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# Evidence for adaptive cortical changes in swallowing in Parkinson's disease

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**Dysphagia is a relevant symptom in Parkinson's disease, whose pathophysiology is poorly understood. It is mainly attributed to degeneration of brainstem nuclei. However, alterations in the cortical contribution to deglutition control in the course of Parkinson's disease have not been investigated. Here, we sought to determine the patterns of cortical swallowing processing in patients with Parkinson's disease with and without dysphagia. Swallowing function in patients was objectively assessed with fiberoptic endoscopic evaluation. Swallow-related cortical activation was measured using whole-head magnetoencephalography in 10 dysphagic and 10 non-dysphagic patients with Parkinson's disease and a healthy control group during self-paced swallowing. Data were analysed applying synthetic aperture magnetometry, and group analyses were done using a permutation test. Compared with healthy subjects, a strong decrease of cortical swallowing activation was found in all patients. It was most prominent in participants with manifest dysphagia. Non-dysphagic patients with Parkinson's disease showed a pronounced shift of peak activation towards lateral parts of the premotor, motor and inferolateral parietal cortex with reduced activation of the supplementary motor area. This pattern was not found in dysphagic patients with Parkinson's disease. We conclude that in Parkinson's disease, not only brainstem and basal ganglia circuits, but also cortical areas modulate swallowing function in a clinically relevant way. Our results point towards adaptive cerebral changes in swallowing to compensate for deficient motor pathways. Recruitment of better preserved parallel motor loops driven by sensory afferent input seems to maintain swallowing function until progressing neurodegeneration exceeds beyond the means of this adaptive strategy, resulting in manifestation of dysphagia.**

**Keywords:** Parkinson's disease; dysphagia; magnetoencephalography; cortical reorganization
**Abbreviations:** MEG = magnetoencephalography

## Introduction

Parkinson's disease has classically been considered as a progressive neurodegenerative movement disorder caused by dopamine depletion in the striatum. Nowadays it is seen as a multisystem disease that gradually affects several components of various functional networks throughout the entire nervous system (Braak *et al*., 2004), accounting for a variety of motor and particularly non-motor symptoms (Dickson *et al*., 2009). Oropharyngeal dysphagia is reported with an incidence of 70–100% (Stroudley and

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Walsh, 1991; Fuh *et al*., 1997; Leopold and Kagel, 1997; Potulska *et al*., 2003). Clinically relevant swallowing impairment is generally associated with advanced stage of the disease. It reduces quality of life, complicates medication intake and leads to malnutrition and aspiration pneumonia, which is a major cause of death in Parkinson's disease (Wermuth *et al*., 1995; Morgante *et al*., 2000). However, formal abnormalities in deglutition have also been found in the earliest stages of Parkinson's disease (Volonte *et al*., 2002; Sung *et al*., 2010).

The pathophysiology underlying Parkinson's disease-related dysphagia is poorly understood. The lack of a clear correlation between dysphagia severity and disease duration or general motor impairment (Nilsson *et al*., 1996; Volonte *et al*., 2002; Monte *et al*., 2005; Lam *et al*., 2007) indicates that disturbance of non-dopaminergic networks may be an important contributor. This would also explain why dysphagia—unlike other motor-related symptoms—responds to dopaminergic treatment only in a small proportion of patients (Hunter *et al*., 1997; Baijens and Speyer, 2009; Menezes and Melo, 2009). Apart from impaired basal ganglia control resulting in disturbance of voluntary, oral components in deglutition, swallowing impairment is attributed to brainstem pathology. Notably, parts of the medullary swallowing central pattern generator, such as the dorsal motor nucleus of the glossopharyngeus and vagus nerves and the surrounding reticular activating system suffer relevant neuronal loss early in the course of Parkinson's disease (Braak *et al*., 2004; Hawkes *et al*., 2010). The pedunculopontine tegmental nucleus, a relay nucleus that provides input to the nucleus of the solitary tract, which constitutes another critical component of the medullary pattern generator, receives pathologically increased inhibitory input from the pallidum and is itself preferentially affected by neuronal degeneration (Grinberg *et al*., 2010).

Recent neuroimaging studies have shown that apart from the brainstem distinct cortical areas, such as the primary sensorimotor cortex, sensorimotor integration areas, insula, anterior cingulate cortex and the adjacent supplementary motor area, are significantly involved in swallowing processing (Hamdy *et al*., 1999*a*; Martin *et al*., 2001; Dziewas *et al*., 2003; Furlong *et al*., 2004). Cortical compensation for dysphagia has been found in stroke (Hamdy *et al*., 1998; Teismann *et al*., 2011*a*) and slowly progressive neurodegenerative disease (Dziewas *et al*., 2009). To our knowledge, the cortical contribution to swallowing processing has not been investigated in Parkinson's disease. In this study, we applied whole-head magnetoencephalography (MEG) to evaluate differences in swallow-related cortical activation in dysphagic versus non-dysphagic patients with Parkinson's disease and healthy control subjects using an established swallowing paradigm (Dziewas *et al*., 2009; Teismann *et al*., 2010, 2011*b*).

We hypothesized a decrease of cortical activation in dysphagic patients with Parkinson's disease because of a disturbance of the swallowing network. We were also looking for a possible compensatory mechanism in non-dysphagic patients on the cortical level that could account for the discrepancy between early affection of the brainstem swallowing centres and late manifestation of severe dysphagia in Parkinson's disease.

# Materials and methods

## Participants

Twenty patients (10 dysphagic and 10 non-dysphagic, classification based on the examination results described later in the text) from our outpatient clinic, diagnosed with Parkinson's disease according to the UK Parkinson's disease brain bank criteria (Hughes *et al*., 1992) and fulfilling the inclusion criteria were recruited for this study (11 male and 9 female subjects, age 65.5 ± 12.6 years). Participants had to be on an optimized stable medication regimen. All examinations were done in the 'ON' phase. Patients were excluded if they were demented or had any other neurological or psychiatric diseases. For technical reasons, subjects unable to sit still in the MEG scanner because of dyskinesia or severe tremor, as well as those being treated with deep brain stimulation, were not eligible to take part.

Disease severity was assessed with the Unified Parkinson's Disease Rating Scale, part III (Fahn and Elton, 1987) and the Hoehn and Yahr disability scale (Hoehn and Yahr, 1967). Disease duration, time between last intake of dopaminergic drugs and the MEG measurement, as well as the L-DOPA (equivalent) dose of each patient's medication were recorded.

Ten healthy age- and gender-matched control subjects (five male and five female subjects, age 66.3 ± 12.4 years) without any history of dysphagia, or any neurological or ear–nose–throat disorder served as control subjects. The local ethics committee approved the protocol of the study. Informed consent was obtained from each subject after the nature of the study was explained, in accordance to the principles of the Declaration of Helsinki.

## Swallowing examination

Fiberoptic endoscopic evaluation of swallowing was performed in all patients in accordance with the standard protocol proposed by Langmore (2001). Briefly, the secretion status was evaluated first. After that, the patient was given standard volumes of puree consistency, liquids and soft solid food. A flexible rhinolaryngoscope (Olympus ENF-P4) was used, attached to a camera and colour monitor. Oropharyngeal dysphagia was deemed to be present when at least one of the following parameters characterizing disturbed swallowing function was found: disturbed management of secretions (i.e. pooling or aspiration of saliva), penetration or aspiration of any food consistency, relevant pharyngeal food residue after the swallow, relevant prolongation of oropharyngeal swallow duration with bradykinetic movements of the base of tongue or pharyngeal muscles, or premature spillage with delayed initiation of the swallowing reflex (Warnecke *et al*., 2010). Patients showing none of these findings were allocated to the non-dysphagic study group.

