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Immunity

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Perspective

What SARS-CoV-2 does to our brains

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https://doi.org/10.1016/j.immuni.2022.06.013

SUMMARY

Neurological symptoms in SARS-CoV-2-infected patients have been reported, but their cause remains unclear. In theory, the neurological symptoms observed after SARS-CoV-2 infection could be (1) directly caused by the virus infecting brain cells, (2) indirectly by our body's local or systemic immune response toward the virus, (3) by coincidental phenomena, or (4) a combination of these factors. As indisputable evidence of intact and replicating SARS-CoV-2 particles in the central nervous system (CNS) is currently lacking, we suggest focusing on the host's immune reaction when trying to understand the neurocognitive symptoms associated with SARS-CoV-2 infection. In this perspective, we discuss the possible immune-mediated mechanisms causing functional or structural CNS alterations during acute infection as well as in the post-infectious context. We also review the available literature on CNS affection in the context of COVID-19 infection, as well as observations from animal studies on the molecular pathways involved in sickness behavior.

INTRODUCTION

With the appearance and global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), many observations of neurological symptoms in SARS-CoV-2-infected patients have been reported. Subsets of infected patients show neurological symptoms in the acute phase, most of which are rather unspecific (general weakness, dizziness, headache, nausea), and among survivors of infection, specific neurological symptoms like taste and smell disturbances (dysgeusia and anosmia) and non-specific symptoms such as fatigue and cognitive impairment appear or are still present even months after the initial infection was resolved (Huang et al., 2021; Figure 1).

However, similar to many initial interventional studies leading to misleading expectations (Janiaud et al., 2021), the early large and highly cited observational studies not only lacked scientifically adequate control groups but lacked any type of control at all (Carfì et al., 2020; Mao et al., 2020) (see Box 1). Without proper controls, one crucial piece of information is lacking: the regular or natural incidence of the observed symptom or disease. If we compare incidences of neurological symptoms among the millions of SARS-CoV-2-infected subjects to the normal (i.e. naturally occurring) incidences of neurological symptoms, we avoid creating a statistical effect that can also be observed when such symptoms are only recorded chronologically in correlation to or as coincidence of SARS-CoV-2 infection. More recent studies try to tackle this issue by including proper controls such as other respiratory infections (Taquet et al., 2021) and by referring to increased incidences and hazard ratios of e.g. stroke, intracranial hemorrhage, dementia, and neuromuscular diseases in patients who required hospitalization or admission to the intensive care unit (ICU). Other recent important large-scale observational studies report on increased incidences of neurocognitive impairments and mental disorders in people who survived mild to moderate SARS-CoV-2 infections (Cohen et al., 2022; Daugherty et al., 2021).

Yet another variable or insecurity is due to the often-imprecise definition of neurological symptoms. Self-reported symptoms that cannot possibly be objectified and different semantic understandings or definitions e.g. of questionnaires can result in rather blurry pictures. In addition, socio-cultural differences in the perception of and/or handling of symptoms may also be confounding factors. Moreover, the cause for the same symptom may vary substantially, which will not be discriminated by the self-reporting person. Dizziness, for example, can result from a rotating vertigo of cochlear origin but can also be caused by a light-headedness because of decreased cardiovascular supply of the brain—while a derealization phenomenon due to a panic attack could equally result in the subjective perception of dizziness. Thus, grouping symptoms of different origins under the same umbrella term inevitably will result in an oversimplification and, subsequently, in erroneous assumptions, possibly creating an unsound basis thwarting further stringent scientific utilization.

To our knowledge, so far, only case reports and series (see Box 1) have suggested COVID-19-associated specific neurological impairments concerning the central nervous system (CNS), such as seizures, meningoencephalitis, and acute disseminated encephalomyelitis (ADEM), or the peripheral nervous system (PNS) (For a detailed review of the current knowledge about the link between peripheral nervous disease and SARS-CoV-2 infection, we recommend Taga and Lauria [2022].), such as Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), mono- or polyneuropathy, and

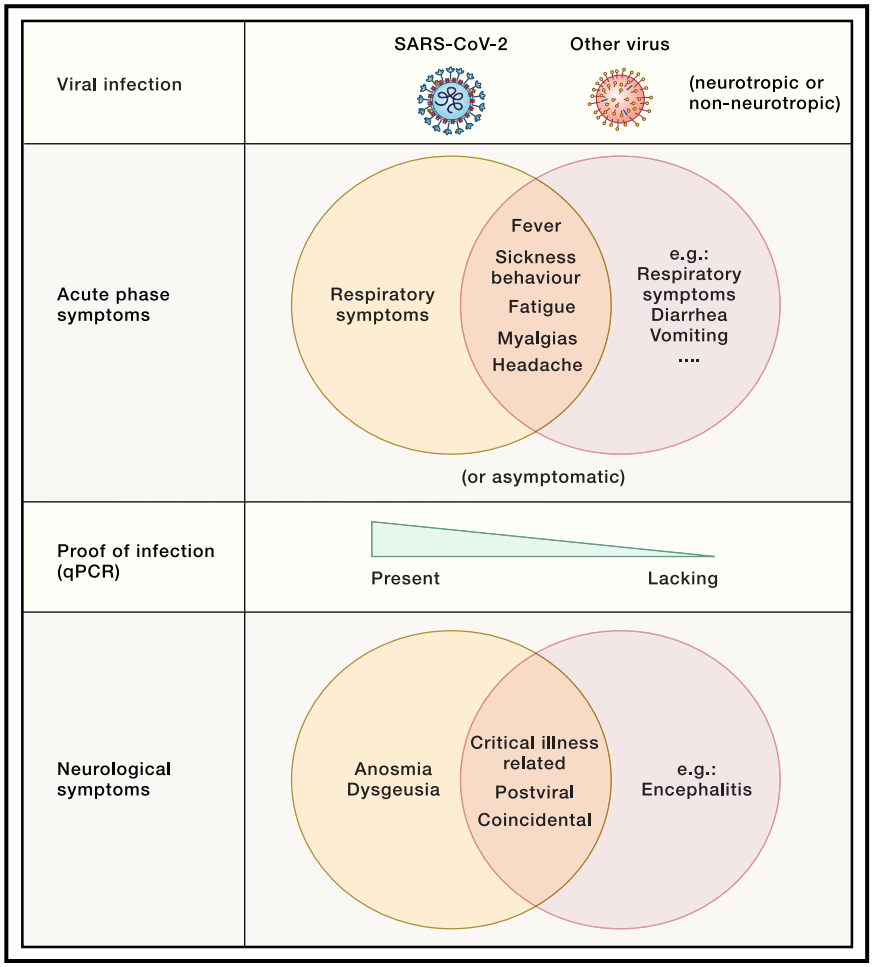

Figure 1. Clinical manifestations of SARS-CoV-2 in relation to other viral agents

