

## Does COVID19 infect the brain? If so, smokers might be at a higher risk

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Running Title: Coronavirus in the brain and the impact of smoking

### Abbreviations:

SARS: Severe acute respiratory syndrome; CoV: coronavirus; nAChR: nicotinic acetylcholine receptor; ACE: angiotensin converting enzyme

### Abstract

COVID19 is a devastating global pandemic with epicenters in China, Italy, Spain, and now the United States. While the majority of infected cases appear mild, in some cases individuals present serious cardiorespiratory complications with possible long-term lung damage. Infected individuals report a range of symptoms from headaches to shortness of breath to taste and smell loss. To that end, less is known about the how the virus may impact different organ systems. The SARS-CoV2 virus, which is responsible for COVID19, is highly similar to SARS-CoV. Both viruses have evolved an ability to enter host cells through direct interaction with the angiotensin converting enzyme 2 (ACE2) protein at the surface of many cells. Published findings indicate that SARS-CoV can enter the human nervous system with evidence from both postmortem brains and detection in cerebrospinal fluid of infected individuals. Here we consider the ability of SARS-CoV2 to enter and infect the human nervous system based on the strong expression of the ACE2 target throughout the brain. Moreover, we predict that nicotine exposure through various kinds of smoking (cigarettes, e-cigarettes, or vape) can increase the risk for COVID19 neuroinfection based on known functional interactions between the nicotinic receptor and ACE2. We advocate for higher surveillance and analysis of neuro-complications in infected cases.

**Significance Statement:** The COVID19 epidemic has spurred a global public health crisis. While many of the cases requiring hospitalization and intensive medical care center on cardiorespiratory treatment, a growing number of cases present neurological symptoms. Viral entry into the brain now appears a strong possibility with deleterious consequences and an urgent need for addressing.

COVID19 belongs to a family of Corona Viruses (CoV) that have evolved in various species (Lam *et al.*, 2016). Human infecting CoV such as SARS and COVID19 have acquired ability to bind the angiotensin converting enzyme 2 (ACE2) on epithelial cells as a primary mechanism of entry into the host (Qi *et al.*, 2020). Critical cases of COVID19 infection commonly manifest as cardiopulmonary symptoms and in severe cases advance into organ failure and sepsis as a result of a “cytokine storm” over activation of the immune system (Guan *et al.*, 2020). The case fatality rate is still unclear but likely anywhere from 0.4-4% and depends critically on the ability of

public health systems to provide intensive supportive care. Recently we have raised the question of whether nicotine exposure through cigarette smoke (and other formulas) is a co-morbidity factor in COVID19 infection and clinical outcome (Olds and Kabbani, 2020). Functional interactions between nicotine exposure and ACE2 expression in lungs and other organ systems such as heart and kidneys, as well as nicotine and other components of the renin angiotensin system (RAS) suggest that smoking can promote COVID19 cellular entry through nicotinic acetylcholine receptor (nAChR) signaling. Notably, nAChRs are known to be on many of the same cells that express ACE2 in the lungs, kidneys, circulation, and in brain (Changeux, 2010; Tolu *et al.*, 2013; Nordman *et al.*, 2014). Thus, smoking can impact COVID19 pathophysiology and clinical outcome in several organ systems.

Differential host factors like age, health, simultaneous infection and genetics are known determinants of susceptibility to a viral infection. Smoking is a strong factor in predicting an individual's likelihood of developing and managing a viral infection and especially a respiratory infection (Razani-Boroujerdi *et al.*, 2004; Eddleston *et al.*, 2010). Here we raise the question of nicotine associated comorbidity to COVID19 in the context of the brain based on published evidence that the viral target receptor ACE2 is expressed in the brain and functionally interacts with nAChRs (Ferrari *et al.*, 2007; J.M. *et al.*, 2018). We consider if neural cells, like epithelial cells, are more vulnerable to infection in smokers because nicotine stimulation of the nAChR can increase ACE2 expression within them (Olds and Kabbani, 2020). This issue is critical because evidence shows that mRNA from the closely related SARS virus, which also binds ACE2 as a mechanism of cell entry, was detected in brain and cerebrospinal fluid of infected individuals (Zhang *et al.*, 2003; Chong *et al.*, 2004; Inoue *et al.*, 2007). Moreover, SARS ability to enter neurons is established in experimental systems using recombinant human ACE2 as the point of entry (Netland *et al.*, 2008; Kaparianos and Argyropoulou, 2011).

