# Neuropsychiatric findings in Post-Acute Sequelae of SARS-CoV-2 Infection

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## Introduction

- Post-acute sequelae of SARS-CoV-2 (PASC) have become increasingly recognized and concerning, yet the syndrome is not well understood.
- We aim to describe the neuropsychiatric findings among patients who presented to our clinic following COVID-19 infection.

## Methods

- We collected data retrospectively (between February 2020 and May 2021) from a cohort (N=100) of patients with persistent PASC symptoms following a short inpatient stay or as outpatients never hospitalized at the Massachusetts General Hospital.
- Patients without confirmed positive SARS-CoV-2 PCR or Antibody diagnostic test were grouped separately as presumptive cases (N=13).
- Demographic characteristics and frequency of neuropsychiatric complaints were compared based on premorbid psychiatric and neurologic history, executive dysfunction findings, and ability to return to work.
- Odds ratios (ORs) and 95% confidence intervals (CIs) of having common neuropsychiatric symptoms of PASC were calculated for the main predictors of interest.
- Phi coefficients were calculated per comparison pair of manifestations, to test how correlated or independent these manifestations were among them.

## Results

- Eighty-seven patients (87.0%) had confirmed SARS-CoV-2 infection and their mean age was 49±15 years old. Of those, 63 (72.5%) patients were female and 65 (75.0%) were white.
- Attention and executive dysfunction were common, with memory-related complaints affecting 58.6% of patients.
- Prior diagnosis of migraine or other headache disorder appeared to predict increased odds of “brain fog” (OR=5.0, 95%CI=1.6-17.6) independent of age, sex, and BMI but not language, education status, and ancestry.

## Results

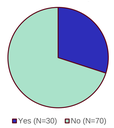
### Study Population

| | Confirmed Cases (N=87) | Presumptive Cases (N=13) |
|---|---|---|
| | M±SD; N (%) | M±SD; N (%) |
| **Ancestry** | | |
| White Non-Hispanic | 65 (74.7) | 9 (69.2) |
| Hispanic | 14 (16.1) | 2 (15.4) |
| Other | 2 (2.3) | 1 (7.7) |
| African American | 4 (4.6) | 1 (7.7) |
| Asian | 2 (2.3) | 0 (0.0) |
| **Highest level of Education[a]** | | |
| Some High School | 5 (5.8) | 1 (7.7) |
| High School | 9 (10.3) | 1 (7.7) |
| Associate degree | 5 (5.8) | 0 (0.0) |
| Some college | 12 (13.8) | 2 (15.4) |
| College | 14 (16.1) | 7 (53.9) |
| Graduate degree/Professional School (MD, JD, MS, PhD) | 32 (36.8) | 1 (7.7) |
| **Employment Status[b]** | | |
| Employed | 64 (73.6) | 10 (76.9) |
| Unemployed | 12 (13.8) | 2 (15.4) |
| Retired | 10 (11.5) | 1 (7.7) |
| **Healthcare worker[c]** | | |
| Yes | 27 (31.0) | 2 (15.4) |
| **Place of Residency** | | |
| Suburban | 42 (48.3) | 8 (61.5) |
| Urban | 31 (35.6) | 4 (30.8) |
| Rural | 14 (16.1) | 1 (7.7) |
| **Body Mass Index (Kg/m$^2$)[e]** | 28.4±6.3 | 25.6±5.6 |

| Frequency of neuropsychiatric manifestations among confirmed cases (n=87) | N (%) |
|---|---|
| Fatigue | 58 (66.7) |
| Brain fog | 52 (59.8) |
| Headache | 48 (55.2) |
| Anxiety | 31 (35.6) |
| Sleep Problems | 26 (29.9) |
| Depression | 20 (23.0) |

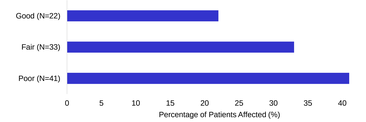
| Frequency of neuropsychiatric manifestations among presumptive cases (n=13) | N (%) |
|---|---|
| Headache | 10 (76.9) |
| Brain fog | 9 (69.2) |
| Fatigue | 9 (69.2) |
| Sleep Problems | 4 (30.8) |
| Anxiety | 2 (15.4) |
| Visual disturbances | 2 (15.4) |