Because heavy fluctuations of symptom presentation can occur in Parkinson's disease, we additionally asked all patients to fill out two validated swallowing questionnaires: the Swallowing Quality of Life Questionnaire (McHorney *et al*., 2000, 2002), which consists of 11 single domains, and the Swallowing Disturbance Questionnaire (Manor *et al*., 2007). The latter was developed especially for patients with Parkinson's disease. Answers to each question can range from 'never' (i.e. 0 points) to 'very frequently' (i.e. 3 points). In doing so, we were able to confirm that the patients' status regarding swallowing function, as judged by endoscopic evaluation, represented their 'true' condition in the longer term and not just a momentary 'best' or 'worst' state.

Immediately before the MEG recording, we carried out a simple clinical dysphagia screening test according to the protocol by Hughes and Wiles (1996) in all 30 participants. Each subject drank 150 ml water from a plastic beaker 'as quickly as is comfortably possible'. The number of swallows was counted by observing the movements of the thyroid cartilage. A stopwatch was started when the water first touched the bottom lip and stopped when the larynx came to rest for the last time. The volume per swallow (ml), time per swallow (s) and swallowing capacity (ml/s) were calculated for each subject. The parameters were used for comparison between patients and control subjects, as we were not able to perform endoscopy on healthy study participants.

## Magnetoencephalography and electromyographic data acquisition

MEG data were collected using a whole head 275-channel sensor array (Omega 275, CTF Systems Inc.). During the MEG measurement of 15 min duration, each subject swallowed self-paced without external cueing. To facilitate volitional swallowing water was infused into the oral cavity via a flexible plastic tube 4.7 mm in diameter attached to a fluid reservoir. The reservoir bag was positioned ~1 m above the mouth of each subject when seated. The tip of the tube was randomly placed in the left or right corner of the mouth between the buccal part of the teeth and the cheek and gently fixed to the skin with tape. The infusion flow was individually adjusted to the subject's request, which ranged between 8 and 12 ml/min. Swallowing acts were identified by surface EMG recording with bipolar skin electrodes (Ag–AgCl) placed on the submental muscle groups (Ding *et al*., 2002; Vaiman, 2007). The electrodes were connected to a bipolar amplifier (DSQ 2017E EOG/EMG system, CTF Systems Inc.). Magnetic fields were recorded with a sample frequency of 600 Hz. During acquisition, the data were filtered using a 150-Hz low-pass filter. The participants' head movements were recorded.

## Data analysis

### Behavioural data

Statistical analyses on patient characteristics, scores of the swallowing questionnaires, swallowing screening parameters and EMG swallow characteristics (see later in the text) were carried out using SPSS 20.0 (IBM Corp.). The assumption of a normal distribution was confirmed in all variables using the Kolmogorov–Smirnov test before analysis. For comparison between features of the Parkinson's disease patient groups, independent-sample *t*-tests were used. Univariate ANOVA was performed to test for differences between all three study groups. Welch's ANOVA was carried out in case the assumption of variance of homogeneity in the data was violated. *Post hoc t*-tests were computed only for the statistically significant variables of the ANOVA analysis using Bonferroni correction for multiple comparisons ($P < 0.05$) or Games–Howell correction if Levene's test for equality of variance turned significant.

### Magnetoencephalography data

MEG data analysis was performed as previously published (Dziewas *et al*., 2009; Teismann *et al*., 2009*a*, 2011*b*). In brief, for event-related analysis of the MEG recordings, each individual's EMG signal was used to mark the beginning of main muscle activation (M1) and the end of the task-specific muscle activity (M2) for every single swallow (Fig. 1). The beginning of the main muscle activation was defined as an enduring >100% increase in amplitude or frequency of the EMG signal after an initial increase of >50% of EMG activity defining the onset of oral swallowing preparation. The end of task-specific muscle activity was defined as a decrease in amplitude or frequency of the EMG signal >50%. To estimate the maximal null distribution (see later in the text), a third marker was set to distinguish background activity from the onset of oral swallowing preparation (M0). EMG data were baseline-corrected and high-pass filtered with 0.1 Hz before markers were manually set. The examiner who set the markers to the data sets was blinded to the study group allocation. For further analysis, time intervals were defined as (i) movement stage: −0.4 to 0.6 s in reference to M1; (ii) resting stage: 0 to 1 s in reference to M2; (iii) background stage 1: −3 to −2 s in reference to M0; and (iv) background stage 2: −2 to −1 s in reference to M0.

To ensure equal swallow behaviour during MEG data acquisition, the mean power (root-mean-square value) and peak-to-peak amplitude of the submental EMG recordings were calculated across the swallowing movement stage in all subjects and statistically compared as described earlier in the text.

To examine the chronological sequence of brain activation, the execution stage was additionally divided into five parts, each lasting 200 ms. Time intervals, including the respective resting and baseline stages for the subsequent analysis, were defined as follows (Fig. 1): (i) Execution stage 1 (A1): −0.4 to −0.2 s in reference to M1; (ii) Execution stage 2 (A2): −0.2 to 0.0 s in reference to M1; (iii) Execution stage 3 (A3): 0.0 to 0.2 s in reference to M1; (iv) Execution stage 4 (A4): 0.2 to 0.4 s in reference to M1; (v) Execution stage 5 (A5): 0.4 to 0.6 s in reference to M1; (vi) resting stage (R): 0 to 0.2 s in reference to M2; (vii) background stage 1 (B1): −2.2 to −2.0 s in reference to M0; and (viii) background stage 2 (B2): −1.2 to −1.0 s in reference to M0.

Synthetic aperture magnetometry, a minimum-variance beamformer technique, was applied for neuronal source localization. This method is capable of analysing induced brain activity, such as event-related desynchronization of cortical rhythms that occurs during motor tasks (Pfurtscheller and Aranibar, 1979; Pfurtscheller and Lopes da Silva, 1999; Taniguchi *et al*., 2000). MEG also detects fields associated with tongue movement during swallowing, as the tongue behaves like a current dipole. The use of synthetic aperture magnetometry, however, overcame the limitations of traditional dipole source analysis as described by Loose *et al*. (2001) because the technique requires no *a priori* estimates of numbers or approximate locations of sources and can separately localize distinct sources that are active at the same time. Although the artefacts caused by oropharyngeal muscle activation during the act of swallowing make it difficult to study activation in subcortical and brainstem structures, the cortical areas can be examined in detail. Synthetic aperture magnetometry has proved to be a reliable approach to examine the complex function of swallowing in humans (Furlong *et al*., 2004; Dziewas *et al*., 2009a; Teismann *et al*., 2009*a*, 2010, 2011*b*). MEG data were filtered within five different frequency bands: theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), low gamma, (30–60 Hz) and high gamma (60–80 Hz). From the filtered MEG data, synthetic aperture magnetometry was used to generate 20 × 20 × 14 cm volumetric pseudo-*t* images (Vrba and Robinson, 2001) with 3-mm voxel resolution. A pseudo-*t* value cancels the common-mode brain activity by subtracting the source power found in a defined control stage from the source power in the active stage. To account for uncorrelated sensor noise, this difference is normalized by the mapped noise power (Vrba and Robinson, 2001). For analysing cortical activity during the movement stage, the corresponding resting stage served as control. The required similarity between the resting stage and the two background stages in patients, as well as in control subjects was proven before by a direct comparison

