Spatially-selective vagus nerve stimulation and fast neural EIT of the cervical vagus nerve

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Abstract – Nerves contain a large number of nerve fibres, or axons, organised into bundles known as fascicles. The new field of bioelectronics medicine, Electroceuticals, involves the electrical stimulation of nerves to treat diseases instead of administering drugs or performing complex surgical procedures. Of particular interest is the vagus nerve, a prime target for intervention due to its afferent and efferent innervation to the heart, lungs and majority of the visceral organs. Vagus nerve stimulation (VNS) is a promising therapy for treatment of various conditions resistant to standard therapeutics. However, due to the unknown anatomy, the whole nerve is stimulated which leads to unwanted off-target effects. Electrical Impedance Tomography (EIT) is a non-invasive medical imaging technique in which the impedance of a part of the body is inferred from electrode measurements and used to form a tomographic image of that part. Micro-computed tomography (microCT) is an *ex vivo* method that has the potential to allow for imaging and tracing of fascicles within experimental models and facilitate the development of a fascicular map. Additionally, it could validate the *in vivo* technique of EIT. Our group has been deciphering the organisation of the porcine vagus nerve fascicular anatomy and function. Understanding and imaging the fascicular anatomy of nerves will not only allow for selective VNS and the improvement of its therapeutic efficacy but could also be integrated into the study on all peripheral nerves for peripheral nerve repair, microsurgery and improving the implementation of nerve guidance conduits.

INTRODUCTION TO VAGUS NERVE STIMULATION

Pharmacological therapy and surgical intervention are the most commonly used approaches for treatment of various pathologies (Mishra, 2017). However, definite side effects continue to prevail for all known drugs, surgeries and non-surgical interventions (de Boer et al., 2013; Dunlop, 1969; Zimmerman, 1999). The brain, nervous system and endocrine system (via neural impulse communications through complex neural circuitry) regulate functions of all internal organs. Most drugs act on or interfere with neurotransmitters and their receptors, or endocrine system mechanisms (Locatelli et al., 2009). In order to avoid these side effects, the new field of bioelectronics medicine, Electroceuticals, was born. Electroceuticals employs electrical stimulation of nerves to treat diseases instead of administering drugs or performing complex surgical procedures (Famm et al., 2013; Kollewe, 2017; Mishra, 2017). Electrical impulses (or action potentials) are the language of the nervous system which result in regulation of virtually all organs and functions (Famm et al., 2013; "The Brain and Nervous System," 2006). Electroceuticals can modulate these neural impulses to recover lost function and revive a healthy balance (Famm et al., 2013; Mishra, 2017).

A prime target for intervention is the cervical vagus nerve (Blount, 2015; Ekmekçi and Kaptan, 2017; Guiraud et al., 2016; Koopman et al., 2016; Pečlin and Rozman, 2014; Smucny et al., 2015). The vagus nerve, also known as cranial nerve X (CN X), innervates numerous visceral organs and muscles, including the pharynx, larynx, heart, lungs, muscles of the bronchi and gut (Fig. 1). The human cervical left and right vagus nerves consist of approximately 5 to 10 individual fascicles (T. J. M. Verlinden et al., 2016), but, surprisingly, the organisation of fascicles within the vagus nerve remains almost completely unknown. The vagus nerve follows a complex anatomical path and crosses several plexuses and ganglia along its thoracoabdominal course. Electrical stimulation of the cervical vagus nerve has been successfully used to reduce depression, arthritis and the frequency of epileptic seizures (Binnie, 2000; De Ferrari and Schwartz, 2011; Ripplinger, 2017). At the moment, however, stimulation techniques and lack of understanding of fascicular anatomy allow for only the entire nerve to be activated or suppressed. Therefore, with the considerable innervation by the vagus nerve, whole nerve stimulation inevitably leads to off-target side effects with organs other than those intended being stimulated (Ripplinger, 2017). Improved knowledge of the functional anatomy of fascicles could not only be helpful in avoiding side effects but in improving the efficacy of vagus nerve stimulation (VNS) overall by better knowledge of the mapping of vagal fibres to both peripheral organs and originating brain regions.

