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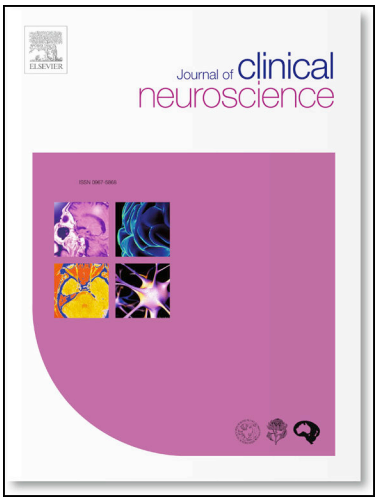

Opinion paper

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DOES COVID-19 IMPAIR ENDOGENOUS NEUROGENESIS?

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Abstract:

Endogenous neural stem cells are thought to continue to generate new neurons throughout life in the human brain. Endogenous neurogenesis has been proposed to contribute to physiological roles in maintaining and regenerating olfaction, as well as promoting normal cognition, learning and memory. Specific impairments in these processes in COVID-19 – impaired olfaction and cognition – may implicate the SARS-CoV-2 virus in attenuating neurogenesis. Furthermore, neurogenesis has been linked with neuroregeneration; and impaired neuroregeneration has previously been linked with neurodegenerative diseases. Emerging evidence supports an association between COVID-19 infection and accelerated neurodegeneration. Also, structural changes indicating global reduction in brain size and specific reduction in the size of limbic structures – including orbitofrontal cortex, olfactory cortex and parahippocampal gyrus – as a result of SARS-CoV-2 infection have been demonstrated.

This paper proposes the hypothesis that SARS-CoV-2 infection may impair endogenous neural stem cell activity. An attenuation of neurogenesis may contribute to reduction in brain size and/or neurodegenerative processes following SARS-CoV-2 infection. Furthermore, as neural stem cells are thought to be the cell of origin in glioma, better understanding of SARS-CoV-2 interaction with tumorigenic stem cells is indicated, with a view to informing therapeutic modulation. The subacute and chronic implications of attenuated endogenous neurogenesis are explored in the context of long COVID. Modulating endogenous neurogenesis may be a novel therapeutic strategy to address specific neurological manifestations of COVID-19 and potential applicability in tumour virotherapy.

Introduction:

Acute COVID-19 presents as a multi-system condition in which approximately 36% of patients have neurological symptoms [1]. These symptoms include impaired or loss of smell, headache, epilepsy, acute cerebrovascular disease, encephalitis and Guillain-Barre syndrome.[2-6] Of concern is the incidence of persistent symptoms for several months after the acute infective process has resolved, i.e. Long-COVID [7, 8]. Although Long-COVID presents with symptoms from multiple organ systems, neurological symptoms (confusion/brain fog, short term memory loss and forgetfulness) were reported in 42% of Long-COVID participants in a longitudinal study of healthcare workers [9]. The same study reported an incidence of anosmia in 18% of participants. An association exists between severity of cognitive impairment and severity of olfactory symptoms in older people recovering from COVID-19 [10].

In addition to olfactory and cognitive deficits, emerging evidence raises concern that COVID-19 may be associated with accelerated neurodegeneration. An interesting recent study utilising advanced neuroimaging techniques has demonstrated generalised reduction in brain volume and markedly so in limbic structures [11]. This paper proposes the hypothesis that SARS-CoV-2 infection may impair endogenous neural stem cell activity. Attenuation of neurogenesis may contribute to reduction in brain size and/or neurodegenerative processes following SARS-CoV-2 infection.

SARS-CoV-2 entry into the Brain and Olfactory system

Over two years into the COVID-19 pandemic, there remains some uncertainty regarding the exact mode(s) of entry of the coronavirus into the brain. Generally accepted routes include via the olfactory nerve/bulb and haematogenous spread [12, 13]. What is certain is that the coronavirus does invade the brain, evidenced by findings of virus within brain cells at autopsy [13-15].