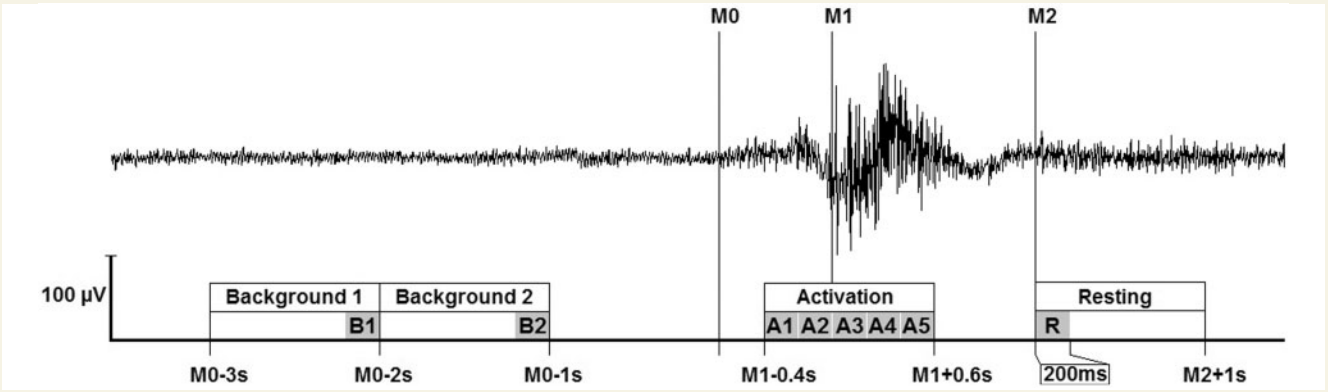


**Figure 1** Definition of execution and resting stage according to swallow-related submental muscle activity. The surface EMG trace of a single swallowing act is shown. To investigate the changes of cortical activation over time, the 1-s swallowing activation stage was divided into five successive 200-ms time intervals (A1–A5). The corresponding resting stage (R) and two background stages (B1 and B2) were also shortened to 200 ms.

of these three stages. Therefore, a standard permutation test for paired samples was performed within each group on these time intervals in which no significant activation was found. For analysis of single conditions, the significance of activated brain regions within each study group was assessed by the permutation test method described by Chau *et al*. (2004). The maximal null distribution was estimated here by comparing background stages 1 and 2. For the comparison between groups, a standard permutation test for unpaired samples was performed (Nichols and Holmes, 2002; Chau *et al*., 2004). Transformation into a common anatomical space is required for these analysis steps. As the MRI scan acquired as part of routine Parkinson's disease patient care did not contain the necessary localization information required for this procedure, normalization was performed as previously published (Steinstraeter *et al*., 2009). Briefly, the individual synthetic aperture magnetometry images were mapped on the MNI (Montreal Neurological Institute) space using the knowledge about the nasion and preauricular point positions in the MEG coordinate system. Then, the rotated synthetic aperture magnetometry image was shifted, so that the centre of the spherical head model used in the synthetic aperture magnetometry calculation coincided with the centre of the head model calculated for the template. In a last step, the size of the synthetic aperture magnetometry image was adjusted, so that the radii of the head models in both images matched. Compared with an established MRI-based normalization procedure (SPM2), this method shows only minor errors of ~0.5 cm in single-subject results, as well as in group analysis (Steinstraeter *et al*., 2009).

Because of recent reports of pathological resting state oscillatory brain dynamics in Parkinson's disease (Bosboom *et al*., 2006; Stoffers *et al*., 2007), we compared the frequency distribution of neural activity during the resting state between groups. We wanted to ensure that swallowing activation pattern changes found in patients as compared with control subjects do not result from baseline differences. This analysis was carried out with custom-made MATLAB (MathWorks Inc.) scripts based on FieldTrip (http://www.ru.nl/fcdonders/fieldtrip), an open source MATLAB toolbox for the analysis of neurophysiological data (Oostenveld *et al*., 2011). Baseline intervals (−3 to −1 s in reference to M0) from each individual subject were averaged across trials. The mean spectral power density in the five frequency bands, which were also used in the beamformer analysis, was calculated over the entire time interval, applying a multitaper frequency transformation implemented in FieldTrip. The 275 channels of the MEG system were afterwards grouped into frontal, central, parietal, temporal and occipital channels, and mean spectral power density per channel group was obtained for each frequency range. Comparisons between the three subject groups were performed using one-way ANOVA and *post-hoc t*-tests as described earlier in the text for the analysis of behavioural data.

# Results

## Clinical data

The demographic and clinical characteristics of the patients with Parkinson's disease are presented in Table 1. The dysphagic patient group turned out to be significantly older than the non-dysphagic group (71.6 versus 59.3 years, $P < 0.05$). Mean disease duration, Hoehn and Yahr scale and Unified Parkinson's Disease Rating Scale, part III scores tended to be higher in dysphagic patients, although the difference did not reach statistical significance between these small study groups. No differences were found in L-DOPA dose and time from last intake of dopaminergic medication until MEG recording.

## Swallowing assessment

In dysphagic patients, salient video-endoscopic findings included bradykinesia of swallowing ($n = 7$), premature spillage and delayed initiation of the swallowing reflex ($n = 7$), relevant pharyngeal residues ($n = 7$), reduced laryngeal elevation ($n = 4$), reduced posterior motion of the tongue base ($n = 2$) and penetration and aspiration of fluids ($n = 1$). Both patient groups differed in the total sum scores and the majority of subdomains of the Swallowing Quality of Life Questionnaire and the Swallowing Disturbance questionnaire (Table 2), confirming that group allocation based on endoscopic results represented the patients' true condition in the longer term. Regarding the swallowing screening test, univariate ANOVA exhibited significant differences for every swallowing parameter between the three study groups. *Post hoc* comparisons

**Table 1 Characteristics of patients with Parkinson's disease [mean ± standard deviation (SD)]**

| Patient characteristics | Non-dysphagic | Dysphagic | *P*-value |
|---|---|---|---|
| Subjects (*n*) | 10 | 10 | |
| Age (years) | 59.3 ± 12 | 71.6 ± 10 | 0.025* |
| Gender (female/male) | 4/6 | 5/5 | |
| Disease duration (years) | 5.3 ± 6.7 | 8.2 ± 4.4 | 0.265 |
| Hoehn and Yahr scale | 2.2 ± 1.0 | 2.8 ± 0.8 | 0.162 |
| UPDRS III (points) | 17.7 ± 8.0 | 22.2 ± 8.5 | 0.239 |
| L-DOPA equivalent dose (mg) | 533 ± 587 | 688 ± 321 | 0.478 |
| Last intake of dopaminergic medication (min) | 111 ± 71 | 181 ± 180 | 0.317 |

*Statistically significant. UPDRS = Unified Parkinson's Disease Rating Scale.

revealed no difference between healthy elderly subjects and patients without dysphagia in any parameter. However, there were obvious differences between patient groups (Table 3). Dysphagic patients had strongly decreased volume and time per swallow, and swallowing capacity was markedly reduced.