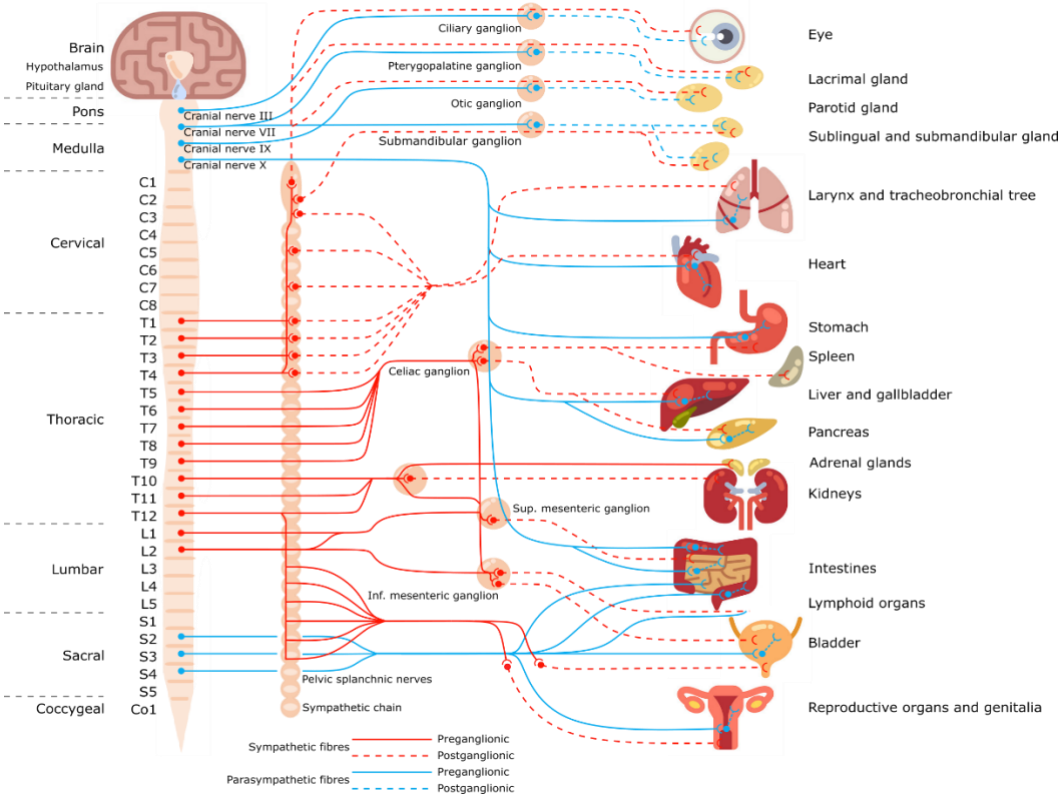

Fig. 1. General schema of the autonomic nervous system. The vagus nerve (represented as cranial nerve X) along with other parasympathetic nerves and fibres are shown in blue. The sympathetic fibres are shown in red. Postganglionic

At the outset of this work, the only evidence of organisation within autonomic nerves was that different functional regions corresponded to cardiac, pulmonary and recurrent laryngeal activity during selective electrical stimulation with a nerve cuff in sheep cervical vagus nerve (Aristovich et al., 2021). It thus seems reasonable to propose that the fascicles within nerves of the autonomic nervous system (ANS) could be organised in an organotopic manner according to organ and/or function in the way that somatic nerves are organised according to function i.e. somatotopically (Bäumer et al., 2015; Stewart, 2003; Zill et al., 1980). However, this required further exploration – shown below.

With a known fascicular organisation of the vagus nerve, selective stimulation could be used to target specific organs or effectors for neuromodulation and avoid adverse off-target effects. Preliminary studies have shown this is possible using cuff electrodes optimised for selective stimulation in sheep, dogs and humans (Aristovich et al., 2021; Pečlin et al., 2009; Rozman and Bunc, 2004). Stimulation through a pair of electrodes in the same radial position on two rings of 14 electrodes in a cylindrical multielectrode nerve cuff array in the sheep allows for selective neuromodulation of cardiac, pulmonary and recurrent laryngeal activity in the vagus nerve; evidence is yet to be obtained to show that function is localised to individual fascicles, but these results already suggest that such function is localised within the nerve (Aristovich et al., 2021). Corresponding localised activity could be imaged using the same nerve cuff and fast neural Electrical Impedance Tomography (FN-EIT) (Aristovich et al., 2021). To account for inter-individual differences, tracing techniques in animal studies may enable estimation of the degree of variation; however, the non-invasive EIT technique could be used to provide subject-specific fascicular mapping and so inform targeted stimulation.

In our research group, we are developing methods to enable selective stimulation of fascicles within the cervical vagus nerve (Aristovich et al., 2021; Chapman et al., 2018; Ravagli et al., 2021, 2020, 2019). In commencing this work, we were surprised at the lack of knowledge of the functional anatomy of the vagus nerve. We have been investigating this using neural tracers, electrophysiology with a multielectrode array, computerised tracing with micro-computed tomography (microCT), the new method of FN-EIT and trial-and-error selective stimulation.

