Perspectives on neuroinflammation contributing to chronic cough


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The mechanisms causing altered neural activity and sensitisation in chronic cough remain largely unknown. Neuroinflammation involving glial cells may contribute to cough pathogenesis, representing a potential novel therapeutic target.

ABSTRACT Chronic cough can be a troublesome clinical problem. Current thinking is that increased activity and/or enhanced sensitivity of the peripheral and central neural pathways mediates chronic cough via processes similar to those associated with the development of chronic pain. While inflammation is widely thought to be involved in the development of chronic cough, the true mechanisms causing altered neural activity and sensitisation remain largely unknown. In this back-to-basics perspective article we explore evidence that inflammation in chronic cough may, at least in part, involve neuroinflammation orchestrated by glial cells of the nervous system. We summarise the extensive evidence for the role of both peripheral and central glial cells in chronic pain, and hypothesise that the commonalities between pain and cough pathogenesis and clinical presentation warrant investigations into the neuroinflammatory mechanisms that contribute to chronic cough. We open the debate that glial cells may represent an underappreciated therapeutic target for controlling troublesome cough in disease.
Introduction
Coughing is a normal physiological process that protects the lung from inhaled irritants and helps clear unwanted airway secretions. However, cough can also present as a troublesome clinical problem. It may present as an acute problem, typically associated with the common cold, which can be quite disruptive but usually settles down quickly (within 2–3 weeks) with minimal intervention [1]. Chronic cough, however, represents one of the most common problems referred to clinicians. Defined as cough lasting for longer than 8 weeks, chronic cough can often bother the patient for many months or years, representing a significant health burden [2]. Systematic diagnostic and treatment pathways focused on asthma, reflux and rhinitis can be effective [3], but for some patients the cough remains unexplained or refractory to trials of treatment [4]. Clinicians are well aware that troublesome coughing presents not only as an isolated clinical condition but also as a distinct and often difficult problem to manage for patients with a range of common lung diseases, including chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis and bronchiectasis [5]. Chronic cough causes considerable distress for patients and this is compounded by the current lack of effective antitussives [6].

Patients with chronic cough typically describe bouts of coughing triggered by low-level physical and chemical stimuli, indicative of cough reflex hypersensitivity arising from sensitisation or dysfunction of the neural pathways responsible for cough [7]. The notion that cough reflex sensitisation may manifest across heterogeneous disease entities has given rise to the unifying clinical concept of cough hypersensitivity syndrome. This was recently defined by a European Respiratory Society Task Force as a “disorder characterised by troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure” [8]. This definition alludes to the fact that affected patients typically describe cough spasms provoked by everyday activities including talking or laughing and changes in ambient air temperature or exposure to aerosols or perfumes [7]. A significant proportion also report abnormal sensations such as a persisting itch or tickle in the upper chest or the feeling of a “lump” in the back of the throat in keeping with neural hypersensitivity or paraesthesia [9]. The underlying pathology for this clinical state likely involves heightened sensitivity of the sensory nerve pathways that ordinarily detect and respond to harmful airway irritants. However, the pathological mechanisms responsible for this sensory sensitisation are not well understood. In this article, we present a back-to-basics perspective on this topic by exploring the role of neuroinflammatory processes, potentially orchestrated or regulated by peripheral and central nervous system glial cells, that may contribute to altered neuronal excitability in chronic cough. The goal of this perspective is to stimulate new discussions and avenues for research into this important clinical problem.

