Bachelor Thesis

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

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Simon Starker

Supervisor: Mgr. Ján Lopatář, Ph.D.

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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 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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I would like to thank my study colleagues, with whom I spent three years of my life and made friends for life with.
Finally, I thank my family for supporting and motivating me through these years.

Content of the thesis

Abstract

Around every third symptomatic COVID-19 patient shows neurologic related symptoms. These can have various forms and are categorized in manifestations of central nervous system, peripheral nervous system, cerebrovascular system and psychiatric manifestations. The most frequent neurological symptoms by far are olfactory and gustatory disorders as anosmia (loss of smell).

Anosmia is a symptom that can have different reasons e.g., viral infections, age, head trauma, neurotoxins, etc. The main principles behind this symptom are referred to as conductive loss or sensorineural loss. Conductive loss is the simpler form resulting in a blockage of odorants reaching the receptors inside of the nose by e.g., swelling, blocked nose, usually resulting in a transient loss of smell. Sensorineural loss is loss of neurons in the sensory neuronal pathway.

The olfactory tract is a direct pathway to the brain and possesses the main entry receptor, ACE2, for SARS-CoV-2 entry. The neurotropic potential of coronaviruses has been shown in the past making a neural origin of anosmia possible. But on the other hand, the regeneration of anosmia due to neural origin normally takes months and in COVID-19 the average regeneration takes only 2 weeks, supporting the theory of conductive loss for the majority of anosmic COVID-19 patients.

The difference of duration in recovery of anosmia in COVID-19 patients and the neurotropic potential of SARS-CoV-2, together with the collected data, points in the direction of a combination of above-named reasons. SARS-CoV-2 most probably enters the olfactory tract, where it starts invading the ACE2-expressing supporting cells around the receptor cells (cilia), resulting in conductive loss due to inflammation and swelling of these cells. Then, if the infection gets worse, the virus could further invade the neuroepithelium where it causes inflammatory impairment to the olfactory neurons resulting in a sensorineural loss and a recovery for around 2 months. There are also patients with a way longer recovery than 2 months and this could be explained by the virus further entering the brain via the olfactory cortex resulting in damage to the olfactory system which could be irreversible.

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 and McIntosh, 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), (Zhong et al., 2003), and in 2012, the Middle East respiratory syndrome (MERS), (Zaki et al., 2012).

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).

TABLE 1: Virus Classification of SARS-CoV-2; (ICTV accessed 02.12.2020)

Realm:	*Riboviria*
Kingdom:	*Orthornavirae*
Phylum:	*Pisuviricota*
Class:	*Pisoniviricetes*
Order:	*Nidovirales*
Family:	*Coronaviridae*
Genus:	*Betacoronavirus*
Subgenus:	*Sarbecovirus*
Species:	*Severe acute respiratory syndrome-related coronavirus*
Strain:	*Severe acute respiratory syndrome coronavirus 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. 3485 different genomes of SARS-CoV-2 have been globally isolated between December 2019 and December 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, (GISAID, accessed December 2020).

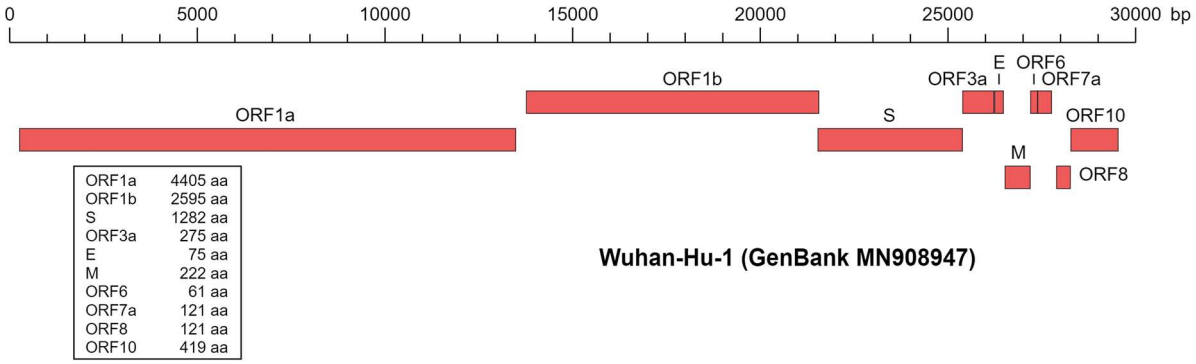

FIGURE 1: Genome of first isolate of SARS-CoV-2, Wuhan-Hu-1; GenBank Acc MN908947; (Wikiwand.com)

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, (Lauer et al., 2020). After that, the first symptoms start to show, most prominently dry cough, fever and fatigue; a rather unusual symptom is the loss of smell (LOS, 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).

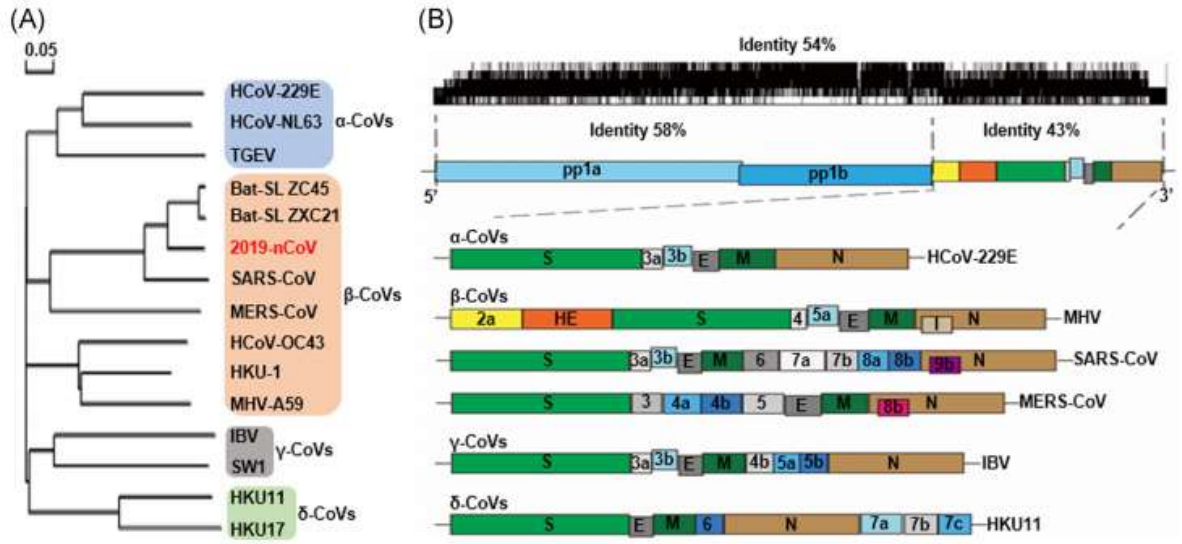

FIGURE 2: The genomic structure and phylogenetic tree of coronaviruses. A. The phylogenetic tree of representative Coronaviruses, with the new coronavirus, SARS-CoV-2, highlighted as 2019-nCov in red. B. The genome structure of four genera of coronaviruses. Pp1a und pp1b represent the two long polypeptides 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, mouse 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, (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 and Netland., 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 3A), (Beniac et al., 2006; Delmas and Laude, 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 and Perlman, 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, (Cui et al., 2015).

For SARS-CoV-2, the transmembrane E-protein is probably located on the endoplasmatic reticulum. 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 and Knapp, 2020).

The N-protein of SARS-CoV-2 binds to the stress granule proteins which is a formation of proteins and RNA in the cytosol. The cytosol 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)

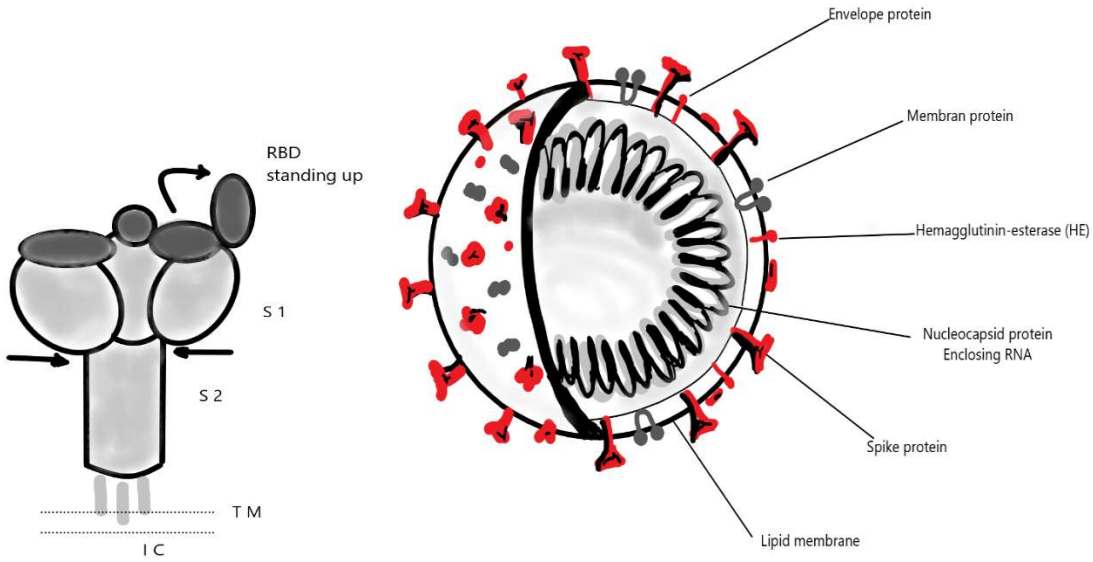

FIGURE 3: (A): Spike Protein of SARS-CoV-2; RBD, receptor binding domain; S1, receptor-binding subunit; S2, membrane fusion subunit; TM, transmembrane anchor; IC, intracellular tail; (B): SARS-CoV-2 Virion; (simplified and adapted from Shang et al., 2020)

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).

