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Concept Paper

Vagal Insufficiency Syndrome (VIS): A Unifying Hypothesis for the Pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long COVID

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Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Long COVID (LC) are chronic multisystem conditions for which no biomarker, or disease-modifying treatment currently exists. This is largely due to the failure to identify the underlying primary pathology as well as the remarkable heterogeneity of patients and their disease severity levels. We propose that ME/CFS and LC are, in most cases, a common dysautonomic state we term Vagal Insufficiency Syndrome (VIS). VIS describes a chronic deficit in vagal tone arising from damage, or dysfunction, of the brainstem-vagus axis (BVA). We argue that the known functions of the vagus nerves map closely onto the symptom profile of both conditions. Additionally, we reason that heterogeneous symptomatology is the expected outcome of vagal neuropathy because they have an organotopic, fascicular structure. In this paper we present the current evidence that the BVA is abnormal in patients, outline potential mechanisms whereby VIS could cause postural orthostatic tachycardia syndrome (POTS) and post-exertional malaise (PEM), and consider potential upstream aetiologies. VIS is offered as a unifying and falsifiable model, with specific research directions and clinical considerations.

Keywords: vagus nerve; ME/CFS; long COVID; vagal neuropathy; postural orthostatic tachycardia syndrome; cholinergic anti-inflammatory pathway; brainstem; craniocervical instability

Introduction

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic, multisystem syndrome, defined by unrefreshing sleep, cognitive impairment, debilitating fatigue and post-exertional malaise (PEM)[1]. ME/CFS is estimated to affect 404,000 people in the UK[2] and although this spans a wide range of severity levels, ~13% are estimated to be housebound or bedbound[3]. These patients are among the most severely ill and suffering patient populations in the world, with health-related quality of life measured as lower than stroke and multiple sclerosis (MS)[4]. The severe patients experience intense symptoms, struggle to even speak or move and require 24/7 care. Importantly, unlike higher mortality rate diseases, ME/CFS patients can persist in this state for decades.

The 2020 SARS-CoV-2 pandemic led to an estimated 2,000,000 people in England and Scotland with persistent symptoms >4 weeks post-acute infection and 381,000 reported continuing to be 'limited a lot'[5]. This became termed 'Long COVID' (LC) and it was quickly noticed that these patients presented with very similar, chronic, multisystem symptoms to those with ME/CFS, again spread across a range of severities. In addition to the human cost, these two pools of patients are estimated to cost the UK up to £4.8 bn for ME/CFS[6] and £10.5 bn for LC[7], in care, lost productivity and welfare, per year. These figures are difficult to reconcile with the historic UK research spend per

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ME/CFS patient being £40, as opposed to £800 for MS (150,000 patients)[8]. There are no approved treatments for either patient group and the NHS care pathway for ME/CFS is limited, consisting of advice to pace and quarterly-yearly care phone calls by their local ME service. Of the 120 LC specialist clinics originally established, only 46 are confirmed to still be open[9]. Care for these patients therefore typically defaults to general practitioners (GPs). Whilst some GPs in primary care are familiar with ME/CFS and Long Covid, most have limited experience in diagnosis or management of these conditions. Patients commonly encounter GPs who are unfamiliar with the relevant NICE guidance NG206 for ME/CFS[1], which covers diagnostic criteria, early recognition, referral and ongoing management, and NG188 for LC[10], joint guidance from NICE, the RCGP and SIGN for diagnosis, assessment and management. Additionally, many patients commonly report clinician disbelief, psychosomatisation and pressure to try contraindicated therapies such as graded-exercise therapy (GET). With no proven central pathology, biomarker or treatment, these patients typically must manage their condition alone.

Nevertheless, the biomedical research has steadily accumulated, with LC massively expanding and accelerating the work done to understand these two syndromes. In fact, a PubMed search returns 8,000-10,000 scientific papers each for ME/CFS and LC[11] respectively. As a result, these patient populations have been increasingly well characterised, and several findings plausibly relate to the disease presentation. However, the patient heterogeneity and multisystem involvement have complicated resolving primary pathology from secondary, and there is not yet a consensus model. Nonetheless, we believe enough convergent evidence has now accumulated to permit the construction of testable unifying hypotheses.

We propose that ME/CFS and LC are clinical expressions of a common dysautonomic state we term Vagal Insufficiency Syndrome (VIS). In the sections that follow, we describe the hypothetical primary pathology of this syndrome and use it as a model to explain how a vagal neuropathy could give rise to the symptomatology seen in ME/CFS and LC patients. In particular, we attempt to use this model to reconcile several areas of the literature and explain two associated, but poorly understood, features; postural orthostatic tachycardia syndrome (POTS) and post-exertional malaise (PEM). We also discuss the current evidence base supporting that the brainstem-vagal axis is abnormal in patients, as well as consider possible upstream aetiologies that can initiate the cascade.

Vagal Neuropathy

We use the term VIS to describe a proposed state of chronic insufficient efferent and/or afferent signalling of the vagus nerves relative to physiological demand. We argue that this deficit, once of sufficient magnitude, could cause the majority of the symptoms afflicting ME/CFS and LC patients. However, we do acknowledge that the ME/CFS and LC categories are diagnostic buckets of idiopathic cases and may contain some patients with a different pathology. For example, some patients diagnosed with LC have obvious damage from a severe acute infection rather than ME/CFS-like sequelae. Nonetheless, despite ongoing debate about how the two conditions relate to each other, they have an undeniably large symptom overlap. A systematic review found that 25 of 29 catalogued ME/CFS symptoms have been reported in at least one LC study[12]. Furthermore, 95% of LC patients[13] and 97% of ME/CFS patients[14] report at least one autonomic symptom, therefore, we will consider them as one dysautonomic syndrome, VIS. While there are, by definition, different precipitating aetiologies that may confer some secondary differences between patients, we make the case that the shared primary pathology is dysautonomia caused specifically by vagal neuropathy.

The autonomic nervous system (ANS) regulates the involuntary functions of the body, across all organs, and is divided into the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) which broadly oppose each other. The vagus nerves are the principal nerves of the PNS and regulate a vast array of functions. Anatomically the two vagus nerves emerge bilaterally from the brainstem and branch to most organs. Despite being the longest cranial nerve in the body, the vagus nerve comprises only ~100,000 axons; 20% efferent and 80% afferent, the latter carrying sensory information back to the nucleus tractus solitarius (NTS) in the brainstem. The cell bodies of the

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afferent limb are located anterior to the atlas in the nodose and jugular ganglia, whereas the efferent cell bodies are the dorsal motor nucleus of the vagus (DMV) and nucleus ambiguus (NA), housed in the brainstem. The vagus nerves are arguably especially vulnerable to damage due to their non-segmental length, proximity to external environments such as in the gut and lungs, primarily unmyelinated axons, high metabolic activity and anatomical bottlenecks, such as the atlanto-styloid interval. However, 'vagal neuropathy' is not generally recognised by clinicians, beyond swallowing and voice issues. Yet the vagal functions are far broader than just pharyngeal motor control and cannot be immune from pathology so we would expect a corresponding patient group. We propose ME/CFS and LC patients sit in this clinical blind spot. Clinicians typically record the patient's dysfunction organ-by-organ and label them 'complex', eventually diagnosing the patient with ME/CFS or LC. However, we feel they may be missing a vagal neuropathy that explains the systemic presentation.

Similarly in biomedical research, the complex and heterogeneous presentation of ME/CFS and LC patients frequently leads to the reasonable conclusion that the core pathology must also be very complex. However, we respectfully reject that logic on the basis that nearly all diseases have systemic signatures and would likely also be considered complex had the central pathology not been discovered. Instead, we asked ourselves, 'what *singular* dysfunctional tissue, organ or system could lead to such a diverse phenotype?' and the vagus nerve emerged as the most compatible, singular candidate. By simply identifying the known functions of the vagus nerve and inverting them to dysregulation, we found they mapped very closely to previous characterisations of the symptom profile of ME/CFS[12] and LC[15] **(Table 1)**. Whilst this is clearly correlative and not systematic, we feel the overlap is significant enough to warrant posing a hypothesis and a further evaluation of its explanatory power.

Importantly, not only is the multiorgan symptom set explainable by vagal neuropathy, but the heterogeneous patient population is an emergent property of this model. The reason being that the vagus nerve has a mostly organotopic fascicular organisation **(Figure 1)**, with fascicular bundles serving distinct target organs and tissues[16,17]. Stochastic patterns of apoptosis, degeneration or dysfunction of fibres across different fascicles, would theoretically generate a population of patients with diverse symptom combinations but who have the same underlying disease process. Furthermore, severity, both overall and per system, could be determined by the degree of axonal loss, or degeneration, per functional cluster. Disease progression could reflect continual axon loss, dysfunction or an accumulation of downstream pathology. Overall, we find vagal neuropathy to be a parsimonious answer to both the question of primary pathology and patient heterogeneity in ME/CFS and LC.