## Magnetoencephalography results

All participants tolerated the MEG examination without any problems. There were no differences regarding head movement [$F(2,27) = 0.805$, $P = 0.457$] and number of swallows taken into account for analysis [$F(2,27) = 1.072$, $P = 0.356$] between groups. In addition, EMG power [$F(2,27) = 0.872$, $P = 0.437$] and amplitude [$F(2,27) = 0.805$, $P = 0.458$] of swallowing acts conducted during MEG acquisition did not differ between groups (Table 3), indicating equal task performance in all participants.

ANOVA of the spectral power density of oscillatory neural activity during the resting state revealed significant differences in single channel groups in the theta and gamma frequency range only (Table 4). *Post hoc t*-tests showed a trend for increased theta in central channels in dysphagic patients compared with healthy subjects ($P = 0.054$) and in temporal channels compared with both other groups, i.e. healthy subjects and non-dysphagic patients ($P = 0.052$ and $P = 0.062$, respectively). The dysphagic group also showed a significant decrease of spectral density in temporal low-gamma power ($P = 0.005$ and $P = 0.028$, respectively) and a trend towards a decrease in temporal high-gamma power ($P = 0.087$ and, $P = 0.070$ respectively).

During swallowing, statistically significant ($P < 0.05$) event-related desynchronization was found within all three study groups in the alpha, beta and low-gamma frequency ranges (Fig. 2) mainly localized around the pericentral cortex (Table 5). The broadest and strongest event-related desynchronization was found in the beta band. The activation in adjacent frequency bands (alpha, low gamma) was similarly located but markedly weaker. In comparison with healthy subjects, peak pseudo-*t*-values in the beta frequency range were 33.1% (left hemisphere) and 20.3% (right hemisphere) lower in non-dysphagic patients. In dysphagic patients with Parkinson's disease, peak values were 43.7 and 47.4% lower, respectively.

In healthy subjects, extensive swallow-related activation was found in primary and secondary sensorimotor cortical areas with activation maxima lying in the rostromedial precentral gyrus bilaterally. Non-dysphagic patients, however, displayed focal activation in caudolateral parts of the primary sensorimotor and premotor cortex and inferolateral parietal lobe. Activation of the supplementary motor area was markedly reduced as compared with the healthy study group ($P < 0.01$). In dysphagic patients, a strong overall reduction of task-related activity was found. Event-related desynchronization was mainly restricted to upper parts of the primary sensorimotor cortex ($P < 0.01$). Fig. 3 shows areas with statistically significant activation differences between patients and age-matched volunteers ($P < 0.01$).

Separate calculation of significant group activation for consecutive 200 ms intervals (Fig. 4) in healthy volunteers showed broad and constant activation peaking in rostromedial parts of the sensorimotor cortex, including the supplementary motor area. In non-dysphagic patients, focal activation of the lateral (pre-)motor cortex was observed from the beginning of movement execution, followed by the lateral parietal cortex at 200–400 ms, whereas the supplementary motor area was activated ~600–800 ms later in time. Again this pattern was not found in dysphagic patients. Activation was continuously centred on the rostromedial pericentral cortex here.

# Discussion

This study examined the cortical representation of volitional swallowing in patients with Parkinson's disease compared with healthy age-matched control subjects. A strong decrease of overall task-related cortical activation in patients was found. Additionally, non-dysphagic patients with Parkinson's disease showed a prominent shift of peak activation towards lateral motor, premotor and parietal cortices starting at movement initiation, whereas activity in the supplementary motor area was markedly reduced and later in time. This distinct pattern was not found in dysphagic patients.

Cortical event-related desynchronization in all three examined groups was observed in bilateral primary sensorimotor areas spreading into secondary motor and sensory regions predominantly in healthy control subjects. This is a well-known phenomenon in functional brain imaging of human swallowing processing. It has been found in several former MEG studies (Dziewas *et al.*, 2003, 2009; Teismann *et al.*, 2009*a*, *b*, 2011*a*). Studies using transcranial magnetic stimulation, PET and MEG led to similar patterns of activation (Hamdy *et al.*, 1998, 1999*b*; Furlong *et al.*,

**Table 2 Results of single domains in the Swallowing Quality of Life Questionnaire and single questions in the Swallowing Disturbance Questionnaire in dysphagic and non-dysphagic patients with Parkinson's disease (mean ± SD)**

| SWAL QOL domains | Maximum achievable score | Non-dysphagic Parkinson's disease | Dysphagic Parkinson's disease | *P*-value |
|---|---|---|---|---|
| Burden | 10 | 10.0 ± 0.0 | 7.8 ± 2.5 | 0.02* |
| Eating duration | 10 | 9.4 ± 2.6 | 6.6 ± 2.4 | 0.02* |
| Eating desire | 15 | 13.8 ± 2.8 | 12.4 ± 2.7 | 0.27 |
| Dysphagia symptoms | 70 | 67.5 ± 3.7 | 54.6 ± 8.6 | 0.001* |
| Food selection | 10 | 10.0 ± 0.0 | 7.8 ± 2.9 | 0.04* |
| Communication | 10 | 7.8 ± 2.0 | 6.3 ± 2.7 | 0.18 |
| Fear | 20 | 19.7 ± 0.9 | 18.1 ± 2.8 | 0.12 |
| Mental health | 25 | 25.0 ± 0.0 | 18.5 ± 4.7 | 0.002* |
| Social | 25 | 25.0 ± 0.0 | 19.5 ± 7.6 | 0.05 |
| Fatigue | 15 | 9.7 ± 2.3 | 8.1 ± 2.1 | 0.12 |
| Sleep | 10 | 8.5 ± 2.8 | 7.8 ± 2.0 | 0.54 |
| Total | 220 | 208 ± 9 | 170 ± 22 | <0.0005* |
| **Swallowing disturbance questionnaire** | | **Non-dysphagic Parkinson's disease** | **Dysphagic Parkinson's disease** | **P-value** |
| 1. Do you experience difficulty chewing solid food like an apple, cookie or a cracker? | | 0.0 ± 0.0 | 0.7 ± 1.2 | 0.09 |
| 2. Are there any food residues in your mouth, cheeks, under your tongue or stuck to your palate after swallowing? | | 0.0 ± 0.0 | 1.5 ± 1.0 | 0.001* |
| 3. Does food or liquid come out of your nose when you eat or drink? | | 0.0 ± 0.0 | 0.3 ± 0.5 | 0.08 |
| 4. Does chewed up food dribble from your mouth? | | 0.0 ± 0.0 | 0.1 ± 0.3 | 0.34 |
| 5. Do you feel you have too much saliva in your mouth; do you drool or have difficulty swallowing your saliva? | | 0.4 ± 0.7 | 2.0 ± 1.2 | 0.001* |
| 6. Do you swallow chewed up food several times before it goes down your throat? | | 0.2 ± 0.6 | 1.0 ± 0.8 | 0.03* |
| 7. Do you experience difficulty in swallowing solid food (i.e. do apples or crackers get stuck in your throat)? | | 0.1 ± 0.3 | 0.8 ± 0.9 | 0.04* |
| 8. Do you experience difficulty in swallowing pureed food? | | 0.1 ± 0.3 | 0.1 ± 0.3 | 1.00 |
| 9. While eating, do you feel as if a lump of food is stuck in your throat? | | 0.2 ± 0.6 | 1.0 ± 0.9 | 0.04* |
| 10. Do you cough while swallowing liquids? | | 0.0 ± 0.0 | 0.8 ± 1.0 | 0.04* |
| 11. Do you cough while swallowing solid foods? | | 0.1 ± 0.3 | 0.8 ± 0.9 | 0.04* |
| 12. Immediately after eating or drinking, do you experience a change in your voice, such as hoarseness or reduced? | | 0.1 ± 0.3 | 1.0 ± 0.9 | 0.02* |
| 13. Other than during meals, do you experience coughing or difficulty breathing as a result of saliva entering your windpipe? | | 0.0 ± 0.0 | 0.4 ± 0.5 | 0.04* |
| 14. Do you experience difficulty in breathing during meals? | | 0.0 ± 0.0 | 0.1 ± 0.3 | 0.34 |
| 15. Have you suffered from a respiratory infection (pneumonia, bronchitis) during the past year? (yes = 2.5 points, no = 0.5 points) | | 0.5 ± 0.0 | 0.7 ± 0.6 | 0.34 |
| Total | | 1.7 ± 2.5 | 11.1 ± 6.2 | 0.001* |

*Statistically significant.
SWAL-QOL = Swallowing Quality of Life Questionnaire.