Now is the time to ask if infection with COVID19 can result in long-term neural damage in both symptomatic and asymptomatic individuals and if chronic nicotine exposure through smoking habits and addiction increases risk of developing COVID19 associated neuropathology through interactions between nAChRs and ACE2 in neurons and glia.

Functional interaction between nicotine and components of the RAS (such as ACE2) are well established in several organ systems including the lungs where smoking is found to impact cardiopulmonary health (Ferrari *et al.*, 2008; Virdis *et al.*, 2010; R.M. *et al.*, 2018). Similar RAS components also exist in the human brain and nicotine exposure is documented to modulate RAS activity in areas as the hypothalamus and brain stem leading to changes in endocrine release as well as hypertension, respectively (Ferrari *et al.*, 2007; J.M. *et al.*, 2018). In the brain as elsewhere ACE2 metabolizes angiotensin II to produce angiotensin 1-7 and this process occurs in neurons as well as astrocytes (Hung *et al.*, 2016). ACE2 signaling is widely thought to oppose oxidative stress and neuroinflammation and disruption in ACE function and balance can drive neurodegeneration of dopaminergic neurons (Labandeira-García *et al.*, 2014). ACE activity may also contribute to cortical cholinergic pathways and participate in the progression of Alzheimer's disease (Kehoe *et al.*, 2009). Figure 1 depicts areas of notable ACE2 mRNA expression such as the cortex, striatum, hypothalamus, and brainstem within the adult human brain as based on microarray data from the Allen Brain Atlas (Jones *et al.*, 2009). These regions, which are known to also express various types of nAChRs (Dani and Bertrand, 2007) are putative sites for primary

infection with COVID19 in the human brain. Interactions between nAChRs and ACE2 have been studied in several of these regions including the ventrolateral medulla (Deng *et al.*, 2019), and smoking may lead to enhanced viral infection through the ability of nicotine to upregulate nAChRs in regions such as the lungs (Plummer *et al.*, 2005; Thorgeirsson *et al.*, 2008; Changeux, 2010). In this case, upregulation of nAChRs in either/both neurons and astrocytes could promote greater viral entry and replication through augmented ACE2 expression in the cell (Fig. 2A).

In conclusion, we suggest, that were COVID19 to breach the blood brain barrier (as evidence suggests for SARS) during the course of ongoing infection, interactions with ACE2 in multiple brain regions would present the virus the opportunity to infect the brain of COVID19 patients. Disruptions to the blood brain barrier may especially be more probable in severe cases of infection and associated with strong immunological responses such as the cytokine storm pathologies as well as adenovirus co-infection (Channappanavar and Perlman, 2017). In one scenario, neural cells could serve as latent reservoirs for the virus, but also produce debilitating neurological symptoms with adverse affect on vascular homeostasis, adaptive immunological responses, and cognitive function (Fig 2). Supporting our concern, a recent report suggests that over 30% of 814 retrospectively studied COVID19 patients showed neurological symptoms (Mao *et al.*, 2020). The above supports the notion that COVID19 may pose a risk for brain infections and suggest that smokers, as well as immune compromised individuals are at higher risk for neurological complications. The evidence calls for careful studies on post-mortem COVID19 patient's brains and for continued surveillance for signatures of the virus beyond lung, cardiac, and renal tissue. Future studies should also include a post-mortem analysis of brains from smokers *vs*, non-smokers.

