



The Psychiatric consequences of Covid-19-infection (SARS CoV-2)

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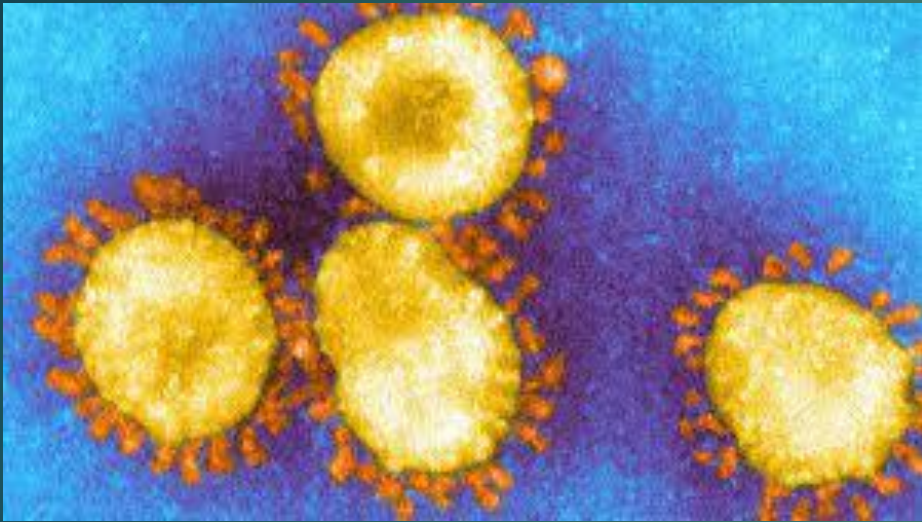
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Coronaviruses are...



- ▶ Enveloped, single-strand RNA viruses
- ▶ Wide range of hosts including avian, wild, domestic mammalian species, and humans
- ▶ Known for their ability to:
 - ▶ mutate rapidly,
 - ▶ alter tissue tropism,
 - ▶ cross the species barrier,
 - ▶ and adapt to different epidemiological situations

6 Corona viruses were known to infect humans since the 1960s.

- ▶ OC43, 229E, NL63, and HKU1
- ▶ 15–30% of upper respiratory tract infections + GIT-infection
- ▶ Other two
 - ▶ Severe acute respiratory syndrome coronavirus (**SARS-CoV**) in 2002–03
 - ▶ Middle East respiratory syndrome coronavirus (**MERS-CoV**) in 2012
- ▶ Occasional disease of the CNS and peripheral nervous system (PNS).

LIFE CYCLE OF THE PANDEMIC CORONAVIRUS

A simplified account of how SARS-CoV-2 enters and exits cells.

Stage 1: Viral entry

The virus's spike protein binds to a receptor on the host cell called ACE2. Then, the host molecule TMPRSS2 cleaves the spike protein, exposing parts that fuse the viral membrane with that of the host.



Stage 2: Inside the cell

Viral RNA is translated into non-structural proteins (NSPs) that quickly suppress the translation of host messenger RNAs in favour of those belonging to the virus.

Endoplasmic reticulum (ER)

Viral proteins (NSPs)

