Bachelor Thesis

Neurological manifestations of SARS-CoV-2 with special focus on anosmia

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Annotation:

The overall aim of the thesis is to explore and categorize currently known neurological symptoms associated with SARS-CoV-2 infection. It should be delved in more detail in SARS-CoV-2-associated loss off smell that has been reported, which is in some countries used as a marker for COVID-19. In particular, the existing evidence should be weighed for neuronal and non-neuronal origin of anosmia, and it should be hinted on the possible mechanism underlying this olfactory perturbation.

Declaration:

I hereby declare that I have worked on my bachelor's thesis independently and used only the sources listed in the bibliography. I hereby declare that, in accordance with Article 47b of Act No. 111/1998 in the valid wording, I agree with the publication of my bachelor thesis, in full form resulting from deletion of indicated parts to be kept in the Faculty of Science archive, in electronic form in a publicly accessible part of the IS STAG database operated by the University of South Bohemia in České Budějovice accessible through its web pages. Further, I agree to the electronic publication of the comments of my supervisor and thesis opponents and the record of the proceedings and results of the thesis defence in accordance with aforementioned Act No. 111/1998. I also agree to the comparison of the text of my thesis with the Theses.cz thesis database operated by the National Registry of University Theses and a plagiarism detection system.

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Abstract

In this thesis, I focused on summarizing previous data about neurological features of SARS-CoV-2 infection and trying to explain a possible mechanism. A special focus was put on the neurological symptom anosmia - lost sense of smell.

It has been shown that SARS-CoV-2 can invade many different cells throughout the human body because of the distribution of its target receptor, ACE2, which could be explaining the diversity of obtained symptoms. It has been shown that SARS-CoV-2 has a similar entry mechanism when compared to SARS-CoV.

Neurological involvement can be caused by direct consequences of the virus affecting the neurons, or indirectly by exerting its actions via cytokines.

The main target for anosmia is most probably the pericytes and glial cells which are either damaged or transferring virus particles through transport of the olfactory system.

Further research should be done in this field to be able to understand the neurotropic mechanisms of SARS-CoV-2.

Aim

Theory

I. INTRODUCTION

Coronaviruses (CoVs) are a group of RNA viruses affecting mammals and have been known for over half a century (Lam et al., 2020). Several animal coronaviruses were discovered by medical researchers even before the first human coronavirus was identified in 1965 (Kahn et al., 2005). Meanwhile, dozens of other coronaviruses have been discovered in wildlife, livestock, and humans. Human coronaviruses (HCoV) such as HCoV-OC43 and HCoV-229E are responsible for up to almost every third case of common colds (Myint, 1995).

Coronaviruses have caused several other epidemics in the past, namely in 2002 severe acute respiratory syndrome (SARS) and in 2012, the Middle East respiratory syndrome (MERS).

SARS-CoV-2 is the new Coronavirus that emerged at the end of 2019 in China. It was first reported in late December 2019 in Wuhan, China. On February 11, 2020, a taxonomic designation "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) became the official name to refer to the virus strain. A detailed classification can be found in Table 1. The novel Coronavirus, SARS-CoV-2, causes the disease called Coronavirus disease 2019 (COVID-19) and has spread across the world causing the current pandemic (Timeline of Covid-19, WHO, 2020).

Realm:	Riboviria
Kingdom:	Orthornavirae
Phylum:	Pisuviricota
Class:	Pisoniviricetes
Order:	Nidovirales
Family:	Coronaviruses
Genus:	Betacoronaviruses
Subgenus:	Sarbecovirus
Species:	Severe acute respiratory syndrome-related coronavirus
Strain:	Severe acute respiratory syndrome coronavirus 2

TABLE 1, Virus Classification of SARS-CoV-2

The RNA sequence of SARS-CoV-2 from patients tested positive for COVID-19 throughout the world was isolated, identified, and compared to the RNA sequences of already known

coronaviruses. 8249 different genomes of SARS-CoV-2 have been globally isolated between December 2019 and June 2020 and the structure of the first successfully isolated and sequenced genome of SARS-CoV-2, called Wuhan-Hu-1, is displayed in Figure 1 (Nextstrain, accessed June 2020).

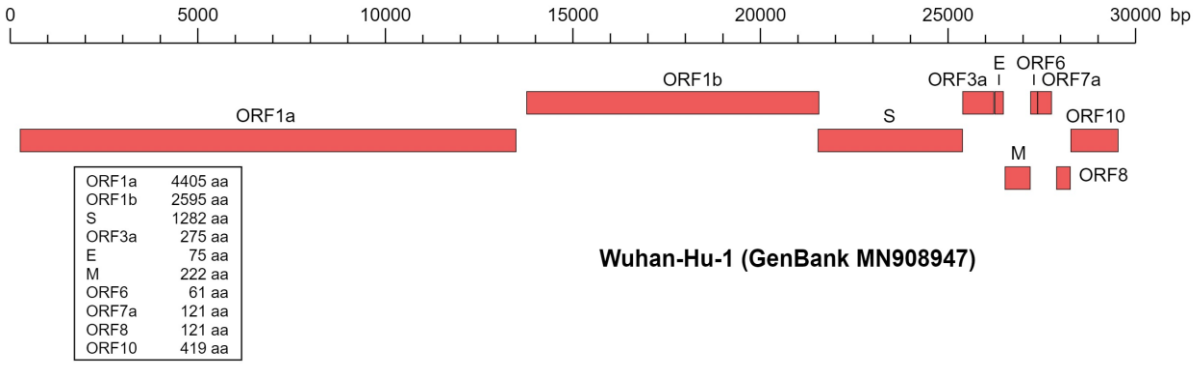

FIGURE 1, Genome of first isolate of SARS-CoV-2, Wuhan-Hu-1; GenBank Acc MN908947; Wikiwand.com

All collected information until now corroborate a natural animal origin (zoonotic origin) of SARS-CoV-2 in humans, most likely from bats, and vitiates that the virus has its origin in a laboratory (Andersen et al, 2020). SARS-CoV-2 has also been reported in minks, tigers, cats and dogs (avma.org, 2020).

As the contact between humans and bats is usually very low, scientists expect that virus transmission occurred through another species, which was believed to be pangolins (Lam et al., 2020).

SARS-CoV-2 has an incubation time of around 5 days. After that, the first symptoms start to show, most prominently dry cough, fever and fatigue; a rather unusual symptom is the disability to smell (anosmia) which may indicate a neurological invasion by SARS–CoV-2. In order to minimize the distribution of this virus, it is necessary to be able to diagnose it in the early stages, which can be done by diagnosing anosmia as one of the key characteristics, since the amount of people suffering from this symptom is as high as 66% of all tested positive.

II. STRUCTURE AND REPLICATION OF CORONAVIRUSES

1. Structure

Coronaviruses are the largest known group of RNA viruses usually consisting of a ~30 kb (kilobases) long positive-sense single-stranded RNA (+ssRNA) strain with a 3'-poly-A tail and 5'-cap structure (Khailany et al., 2020; Marra et al., 2003). Considering its length, coronaviruses are very untypical viruses because the genome of RNA viruses usually consists of less than 10kb. RNA compared to DNA viruses have a much higher mutation rate (Belshaw et al., 2007).

The genome of SARS-CoV-2 is a 29,903 bp (basepairs) ss-RNA coronavirus, with ID NC_045512. Analysis of SARS-CoV-2 also shows that it belongs to the genera of betacoronaviruses. In Figure 2A it can be seen that SARS-CoV-2 is more closely related to bat-SL-CoV ZC45 and bat-SL-CoV ZXC21. On the other side, SARS-CoV-2 is more distantly related to SARS-CoV (80% similarity, Xu J et al, 2020a), the virus behind the 2003 outbreak of SARS.

Typically, the RNA of coronaviruses code for at least 6 ORFs (*open reading frames*). The first *orf*s (orf1a/b) occupy already two thirds of the whole genome and encodes 16 NSPs (*non-structural proteins*). Two polypeptides, PP1a and PP1ab are created due to a -1 frameshift between *orf1a* and *orf1b* and further processed into 16 NSPs (Masters, 2006; Ziebuhr J et al, 2000).

On the other third of the genome near the 3' end are ORFs located that encode for at least four main structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins (detailed explanation in Chapter 2.2 "Functions of Proteins"). As this is true for all coronaviruses, different coronaviruses may produce different additional structural and accessory proteins, which are all translated from subgenomic RNA (sgRNA) (Hussain et al, 2005).

