MedStar National Rehabilitation Network

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Long-COVID/PASC: Persistent Neurocognitive and Psychological Impact Following COVID-19 Illness

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COI Disclosure

Professional Roles

- Director of Psychology MNRN
- Faculty, Neuropsychology Fellowship, Brain Injury Medicine Fellowship
- Consultant to NFL Player Disability Plans
- Forensic Expert Witness: Civil and Criminal Matters

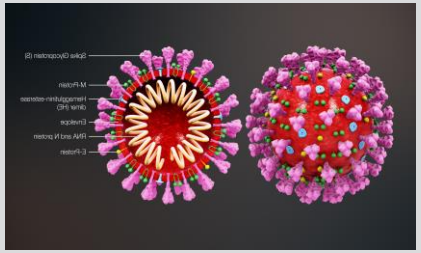
Conflict of Interest Disclosure

- No known conflicts of interest related to this talk
- I have no financial relationships to disclose related to this content

Opinions expressed reflect presenter's professional ideas/opinions

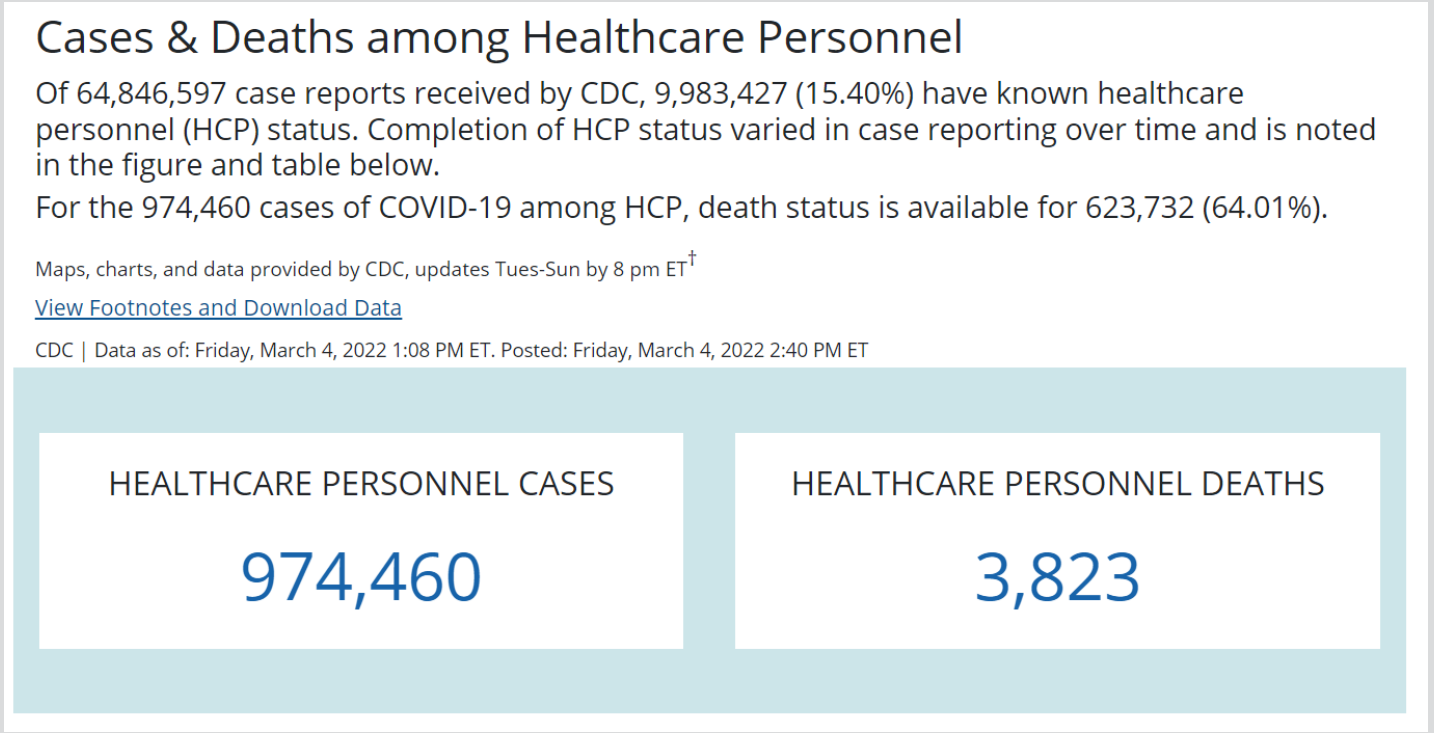
Objectives

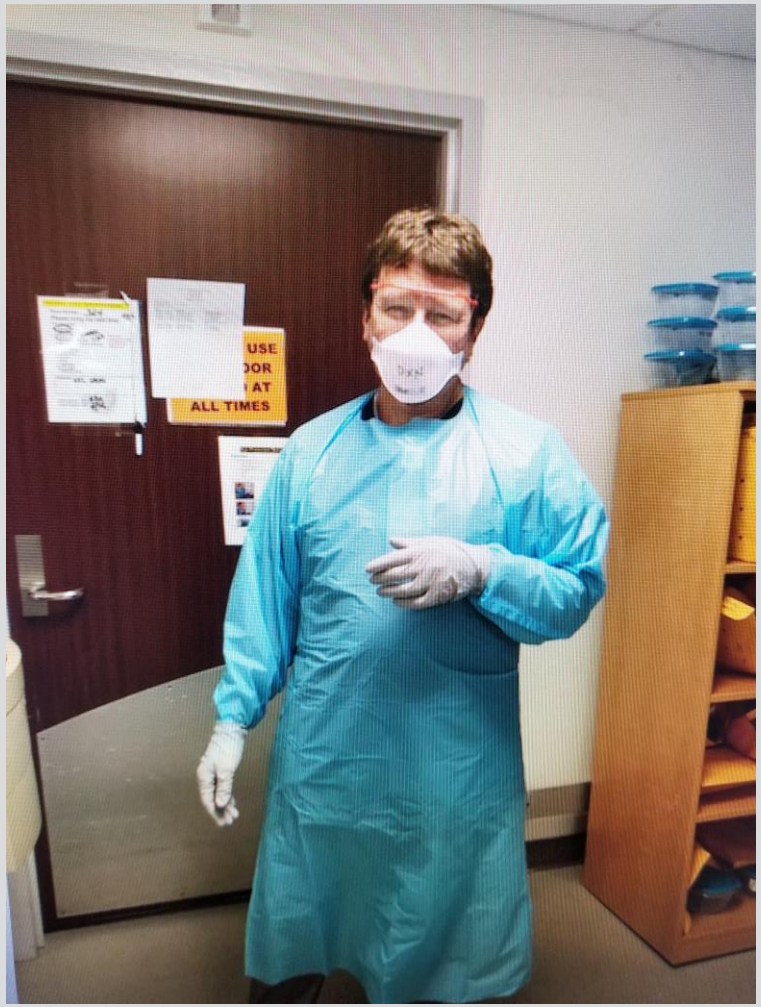
1. Understand mane research challenges in pandemic and global context
2. Review current research on long-term neurocognitive effects following COVID-19 illness
3. Review neuropsychological data from MNRN clinical sample of Long-COVID-19 patients.
4. Discuss rehabilitation approach to long-COVID-19 patients



