CIFAR Manulife

Seeing Through Brain Fog:

Disentangling the cognitive, physical, and mental-health sequelae of COVID-19.

Adrian M. Owen

Department of Physiology & Pharmacology and Department of Psychology,
Western Institute for Neuroscience
The University of Western Ontario, Canada

owenlab.org

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

NSERC CRSNG

CIFAR
CANADIAN INSTITUTE FOR ADVANCED RESEARCH

Canada Excellence Research Chairs
www.cerc.gc.ca

JAMES S. MCDONNELL FOUNDATION

Canada Foundation for Innovation
Fondation canadienne pour l'innovation

Cell Reports Medicine

CellPress
OPEN ACCESS

Article

Disentangling the cognitive, physical, and mental health sequelae of COVID-19

Conor J. Wild,[1,2,9,*] Loretta Norton,[1,3] David K. Menon,[4] David A. Ripsman,[5] Richard H. Swartz,[6,8] and Adrian M. Owen[1,2,7,8]

[1]Western Institute for Neuroscience, Western University, London, ON N6A 3K7, Canada
[2]Department of Physiology and Pharmacology, Western University, London, ON N6A 3K7, Canada
[3]Department of Psychology, King's University College, Western University, London, ON N6A 3K7, Canada
[4]Division of Anaesthesia, Department of Medicine, University of Cambridge, Cambridge CB2 2QQ, UK
[5]Faculty of Medicine, Department of Neurology, University of British Columbia, Vancouver, BC V6T 2B5, Canada
[6]Department of Medicine (Neurology), Hurvitz Brain Sciences Program, Sunnybrook Health Sciences Center, University of Toronto, Toronto, ON M4N 3M5, Canada
[7]Department of Psychology, Western University, London, ON N6A 3K7, Canada
[8]Senior author
[9]Lead contact
*Correspondence: cwild@uwo.ca
https://doi.org/10.1016/j.xcrm.2022.100750

Wild *et al*., 2022

COVID-19 and the Brain

Headaches
Aches and Pains
Loss of Smell

Blurred Vision
Strokes
Seizures
Delirium

Impaired Cognition

“Brain Fog”

Neurologic Features in Severe SARS-CoV-2 Infection

June 4, 2020
Created On May 20, 2020
N Engl J Med 2020; 382:2268-2270
DOI: 10.1056/NEJMc2008597
Metrics

Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study

Aravinthan Varatharaj, Naomi Thomas, Mark A Ellul, Nicholas W S Davies, Thomas A Pollak, Elizabeth L Tenorio, Mustafa Sultan, Ava Easton, Gerome Breen, Michael Zandi, Jonathan P Coles, Hadi Manji, Rustam Al-Shahi Salman, David K Menon, Timothy R Nicholson, Laura A Benjamin, Alan Carson, Craig Smith, Martin R Turner, Tom Solomon, Rachel Kneen, Sarah L Pett, Ian Galea, Rhys H Thomas*, Benedict D Michael*, on behalf of the CoroNerve Study Group†*

BBC.COM

How Covid-19 can damage the brain

Some scientists suspect that Covid-19 causes respiratory failure...

June 22, 2020

The New York Times

Some Coronavirus Patients Show Signs of Brain Ailments

Doctors have observed neurological symptoms, including confusion, stroke and seizures, in a small subset of Covid-19 patients.

April 2, 2020

Scientists warn of potential wave of COVID-linked brain damage

Neuroscientists and specialist brain doctors say emerging evidence of its impact on the brain is concerning

REUTERS

Reuters
Kate Kelland

July 9, 2020

COVID-19 and the Brain

Direct Effects

Indirect Effects

- Inflammation
- Blood Clots
- Low Oxygen Levels
- Sedation
- Ventilator
- ICU

nature

SARS-CoV-2 is associated with changes in brain structure in UK Biobank

https://doi.org/10.1038/s41586-022-04569-5

Received: 19 August 2021

Accepted: 21 February 2022

Published online: 7 March 2022

Open access

Check for updates

Gwenaëlle Douaud[1]✉, Soojin Lee[1], Fidel Alfaro-Almagro[1], Christoph Arthofer[1], Chaoyue Wang[1], Paul McCarthy[1], Frederik Lange[1], Jesper L. R. Andersson[1], Ludovica Griffanti[1,2], Eugene Duff[1,3], Saad Jbabdi[1], Bernd Taschler[1], Peter Keating[4], Anderson M. Winkler[5], Rory Collins[6], Paul M. Matthews[7], Naomi Allen[6], Karla L. Miller[1], Thomas E. Nichols[8] & Stephen M. Smith[1]

There is strong evidence of brain-related abnormalities in COVID-19[1–13]. However, it remains unknown whether the impact of SARS-CoV-2 infection can be detected in milder cases, and whether this can reveal possible mechanisms contributing to brain pathology. Here we investigated brain changes in 785 participants of UK Biobank (aged 51–81 years) who were imaged twice using magnetic resonance imaging, including 401 cases who tested positive for infection with SARS-CoV-2 between their two scans—with 141 days on average separating their diagnosis and the second scan—as well as 384 controls. The availability of pre-infection imaging data reduces the likelihood of pre-existing risk factors being misinterpreted as disease effects. We identified significant longitudinal effects when comparing the two groups, including (1) a greater reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus; (2) greater changes in markers of tissue damage in regions that are functionally connected to the primary olfactory cortex; and (3) a greater reduction in global brain size in the SARS-CoV-2 cases. The participants who were infected with SARS-CoV-2 also showed on average a greater cognitive decline between the two time points. Importantly, these imaging and cognitive longitudinal effects were still observed after excluding the 15 patients who had been hospitalised. These mainly limbic brain imaging results may be the in vivo hallmarks of a degenerative spread of the disease through olfactory pathways, of neuroinflammatory events, or of the loss of sensory input due to anosmia. Whether this deleterious effect can be partially reversed, or whether these effects will persist in the long term, remains to be investigated with additional follow-up.

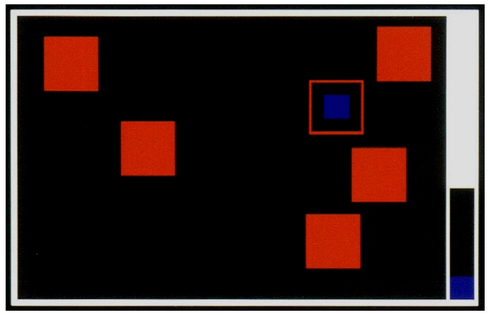
Douaud *et al.*, 2022

The Problem

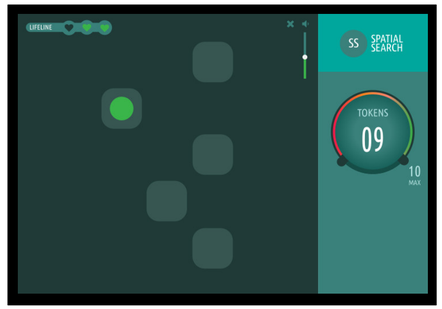
There are now more than 630 million people in the world who have had COVID-19 and 4.3 million in Canada alone. Even if only a small proportion of these individuals go on to develop cognitive problems and/or mental health issues, the result will create an enormous economic and societal burden.

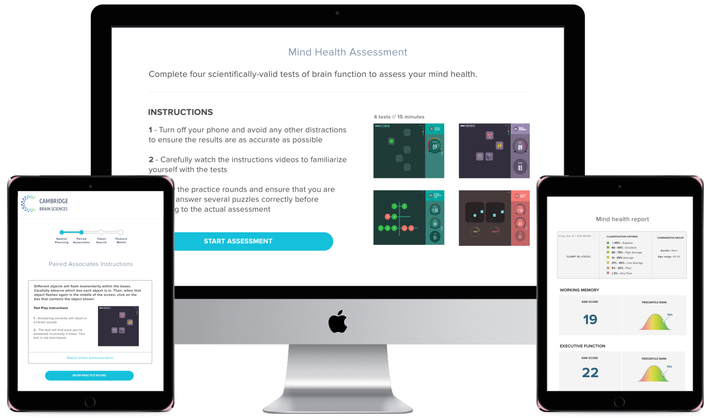
1988 - 2022
The Evolution of Computerised Cognitive Testing

