# Catecholaminergic neurons in the peripheral nervous system

# Impact

Progress in science is dependent on (interdisciplinary) collaboration. Appropriate collaboration is dependent on language. The anatomical nomenclature is one of the fundamental languages of neuroscience important for (interdisciplinary) communication. The unambiguous description of thousands of structures is made possible with an extensive number of highly specialized terms that are used to the exclusion of any other. In this thesis we conclude that neurons, nerves and ganglia are best labelled according to topography.

## Implications from this thesis for peripheral nerve stimulation treatments

A common form of generalization is the classification of nerves and ganglia based on their dominant feature alone. The vagus nerve for example has become known as a parasympathetic nerve, and the phrenic nerve as a somatic nerve (Chapters 2,3).

Direct implications from such classifications can be observed in “peripheral nerve stimulation treatments”. This therapy involves delivering electrical impulses to specific nerves. The treatment involves surgery in which a small generator is usually implanted under the patients’ skin. Lead wires from the generator are tunneled up to the area of interest where the electrode is than wrapped around the entire nerve.

Well known examples are vagus and phrenic nerve stimulation treatments. Because of the classification of nerves on their dominant physiologic characteristic, phrenic nerve stimulation is mainly known for pacing the diaphragm (Chapter 2). Vagus nerve stimulation has, as such, become known for increasing ‘parasympathetic tone’ (Chapter 3). Other events that appear on vagus nerve stimulation, such as voice alteration and hoarseness, cough and dysphagia are called adverse effects, but are common and can be ascribed to other properties of the vagus nerve.

In this thesis, we studied the morphological composition of both vagus and phrenic nerves at the typical levels of nerve stimulation therapies. We demonstrated that both nerves also contain catecholaminergic fibers. We described the distribution of myelinated and non-myelinated nerve fibers within the left and right or along the proximo-distal course of these nerves. Such information is important for nerve stimulation, because myelinated nerve fibers have a much lower amplitude-duration threshold than non-myelinated fibers. Typical stimulation protocols for nerve stimulation can vary up to a hundred-fold in intensity, 5-fold in duration and 2-fold in frequency. If

applied for central sleep apnea, we suggest that the stimulation should target the myelinated fibers and should, therefore, be accomplished with the lowest possible amplitude-duration thresholds that result in the intended rhythmic activation of the diaphragm. This is necessary to prevent any undesired stimulation of the nonmyelinated catecholaminergic fibers that we demonstrated within the phrenic nerve (Chapter 2). Stimulation of these fibers may further increase the chronic upregulation of sympathetic activity that is already present in patients with central sleep apnea and is associated with increased mortality these patients. Furthermore, we demonstrated that the right cervical vagus nerve contains significantly more catecholaminergic fibers than the left (Chapter 3).

## Providing morphological support for novel molecular findings

The universally accepted model of the sympathetic and parasympathetic efferent limbs of the autonomic nervous system was formulated at the turn of the 19$^{th}$ to the 20$^{th}$ century. The tenability of this classic model, however, is challenged by progressive insights from novel molecular techniques (Chapter 5). Collectively, these studies however, struggle in refuting the longstanding anatomical arguments that are used for the classic subdivision of the spinal autonomic outflow in sympathetic (thoracolumbar) and sacral (parasympathetic) divisions. The proposed paradigm shift to classify the sacral autonomic outflow as sympathetic, met as such, considerable resistance in the field.

In this thesis, we assembled all available data on the peripheral distribution of catecholaminergic neurons, and used the outcome to re-evaluate the anatomical arguments on which the sympathetic-parasympathetic model is based (Chapter 5). We conclude that the anatomy of the autonomic outflow actually displays a conserved architecture along the entire spinal axis. The perceived differences in the anatomy of the thoracolumbar and sacral outflow are the result of a gradient of anatomical characteristics that progressively change from the thoracic level towards those that are typical for the sacral autonomic outflow. This finding provides the morphological support that, up until know, was lacking for the novel molecular finding that the autonomic outflows at the thoracolumbar and sacral levels possess a highly similar molecular signature. Aiding to appropriate interdisciplinary communication, we also show in this thesis (Chapter 5) that it is better to label preganglionic neurons according to topography (i.e. spinal vs. cranial), since the term sympathetic has become polysemous over time (Chapter 1).