Table 1 shows the known functions of the vagus nerves, the predicted consequence of dysfunction and the symptom prevalence of similar issues in ME/CFS and LC. Table 1 was constructed by identifying tissues the vagus nerves are known to innervate, and then cataloguing the functions attributed to vagal signalling in each region from physiology literature. A function was included irrespective of whether any corresponding symptom had been reported in ME/CFS or LC. Prevalences were retrieved from the largest available symptom-frequency studies in each condition reporting symptom-level rather than diagnosis. Where there were prevalences in more than one paper, both are shown irrespective of agreement. 'NR' indicates that no published prevalence estimate was found, not that the symptom is necessarily absent. This was not intended to be fully systematic, nor do we claim it to be exhaustive.

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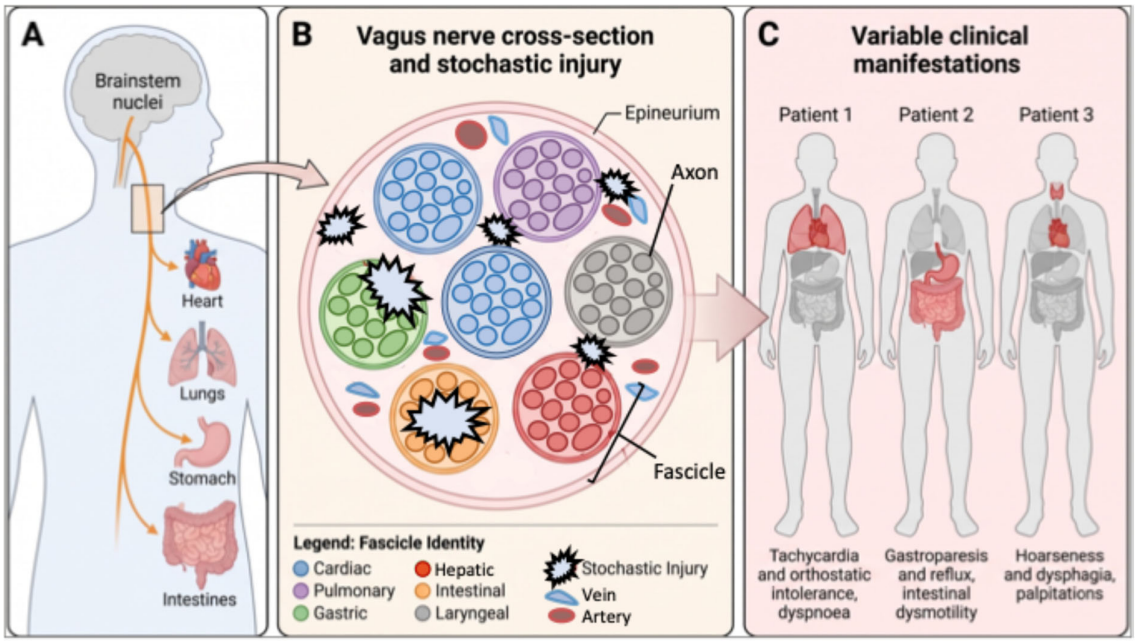

Figure 1. Schematic illustrating how stochastic injury pattern in the vagus nerve can give rise to a heterogeneous patient population. (a) Overview of the path of the vagus nerve from the brainstem nuclei, branching to the corresponding organs. (b) Cross section of the vagus nerve showing its fascicular structure and an example pattern of injury 'Patient 2'. (c) Hypothetical patient population with a heterogeneous symptom portfolio dependent on which fascicles were affected.

Table 1. Known functions of the vagus nerve and their proposed matching ME/CFS and LC symptoms when vagal tone is insufficient.

Vagal function	Evidence level	Corresponding symptoms of dysfunction	Symptom prevalence	
			ME/CFS	LC
Cardiac				
Slows heart rate via sinoatrial and atrioventricular nodes [18]	Established, human	Inappropriate sinus tachycardia and impaired heart rate recovery	23.5%[13]	61.4%[15], 28.7%[13]
Reduces the force of cardiac contraction at rest [19–21]	Established, human	Palpitations	23.4%[22]	67.4%[15], 57%[23]
Preserves inotropic responsiveness[24] and increases coronary flow during exercise[25]	Established, animal	Exercise intolerance, vasospasms and angina.	86.4%[22]	89.1%[15], 87%[23]

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Suppresses atrial and ventricular ectopy and arrhythmia [19,26]	Established, animal	Ectopic heartbeats and arrhythmia	23.4%[22]	NR
Vascular and blood pressure regulation				
Facilitates the baroreflex [21,27]	Established, human	Orthostatic intolerance, cerebral blood flow abnormalities and intracranial hypoperfusion	86%[28]	70%[29]
Signals arterial pressure from the aortic arch baroreceptors [27]	Established, human	Orthostatic hypotension and blood pressure lability contribution to orthostatic intolerance	18.8%[13]	21.0%[13], 11.8%[15]
Detects low blood volume via cardiopulmonary stretch receptors[30]	Established, animal	Hypovolaemia, orthostatic intolerance and POTS	28%[28]	36%[29]
Dilates coronary arteries via nitric oxide-dependent tone[31,32]	Established, animal; supported in human	Exertional chest pain and vasospasm	18.0%[22]	53.1%[15], 26%[23]
Respiratory and airway				
Regulates bronchomotor tone and airway mucus secretion[33]	Established, animal; supported in human	Breathlessness, air hunger and chest tightness	35.4%[22], 28.2%[13]	77.4%[15], 36%[23]
Detects airway stretch and contributes to respiratory rhythm[34]	Established, animal	Central sleep apnoea	NR	7.1%[15], 36%[23]
Pharyngolaryngeal				

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Innervates the pharyngeal, laryngeal, soft palate and palatoglossus musculature[35]	Established, human	Dysphagia, hoarse voice and eustachian tube dysfunction	32.6%[36]	32.5%[15]
Mediates the cough, gag, swallow and vomiting reflexes[37]	Established, human	Impaired gag reflex, chronic cough and swallowing difficulties	39.2%[36]	66.2%[15], 33%[23]
Gastrointestinal				
Drives oesophageal, gastric, and small-intestinal motility and gastric emptying[38–40]	Established, human	Gastroparesis, early satiety, constipation and irritable bowel symptoms	47.7%[22]	30.8%[15], 59%[23]
Stimulates gastric acid, digestive enzymes and mucus secretion[37,41]	Established, human	Maldigestion, malabsorption and bloating	47.9%[22]	35.0%[15]
Maintains mast cell regulation and gut barrier immune tolerance[39,42,43]	Established, animal	Mast cell activation syndrome and food sensitivities	42.4%[22]	20.3%[15]
Signals satiety and energy balance[44]	Established, human	Appetite change and unintentional weight gain	37.2%[22]	51.6%[15]
Hepatic, metabolic and fluid balance				
Regulates pancreatic secretion and hepatic glucose-sensing[41,45–47]	Established, animal	Impaired digestion and dysregulated glucose homeostasis	NR	33.7%[48]
Senses portal vein osmolarity and blood volume[49,50]	Established, animal	Altered thirst	NR	35.8%[15], 40%[23]

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Relays thermal information by hepato-vagal afferents via the NTS to hypothalamic circuits[47,51]	Established, animal	Temperature dysregulation, heat or cold intolerance.	54.7%[22]	58.2%[15], 35%[23]
Urinary				
Contributes to bladder control[52,53]	Inferred	Urinary retention or incontinence	30.6%[22]	14.1%[15], 30%[23]
Immune and inflammatory				
Suppresses systemic cytokine production via the cholinergic anti-inflammatory pathway[54,55]	Established, animal	Chronic low-grade inflammation and flu-like symptoms	54.3%[22]	59.5%[15]
Suppresses joint and systemic inflammation[54,56,57]	Established, animal; supported in human	Myalgia and arthralgia	73.9%[22]	69.1%[15], 39%[23]
Relays to splenic immune output via the splanchnic nerve[58,59]	Established, animal	Immune dysregulation and raised autoantibody titres	29.5%[60]	NR
Central and neuroendocrine				
Regulates the behavioural sickness response to infection[37,61–63]	Established, animal	Fatigue and malaise	93.1%[22], 87.3%[3]	98.3%[15], 85%[64]
Promotes sleep-onset [65] and slow-wave sleep depth[66,67]	Established, human	Insomnia and non-restorative sleep	90.7%[22], >90%[68]	68.6%[15], 32%[23]
Supports glymphatic clearance of brain metabolites during sleep [69,70]	Inferred	Unrefreshing sleep and brain fog	>90%[68], 80.1%[22]	85.1%[15], 64%[23]

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Conveys interoceptive information from the thoracic and abdominal viscera[71]	Established, human	Malaise, air hunger, nausea, loss of sense of wellbeing and central sensitisation.	85.4%[13], 25.0%[22]	78.1%[13], 47.8%[15]
Modulates limbic GABAergic tone via afferent input to the NTS [72–74]	Established, animal; supported in human	Anxiety and panic attacks	37.6%[75]	57.9%[15], 27%[23]
Modulates hypothalamic-pituitary-adrenal axis output via the NTS to hypothalamic corticotropin-releasing hormone[76–78]	Established, animal	Blunted cortisol, fatigue, weakness, hypotension.	67.1%[22]	44.5%[15], 42%[23]
Normalises central auditory gain[79]	Inferred	Tinnitus	52.1%[36]	34.0%[15]

Orthostatic Intolerance and POTS

Orthostatic intolerance is among the most consistent findings in ME/CFS and LC, and its most recognised form, POTS, requires a deeper explanation than just the functional inversions of **Table 1**. By strict tilt-table-based criteria (HR rise ≥30 bpm within 10 min of standing), ~28% of ME/CFS patients[28], and ~36% of LC patients[29], have POTS. However this may substantially underestimate the true burden of vascular-autonomic dysfunction, as 90% of ME/CFS patients show abnormal cerebral hypoperfusion on tilt, including 82% of those whose heart rate and blood pressure responses appear entirely normal[28]. This may explain why the prevalence of orthostatic intolerance, where symptoms emerge or worsen upon upright posture and lessen by recumbence, is greater than that of POTS, estimated at ~86% for ME/CFS[28] and ~70% for LC[29]. We propose that POTS in these conditions is not a discrete disease but instead another consequence of vagal neuropathy, with overlapping subtypes (neuropathic, hypovolaemic and hyperadrenergic) representing different points of failure along the vagally-mediated baroreflex circuits.