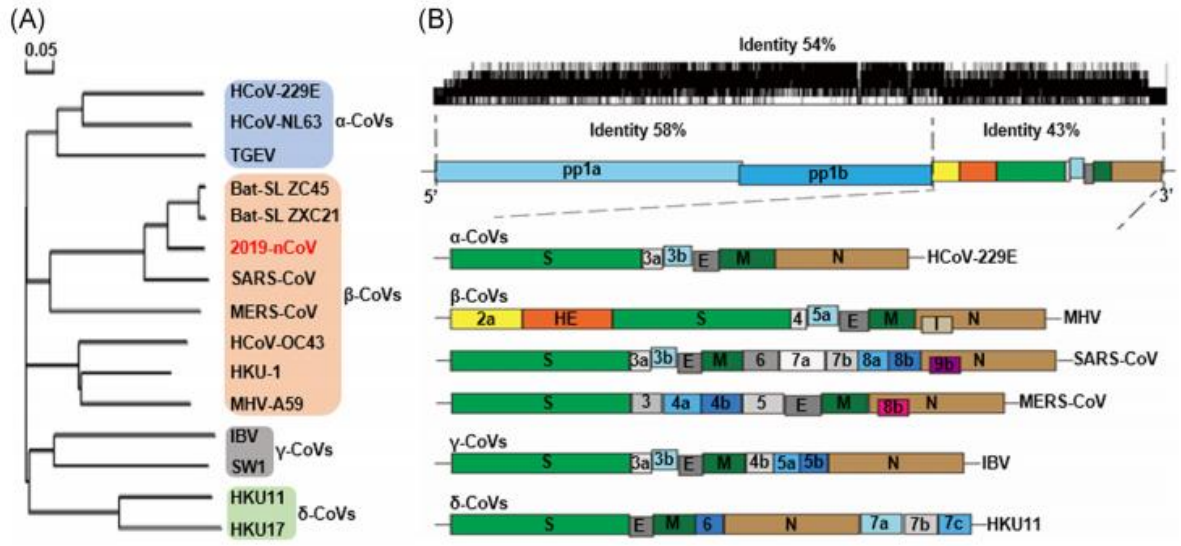

FIGURE 2: The genomic structure and phylogenetic tree of coronaviruses. A. The phylogenetic tree of representative Coronaviruses, with the new coronavirus, SARS-CoV-2, highlighted as 2019-nCov in red. B. The genome structure of four genera of coronaviruses. Pp1a und pp1b represent the two long polypeptides that are processed into 16 nonstructural proteins. S, E, M, and N indicate the four structural proteins spike, envelope, membrane, and nucleocapsid. 2019-nCov, SARS-CoV-2; CoVs, coronavirus; He, hemagglutinin-esterase. Viral names: HKU, coronaviruses identified by Hong Kong University; HCov, human coronavirus; IBV, infectious bronchitis virus; MHV, murine hepatitis virus; TGEV, transmissible gastroenteritis virus, (Chen Y et al, 2020).

2. Replication

2.1 Replication of Coronaviruses

The most important steps of the Replication of Coronaviruses are the following:

- RNA is used as a template to directly translate *pp1a* and *pp1ab* (Polyprotein 1a/1ab), which holds the information of NSPs to form a replication-transcription complex (RTC) in a double membrane vesicles (DMVs) (Snijder et al, 2006).
- Next, RTC initiates discontinuous transcription which is followed by the synthesis of sgRNAs, (Hussain et al, 2005). These subgenomic messenger RNAs (mRNAs) possess common 5′-leader and 3′-terminal sequences.
- The end of transcription and following leader RNA acquisition takes place between open reading frames ORFs. Subgenomic mRNAs are produced by these minus-strand sgRNAs (Sawicki et al, 2007; Perlman et al, 2009).

2.2 Functions of Proteins

Most of the NSPs play an important role during replication while some nsps' function is still unknown.

For virion assembly and infection of CoV, four structural proteins (Figure 3B) are important:

- S-protein homotrimers are spikes on the viral surface, which are used to bind to host receptors (Figure 3) (Beniac et al, 2006; Delmas et al, 1990).
- The M-protein contains three transmembrane domains. It is responsible for the virion shapes, binding to the nucleocapsid and it promotes membrane curvature (Nal et al, 2005; Neumann et al, 2011).
- The transmembrane E-protein is involved in viral pathogenesis and triggers virus assembly and release (DeDiego et al, 2007; Nieto-Torres et al, 2014).
- The N-protein can bind virus RNA genome with both of its two domains via different mechanisms. The N-protein has the ability to bind to an NSP3 protein, which helps to tie the genome and RTC together. The encapsulated genome can then be packed into virions (Fehr et al, 2015; Chang et al, 2006; Hurst et al, 2009). N also appears to be beneficial for the replication of the virus with its abilities of a viral encoded repressor of RNA interference and antagonist of interferon (IFN) (Cui et al, 2015).

For SARS-CoV-2, the transmembrane E-protein is probably located on the endoplasmatic reticulum (ER). The Golgi intermediate compartment and Golgi membranes bind to two members of the bromodomain and extra-terminal domain family. These bind further to acetylated histones to regulate transcription (Faivre et al., 2020). The C-terminal region of the E-protein probably has a sustaining function as it looks like the N-term of histone H3. Histone H3 is interacting with bromodomains (Filippakopoulos et al., 2020).

SARS-CoV-2's N-protein binds to the stress granule proteins, a formation of proteins and RNA in the cytosol, whose formation is thought to be a primary antiviral response. The N-protein also binds to other host mRNA-binding proteins. It is natural for *Coronaviridae* to manipulate the stress granule and the related RNA biology (Nakagawa et. al., 2018; Raaben et al., 2007; Thompson et al., 2019).

A B

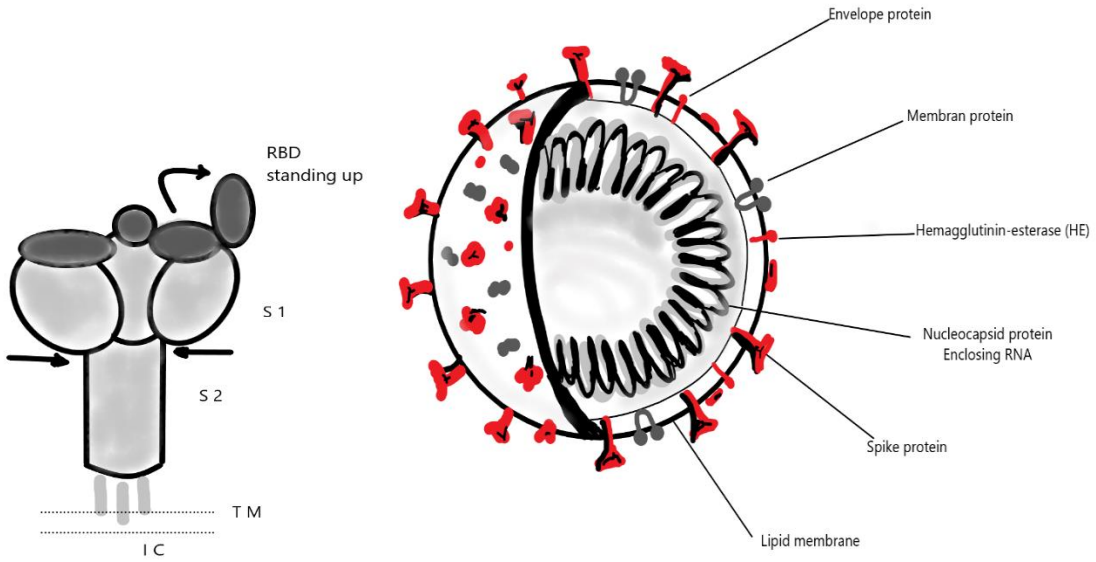

FIGURE 3: A: Spike Protein of SARS-CoV-2; RBD, receptor binding domain; S1, receptor-binding subunit; S2, membrane fusion subunit; TM, transmembrane anchor; IC, intracellular tail; B: SARS-CoV-2 Virion; (simplified and adapted from Shang et al., 2020)

2.3 Target Proteins in human

SARS-CoV's S-Protein is known to target angiotensin converting enzyme 2 (ACE2). A SARS-CoV-2 Spike-protein modeling indicates enough affinity to the ACE2 receptor to explain a mechanism of cell entry in human,(Xu et al, 2020).

SARS-CoV-2 S-Protein was shown to bind to the endogenously expressing hACE2 cells, Calu-3 cells (human lung epithelial cells) and MRC-5 cells (human lung fibroblast cells), as well as the exogenously expressing hACE2 HeLa cells (human cervical cells).

ACE2 belongs to the family of angiotensin-converting enzymes of dipeptidyl-carboxydipeptidase and appears to be very similar to angiotensin converting enzyme 1 (ACE1). Both, ACE1 and ACE2, produce angiotensin (Ang) 1-9 from angiotensin 1 and Ang 1-7 from angiotensin 2. A lot of physiological functions, like blood pressure, fluid balance, inflammatory response, are triggered by ACE2 (Zhang et al., 2020). As mentioned above, ACE2 is particularly expressed in many organs and tissues leading to the assumption that it is a cruicial enzyme in cardiovascular, renal and reproductive functions (Richards et al., 2018; Hamming et al., 2004).