Neural mechanisms in cough
The act of coughing presents as a simple respiratory behaviour in response to an airway irritation, yet the neurophysiological processes that govern cough are surprisingly complex. In many instances cough is a reflex, initiated when vagal sensory nerve endings in the airways, and perhaps lungs, are activated by noxious or potentially noxious stimuli [10], although stimuli to other territories of the vagus nerve, such as the external ear or oesophagus, may also sometimes evoke or facilitate coughing [10]. Within the respiratory system, the extrapulmonary airways (larynx, trachea and mainstem bronchi) are important reflexogenic sites essential for preventing the inhalation of noxious chemicals, aspiration of foodstuffs and accumulation of excess mucous secretions, all of which can produce reflex coughing [11]. The first level of complexity in the neurophysiology resides in the fact that these diverse stimuli induce cough via at least two sensory neural pathways (figure 1a) [10]. Studies in guinea pigs have described a sensory neuron subtype that induces coughing, known as airway mechanoreceptors or simply “cough receptors” [12]. This neuron subtype is derived from the nodose vagal ganglia, which is a collection of visceral sensory neurons associated with the vagus nerves [10, 11]. Similar receptors are described in humans [13]. A second sensory neuron type evoking cough in animals and humans is composed of the bronchopulmonary chemoreceptors or nociceptors, which likely originate from the jugular vagal ganglia and are responsible for detecting noxious chemical stimuli [10, 11]. Nodose and jugular sensory neurons are derived from different embryological lineages, and studies in mice, rats and guinea pigs have shown them to be quite different in their molecular phenotype, physiological responsivity and neuroanatomical organisation (reviewed elsewhere [11]). However, collectively these two types of sensory neurons afford the ability to detect the wide variety of noxious stimuli that drive reflex coughing.

A second level of complexity in the neural control of cough lies in the central neural circuits that receive inputs from vagal cough sensory neurons. Two parallel neural cough pathways have been described in the brainstem and brain of rats and guinea pigs [14, 15]. One major difference is in the brainstem processing nuclei that receive nodose and jugular vagal sensory inputs. Nodose-derived airway sensory neurons project almost exclusively to a brainstem nucleus called the nucleus of the solitary tract, well known for its involvement in processing many sensory inputs from the visceras (figure 2a) [14, 15]. By contrast, the jugular-derived neurons project to a different and poorly studied brainstem region, the paratrigeminal...
The brain circuits arising from the nucleus of the solitary tract and the paratrigeminal nucleus show important differences [14], and this may contribute to heterogeneity in the presentation and management of cough in health and disease [5, 10].

A third level of complexity is that cough is not purely reflexive. Rather, studies in humans have shown that inputs from the airways and lungs to the higher brain allow for conscious perception of airway irritation, which in turn leads to behavioural modifications of coughing [16]. Clinically, this perceived sensation is defined as the urge to cough and it commonly precedes the motor act of coughing [17]. Notably, cough can be voluntarily produced even in the absence of any sensory inputs from the airways, or actively inhibited by conscious or subconscious higher brain processes (figure 2a). The higher brain circuits that allow for this level of control have been investigated in humans using functional magnetic resonance imaging (fMRI) [10, 11, 16] and changes in the activity of these circuits have been demonstrated in patients with altered cough sensitivity [18, 19].

The relevance of these neurophysiological processes is apparent when considering the mechanisms that underpin the development of cough hypersensitivity syndrome. Excessive coughing, especially that evoked by stimuli which are ordinarily considered innocuous, is highly consistent with sensitisation and excessive activity in the neural pathways regulating cough [7]. However, what is less clear is where in the neural circuitry these functional changes take place. One likely possibility is the vagal sensory neurons innervating the airways and lungs. Indeed, in other clinical conditions characterised by hypersensitivity (e.g. chronic pain), primary sensory neurons show enhanced excitability through a process known as peripheral sensitisation [20]. In this regard, the clinical symptoms associated with chronic pain also present many overlapping characteristics with chronic cough. These include hyperalgesia/hypertussia (increased pain/cough sensitivity to noxious stimuli) and allodynia/allotussia (increased pain/cough responsivity to innocuous stimuli) [7, 21]. In cough, one of the mediators that appears to contribute to this peripheral neural hyperexcitability is ATP [22] and recent clinical trials with purinergic P2X3 receptor antagonists, such as the Merck compound gefapixant, demonstrate promising antitussive activity.

