LONG COVID AND COGNITION

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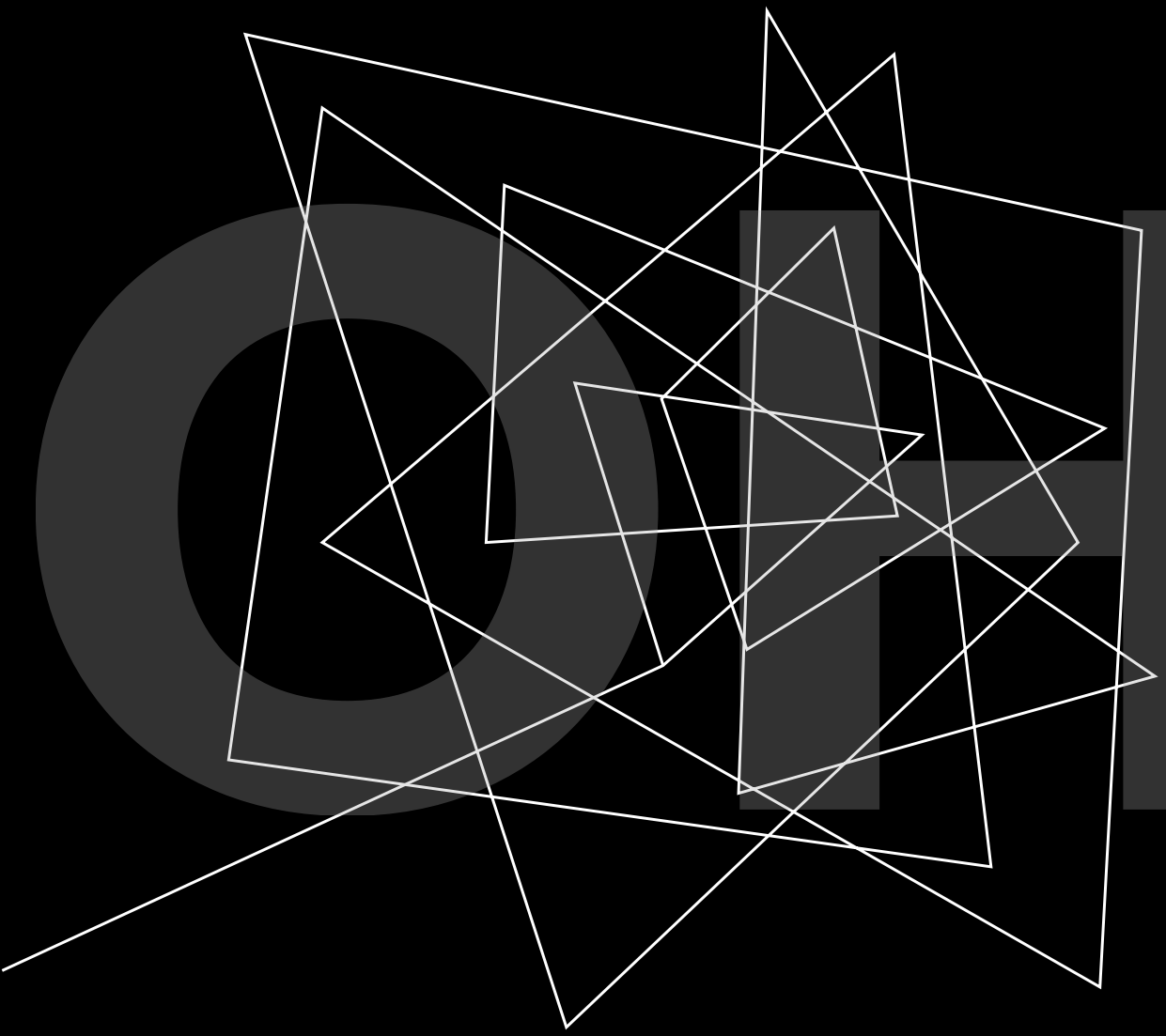
OBJECTIVES

Definitions & Observations
- What is Long COVID?
- “Brain Fog” / primary cognitive symptoms & deficits

Pathophysiology
- What causes it?