Hamming et al, 2004, explored where the ACE2 protein is located in various human organs (oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain). They found a surface expression of ACE2 protein on lung alveolar epithelial cells and enterocytes of the small intestine. ACE2 was also present in all the organ systems analyzed, in arterial and vein endothelial cells, and in vascular smooth muscle cells (Igase et al., 2008). ACE2 expressions have also been found in other systems in the human body, suggesting that, besides the respiratory system, the virus SARS-CoV-2 also targets digestive system, urogenital system, central nervous system (CNS), and circulatory system (Hamming et al., 2004). ACE2 receptors detected in glial cells and neurons (Gallagher et al., 2006), were reported to be expressed by the brain, making it a potential target for COVID-19. The great distribution of ACE2 in combination with the cell entry mechanism of SARS-CoV-2 explains the huge variety of pulmonary and gastrointestinal symptoms associated with COVID-19.

Patients with acute SARS-CoV illness have also demonstrated the presence of the virus in cerebrospinal fluid (Chin Neuro, 2020). SARS-CoV was also found to be present in the gastrointestinal tract because traces of its RNA were found in stool explaining diarrhea as possible symptom (Mao et al, 2020). The human digestive tract also possesses ACE2 receptors making it a possible target for SARS-CoV-2.

Viral nucleic acid of SARS-Cov-2 was found in patients´ cerebrospinal fluid and in their brain tissue. Moreover, SARS-CoV-2 was found in urine, blood and oropharyngeal swab samples from people tested positive for the virus (Peng et al, 2020). Because of this, it is suggested that the novel Coronavirus may be transported by blood flow and could reach the CNS via the brain-blood barrier (Li et al., 2020).

3. Cell entry mechanism

To invade a cell, the coronavirus binds to a receptor on the surface of the cell, subsequently enter endosomes and finally, fuse lysosomal and viral membranes (Figure 4) (Li, 2016; Perlman et al., 2009). The cell entry of coronaviruses is regulated by a spike protein, which is attached to the surface of the virus and on fully developed viruses the spike exists as a trimer (see Figure 3). This trimer has a membrane fusion subunit (S2) stalk for trimeric membrane fusion and on top, three receptor-binding subunit (S1) heads, which are responsible for receptor-binding. It is important to understand the mechanism of cell entry as the

understanding of how a virus enters the cell is one of the main targets for drug development against SARS-CoV-2.

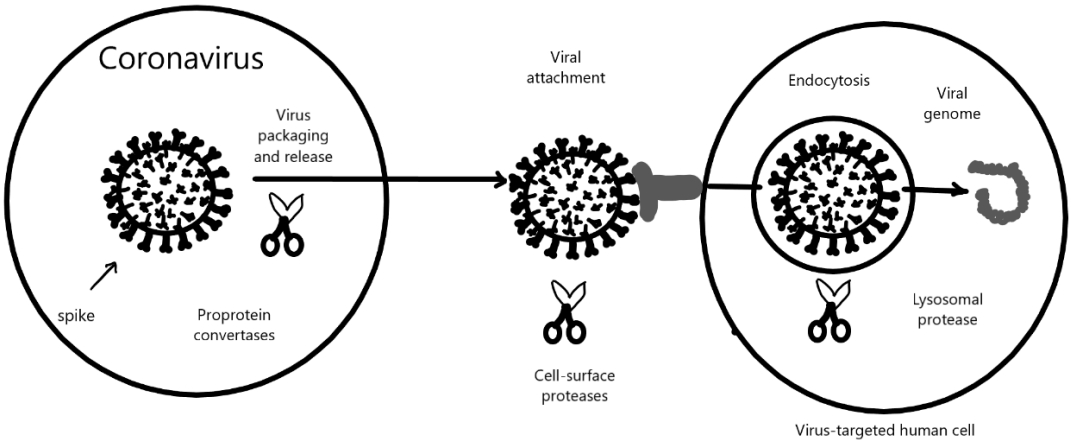

FIGURE 4, Viral exit of SARS-CoV-2 from a human cell, viral attachment onto hACE2 receptor, followed by viral entry of the endosome and fusion with human lysosome, release of viral genome (simplified and adapted from Shang et al., 2020)

RBD hiding:

Coronaviruses usually hide their crucial parts and RBD (receptor-binding domain) using 2 methods. The first one is called conformational masking and here the virus covers its RBD in surface depressions (canyon-like structures), which are inaccessible for antigens (Rossmann, 1989).

In the second one, glycan shielding, the virus is hiding its crucial parts of its spike behind glycan cluster (Vigerust et al., 2007).

Conformational masking is one of the hiding strategies of SARS-CoV-2 and takes part in immune evasion. It is expected that a hidden RBD leads to poor recognition of the host receptor and inefficient entry. SARS-CoV-2 coped this by evolving a RBD with high hACE2 binding affinity and a Furin motif for spike preactivation, (Shang et al., 2020). Furin, a proprotein convertase, preactivates other proteins resulting in an easier cell entry. Preactivation of Furin occurs by removing some sections of the translated, inactive proteins making them active. Furin can be found in the Golgi apparatus (Thomas, 2002).

3.1. Mechanism of cell entry for SARS-CoV

The S1 head of SARS-CoV includes a receptor binding domain (RBD) which individually identifies angiotensin-converting enzyme 2 as its receptor and binds to it (Li, 2015; Li et al.,

2003; Li et al., 2005). The RBD can either be in an upstanding state for receptor binding, or a down lying state for immune evasion. The state of the RBDs switches between those (Yuan et al., 2017; Gui et al., 2017).

The spike needs to be proteolytically activated to be able to fuse membranes. The activation needs to take place at the S1/2 boundary where the S1 dissociates and the S2 undergoes a drastic change in structure. SARS-CoV interacts with human cell surface transmembrane protease, serin 2 (TMPRSS2) and lysosomal proteases cathepsins excluding Furin in order to enter the cell (Shang et al, 2020).

3.2 Mechanism of cell entry for SARS-CoV-2

3.2.1 Receptor binding

SARS-CoV-2 targets human ACE2 (hACE2) as its receptor as well but the crystal structure of its RBD revealed a higher binding affinity than SARS-CoV RBD. Nevertheless, SARS-CoV-2 RBD is mostly in the down lying state (Figure 5) which means ineffective receptor binding (Gui M et al, 2017). Also, TMPRSS2 and lysosomal proteases are important for SARS-CoV-2 entry. Although SARS-CoV-2 has a proprotein convertase (PPC) motif at the S1/2 boundary (see Figure 3A) of the S-protein , PPC cleavage of the S-protein does not improve cell entry (Shang et al, 2020), but preactivation by furin does.

Although its RBD has a higher binding affinity, SARS-CoV-2's overall spike has a lower binding affinity and is less accessible than the S of SARS-CoV. Because of this, SARS-CoV-2 must have a second strategy additional to receptor-binding to keep its high infectivity (Shang et al., 2020).

3.2.2 Host protease activation

The entry of SARS-CoV-2 is activated by both, TMPRSS2 and lysosomal cathepsins which have cumulative effects with Furin. Furin preactivation increases its ability to enter some cells - preferably cells with low lysosomal cathepsin and/or TMPRSS2 expressions (Shang et al., 2020). Because of its ability of preactivation, SARS-CoV-2 is less dependent on target cells.

Protease activation leads to the irreversible, tightly regulated, final structural change in S2 needed for membrane fusion. On SARS-CoV-2 particles, most of the spikes already went through the process of structural change (Liu et al., 2020)