There are two baroreflex circuits; 1) the arterial (high pressure) baroreflex which has two distinct afferent arms and, 2) the cardiopulmonary (low pressure) baroreflex. The arterial baroreflex depends on blood pressure sensors located on vagal afferents in the aortic arch and glossopharyngeal afferents in the carotid artery. These receptors fire under arterial stretch, signalling to the NTS, prompting it to suppress heart rate via vagal efferent signalling to the sinoatrial node (SAN), and lower vascular tone by inhibiting sympathetic efferent vasomotor signalling. Both afferent limbs contribute to negative inotropy (via sympathetic efferents) and negative chronotropy (via vagal efferents) when fired, but asymmetrically, with the aortic afferent limb contributing up to 70% of vagal efferent chronotropic control[80,81]. In contrast the split for sympathetic vasoconstriction (muscle sympathetic nerve

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activity, MSNA) and renal sympathetic nerve activity (RSNA) is thought to be roughly equal[80]. The vagus nerve is therefore the dominant brake on heart rate and its withdrawal can cause tachycardia if dysfunctional. Furthermore, once the heart rate is elevated, vagal dysfunction would be expected to cause low heart rate recovery (HRR), a common finding in patients[82]. The disinhibition of sympathetic outflow when pressure is low is important for beat-to-beat blood pressure normalisation upon orthostatic challenge by MSNA and then tonically by both RSNA and activation of the renin-angiotensin-aldosterone system (RAAS).

The cardiopulmonary baroreflex is even more sensitive to orthostatic challenge and therefore especially relevant to POTS. Similar to the arterial baroreflex, this circuit consists of vagal afferents that fire when receptors detect stretch, except these are located on the cardiac atria and pulmonary veins, allowing them to detect blood volume. As before, when stretched they signal to the NTS and suppress vasoconstriction by inhibiting sympathetic efferents [83]. In the context of low blood pressure the cardiopulmonary baroreflex disinhibits vasoconstriction of muscle, splenic and renal vascular beds as well as RAAS. This reflex is more sensitive and faster than the arterial baroreflex, with lower body negative pressures that decrease venous but not arterial pressures, eliciting a clear increase in vascular resistance[84]. Thus suggesting that a dysfunction in this circuit could trigger orthostatic hypotension and compensatory tachycardia via the arterial baroreflex. Additionally, vagal knock-outs of the stretch receptor PIEZO2 become insensitive to hypovolaemia[30,83] and approximately 70% of POTS patients are hypovolaemic[85], theoretically linking hypovolaemic POTS to vagal neuropathy mechanistically. This desensitisation to blood volume may also explain the 'renin-aldosterone paradox' in POTS where aldosterone is paradoxically low despite reduced plasma volume that would normally trigger renin release and consequent aldosterone secretion[86].

A potential non-vagal failure point is the efferent sympathetic limb itself. In the neuropathic POTS subtype, which accounts for roughly 33-50% of POTS, small-fibre neuropathy (SFN) damages the postganglionic sympathetic vasomotor fibres that normally constrict the lower-limb vasculature on standing[87,88]. Without adequate vasoconstriction, blood pools in the legs, venous return and preload fall, and the heart rate increases to defend cardiac output. Small-fibre neuropathy may be the cause of POTS in some, or a modifier of severity in others. There is also the possibility that some patients won't have true SFN but chronic low tone in these fibres due to a failure located in the upstream NTS, such as has been suggested in craniomedullary syndrome[89].

It seems highly likely that, in many patients, orthostatic intolerance and POTS are yet another consequence of vagal neuropathy, via baroreflex failure. However, a pertinent mechanistic objection must be addressed. Given the sympathoinhibitory organisation of the baroreflex circuits, one might expect that deletion of the vagal afferent limb would produce chronic hypertension and tachycardia, rather than the blood pressure lability and orthostatic intolerance actually seen in patients. Nonetheless, empirically, this is not what happens in animals with sinoaortic denervation. Vagal baroreceptor denervation in animals consistently causes a temporary rise in mean arterial pressure (MAP) which resolves to near normotension within hours to weeks[90–92]. The consistent phenotype in these animals is marked blood pressure lability, as it is in human baroreflex failure[93]. The reason is that basal sympathetic activity and MAP are set independently of the baroreflexes by a central set point and renal pressure natriuresis[94]. Loss of the vagal fibres and baroreflexes may simply remove the ability to respond acutely to blood pressure, or volume changes, potentially resulting in orthostatic intolerance and POTS[95]. Additionally, our stochastic injury model implies partial retention of cardiac efferent and afferent vagal fibres. This would still enable some response to orthostatic challenge, albeit a delayed and abnormal one such as tachycardia. Another example would be the compensatory central sympathetic surge seen in the hyperadrenergic subtype, in which upright plasma noradrenaline is markedly elevated[96]. Consistent with these ideas, baroreflex sensitivity is reduced in severe ME/CFS[97] and afferent baroreflex failure has been documented following COVID-19, with one case, presenting with normal MAP but severe blood pressure lability and orthostatic intolerance [98]. Viewed together, the neuropathic, hyperadrenergic, and hypovolaemic subtypes of POTS need not be regarded as separate diseases requiring separate

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explanations. Each may represent a different manifestation of failure on one autonomic circuit whose integrity depends on the vagus nerves and coordinated sympathetic output.

Fatigue and Post-Exertional Malaise

Fatigue is a defining feature of ME/CFS and found in 87-100% of LC patients, yet, despite prioritised study, it is still not understood[15]. Patients can feel fatigued from minimal activity and even at rest, to the point of 24/7 bedbound exhaustion in severe cases. While technically the fatigue is multifactorial, with contributions from a collective burden of secondary symptoms such as unrefreshing sleep, systemic inflammation and preload failure; patients report the fatigue as more profound than can be explained by these alone. Indeed, patients with other diseases with those pathologies do not exhibit the same severity or pattern of fatigue, so there is likely a more intrinsic cause. We believe the mechanism is vascular dysfunction, downstream of low vagal tone.

The evidence points toward a haemodynamic failure at the level of respiring tissue. In both conditions, invasive cardiopulmonary exercise testing (iCPET) studies have demonstrated impaired peripheral oxygen extraction and utilisation, independent of cardiac output[99,100]. This is further supported by findings of decreased pyruvate dehydrogenase flux[101], decreased anaerobic threshold[100] and excess lactate on exertion and at rest[102,103], consistent with a greater reliance on glycolysis and a reduced capacity to meet ATP demands aerobically. Importantly a recent study found that skeletal-muscle mitochondrial capacity does not correlate with VO_2 max in ME/CFS patients, as it does in healthy and deconditioned controls[104], suggesting that the aerobic limitation is upstream of, or unrelated to, mitochondrial dysfunction. Together, these data suggest fatigue is not primarily due to a cardiac deficit, nor only a mitochondrial deficit but instead a peripheral vascular one, where blood and oxygen fail to reach or be extracted by respiring tissue[99,100].

Intriguingly, fatigue increases, and exercise capacity decreases, 1-2 days after exercise; a phenomenon definitional to ME/CFS known as post-exertional malaise (PEM)[105,106]. In LC, pre and post-exercise biopsies revealed lower muscle oxidative phosphorylation capacity, lowered anaerobic threshold and increased glycolytic type IIX fibres, signatures that worsened after exercise, objectively confirming patient reports that LC features PEM too[107]. Concerningly, patients often report a permanent lowering of baseline after such exercise, and there is evidence of subsequent damage to the muscle tissue, such as focal necrosis, signs of chronic muscle regeneration[107] and mitochondrial damage[108,109]. The kinetics also mirror those of delayed onset muscle soreness (DOMS) in healthy people, which peaks 24-72 hours post exercise, albeit at much higher provoking intensities[110,111]. We therefore distinguish the physiological limitation present during exertion from the delayed post-exertional response. The former may generate the initiating cellular stress, whereas failure to resolve that stress during recovery produces PEM.