Management
- AAPM&R Guidelines
- Cognitive Rehabilitation
- Energy Conservation
- Pharmacotherapy

Future Directions
- Long term impact
- Dementia risk?



DEFINITIONS AND OBSERVATIONS

DEFINITIONS – “LONG COVID”

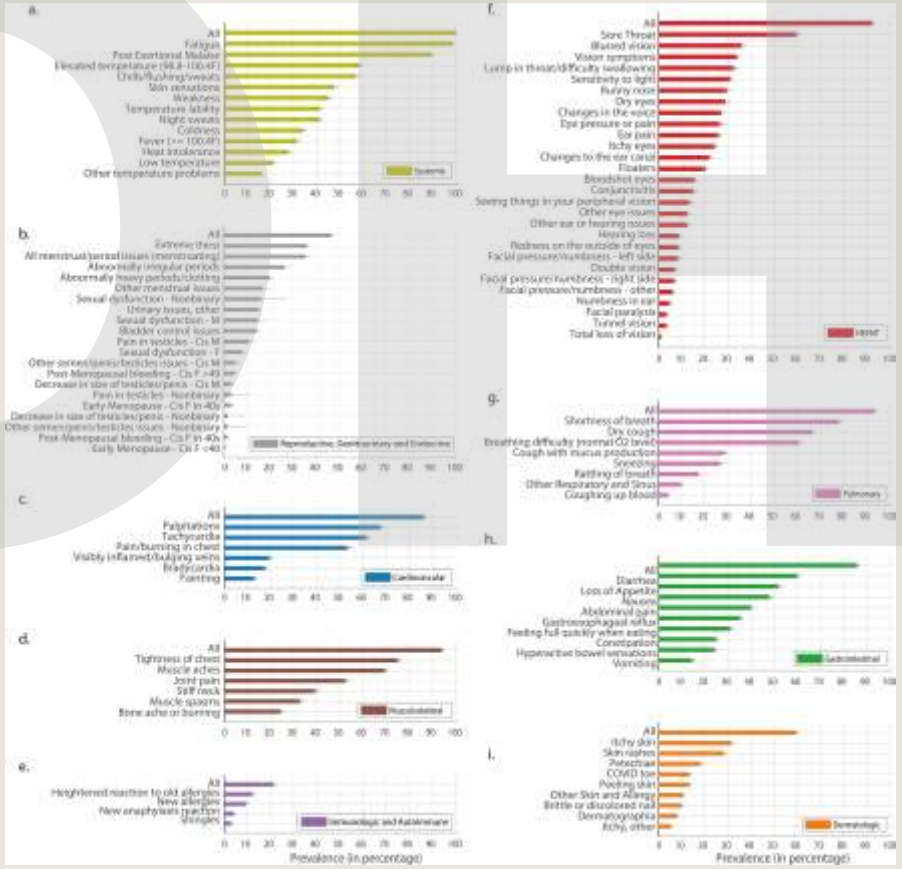
New or persistent health problems experienced **four or more weeks** after the initial COVID infection

Also known as:

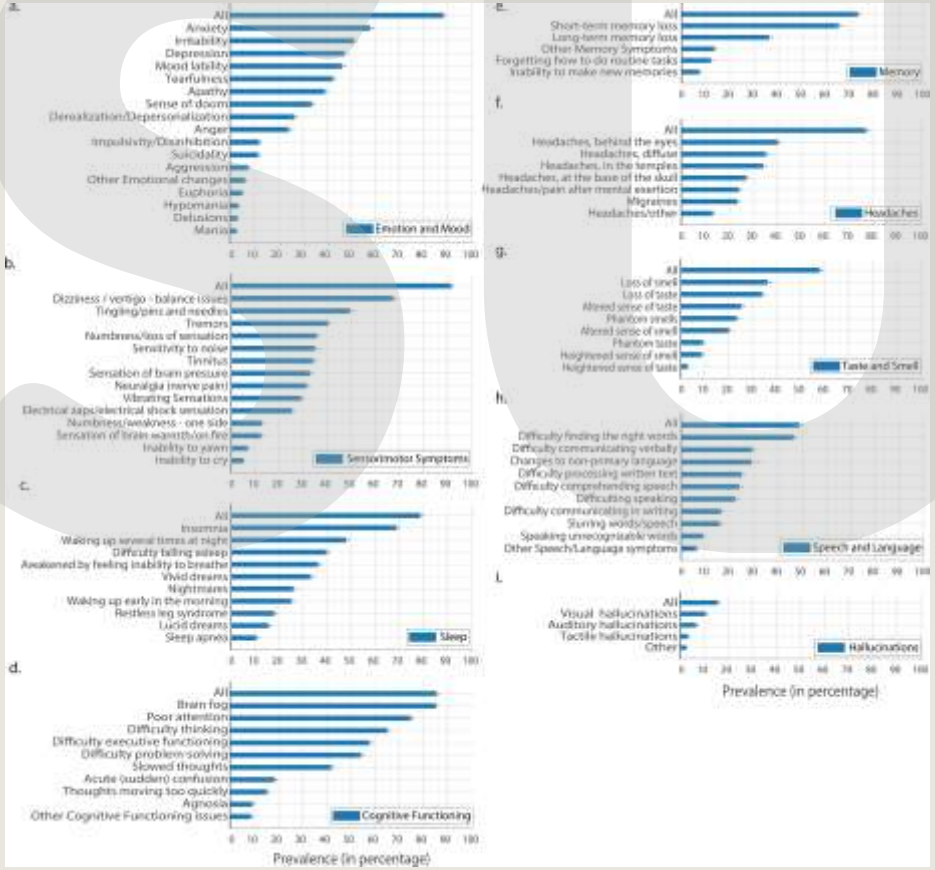
- Chronic COVID
- PASC = Post Acute Sequela of SARS-CoV-2 (Research term)

CHARACTERIZING LONG COVID IN AN INTERNATIONAL COHORT: 7 MONTHS OF SYMPTOMS AND THEIR IMPACT DAVIS ET AL 2021 *ECLINICALMEDICINE*