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, (Xu and Lazartugues, 2020), 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.

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 enters endosomes and finally, fuses lysosomal and viral membranes (Figure 4), (Li, 2016; Perlman and Netland, 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 (Figure 3A). 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.

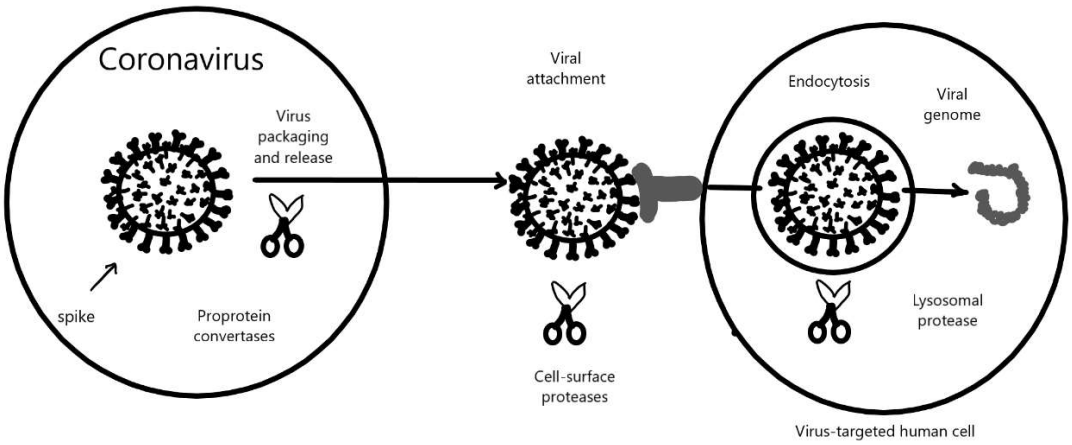

FIGURE 4, Viral exit of SARS-CoV-2 from a human cell, viral attachment onto hACE2 receptor, followed by viral entry of the endosome and fusion with human lysosome, release of viral genome, (simplified and adapted from Shang et al., 2020)

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 and Shephard, 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 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 boundary of the subunits S1 and S2 where the S1 subunit dissociates and the S2 subunit 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 motif at the S1/2 boundary (Figure 3A) of the S-protein , proprotein convertase 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).

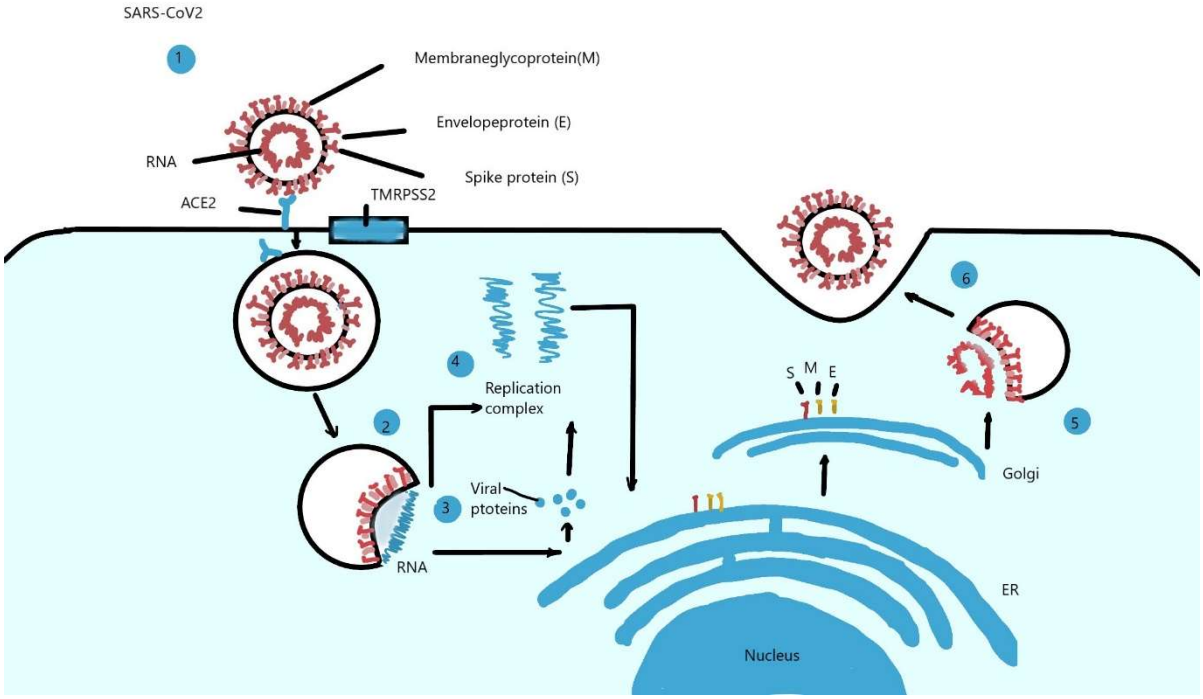

FIGURE 5: SARS-CoV-2 invading a cell. 1) entry. 2) RNA release of virus and membrane fusion. 3) Translation. 4) Proteins from step 3 and RNA from step 2 produce more RNA by forming a replication complex. 5) Packing in Golgi. 6) Release of SARS-CoV-2. (adapted and modified from Zhang et al., 2020)

III. COVID-19

COVID-19 is the name of the disease caused by the virus SARS-CoV-2 (coronavirus disease 2019). As of 03.12.2020, there were 66 million people with confirmed SARS-CoV-2 infection, (ecdc.europa.eu). Around 42.5 million people recovered and 1.52 million people died from COVID-19 so far. Figure 6 is displaying the number of people that had died from COVID-19 for 5 different countries per million people.

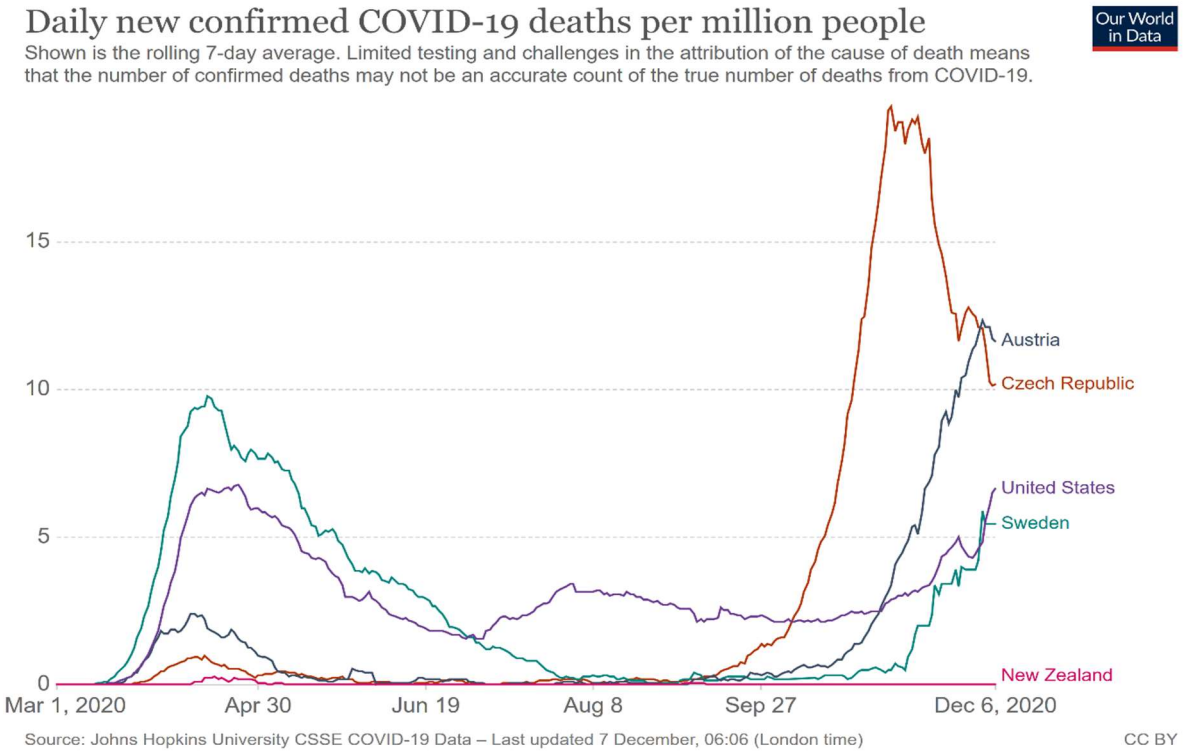

FIGURE 6: Daily new confirmed deaths attributed to COVID-19 in different countries over time; (Ourworldindata.org)

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:

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

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

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 and Topol, 2020).

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

Physiological tracts and systems	**Major symptoms**	**Percentage 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%	

After the average incubation time of about five days, (Lauer et al., 2020), 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. and Byrareddy, 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.

Chronic diseases like hypertension, kidney disease or diabetes are known to increase 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 effect means that the virus is causing the damage as a consequence for instance 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 (peripheral nervous system) and CNS diseases have already been associated with two relatives of SARS-CoV-2, SARS and MERS, (Ellul et al., 2020). According to the current situation, it is expected to have in between 24,818 and 132,976 patients with CNS complications and in between 33,096 and 106,383 patients with PNS complications, (assumption: 66 million cases, Ellul et al., 2020). As of 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).

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

Description	Conditions	Percentage
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%

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 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

Most of the psychiatric problems are secondary which means as a consequence of external factors such as habit- or lifestyle changes. If a virus affects the body and the brain and then causes a psychiatric disorder, it is referred to as a primary psychiatric disorder. Most of the presented symptoms are secondary psychiatric symptoms. Viruses can enter the brain so it is possible that they can cause a real psychiatric disease which is yet unknown.

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.