FIGURE 1 Peripheral glial mechanisms of sensitisation. a) The airways and lungs receive axons from two types of vagal sensory neurons capable of detecting cough-specific stimuli. Nodose ganglia mechanoreceptors (“cough receptors”) detect the physical presence of foreign material in the airways as well as respond to rapid acidification (e.g., gastro-oesophageal reflux). Jugular ganglia nociceptors are broadly chemosensitive and respond to a myriad of noxious chemicals and inflammatory mediators. b) In the airways and lungs (airway smooth muscle (ASM) and epithelium), myelinating and nonmyelinating Schwann cells likely contribute to the inflammatory milieu accompanying chronic cough, leading to peripheral sensitisation of cough-evoking sensory fibres. c) Peripheral sensitisation can also involve inflammatory events in the vagal sensory ganglia, extrinsic to the airways and lungs. Ganglia inflammation is typically orchestrated by infiltrating inflammatory cells and resident satellite glial cells and Schwann cells. Collectively, these events reduce the stimulus threshold required to induce cough, resulting in hypertussia. See text for specific details of the mediators and mechanisms involved. CNS: central nervous system.
However, the source of extracellular ATP is currently unknown. In guinea pigs, ATP can be released into the extracellular environment from (unknown) airway cells via a process involving the transient receptor potential cation channel subfamily V member 4 (TRPV4) [22]. Consistent with this, TRPV4 agonists induce coughing in guinea pigs [22] while inhaled ATP sensitises cough evoked by inhaled citric acid [24], both of which are dependent on a mechanism involving P2X3 receptor activation. This axis of ATP release mechanistically underpinned a recent clinical trial assessing a TRPV4 antagonist (GSK2798745) in chronic refractory cough, although this trial failed to show clinical efficacy, raising questions about the mechanism of ATP release in humans, and suggests a reappraisal of the role of TRPV4 in cough [25]. However, it was not validated whether target engagement of the antagonist was achieved in this study and additional trials may be warranted. Whether other peripheral mediators contribute to peripheral sensitisation and excessive activation is currently not clear.

Importantly, as in chronic pain, it seems unlikely that peripheral sensitisation alone is responsible for chronic cough. Instead, central sensitisation involving changes in the efficacy of neurotransmission in the brainstem and brain pathways that produce reflex and behavioural regulation of coughing are undoubtedly also involved [7, 10, 18]. Drugs with a central mode of action are sometimes used to control chronic cough, with opiates representing a prime example of a drug with antitussive properties, although a limiting tolerance profile. Gabapentin and pregabalin are both analogues of the neurotransmitter γ-aminobutyric acid with a presumed central mode of action, and are currently approved for the treatment of post-herpetic neuralgia, diabetic neuropathy and fibromyalgia [26]. Recent European Respiratory Society guidelines suggest a trial of gabapentin or pregabalin in adults with chronic refractory cough, albeit based on low-quality evidence [27]. In one randomised controlled trial of gabapentin, patients experienced improvements in cough severity, quality of life and cough frequency (although only measured over a single-hour duration) [28]. Interestingly, those with clinical features of central cough sensitisation reported greater treatment efficacy than those without. Pregabalin together with speech pathology therapy improved cough quality of life and cough severity, but had no significant reduction in cough frequency [29]. In unrelated trials, the centrally acting neurokinin-1 receptor antagonist orvepitant is also showing clinical efficacy in refractory cough, providing further support for altered central nervous system processing in

FIGURE 2 Central glial mechanisms of sensitisation. a) Nodose and jugular ganglia sensory neurons terminate in distinct nuclei of the brainstem: the NTS and the Pa5. These inputs can evoke reflex coughing via local brainstem circuits that regulate the CPG. Alternatively, sensory inputs can ascend the neuraxis to higher brain regions in the cerebrum and generate the urge to cough, leading to volitional control of coughing through pathways that descend on the CPG. Pa5: paratrigeminal nucleus; NTS: nucleus of the solitary tract; CPG: cough pattern generator. b) In the brainstem sensory integration nuclei, and perhaps elsewhere in the cough neural network, activated glial cells likely enhance cough circuit excitability. Persistent sensory neuron inputs are known to activate astrocytes, oligodendrocytes, and resident and recruited microglia, leading to the release of a wide variety of neuroactive and inflammatory mediators. Central sensitisation produces long-lasting effects on synaptic efficacy, network excitability and neuroplasticity, which typically become less dependent on the peripheral inputs over time. Clinically central sensitisation is thought to result in allotussia, i.e. the occurrence of cough in response to normally innocuous stimuli. See text for specific details of the mediators and mechanisms involved.

https://doi.org/10.1183/13993003.00758-2020
chronic cough [30]. It is possible that these centrally acting agents alter the perception of cough rather than exerting a direct antitussive effect. In turn, the development of effective treatments for chronic cough may require an approach that targets peripheral and central neural plasticity. Here, we present the case outlining why peripheral and central neuroinflammatory processes, especially those involving the glial cells of the nervous system, might be critically involved in cough sensitisation.