FAST NEURAL EIT AND DEVELOPMENTS IN HARDWARE

In recent advances in biomedical engineering, specifically in our research group, a cervical vagus nerve implantable multi-electrode cuff stimulator has been designed that enables selective stimulation of fascicles or specific regions of the nerve as well as FN-EIT (Aristovich et al., 2021). This is possible due to the configuration of the cuff with two rings of 14 pairs of electrodes formulated with optimal specifications and spacing within the array. Individual pairs can be stimulated at one time, allowing for specificity of activation within the nerve.

EIT has a range of clinical applications such as the detection of breast cancer (Cherepenin et al., 2002), monitoring of lung function (Frerichs et al., 2002), differential diagnosis of stroke (Clay and Ferree, 2002; Dowrick et al., 2016), measuring normal and pathological gastrointestinal activity (Nour et al., 1995), and detection of epileptic seizure onset zones (Witkowska-Wrobel et al., 2018). One of its biomedical applications, FN-EIT, has recently been demonstrated by our group as a method for imaging evoked compound activity in peripheral nerves (Aristovich et al., 2018a).

Optimisation of peripheral nerve EIT related technical aspects has included electrode design and fabrication (Chapman et al., 2018), proof of principle and validation against basic histology (Aristovich et al., 2018a), optimisation of current injection protocols (Ravagli et al., 2019), and EIT frequency range (Hope et al., 2019).

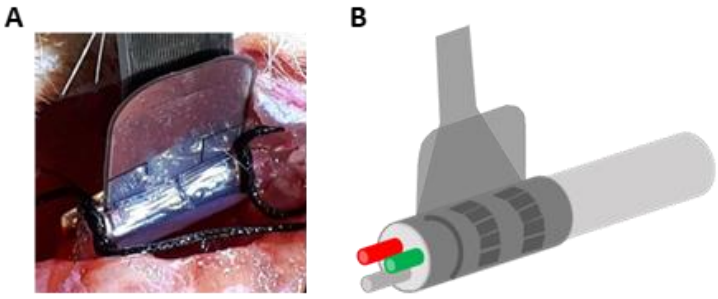

Fig. 2. Example and schematic of nerve cuff. A. Electrode cuff placed around a nerve in vivo. B. Schematic of a nerve cuff wrapped around a nerve with its fascicles (green, red and grey) running through which will subsequently be able to be imaged – the cuff comprises two arrays of 14 electrodes arranged in a circumferential ring with one reference electrode placed at the extremity of the cuff.

In FN- EIT of the peripheral nerve, impedance changes are imaged that arise during neuronal depolarisation as a result of the opening of voltage-dependant ion channels in the neuronal cell membrane of nerve fibres during evoked activity. This generates a decrease in the bulk electrical impedance of ≈0.1%, which can be imaged with a cuff-like circumferential array of surface electrodes placed around the nerve (Fig. 2). Sequential switching of sub-threshold AC injections of ≈10μA at ≈6kHz through pairs of electrodes within the array is achieved using electronic multiplexers and the resulting voltages are recorded on each electrode in the array resulting in a data set of transfer impedances. Because of low signal-to-noise ratio (SNR), averaging over several hundred evoked action potentials is required, but the resulting dataset allows imaging neuronal depolarisation with high spatio-temporal resolution of <1 ms and 200 μM in rat sciatic nerve (Aristovich et al., 2018a). Neuromodulation of the vagus nerve in conjunction with monitoring and recording heart rate, blood pressure, and respiratory rate allowed for identification of regions within the nerve that selectively reduced respiratory and heart rates without affecting the other, respectively. It is therefore hypothesis that there is functional organotopic organisation of the fascicles in the cervical vagus nerve (Aristovich et al., 2021; Prechtl and Powley, 1987). The evidence for organisation of the fascicles thus far is, from the abovementioned research, organotopic organisation with three notable regions identified: cardiac, pulmonary and recurrent laryngeal. Selective stimulation and EIT with a nerve cuff identified these three separate regions in sheep cervical vagus nerve (Aristovich et al., 2021).

ADVANCES IN UNDERSTANDING VAGUS NERVE ANATOMY

The functional anatomy of somatic peripheral nerves has been well-studied with serial histological tracing. It has been shown that fascicles observed on a nerve cross section map reasonably logically to supplied dermatomes and muscle groups (Bäumer et al., 2015; Stewart, 2003; Sunderland, 1945). The human vagus nerve is the main peripheral nerve of the ANS and provides innervation to about eight visceral organs in the thorax and abdomen as well as the larynx. It contains an average of 5 to 8 fascicles but may contain up to 21 fascicles at the cervical level (Hammer et al., 2018; T. J M Verlinden et al., 2016), but, in contrast to the somatic case, their anatomical relation to supplied organs and function is almost entirely unknown (Pelot et al., 2020; Ravagli et al., 2020; Rea, 2014). By homology to the somatic nervous system, it seems reasonable to postulate that fascicles are arranged according to their supply to individual organs and possibly specific functions.

