Staring Down the Barrel of a Gun: A Potential Pain Pandemic Following COVID-19 Infection.

M.A.Thacker and M. Mansfield

Pain Research Cluster.

Ageing, Acute and Long Term Conditions Research Group

School of Health and Social Care.

London South Bank University

**Introduction**

**“*If anything is likely to kill over 10 million people in the next few decades, it’s likely to be a highly infectious virus rather than a war….Not missiles but microbes”***

These highly prophetic words were spoken by Bill Gates during his TED talk in 2015 (see <https://www.youtube.com/watch?v=6Af6b_wyiwI>). Fast forward four or five years to the present time and we are living through the very scenario Gates was describing.

In December 2019 several people presented with an acute atypical respiratory disease in Wuhan, China. Soon after, several new cases of infection were reported across mainland China and then spread rapidly across the globe. Following extensive research, it was established that a novel (to humans) coronavirus was responsible, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2, 2019-nCoV); the virus was named due to its high homology (~80%) to Severe Acute Respiratory Syndrome (SARS-CoV), which caused acute respiratory distress syndrome (ARDS) and high mortality during 2002–2003 (25, 36). The human disease caused by this virus was given the name Coronavirus disease 19 (abbreviated to COVID-19) and eventually a global pandemic was declared by The World Health Organization (WHO). COVID-19 has had, and is still having, a massive impact, being reported in approximately 200 countries and territories and infecting a huge number of people worldwide. As of June 12th 2020, 7.27 million people world-wide have had a confirmed diagnosis of COVID-19, which includes 293 000 confirmed cases and 41 481 deaths in the United Kingdom (UK), with these figures continue continuing to grow.

Coronaviruses have been identified in several non-human mammalian species, including rats, mice, cattle, swine, cats, dogs, rabbits and horses and, notably for this infection, bats. In these species (36), Coronavirus infection often causes devastating respiratory or enteric diseases (25,36). Several coronaviruses have been identified since the mid-1960s. Prior to the SARS-CoV outbreak in the early 2000s, coronaviruses were only thought to cause mild, self-limiting respiratory infections in humans, commonly referred to as “colds”. These viruses are endemic among the human populations, causing 15–30 % of respiratory tract infections each year (25,36). Whilst rare, it is known that these viruses can cause lower respiratory tract infections (25,36).

The majority of people with SARS-CoV-2 virus who become symptomatic, report a typical presentation of fever, dry cough and dyspnoea consistent with the primary viral effects on the respiratory system (24). The developed respiratory symptoms of Covid-19 are extremely heterogeneous, ranging from minimal to significant hypoxia and in severe cases the development of Adult Respiratory Distress Syndrome (ARDS) (26). In addition, there is increasing evidence that other organ systems may be either primarily or subsequently involved, including renal, cardiac, hepatic and the nervous systems (15,21,22,24). Several symptoms associated with COVID-19 including, headache, dizziness, generalized weakness and fatigue as well as vomiting and loss of taste and/or smell have been linked to alterations within the Central Nervous System (CNS) (25). It has been suggested that about 88% among severely affected patients (those requiring respiratory support) display neurologic manifestations including acute cerebrovascular disease and impaired consciousness (23,31,32) and there is now an agreement that the headache reported by around 8% of infected individuals is of neural origin (22,29,36,39).

The exact pathophysiological mechanisms operating outside of the pulmonary system in COVID-19 are currently undetermined but are thought to involve an interplay between the primary actions of the virus and the body’s defensive systems with a particular emphasis on the immune system (15,22,31,38). COVID-19 leads to a fast activation of innate immune cells following viral contact and the magnitude of this response has been shown to be greater in those patients who develop more severe disease/symptoms (15,21,31,38). Indicators of immune facilitation in COVID-19 include an increase in the number of circulating neutrophil and a marked lymphocytopenia that mostly targets all the sub-types (effector, memory and regulatory) of CD4+ T cells (38,40). These changes are consistent with neuro-immune alterations that have been observed following somatic injury/inflammation and associated with nociception (8,17,19,20,35). It is this nervous system-immune system interaction and their potential involvement in the development of clinical pain that caught our attention in the early phase of COVID-19.

 Here we outline our hypothesis that those who have been infected with SARS-CoV-2 and developed symptoms may have an increased propensity to develop a clinically significant pain state/s due to the associated neuro-immune interactions. These interactions and the subsequent neuro-inflammation produce a series of neuroplastic responses within the nervous system that are well established as important mechanisms in the generation and maintenance of several clinical pain states (8,17,19,20,35). A full exposition of neuroimmune interactions in both pain and COVID-19 are beyond the scope of this extended editorial so here we briefly highlight several important features of COVID-19 infection that mirror neuroimmune mechanisms associated with the development and maintenance of pain. We aim to demonstrate our concern that we are potentially on the brink of a POST COVID-19 “pain pandemic” as a result of the neuroinvasive potential of the SARS-CoV-2 virus (see also 40 & 41).