United States COVID-19 Impact on Healthcare Workers

(Data from March 4, 2022)




ALL TIMES

Complex Landscape of Integrating Research: Methodologic Challenges

- Shifting landscape
  - Treatments, virus variants, societal controls/regulations have evolved – are data from 2020 fully comparable to today?
  - Antonelli et al (2022): Long-COVID less common with omicron variant?
- NP and Psych Tests capture broad amount of variance in behavior
- Non-specific effects of pandemic on health and cognitive/psychological well-being
- Construct Shift?
  - Does somatic preoccupation mean something different in midst of global pandemic?
- ‘Big Data’ – Big Confusion?

‘Big Data’ Studies

- Enable collection of huge sample sizes, and potential to identify trends and control variables (post-hoc) in ways not possible with smaller studies and RTCs
- Dependent on quality of entries made into the EMR
- Cannot control for reliability of use of ICD-10/DSM-V codes across examiners
- Over-reporting risk?: A diagnostic code entered may or may not be corroborated, but might stay in the record
- Under-reporting risk?: May not capture conditions that are presented but not coded, and those that never made it to the clinic visit
- Utilize methodology unfamiliar with many professionals – difficult for many (most?) professional readers to critique

COVID-19 Neuropsychological Manifestations: Methodologic Challenges

- Publications from centers across the world may use similar terms without clarifying operational definitions
- Health disparities may limit subject enrollment
- Selection Bias and convenience samples
- Small sample size studies
- Intermixing of confirmed positive and non-confirmed cases
- Variable range of time since illness onset
- Reliance on self-report without controlled, objective assessment
- On-line assessment (not de facto a problem)
- Variable level of control or corrections for important covariates
- Are effects COVID-19 specific or non-specific? (e.g., other viral encephalopathies, hypoxia, and post-delirium)

COVID-19 Neuropsychological Manifestations: What is Impaired Cognition?

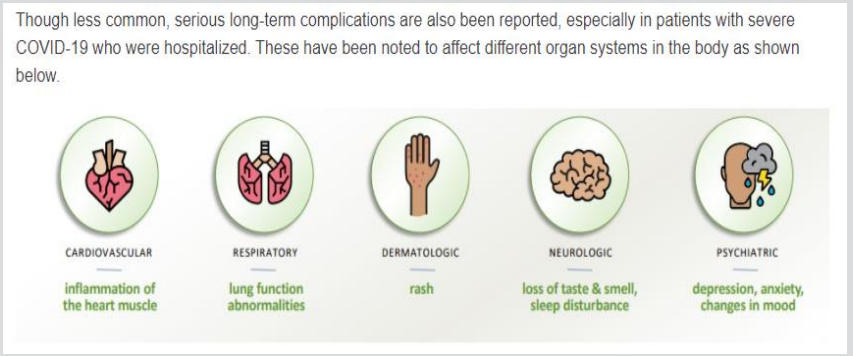
- Self-Report versus objective testing
- Screening instruments versus detailed batteries
- Performance validity infrequently addressed
- Statistically lower than standardized test mean
- Group-wise statistically significant score differences
- Numbers of low scores compared to expected base rates
- What is a ‘low score?’
  - >1 SD below the mean
  - >1.5 SD below the mean
  - >2.0 SD below the mean
- Variable use of demographic adjustments
- Stronger emphasis on sensitivity or specificity?

Proposed Mechanisms for Direct/Indirect Neurocognitive/Neurological Impact Following COVID-19

- Direct Neurologic SARS-CoV-2 Damage
  - Blood-brain-barrier compromise
  - Transmission into CNS through cranial nerves
- Indirect Sources of Neurologic Insult
  - Post-ICU delirium (short and long-term)
  - Hypoxia from ARDS
  - Thrombotic Events
  - Exacerbation of pre-existing comorbidities
  - Medication effects
- Potential for impact expressed later (heightened neurodegeneration risk)
- Psychological/Psychiatric Factors
  - Acute Stress Response
  - PTSD
  - Cognitive dysfunction from depression, anxiety, pain
  - Somatic Symptom Disorder

Lasting Effects of COVID-19 –
‘Long COVID’ – ‘Long-Haulers’
Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

- World Health Organization (Long COVID)
  - History of confirmed or probable SARS CoV-2 Infection
  - Symptom onset within 3 months of illness, lasting at least 2 months
  - Not explainable by alternate diagnosis
  - Common symptoms: Fatigue, Dyspnea, Cognitive Dysfunction, also others
  - Have meaningful impact on daily functioning
  - May fluctuate or relapse over time



Persistent Problems Following COVID-19

Persistent Problems Following COVID-19

- Meta-Analyses and Scoping Reviews (a few examples)
  - Lopez-Leon et al (2021)
  - Ceban et al (2022)
  - Akbarialiabad et at (2021)
  - Crivelli et al (2021)
  - May (2022)
  - Bertuccelli et al (2022)
  - Shou et al (2021)

- Challenge to compare across studies
  - Cross-sectional, Retrospective, Longitudinal (few)
  - Hospitalized, Non-hospitalized, Mixed
  - Major Cohort Differences
  - Self-Report, Structured Questionnaires, Objective Measures
  - Imprecise Operational Definitions
  - Lack of Common Nomenclature and Criteria

Meta-Analyses of Long-Term Effects of COVID-19

- Ceban et al. (2021) – focus on fatigue and cognition
  - 12 weeks or more post-illness – primarily hospitalized samples
  - 32% persistent fatigue (pooled proportions)
  - 22% persistent cognitive impairment (pooled proportions)
  - Studies using objective versus subjective assessment reported higher rates for both
  - 21-63% reduced Quality of Life
  - Elevated rates of pro-inflammatory markers in symptomatic groups
  - Predictors: Older age, initial illness severity, female sex, pre-existing comorbidities

- Premraj et al. (2022) - long-term neurologic and psychiatric
  - <3 and >3 months, hospitalized and non-hospitalized cohorts
  - 37% persistent fatigue
  - 22-32% persistent cognitive (depending on how defined)
  - 31% sleep disturbances
  - 23% anxiety
  - 17% depression
  - Anxiety, depression, sleep disturbance increased over time
  - Illness severity variably related to differing outcomes

Large Data Medical Records Studies
JAMA Psychiatry (2022) – Global Burden of Disease Long-COVD Collaborators