Vagal tone is highly implicated in fatigue, exercise and recovery. Estimated by the proxy of high frequency heart rate variability (HRV), low vagal tone has been associated with fatigue in healthy adults across a wide range of occupations[112–115], and at the extremes of health such as in elite endurance athletes[116] and sick patient populations [117–121]. A systematic review across seventeen medical populations found the association in fourteen[122]. Notably, fatigue is preceded, not merely accompanied, by reduced vagal tone in health[123] and disease[124,125], and interventional raising of vagal tone reduces fatigue in cancer survivors[126], primary Sjögren's syndrome[120] and in two small Long COVID pilot trials[127,128], supporting a causal link. ME/CFS[124] and Long COVID[129] appear to represent a pathological extreme of this general relationship.

The vagus nerve is also specifically implicated in exercise itself. Vagal tone scales with physical fitness, both cross-sectionally and with interventional exercise[130,131]. Structural and functional vagal adaptations to exercise have been quantified in rats, including increased firing of vagal preganglionic neurons[132], increased axon diameter, neurofilament density, microtubule density and myelin sheath thickness in myelinated fibres[133]. Recent transcutaneous vagus nerve stimulation (tVNS) trials in healthy adults demonstrated increased VO_2-peak, a reduced

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inflammatory response, 3.5 fold faster lactate clearance and lower perceived fatigue in post-exercise recovery[134,135].

In order to understand exactly how vagal function may be important in exercise and therefore potentially in ME/CFS and LC, it is useful to first understand the main cardiovascular cascade during exercise. Heart rate rises at onset by vagal withdrawal, followed by central sympathetic activation that increases cardiac output and, via α-adrenergic tone, constricts low-respiring vascular beds to bolster arterial pressure[136]. Respiring capillary beds in exercising muscle are subject to α-adrenergic tone also but this vasoconstriction is partially overridden locally by vasodilators such as nitric oxide, adenosine, H^+, and ATP, released by endothelial cells and deoxygenating erythrocytes in proportion to demand. Oxygen delivery and the convective washout of H^+, lactate, and carbon dioxide are both coupled to tissue perfusion. When exercise ceases, the muscle pump stops, and continued metabolite removal is supported by sustained post-exercise hyperaemia. Skeletal muscle itself is not vagally innervated, making it initially unclear how vagal insufficiency could give rise to the peripheral vascular phenotype. However, the consensus view that the vagus fully withdraws, and that exercise is primarily sympathetically regulated, has been updated in recent years.

There are now several recognised mechanisms by which the vagus nerves participate in the exercise response. Elegant single-unit carbon-fibre recordings from vagal preganglionic neurons in the nucleus ambiguus and dorsal vagal motor nucleus of rats have shown that vagal firing frequency increases 33% during simulated exercise, recruiting additional units that would otherwise have been silent[132]. Exercise training increases resting dorsal vagal motor nucleus firing rates by 73% and this finding has been replicated in the cardiac vagal branches of treadmill-exercising sheep, demonstrating that exercise does not induce vagal withdrawal but that vagal tone actually increases[25]. A reanalysis of earlier human data supported the same paradigm, favouring sympathetic-parasympathetic co-activation over parasympathetic withdrawal[137]. Subsequent human experiments confirmed that some vagal withdrawal does occur at exercise onset but this is not representative of exercise as a whole, and that HRV does not correlate with vagal firing during exercise[132,138,139]. Two functions of this maintained vagal activity have so far been identified, both cardiac since that is where the initial studies have looked. Cardiac vagal efferents release vasoactive intestinal peptide (VIP), a powerful vasodilator, to increase coronary blood flow during exercise[25] and, counterintuitively, vagal efferents increase contractility by suppressing β-adrenoceptor desensitisation, preserving inotropic responsiveness to sympathetic drive[24]. These cardiac studies may go some way toward explaining reduced exercise capacity in ME/CFS and LC, but they do not explain the impaired peripheral oxygen extraction and post-exertional muscle pathology indicated in the iCPET and muscle biopsy data respectively. We therefore reason that the vagus nerve must have an additional, unrecognised role beyond the heart.

We propose that PEM and fatigue are the end results of chronic vascular dysfunction that begins with vagal insufficiency of the cholinergic anti-inflammatory response. Contracting muscle generates transient redox, metabolic and immune signalling proportional to the intensity and duration of the exercise[140]. In direct response to these signals[141], there is a coupled pro-resolving response consisting of lipoxins, resolvins, protectins and likely other effectors[142]. Exercise is therefore tightly regulated immunologically to limit damage and facilitate repair and subsequent adaptation of tissues to their workload. The vagus nerve has emerged as a potent central regulator of inflammation, capable both of sensing inflammation with various receptors on its afferent limb such as IL-1R and TLR4, and of resolving inflammation via its efferent limb[54,55]. This circuit is known as the cholinergic anti-inflammatory pathway (CAP) as it acts primarily via the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$nAChR). Importantly, experiments in $\alpha 7$nAChR null mice and using interventional stimulation of the vagus nerve, have demonstrated the CAP to increase macrophage efferocytosis and shift biosynthesis of lipid mediators toward ALOX15-dependent resolvins and maresins[143]. These effectors overlap with those of the exercise resolution phase, and there is early evidence in mice that vagotomy abolishes the effect of exercise on lowering inflammatory cytokines such as TNF-

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α[144]. Therefore, a deficit in the parasympathetic dominant post exercise repair and resolution phase of ME/CFS and LC patients is plausible.

Parasympathetic reactivation after exercise is impaired and delayed in both ME/CFS[145] and LC, including suppressed vagal tone (HRV) for at least 24 hours post exercise cessation[146]. The timing of this deficit is important as it infringes on sleep, when vagal tone typically increases several fold in healthy humans. Sleep itself is crucial for exercise recovery, sleep disturbance is known to reduce the concentration of circulating pro-resolving mediators[147] and parasympathetic activity is specifically reduced during slow-wave sleep in ME/CFS[148].

If the CAP is a key component of exercise recovery, chronic CAP insufficiency may affect the structure and function of the vasculature, which sits at the interface of several cellular stressors during exercise. In α7nAChR knockout mice, arterial injury not only induces an exaggerated cytokine response but additional oxidative stress, vascular smooth muscle proliferation, collagen deposition and neointima, compared to wildtype (WT)[149]. Furthermore, these maladaptations were significantly reduced in WT subjected to the same injury but treated with a selective α7nAChR agonist. Similarly, vagus nerve stimulation (VNS) ameliorated vascular dysfunction, vascular TNF-α and structural changes, in distal mesenteric arteries following myocardial ischemia-reperfusion injury in rats[150]. In humans, a randomised controlled trial (RCT; n=50) treating heart failure patients with reduced ejection fraction using VNS, found improved arterial flow-mediated dilation (FMD) compared to sham[151]. A smaller study (n=8-11) by the same group in acute decompensated heart failure demonstrated VNS treatment to reduce serum IL-6 by 69% and oxidative stress in cultured coronary endothelial cells exposed to patient serum by 28%, relative to sham[152]. These studies demonstrate that vagal activity is capable of regulating vascular outcomes, although endothelial autocrine cholinergic signalling may also contribute to vascular health in homeostasis.

The vascular phenotype of ME/CFS and LC is compatible with such injuries. Muscle biopsies of LC patients show thickened capillary basement membranes and increased CD169+ macrophages (correlated at r=0.53)[153] as well as capillary rarefaction in both conditions[104,154]. A LC study performed *in vivo* measurements of retinal vasculature, finding narrower arterioles and a decreased ability for the venules to dilate upon light stimuli relative to COVID-recovered controls[155]. Endothelial dysfunction as measured by reduced FMD has been found repeatedly in ME/CFS and LC, typically endothelium-dependent when pharmacologically differentiated[156–160]. Taken together, LC and ME/CFS patients show remodelling and vascular dysfunction compatible with vascular injury and we hypothesise this injury could be caused by delayed resolution of inflammation and impaired tissue repair following exertion.

Current evidence points to impaired oxygen extraction but cannot discern between, or weight, the possible upstream mechanisms of muscular maldistribution of blood; 1) blood flow shunting to non-exercising beds or 2) impaired capillary to myocyte transfer[99,100,161]. It may be that endothelial responsiveness to metabolic and shear-mediated vasodilatory signals is impaired such that greater metabolic and shear stress is required to achieve comparable vasodilation and adequately perfused capillary beds. Consequently, this greater metabolic and haemodynamic challenge may increase cellular stress for a given workload and maldistribute flow. Combined with structural abnormalities such as capillary rarefaction and thickened basement membranes, this may further impair capillary-to-myocyte oxygen transfer and potentially slow tissue-to-blood metabolic efflux, even where bulk post-exercise hyperaemia is preserved. However, post-exercise muscle hyperaemic flow appears normal in ME/CFS, arguing against a simple convective washout failure[162].