**COVID-19 is Neuroinvasive**

A growing body of evidence shows that neurotropism, defined as an ability to invade, infect and live in neural tissue, is a common feature of CoVs (15,36,38). Most CoVs share a similar viral structure and infection pathways. The neuro-invasive propensity of CoVs has been documented for almost all of the CoVs, including SARS CoV and is likely to be the same for SARS-CoV-2 (15,36,38). Work on the original SARS CoV virus demonstrated entry of particles in the brain, where they were located almost exclusively in neurons (15,38). Several regions of the brain have demonstrated detectable viral levels including the hypothalamus, basal ganglia, mid brain structures including the locus coeruleus, dorsal tegmentum, dorsal raphe magnus, with the brainstem the most heavily infected by SARS-CoV-2 (15,36,38). This concentrated spatial distribution has obvious importance for respiratory function due to the neural systems that control site respiratory (and cardiac) function. Closer inspection reveals several key structures with established roles in the processing of nociception with particular bias towards regions normally involved in the inhibition of nociceptive processing (1,7,8). Therefore, altered function induced by the virus may not only lead to altered respiratory function but a reduction in inhibitory modulation of nociception.

The exact route by which SARS CoV enters the CNS is still not certain. However, direct entry via the circulatory or lymphatic systems appear unlikely, especially in the early stage of infection, since almost no virus particles are detected in the non-neuronal cells in the infected brain areas (15,27,36). Evidence suggests that CoVs first invade peripheral nerve terminals within the respiratory and/or enteric systems and then gain access to the CNS via a synapse to synapse connected route (16, ,2938). The transsynaptic transfer has been well documented for other CoVs (16, ,29, 38) and also for molecules involved in immune signalling including cytokines and chemokines (1,7,8,18,37). Consistent with this is the unequivocal evidence that peripheral inflammation causes a “remote” inflammatory response in the CNS, characterised by infiltration of circulatory cells and both the influx and synthesis and action of cytokines from within the brain (1,7,8,20,37). The concentration of viral antigens detected in the brainstem (where the infected regions included the nucleus of the solitary tract and nucleus ambiguous), midbrain and hypothalamus further suggest a highly targeted mechanism of neuroinvasion is at play. Furthermore, early epidemiological surveys on COVID-19 patients (36) suggest that the median time from the first symptom to dyspnoea is 5.0 days, to hospital admission is 7.0 days, and to intensive care is 8.0 days (25,36). The noted latency period adds to the evidence that the virus and/or specific viral particles are specifically transported to, enter and destroy the specific supraspinal neuronal pools (28,36,38).

There is a large body of evidence to demonstrate that the vagal afferent pathway is operational in many respiratory conditions and emerging evidence that this includes COVID-19 (10,11,13,40). Approximately 80% of the vagus’ neurons serve afferent functions. (13). Vagal afferents sample the tissue environment of almost all the viscera providing a major surveillance system for inflammatory and immune cells and mediators (13). Sensory information from mechanoreceptors and chemoreceptors in the lung and respiratory tract are relayed via the vagal afferents and impinge directly on the nucleus tractus solatarius in the brain stem. Furthermore, the same mechanism has been identified as a key player in neuroimmune interactions that lead to the development of pain and several neurological (mental health) conditions including depression, bipolar disorder and schizophrenia (18,35). The vagal afferents are largely C peptidergic fibres, a percentage of which have confirmed pro-nociceptive phenotypes that appear analogous with the so-called silent nociceptors in peripheral nerve trunks (13). This population of fibres have received particular attention and demonstrate a unique response profile remaining quiescent in healthy tissues but discharging to mechanical and chemical stimuli following infection and /or irritation of the respiratory tract even at low thresholds (13). This response profile is identical to the somatic silent nociceptors, whose discharge is associated with increased peripheral nociceptive activity (9,13,35). Furthermore, these vagal silent fibres have been shown to induce alterations in the sensitivity of neurons on which they synapse, leading to classical sensitisation and long-term potentiation in a fashion also identical to that noted for the somatic afferents. It has been proposed that these fibres therefore should be considered outright nociceptors (13) capable of inducing potentially long-lasting neuroplastic effects within the CNS (10,11,13).