Patients Reporting Sleep Problems Across All the Cohort (N=96)*

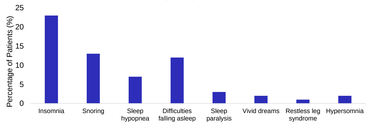



*4 missing data points

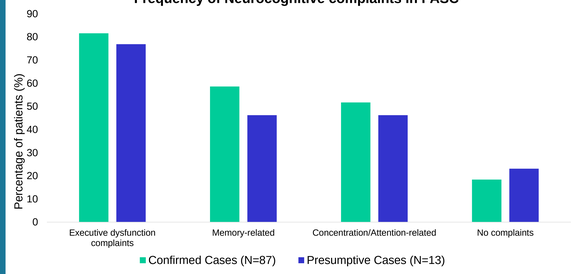
Self-reported sleep quality (N=96)*



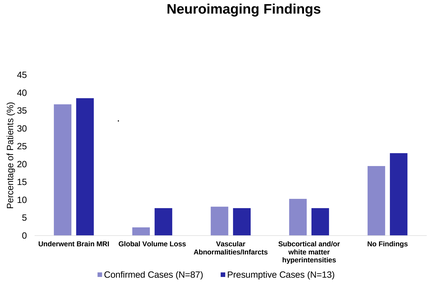

Specific Sleep Complaints Reported by the Study Sample (N=96)*



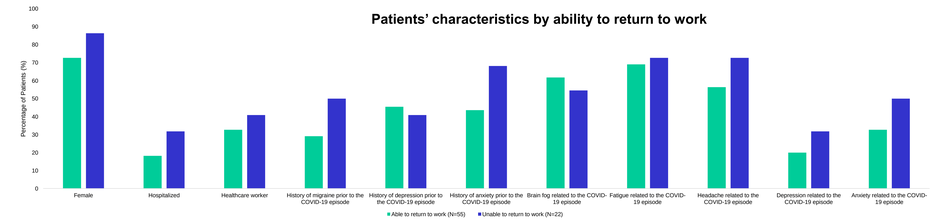

Frequency of Neurocognitive complaints in PASC




Neuroimaging Findings

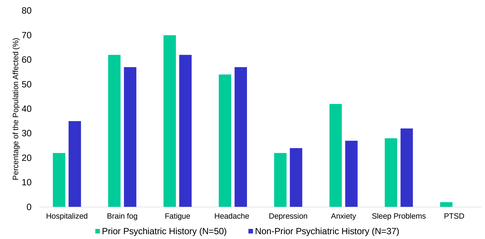



Patients’ characteristics by ability to return to work

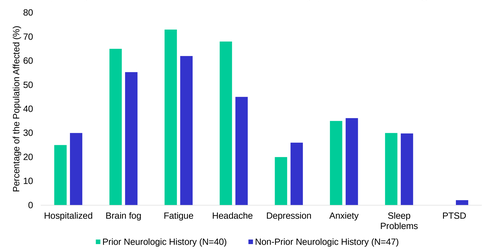



## Results

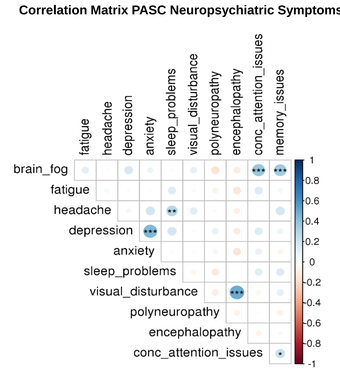
Frequency of PASC manifestations stratified by previous psychiatric disease




Frequency of PASC manifestations stratified by previous neurologic disease



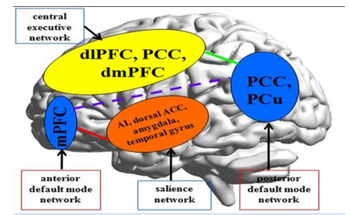

Correlation Matrix PASC Neuropsychiatric Symptoms




## Discussion

To this date, the pathophysiology of PACS remains elusive. As we continue to observe this cohort and others do the same across the world, some hypotheses could be entertained such as the potential dysfunction of the GABA-ergic networks leading to fatigue and confusion (even frank delirium at times) or the involvement of the fronto-subcortical system highly sensitive to inflammation and white matter insults (1,2).

In fact, neuroimaging studies described vascular/ischemic findings in population of COVID-19 survivors and non-survivors (3,4,5). Endotheliitis has been proposed (6). In addition, the immune system may play a role in having symptoms linger by keeping a steady low-level brain inflammation, reducing the ability to respond to new antigens and amassing memory T cells – the hallmark of brain insults (7).




Pathophysiology of loop dysfunction in executive dysfunction. *Adapted from Bonelli et al. (2)*

## Conclusions

- Our findings suggest that PASC present with heterogenous symptoms including executive dysfunction and attention difficulties.
- In our cohort, high burden of vascular abnormalities on imaging were more frequent among patients with executive dysfunction.
- A history of headache disorder increased the likelihood of “brain fog” and a prior history of mental illness reflected on ability to return to work.
- A larger and more diverse cohort is needed to better characterize PASC and offer equitable care.

## References

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