A healthy person performing unaccustomed exercise may experience DOMS 1-3 days post-exercise and then adaptation, whereas a ME/CFS/LC patient may experience PEM and maladaptation in the form of a lowered future PEM threshold. Tissue injury or stress may only persist for minutes, but the conserved inflammatory and reparative cascade it triggers canonically evolves over the following days[163], explaining why a patient may complete exertion without immediate distress then deteriorate two days later and take weeks to fully recover[164]. This is because although both groups' bouts exceeded the body's ability to buffer the cellular stress, the healthy body with a

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competent CAP can resolve the inflammation and trigger the repair and adaptation process in a complete and timely manner. An individual's PEM threshold may therefore be a function of CAP capacity and their vasodilatory response in legacy of past bouts, whereas fatigue at baseline may largely reflect accumulated vascular and mitochondrial dysfunction and the energy burden of other chronic symptoms. An individual will therefore exist on a spectrum of exercise tolerance between DOMS and severe PEM. Indeed, many ME/CFS patients report some degree of exercise intolerance before ME/CFS onset proper, in the so-called prodromal phase[165]. The vicious circle occurs by progressively impaired haemodynamics which in turn increase the cellular stress of exercise, maladaptation and so on. Our hypothetical mechanism is necessarily speculative, but it is grounded in established inflammatory and vascular physiology and in emerging ME/CFS and LC pathology.

Evidence for Brainstem-Vagus Axis Abnormality in ME/CFS and LC Patients

The previous sections outlined how vagal insufficiency could theoretically lead to the majority of symptoms in ME/CFS and LC, including definitional features such as fatigue and PEM. Whilst this exercise is itself supportive of the VIS model, it is also largely correlative and falls short of direct evidence. In this section we will highlight more direct sources of evidence in support of damage to and dysfunction of the brainstem-vagus axis in ME/CFS and LC patients. We will also present evidence that indicates vagal insufficiency is a primary rather than secondary pathology as this is a key differentiator amongst competing pathophysiological hypotheses.

Firstly, we can say with a high degree of confidence that low vagal tone is a very reproducible feature of ME/CFS and LC patients. In ME/CFS, low HRV has been identified in at least fifteen independent cohorts spanning three decades, using resting, orthostatic, exercise, and nocturnal paradigms[124,129,166–178], a consistency corroborated at the meta-analytic level[179]. The same finding has been reproduced in LC in at least 16 independent cohorts[180–196]. The magnitude of reduced HRV predicts fatigue severity[124,169], impaired cognitive performance[129], and poor sleep quality[167]. To know the exact prevalence for low HRV is not possible because HRV is a continuous variable without agreed clinical thresholds. However, the broader construct it indexes, cardiovascular autonomic dysfunction, correlates strongly with other measures of general autonomic function upon formal testing[197]. Autonomic failure, spanning cardiovagal, adrenergic, and sudomotor domains has been documented in 89% of ME/CFS and 95% of LC patients[13]. Furthermore, 97% of ME/CFS patients report at least one autonomic symptom[14]. As has already been covered in depth, continuous wearables recording HRV have demonstrated predictive power for both fatigue and PEM[125,146]. Together, these data show that cardiac vagal efferent tone is, at the very least, typically dysregulated in patients and directly related to some of their symptoms.

Ideally, the best way to assess for damage to the vagus nerves would be histological. However, imaging of the vagus nerve has been rare, likely due to the lack of standardised radiological reference ranges but also due to its small cross-sectional area, making *in vivo* imaging difficult. Nonetheless, a small (n=14-30) neck ultrasound study was performed comparing the vagus nerves of LC patients who had at least one verified vagus nerve related symptom (67%) to COVID-19 recovered and uninfected controls[198]. LC patients displayed hyperechogenic vagus nerves with a trend for larger cross-sectional areas (p=0.08) compared to both control groups, similar to that seen in inflammatory neuropathies such as Guillain-Barré syndrome[199]. Interestingly, a similar ultrasound study (n=20-40) by another group found a significant difference in the cross-sectional area of LC patients vs controls but in contrast, the area was smaller in LC patients, suggestive of degeneration[200]. It may be that these studies captured different stages of injury, with thickening being the early inflammatory stage and the thinning being the later degenerative stage once axons have been lost. Indeed, a recent study analysed gastric mucosa biopsies of LC patients by immunohistochemistry, finding approximately a 50% reduction in VIP^+ cholinergic neurons compared to dyspepsia patient controls[201]. Although the study's staining methods are insufficient to confirm the precise identity of these fibres, the degree of denervation in the fundus layer was found to negatively correlate with HRV. This links the structural finding to vagal insufficiency and also suggests this denervation may

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not be limited to the stomach. An autopsy study of those who died of acute COVID-19 showed inflammatory cell infiltrate and transcriptomic inflammatory signal in the vagus nerves, so there may well be an injury upon infection in some individuals[202].

Unfortunately, to our knowledge there are no analogous structural evaluations of the vagus nerve in ME/CFS. However, there are several brainstem MRI studies, in both populations, that have noted structural and functional abnormalities in the relevant autonomic structures, including those that host the vagal efferent nuclei. Most strikingly, ultra-high-field imaging using 7 Tesla MRI (n=8-10) found the brainstem and pons to be significantly enlarged in LC and ME/CFS patients, relative to healthy controls[203]. The increase was the same in each population and additional changes in midbrain volume negatively correlated with breathing difficulty, suggesting a similar pathology and one that may be affecting autonomic function. Interestingly, another group performed a similar MRI volumetric study, in an independent ME/CFS cohort (n=30-45), finding reduced white matter volume in the midbrain, pons and right temporal lobe and increased grey-matter volume in insula and amygdala[204]. These somewhat contrasting studies echo the contrasting vagal sonography studies, suggesting neurodegeneration of autonomic circuits and potential compensatory hypertrophy of interconnecting regions.

Sophisticated functional analyses of these regions have found similar deficits localised to the brainstem. One such ME/CFS MRI study used voxel-wise interaction regressions against distributions of steady state autonomic measures, heart rate and blood pressure to identify regions of abnormal autonomic function. Abnormal regression slopes were found in voxels of vasomotor centre and midbrain reticular nuclei, in ME/CFS patients. This is despite no structural abnormality, suggesting that the issue could be communication between these autonomic nuclei. Notably, identified areas are adjacent or overlapping to several of the vagal nuclei in the medulla oblongata[205]. A functional MRI (fMRI) study (n=27-43) further interrogated functional interconnectivity of brain regions, finding that specifically during cognitive exertion, interconnectivity between the rostral medulla and the midbrain was altered in patients and correlated with worse symptoms[206]. A related result was found in LC patients in a follow-up study (n=10-13) although interestingly, that circuit's connectivity was diminished in the ME/CFS cohort but increased in the LC cohort[207]. These changes were replicated a third time in an ME/CFS and LC cohort (n=19-32) and correlated to respiratory dysfunction[208]. An earlier study (n=14-27) had also found reduced brainstem myelin-sensitive signal in the pons and medulla, with apparent compensatory change in the sensorimotor cortex[209]. Although these cohorts are all of a modest size and difficult to interpret, they most commonly localise to the same area of the brain as the vagal nuclei. Importantly, however, no overt focal lesions have been reported in the brainstem beyond the changes in white matter and connectivity. The authors of these studies generally interpret these findings as evidence of a compensatory response to dysautonomia, one which we feel is not only compatible with damage to the brainstem-vagal axis but strongly implicates it.

Thus far the evidence presented has been in support of vagal insufficiency in ME/CFS and LC, but does not differentiate between it being a secondary or primary pathology. A logical way to discern these is to investigate if damage or disruption to the vagal circuits in other contexts is sufficient to generate an ME/CFS/LC-like phenotype. Whilst this hasn't been formally tested, there are many incidental examples across disease, animal models, and human surgery and injury. For example, a case study reports that during the surgical removal of a tumour from the 4th ventricle of a cancer patient, the medulla oblongata was damaged, causing the patient to suffer long term blood pressure lability, sensitivity to environmental stress, POTS and a myriad of general dysautonomic symptoms such as sweating[210]. In diabetic cardiac autonomic neuropathy, the vagus degenerates early, producing early HRV decrease, POTS and exercise intolerance [211,212]. Chronic acetylcholinesterase-inhibitor exposure in Gulf War illness generates a multi-symptom, fatiguing illness phenotypically overlapping ME/CFS[213,214]. These examples are not completely vagus specific but there are also specific surgical injuries or transections to the vagus that have fewer confounders. For example, in humans, iatrogenic vagal injury during anterior cervical spine surgery

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has produced chronic, exertion-worsened tachycardia with an otherwise negative cardiac evaluation, the injury confirmed by vagal thickening on ultrasound, as in LC[215]. Similarly, deliberate truncal vagotomy for peptic ulcer disease produces a chronic 'Dumping Syndrome' in roughly a quarter of patients, comprising gastroparesis, orthostatic intolerance, blood pressure lability, fatigue, tachycardia, and diarrhoea[216]. Although there is no perfect analogue of the vagal injury we describe, the parallels we do have suggest damage and dysfunction to these structures can produce similar phenotypes to ME/CFS and LC.