- Extracted data from 54 international cohort studies and 2 medical records databases in the U.S. – statistically used pooled data
- Examined 3 ‘clusters’ of common Long-COVID effects (based on frequency reporting and the WHO Delphi consensus determination process)
  - Persistent fatigue with body pain or mood swings
  - Cognitive problems
  - Persistent respiratory problems
- Outcome Measures: Proportion of at least 1 cluster, 3 months and 12 months post-symptomatic SARS-CoV-2 infection

Large Data Medical Records Studies
JAMA Psychiatry (2022) – Global Burden of Disease Long-COVD Collaborators

	% - 3 Months Post	% - 12 Months Post
Full Sample	6.2	0.9
Hospitalized		
General Ward	27.5	11.1
ICU	43.1	15.1
Non-Hospitalized	5.7	0.7

- Long-COVID clusters significantly more common in females
  - Note: Females tend to have less severe disease from viruses and higher antibody responses
- 38% of Long-COVID cases had 2 or 3 of the symptom clusters overlapping
- Suggests that the majority of Long-COVID cases resolve with time (no study included went beyond 12 months)
- Authors point to methodological factors that may impact results
- Unable to analyze new-onset diseases/illnesses that might occur with greater frequency following COVID-19 illness

Studies of Long-COVID-19

Ferrando, et al. (2022)
Post-COVID-19: Treatment-Seeking Versus Non-Treatment-Seeking

- N = 60 (32 ‘clinical’ and 28 ‘non-clinical’)
- Mean = 7 months post-onset
- 7 hospitalized (6 in the clinical group) – none in ICU
- Clinical group
  - lower current employment rates
  - Higher depression and trauma scores
  - Greater number of comorbidities
  - Greater total symptom score
- Neurocog Battery: RBANS, Trail Making, Verbal Fluency, Color-Word
- Comparing Groups:
  - Non-clinical: Significantly lower than standardized norms on 1 of 11 scores
  - Clinical: Significantly lower than standardized norms on 8 of 11 scores
  - Clinical: Significantly greater number of extremely low scores (38%)
- Predictors of low scores in clinical group included initial symptom severity, depression, # of comorbidities, subjective complaints

Hampshire, et al. (2021)
Cognitive deficits following recovered COVID-19

- Predominantly UK sample of post-COVID-19 subjects, selected from a large sample study of the normal population
- “Collaborative citizen science project” - on-line demographic and health-related questionnaires, and a cognitive assessment battery
- Extracted approximately 13,000 COVID-19 subjects
- Hospitalized, ventilated COVID-19 subjects showed a global performance deficit in the range of .47 SD
- Non-hospitalized biopositive COVID-19 subjects showed .23 SD global performance deficit
- Differential levels of impairment were evident depending on the domain assessed

Hampshire, et al. (2021)

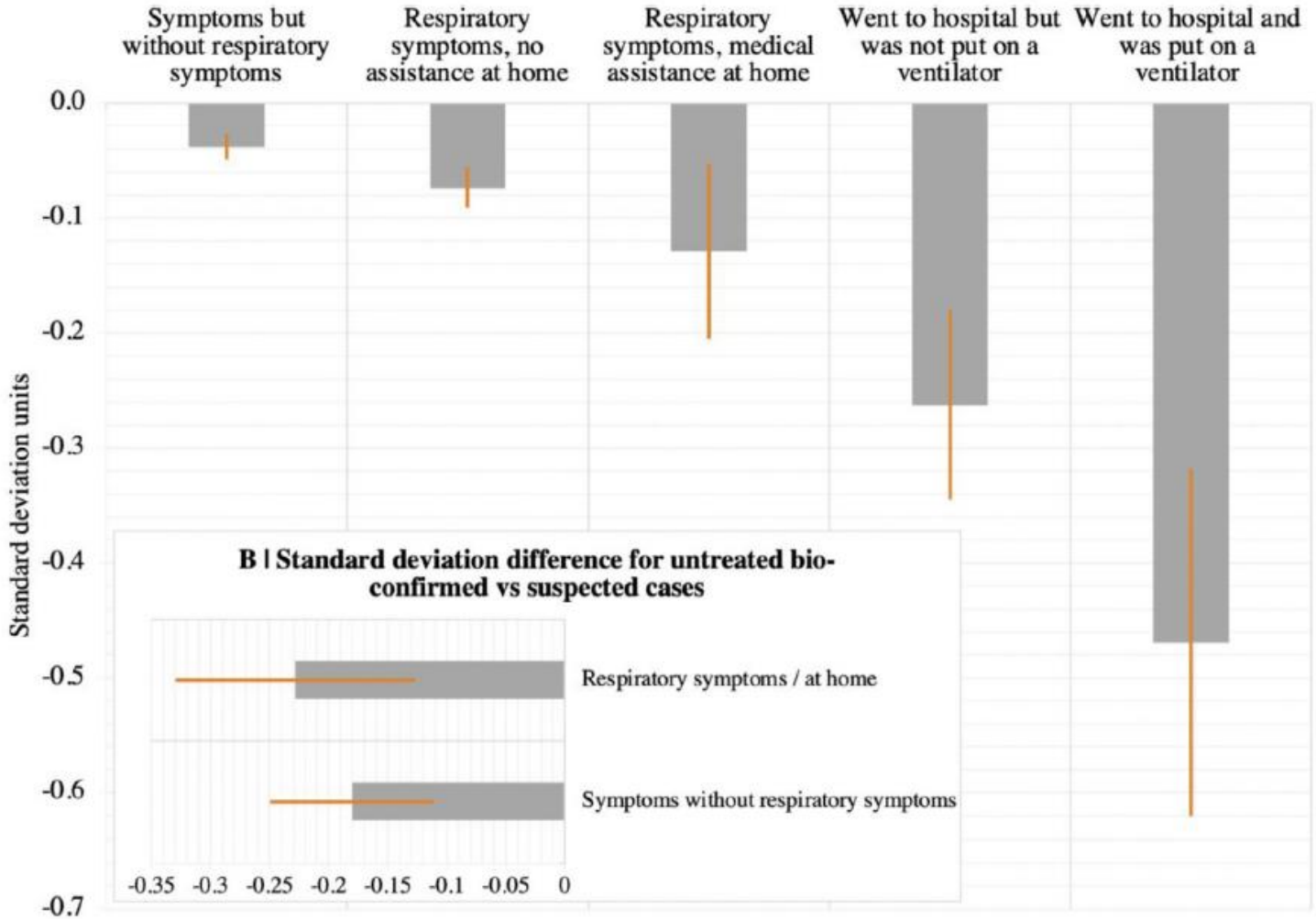


Fig. 2. . Cognitive deficits in people with suspected and confirmed COVID-19 illness.
A | People who reported having recovered from COVID-19 performed worse in terms of global score. The scale of this deficit increased with the level of treatment received for respiratory difficulty. B | In individuals who did not receive medical assistance, the scale of this deficit was greater in biologically confirmed cases versus suspected cases of COVID-19. Error bars report the standard error.