Cytokine storm and neuroinflammation are widely document in the presence of systemic COVID-19 infection and evidence of neural damage demonstrated by increased glial fibrillary acidic protein and neurofilament light chain protein in patients with severe disease [16-18]. However, direct association between neuroinflammatory findings and neuronal coronavirus infection is difficult to unravel. A post-mortem case series on 43 people who has died while PCR positive for SARS-CoV-2 identified cytotoxic T-cell infiltration and microglial activation in the brain but the presence of intracranial coronavirus was not

associated with severity of the neuropathological findings [15]. That said, neuroinflammation, irrespective of mechanism, must be a serious contender to explain the neurological sequelae of COVID-19. Given that neuroinflammation impairs neurogenesis[19], dysfunction of neural stem cells must be factored in.

COVID-19 and Olfaction

Entry of cells by SARS-CoV-2 is mediated by angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) expressing cells in the nasal mucosa, olfactory epithelium and thenceforth through the olfactory bulb [20]. The mechanism by which SARS-CoV-2 causes anosmia is thought to be mediated by direct effects on the olfactory bulb and epithelium, with subsequent inflammation resulting in neuronal damage and impairment of regenerative ability [21, 22]. The inflammatory processes result in anosmia [6]. Recovery of olfactory function in some patients after the acute illness may be as a result of resolution of inflammation as well as regeneration of damaged cells by neural stem cells. Persistent symptoms may therefore be a result of ongoing inflammation overwhelming regenerative capacity with the possibility of impaired neural stem cells. From the olfactory bulb the virus potentially gains access to a variety of locations within the neuraxis [21, 23].

Neurogenesis, COVID-19, Olfactory function and Parkinson's disease

The exact nature, anatomical extent and amount of post-natal and adult human neurogenesis continue to be debated [24-26]. However, there is substantial experimental and clinical evidence that endogenous neurogenesis contributes significantly to physiological olfaction and associated limbic system functions including cognition [27]. Neural stem cells may also have a role in brain repair and regeneration [28]. Neurogenic niches containing neural stem/progenitor cells have been demonstrated in the lateral walls of the lateral ventricles and in the hippocampal formation [29-31].

SARS-CoV-2 has been demonstrated to significantly attenuate the viability of induced pluripotent stem cell derived human neural precursors, neurospheres and brain organoids [32]. The molecular apparatus implicated in viral entry into human cells including ACE2, TMPRSS2, cathepsin L and furin were widely detected on the neural precursor cells. SARS-CoV-2 was found to readily infect and replicate in human neural stem cells and resulted in significant cytotoxicity [32]. These findings mirrored earlier findings that Zika virus

abrogates neurogenesis during human brain development through direct infection of neural stem cells [33]. The possibility of endogenous neurogenesis being impaired in COVID-19 is thus raised.

In addition to a primary cytotoxic effect on neural stem cells, neuroinflammatory sequelae of COVID-19 infection have also been implicated in attenuating neurogenesis [34]. Pro-inflammatory cytokines upregulated in CSF during acute and post-acute phases of COVID-19 infection include IL-1β, TNF-α, IL-8, IL-6, IL-15, MCP-1 and MIP-1β [35, 36]. These inflammatory cytokines are well recognised to target neural stem cells and attenuate neurogenesis [37].

One of the chemokines upregulated following SARS-CoV-2 infection is CCL11 [38]. Peripheral CCL11 levels have previously been shown to strongly correlate with decreased adult neurogenesis and impairments in learning and memory [39]. In patients in the post-acute phase of COVID-19 infection, CCL11 levels correlate with severity of cognitive deficit [38]. Further, in a mouse model, decreased hippocampal neurogenesis was demonstrated following even mild SARS-CoV-2 infection, but not other respiratory viral infections [38]. Similar findings of decreased hippocampal neurogenesis following COVID-19 infection were demonstrated by another group in a rodent model [40]. Post-mortem examination of the brains of patients with COVID-19 (who died of other unrelated causes) also demonstrated evidence of decreased neural stem cell maturation and/or increased neuroblast death [40]. Taken together, COVID-19 infection may attenuate neurogenesis through two distinct processes – direct and selective SARS-CoV-2-mediated cytotoxicity of neural stem cells and upregulation of cytokines which are known to attenuate neurogenesis.

