

Global consortium studies: neuropsychiatric sequelae of SARS-CoV-2 infection

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Harmonization of data collection

- Clinical data
- Cognitive assessments
- Brain imaging
- Blood and genetic markers

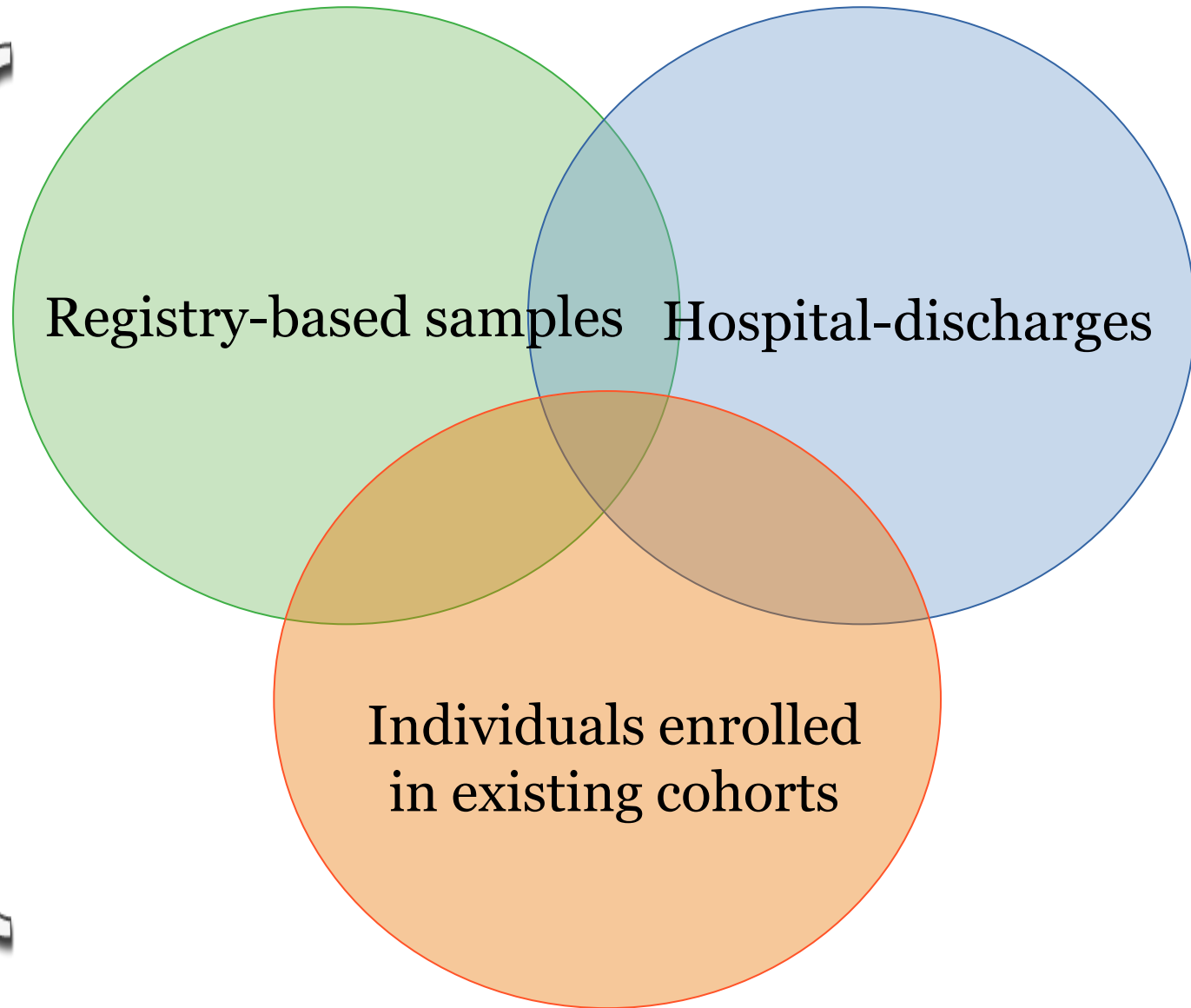
Flexibility of design

Unique opportunity to address:

- Risk factors for chronic adverse outcomes (modifiable?)
- Cultural influences (such as stigma-associated outcomes)
- Impact of genetic variations (viral and host) and environmental effects

TARGET SAMPLE SIZE = 1,000 persons per cohort (20 to 40,000 total participants)