Viral infections can lead to acute phase symptoms that are largely unspecific with regards to the viral agent in question, such as fever, fatigue, myalgias, and headache. Depending on the virus and its tropism, more specific effects can also be observed. Any viral infection can, however, also be asymptomatic. One notable difference between infections with SARS-CoV-2 in comparison to other viruses is the frequency of testing. Because of the high number of diagnostic qPCR tests, many asymptomatic or mild symptomatic infections were identified or "proven," which is much less frequently the case with most other (respiratory) viruses. Neurological symptoms occurring after an infection with SARS-CoV-2 could therefore have been more often causally linked to that infection, compared to instances of neurological symptoms occurring after a viral infection that was not clearly identified as such (e.g. where the viral agent went undiagnosed). Furthermore, neurological symptoms chronologically occurring after any type of infection can be coincidental or due to co-occurring factors (such as critical illness related in severely ill patients).

myasthenia gravis (Mahmood et al., 2022; Morgello, 2020; Restivo et al., 2020; Sohal and Mansur, 2020; Song et al., 2021; Srivastava et al., 2021).

Because of the high number of newly occurring infections in a global pandemic, however, case studies need to be regarded with even more precaution than in non-pandemic times. Moreover, observed effects need to be put into context and in relation to the number of cases: if an infection with a viral agent occurs that only a few people encounter globally, effects, symptoms, and consequences have more weight than those of few individuals in a cohort of millions of infected people—even if each patient and situation per se, without any doubt, is a relevant one. Along those lines, whereas GBS has been associated with COVID-19 in case studies, in a more rigorous epidemiological and cohort study approach, no association between COVID-19 and GBS was detected (Keddie et al., 2021) (see Box 1).

The CNS and the immune system are the most complex systems in our body and tightly interact via the neuroimmune axis. We therefore provide a brief summary of the main players and components of these two systems, with a special focus dedicated to the barriers and interfaces of the CNS (Box 2).

The main question we aim to discuss in the following is whether the neurological symptoms (or presumed neurological symptoms, see introduction) observed after SARS-CoV-2 infection are (1) directly caused by the virus infecting host cells, (2) indirectly caused by our body's local or systemic immune response toward the virus, (3) caused by co-occurring phenomena, or (4) a result of a combination of (1)–(3). Furthermore, we provide insights into possible autoimmune mechanisms behind neuroimmunological manifestations in a post-infectious context. The almost indigestible plethora of SARS-CoV-2-related publications over the last two years, generated and published under the pressure of the global pandemic, resulted in a temporary sleep mode of the typically applied (and required) stringent scientific peer review rules and procedures. We propose a critical reevaluation as well as an interdisciplinary discussion of the scientific findings so far between the various disciplines, including neurosciences and immunology.

CNS and SARS-CoV-2–what do we know so far?

Single cases of SARS-CoV-2 RNA detection in cerebrospinal fluid (CSF) or the CNS parenchyma have been described (Moriguchi et al., 2020), but larger case series of patients with acute COVID-19 and neurological symptoms did not find SARS-CoV-2-RNA nor increased numbers of leukocytes in the CSF (Alexopoulos et al., 2020; Neumann et al., 2020; Normandin et al., 2021; Placantonakis et al., 2020). However, levels of intrathecal interleukin (IL)-6, IL-8, IL-15, and macrophage inflammatory protein-1β (MIP-1β) were increased in a subset of patients and apparently correlated with signs of BBB disruption (Normandin et al., 2021). On the other hand, the concentration of intrathecal proinflammatory cytokines appeared to be lower when compared to patients with viral encephalitis or various neuroinflammatory diseases (Bernard-Valnet et al., 2021; Heming et al., 2021). Anti-SARS-CoV-2 antibodies were described in the

Box 1. Hierarchy of evidence

How can we address the relation between SARS-CoV-2 infection and neurological symptoms? Here, we present some possible scientific approaches, starting with methods with low levels of relative strength and going to more powerful methods.

DESCRIPTIVE STUDIES

Case report: report of one or a few (usually not more than four) case(s) with a specific neurological affection during or after SARS-CoV-2 infection.
Case series: similar to case reports but with more patients of similar cases. No upper or lower limit of numbers exists, but usually there are more than four and less than ten.

BIOLOGICAL MODELS

Animal study: testing single factors and/or effects in model organisms to prove biological plausibility. The important challenge is the translation to the human situation.
In vitro study: testing single factors on brain cells and/or tissue of human or non-human origin, missing the complex interactions between physiological systems (e.g. immune and nervous systems).

OBSERVATIONAL STUDIES

Cross-sectional study: at one given time point, groups, e.g. SARS-CoV-2 infected and uninfected individuals, are compared according to one or more neurological signs. This implies no directionality between cause (infection) and effect (neurological sign). One only can calculate measures of association.
Case-control study: compares patients and/or diseases with and without the respective neurological sign retrospectively, e.g. patients with fatigue (cases) and without fatigue (controls). The design needs a definition of cases based on inclusion and exclusion criteria. The effect (neurological sign) to cause (infection) is investigated. The researchers are setting the prevalence, so this is good for rare effects and long latencies but more susceptible to selection bias compared to cohort studies.
Cohort study: longitudinally, in a group of individuals (cohort) coming from the same source population, regardless of their infection status or neurological signs, researchers can determine outcomes. The cause (e.g. infection) to effect (e.g. neurological sign) is observed and risk ratios are calculated. Prospectively (looking forward), these studies can address the temporal relationship between cause and effect. No control cohort is defined; the comparison is between different outcome groups of the same cohort. This design needs very large sample sizes for rare outcomes.

RANDOMIZED CONTROLLED CLINICAL TRIALS

The best way to identify causal effects on the CNS of SARS-CoV-2 because they theoretically eliminate all preexisting differences between the infected and control group. However, it is questionable whether this design is appropriate in this context, as exposure to SARS-CoV-2 is a risk factor for negative health effects.

