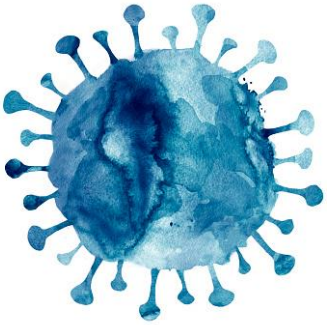

Estudio del funcionamiento neuroconductual, neuropsicológico y de la conectividad cerebral a largo plazo en personas infectadas por SARS-CoV-2

Daniela Ramos Usuga

Director: Dr. Juan Carlos Arango Lasprilla

2023

eman ta zabal zazu

Universidad del País Vasco

Euskal Herriko Unibertsitatea

A mi pequeña gran familia, Nury, Hugo y Lucía

CONTENIDO

AGRADECIMIENTOS

No creo en el destino sino en casualidades, que, en ocasiones, me pone en el camino a personas maravillosas que me acompañan en la vida. Algunos encuentros son fugaces, otros perennes, pero de alguna forma todos aportan a mi crecimiento. Quiero dedicar unas palabras de agradecimiento a todas las personas que me han apoyado durante estos cuatro años de doctorado, sin ellas este trabajo no habría sido posible.

En primer lugar, quiero expresar mi más sincero agradecimiento a mi director y amigo, Juan Carlos Arango-Lasprilla. Desde el primer momento me abrió las puertas de su laboratorio, poniendo toda su confianza en mí y ofreciéndome tantísimas oportunidades. Con mucha paciencia, dedicación y cariño me ha guiado a lo largo de mi viaje académico y me ha enseñado, no solo a trabajar con pasión y esmero, sino muchos valores esenciales que he trasladado a mi vida personal. Es una fortuna haberlo tenido como mentor y seguir teniéndolo como una parte muy importante de mi vida. También quiero agradecer a Heather Lynn Rogers por todas las oportunidades que me ha brindado y por regalarme un poco de su sabiduría. Siento una profunda admiración por los dos, son toda una inspiración para mí.

A todas las personas que han sido parte de mi grupo de investigación, pero principalmente a Diego Rivera y Laiene Olabarrieta, por sus enseñanzas, porque siempre están dispuestos a ayudarme y porque me tienen en mente para todo. También a Itziar Benito, por haber sido mi confidente y compañera de aventuras durante estos años, y por alegrarme incluso en los días más difíciles. Más que compañeros de trabajo, son mis amigos.

A Antonio Jiménez, por caminar a mi lado con amor, respeto y lealtad. Ha sido un apoyo incondicional y una fuente de aprendizaje para mí.

Al Dr. Jesús Cortés y a todos los integrantes de su grupo de investigación "Neuroimagen computacional", por haberme hecho sentir como un miembro más de su equipo.

A los colegas de Estados Unidos, Paul B Perrin, Elisabet Alzueta, Samuel J West, Kritzia Merced, Daniel W Klyce, Fiona C Baker, Stella Iacovides, Mar Cortes, Anthony H Lequerica y Yelena Bogdanova, con quienes he tenido la gran oportunidad de colaborar y llevar a cabo dos de los estudios que forman parte de la presente tesis doctoral.

A los médicos de la Unidad de Cuidados Intensivos del Hospital de Cruces, Victoria Boado, Fermín Labayen y Elena Panera; al Dr. Alberto Cabrera-Zubizarreta, radiólogo del Hospital de Galdakao; a mis colegas del grupo de "Neuroimagen computacional", Jesús Cortés, Antonio Jiménez y Endika Martínez-Gutiérrez; y mis compañeros Itziar Benito y Diego Rivera, quienes han sido clave en el desarrollo del último estudio que se incluye en la presente tesis doctoral.

A los colegas de Puerto Rico, Rafael Oliveras, Walter Rodríguez e Ivonne Romero, con quienes he tenido el placer de colaborar en múltiples proyectos y de quienes siempre aprendo algo nuevo.

A la Dra. María Jesús Gómez y todo el equipo de la Clínica Uner, por haberme recibido y acogido en su equipo durante los dos meses de estancia.

Al Dr. Francisco Lopera y todos los integrantes del Grupo de Neurociencias de Antioquia, por hacer de mi estancia una experiencia inolvidable y llena de aprendizaje.

A los Dres. Yaneth Rodríguez, María González, José Vicente Lafuente, Fernando Maestu Unturbe, Guido Mascialino y Andone Sistiaga, por haber aceptado formar parte de mi tribunal de defensa.

A todos los participantes de los estudios, los protagonistas de este trabajo.

A Gabriel Rivas y Bidane Gartzia, de Neuropsychology Learning, por darme la oportunidad de colaborar con ellos y por la confianza que han puesto en mi trabajo.

A mis mejores amigos, Laura Manzanal, David Rodríguez y Luisa Blanco por dejarme formar parte de su vida.

Y por supuesto, a mi familia por todo su apoyo, amor incondicional y por creer en mí.

Finalmente, agradecer al Gobierno Vasco por otorgarme la beca predoctoral (PRE_2019_1_0164) que ha hecho posible llevar a cabo este trabajo.

ÍNDICE DE TABLAS

ÍNDICE DE FIGURAS

Figure 4.2. Salience connectivity alterations in critically ill COVID-19 patients.

Figure 4.3. Association between functional connectivity of the salience network and cognitive performance in critically ill COVID-19 patients.

ABREVIATURAS

Español	Inglés
AEMPS: Agencia Española de Medicamentos y Productos Sanitarios	ACE-2: Angiotensin-Converting Enzyme 2
ARN: Ácido ribonucleico	AD: Alzheimer's disease
ARNm: ARN mensajero	ACC: Anterior Cingulate Cortex
ECA2: Enzima Convertidora de Angiotensina 2	BOLD: Blood oxygenation level dependent
Enfermedad por coronavirus 2019: COVID-19	BNT: Boston Naming Test
FMO: Fallo Multiorgánico	BTA: Brief Test of Attention
IL: Interleuquina	DoC: Disorders of Consciousness
OMS: Organización Mundial de la Salud	fMRI-resting state: Functional Magnetic Resonance Imaging-resting state
RMf: Resonancia magnética funcional	Food and Drug Administration: FDA
RND: Red Neuronal por defecto	FWHM: Full width at half maximum
SNC: Sistema Nervioso Central	HCoV: Human Coronavirus
SNP: Sistema Nervioso Periférico	HVLT-R: Hopkins Verbal Learning Test-Revised
TMPRSS2: Proteasa transmembrana serina 2	ICU: Intensive Care Unit
UCI: Unidad de Cuidados Intensivos	LCI: Lower-bound of the confidence interval
	MERS-CoV: Middle East Respiratory Syndrome Coronavirus
	MMSE: The Mini-Mental State Examination
	MOF: Multiorgan Failure

MRIs: Brain Magnetic Resonance Images

M-WCST: Modified Wisconsin Card Sorting Test

NSI: Neurobehavioral Symptom Inventory

PCR: Polymerase chain reaction

PHQ-9: Patient Health Questionnaire–9

ROCF: Rey-Osterrieth Complex Figure

RSN: Resting State Networks

SBC: Seed-based-correlation

SD: Standard Deviation

SDMT: Symbol Digit Modalities Test

SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus

SOFA: The Sequential Organ Failure Assessment

TMT: Trail Making Test

UCI: Upper-bound of the confidence interval

VBM: Voxel-based morphometry

VAN: Ventral Attention Network

VFT: Verbal Fluency Test

WM: White matter

GLOSARIO[1]

Aparato de Golgi: orgánulo celular que ayuda en la fabricación y empaquetamiento de las proteínas y los lípidos, especialmente de aquellas proteínas destinadas a ser exportadas por la célula.

ARN mensajero (ARNm): es un tipo de ARN de cadena única que participa en la síntesis de las proteínas.

Blood oxygenation level dependent (BOLD): cambios en el nivel de oxigenación de la sangre que están asociados con la actividad neuronal, y que pueden medirse a través de la resonancia magnética funcional.

Citoplasma: líquido gelatinoso que llena el interior de una célula.

Endocitosis: Proceso por el cual la célula introducen moléculas grandes o partículas a su interior

Enterocito: tipo de célula del epitelio intestinal que recubre toda la superficie interna del intestino delgado. Su función es la de digerir los alimentos y absorber sus nutrientes.

Exocitosis: Proceso por el cual la célula transporta al exterior moléculas grandes o partículas a través de su membrana.

Genoma: conjunto del material hereditario de un organismo.

Glicoproteína: moléculas compuestas por una proteína unida a uno o varios glúcidos.

[1] Las palabras incluidas en el glosario se han señalado en negrita en el texto.

Patogenicidad: la capacidad de los parásitos para infectar un huésped y causar enfermedad.

Proteína ARN polimerasa: proteína de carácter enzimático cuya función es copiar el ARN genómico viral para permitir la replicación y transcripción de los genes virales.

Proteínas ARN-polimerasas: conjunto de proteínas con carácter enzimático capaces de polimerizar los ribonucleótidos para sintetizar ARN a partir de una secuencia de ARN viral que sirve como patrón o molde.

Proteólisis: degradación de proteínas ya sea mediante enzimas específicas, llamadas proteasas, o por medio de digestión intramolecular.

Retículo endoplásmico: orgánulo celular, que puede ser liso o rugoso, y cuya principal función es producir proteínas para que el resto de la célula pueda funcionar.

Ribosoma: orgánulo celular encargado de unir aminoácidos para formar proteínas.

Traducción: proceso mediante el cual se produce la síntesis de las proteínas a partir de la unión de cadenas de aminoácidos. Este proceso tiene lugar gracias a la codificación de la información del ARNm.

Transcripción: proceso mediante el cual una célula elabora una copia de ARN a partir de una pieza de ADN. Esta copia de ARN, que se llama ARN mensajero (ARNm), transporta la información genética que se necesita para elaborar las proteínas en una célula. En el caso de los virus ARN monocatenario positivos, la transcripción se realiza del ARN viral al ARNm.

Capítulo 1. Marco teórico

1.1. Coronavirus

Coronaviridae es una familia de virus compuesta por dos subfamilias, Letovirinae y Orthocoronavirinae. A esta última subfamilia pertenecen los coronavirus, los cuales pueden ser de cuatro géneros: Alphacoronavirus, Betacoronavirus, Gammacoronavirus y Deltacoronavirus. Los coronavirus humanos (HCoV) pertenecen a los géneros Alphacoronavirus y Betacoronavirus. Si bien cada género tiene sus particularidades, esta familia de virus se caracteriza por tener un genoma de ARN monocatenario (cadena sencilla) de sentido positivo (ARN sentido +). Esto implica que el genoma del ARN viral es igual al del ARN mensajero (ARNm) de las células, lo que hace que la célula lo reconozca como su propio material genético y realice la traducción directamente a las proteínas virales en su citoplasma. Esta característica permite a los coronavirus replicarse e infectar a las células huésped con mayor rapidez que otros virus (1).

A nivel estructural, el virión o partícula vírica de la mayoría de los coronavirus guarda su ARN en una cápside (cubierta proteica) y se compone principalmente de cuatro proteínas estructurales: la glicoproteína de espiga (S), la glicoproteína transmembrana (M), la proteína de la nucleocápside (N) y la proteína de la envoltura (E) (ver Figura 1.1.). Las glicoproteínas M y S se encuentran en la envoltura del virión, otorgándole el aspecto de corona, y participan principalmente en la unión y ensamblaje del virus a las células. En particular, la glicoproteína S tiene un papel protagonista en la infección ya que es la que se une al receptor de la célula para mediar la entrada del material vírico. Por otra parte, la proteína N es la que forma la cápside que protege el ARN, mientras que la proteína E participa en el ensamblaje y liberación del virión de la célula huésped (1).

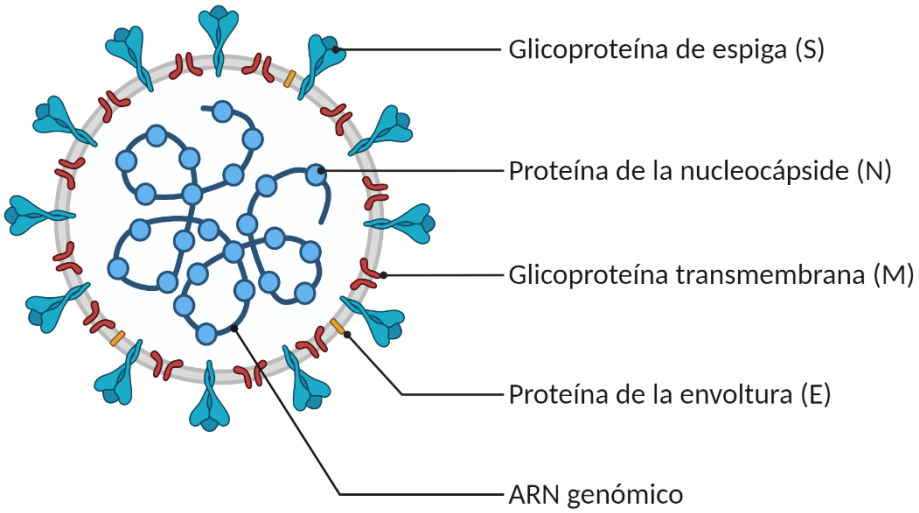

Figura 1.1. Estructura del SARS CoV-2

Nota: Imagen creada con BioRender.

Existen innumerables tipos de coronavirus, de los cuales solo siete pueden infectar a los humanos. En estos casos, la infección puede darse directamente entre los humanos o a través de animales, que actúan como vectores para transmitir el virus (2).

Los dos primeros coronavirus humanos (HCoVs), el HCoV-229E y el HCoV-OC43, aparecieron por primera vez en la década de los 60, causando síntomas similares a los del resfriado común. A pesar de que se consideran virus de baja patogenicidad, y en la mayoría de los casos, la enfermedad se resuelve sin ninguna complicación, en personas mayores o con el sistema inmunológico debilitado los síntomas pueden ser graves (3).

En 2002 se detectó en China el *Severe Acute Respiratory Syndrome Coronavirus* (SARS-CoV), que tal y como indica su nombre, provoca problemas respiratorios graves (3). Este virus se extendió a 29 países y regiones, dando lugar a la primera epidemia por coronavirus, en la que 8098 personas fueron infectadas (4). Desde el 2004 no se ha reportado casos nuevos de esta enfermedad (5).

