

THE EFFECT OF THE SARS-COV-2 PANDEMIC ON THE INCIDENCE OF PSYCHIATRIC DISORDERS: AN OVERVIEW

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Summary

The SARS-CoV-2 pandemic exerted an unprecedented threat to the population worldwide. This led to a sharp increase in symptoms of depression, anxiety, and PTSD, especially in the early phase of the pandemic. As far as data allowed a comparison with the pre-pandemic era, an increase by odds ratios of up to 3,5 was found. People affected by the virus showed an even greater amount of symptomatology as compared to the general population. Next to psychological stress, direct and indirect effects of the virus on the brain in these persons could be observed. Only on very few occasions, a direct invasion of the virus in the brain could be observed. Yet far more important seems to be the induction of a low-grade inflammation in the brain ("neuroinflammation"). This kind of processes have been observed earlier accompanying many psychiatric and neurologic diseases. In this way, especially cognitive symptoms might persist long after the acute infection has abated.

Keywords: SARS-CoV-2, COVID-19, depressive disorders, cognitive disorders, psychosis, neuroinflammation

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INTRODUCTION

The SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus-Type-2) pandemic led to a worldwide unprecedented state of emergency. During the first months, the mortality rate was highest, reaching up to 20% of hospitalized patients (Adjei et al. 2022) and exerted extreme stress on the public and decision makers. Lockdowns were applied to curb the propagation of the virus which led to further stressors, as the breakdown of everyday life, isolation of individuals, sharp decline of business life with ensuing economic troubles (Aly et al. 2020, Holmes et al. 2020). It turned out the virus came in waves with various variants displaying differences in infectivity, symptomatology, and mortality. Fortunately, as of beginning of 2022, the omicron variant became predominant, displaying high contagiousity yet far less severe symptoms (Adjei et al. 2022). Together with the repeated vaccination of broad parts of the population and the improved possibilities to treat the acute symptoms of the infection, the threat of the virus abated and ultimately led to an end of the state of pandemic.

The effect of SARS-CoV-19 on the incidence of psychiatric disorders thus can be viewed in two aspects (Rittmannsberger et al. 2022). On the one hand, the effects of the pandemic on the population as a whole, and on the other hand the effects on persons actually infected with the virus. The latter are affected by all fears and troubles afflicting the population as a whole, plus the psychological burden of being a victim of the virus themselves, plus

the possible effects of the virus and the resulting somatic sequelae on the brain. Both aspects will be discussed in the following passages.

EFFECTS OF PANDEMIC ON THE GENERAL POPULATION

There are numerous studies dealing with the state of the general population during the pandemic, covered by various meta-analyses, summed up in Table 1. Studies mostly dealt with symptoms of depression, anxiety, post-traumatic stress disorder (PTSD), stress and insomnia and all found very high proportions of affected people. As far as comparisons with investigations prior to the pandemic were possible, numbers were 3 to 4 times higher (Cénat et al. 2021). Yet these numbers must not be equated to diagnoses since these investigations usually were done by rating scales applied online or by telephone, defining cases by exceeding certain thresholds in the scales. As for PTSD, usually only symptoms were counted without making sure that a traumatic experience preceded the symptoms. In most instances samples were not representative. Nevertheless, these results depict a high load of symptoms in the population.

Methodologically more sound are investigations relying on data gathered already before and repeated during the pandemic. For example, the US Census Bureau yearly conducts an investigation on anxiety and depression of the American population. Though rating scales are applied

Table 1: Meta-analyses on psychiatric symptoms during the COVID-19 pandemic (in chronological order concerning endpoint of data collection)

Symptoms	Wu et al. (2020)	Krishnamoorthy et al. (2020)	Xiong et al. (2020)	Cénat et al. (2021)	Lakhan et al. (2020)	Bonati et al. (2022)
Anxiety	32	26	6-60	15	35	6-70
Depression	31	24	15-48	17	20	3-83
PTSD		15	7-54	22		5-30
Insomnia		34		16		
Stress	41	26	8-82	10	53	15-40
N studies/persons	53/222.000	50/172.000	19/93.000	68/189.000	16/113.000	105/n.a.
Publications covered till	3/2020	4/2020	5/2020	5/2020	6/2020	4/2021