Silent afferent fibres are also present in the gastrointestinal tract (13). These fibres have identical properties and effects as those in the respiratory and somatic systems (13). Alterations in gastrointestinal function are considered cardinal features of COVID-19 infection (25,36). Several gastrointestinal symptoms associated with COVID-19 have previously been shown to be associated with alterations in CNS neuronal sensitivity and a direct link between these alterations and those associated with somatic nociception are widely accepted (see 5). This adds further to the evidence we provide that COVID-19 has the potential to induce CNS alterations that may lead to the generation and maintenance of nociception and pain.

Neuronal driven direct molecular contact signalling across the blood brain barrier (BBB) appears therefore to be the dominant mechanism by which the brain is affected by peripheral signals (18,35,38). The increased permeability of the BBB is thought to be enhanced by pro inflammatory cytokine activation of the cerebral endothelium. Cytokines are small signalling proteins secreted primarily by cells of the immune system, including monocytes, macrophages, microglia), astrocytes, lymphocytes (B and T cells), and vascular endothelial cells that signal the coordinated detection of pathogens in order to activate cellular networks to mount appropriate immunological responses (17,18,29,35).

**COVID-19 induces a cytokine storm**

The levels of several cytokines including TNFα IL-1β, IL-6, IL-8, G-CSF and GM-CSF, as well as chemokines, such as CCL2 (MCP1), CXCL10 (IP10) and CCL3 (MIP1α) have been shown to be elevated in individuals with COVID-19 and may become dangerously high in those who are critically ill/displaying more severe symptomology (3,15,21,31,36,37,38). The unfortunate, extreme, end point of these immune/cytokine responses in COVID-19 is what has been labelled “the cytokine storm” (3,21). This state resembles secondary haemophagocytic lymphohistiocytosis, a hyperinflammatory state known to be triggered by viral infections (3,21). Existing literature on Adult Respiratory Distress Syndrome (ARDS) identifies the cytokine storm as a significant risk factor for mortality (3,21,22,24,37). This and other work on respiratory cytokine storms have demonstrated that both peripheral mediated and CNS expressed cytokines play major roles in the overall response (3,21,24,37).

There are many classes of cytokines including interleukins, lymphokines, chemokines, hematopoietins, interferons, and tumour necrosis factor (TNF). In addition, several families of growth factors whose immune function is identical with that of cytokines have been identified (8,19,33). Here we will make use of the generic term cytokines to include all these sub families unless specifics are required. Cytokines perform roles in normal central nervous system (CNS) function, including neural development, maturation and required apoptosis (7,8,17,19,20,33). These actions are carefully controlled in terms of the spatial and temporal pattern of cytokine release and activity. Excessive or prolonged release leads to alterations in both activity and function of the neural structures, which may be considered pathological (7,8,17,19,20,32,33). There is an extensive body of research that confirms the role of cytokines as mediators of altered CNS function during inflammatory states associated with bacterial and viral infections affecting either the brain or the periphery (15,31,38).

Peripheral inflammation of tissues including the viscera leads to increased circulatory and local (including the nervous) tissue levels of pro-inflammatory effector cytokines (13,18,33,35,40). There is now unequivocal evidence that peripheral inflammation causes a “remote” inflammatory response in the CNS, characterised by infiltration of circulatory cells which is controlled and influenced by cytokines released from both the periphery and cells of the CNS (7,8,17,18,35). Signalling across an intact but leaky BBB appears to be the usual and dominant mechanism means by which the brain is affected by peripheral signals (7,8,18,35). The effects of cytokines within the nervous system are dependent on the expression of their receptor complexes within the CNS (7,8,18,35). Expression of cytokine receptors has been localised to vascular endothelial and perivascular cells, microglia, astrocytes and neurons and is known to be elevated following peripheral (including visceral) or direct neural injury/inflammation and also viral infection (7,8,35). Moreover, these alterations are strongly associated with the generation and maintenance of nociceptive signalling (see for extensive reviews within the peripheral and central nervous systems (7,8,17,18,19,20,33,35) and also with COVID 19 infection (3,36,37).

Although the precise mechanisms of CNS synthesis of cytokines are still being delineated, there is irrefutable evidence for a *de novo* expression of cytokines in the brain from several sources including microglia, invading inflammatory cells, microvessel endothelial cells, pericytes, choroid plexus, astrocytes in response to infection and injury (7,8,35). Cytokine production by microglia is related to a characteristic morphological change (from quiescent ramified to activated amoeboid states) associated with their activation that can be readily visualised with appropriate techniques, allowing diagnostic confirmation (1,7,8,20). Importantly, there is a direct expression of cytokines and chemokines from several neuronal populations in the spinal cord and brain, suggesting a phenotypic switch of neurons from neuronal to immune profile following injury and infection (7,8,17,18,19,20,32,33,35). In addition, cytokines are also thought to be transported to and released into the CNS via the afferent vagal system in a manner consistent with the process outlined above. Following invasion of the CNS a series of long-lasting events that impact on normal CNS processing are generated, which we believe have implications for COVID-19 affected individuals.

