swallowing, mouthing, and chewing in monkeys. Oralimentary behavior, including motor automatisms, has been described during epileptic seizures originating in this part of the insula. Lesion patients with discrete lesions of the anterior insula have been shown to suffer from dysphagia in small case studies. Furthermore, sensory and motor signaling from and to various areas might be mediated by the insula (eg, interacting with the oropharynx and the esophagus). A magnetoencephalographic study demonstrated consistent long-lasting activation of the insular cortex before swallowing. Taken together we posit a major role of the insula in elevating the risk of aspiration as it may function as a key area in the regulation of both voluntary and automatic swallowing.

Lesions of the caudal primary sensorimotor and premotor cortex did not prove significant as predictors of aspiration risk. These findings contrast with the results of functional imaging studies of swallowing in healthy individuals, which have found marked cortical activations around the central sulcus. However, activation of these regions was also observed in lip pursing, tongue rolling, and tongue tapping, thus suggesting that activation of these areas may not be specific to swallowing per se, but might rather represent an interference and modulation of swallowing-related tasks.

Additionally we have confirmed that subcortical stroke can lead to acute risk of aspiration, as it was observed previously. In fact, lesions of the internal capsule were the best predictors of aspiration risk in our study group. The internal capsule and the PVWM are known to comprise ascending sensory and descending motor pathways. We hypothesize that lesions of the white-matter tracts passing these structures disrupt cortical swallowing centers and the central pattern generator in the brain stem (eg, the nucleus of the solitary tract). Chronic white matter lesions, assessed with an age-related white-matter changes rating scale, did not influence the risk of aspiration or its recovery.

No between-group differences related to the lesioned hemisphere were observed in our study. Previous research suggested a right-hemispheric dominance of insular activation during swallowing and a left-hemispheric dominance of dysphagia after lesions to the PVWM. Furthermore, it has been argued that cortical swallowing centers might be represented bilaterally but asymmetrically with interindividual differences. The absence of significant effects in lesion laterality in our study suggests that previous findings resulted from smaller patient collectives.

Summarizing the results of the multivariate analysis, specific stroke location is more important than lesion size or stroke severity in predicting aspiration risk. Nevertheless, larger lesions are more likely to damage critical nodes for swallowing. In this respect, odds ratios of lesion size (Table 4) have to be analyzed with caution, because they represent a 1-unit (1 mL) change of lesion volume. Furthermore, swallowing is a multisensory process dependent on several sensory modalities. Consequently, more severe neurological deficits, for example, sensory, visual, or attention deficits are likely to interfere with the consecutive timing of oral and pharyngeal phases of deglutition.
Factors Influencing Recovery of Aspiration Risk

Identifying predictors for recovery of aspiration risk in the early subacute phase might be important for timely and potentially life-saving management, as half of the initially affected patients were still at risk of aspiration at 1 week, had worse outcome, and had more frequent medical complications during hospitalization (Table 1). Lesions of the frontal operculum (BA 44) have been shown to substantially impair the recovery of aspiration risk. Three explanations may be considered for this finding.

First, BA 44 as part of Broca’s area is classically considered to subserve motor speech production and, according to recent research, also nonlanguage-related motor functions and control of orofacial sensorimotor behavior. Depending on stimulation intensity, the frontal operculum evokes mastication at low levels and swallowing sequences at high levels of stimulation. Furthermore, there is evidence for an overlap of BA 44 with the ventral premotor cortex. Hence, a lesion of this premotor area might disrupt its access to the primary motor cortex and, thus, the descending motor pathway.

Second, the frontal operculum might play a role in peri-infarct tissue recruitment after insular stroke. In motor and aphasic stroke rehabilitation, recent evidence suggests that peri-infarct cortical reorganization is associated with favorable functional outcome. Similarly, damage of the frontal operculum would likely compromise such a cellular and molecular repair mechanism in the transition area to the insular cortex and impair the recruitment of peri-infarct tissue after insular stroke.

Third, parts of the frontal operculum in the transition zone to the insular cortex might exhibit similar features with respect to swallowing as the insula, which has been revealed by human and animal studies. Damage to both areas might therefore cause a more severe and longer-lasting risk of aspiration. Additionally, there is evidence that the insulo-opercular transition zone represents a primary gustatory cortex. Hence, damage to this area might diminish sensory outflow to the frontal operculum, for planning and preparation of the compound variables in the multivariate analysis. In contrast, patients with isolated lesions of the insula but an intact frontal operculum recovered within 1 week. And patients with infarctions of the frontal operculum but an undamaged insular cortex were not at risk of aspiration at all. The close structural interconnection of the frontal operculum and the anterior insula has been confirmed both in the human and monkey brain.