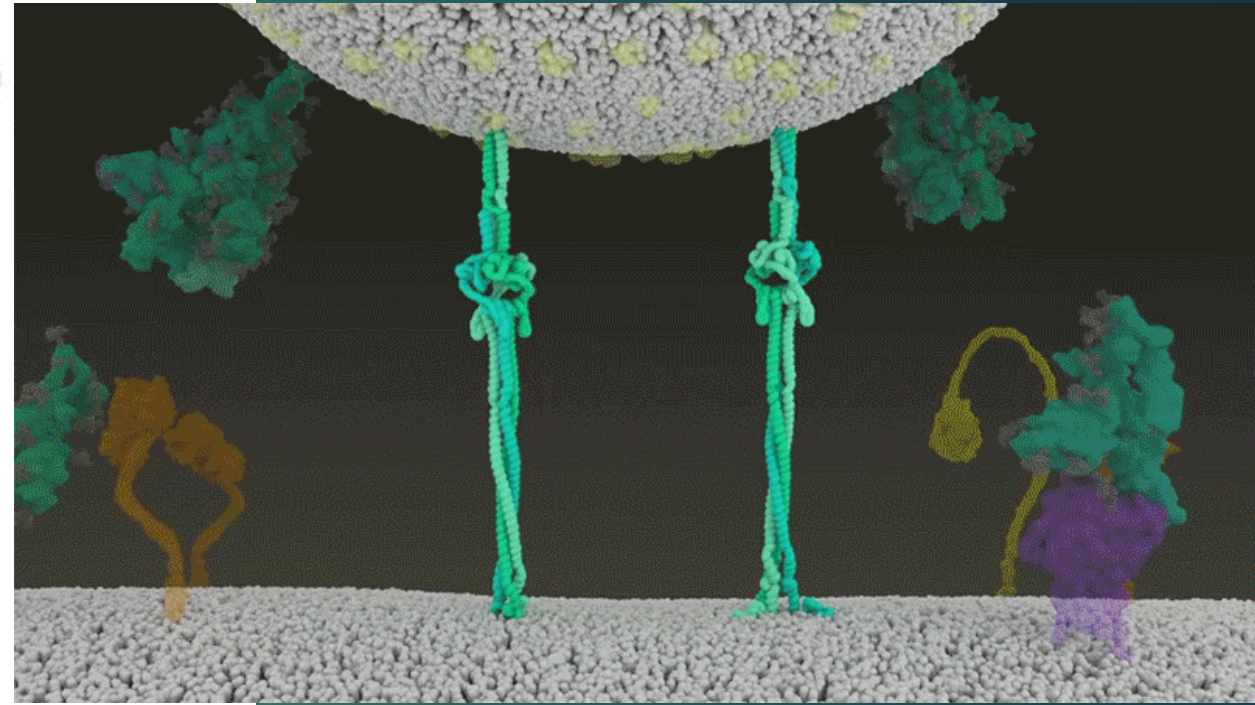
Viral RNA

Ribosome

NSPs

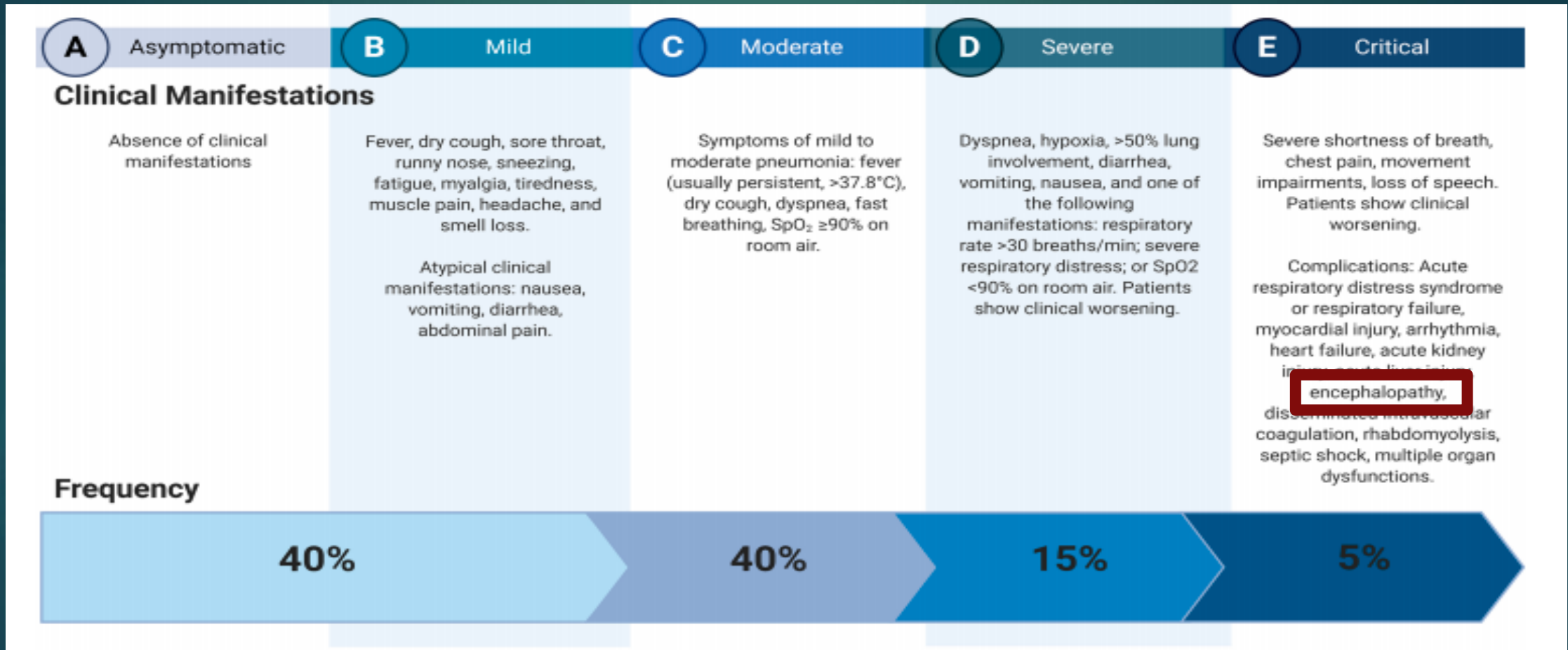
ER remodelling

The spikes unravel and pull the membrane of the virus and host cell together

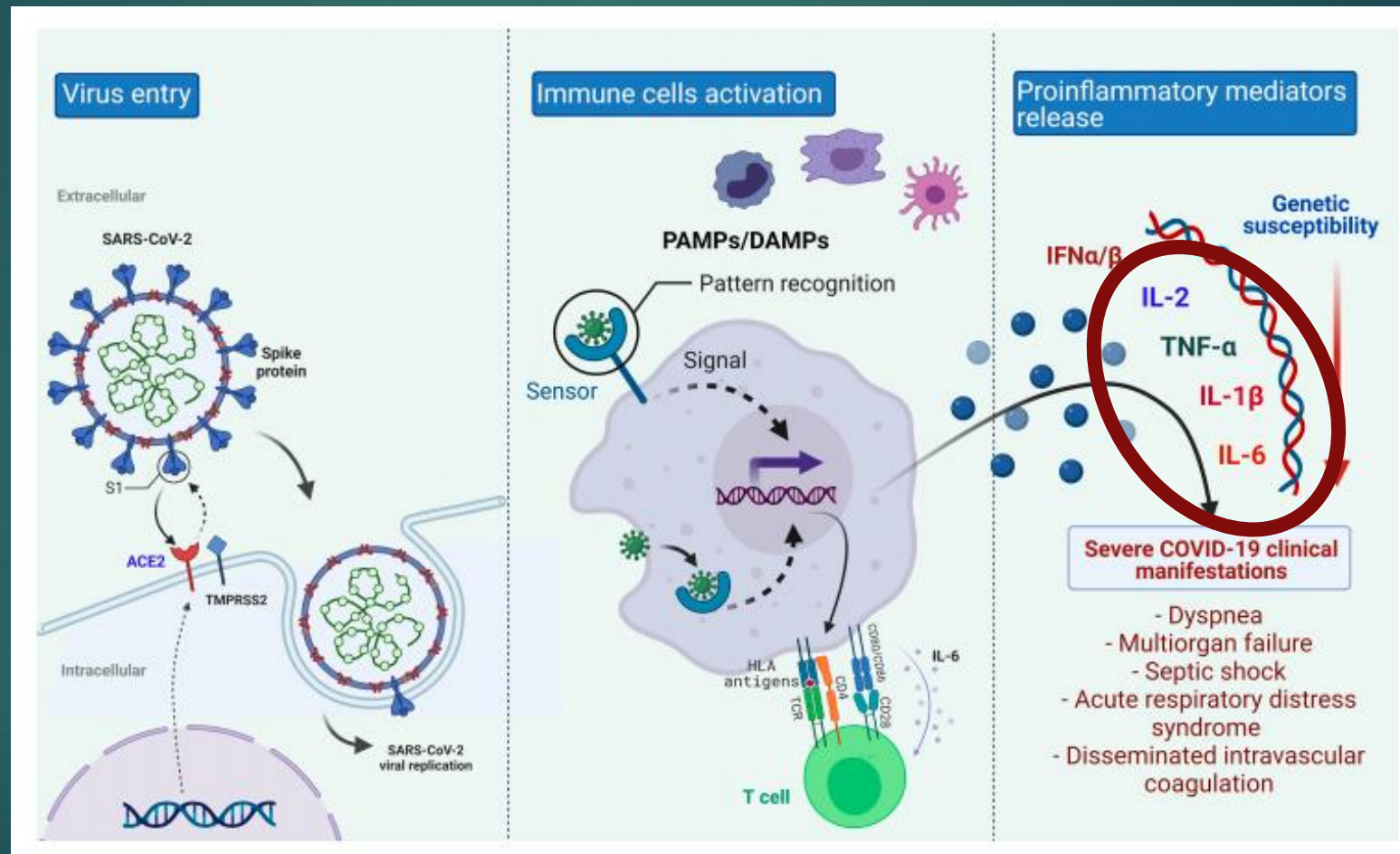


An animation of the way SARS-CoV-2 fuses with cells. Credit: Janet Iwasa, University of Utah