CSF of patients with COVID-19 and, in the majority of cases, these appeared to originate from the peripheral blood rather than being generated intrathecally (Alexopoulos et al., 2020; Bernard-Valnet et al., 2021). Moreover, autoantibodies against neuronal and glial antigens could be identified in critically ill COVID-19 patients with pronounced neurological symptoms (Franke et al., 2021; Song et al., 2021), raising the question of an autoimmune pathomechanism at work. In line with this, critically ill COVID-19 subjects showed signs of extrafollicular B cell activation reminiscent of what can be seen in certain autoimmune diseases (Woodruff et al., 2020). Other findings suggest a compartmentalized immune response, with clonal expansion of $CD4^+$ T cells in the CSF that could not be found in the blood (Heming et al., 2021). Similarly, B cells and plasma cells in the CFS seem to differ from the ones in the blood in patients with COVID-19, resulting in different anti-SARS-CoV-2 antibody profiles.

Several studies in the first year of the pandemic—including one from our group—reported the detection of SARS-CoV-2 RNA in the CNS parenchyma or adjacent structures (Matschke et al., 2020; Meinhardt et al., 2021; Puelles et al., 2020; Solomon et al., 2020). This fueled the speculation about a multi-organ tropism of SARS-CoV-2. However, the initial interpretations of immunohistochemical and *in situ* hybridization with respect to the presence of SARS-CoV-2 need to be re-assessed critically, because in the meantime it has become clear that control samples of non-COVID-19 subjects can also give rise to similar signals (Meinhardt et al., 2021). Importantly, so far no overt viral particles could be identified within the CNS by electron microscopy that fulfill the minimal ultrastructural criteria of coronavirus-like particles as ultimate proof for SARS-CoV-2 infection (Dittmayer et al., 2020; Goldsmith et al., 2020), in contrast to other tissues including olfactory mucosa, where intact viral particles have been shown and SARS-CoV-2 infection of neurons within the mucosa occurs presumably stochastically (Meinhardt et al., 2021).

Detecting viral RNA in a tissue does not equal a genuine infection of this tissue and does not necessarily indicate active replication of the virus. Detection of SARS-CoV-2 RNA in the CSF or

Box 2. Components of the CNS

The CNS is undoubtedly greater than the sum of its parts, but knowing the latter is a required starting point: the most abundant cellular components of the mammalian brain and spinal cord are glial cells (astrocytes, oligodendrocytes, and microglia) and neurons, both summing up to around 85 billion cells per adult—in contrast to the 10:1 ratio that was assumed in the 20th century (Azevedo et al., 2009; von Bartheld et al., 2016). These functional and supportive cellular units of the CNS parenchyma are surrounded by distinct barriers (*glia-limitans*; *pia, arachnoid,* and *dura mater*; skull, vertebrae) and fluid-filled or virtual spaces (ventricles, subarachnoid space, subdural space, perivascular space).

The historical paradigm of the CNS parenchyma being an immunologically tolerant or privileged site has been regularly challenged over time (Hasek et al., 1977; Medawar, 1948) and as of today, we can conclude: it is complicated. The CNS is *immunologically specialized*, in the sense that it shows tighter mechanisms of immune regulation and a more immunosuppressive microenvironment in comparison to other organs (Forrester et al., 2018; Streilein, 1993). It is important to note, however, that the meninges and ventricles behave differently from the CNS parenchyma, and foreign tissue grafted there provokes an immune response comparable to that in other organs (Mason et al., 1986).

In the parenchyma, microglia constitute by far the largest resident population with immune cell properties. They are brain resident innate immune "watchdogs" and play a fundamental role in regulation of immune reactions and homeostasis (Hickey and Kimura, 1988; Prinz et al., 2021). Besides microglia, other tissue-resident myeloid populations including perivascular, choroid plexus (CP), and meningeal (dural and leptomeningeal) macrophages (border-associated macrophages, BAMs), as well as dendritic cells (DCs), monocytes, and granulocytes (neutrophils, basophils, and eosinophils), have been identified within meninges, perivascular spaces, and the ependyma of mice (Goldmann et al., 2016; Mrdjen et al., 2018). Non-myeloid immune cells are scarce or absent in the CNS parenchyma, but several distinct subsets of B cells, T cells, and innate lymphoid cells (ILCs) can be found within the meninges (Korin et al., 2017; Mrdjen et al., 2018; Schafflick et al., 2021).

Recent studies in mice revealed that myeloid cells and B cells next to CNS borders can migrate from the bone marrow of adjacent bony structures to the meninges via specialized channels (Brioschi et al., 2021; Cai et al., 2019; Cugurra et al., 2021). Under the pretense that we can extrapolate this to humans, this adds a fourth route for immune cell migration into the CNS, in addition to (1) the blood to CSF via the CP route, (2) blood to subarachnoid space via the meningeal vessels route, and (3) the blood to perivascular spaces route (Ransohoff et al., 2003).

In addition to the immune cells mentioned so far, the CNS harbors other cells that are not primarily seen as immune cells but are more and more understood to significantly contribute to immune reactions as well: endothelial cells, pericytes, smooth muscle cells, mesenchymal cells, and epithelial cells.

INTERFACES BETWEEN CNS PARENCHYMA AND CIRCULATING FLUIDS

Arterial vessels located in subarachnoid space and the ones penetrating into the CNS parenchyma are composed of non-fenestrated endothelial cells with tight junctions and arteries penetrating into the CNS parenchyma. They form, together with astrocytic end feet and pericytes, the well-known (but ill-termed) blood-brain-barrier (BBB) (Derk et al., 2021).