1988



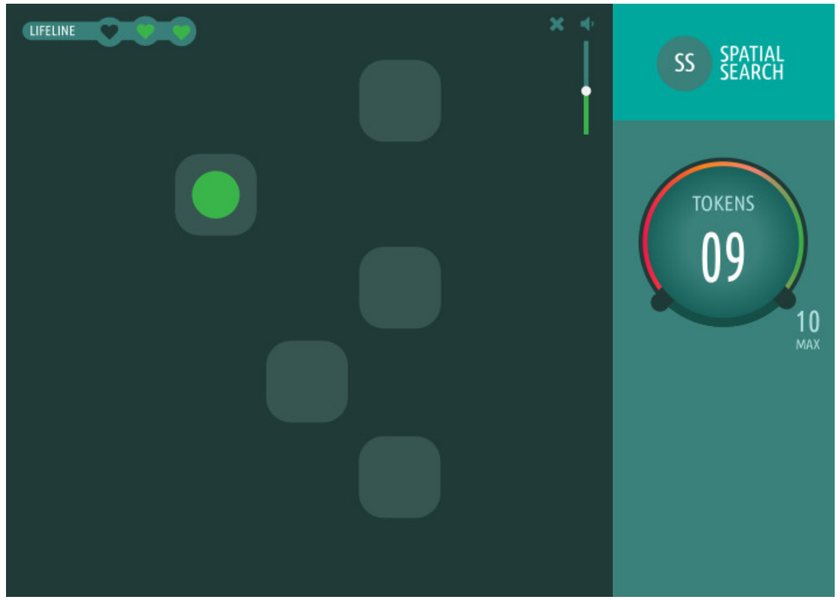
2022

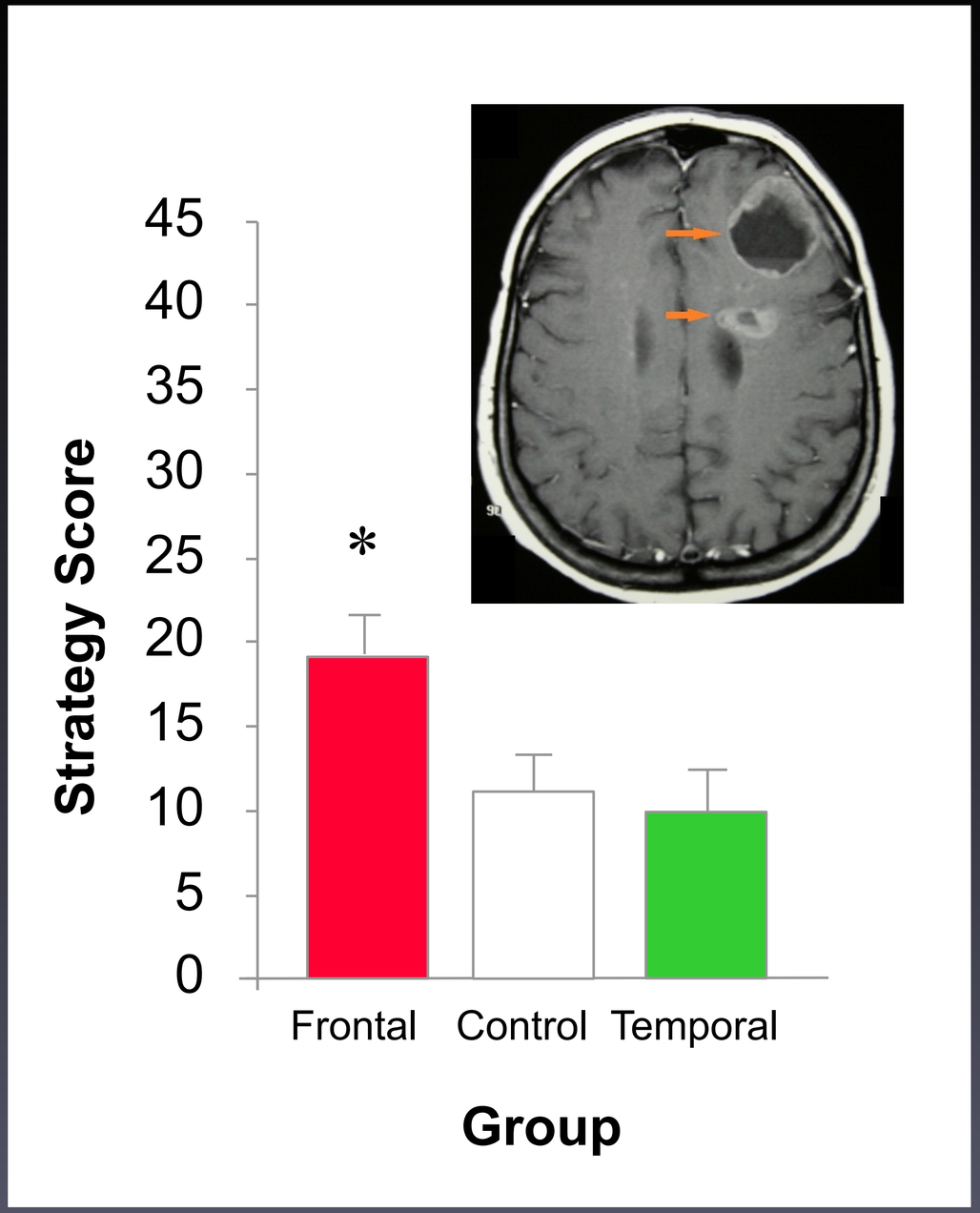




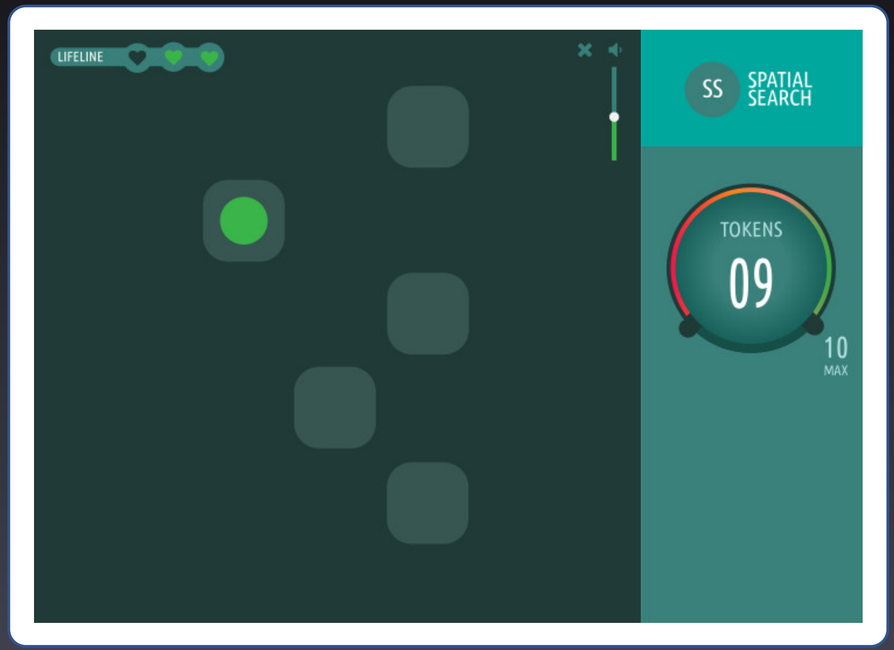
Radial Arm Maze

Token Search Test



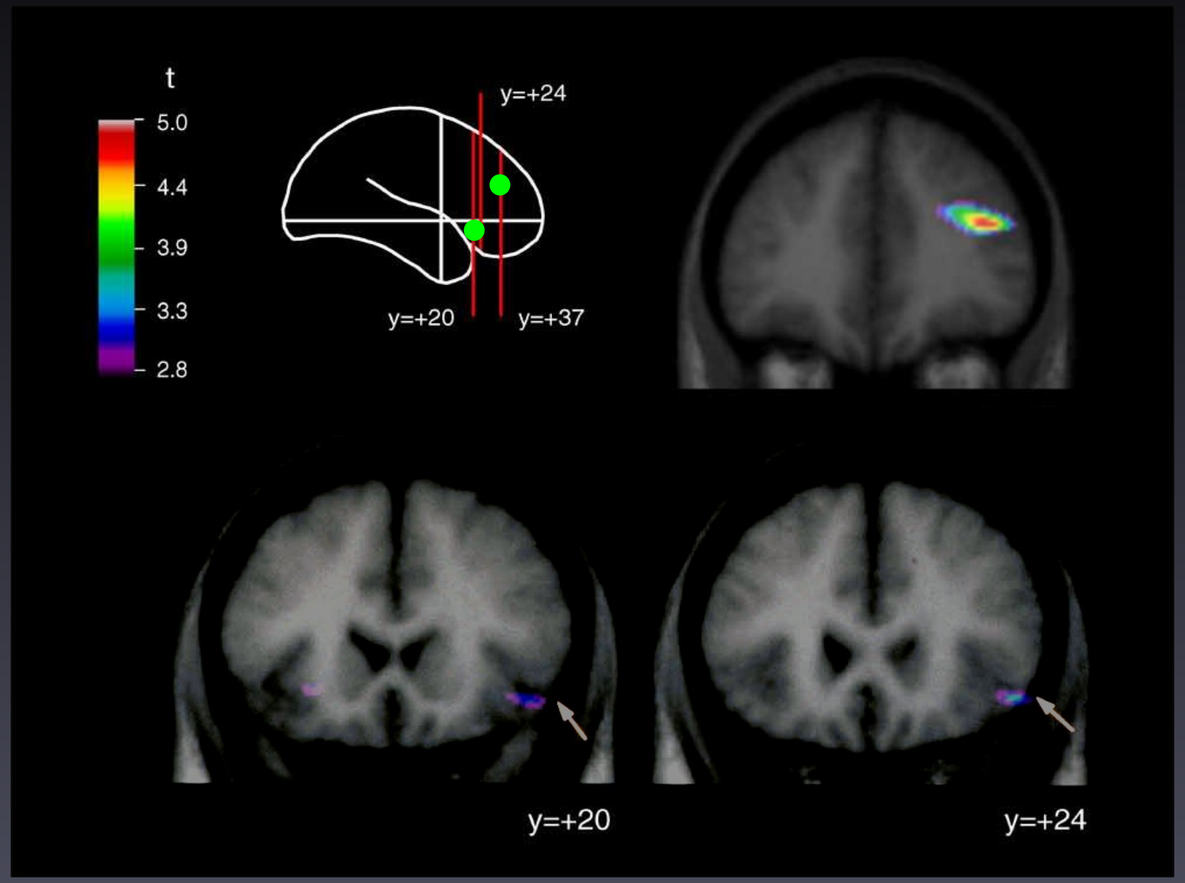


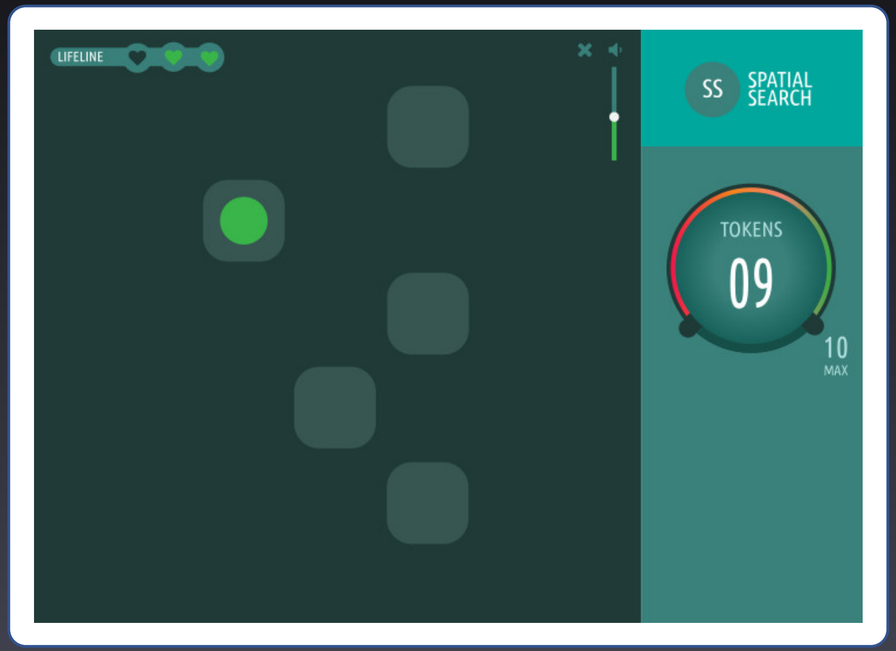
Performance of these tests is sensitive to specific types of *brain* damage



Owen *et al*., 1990; 1992; 1992; 1993; 1995; 1996.