**COVID-19 induces (Bio)Neuroplasty**

The above processes demonstrate a clear link between visceral and somatic neuroimmune/inflammation in COVID-19. We have attempted to establish that these neuroimmune interactions act as potential, and powerful, causal mechanisms for several symptoms displayed by and diagnostic for COVID-19. We now outline how these ‘peripheral’ cellular and chemical pathways have direct effects on structural, functional and chemical (bio)neuroplasticity within the CNS with implications for both nociception and respiratory dysfunction associated with COVID-19.

(Bio)Neuroplasticity allows the nervous system to adapt to changing conditions. Traditionally, this has been described as direct interactions between neurons; a prominent example of such an interaction is the induction of LTP at glutamatergic synapses associated with increased CNS responses to afferent stimuli. We have intentionally used the (Bio) prefix here, as we now know that CNS adaptions including LTP are not solely dependent on neuronal signalling but are also dependent on other cell types. Glial cells (used here as a generic term used for microglia and astrocytes) and several products they release including pro- and/or anti-inflammatory mediators have essential roles to play in (bio)neuroplastic alterations throughout the CNS.

An important element therefore in any consideration of neuro-immune interactions are multipartite (tri quadra, tetra and pentapartite) synapses within the CNS. These complex functional units occur throughout the neuraxis and are dynamically involved in the function of neurotransmission. Their anatomical make up can be any combination of neurons, astrocyte, microglia, astrocytes, T cells and includes signalling mechanisms via the extracellular matrix (7,8,20). This arrangement is likely to differ between CNS regions and provide different functional roles, for example astrocytes express glutamate transporters that remove glutamate from the extracellular space that are upregulated by neuronal activation providing the potential to reduce glutamate excitotoxicity (7,8,20). These dynamic units are integral of the neuro-immune interactions including those linked to pain and plasticity (7,8,19,20). Several well-established signalling pathways have been identified for nociception (7,8,12,19,20) and also for signalling in the respiratory control systems of the brain (9,10,11,12). Whilst there are variations and specifics in each case there is also much overlap and discussion about how various pathologies lead to cross talk between normally functionally isolated units. Interestingly, (bio)neuroplasticity associated with neuroimmune/inflammation processes has been the focus of recent attention in the respiratory disease literature (9,10,11,12,26). Several plasticity induced alterations in structure and function within the CNS have been linked to respiratory dysfunction, including ARDS (9,10,11,12,26) At present the paucity of research on COVID-19 limits our ability to fully investigate the potential for these interactions in COVID-19, although the current mobilisation of resources focused on umderstanding the disease may provide a unique opportunity to fully investigate nociceptive-respiratory interactions.

**COVID-19 and nociception,**

The above account has touched upon shared mechanisms of neuroimmune interactions that link COVID-19 and nociception. Here we offer a finer grained perspective focusing on these mechanisms in respect to nociceptive processing.

Detailed knowledge about neuroimmune responses associated with nociception has been gained primarily at the level of the spinal dorsal horn (7,8,17,19,20,32). These processes are the result of aberrant signalling involving activation of nociceptors and/or neural injury. Altered discharge of nociceptors (in particular C peptidergic fibres) lead to long-term (neuroplastic) changes in the processing of sensory information in the spinal dorsal horn (7,8,17,20,32). Ongoing activation of peptidergic C fibres leads to the release of various mediators, including glutamate, substance P, calcitonin gene-related peptide (CGRP), brain-derived neurotrophic factor (BDNF), fractalkine and ATP within the spinal dorsal horn (7,8,17,19). Receptors for these neurotransmitters and neuropeptides are expressed by cells of the immune system, vascular endothelial cells and higher-order neurons that link the cord to the brain (1,7,8,17,19,20,33). Several of these neurotransmitters also function as mediators of neurogenic neuroinflammation in both the periphery and also the CNS including BDNF, ATP, TNFα and IL-1β (7,8,33). These compounds are known to be essential for induction of LTP within the CNS, an established process in nociception and respiratory conditions andtherefore likely to occur in COVID-19.