Arterial vessels in the dura, the leptomeningeal space, and CPs, on the other hand, possess fenestrated endothelia that lack tight junctions, and blood flowing through these is separated from the CSF by a monolayer of cells (arachnoid and ependymal layer, respectively) tied together by tight junctions, constituting the BCSFB (Engelhardt and Ransohoff, 2012). CSF is mostly produced by CP cells but also consists partly of interstitial fluid derived from the CNS parenchyma and filtered through the BBB. It circulates through the subarachnoid space, the ventricles, and the central canal of the spinal cord and is renewed several times per day (Damkier et al., 2013). CSF drains through arachnoid granulations via dural venous sinuses into the blood stream and through dural lymphatics at the base of the skull and spinal nerve roots to cervical and lumbar lymph nodes, as well as through nasal lymphatics via the cribriform plate to cervical lymph nodes (Foldi et al., 1966; Kida et al., 1993; Widner et al., 1988). The rediscovery of meningeal lymphatic vessels created an increased awareness for that route in the last decade and there is evidence that antigen-presenting cells (APCs) can exit the CNS via this path (Aspelund et al., 2015; Louveau et al., 2015; Ma et al., 2017). This challenges the previously held understanding that the afferent arm of the adaptive immune response to CNS infections only relies on the drainage of soluble antigen to peripheral lymphoid structures (Galea et al., 2007a).

So far, lymphatic vessels have not been identified within CNS parenchyma. Instead, interstitial fluid drains—in addition to the route of CSF—from the parenchyma into the intramural perivascular spaces between endothelial cells and astrocytic endfeet (Virchow-Robin space) around arterioles and venules of the white matter and basal ganglia toward cervical lymph nodes (Cserr et al., 1981; Lam et al., 2017; Szentistvanyi et al., 1984; Zhang et al., 1990). This "glymphatic pathway" is separated from the CSF by the pia mater (Iliff et al., 2012) and is considered a second route of the afferent arm of the immune system, carrying antigens (but not APCs) from the CNS parenchyma to regional lymph nodes (recommended reviews: Engelhardt et al.,2016, Ampie and McGavern, 2022).

In the cerebral cortex, the perivascular space is only virtual, in contrast to what was first assumed from erroneous interpretations of sample preparation artefacts (Morris et al., 2016).

Circumventricular organs (CVO), midline anatomical regions (subfornical organ [SFO], area postrema [AP], vascular organ of lamina terminalis [VOLT], median eminence, pituitary neural lobe, pineal gland) around the third and fourth ventricles, lack a classical BBB

(Continued on next page)

Box 2. *Continued*

but instead possess highly permeable fenestrated capillaries that are lined by tanycytes, specialized ependymal and/or glial cells, allowing the passage of peptides and hormones from the CNS to circulating blood (Kaur and Ling, 2017; Wislogki and King, 1936). These "windows of the brain" create a close contact between blood, CSF, and CNS (neurons and tanycytes) (Gross and Weindl, 1987), allowing for the transformation of neural information into humoral responses and thus affecting various aspects of full body homeostasis, ranging from metabolism to cardiovascular finetuning, hormone regulation, and even behavior (Cardinali, 1983).

INTERFACE BETWEEN THE CNS PARENCHYMA AND ITS NEIGHBORS

The meninges around the CNS are far from being mere mechanical barriers but rather active parts of CNS immunity and homeostasis, constituting a meeting point between circulating immune cells and CNS antigens (Bartholomaus et al., 2009). A large population of resident immune sentinels including B and T cells, macrophages, DCs, mast cells (MCs), and ILCs has been described in the dural layer of the meninges of rodents, even in the absence of neuroinflammation (Schafflick et al., 2021). Ectopic follicle-like structures harboring B cells were found in the meninges in many patients with secondary progressive multiple sclerosis (Howell et al., 2011).

Recent evidence suggests that antigens from the CNS parenchyma passing through the CFS are additionally processed by APCs in the dural sinuses, where they are presented to circulating T cells (Rustenhoven et al., 2021). This can be viewed as an additional peak hole for circulating immune cells to monitor CNS infections, thus making the dural sinuses an important neuroimmune interface.

Other interfaces of the CNS and the outside or inside world are: eyes (neural retina, blood-retinal barrier), nose (cribriform plate, olfactory nerve and bulb), ears (blood-labyrinth barrier), peripheral nerves, and nerve roots of the spinal cord.

CELL TRAFFICKING

The differences in barrier composition and integrity of the interfaces affect pathogen entry, cell trafficking, antigen presentation, waste drainage, and bioavailability of chemical or pharmaceutical substances to the brain. Moreover, there is a plasticity allowing for adaptation to different physiological or pathological conditions. This is especially true for immune cell trafficking, with e.g. the BBB becoming more permeable in the context of inflammation, allowing for transmigration of immune cells that under normal conditions would not be able to cross from the blood to the CNS parenchyma (Alvarez et al., 2011; Engelhardt and Ransohoff, 2012; Galea et al., 2007b). Further data suggest that in experimental autoimmune encephalomyelitis (EAE), autoaggressive T cells pass through lung tissue first, where their gene-expression profile substantially changes, with upregulation of proteins facilitating endothelial barrier transgression ("migratory mode") and antigen encounter, thus potentially allowing them to cross an intact BBB. (Odoardi et al., 2012).

There is also evidence suggesting a recruitment of circulating immune cells from the blood to the CSF via the highly vascularized CPs (Haas et al., 2020; Kivisakk et al., 2003; Kunis et al., 2013; Shechter et al., 2013; Strazielle et al., 2016).

At homeostasis, the CSF contains around 3,000 leukocytes per mL, 80% of which are T cells with an increased CD4 to CD8 ratio as compared to the blood (Ransohoff et al., 2003). In rats it was shown that T cells enter the CSF from the leptomeninges in an experimental model of CNS inflammation (Schlager et al., 2016).

VIRAL INFECTIONS OF THE CNS

From a theoretical point of view, intact viral particles or viral antigens can access the CNS via all of the mentioned interfaces. In cases of viremia, the fenestrated capillaries of the CP and CVO can be a potential entry route (hematogenic route), with or without direct infection of endothelial cells (Moses et al., 1993; Verma et al., 2009). Viruses capable of infecting circulating blood cells can enter the CNS on the sites of cell trafficking inside these (Trojan horse entry) (Clay et al., 2007). Certain viruses can reach the CNS parenchyma by retrograde axonal migration along cranial or peripheral nerves (Barnett et al., 1993; McGavern and Kang, 2011). Finally, some viruses seem to travel within a host via extracellular vesicles (Altan-Bonnet, 2016).