Non-neuropsychiatric symptoms

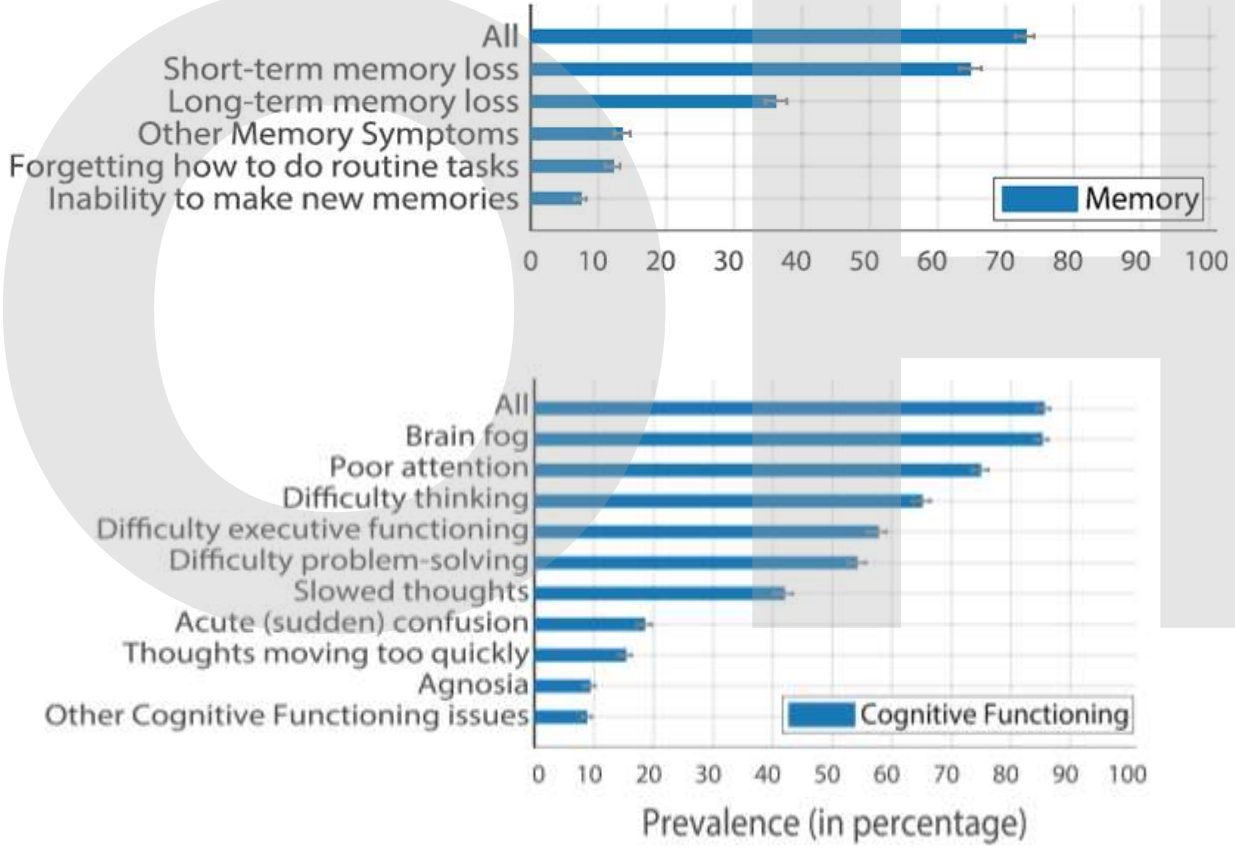


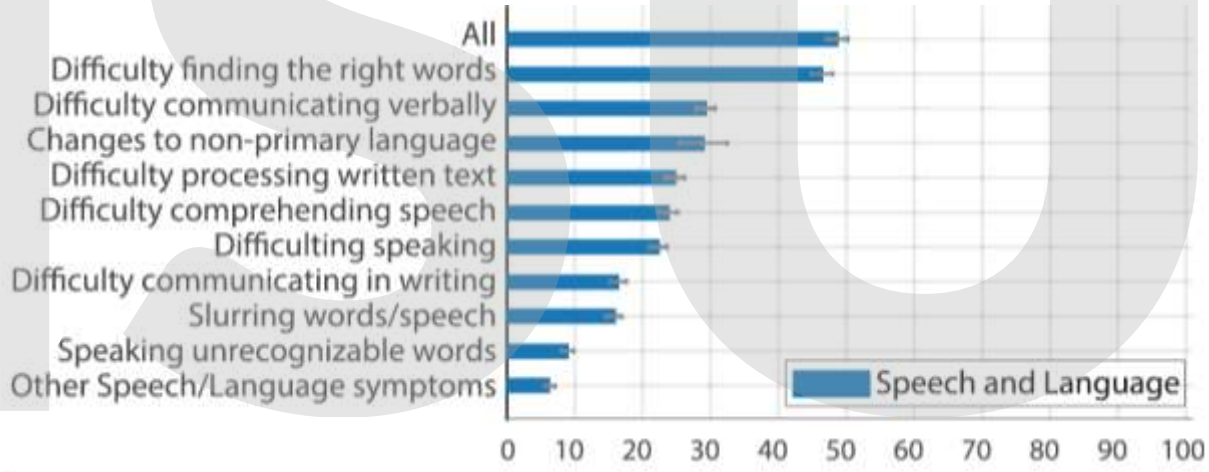
Neuropsychiatric symptoms



COGNITIVE SYMPTOMS

DAVIS ET AL 2021 *ECLINICAL MEDICINE*





COGNITIVE SYMPTOMS

BECKER ET AL 2021 *JAMA NETWORK OPEN*

Table 2. Prevalence of Cognitive Impairment After COVID-19 Infection

Cognitive domain	Impaired (*z* score ≤1.5), No. (%)				Adjusted odds ratio (95% CI)[a]	
	Total (N = 740)	Outpatient (n = 379)	ED (n = 165)	Hospitalized (n = 196)	ED vs outpatient	Hospital vs outpatient
Attention	74 (10)	19 (5)	10 (6)	29 (15)	0.8 (0.3-2.0)	2.8 (1.3-5.9)
Working memory	74 (10)	30 (8)	17 (10)	29 (15)	1.0 (0.5-2.2)	1.7 (0.8-3.3)
Processing speed	133 (18)	57 (15)	21 (13)	55 (28)	0.7 (0.4-1.3)	1.4 (0.8-2.5)
Executive functioning	118 (16)	45 (12)	23 (14)	53 (27)	1.0 (0.5-1.8)	1.8 (1.0-3.4)
Phonemic fluency	111 (15)	42 (11)	25 (15)	39 (20)	0.9 (0.5-1.8)	1.5 (0.8-2.8)
Category fluency	148 (20)	49 (13)	35 (21)	69 (35)	1.8 (1.1-3.1)	3.0 (1.7-5.2)
Memory encoding	178 (24)	61 (16)	43 (26)	73 (37)	1.7 (1.0-3.0)	2.3 (1.3-4.1)
Memory recall	170 (23)	45 (12)	38 (23)	76 (39)	1.5 (0.9-2.6)	2.2 (1.3-3.8)
Memory recognition	74 (10)	34 (9)	20 (12)	25 (13)	1.5 (0.8-3.0)	1.1 (0.5-2.4)

COGNITIVE SYMPTOMS
BECKER ET AL 2021 *JAMA NETWORK OPEN*

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Phonemic fluency	111 (15)
Category fluency	148 (20)
Memory encoding	178 (24)
Memory recall	170 (23)