**Table 3 Results of the swallowing screening test and EMG swallow characteristics during MEG data acquisition in patients with Parkinson's disease and healthy age-matched control subjects (mean ± SD)**

| Swallow parameter | Healthy aged-matched control subjects | Non-dysphagic Parkinson's disease | Dysphagic Parkinson's disease | *P*-value |
|---|---|---|---|---|
| Volume per swallow (ml) | 22.54 ± 10.54 | 24.99 ± 9.26 | 14.13 ± 1.67 | 0.028[a,*] |
| Time per swallow (s) | 1.38 ± 0.38 | 1.45 ± 0.27 | 2.67 ± 0.92 | 0.006[a,*] |
| Swallowing capacity (ml/s) | 16.68 ± 5.41 | 17.95 ± 7.88 | 5.83 ± 2.56 | 0.002[a,*] |
| EMG power (μV) | 63.01 ± 30.08 | 87.23 ± 50.09 | 74.50 ± 25.73 | 0.437[b] |
| EMG amplitude (μV) | 376.0 ± 117.6 | 445.5 ± 185.7 | 449.4 ± 126.0 | 0.458[b] |

a *Post hoc t*-test between patient groups only, adjusted *P*-value.
b ANOVA.
*Statistically significant.

**Table 4 Spectral power density (ft/√Hz) of baseline oscillatory brain activity per frequency range and channel area in all three study groups (mean ± SD)**

| Frequency range / channel area | Healthy aged-matched control subjects | Non-dysphagic Parkinson's disease | Dysphagic Parkinson's disease | *P*-value |
|---|---|---|---|---|
| Theta (4–8 Hz) | | | | |
| Frontal | 25.53 ± 6.44 | 26.13 ± 8.88 | 32.52 ± 11.27 | 0.182 |
| Central | 22.06 ± 4.43 | 25.68 ± 4.70 | 34.31 ± 13.88 | 0.035* |
| Parietal | 29.59 ± 6.09 | 29.68 ± 11.00 | 42.18 ± 16.70 | 0.117 |
| Temporal | 35.84 ± 9.82 | 35.33 ± 15.40 | 52.01 ± 17.71 | 0.026* |
| Occipital | 38.16 ± 11.00 | 43.02 ± 23.74 | 48.93 ± 15.99 | 0.407 |
| Alpha (8–13 Hz) | | | | |
| Frontal | 24.58 ± 7.20 | 20.28 ± 5.94 | 25.62 ± 8.34 | 0.234 |
| Central | 28.51 ± 11.04 | 24.04 ± 6.99 | 31.21 ± 11.51 | 0.290 |
| Parietal | 42.95 ± 12.80 | 31.89 ± 13.96 | 43.93 ± 18.83 | 0.172 |
| Temporal | 44.25 ± 16.18 | 36.94 ± 22.35 | 54.29 ± 23.63 | 0.197 |
| Occipital | 37.71 ± 14.87 | 33.33 ± 13.17 | 45.07 ± 16.21 | 0.219 |
| Beta (13–30 Hz) | | | | |
| Frontal | 17.33 ± 3.97 | 15.62 ± 4.48 | 15.37 ± 4.99 | 0.577 |
| Central | 22.97 ± 8.92 | 19.27 ± 6.13 | 19.52 ± 6.15 | 0.449 |
| Parietal | 28.58 ± 8.17 | 20.99 ± 8.75 | 21.15 ± 6.77 | 0.068 |
| Temporal | 24.72 ± 5.70 | 21.23 ± 8.44 | 21.34 ± 6.84 | 0.467 |
| Occipital | 21.82 ± 4.53 | 20.47 ± 5.76 | 20.95 ± 4.25 | 0.824 |
| Low gamma (30–60 Hz) | | | | |
| Frontal | 6.82 ± 1.26 | 7.13 ± 1.72 | 7.67 ± 4.29 | 0.792 |
| Central | 6.99 ± 1.31 | 7.18 ± 1.04 | 6.82 ± 1.69 | 0.838 |
| Parietal | 8.18 ± 1.13 | 7.56 ± 1.67 | 6.82 ± 1.45 | 0.121 |
| Temporal | 9.18 ± 0.94 | 9.90 ± 2.19 | 7.64 ± 0.95 | 0.003* |
| Occipital | 8.61 ± 1.33 | 10.01 ± 2.37 | 9.27 ± 3.10 | 0.431 |
| High gamma (60–80 Hz) | | | | |
| Frontal | 5.56 ± 1.41 | 5.77 ± 2.50 | 6.57 ± 4.04 | 0.764 |
| Central | 4.32 ± 0.46 | 4.60 ± 0.79 | 4.67 ± 1.47 | 0.716 |
| Parietal | 4.68 ± 0.48 | 4.79 ± 0.71 | 4.38 ± 1.05 | 0.494 |
| Temporal | 6.32 ± 0.87 | 7.40 ± 2.35 | 5.42 ± 0.91 | 0.031* |
| Occipital | 7.09 ± 1.84 | 8.52 ± 3.50 | 7.78 ± 3.37 | 0.571 |

*ANOVA, statistically significant.

2004). Projections to and from the swallowing tract represented in non-primary motor areas were suggested by Hamdy *et al*. (1998) as reason for this widespread cortical involvement. Additionally, an age-related increment of swallowing activation with further expansion over cortical regions and frequency ranges was previously shown (Teismann *et al*., 2010). Following our expectations based on these results, activation not only centred in the beta frequency band but also reached into adjacent alpha and gamma frequency ranges.

## Non-dysphagic patients with Parkinson's disease

In non-dysphagic patients with Parkinson's disease, the first finding was a strongly reduced activation in the supplementary motor area, which occurred later, as compared with healthy subjects. This is the major cortical projection area of the putamen (Alexander *et al*., 1986). Degeneration of nigroputaminal projections occurs early in the disease, whereas nigrocaudate dopaminergic projections are relatively spared (Brooks *et al*., 1990). Thus, hypoactivation of the supplementary motor area is caused by impaired putaminal output, resulting in excessive inhibitory pallidal outflow to thalamic motor nuclei with subsequent functional deafferentation of frontal cortical areas (DeLong, 1990). Our finding is in line with previous neuroimaging studies in Parkinson's disease, depicting hypoactivation of the supplementary motor area during self-initiated finger lifting (Jahanshahi *et al*., 1995), joystick movements (Jenkins *et al*., 1992; Playford *et al*., 1992; Haslinger *et al*., 2001), finger-to-thumb opposition (Rascol, *et al*., 1992) and more complex sequential finger movement tasks (Samuel *et al*., 1997; Sabatini *et al*., 2000). The supplementary motor area is considered to be involved in motor programming, initiation and movement execution. Failure of this structure can explain impaired voluntary movement initiation and bradykinesia in patients with Parkinson's disease (Nachev *et al*., 2008).