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

Symptom	**Percentage**
Anxiety	6.3% - 50.9%
Depression	14.6% - 48.3%
Post-traumatic stress disorder	7% - 53.8%
Psychological distress	34.4% - 38%
Stress	8.1% - 81.9%

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, (Figure 7; Varantharaj et al., 2020).

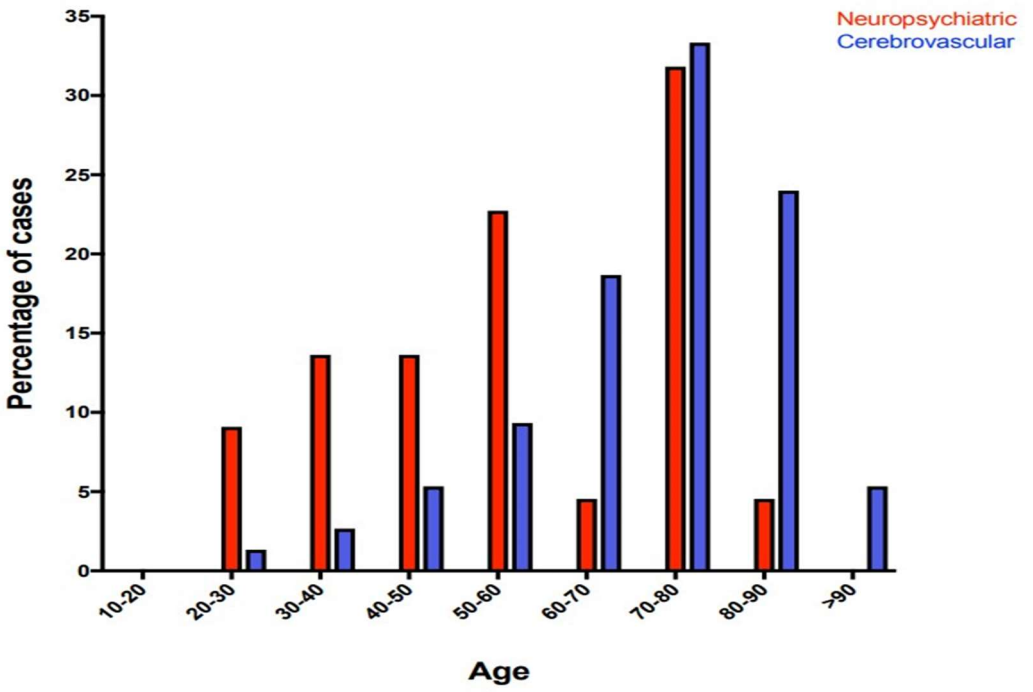

FIGURE 7: Age distribution of cerebrovascular (blue) and neuropsychiatric events (red), (Varatharaj et al., 2020)

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 L. et al., 2020). Confusion and headache are nonspecific neurological symptoms of patients with COVID-19 illness, (Asadi-Pooya and Simani, 2020). 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.

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

Symptom	**Conditions**	**Reference**
Headache	6-8 %	Roman et al., 2020
Agitation and Delirium	69%	Ftiha et al., 2020
Delirium	65%	
Impaired Consciousness	22 % (fatal cases) 14.8 % (severe cases)	
Dizziness		Ftiha et al., 2020
Global confusion		Najjar et al., 2020
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	

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 as ischemic (restriction of blood supply) or hemmorrhagic (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
- 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 including astrocytes, neurons), or indirectly by exerting its actions via cytokines. Both, neurons and glial cells possess the main entry receptor, ACE2, (Xu and Lazartugues, 2020). Viruses with the ability to enter neurons/ glial cell are called neurotropic. Also other coronaviruses exist with neurotropic abilities, (Desforges et al., 2014). 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 could be 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, as documented by electron microscopy and RT-PCR, and localized in the hypothalamus and the cortex of six out of eight deceased SARS-suffering patients.

Meinhardt et al., 2020, showed the neurotropic potential of SARS-CoV-2 by showing the presence of intact CoV-particles and SARS-CoV-2 RNA in the olfactory mucosa and neuroanatomical locations when performing immunohistochemical staining techniques of deceased COVID-19 patients. This study further gave insight on the SARS-CoV-2 pathway to the brain. They found that the virus enters the neuroepithelium through the nose and via neuronal paths, invades the brainstem, which controls respiration potentially explaining the respiratory problems in COVID-19 patients, (Meinhardt et al., 2020).

Invading neurons is not the only way how to affect them. SARS-CoV-2 activates pathogenic cells (T cells) and releases a huge number 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 severe COVID-19.

Postulated entry of the virus of CNS through PNS

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. These symptoms could be due to the virus entering the brain from the periphery and affecting the brain cells directly.

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, the

symptoms 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).

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 where the cilia are located, the olfactory epithelial cells are activated, (Díaz 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, also called nasal conchae which are bony elements that are forming the upper chambers of nasal cavities. The cilia in the olfactory vesicles are responsible for transduction of odor stimuli. They are hair-like receptors which are made of specialized epithelial cells, (Vokshoor and McGregor, 2015).

(A) (B)

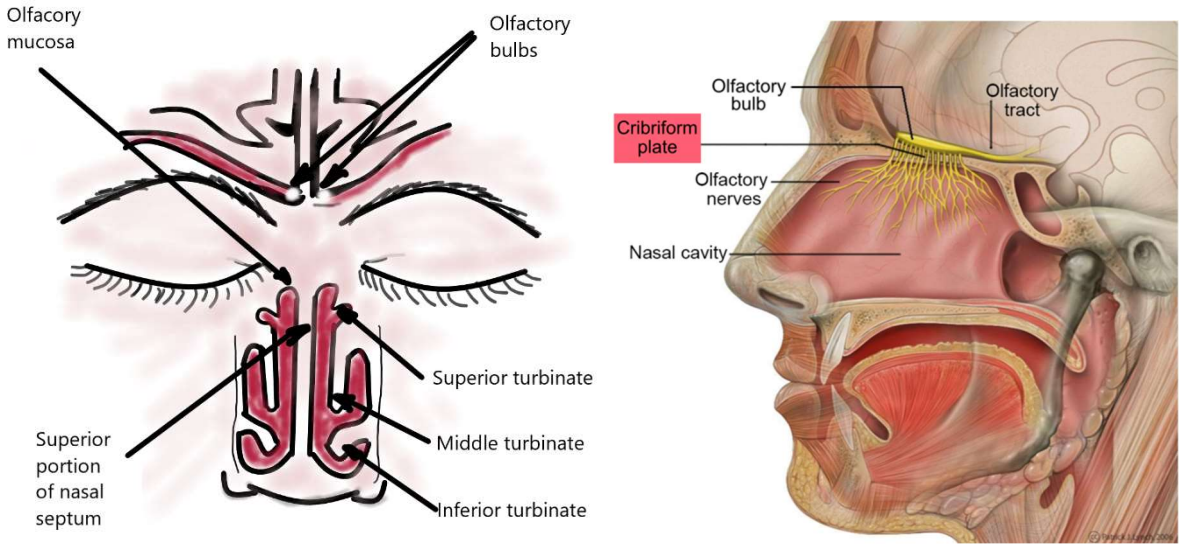

FIGURE 8: (A): Head anatomy with olfactory nerve illustrated and simplified; (B): Head anatomy with focus on the Cribriform plate and olfactory system; Original work: Patrick J. Lynch, medical illustratorDerivative (https://upload.wikimedia.org/wikipedia/commons/9/9d/Head_Olfactory_Nerve_Labeled_-_Cribriform_plate_highlighting.png)

1. Anatomy and Physiology

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

1. Basal stem cells: are stem cells that transform into olfactory receptor cells. The constant transformation and new supply are unique, (Vokshoor et al., 2015).
2. Supporting (goblet) cells: empty their contents onto the mucosal surface via microvilli and secretory granules. They are distributed among receptor cells, (Morrison and Costanzo, 1990).
3. Olfactory receptor cells: are bipolar neurons. They are highly adapted and represent one of the few classes 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), (Vokshoor and McGregor, 2015).

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. The cribriform plate is a sieve-like structure and part of the ethmoid bone (Figure 9 (B), light horizontal layer), (Kalmey et al., 1998).