An interesting article links olfactory disturbance in COVID-19 to virus mediated inflammatory disturbance of neurogenesis in the olfactory bulb [41]. Further, the authors associate olfactory deficits in COVID-19 and Parkinson's disease with regenerative failure in replenishment of dopaminergic neurons in the olfactory bulb and epithelium. Indeed, possible links between COVID-19 and Parkinson's disease have been described; specifically there is evidence that COVID-19 aggravates specific motor and non-motor symptoms [42].

The possibility of SARS-CoV-2 impeding neurogenesis in a more widespread anatomical distribution, larger than the olfactory bulb, is highly likely. A number of clinical and molecular rationales to explain the possibility of post-viral Parkinsonism have been put forth and are reviewed elsewhere [42, 43]. Analogous to impaired olfactory system neurogenesis and associated loss of dopaminergic neurons as suggested by Rethinavel et al [41], interactions between nigrostriatal dopaminergic systems and endogenous neurogenesis may

be impeded in coronavirus infection. Experimental data supports the existence of neurogenesis in the adult substantia nigra and its role is surmised to include maintenance and regeneration [44, 45]. As alluded to above, there remains debate regarding how widespread neurogenesis is in the adult brain, although enhancing endogenous neurogenesis is being evaluated as treatment in Parkinson's disease [46-48]. Taken together, it is possible that wider impedance of neurogenesis to limit dopaminergic processes – beyond olfactory circuits – could explain how coronavirus infection may induce a post-viral Parkinsonism. A number of other viruses have been linked with secondary parkinsonism including human immunodeficiency virus (HIV), Japanese encephalitis, coxsackie viruses, Herpes simplex 1, Epstein-Barr, hepatitis C and influenza A [49]. At the same time, several of these viruses have been shown to cause inflammatory olfactory bulb dysfunction as they gain their entry to the neuraxis through this route [50]. Viral infection as an antecedent to various neurodegenerative diseases have been previously hypothesised [51]. A mechanism that inhibits endogenous neural stem cell activity is possible and may require further investigation.

COVID-19 and Dementia

Previous COVID-19 infection is associated with cognitive impairment, with well-described patterns of impairment in memory, attention and executive functions [52]. Similarly, COVID-19 has been associated with exacerbating or accelerating dementia [23]. This is further supported by the finding of accelerated rates of cognitive decline in patients with Alzheimer's disease who develop COVID-19 in other studies [53]. Indeed, cognitive impairment has been well documented in patients with a history of COVID-19 infection [54-56]. In the context of dementia, while it is possible that decreased social interactions may contribute to cognitive impairment, there is also biochemical evidence that COVID-19 may accelerate the pathophysiology of Alzheimer's disease. Serum biomarkers of neuronal injury and neuroinflammation including neurofilament light chain, total tau, glial fibrillary acid protein, ubiquitin carboxyl-terminal hydrolase L1 and others were found to correlate strongly in the setting of neurological symptoms in patients with COVID-19 [57]. These findings contribute to the evidence that patients who have had COVID-19 may have acceleration of symptoms and pathology of Alzheimer's disease and related dementias. A wider role of SARS-CoV-2 in promoting neurodegeneration has been reported and an inflammatory basis has been averred [58-62]. An intriguing paper links COVID-19 associated

neuroinflammation with disordered iron metabolism, culminating in accelerated cellular senescence as intracellular inclusion bodies accumulate [63].