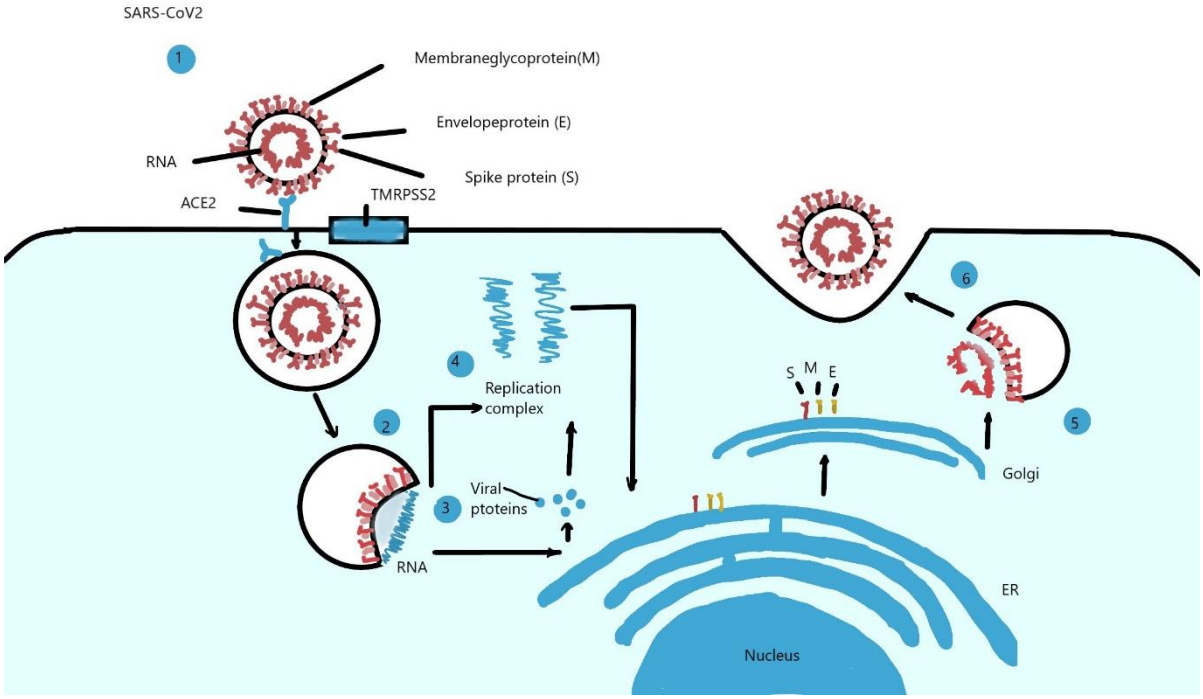

FIGURE 5: SARS-CoV-2 invading a cell. 1) entry. 2) RNA release of virus and membrane fusion. 3) Translation. 4) Proteins from step 3 and RNA from step 2 produce more RNA by forming a replication complex. 5) Packing in Golgi. 6) Release of SARS-CoV-2. (adapted and modified from Zhang et al., 2020)

III. COVID-19

COVID-19 is the name of the disease caused by the virus SARS-CoV-2 (Coronavirus disease 2019). As of 08.08.2020, there were 19.5 million people with confirmed SARS-CoV-2 infection (ecdc.europa.eu). Around 10.2 million people recovered, and 674,000 people died from COVID-19 so far. The case fatality rate (CFR) is the number of confirmed infections divided by the number of confirmed deaths and for COVID-19, it differs by location. The CFR is reflecting the severity of a disease at a specific time, in a specific population and a specific context, i.e. the case fatality rate of Czech Republic or Austria from July 31st, 2020 is 2.3% and 3.4% (can be seen in Figure 6).

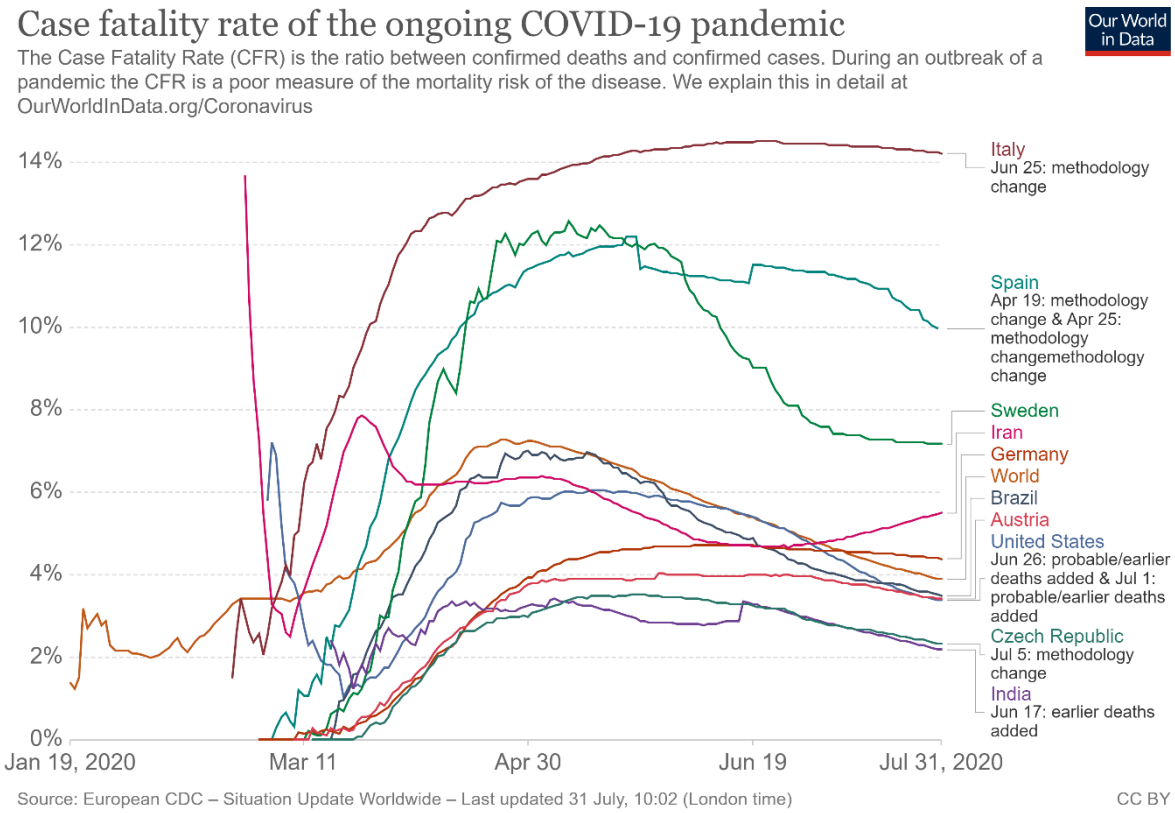

FIGURE 6: Case fatality rate of different countries over time; (Ourworldindata.org)

1. Symptoms and targeted organs

The main common symptoms of the disease COVID-19 referring to the world include fever, dry cough, and others and are listed in Table 2:

Symptoms	**% of people with symptoms**
Fever	78
Cough	57
Fatigue	31
Anosmia	66
Difficulty in breathing	23

TABLE 2: Common symptoms of 24,410 symptomatic adults infected worldwide by COVID-19; Grant M.C. et al., 2020

Besides the common symptoms, there is also a wide variety of other symptoms of patients with confirmed COVID-19 (see Table 3 below). Importantly, 40-45 % of infected people show

no symptoms at all and they can transmit the virus to others for more than 14 days, (Oran. et al., 2020).

Physiological tracts and systems	**Major symptoms**	**% of infected patients**	**References**
Respiratory system			
	Cough	57	Grant M.C. et al., 2020
	Shortness of breath	18.6	Report of WHO China, (02.2020)
	Sore throat	13.9	
Digestive system			
	Diarrhea	19.4	Han C. et al., 2020
	Vomiting	3.6- 15.9	Tian Y. et al., 2020
	Loss of appetite	39.9- 50.2	
Neurological symptoms			
	See Table 4 below		
Immune system			
(for people suffering from autoimmune disease)	Pneumonia	Up to 20	Ehrenfeld et al, 2020
Other…	Headache	13.6	Report of WHO China, (02.2020)
	Chills	11.4	

TABLE 3: List of the most important symptoms with the disease COVID-19 referred to attacked systems

After the average incubation time of about five days, the first symptoms such as fever, cough, fatigue, headache, show among others. Symptoms for extreme cases are pneumonia, acute respiratory distress syndrome, acute cardiac problems, and multiorgan failure (Rothan H.A. et al, 2020).

Also very specific types of symptoms have been characterized. Neurological manifestations like febrile seizures, convulsions, change in mental status, and encephalitis have been associated with SARS-CoV-2 and other respiratory viruses (Desforges et al, 2020; Bohmwald et al., 2018). A study posted in medRxiv (Mao L et al., 2020) that involved 214 patients has reported neurological manifestations in 78 (36.4%) COVID-19 patients.

Some prior, chronic diseases like hypertension, kidney disease or diabetes are correlated with increasing the mortality and severity of COVID-19. On the other hand, no correlation between the severity and chronic liver disease was found while acute cardiac and liver injury are extraordinarily associated with severity (Liu H. et al., 2020)

2. Neurological symptoms

Neurological manifestation can be due to direct or indirect effects of the virus on the nervous system. Direct effects mean that the virus is causing the damage at the neurons. Indirect effects would be after the disease because of the change of immune responses caused by the virus. Neurological manifestations like occasional PNS and CNS diseases have already been associated with SARS-CoV-2's relatives, SARS and MERS (Ellul et al., 2020). According to the current situation, it is expected to have between 3,610 and 19,342 patients with CNS and between 4,814 and 15,474 patients with PNS complications (assumption: 9,6 million cases, Ellul et al, 2020). As for now, August 2020, neurological manifestations (Table 4) of SARS-CoV- 2 have been found in the CNS, PNS, and vasculature and psychiatric diseases have been associated with COVID-19 (Ellul et al, 2020).