**Evidence for peripheral and central sensitisation in chronic cough**

Pre-clinical animal studies provide strong evidence that airways inflammation is directly associated with sensitisation and plasticity of vagal sensory neurons (figure 1b and c). This is demonstrated by increased production and expression of neuropeptides (i.e. substance P and calcitonin gene-related peptide), upregulation of nociceptive ion channels (e.g. TRPV1) and glutamate receptors, and alterations in the threshold for activating sensory evoked responses, including cough [7, 11]. In the airways, the upregulation of neuropeptides is a key feature of inflammatory states associated with allergen or viral exposure in guinea pigs [11, 31] and this upregulation is predominately observed in airway sensory neurons of the nodose ganglia that do not usually express such neuromodulators. Human airways also display altered nerve profiles and neuropeptides in conditions of chronic cough [32, 33]. Together, these effects expand the stimuli that can elicit cough-evoking responses forming the basis of hypertussia in chronic cough patients, although a specific role for peripheral glial cells in mediating this has not been investigated.

Peripheral sensitisation of vagal sensory neurons may lead to central sensitisation of cough pathways in the brain (figure 2b). For example, electrical stimulation of the vagus nerve in animals has been shown to acutely activate both the neurons and the glial cells in the nucleus of the solitary tract [34]. Furthermore, animal experiments show that chronic exposure of the airways to environmental pollutants or irritants (e.g. cigarette smoke, ozone, allergens or respiratory tract viruses) enhances the general excitability of neurons in the nucleus of the solitary tract, and promotes glial cell activation and expansion (gliosis) [35]. These processes leave the central neural circuit more sensitive to incoming sensory information. Glial-dependent neuroinflammation in the paratrigeminal nucleus, which also processes cough sensory inputs, has not been studied but may be expected. Importantly, fMRI studies in humans suggest that changes in cough sensitivity, like that in pain, are accompanied by altered activity across several brain regions. For example, in patients demonstrating cough hypersensitivity, fMRI studies have shown that altered sensitivity to inhaled airway irritants is associated with increased activity in the brainstem and sensory cortex, and reduced activity in inhibitory control networks that ordinarily suppress coughing [18]. Conversely, cigarette smokers demonstrate a reduction in cough reflex sensitivity, despite a propensity to develop chronic cough [19]. This is associated with concomitant increased activity in cough sensory processing and cough suppression networks in the brain [19]. These data argue that an imbalance of excitatory and inhibitory neural processing in the brain can alter cough sensitivity and that central sensitisation, as described for chronic pain [5, 7, 10], may contribute to the development of chronic cough.

**Overview of glial cell biology**

Glia cells are nonneuronal cells and were originally thought of rather simply as the “glue” of the peripheral and central nervous system. However, glial cells have now been attributed to many important functions, including providing structural and trophic support for neurons, regulating neurotransmission, and clearing cellular debris and pathogens, and are integral regulators of the response to cell injury [36]. Although a detailed review of glial cell function is beyond the scope of this perspective article, we provide a brief summary of the various glial cell types and their potential roles in chronic cough.

Glia cells of the peripheral nervous system include Schwann cells and satellite glial cells (SGCs). Schwann cells are abundant and well known to myelinate peripheral axons, contributing to the propagation of action potentials and to axonal maintenance and growth (figure 1b) [37]. However, not all Schwann cells are myelinating. Unmyelinated nociceptors in body tissues are generally unsheathed and supported by nonmyelinating Schwann cells (figure 1b), forming so-called Remak bodies [38]. These nonmyelinating Schwann cells have recently received significant interest because of their responsivity to ATP and likely role in regulating sensory neuron excitability [38, 39, 40]. Notably, nonmyelinating Schwann cells were recently described in the lung, although their function is yet to be elucidated [37]. SGCs are located around the neuronal cell bodies in the sensory and autonomic ganglia where they help to regulate neuronal activity through bidirectional communication with their associated neurons. Because SGCs express receptors for a range of tissue and inflammatory factors, they can influence neuronal activity dependent upon changes in the local tissue environment [41].