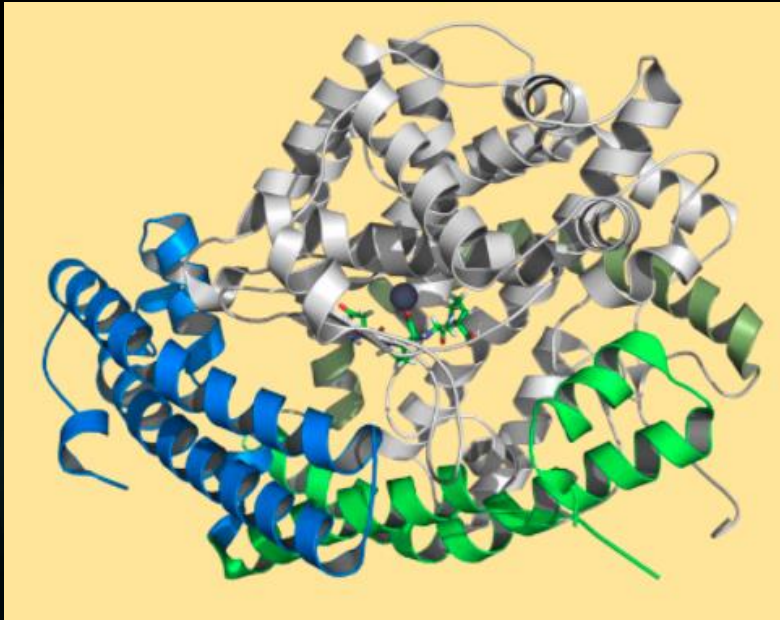
Clinical courses of COVID-19.



Different genes could be implicated in the disease's differential clinical outcome