Performance of these tests activates specific *networks* in the brain

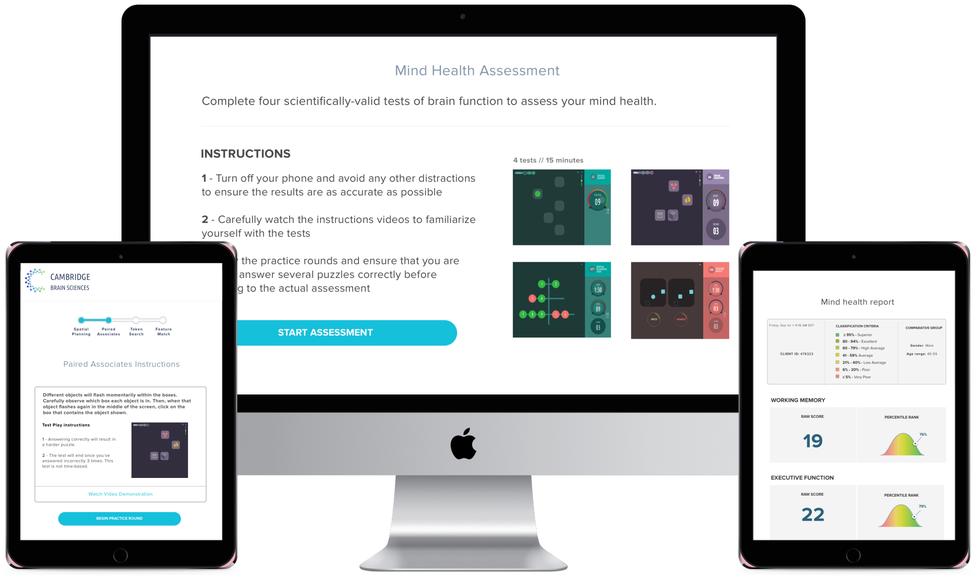




Owen *et al*., 1996; 1997; 1998; 1999; 2000

CAMBRIDGE BRAIN SCIENCES

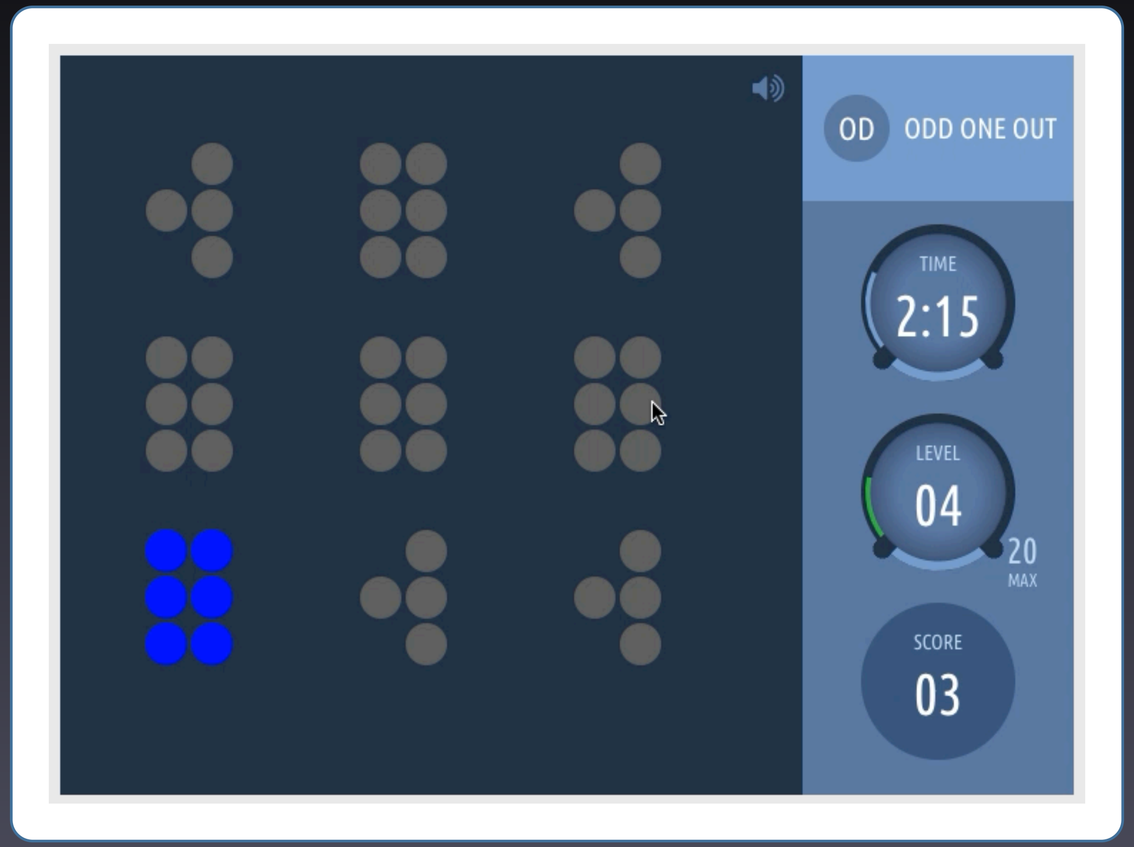
12 short tasks measuring core aspects of cognition, such as working memory, attention, planning, reasoning, decision-making, problem-solving and verbal abilities.



Key Highlights

- ✓ Over 10 million tests completed globally
- ✓ Low cost and high convenience (1.5 – 3 mins per task)
- ✓ Large normative database (75,000), broken down by age for comparative purposes
- ✓ Web-based data correlates highly with lab-based testing
- ✓ Test-retest reliability is excellent
- ✓ 300+ peer-reviewed behavioural and neuroimaging studies in neuropsychological and neurodegenerative populations.

ODD ONE OUT (REASONING)



***Nature* 2010**
(n = 11,430)

Vol 465|10 June 2010|doi:10.1038/nature09042 nature

LETTERS

Putting brain training to the test

Adrian M. Owen[1], Adam Hampshire[1], Jessica A. Grahn[1], Robert Stenton[2], Said Dajani[2], Alistair S. Burns[3], Robert J. Howard[2] & Clive G. Ballard[2]

'Brain training', or the goal of improved cognitive function through the regular use of computerized tests, is a multimillion-pound industry[1], yet in our view scientific evidence to support its efficacy is lacking. Modest effects have been reported in some studies of older individuals[2,3] and preschool children[4], and video-game players outperform non-players on some tests of visual attention[5]. However, the widely held belief that commercially available computerized brain-training programs improve general cognitive function in the wider population in our opinion lacks empirical support. The central question is not whether performance on cognitive tests can be improved by training, but rather, whether those benefits transfer to other untrained tasks or lead to any general improvement in the level of cognitive functioning. Here we report the results of a six-week online study in which 11,430 participants trained several times each week on cognitive tasks designed to improve reasoning, memory, planning, visuospatial skills and attention. Although improvements were observed in every one of the cognitive tasks that were trained, no evidence was found for transfer effects to untrained tasks, even when those tasks were cognitively closely related.

To investigate whether regular brain training leads to any improvement in cognitive function, viewers of the BBC popular

broader range of cogni
term memory, attentic
similar to those comm
training devices. The d
participants improved
formance and maximiz
did not formally pract
'training' sessions, but
categories using any ava
marking assessment wa
were compared. The di
measure of generalized
ing. Similarly, for each
compared to give a me

Of 52,617 participan
completed both bench
training sessions during
completed 24.47 (s.d.
sessions). The three gr
39.65 (11.83), 40.51
male = 5.5:1, 5.6:1 and

Numerically experi

***Neuron* 2012**
(n = 44,600)

Neuron
Article

Cell PRESS

Fractionating Human Intelligence

Adam Hampshire,[1,*] Roger R. Highfield,[2] Beth L. Parkin,[1] and Adrian M. Owen[1]
[1]The Brain and Mind Institute, The Natural Sciences Centre, Department of Psychology, The University of Western Ontario, London ON, N6A 5B7, Canada
[2]Science Museum, Exhibition Road, London SW72DD, UK
*Correspondence: ahampshi@uwo.ca
http://dx.doi.org/10.1016/j.neuron.2012.06.022

SUMMARY

What makes one person more intellectually able than another? Can the entire distribution of human intelligence be accounted for by just one general factor? Is intelligence supported by a single neural system? Here, we provide a perspective on human intelligence that takes into account how general abilities or "factors" reflect the functional organization of the brain. By comparing factor models of individual differences in performance with factor models of brain functional organization, we demonstrate that different components of intelligence have their analogs in distinct brain networks. Using simulations based on neuroimaging data, we show that the higher-order factor "g" is accounted for by cognitive tasks corecruiting multiple networks. Finally, we confirm the independence of these components of intelligence by dissociating them using questionnaire variables. We propose that intelligence is an emergent property of anatomically

as opposed to a bias in testing
components of a more complex
1981; Horn and Cattell, 1966; Ma
the past 100 years, there has bee
general intelligence is unitary or
(Carroll, 1993; Cattell, 1949; Catt
and Bouchard, 2005). This debate
that test measures tend to form
combined with the intractability
sure individual cognitive process
complex set of factors contribute
(Carroll, 1993).

Defining the biological basis
challenge, however, due in part t
factor analyses. More specifically
do not provide an unambiguous
tive architecture, as the factors
being measured indirectly by e
from correlations between the p
ferent tests. Thus, for a given set o
are many factor solutions of vary
of which are equally able to accou

***Sleep* 2018**
(n = 10,000)

OXFORD Sleep Research Society®

SLEEP, 2018, 1–11
doi: 10.1093/sleep/zsy182
Advance Access publication Date: 13 September 2018
Original Article

ORIGINAL ARTICLE

Dissociable effects of self-reported daily sleep duration on high-level cognitive abilities

Conor J. Wild[1,*,•], Emily S. Nichols[1], Michael E. Battista[2], Bobby Stojanoski[1] and Adrian M. Owen[1,2]

[1]The Brain and Mind Institute, Western University, London, ON, Canada and [2]Department of Psychology, Western University, London, ON, Canada

*Corresponding author. Conor J. Wild, The Brain and Mind Institute, Western University, London, ON N6C 5B7, Canada. Email: cwild@uwo.ca.

Abstract

Most people will at some point experience not getting enough sleep over a period of days, weeks, or months. However, the effects of this kind of everyday sleep restriction on high-level cognitive abilities—such as the ability to store and recall information in memory, solve problems, and communicate—remain poorly understood. In a global sample of over 10 000 people, we demonstrated that cognitive performance, measured using a set of 12 well-established tests, is impaired in people who reported typically sleeping less, or more, than 7–8 hours per night—which was roughly half the sample. Crucially, performance was not impaired evenly across all cognitive domains. Typical sleep duration had no bearing on short-term memory performance, unlike reasoning and verbal skills, which were impaired by too little, or too much, sleep. In terms of overall cognition, a self-reported typical sleep duration of 4 hours per night was equivalent to aging 8 years. Also, sleeping more than usual the night before testing (closer to the optimal amount) was associated with better performance, suggesting that a single night's sleep can benefit cognition. The relationship between sleep and cognition was invariant with respect to age, suggesting that the optimal amount of sleep is similar for all adult age groups, and that sleep-related impairments in cognition affect all ages equally. These findings have significant real-world implications, because many people, including those in positions of responsibility, operate on very little sleep and may suffer from impaired

Measuring Cognitive Performance

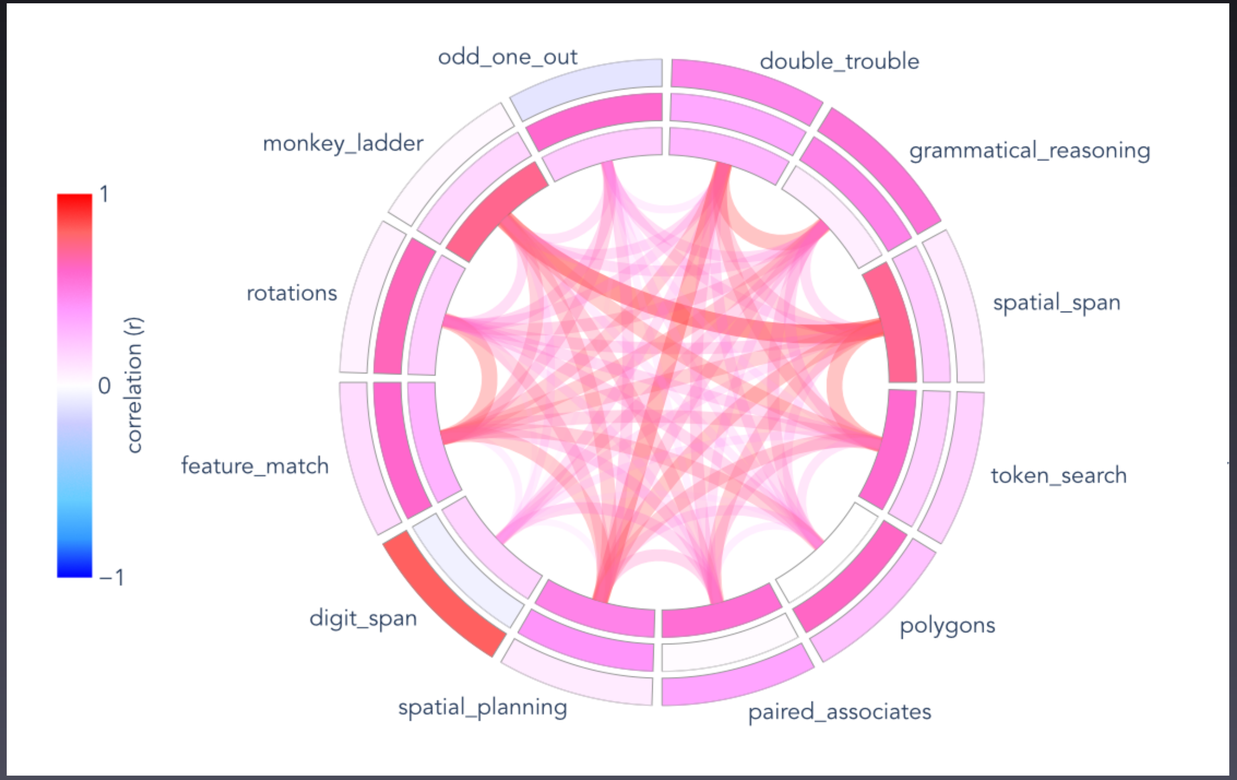
Principal Component Analysis (PCA w/ Varimax)

Factor 1 “Short Term Memory (STM)”

Factor 2 “Reasoning”

Factor 3 “Verbal Abilities”

Pre-Pandemic Norms (N = 7,832)



Wild *et al*., 2018

Participate in the COVID-19 Brain Study—a global study of how the virus affects cognition

COVID-19 may have direct and indirect effects on the brain. If you have been diagnosed with COVID-19, help world-renowned neuroscientists discover its effects on cognition by signing up for this important global study.