Whilst the anatomy of the visceral sensory system differs from that of the somatic nervous system the mechanisms of transduction and transmission of sensory (nociceptive) afferent inputs remain highly consistent. Here too, significant aberrant sensory inputs lead to similar effects in terms of alterations in sensory processing (10,11,13,40). These changes occur rapidly i.e. C fibres induce a rise in intracellular Ca2+ concentrations in spinal astrocytes within seconds. Both vagal and somatic signalling also result in direct glial cell activation following the release of putative agents from primary afferent fibres (11,13,40). In turn, several markers of activation (secondary singling cascades) are upregulated in CNS microglia and astrocytes within minutes of enhanced neuronal activity (11,13). In addition, several neurotransmitters released only by CNS neurons also have actions on both astrocytes and microglia, for example glycine and GABA, released from both spinal interneurons, and noradrenaline, serotonin and dopamine released from descending supraspinal neurons (7,8). These neurotransmitters modulate the functions of microglia, astrocytes and vascular endothelial cells throughout the neuraxis (1,7,8,17,19,20). Noradrenaline causes retraction of microglial processes and serotonin increases microglial motility under pro-inflammatory conditions (7,8).

Unlike neurons, the activation of microglia is not an ‘all-or-none’ process and does follow a linear path with fixed uniform outcomes. Glial cells are permanently active but under normal conditions function only in a surveillance mode (1,7,8,17,19,20). Glial cells switch to distinct and finely tuned executive phases in response to neuronal activity, inflammation and /or neuronal injury and during infections (1,7,9,17,19,20). The innate immune response profile to infection of both microglia and astrocytes is dependent on the activation of pattern- and danger-recognition receptors. The major family of pattern and danger recognition receptors in the human nervous system are the Toll-Like Receptors (TLRs) that function to bind microbial products of both bacterial and viral origin (7,8,14,20,35); microglia and astrocytes express numerous TLRs. Activation of TLRs and the responses they generate have a confirmed role in the generation of nociceptive activity and spinal sensitisation (7,8,14). Importantly, dysregulation of TLRs has also been identified as a significant risk factor for fatality from ARDS (26).

Once activated, glial cells display an exhaustive biology that has two major components: i) a direct immune role (including phagocytosis and antigen presentation) and ii) a neural signalling role. The latter has been implicated in the amplification of the nervous systems response to further afferent inputs, consistent with alterations in CNS sensitivity associated with increased nociceptive signalling (1,7,8,17,19,20,35,40). Their ongoing activity may also be instrumental in processes that negate the need for further afferent signalling from the periphery, i.e. they become the source of nociceptive inputs to other areas of the CNS (1,7,8,17,19,20,35,40). Equally astrocytes have been shown to have overlapping roles in similar neural signalling processes throughout the nervous system have also been implicated in altered nociceptive signalling (7,8,17,19,20). It is our proposal, that these mechanisms are likely to be/become operational in those affected by COVID-19, in particular those at the more severe end of the disease spectrum.

In addition, members of T cell family express a similar repertoire of neurotransmitter receptors to glial cells and may be activated in an antigen-independent fashion by glutamate, substance P, CGRP, somatostatin, BDNF and neuropeptide Y released directly from nociceptive primary afferents in response to neuronal activity (7,8,18,20,23) Furthermore, naive T cells are recruited to the CNS by chemoattractant signals produced by activated neurons or glia (primarily via chemokines including CCL2). Both infection and neural activity (including that in nociceptors) seems to be a powerful trigger of innate and adaptive T cell activation within the CNS.

There is evidence that continued activation of T cells leads to an eventual “fatigue” in their functioning and may eventually lead to selective apoptosis (4). Failure of the T cell system is a serious proposition and renders the host vulnerable to infection and immune compromise. There is emerging evidence that COVID 19 patients with severe disease exhibit such T cell fatigue (4). Whilst counter intuitive this may also have serious implications for the generation of pain as T cells serve both pro and anti-inflammatory roles linked with increased and decreased nociception respectively based in part on the release of specific cytokines (23). This is one example of an important caveat to much of this account;, not all neuro-immune/cytokine responses are pro-inflammatory or algogenic, in fact several including Il-1ra,IL-4, Il-6,IL-10, IL-11, IL-13, TGF-β may all be considered anti-inflammatory in specific situations and/or concentrations (7,8).

As detailed above cytokines are key determinants of neuroimmune interactions within the CNS cytokines. Almost all of the cytokines that have been identified in COVID-19 patients have established roles in nociception. Many of these including TNFα and CCL2 have identified roles in the peripheral and central nervous system (1,7,8,17,19,20,32,33,35,40). Following injury or inflammation both are transported in an anterograde direction in sensory nerve fibres from the peripheral tissues (including the lung parenchyma) centrally to the CNS (7,8,18,19,33,40). In addition, both are released centrally following peripheral injury/inflammation, nerve injury and infection where they further activate immune cells including microglia and astrocytes and facilitate release of several other cytokines and chemokines (7,8,17,19,20,33,35,40). These processes amplify the initial response and may lead to the spread of neuroinflammation to sites outside of the initial neural receptive field (7,8,17,19,20,32,35). These processes have been linked to patterns of symptoms associated with ongoing pain states, which are often labelled as ‘central sensitisation’ (7,8,17,19,20,32,35).

