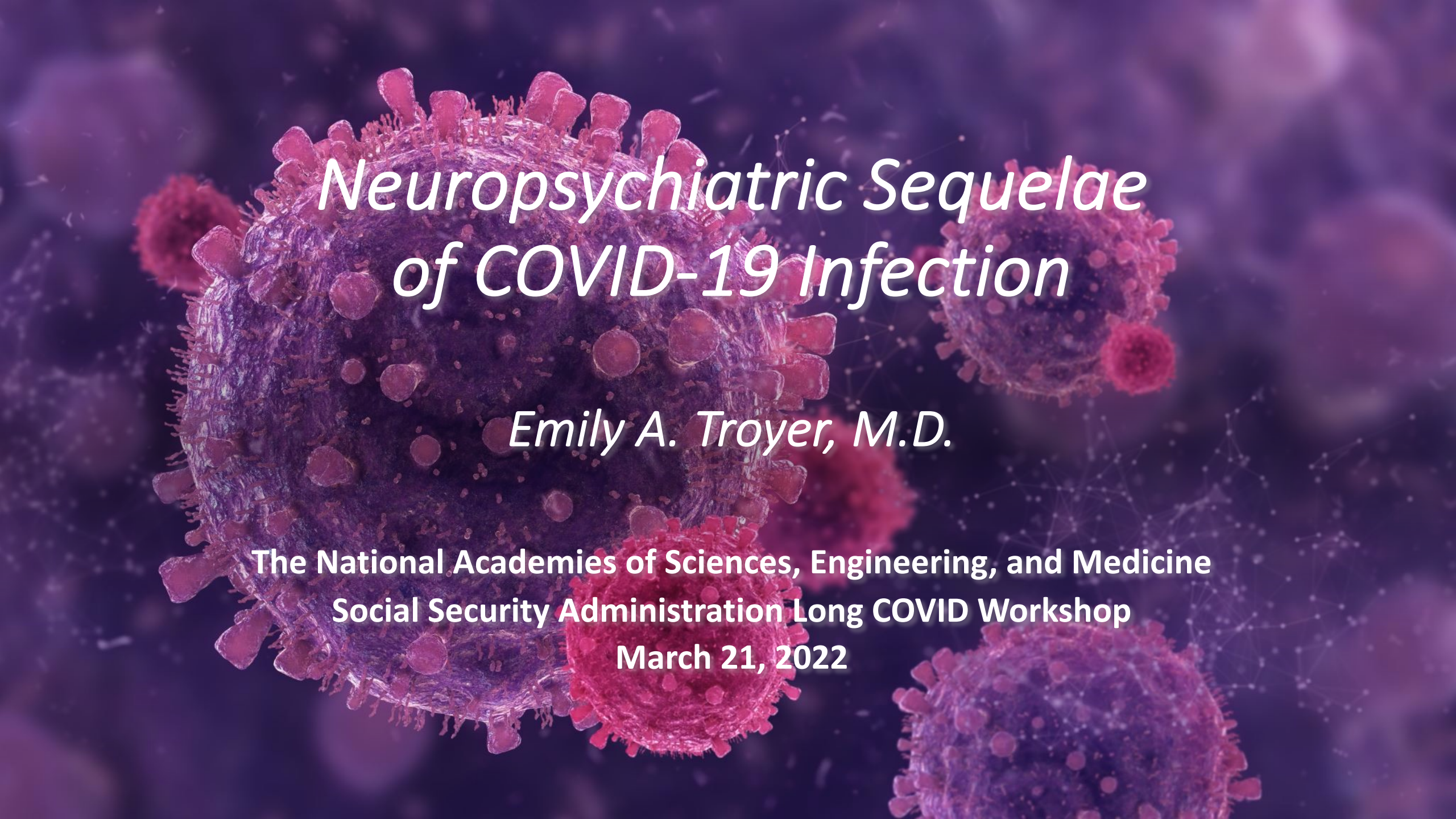

Neuropsychiatric Sequelae of COVID-19 Infection

Emily A. Troyer, M.D.

The National Academies of Sciences, Engineering, and Medicine
Social Security Administration Long COVID Workshop
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Historical Perspective

"The outcome for almost all encephalitis lethargica (EL) patients was some form of tragedy: death, trouble with the law, inability to maintain stable relationships within their family or with others, physical disability, incarceration as children or young adults in mental hospitals and geriatric homes. The social aspects of EL concerned investigators and governments from around 1920, when it became clear that for a majority of patients – at least– there was no true post-EL period, as full recuperation could not be expected. 'Recovery' was often defined as the ability to work, even where this meant, for example, that a former teacher was now employed to undertake restricted gardening activities. **Physical incapacity was a problem for most patients, whether because of parkinsonism or other neurologic symptoms, or because the long term mental effects – bradyphrenia, memory lapses, lack of concentration – prevented resumption of their pre-EL occupations."**