Español | Français

Sign Up Now

covidbrainstudy.com

English/French/Spanish

DESIGNED BY RESEARCHERS FROM WESTERN UNIVERSITY, THE UNIVERSITY OF TORONTO, AND SUNNYBROOK HEALTH SCIENCES CENTRE

Western
The Brain and Mind Institute

UNIVERSITY OF CAMBRIDGE

UNIVERSITY OF TORONTO

Sunnybrook
HEALTH SCIENCES CENTRE

Key Questions

Does COVID-19 infection result in significant cognitive impairment? If so, what cognitive domains are most affected?

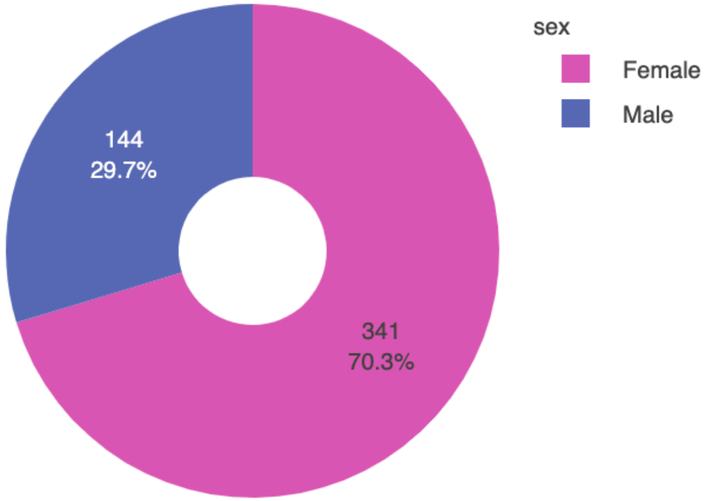
Is the burden of cognitive impairment greater in those who require ICU stay versus those hospitalized outside the ICU versus those in the community?

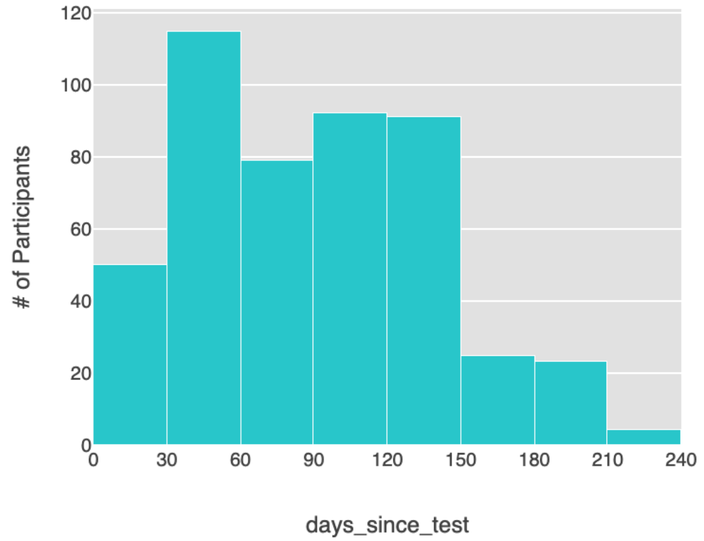
Are COVID-19 patients are getting better or worse over time? (3 mo & 1 yr longitudinal follow-up)

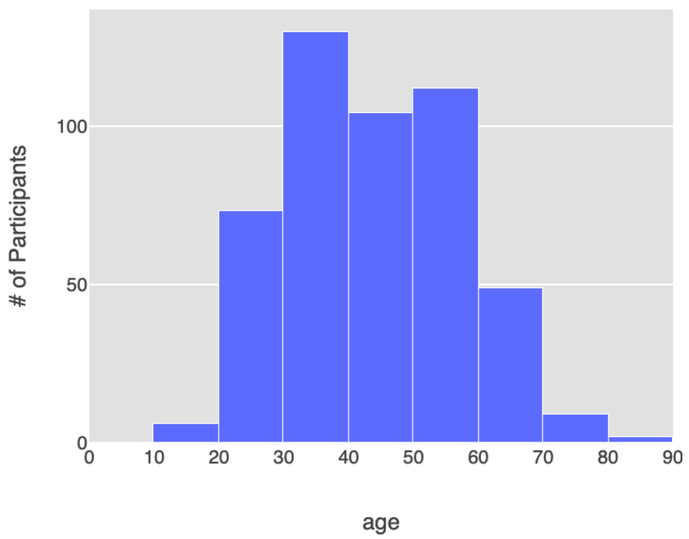
Are there interactions with sex, age and medical risk factors that result in greater impact in some populations?

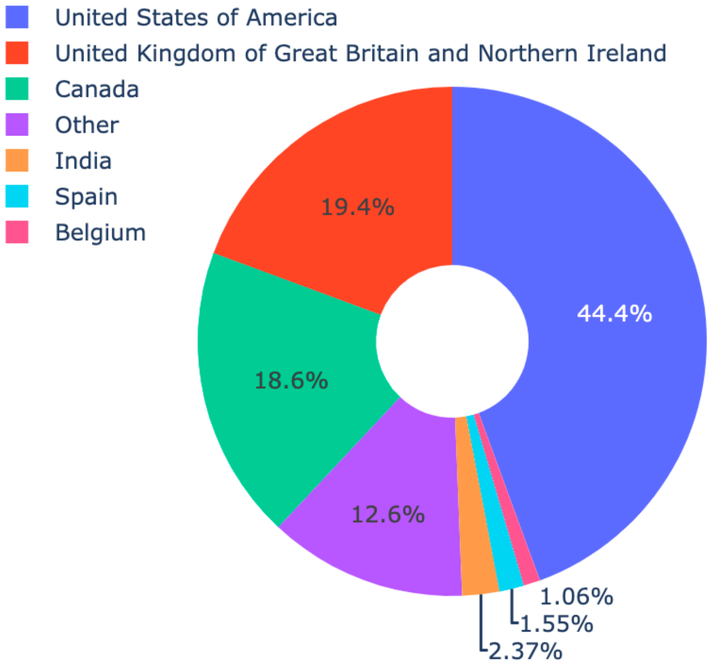
Final Study Sample:

- 1,455 with questionnaire & CBS data
- 942 after filtering (outliers, invalid responses, missing values, etc.)
- **478 reported a positive COVID test (COVID+)**