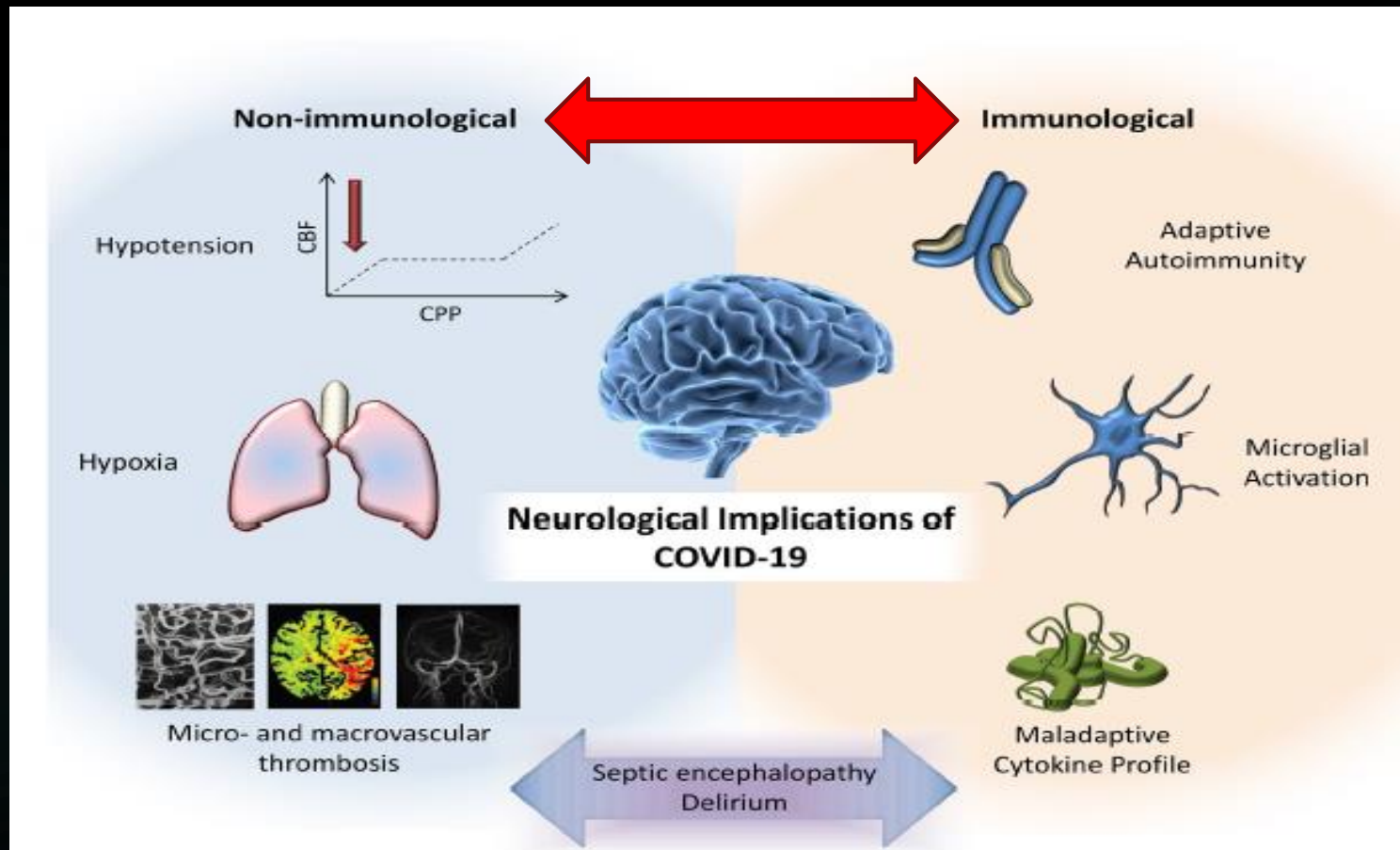


Angiotensin Converting Enzyme 2

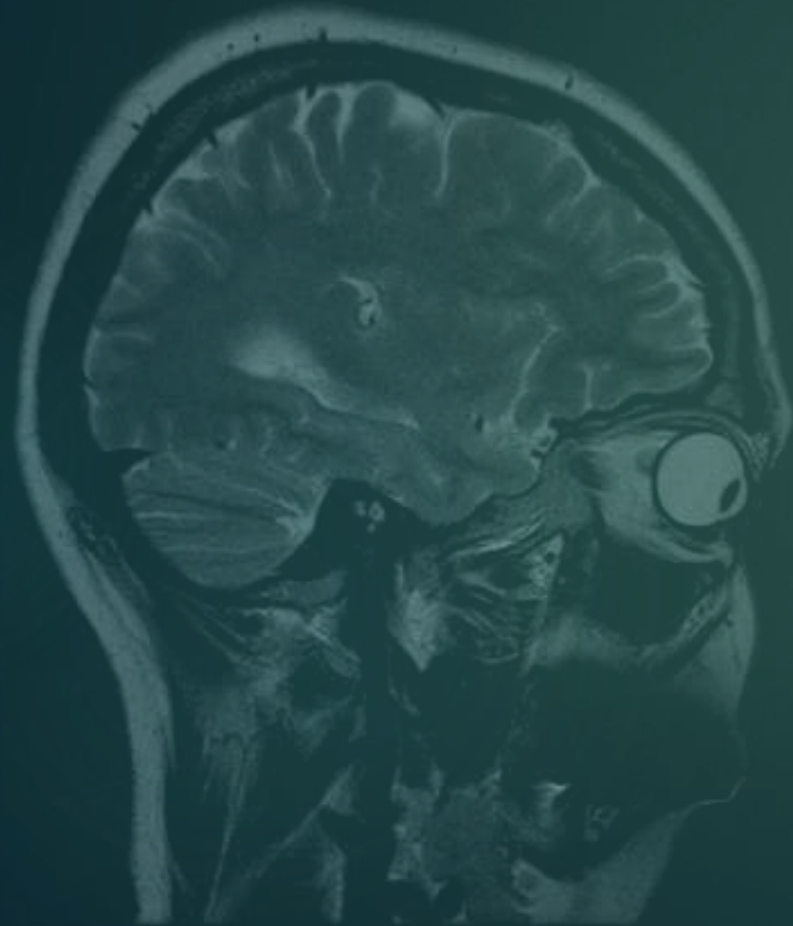


- ▶ Converts AT II > AT I
- ▶ AT I reduced / major anti-inflammatory effect
- ▶ COVID-19 is associated with ACE2 expressed in neurones and in neuroglialia

Putative mechanisms underlying neurological consequences of COVID-19

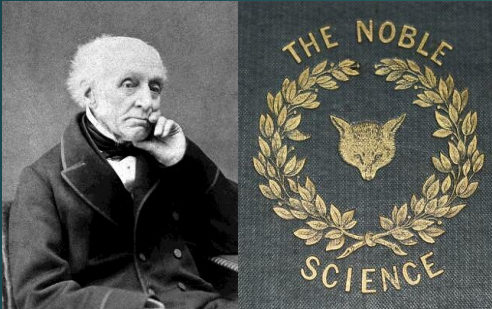


Neurological Syndromes



- SARS-CoV-2 meningitis, encephalitis, Transversemyelitis, or CNS vasculitis
- Acute disseminated encephalomyelitis* associated with SARS-CoV-2 infection
- Stroke associated with SARS-CoV-2 infection
- Intracerebral haemorrhage
- Cerebral venous sinus thrombosis
- Rhabdomyolysis and other muscle disease
- Guillain-Barré syndrome, and other acute neuropathies associated with SARS-CoV-2 infection
- Anosmia and ageusia

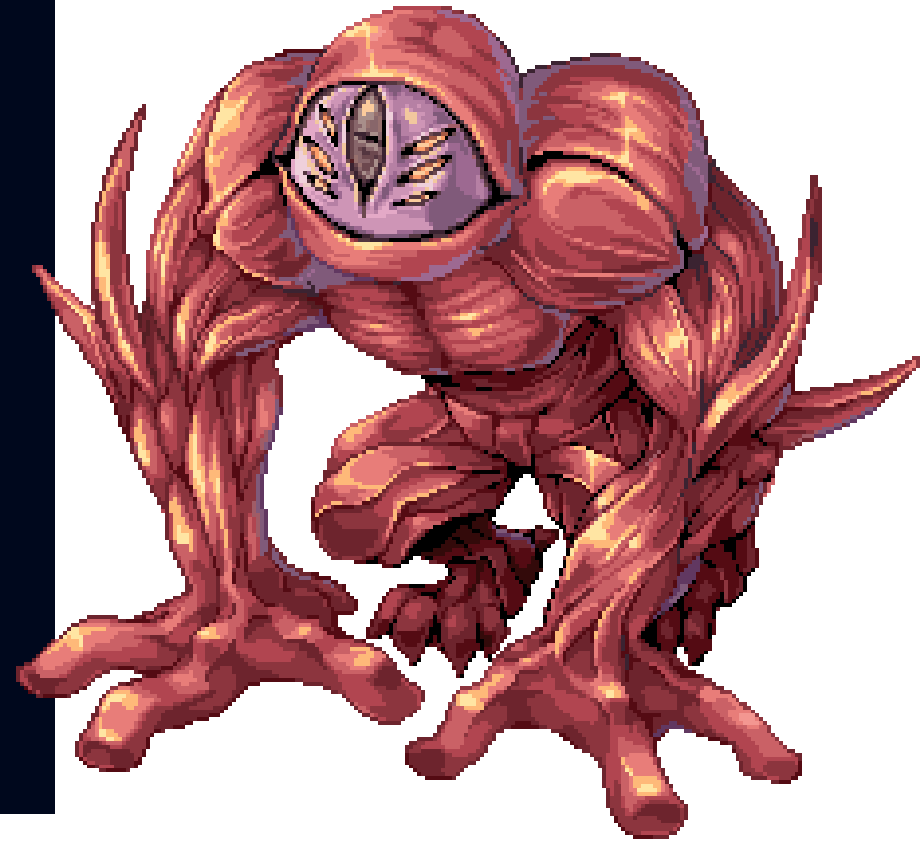
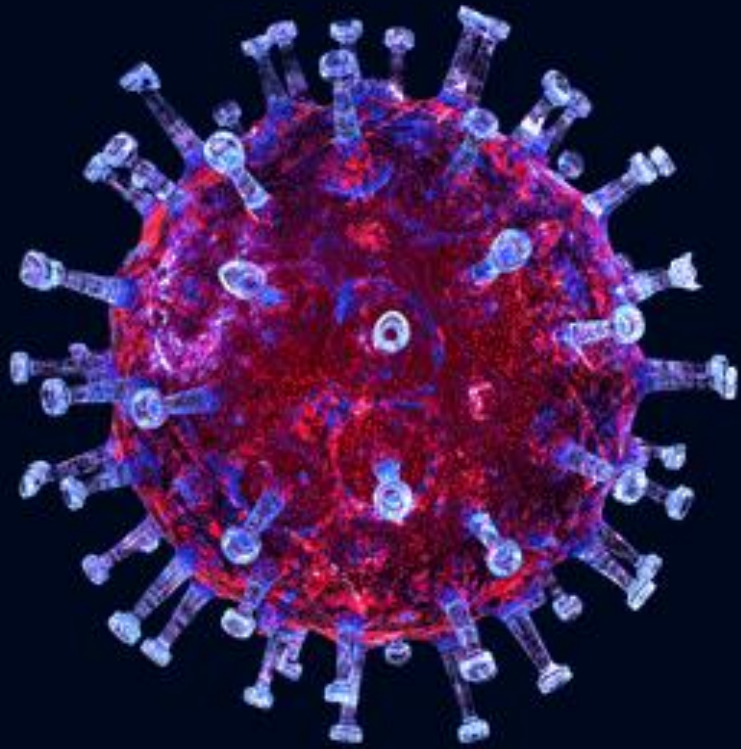
Onset of psychiatric diseases following viral epidemics begun in 19 Century