When, by one way or another, a virus manages to reach the CNS, there are different potential outcomes: acute replication, elimination, and persistency or latency. As with any other organ, these outcomes dependent on multiple factors, including the expression of certain cell surface receptors allowing cell entry, replication, etc. and the local and systemic immune response of the host. The immune response toward a viral entity that reaches the CNS or its borders is in large parts similar to any other organ, with sensing of antigens or viral RNA via pattern recognition receptors (PRRs), toll-like receptors (TLRs), RIG-I-like receptors (RIGs), etc., resulting in innate immune cell activation (microglia, CNS macrophages, ILCs, DCs), response of the local cellular environment (activation of astrocytes, endothelial cells, neurons, etc.), and adaptive immune responses generating virus-specific T and B cells (Kawai and Akira, 2009; Pichlmair and Reis e Sousa, 2007). The inflammatory response to an intruding virus (or other pathogen) needs to be controlled in a narrow range (as little as possible, as much as necessary) in order to not damage non-renewable cells such as neurons while at the same time getting rid of the intruder.

KEY MESSAGES

- SARS-CoV-2 is not neurotropic; to date there is no indisputable evidence of replicating SARS-CoV-2 particles (i.e. intact virus) in the CNS
- Neuroimmune axis alterations in COVID-19 vary with disease severity and disease course
- Sickness behavior is mainly due to cytokines affecting the CNS
- Prolonged cognitive impairment after mild infection could be due to protracted cytokine release
- Encephalopathy in critically ill individuals has a multi-factorial pathogenesis beyond SARS-CoV-2 infection (which may act as a trigger)
- Neuroimmunological diseases associated with COVID-19 are rare but potentially constitute post-infectious syndromes or autoimmune-mediated processes triggered by an acute viral infection

the CNS parenchyma is possibly due to a contamination from the blood, if the permeability of the BBB or blood-CSF-barrier (BCSFB) are altered as a result of systemic inflammation (Krasemann et al., 2022b). Alternatively, SARS-CoV-2 RNA may also be the result of migration of immune cells that opsonized the virus or viral particles in the periphery (Trojan horse entry). Therefore, postulating SARS-CoV-2 neurotropism solely on the basis of detectable RNA is problematic.

Postmortem histopathological examinations of patients deceased from or with COVID-19—a most valuable source for scientific insights, even in light of the fact that this group of COVID-19 subjects represents those with the worst possible outcome—only revealed few cytotoxic T cells in the CNS parenchyma, arguing against a manifest viral encephalitis, at least in immunocompetent hosts. However, there is evidence for increased numbers of T cells in the perivascular niche and close to microglia nodules (Schwabenland et al., 2021; Thakur et al., 2021). One study found indirect evidence for damage of neurons and astrocytes in severe COVID-19 patients (Kanberg et al., 2020). The lack of an adequate control group—see introduction—makes proper interpretation and placement of such findings difficult, as the confounders of critical illness conditions (such as sepsis, hypoxia, altered metabolism, polypharmacotherapy, invasive treatments) commonly associated with severe COVID-19 result in manifest CNS stress and damage on their own. For example, signs of activation of astrocytes and microglia in deceased COVID-19 patients did not correlate with the presence of SARS-CoV-2 RNA in those brains (Matschke et al., 2020; Thakur et al., 2021), and such activation—which can also be regularly detected in patients with certain comorbidities such as dementia (Poloni et al., 2021)—can equally be found in septic non-COVID-19 patients (Deigendesch et al., 2020).

In sum, the absence of arguments for active viral replication and substantial cellular inflammation in the CNS suggests that neurological symptoms occurring during or after COVID-19 are rather due to indirect causes, namely neuroimmune actions, than a direct effect or consequence of the pathogenic neurotropism of SARS-CoV-2. Similar arguments speaking in favor of immune-mediated consequences rather than direct virus-induced pathology could be found in COVID-19-associated myopathy (Aschman et al., 2021).

Many studies report signs of activation of mainly the innate arm of the immune system, reflected by activation of myeloid cells and/or microglia as well as astrocytes (astrogliosis), and it will be of great interest not only for COVID-19 research but for neurosciences as such to investigate whether these changes per se are sufficient to explain neurocognitive symptoms during or after viral infections in general and during or after COVID-19 in particular (although admittedly this will be challenging to approach experimentally).

Neuroimmune axis—sickness behavior

Probably everybody knows what it means to be sick. Seasonal flu was largely unavoidable in pre-mask-wearing-eras, and especially children are regularly ill from viral infections. Phenomenologically speaking, being sick is very different from not being sick: even small tasks seem to require huge efforts, and activities that usually are associated with pleasure can seem utterly unappealing. Cognitive processes are slowed down, outside sensory stimuli are sensed less intensely. From an evolutionary standpoint, one plausible explanation is that sickness behavior affects mood, drive, and motivation, ultimately resulting in an intrinsic withdrawing of the infected from social interactions or other activities, thus contributing to saving energy for combating the infection but also for limiting the spread of the infectious agent (Shakhar and Shakhar, 2015; Shattuck and Muehlenbein, 2015). Along this line it is interesting to learn that SARS-CoV-2 viral loads of asymptomatic people, while being equal in numbers to those in symptomatic individuals, were cleared faster (Bouayed and Bohn, 2021). The prevalence of symptoms related to sickness behavior in people infected with SARS-CoV-2 are estimated to be up to 60% (Oran and Topol, 2020).

Signs of sickness behavior are not SARS-CoV-2- or, generally speaking, virus-specific but can also be present in patients with systemic autoimmune or chronic inflammatory diseases. Many patients with systemic lupus erythematosus (SLE), for example, display a chronic fatigue and neurocognitive impairment, reminiscent of what can be experienced during viral infections (Ahn and Ramsey-Goldman, 2012; Maes et al., 2012) and which may be explained by the type of immune response, in the mentioned example of SLE, the strong type I interferon (IFN) imprint (Ytterberg and Schnitzer, 1982). The difference from viral infections is, of course, that there seems to be no evolutionarily plausible benefit from these consequences of illness. Nonetheless, the apparent neurocognitive changes in viral infections

and autoimmune or chronic inflammatory diseases strongly indicate that systemic illness can influence higher cognitive functions and thereby the CNS—however, by what means?

Most available data on this topic stem from animal studies. What needs to be considered here: behavioral changes are difficult to reflect in animal models of diseases, and rodents show different responses to infection. A most obvious example is the drop of body temperature in various animal species compared to humans, who generally develop fever upon infection (Cavaillon et al., 2020). Standardized animal studies are nevertheless of great importance in helping to understand the molecular mechanisms associated with infections, which is even more vital in light of mostly correlative data coming from humans. While human studies are typically conducted in a more physiological, i.e. authentic, setting than animal studies, behavioral and biological endpoints are often measured in parallel and hence do not allow for inferences regarding the direction of causation, i.e. they suffer from the classical hen and egg dilemma. This also applies to the (COVID-19-associated) correlation of the cytokine storm intensity and the severity of neurological manifestations (Lee et al., 2019).