Interestingly, lesions of the frontal operculum did not lead to acute risk of aspiration, however, they impaired recovery of aspiration risk. A similar finding has been observed in motor stroke, where the recovery of motor deficits was influenced by cortical sensory areas, which would not cause paresis in the acute phase. Accordingly, a recent study showed that lesions to the somatosensory cortices impaired recovery from hand paresis in stroke. We suggest a similar function of the frontal operculum in risk of aspiration after stroke, modulating the recovery of swallowing function.

Subcortical lesions as investigated by the ROI approach did not disclose any interference with the recovery of aspiration risk. Although lesions of the internal capsule and the PVWM were likely to cause acute risk of aspiration, they did not increase the odds for extended risk of aspiration. In accordance with other authors, we assume that the interruption of pathways between the cortex and the swallowing pattern generator in the brain stem is likely to improve rather fast via a bypass of the damaged segment.

The limitations of this study may be summarized as follows: On the one hand, the ROI-based approach allows a comprehensive lesion analysis in relation to the literature. On the other hand, it cannot directly evaluate lesion patterns within the selected ROI and may be prone to confounding with neighboring regions. The interpretation of the results has to take into consideration that risk of aspiration was assessed clinically and not confirmed by instrumental testing. However, patients with extended risk of aspiration had worse swallowing outcome as compared with those with transient or no risk of aspiration, implying the clinical relevance of the subgroup classification. Because of the strict inclusion criteria, these results might primarily apply for patients with mild strokes. Because of sample size limitations, absolute effect sizes have to be interpreted with caution. In this respect, we cannot evaluate the relevance of the anterior cingulate cortex for the risk of aspiration because there were only few strokes in the anterior cerebral artery territory in our cohort. Finally, we analyzed only the early subacute phase after stroke, whereas recovery of swallowing function continues well beyond the first 7 days. This later time frame was not assessed in this study and, thus, our results cannot address the chronic phase or the need of long-term percutaneous endoscopic gastrostomy feeding.

Conclusions

Data on lesion location derived from MRI brain scans facilitate early differentiation between patients with transient and those with extended risk of aspiration in the early subacute phase after supratentorial ischemic stroke. Risk of aspiration is likely to persist beyond the first week in cases with combined affection of the insular cortex and the frontal operculum. If those areas are affected by ischemic stroke, the clinician might consider timely enteral tube feeding of these patients.

Sources of Funding

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Disclosures

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References


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Marian Galovic, Natascha Leisi, Marlise Müller, Johannes Weber, Eugenio Abela, Georg Kägi and Bruno Weder

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Lesion location predicts transient and extended risk of aspiration after supratentorial ischemic stroke.

Marian Galovic, Natascha Leisi, Marlise Müller, Johannes Weber, Eugenio Abela, Georg Kägi, Bruno Weder
Supplemental methods

Image acquisition
Our standard stroke imaging protocol comprised transverse T2, T1, FLAIR (5 mm) and sagittal T2 images (4.5 mm), isotropic DWI sequences (b=1000 s/m²) with transverse slices (4 mm) and integrated ADC map calculation and an intracranial arterial time-of-flight (TOF) sequence acquired either on a 1.5T Siemens Avanto or 1.5T Siemens Symphony or a 3T Verio MRI system (Siemens, Erlangen, Germany). The whole brain was covered with all sequences.

Lesion overlap map of the frontal operculum (BA 44, Figure 1 in print publication)
We have generated a lesion overlap map of the frontal operculum to demonstrate the morphological distribution of lesions in this ROI and proceeded as follows: DWI scans were used for lesion definition, since they provided a high contrast between ischemic injury and healthy tissue. T1-images were used to calculate normalization parameters for transformation of images into stereotaxic space. First, binary lesion maps were generated by manually outlining the regions of ischemic injury using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/) and leftsided lesions were flipped to the right side. Next, lesion maps were transformed into stereotaxic space by warping the individual brains to match a standard brain template ("spatial normalisation") as defined by the Montreal Neurological Institute (MNI). Normalization to MNI-space provided an approximate one-to-one mapping of individual brains. Spatial normalization was carried out in SPM8 (a Matlab-based library of neuroimaging analysis routines, available at http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). DWI scans and lesion maps were coregistered to the T1-images. The latter were then used to calculate the normalization parameters that encoded the deformations necessary to match the individual patient images to the standard T1 brain template in MNI-space. These parameters were applied to the coregistered lesion maps. During spatial normalization, lesioned areas were masked out from the normalization algorithm to avoid image distortions. Finally a lesion overlap map was generated using MRIcron and masked for BA 44 using an anatomical template*.