Posteriormente, en el 2004 y el 2005 se descubrieron otros dos coronavirus, el HCoV-NL63 y HCoV-HKU1, respectivamente. En el primer caso, los pacientes suelen desarrollar infecciones respiratorias que, en algunos casos, pueden llegar a ser graves en niños, ancianos o pacientes inmunodeprimidos, mientras que el HCoV-HKU1 provoca principalmente fiebre, tos, rinorrea y sibilancias, e infecciones respiratorias en pacientes vulnerables. Estos dos virus también tienen una baja patogenicidad (3).

Siete años más tarde apareció el *Middle East Respiratory Syndrome Coronavirus* (MERS-CoV) en Arabia Saudí. Al igual que el SARS-CoV, este virus da lugar, principalmente, a complicaciones respiratorias, no obstante, también se han reportado alteraciones gastrointestinales, cardiovasculares, renales y neurológicas (3). Si bien la baja tasa de contagio y la alta letalidad (35% de muertes tras la infección) (6) del virus limitó su

expansión, el MERS-CoV ha sido el protagonista de la segunda epidemia por coronavirus, que afectó a 27 países en Asia, América, Europa y África (3).

Finalmente, en diciembre del 2019 se detectó en Wuhan, China el primer caso de infección por el *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2). Este nuevo virus, muy similar al SARS-CoV, se expandió por todo el mundo a gran velocidad, dando lugar a la pandemia de enfermedad por coronavirus 2019 (COVID-19). Los datos más recientes indican que, a nivel mundial, aproximadamente 771,679,618 personas han sido contagiadas por el virus, de las cuales 6,977,023 han fallecido (7). Durante esta situación de emergencia sanitaria internacional, el mundo fue testigo de una carrera, por parte de toda la comunidad científica, en búsqueda de la vacuna para la COVID-19. Como resultado, cinco vacunas han sido aprobadas por la Administración de Alimentos y Medicamentos de los Estados Unidos (FDA, por sus siglas en inglés) (8) y ocho por la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) (9), lo que ha contribuido a que lentamente se haya logrado frenar la expansión del virus hasta el punto de que el 5 de mayo de 2023 se declarase el fin de la pandemia. A pesar de ello, la COVID-19 sigue siendo un gran problema de salud pública para muchos países del mundo (3).

1.2. SARS-CoV-2 y COVID-19

El SARS-CoV-2 pertenece al género Betacoronavirus y comparte su genoma en un 70% y un 40% con el del SARS-CoV y MERS-CoV, respectivamente. Tal y como se detallará a continuación, una parte esencial del mecanismo de infección de los coronavirus es la unión entre la glicoproteína S del virus y un receptor de la célula huésped, el cual es específico para cada tipo de coronavirus. Dicho receptor determina el modo en el que el virus entra a la célula y los órganos que son vulnerables a la infección. El SARS-CoV-2, en

particular, se une únicamente al receptor de la enzima convertidora de angiotensina 2 (ECA2) (2), que se encuentra principalmente en las células epiteliales del pulmón, las glándulas salivales y de la lengua, así como en los **enterocitos** del intestino delgado (10).

1.2.1. MECANISMO DE INFECCIÓN DEL SARS-COV-2

La infección del SARS-CoV-2 inicia con la unión de la glicoproteína S del virus con el receptor ECA2 presente en la superficie de la célula huésped. A continuación, se produce la fusión de la envoltura viral con la citomembrana de la célula gracias a una serie de proteasas, principalmente la proteasa transmembrana serina 2 (TMPRSS2), cuya función es cortar la glicoproteína S en dos (11–13).

El virus entra a la célula huésped por **endocitosis**, libera su genoma viral en el citoplasma celular, y dado que actúa como un **ARNm**, la célula lo reconoce como su propio material genético. Esto activa la maquinaria celular, de modo que el **ribosoma** inicia el proceso de **traducción** del ARN genómico para formar una serie de poliproteínas, que, mediante la **proteólisis**, se dividen en proteínas más pequeñas, entre las que se encuentra la **proteína ARN polimerasa** y las **proteínas no estructurales**. (11–13).

Este conjunto de proteínas forma el complejo de replicación y transcripción, con el que se inicia el proceso de replicación del genoma viral. Durante este proceso, a partir del ARN genómico (sentido +) que ha ingreso a la célula y que sirve como plantilla, se crea una copia de ARN genómico (sentido -). Esta copia se transcribe de nuevo para generar un ARN genómico (sentido +), que será el genoma viral de los nuevos virus, así como un ARN subgenómico (sentido +) que traducirá y formará las proteínas estructurales (M, S, N y E) (11–13).

Una vez sintetizadas, las proteínas M, S y E se unen al retículo endoplásmico, donde se terminan de formar, mientras que la proteína N envuelve el genoma viral, dando lugar a la nucleocópside. Después, las proteínas M, S y E pasan al aparato de Golgi a través del compartimento intermedio del retículo endoplásmico-Golgi (ERGIC). En el aparato de Golgi se ensamblan las proteínas M, S y E con la nucleocápside y se finaliza la maduración del virión, el cual es liberado al exterior de la célula a través de una exocitosis (ver Figura 1.2.) (11–13).

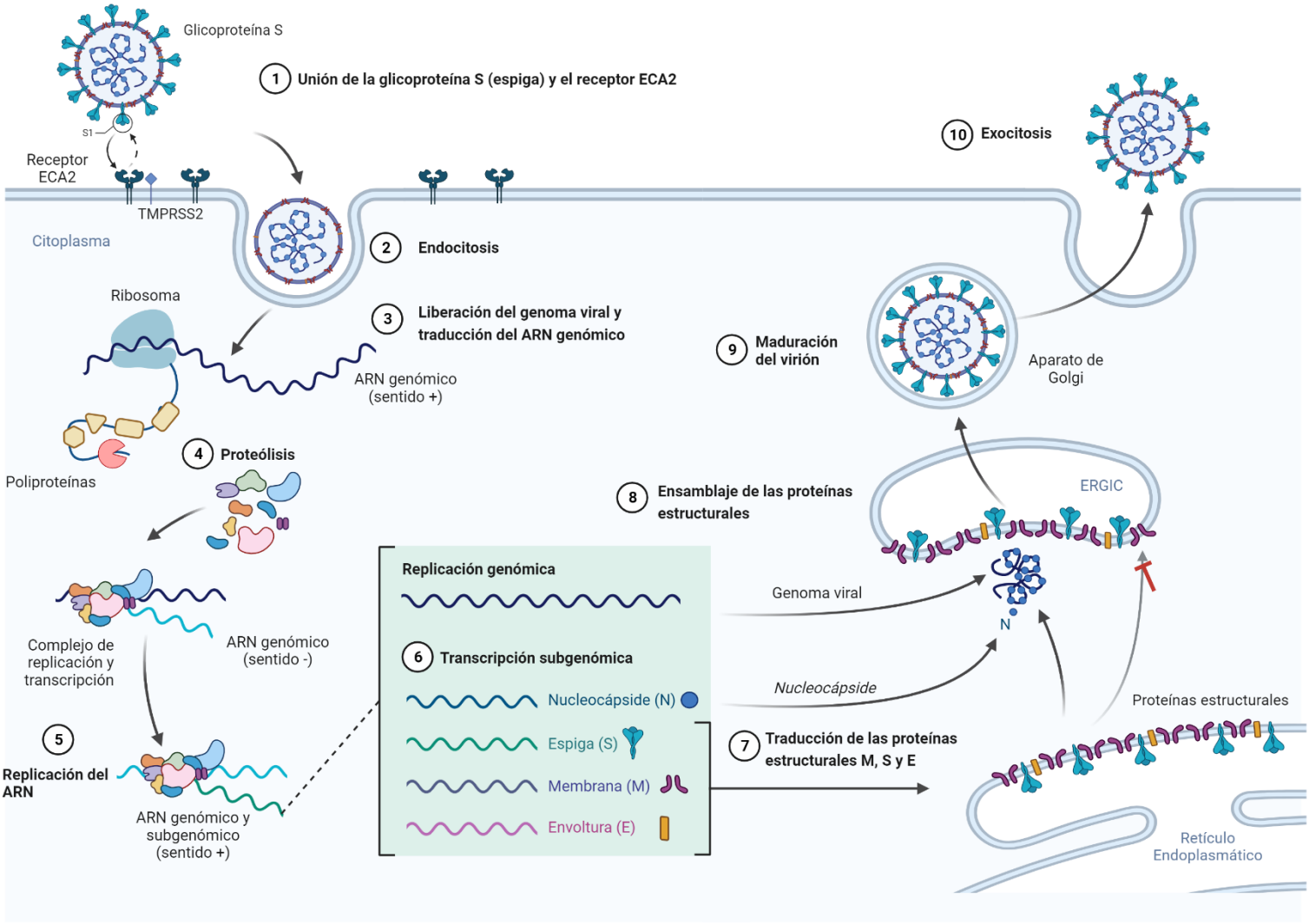

Figura 1.2. Mecanismo de infección del SARS CoV-2

Nota: Imagen creada con BioRender.

1.2.2. RESPUESTA DEL SISTEMA INMUNOLÓGICO ANTE EL SARS-COV-2

Tras la infección por SARS CoV-2, se produce una respuesta por parte del sistema inmunológico, que puede ser innata o adquirida. Por una parte, la inmunidad innata, es la primera que sale a combate y proporciona una respuesta inmediata en el momento en el que se detecta el virus. Si bien este tipo de inmunidad nos protege frente a muchos patógenos, es muy poco específica y activa el mismo mecanismo de acción independientemente del patógeno, por lo que no es suficiente en algunos casos. Por ello, cuando la inmunidad innata no consigue controlar la infección, se activa la inmunidad adaptativa, la cual sí es capaz de reconocer las diferencias entre los microorganismos, toxinas o antígenos y dar una respuesta específica. Además, cuenta con memoria inmunológica, es decir, que reconoce los patógenos que ya han sido combatidos en infecciones anteriores para atacarlos con mayor eficacia (14).

En cada uno de los tipos de inmunidad se ponen en acción diferentes células y proteínas que abordan la infección de determinada manera, dando lugar a gran parte de los síntomas de la enfermedad. Sin embargo, en ambos casos, uno de los principales mecanismos es la inflamación, la cual es posible gracias a la secreción de un tipo de proteína llamada citoquina o interleuquina (IL) (14).

En algunos casos, esta respuesta inflamatoria es descontrolada y se produce una tormenta de citoquinas, en la que no solo se ataca a los virus y células infectadas, sino que también se lesiona los tejidos y órganos sanos (14). Esta respuesta es la protagonista de los casos más severos de la COVID-19, y puede inducir, a su vez, un fallo multiorgánico (FMO) (15,16), caracterizado por la alteración de más de un sistema orgánico vital, principalmente los sistemas respiratorio, cardiovascular y nervioso (17).

1.2.3. CARACTERÍSTICAS CLÍNICAS DE LA COVID-19

La respuesta del sistema inmunológico ante el virus es la que determina, en parte, los síntomas de la enfermedad y su gravedad. Además, la presencia de comorbilidades (p. ej., obesidad, hipertensión, enfermedades pulmonares etc.) y las características demográficas como una edad avanzada, el género masculino, así como el tabaquismo o alcoholismo son factores de riesgo para tener síntomas más graves (18,19). Por lo tanto, la presentación de la COVID-19 puede variar desde un cuadro asintomático, que representa el 40% de todos los casos, hasta personas que desarrollan síntomas críticos, o incluso puede causar la muerte (20).

Según la Organización Mundial de la Salud (OMS) (21) los síntomas más comunes de la COVID-19 son la fiebre, escalofríos y dolor de garganta, aunque también pueden aparecer otros síntomas como dolores musculares, fatiga, congestión nasal, dolor de cabeza, mareo, tos, opresión o dolor en el pecho, dificultad para respirar, anosmia y ageusia, pérdida de apetito, náuseas, vómitos, dolor abdominal o diarrea. Estos síntomas suelen ser parte de un cuadro leve de la enfermedad, y normalmente aparecen entre 2 y 7 días después de la exposición al virus, y suelen durar aproximadamente una semana.

En los casos moderados a graves, los pacientes desarrollan neumonía e/o hipoxia, y, por lo general, requieren hospitalización, mientras que en los casos críticos se puede producir una insuficiencia respiratoria, shock séptico o un FMO, lo que conlleva el ingreso de la persona en la Unidad de Cuidados Intensivos (UCI) y, por consiguiente, la asistencia respiratoria mecánica, y en casos mucho más severos incluso la muerte (22,23).

A pesar de que el sistema respiratorio, donde hay una mayor expresión de la ECA2 (24), es el principal afectado en esta enfermedad, existe un porcentaje de pacientes que

cursan con alteraciones cardíacas, gastrointestinales, renales, hepáticas, endocrinológicas, dermatológicas, oculares, neurológicas o neuropsicológicas (25).

1.3. Alteraciones neurológicas

Según la literatura más reciente, entre un 35% y 85% de los pacientes infectados por el SARS CoV-2 presentan alteraciones del sistema nervioso, tanto periférico (SNP) como central (SNC) (26). Las alteraciones del SNP tienden a ser las más leves e incluyen principalmente anosmia, ageusia y mialgia (27,28), mientras que las lesiones del SNC dan lugar a alteraciones más graves como la pérdida del conocimiento, enfermedad cerebrovascular isquémica, encefalopatía, encefalopatía hemorrágica necrotizante aguda, encefalitis, meningitis, ataques epilépticos y enfermedades desmielinizantes como el síndrome de Guillain Barré (27–30). La presencia de estas alteraciones neurológicas en la COVID-19 empeoran el pronóstico de los pacientes. Por ejemplo, se ha visto que la encefalopatía se relaciona con ingresos hospitalarios más largos, una peor funcionalidad tras el alta y una mayor tasa de mortalidad. De igual manera, casi un tercio de los pacientes infectados por SARS CoV-2 y que presentan enfermedad cerebrovascular fallecen (31).