Elucidating the organisation of the fascicles in the vagus nerve would be a paradigm shift in the largely unknown functional anatomy of ANS, providing a scientifically advanced understanding of the systems organisation of these nerves. This will improve understanding of neurobiological principles and be seminal in assisting studies on neural control (Ardell et al., 2015; Bai et al., 2019; Plachta et al., 2014), neurophysiology, neurological disease and dysfunction (Asad and Stavrakis, 2019; De Ferrari et al., 2017; Drewes, 2021; Rajendran et al., 2016), and ephaptic interactions (Bokil et al., 2001; Capllonch-Juan and Sepulveda, 2020; Sheheitli and Jirsa, 2020). In addition, these findings will be of value in the clinical applications of nerve repair and regeneration (Isabella et al., 2021) and vagus nerve stimulation (VNS) (Mastitskaya et al., 2021; Rajendran et al., 2019; Thompson et al., 2019). Specifically, the latter could be improved with the knowledge of the fascicular anatomy of the vagus nerve by allowing spatial-selectivity thereof and thus avoidance of off-target effects that are frequently experienced such as cough, dyspnoea, and bradycardia (Fitchett et al., 2021; Mulders et al., 2015).

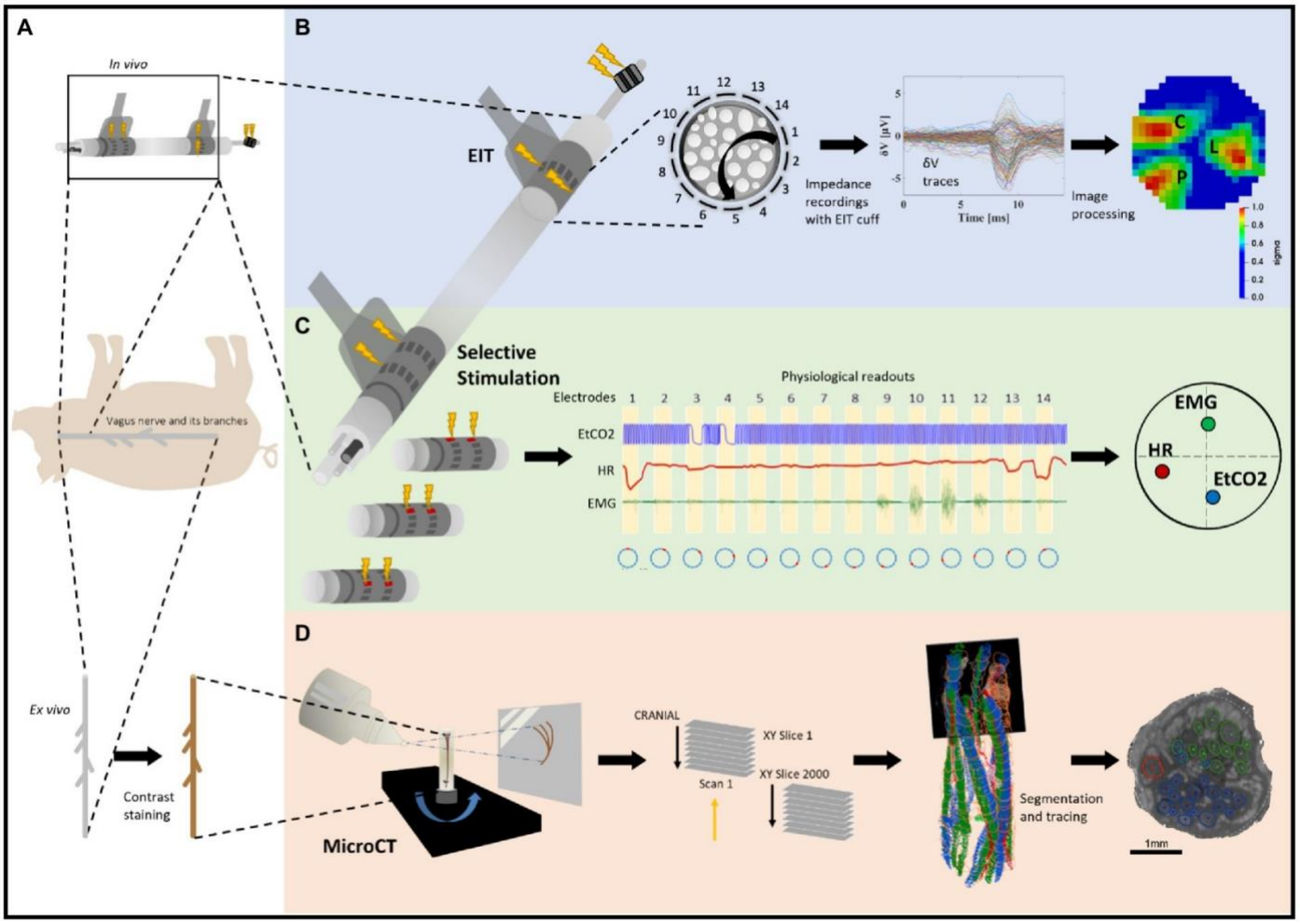

Fig. 3. Experimental design for pig cervical vagus nerve imaging with Electrical Impedance Tomography (EIT), selective stimulation (SS), and micro-computed tomography (microCT). A. *in vivo* experiment in pigs with EIT and SS cuffs placed around the left vagus nerve (N=4) followed by dissection of the nerve from cervical level to below the pulmonary branches, including the cardiac and laryngeal branches, for ex vivo microCT. B. Identification of the areas responsible for cardiac (C), pulmonary (P) and laryngeal (L) functions in the cervical vagus nerve with EIT. The colour scale is arbitrary units (Z score of relative change in the modulus of the impedance). C. Selective stimulation through individual electrode pairs applied sequentially around the circumference of the cuff (pairs 1-14) with resulting physiological changes, such as heart rate (HR, red, cardiac), electromyography (EMG, green, recurrent laryngeal) and end-tidal carbon dioxide (EtCO2, blue, pulmonary), to determine cross-sectional location of the fascicular groups responsible for the respective functions. D. MicroCT scanning of the full dissected vagus nerve followed by segmentation and tracing from the point of organ-specific branching up to the cervical level of cuff placement to identify the location of organ-specific fascicles (cardiac, red; laryngeal, green; and pulmonary, blue).