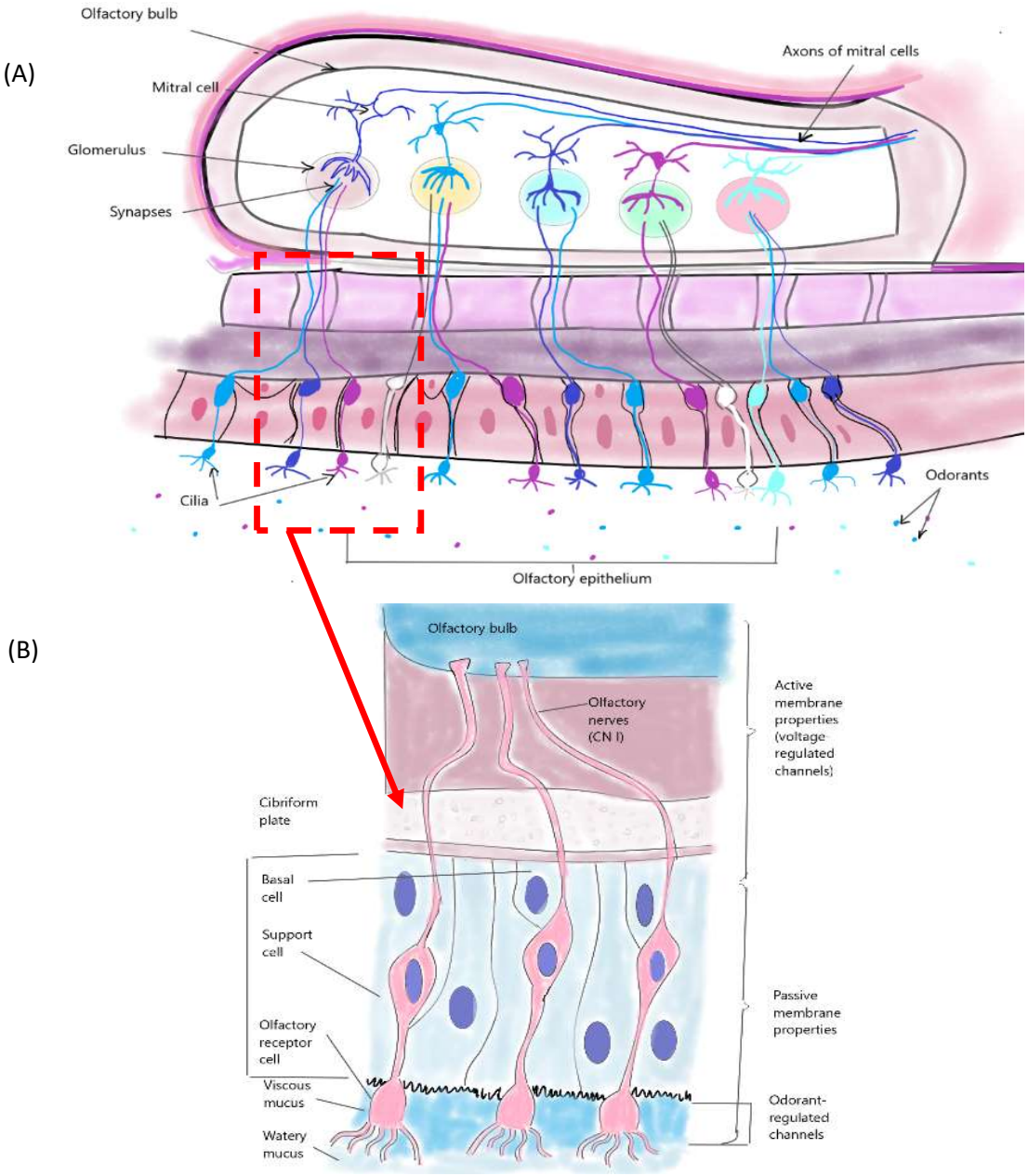

FIGURE 9: A: Olfactory bulb; B: different epithelial cells inside of the olfactory bulb, (adapted and simplified from https://mammothmemory.net/biology/coordination-and-response/sensory-receptors/olfactory-bulb.html)

Olfactory bulb (OB)

Is a highly structured system with synaptic specializations of following diverse layers, (outside to center; summarized by Vokshoor and McGregor., 2015):

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).

2. From odiferous molecule to the brain

Smelling is one of the most primitive sensory systems. We need it to distinguish between rotten and fresh food, genetically equivalent partners or dangers and hazards like poisonous gases. Odorants are molecules that can bind to out of 5 families of odorant receptors. It is suggested that humans can distinguish around 1 trillion different odorants which are detected by a combination of different odorant receptors, (Munger et al., 2009; Bushdid et al., 2014).

To enable a person to distinguish between good or bad odorants, signaling transmission in olfactory sensory cells occurs as following:

First, the odor molecule needs to enter the nasal cavities where it can attach to an odorant receptor located on an olfactory receptor cell. A depolarized receptor potential emerges in the sensory cells and after exceeding a threshold value, an action potential cascade is initiated. This odorant-receptor-interaction leads to olfactory G-Protein activation which turns on Adenylatcyclase type III. The second messenger cAMP (cyclic adenosine monophosphate) is synthesized by the adenylatcyclase and opens non-selective cyclic nucleotide-gated channels where Na^+ and Ca^{2+} Ions that are in the olfactory mucosa can travel through to accumulate in the cilia of sensory cells leading to a depolarization of cilia membrane. The Ca^{2+} Ions

streaming into the cells are opening Cl^- Ion channels where Cl^- Ions are flowing out of the cells increasing transduction signaling, (Liberles, 2014; Munger et al., 2009).

Na^+/ K^+/ $2Cl^-$ cotransporters, Cl^-/HCO_3^- exchangers and Na^+/ Ca^{2+} exchangers are expressed in the cilia membranes and are responsible for transporting Cl^- back in, and Ca^{2+} back out of the cilia. This active transport is maintaining the correct electrochemical ion gradient, which is needed for signal transduction, (Manzini et al., 2014). If continuously exposed to an odorant, stimulus response is decreasing drastically after a short amount of time by reduced sensitivity to cyclic adenosine monophosphate and internalization of receptors. In this process calmodulin is playing a central role, (Munger et al., 2009). Calmodulin is a multifunctional, Ca^{2+}-binding messenger protein that is present in all eukaryotic cells.

Beside the odorant receptors, also other G-protein-coupled and ionotropic receptors like cannabinoid receptors, purinergic-, adrenergic-, and cholinergic receptors are expressed in the sensory cells and the activation of these receptors leads to a modulation of the odorant information already in the OE, (Lucero, 2013).

The olfactory cell axons form the olfactory nerve and end in the OB. The synapses between the mitral cells (downstream projection neurons) and these axons lie in so-called glomeruli. All sensory cells expressing the same type of odorant receptors are converging into the same glomeruli. The information is transmitted to higher olfactory centers through the tractus olfactorius which is made of axons of mitral cells. Before leaving the bulb, granule cells and periglomerular cells are modulating olfactory information, (Mori and Sakano, 2011). Usually, single odorants are activating several glomeruli and single glomeruli are activated by several odorants. In the recognition of an odorant, a complex activity pattern of several glomeruli is occurring where the temporal activation course also takes part. The spatial and temporal information enables the olfactory system to distinguish more odorants than it has receptors, (Mori and Sakano, 2011).

The olfactory information is leaving the OB via the mitral axons and is, compared to other senses, not obligatory connected to the thalamus but it reaches different cortex regions (orbital surface of frontal lobe & dorsomedial surface of temporal lobe after the olfactory tubercle via the lateral branch of the tractus olfactorius). The areas receiving direct input of the OB are summarized as primary olfactory cortex including piriform cortex at the transition between frontal and temporal lobes, the amygdala and rostral entorhinal cortex (both of which are located in the temporal lobe, (Gottfried, 2006; Price, 1973). All of these brain regions are part

of the limbic system and have even more functions than just detecting odorants, like processing of emotions, (Manzini et al., 2014). So only a few parts of the limbic system take part in the process of odour identification as can be seen in Figure 10.

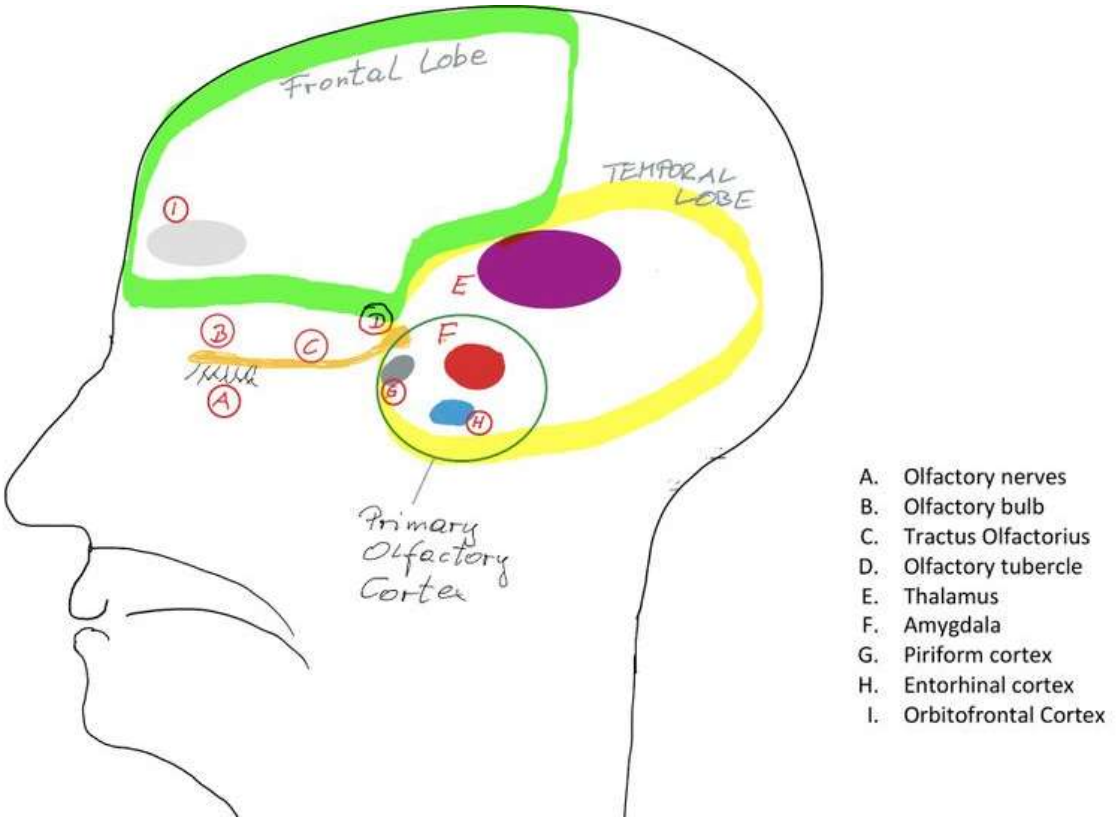

FIGURE 10: Head sketched from the side to highlight the brain regions that take part in the smelling process.

3. Disorders of the olfactory system

Dysfunctions of the Olfactory System can take various forms and have various reasons (e.g., sex, smoking behavior, prior infections, intranasal neoplasms …).

Olfactory dysfunction can be total (anosmia) or incomplete (partial anosmia, hyposmia, microsmia). It can reflect spontaneous sensations (phantosmia: smelling without stimulus) or distortions (dysosmia: smelling something else, e.g., to smell rotten from flowers). A decreased sense of smell is called hyposmia and if it is not possible to recognize the odorant independently of a normally functioning olfactory system, it is called olfactory agnosia. These forms can occur bilateral or unilaterally. These conditions can be either permanent or temporary (Doty, 2009).