An important recent study has demonstrated that SARS-CoV-2 infection is associated with structural changes in the brain [11]. The UK Biobank study is a population-based cohort of 500,000 adult participants recruited between 2006 and 2010 and a proportion of these participants underwent detailed neuroimaging by means of magnetic resonance imaging (MRI) in the world's largest multi-modal imaging study [64]. Data released demonstrated that on comparison of imaging before and after testing positive for COVID-19, a number of significant structural changes were found when compared with controls. Significant longitudinal effects were found in that there was a greater reduction in global brain size in those who tested positive for COVID-19 [11]. Additionally, there was significant reduction in tissue integrity and evidence of tissue damage in the orbitofrontal cortex, parahippocampal gyrus and brain regions associated with the primary olfactory cortex. Authors concluded that the structural appearances could suggest of degenerative or neuroinflammatory spread through limbic pathways.

Consistent with these findings, a systematic review of brain imaging changes following COVID-19 reported abnormalities in the olfactory brain network including rhinencephalon and hippocampal formation, extending to the cingulate gyrus, corpus callosum and insula [65]. The size/volume of limbic structures, in particular the hippocampal formation, is thought to correlate with the extent of adult neurogenesis [66, 67]. Therefore, it is possible that COVID-19 infection may particularly influence neurogenesis with resulting structural changes and deficits in olfaction and cognition. Limitations of this supposition a priori are twofold – firstly that most supporting data originates from animal studies; and secondly that mechanisms causing hippocampal volume loss are manifold, including neuronal and glial cell death.

That said, neurodegenerative processes spreading distally through the limbic system are reminiscent of Alzheimer's disease, whose clinical and pathological stages progress as amyloid and neurofibrillary changes progress from transentorhinal (Stages I-II), limbic (Stages III-IV) and isocortical (Stages V-VI) [68, 69]. Moreover, the phenotypic association of hyposmia/anosmia and dementia in neurodegenerative diseases is ubiquitous [70, 71].

Neural stem cells, Olfactory function and Neurodegenerative Disorders

The mechanistic basis by which COVID-19 results in cognitive impairment, neurodegeneration and hyposmia/anosmia may involve the impedance of endogenous neural stem cell physiology. Neurogenesis in the olfactory bulb contributes to the maintenance and regeneration of olfactory mechanisms [72, 73]. Similarly, endogenous neural stem cell activity has several important roles in promoting cognition [74, 75]. Indeed, the suggestion that neurodegeneration involves a failure of endogenous neuroregeneration is not new [76, 77]. According to this theory, primary deficits in neural stem cell proliferation, migration and/or differentiation may contribute to the net cell loss and neural circuit disruption in neurodegenerative diseases. Taken together, as COVID-19 appears to downregulate processes mediated by neurogenesis, it is hereby hypothesised that SARS-CoV-2 infection has a direct effect on endogenous neural stem cells. Further studies are indicated.

In a broader viewpoint, olfactory dysfunction features in most neurodegenerative conditions albeit to varying degrees [70, 71]. Olfactory dysfunction is relatively profound in Alzheimer's disease and Parkinson's disease, significantly but less impaired in Huntington's disease and amyotrophic lateral sclerosis, and slightly impaired in progressive supranuclear palsy [78, 79].

While the existence of a common pathophysiological substrate between olfaction and neurodegeneration has been proposed, this has not yet been definitively described [80, 81]. It is hereby hypothesised that impaired neural stem cell activity in neurodegenerative diseases may account for such a substrate. Impairments in neurogenesis, which have been demonstrated in several neurodegenerative disorders, could contribute to hyposmia and neurodegeneration (Figure 1).

Consistent with this notion, chronic cognitive impairment has been shown to correlate with olfactory dysfunction due to COVID-19 [10]. Hyposmia during acute COVID-19 was linked with increased vulnerability in memory functions in several studies [82-84]. Again, it is conceivable that the effects of SARS-CoV-2 on attenuation of neural stem cell activity in this group of patients are longer acting and/or slower to recover. Similarly, patients with long COVID frequently have persistent olfactory dysfunction. These patients are also frequently symptomatic with fatigue, decreased cognition, depression and anxiety [85]. There may be merits in exploring therapeutic strategies to modulate neural stem cell activity in these patients. There is evidence that psychotropic medication and neuromodulation/neurostimulation may influence neural stem cell activity [86-89].