Sampling strategies



Domain	Measures	
Clinical, Cognitive and Psychosocial Assessments		
Cognitive domains	Orientation & language*	ACE III and Shortened Boston naming test
	Memory	Episodic: Visual Paired Associates
		Working: Corsi Block Test
		Semantic: Cactus & Camel Test
	Executive function	Inhibition (& psycho-motor speed): Color (or Size) Stroop
		Planning - Problem solving: Tower of Hanoi
		Decision making – Impulsivity: Iowa, Gambling task
	Psychomotor speed	Symbol substitution test
	Attention & Visuo-Spatial abilities	Search Neglect: Bell cancellation
		Perception Apperceptive Agnosia: Poppelreuter-Ghent's overlapping figures test
Social Cognition	Theory of Mind: Frith-Happé animations	
Neuropsychiatry and Behavioral Neurology	World Health Organization Schedules for Clinical Assessment in Neuropsychiatry (WHO SCAN)	
Clinical evaluation of neurodegenerative disorders	The National Alzheimer's Coordinating Center Uniform Dataset (NACC UDS)	
Emotional reactivity assessment	The Perth Emotional Reactivity Scale (PERS) ^{§1}	
Clinical Cognitive Diagnosis	Mild Cognitive Impairment (amnesic or non-amnesic MCI), and dementia	
Psychosocial measures	Quality of life measures; stressful life events; poverty and financial hardship	
Semiquantitative Clinical Variables	Anosmia/Hyposmia smell recognition test; 2-min walk test of fatigability	

Neuroimaging	
Structural MRI	Region specific volumetric, cortical surface White matter hyperintensities as a proxy for vascular disease Vascular lesion burden: Infarcts, microbleeds
Diffusion Tensor Imaging	Tract-Specific Fractional Anisotropy (FA) and Mean Diffusivity (MA)
BOLD fMRI	Data from functional connectivity (FC) analyses BOLD-derived voxel-based physiological (VBP) indices of neurovascular coupling
¹⁸ F-DG PET (Only at UTHSA site)	Region-specific glucose uptake as markers of tissue metabolism and synaptic integrity
Blood-based biomarkers	
AD-specific biomarkers	A β 42, A β 40, P-tau ₁₈₁ , P-tau ₂₁₇
Neurodegeneration and neuronal activity/injury	NfL, GFAP, sTREM-2
Inflammatory biomarkers	Bio-Plex Pro Human Cytokine panel: FGF basic, Eotaxin, G-CSF, GM-CSF, IFN- γ , IL-1 β , IL-1ra, IL-1 α , IL-2Ra, IL-3, IL-12 (p40), IL-16, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, GRO- α , HGF, IFN- α 2, LIF, MCP-3, IL-10, IL-12 (p70), IL-13, IL-15, IL-17A, IP-10, MCP-1 (MCAF), MIG, β -NGF, SCF, SCGF- β , SDF-1 α , MIP-1 α , MIP-1 β , PDGF-BB, RANTES, TNF- α , VEGF, CTACK, MIF, TRAIL, IL-18, M-CSF, TNF- β
Genetics	
DNA collection for GWAS or Whole Genome Sequencing	

2.A. Characteristics of Site Populations

Site	San Antonio	Laredo	Seattle	Bronx	Jujuy	Ibadan (Oyo)
<i>Population</i>	2,003,554.00	276,652.00	2,252,782.00	1,418,782.00	770,881.00	3,649,000.00
<i>Population density (per sq mile)</i>	1,615.00	82.00	1,065.00	33,727.00	33.00	2,551.00
<i>Population over 60 years</i>	240,426.48	27,665.20	315,389.48	184,441.66	92,506.00	120,417.00
<i># of COVID-19 cases (12/31/2021)</i>	340,000.00	58,076.00	200,873.00	244,271.00	50,035.00	8,767.00
<i>% of population infected (12/31/2021)</i>	16.97	20.99	8.92	17.22	6.49	0.24