Memory recognition	74 (10)

"The relative sparing of memory recognition in the context of impaired encoding and recall suggests an executive

pattern.

This pattern is consistent with early reports describing a dysexecutive syndrome after COVID-19 and has considerable implications for occupational, psychological, and functional outcomes"

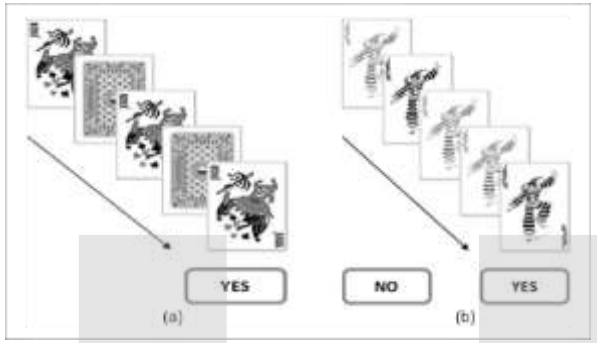
COGNITIVE SYMPTOMS

Other studies showing cognitive symptoms / deficits

- Ritchie K, Chan D. The emergence of cognitive COVID. World Psychiatry. 2021;20(1):52-53. doi:10.1002/wps.20837
- Jaywant A, Vanderlind WM, Alexopoulos GS, et al. Frequency and profile of objective cognitive deficits in hospitalized patients recovering from COVID-19. Neuropsychopharmacology. 2021; 46:2235-2240. doi:10.1038/s41386-021-00978-8
- Zhou H, Lu S, Chen J, et al. The landscape of cognitive function in recovered COVID-19 patients. J Psychiatr Res. 2020;129:98-102. doi:10.1016/j.jpsychires.2020.06.022
- Hampshire A, Trender W, Chamberlain SR, et al. Cognitive deficits in people who have recovered from COVID-19. EClinicalMedicine. 2021;39:101044. doi:10.1016/j.eclinm.2021.101044

OTHER OBSERVATIONS:

POTS



Attention and executive function are impaired during active standing in postural tachycardia syndrome

- Miller at al 2020 *Autonomic Neuroscience*
- Executive function – Stroop Word-Color test
- Visual attention – Cogstate Identification task