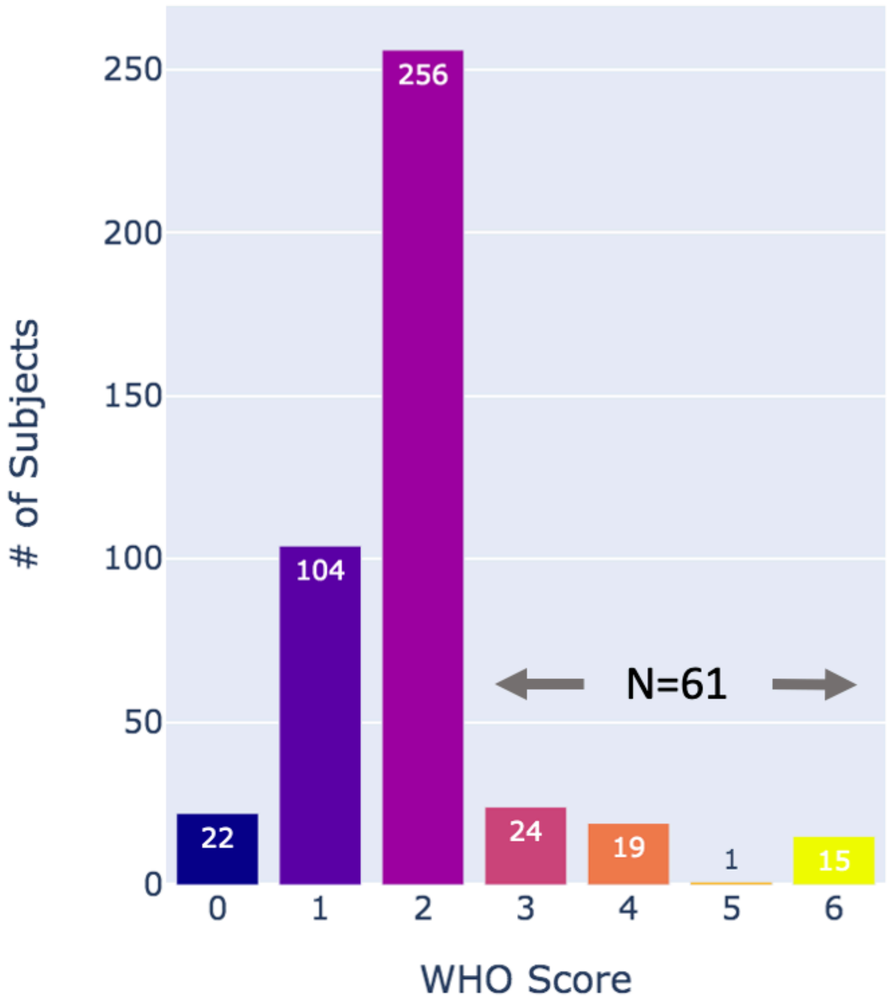






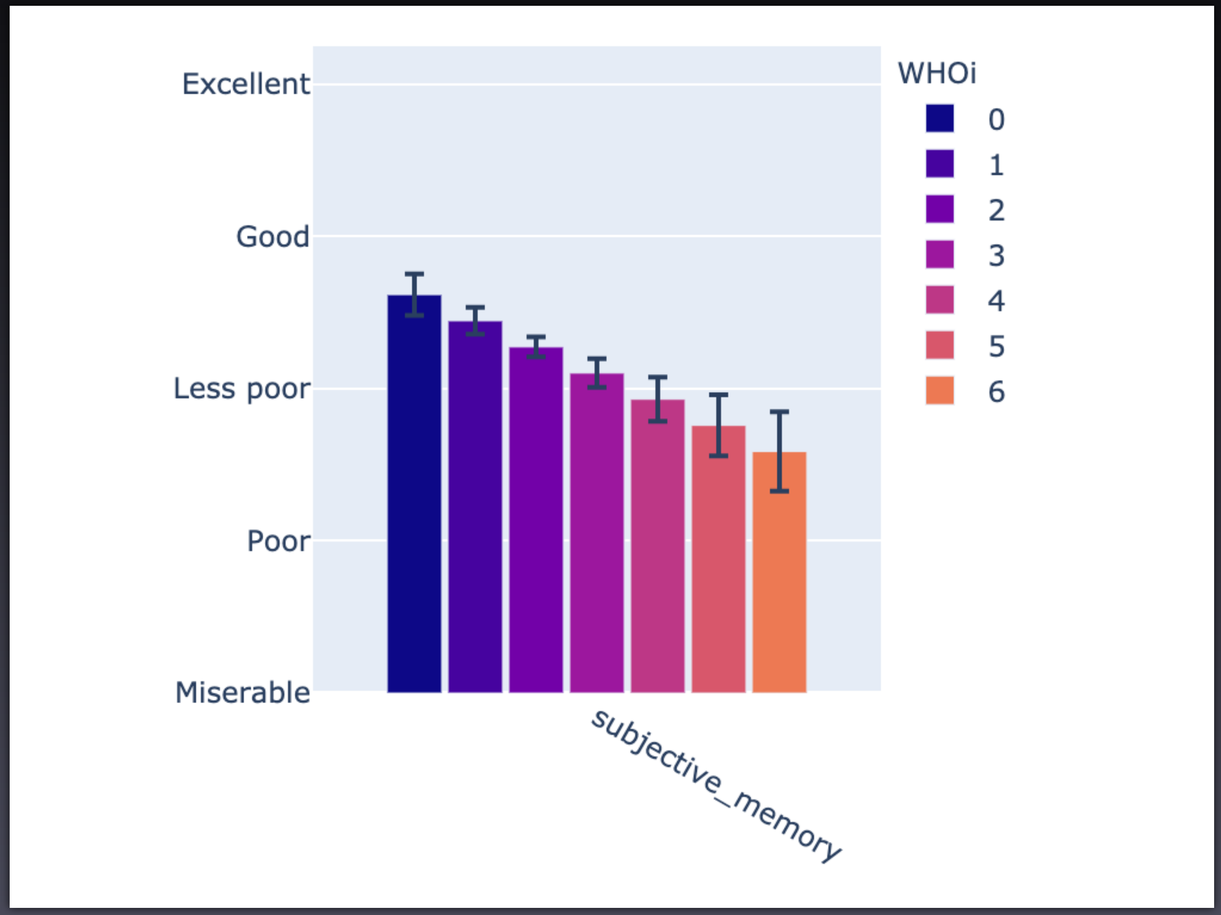
Assessing COVID-19 Illness Severity

WHO	Y/N	Question
0	✗	Symptoms
	✗	Hospital
1	✓	Symptoms
	✗	(Not) Daily Routine
	✗	Hospital
2	✓	Symptoms
	✓	(Not) Daily Routine
	✗	Hospital
3	✓	Hospital
	✗	O2 (Hospital)
	✗	ICU
4	✓	Hospital
	✓	O2 (Hospital)
	✗	ICU
5	✓	Hospital
	✓	ICU
	✗	O2 (ICU)
6	✓	Hospital
	✓	ICU
	✓	O2 (ICU)



Wild *et al*., 2022

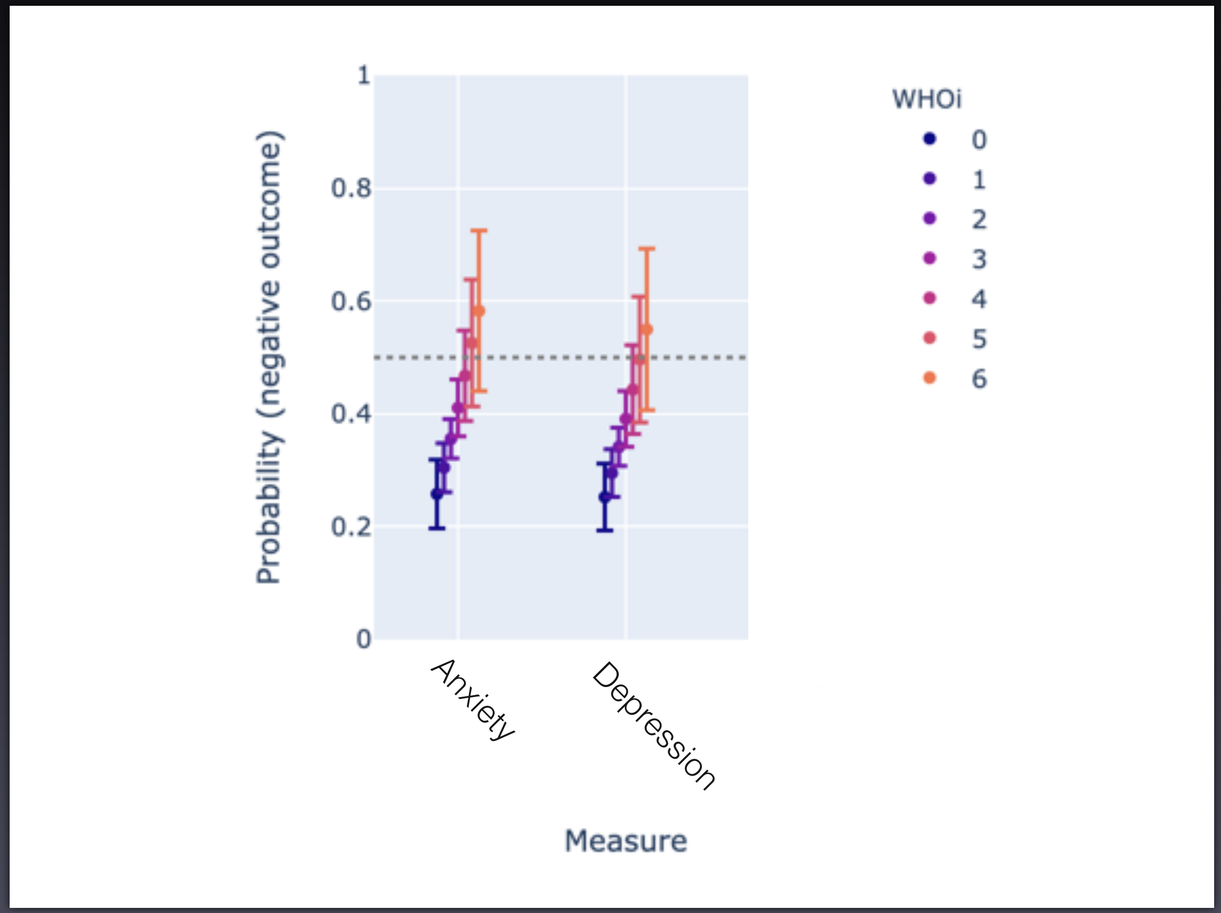
Results



Increasing COVID-19 severity is strongly associated with subjectively poorer memory ratings.

Wild *et al*., 2022

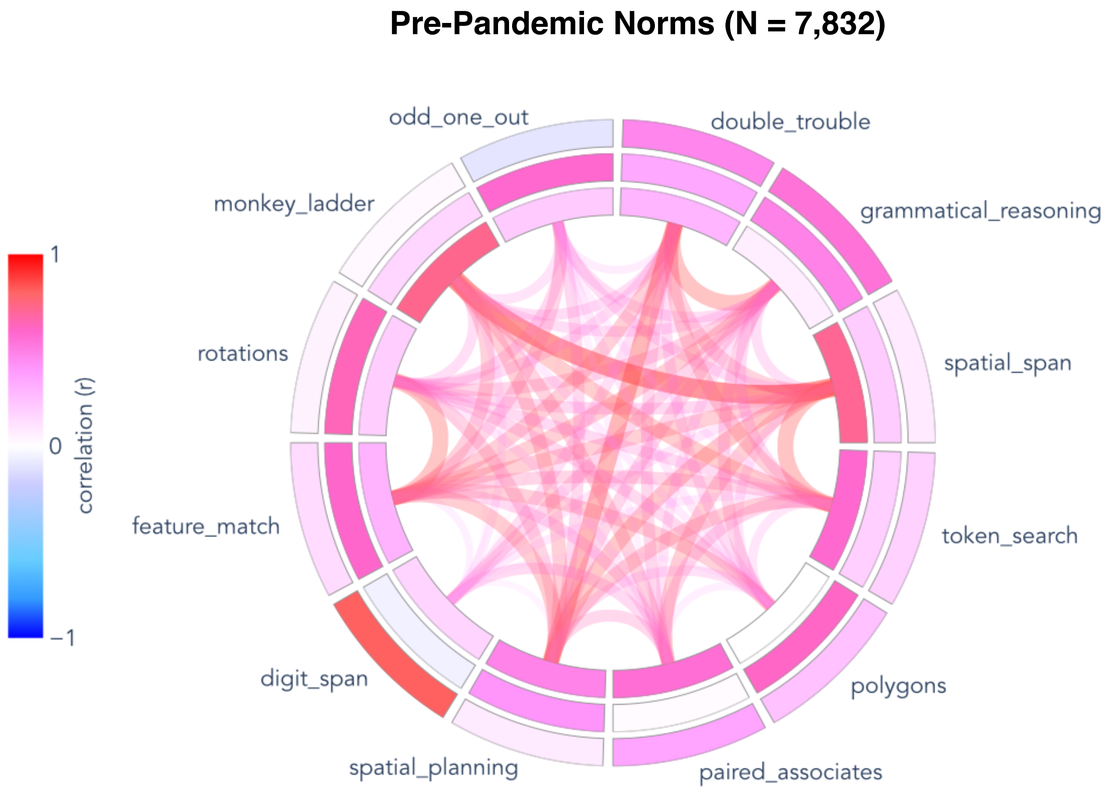
Results



Increasing COVID severity is strongly associated with subjectively greater levels of anxiety and depression.

Wild *et al*., 2022

Measuring Cognitive Performance



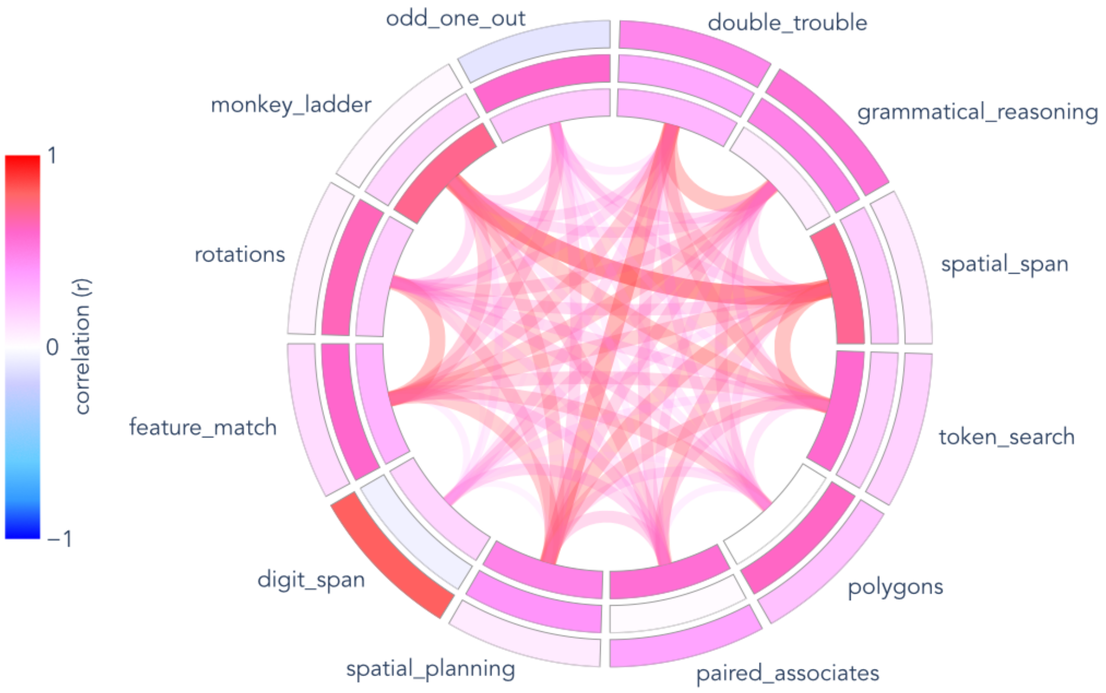
Principal Component Analysis (PCA w/ Varimax)