Techniques allowing imaging of the anatomy of peripheral nerve *in vivo* include photoacoustic tomography, magnetic resonance imaging (Rangavajla et al., 2014), optical coherence tomography (OCT) (Carolus et al., 2019; Hope et al., 2018; Raphael et al., 2007; Vasudevan et al., 2019) and ultrahigh-frequency and high-resolution ultrasound (Beekman and Visser, 2004; Cartwright et al., 2017; Settell et al., 2021). Unfortunately, none have sufficient tissue contrast, resolution, clarity and penetration depth to trace fascicles confidently along the entire length of the vagus nerve which is >60cm in large animals such as the pig or humans. In addition, these techniques are highly invasive, requiring a large surgical opening to visualise the origin of the fascicles present at the cervical level.

In peripheral nerves, FN-EIT and selective neuromodulation is performed with a circumferential electrode array set on a nerve cuff, and thus is non-penetrating. The former has been demonstrated in rat sciatic nerve with an accuracy of 1 msec and <200µm (Aristovich et al., 2018b; Ravagli et al., 2019, 2020, 2021). EIT can be used to image and identify organ-specific fascicles within the vagus nerve by correlation of electrical CAPs within the nerve with spontaneous rhythmical physiological activity, such as the heartbeat, lung inflation/deflation, or bowel movement (Ravagli et al., 2020).

Micro-computed tomography (microCT) of peripheral nerve after iodine staining allows *ex vivo* 3D tomographic imaging of the vagus nerve with a spatial resolution of ≈4 µm. This method has been developed and validated for the task of the tracing of fascicles over tens of cm from the innervated organ neural stimulation site to the cervical level in large animals such as the pig or man. This provides independent anatomical validation of any functional connections identified with FN-EIT and selective electrical stimulation (Thompson et al., 2020).

The three methods have enabled the fascicular organisation of the cervical vagus nerve at the level of VNS cuff placement to be deciphered for the first time (Fig. 3). It was possible to identify three spatially separated fascicular groups which correlated with cardiac, pulmonary and laryngeal (thoracic) activity with FN-EIT and selective VNS, and

this correlated closely with microCT tracing of the organ branches from their entry into the vagus nerve up to the cervical level (N=4, ~28 cm) (Fig. 4). The cervical vagus nerve is arranged organotopically with respect to these three fascicular groups. These findings were consistent between nerves and the functional and structural imaging techniques. In a cross section, if recurrent laryngeal is placed at the top (12 o'clock), pulmonary and cardiac follow in clockwise order (c. 5 o'clock and 9 o'clock, respectively). These findings support the hypothesis based on somatic fascicle organisation that cervical vagus nerves are organised organotopically.