Aunque los mecanismos que subyacen a la alteración neurológica tras la infección por el SARS CoV-2 siguen siendo motivo de debate, hay tres teorías que han obtenido un mayor apoyo científico. Una primera hipótesis postula que hay una infección directa del virus al cerebro; algunos autores indican que el acceso se da mediante la mucosa nasal, la lámina cribiforme y el bulbo olfatorio, y que por ello uno de los síntomas es la anosmia (25), mientras que otros sostienen que se produce a través de las terminaciones nerviosas del SNP o del torrente sanguíneo (32,33). Independientemente de la vía de acceso, en

diversos estudios se ha reportado la presencia de partículas víricas tanto en el líquido cefalorraquídeo como en el cerebro de personas infectadas (34,35). La segunda hipótesis propone que el daño cerebral es el resultado de la respuesta inflamatoria orquestada por la tormenta de citoquinas, que altera el sistema vascular del cerebro y la barrera hematoencefálica (36). Una última hipótesis sugiere que el bloqueo del flujo sanguíneo en el cerebro causa hipoxia, que provoca lesiones en el tejido del cerebro y da lugar a manifestaciones neurológicas y cognitivas (37).

1.4. Alteraciones neuropsicológicas

De manera similar a lo que sucede típicamente en estas afecciones, el daño neurológico mediado por el SARS-CoV-2 puede provocar secuelas a corto y largo plazo que afectan tanto el funcionamiento cognitivo como la salud mental de los pacientes. No obstante, se ha visto que incluso las personas que han tenido presentaciones leves de la enfermedad y que no han requerido de hospitalización también pueden presentar secuelas cognitivas y emocionales tras ser infectados por el virus. De hecho, la presencia de síntomas como fatiga mental, problemas de concentración, confusión, olvidos recurrentes, pensamiento lento e incluso desorientación hacen parte del cuadro clínico conocido coloquialmente como “niebla mental” (38,39). Aunque estos síntomas pueden desaparecer poco después de recuperarse de la enfermedad, muchas personas continúan experimentándolos durante más de dos meses después de la infección. La presencia de estos problemas cognitivos, junto con otros síntomas físicos/somáticos (p. ej., fatiga, problemas respiratorios y digestivos) y emocionales (p. ej., ansiedad, depresión, apatía) a largo plazo es lo que se ha denominado como “síndrome post-COVID persistente” o “COVID persistente” (38,39).

A pesar de que las secuelas de la COVID-19 tienen un fuerte impacto en el funcionamiento y la calidad de vida de las personas (40), gran parte de la investigación en este ámbito se centra principalmente en reportar las alteraciones a través de estudios de casos (41) y desde una perspectiva puramente diagnostica. Sin embargo, son escasos los estudios en los que se utilizan otras herramientas para examinar dichas secuelas, como las pruebas neuropsicológicas, la resonancia magnética funcional (RMf) u otros instrumentos estandarizados/validados.

Por ejemplo, Zhou et al. (2020)(42) encontraron que, en comparación con los controles sanos, los 29 pacientes de su muestra obtuvieron peores resultados en las pruebas que evaluaban atención sostenida. Por su parte, Ferrucci et al. (2021) (43) realizaron una evaluación neuropsicológica a 53 pacientes a los 5 y 12 meses después de ser dados de alta del hospital. Los autores encontraron que el 63.2% de los participantes obtuvo un bajo rendimiento en al menos una de las pruebas. Aunque las puntuaciones mejoraron al año, la velocidad de procesamiento y la memoria verbal y espacial continuaron afectadas. Poletti et al. (2021) (44) reportaron resultados similares, donde un alto porcentaje de los pacientes con COVID-19 obtuvo puntuaciones bajas en al menos un dominio cognitivo al mes (79%) y a los 3-6 meses (75%) después de la infección. Además, al compararlos con controles sanos, los pacientes rindieron peor en las pruebas de velocidad de procesamiento y coordinación motora. Miskowiak et al. (2021) (45) también encontraron que entre el 59% y 65% de su muestra de 29 participantes con COVID-19 mostró alteraciones cognitivas, principalmente en memoria verbal y funciones ejecutivas 3-4 meses después del alta hospitalaria. Más recientemente, Schild et al. (2023) (46), en un estudio transversal, encontraron que de los 52 pacientes con síndrome post-COVID-19 que evaluaron, más de la mitad presentaban un trastorno neurocognitivo,

con alteraciones en la memoria y las funciones ejecutivas (60.7%), atención (51.6%), lenguaje (35.5%) y las habilidades perceptivas y motoras (29%).

Otros grupos de investigación han explorado la presencia de síntomas persistentes tras la COVID-19 a través de autoreportes en encuestas en línea. Así pues, Orrú et al. (2021) (47) encontraron que los problemas de concentración estaban dentro de los síntomas más reportados por los 507 pacientes que contestaron a su encuesta, junto con el dolor de cabeza, la fatiga y la mialgia. Davis et al. (2021) (48) recogieron información sobre la prevalencia de 203 síntomas en una muestra de 3762 personas, de las cuales 1020 habían tenido COVID-19 confirmado por un test y el resto sospechaba haber tenido la enfermedad sin haber sido comprobada. Estos autores encontraron que, incluso 7 meses después de la infección gran parte de su muestra continuaba presentando síntomas, principalmente problemas cognitivos (88%), fatiga (86.7%) y malestar después de hacer esfuerzo (85.9%). En el estudio de Frontera et al. (2021) (49) los 999 pacientes con COVID persistente reportaron principalmente ansiedad, confusión mental, dificultad para concentrarse y olvido. Además, encontraron que las mujeres jóvenes hispanas eran más vulnerables a desarrollar estos síntomas. Ziauddeen et al. (2022) (50) obtuvieron datos acerca de los síntomas persistentes de 2550 participantes de Reino Unido, y encontraron que el 88.8% refería síntomas cardiopulmonares, cognitivos y fatiga. Además, una mayor gravedad de los síntomas se asoció con ser mujer, tener ingresos más bajos y tener problemas de salud previos a la infección por el SARS CoV-2. En Malasia, Moy et al. (2022) (51) encontraron que el 44% de los 732 pacientes que respondieron a su encuesta reportaron síntomas persistentes, siendo la fatiga, la confusión mental, la depresión, la ansiedad y el insomnio los más prevalentes. Al igual que en los estudios de Frontera et al. (2021) (49) y Ziauddeen et al. (2022) (50), estos

autores también reportaron que las mujeres tenían mayor riesgo de presentar estas secuelas. Los resultados de Kim et al. (2022) (52) son muy similares a los de Moy et al. (2022) (51) en cuanto a que los síntomas persistentes más reportados por su muestra de 454 personas fueron la fatiga, los problemas de concentración y memoria, depresión y ansiedad. Por último, en la encuesta de Mclaughlin et al. (2023) (53) 253 personas de Escocia indicaron que los síntomas persistentes más prevalentes eran malestar por esfuerzo (95%), fatiga (85%) y problemas cognitivos (68%).

Aunque una de las mayores limitaciones del uso de encuestas en línea es que no se puede garantizar la veracidad de lo informado por los participantes, es una herramienta muy útil y válida para obtener información de muestras muy grandes y de diversas regiones del mundo, lo que facilita la representatividad de la población y la generalización de los resultados.

Por otra parte, varios estudios de neuroimagen han concluido que estas alteraciones neuropsicológicas podrían estar relacionadas con lesiones estructurales y cambios metabólicos en el cerebro, principalmente en la sustancia blanca (54). Asimismo, algunos estudios han encontrado que la conectividad estructural y funcional también se encuentra alterada en estos pacientes. Por ejemplo, Fischer et al. (2022) (55) compararon la conectividad funcional y estructural de 11 pacientes con trastorno de la conciencia (DoC, por sus siglas en inglés) debido a la COVID-19, 18 pacientes con DoC por traumatismo craneoencefálico severo (TCE) y 14 controles sanos. Dentro de los hallazgos, se destaca que, en comparación con los controles sanos, los pacientes con COVID-19 mostraron una reducida conectividad de la red neuronal por defecto (DMN), así como una reducción en la conectividad entre la DMN y la red de saliencia (SN). De manera similar, Díez-Cirarda et al. (2022) (56) realizaron un estudio transversal de neuroimagen

funcional y estructural, además de una evaluación neuropsicológica a 86 pacientes con COVID persistente y 36 controles sanos, encontrando alteraciones principalmente en atención y memoria, así como hipoconectividad entre la circunvolución parahipocampal izquierda y derecha, y entre el cerebelo III izquierdo y la corteza orbital superior frontal izquierda y derecha.

A excepción de la investigación de Fischer et al. (2022) (55) y Díez-Cirarda et al. (2022) (56), la mayoría de los estudios realizados con neuroimagen, incluidos aquellos que combinan esta herramienta con la neuropsicología (57,58), se centran en la evaluación de cambios estructurales o metabólicos en el cerebro de los pacientes con COVID-19 (41,54,59,60), sin incluir la evaluación funcional.

El estudio de la conectividad funcional, y en concreto, en estado de reposo (fMRI-resting state) ha demostrado tener múltiples ventajas tanto en investigación como en la clínica y ser una herramienta sumamente útil para la evaluación de diversas enfermedades del SNC (61), las cuales parecen tener la etiología en desordenes de la conectividad cerebral (62–66). Por ello, el uso de estas técnicas de neuroimagen y su combinación con el examen neuropsicológico podría suponer un avance para la comprensión de alteraciones neuropsicológicas que presentan algunas personas que han tenido COVID-19. Además, teniendo en cuenta que muchos de estos pacientes presentan secuelas a largo plazo, es preciso realizar estudios longitudinales.

1.5. Limitaciones de la literatura

No cabe duda de que la comunidad científica se ha volcado en el estudio del SARS CoV-2 y la COVID-19 desde el momento en el que se reportaron los primeros casos. Así, en un tiempo record, los investigadores pudieron secuenciar el genoma del virus y

conocer su mecanismo de infección, algo sumamente importante para la búsqueda de opciones terapéuticas. Además, el desarrollo de pruebas diagnósticas con alta fiabilidad y especificidad facilitó la detección de las personas realmente infectadas por el virus, permitiendo la descripción de las características clínicas de la enfermedad. En última instancia, el desarrollo de diferentes vacunas en tan poco tiempo ha sido un verdadero hito de la ciencia.

Por otro lado, la investigación ha proporcionado información muy relevante sobre las posibles secuelas neuropsicológicas de las personas que han tenido COVID-19, no obstante, se requiere de más estudios en este tema que suplan las limitaciones que tiene la literatura disponible hasta la fecha. En primer lugar, la mayoría de los estudios que evalúan la presencia de síntomas persistentes tras la COVID-19 a través de encuestas en línea no utilizan instrumentos estandarizados/validados, sino que incluyen preguntas creadas por los propios autores. Además, la muestra de la mayor parte de los estudios es relativamente pequeña a pesar del alcance que puede tener este tipo de diseños, y proviene principalmente de países anglosajones, sin incluir personas de otras regiones del mundo. De hecho, tal y como ocurre en otros en otros ámbitos científicos, los estudios que incluyen poblaciones de habla hispana son mínimos. Esto supone una gran limitación teniendo en cuenta que los países latinoamericanos, donde se concentra la mayor parte de los hispanohablantes, han sido gravemente afectados por la pandemia de COVID-19, tanto a nivel sanitario, quedando patentes las debilidades de los sistemas de salud, como a nivel socioeconómico, aumentando las desigualdades existentes en estos países. Cabe señalar también que son pocos los estudios que exploran otros aspectos relevantes más allá de los propios síntomas, como factores de riesgo para el desarrollo de las secuelas y variables que intensifican los síntomas.

En cuanto a los estudios que evalúan las secuelas cognitivas a través de técnicas más directas y objetivas como la evaluación neuropsicológica y/o las técnicas de neuroimagen, es preciso señalar que son muy limitados los que combinan estas dos herramientas de evaluación. Además, la gran mayoría de estudios de neuroimagen, incluidos los pocos que también incluyen medidas cognitivas, evalúan cambios estructurales o metabólicos en el cerebro, dejando de lado la conectividad funcional.

Finalmente, una de las mayores limitaciones se relaciona con el diseño transversal que tiene la mayoría de los estudios. Teniendo en cuenta la presencia de las secuelas a corto y a largo plazo de la enfermedad, se hace necesario realizar estudios longitudinales que permitan seguir la evolución de los síntomas y comprenderlos mejor, con el objetivo último de poder desarrollar programas de manejo e intervención que mejoren la funcionalidad y la calidad de vida de estas personas.

1.6. Justificación del trabajo

En la presente tesis se han llevado a cabo dos investigaciones paralelas. En la primera, se recogió información, a través de una encuesta en línea distribuida globalmente, sobre la presencia de síntomas neuroconductuales antes, durante y después de la infección por el SARS CoV-2. Estos síntomas fueron reportados a través del *Neurobehavioral Symptom Inventory (NSI)*. Además, se recogieron datos demográficos e información sobre la gravedad de los síntomas y las intervenciones médicas recibidas. De esta investigación se han publicado dos artículos, que se incluyen en el capítulo 2 y capítulo 3 de la tesis.

En el primer artículo, se comparó la presencia de los síntomas neuroconductuales reportados por los participantes en los tres tiempos, permitiendo observar su evolución.

Además, se evaluaron los posibles factores de riesgo para el desarrollo de dichos síntomas. Finalmente, dado que se cuenta con una muestra grande de personas de diferentes países, se hizo una comparación de la presencia de los síntomas por regiones del mundo.

En el segundo artículo, se aplicó un novedoso análisis de redes psicométricas que permitió examinar las interconexiones entre los síntomas neuroconductuales persistentes de la COVID-19 (cognitivos, afectivos y somáticos). Para ello, se utilizó únicamente la muestra de participantes hispanohablantes infectados por el SARS CoV-2 (n=650) y se comparó con un grupo de personas, también hispanohablantes, que habían completado el NSI antes de la pandemia (n=443), como parte de un estudio anterior.

Por último, en la segunda investigación, la muestra estuvo compuesta por un grupo de pacientes ingresados en la UCI a causa de un FMO. La mitad de los pacientes tuvieron el FMO por la infección del SARS CoV-2 y la otra mitad por insuficiencia respiratoria, shock cardiogénico o shock séptico. Además, se incluyó una muestra de participantes sanos. A todos ellos se les evaluó, a los 6 y 12 meses después del alta de la UCI de los pacientes, mediante una batería de pruebas neuropsicológicas y resonancia magnética funcional, con el objetivo de comparar el rendimiento neuropsicológico, los cambios en la conectividad funcional y la relación entre ambas medidas.