UK: Henry Holland (1839)

"... flu was responsible "of featured impairments of mental functions almost in the same ratio of the body and that the behavioural alterations were not comparable to those secondary to other fevers".

THE TWO FACES OF COVID-19

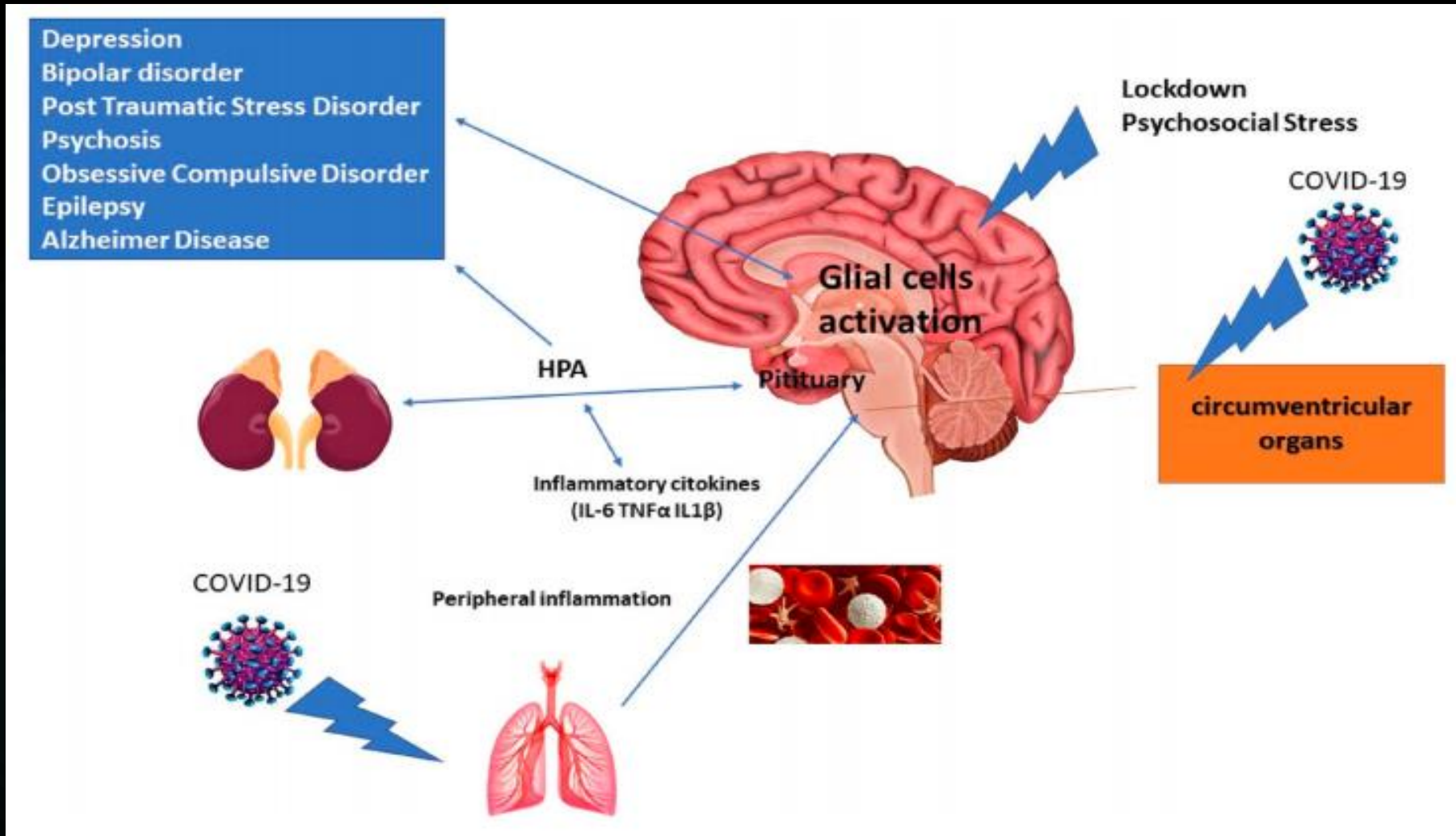


Aetiologic role of viruses



- ▶ Not only the organic mental disorders induced by encephalitis
- ▶ but also **functional psychiatric diseases** such psychosis, depression and bipolar disorder
- ▶ Now accepted that combination of:
 - ▶ systemic infection,
 - ▶ viral neurotropism
 - ▶ and environmental stress
- ▶ facilitates or even induces development of psychiatric pathologies

Neuropsychiatric sequelae of COVID-19.