Al-Aly, et al (2021)
Characterization of Post-Acute Sequelae

- Examined U.S. Department of Veterans Affairs healthcare databases to identify 6-month sequelae in survivors of COVID-19
- Found a ‘risk gradient’ for persistent problems positively related to acute illness severity
- Higher risk of death
- Records show, beyond first 30 days of illness, increased incidence of health multi-system health issues including pulmonary, nervous system/neurocognitive, cardiovascular, gastrointestinal, mental health, general malaise indicators, pain, etc.
- Increased risk of using several classes of medication (pain, antihypertensive, antihyperlipidemic, antidepressants, anxiolytic, etc.)
- Increased risk and burden of post-acute sequelae evident even in those not requiring hospitalization during acute illness
- Post-acute burden worse for those hospitalized for COVID-19 than for influenza

Xie, et al. (2022)
Risks of Negative Mental Health/Neurocognitive Outcomes

- V.A. Health System electronics records
- Compared COVID-19 patients to contemporary and historical medical control cohorts
- 1 year post-COVID-19 group showed higher risk for behavioral health (anxiety, depression, stress disorders, etoh/substance abuse, sleep) and neurocognitive diagnoses
- Increased risk relative to control cohorts for hospitalized and non-hospitalized subjects
- Use of contemporary medical cohort helped control for general pandemic-related mental health burdens
- Suggest a ‘bidirectional connection between mental health and COVID-19

Xu, et al. (2022)
Risks of Negative Neurologic Outcomes

- V.A. Health System electronics records (Al-Aly and Xie studies)
- Compared COVID-19 patients to contemporary and historical medical control cohorts
- 1 year post-COVID-19 group showed higher risk for neurologic disorders
  - Cognitive disorders
  - CVA
  - Extrapyramidal and Movement disorders
  - Peripheral Nervous System disorders
  - Sensory disorders
  - Others (e.g., Guillain-Barre)
- Risks persist against historical and contemporary control groups
- Risks evident in multiple subgroups, hospitalized and non-hospitalized

Longitudinal Studies

- Del Brutto et al. (2021)
  - Atahualpa Longitudinal Study – rural Ecuador
  - Pre-pandemic serial cognitive and health assessments, baseline MRIs
  - Existing longitudinal data on MOCA score changes over time
  - Compared mild COVID-19 cases to healthy controls
  - Six-months post-illness, COVID-19 group showed larger MOCA score decline against prior testing, compared to healthy controls
  - Cognitive decline seen in 21% of COVID-19 cases compared to 2% controls

- Del Brutto et al. (2022)
  - Follow-up with the same population cohort
  - 12-month post-illness assessments
  - COVID-19 cohort showed improved MOCA scores, no longer different from healthy controls
  - Conclusion: Post-COVID-19 cognitive impairment may not be permanent

Cross-Sectional Studies

- Delgado-Alonso, et al. (2022)
  - N=50 post-COVID-19 subjects compared to healthy controls
  - COVID-19 group showed lower scores on several domains (incl. attention, memory, executive functions)
  - Effects sizes generally in the low range
  - Psychiatric scales showed low correlations with cognitive performance

- Kay, et al. (2022)
  - Multi-Center, international, cross-cultural study
  - Frequency of cognitive impairment varied across sites
  - Significant numbers had one domain ≥1.5 SD below mean)
  - Most common domains impaired: Attention, working memory, executive
  - Impairments typically in mild range
  - Elevated rates of depressive and anxiety symptoms

Elevated Risk for Dementia?

- Liu, et al. (2022)
  - Cohort study of older adults hospitalized with COVID-19 (Wuhan)
  - In severe-illness group, 15% identified with dementia at 12 months, 26% with MCI
  - Evidence of progression of cognitive decline in some subjects
  - In non-severe illness group, rates of MCI and dementia did not differ with controls
  - Non-severe group compared to paired controls did show elevated cognitive impairment at 12 months

- Wang, et al. (2022)
  - Electronic Health Records study (propensity-score matching)
  - COVID-19 cohort: Increased risk for new Alzheimer's dx compared to matched non-COVID-19 cohort
  - Highest risk groups: Over age 85 and females

Studies not showing significant evidence of impairment

Whiteside et al., 2022a, 2022b: Outcomes in Post-Acute COVID-19 at Six Months Post-Infection: Cognition and Psychological Functioning

- N=49 consecutive referrals to Post-COVID-19 clinic with concerns about cognitive functioning (PVT failures removed)
- High rates of premorbid behavioral health diagnoses
- Conclusions:
  - Low rates of cognitive impairment in the overall sample
  - Presence of low scores consistent with base-rate estimate studies from nonclinical studies
  - Current emotional distress accounted for significant variance in cognitive performance (along with education)
  - Disconnect between subjective cognitive symptom reporting and objective testing
  - Authors recognize limitations, including sample not reflecting groups most vulnerable to severe COVID-19 illness
- PAI results
  - DEP: (Mean T=64); 28% showed T>70
  - SOM: (Mean T=69); 44% showed T>70
  - Psychological factors biggest driver of subjective cognitive issues post-COVID-19

Behavioral Health Outcomes

Psychiatric Symptoms in Long-COVID-19

- Mazza et al. (2021)
  - N=226 post COVID-19 subjects
  - Hospitalized sample 1 and 3 months post-discharge
  - 3 month Self-Report: 36% reported self-rate symptoms in clinical range for at least one behavioral health condition (anxiety, depression, PTSD, OCD)
  - 3 month Psychiatric interview: 24% met DSM-V criteria for a behavioral health diagnosis
  - Change over 1-3 months: PTSD, anxiety symptoms decreased, depression stayed same, OCD symptoms increased
  - Inflammatory biomarkers correlated with depression trajectory
  - Female sex and prior psychiatric history increased risk
  - High rates of impaired cognitive scores – strong relation to psychopathology symptoms
  - Systemic inflammation markers may relate to both cognitive and behavioral health symptoms

Psychiatric Symptoms in Long-COVID-19

- Mazza et al. (2022)
  - Longitudinal cohort followed up to 1 year post-hospitalization
  - 6 and 12 months: 45% of sample were above clinical threshold for behavioral health condition on at least one self-report measure
  - 28% had been prescribed a medication for behavioral health conditions
  - 11% had sought mental health care over the year
  - 33% reported high levels of persistent fatigue
  - Prior psychiatric history and female sex more strongly related to psychological symptoms
  - Illness severity variables not strongly related to psychological symptoms
  - Posit a link between inflammatory process and psychological symptoms

Psychiatric Symptoms in Long-COVID-19

- Poletti et al. (2021)
  - Hospitalized cohort followed at 1, 3, 5 months post-illness
  - Compared to healthy controls and MDD group
  - On mood scale, significant depressive symptomatology ranged from 23-27% of post-COVID-19 group across 6 months
  - Cognitive impairment shown in 75% of post-COVID-19 group up to 6 months (in at least 1 domain)
  - Strong relationship between depression and cognitive impairment – possible common inflammatory process hypothesized

Behavioral Health Diagnoses as Risk Factor?