The fact that our patients showed no clinical signs of dysphagia despite strongly reduced and delayed supplementary motor area activation during voluntary initiated swallows may be attributed to our second finding: non-dysphagic patients demonstrated a prominent shift of task-related activation towards the lateral motor, premotor and inferolateral parietal cortices. This activation was

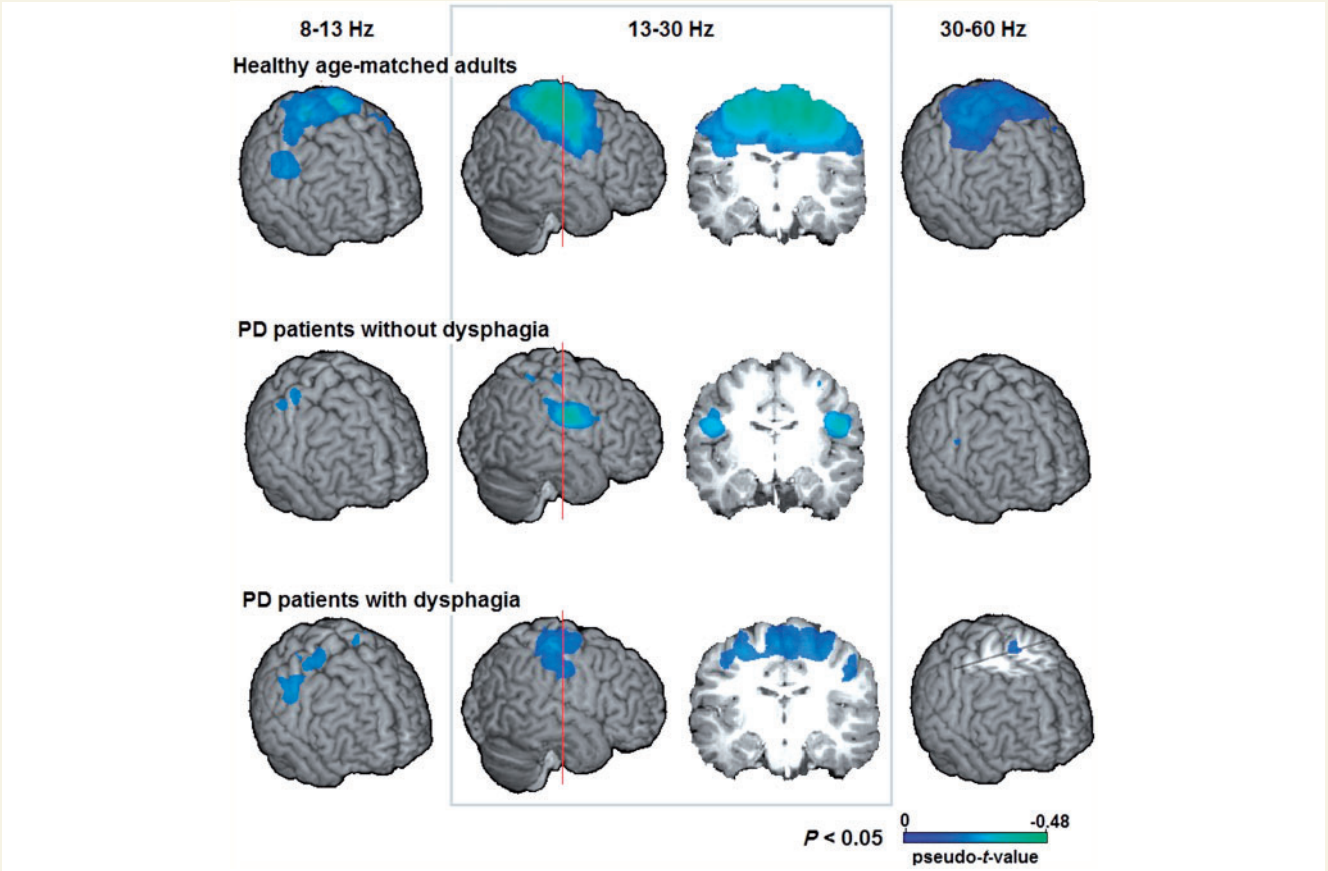


**Figure 2** Group results of significant cerebral event-related desynchronization during swallowing in alpha (8–13 Hz), beta (13–30 Hz) and low-gamma (30–60 Hz) frequency bands. PD = Parkinson's disease.

**Table 5 Localization of significant swallowing-associated cortical activation per group ($P < 0.05$)**

| Study group | Peak location (*x*, *y*, *z*) | Pseudo *t*-value | Cortical label | BA |
|---|---|---|---|---|
| Healthy aged-matched subjects | | | | |
| 8–13 Hz | l: (−21, −36, 60) | −0.3320 | GPrC, GPoC, GFm | 1, 2, 3, 4, 6 |
| | r: (15, −33, 69) | −0.3320 | GPrC, GPoC, GFm | 1, 2, 3, 4, 6 |
| 13–30 Hz | l: (−18, −30, 69) | −0.4705 | GPrC, GPoC, GFm/s, LPi | 1, 2, 3, 4, 5, 6, 40 |
| | r: (12, −27, 66) | −0.4815 | GPrC, GPoC, GFm/s, LPi | 1, 2, 3, 4, 5, 6, 40 |
| 30–60 Hz | l: (−30, −30, 63) | −0.2008 | GPrC, GPoC, GFm/s, LPi | 1, 2, 3, 4, 6 |
| | r: (30, −24, 66) | −0.2180 | GPrC, GPoC, GFm/s, | 1, 2, 3, 4, 6 |
| Non-dysphagic Parkinson's disease | | | | |
| 8–13 Hz | l: not significant | | | |
| | r: (42, −39, 48) | −0.2189 | GPrC, GPoC, LPi | 1, 2, 3, 4, 40 |
| 13–30 Hz | l: (−48, −21, 39) | −0.3148 | GPrC, GPoC, LPi | 1, 2, 3, 4, 6, 40, 43 |
| | r: (54, −6, 27) | −0.3839 | GPrC, GPoC, GFi | 1, 2, 3, 4, 6 |
| 30–60 Hz | l: not significant | | | |
| | r: (54, −9, 30) | −0.1668 | GPrC | 6 |
| Dysphagic Parkinson's disease | | | | |
| 8–13 Hz | l: (−33, 33, 57) | −0.2420 | GPrC, GPoC | 1, 2, 3, 4 |
| | r: (51, −24, 36) | −0.2411 | GPrC, GPoC | 1, 2, 3, 4 |
| 13–30 Hz | l: (−33, 30, 57) | −0.2651 | GPrC, GPoC, GFm | 1, 2, 3, 4, 6 |
| | r: (24, −27, 60) | −0.2532 | GPrC, GPoC, GFm | 1, 2, 3, 4, 6 |
| 30–60 Hz | l: (−15, −18, 60) | −0.1465 | GPrC, GFm | 6, 4 |
| | r: (15, −18, 63) | −0.1255 | GPrC | 6 |

BA = Brodmann area; GPrC = gyrus precentralis; GPoC = gyrus postcentralis; GFm = gyrus frontalis medialis; GFs = gyrus frontalis superior; GFi = gyrus frontalis inferior; LPi = lobulus parietalis inferior; l = left hemisphere; r = right hemisphere.

