Sir, we read with great interest the article by Schwarzacher et al. (2011) describing the neuroanatomical characteristics of the human pre-Bötzinger complex and its involvement in multiple system atrophy and spinocerebellar ataxia 3 (SCA3). In this study, the authors provide a thorough analysis of the pre-Bötzinger complex and demonstrate that somatostatin and neurokinin 1 receptor expressing neurons are severely reduced in a neurodegenerative disorder presenting with severe central respiratory dysfunction (multiple system atrophy), but spared in patients with no history of such respiratory deficits (SCA3). This study provides strong neuropathological evidence that degeneration of the pre-Bötzinger complex occurs in multiple system atrophy and extends previous findings showing a drastic reduction of putative brainstem chemosensory neurons in this disease (Benarroch, 2007). Altogether, these findings strongly support the hypothesis that degeneration of these brainstem respiratory neurons underlies respiratory dysfunction in multiple system atrophy.

In addition to the characterization of the pre-Bötzinger complex, Schwarzacher et al. (2011) also provide a detailed analysis of the nucleus ambiguus in multiple system atrophy and SCA3. In both diseases, the ventral part of the nucleus ambiguus (containing pre-ganglionic cardiovagal neurons) display severe neuronal loss, which also has been shown by others (Benarroch et al., 2003, 2006). Although less documented for SCA3, these findings may explain altered heart rate control occurring in both diseases (Cohen et al., 1987; Pradhan et al., 2008). Analysis of the dorsal portion of the nucleus ambiguus (which contains branchiomotor neurons innervating the larynx, pharynx and oesophagus) revealed a drastic reduction of the number of cholinergic neurons in patients with SCA3. Conversely, this dorsal portion of the nucleus ambiguus was spared in patients with multiple system atrophy, in accordance with previous results (Benarroch et al., 2003). Clinical and pathological data from patients with SCA3 support the authors’ conclusions that degeneration of ambi-gual motoneurons is one of the underlying mechanisms of dysphagia in this disease.

However, if dysphagia is a prominent clinical feature of SCA3, affecting >60% of patients (Jardim et al., 2001), it is also commonly observed in multiple system atrophy. Accordingly, severe dysphagia has been described in 32% of patients with multiple system atrophy in one post-mortem study (O’Sullivan et al., 2008) and dysphagia was a subjective complaint in 73% of patients with multiple system atrophy in a smaller post-mortem study (Muller et al., 2001). In both studies, the presence of dysphagia was unequivocally associated with a bad prognosis and a short survival time.

In our prospective cohort of patients with multiple system atrophy who are followed at the French multiple system atrophy reference centre, we found that 64.1% of the patients (n = 78) who were examined in 2010 with the Unified Multiple System Atrophy Rating Scale (UMSARS) displayed at least some degree of dysphagia (Table 1 and Fig. 1A). Moreover, of the 12 patients with multiple system atrophy who died in 2010, 25.0% received gastrostomy feeding at the end of life. The severity of dysphagia...
(UMSARS I, item 2) was further associated with UMSARS I (activities of daily living, Fig. 1B, \( P < 0.001 \)), UMSARS II (motor score, Fig. 1C, \( P < 0.001 \)) and UMSARS IV scores (disability score, \( P < 0.001 \)), as well as disease duration (\( P < 0.05 \)) in a univariate regression analysis. In a multivariate regression, only the association with UMSARS I scores was found. No association was observed with age and multiple system atrophy subtype (parkinsonian versus cerebellar).

Despite all recent progress, the underlying neuronal mechanisms of dysphagia in multiple system atrophy remain poorly understood. Parkinsonism and cerebellar dysfunction may further distinctly contribute to dysphagia in patients with multiple system atrophy. Accordingly, delayed bolus transport from the oral cavity to the pharynx may be due to bradykinesia or disturbed tongue coordination. Furthermore, cerebellar dysfunction seems not to considerably impair cricopharyngeal muscle relaxation (Higo et al., 2005), while parkinsonism does (Alfonsi et al., 2007). The exact contribution of parkinsonism and cerebellar dysfunction are unknown as no comparative study has been conducted so far.

The brainstem swallowing network includes a dorsal and a ventral swallowing group located within the nucleus of the tractus solitarius and the reticular formation adjacent to the nucleus ambiguous (Jean, 2001). Impaired cricopharyngeal muscle relaxation further points to an involvement of the pedunculopontine tegmental nucleus that is included in the neurodegenerative process in multiple system atrophy (Schmeichel et al., 2008).

Altogether, the results presented by Schwarzacher et al. (2011) raise several important questions that may ultimately help improve our understanding of the underlying causes of dysphagia in multiple system atrophy. As such, it would be interesting to have more clinical information about the patients with multiple system atrophy included in their study and to know whether any of these patients displayed signs of dysphagia during the course of the disease.

Finally, further clinicopathological studies in multiple system atrophy will help to identify the underlying causes of dysphagia in this neurodegenerative disorder. Since some of the nuclei involved in the brainstem swallowing network are located at the same anatomical level as the pre-Bötzing complex and the nucleus ambiguus, Schwarzacher and colleagues are in the best position to apply their expertise and elegant methodology to extend their findings in multiple system atrophy to the nuclei of the brainstem swallowing network.

### Table 1 Demographic data (mean ± SD)

| Age (years) | 64.8 ± 8.3 |
| Disease duration (years) | 6.4 ± 3.0 |
| UMSARS I | 24.2 ± 9.3 |
| UMSARS I, item 2 (dysphagia) | 1.2 ± 1.2 |
| UMSARS II | 27.2 ± 7.6 |
| \( \Delta \) Systolic BP (mmHg) during stand test | −30.2 ± 19.0 |
| \( \Delta \) Diastolic BP (mmHg) during stand test | −15.6 ± 10.9 |
| UMSARS IV | 2.8 ± 1.1 |
| Multiple system atrophy-P versus multiple system atrophy-C | 65.4% versus 34.6% |
| Probable versus possible multiple system atrophy | 89.7% versus 10.3% |
| Males versus females | 51.3% versus 48.7% |

### Figure 1

Severities of dysphagia in patients with multiple system atrophy. (A) Distribution of dysphagia severity as assessed by UMSARS I, item 2 scores. Dysphagia severity is associated with disability in activities of daily living (B) and motor impairment (C).

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### References