- Ranger et al. (2022)
  - Pandemic cohort compared to pre-pandemic cohort – medical records study
  - Compared risk for severe outcome in those with pre-existing psychiatric diagnoses
  - Those with psychiatric diagnoses (including dementia) had increased risk of severe outcome following COVID-19 and other SARIs.
  - Prescription for antidepressant medication (even with not psych diagnosis listed) had increased risk of severe outcome
  - No difference in risk of severe outcome between COVID-19 and other SARIs
  - Psychiatric history did not increase risk for contracting SARS-CoV-2

- Ceban et al. (2021):
  - Meta-analysis reached similar conclusions

MedStar COVID-19 Outpatient Recovery Program

What is the COVID Recovery Program?

The COVID Recovery Program is a collaboration among medical specialists across all MedStar Health hospitals. Our team aims to support patients recovering from COVID-19 with persistent symptoms such as:

- Fatigue
- Pain
- Persistent shortness of breath
- Thinking, focus, and memory issues
- Weakness

We will support your recovery by offering a wide range of services from a team of medical specialists that will help you return to your normal activities as soon as possible. Our team is led by physical medicine and rehabilitation physicians and advanced practice providers who specialize in the rehabilitation of patients with a variety of physical impairments. Our team will perform a detailed evaluation and provide necessary referrals to specialists who can further address your symptoms. A patient navigator and community health advocate will assist you with scheduling and managing your plan of care. Visits may be via telemedicine or onsite at MedStar National Rehabilitation Hospital.

MedStar COVID-19 Outpatient Recovery Program

- At least six-weeks post-onset, still report at least two major symptoms, and have a history of a positive test
- Initial assessment done by Rehabilitation Medicine
- Neuropsychology/Rehabilitation Psychology among the most frequent referrals
- Most prominent symptoms are fatigue and ‘brain fog’
- Most prominent cognitive complaints (as part of ‘brain fog’) include concentration, memory, slowed processing, and word-finding
- On self-report, patients report high levels of occupational disruption
- Referrals may include PT, Neuropsychology or Rehabilitation Psychology, Cardiology, Pulmonary, Neurology, Psychiatry, Sleep Medicine, other rehabilitation therapies
- **Selection bias: Symptomatic clinical population with access to health care system**

MNRN COVID-19 Recovery Program
Neuropsychology Evaluations
Full Sample (N=135)

	Age	Education
Mean	46.6	16.4
Median	48	16
Standard Deviation	12.9	2.1
Range	58	9
Minimum	21	11
Maximum	79	20

	%
Sex	
Female	74
Male	26
Race	
White	69
African American	19
Hispanic	5
Other	7
Relationship Status	
Single	31
Married	49
Long-Term Partner	9
Divorced	9
Widowed	2
Pre-Illness Employment	
Full-Time	87
Part-Time	4
Disability/Med Leave	1
Student	2
Retired	5
Unemployed	1

Acute Hospitalization and Time Since Onset Full Sample (N=135)

Acute Illness Hospitalizations	
Acute Hospitalization	N=31 (23%)
Length of Stay (Mean)	12 Days
Range	1 – 60 Days
# in ICU	7
# ARDS/Mechanical Vent	3

Weeks/Months Post-Illness Onset at Time of Evaluation	
Weeks post-onset (Mean/SD)	38 (24.1)
Range (in weeks)	7-109
2-3 Months	11%
4-6 Months	23%
6-8 Months	14%
8-12 Months	22%
>12 Months	30%

Pre-Illness Developmental and Mental Health Conditions Full Sample (N=135)

	%
ADD/ADHD	
No	83
Yes	17
Learning Disability	
No	90
Yes	10
Mental Health History	
No	32
Yes	68
Primary Diagnosis	
Adjustment Disorder	10
GAD/Other Anxiety	27
MDD/Other Depression	17
Co-Occurring GAD-MDD	34
PTSD/ASD	10
Bipolar Illness	2
Trauma History	
No	63
Yes	37
Etoh/Subs History	
No	97
Yes	3

Pre-Illness Medical Conditions (Self-Report)
Full Sample (N=135)

	%
Neuro/Brain Injury	29
Diagnoses	
MTBI	77
Mod/Severe TBI	14
Other (migraines)	9
Seizures	6
Diabetes (I or II)	10
Hypertension	22
Cardiac Disease	18
Cancer (any)	5
Chronic Kidney Disease	3
Chronic Liver Disease	1
Chronic Lung Disease	17
Sleep Apnea	36
Rheumatologic Disease	12
Chronic Pain	39
Auto-Immune Illness	6

# of Comorbid Conditions	%	Cum %
0	33	33
1	32	65
2	17	82
3	10	92
4	6	98
5	2	100

Mean # of Comorbid Conditions = 1.3

Comorbidities, Age, Hospitalization Status

- Correlations with # of comorbidities:
  - Age =.40 (p<001)
  - Race not significant
  - BDI-II, BAI, PCL-5 not significant

- Hospitalized subjects had greater # Comorbidities relative to non-hospitalized (t= -2.1, p<.04)
  - Hospitalized Mean: 1.8 (SD=1.7)
  - Non-Hosp. Mean: 1.2 (SD= 1.1)

- Hospitalized subjects significantly older relative to non-hospitalized (t=4.11, p,>001)
  - Hospitalized Mean: 55.5 yrs. (12.2)
  - Non-Hosp. Mean: 43.2 yrs. (11.1)

Neuropsychological Test Battery

- Core Elements
  - WAIS-IV: Similarities, Block Design, Digit Span, Arithmetic
  - Trails A & B
  - SDMT
  - RAVLT
  - WCST
  - Phonemic and Semantic Fluency
  - Rey-Osterrieth Complex Figure
  - Boston Naming Test
  - TOMM, RDS, other embedded
  - BDI-II, BAI
  - PCL-5
  - CD-RISC-10

- Less Frequently
  - Trails-X
  - D-KEFS Color-Word
  - WMS-IV: LM and VR
  - BVMT-R
  - PAI
  - TOPF

- Telehealth Assessments
  - Oral SDMT
  - Oral Trails

Post-COVID-19 Recovery Subjects

- Full Sample = 135 unique cases
- Performance Validity ‘Pass’ = 127 Cases (TOMM, RDS, others)
- Performance Validity Failures = 8 cases
- Final sample for analyses = 127 cases, all first-time evaluations
- Most In-Person Assessments
- All evaluations clinical referrals, conducted by five different neuropsychologists and two post-doctoral fellows
- Test battery sometimes modified based on clinical or logistical factors

Pre- and Post-Illness Employment, Change in Status, Disability Applications Valid Cases

Pre-Illness Employment	**%**
Full-Time	87
Part-Time	4
Student	2
Retired	6
Unemployed	1
Employment Stats – At Evaluation	**%**
Full-Time	57
Part-Time	8
Disability/Med Leave	19
Student	2
Retired	7
Unemployed	7