On a molecular level it is known that circulating pathogen-associated molecular patterns (PAMPs), which are small molecular motifs conserved within a class of pathogens, can reach the CNS via the CP and the circumventricular regions (Quan et al., 1998). Peripheral administration of lipopolysaccharides (LPSs), components of Gram-negative bacteria in the outer membrane, or of the cytokine IL-1 induces cytokine receptor expression in the CNS and, subsequently, sickness behavior in rodents (Bluthe et al., 1994; Bret-Dibat et al., 1995; Laye et al., 1994; Quan et al., 1998; van Dam et al., 1992), which can be reversed by administration of IL-10 and insulin-like growth factor I (IGF-I) (Bluthe et al., 1999; Dantzer et al., 1999). Mice treated with LPS are known to show impaired learning skills, which appears to be mediated by IL-6 signaling (Sparkman et al., 2006). Similarly, viral or synthetic double-stranded (ds)RNA induces sickness behavior identical to that of a proper infection with an influenza virus (Kimura-Takeuchi et al., 1992). An effect of type I IFN on cognition and behavior has been assumed for a while (Leuschen et al., 2004; Mendoza-Fernandez et al., 2000), but the underlying mechanisms are not well characterized. Studies in mice revealed that IFN responses to single-stranded (ss)RNA viruses or dsRNA ligands of brain endothelial and epithelial cells mediated depressive-like sickness behavior, and administration of IFN-β resulted in decreased spatial learning and decreased memory recall, which appeared to be mediated locally by soluble factors such as the chemokines CXCL10 and CXCR3, produced by CNS endothelial and epithelial cells (Blank et al., 2016). Notably, a recent study in mice showed that IFN-I signaling induced by the rodent-borne lymphocytic choriomeningitis virus (LCMV) infection negatively affected tissue repair processes and recovery of neurological functions after experimental traumatic and cerebrovascular brain injury. The fact that the LCMV infection was also shown to go along with an increased and persistent permeability of the BBB, which was mediated through the IFN-α/β receptor (*IFNAR*) and MDA5, a pattern-recognition receptor for dsRNA (Mastorakos et al., 2021), seems to be equally important in this context.

But not only the CNS-intrinsic innate cells, namely microglia and CNS-resident macrophages (Tsuda et al., 2009), are susceptible to IFN-I signaling: inhibitory neurons located in close proximity to the brain surface and CSF were also shown to respond to IFN-γ treatment in mice. This had effects on their social behavior, and rodents that were forced into social isolation showed a decreased IFN-γ gene signature, indicating a role of that cytokine in shaping behavior even in the absence of infection (Filiano et al., 2016).

Post-viral syndromes

It has been known for many decades that certain symptoms associated with acute illness like muscular fatigue, pain, and neurocognitive impairment (concentration difficulties, impaired memory, decreased motivation and drive, etc.) can last for many weeks, months, and sometimes even years in a subset of individuals, even after the acute viral infection has resolved. This so-called post-viral syndrome has been described to occur sporadically and along epidemics and pandemics (Acheson, 1959; Bannister, 1988; Calder et al., 1987; Hotchin et al., 1989; Parish, 1978). Post-infectious, post-acute, or long COVID-19, a condition where clinical symptoms prevail long after the initial infection with SARS-CoV-2, shares many similarities with other post-viral syndromes. Because of the lack of solid evidence of neurotropism, the possibility of persistent cerebral viral infection—as discussed in other organs (Mehandru and Merad, 2022) with reported long term viral shedding (Cevik et al., 2021)—is not very likely to be the reason for CNS long COVID-19 symptoms. We suggest that post-acute COVID-19 with CNS symptoms could be seen as a protracted sickness behavior due to unresolved systemic or local pro-inflammatory states of our immune system. In this state, where the acute inflammation has resolved, CNS residential cells (microglia, astrocytes, and/or endothelial cells) potentially continue to produce or are exposed to systemically produced pro-inflammatory cytokines, ultimately leading to fatigue, neurocognitive impairment, or other neurological and/or psychiatric post-COVID or long COVID signs and symptoms.

Certainly, because of the millions of SARS-CoV-2 infections worldwide, post-infectious syndromes or autoimmune diseases directly or indirectly triggered by the virus—even if not occurring at a higher rate compared to other virus infections—are of major public health interest because a relatively small subset of an obviously large cohort results in a high number, in absolute terms, even when considering the intrinsic inaccuracy in defining the symptoms properly in the context of a COVID-19- and long COVID-19-alerted global community (see Introduction).

Neuroimmune axis—critical illness

The majority of SARS-CoV-2-infected individuals have an asymptomatic or mild disease presenting with temporal loss of olfaction and taste as characteristic neurological symptoms, due to local infection of the olfactory mucosa. However, few infected individuals show a severe systemic immune dysregulation with neurological alterations similar to sepsis-associated encephalopathy. Fever, cytokine storm, medical treatment (sedatives, myorelaxants, analgesics, antibiotics), peripheral organ dysfunction, artificial nutrition, immobility, comorbidities, and social isolation have their impact on the CNS, especially in

severe COVID-19 cases. Along with pneumonia, due to SARS-CoV-2 or exacerbated because of bacterial superinfection, its functional consequences, resulting in acute respiratory distress syndrome (ARDS) or hypoxia, can further challenge neuronal function. Septic conditions in general are a tremendous burden for the cardio-circulatory system and, last but not least, therapeutic attempts, hospital admission, drug therapy, and mechanical or assisted ventilation have an impact on body function that co-orchestrate and substantially influence the challenge provided by the sole viral infection itself. These additional factors need to be considered, as they might contribute to the development and persistence of neurological alterations or encephalopathy of survivors of severe COVID-19, including preexisting (potentially not yet diagnosed) CNS pathology, side effects of sedatives, renal dysfunction, and latent virus reactivation following immunosuppression induced by corticosteroid treatment.