SARS-CoV-2 as a potential anti-glioma strategy

While the mechanisms by which SARS-CoV-2 invades the central nervous system are being explored, the exact molecular bases of neural stem cell dysfunction require further study [32, 41]. Preliminary studies support the notion that SARS-CoV-2 infection may downregulate neural stem cell activity. If this finding is corroborated in human studies, there may be a role for SARS-CoV-2 virotherapy as a novel anti-glioma agent (Figure 2).

Despite recent advances in cancer therapy, the prognosis of patients with glioma remains poor, especially patients with glioblastoma. Viruses have been studied in the context of oncolytic virotherapy as well as viral delivery of gene therapy, although few of these have advanced to clinical studies [90]. Oncolytic virotherapy for glioma has included several classes of virus including viruses with human pathogenicity such as Herpes simplex virus, Adenovirus, measles virus, Poliovirus and Reovirus [91]. Genetic alterations such as mutated or deleted viral genes allow for a reduction in neurotoxicity while not affecting infection of dividing cells [92]. Cancer stem cells are a small subpopulation of cells within tumours that possess capabilities of self-renewal, differentiation and tumorigenicity [93]. A virus bearing additional and/or particular cytotoxicity to a cancer stem cell can be expected to be a legitimate virotherapy agent. Herein lies an advantageous role for SARS-CoV-2 in glioma.

The cells of origin in gliomas are thought to be neural stem cells [94-96]. Neural stem cells from subventricular zone niches have been shown to carry driver mutations which lead to the development of malignant gliomas, even in anatomically distant regions [97]. Modulation of neural stem cell activity could potentially be harnessed for therapeutic purposes in glioma.

Glioma/glioblastoma stem cells mediate phenotypic diversity in a tumour leading to resistance to oncological treatments – their selective targeting may improve outcomes [98]. There are significant molecular similarities between neural stem cells and brain tumour stem cells [99, 100].

Other viruses are known to have tropism towards neural stem cells and/or ablate neurogenesis [101]. Zika virus infection attenuates neural stem cell activity by inducing mitotic abnormalities and apoptosis [33, 102]; attenuates glioblastoma stem cell viability and proliferation [103]; and is therefore being investigated as a novel treatment in glioma [104, 105]. In experimental conditions human neural stem cells were permissive to SARS-CoV-2 (but not SARS-CoV) infection and resulted in significant cytotoxicity [32, 38]. As with other oncolytic viruses in glioma, it may be that genetic modification is required to increase

precision and reduce collateral neurotoxicity. If similar effects can be confirmed in vivo, a potential role in brain tumour research and treatment may be explored.

Conclusion:

In summary, this paper puts forth a few novel hypotheses (see Figures 1 and 2).

1. SARS-CoV-2 infection may impair neural stem cell activity resulting in cognitive impairment and hyposmia/anosmia by impeding hippocampal and olfactory neurogenesis respectively. This hypothesis could be tested through analysis of post-mortem tissue, although molecular markers of neurogenesis are controversial [106, 107]. There remains disagreement in the scientific community regarding the appropriateness and significance of markers of neurogenesis. Although data supporting this hypothesis have been provided by one good-quality study [40], further studies evaluating this are indicated. Advanced neuroimaging techniques including positron emission tomography, magnetic resonance imaging and spectroscopy studies may be used to study neurogenesis in vivo [108, 109]. However, contemporary neuroimaging techniques lack sensitivity in demonstrating human neurogenesis, not least because of the small size of the anatomical areas thought to bear the most neurogenic potential.