3.1. Reasons for dysfunctions in the Olfactory System:

Viral infections:

The simplest example for dysfunction of the olfactory system is due to inflammation initiated by a flu or cold. This usually results in a blocked nose and in most cases, the olfactory dysfunction is temporary (see section on Conductive loss). Different inflammation mechanisms can also have influence on the onset and severity of the disorder, (Welge-Luessen, 2009).

Upper respiratory tract infection (URI), in nature mostly viral infection, are the most frequent reason of permanent anosmia or hyposmia, (Deems et al., 1991; Murphy et al., 2003), which show no fluctuation over time when comparing to nasal inflammatory disorders. The severity of the olfactory dysfunction can relate to the damage of the OE and in a few cases the virus can enter the brain and cause damage to the central olfactory structures (Figure 10), which are brain regions responsible for the identification and processing of the sense of smell, (Doty, 2009).

The common cold, hepatitis, flu-like infections, and herpes simplex encephalitis are disorders related to virus infections and show damage to the olfactory neuroepithelium, (Stroop, 1995).

Viruses can cause olfactory dysfunction either via immune system, or directly by invading the olfactory structures. If viruses invade neurons, including those in the olfactory system, they are called neurotropic. Neurotropic viruses that are known to invade the peripheral olfactory structures are, (Baker and Genter, 2007):

- Polio, the Indiana strain of wild-type vesicular stomatitis
- Rabies
- Herpes simplex types 1 and 2
- Mouse hepatitis virus
- Herpes suis
- Borna disease
- Canine distemper viruses

It is called a "postviral olfactory disorder" when the effect of acute rhinitis decreases and olfactory disorders are still ongoing. Post upper respiratory disorders are another common form of olfactory disorders. Around 33% suffering from upper respiratory disorders experience spontaneous recover within the first 2 years, (Duncan, 1997).

Age-related changes in nose function or defense mechanisms, diet, drugs, genetic factors, or diseases can result in a reduced or inhibited mucociliary transport causing increased likelihood to viral damage, (Brownstein, 1987).

Some viruses are able to change from non-neurotropic to neurotropic after entering the nose like the NWS strain of influenza virus. When inoculated into the nose of mice, this influenza virus can spread to the brain via olfactory and trigeminal nerves, (Reinacher et al., 1983). On the other hand, intraperitoneal injection into mice typically results in the perivenous spread of the virus and the viral antigen is limited to the meninges, chorois plexus, ependymal cells and perivascular locations within the brain parenchyma, (Zaidel et al., 1995). So how and where a virus is entering, has an influence on the way the virus is acting or the body is responds to the infection.

Age:

Age is the most influential factor in the decline of olfactory function in healthy adults. The progress of people suffering from chronic decreased sense of smell by age can be seen in Figure 11 and, in this case, is more severe for men than women, (Doty, 2009):

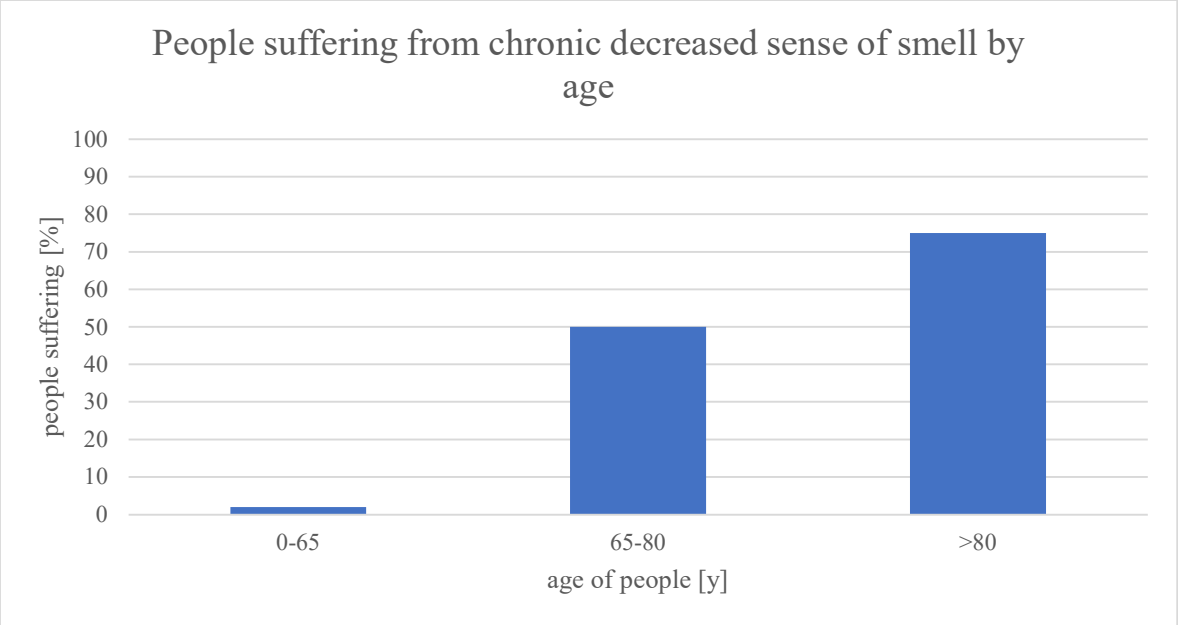

FIGURE 11: Ratio of people suffering from chronic decreased sense of smell divided into different age groups, (exact values from left to right: 2%, 50%, 75%)

The origin of age-related decreased olfactory function can be various ones. They include ossification and closure of the foramina of the cribriform plate, (Krmpotic´-Nemanic´, 1969;

Kalmey et al., 1998), cumulative damage to the olfactory receptors from repeated viral and other disruptions throughout life, (Breihpol et al., 1986).

Toxic Chemicals and Nanoparticles:

Heavy metals (like cadmium, chromium, nickel, and manganese), herbicides, solvents and pesticides are able to influence the olfactory function, especially when exposed chronically, (Doty and Hastings, 2001). Nanoparticles and heavy metals damage the OE and likely enter the brain via the olfactory mucosa. The olfactory sensory neurons (OSN) can absorb cadmium, gold, and manganese and move them with 2.5-3 mm/h to the OB, (Gottofrey, Tjalve, 1991; Tjalve et al., 1996; Tjalve, Henricksson, 1999).

Neurodegenerative diseases:

Olfactory dysfunction is a cardinal feature of several neurodegenerative diseases such as Alzheimer's Disease and Parkinson's' Disease. The deficit in olfaction for both diseases in early-stage patients occurs in 85-90% of cases. Functional imaging measurement showed decreased activation of central odor processing structures, (Doty et al., 1992a; Doty et al., 1992b; Quinn et al., 1987).

Head Trauma:

4-15% of the general population show a trauma-related olfactory dysfunction, (Doty et al., 1997). Smell loss does occur when experiencing skull fractures or fractures of the cribriform plate area but on the other hand, a fracture of the cribriform plate or skull can cause olfactory dysfunction. The average recovery – if it occurs – takes place within one year of the injury, (London et al., 2008). The probability of suffering of loss of smell (LOS) from head trauma is directly relatable to the severity of the trauma, (Doty et al., 1997).

Other disorders:

The LOS has been documented to be linked with cerebellar degeneration. The neurodevelopmental disease, schizophrenia, is indicated by the LOS, (Doty, 2003). Apparent congenital anosmia patients often lack or have hypoplasia of the OB and stalks as shown in 100% patients tested with MRI (magnetic resonance imaging), (Doty, 2009). A summarized distribution of the above-named reasons for olfactory impairment can be seen in the following Figure 12.

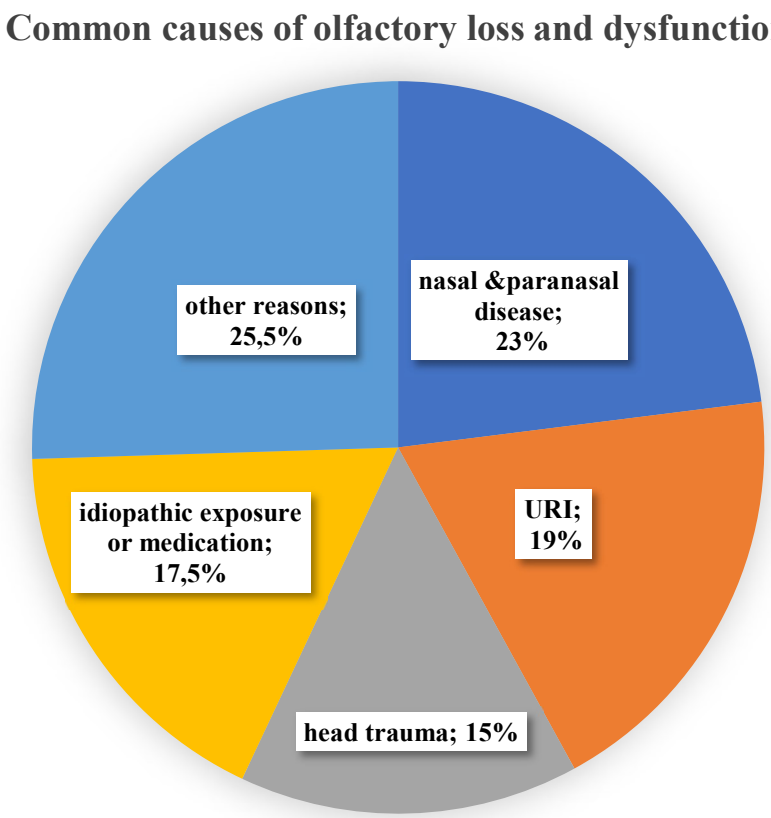

FIGURE 12: Distribution of general olfactory disorders; the ranged percentage of idiopathic exposure or medication was set to 17.5% (actual range: 10-25%); (Adapted and simplified from Daroff and Aminoff, 2014)

3.2. Anosmia

Not being able to smell – anosmia – is a dysfunction of the olfactory system and can have a tremendous impact on people's quality or even affect their health situation. 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).

