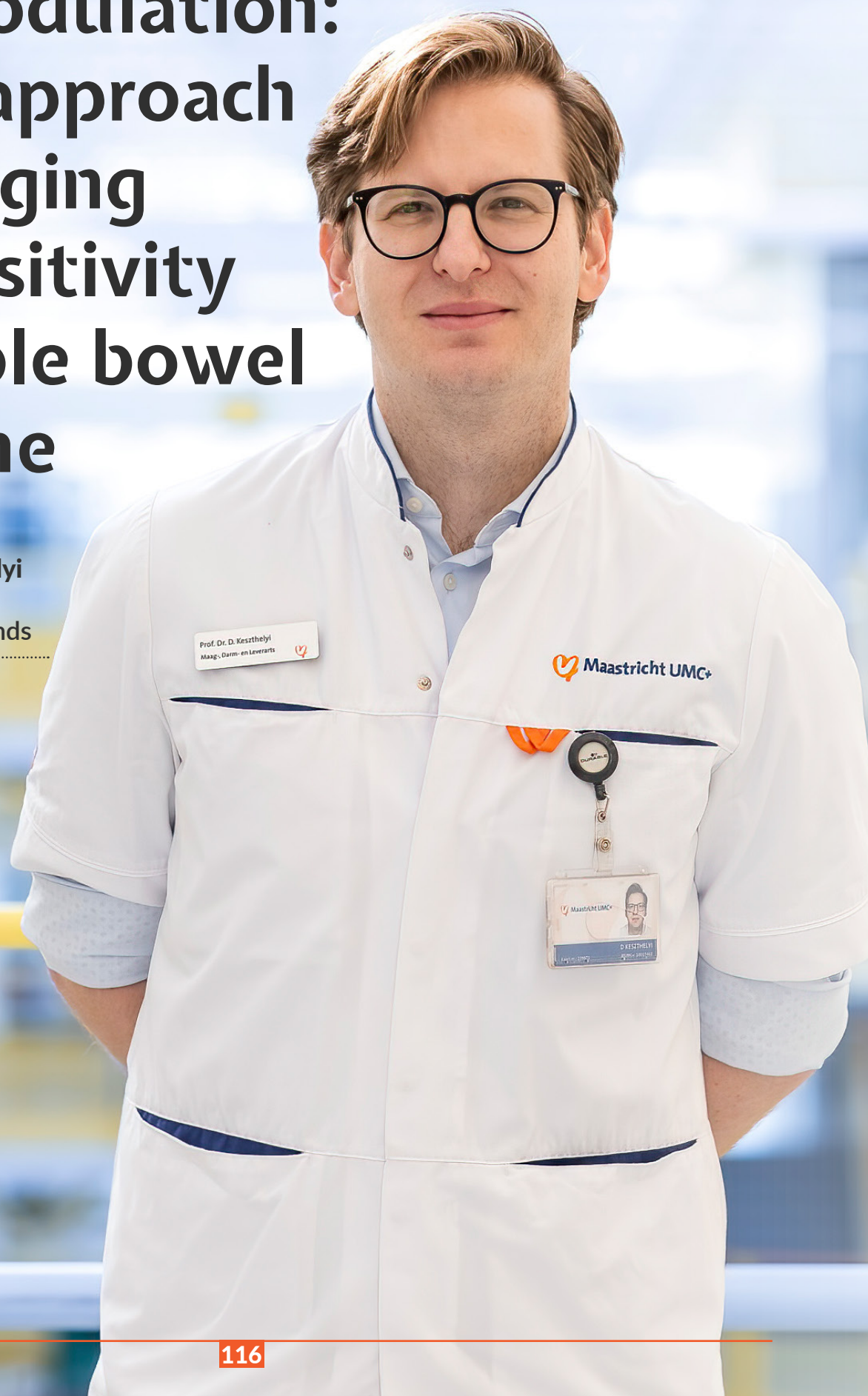


Exploring vagal neuromodulation: a novel approach to managing pain sensitivity in irritable bowel syndrome

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Common colloquial phrases like ‘gut feeling’ or ‘butterflies in my belly’ are not just idioms but reflect the unique communication between gut and brain. The principal interface for this interaction is the autonomic nervous system—a largely subconscious system that manages bodily functions through a delicate balance between its two branches: the sympathetic and parasympathetic nervous systems. The vagus nerve is the main component of the latter. Diminished vagal tone resulting in increased sensitivity to pain is characteristic of many chronic pain disorders, including irritable bowel syndrome (IBS). Correction of vagal dysfunction could, therefore, offer a novel therapeutic avenue to achieve symptom control.