Glia cells of the central nervous system include the astrocytes, oligodendrocytes and microglia. Astrocytes are the most prevalent, with important physiological roles in the organisation of neuronal networks, formation of the blood–brain barrier, neuronal development and response to injury [42, 43, 44]. These
cells are not equipped with the cellular machinery necessary for generating action potentials; however, when activated, astrocytes release gliotransmitters such as ATP, d-serine and glutamate, which in turn act on neurons to influence and enhance synaptic transmission and neurovascular coupling. Astrocytes also form a central component of the astrocyte-neuron lactate shuttle whereby lactate produced by astrocyte metabolic activity is used as an energy source for neuronal production of ATP [45]. Oligodendrocytes create the myelin sheath that provides support and insulation to axons in the central nervous system, in much the same way Schwann cells do in the peripheral nervous system. Their role extends beyond this and includes providing trophic support for axons, angiogenesis and supporting blood–brain barrier integrity [44, 46]. Microglia are of erythromyeloid origin and are considered the resident macrophages of the spinal cord and brain. They have key physiological roles in the phagocytosis of apoptotic cells, maintenance and reorganisation of neuronal networks, and inflammatory and immune responses to injury and infection [47, 48].

**Glial cells and hypersensitivity: relevance to chronic cough**

Glial cells are key drivers of neuroinflammation in disease, both acutely and in the maintenance phase that leads to chronicity. This pathogenic role is considered important in the development and maintenance of pain hypersensitivity and chronic itch, but in this perspective article we suggest it may also be highly relevant to cough hypersensitivity. In pain, glial cell-derived neuromodulators, including cytokines, chemokines, growth factors and gliotransmitters, establish a positive feedforward cycle between neurons and glial cells, enabling persistent changes in neuronal excitability [21, 41, 42, 43, 44]. Similarly, itching associated with allergic skin diseases is dependent on upregulated immune cell (particularly eosinophils) activation of glial and neuronal activity [49]. Chronic cough presents clinically as a neuronal hypersensitivity and is common in pathologies with increased eosinophils in the airways, including eosinophilic bronchitis and asthma [50], suggesting a similar signalling axis between immune cells, glia and neurons could exist in the airways. Peripheral immune and glial cells respond rapidly to tissue and nerve damage, contributing to the establishment of peripheral sensitisation (figure 1b and c). Consequently, sensory input into the central nervous system is increased almost immediately and sustained while injury and inflammation persist. This in turn promotes important changes in the excitability of central neural pathways that become progressively dependent upon central glial cell activation [20]. Such changes are collectively referred to as central sensitisation and drive a state whereby evoked responses are uncoupled from direct sensory nerve stimulation leading to the development of secondary hyperalgesia and allodynia, which are clinically evident in chronic pain syndromes [20, 44]. These disease states are considered akin to the clinical phenomena of hypertussia and allotussia that are described in chronic cough [7, 10, 51], and evidence for upregulated central neural processing in cough hypersensitivity has been described [18]. Perhaps also supportive of our assertions, cough is a frequently observed clinical symptom in a number of conditions in which there is direct evidence of neuroinflammation, including diabetes, obesity and HIV infection [52, 53, 54].