Finally, if insufficient vagal tone is causal, rather than merely correlated with disease, then theoretically increasing vagal tone should improve the affected functions. The problem is that this approach potentially relies on upregulating a system that is, by premise, damaged. Nevertheless, in ME/CFS RCTs, the cholinesterase inhibitor pyridostigmine increased peak oxygen uptake, improved cardiac output and filling pressures [217], and also improved POTS[218]. In contrast, the stimulation of the vagus via tVNS has led to mixed results. In pilot LC cohorts it improved fatigue, cognition, and autonomic parameters [127,128], whereas the recent COVIVA RCT (n=45) tVNS showed no benefit to fatigue or quality-of-life score over sham[219]. Finally, interventions that raise vagal tone through slow, paced breathing, successfully reduced symptoms[220]. All of these are small studies but given the lack of positive responses in almost all other interventional trials, the selective responsiveness to vagal augmentation is difficult to reconcile with vagal insufficiency only being incidental. On the contrary, it is what would be expected if vagal insufficiency were the driving pathology.

Candidate Aetiologies of Vagal Insufficiency Syndrome

Our model theoretically allows for any aetiology that could conceivably cause damage or dysfunction to the vagus nerves resulting in vagal insufficiency. This would be similar to other organ or system failures, such as heart failure which can have many potential causes. However, that is not to say every aetiology is equally likely and therefore of equal incidence or necessarily stratifies evenly between syndromes. Indeed, definitionally LC patients have a viral onset and a recent large (>10,000 patients) study by DecodeME found 2/3rds of ME/CFS patients report a viral onset[3]. In the context of our model, the question becomes 'how did the trigger cause vagal insufficiency' which requires a greater explanation than the trigger itself.

Several intriguing primary pathologies have been proposed for LC and ME/CFS. Many of these are compatible with VIS, either as downstream pathologies or as upstream aetiologies linking infection to vagal insufficiency. Admirable work has been carried out on each, but it is beyond the scope of this paper to review their individual merits and limitations in detail. Instead, we will focus on the two candidate injury mechanisms most easily integrated into the proposed model of VIS: 1) Thrombogenesis, 2) Craniocervical instability (CCI).

A thrombogenic signal was detected early in the pandemic in acute COVID-19 infections[221,222] and then later in COVID-19 vaccinations[223,224]. Clotting is part of the classical innate immune containment response to infection via TNF-α release and so not entirely unexpected. However, SARS-CoV-2 spike protein was also demonstrated to bind fibrin to form abnormal, proinflammatory clots resistant to fibrinolysis[225,226], supporting the idea that COVID-19 could be especially thrombogenic. Confirming this, an autopsy study found widespread microthrombi in the lungs of patients who died from COVID-19; 9x more than in the control lungs of patients who died from influenza[227]. Thrombosis is therefore confirmed as a feature of acute COVID-19 infection and given the thrombi's resistance to fibrinolysis, many have hypothesised it may drive LC.

Unfortunately, despite promising early case reports[228], RCTs of therapies to target clotting have failed to show clinical benefit in treating LC[229,230]. We therefore wonder whether microvascular thrombotic ischemia could have damaged the vagus nerve, and indeed other nerves. An injury might explain why these thrombolytic therapies have failed to produce benefit as the damage is already done. There is no direct evidence of ischemic injury but given the high metabolic demands of the vagus nerve it seems plausible that it could be vulnerable to proximally located

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thrombi. The infamous post-COVID-19 infection anosmia might be an example of a similar phenomenon in the olfactory nerve, likewise unconfirmed to be ischemic injury[231].

The second aetiology, CCI, is a pathology where excess relative movement of the upper cervical vertebrae and skull leads to transient or chronic neurovascular abrasion or compressions, resulting in neurological symptoms. We propose CCI as a candidate upstream cause of VIS in a significant subset of ME/CFS cases and LC cases. In this model, viral infection could, in predisposed individuals, lead to excessive degradation of connective tissue via matrix metalloproteinases (MMPs) as part of the inflammatory response. Indeed, elevated serum MMPs have been observed in both patient groups[232] and recently serum MMP-9 was shown to fully separate ME/CFS patients from controls[233]. A peak area for inflammation during viral infection is the back of the mouth and throat, a region directly anterior to the craniocervical ligaments and articular facet cartilage of the upper cervical spine. This inflammatory response may weaken the ligaments or diminish the cartilage, causing joint laxity such that the craniocervical junction becomes hypermobile and able to cause neurological injury and/or dysfunction. Specifically, the clivo-axial angle **(Figure 2a & 2b)** can become too low, simultaneously deforming the brainstem and reducing the available space for the vagus nerves and internal jugular veins as they pass in front of the atlas **(Figure 2d)**. Additionally, when the atlas becomes hypermobile it may be able to rotate relative to the skull occiput or translate forward **(Figure 2g & 2f)**, as has been recorded by clinicians using fluoroscopy and varipose cone-beam ct and MRI. This has the potential to compress the vagus nerve at its bottleneck between the anterior lateral mass of the atlas and the bony styloid of the stylohyoid ligament **(Figure 2e)**, during excess movement or during sleep when the stabilising muscles relax. Notably, the afferent vagal cell bodies are found in the nodose ganglion, directly anterior to C1/C2, potentially making the consequences of compression more serious. These structural issues are recognised pathologies in CCI patients, a group who have significant symptom overlap with ME/CFS many of whom have both diagnoses.

Interestingly, this model of VIS onset might explain why joint hypermobility appears to be associated with these types of syndromes, being detected in 49% of ME/CFS patients, 30% of LC patients and 57% of all patients with POTS vs approximately 15% of controls[234]. CCI would also be a simple explanation for two of the most consistent features of ME/CFS, cerebral hypoperfusion (even whilst supine)[235] and intracranial hypertension (ICH; estimated at 55-83% of patients by MRI measurements)[236]. Venous outflow obstruction concomitant with CCI-induced misalignments could contribute to ICH and hypoperfusion, which in turn could explain the cerebral hypoxia found via lactate imaging on MRI[237,238]. Similarly, hypoxia is a potent inducer of inflammation so this may explain the repeated finding of neuroinflammation and activated microglia in the brains of ME/CFS patients[238]. However, direct evidence for CCI driving ME/CFS is currently weak, limited to a handful of anecdotal patient reports and interventional case studies where the craniocervical junction has been surgically fused[89,239,240], or the jugular veins and vagus nerves have been decompressed, leading to partial to complete recovery[241]. As CCI is a dynamic phenomenon, it is difficult to diagnose, even with high quality imaging. Few clinicians are even aware of CCI as a chronic disease, let alone CCI's connection to ME/CFS and POTS. Nevertheless, we predict CCI to be a foremost aetiology because of its ability to reconcile such well-established, but otherwise disparate, features of ME/CFS and LC.

In summary, there might be several aetiologies for VIS but we favour CCI and thrombosis for the reasons laid out in this section. These routes are not exhaustive and the downstream VIS hypothesis does not depend on either being the true predominant aetiology. Importantly, these need not be mutually exclusive; there may be multiple 'hits' that push a person along the spectrum of VIS until they cross the threshold for detectable disease.