Author Contribution: NK and JLO wrote the paper.

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## Figure legends

**Figure 1.** Images taken from the Allen Human Brain Atlas (<http://www.proteinatlas.org>) show the expression of the CoV target ACE2 in the adult human brain. ACE2 mRNA distribution is widespread throughout the brain with notable strong expression in some of the indicated regions. Images shown are from a search for the human adult ACE2 gene ([http://human.brain-map.org/microarray/search/show?exact\\_match=true&search\\_term=ACE2&search\\_type=gene&donors=10021,15496,14380,12876,9861,15697](http://human.brain-map.org/microarray/search/show?exact_match=true&search_term=ACE2&search_type=gene&donors=10021,15496,14380,12876,9861,15697)). Areas of possible COVID19 infection include the cortex, striatum, hypothalamus, medulla, and brainstem nuclei important for hearing and balance.

**Figure 2.** Mechanisms of ACE2 entry and COVID19 infection in neural cells. A. A role for nicotine associated upregulation of nAChRs in ACE2 expressing astrocytes and neurons. Based on published findings, upregulation of nAChRs can also increase ACE2 cell surface expression thereby enhancing viral entry and infection. B. A putative clinical timeline for progression of COVID19 into the brain.

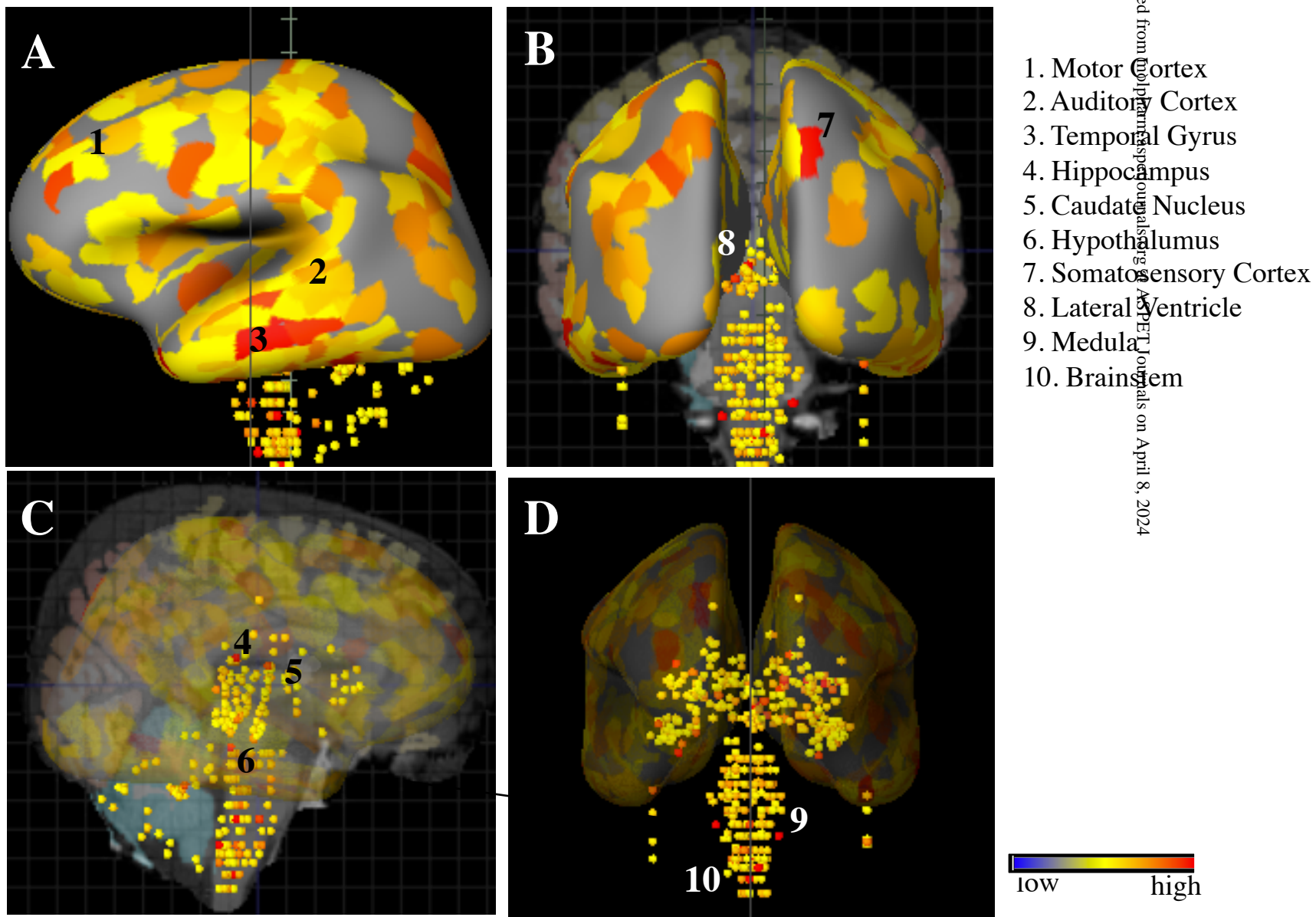


Figure 1

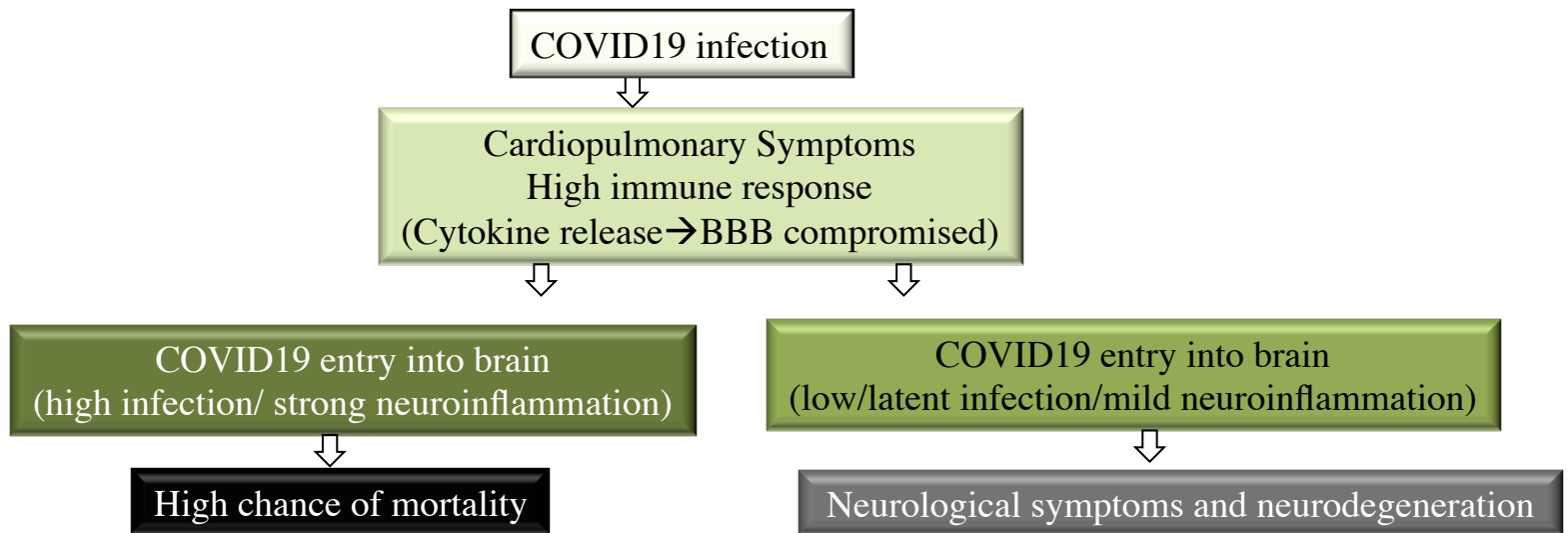
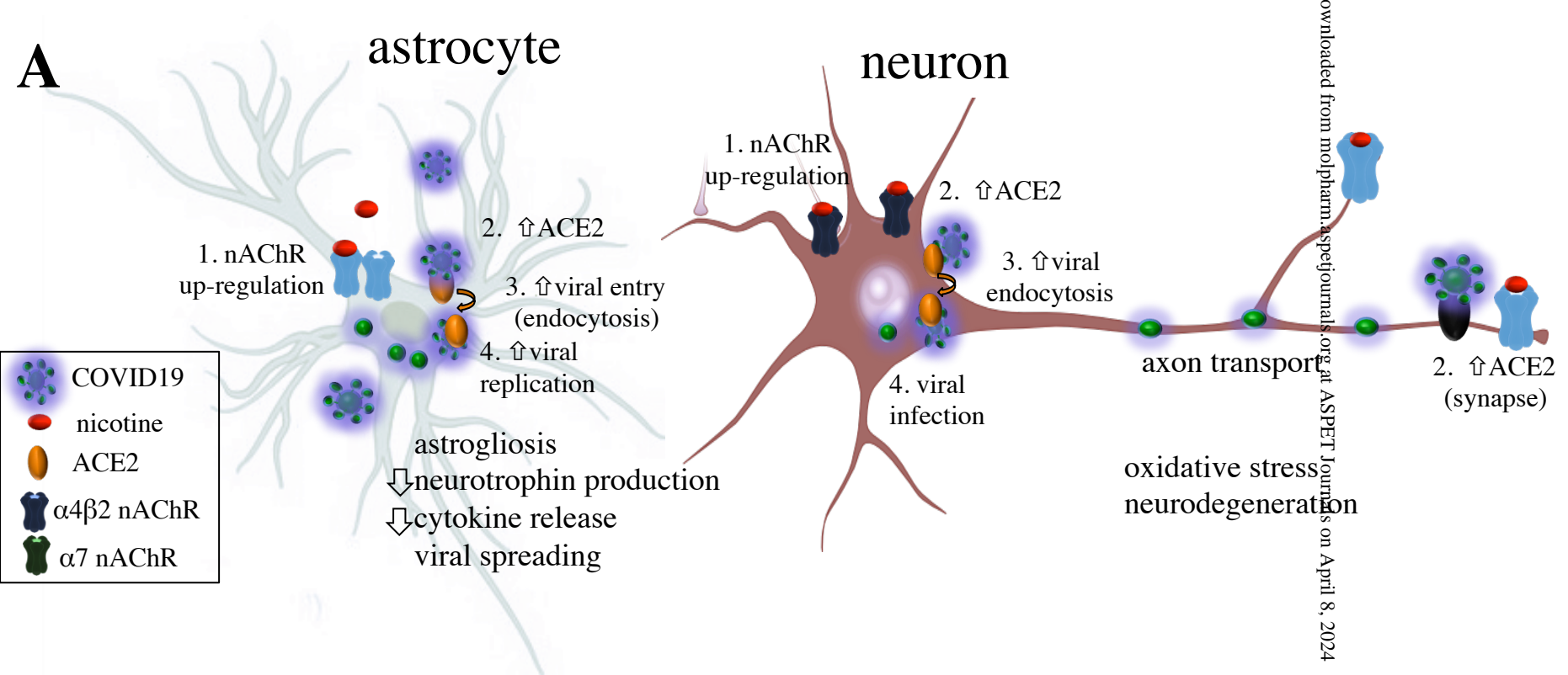


Figure 2