Employment – Change in Status	**%**
No Change	55
Not Working	28
Reduced Hours/Responsibility	16
Compensation Status – At Evaluation	**%**
No STD/LTD/FMLA	74
On Disability or Applied	26

Notes:
- Multiple factors for those on disability
- Failed Effort Group: 5 of 8 on Medical Leave or Disability

Psychological Symptoms at Time of Evaluation
Valid Cases

	BDI-II	BAI	PCL-5	CD-RICS-10
Mean	16.4	12.1	23.4	26.3
(SD)	9.2	8.5	14.2	6.9
Median	15.0	12.0	22	27.0
Minimum	1	0	0	4
Maximum	44	40	54	40

PAI – Select Validity and Clinical Scales:
Note – small sample size (n=15)

	Mean (T)	SD	Range
ICN	56.4	7.6	43-67
INF	53.5	7.1	40-67
NIM	55.8	7.0	47-66
SOM	63.3	12.8	45-86
ANX	62.9	13.5	45-92
ARD	61.1	12.0	36-78
DEP	67.1	15.6	44-96

Correlations: BDI-II, BAI With

Demographics

Neurocognitive Scores

Valid Cases

Correlations of NP Test Scores and Beck Scales (significant values in Yellow/Bold)

Test	BDI-II	BAI
Age	**-.19**	-.05
Education	-.10	-.11
# of Comorbid Conditions	-.08	-.09
# Weeks Post-Onset	-.06	-.11
WAIS-IV Similarities	-.01	-.04
WAIS-IV Block Design	-.004	-.06
WAIS-IV Digit Span	-04	-.06
WAIS-IV Arithmetic	-.00	-.14
Trails A	-.15	**-.22**
Trails B	-.07	-.13
SDMT Written	.01	.03
SDMT Oral	-.07	-.09
WCST Categories Completed	-.08	-.15
WCST Perseverative Responses	-.01	-.11
COWAT	-.09	-.07
Semantic/Animal fluency	-.06	-.14
RAVLT Trial 1 T-score	-.14	**-.27**
RAVLT Trials 1-5 T-score	-.03	-.13
RAVLT List B T-score	-.14	**-.23**
RAVLT Immediate Free Recall T-score	.11	-.02
RAVLT Delayed Free Recall T-score	.09	-.09
Boston Naming Test	-.05	-.06
Rey-Osterrieth Figure Copy	-.06	-.12

Comparing Impaired and Unimpaired Subjects – Valid Cases

- Neuropsychologist Clinical Determination
  - Not Impaired, Impaired, Indeterminate
- 125 cases:
  - 85 (68%) rated Not-Impaired
  - 31 (25%) rated Impaired
  - 9 (7%) rated Indeterminate
- No significant differences in numbers of comorbid conditions
- No significant differences in BDI-II
- Significant difference in BAI scores (Indeterminate group)
- No significant difference in Age & Education

	Not Impaired	Impaired	Indeterminate	ANOVA
Age (SD)	45.2 (13.2)	49.4 (13.0)	41.4 (8.5)	F=1.75, ns
Education (SD)	16.7 (2.0)	15.9 (2.1)	17.0 (1.7)	F=1.9, ns
BDI-II (SD)	16.6 (9.5)	15.4 (7.9)	19.0 (10.8)	F=.56, ns
BAI (SD)	11.4 (8.1)	11.6 (7.9)	21.6 (8.4)	F=6.5, p=.002
PCL-5 (SD)	22.7 (14.8)	23.7 (13.2)	32.5 (4.8)	F=.89, ns

Post-hoc tests: Indeterminate Group differs from Not-Impaired and Impaired Groups

Impaired and Unimpaired Subjects
Change in Employment Status at Time of Evaluation
Valid Cases

	Not Impaired (%) (n=84)	**Impaired (%) (n=29)**
No Change from Pre-Illness	55%	52%
Not Working At All	25%	32%
Reduced Hours/Responsibilities	18%	9%

Impaired and Unimpaired Subjects
Acute Illness Hospitalization Status
Valid Cases

		Current Neurocognitive Disorder		
		No	Yes	Total
Hospitalization Status	No	70	17	87
	Yes	15	14	29
	Total	85	31	116

$X^2 = 9.17$, p=.002

48% of hospitalized subjects Impaired
19% of non-hospitalized subjects Impaired

Impaired and Unimpaired Subjects

- No significant differences found:
  - WAIS-IV Similarities and Block Design
  - Executive Functioning Tasks (WCST, COWAT, D-KEFS, Trails-X)
  - Verbal Fluency (phonemic, semantic)

- Significant differences found:
  - Processing Speed (Trail Making, SDMT)
  - Attention/Working Memory (Digit Span, Arithmetic, RAVLT Trial 1)
  - New Learning/Recent Memory (RAVLT learning, immediate recall, delayed recall)

- Impaired group showed higher frequencies of low scores
  - ≥1.5 SD below mean

Comparing Impaired and Unimpaired Subjects

Processing Speed, Attention/Working Memory, New Learning/Recent Memory

	Not Impaired	Impaired	p	Cohen's D
WAIS-IV Similarities	54.1 (10.9)	51.7 (8.5)	.27	N/A
Trail Making A	51.2 (11.9)	45.5 (9.6)	.05	.59
Trail Making B	51.8 (9.6)	45.9 (10.8)	.02	.55
SDMT - Written	50.9 (8.5)	43.8 (10.9)	.002	.79
SDMT - Oral	52.1 (9.3)	45.4 (8.9)	.003	.73
WAIS-IV Digit Span	51.8 (10.6)	44.9 (7.5)	.001	.68
WAIS-IV Arithmetic	48.9 (10.4)	43.6 (7.9)	.01	.54
RAVLT Trial 1	53.6 (11.3)	41.7 (10.8)	<.001	1.06
RAVLT Trial 5	57.1 (7.6)	44.6 (11.3)	<.001	1.42
RAVLT Trials 1-5 Total	58.4 (9.0)	43.1 (11.4)	<.001	1.58
RAVLT Immed. Free Recall	57.3 (8.5)	44.3 (9.1)	<.001	1.50
RAVLT Delayed Free Recall	57.5 (8.5)	43.2 (9.9)	<.001	1.60
Rey-Osterrieth 3 Min. Recall (Raw)	22.5 (5.6)	16.6 (6.2)	<.001	1.03

Frequency of Low Scores – Not-Impaired v Impaired Groups
Valid Cases

Frequencies of Low Scores (≥1.5 SD Below Mean) Non-Impaired v Impaired Groups		
Test	**Not Impaired**	**Impaired**
Trails A	7%	14%
Trails B	4%	18%
SDMT Written	4%	23%
SDMT Oral	3%	14%
WAIS-IV Digit Span	5%	10%
WAIS-IV Arithmetic	10%	19%
RAVLT Trial 1 T-score	5%	23%
RAVLT Trials 1-5 T-score	3%	26%
RAVLT Immediate Free Recall	4%	19%
RAVLT Delayed Free Recall	3%	26%