1.7. Objetivos

1.7.1. OBJETIVO PRINCIPAL

Estudiar los cambios en el funcionamiento neuroconductual, cognitivo y de conectividad cerebral funcional tras la infección por el SARS CoV-2.

1.7.2. OBJETIVOS ESPECÍFICOS

Estudio 1

Objetivo 1. Comparar la presencia de síntomas neuroconductuales (cognitivos, afectivos y somáticos), evaluados a través del NSI, en una gran muestra de personas antes de la infección por el SARS CoV-2, durante la infección y después (al momento de participar en el estudio).

Objetivo 2. Examinar los factores de riesgo para el aumento de los síntomas neuroconductuales de la COVID-19, incluidas las variables demográficas, la gravedad de la infección y las características de la intervención.

Objetivo 3. Comparar la presencia de los síntomas neuroconductuales de la COVID-19 entre las regiones de Europa y Asia Central, Latinoamérica y el Caribe, Norte América y África Subsahariana.

Estudio 2

Comparar los patrones de interconectividad entre los síntomas neuroconductuales, a través del análisis de redes psicométricas, entre una muestra de individuos hispanohablantes afectados por la COVID-19 y una muestra de personas controles sin COVID-19.

Estudio 3

Objetivo 1. Comparar el funcionamiento cognitivo dos grupos de individuos con fallo multiorgánico (FMO), uno por COVID-19 y otro por otra causa, y un grupo de controles sanos a los 6 y 12 meses después del alta de la UCI.

Objetivo 2. Evaluar las diferencias de conectividad funcional entre el grupo con COVID-19 y el grupo de controles sanos, corrigiendo por el grupo FMO.

Objetivo 3. Evaluar la asociación entre el funcionamiento cognitivo y la conectividad funcional en los tres grupos.

CAPÍTULO 2. MODERATE, LITTLE, OR NO IMPROVEMENTS IN NEUROBEHAVIORAL SYMPTOMS AMONG INDIVIDUALS WITH LONG COVID: A 34-COUNTRY RETROSPECTIVE STUDY[2]

[2] Ramos-Usuga, D., Perrin, P. B., Bogdanova, Y., Olabarrieta-Landa, L., Alzueta, E., Baker, F. C., Iacovides, S., Cortes, M., & Arango-Lasprilla, J. C. (2022). Moderate, Little, or No Improvements in Neurobehavioral Symptoms among Individuals with Long COVID: A 34-Country Retrospective Study. International journal of environmental research and public health, 19(19), 12593. https://doi.org/10.3390/ijerph191912593

Some individuals who have had COVID-19 develop a range of symptoms that last for several months after infection, a syndrome known as long COVID. These symptoms, which vary widely in nature, interfere with the daily functioning of these individuals, significantly worsening their quality of life. Due to its significant implications, various research efforts have been undertaken with the goal of obtaining as complete a picture as possible of this pathology and thus, developing therapeutic options to address this issue. Therefore, the present study was conducted, in which neurobehavioral symptoms (cognitive, affective, and somatic) were evaluated in a broad population infected by SARS-CoV-2, using the Neurobehavioral Symptom Inventory (NSI). This inventory is validated and is the most widely used tool to assess these types of symptoms in both clinical and non-clinical populations. Along with the NSI, questions related to demographic variables, medical interventions, and the severity of the disease were included, which have allowed for the determination of certain risk factors for the development of these sequelae.

2.1. Methods

2.1.1. PARTICIPANTS

To participate in this retrospective study, the inclusion criteria were: (a) age 18 years or older, and (b) self-report of having tested positive for COVID-19 through a viral and/or antigen test. A total of 1,049 participants completed the survey. Of those, 23 participants were removed who did not respond to the item asking if they had tested positive for COVID-19, 8 who did not report a diagnosis year, 10 who reported a diagnosis date before 1 March, 2020, and 7 who reported a diagnosis date after the date they took the survey or on a date that had not occurred yet. Therefore, the final sample included 1,001 participants.

2.1.2. MEASURES

Through an online survey, the following information was collected: (a) demographic information (gender, age, romantic relationship status, educational background, work status, and country of residence); (b) pre-existing chronic health condition status; (c) COVID-19 infection characteristics and treatment (date of diagnosis, severity of symptoms, and COVID-19 details of medical intervention).

The NSI (67) was used to evaluate persistent symptoms. It is a self-report questionnaire used to assess cognitive, affective, and somatic neurobehavioral symptoms in people with post-concussion syndrome. It consists of 22 items that are scored on a 5-point Likert scale according to symptom severity (0 = None; 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very Severe) (See Anexo I). In the current survey, participants were asked to report the presence of each symptom at three different time-points: before COVID-19 diagnosis, during the infection, and now (when completing the survey). The English and previously validated Spanish version of the NSI were used (68), depending on the global region where participants lived.

2.1.3. PROCEDURE

A team of researchers with expertise in COVID-19 from Spain and the United States of America developed the survey, originally in English and then translated into Spanish. The survey was hosted on Qualtrics and, once the study was approved by the Ethics Committee of the Public University of Navarra, it was distributed through (a) professional mailing lists and collaborators' contact networks; (b) Facebook groups and advertisements; and (c) a database of individuals with COVID-19 from one of the collaborating centers (Icahn School of Medicine at Mount Sinai in New York City, USA).

Data collection took place from 9 March to 7 June, 2021. Individuals were invited to participate if they had previously tested positive for COVID-19.

Information about the study was included in the first page of the survey, the social media advertisements, and the recruitment email. This information emphasized that participation was voluntary, data would be anonymous, and there was no financial compensation for participation. To proceed to the survey, informed consent was provided by an affirmative answer to the question "Do you want to participate in this study?" The study was conducted in compliance with the declaration of Helsinki.

2.1.4. DATA ANALYSES

All descriptive statistics and analyses were conducted using IBM SPSS Statistics 27. In order to determine whether there were differences in neurobehavioral symptoms by domain (subscale) and by symptom (item) as recalled before participants' COVID-19 diagnosis, during the infection, and now (when completing the survey), a series of paired-samples t-tests was conducted. In each analysis, the independent variable was time (before COVID-19 diagnosis, during the infection, and now), and the dependent variable was the NSI subscale score or item. For each analysis, a Cohen's d effect size was calculated taking into account the longitudinal correlation between subtotal scores or items. Because of the large sample size, Cohen's d cutoffs and descriptors of 0.2 (small), 0.5 (large), and 0.8 (large) were used rather than p-values.

In order to investigate demographic characteristics, presence of a chronic health condition, COVID-19 medical intervention characteristics, COVID-19 symptom severity, and days since COVID-19 diagnosis as predictors of current neurobehavioral symptoms, three hierarchical stepwise linear regressions were computed with neurobehavioral

symptom domain (cognitive, affective, or somatic) as the outcome variable. For reference, a bivariate correlation matrix was created between these sets of relationships as well. In these regressions, demographic characteristics (man vs. woman or non-binary/trans, age, education level [with continuous coding as specified in Table 2.1], employed vs. unemployed [with full-time, part-time, and student coded as "employed" and all other categories coded as "unemployed"], and romantically partnered vs. not partnered) and whether participants reported another chronic health condition were included as Step 1 variables. Step 2 included COVID-19 intervention characteristics (hospitalization, oxygen therapy, Intensive Care Unit (ICU) stay, noninvasive ventilation, invasive ventilation, and induced coma), participants' self-reported level of COVID-19 symptom severity while positive, and number of days since the COVID-19 diagnosis.

Table 2.1. Sociodemographic characteristics of the study cohort (N=1001).

Variable	Value	
Age (years), M[1], SD[2]	43.5	12
Gender, N, %		
Man	213	21
Woman	782	78
Non-binary, transgender, or other	6	1
Country region, N, %		
Europe and Central Asia	147	15
Latin America and the Caribbean	516	51
North America	218	22
South/East Asia and the Pacific	4	0.4
Sub-Saharan Africa	116	12
Work status, N, %		
Full-time employed	571	57
Part-time employed	145	14
On leave	63	6
Volunteering	10	1
Student	48	5
Unemployed	56	6
Retired	42	4
Staying at home/homemaker	49	5
Disability	17	2
Highest level of education completed, N, %		
Some primary education (elementary school)	5	0.5
Completed primary education (graduated elementary school)	5	0.5

Some secondary education (high school)	10	1
Completed secondary education (graduated high school)	57	6
Trade/technical/vocational training	90	9
Some undergraduate education (college or university)	121	12
Completed undergraduate education	301	30
Some postgraduate education	145	15
Completed postgraduate education (masters or doctorate)	267	27
Romantic relationship status, N, %		
Partnered	717	72
Single	284	28
Past chronic health condition, N, %		
At least one past chronic health conditions	586	59
No other chronic health condition	415	41
Hospitalized, N, %	111	11
Oxygen Therapy, N, %	82	8
ICU[3] Stay, N, %	25	3
Noninvasive Ventilation, N, %	15	2
Invasive Ventilation, N, %	7	.7
Induced Coma, N, %	5	.5
Days from COVID-19 diagnosis M, SD	175	118
Severity of the symptoms while positive for COVID-19, N, %		
No symptoms (asymptomatic)	35	4
Some mild symptoms (no need for treatment)	309	31
Moderate symptoms (needed treatment, but no hospitalization)	546	55

Severe symptoms (hospitalization)	84	8
Critical symptoms (intensive care unit)	27	3

Note: [1] Mean; [2] Standard Deviation; [3] Intensive care unit

Then, neurobehavioral symptom category scores were compared by global region using analyses of covariance (ANCOVAs). Demographics included in Step 1 of the previous regressions were included as covariates. Participants from South Asia, as well as East Asia and the Pacific were excluded from the ANCOVAs because the small group size precluded meaningful comparisons (n = 4).

2.2. Results

2.2.1. SOCIODEMOGRAPHIC CHARACTERISTICS

A total of 1,001 participants from 34 different countries (see Figure 2.1) completed the survey. Most of the participants were women (n= 782; 78%) with a mean age of 43.5 years (SD= 11.9), and with university studies (n= 713; 71%). More details of the sociodemographic information can be found in Table 2.1.

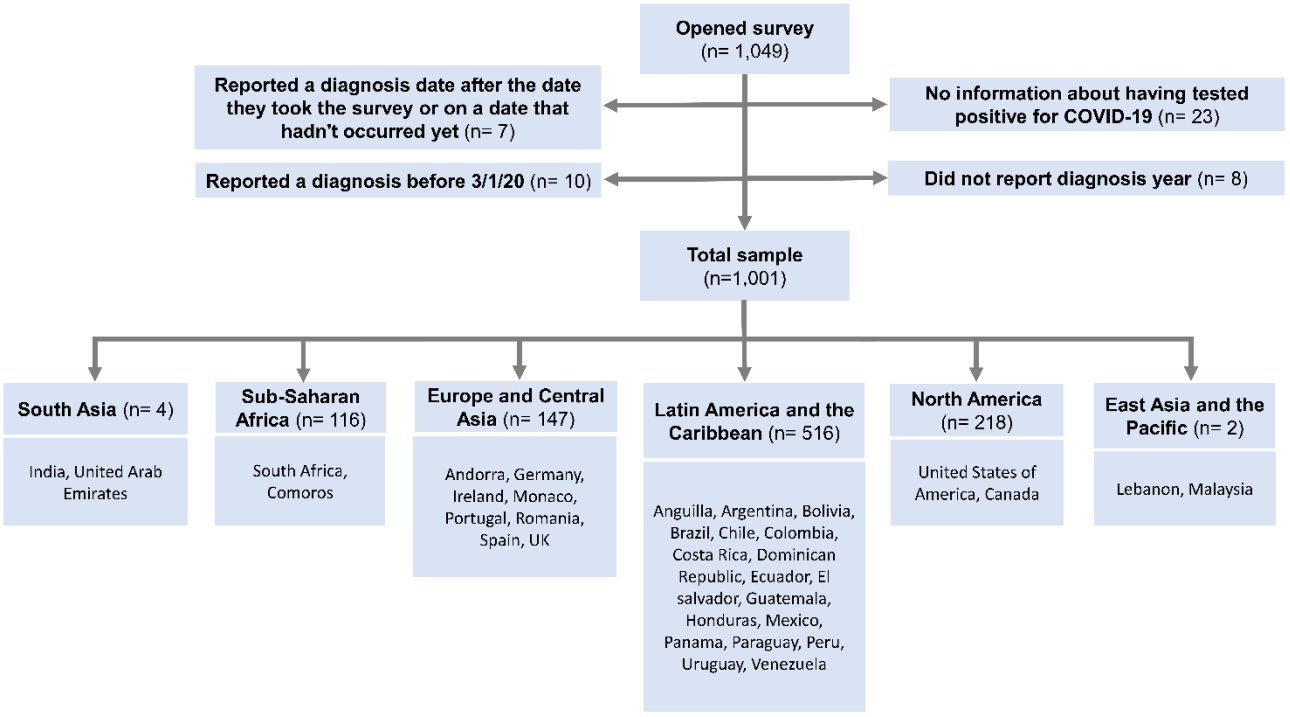

Figure 2.1. Sample Size by countries.

2.2.2. CHANGES IN NEUROBEHAVIORAL SYMPTOMS OVER TIME

The results of the paired-samples t-tests comparing neurobehavioral symptoms before the COVID-19 diagnosis, during the infection, and now (when completing the survey) are presented in Table 2.2. At the symptom domain level, participants reported large-sized increases during vs. before infection in all domains (somatic, cognitive, and affective). Participants reported a medium-sized improvement (during infection vs. now) in somatic symptoms and a small-sized improvement in affective symptoms, but the improvement in cognitive symptoms was very minor and did not reach a small-sized effect.

Table 2.2. Neurobehavioral symptoms before COVID-19 diagnosis, during infection, and now (N=1001).