(Foley, 2018; Welfare Council of New York City, 1935)

Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic

Jonathan P Rogers, Edward Chesney*, Dominic Oliver, Thomas A Pollak, Philip McGuire, Paolo Fusar-Poli, Michael S Zandi, Glyn Lewis, Anthony S David*

- Cognition:
  - 27.9% with *acute* confusion → **18.9%** with *post-illness* memory impairment
- Mood:
  - 32.6% with depressed mood *acutely* → **14.9%** with *post-illness* depression
- Trauma:
  - **32.2%** with PTSD at long-term follow-up
- Psychosis:
  - Acutely: 4.7% auditory hallucinations, 2% visual hallucinations, 3.9% persecutory beliefs
  - Long-term: **1%** with auditory hallucinations, **2%** persecutory beliefs
- Function:
  - **23.1%** without return to work

(Rogers et al., 2020)

COVID-19 ← → Neuropsychiatric Symptoms

- Prevalence of neuropsychiatric complaints in patients with acute COVID-19 = **22.5%** (*n*=40k)
- COVID-19 → incident psychiatric disorders in first 3 months is **18%** (**6%** new onset) (*n*=62k)
- Pre-existing psychiatric disorder → increased risk of COVID-19 infection, hospitalization, and death

Image Source: trinetx.com

(Garcia-Azorin et al., 2020; Jeon et al., 2020; Li et al., 2020; Nalleballe et al., 2020; Taquet et al., 2020; Yang et al., 2020)

Image Source: Healthline

Psychiatric Symptoms in COVID-19 Survivors

- Sleep disturbance ~ 10 – 55%
- Depression ~ 5 – 50%
- Anxiety ~ 5 – 50%
- PTSD/PTSS ~ 5 – 45%
- Psychosis rarer but reported

(Akter et al., 2020; Badenoch et al., 2021; Bellan et al., 2021; Cai et al., 2020; D'Cruz et al., 2020; Einvik et al., 2021; Ferrucci et al., 2021; Garrigues et al., 2020; He et al., 2020; Huang et al., 2021; Islam et al., 2021; Ju et al., 2020; Liu et al., 2020; Lorenzo et al., 2020; Mandal et al., 2021; Mazza et al., 2020; Oh et al., 2021; Perlis et al., 2021; Rogers et al., 2021; Simani et al., 2021; Skyes et al., 2021; Sonnweber et al., 2020; Taboada et al., 2021; Tomasoni et al., 2020; Van den Borst et al., 2020; Van de Sar et al., 2021; Wu et al., 2020; Yan et al., 2020; Yuan et al., 2021; Zhu et al., 2020)

Psychiatric Symptoms in COVID-19 Survivors

6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records

Maxime Taquet, John R Geddes, Masud Husain, Sierra Luciano, Paul J Harrison

- Incidence of *any* neuropsychiatric outcome = **33.62%**
- Incidence of *first* neuropsychiatric outcome = **12.84%**
- *Any* incident mood, anxiety, or psychotic disorder = **23.98%**
- *First* incident mood, anxiety, or psychotic disorder = **8.63%**

(Taquet et al., 2021)

6-Month Outcomes Continued

- First incident PTSD in 6 months post-COVID = 0.58% (v. 0.26% post-influenza, HR = 2.12, $p < 0.0001$)