only online as well, the results between time points show excellent comparability as of the fixed methods and the samples' carefully weighting to be representative und adjusted for nonresponse. Collating results gained during April and May 2020 with the those of 2019 showed an increase of relative risk by an odds ratio of 3,5 in 2020 (Twenge & Joiner 2020). The Global Burden of Diseases Study found an increase of depression of 28% and of 26% for anxiety disorders during the year 2020, amounting to a plus of 53 million cases of depression and 76 million cases of anxiety disorders worldwide (COVID-19 Mental Disorders Collaborators 2021). Of course, depression, anxiety and PTSD were not the sole disorders affected by the pandemic. Especially in the first year of the pandemic increased symptoms (concerning severity as well as frequency) of obsessive-compulsive disorders (OCD) were reported (Benatti et al. 2020, Prestia et al. 2020, Storch et al. 2021). For alcohol use, most studies found an increase, especially in those persons already showing a pathological consume pattern (Weerakoon et al. 2020) or more affected by anxiety or depression (Capasso et al. 2021, Oksanen et al. 2020, Yazdi et al. 2020), whereas consumers of illegal drugs showed no change (Fuchs-Leitner et al. 2020).

Longitudinal studies showed that with time passing numbers of symptomatic persons decreased as people became more accustomed to the pandemic (Bendau et al. 2021, van der Velden et al. 2021).

PSYCHIATRIC SYMPTOMS IN PERSONS INFECTED WITH SARS-COV-2

As already mentioned, the stress exerted by the pandemic should be felt still more by people suffering from COVID-19, especially if they needed inpatient treatment. A meta-analysis (Krishnamoorthy et al. 2020) comparing depression, anxiety, and PTSD in persons of the general population with persons hospitalized for COVID-19 showed increased rates of the three symptom clusters in the affected patients.

Yet in these persons also biological processes affecting the brain can contribute to the symptoms, in the acute phase as well as in the time thereafter, usually termed "Long-Covid" (Rabady et al. 2021). To understand these processes, it is necessary to take a closer look at the effects the virus exerts on the brain.

Very soon after the beginning of the pandemic one had to recognize that SARS-CoV-2 affects not only the respiratory system but other organs too, among them the brain. This became obvious when cases of COVID-19 with neurological symptoms appeared (Mao et al. 2020, Varatharaj et al. 2020). A metanalysis showed that up to one third of hospitalized patients showed at least one neurological symptom (Misra et al. 2021). Various ways in which the virus might enter the brain were discussed: retrograde passage through cranial nerves, especially N. olfactorius, but also N. glossopharyngeus and N. vagus (Bodnar et al. 2020, Ritchie & Chan 2021), via the hematogenous route by damaging the blood-brain-barrier (BBB) or via spaces lacking the BBB as the periventricular organs or the

choroid plexus, or through infected cells of the immune system as “trojan horses” (Steardo et al. 2020). None of these possibilities could be definitely proven yet it turned out, that even in cases with neurological symptoms the virus could be detected in the brain of only a minority of patients (Fotuhi et al. 2020, Schweitzer et al. 2022).

The most frequent psychiatric disorder in severely ill patients with COVID-19 is delirium (Butler et al. 2022). Up to 32% of inpatients suffer from delirium (Shao et al. 2021) rising to up to 80% in patients on intensive care units (ICU) (Hawkins et al. 2021, Pun et al. 2021, Ragheb et al. 2021). As always in delirium there are multiple causal contributions. Since COVID-19 mainly is an infection of the respiratory tract, hypoxemia is of importance. Then the virus causes an intensive systemic inflammation (often termed as “cytokine storm”) and a prothrombotic state. Finally, failure of other organs, as kidneys, heart or liver can contribute to compromise brain function. Delirium may be the starting point of several other disadvantageous outcomes. It increases the risk of death by factor 2-3 (Hariyanto et al. 2021, Pranata et al. 2021, Shao et al. 2021). Many patients after ICU treatment for COVID-19 show long lasting cognitive impairments and symptoms of depression, anxiety and PTSD forming an overlap of Long Covid with “post intensive care syndrome” (PICS) (Stracciari et al. 2021, Vialatte de Pémille et al. 2022). The duration of the delirious state is a predictor of the intensity of cognitive damage thereafter (Kotfis et al. 2020, Ramage 2020).