Neurobehavioral Symptom	*M*(*SD*) Before	*M*(*SD*) During	*M*(*SD*) Now	*d* Before vs. During	*d* Before vs. Now	*d* During vs. Now
Somatic	13.33(3.25)	21.74(7.96)	18.20(6.92)	-1.15	-0.76	0.61
Dizzy	1.22(0.51)	2.15(1.09)	1.75(0.92)	-0.87	-0.58	0.40
Balance	1.14(0.43)	1.79(1.03)	1.53(0.82)	-0.66	-0.51	0.31
Coordination	1.16(0.44)	1.76(1.00)	1.56(0.84)	-0.63	-0.51	0.25
Nausea	1.13(0.44)	1.89(1.10)	1.48(0.84)	-0.73	-0.43	0.44
Vision	1.36(0.65)	1.86(1.00)	1.82(0.96)	-0.57	-0.55	0.06
Light Sensitivity	1.29(0.63)	1.80(1.06)	1.60(0.90)	-0.54	-0.40	0.26
Hearing	1.22(0.55)	1.44(0.78)	1.45(0.78)	-0.35	-0.37	-0.02
Noise Sensitivity	1.27(0.58)	1.75(1.02)	1.66(0.92)	-0.54	-0.48	0.12
Numb/Tingling	1.27(0.55)	1.94(1.09)	1.81(0.99)	-0.65	-0.58	0.14
Taste/Smell	1.07(0.38)	2.85(1.45)	1.80(1.07)	-1.21	-0.68	0.84
Appetite	1.19(0.52)	2.50(1.20)	1.72(0.95)	-1.05	-0.55	0.67
Cognitive	5.09(1.68)	8.74(4.15)	8.21(3.94)	-0.91	-0.81	0.17

Concentration	1.29(0.56)	2.43(1.22)	2.20(1.15)	-0.95	-0.80	0.22
Forgetfulness	1.37(0.59)	2.22(1.17)	2.23(1.11)	-0.76	-0.78	-0.01
Making Decisions	1.22(0.49)	1.88(1.09)	1.75(0.98)	-0.65	-0.57	0.17
Slowed Thinking	1.21(0.51)	2.20(1.21)	2.03(1.12)	-0.85	-0.75	0.17
Affective	10.52(3.57)	17.38(6.04)	15.33(6.13)	-1.24	-0.86	0.46
Headaches	1.71(0.87)	2.87(1.19)	2.16(1.08)	-0.93	-0.41	0.63
Fatigue	1.36(0.63)	3.35(1.18)	2.64(1.20)	-1.61	-1.05	0.62
Sleep	1.50(0.78)	2.35(1.29)	2.24(1.18)	-0.68	-0.69	0.11
Anxious	1.63(0.78)	2.48(1.19)	2.24(1.09)	-0.77	-0.61	0.26
Depressed	1.43(0.72)	2.23(1.19)	2.04(1.10)	-0.74	-0.60	0.20
Irritability	1.49(0.68)	1.99(1.03)	1.98(1.01)	-0.54	-0.54	0.02
Frustration	1.41(0.64)	2.10(1.16)	2.03(1.10)	-0.66	-0.62	0.09

Within the somatic symptom domain, the largest symptom increase during vs. before infection occurred with changed in taste/smell, appetite, and dizziness. Changes in taste/smell and appetite-related symptoms showed large-sized improvements (now vs. during infection). Estimated marginal means of each somatic symptom can found in Figure 2.2. Within the cognitive symptom domain, the large-sized symptom increases during vs. before infection occurred with concentration and slowed thinking. All four cognitive symptoms showed extremely low levels of improvement (now vs. during infection) with only concentration symptoms just surpassing the threshold for a small-sized effect and forgetfulness showing no improvement. Estimated marginal means of each cognitive symptom can found in Figure 2.3. Within the affective symptom domain, large-sized symptom increases during vs. before infection occurred with fatigue and headaches. These two symptoms also showed medium-sized improvements (now vs. during infection), although improvements in difficulty falling or staying asleep, irritability, and frustration tolerance failed to reach a small-sized effect. Estimated marginal means of each affective symptom can found in Figure 2.4.

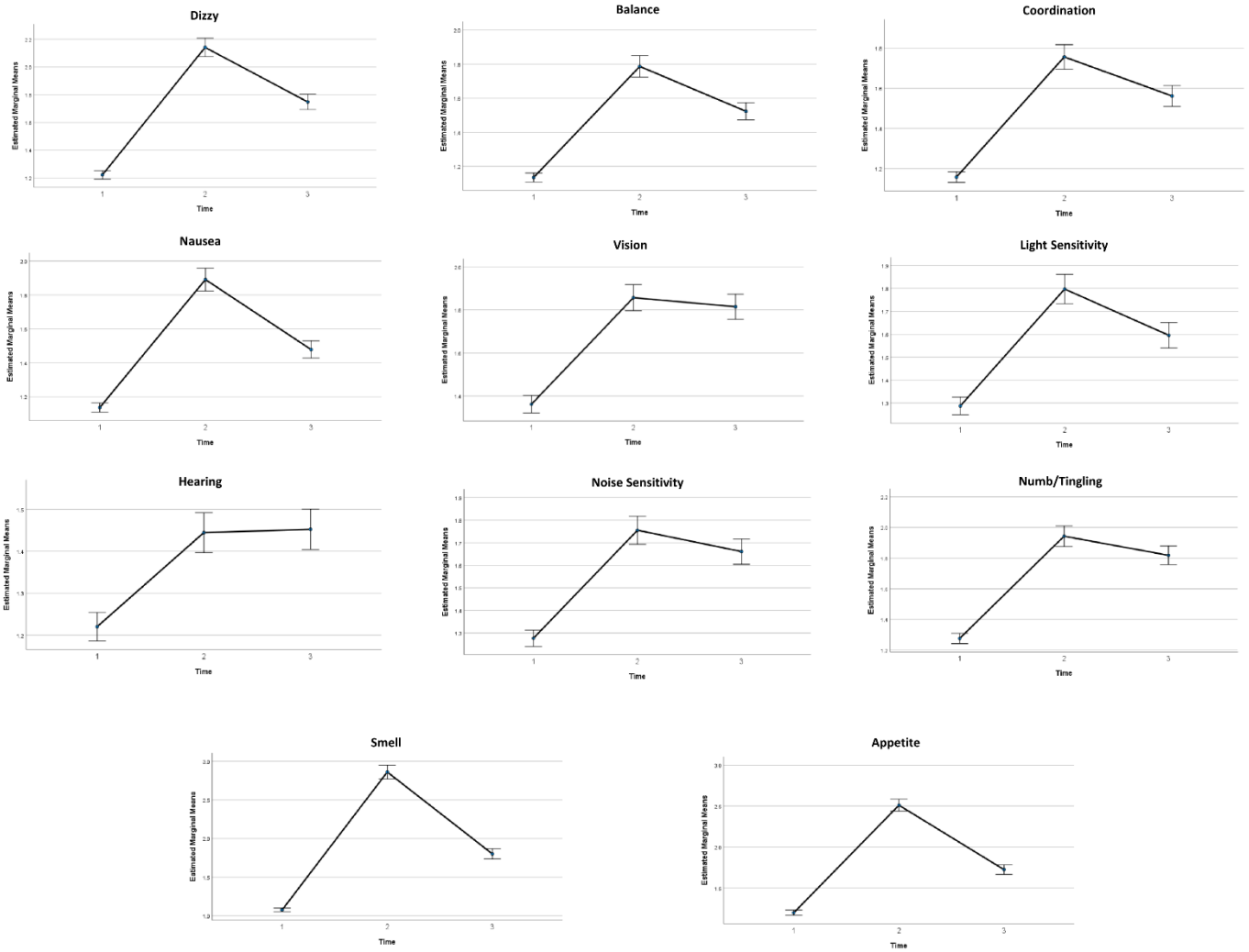

Figure 2.2. Estimated marginal means of somatic symptoms.

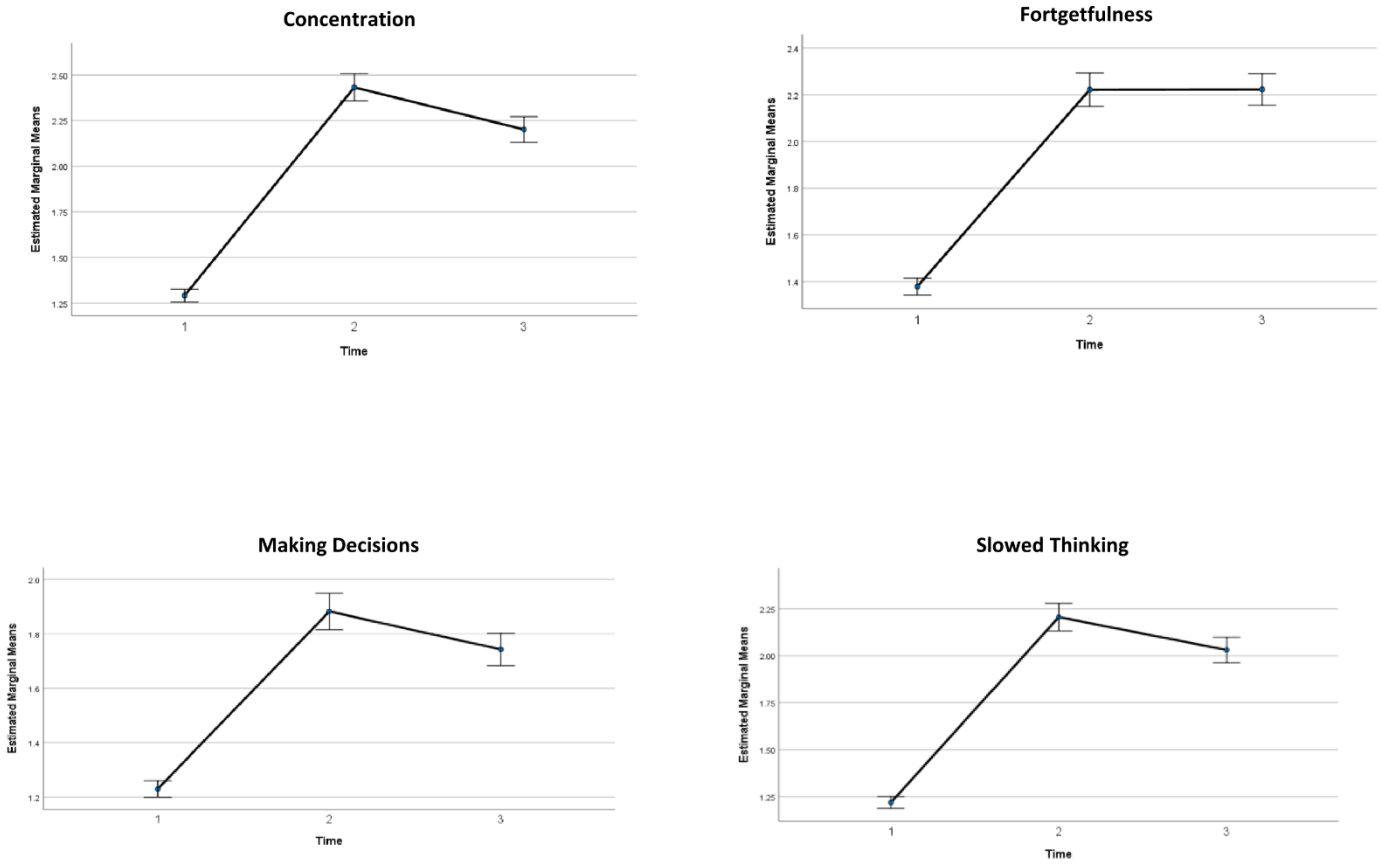

Figure 2.3. Estimated marginal means of cognitive symptoms.

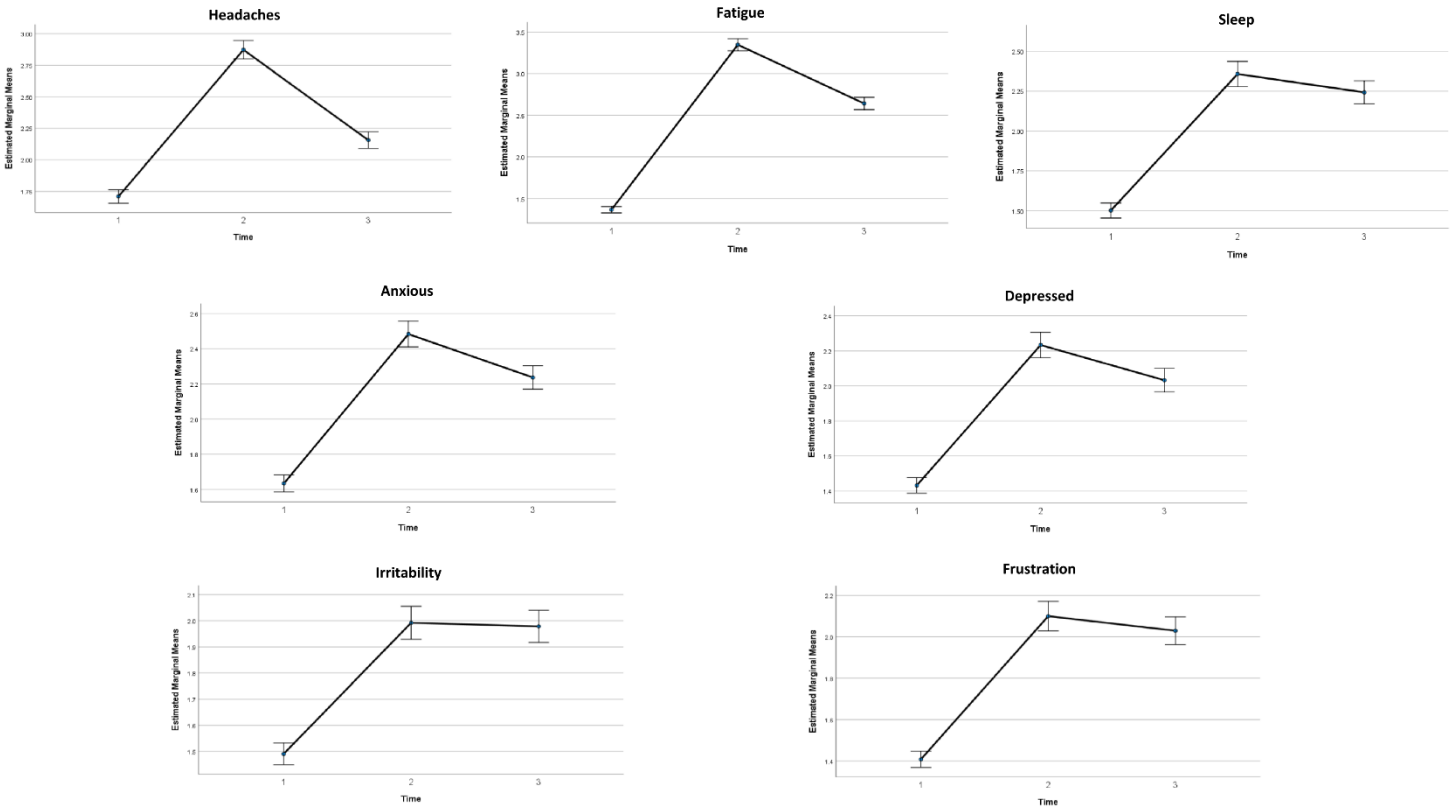

Figure 2.4. Estimated marginal means of affective symptoms.