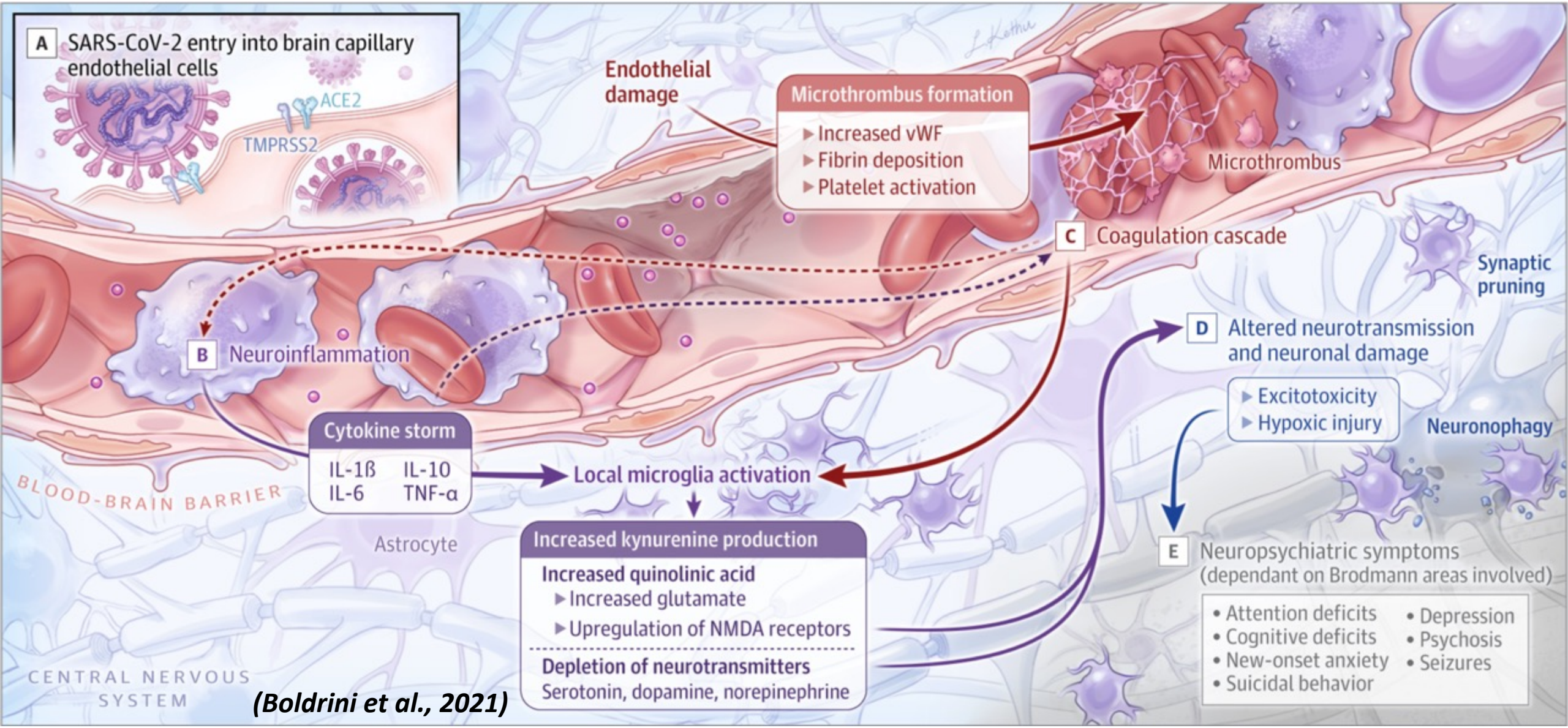
(Taquet et al., 2021)

	COVID-19 *vs* influenza (N=105 579)*		COVID-19 *vs* other RTI (N=236 038)*	
	HR (95% CI)	p value	HR (95% CI)	p value
Mood, anxiety, or psychotic disorder (any)	1·46 (1·43–1·50)	<0·0001	1·20 (1·18–1·23)	<0·0001
Mood, anxiety, or psychotic disorder (first)	1·81 (1·69–1·94)	<0·0001	1·48 (1·42–1·55)	<0·0001
Mood disorder (any)	1·47 (1·42–1·53)	<0·0001	1·23 (1·20–1·26)	<0·0001
Mood disorder (first)	1·79 (1·64–1·95)	<0·0001	1·41 (1·33–1·50)	<0·0001
Anxiety disorder (any)	1·45 (1·40–1·49)	<0·0001	1·17 (1·15–1·20)	<0·0001
Anxiety disorder (first)	1·78 (1·66–1·91)	<0·0001	1·48 (1·42–1·55)	<0·0001
Psychotic disorder (any)	2·03 (1·78–2·31)	<0·0001	1·66 (1·53–1·81)	<0·0001
Psychotic disorder (first)	2·16 (1·62–2·88)	<0·0001	1·82 (1·53–2·16)	<0·0001
Substance use disorder (any)	1·27 (1·22–1·33)	<0·0001	1·09 (1·05–1·12)	<0·0001
Substance use disorder (first)	1·22 (1·09–1·37)	0·0006	0·92 (0·86–0·99)	0·033
Insomnia (any)	1·48 (1·38–1·57)	<0·0001	1·15 (1·10–1·20)	<0·0001
Insomnia (first)	1·92 (1·72–2·15)	<0·0001	1·43 (1·34–1·54)	<0·0001
Any outcome	1·44 (1·40–1·47)	<0·0001	1·16 (1·14–1·17)	<0·0001
Any first outcome	1·78 (1·68–1·89)	<0·0001	1·32 (1·27–1·36)	<0·0001

Additional details on cohort characteristics and diagnostic subcategories are presented in the appendix (pp 29–33). HR=hazard ratio. RTI=respiratory tract infection. *Matched cohorts.