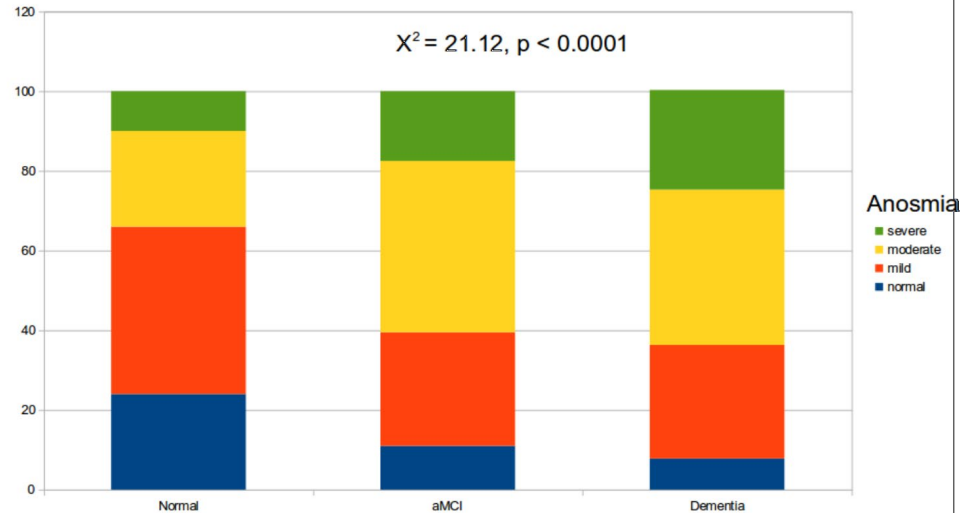
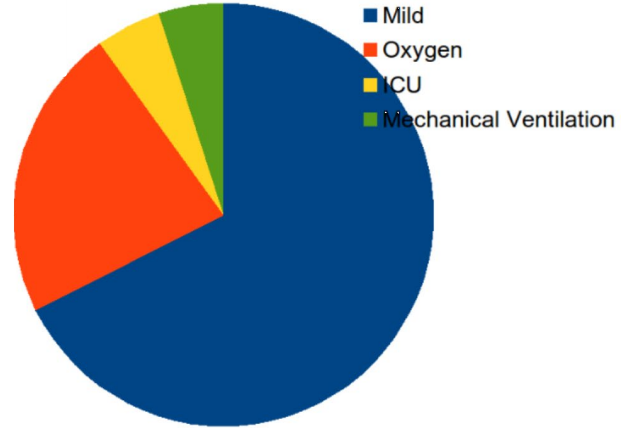
2.B. Recruitment Targets per Site

<i>n</i>	250	250	250	250	3000	300
Non-white Hispanics	250	250	-	15	-	-
White Hispanics	-	-	-	85		
Indigenous West African/African-American	-	-	-	125	-	300
Amerindian	-	-	125	-	3,000	-
Non-Hispanic white	-	-	125	25	-	-

Cohort ~850 participants
Mean age = 69
SARS-CoV-2 positive ~700
Vaccination rate > 95%
Reinfection rate ~ 9 %

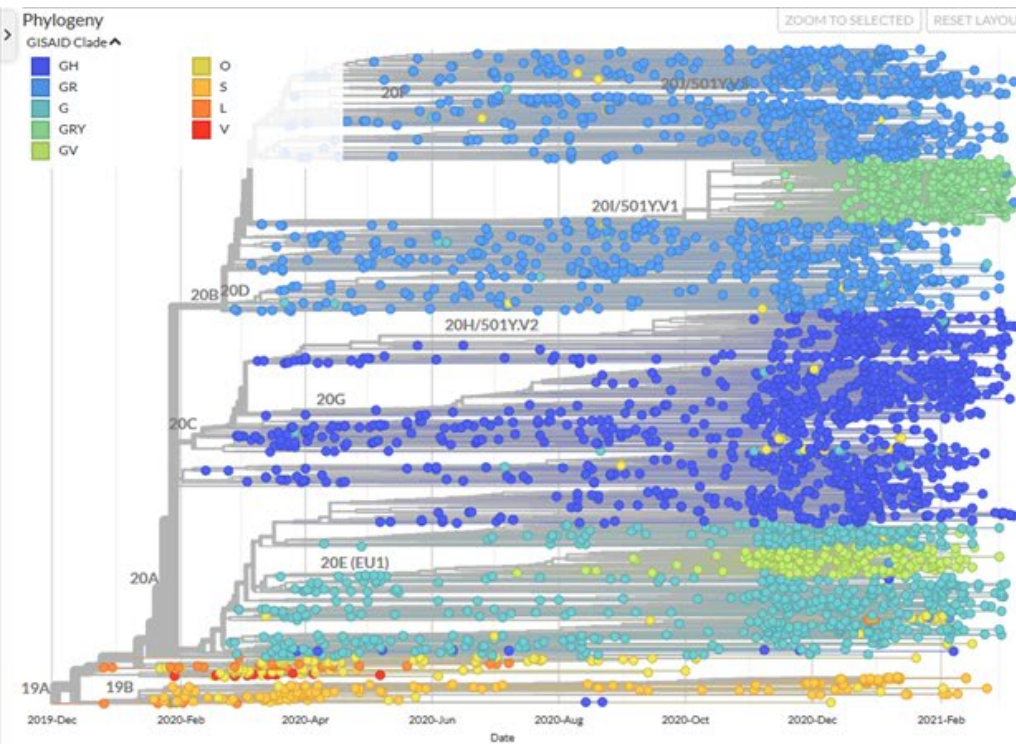
Task	NC	MO	MDI	Mean	SD	F	p
n	104	49	80				
Shortened Boston Naming Test				8.3	3.2	18.5	0.000
Weschler Memory Scale-Long Term Recall	-0.2	-1	-2.2	5.3	2.3	108.6	0.000
Weschler Memory Scale-Short Term Recall	-0.9	-2	-2.1	5.8	2.3	46.4	0.000
Weschler Memory Scale-Recognition	-0.7	1	-1.5	21.1	2.6	13.7	0.000
Corsi Blocks direct	0	0.3	-3	6.4	2	10.7	0.000
Corsi Blocks inverse	-0.4	-0	-1.1	5.2	2.1	16.5	0.000
Cactus and Camel				27.3	4.9	16.6	0.000
Oral Trails Verbal Search (time in seconds)	0.39	0.5	0.91	33.8	19.8	7.8	0.000
Oral Trails Verbal Search errors	-1	1	2.33	0.3	0.8	4.5	0.013
Oral Trails Visual Search (time in seconds)	0.56	0.8	1.23	71.4	38.8	12.8	0.000
Oral Trails Visual Search errors	0.14	0.4	0.23	0.4	1.4	1.6	0.211
Oral Trails Mental Search (time in seconds)	0.92	1	1.5	86.2	58.4	17.7	0.000
Oral Trails Mental Search errors	0.05	0.8	1.08	2.2	3	11.6	0.000
Oral Trails Visual-Mental Search (time in seconds)	0.99	1.3	1.7	103.7	55.6	29.6	0.000
Oral Trails Visual-Mental Search errors	0.46	0.54	0.72	1.9	4.2	7.6	1.000
Oral Trails Mental Switching (time in seconds)	0.1	1.1	1.56	90.6	57.9	29.8	0.000
Oral Trails Mental Switching errors	0.64	0.6	1	3.1	4.4	17.4	0.000
Digit Symbol score				35.9	17.7	34.9	0.000
Tower of Hanoi				10.2	3.8	4.4	0.014
Five Digit Test reading time	0.49	0.4	1.16	38.5	22.7	18.4	0.000
Five Digit Test reading errors	0.05	0	0.32	0.6	4.7	2.4	0.090
Five Digit Test counting time	0.4	0.4	1	40.9	23.5	18.8	0.000
Five Digit Test counting errors	0.1	0.3	0.29	0.7	4.7	2.3	0.100
Five Digit Test selecting time	1.04	0.3	1.2	62.5	35.8	27.8	0.000
Five Digit Test selecting errors	-1.2	0.3	0.5	2.3	4.9	8.5	0.000
Five Digit Test switching time	0.72	0.4	1.53	87.1	44.9	40.5	0.000
Five Digit Test switching errors	0.17	0.2	0.82	4	5.7	1661	0.000