3.2.1.Reasons for anosmia

It is very difficult to identify the origin of olfactory disorders. Usually the clinician is not able to identify the etiology right away and is forced to perform a neuroradiologic evaluation which also does not give enough insight in the underlying reason for the disorder.

Sensory (URI) or neuronal (head trauma) damage is the most abundant reason for olfactory loss. Contrary to this, a conductive loss is a loss secondary to nasal or sinus pathology meaning that odorants are hindered to reach the receptors and nasal vault while the neuroepithelium is

still intact. A proper diagnosis is very important because a conductive loss needs to be treated in a different way than a sensorineural loss (due to secondary damage). It is crucial to treat obstructions and inflammations of the nose which are interfering with the olfactory transport because there is no specific treatment for sensorineural loss, (Goncalves and Goldstein, 2016).

Anosmia can have various reasons. In the following Table 7, I will list some common examples for reasons for anosmia but the distribution of the most common reasons for olfactory dysfunction and disorders are shown in Figure 12:

TABLE 7: Common examples for reasons for anosmia

Reason for Anosmia	Reference
Alzheimer's disease	Murphy, 1999
Cerebral aneurism	Eriksen et al, 1990
COVID-19	Grant et al, 2020
Head trauma, ethmoid bone damage	Doty et al 1997
Myasthenia gravis	Leon-Sarmiento et al, 2012
Nasal polyps	Ta, 2019
Neurotropic virus	Seo et al, 2009
Old age	Doty (a) et al, 1984
Paget's disease of bone	Wheeler et al, 1995
Parkinson's disease	Doty et al, 1988
Sarcoidosis	Kieff et al, 1997
Schizophrenia	Rupp et al, 2005
Snakebite	Churchman et al, 2010
Toxins (especially acrylates)	Schwartz et al, 1989
URI (sinusitis, cold)	Doty (a), 2001
Zinc-based intranasal cold products, including homeopathics	Harris, 2009

Conductive loss

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.

The mechanism of conductive loss by inflammation and edema is described best in the setting of allergic rhinitis. Nasal congestion is one of the symptoms and underlying the early phase

and late phase of allergic inflammatory response. Crosslinking of (IgE) receptors on mast cells is happening by the contact of an antigen with the nasal mucosa. The crosslinking cells are degranulated and histamine is released, (Pearlman, 1999; White, 1999; Quraishi et al., 2004; Bascom et al., 2012; Bascom et al., 1988; Minshal et al., 1998). In the early phase of the release of inflammatory mediators, leukotrienes, prostaglandins, (TNF)-α and (IL)-4 are produced and released, (Pearlman, 1999; Bachert et al., 1998; Wachs et al., 1989). These mediators cause fluid secretion, congestion and other symptoms, (Bachert et al., 1998). In the chronic, late phase, cytokine or mediator release results in inflammatory cells (including neutrophils, basophils, lymphocytes, eosinophils and mast cells) getting infiltrated by these cells, (Gelfand, 2004).

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). Figure 13 shows the distribution of the pathological site of anosmic patients with conductive loss:

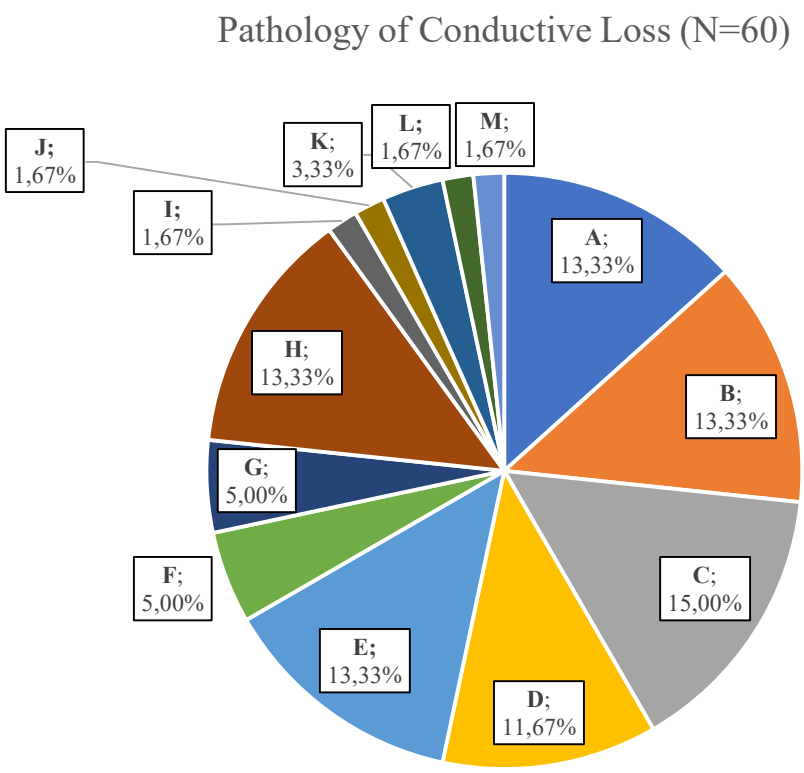

FIGURE 13: Pathological site of 60 patients with conductive olfactory loss; A: Diffuse nasal polyps, an overgrowth of mucus membranes; B: Polyps at the middle meatus (location between the middle turbinate and lateral nasal wall); C: Polyps at the nasal vault (one of two nasal bones; the superior wall of the nasal cube); D: Ostiomeatal (channel linkink frontal sinus, anterior ethmoid air cell and maxillary sinus to middle meatus) disease; E: Chronic ethmoid sinusitis (inflammation in hollow spaces in bones around the nose between nose and eyes); F: Chronic ethmoid and maxillary sinusitis (inflammation of paranasal sinuses); G: Pansinusitis (both sinuses are inflammated); H: Allergic rhinitis (inflammation and swelling of mucus membrane); I: Rhinitis (atrophic); J: Inverting papilloma (non-cancerous tumors in nasal cavities); K: Previous surgery; L: Sphenoid sinusitis (rare disease with potentially devastating complications like brain abscess and meningitis); M: Sarcoid (inflammatory cells forming lumps known as granulomas); (adapted and simplified form: Seiden, 2001).

Sensorineural loss

It can be induced after a trauma or a cold or a post URI. 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 URI, infection with damage on sensory structures, and ciliopathy, (Goncalves and Goldstein, 2020).

Repair of the olfactory functionality is due to the production of new olfactory neurons which are made of basal stem cells. Olfactory sensory neurons are usually replaced every one to two

months, (Graziadei and Montigraziadei, 1979). The OSNs can only be replaced when cytokine production is interrupted.

V. COVID-19 AND ANOSMIA

Prevalence

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, (Heidari et al., 2020).

The first time that the terms “anosmia” and “COVID-19” were mentioned together in google scholar, was by Pérez, 2020.

The first paper that mentions reports of anosmia due to COVID-19 was published in early 2020 by Kowalski.

Age

There exists a risk group for SARS-CoV-2 infection. The older people get, the more the olfactory function decreases, (Ship et al., 1996), and the higher the levels of ACE2 gene expressions was found in the nose of people in between 4-60 years, (Bunyavanich et al., 2020).

Recovery

88 patients self reported suffering from anosmia according to Vaira et al., 2020. They observed, that 79.5% of these patients fully recovered from the dysfunction within 2 months. Typical anosmia, after viral infection (postviral infection), lasts for several months and is due to sensorineural losses (Goncalves and Goldstein, 2020), while in comparison, SARS-CoV-2 induced anosmia - in most cases - lasts just for weeks (Figure 14), (Vaira et al., 2020). Relatively fast recovery and olfactory dysfunction after or at the same time as general or ear-nose-throat symptoms in COVID-19 patients support the theory of conductive loss for the majority of cases, (Lechien et al., 2020, Spinato et al., 2020).

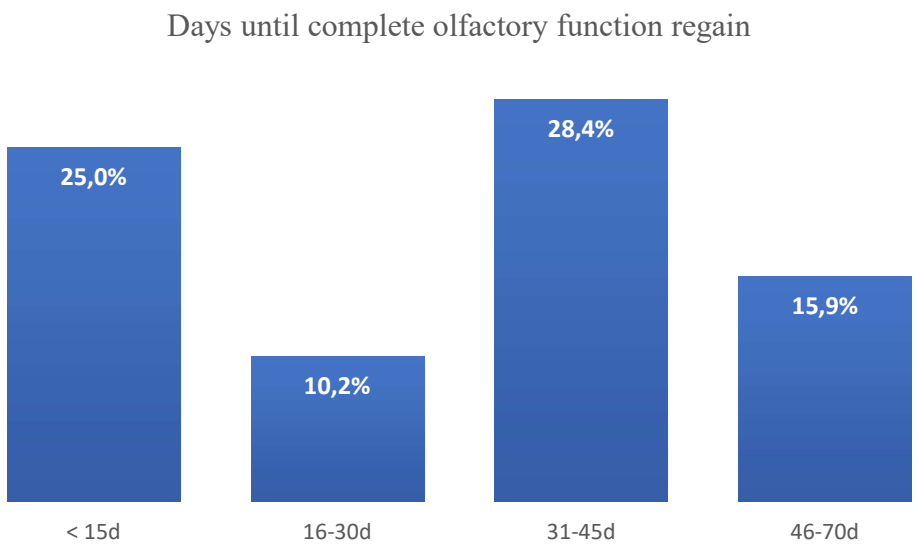

FIGURE 14: Complete recovery duration of olfactory function of selfreported, anosmic, COVID-19 patients; missing patients recovered after 70 days or did not get their sense of smell back until this study was published (Vaira et al., 2020)

Patients with a severe form of COVID-19, show significantly higher Immunoglobulin-G (IgG) levels in nasal secretion and serum than mild cases. IgG is the most common antibody in our blood and extracellular fluid proving a worse spread of SARS-CoV-2 in severe than in mild cases.