“Pandemic Brain Fog”



- ▶ " like an inability to focus, difficulty sleeping, feelings of negativity and more.
- ▶ caused by a wide range of factors including
 - ▶ Isolation
 - ▶ Anxiety
 - ▶ Lack of sleep
 - ▶ Decreased level of exercise and more
- ▶ Especially the frontal network, which contributes to memory, recall and attention.
- ▶ Social distancing also removes some mental stimulation.

Effects of quarantine and after

- ▶ Stress,
- ▶ Depression,
- ▶ Irritability,
- ▶ Insomnia,
- ▶ Fear,
- ▶ Confusion,
- ▶ Anger,
- ▶ Frustration,



- ▶ Boredom,
- ▶ And stigma associated with quarantine
- ▶ Specific stressors included;
 - ▶ Greater duration of confinement,
 - ▶ Having inadequate supplies,
 - ▶ Difficulty securing medical care and medications,
 - ▶ Esulting financial losses.

COVID-Phobia

- ▶ Making the well sick and the sick sicker



- ▶ Hypochondriasis- morbid preoccupation of getting infected with COVID-19 at first sneeze
- ▶ Panic attacks with dread of losing control
- ▶ Impending doom and getting home-bound
- ▶ Thanatophobia-dread of death

Genetically predisposed vulnerable population or in mentally ill patients



- ▶ Flare-up of **OCD**
- ▶ **Hysterical contagion** (mass hysteria)
- ▶ **Chronophobia**
 - ▶ dread of passing time is a common experience for those in quarantine;
- ▶ “At a later stage, people become **phlegmatic automatons** who live by the ‘clock’- wondering when the 14-day isolation is over, when curfew is over, and most importantly when this hardship is over. “

Study of neuropsychiatric consequences of SARS-COV-1 performed at 30–50 months after the infection



- ▶ 40% of posttraumatic stress disorder (PTSD)
- ▶ 36.4% of depression
- ▶ 15.6% of obsessive compulsive disorder / anxiety disorders
- ▶ Neurocognitive deficits up to 18 months post-discharge
- ▶ Including mild cognitive impairment
- ▶ Promotes cognitive disorders with emergence of delirium, acute psychosis
 - ▶ Exacerbation of mild cognitive impairment
 - ▶ Accelerating of dementia associated with various neurodegenerative conditions, including Alzheimer's disease

COVID-19 and major depression



- ▶ Changes in lifestyle and interpersonal relationships
- ▶ Loneliness
- ▶ Decreased control over impulsivity and feelings of fear in combination with inflammatory challenges to the brain might increase the risk of suicide.
- ▶ MDD > inflammatory injury to the brain
- ▶ Severe cases of COVID-19 accompanied with excessive host immune response
 - ▶ Massive increase in plasma levels of IL-6
 - ▶ Correlates with an unfavourable outcome of the disease
 - ▶ Abnormally high concentrations of IL-6 were detected in the cerebral spinal fluid of
 - ▶ suicide attempters
 - ▶ depression
 - ▶ schizophrenia
 - ▶ postpartum depression

COVID-19 and bipolar disorder



- ▶ ??
- ▶ Increased cortisol
- ▶ Worsening of BD
- ▶ Social isolation....

COVID-19 and reactive psychosis



- ▶ 1-4%
- ▶ Differentiate from delirium
- ▶ Enhanced inflammation in psychosis
- ▶ FEP patients showed an up-regulation of IL-6, TNF- α and IL-1 β generating the inflammatory-related psychotic reactions

Dementia



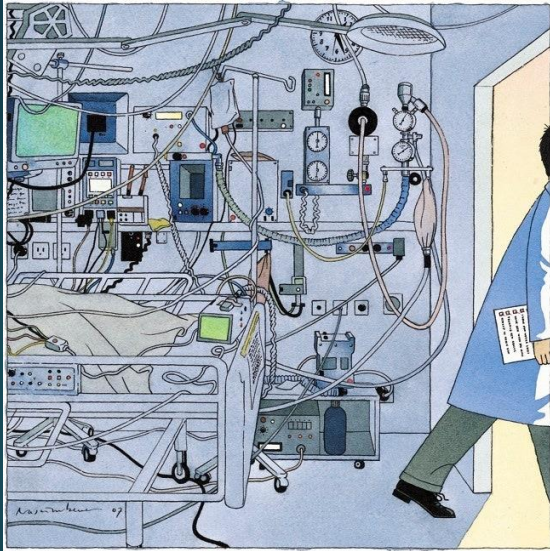
- ▶ Leuco-encephalopathy
- ▶ Existing dementia worse
- ▶ Hypoxia / ventilation / drugs in ICU
- ▶ Post-delirium

COVID-19 and OCD



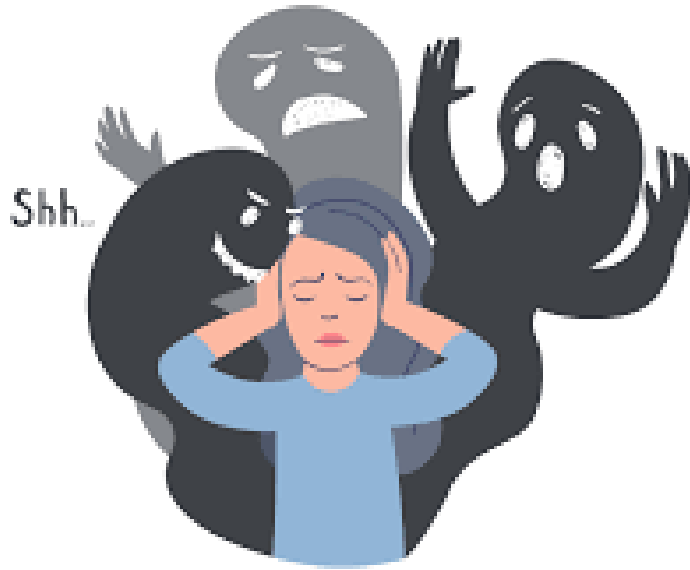
- ▶ PANDAS
 - ▶ “Paediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus”.
- ▶ Inflammation plays role
- ▶ Systemic inflammation which is the prominent feature of COVID-19 may therefore trigger OCD in surviving subjects.