1. Short Term Memory (STM)
2. Reasoning
3. Verbal

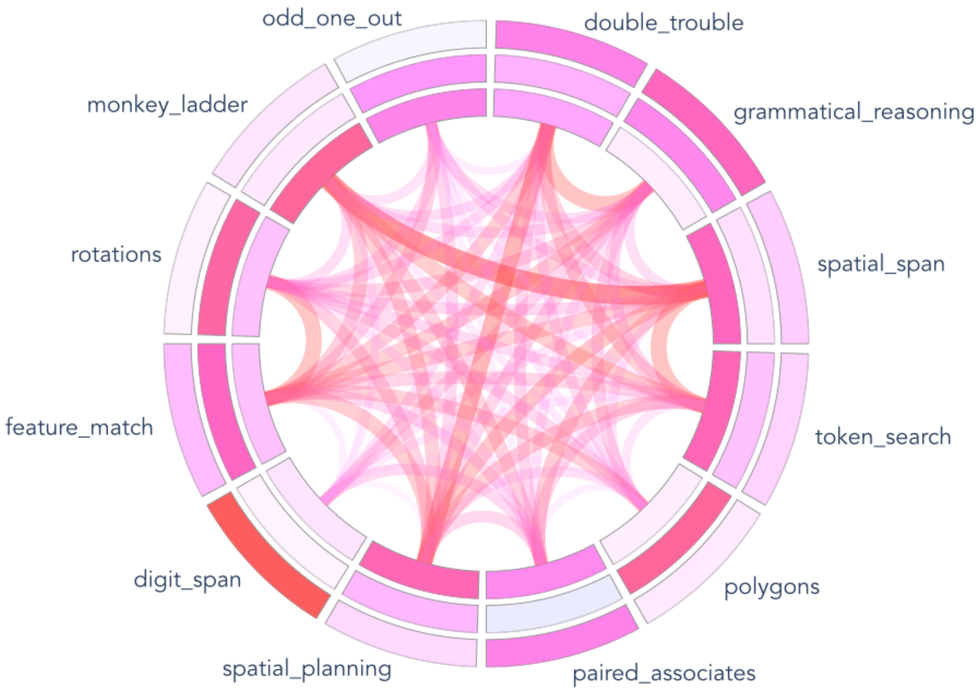
Wild *et al.*, 2022

Measuring Cognitive Performance

Pre-Pandemic Norms (N = 7,832)



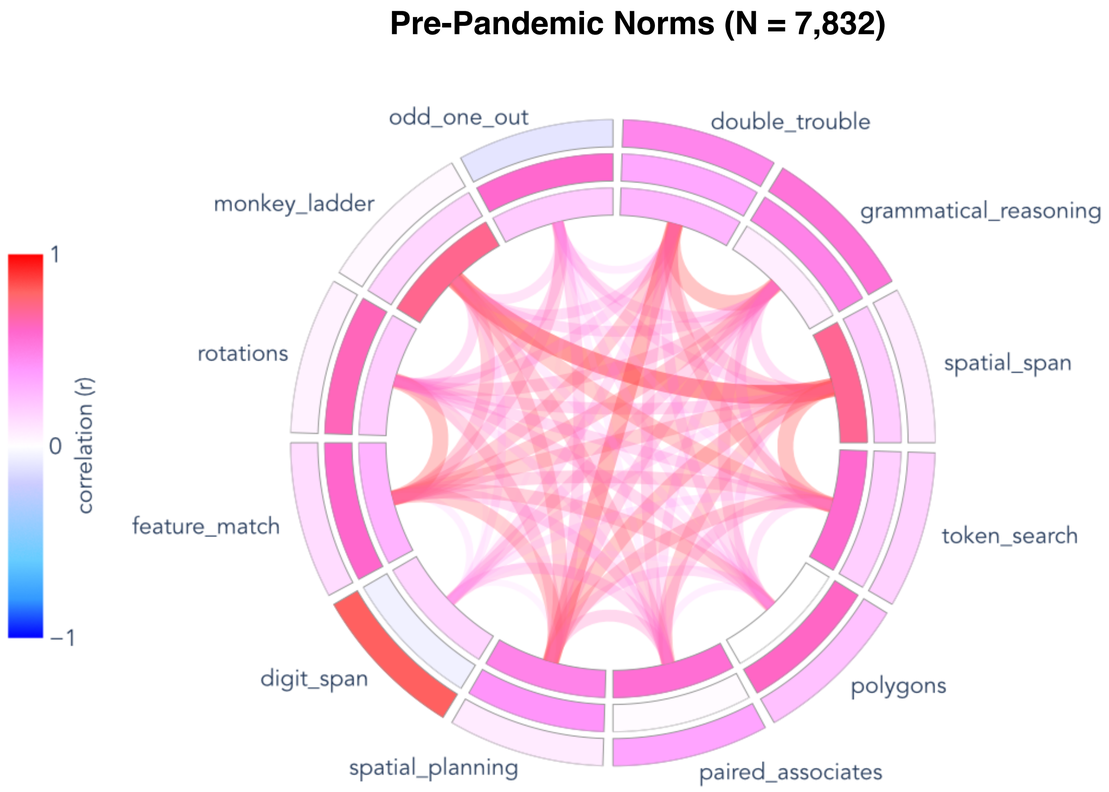
COVID+ (N = 478)



(Congruence coefficient > 0.95 for three factors)

Wild *et al.*, 2022

Measuring Cognitive Performance



Three Domain Scores:

1. Short Term Memory (STM)
2. Reasoning
3. Verbal

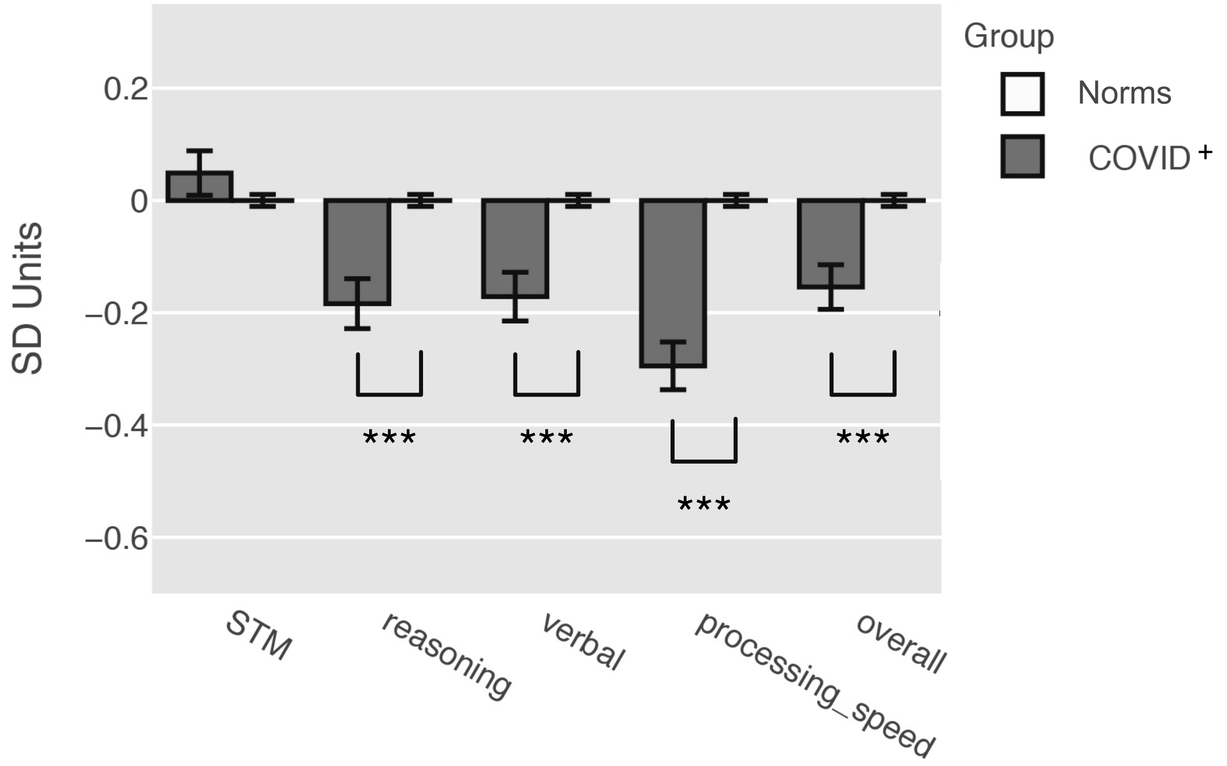
Two Additional Scores:

4. Overall (Average) Performance
5. Processing Speed (faster = better)

Wild *et al.*, 2022

Cognitive Performance: COVID+ vs. Norms

- COVID+ participants were significantly impaired relative to pre-pandemic controls on 4/5 cognitive measures.

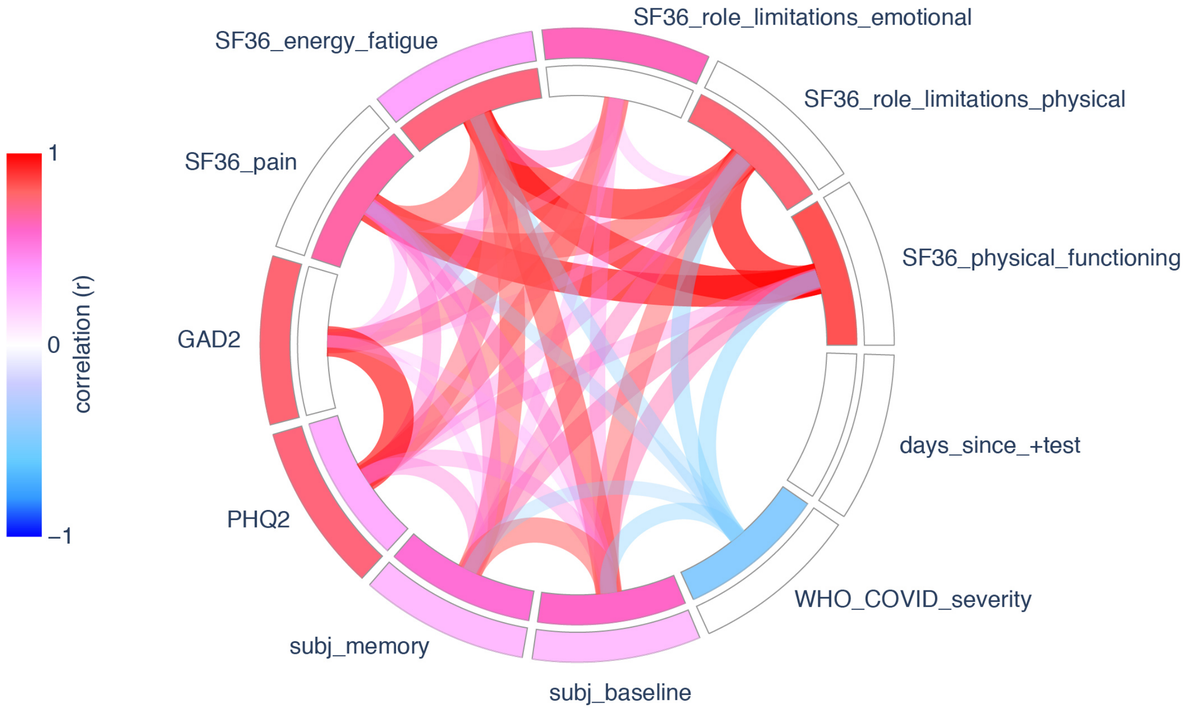


(error bars are SEMs)

(scores are corrected for age, sex, level of education, socio-economic status, amount of exercise, and drug use)

Wild *et al*., 2022

Other Measures of Health (COVID+)



Two Health Factors:

- **F1**: Overall physical health, including COVID severity
- **F2**: Mental health & wellness

10 Questionnaire Scales:

↑ WHO COVID Severity

↑ SF-36 Pain Scale

↑ SF-36 Physical Functioning

↑ SF-36 Role limitations (physical)

↑ SF-36 Energy / Fatigue

↑ SF-36 Role limitations (emotional)

↑ GAD-2 (anxiety)