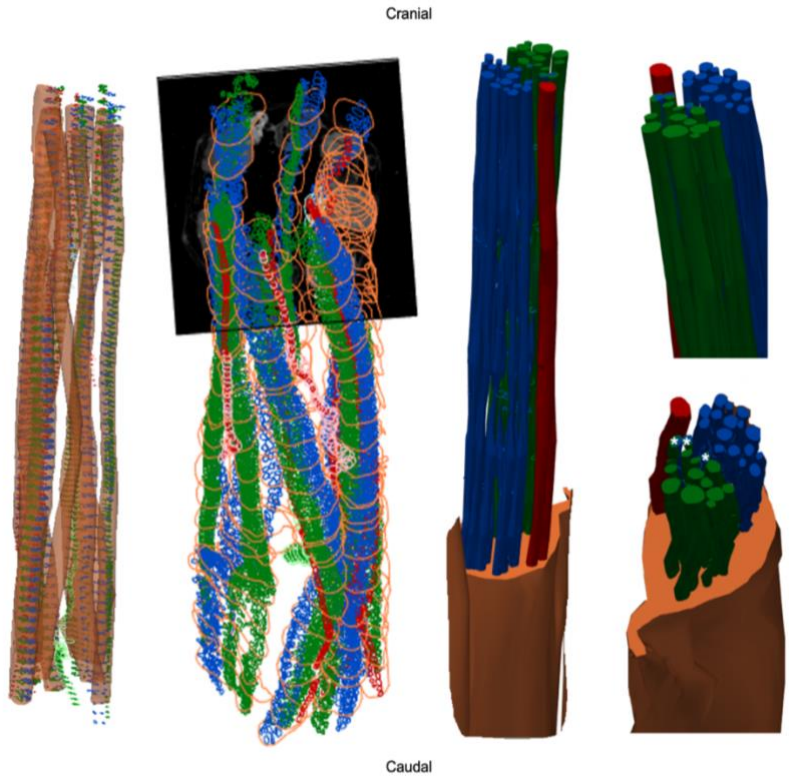

Fig. 4. 3D shelled segmentation of fascicles in the nerve. Laryngeal in green, pulmonary in blue and cardiac in red.

POTENTIAL APPLICATIONS

VNS has been successfully used to reduce depression, arthritis, the frequency of epileptic seizures, and bronchoconstriction associated with asthma, as well as to improve outcomes of heart failure (Binnie, 2000; De Ferrari and Schwartz, 2011; Klein and Ferrari, 2010; Mehmed, 2015; Ripplinger, 2017).

More specifically, VNS has been used to treat epilepsy with a significant reduction in epileptic seizures (Johnson and Wilson, 2018). VNS was approved for use in patients with refractory epilepsy in 1997 through invasive left vagus nerve stimulation at the cervical level (Farmer et al., 2016). Use of VNS for epilepsy has shown measurable improvement in patient condition – mean seizure frequency after one year decreased by 26%, after five years decreased by 30% and decreased by 52% after twelve years with VNS treatment (Uthman *et al.*, 2004). Stimulation currents for epilepsy start at 0.25mA and can increase up to 1.25-2mA over several weeks (Uthman et al., 2004).

VNS has potential to treat chronic heart failure. Increased heart rate and diminished vagal activity are indicators of a high mortality rate in heart failure (Sabbah et al., 2011). It has been shown in animals with heart failure that VNS improves left ventricular function and has the potential to prevent sudden cardiac death and suppress ventricular arrhythmias (Sabbah et al., 2011). Chronic VNS in symptomatic chronic heart failure patients has been shown to be safe and tolerable, with an increase in left ventricular ejection fraction from 22% to 29% in six months. Use of chronic VNS for treatment of chronic heart failure was in the right vagus nerve (De Ferrari and Schwartz, 2011). Chronic VNS also has potential applications in inflammatory bowel disease (IBD) patients since it has anti-inflammatory properties. Five out of seven patients with moderate Crohn's Disease in a pilot study were in deep clinical, biological and endoscopic remission after three months of VNS (Bonaz et al., 2017). VNS has also been hypothesised as effective at reducing pain in humans. Under chronic VNS, an increase of pressure and mechanical pain threshold was found alongside a reduction in mechanical pain sensitivity (Busch et al., 2013).