Description	**Conditions**	**%**
Cerebrovascular manifestation	Retrospective series from Wuhan, out of 221 (Li Y et al, 2020)	6%
Ischaemic stroke		5%
Intracerebral haemorrhage		<1%

Cerebral venous sinus thrombosis		<1
stroke	388 patients (Lodigiani et al, 2020)	2%
Encephalopathy	901 patients (Ellul et al, 2020)	10%
Thereof encephalitis		<1%
Peripheral Nervous System		
Guillian-Barré syndrome	214 infected (Mao et al, 2020)	9%
Olfactory dysfunction	417 patients (Lechien et al, 2020)	86%
Gustatory disorders		82%
Central nervous system	Wuhan study of 214 infected, (Mao et al, 2020)	25%
Dizziness		17%
Headache		13%
Impaired consciousness		7%

TABLE 4, SARS-CoV-2 cerebrovascular manifestations, PNS, CNS

2.1 PNS involvement

Guillain-Barré syndrome, a rare disease in which the body's immune system attacks its own nerves, was found as a common PNS event in different variations in COVID-19 patients. Some patients had Miller Fisher variant with areflexia (no muscle response to stimuli), ataxia (damage of cerebellum), or weakness or paralysis of eye muscles.

The most common symptoms of the peripheral nervous system of COVID-19 patients are anosmia (loss of smell) and ageusia (loss of taste). They can occur alone or in concert with other symptoms. There were more frequent records of anosmia and ageusia in COVID-19 patients than in any influenza cluster documented so far which makes it very specific symptoms for an infection by SARS-CoV-2, (Román et al, 2020).

2.2 Psychiatric problems

The outbreak of the SARS-CoV-2 pandemic has caused an extraordinary number of mental health disorders which varies among countries. Up to every second person is suffering from anxiety, depression, post-traumatic stress disorder and more than every third, and two out of

three people are suffering from psychological distress and stress, respectively. These are just the most common symptoms (Raijkumar, 2020). A more detailed description of these symptoms is visualized in Table 5.

Symptom	**Percentage**
anxiety	6.33% - 50.9%
depression	14.6% - 48.3%
post-traumatic stress disorder	7% - 53.8%
psychological distress	34.43% - 38%
stress	8.1% - 81.9%

TABLE 5, psychiatric symptoms of people during COVID-19 pandemic (Xiong et al, 2020)

Other psychiatric COVID-19 symptoms include inattention, confusion, disorientation and insomnia (Rogers et al, 2020)

This current pandemic has a huge influence on our daily activities. Lockdown, home-office and other factors influence our daily routines which can result in psychological distress. There are a lot of factors that are related to distress during this pandemic. Some of them are (Xiong et al, 2020):

- Female gender
- Groups until the age of 40
- Previous psychiatric or chronic illnesses
- Employment status (unemployed, students)
- Frequent exposure to social media or news related to SARS-CoV-2

Another variable influencing the number and severity of those psychiatric disorders is the high-, middle, or low capitalization and economic status of countries. The better a social economy is, the less likely it is for its inhabitants to get these symptoms. Countries with better economy usually provide free psychological assistance. Looking at a level of a single person, people can develop maladaptive behaviors like avoiding consultations of doctors even when being sick, hoarding of specific items or frequently asking for medical help (Rajkumar, 2020)

Altered mental status and cerebrovascular events have been diagnosed in all age groups. But their distribution occurs unequally. It is remarkably interesting that neuropsychiatric problems are found more often in young people than cerebrovascular symptoms. The older the tested group gets, the more the cerebrovascular gets compared to altered mental events. From the age

of 60 years and on – which is described as the risk group because they are suspected to have a more severe course - cerebrovascular events predominate (Fig 7).

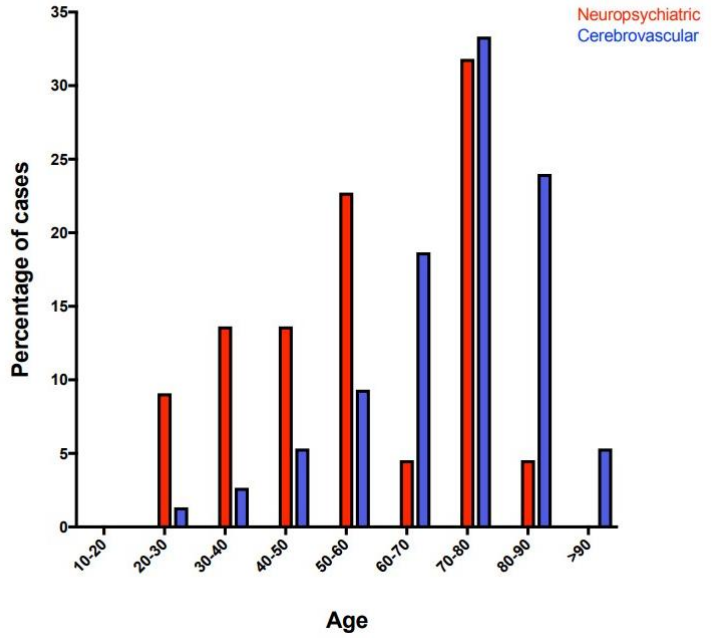

FIGURE 7, Age distribution of cerebrovascular (blue) and neuropsychiatric events (red) (Varatharaj et al, 2020)

After recovery from SARS and MERS infections, in more than 15% of cases, following symptoms have been reported in between 6 weeks and 36 months (Rogers et al, 2020):

- Sleep disorder
- Frequent recall or traumatic memories
- Emotional lability
- Impaired concentration
- Impaired memory
- Fatigue

This is an important indicator for future studies to have a look on the psychiatric effects of SARS-CoV-2 as, until this point, August 2020, just a few studies have been published in this field. Moreover, some psychological diseases can take years to develop, so long term effects are yet to be discovered.

2.3 CNS involvement

One-quarter of the hospitalized patients which were tested positive of severe acute respiratory syndrome from SARS-CoV-2 infection had manifestations of CNS involvement (Mao et al, 2020). Confusion and headache are nonspecific neurological symptoms of patients with COVID-19 illness. A summarized list of the main CNS-symptoms of SARS-CoV-2 infection that have been reported to date is listed below in Table 6.

Symptom	**Conditions**	**Reference**
Headache	6-8 %	Roman et al, 2020
Agitation and Delirium	69%	Ftiha et al, 2020
Delirium	65%	
Impaired Cocnsciousness	22 % (fatal cases) 14.8 % (severe cases)	
Dizziness		Ftiha et al, 2020
Global confusion		Najjar et al.
Syncope		
Encephalitis		
Frontotemporal hypoperfusion	58 ICU* patients with severe COVID-19, 45 survived (33 % had frontal lobe behavioral signs)	Roman et al, 2020
Arterial and Venous Thromboses	31 % thrombotic complications inc. pulmonary embolism in 81 % 27 % venous thromboses 3.7 % arterial thromboses	

TABLE 6, summarized CNS symptoms found in COVID-19 patients**;** *) ICU: (intensive care unit)

2.3.1 Cerebrovasculature diseases

SARS-CoV-2 can affect endothelial cells lining the vasculature. Viral infection of the endothelial cells will lead to vasoconstriction, edema, and pro-coagulation state, which could lead to stroke (blocking of a vein in the brain).

Cerebrovascular disease such as strokes can occur ischemic (restriction of blood supply) or hemorrhagic (broken blood vessel releasing blood) due to COVID-19 (Najjar et al, 2020).

The most typical and a frightening cerebrovascular symptom of COVID-19 is acute ischemic stroke (AIS) affecting up to 2,7% (Klok et al, 2020) of infected. AIS is defined as a failure of neurological tasks because of a rapid failure of blood circulation in parts of the brain. Ischemic

stroke is often poorly diagnosed because the masking of symptoms from SARS-CoV-2 makes it hard to detect. The most important clinical statements for AIS patients with COVID-19 are pointed out (Tan et al, 2020):

- 40.9% show large vessel occlusion (LVO)
- AIS in COVID-19 patients is moderate to severe
- 38% of AIS patients die
- AIS mean onset duration of 10 ± 8 days (n=54) of COVID-19
- Mean age of AIS patients is 63.4 ± 13.1 years (n=54)
- 24% of AIS patients did not show symptoms of COVID-19 at all

AIS patients also show more severe strokes while also showing COVID-19 symptoms. The majority of AIS patients had unusual subtypes of AIS like large vessel thrombosis, embolism, or a lowered percentage of small vessel stroke (Tan et al, 2020)
The documented stroke patients have been mainly people above 60 years and/or with known cerebrovascular disease-risk, hypertension diabetes, vascular disease and hyperlipidemia (Ellul et al, 2020)

2.3.2 Possible mechanisms for CNS involvement

Neurological involvement can be either as a direct consequence of the virus affecting the nervous system (glial cells, neurons), or indirectly by exerting its actions via cytokines. Both, neurons and glial cells possess the main entry receptor, ACE2. Viruses with the ability to enter neurons/ glial cell are called neurotropic. Also other Coronaviruses exist with neurotropic abilities (Desforges et al, 2020). Neuronal pathways are important vectors for entry of CNS for neurotropic viruses. The viruses can retrograde or anterograde neural transportation under the action of motor proteins, dynein and kinesins. The unique anatomy of olfactory bulb and olfactory nerves allows it to act as a channel between the CNS and nasal epithelium. Olfactory tract is a major route for virus dissemination to the brain in the early stage of SARS-CoV-2 respiratory system infection (Zhang et al., 2020). Gu et al, 2005, showed that coronaviruses can enter the CNS from periphery via neural pathways.