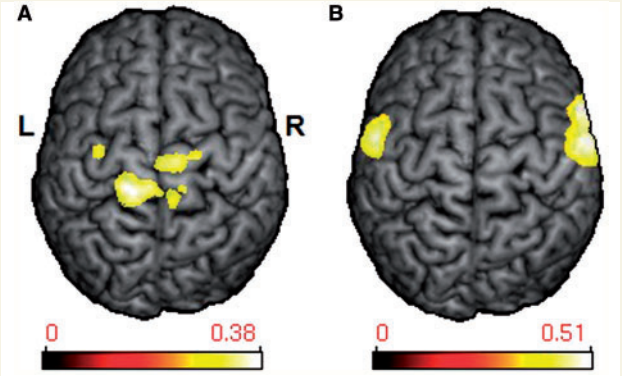


**Figure 3** Cortical areas showing a significant reduction of swallowing-associated activation in non-dysphagic (**A**) and dysphagic (**B**) patients with Parkinson's disease compared with healthy aged-matched subjects, (13–30 Hz, $P < 0.01$). The relative decrease of event-related desynchronization is colour-coded.

present from movement initiation and occured substantially before supplementary motor area activation. The relevance of this cortical recruitment pattern becomes clear when considering that the functional architecture of the basal ganglia networks is parallel in nature (Alexander and Crutcher, 1990). Two loops for movement execution have been proposed: a frontal striato-thalamocortical loop mainly projecting to the supplementary motor area, which is concerned with internally generated movements; and a cerebellar-parietal-premotor loop responsible for externally or sensory cued movements (Roland, 1984). Parallel cortical network organization with close functional coupling of the parietal and premotor cortex was also explicitly demonstrated for the volitional control of swallowing (Mosier and Bereznaya, 2001). These latter areas are functionally well preserved in Parkinson's disease because projections to the dorsolateral premotor cortex primarily originate in the relatively unaffected caudate nucleus (Alexander and Crutcher, 1990; Brooks *et al*., 1990). Moreover, the lateral premotor cortex receives dense projections from intact deep cerebellar nuclei and the parietal association cortex, which again projects to the cerebellum (Strick, 1985; Yeterian and Pandya, 1993; Nakano, 2000) and does not itself receive direct input from the basal ganglia (Samuel *et al*., 1997). In keeping with this model and similar to our findings, Samuel *et al*. (1997) observed overactivity in lateral premotor cortex and inferolateral parietal regions during a complex, sequential finger movement task in patients with Parkinson's disease. They were the first to suggest a switch from the use of defective striato-mesial frontal towards better preserved parietal–lateral premotor circuits in Parkinson's disease as an adaptive strategy to facilitate volitional movement performance. Their results were confirmed by PET (Catalan *et al*., 1999) and functional MRI studies in akinetic patients with Parkinson's disease (Sabatini *et al*., 2000; Haslinger *et al*., 2001). Concerning the role of the parietal cortex as integrator of sensory, motivational and attentional inputs and the importance of the lateral premotor cortex in sensory processing, Samuel *et al*. (1997) argued that patients subconsciously use sensory guidance for movement execution, thereby avoiding the need for intact basal ganglia–mesial frontal circuits. Evidence suggests that overactivation increases with task difficulty (Samuel *et al*., 1997; Catalan *et al*., 1999), and it is a well-known phenomenon that motor performance in Parkinson's disease improves with external cues (Siegert *et al*., 2002). In support of this hypothesis, a single photon emission tomography study by Hanakawa *et al*. (1999) revealed overactivation of the premotor cortex accompanied by clinical improvement during sensory-cued 'paradoxical gait' in patients with Parkinson's disease, thereby linking neuroimaging and clinical results.

Here, we showed for the first time that this compensatory mechanism also occurs during a complex motor task that requires the bilateral coordination of midline structures. Capitalizing on the high time resolution MEG offers, we were able to demonstrate the shift in activation pattern not only in space but also in time. More than 25 pairs of muscles are involved in a swallow, but deglutition also provides continuous oropharyngeal sensory feedback to guide motor performance. The adaptive switch towards parietal–lateral premotor circuits seems to be effective, as endoscopic evaluation confirmed that none of these patients had clinical signs of dysphagia. Concluding that cortical compensation is driven by sensory afferent input has important implications for therapeutic strategies in patients with Parkinson's disease. New methods in dysphagia treatment should rely on sensory stimulation, such as the pharyngeal electrical stimulation proposed by Hamdy *et al*. (1998). Extracranial stimulation techniques like transcranial direct current stimulation, which have recently been applied for swallowing rehabilitation (Jefferson *et al*., 2009; Kumar *et al*., 2011; Yang *et al*., 2012) should target the lateral premotor and inferolateral parietal cortex in Parkinson's disease. Adequate oropharyngeal sensory and gustatory input should be provided in parallel to enhance the stimulation effect.

## Dysphagic patients with Parkinson's disease

In dysphagic patients, the activation pattern was mainly restricted to primary sensorimotor areas. One may argue that the dysphagic patients look more similar to the control group than the non-dysphagic patients. However, their activation was strongly reduced compared with healthy subjects. The activation pattern changes observed in non-dysphagic patients were not present. We assume this to be because of the fact that the compensatory pathways were no longer recruitable in dysphagic patients. One reason for this is that with progressing neuronal degeneration, the relevant neocortical secondary sensorimotor and association regions themselves become increasingly involved in the disease process, whereas primary sensorimotor areas, in which activation was still found, remain relatively preserved until the latest stages of Parkinson's disease (Braak and Del Tredici, 2008). Additionally, progressive affection of brainstem swallowing centres may contribute to emerging dysphagia at this point. In particular, the integrity of the nucleus of the solitary tract being the main afferent central structure in deglutition and containing the 'trigger neurons' for swallowing, but also the pontine sensory relay neurons receiving information from oropharyngeal receptors (Jean, 2001) are crucial for sensory feedback-dependent swallow performance. Dysphagic