Supplementary tables and figures

Supplementary Table I: Two out of six scale

<table>
<thead>
<tr>
<th>Two out of six scale</th>
<th>□ Dysphonia</th>
<th>□ Dysarthria</th>
<th>□ Abnormal gag reflex</th>
<th>□ Abnormal volitional cough</th>
<th>□ Cough after swallow</th>
<th>□ Voice change after swallow</th>
</tr>
</thead>
</table>

Interpretation

Score 0-1: No risk of aspiration, normal or mild dysphagia.
Score 2-6: Risk of aspiration, moderate to severe dysphagia.

Validation

Established and validated in by Daniels et al.* The presence of two or more features provides an objective indicator of moderate to severe, i.e. significant, dysphagia due to the associated risk of aspiration, whereas less than two features indicate no or mild dysphagia without risk of aspiration (sensitivity 92.3, specificity 66.7, p=0.00005, referenced to a videofluoroscopic swallowing study).

### Supplementary Table II: BODS-2: Bogenenhausener dysphagia score; a measure of functional oral intake*

<table>
<thead>
<tr>
<th>Score</th>
<th>Functional oral intake (BODS-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Total oral diet with no restrictions.</td>
</tr>
<tr>
<td>2</td>
<td>Total oral diet with minor restrictions: multiple consistencies without compensatory techniques or compensatory techniques without diet restrictions.</td>
</tr>
<tr>
<td>3</td>
<td>Total oral diet with moderate restrictions: multiple consistencies with compensatory techniques.</td>
</tr>
<tr>
<td>4</td>
<td>Total oral diet with severe restrictions: single consistency with or without compensatory techniques.</td>
</tr>
<tr>
<td>5</td>
<td>Predominantly oral diet with additional tube feeding.</td>
</tr>
<tr>
<td>6</td>
<td>Partially oral diet (&gt; 10 teaspoons daily), predominantly tube feeding.</td>
</tr>
<tr>
<td>7</td>
<td>Minor oral intake (≤ 10 teaspoons daily), primarily tube dependent.</td>
</tr>
<tr>
<td>8</td>
<td>Tube dependent, nothing by mouth.</td>
</tr>
</tbody>
</table>

Supplementary Table III: Detailed overview of supratentorial regions of interest involved in swallowing and selected references

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Assumed function</th>
<th>DCS</th>
<th>TMS</th>
<th>fMRI</th>
<th>PET</th>
<th>SPECT</th>
<th>MEG</th>
<th>LBM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudal sensorimotor and premotor area (BA 1-4, 6)</td>
<td>Motor and sensory control of swallowing.1-4</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Superior parietal cortex (BA 5, 7)</td>
<td>Higher order processing of sensation.5,6</td>
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<tr>
<td>Frontal operculum (BA 44, 47)</td>
<td>Control of non-speech orofacial sensorimotor behaviors.5,7,8</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insular cortex (BA 13, 14, 16)</td>
<td>Voluntary initiation of swallowing.5,7,9-11</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td></td>
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<tr>
<td>Superior temporal cortex (BA 21, 22)</td>
<td>Somatosensory and gustatory perception.5,7,12</td>
<td></td>
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<tr>
<td>Parieto-occipital cortex (BA 19, 31)</td>
<td>Processing of the cue to swallow.13,14</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Anterior cingulate cortex (BA 24, 32, 33)</td>
<td>Attentional processing in voluntary swallowing.7,15,16</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Basal ganglia</td>
<td>Gating of sensory input for control of motor swallowing function.16,17</td>
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<tr>
<td>Internal capsule</td>
<td>Functional connection of the cerebral and brain stem swallowing relay nodes.18,19</td>
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<tr>
<td>Periventricular white matter</td>
<td>Functional connection of the cerebral and brain stem swallowing relay nodes.20,21</td>
<td></td>
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<tr>
<td>Thalamus</td>
<td>Sensory-motor integration through thalamo-cortical or thalamo- striatal pathways.16,22</td>
<td></td>
<td></td>
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<td></td>
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<td>x</td>
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</tbody>
</table>

BA = Brodmann area, DCS = direct cortical stimulation, TMS = transcranial magnetic stimulation, fMRI = functional magnetic resonance imaging, PET = positron emission tomography, SPECT = single-photon emission computed tomography, MEG = magnetoencephalography, LBM = lesion behaviour mapping

Selected supplemental references:


Supplementary Figure I: Distribution of lesions in patients with no, transient or extended risk of aspiration