2.3.3 Invading neurons

Invading neurons is not the only way how to affect them. SARS-CoV-2 activates pathogenic cells (T cells) and releases a huge amount of inflammatory cytokines (i.e. IL-1, IL-6). These

in return, activate other cells (i.e. CD14+), which again lead to the release of even more cytokines resulting in an inflammatory cascade (Zhang et al, 2020).

Some Coronaviruses are able to enter the lungs and airways and reach the brainstem, the center of our body that is controlling vital functions, via synapse linked pathways (Li Y.C. et al., 2020). This might be a reason for respiratory failure as one of the symptoms of COVID-19.

Postulated entry of the virus of CNS through PNS

Most patients with infections of coronaviruses in a physically fit state, show just mild respiratory symptoms proposing its viral entry to begin in the lungs. From there on, they can spread to the CNS via neurological pathways. SARS, for instance, is proven to invade the CNS (Xu J. et al, 2005). Peripheral organs are highly supplied with nerves which are connecting the PNS to the CNS. Several strategies for entering the CNS have evolved from viruses invading neuronal systems. In order to replicate in the CNS, some viruses change the neuronal cytoskeleton machinery and send viral particles from the PNS over retrograde and anterograde pathways. Presynaptic neurons are then invaded by viral particles which were released into the synaptic cleft (Alam et al, 2020)

Several patients with a confirmed infection of SARS-CoV-2 show symptoms related to intracranial (inside of the head) infection including specific headache, confusion, and epilepsy. Some patients got intracranial-related symptoms even before they showed pulmonary symptoms like dyspnea and cough (Zhang et al., 2020).

Regarding the non-direct ways, how the virus can affect the neurons is by invading glial cells which, in turn, cause CNS damage by releasing inflammatory factors (IL-6, IL-12, IL-15, TNF-α)in a significant amount. Additional to direct, ACE2-related damage, some other frequently pathological changes, such as diffuse alveolar damage, edema, exudation of interstitial inflammation occur, when SARS-CoV-2 replicates in lung tissue cells (Wu et al., 2020; Li et al., 2020). These changes would result in hypoxia which would be another possible way of how to affect the nervous system indirectly.

IV. Olfactory System

The olfactory system is a chemical sensor and one of the oldest mechanisms to detect food and has an impact on how people behave socially or sexually. As soon as odiferous molecules

interact with the olfactory vesicles, the olfactory epithelial cells are activated (Diaz et al., 2013).

The olfactory epithelium (OE) which possesses more than 100 million receptor cells and is just a few centimeters broad, is in the upper posterior region of the head (Figure 8). The inspired air is forwarded here by the turbinates or nasal conchae which are located within the nasal cavity. The cilia in the olfactory vesicles are hair-like receptor cells, which are responsible for transduction of odor stimulus are made of specialized epithelial cells (Vokshoor et al., 2015).

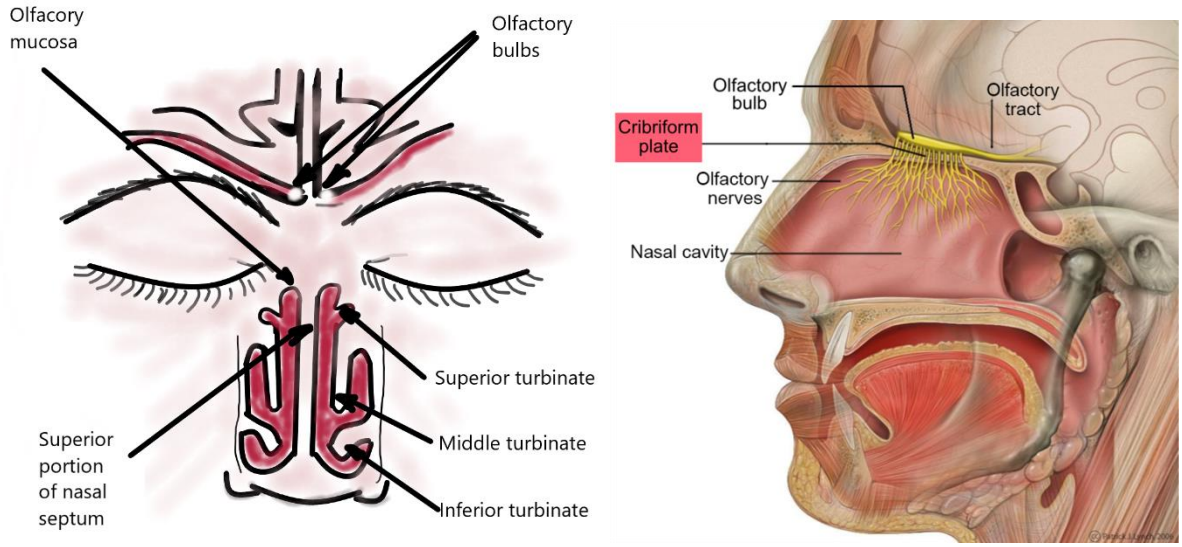

FIGURE 8: left: Head anatomy with olfactory nerve illustrated and simple; right: Head anatomy with focus on the Cribriform plate and olfactory system; Original work: Patrick J. Lynch, medical illustratorDerivative version: User:Opt1cs / CC BY (https://creativecommons.org/licenses/by/2.5)

The olfactory epithelium is made up of 3 different types of cells (Figure 9):

1. Basal cells: are stem cells that transform into olfactory receptor cells. The constant transformation and new supply are unique.
2. Supporting (goblet) cells: empty their contents onto the mucosal surface via microvilli and secretory granules. They are distributed among receptor cells, (Morrison et al.), 1990.
3. Olfactory receptor cells: are bipolar neurons. They are highly adapted and represent the only class of regenerative neurons. Every single one has a dendritic rod with specialized cilia (transduction surface for odors) from the olfactory vesicle and the fila olfactoria (olfactory nerve fibers).

The olfactory nerve fibers pass through lots of tiny foramina, on the cribriform plate. Foramina are tiny tunnels inside of the body through which e.g. nerves, veins, muscles can fit to connect different parts of the body.

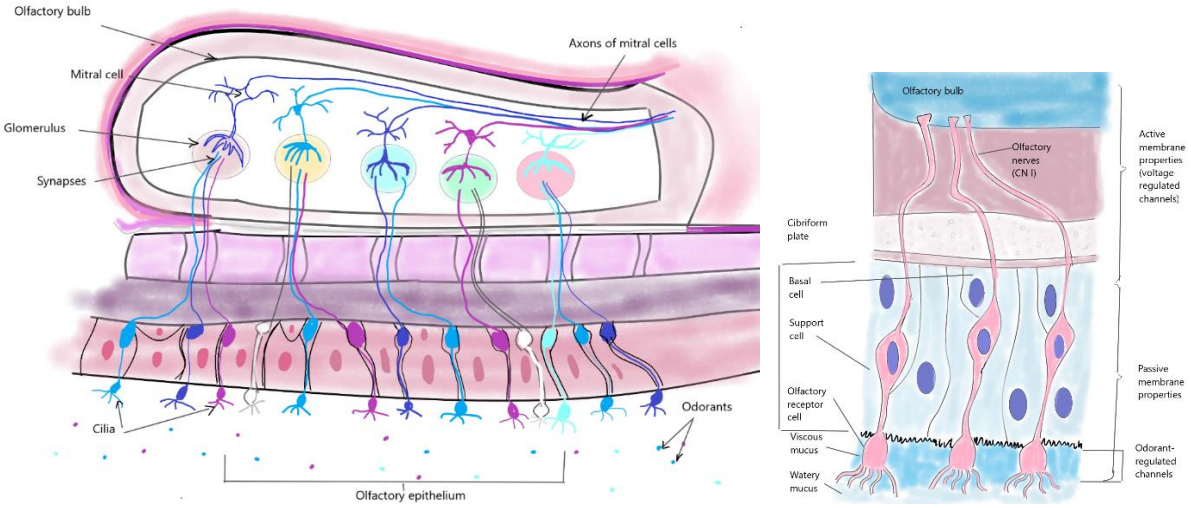

FIGURE 9: Olfactory bulb and different epithelial cells. Adapted and simplified

1. Olfactory bulb (OB):

Is a highly structured system with synaptic specializations of following diverse layers (outside to center):

Glomerular layer: most superficial layer of glomeruli, fila olfactoria, periglomerular cells

Periglomerular cells: interact with various mitral cell dendrites; lateral, adjacent, glomeruli-inhibition while allowing excitation of explicit mitral cell dendritic tree

External plexiform layer: incorporates mitral cells' passing dendrites and some tufted cells (same size as mitral cells, get granule cell input)

Mitral cell layer: at least 1000 olfactory nerve fibers interact with one mitral cell at glomerular layer, these cells are second-order neurons

Internal plexiform layer: containing largest neurons (pyramidal mitral cells) of the olfactory bulb in between internal and external plexiform

Granule cell layer: containing numerous, tiny, round, axon-lacking neurons. Some of its plexiform layer dendrites message mitral cell dendrites.