COVID-19 and PTSD



- ▶ Can be a likely outcome for COVID-19 sufferers
- ▶ Severity of systemic inflammation and viral invasion into the brain,
- ▶ Gravity of stress caused by an unexpected pandemic with high mortality > catastrophic stress
 - ▶ Death of loved ones
 - ▶ Exposure to death in ICU
 - ▶ Own complications / intubation etc.

Schizophrenia and viral infection



- ▶ COVID-19 patients with recent onset of psychotic episodes :
 - ▶ Auditory and visual hallucinations and delusions
- ▶ Although there are no evidence directly linking COVID-19 with the risk of schizophrenia
- ▶ Increased risk of death from COVID-19 in Schiz

Unique aspects to treatment



- ▶ Azithromycin / Vit C / Steroids induce depression
- ▶ IL6-inhibitors Rx for MDD
- ▶ Anxiety and agitation not benzo's
 - ▶ Gabapentin
 - ▶ SSRI's
 - ▶ Antipsychotics
- ▶ Fluvoxamine / haloperidol / Valproate against COVID

The brain effects of social isolation

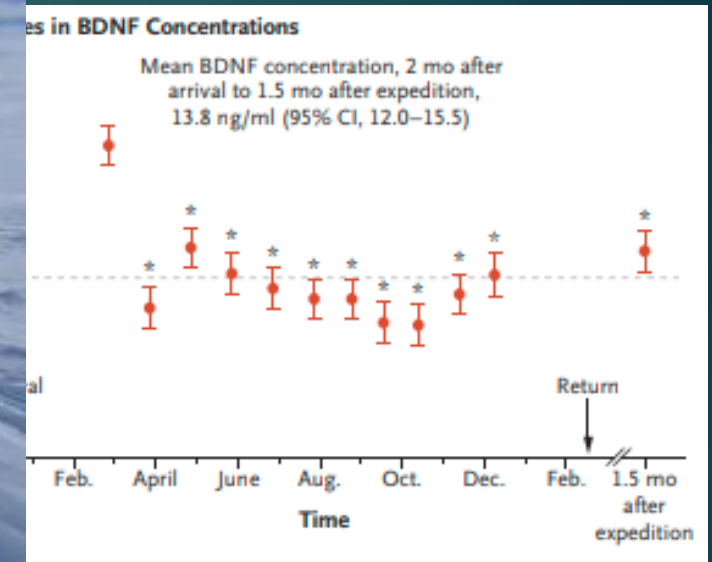
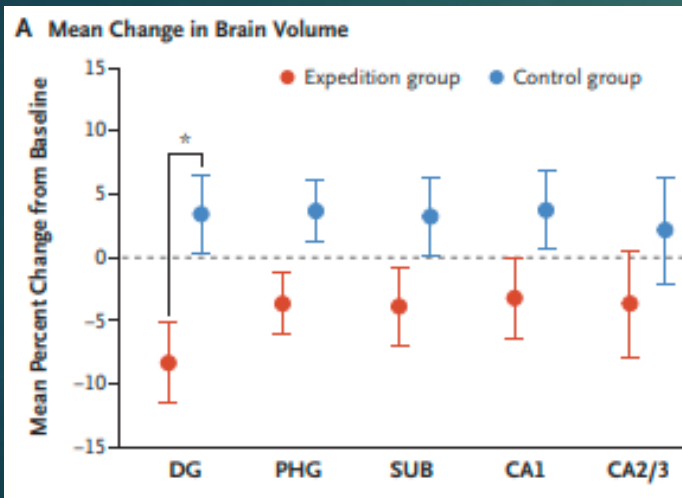


- ▶ Severe psychological effects in humans
- ▶ Neural bases poorly understood
- ▶ 2 weeks of social isolation stress (SIS) caused multiple behavioral changes in mice