OBSERVATIONS

Whiteside et al 2022 *The Clinical Neuropsychologist*

- Significant correlations between cognition and mood/anxiety measures
- Psychological distress prominent in PASC and related to objective cognitive performance,
  - BUT objective cognitive performance was unrelated to cognitive complaints
- Personality Assessment Inventory (PAI) scales measuring psychological distress, particularly *somatic preoccupation and depression*, were the most frequently elevated

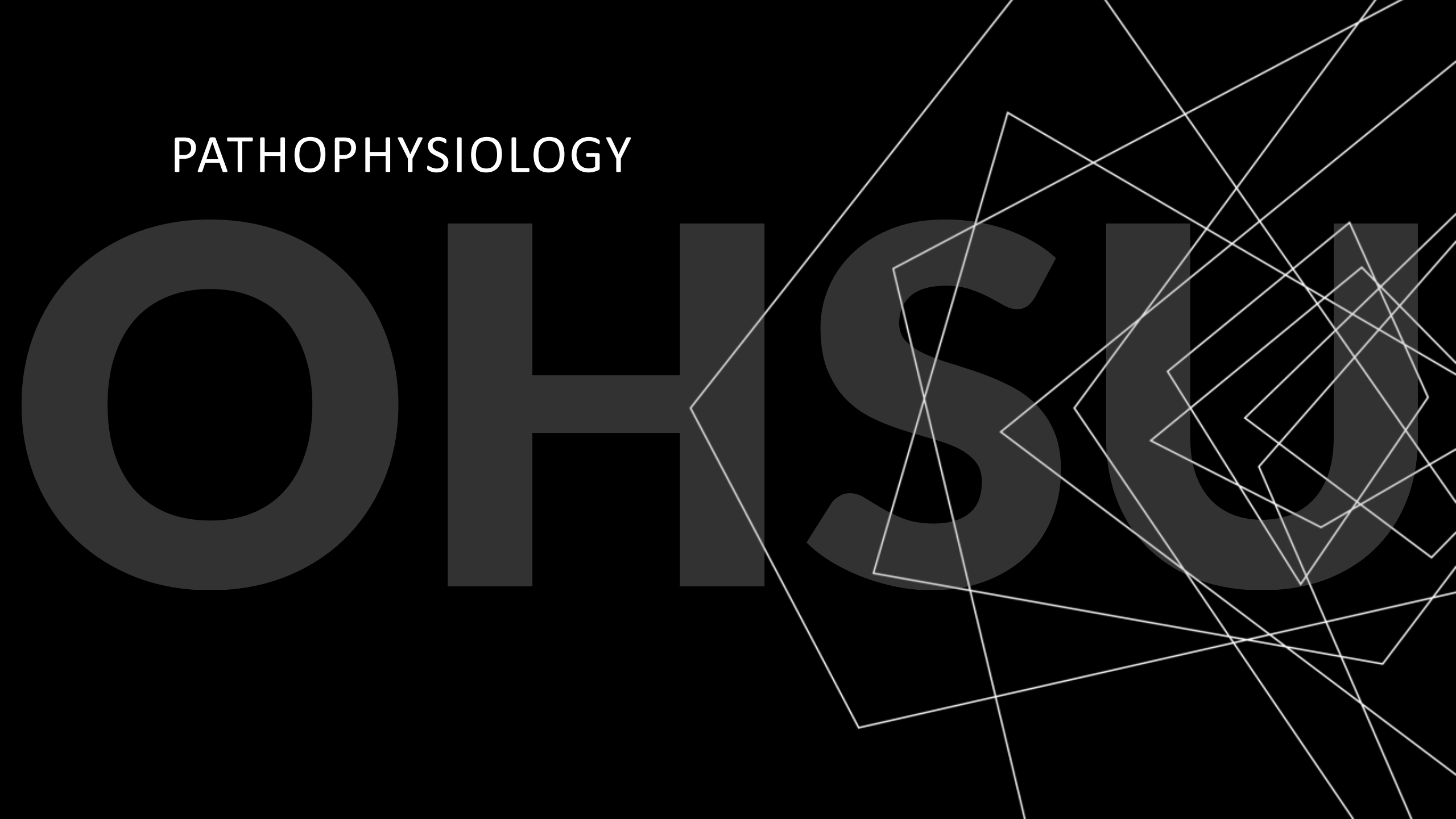
Outcomes in post-acute sequelae of COVID-19 (PASC) at 6 months post-infection Part 1: Cognitive functioning