Until recently a link between infection and nociception was not well determined (2). We now know that there is the potential for viral and bacterial infection to directly activate the nociceptive system and to promote neuroplastic alterations within the CNS consistent with mechanism outlined above and that act to amplify noxious sensory inputs. We believe there is the potential for COVID-19 infection to be a primary cause of nociception in addition to the processes highlighted throughout the account.

We have cherry-picked our way through the complex landscape of neuro-immune inflammation as it pertains to pain and COVID-19. We hope the reader now has some appreciation of the potential for the development of pain due to the shared mechanism of neuro -immune, -inflammation in both pain states and COVID-19. Neurogenic neuroinflammation has roles in tissue metabolism, synaptic plasticity, modulation of neuronal excitability, degeneration and regeneration within the CNS. It is important to note that neurogenic induced neuroinflammation may also prove beneficial although this account has focused largely on its detrimental effects and outcomes. The dominant effect of these processes is likely to reflect the context and specifics of the responses, for example the magnitude of cytokine release.

**Conclusion**

Up to now the focus of the pain community during the pandemic has been on the provision of care for those already living with pain, especially in those countries where lock down restrictions have been put in place. This has had the unfortunate consequence that research into the clinical and basic science of nociceptive processes in COVID-19 has received little attention.

Here we have outlined our thoughts on why we think there is the potential for a large number of people to develop pain following COVID-19 infected. Specifically, similar processes are at play within the visceral and somatic nociceptive systems and that neuroimmune/inflammation is a potential (and powerful) causal mechanism for several symptoms displayed by and diagnostic for COVID-19. Furthermore, these ‘peripheral’ cellular and chemical pathways have direct effects on structural, functional and chemical (bio)plasticity within the CNS with implications for both pain and also respiratory function. Altered CNS function associated with neuroimmune dysfunction is known to be long lasting and refractory to treatment. Perhaps it is too early to declare COVID-19 a neurological condition but this in our opinion is a serious consideration.

We encourage the clinical and research pain communities to turn their focus to addressing the potential for a post COVID-19 ‘pain pandemic’ and to instigate programs of research and clinical based monitoring that takes this proposal seriously.

Normally as researchers we hope that our hypotheses are correct but in this case, we really do hope that we have got it wrong!

Acknowledgements

Thanks to Kath Thacker and the journal editorial term for their useful feedback and comments on the manuscript.

Dedication

We would like to dedicate this account to the memory of all those who have lost their life or been affected by COVID-19. We would also like to extend this dedication to the life of George Floyd and all those affected by racism/prejudice of all forms.