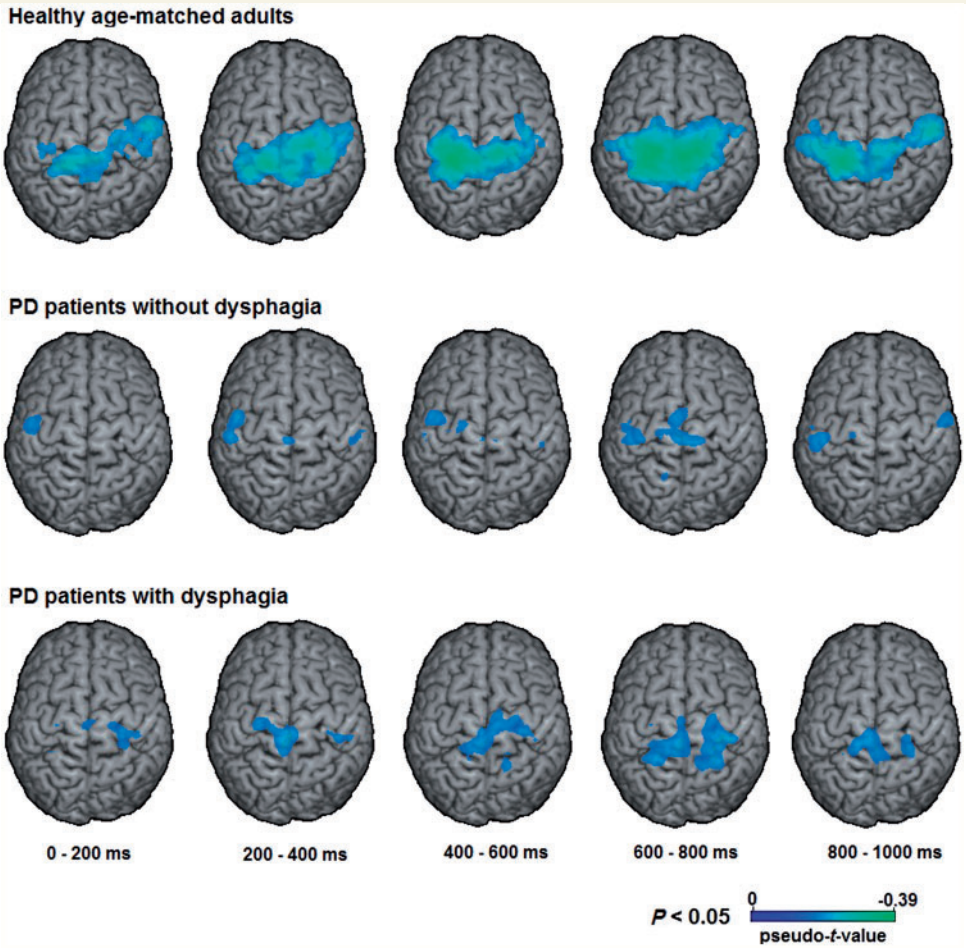


**Figure 4** Time course of significant activation (13–30 Hz) per group during the five successive 200-ms time intervals of the swallowing execution phase. PD = Parkinson's disease.

patients were ~10 years older than non-dysphagic patients, and those with an older age at onset tend to have more rapid disease progression (Jankovic and Kapadia, 2001). There may also be a limited capacity of the aged neurodegenerated brain for functional plasticity. Dysphagia seems to occur when the cumulative affection of relevant swallowing network structures at different levels of the CNS exceeds beyond the capabilities of the aforementioned compensatory mechanisms. However, whether the observed changes in the patient groups are two snapshots of one continuous disease process, or if there are currently unknown additional factors that enable some patients to compensate, whereas others cannot, remains to be elucidated. It will, therefore, be interesting to re-evaluate our non-dysphagic patient cohort, when they have developed dysphagia, to determine whether they have lost the cortical compensation pattern.

## Methodological considerations

With regards to resting-state activity, significant differences were found only in single channel groups in the theta (central and temporal channels) and low- or high-gamma frequency range (temporal channels). Regarding levels of alpha and—most relevant—beta activity, however, where swallowing activation was mainly found and afterwards statistically compared between groups, no significant baseline power differences were observed. Thus, we conclude that the cortical activation pattern differences observed during swallowing do not result from differences in the resting stage, which was used as a baseline contrast for the beamformer analysis.

The intake of dopaminergic medication introduces a difference between patients and control subjects. In some studies, similar activation patterns to those reported here were only observed in patients 'OFF' medication (Playford *et al*., 1992; Samuel *et al*., 1997; Catalan *et al*., 1999; Sabatini *et al*., 2000). Others found that dysfunctional changes were (partly) reversed by dopaminergic treatment (Jenkins *et al*., 1992; Rascol *et al*., 1992; Haslinger *et al*., 2001; Buhmann *et al*., 2003). These studies applied imaging methods that do not measure neuronal activity directly but rely on surrogate markers, such as regional cerebral blood flow, knowing that the effect of levodopa on neurovascular coupling mechanisms is still unclear (Haslinger *et al*., 2001). MEG may be more sensitive to detect even slight cortical activation changes in medicated

patients. Considering that levodopa leads to a relative normalization, it can be assumed that the changes of task-related event-related desynchronization observed in our patients would have been even stronger after drug withdrawal. Nevertheless, it would be of interest for future studies to investigate the modulatory effect of L-DOPA on the cortical representation of swallowing in more detail by comparing patients ON and OFF medication. In the present study, however, patients were required to be in the ON phase, so they could perform the MEG measurement equally well as healthy control subjects. Many of the patients would otherwise have not been able to maintain a stable sitting position for >15 min.

The MEG results rely on accurate allocation of patients to the dysphagic or non-dysphagic group. Swallowing was carefully assessed using fiberoptic endoscopic evaluation, which is currently one of the gold standard methods in dysphagia diagnostics (Langmore, 2001). Swallowing performance in non-dysphagic patients was comparable with control subjects in the screening test. Moreover, questionnaires and behavioural data strongly confirmed that patient group allocation was correct. Finally, it seems unlikely that varieties in task performance (e.g. resulting in different signal-to-noise ratio) account for the observed differences taking into account that swallowing in the MEG was done in a physiological upright sitting position at a low frequency and with small amounts of water. Participants were continuously monitored via a video camera for correct task execution and did not differ in the recorded head movement, the number of swallows or the EMG characteristics of swallowing.

Our study has some limitations: severely dysphagic patients could not take part because of increased aspiration risk during the MEG task. Patients with tremor-dominant type of Parkinson's disease also had to be excluded for technical reasons. Therefore, the results were obtained from patients with equivalent and akinetic-rigid disease type only. It is conceivable that adaptive changes in subcortical structures and cerebellum, the basal ganglia or brainstem may have been missed in the present study because of technical limitations of MEG. However, it is methodologically difficult to measure subcortical activation during swallowing in patients with functional neuroimaging modalities and has rarely been achieved. Functional MRI provides this opportunity but requires an unphysiological supine position during swallowing, which can be harmful, as aspiration is likely to occur. Also coughing and related movement artefacts in the scanner might impair the image quality. Thus, in spite of its limitations, we are certain that MEG is currently the neuroimaging modality best suited for the investigation of swallowing-associated brain activity in handicapped and dysphagic patients. From our point of view, there is little chance that such a distinct cortical activation pattern as found in non-dysphagic patients with Parkinson's disease, which has been identified as a compensation strategy to facilitate limb movement in Parkinson's disease, should just be a reflection of changes in basal ganglia and brainstem swallowing centres without direct cortical reorganization. As subcortical structures are affected earlier and more severely in Parkinson's disease, it seems likely that the less affected cortical regions have a higher potential for adaptive reorganization. Moreover, the relevant cortical areas depicting adaptive changes receive input from relatively unaffected parts of the basal ganglia or from intact cortical areas via intracortical connections, as outlined earlier in the text. Finally, following the concept that the swallowing centres in the brainstem are being volitionally triggered by descending input from higher centres in the cerebral cortex to generate the swallowing reflex (Hamdy *et al*., 1999*b*), which is top-down rather than bottom-up regulation, an effective compensatory strategy would be expected at a cortical level rather than in brainstem structures.

# Conclusion

To the best of our knowledge, the present study is the first to examine the pattern of cortical swallowing processing in patients with Parkinson's disease. We were able to contribute to the understanding of the (patho)physiology of deglutition in Parkinson's disease by showing that not only brainstem and basal ganglia circuits but also cortical areas modulate swallowing function in a clinically relevant way. The observed compensational mechanisms may be relevant for future therapeutic approaches.

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