Douglas M. Whiteside[a], Michael R. Basso[b], Savana M. Naini[a,c], James Porter[a], Erin Holker[a], Eric J. Waldron[a], Tanya E. Melnik[a], Natalie Niskanen[a] and Sarah E. Taylor[a]

Outcomes in post-acute sequelae of COVID-19 (PASC) at 6 months post-infection part 2: Psychological functioning

Douglas M. Whiteside[a], Savana M. Naini[a,c], Michael R. Basso[b], Eric J. Waldron[a], Erin Holker[a], James Porter[a], Natalie Niskanen[a], Tanya E. Melnik[a] and Sarah E. Taylor[a]

PATHOPHYSIOLOGY



PATHOPHYSIOLOGY

Similarities to chemo-treatment-related cognitive impairment. Fernandez-Castenada 2022

- Impaired hippocampal neurogenesis, decreased oligodendrocytes and myelin loss in subcortical white matter persisted at least 7 weeks following mild SARS-CoV-2 infection in mice

Changes in brain structure on MRI. Douaud 2022

- Greater reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus
- Greater changes in markers of tissue damage in regions functionally connected to primary olfactory cortex
- Greater reduction in global brain size
- Neurodegenerative spread via olfactory pathways?

Redox imbalance similar to myalgic encephalomyelitis / chronic fatigue syndrome. Paul et al 2021

- Elevated levels of pro-oxidants; reduced levels of small molecule antioxidants
- Mitochondrial dysfunction
- Combination leads to chronic inflammation

PATHOPHYSIOLOGY

Focal hypometabolism on FDG-PET

- Sollini et al 2021
  - Orbitofrontal cortex, parahippocampal gyrus, thalamus
- Guedj et al 2021
  - Olfactory gyrus, right temporal lobe (incl amygdala and hippocampus), right thalamus, bilateral pons/medulla, bilateral cerebellum
    - Worse in patients on an ACE inhibitor, better in patients using nasal decongestant spray during the infectious stage
      - ➢ Possible role of ACE receptors as an olfactory gateway for neurotropism

OHSU

MANAGEMENT

MANAGEMENT

AAPM&R Consensus Guidance Statement

Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of cognitive symptoms in patients with post-acute sequelae of SARS-CoV-2 infection (PASC)

Jeffrey S. Fine MD, FAAPMR[1] | Anne Felicia Ambrose MD, MS[2] | Nyaz Didehbani PhD[3] | Talya K. Fleming MD[4] | Lissette Glashan MS, CCC-SLP, CBIS[5] | Michele Longo MD, MPH[6] | Alexandra Merlino MS, CCC-SLP[7] | Rowena Ng PhD[8] | Gerald J. Nora MD, PhD[9] | Summer Rolin PsyD[10] | Julie K. Silver MD[11] | Carmen M. Terzic MD, PhD[12] | Monica Verduzco-Gutierrez MD[13] | Sarah Sampsel MPH[14]

MANAGEMENT

AAPM&R Consensus Guidance Statement (Paraphrased)

1. Screen with validated instruments (MOCA, MMSE, SLUMS).
2. Screen for comorbidities that impact cognition**:
   - Sleep impairment
   - Mood, including anxiety, depression, and posttraumatic stress disorder
   - Fatigue
   - Endocrine abnormalities
   - Autoimmune disorders

**Note: Avoid misattributing symptoms to psychological factors

MANAGEMENT

AAPM&R Consensus Guidance Statement

3. Perform Neurologic exam. Refer or order neuroimaging if necessary.
4. Labs

   CBC, B12, thiamine, folate, vitamin D, CMP, LFTs, thyroid function, HIV/RPR if high risk