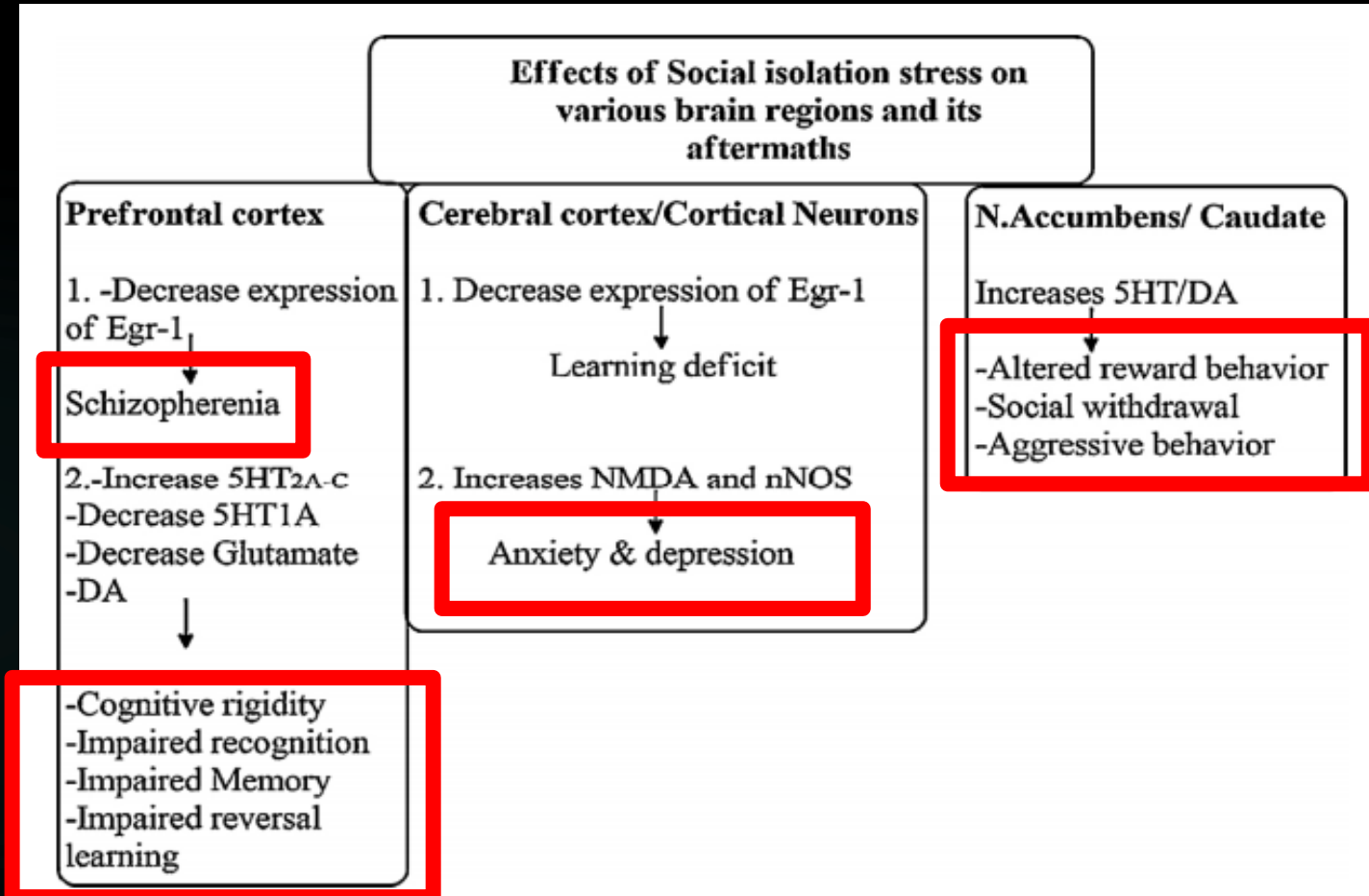
BDNF

- ▶ Development and maintenance of neural connections are disrupted in major mental disorders,
- ▶ Indicates that neurotrophic factors could play a critical role in their pathogenesis.
- ▶ Stress is a well-established risk factor for psychopathology
- ▶ Disrupted signaling via brain-derived neurotrophic factor (BDNF) may be involved in mediating the negative effects of stress on the brain.
- ▶ Downregulation of BDNF seems to be associated with increased anxiety-like symptoms
- ▶ Mechanisms linking chronic social isolation, BDNF expression and the elicited behavioral alterations are currently unknown.

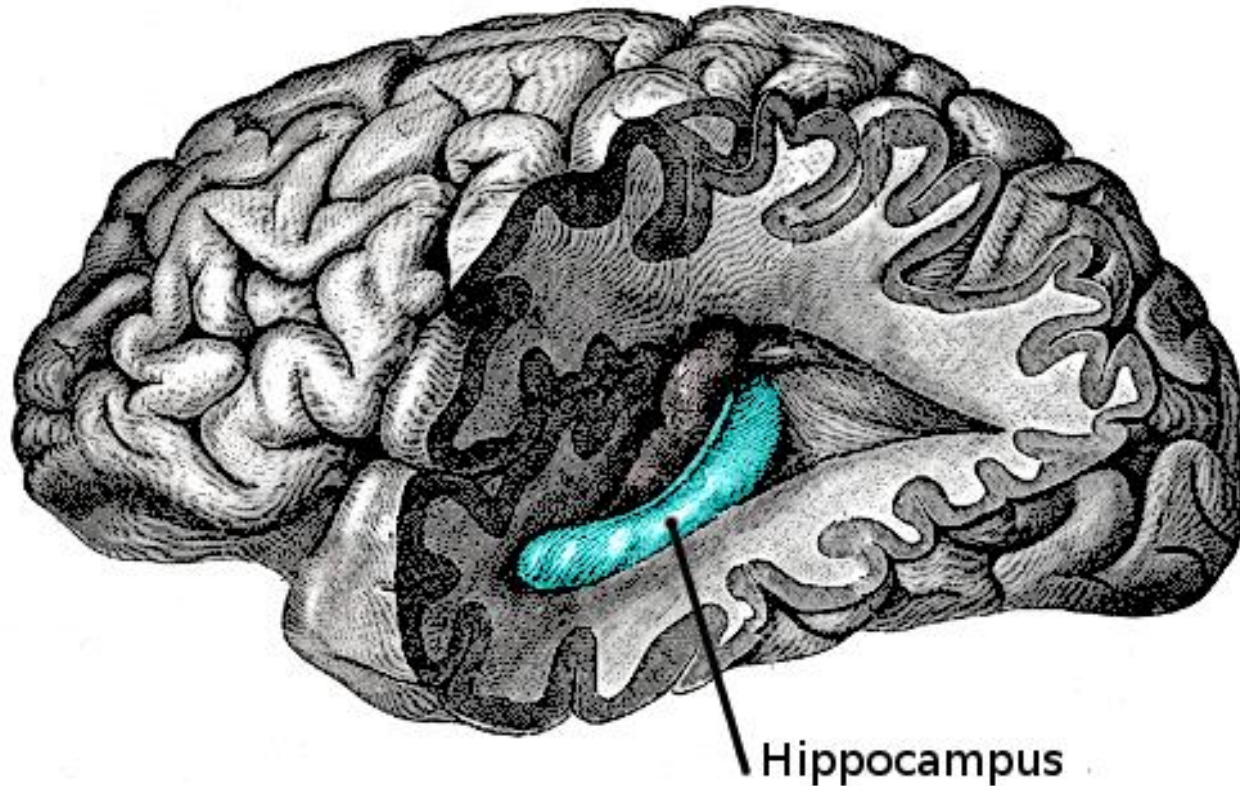
Changes in hippocampal subfields in 8 Antarctic expeditioners and nine age- and sex-matched controls.



Social isolation stress and its consequences on various brain regions.



Social isolation stress and its consequences on hippocampus.



How mental health care should change as a consequence of the COVID-19 pandemic

*Carmen Moreno, Til Wykes, Silvana Galderisi, Merete Nordentoft, Nicolas Crossley, Nev Jones, Mary Cannon, Christoph U Correll, Louise Byrne, Sarah Carr, Eric Y H Chen, Philip Gorwood, Sonia Johnson, Hilikka Kärkkäinen, John H Krystal, Jimmy Lee, **Jeffrey Lieberman**, Carlos López-Jaramillo, Miia Männikkö, Michael R Phillips, Hiroyuki Uchida, **Eduard Vieta**, Antonio Vita, Celso Arango*

Normalizing milder reactions...



- ▶ By providing information about usual reactions to this kind of stress
- ▶ Pointing out that people can and do manage even in the midst of dire circumstances.
- ▶ Health care providers can:
 - ▶ Offer suggestions for stress management and coping (such as structuring activities and maintaining routines),
 - ▶ Link patients to social and mental health services,
 - ▶ And counsel patients to seek professional mental health assistance when needed.
- ▶ Contact with pandemic-related news limited.
- ▶ Address children's reactions and concerns.