While infected, SARS-CoV-2 might be accumulated in nasal goblet cells. These cells and the ciliated cells showed high expressions of ACE2 and TMPRSS2, measured by single cell RNA sequencing, (Sungnak et al., 2020).

For SARS-CoV, a high expression of ACE2 in the nasal respiratory epithelium was shown, (Bertram 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 and Holen, 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.

1. An insight from animal models

Scientists are not always able to experiment ethically correct on humans. Therefore, it is very important to have an insight from animal models.

First, impaired ON function is shown in mice where inflammatory cytokines can be inducibly expressed in the supporting cells of the OE, (Lane et al., 2010). Later on, with continuous production of the imflammatory cytokines, the olfactory neurons are killed. Recovery can be induced by stopping the overproduction of these cytokines. Then, new neurons can be produced by the basal stem cells, (Turner et al., 2010).

Another mouse study performed by Netland et al., observed antigen expressions of SARS-CoV in the brain of transgenic mice and therefore assumed a possible route from OB to the brain. The first antigen expression of SARS-CoV was found around 2.5 days after infection and was most abundant in the OB, (Netland et al., 2008). A large amount of SARS-CoV was also found after 3 days in regions of the cortex, basal ganglia and midbrain which is connected to the olfactory bulb, (Netland et al, 2008). If the virus SARS-CoV-2 is also able to follow the olfactory tract leading to rapid transneural spread, it may explain anosmia as a symptom.

Van Riel et al demonstrated in mouse models that apoptosis (excretion of old, dead cells) of infected olfactory sensory neurons (OSNs) can prevent the virus from spreading to the OB and CNS. As the OSN can be regenerated, this may be a programmed defensive response to neurotropic viruses reducing severity. The low prevalence of severe, anosmic cases due to COVID-19 could be explained by a failure of this defensive response.

2. Possible mechanisms for the non-transient anosmia in COVID-19

Permanent anosmia in COVID-19 patients could potentially suggest permanent damage to the neuronal pathways in the CNS responsible for analysing and processing of the sense of smell.

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, (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).

Most CoVs and many other viruses, invade the OB by proliferation through the cribriform plate. The rodent CoV, mouse hepatitis virus (MHV), whose olfactory sensory neurons (OSNs) do not possess expressions of its MHV receptor, can reach the OB from the nose. Looking at this, it is expected that CoVs can infect the brain from the nasal mucosa, (Butowt and Bilinska, 2020).

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 H 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., 2008). In human brains that were virally invaded by SARS-CoV, a similar pattern was discovered, (Gu et al., 2005).

3. Diagnosis and Treatment

A smell disorder needs to be correctly diagnosed by electrophysiologic, psychophysiological and psychophysical tests, (Doty, 2007; Kobal, 2003). The assessment of smell function usually occurs via the so-called UPSIT (University of Pennsylvania Smell Identification Test), a

psychophysical test, where 40 different odorants are tested and the test can be self-administered within around 15 minutes, (Doty et al., 1984).

Threshold olfactory tests usually consist of a dilution series of an odorant and blank samples, (Laing and Doty, 2003). This test aims to quantify the extent of hyposmia, or identify anosmia.

Because there are a some different reasons for hyposmia and anosmia, and each type of olfactory dysfunction needs to be treated in a different way, some treatment options and future therapy targets are summarized from Saussez et al in Table 8.

People are suffering under rhinosinusitis if an inflammation of the nasal mucosa (Rhinitis) and an inflammation of the mucosa in the nasal sinuses (Sinusitis) occur simultaneously. Etiology of anosmia due to rhinosinusitis is thought to occur because of olfactory cleft obstruction and/or inflammation causing sensorineural dysfunction. An endoscopic sinus surgery for treating the chronic disease (like polyps), together with maximal medical therapy –may improve the healing process. Maximal medical therapy often included oral steroids, (Goncalves and Goldstein, 2016). Therefore, another treatment target for rhinosinusitis as a cause of conductive loss could be olfactory cleft inflammation where new anti-inflammatory as well as new topical delivery methods could lead to an improvement in treating this disease.

Ciliopathy is a disease where the formation of cilia or their function is modified or missing. Anosmia due to ciliopathy can occur if the odorant receptors cannot locate the transduction machinery or the above-named reasons. Most of the mutations occurring in ciliopathy is the loss-of-function alleles, (Goncalves and Goldstein, 2016). As there is currently no treatment for genetic ciliopathy, an option to cure the lack of a gene could be gene replacement via viral gene therapy, where a gene is delivered via a viral system that could express this gene in the targeted cells.

For post-viral olfactory disorder there is currently no treatment option because the exact etiology is still unclear. Scientists expect either an inflammatory response impairing OSN and/or the basal stem cells that are producing new OSNs, or a reduction of basal stem cells due to infection. Olfactory training therapy can be used to treat this disorder by sniffing different odorants twice for 15 seconds throughout the day to train your sense of smell, (Damm et al., 2014). A potential treatment target could therefore be to analyse basal cell signalling pathways in which basal stem cells are forming OSN. Wnt-signalling pathway has an influence on certain basal stem cells. Wnt-signalling is a transduction pathway starting at a specific

protein which is transducing a signal via a receptor on the cell surface to the inside of the cell, (Wang et al., 2011).

Currently there are no specific treatments for anosmia due to head injury. It can be caused by stretching or shearing along the cribriform plate resulting in neuronal death or olfactory fibre damage (temporary). If post traumatic anosmia is due to sensory loss, other reasons must be the cause like damage to the olfactory pathways or OB. Glial scarring could be another cause and potential treatment target. In glial scarring, axons could be prevented from building new synaptic connections, (Goncalves and Goldstein, 2016), and targeting this pathway could lead to a better olfactory treatment option.

TABLE 8: Major causes of olfactory impairment, treatment option, and possible therapeutic trargets, (adapted from Saussez et al., 2020)

Cause	**Current treatment option**	**Potential therapeutic targets**
Rhinosinusitis (a common form of conductive loss)	Maximal medical therapy; Endoscopic sinus surgery	Olfactory cleft inflammation
Genetic Ciliopathy	none	Gene replacement via viral gene therapy
Post-viral olfactory disorder	Olfactory training therapy	Inflammation; Basal cell signalling pathways
Head injury	supportive	Neuron degeneration; Glial scarring

Treatment of anosmia in COVID-19:

Hopkins et al., 2020 formed an expert panel to analyse and suggest possible treatment methods for anosmia in COVID-19 patients. They differentiate between isolated loss of smell and loss of smell related to nasal symptoms.

TABLE 9: List of different treatment options sorted out by an expert panel

Treatment	**Description**
Olfactory training and support	Recommended for LOS durations of more than 2 weeks
Intranasal corticosteroid sprays	Recommended for LOS durations of more than 2 weeks; related to nasal symptoms
Intranasal corticosteroid drops or rinses	Optional for LOS durations of more than 2 weeks; related to nasal symptoms
Oral corticosteroids	NOT recommended for LOS durations of more than 2 weeks with persistent COVID-19 symptoms Optional for LOS durations of more than 2 weeks
Vitamin A drops	No recommendation due to disagreement of the expert panel
Alpha-lipoic acid	NOT recommended for LOS durations of 2 weeks as an isolated symptom or following resolution of any other COVID-19 symptoms
Omega-3 supplements	Optional for LOS more than 2 weeks as an isolated symptom or following resolution of any other COVID-19 symptoms

These are of course just recommendations and each patient should be checked on an individual level.

There are no treatment recommendations for LOS of less than two weeks. Treatment may not be required as most of the treatment should only be applied if the LOS occurs isolated. Most of the patients recover their ability to smell within the first two weeks and therefore no treatment is needed. Optional could be smell training, (Hopkins et al., 2020).

The expert panel also proposed a flowchart to visualize how to diagnose and treat anosmic COVID-19 patients and it is shown below in Figure 15 for general interest.