In the first hierarchical linear regression predicting current somatic symptom severity, Step 1 was statistically significant, $F(6, 994) = 16.56$, $R2 = 0.091$, $p < 0.001$ (Table 2.3 with standardized β weights). Greater somatic symptom severity was significantly and uniquely associated with female or trans vs. male gender, lower education level, being unemployed, and having another chronic health condition. With the addition of COVID-19 intervention characteristics, COVID-19 symptom severity, and number of days since the COVID-19 diagnosis as a predictor in Step 2, the overall model was still statistically significant, $F(14, 986) = 18.80$, $R2 = 0.211$, $p < 0.001$. Within this step, all previously significant predictors were still statistically significant and associations in the same directions, with the addition of greater age now significantly predicting lower somatic symptom severity. Greater somatic symptom severity was uniquely associated with higher COVID-19 severity while positive and greater number of days since participants' COVID-19 diagnosis.

Table 2.3. Neurobehavioral symptom domain multiple regressions with standardized B-weights and p-value (N=1001).

	Somatic		Cognitive		Affective	
Predictor	β	*p*-value	β	*p*-value	β	*p*-value
Step 1:						
Male Gender	-.13	<0.001	-.09	0.004	-.12	<0.001
Age	.00	0.896	-.03	0.364	-.06	0.040
Education	-.08	0.013	-.01	0.859	-.10	0.002
Employed	-.16	<0.001	-.16	<0.001	-.16	<0.001
Partnered	-.06	0.072	-.06	0.071	-.04	0.178
Other Chronic Condition	.15	<0.001	.14	<0.001	.19	<0.001
Step 2:						
Male Gender	-.15	<0.001	-.10	<0.001	-.14	<0.001
Age	-.07	0.031	-.08	0.007	-.12	<0.001
Education	-.11	<0.001	-.04	0.171	-.13	<0.001
Employed	-.10	0.001	-.11	<0.001	-.10	0.001
Partnered	-.04	0.155	-.04	0.162	-.03	0.313

Other Chronic Condition	.12	<0.001	.12	<0.001	.16	<0.001
Hospitalized	.08	0.198	.18	0.003	.08	0.192
Oxygen Therapy	-.01	0.898	-.15	0.006	-.06	0.282
ICU Stay	-.02	0.769	-.05	0.303	-.09	0.062
Noninvasive Ventilation	.00	0.924	-.02	0.748	.02	0.710
Invasive Ventilation	-.02	0.707	-.02	0.744	-.02	0.788
Induced Coma	.04	0.422	.02	0.695	.07	0.223
COVID-19 Severity	.24	<0.001	.27	<0.001	.29	<0.001
Days Since Diagnosis	.18	<0.001	.20	<0.001	.19	<0.001

In the second hierarchical linear regression predicting current cognitive symptom severity, Step 1 was statistically significant, $F(6, 994) = 11.62$, $R2 = 0.066$, $p < 0.001$ (Table 2.3). Greater cognitive symptom severity was significantly and uniquely associated with female or trans vs. male gender, being unemployed, and having another chronic health condition. With the addition of the Step 2 predictors, the overall model was still statistically significant, $F(14, 986) = 16.98$, $R2 = 0.194$, $p < 0.001$. Within this step, all previously significant predictors were still statistically significant and associations in the same directions, with the addition of greater age now significantly predicting lower cognitive symptom severity. Greater cognitive symptom severity was uniquely associated with having been hospitalized, higher COVID-19 severity while positive, and greater number of days since participants' COVID-19 diagnosis. Conversely, lower cognitive symptom severity was associated with having received oxygen therapy.

In the third hierarchical linear regression predicting current affective symptom severity, Step 1 was statistically significant, $F(6, 994) = 19.16$, $R2 = 0.104$, $p < 0.001$ (Table 2.3). Greater affective symptom severity was significantly and uniquely associated with female or trans vs. male gender, younger age, lower education, being unemployed, and having another chronic health condition. With the addition of the Step 2 predictors, the overall model was still statistically significant, $F(14, 986) = 21.23$, $R2 = 0.232$, $p < 0.001$. Within this step, all previously significant predictors were still statistically significant and associations in the same directions. Greater affective symptom severity was uniquely associated with higher COVID-19 severity while positive and greater number of days since participants' COVID-19 diagnosis. Correlations between neurobehavioral symptoms and predictors can be found in Table 2.4.

Table 2.4. Bivariate correlations (r) between neurobehavioral symptoms and predictors.

Variable	Somatic	Cognitive	Affective
Male Gender	-0.157**	-0.110**	-0.153**
Age	0.044	0.022	-0.010
Education	-0.123**	-0.048	-0.142**
Employed	-0.192**	-0.176**	-0.187**
Partnered	-0.064*	-0.064*	-0.051
Other Chronic Condition	0.180**	0.166**	0.208**
Hospitalized	0.254**	0.224**	0.216**
Oxygen Therapy	0.218**	0.142**	0.166**
ICU Stay	0.140**	0.069*	0.082**
Noninvasive Ventilation	0.102**	0.035	0.063*
Invasive Ventilation	0.100**	0.044	0.089**
Induced Coma	0.102**	0.050	0.100**
COVID-19 Severity	0.326**	0.306**	0.316**
Days Since Diagnosis	0.198**	0.228**	0.208**

Note: * = $p < 0.05$; ** = $p < 0.01$.

2.2.3. DIFFERENCES IN COVID-19 NEUROBEHAVIORAL SYMPTOMS BY GLOBAL REGION

In the ANCOVA predicting current somatic symptom severity, there was a statistically significant effect of global region, $F(3, 987) = 19.67$, $p < 0.001$, partial-eta2 = 0.056 (Figure 2.5). Bonferroni-corrected post hoc pairwise comparisons showed that participants from Europe and Central Asia (covariate-adjusted M = 20.13, SE = 0.54) and North America (covariate-adjusted M = 20.42, SE = 0.44) reported significantly greater somatic symptom severity than participants from Latin America and the Caribbean (covariate-adjusted M = 16.99, SE = 0.29) and Sub-Saharan Africa (covariate-adjusted M = 17.10, SE = 0.60), all $p < 0.001$.

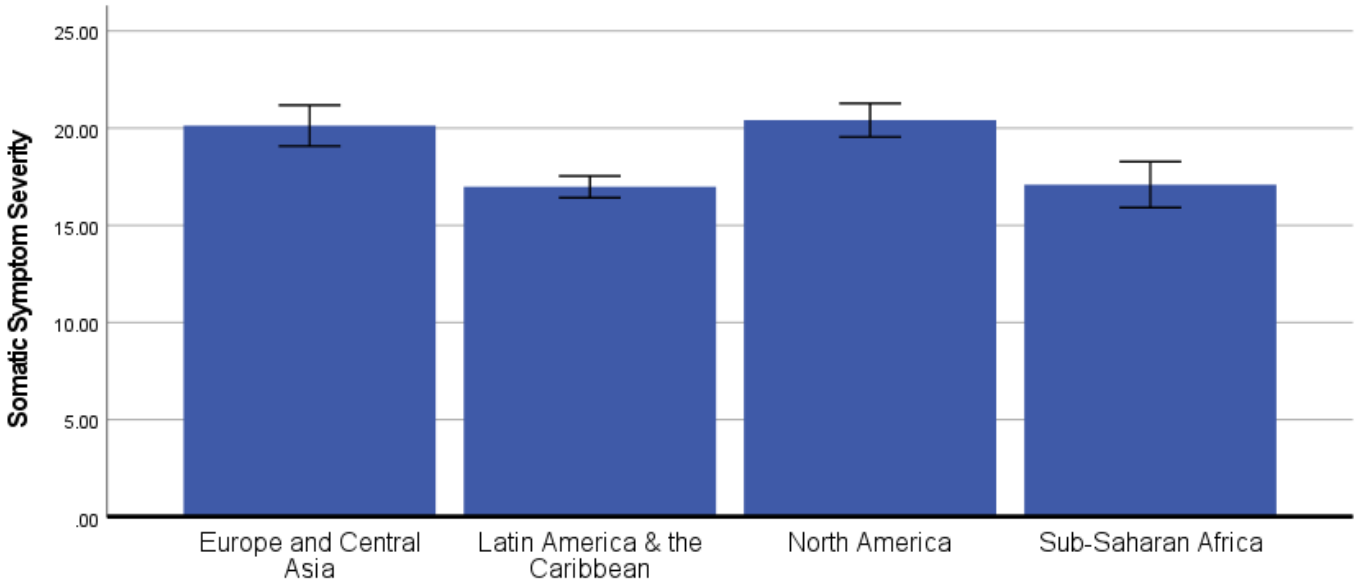

Figure 2.5. Covariate-adjusted somatic symptom severity scores (mean with 95% confidence interval) by global region.

Note: A graphic that shows the differences in somatic symptoms by Global Region. The participants from Europe and Central Asia and North America reported significantly greater somatic symptom severity than participants from Latin America and the Caribbean and Sub-Saharan Africa.

In the ANCOVA predicting current cognitive symptom severity, there was a statistically significant effect of global region, $F(3, 987) = 39.31$, $p < 0.001$, partial-eta2 = 0.107 (Figure 2.6). Bonferroni-corrected post hoc pairwise comparisons showed that participants from Europe and Central Asia (covariate-adjusted M = 9.12, SE = 0.30) reported significantly greater cognitive symptom severity than participants from Latin America and the Caribbean (covariate-adjusted M = 7.22, SE = 0.16, $p < 0.001$) and Sub-Saharan Africa (covariate-adjusted M = 7.72, SE = 0.34, $p = 0.013$), but lower severity than participants from North America (covariate-adjusted M = 10.28, SE = 0.25, $p = 0.019$). Participants from North America also reported greater cognitive symptom severity than those from Latin America and the Caribbean ($p < 0.001$) and Sub-Saharan Africa ($p < 0.001$).

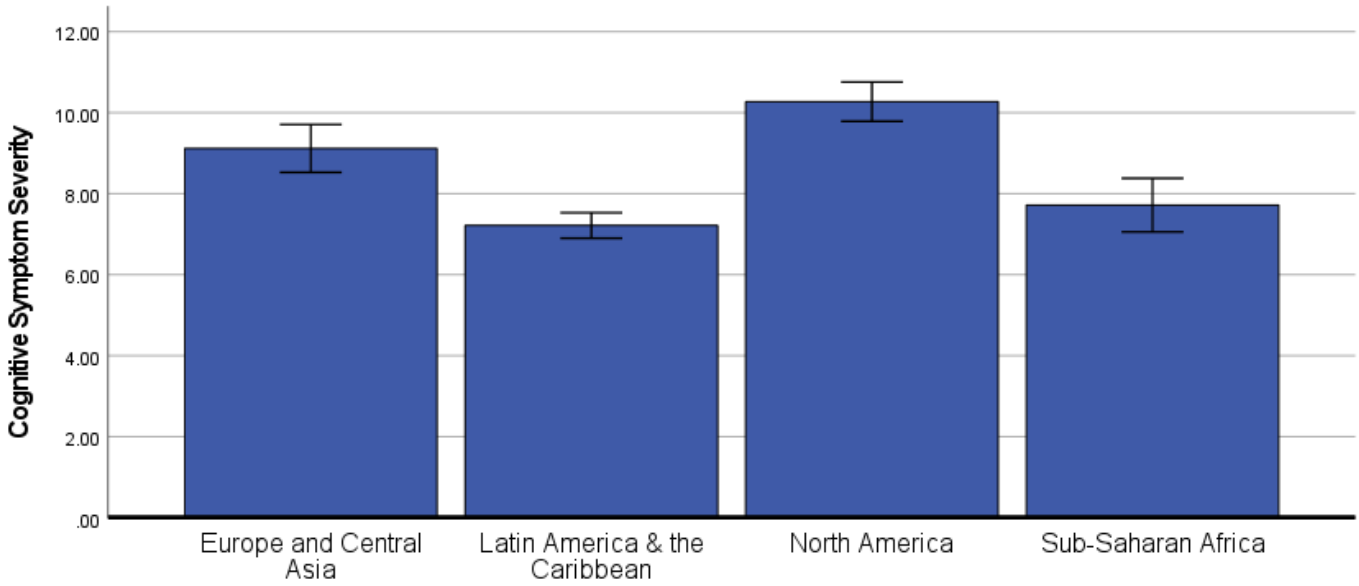

Figure 2.6. Covariate-adjusted cognitive symptom severity scores (mean with 95% confidence interval) by global region.

Note: A graphic that shows the differences in cognitive symptoms by Global Region. The participants from North America reported the greatest cognitive symptoms. Additionally, participants from Europe and Central Asia reported significantly greater cognitive symptom severity than participants from Latin America and the Caribbean and Sub-Saharan Africa.

In the ANCOVA predicting current affective symptom severity, there was a statistically significant effect of global region, $F(3, 987) = 29.26$, $p < 0.001$, partial-eta2 = 0.082 (Figure 2.7). Bonferroni-corrected post hoc pairwise comparisons showed that participants from Latin America and the Caribbean (covariate-adjusted M = 13.87, SE = 0.25) reported significantly lower affective symptom severity than participants from Europe and Central Asia (covariate-adjusted M = 16.46, SE = 0.47, $p < 0.001$), North America (covariate-adjusted M = 17.98, SE = 0.38, $p < 0.001$), and Sub-Saharan Africa (covariate-adjusted M = 15.50, SE = 0.52, $p = 0.030$). Participants from Sub-Saharan Africa also reported lower affective symptom severity than those from North America ($p < 0.001$).