Predictors:

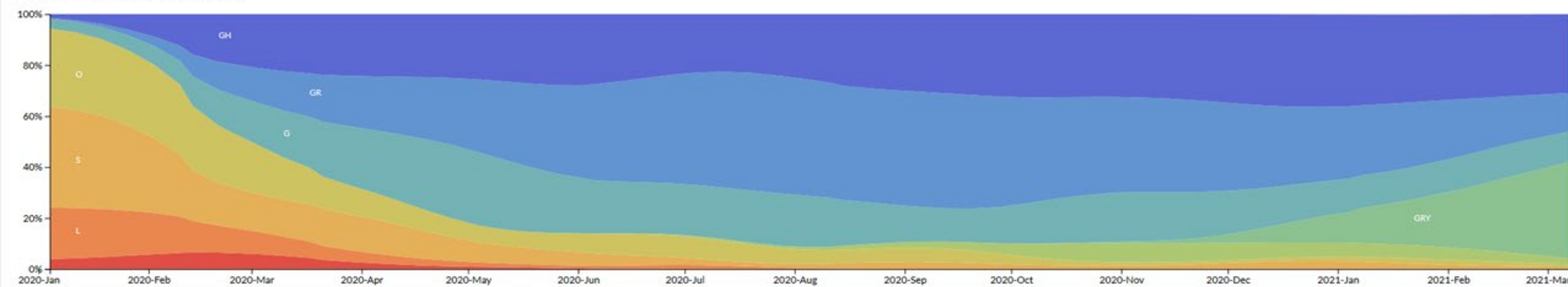


Preliminary Data:

- Mild cognitive impairment (of new onset) is common in older adults positive for SARS-CoV2 regardless of COVID-19 symptom severity. Typical CDR is 0.5.
- Anosmia is commonly associated with cognitive impairment.
- Fatigability and decreased stamina are also nearly always present.
- Emotional indifference and (less commonly) hypomanic or manic symptoms are frequent, but not as common as cognitive decline.
- Depression of new onset is rare. The cases seen may not be more frequent than in the general population of the same age.
- Motor slowness is common, but hard to distinguish from overall fatigability.



Frequencies (colored by GISAID Clade)



- What is the longitudinal course of cognitive changes post-infection?
- What are the biomarkers of cognitive change post-infection?
- What is the role of host-virus genetic interactions on the risk?
- What are the environmental factors that affect disease risk and recovery?

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