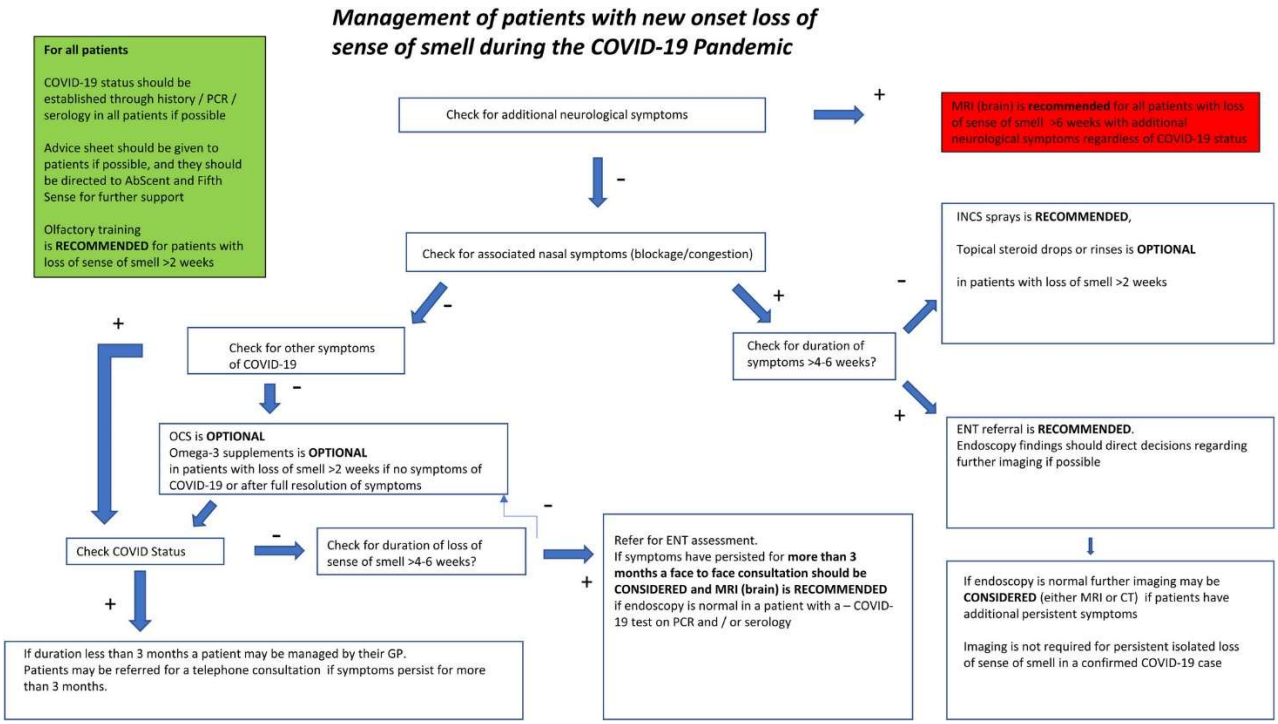

FIGURE 15: Flowchart for management of new onset loss of sense of smell during the COVID-19 pandemic. INCS, intranasal corticosteroids; OCS, oral corticosteroids. Optional indicates that consensus was achived at the 60% and not the 70% threshold, highlighting ongoing uncertainty regarding the usage, (Hopkins et al., 2020).

Materials and methods

A search of literature using different keywords or a combination of them was carried out ('COVID-19', 'SARS-CoV-2', 'SARS', 'neurological symptoms', 'anosmia', 'loss of smell', 'CNS', 'PNS', 'ACE2', 'Olfactory dysfunction', etc.). The search resulted in scientific articles (original or reviews) that were used and, in which other useful references were found and followed. For big topics like the proposed information on SARS-CoV-2 related loss of smell, the same search was performed several times in order to check for updates.

The main websites used for literature research for this thesis were search engines like Google Scholar, PubMed, medRxiv, major journals like Nature, Science, BMJ, and publishers such as Elsevir, Springer, and AAN, and searched up until December 03, 2020. The research on SARS-CoV-2 was limited by December 2019 as COVID-19 was first published early 2020. The huge number of upcoming articles and the fact that this novel disease has been recognized by scientist only for a year up to now limited this research.

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 *Coronaviridae* 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 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 of sense of smell, (Grant et al., 2020). Not being able to smell is a very untypical symptom related to coronavirus infection that can 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 L. et al., 2020).

The main CNS symptoms include headache, arterial and venal thromboses, impaired consciousness and encephalitis, (Mao et al., 2020), and the main PNS symptoms include Guillian-Barré syndrome, (Mao et al., 2020), gustatory and olfactory disorders, (Lechien et al., 2020) including loss of smell (anosmia).

ACE2, the main target for SARS-CoV-2 cell entry, is found in many cells throughout the human body, (Hamming et al., 2004), potentially explaining the many different forms of symptoms of COVID-19. SARS-CoV-2 causes the neuronal problems either direct (conventional) by invading neurons or glial cells, or indirect by secondary factors such as inflammatory responses by cytokines. Indeed, evidence shows that SARS-CoV-2 is capable

of entering the CNS via neuroinvasion at the neural-mucosal interface. As documented by Meinhardt et al., 2020, who showed that RNA and proteins of SARS-CoV-2 were present in anatomically distinct nasopharynx, and brain regions. The olfactory system acts as a neuronal pathway from the epithelium, expressing ACE2, to the CNS, (Desforges et al., 2020). This was shown in other viruses like SARS by Netland et al., 2008. As for SARS-CoV-2, evidence of a similar route exists according to a recent study from Meinhardt et al., 2020, where they supposed the route of SARS-CoV-2 from the nose to the neuroepithelium and via neuronal pathways to the brain stem which is managing respiratory function. Not only neuronal pathways could be the reason for affecting the CNS.

Regarding the indirect way of SARS-CoV-2 affecting the CNS, 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).

Two recent studies analysed human brain tissues of dead COVID-19 patients and did not find enough evidence of SARS-CoV-2 infection to cause local damage in the brain, (Coolen et al., 2020). These two studies therefore indicate a secondary pathway because they found ischemic signs (little blood flow) in the infected tissues, (Solomon et al., 2020), which could be a result of inflammatory immune responses.

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 in the epithelium, which are closest to the environment, (Brann et al., 2020). SARS-CoV-2 RNA and protein expressions have been found in brains of dead COVID-19 patients (Meinhardt et al., 2020; Coolen et al., 2020), but these expressions were not significant. These data suggest that SARS-CoV-2 could enter the supporting cells and further invade the neuronal pathway to the brain. On the other hand, because not a lot of SARS-CoV-2 expressions were found, the virus most probably enters the body 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, in the majority of cases, was found to be a temporary damage in COVID-19, (Klopfenstein et al., 2020).

At the very beginning of the COVID-19 pandemic, three main theories trying to explain the etiology of olfactory disorders related to SARS-CoV-2 infection were proposed:

- Inflammation and obstruction of the olfactory cleft resulting in a conductive loss,
- An injury to the sustentacular (supporting) cells in the OE
- Because of the known neurotropic potential of CoV's: invasion and damage of the neurons in the olfactory tract

Whether or not these hypothesises are true is still not completely understood but research points in the direction of supporting all of them.

Referring only to the course of anosmia in COVID-19 patients, all of the above named hypothesis are possible.

I divided those disease progressions into 3 groups:

The first one is recovery of ability to smell within the first 2 weeks, which encompasses the majority of patients suffering from COVID-19 related anosmia. This group may support the first hypothesis of conductive loss. For conductive loss due to other reasons was shown to follow a quick recovery of olfactory function. Conductive loss can have various primary reasons but the closest one is an URI followed by swollen tissue which blocks the odorants from reaching the receptors within the Olfactory System. URI often results in inflammatory immune responses. Most probably the virus enters the supporting cells that are distributed all around the cilia in the OE, (Morrison and Costanzo, 1990). The supporting cells show the highest amount of ACE2 expressions, (Brann et al., 2020), and inflammation and swelling around the receptor cells could result in a conductive loss. Goncalves and Goldstein, 2016, showed that transient anosmia can be induced by edema of the nasal respiratory epithelium or congestion of the nose from nose polyps or chronic rhinositis, supporting this theory of conductive loss.

Sometimes, these immune responses can get worse resulting in an inflammatory cascade. This cascade can result in an impairment or death of neurons. Basal stem cells are producing new olfactory neurons every one to two months which fits perfectly in the second group where recovery can take up to two months (Graziadei and Montigraziadei, 1979).

Group three is a minority of around 20% of anosmic COVID-19 patients which did not regain their sense of smell back within the first two months from infection. Some of these patients needed more time to recover and some of them did not even gain their senses back yet. This could be due to the neurotropic potential of coronaviruses resulting in impairment of basal stem cells, damaging the machinery that is reproducing new neurons. This is supported by Meinhardt et al., 2020, who showed the neurotropic potential of deceased COVID-19 patients.

COVID-19 related anosmia is very rare in children, (Erdede et al., 2020), and affects the highest number of patients between the age of 40-50, (Klopfenstein et al., 2020). Therefore, I think of a correlation of age, severity and ACE2 expression. This could lead to the assumption that COVID-19 patients from the second or third group explained above could be the older, risk group. The correlation of age and anosmic recovery should therefore be covered in future studies.

Although not a scientific observation per se, 10 friends of mine (age < 30y) who experienced anosmia due to SARS-CoV-2 infection, recovered within the first week since onset of symptoms. Surprisingly, the 3 youngest ones, did only show anosmic symptoms for less than 3 days supporting the assumption of correlation of age and duration of anosmia in COVID-19 patients. This is in line with the proposition outlined here.

In summary, there is some evidence of how SARS-CoV-2 can enter the central nervous system. Research showed that SARS-CoV-2 damages the CNS and that SARS-CoV-2 related anosmia is a major, coronavirus-related untypical symptom. The possibility of SARS-CoV-2 entering the CNS via the OB could be a possible pathway. So far, research indicates an indirect effect of SARS-CoV-2 on the CNS and on the olfactory system via cytokines and other inflammatory molecules. Nevertheless, further investigations of the brain of COVID-19 patients, amongst other things, is crucial in order to get evidence of the entry mechanism of SARS-CoV-2. As of anosmia in COVID-19 patients, it is very likely that, as the receptor neurons do not express ACE2, the cause of the lost ability to smell in the majority of anosmic COVID-19 patients is because of conductive loss due to SARS-CoV-2 invasion of the supporting cells resulting in swelling and the inability of odor molecules to reach the receptors. For patients with a recovery duration of around 2 months, this invasion could be worse, resulting in inflammation and sensorineural loss. More investigation is needed on the patients suffering from anosmia for more than 2 months.

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Abbreviation Appendix

Abbreviation	Meaning
ACE2	Angiotensin-converting enzyme 2
AIS	Acute ischemic stroke
CNS	Central nervous system
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
hCoV	Human coronavirus
HCoV-229E	Type of „human coronavirus“
HCoV-OC43	Type of „human coronavirus“
ICU	Intensive care unit
kb	Kilobases
LOS	Loss of smell
MERS	Middle East respiratory syndrome
MHV	Mouse Hepatitis Virus
NSP	Non structural proteine
OB	Olfactory bulb
OE	Olfactory epithelium
ORF	Open reading frame protein
OSN	Olfactory sensory neurons
orf	Open reading frame gene
PNS	Peripheral nervous system
pp1a	Polypeptide 1a
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
TMPRSS2	Transmembrane protease, serine 2
URI	Upper respiratory infection
WHO	World health organization

Figure appendix

Table appendix