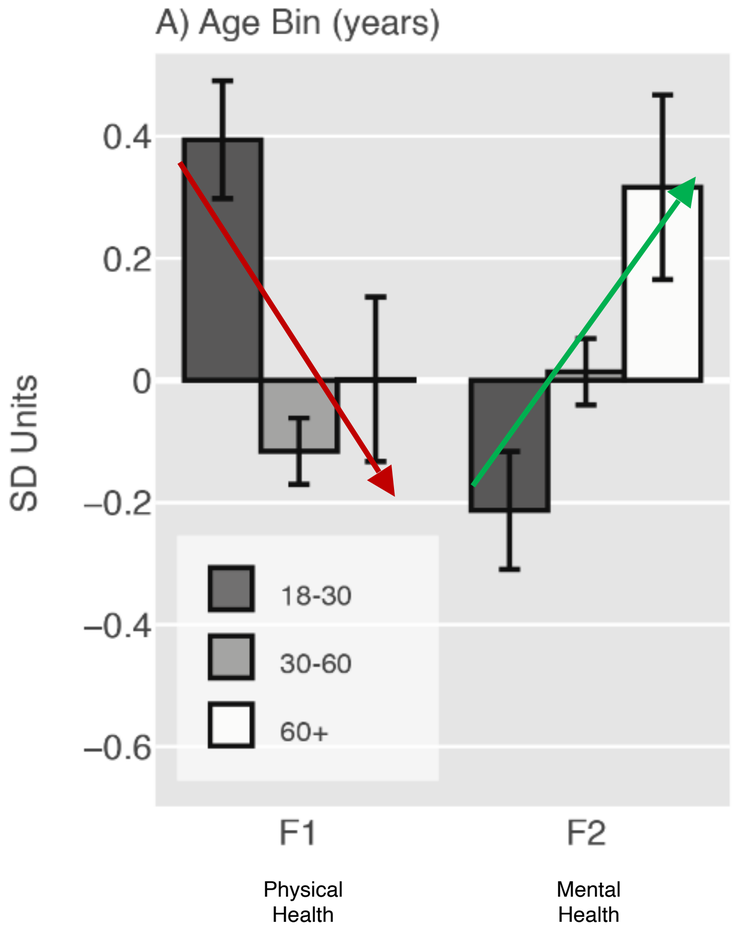
↑ PHQ-2 (depression)

↑ *"… back to your baseline… ?"*

↑ *"How would you describe your memory?"*

Wild *et al.*, 2022

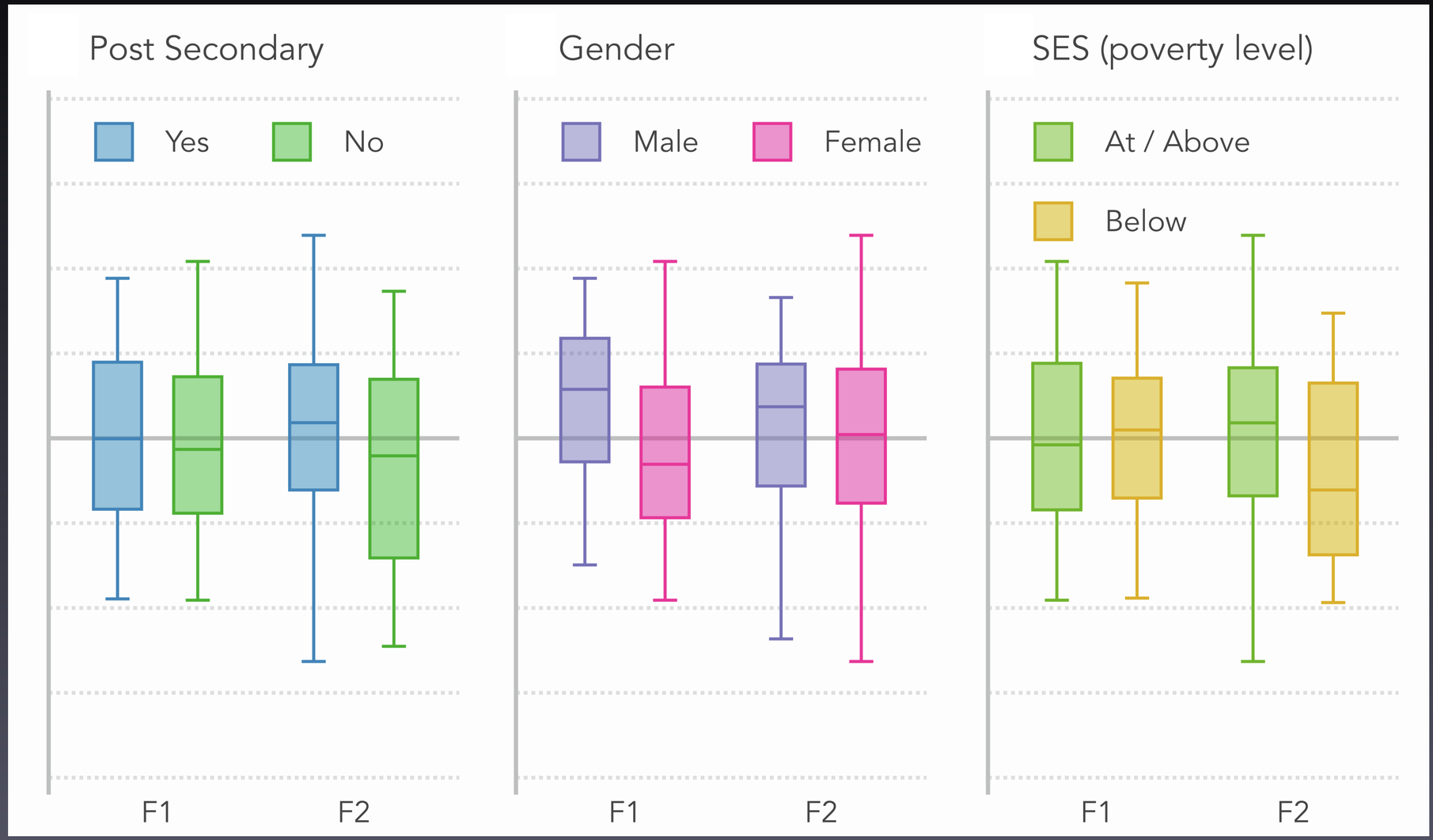
How do health factors relate to demographics?



Two distinct, *but not mutually exclusive*, factors that characterize post COVID-19 syndrome.

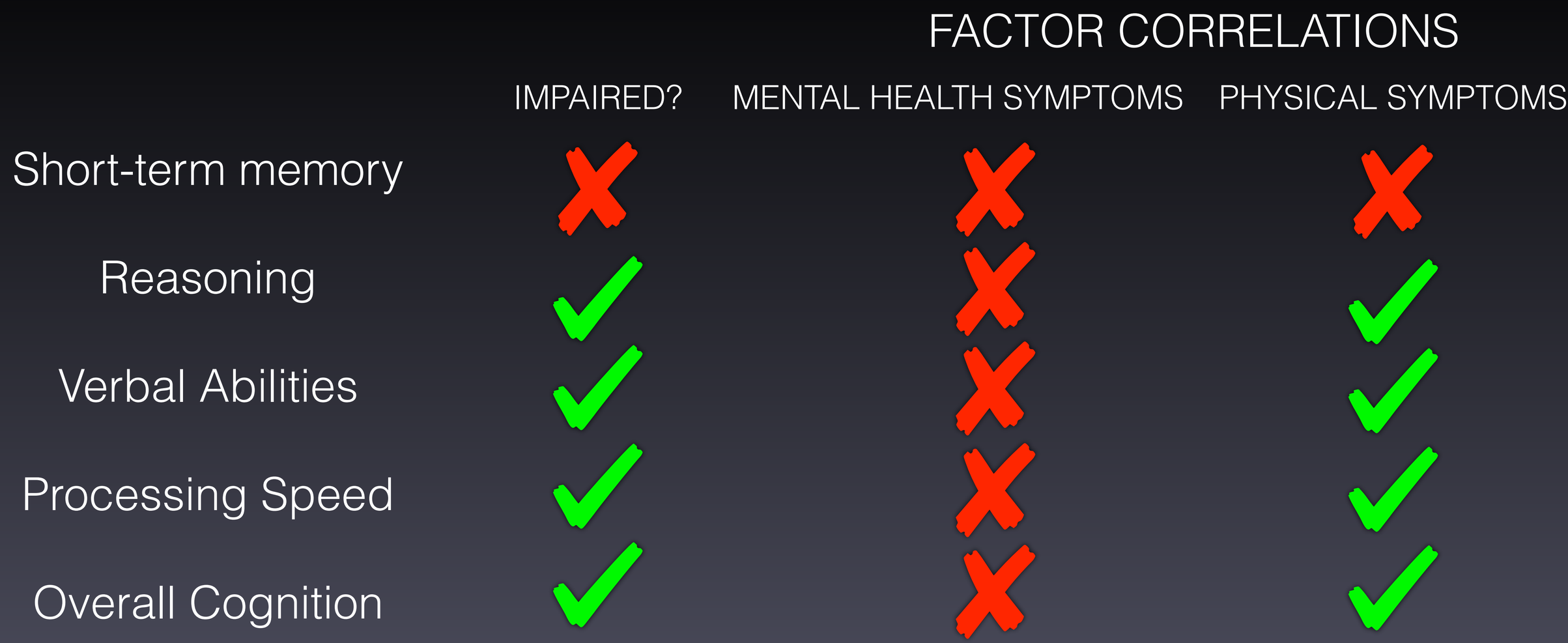
Wild *et al*., 2022

How do health factors relate to demographics?