Glial cells are present in the olfactory bulb of adult mammals (Doucette, 1993). After nasal infection, inflammation and demyelination are symptoms caused by the human coronavirus (hCoV) when entering the CNS through the olfactory bulb (Bohmwald et al., 2018).

2. Infection of the olfactory system

The ability to smell is hampered by virus or bacteria infections, of which the most common symptoms are local nasal- and upper respiratory infections (URI). The OE is believed to be damaged by viral infections. Anosmia is very frequent for severe infection of the upper respiratory system (Thomas et al, 2020). Two possible ways of SARS-CoV-2 invasion into the CNS are proposed by (Baig et al, 2020):

- Through circulation or
- Through the olfactory nerve entry across the cribriform plate

CoVs, enteroviruses, rhinoviruses, influenza viruses and more were already found in the olfactory system. Coronaviruses may be one clinical cause for postviral olfactory dysfunctions (PVOD) (Suzuki, 2007). Other RNA viruses like influenza, rhabdoviruses, as well as coronaviruses can invade the olfactory bulb as has been shown a mouse inoculation experiment (Park et al., 2002; Christian et al., 1996; Goverdhan et al., 1992).

Most CoVs and many other viruses, invade the OB by proliferation through the cribriform plate. The rodent CoV, mouse hepatitis virus (MHV), whose OSNs (olfactory sensory neurons) do not possess expressions of its MHV receptor, can reach the OB from the nose. OSNs, are sensory neurons that interact with odors. Looking at this, it is expected that CoVs can infect the brain from the nasal mucosa (Youngentob et al, 2001).

V. ANOSMIA

1. What it is:

The sense of smell nowadays, is important for collecting enormous amount of information from the environment. We can detect harmful odors, enjoy a meal, walk in a forest, feel attracted to someone, and many more. Therefore, not being able to smell – anosmia – is a dysfunction of the olfactory system and can have a tremendous impact on people's quality of living or even affect their health situation.

Olfactory disorders are divided into 3 categories, anosmia, hyposmia (reduced ability to smell) and hyperosmia (increased sense of smell). Based on the cause, it is either local or systemic. Usually, olfactory disruption is caused by local nasal diseases which result in conductive and inflammatory consequences. If this does not to occur to happen locally, it could be a consequence of olfactory cortex problems (i.e. CNS problem, rather than the periphery nervous problem, epithelial problem or any other local problem of the nose). Bacterial, viral and fungal infections can be related with olfaction disorders. Moreover, neurodegenerative diseases, like Parkinson´s and Alzheimer´s disease are related to those dysfunctions and suspected to be indicated by them (Thomas et al, 2020)

Already 3,2% of people older than 40 years suffer from anosmia in the US, (Hoffman et al., 2016). For people being 60 years and older, this number increases to about 14-22%, (Pinto et al., 2014; Hoffman et al., 2016; Kern et al., 2014).

About two thirds of people suffering from COVID-19 suffer from anosmia and more than half showed taste dysfunction (Lechien et al., 2020). The number of infected people suffering from anosmia increased over time from 25% at the beginning to around 66% now, as of 08.08.2020. This makes it a new prominent symptom for the diagnosis of SARS-CoV-2 infection.

2. Reasons for anosmia

A reason for anosmia could be the deformed or missing cilia which are responsible for odor detection (Goncalves et al, 2020). If the cilia of OSN is not connected properly to the transduction machinery, mutation, or deletion of ciliacan result in anosmia (Gonzalves and

Goldstein, 2016). The machinery replaces olfactory sensory neurons usually every one to two months (Graziadei and Montigraziadei, 1979).

Anosmia may be loosely classified as sensorineural or conductive olfactory loss (Goncalves et al., 2016).

2.1 Conductive loss (CL)

It can be caused by stopped air intake, combined with edemas and infections. Conductive loss can also be caused by the inhibition of the transduction of odor molecules to the olfactory epithelium and sinonasal conditions that are influencing airflow.

2.2 Sensorineural loss

It can be induced after a trauma or a cold or a post URTI (upper respiratory tract infection). Sensorineural loss is referred to the damage of olfactory neurons and or their central projection. Sensorineural impairment indicates an olfactory epithelium dysfunction that is irreversible or can have a longer rehabilitation time. It can be caused by genetic mutations, prior URTI, infection with damage on sensory structures, and ciliopathy (Goncalves and Goldstein, 2016). For SARS-CoV-2 anosmia, several potential mechanisms are proposed which may induce anosmia on its own or in combination. Olfactory neurons can be harmed or destroyed by inflammation and die with increasing productions of cytokines.

Repair of the olfactory functionality is due to the production of new olfactory neurons which are made of basal stem cells (BSC). This is just valid if an interrupted inflammatory cytokine production occurs. Out of all patients diagnosed with anosmia before COVID-19, due to sinonasal disease, 14-30% of patients had temporary anosmia. It was shown that transient anosmia can be induced by edema of the nasal respiratory epithelium or congestion of the nose from nose polyps or chronic rhinositis (Goncalves and Goldstein, 2016). Some research indicates that SARS-CoV-2 induces a transient loss of taste and smell. Typical anosmia, after viral infection (postviral infection), lasts for several months and is due to sensorineural losses, while in comparison, SARS-CoV-2 induced anosmia - in most cases - lasts just for weeks. Relatively fast recovery and olfactory dysfunction after or at the same time as general or ear-nose-throat (ENT) symptoms in COVID-19 patients support the theory of conductive loss (Lechien J.R. et al., 2020, Spinato G. et al., 2020).

3. Mechanisms

Viral tropism could lead to respiratory failure and could be happening in COVID-19 patients because the virus could enter the olfactory nerve followed by olfactory cortex and brain stem (Li et al, 2020). Investigation in animal models showed that neurotropic viruses usually reach the brain through the nasal pathway (Baig, 2020). Another experiment with transgenic mice expressing human ACE2 showed that in order to enter the brain, SARS-CoV-2 enters the olfactory bulb. From there, the virus immediately disseminates to the olfactory cortex, and other areas close by, like midbrain nuclei or basal ganglia. In absence of encephalitis, it causes neuronal death (Netland et al, 2020). In human brains that were virally invaded by SARS-CoV, a similar pattern was discovered (Gu et al, 2005).

Odors are sensed by OE where mature OSNs (mOSNs) are interacting with scents using receptors on their dendritic cilia. OSN premors transport the information about the odors from OE to the brain. These axons perforate the cribriform plate (Figure 8) at the skulls base and end up in the OB where odor information is processed and then sent to the higher brain centers (Figure 9). While infected, SARS-CoV-2 might be accumulated in nasal RE goblet cells. These cells and the ciliated cells showed high expressions of ACE2 and TMPRSS2, measured by single cell RNA sequencing (Sagnak et al, 2020).

For SARS-CoV, a high expression of ACE2 in the nasal respiratory epithelium was shown (Bertram S. et al., 2012). In more detail, intranasal entry of the virus is suggested due to the high expression of ACE2 on the ciliated cells (olfactory receptor cells) (Sims et al., 2005; Hamming et al., 2004), additionally to the previous studies, identified ACE2 also in the basal layer.

For SARS-CoV-2, a high ACE2 expression was found in nasal respiratory epithelium goblet cells (Sungnak et al., 2020; Ziegler et al., 2020). Even though the olfactory epithelium and the OSNs (the actual neurons) do not have ACE2 (Solbu et al, 2012), ACE2 expression in nonneural cells, like stem-, supporting-, and perivascular cells, has been shown by Brann et al., 2020. ACE2 is located on nearby tissue, including vascular pericytes. Pericyte infection could alter the sense of smell by causing an inflammatory response. This might damage cells and change any signaling from the sensory neurons to the brain or modify the functionality of olfactory neurons. The main cell targets for SARS-CoV-2 entry are supporting cells, also playing a crucial role in maintenance in the neuroepithelium and are facing the nasal cavity (Fodoulian et al., 2020).

As the similarity of SARS-CoV and SARS-CoV-2 is 80% (Xu J et al, 2020) and they are attracted to the same receptor, it is very likely that these two viruses share similar mechanisms. The fact that anosmia is temporary in most patients, tends to make it unlikely that viruses will directly invade and later destroy olfactory neurons.