Severe COVID-19 cases occur most frequently in either multimorbid, elderly individuals that unfortunately quickly succumb to the disease or in subjects with more resistance to disease that survive peracute COVID-19 but develop complications such as bacterial superinfection, sepsis, multiorgan failure, thrombosis, and/or other problems during their sometimes week- or month-long stay at the ICU. In critically ill patients—independent of SARS-CoV-2 infection—indicators of encephalopathy constitute a stand-alone predictor of mortality, which is associated with long-term cognitive dysfunction (Gordon et al., 2004). Given that cognitive impairment and delirium are frequent in critically ill patients, they seem to be even more prevalent in critically ill patients with COVID-19 (Helms et al., 2020). Along that line, it is important to note that systemic inflammation during sepsis can induce an associated encephalopathy with cognitive impairment, especially in ICU patients (Sonneville et al., 2017), and, additionally, increases the risk of dementia, especially in older patients (Iwashyna et al., 2010; Muzambi et al., 2021).

In some individuals with severe COVID-19, the innate immune response results in numerous and highly activated cellular players, resulting in the massive release of cytokines, similar to what can be observed during influenza (Lucas et al., 2020). However, there is no clear knowledge of which type of cytokine needs to be present at which level per given time point upon infection to be regarded as physiological, i.e. required to resolve infection, and where the so-called cytokine storm starts, i.e. a qualitatively and quantitatively pathological ''above-threshold'' mixture of cytokines (Fajgenbaum and June, 2020).

Peripherally released cytokines are capable of traveling quickly to remote body areas such as the CNS via the blood. Although cytokines such as IL-1α, IL-1β, IL-6, and TNF have saturated receptors on the BBB (Banks et al., 1995), during the cytokine storm the BBB shows signs of disruption (Normandin et al., 2021), enabling small-sized soluble molecules and cytokines to also enter the CSF and the CNS parenchyma. Levels of inflammatory intrathecal cytokines such as IL-6, IL-8, IL-15, and MIP-1β were increased in a subset of COVID-19 patients with altered BBB (Normandin et al., 2021)—an important finding in light of the known cytokine-induced toxicity in the brain resulting in a worsening of cognitive functions (Cape et al., 2014; de Rooij et al., 2007; van Munster et al., 2008).

Quantifying cellular or tissue damage in the CNS of critically ill individuals suffers from the obvious lack of adequate data in humans. However, a first study hints at a disturbed microglial homeostasis and suggests an association with synaptopathy similar to Alzheimer's disease based on protein expression signatures in the CSF of COVID-19 cases with infectious delirium (Peters van Ton et al., 2020). In addition, fever as a hallmark of systemic infection is regulated in clusters of thermo-sensitive hypothalamic neurons via cytokine-triggered prostaglandin E2 (PGE2) production in the CVO (for more information on CVO see Box 2), enabling an immune-triggered crosstalk between blood and/or the periphery and neurons of the hypothalamus (Biddle, 2006). In addition to direct cytokine-mediated effects, cerebral functions can be affected by cytokine-dependent alterations in the cells' ion channel homeostasis (Van Hook, 2020), eventually triggering seizure activity. While in severe COVID-19 the association between seizures and the severity of COVID-19 is not clear (Hepburn et al., 2021; Romero-Sanchez et al., 2020), there appears to be a link of experiencing seizures with a history of cognitive impairment, higher age, and higher levels of creatine-kinase and C-reactive protein as described also for non-COVID-19 patients with encephalopathy (Asadi-Pooya, 2020).

Per definition, sepsis-related encephalopathy and its neuroinflammatory changes are not due to a direct infection of neurons or glial cells but mediated by systemic inflammation. Cellular changes in the CNS are very similar to what is described in COVID-19-related neuroinflammation with microglial activation and astrogliosis as well as BBB alterations, the presence of inflammatory cytokines in the CSF (Lemstra et al., 2007; Zrzavy et al., 2019), alterations in neuronal synapses, and neurovascular changes (Ehler et al., 2017; Peters van Ton et al., 2020).

CONCLUDING REMARKS

Many questions and many answers around SARS-CoV-2 have arisen since its first recognition, culminating in—as of June 2022—266,000 publications on COVID-19 (PubMed). From a purely biological perspective, our central nervous system is what makes us human—not our hearts, kidneys, or livers. Not only for this (pretty good) reason, the widespread concerns due to the observed neurological symptoms in SARS-CoV-2-infected patients early in the pandemic is and was entirely understandable. With some distance it seems safe to spread some reassuring perspective: SARS-CoV-2 does not seem to be a primarily neurotropic virus, as none of the many even severely diseased patients that were autopsied presented an undisputable proof for proper SARS-CoV-2 infection of the CNS, nor considerable CNS inflammation and structural damage in those severe COVID-19 cases succumbing to death, and among the living patients CSF findings strongly argue against a relevant ongoing, i.e. chronic, neuroinflammation.

This does not mean that SARS-CoV-2 is entirely harmless to our brain—both functionally and structurally—at all occasions. This also does not mean that occasionally the virus (or viral proteins) cannot end up within the boundaries of the CNS, including vascular-perivascular niche and the meninges, or even in cells of the CNS parenchyma in very specific circumstances. At the end of the day only time will answer the current controversy around

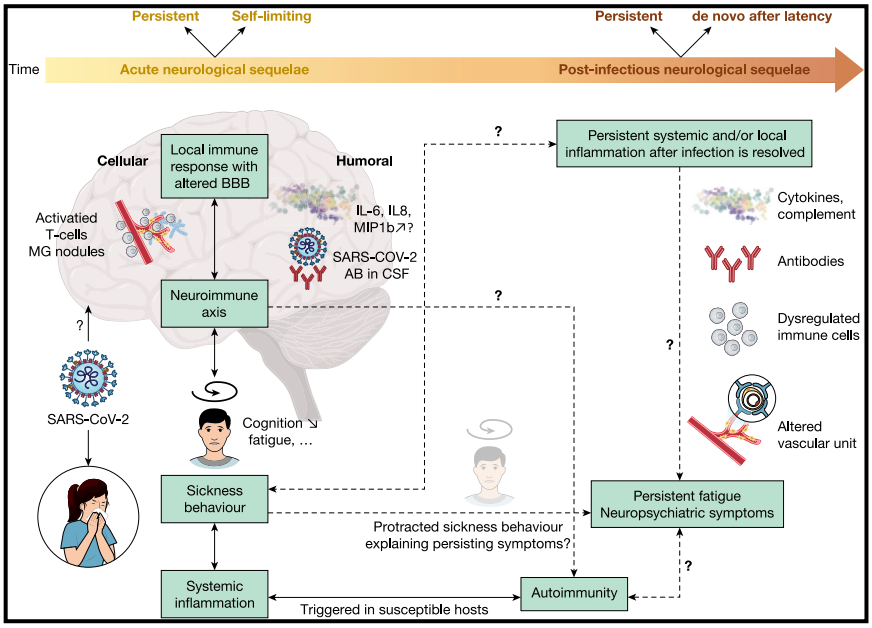

Figure 2. Potential pathomechanisms behind SARS-CoV-2-related neurological sequelae