***Table* 3: HRs for the major outcomes in patients after COVID-19 compared with those after influenza and other RTIs**

Potential Pathogenic Mechanisms



(Boldrini et al., 2021)

Pediatric Long COVID & Psychiatric Symptoms

- Prevalence of pediatric long COVID ~1-5%
- Neuropsychiatric symptoms
  - Fatigue = 5-85%
  - But… 40% of youth with anxious/depressive symptoms, regardless of COVID-19 infection history
- Functional impact in Danish youth 15-18 years of age (*n*=28,270)
  - 16+ sick days:
    - 18.2% (COVID-19+) versus 11.6% (HCs), $p<0.0001$
  - 16+ days of school absence:
    - 10.5% (COVID-19+) versus 8.2% (HCs), $p<0.0001$

Image Source: San Diego Union Tribune

(Gurdasani et al., 2022; Kikkenborg Berg et al., 2022; Molteni et al., 2021; Radtke et al., 2021; Stephenson et al., 2021)

Developmental Perspective

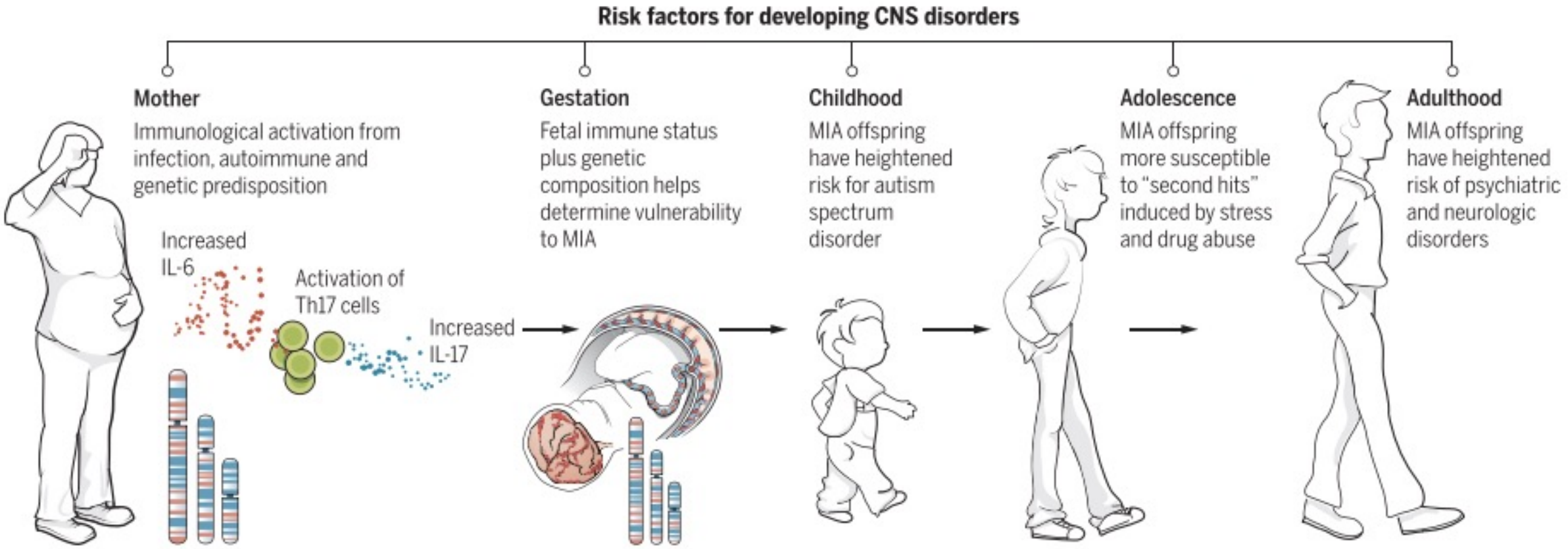


Fig. 1. MIA as a disease primer. This schematic depicts the current model for how MIA leads to psychiatric disorders in offspring. Infection leads to release of pro-inflammatory cytokines and activation of T_H17 cells in the mother's bloodstream (*6*, *19*). A combination of genetic background, autoimmune status, and second hits during childhood and adolescence (including stress and drug abuse) combines with the consequences of maternal infection to increase the likelihood of offspring developing psychiatric disorders as adults (*3*, *6*, *14*, *37*).

(Brown & Derkits, 2010; Estes & McAllister, 2016; Kępińska et al., 2020; Khandaker et al., 2012; Menninger, 1926)

Summary

- COVID-19 infection is associated with risk for exacerbation of and new-onset psychiatric disorders, including mood, anxiety, and trauma-related disorders, as well as sleep disturbances
- Nearly all studies to date have been conducted in adult samples, and findings may not be generalizable to other stages of development
- Longer term outcomes, pathogenic mechanisms, biomarkers, and effective treatments for post-COVID psychiatric disorders remain to be elucidated
- Disentangling effects of COVID-19 infection versus pandemic-related stress will be difficult, as both may contribute to long-term sequelae via neuroimmune mechanisms
- The scale of the pandemic will require that brain and mental health be integral components of research and clinical and social service planning in the coming years

Thank You!

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