The anatomical knowledge of the fascicular organisation in the cervical vagus nerve is an important novel scientific finding alone, but in addition, it could aid the following fields in neuroscience: 1) More precise investigations of healthy neural control of visceral organs as the neural efferent and afferent signals within the vagus nerve can be separated and organ-specific fibres identified; As an example, the cardiac neural control is of great interest, especially with respect to afferent VS efferent traffic and how this could be leveraged to understand and precisely control the autonomic system remodelling in chronic heart failure (Ardell et al., 2017, 2015; Ardell and Armour, 2016). 2) The investigation of neurological disease and dysfunction of the autonomic neural control can be greatly enhanced by studying fibre and cell function, structure and neurodegeneration overlayed on the organotopic functional map. This will be useful in studies of pain (Busch et al., 2013), interactions between sympathetic and parasympathetic systems (Bonaz et al., 2021; Deuchars et al., 2018; Kamiya et al., 2021), and mechanisms of various conditions caused by autonomic nervous system dysfunction. 3) Organ-specific invasive autonomic neurophysiology is now possible using electric (Fitchett et al., 2021), optical (Fontaine et al., 2021), or chemical (Ahmed et al., 2022) methods, by isolating the organ-specific fascicles from the vagus. In some cases, this could be the only method as it is impossible to localise and isolate all organ-specific fibres at the organ level due to sprouting (Jensen et al., 2013) or joining of other neural

structures such as ganglia (Bratton et al., 2012). 4) The studies of ephaptic coupling (Anastassiou et al., 2011) and interactions would be greatly aided by the knowledge of the organ-specific fibre locations. As an example, the mechanisms of visceral pain could be studied with a clear prediction mechanism (Finnerup et al., 2021).

These results also lend hope to more clinical applications: the improvement of nerve repair and regeneration, microsurgery, and possible use of selective VNS in the future. The latter is currently accomplished with stimulation of the entire cervical vagus nerve; this indiscriminately modulates all organs supplied and consequent unwanted side-effects, such as cough, dyspnoea, hoarseness, shortness of breath and bradycardia (Mulders et al., 2015), limit therapeutic efficacy (Howland, 2014; Ripplinger, 2017; Thompson et al., 2019). In principle, this could be avoided by spatially selective stimulation of individual fascicles with knowledge of the fascicular organisation of the vagus. This can allow expansion of VNS from its current use in the treatment of drug-resistant epilepsy and depression (Fisher et al., 2021; Nemeroff et al., 2006) to cardiovascular disorders and heart failure, lung injury, asthma, sepsis, arthritis, diabetes, pain management, and even immune function (Asad and Stavrakis, 2019; Chakravarthy et al., 2015; Drewes, 2021; Li et al., 2021; Marsal et al., 2021; Mehmed, 2015). The recurrent laryngeal fascicles identified at the cervical level accounted for roughly a half of fascicles present, correlating with previous studies (Settell et al., 2020). Avoidance of undesired stimulation of vagal outflow to the larynx alone could improve tolerability and efficacy of VNS.

WORK IN PROGRESS

The novel techniques of FN-EIT and trial-and-error selective stimulation show promise for in vivo imaging of functional fascicular organisation and localisation clinically in humans with an accuracy sufficient for targeted VNS. Clinical trials are underway to determine the functional anatomy of human vagus nerves *in vivo* using trial-and-error selective neuromodulation and FN-EIT using the electrode cuff designed and made in our laboratory.

As shown above, the organisation of the cervical vagus nerve in swine was investigated by Thompson *et al* (2023), which showed a degree of cross-sectional organisation for branches innervating the larynx, heart and lungs, cross-correlated between spatially selective VNS, microCT and FN-EIT. Similar conclusions were drawn in another recent swine study (Jayaprakash et al., 2022). However, a deeper understanding of the functional and anatomical organisation of cardiac nerve fibres in the cervical vagus is needed to perform spatially selective VNS to treat heart failure. The key to effectively treat heart failure and having therapeutic efficacy is stimulating the efferent vagal fibres whilst simultaneously avoiding the afferents. Vagal efferent fibres regulate heart rate, contractility and excitability and when active, heart rate along with atrial and ventricular contractility is decreased (Hsieh et al., 1998). However, the location and organisation of these respective fibre groups within the vagus nerve is unknown.