Irritable bowel syndrome and the unmet clinical need

IBS is characterised by chronic abdominal pain and occurs in 5 per cent of the general population (Van den Houde *et al.*, 2019). IBS affects all age groups across the life span, generally appearing in late adolescence/early adulthood (Canavan, West and Card, 2014). The impact of IBS symptoms is substantial: survey results indicate that people with IBS would be willing to give up 15 years of their remaining life in exchange for perfect health (Drossman *et al.*, 2009). Despite the impact of IBS, its pathophysiology still remains unclear. In clinical practice, diagnosis generally relies on the exclusion of organic diseases as a cause of abdominal pain and altered bowel function (Mujagic *et al.*, 2017). Consequently, this trajectory selects patients with no identified cause for their symptoms, which results in a very heterogenous patient group. Because of this, treatment is largely a ‘trial-and-error’ process. Patients often undergo several cycles of treatment before reaching a sufficient treatment response, if ever.

Therefore, there is a need to develop novel, effective treatments and better strategies to identify which patients would benefit most from the specific treatment options, enabling an unprecedented, personalised approach to IBS. A more in-depth understanding of the pathogenesis of IBS is paramount to establishing more efficacious treatment strategies. Current consensus considers

IBS a disorder of the gut-brain interaction, reflecting the unique bidirectional communication between these two organ systems (Mearin *et al.*, 2016). However, despite this consensus, insight into the exact functioning of the gut-brain axis is still lacking and remains limited to mere concepts rather than clinically applicable therapeutic strategies.

This project will focus on understanding the processes of pain symptom generation in IBS and developing novel interventions to restore this crosstalk between gut and brain as an opportunity for adequate management of symptoms. Central to this effort is the vagus nerve. IBS has indeed been associated with reduced parasympathetic tone, contributing to heightened pain sensitivity (Chang, 2011). The vagus nerve offers a unique window to the autonomic nervous system through a single peripheral branch (the auricular branch), innervating the external ear. Given its accessibility, the auricular vagus nerve is targeted for

transcutaneous vagus nerve stimulation (tVNS), which offers a remarkable therapeutic approach. Previous studies piloting the efficacy of tVNS have indeed shown promising results in diverse clinical conditions associated with chronic pain, including migraine and fibromyalgia (Kaniusas *et al.*, 2019).

Non-invasive vagus nerve stimulation

The non-invasive transcutaneous VNS (tVNS) method consists of small electrodes that interface with the concha of the outer ear. The auricular branch of the vagus nerve innervates the concha of the ear and is located directly under the skin, making it a suitable target for transcutaneous stimulation (Kaniusas *et al.*, 2019). tVNS has been demonstrated to be safe and well-tolerated, and the potential widespread accessibility of the technology adds to its appeal (Kaniusas *et al.*, 2019).

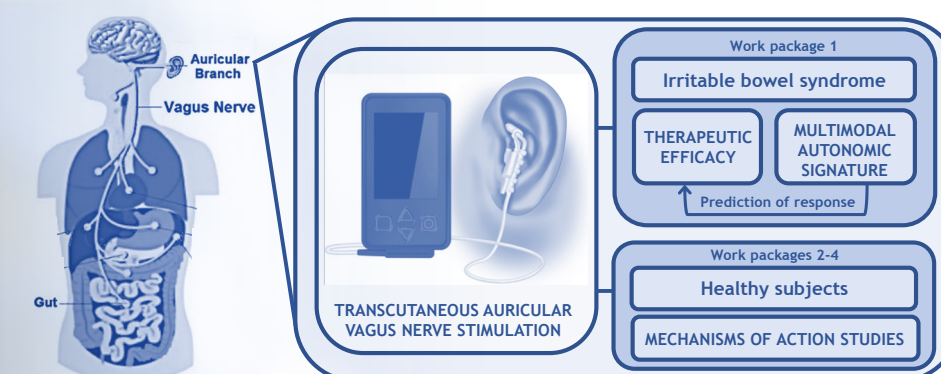


Figure 1: Work packages for auricular vagus nerve stimulation study in the RESILIENCE project.

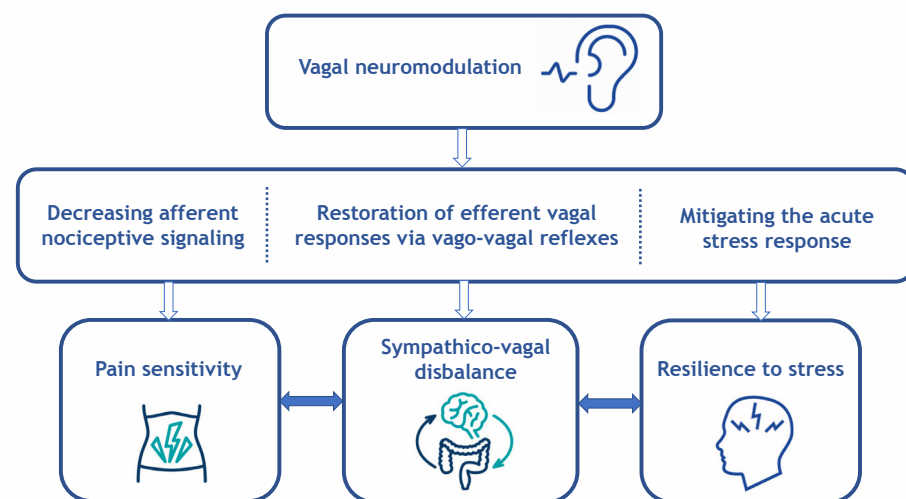


Figure 2: Visual representation of vagal neuromodulation effects on pain sensitivity, sympathico-vagal disbalance and stress resilience.