Other molecules could also contribute SARS-CoV-2 entry without expressions of ACE2 (Lamers et al, 2020). Moreover, it may be possible for infected cells to form multinucleate cells (resulting from multiple cell fusions) with cells not expressing ACE2 at all, (Brann et al, 2020).

Materials and methods

This thesis is a theoretical work, and only literature noted at the end of the thesis was used as the sources for writing of the thesis.

Discussion and Conclusion

Coronavirus is a word that became famous in 2020 due to the current pandemic. The word has been existing for a long time and scientists already knew *Coronavirae* affecting mammals for more than 50 years now (Lam et al, 2020). Most of coronaviruses have not been able to infect humans. Two more famous coronaviruses have been reasons for epidemics and pandemics before, namely the coronavirus SARS in 2002 and MERS in 2012 (Lam et al, 2020). Moreover, 6 coronavirus strains are causing about every third case of the common cold year after year (Myint, 1995). The new coronavirus, SARS-CoV-2, has an incubation period of about 5.1 days (Lauer et al, 2020), which means that infected people do not show symptoms for that amount of time being able to spread the virus to others without being aware of it. This makes it extremely dangerous and justifies lockdowns or other measures in order to suppress spreading.

The new coronavirus, causing the disease COVID-19 (coronavirus disease 2019), has various symptoms. Some of the most frequent ones are dry cough, fever, heavy breathing, and anosmia – loss sense of smell (Grant et al, 2020). Not being able to smell is a very untypical symptom related to coronavirus infection that can tremendously decrease living quality (Thomas et al, 2020). The awareness of neurological symptoms of COVID-19 is increasing every day. More than every third person that is symptomatic – 40% to 45% of infected are asymptomatic – has neurologically related symptoms including peripheral nervous system (PNS), central nervous system (CNS), vasculature system and psychiatric symptoms (Mao et al, 2020).

It is known that the coronavirus causing SARS, (SARS-CoV), has an 80% similar genomic RNA sequence when compared to the novel coronavirus and that the human ACE2 receptor is the main target for both viruses (Xu et al, 2020). ACE2 is found in many cells throughout the human body (Hamming et al, 2005), potentially explaining the many different forms of symptoms of COVID-19. ACE2 has a lot of functions in our bodies such as blood pressure regulation, fluid balance, inflammatory response and many more (Wang W et al, 2016). SARS-CoV-2 enters the cell by binding and subsequent fusion to this ACE2 receptor on the cell surface of the target cell. Afterwards, the virus enters the endosome, fuses lysosomal and viral membranes, and finally, new replicates are released. The cell entry of SARS-CoV-2 is activated by TMPRSS2 and cathepsins which have cumulative effects with furin. Preactivation by furin promotes cell entry.

The symptoms exerted by SARS-CoV-2 on the CNS could either be direct, affecting the nervous system or indirect by exerting its actions via cytokines. The major channel for a virus to the the brain is the olfactory tract which contains ACE2 and therefore, is a possible pathway for SARS-CoV-2 invasion.

Other neurotropic coronaviruses, like SARS-CoV, are already known to be able to enter the CNS via neuronal pathways from PNS (Gu et al, 2005).

Most coronavirus patients in a physically fit state just show mild respiratory symptoms suggesting that the infection begins in the lungs (Xu J et al, 2005). A number of patients with COVID-19 show specific intracranial (inside of the head) symptoms. Some of those COVID-19 patients developed intracranial related symptoms even before pulmonary symptoms, (Zhang et al, 2020). This controversy makes it unclear if the infection starts in the head or lungs. Further investigation is needed here.

The virus causes the neuronal problems either directly (conventional) causing entry invading neurons or glial cells, or indirect causing entry by secondary factors such as inflammatory responses by cytokines. The olfactory system acts as a neuronal pathway from the epithelium, expressing ACE2, to the CNS (Desforges et al, 2020). Not only neuronal pathways could be the reason for affecting the CNS.

With regard to the indirect way, a special focus has to be given to severe COVID-19 patients because of the risk of a cytokine cascade which can result in organ failures. SARS-CoV-2 activates an enormous response of the immune system and inflammatory response and releases a huge amount of inflammatory cytokines. These in return, activate other cells, which again lead to the release of even more cytokines resulting in an inflammatory cascade (Zhang et al, 2020). Whether the origin of CNS invasion is direct or indirect is still to be investigated in further studies but 2 recent studies where they analyzed human brain tissues of dead COVID-19 patients, indicate a secondary pathway because they found ischaemic signs (little blood flow) in the infected tissues (Solomon et al, 2020) and not enough evidence of presence of SARS-CoV-2 infection (Coolen, 2020) was found in the brain.

Over time, anosmia became more and more relevant as an indication symptom of COVID-19. At the beginning of this pandemic, not a lot of patients were diagnosed with it because patients did not really realize the occurrence of anosmia. As studies nowadays already confirmed, this symptom occurs to affect two out of three COVID-19 patients, upgrading it to a diagnostic symptom for SARS-CoV-2 infection (Lechien et al, 2020).

Anosmia can occur because of sensorineural or conductive loss (Goncalves et al, 2016). Conductive loss can occur because of blocked air intake, combined with edemas and infections. Olfactory neurons, which do not possess ACE2 (Solbu et al, 2012), can be destroyed by inflammation and die from cytokine production (Turner et al, 2010), resulting in an irreversible anosmia or recovery takes several months. ACE2 is located on nearby tissue, including vascular pericytes, whose infection could alter the sense of smell by causing an inflammatory response. This might damage cells and change any signaling from the sensory neurons to the brain or modify the functionality. Sensorineural degradation is causing irreversible damage to the olfactory epithelium and is associated with a much longer recovery. Because anosmia in COVID-19 patients can be reversed in most of the patients, and it for 50% of people it takes around 3 weeks from onset to recover (Cocco et al, 2020), it is interesting to speculate that anosmia in SARS-CoV-2 patients might be caused by sensorineural conditions.

A virus can enter neurons in the periphery or in the central nervous system. These neurons have to be present in the environment of the virus in order to get attacked. ACE2 expression was not found in sensory neurons and no expression of SARS-CoV-2 has been found in brains of dead COVID-19 patients. These information leads to the conclusion that the virus SARS-CoV-2 does not directly enter the CNS. The virus most probably enters by infecting the lungs, pericytes in the blood stream or supportive cells in the olfactory system. Then, SARS-CoV-2 initiates immune responses and cytokine cascades leading to issues in the brain that would explain the neurological symptoms. Anosmia was found to be a temporary damage. It is very likely that, as the receptor neurons do not express ACE2, the cause of the lost ability to smell is because of local inflammations and the inability of odor molecules to reach the receptors.

In summary, there is no clear evidence of how SARS-CoV-2 can enter the central nervous system and further cause anosmia. Research showed that SARS-CoV-2 damages the CNS (Kranberg et al, 2020) and that SARS-CoV-2 related anosmia is a major, coronavirus-related untypical symptom. So far, research indicates an indirect entry of SARS-CoV-2 into the CNS from the olfactory system over the PNS. Nevertheless, further investigations of the brain of COVID-19 patients, amongst other things, is crucial in order to get evidence of SARS-CoV-2's entry mechanism.

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Abbreviations Appendix

Abbreviation	Meaning
ACE1	angiotensin-converting enzyme 1
ACE2	angiotensin-converting enzyme 2
AIS	acute ischemic stroke
Ang	angiotensin
bp	basepairs
CNS	central nervous system
CL	Conductive Loss
COVID-19	Coronavirus disease 2019
DMV	Double membran vesciles
ENT	ear-nose-throat
ER	endoplasmatic reticulum
hCoV	human coronavirus
HCoV-229E	type of „human coronavirus“
HCoV-OC43	type of „human coronavirus“
HSE	herpes simplex encephalitis
ICU	Intensive care unitLiebe WINCAMPSer
IFN	Interferon
kb	kilobases
LVO	large vessel occlusion
MERS	Middle East respiratory syndrome
MHV	Mouse Hepatitis Virus
mRNA	messenger RNA
NSP	non structural proteine
OB	Olfactory bulb

OE	Olfactory epithelium
ORF	Open reading frame protein
orf	Open reading frame gene
pp1a	Polypeptide 1a
PPC	Proprotein convertase (PPC)
PVOD	Postviral olfactory dysfunctions
RBD	receptor binding domain
RNA	ribonucleic acid
RTC	replication-transcription complex
S1 head	receptor-binding subunit
S2 stalk	membrane fusion subunit
SARS	severe acute respiratory syndrome
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sgRNA	subgenomic RNA
+ssRNA	positive-sense-single-stranded RNA
TMPRSS2	transmembrane protease, serine 2
URI	upper respiratory infection
URTI	upper respiratory tract infection
WHO	World health organization

Figure Appendix

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