After SARS-CoV-2 enters the body via upper respiratory tracts, systemic immune activation leads to unspecific general symptoms of infection including sickness behavior and more specific symptoms (anosmia, dysgeusia). While there is no robust evidence for a viral replication of SARS-CoV-2 in the CNS, multiple observations suggest a local immune response in the CNS parenchyma (activated T cells, microglia nodules) as well as in the cerebrospinal fluid (CSF), with increased production of proinflammatory cytokines and anti-SARS-CoV-2-specific antibodies. In the majority of cases, sickness-behavior-associated symptoms will disappear once the infection is resolved. In some cases, similar symptoms might either persist or reappear after a phase of latency. The reasons behind this are likely heterogeneous, including, for instance, cases of autoimmunity triggered by the viral infection or a dysregulated immune system resulting in persistent systemic and/or local inflammation or sustainably altered vascular units.

BBB, blood-brain barrier; MG, microglia; AB, antibodies; CSF, cerebrospinal fluid

the topic of neurotropism, and rigorous scientific criticism is needed to avoid misleading interpretations, e.g. of light or of electron microscopy images (Krasemann et al., 2022a).

While it is, of course, important to understand which cells are genuinely infected, it is undebatable that the virus enters our system initially via the respiratory tract. A pragmatic approach to avoiding academic dispute over the question of whether the virus is within the CNS proper or not—if at all it will be small in number and only in rare cases—is to focus on the host, i.e. recipient, side and the hosts' way to deal with SARS-CoV-2 infection. Regardless of whether a specific cell X is directly infected or not, there is a reaction of our immune system to this virus, directly or indirectly, and this immune reaction has a local and a systemic projection. As we know from many other viruses and also autoimmune or chronic inflammatory diseases, our immune systems are diverse and different. Viral infections are well-known triggers for autoimmune reactions, either by sparking disease onset or affecting disease progression by causing flares, as has been described in many different diseases like autoimmune encephalitis, GBS, myasthenia gravis, CIDP, multiple sclerosis, SLE, etc., even in the absence of wet lab arguments proving or disproving a molecular mimicry mechanism (Armangue et al., 2018; Bouchard et al., 1999; Korn and Abramsky, 1981; Pruss, 2017; Smatti et al., 2019). Of note in this context are recent observational data on the presumable connection of precedent Epstein-Barr virus infection and chronic inflammatory demyelination of the CNS based on data from millions of US military recruits monitored over a 20-year period (Bjornevik et al., 2022).

Depending on the host, infection with the same virus strain could potentially result in different disease phenotypes, not only regarding disease severity but also with respect to neurological affection and distinct autoimmune responses. Some patients with constitutional or environmental susceptibility to, for example, chronic fatigue, GBS, or other autoimmune diseases could, in principle, be pushed into a pathogenetic-prone direction by any given (viral) infection acting as a trigger. As for SARS-CoV-2, which was and still is spreading rather efficiently around the globe, one cannot exclude that our SARS-CoV-2-wise rather than inexperienced immune systems may react more strongly and less directed when compared to other more known pathogens, possibly resulting in an increased production of proinflammatory cytokines. On the other hand, the latter is purely speculative because (1) we have no proper comparison and reference points (humankind never monitored a novel virus with this degree of stringency), and (2) multiple findings suggest that SARS-CoV-2 directly interacts with our immune system, which results e.g. in impaired transforming growth factor β (TGF-β) and IFN-I signaling (Hadjadj et al., 2020; Witkowski et al., 2021), possibly guiding the immune response into a certain direction, potentially depending on the host's constitution.

We therefore hypothesize that SARS-CoV-2 can affect an immune system's response both acutely and long term in potentially different ways depending on the host, leading to ongoing inflammatory or autoimmune signaling even after clearance of the viral particles, and thus resulting in or contributing to post-viral syndromes in some but not in others. It will be of interest to investigate whether post-viral syndromes—including post-acute or long COVID—are forms of protracted sickness behavior due to unresolved systemic proinflammatory states in a susceptible host (Figure 2).

To us, it seems of utmost importance to tackle the question of neurological impairment upon SARS-CoV-2 infection by sticking to the following: not to overinterpret observational studies that lack (often for understandable, practical reasons) adequate control groups; instead, we must rely on methodologically well-done, ideally prospective, studies comparing SARS-CoV-2 positive and SARS-CoV-2 negative cohorts with as few as possible confounding factors to evaluate the real relative risk of neurological symptoms that can solely be attributed to the viral infection and the host's resulting immune response. Once a definitive association of such symptoms or diseases with COVID-19 is established, these symptoms must be categorized

and characterized as precisely as possible. The mechanisms at cause in the case of a post-viral lasting fatigue or muscular weakness can be presumably quite different from the mechanisms behind the post-viral occurrence of an identifiable demyelinating autoimmune disease, with identification of autoantibodies or measurable parameters of immune system (over) activation. Once distinct post-viral disease phenotypes with a clear link to the infection are identified and precisely defined, we can precisely dissect the underlying pathomechanisms.

On the positive side, this global pandemic with all its devastating consequences can also be a unique opportunity—if done correctly—to learn and better understand the way in which our immune system reacts to an invading viral pathogen and how this impacts our CNS, both on a functional as well as a structural level, thus paving new paths for therapies aiming at reducing negative side effects of CNS-related sickness behavior related to distinct underlying causes.

ACKNOWLEDGMENTS

This work was supported by the Federal Ministry of Education and Research within the framework of the network of university medicine (NATON 01KX2121). F.L.H. is funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy – EXC-2049 – 390688087.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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