The therapeutic potential of tVNS is assumed to be the result of the fact that tVNS can impact the sensory feedback from the body to the brain. tVNS is purported to work through vagal afferents terminating in the nucleus of the solitary tract (NTS), the primary relay station for sensory vagal afferents in the brainstem. NTS, in turn, has direct or indirect projections to the nuclei, providing noradrenergic, endorphinergic and serotonergic fibres to different parts of the brain (Kaniusas *et al.*, 2019). Then, efferent outflow is generated either via efferent vagus via the vago-vagal reflex loop or from the brain to the spinal cord and then the spinal cord via splanchnic nerves towards the intestine and other organs. tVNS has been postulated to be able to restore the missing or altered signalling of intestinal afferents (Guiraud

et al., 2016). This way, neuromodulation directed at the vagus nerve can positively affect impaired synchronicity of synaptic activity between brain regions in order to improve maladaptive neuronal plasticity and, therefore, has the potential to exert both acute and chronic effects on pain sensitivity.

Project objectives

The principal hypothesis of the project is that restoring the sympathico-vagal disbalance through tVNS can decrease sensitivity to pain in IBS. In addition, the project postulates that IBS patients present with distinct neurological profiles of pain sensitivity, which can be used to predict response to tVNS. To test this, we will develop a novel 'vagal-autonomic

neurosignature' using different biometrics and high power-field neuroimaging. In parallel, we will unravel the exact mechanisms of action of tVNS, which remain unknown.

Organisation of project

The project will build on two recent methodological innovations:

- real-time symptom registration in IBS using a validated smartphone application based on the experience sampling method (ESM) (Vork *et al.*, 2018), which is able to select patients according to their stress-related pain sensitivity (Vork *et al.*, 2020); and
- a human experimental visceral pain model developed and validated for high power-field (7T) fMRI (Beckers *et al.*, 2021). Activities will be organised into four work packages (WP) addressing six key objectives. WP1 involves a large clinical study of IBS patients undergoing tVNS treatment, including extensive phenotyping. WPs 2–4 investigating mechanisms of action will be performed in healthy subjects.

The project will aim to answer questions in the following categories:

Novel therapeutic concept

- Can restoring the sympathico-vagal disbalance through vagal neuromodulation (i.e. tVNS) reduce sensitivity to pain and thereby decrease symptom burden in IBS patients? Clinical efficacy; WP1, objective 1.)

Development of a multimodal vagal-autonomic neurosignature for patient stratification in IBS

- Is it possible to define distinct patterns in pain sensitivity based on the combination of actively and passively recorded biometrics and neuroimaging? (Biomarker development and validation; WP1, objective 2.)
- Does this profiling allow for the accurate identification of patients who benefit from tVNS? (Prediction; WP1, objective 3.)

Mechanisms of action of tVNS in healthy subjects (WPs 2–4)

- Is tVNS able to interrupt incoming nociceptive signals of intestinal origin, resulting in decreased activation of higher cortical areas responsible for pain perception? (Afferent function; WP2, objective 4.)
- Does tVNS influence the motor response in the gastrointestinal (GI) tract? (Efferent function; WP3, objective 5.)

- Does tVNS have the potential to mitigate the acute response to stress? (Stress response; WP4, objective 6)

The project is foreseen to fundamentally change the therapeutic landscape of IBS and other pain disorders by providing high-quality clinical and mechanistic evidence for the efficacy of vagal neuromodulation. Identifying the neurological signatures of patients who likely benefit from this approach would represent a major breakthrough in individualising therapeutic efforts in IBS.

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PROJECT NAME

Rediscovering the Wanderer: restoration of sympathico-vagal disbalance in irritable bowel syndrome by neuromodulation — a novel therapeutic concept (RESILIENCE)

PROJECT SUMMARY

Irritable bowel syndrome (IBS) is a common, chronic gastrointestinal disorder characterised by recurring abdominal pain and discomfort. This project will work under the hypothesis that IBS is linked to a malfunctioning of the brain-gut communication axis and proposes to address this dysfunction through transcutaneous electrical vagus nerve stimulation. To assist in identifying IBS patients suitable for this treatment, the study team aims to develop a neural signature using biometrics and neuroimaging. The study has the potential to revolutionise the treatment of IBS and other pain disorders, providing personalised and effective therapies.

PROJECT LEAD PROFILE

Daniel Keszthelyi is a professor of Gastroenterology and Head of the Department of Gastroenterology at the Maastricht University Medical Center, Maastricht, the Netherlands. His main research interests relate to investigating the pathomechanisms of chronic abdominal pain and disorders of gut-brain interactions, including neuroimaging studies. He received the United European Gastroenterology (UEG) Rising Star Award and the Rome Foundation International Research Award.

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