Sir, we are grateful for the opportunity to respond to the correspondence from Fernagut et al. (2011) on the ambiguity of dysphagia in multiple system atrophy. We thank the authors for their comments and their interest in our article on the human pre-Bötzing complex (Schwarzacher et al., 2011). As they point out, the main focus of our study was the localization and characterization of the pre-Bötzing complex in health and in two diseases of severe brainstem degeneration, multiple system atrophy and spinocerebellar ataxia 3 (SCA3). We characterized putative pre-Bötzing complex neurons using immunostaining for neurokinin-1 receptor (NK-1) and somatostatin (SOM), two reliable markers of pre-Bötzing complex neurons in experimental animals (Gray et al., 1999; Stornetta et al., 2003). Furthermore, the population of pre-Bötzing complex neurons showed a characteristic somatic shape on conventional pigment Nissl-stained sections, making neuropathological investigations of pre-Bötzing complex neurons in human brains feasible.

Interestingly, neurons of the presumed pre-Bötzing complex were not affected in patients with SCA3, and these findings correlated well with the absence of respiratory deficits in the clinical reports of these patients. In contrast, putative pre-Bötzing complex neurons were severely reduced in the brains of patients with multiple system atrophy. This reduction was in accordance with the respiratory dysfunctions often reported in this disease (Nogues and Benarroch, 2008). We used the selective vulnerability of the pre-Bötzing complex neurons as indirect, but yet to some extent functional evidence for the identification of pre-Bötzing complex neurons in human. This view is supported by the large body of experimental evidence that indicates that the pre-Bötzing complex is essential for breathing, as stated by Ramirez’s scientific commentary on our study (Ramirez, 2011).

We further examined the distribution of motoneurons forming the ambigual complex in control, SCA3 and patients with multiple system atrophy. Neurons of the ventral portion of the ambigual nucleus were reduced in both SCA and patients with multiple system atrophy. In addition, the dorsal portion of the ambigual complex, that innervates swallowing muscles, was strongly reduced in SCA3 brains, consistent with the clinical picture of severe and ultimately lethal dysphagia, observed in patients with SCA3 (Rüb et al., 2008). Interestingly, the dorsal portion of the ambigual complex was unaffected in the brains of patients with multiple system atrophy. Fernagut et al. (2011) now present interesting clinical data from a prospective cohort of patients with multiple system atrophy who were followed by the French multiple system atrophy reference centre. Twenty-five per cent of 12 patients with multiple system atrophy, who died in 2010, received gastrostomy feeding at the end of life, in line with prior reports of dysphagia in patients with multiple system atrophy, cited by the authors (Muller et al., 2001; O’Sullivan et al., 2008). A majority of 64.1% of patients with multiple system atrophy examined by Fernagut et al. (2011) using the Unified Multiple System Atrophy Rating Scale (UMSARS) displayed at least some degree of dysphagia, and these authors reported dysphagia as a typical sign of multiple system atrophy in a recent study (Meissner et al., 2010). Although the dorsal portion of the ambigual complex was unaffected in the brains of the patients with multiple system atrophy in our study, we cannot exclude disturbances of the upper alimentary system in these patients, since the central control of
swallowing is a complex process and involves a number of other brainstem areas (Lang, 2009). This aspect was not investigated in detail in our study, which focused on central respiratory control and the pre-Bötzinger complex. Nevertheless, it is very interesting and certainly warrants further investigations.

The phases of swallowing are controlled by at least three separate sets of brain stem nuclei (Lang, 2009) and appear to involve both the dorsal and ventral ambigual nucleus. Whereas the oral phase is controlled by the trigeminal nucleus and reticular formation, the nucleus tractus solitarius contains the second-order sensory neurons as well as the pattern-generating circuitry of both the pharyngeal and oesophageal phases of swallowing (Jean, 2001). The nucleus ambiguous and the surrounding ventrolateral medulla contain the motoneurons of the pharyngeal and oesophageal phases of swallowing as well as a second pattern generator of premotor neurons (Jean, 2001). Ambigual motoneurons involved in swallowing have extensive dendritic arborizations that terminate within the adjacent ventrolateral reticular formation, where swallowing premotor neurons are located (Broussard and Altschuler, 2000). In a thorough study in cats, Lang et al. (2004) found that among activation of different subnuclei of the nucleus tractus solitarius and the dorsal vagal nucleus, the pharyngeal phase was associated with an elevated number of c-fos-positive neurons in the dorsal nucleus ambiguous, whereas the oesophageal phase was associated with activation of the ventral nucleus ambiguous. Therefore, the reduction of ventral ambiguous motoneurons in both multiple system atrophy and SCA3 found in our study could well serve as part of the mechanisms underlying swallowing problems in both diseases. In addition, other brainstem nuclei of the central swallowing network could well be affected in multiple system atrophy, which we did not investigate. Prospective clinical studies, such as the study by Fernagut et al. (2011), are of great value to correlate clinical symptoms with neuropathological changes, in particular in rare diseases, such as multiple system atrophy. We fully agree with Fernagut et al. (2011), that this kind of prospective research will lead to a better understanding of the underlying causes of functional disturbances.

Finally, we would like to point out that we found an intriguing similarity of the formation of the different subnuclei of the ambiguous complex in humans in comparison to experimental animals. The rostrocaudal organization of the ambiguous subgroups can help to delineate a concept of the arrangement of the different respiratory groups in humans (Fig. 5 in Schwarzacher et al., 2011). As pointed out by Ramirez (2011), the specific human neuropathology found in SCA3 and multiple system atrophy neurodegenerative diseases can then reversely be compared with insights gained in animals that are amenable to experimental manipulations. Taken together, this comparative approach will ultimately result in a better understanding of the neuronal determinants of human breathing, as well as other complex motor networks such as swallowing.

References