2. Neural stem cell dysfunction may be a neuropathological substrate linking neurodegeneration and hyposmia. Again, post-mortem studies and advanced neuroimaging may ultimately shed more light, but as described above there are shortcomings in these techniques. As an example, a neuroinflammatory component of the pathophysiology of a neurodegenerative disease may be the driving factor in inhibiting neurogenesis, although what may be experimentally observed is a compensatory increase in neurogenesis. Furthermore, there is considerable heterogeneity in inflammatory cascades and mechanisms of cell death underlying neurodegeneration. Indeed, there are risks of bias from common contributing factors, for example increasing age and frailty, which themselves are risk factors for hyposmia.

3. Long COVID symptoms may include elements of decreased neural stem cell activity and may be ameliorated by their pharmacological/therapeutic upregulation. To this

end, a role for antidepressant medications and vagus nerve stimulation (which are thought to upregulate neural stem cell activity) are already being investigated as treatments for long COVID [110, 111]. Critically appraising this hypothesis, it is unclear then why some patients and not others develop long COVID. One possibility that has been proposed elsewhere is that there may be a larger pool or "reserve" of neural stem cells in some patients, which confer the ability to recover or regenerate [40].

4. Decreasing neural stem cell activity, using SARS-CoV-2 virotherapy, may be a viable target for future research into potential anti-glioma therapies. Preclinical studies of SARS-CoV-2 interactions with neural stem cells and glioma stem cells would be valuable – specifically evaluating viral entry and ensuing cell death processes. As with other oncolytic viruses being investigated as treatments for glioma, genetic modifications to increase efficacy and decrease neurotoxicity are possible. Neural stem cells and glioma stem cells share a multitude of molecular similarities – a particular predilection of SARS-CoV-2 in the death of neural stem cells, may translate in suppression of glioma stem cells which propagate brain tumours.

A limitation of this paper is that the extent and physiological relevance of neurogenesis in post-natal humans remains a source of much debate. On one extreme, the very existence of postnatal neurogenesis and plasticity is questioned [26, 112]. Some of what is understood is derived from animal studies and clearly these do not translate a priori in humans. Nonetheless, resultant observations and insights gained can be the basis of future hypothesis-driven work.

Further studies are indicated. While it is hoped that a "dementia pandemic" does not follow, it is perhaps too early to know the natural history of neurological damage post-COVID-19 [113-115]. Principally, large prospective, collaborative studies will inform the direction that future research will take in COVID-19 and beyond.

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Conflicts of interest:

None to report

Figure legends:

Figure 1: Neural stem cells residing in periventricular niches are the substrate of neurogenesis. Under physiological conditions endogenous neurogenesis has been proposed to contribute to maintaining and regenerating olfaction, as well as promoting normal cognition, learning and memory. Specific impairments in these processes in COVID-19 – impaired olfaction and cognition – may implicate the SARS-CoV-2 virus in attenuating neurogenesis. Furthermore, neurogenesis has been linked with neuroregeneration; and impaired neuroregeneration has previously been linked with neurodegenerative diseases. Emerging evidence supports an association between COVID-19 infection and accelerated neurodegeneration. This paper proposes the hypothesis that SARS-CoV-2 infection may impair endogenous neural stem cell activity. An attenuation of neurogenesis may contribute

to reduction in brain size and/or neurodegenerative processes following SARS-CoV-2 infection.

Figure 2: The SARS-CoV-2 virus has been shown to infect and replicate in neural stem cells, resulting in significant attenuation of their viability and proliferative turnover. Neural stem cells and/or their derivatives are thought to be the cells of origin in glioma, namely brain tumour stem cells or glioma stem cells. Neural stem cells and glioma stem cells share a multitude of molecular similarities – a particular predilection of SARS-CoV-2 in the death of neural stem cells, may translate in suppression of glioma stem cells which propagate brain tumours.

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Highlights:

- COVID-19 associated impairment in neural stem cell activity may contribute to cognitive impairment and hyposmia
- Neural stem cell dysfunction may be a neuropathological link between neurodegeneration and hyposmia
- Therapeutic upregulation of neural stem cell activity may improve symptoms of long COVID
- SARS-CoV-2 may have a role in oncolytic virotherapy by targeting brain tumour stem cells