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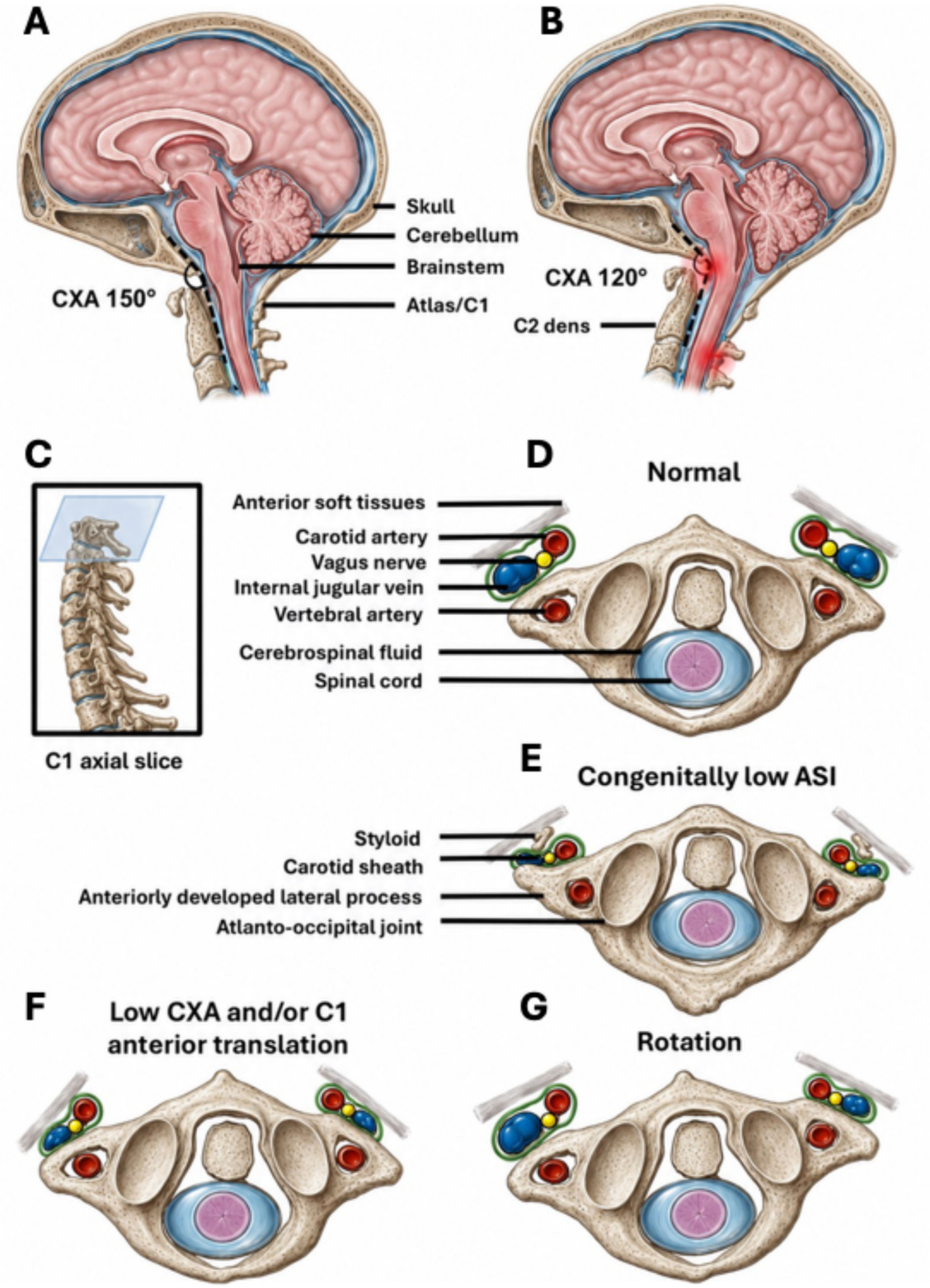

Figure 2. Illustration of anatomical alignments that can cause irritation or injury to neural and vascular tissues. (a) Labelled illustration of a sagittal midline slice view of the brain and upper cervical spine where the clivoaxial angle (CXA) is normal (150°) and (b) abnormal (CXA=120°) with areas of irritation/compression seen as a red haze. (c) upper cervical spine showing the axial slice location for illustrations D-G. (d) Axial view 3D render of the atlas/c1 vertebrae and neurovascular structures, as labelled in the figure, in normal spacing and

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alignment and (e-g) in abnormal alignment and or spacing due to CCI leading to unilateral or bilateral compression of the internal jugular veins (IJVs) and vagus nerves.

Discussion

Whilst dysautonomia is a frequently mentioned component in discussions of ME/CFS and LC, the role of the vagus nerves is often either omitted or referenced briefly as one of many secondary problems in a complex disease. Vagal neuropathy is not commonly diagnosed in the clinical setting, and when it is, it is identified on a per specialty basis in a small number of functions such as gut motility, heart rate, swallowing issues and voice hoarseness. A recent review concluded that there are three main reasons: (1) Vagal sensory function rarely causes overt pain, producing instead diffuse, non-specific symptoms easily attributed to other illnesses or stress; (2) diagnostic access to vagal fibres is limited, since, unlike other peripheral nerves, the vagus cannot be assessed by skin biopsy or electromyography; and (3) neuropathy research has historically focused on painful conditions and vagal dysfunction is often labelled as neuroplasticity, rather than neuropathy[242]. We agree with these conclusions and believe they go some way towards explaining a potential under-identification of vagal neuropathy in ME/CFS and LC.

An additional issue is that the range of vagally regulated processes is underappreciated by researchers and clinicians alike, and this presents a barrier to linking vagal neuropathy to multisystem illnesses. We hope to have at least illuminated this blind spot somewhat by highlighting the wide range of vagal functions and how their dysfunction overlaps with the symptoms seen in ME/CFS and LC **(Table 1)**. It is this functional diversity that gives VIS **(Figure 3)** its explanatory economy, where a single point of dysfunction can reconcile seemingly disparate but highly replicable findings. The model also accommodates the established observation of a disease spectrum spanning healthy, prodromal and patients. Furthermore, because the vagus is fascicular and composed of discrete units, that spectrum is multidimensional, matching the stochastic pattern of symptoms in the patient population. Importantly, our model does not predict per symptom randomness, it is highly likely that certain regions of the vagus are more vulnerable than others and some vagally regulated processes may share symptoms when dysregulated. Similarly, there may be more functional reserve for certain bodily functions served by the vagus, or simply more axons and therefore potentially more redundancy.

There may also be positive feedback loops that maintain chronicity or even promote disease progression. One that is often discussed is mast cell activation syndrome and the release of enzymes such as tryptase and cathepsins, which may further degrade the connective tissue in these patients, which in turn could worsen CCI and therefore dysautonomia. A simple mechanism could be the degradation of ligamentous elastin, reducing the ability of ligaments to return to their original length after strain, leading to laxity. Degranulation of mast cells also releases inflammatory mediators including histamine that can cause gastrointestinal upset, vasodilation and tachycardia, which could exacerbate POTS in those affected. Similarly, we have already discussed the cyclical nature of PEM and highlight it as a major roadblock to recovery and therefore high priority target for clinical intervention.

The NICE evidence review for ME/CFS[1] specifically identified insufficient professional knowledge, lack of medical legitimacy and inadequate training as barriers to diagnosis. It also reported that patients sometimes must consult multiple doctors or take a particularly proactive role in obtaining a diagnosis. The absence of a biomarker can create uncertainty among GPs who are accustomed to diagnosing conditions through measurable abnormalities. Major difficulties can arise when normal results are interpreted as evidence that the patient does not have a significant physical illness. Therefore, finding a biomarker of high inclusivity, sensitivity and fidelity is often cited as top priority. However, the physiological search space is vast and so focusing on first determining the primary pathology may be a faster route to a clinically viable biomarker. Furthermore, identification of the primary pathology would allow for robust validation of the biomarker. Plausible hypotheses

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also help narrow the search space. For example, the VIS hypothesis would suggest nocturnal HRV could form the basis of a candidate biomarker for ME/CFS and LC.