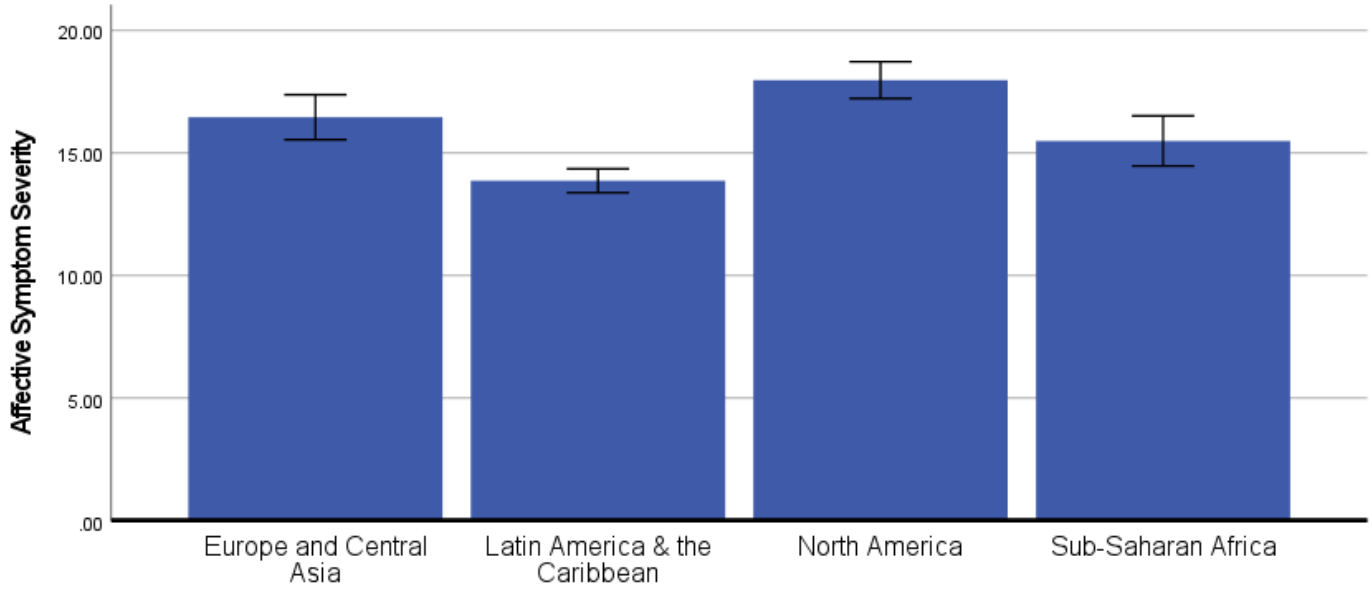

Figure 2.7. Covariate-adjusted affective symptom severity scores (mean with 95% confidence interval) by global region.

Note: A graphic that shows the differences in affective symptoms by Global Region. The participants from Latin America and the Caribbean reported significantly lower affective symptom severity than participants from Europe and Central Asia, North America, and Sub-Saharan Africa. Participants from Sub-Saharan Africa also reported lower affective symptom severity than those from North America.

2.3. Discussion

This retrospective study (a) compared the presence of somatic, cognitive, and affective neurobehavioral symptoms in a large international sample of individuals before their COVID-19 diagnosis, during the SARS CoV-2 infection, and currently, and (b) examined risk factors for increased Long COVID neurobehavioral symptoms including demographic variables, COVID-19 infection severity, and intervention characteristics. Participants showed large-sized symptom increases in all three neurobehavioral domains (cognitive, affective, and somatic) during their infection, consistent with commonly reported COVID-19 symptoms (38,47,69,70). However, there were marked differences in the patterns of post COVID-19 recovery as a function of symptom domain. Specifically, changes in taste/smell, appetite, and dizziness (somatic symptoms) showed large increases during participants' COVID-19 infection, with only taste/smell showing a large improvement post COVID-19. Within the affective domain, fatigue and headaches showed large increases during COVID-19, but also medium-sized improvements post COVID-19; whereas there were extremely minimal improvements in sleep, irritability, and frustration. Regarding cognitive symptoms, concentration problems and slowed thinking demonstrated the largest increases during COVID-19. However, all four cognitive symptoms showed very low levels of improvement or no improvement (forgetfulness). The distinct long recovery trajectories in these domains may reflect multiple factors, ranging from pre-existing individual health conditions and vulnerabilities, to specific pathway/s of viral attack, or specific brain regions or neural networks affected by the virus. Further research, and more specifically, longitudinal, neuroimaging, and neurobiological studies, may provide further evidence and insight into specific

neurobiological mechanism/s of cognitive impairments associated with COVID-19 infection and help identify additional risk and protective factors.

This study identified several risk factors associated with higher symptom severity. First, the sociodemographic characteristics consistently associated with greater severity of symptoms across the three domains were being female, younger, lower education, being unemployed, and having another chronic health condition. These findings are consistent with a study by Frontera et al. (49), in which participants reporting prolonged COVID-19 symptoms were more often younger, female, Hispanic, with a history of a mental health disorder, unemployed, and with financial insecurity. In fact, several studies from different geographic regions have also reported that females have been disproportionately affected by Long COVID as compared to males (50,70–72). Moreover, other studies have found that females have experienced higher psychosocial distress and neurobehavioral symptoms than males during the COVID-19 pandemic, even those who had not contracted COVID-19 (49,73,74). According to Kolakowsky-Hayner et al. (2021) (75), these differences may be due to genetics or hormonal factors, structural gender inequity at the societal level, or coping strategies. Therefore, women's susceptibility to reporting greater mental health symptoms may exacerbate neurocognitive symptoms after COVID-19 infection and maintain them over time.

On the other hand, though older adults are at a greater risk for serious complications of COVID-19, several cross-sectional studies in the general population reported age differences in mental health outcomes during the COVID-19 pandemic, with the younger group being the most psychologically impacted by the pandemic (76–78). Older adults have been shown to have better emotional regulation and engage in

proactive coping (79,80), as well as better emotional well-being, a more positive outlook, and emotional resilience, despite prolonged stress of the COVID-19 pandemic (81). This population also has better coping skills and more stable social/family connections than younger adults which may serve as protective factors against psychosocial distress during the pandemic (78). The current findings provide additional evidence of this hypothesis.

The current study results showed that participants with lower education levels reported higher somatic and affective symptoms. While there were no reports in the literature directly addressing the association between low educational level and somatic and affective neurobehavioral symptoms in Long COVID, a cross-sectional study from Poland (n = 1,002) reported that higher education level and male gender were associated with lower psychopathological symptoms in a general sample during the COVID-19 pandemic. The authors also reported that greater knowledge about COVID-19 was associated with lower symptom severity (73). Another study showed that greater knowledge about COVID-19 was associated with a more optimistic outlook and the use of preventive measures in a general Chinese sample (82). Both studies reported that greater knowledge was associated with higher education and the male gender in their respective countries. In many societies and cultures across the globe, higher education is often a pre-requisite and a pathway to a higher paying job/occupation, and consequently, may provide better access to medical care, child and elder care, access to information and support systems, shelter, and food security.

Regarding unemployment, our results coincide with that found by Frontera et al. (2021) (49), where this variable is associated with persistent symptoms after COVID-19. Some reports indicated that low socio-economic level, escalated during a public health

crisis, can have an adverse effect on physical and mental health and has been associated with higher levels of psychosocial distress (83,84). Additionally, the lack of employment and low economic resources may mean less access to health care in some regions where healthcare is private, limiting one's ability to obtain medical assistance, assistance to rehabilitation programs, and needed medications, etc. Likewise, being unemployed is a highly stressful situation for many that may be at the root of many of the affective symptoms reported by the participants of the present study, such as anxiety. Future studies should investigate this potential explanation further, comparing the presence of persistent symptoms in people with high and low socioeconomic status, or employed vs. unemployed.

Having another chronic health condition was also associated with all three neurobehavioral domains. This is consistent with previous research that has found that individuals with previous chronic diseases such as diabetes (85), asthma (86), hypertension (87), cardiovascular diseases (88), and malignancy (89), or human immunodeficiency virus (HIV) (90) have more complications from being infected with SARS-CoV-2 than those without chronic health conditions. This is possibly due to two mechanisms: a) a deficient immune system, as in the case of HIV or cancer, or b) some diseases such as diabetes cause an increase in Angiotensin-Converting Enzyme 2 (ACE-2) receptors (91). The results of the present study increase the evidence of the vulnerability of individuals with chronic health conditions.

Some studies have documented a relationship between the presence of persistent symptoms and greater severity of COVID-19, the need for mechanical ventilation, an ICU stay, and a longer hospitalization (71). For example, Daste et al. (2021)

(92) found that 3 months after ICU discharge, persons reported clinically relevant physical impairment (shoulder and peripheral nerve injuries), cognitive alterations (in memory, attention, processing speed, and executive function), and emotional problems (anxiety, depression, and posttraumatic stress disorder). Many of these authors have suggested that people with these characteristics have long-term tissue damage that may be associated with persistent symptoms. In the current sample, greater SARS CoV-2 infection severity predicted greater current symptom severity across all three neurobehavioral domains, however, the other variables such as ICU stay, noninvasive or invasive ventilation, and induced coma were not associated with Long COVID symptoms. The inconsistency and variability of reported post-COVID-19 outcomes in the current literature are likely to reflect the heterogeneity of the population samples, assessment measures, clinical presentations, and recovery trajectories of individuals with prolonged COVID-19 symptoms.

The current study results also showed that cross-sectionally across the sample, greater time since the infection was associated with increased neurobehavioral symptoms. This finding may potentially reflect the natural course of post-COVID recovery, where milder symptoms get resolved soon after the infection, and more severe symptoms continue to develop and/or linger for a longer period of time. However, the emerging literature investigating post-COVID recovery and Long COVID symptoms indicates the possibility of different trajectories determined by distinct temporal subtypes or phenotypes (48). For instance, a study by Davis et al. (2021) (48) reported a continuous increase in cognitive symptoms (brain fog, attention, and memory impairment) in the first few months after the infection which is consistent with the current findings of persistent cognitive symptoms showing no improvement over time in

the longitudinal analyses. At this point in time, only limited data are available on the temporal recovery trajectory of Long COVID, and future longitudinal studies using large samples may provide further insight and help to identify and evaluate potential phenotypes.

Lower cognitive symptom severity was uniquely predicted by having received oxygen therapy. Though there is limited literature available on oxygen therapy in individuals with COVID-19, it has been suggested that oxygen treatment, and hyperbaric oxygen therapy in particular, may improve oxygenation and reduce tissue inflammation (93). A systematic review reported that hyperbaric oxygen treatment improved severe COVID-19 symptoms and increased general wellbeing, while correcting hypoxia and elevating O2 saturation, in several small samples of individuals with COVID-19 (94). To the authors' knowledge, the current study is the first to report an association between having received oxygen therapy during COVID-19 and lower cognitive symptoms post COVID-19 infection in a large international sample.

Finally, after controlling for demographics, participants from North America, Europe, and Central Asia generally reported the highest levels of symptoms across all domains relative to other global regions. Although it may seem counterintuitive that people from high-income countries present more sequelae than those from low-income countries taking into account that they have greater access to resources such as health, hygiene, food, etc., data from the Institute of Health Metrics and Evaluation (95) indicated that the incidence of mental disorders in the North American, European, and Central Asian regions were much higher than in Latin America and Africa. These alterations, as suggested by Benzakour et al. (2021) (96), can exacerbate cognitive

problems, which would explain the results obtained in the present study. However, further research is required in this area.

2.3.1. IMPLICATIONS

Compared to previous literature, this study has a number of strengths that should be highlighted. Most of the research carried out on COVID-19 or Long COVID is based on case studies or small samples. The current study presents results obtained from a sample of more than 1,000 people which facilitates generalization of the results. In addition, the participants came from different countries, allowing comparisons by global regions which is unique in the literature to date. Although there is much research on certain risk factors that promote the development of Long COVID symptomatology, in the present study, novel factors such as low education and the absence of oxygen therapy were identified as important that have not been previously taken into account. In fact, these unique characteristics predictive of Long COVID symptoms underscore risk factors related to healthcare access, including unemployment, education, and services such as oxygen therapy. Nonetheless, the sample was a convenience sample and therefore not representative in terms of age, education, or geographic region, so conclusions must be tempered accordingly. Clinically, these findings have important implications for Long COVID, highlighting the necessity to assess, monitor, and treat somatic, cognitive, and affective neurobehavioral symptoms in the general population during and after COVID-19, especially targeting the most at-risk groups for higher Long COVID symptom severity (younger age, female or trans gender, unemployed, and having chronic health conditions, and lower educational level). In addition, periodic evaluations of these patients must be

carried out, taking into account that the symptoms, in many cases, tend to persist over time.

Moreover, these results open the way to new research that investigates the characteristics of the presentation of symptoms, and taking into account, mainly, the differences between the different regions of the world. Based on our results, it is possible that there are other environmental and cultural factors that are not being taken into account and that may be influencing not only the appearance of symptoms, but also their reporting. In sum, the risk factors identified provide evidence and future directions for both research and clinical developments.

2.3.2. LIMITATIONS

The results of current study must be interpreted in light of several limitations. The inconsistency and variability of reported post-COVID-19 outcomes in the current literature are likely to reflect the heterogeneity of the population samples, assessment measures, clinical presentations, and recovery trajectories of individuals with prolonged COVID-19 symptoms. For instance, first, the survey was distributed online, so the veracity of what was reported by participants cannot be guaranteed versus if objective indices of the constructs had been collected (e.g., neuropsychology test performance, sleep monitoring study, etc.). Second, people with limited or no access to the internet were unable to participate in this study; previous research has suggested that people from low or very low socioeconomic areas may be differentially impacted by the COVID-19 pandemic compared to those in higher socioeconomic areas (97). Therefore, the current study likely over-sampled participants of higher educational and income backgrounds. Third, as the study was retrospective, participants responded according to their recall of

symptoms at various stages in the COVID-19 infection course. Participants with greater psychological distress may have had a more biased, exacerbated recall of their COVID-19 symptoms or premorbid functioning. Fourth, this study was only focused on adults with COVID-19, and future studies should include adolescents and children to increase the field's knowledge about neurobehavioral symptoms in Long COVID among these groups as well. Fifth, although data were collected from 34 countries, the fact that the survey was only available in English and Spanish likely limited the number of participants from Asia, Africa, or Europe. Sixth, participants with severe and critical symptoms are underrepresented in the cohort since they represent only 11% of the sample. Seventh, given the study's recruitment approach, the total number of individuals who saw the study invitation is unknown, and differences between those who participated vs. did not participate in the study are similarly unknown. Finally, as vaccine campaigns increase, future studies should follow up with people who have received the vaccine and become infected after vaccination to determine whether neurobehavioral symptomatology is similar or different compared to those who are unvaccinated.