1. Austin P.J., Fiore N.T. (2019) Supraspinal neuroimmune crosstalk in chronic pain states Current Opinion in Physiology 2019, 11:7–15
2. Chiu I.M., Heesters B.A., Ghasemlou N., Von Hehn C.A., Zhao F., Tran J. Wainger B., Strominger A., Muralidharam S., Horswill A.R., Wardenburg J.B., Hwang S.W., Michael C. Carroll M.C., Woolf C.J. (2013) Bacteria activate sensory neurons that modulate pain and inflammation N*ature*. 2013 September 5; 501(7465): 52–57.
3. Coperchini F., Chiovato L., Croce L., Magri F., Rotondi M. (2020) The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine. Cytokine and Growth Factor Reviews. https://doi.org/10.1016/j.cytogfr.2020.05.003
4. Diao B., Wang C, Tan ., Chen X., Liu Y., Ning L., , Li Chen L. Li M., Liu Y, Wang G., Yuan Z, Feng Z., Wu Y., Chen Y (2020) Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19) MedRxix https://doi.org/10.1101/2020.02.18.20024364
5. Farmer A.D., Aziz Q. (2014) Mechanisms of Visceral Pain in Health and Functional Gastrointestinal Disorders. Scandinavian Journal of Pain ;5(2):51-60.
6. Fukushi I., Shigefumi Yokota S., Okada Y. (2019) The role of the hypothalamus in modulation of respiration Respiratory Physiology & Neurobiology 265;172-179
7. *Gonçalves dos Santos G., Delay L., Yaksh T.L., Corr M. (2020)* Neuraxial Cytokines in Pain States. Frontiers in Immunology | www.frontiersin.org **1** January 2020 | Volume 10 | Article 3061
8. Grace P.M., Hutchinson M.R., Maier S.F., Watkins L. (2014) [Pathological pain and the neuroimmune interface.](https://pubmed.ncbi.nlm.nih.gov/24577438/?from_term=neuroimmune+and+pain+reviews&from_pos=1) Nat Rev Immunol. 14(4):217-31
9. Guyenet P.G., Bayliss G.D. (2015) Neural control of breathing and CO2 homeostasis*Neuron*. September 2; 87(5): 946–961. doi:10.1016/j.neuron.2015.08.001.
10. Hocker A.D., Stokes J.A., Powell F.L., Adrianne G. Huxtable A.G. (2017) The impact of inflammation on respiratory plasticity Experimental Neurology 287; 243-253.
11. Huxtable A.G., Vinit S., Windelborn J.A., Crader S.M., Guenther C.H., Watters J.J., Mitchell G.S. (2011) Systemic inflammation impairs respiratory chemoreflexes and plasticity Respiratory Physiology & Neurobiology 178;482-489.
12. Jiang M, Alheid G.F., Calandriello T, McCrimmon D. (2004) Parabrachial–lateral pontine neurons link nociception and breathing Respiratory Physiology & Neurobiology 143; 215–233
13. Kollarik M., Ru F., Brozmanova M. (2010) Vagal afferent nerves with the properties of nociceptors *Auton Neurosci*. 2010 February 16; 153(1-2): 12. doi:10.1016/j.autneu.2009.08.001.
14. Lacagnina MJ, Watkins LR, Grace PM. (2018) T[oll-like receptors and their role in persistent pain.](https://pubmed.ncbi.nlm.nih.gov/28987324/?from_term=neuroimmune+and+pain+reviews&from_pos=4) Pharmacol Ther. 184:145-158
15. Li Y.C., Bai W.Z., Hashikawa T. (2020)The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020;92:552–555
16. Mahammedi A., Saba L., Vagal A., Leali M., Rossi A., Gaskill M., Sengupta S., MD, PHD; Zhang B., Carriero A., Bachir S., Crivelli P., Paschè M., Premi E., Padovani A., Gasparotti R. (2020) Imaging in Neurological Disease of Hospitalized COVID-19 Patients: An Italian Multicenter Retrospective Observational Study. Radiology.
17. Marchand F., Perretti M., McMahon S .B. (2005) Role of the immune system in chronic pain. Nat Rev Neurosci.; 6(7):521-32.
18. Mao L., Jin H., Wamg M., Hu Y., Chen S., He Q., , Chang J., Hong C., Zhou Y., Wang D., Miao X., Li Y, Hu B. (2020) Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China JAMA Neurol Apr 10;e201127. doi: 10.1001/jamaneurol.2020.1127. Online ahead of print.
19. Marques-Deak A., Cizza G., Sternberg E. (2005) Brain-immune interactions and disease susceptibility Molecular Psychiatry 10, 239–25
20. McMahon SB, Cafferty WB, Marchand F. [Immune and glial cell factors as pain mediators and modulators.](https://pubmed.ncbi.nlm.nih.gov/15755561/?from_term=MCMAHON+AND+MARCHAND+REVIEWS&from_pos=2) Exp Neurol. 2005 Apr;192(2):444-62.
21. McMahon S.B., Malcangio M. (2009) [Current challenges in glia-pain biology.](https://pubmed.ncbi.nlm.nih.gov/19840548/?from_term=MCNAHON+AND+MALCANGIO+REVIEWS&from_exact_term=mcmahon+AND+MALCANGIO+REVIEWS&from_pos=2)

Neuron. 2009 Oct 15;64(1):46-54.