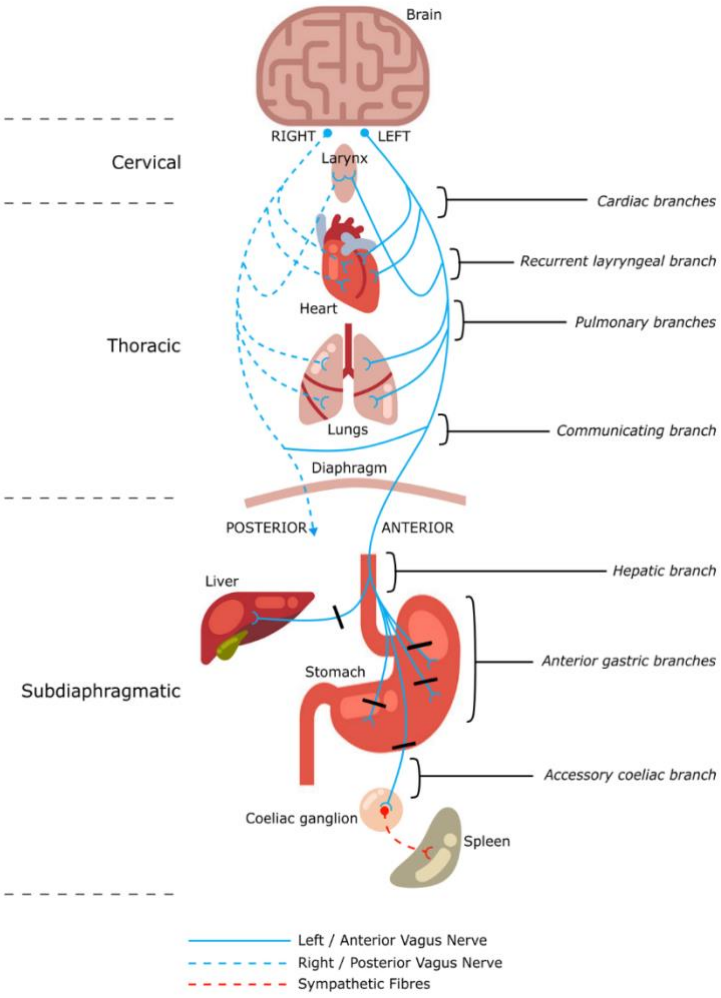

Fig. 5. Schematic of thoracic and subdiaphragmatic branches of the left vagus nerve. The left vagus nerve (solid blue line) becomes the anterior vagus nerve after passing through the diaphragm. It then goes on to supply the hepatic, anterior gastric and accessory coeliac branches. The branches were cut (short black line) as close to the organs of interest as possible. The longest branch running over the surface of the stomach was cut and labelled as the accessory coeliac ganglion.

Additionally, the three techniques, in conjunction with analysis of blood from the splenic vein for increase noradrenaline, are being used to determine the fascicular anatomy of the subdiaphragmatic fascicles amongst and in addition to the thoracic branches. This includes the gastric, hepatic and coeliac branches of the anterior vagus nerve which is derived from the left vagus nerve (Fig. 5). By activating the fibres that indirectly innervate the spleen via the coeliac ganglion, the cholinergic anti-inflammatory pathway (CAIP) could be activated. The spleen is the major source of cytokine production in conditions of systemic inflammation such as sepsis; thus, the CAIP is a potent mechanism exploited by VNS for treatment of inflammatory diseases.

IMPACT

In the future, implanted electroceutical hardware could contain a multielectrode cuff able to stimulate or block a fascicle of interest identified empirically by trial-and-error selective stimulation or from EIT. At the present time, the cervical vagus nerve has been identified as the target for initial study because it is surgically easily accessible and provides access at one site to multiple organs in the thorax and abdomen including the heart, lungs, visceral organs and gastrointestinal tract to the descending colon; one implanted electrode cuff could be used selectively to control many different autonomic organs and functions. For example, it was used as the site in a recent trial in which rheumatoid arthritis was improved by electrical stimulation (Koopman et al., 2016).

Selective stimulation is likely to be paramount in order to avoid off-target effects. Currently, whole nerve stimulation of the vagus nerve is performed which is not selective as the vagus nerve innervates numerous organs and functions. Until now, the side effects of stimulation for its principal use in epilepsy have been minor. They have mainly been hoarseness due to stimulation of the recurrent laryngeal nerve. However, in this application, the stimulation is relatively sparse. For Electroceuticals, stimulation may be more continuous and at higher frequencies, especially if blocking is the paradigm. In this case, side effects may be critical. For example, in a study of the use of beta-blockers to treat acute respiratory distress syndrome, mortality was not improved, and this was considered to be due to off-target cardiac effects (Gao Smith et al., 2012).

The hypothesis underlying this proposal is that autonomic nerves, in particular the cervical vagus, are organised according to organ origin and physiological function, so that selective stimulation will be achievable. With the map of the vagus nerve, this newly developed technology could be used accurately and targeting of specific regions, functions or organs could be possible thereby improving the therapeutic treatment of a variety of disorders.

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