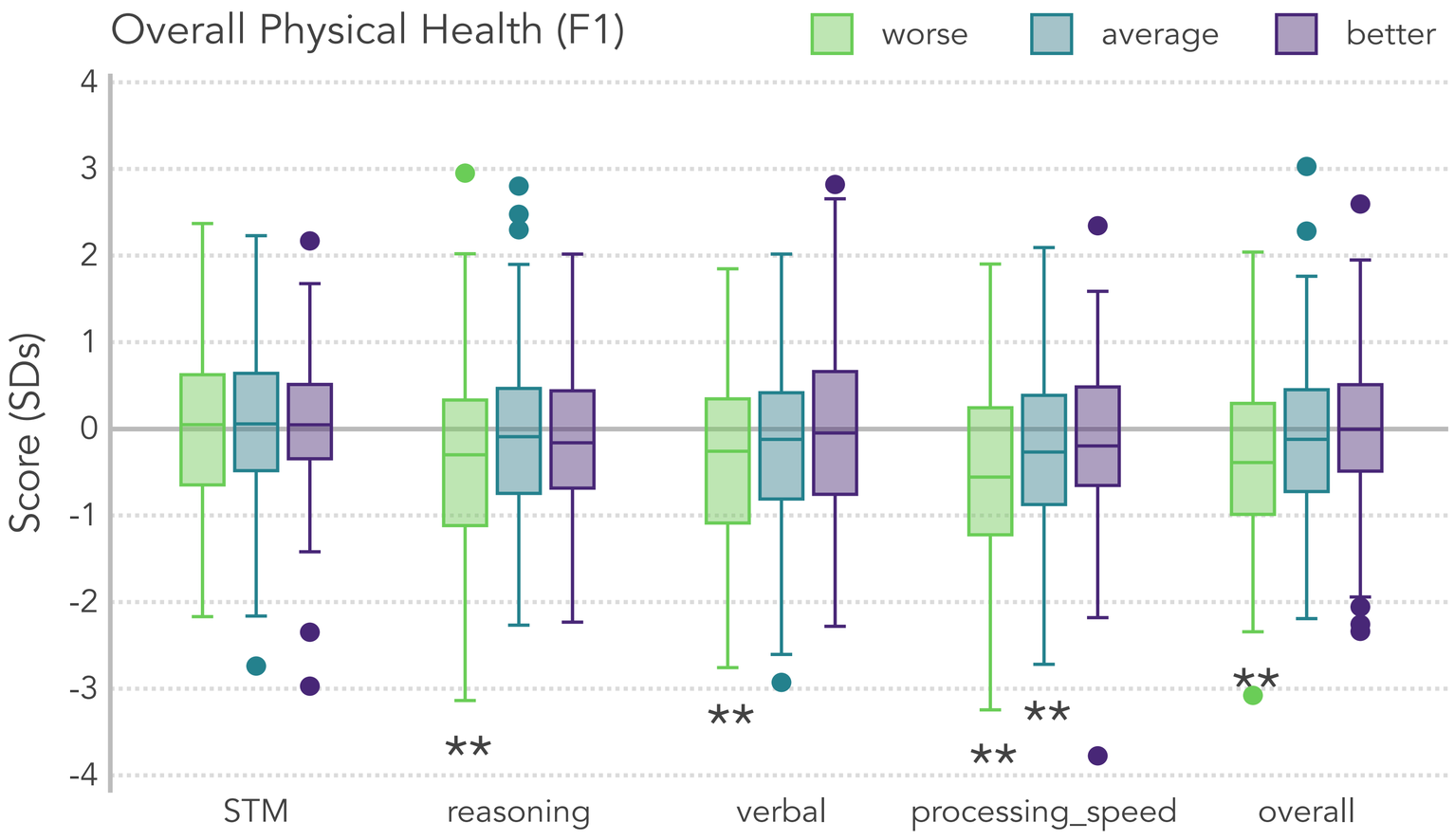


Wild *et al*., 2022

Results

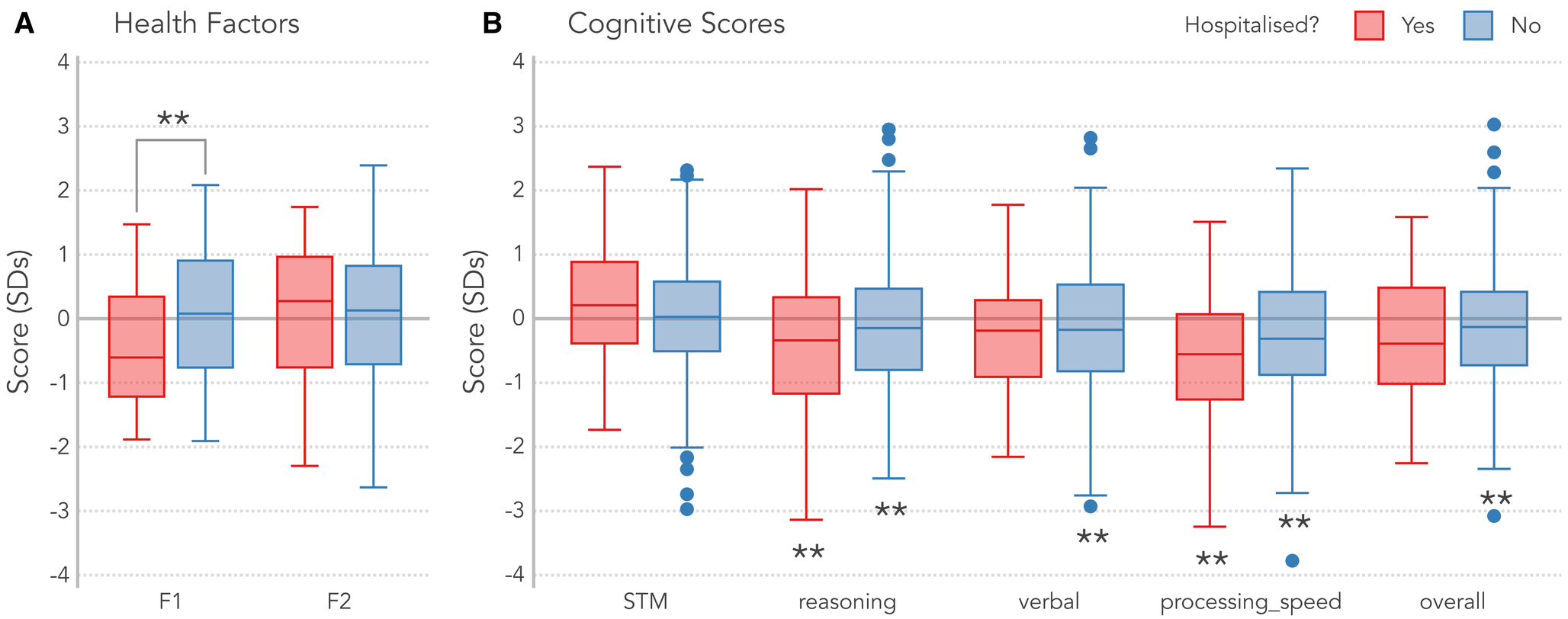


Wild *et al*., 2022



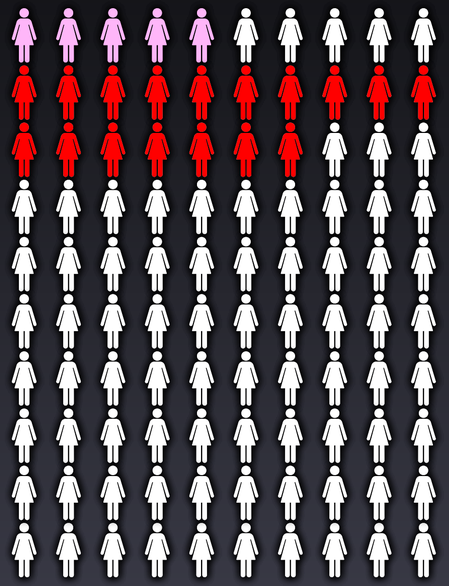
Wild *et al*., 2022

Is this just a matter of hospitalisation?



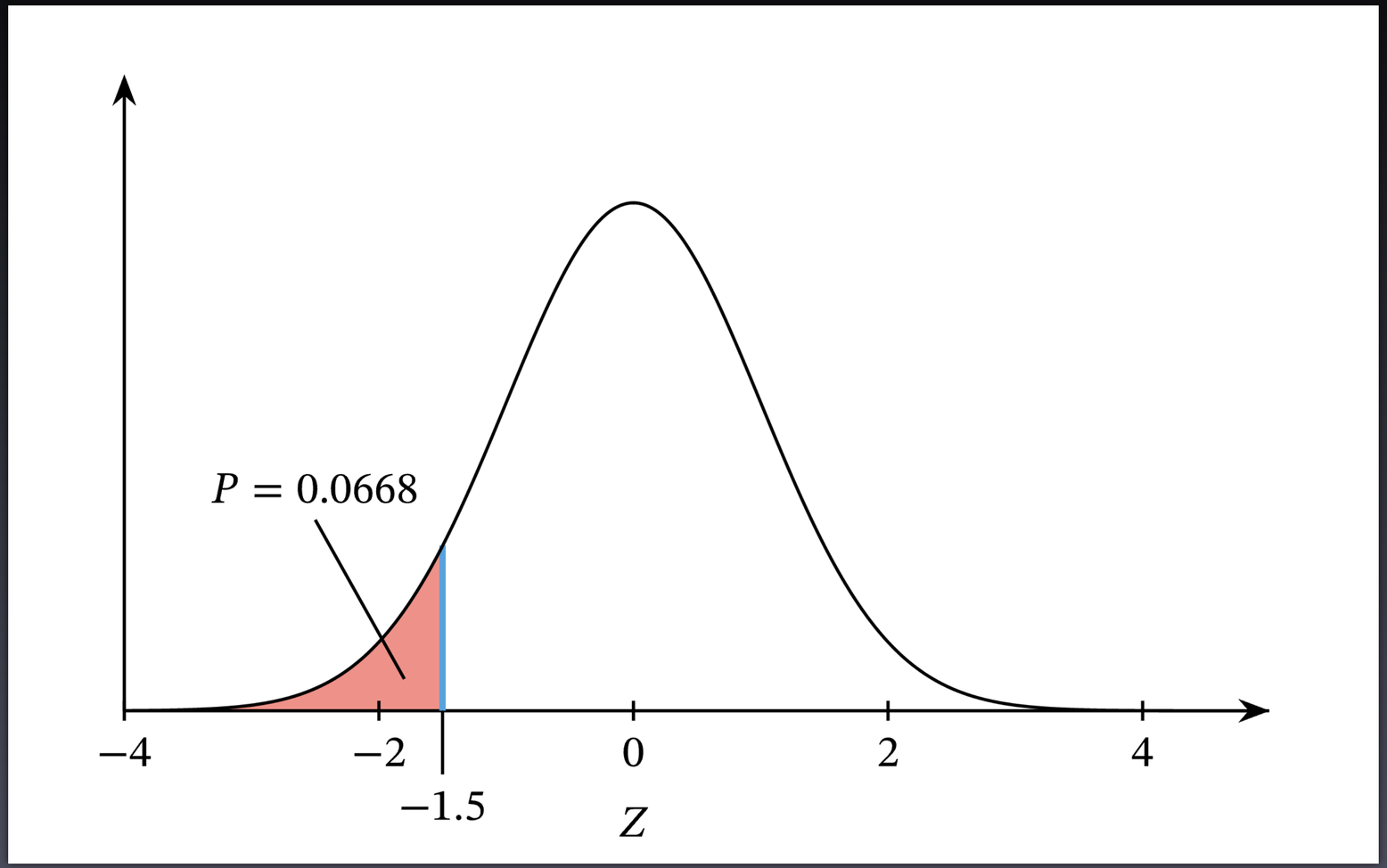
Wild *et al*., 2022

What proportion of participants were “impaired”?



≈ 737,000 Canadians

≈ 107M Worldwide



……of known COVID-19 cases

Wild *et al*., 2022

Conclusions

1. There are two dimensions that describe post-COVID-19 syndrome; one that primarily affects aspects of physical health and is related to COVID severity, and one that primarily affects mental health and is unrelated to COVID severity.

2. Our objective measures of cognition related to the *physical* rather than the *mental health* symptoms; that is, the worse your physical symptoms, the worse your cognitive outcome, but this was not true of the relationship between mental health and cognition.

3. “Brain Fog”/“Long COVID” relates to physical symptoms and cognitive deficits (rather than mental health impairments).

Wild *et al*., 2022

Cell Reports Medicine

CellPress
OPEN ACCESS

Article

Disentangling the cognitive, physical, and mental health sequelae of COVID-19

Conor J. Wild,[1,2,9,*] Loretta Norton,[1,3] David K. Menon,[4] David A. Ripsman,[5] Richard H. Swartz,[6,8] and Adrian M. Owen[1,2,7,8]

[1]Western Institute for Neuroscience, Western University, London, ON N6A 3K7, Canada
[2]Department of Physiology and Pharmacology, Western University, London, ON N6A 3K7, Canada
[3]Department of Psychology, King's University College, Western University, London, ON N6A 3K7, Canada
[4]Division of Anaesthesia, Department of Medicine, University of Cambridge, Cambridge CB2 2QQ, UK
[5]Faculty of Medicine, Department of Neurology, University of British Columbia, Vancouver, BC V6T 2B5, Canada
[6]Department of Medicine (Neurology), Hurvitz Brain Sciences Program, Sunnybrook Health Sciences Center, University of Toronto, Toronto, ON M4N 3M5, Canada
[7]Department of Psychology, Western University, London, ON N6A 3K7, Canada
[8]Senior author
[9]Lead contact
*Correspondence: cwild@uwo.ca
https://doi.org/10.1016/j.xcrm.2022.100750

Wild *et al*., 2022

CIFAR Manulife

Acknowledgements

Rick Swartz (Sunnybrook)
David Menon (Cambridge, UK)
Conor Wild (Western)
Loretta Norton (Western)
David Ripsman (Ottawa)

owenlab.org

Western The Brain and Mind Institute
UNIVERSITY OF CAMBRIDGE
UNIVERSITY OF TORONTO
Sunnybrook HEALTH SCIENCES CENTRE