**Peripheral glial cells**

Following peripheral nerve injury, activated Schwann cells mediate the breakdown of the blood–nerve barrier via the secretion of matrix metalloproteinase-9, which promotes the recruitment of immune cells from the vasculature and their subsequent release of inflammatory mediators (figure 1b and c) [55]. Infiltration of immune cells can affect neurons either through direct action on sensory neuron cell bodies and/or their terminals, or indirectly through activating axon-associated Schwann cells or SGCs within the sensory ganglia [41, 44]. Indeed, in the skin, nonmyelinating Schwann cells form a glial network that encases unmyelinated nociceptor fibres, playing an important role in the transduction of noxious stimuli [38]. Schwann cells have also recently been shown to express functional transient receptor potential cation channel subfamily A member 1 (TRPA1) channels, which contribute to the development of allodynia and chronic pain following nerve crush or excessive alcohol intake, by driving local oxidative stress responses and inflammation around nociceptive nerve fibres [39, 40]. This is an intriguing discovery given that TRPA1 is also implicated in cough reflex regulation. However, it should be noted that a clinical trial of a TRPA1 antagonist (GRC 17536) failed to demonstrate cough suppression in chronic cough, albeit with the caveat again that adequate target engagement of the drug was not validated [56]. Glial involvement in sensory neuron sensitisation, however, is probably not confined to the peripheral nerve ending. In sensory ganglia during chronic pain, bidirectional cross-talk is increased between the sensory neurons and their surrounding SGCs [41, 57]. This cross-talk is predominately mediated by ATP release from both neurons and “activated” SGCs (figure 1c), which also exhibit increased expression of the proteins that form the gap junctions between adjacent SGCs [41, 57]. In animal models of chronic pain, the pannexin-1 channel, which is responsible for ATP release, has been implicated as a key contributor of enhanced neuronal activity and is thus considered a druggable target. Pannexin channels represent a potential therapeutic target to investigate in chronic cough as they are reportedly involved in ATP release in the airways [22].
Mainstream treatments for chronic cough (e.g. disease-modifying therapies or nonspecific antitussive including opioids and gabapentin) have proven efficacious in some patients, but fail to adequately relieve excessive cough in many others [69]. These treatments either modify peripheral pathologies (including classic immune mechanisms of disease) or inhibit the neural processes that are important for cough. However, they do not directly target the glial cell neuroinflammatory axis proposed earlier and, conceivably, this is a reason for limitations in their effectiveness. Although speculative at this stage, therapies that target multiple components of this signalling axis might afford better control of chronic cough. A better mechanistic understanding of glial biology in cough is therefore warranted to advance this hypothesis, which could be achieved with cell, animal and human experimentation. For example, in vitro animal or stem cell-derived cell culture systems exist for modelling mechanisms involved in peripheral cough neuron–glia cross-talk [70], the discoveries from which would lead to testable hypotheses and pre-clinical trials in animal (e.g. guinea pig) models of cough and cough hypersensitivity. Additionally, animal studies of altered central glial cell activity in models of lung disease have been published [35, 71, 72] and these could be adapted for investigations of central glial contributions to cough hypersensitivity. Notably, experimental approaches in humans also exist, especially for investigating central glial activity in
disease. For example, with appropriate radioligands, advanced targeted positron emission tomography imaging is a novel approach to image brain microglia and astrocytes [73], and this could be employed in patients with chronic cough to investigate regional brain glial activation profiles and their relationship to the altered functional brain responses already reported [18, 19].

Conclusions
The clinical manifestation of chronic cough, in particular the disruptive bouts of coughing elicited by relatively innocuous stimuli, is extremely troublesome for patients. The mechanisms responsible for chronic cough have parallels with those considered important in chronic pain. In this perspective article, we have considered the evidence for a mechanistic role for glial cells, a specific category of nonneuronal cells integral to peripheral and central neural processing, in the development of chronic pain. We propose that glial cells may similarly impact the peripheral and central nervous system control of coughing, contributing to neuroplasticity and cough hypersensitivity. The notion that glial cells function solely to nurture neurons is now redundant and an improved understanding of their mechanistic role in cough will identify potential novel targets for drug development.

Author contributions: Article concept: L.P. McGarvey, S.B. Mazzone and F.T. Lundy; drafting of manuscript: all authors; critical revision of manuscript for important content: all authors.

Conflict of interest: A-C. Devlin has nothing to disclose. F.T. Lundy has nothing to disclose. S.L. Martin has nothing to disclose. G.P. Sergeant has nothing to disclose. S.B. Mazzone reports grants and personal fees for consultancy from Merck, personal fees for consultancy from NeRRe, outside the submitted work. L.P. McGarvey reports grants and personal fees from Merck, personal fees from NeRRe, Chiesi, GSK and Shionogi, outside the submitted work. A.K. Driessen has nothing to disclose.

Support statement: This work was part of the BREATH project by the European Union under the Interreg VA Health and Life Science Programme. The views and opinions expressed in this paper do not necessarily reflect those of the European Commission or the Special European Union Programmes Body.

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