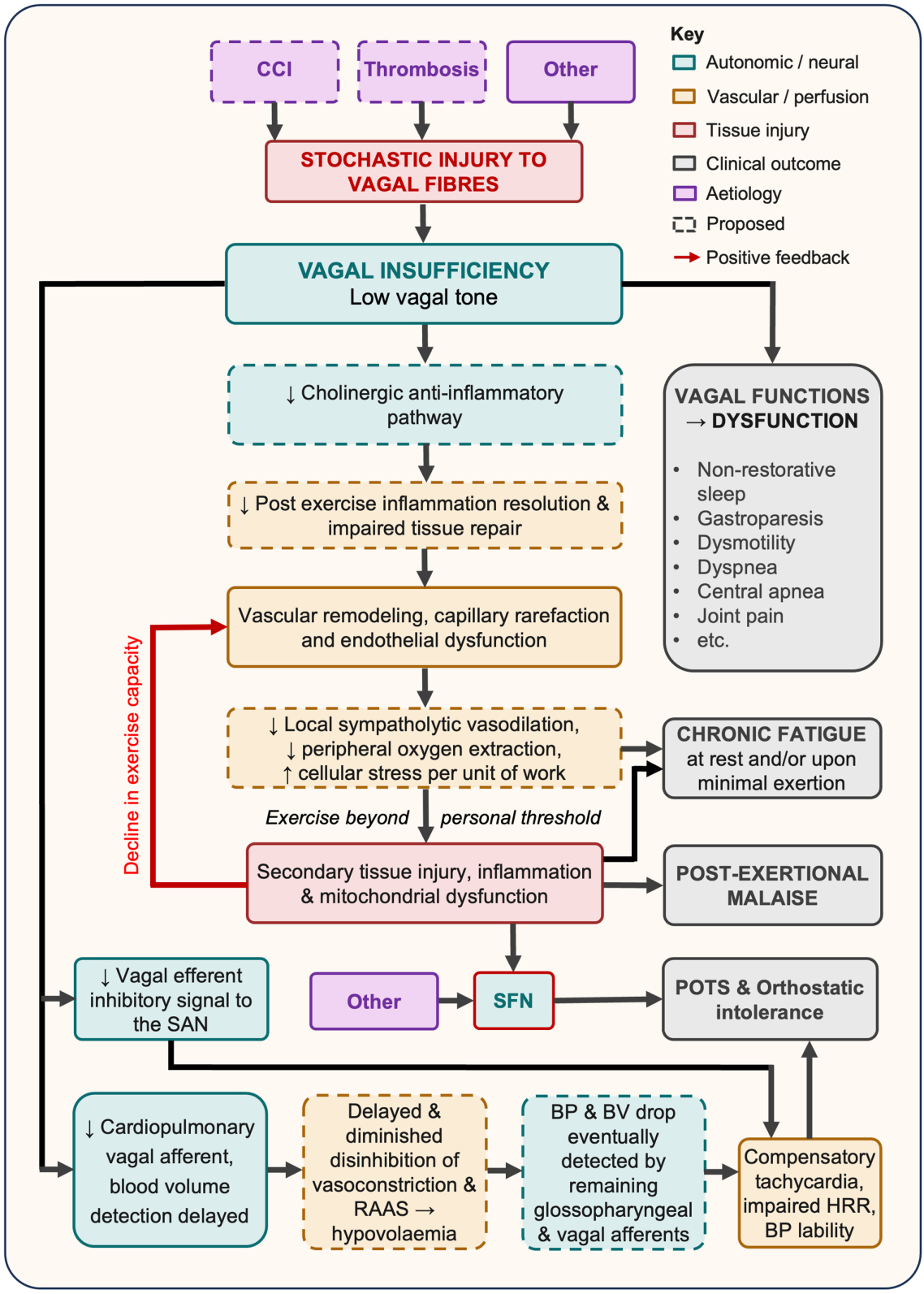

Figure 3. Flow chart summarising the mechanisms of vagal insufficiency syndrome. This flow chart shows the core mechanistic steps that follow vagus nerve injury and how they manifest as dysautonomic symptoms, including POTS, fatigue and PEM. The key to the colour-coding and outlines is in the figure. CCI = Craniocervical

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instability, CAP = Cholinergic anti-inflammatory pathway, SAN = Sinoatrial node, SFN = Small fibre neuropathy, RAAS = Renin-angiotensin-aldosterone system, BP = Blood pressure, BV = Blood volume, POTS = Postural orthostatic tachycardia syndrome and HRR = Heart rate recovery.

Importantly, we do not suggest that other leading hypotheses are necessarily wrong, in contrast, many are well evidenced with high quality studies and are doubtless real phenomena. Rather, it is a question of hierarchy in assignment of primary or secondary pathology, and prevalence, in the case of heterogeneous aetiology. For example, our hypothesis is principally one of vagal insufficiency but the model implies vascular dysfunction is downstream of dysautonomia and mitochondrial dysfunction is downstream of vascular dysfunction. Whereas other putative mechanisms, such as clotting and CCI, are placed upstream as aetiologies. Others are suggested by us to be concomitant with the upstream aetiology, such as ICH and hypoperfusion, albeit the latter likely being affected by orthostatic intolerance also. This is another property of our model; that there are likely multiple contributors to singular symptoms, as can be seen in **Table 1**.

One hypothesis that is particularly similar to our own, proposes ME/CFS might be caused by persistent infection of the vagus nerves, leading to dysregulated vagal signals[243,244]. Vagal afferents are understood to detect inflammatory cytokines and pathogen-associated molecular patterns, then promote centrally mediated 'sickness behaviour' (fatigue, fever, myalgia, depression and others)[245]. ME/CFS and LC patients would be assumed to be experiencing a dysregulated, chronic version of this response. It is an intriguing idea due to the common viral onset and how the vagus nerve could be a strategic target tissue for pathogens due to its proximity to the outside, length and immune regulatory role. The idea also highlights a possible contradiction to our own model, that vagotomy in animals reproducibly attenuates or blocks the ability of animals to mount the sickness response in reaction to inflammatory stimuli[245,246]. However, we do not believe sickness behaviour to be entirely the same as ME/CFS as the former is a very broad set of 'flu-like' symptoms rather than the characteristic dysautonomic profile of ME/CFS and LC. Furthermore, a peculiar but common observation among ME/CFS and LC patients is that their perceived rate of acute viral infection is significantly lower than pre-ME/CFS, even when their household members catch viruses[3,247]. Additionally, on the rare occasion patients do report catching a cold, they report improvements in their symptoms[248]. Likewise the few who partially or fully recover from ME/CFS report the return of normal immune responses[247]. Such phenomena are readily explainable under a VIS model as the vagal sickness response may be diminished, reducing the perception or expression of minor infection, while a sufficiently strong immune challenge transiently recruits surviving vagal afferents and downstream inflammatory-reflex circuitry. Efficacy of tVNS demonstrates that seemingly unrelated afferents (e.g. the auricular branch) can raise efferent tone systemically; perhaps this occurs via the CAP and relieves symptoms. Nevertheless, we acknowledge that chronic vagal infection and overactivation of the sickness response could represent a subset of patients, but that further work is needed to test this possibility.

To test our own core hypothesis of vagal insufficiency directly is quite challenging. The most direct finding that would falsify our model would be evidence that there is no difference in function, in any of the vagal branches, between ME/CFS and LC patients, and healthy age-matched controls. However, there are not yet non-invasive methods to measure aggregate nerve function for the vagus nerves in humans. There are invasive methods such as extraneural cuff electrodes but aggregate and circadian data from an autonomic nerve would be difficult to interpret and require day long recordings. Fascicular level deficits might not be able to be resolved at the cervical level, requiring the cuffing of multiple branches. These limitations make this approach difficult even in one patient and so scalability to a cohort is not feasible. Instead, we suggest a less direct approach, in the form of four research priorities that would facilitate the accumulation of evidence useful in determining the accuracy of the VIS hypothesis **(Table 2).**

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Table 2. Recommended research directions in service of testing vagal insufficiency as the primary pathology of ME/CFS and LC.

Research Priority	Rationale	Methodology	Challenges
Establish animal models of vagal insufficiency	Interventional loss of function experiments to test if vagal neuropathy is sufficient to induce an ME/CFS and LC-like phenotype. If successful, the field would gain an animal model for accelerated pre-clinical research.	A surgical crush injury model could be considered. Sophisticated transgenic animals could be generated; spatially and temporally conditional, reversible nerve silencing for powerful insight. E.g. the DREADD and CreER-Lox systems.	Costly. Specific but inclusive promoters for driver lines could be challenging and ultimately a compromise. Difficult to establish ME/CFS/LC phenotypic success criteria.
Small combinatorial human trials aiming to increase vagal tone	Interventional gain of function experiment to assess if correcting low vagal tone in patients is possible and which, if any symptoms improve. This provides insight into the pathology and, if successful, a treatment candidate for clinical trials.	Vagal tone raising therapies and medications such as tVNS, box breathing, cold therapy and pyridostigmine could be combined. Maximising chance of positive result at the cost of interventional clarity. 24/7 HRV, cervical high-resolution ultrasound and symptom scores would be feasible outcome measures.	It may be difficult to raise vagal tone if the vagus nerves are indeed damaged. Patient heterogeneity and low patient numbers may lessen statistical power.
Large vagus nerve histological studies on ME/CFS and LC post-mortem	Observational and correlative study. Histology can test if patients have signs of vagal neuropathy. The resolution would far	Deep quantification of healthy vs ME/CFS and LC, axons, myelination and subcellular organelles by transmission electron	Establishing a normal histological range for vagus nerve structural metrics may require a

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	exceed live imaging approaches and all branches could be assessed separately.	microscopy. Particularly axon number per branch and correlation to symptoms. Immunohistochemistry for markers of neuropathy e.g. ATF3	large n but samples are scarce. Patient samples will also be scarce.
Structural and functional comparison of the vagus nerves in healthy vs ME/CFS and LC	Observational and correlative study. Thus far there are only small studies comparing vagus nerve structure in LC to controls. Comparisons in living patients allow large sample sizes and correlation with large symptom and severity data.	Imaging modalities such as high-resolution ultrasound for high throughput morphological analysis of cervical vagus nerves. 24/7 HRV monitoring as a proxy for vagal tone. fMRI could be used on smaller samples of patients to examine nerve and brainstem nuclei function. CT venograms to check for surrounding structural and vascular compressions.	Spatial resolution of vagus nerve structure is limited in imaging modalities suitable for live patients. Functional measures of vagal function are currently very limited.

The main limitation of our model is that the intense fatigue, characteristic of ME/CFS and LC patients, is not a clear one-step consequence of vagal dysfunction. Rather, currently several steps are required to explain fatigue using our model, some of which are based on only a few studies and some of which are speculation. There may well be mechanisms yet unknown to the field that explain the link more simply, reducing the probability of error. For example the very recent discovery of vagal-mediated coronary vasodilation mentioned previously. Importantly, the proposed mechanism of fatigue is not central to our model and is primarily an exercise in the limits of its explanatory power.

In conclusion, we propose that ME/CFS and LC are, in a majority of cases, clinical expressions of a dysautonomic state arising from damage to, or dysfunction of, the brainstem-vagus axis, resulting in vagal insufficiency. If VIS is demonstrated to be the correct primary pathology, then measures of vagal function could provide objective stratification of patients and outcome measures. The field would also have a clear anatomical target for therapeutics, though these would likely be challenging depending on the extent of neuropathy, perhaps requiring novel, multi-tissue regenerative approaches. Given the scale of the illness burden, absence of effective treatment and the evidence outlined in this paper, we believe vagal neuropathy in ME/CFS and LC warrants extensive investigation.

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