Cognitive dysfunctions are not constrained to patients during severe or after severe illness but are also found in patients with less severe or even asymptomatic courses of infection (Douaud et al. 2022, Hampshire et al. 2021). A meta analysis of studies on long covid more than a year after infection revealed cognitive complaints concerning memory and concentration in 19% of patients (Han et al. 2022). In neurologic outpatient clinics for post Covid-19 sequelae patients with “brain fog” comprise up to 80% of patients (Graham et al. 2021). Yet often cognitive complaints are not detectable by neuropsychological tests and seem to be more closely related to affective disorders (Finsterer & Mehri 2023, Krishnan et al. 2022, Sia et al. 2023).

This leads us back to the question whether SARS-CoV-2 can damage the brain even in mild cases of infection, the issue of “neuroinflammation (NIF)” or “mild encephalitis”. As already mentioned, SARS-CoV-2 even in cases with severe symptoms only rarely is found in the brain. Yet this does not mean that the infection has no effect on the brain at all and signs of a low-grade inflammation are frequently found (Cosentino et al. 2021, Matschke et al. 2020). SARS-CoV-2 has a high affinity

for vascular endothelium, spreads easily to different organs besides the respiratory tract and therefore has been called a “vascular disease”(Jonigk et al. 2021). It fosters a sometimes most intensive systemic inflammation (often called “cytokine storm”) and prothrombotic state. All these mechanisms together can contribute to mediators of inflammation to cross the BBB and induce NIF. The main process of NIF is activation of microglia and astrocytes, being the brain’s autochthonic immune cells. Activated microglia change their morphologic appearance to macrophage and turn their function from homeostatic support of neurons to massive production of proinflammatory cytokines, which not only intensify inflammation but also compromise neurons and myelin sheets of their axons (Solomon 2021, Woodburn et al. 2021). NIF is known to accompany many psychiatric disorders, as affective (Hodes et al. 2014), psychotic (Barron et al. 2017, Doorduin et al. 2009) and degenerative disorders like dementia (Domingues et al. 2020, Gonçalves de Andrade et al. 2021). Epigenetic mechanisms can extend the activated state of microglia far beyond the acute infection making the brain more vulnerable for further stressors (Tizenberg et al. 2021). There are data supporting the view that COVID-19 has special effects on the brain compared to other infections as the group at the University of Oxford could show in a series of consecutive papers (Ley et al. 2023, Taquet et al. 2020,2021,2022). An analysis of electronic health records of 89 Million patients comparing patients after COVID-19 with controls found an increased risk for psychiatric disorders in the aftermath (Taquet et al. 2020). Six months after infection with COVID-19 data showed that neurologic and psychiatric disorders were more frequent after COVID-19 than in persons with other respiratory infections (Taquet et al. 2020). This could be still found after 2 years (Taquet et al. 2022). Yet while the prevalence of depressive, anxiety and sleep disorders returned to the level seen with the other infections, dementia, cognitive disorders, and psychosis remained elevated (Ley et al. 2023).

Especially in the early days of the pandemic, the possibility of an increase in psychotic disorders was discussed (Brown et al. 2020, Kępińska et al. 2020, Vasilevska et al. 2021, Watson et al. 2021), referring to the influenza pandemic of 1918/19 when in the aftermath of the infection a great deal of cases with encephalitis lethargica and psychoses, then mistakenly diagnosed as dementia praecox, were observed (Menninger 1919). Reviews of case reports of psychoses on the context of COVID-19 showed that only a modest number of cases were reported and that a good deal of these cases were difficult to distinguish from delirium. An interesting finding was an almost equal number of reports in persons without infection in

whom most probably the stress induced by the pandemic had led to a kind of reactive psychosis. The importance of situational factors is underlined by the finding that all cases were reported during the first half year of the pandemic and that thereafter the reporting about this type of psychosis ceased whereas the reports of psychotic patients with SARS-CoV-2 infection further continued.

CONCLUSION

The SARS-CoV-2 pandemic has had widespread effects on the psychological wellbeing of the population. In this paper we wanted to focus on the reactions of people to the emergence of the pandemic and on the possible effects of the virus on the affected persons brains. Since our possibilities to assess molecular processes in the

brain, despite the huge scientific advances during the last decades, still are very limited, as well as our knowledge about the physiological processes of psychiatric diseases, much has to remain uncertain or hypothetical. Still, there is much evidence that COVID-19 not only affects us psychologically, but also through changes in brain metabolism and function. The widespread societal sequelae of the pandemic which maybe are still more enduring could not be covered by this paper.

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