Impaired Group:
- Mean # Scores >1.0 SD below mean = 7.3
  Range: 0-17
- Mean # Scores ≥ 1.5 SD below mean = 4.7
  Range: 0-14

Conclusions – MNRN Neurocognitive Data

- Most typical neuropsychological profile in long-COVID-19 is absence of objective impairment – irrespective of early illness severity
- 25% of patients showed neurocognitive impairment –
  - Impairments typically in mild range, involving processing speed, attention, working memory, new learning/recent memory
  - Learning/Recent Memory and Processing Speed strongest effect in this sample
  - Impairments most typically in mild range
- Impairment not predicted by psychological symptoms
- Severity Gradient: Greater proportion of hospitalized in Impaired group
- Unclear whether a sample with more severe illness course would show different pattern
- Findings show general consistency with many other studies

Long COVID-19 - Summary

- Elevated risk for neurocognitive and behavioral health conditions post COVID-19
- Risk persists controlling for health comorbidities
- Long-COVID-19 symptoms generally improve over time (not all agree)
- Relationship of acute illness severity to Long-COVID not well-understood (‘risk gradient’)
- Self-report of Long-COVID-19 symptoms not consistently related to initial illness severity
- Roughly, 20-35% post-COVID-19 self-report cognitive impairment, mood symptoms, and vegetative struggles (fatigue, sleep)
- Behavioral health disorders are a risk factor for more severe illness course, and a common element of persistent/long-COVID-19
- Neurocognitive impairments may be more easily seen in population-based studies (e.g., Hampshire et al), in part because syndromes tend to be objectively will be mild, and not easily seen in individual or small sample cases

Long-COVID - Summary

- Multi-factorial pathway to Long-COVID – no single etiology
- Persistent cognitive symptoms in long-COVID-19 reflect heterogeneous and interactive factors across individuals:
  - acquired neurocognitive impairment
  - Sleep disorders, fatigue, pain
  - Impact of anxiety, depression
  - Pre-existing psychological adjustment factors
  - Impact of premorbid conditions with neurocognitive risk factors (possibly interactive)
  - Medications
- Leading hypotheses for etiology of prolonged difficulties include, persistent inflammatory processes, autoimmune dysregulation, in more severe cases interacting with ARDS/post-ICU, worsening of pre-existing conditions.
- Unclear whether cognitive impairment following SARS-CoV-2 has unique features or high similarly to neurocognitive disorders that may follow from other viral illnesses
- The political and social zeitgeist of the pandemic cannot be ignored as a factor impacting symptom presentation

Neuro-Rehabilitation for Long-COVID-19
WHO Recommendations

- "Limited data are available on rehabilitation for cognitive impairment in post COVID-19 condition *(399)(411)*. No RCT or non-randomized study of interventions (NRSI) with comparator have been identified for the rehabilitation management of cognitive impairment. Hence, no GRADE certainty of evidence assessment has been applied"
- Recommend compensatory, restorative interventions, and environmental adjustments, depending on nature and extent of impairments
- Cognitive impairments often "overlap" or "cluster" with non-neurologic issues (fatigue, sleep, mental health, etc.) – need to take these into account for treatment planning
- Subjective cognitive symptoms don't always associate with objective test results – rehab focus for those may need to be different
- Consider potential for episodic, fluctuating nature of cognitive impairments

Clinical management of COVID-19: living guideline, 15 September 2022. Geneva: World Health Organization; 2022 (WHO/2019-nCoV/Clinical/2022.2).

MedStar COVID-19 Outpatient Recovery Program

What is the COVID Recovery Program?

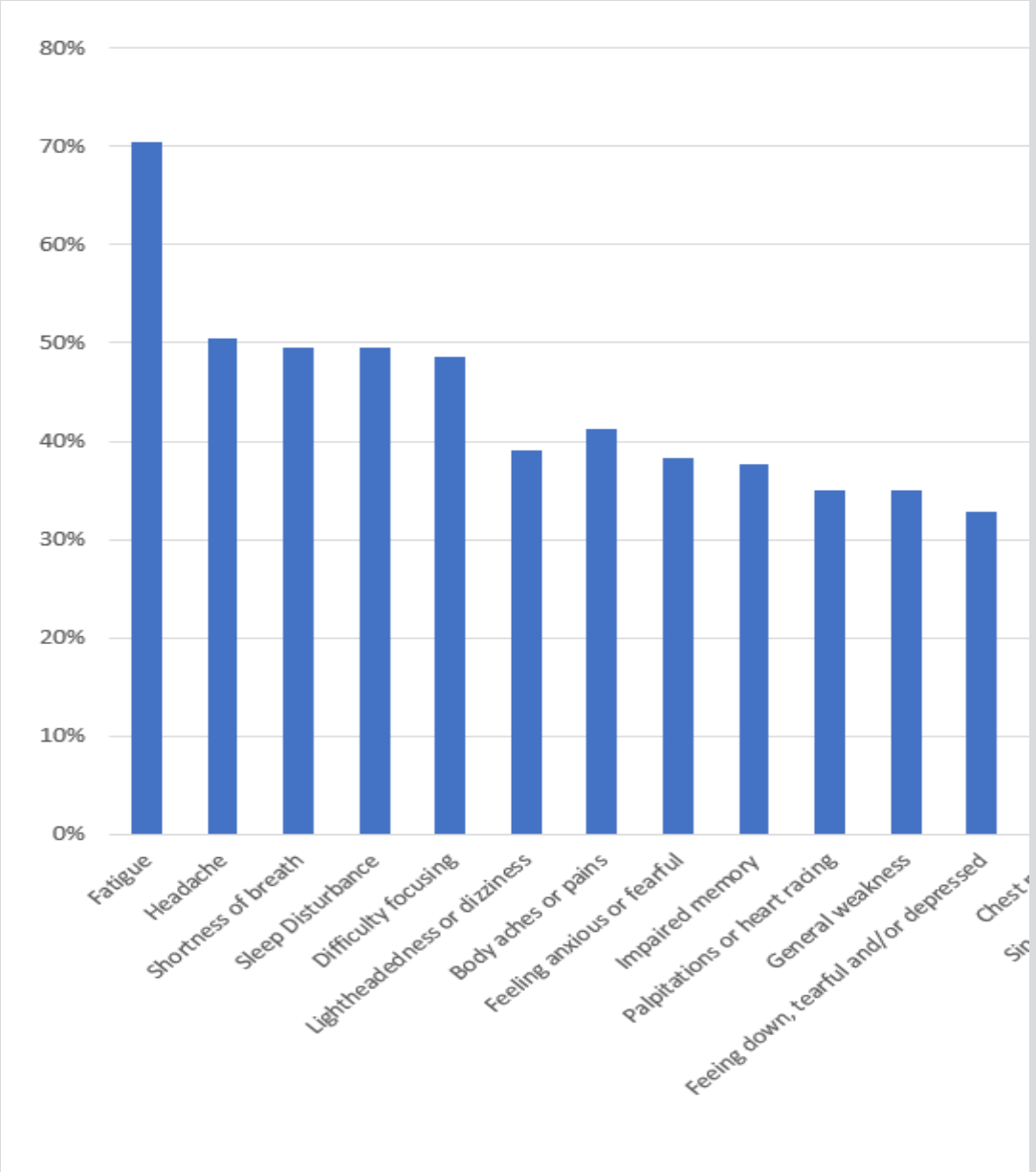
The COVID Recovery Program is a collaboration among medical specialists across all MedStar Health hospitals. Our team aims to support patients recovering from COVID-19 with persistent symptoms such as:

- Fatigue
- Pain
- Persistent shortness of breath
- Thinking, focus, and memory issues
- Weakness

We will support your recovery by offering a wide range of services from a team of medical specialists that will help you return to your normal activities as soon as possible. Our team is led by physical medicine and rehabilitation physicians and advanced practice providers who specialize in the rehabilitation of patients with a variety of physical impairments. Our team will perform a detailed evaluation and provide necessary referrals to specialists who can further address your symptoms. A patient navigator and community health advocate will assist you with scheduling and managing your plan of care. Visits may be via telemedicine or onsite at MedStar National Rehabilitation Hospital.

Most Common Self-Reported Post-COVID-19 Symptoms

Highest Percentage of referrals to PT, Neuropsych/Rehab Psych



Treating Patients With Long-COVID-19
What Are We Treating?

- Somatic Symptom Disorder – in a new package?
  - Yes, in at least some
  - Not strongly evident in most of our sample

- Recovery Trajectories
  - Most Long-COVID-19 patients get better over many months (some > a year)
  - Atypical for someone not to improve with time (some disagree)
  - Improvement often uneven, and with recurrence of some symptoms
  - Most specialty evaluations (cardiology, pulmonology, etc.) – negative results
  - Atypical symptoms – often not atypical
  - Subgroup found to have organ system damage - need ongoing monitoring

- Significant social context of ‘anti’ views impact patients

- Compensation-seeking context may mediate recovery patterns for some

Treating Patients With Long-COVID-19
What Are We Treating?

- Treatment still primarily targets active symptoms/disruptions
- Patients with no evidence of cognitive impairment – NP assessment as intervention
- Primary Targets: Fatigue, dizziness, deconditioning, cognition, sleep, autonomic dysregulation, anxiety/depression
- Strong focus on
  - Creating expectation for recovery
  - Normalizing life patterns (physical, social, cognitive activation)
  - Reframing misattributions when seen
- Try to avoid over-treatment – a common slippery slope
- Medications typically used for symptoms (not an underlying core condition)
- Treat one – treats them all
- Neurorehabilitation setting a good ‘home’ for treatment
  - Multi-disciplinary
  - Existing programs for multi-faceted interventions (draw from other conditions)

Treating Patients With Long-COVID-19
Neuropsychology Assessment and Intervention

- Neuropsychological evaluation - rule-in or rule-out neurocognitive impairment.
- Patients with no evidence of cognitive impairment – NP assessment as intervention
- Patients with objective evidence of cognitive impairment:
  - Possibly more in-depth neurologic and imaging studies
  - Thorough evaluation of metabolic and other conditions potentially contributing
  - Address fatigue and deconditioning
  - Dizziness and vertigo
  - Sleep disruption
  - Anxiety/dysphoria
  - Pain
- Possibly referral for cognitive rehabilitation
- Many seen for individual treatment with neuropsychologists or rehab psychologists

MedStar COVID-19 Outpatient Recovery Program- Neuropsychology Assessment and Intervention

- Extensive psychoeducation about:
  - Multiple factors that contribute to objective and subjective cognitive impairment
  - Role of sleep, exhaustion, pain, emotional well-being
  - Importance of normalizing daily activities within capabilities
  - Expectation of recovery with time
- Providing or referring for treatment of anxiety, depression, post-traumatic symptoms
- Strong focus on attributions, reframing, normalizing, and the social context of the illness experience
- Address premorbid factors exacerbating current disruption
- Initiating group-based psycho-education to emphasize health behaviors, efficient daily functioning, psychological health

MedStar COVID-19 Outpatient Recovery Program- Neuropsychology Interventions

- Neuropsychology/Rehabilitation Psychology Psychoeducation Group for Long-COVID-19 Patients
- Consistent with emerging trends in rehabilitation, focus on specific presenting issues and larger healthy lifestyle factors that exacerbate impact
- Psychoeducation group done via telehealth
- Each session focuses on a specific topic
  - Adapting to cognitive changes
  - Positive health behaviors that facilitate recovery (exercise, nutrition, etc.)
  - Sleep hygiene
  - CBT approaches for depression and anxiety
  - Psychological strategies for pain
  - Coping with anosmia/dysgeusia
  - Skills for mindfulness, reframing, normalizing,

Important Role of Neuropsychology in Assessment and Management of COVID-19

- Acute and Inpatient COVID-19 Rehabilitation Units
  - Screening assessments (MOCA, O-Log/C-Log, RBANS, etc.) of cognition to contribute to decisions about capacity, treatment impact, need for formal rehabilitation, judgement/impulsivity, etc.
  - Interventions to address psychological well-being and adaptation in an intensely stressful and isolated environment, and to help 'inoculate' against emergence of future psychological disorders
- Post-Acute/Outpatient Settings
  - Assessment of potential lasting effects of COVID-19 on neurocognitive functioning and psychological well-being
  - Neuropsychological intervention to treat those who show persistent neurocognitive impairment
  - Likely that in addition to those with persistent neurocognitive disorders there will be elevated levels of anxiety and depression, possibly PTSD, and somatic symptom disorders
- Development of/Participation in Research
  - An exciting opportunity to be part of the development of an entirely new area of science
  - Past pandemics have led to new innovations and approaches in medicine and science
  - Is there undetected neurologic/neurocognitive damage in infected but mild cases?
  - Could research help reduce likelihood/impact of new variants of somatic symptom disorders?
- Forensic Applications
  - Almost certainly will be forensic developments emerging from the pandemic (civil and criminal)

COVID-19 Special Interest Groups

- Neuro-COVID Discussion Group and Listserv
  - On-line listserv discussion group and Google-docs spreadsheet of publications
  - Moderated by Michelle Imber, Kristin Fiano, William Garmoe
  - Contact one of us to be added

- INS Neuro-COVID-19 SIG
  - https://www.the-ins.org/sigs/
  - Co-Chairs: Lucette Cysique, Emilia Lojek, Bernice Marcopulos

MNRN Neuropsychology COVID-19 Research Team

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