MANAGEMENT

AAPM&R Consensus Guidance Statement

5. Comprehensive History
   - Preexisting conditions (medical, neurologic, psychiatric)
   - Standard mental health scales if indicated (PHQ9, GAD7, PCL5)
   - Prior level of function vs current level of function
   - Medications and supplements (eg antihistamine, anticholinergic, antidepressant/anxiolytics?)
   - Collateral history if available
6. Assess impact of cognitive struggles on quality of life; distinguish *cognitive fatigue* from *general or exertional fatigue*

MANAGEMENT

AAPM&R Consensus Guidance Statement – Treatment Recommendations (Paraphrased)

1. Refer to specialists for cognitive rehab if available (ST, OT, Neuropsychology)
2. Treat underlying medical conditions that contribute
   - Pain
   - Sleep disorders
   - Mood disorders
   - Other medical (dysautonomia, thyroid)

MANAGEMENT

AAPM&R Consensus Guidance Statement – Treatment Recommendations

3. Reduce polypharmacy, taper/stop drugs that negatively impact cognition
4. Reinforce sleep hygiene

MANAGEMENT

AAPM&R Consensus Guidance Statement – Treatment Recommendations

5. Begin an individualized and structured, titrated return to activity program
   - Avoid flaring symptoms (overexertion)
   - Frequently assess impact of return to normal, daily activities
   - Exercise may only be helpful for cognition if patient is able to return to normal daily routine and tolerate exercise 2-3x/week

MANAGEMENT

OHSU: Cognitive Rehab via Speech Therapy

Spoon theory – energy conservation

MANAGEMENT

Pharmacotherapy

?

MANAGEMENT

Pharmacotherapy – What I've tried

- Stimulants
  - Dextroamphetamine and amphetamine (Adderall)
  - Methylphenidate (Ritalin)
  - Lisdexamfetamine (Vyvanse)
  - Modafinil (Provigil)
- Non-stimulant ADHD medications
  - Atomoxetine (Strattera)
  - Clonidine
  - Guanfacine (+NAC)
- Other
  - Amantadine
  - Memantine

MANAGEMENT

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MANAGEMENT

Pharmacotherapy

Clinical experience with the α2A-adrenoceptor agonist, guanfacine, and N-acetylcysteine for the treatment of cognitive deficits in "Long-COVID19"

Arman Fesharaki-Zadeh [a,b,*], Naomi Lowe [a], Amy F.T. Arnsten [c]

[a] *Departments of Neurology, Yale Medical School, New Haven, CT USA 06510*
[b] *Psychiatry, Yale Medical School, New Haven, CT USA 06510*
[c] *Neuroscience, Yale Medical School, New Haven, CT USA 06510*

FUTURE DIRECTIONS

FUTURE DIRECTIONS

- FDG –PET as a biomarker?
- Drugs targeting redox imbalance?
- Improve education
- How will long COVID affect cognition long-term?

LONG COVID VS ALZHEIMER'S?

"Brain Fog" by COVID-19 or Alzheimer's Disease? A Case Report

Jordi A. Matias-Guiu[1], Cristina Delgado-Alonso[1], Miguel Yus[2], Carmen Polidura[2], Natividad Gómez-Ruiz[2], María Valles-Salgado[1], Isabel Ortega-Madueño[3], María Nieves Cabrera-Martín[4] and Jorge Matias-Guiu[1]*

"In our case, the finding of an isolated episodic memory deficit, suggestive of hippocampal dysfunction, led to investigate AD biomarkers.

In this regard, some findings, such as an episodic memory deficit with preserved attention, a low benefit through category cues during controlled learning tests for episodic memory assessment, or failure to recover from proactive semantic interference (closely associated with amyloid deposition and AD; Loewenstein et al., 2018), should be considered as patterns highly suggestive of Alzheimer's pathology, as we observed in this patient."

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QUESTIONS?