1. Mehta P., McAuley D.F., Brown M., Sanchez E., Tattersall R.S., Manson J.J., (2020) COVID-19: consider cytokine storm syndromes and immunosuppression The Lancet https://doi.org/10.1016/ S0140-6736(20)30628-0.
2. Moalem G., [Xu](https://pubmed.ncbi.nlm.nih.gov/?term=Xu+K&cauthor_id=15541898) K., Yu L. (2004) T Lymphocytes Play a Role in Neuropathic Pain Following Peripheral Nerve Injury in Rats Neuroscience 129(3):767-77.
3. Montalvan V., J. Lee J., Bueso T., De Toledo J., K. Rivas K. (2020) Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review Clinical Neurology and Neurosurgery 194; 105921.
4. Pascarella G., Strumia A., Piliego C., Bruno F., Del Buono R., Costa F., Scarlata S., Agrò FE. (2020) COVID-19 Diagnosis and Management :A Comprehensive Review. J Intern Med. Apr 29:10.1111/joim.13091. doi: 10.1111/joim.13091.
5. Peña-Ortega F. (2019) Clinical and experimental aspects of breathing modulation by inflammation Autonomic Neuroscience: Basic and Clinical 2016;72-89.
6. Ramirez Cruz N., Maldonado Bernal C., Cuevas Uriostegui M.L., [Castañoń](https://pubmed.ncbi.nlm.nih.gov/?term=Casta%C3%B1o%C5%84+J&cauthor_id=15794413) J.,  [López Macías](https://pubmed.ncbi.nlm.nih.gov/?term=L%C3%B3pez+Mac%C3%ADas+C&cauthor_id=15794413) C.,  [Isibasi](https://pubmed.ncbi.nlm.nih.gov/?term=Isibasi+A&cauthor_id=15794413) A. (2004)Toll-like Receptors: Dysregulation in Vivo in Patients With Acute Respiratory Distress Syndrome ; Reviews in Allergy Mexico 51(6):210-7.
7. Román G.C., Spencer P.C., Reis J , Buguet A , El Alaoui Faris M. ,Sarosh M. Katrak S.A., Láinez M, Tulio Medina M., Meshram C., Mizusawa H,. ÖztürK S., Wasay M. (2020) The neurology of COVID-19 revisited: A proposal from the Environmental Neurology Specialty Group of the World Federation of Neurology to implement international neurological registries. Journal of the Neurological Sciences 414; 116884.
8. Romoli M., Jelcic I., Bernard-Valnet R., García Azorí D., Mancinelli L., Akhvlediani T., Monaco S., Taba P., Sellner J. (2020) A systematic review of neurological manifestations of SARS-CoV-2 infection: the devil is hidden in the details doi: 10.1111/ENE.14382
9. Rogers J.P, Chesney E., Oliver D., Pollak T.A., McGuire P., Fusar-Poli P., Zandi M.S., Lewis G., David A.S. 2020. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic www.thelancet.com/psychiatry Published online May 18, 2020 https://doi.org/10.1016/S2215-0366(20)30203-0
10. Schett G., Sticherling M., Neurath M.F. (2020) COVID-19: risk for cytokine targeting in chronic inflammatory diseases? NATURE REVIEWS **|** Immunology volume 20 ://doi.org/10.1038/ s41577-020-0312-7
11. Thacker M.A., Clark A.K., Bishop T., Grist J., Yip P., Moon L.D.F., Thompson S.W.N., Marchand F., McMahon S.B. (2009) CCL2 is a key mediator of microglia activation in neuropathic pain states. European Journal of Pain 13 (2009) 263–272
12. Thacker M.A., Clark A.K., Marchand F., McMahon S.B. (2007) Pathophysiology of Peripheral Neuropathic Pain: Immune Cells and Molecules. Anesthesia & Analgesia: 105; 3; 838-847.
13. Vidya M.K., Kumar V.G., Sejian V., M Bagath M., Krishnan G. , Bhatta R (2017) Toll-like receptors: Significance, ligands, signalling pathways, and functions in mammals. International Reviews of Immunology. https://doi.org/1080/08830011852017.1380200
14. Watkins L.R., Maier S.F., THE PAIN OF BEING SICK: Implications of Immune-to-Brain Communication for Understanding Pain Annu. Rev. Psychol. 2000. 51:29–57
15. Yuki K., Fujiogi M., Koutsogiannaki S. (2020) COVID-19 pathophysiology: A review. Clinical Imunology: 215; 108427.
16. Jianzhong Yang\*, Mayra Azat\*, Peng Peng, Yiping Chang, Ranran Gao, Wenli Li, Jiming Li, Yage Chai, Dandan Li Serum levels of TNF-α, IL-1β, IL-9, and IL-15 in acute respiratory distress syndrome Int J Clin Exp Pathol 2017;10(1):781-788
17. Zhiqiang Z., Huicong Kang H., Li S., Zhao X. (2020) Understanding the neurotropic characteristics of SARS‐CoV‐2: from neurological manifestations of COVID‐19 to potential neurotropic mechanisms Journal of Neurology https://doi.org/10.1007/s00415-020-09929-7

**Additional References Added Following Review:**

1. Bolay H., Gül A., Baykan B. 2020 COVID-19 is a Real Headache! Headache; doi: 10.1111/head.13856
2. Ray, P.R., Wangzhou, A., Ghneim, N., Yousuf, M.S., Paige, C., Tavares-Ferreira, D., Mwirigi, J.M., Shiers, S., Sankaranarayanan, I., McFarland, A.J., Neerukonda, S.V., Davidson, S., Dussor, G., Burton, M.D., Price, T.J., A pharmacological interactome between COVID-19 patient samples and human sensory neurons reveals potential drivers of neurogenic pulmonary dysfunction, *Brain, Behavior, and Immunity* (2020), doi: <https://doi.org/10.1016/j.bbi.2020.05.078>
3. Su S., Cui H., Wang T, Shen X, Ma C. 2020 Pain: A potential new label of COVID-19Brain, Behaviour, and Immunity 87 (2020) 159–160