2.4. Conclusions

This study found that COVID-19 might result in long-term neurobehavioral symptomatology, with medium-size improvements in somatic and affective domains, but small-sized or non-existent improvements in the cognitive domain. Evaluation and monitoring of neurobehavioral symptoms after COVID-19 are warranted. Moreover, the results reported here allow clinicians to identify early individuals who are at an increased risk of developing long-term neurobehavioral symptoms, and thus start with early intervention for groups including: younger age, being female or trans, having low

education, having another chronic health condition, being unemployed, and higher COVID-19 severity. Finally, global region differences arose, with North America, Europe, and Central Asia participants generally reported the highest levels of symptoms across all domains relative to other global regions. This may reflect social inequalities making the COVID-19 pandemic worse in particular global regions.

CAPÍTULO 3. NETWORK ANALYSIS OF NEUROBEHAVIORAL SYMPTOM PATTERNS IN AN INTERNATIONAL SAMPLE OF SPANISH-SPEAKERS WITH A HISTORY OF COVID-19 AND CONTROLS[3]

[3] Perrin, P. B., Ramos-Usuga, D., West, S. J., Merced, K., Klyce, D. W., Lequerica, A. H., Olabarrieta-Landa, L., Alzueta, E., Baker, F. C., Iacovides, S., Cortes, M., & Arango-Lasprilla, J. C. (2022). Network Analysis of Neurobehavioral Symptom Patterns in an International Sample of Spanish-Speakers with a History of COVID-19 and Controls. International journal of environmental research and public health, 20(1), 183. https://doi.org/10.3390/ijerph20010183

Psychometric network analysis provides a novel statistical approach to model related symptom clusters as a dynamic system. Given that patients with Long COVID present a broad spectrum of neurobehavioral symptoms, the present study was conducted with the aim of analyzing the dynamics of these symptoms in a population of Spanish-speaking persons who have been infected with SARS CoV-2. In addition, in order to compare the symptom dynamics of patients with Long COVID with those of persons without this disease, a sample was taken from a pre-pandemic study in which participants also reported neurobehavioral symptoms through the NSI.

3.1. Methods

3.1.1. PARTICIPANTS

The inclusion criteria to participate in the present study were: (a) age 18 years or older, and (b) self-report of having tested positive for COVID-19 through a viral and/or antigen test. For this study, only Spanish-speaking participants have been included. So, the sample consisted of 1,093 adults; 650 of these participants from 26 countries reported having previously tested positive for COVID-19 (COVID+) through a viral and/or antigen test (range: 1-383 days since positive test). The remainder consisted of 443 adults from 20 countries who participated in other study (68) prior to the COVID-19 pandemic (COVID–) (Figure 3.1). See Table 3.1 for participant demographic information.

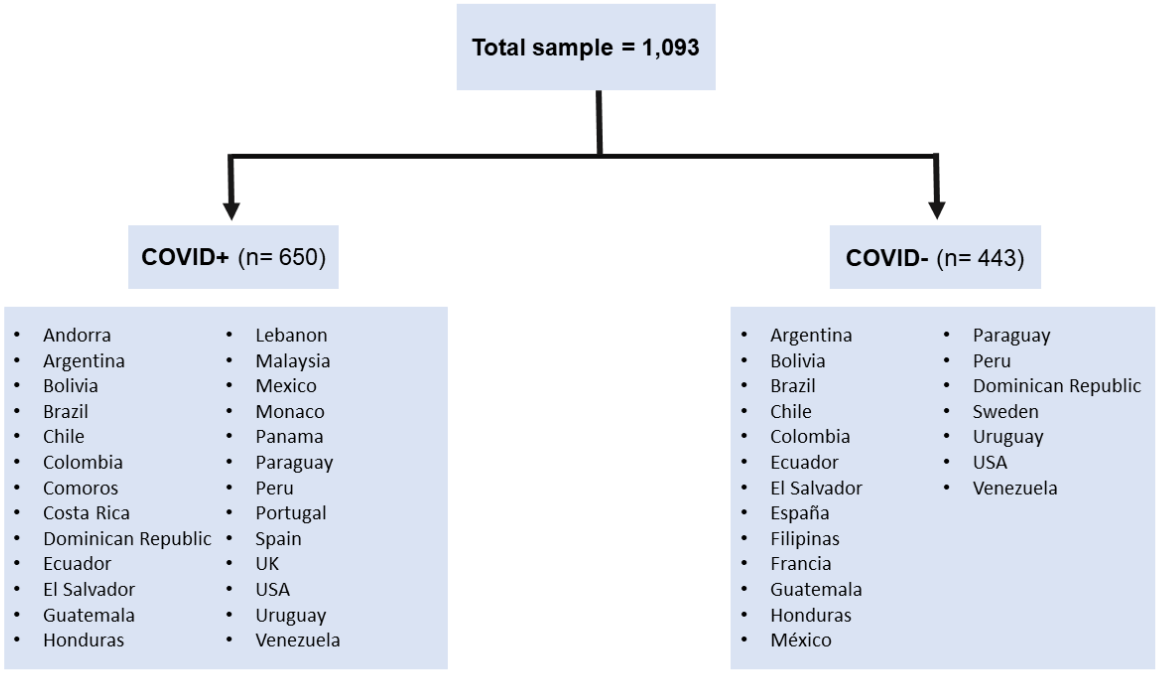

Figure 3.1. Countries included in the sample.

Table 3.1. Sociodemographic characteristics of the study cohort (N=1093).

Variable	COVID+		COVID-	
Age (years), M[1], SD[2]	43.5	11.9	33.9	13.2
Gender, N, %				
Man	130	20.0	140	31.6
Woman	519	79.8	303	68.4
Non-binary, transgender, or other	1	0.2	0	0
Highest level of education completed, N, %				
Some school education	12	1.8	54	12.4
Graduated High School	31	4.9	40	9.1
Some college/Technical degree	145	22.3	69	15.7
Completed undergraduate education	201	30.9	47	10.9
Postgraduate education (some or completed)	261	40.1	230	51.9
Days from COVID-19 diagnosis, M, SD	147.6	98.9	-	-

Note: [1]Mean; [2] Standard Deviation

3.1.2. MEASURES

Participants completed items assessing demographic information and in the COVID-19 group, days since COVID-19 diagnosis.

The Neurobehavioral Symptom Inventory (NSI) (67) is a self-report assessment of cognitive, affective, and somatic neurobehavioral symptoms. It consists of 22 items scored on a 5-point Likert scale according to severity (0 = None; 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very Severe). The NSI was administered in Spanish (68).

3.1.3. PROCEDURE

The Qualtrics survey was distributed online through (a) professional mailing lists and collaborators' contact networks; (b) Facebook groups and advertisements; and (c) a COVID-19 patient database from one of the collaborating centers. The study was approved by the Ethics Committee of the Public University of Navarra (PI-003/21). An informed consent document specified that participation was voluntary, data were anonymous, and there was no financial compensation for participation. The study was conducted in compliance with the declaration of Helsinki.

3.1.4. DATA ANALYSES

A psychometric network analysis was applied to the 22 items of the NSI. In the current network analysis, *nodes* represented cross-sectional variables (e.g., individual NSI symptoms) and *edges* represented the regularized partial correlation between any two nodes. We also estimated the strength centrality of each node in our networks. *Strength* centrality refers to the overall influence of a node within a network (e.g., the absolute sum of all edges connecting to a given node). We estimated our networks using the *estimateNetwork* function from the bootnet package for R version 4.1.1 (98,99). We

implemented the EBICglasso routine which attempts to finds a relatively sparse network that best fits the data by reducing the smallest edges in the network to zero and examining the model fit until maximal fit is achieved (98,99). Network stability and accuracy were examined by two 1,000-sample bootstraps (e.g., case-dropping and non-parametric) using the bootnet function from the bootnet package (98,99). Pairwise deletion was used for missing values. The average network layout was computed using the averageLayout function from the qgraph package prior to visualization to aid in comparison (100,101). Finally, we compared our networks (COVID+ versus COVID–) statistically using a 1,000-iteration permutation test from the NetworkComparisonTest package (102).

To facilitate the graphical representation of the symptom network, some names were slightly modified with respect to those of the NSI, as presented in Table 3.2.

Table 3.2. NSI's symptoms names.

NSI name	Network analysis
Cognitive	
Concentration	Concentrate
Forgetfulness	Forgot
Making Decisions	Decide
Slowed Thinking	Organized
Affective	
Headaches	Head
Depressed	Sad
Anxious	Tense
Frustration	Frustrated
Irritability	Annoyed
Somatic	
Taste/smell	Taste
Coordination	Clumsy
Light Sensitivity	Light
Noise Sensitivity	Noise

3.2 Results

Descriptive statistics are presented in the Table 3.3 and Table 3.4. No variables in the current study demonstrated substantial skew excepting the Appetite node among the COVID– participants. Applying the nonparanormal transformation to this variable did not improve the skew, and thus the original data were retained (103). We screened both datasets separately for univariate outliers (e.g., beyond +/- 3SD from the mean), which were Winsorized prior to network estimation. Correlation stability coefficients were ideal for edge weights (*CS* = .75) and strength centrality estimates (*CS* = .67) in the COVID+ network. Similar stability was found in the COVID– network for edges (*CS* = .44) but strength centrality was relatively lower (*CS* = .36), though still acceptable. Both networks demonstrated accuracy in relation to the estimated edges, as only a single edge (Clumsy—Organize from the COVID+ network) was absent in more than 50% of the nonparametric bootstrap samples. Full edge weights estimate and related bootstrapped values are presented in the Table 3.5 and Table 3.6.

Table 3.3. Descriptive Statistics from the COVID- Group.

Variable	*M*	*SD*	Min	Max	Skew	Kurtosis	*SE*
Annoyed	1.88	0.88	1	4	0.70	-0.37	0.04
Appetite	1.17	0.48	1	4	3.18	11.11	0.02
Balance	1.38	0.67	1	4	1.89	3.47	0.03
Clumsy	1.43	0.68	1	4	1.55	1.96	0.03
Concentrate	1.64	0.86	1	4	1.20	0.54	0.04
Decide	1.88	0.86	1	4	0.69	-0.30	0.04
Dizzy	1.58	0.75	1	4	1.18	0.80	0.04
Fatigue	1.60	0.88	1	4	1.31	0.67	0.04
Forget	1.86	0.97	1	4	0.85	-0.37	0.05
Frustrated	1.77	0.88	1	4	0.95	0.07	0.04
Head	1.52	0.78	1	4	1.44	1.36	0.04
Hearing	1.65	0.85	1	4	1.15	0.44	0.04
Light	1.71	0.85	1	4	0.95	-0.07	0.04
Nausea	2.15	0.91	1	4	0.28	-0.85	0.04
Noise	1.35	0.66	1	4	2.02	3.80	0.03
Numb	1.51	0.79	1	4	1.50	1.51	0.04
Organize	1.63	0.81	1	4	1.13	0.52	0.04
Sad	1.83	0.91	1	4	0.87	-0.16	0.04
Sleep	2.00	0.93	1	4	0.55	-0.64	0.04
Taste	1.67	0.82	1	4	1.10	0.53	0.04
Tense	2.01	0.93	1	4	0.51	-0.72	0.04
Vision	1.37	0.62	1	4	1.65	2.57	0.03

Table 3.4. Descriptive Statistics from the COVID+ Group.

Variable	*M*	*SD*	Min	Max	Skew	Kurtosis	*SE*
Annoyed	1.87	0.94	1	5	0.98	0.47	0.04
Appetite	1.78	1.02	1	5	1.17	0.55	0.04
Balance	1.46	0.75	1	5	1.69	2.61	0.03
Clumsy	1.50	0.77	1	5	1.67	2.87	0.03
Concentrate	1.66	0.90	1	5	1.21	0.78	0.04
Decide	2.07	1.03	1	5	0.67	-0.33	0.04
Dizzy	1.69	0.84	1	5	1.06	0.47	0.03
Fatigue	2.05	1.11	1	5	0.76	-0.34	0.04
Forget	2.05	1.07	1	5	0.75	-0.28	0.04
Frustrated	1.87	0.99	1	5	1.01	0.34	0.04
Head	1.86	1.03	1	5	1.06	0.34	0.04
Hearing	1.53	0.80	1	5	1.43	1.35	0.03
Light	1.83	0.96	1	5	0.85	-0.28	0.04
Nausea	2.07	1.04	1	5	0.68	-0.3	0.04
Noise	1.40	0.73	1	5	1.93	3.75	0.03
Numb	1.58	0.84	1	5	1.5	2.05	0.03
Organize	1.58	0.86	1	5	1.4	1.19	0.03
Sad	1.94	1.04	1	5	0.87	-0.04	0.04
Sleep	2.43	1.14	1	5	0.42	-0.62	0.04
Taste	1.75	0.93	1	5	1.07	0.47	0.04
Tense	2.11	1.03	1	5	0.62	-0.33	0.04
Vision	1.39	0.74	1	5	1.92	3.05	0.03

Table 3.5. Edge Weight Estimates and Bootstrap Results for All Edges Included in the COVID- Network.

Edge	Weight	Mean	SD	LCI	UCI	P0
Annoyed--Frustrated	0.36	0.35	0.05	0.26	0.45	0.00
Appetite--Organize	0.16	0.12	0.10	-0.03	0.36	0.39
Balance--Clumsy	0.24	0.23	0.07	0.10	0.38	0.06
Clumsy--Light	0.18	0.14	0.10	-0.03	0.39	0.34
Concentrate--Forget	0.21	0.19	0.06	0.08	0.33	0.06
Decide--Annoyed	0.13	0.08	0.08	-0.03	0.29	0.49
Decide--Head	0.14	0.10	0.08	-0.03	0.31	0.37
Dizzy--Balance	0.32	0.31	0.05	0.22	0.43	0.00
Dizzy--Nausea	0.27	0.26	0.05	0.16	0.37	0.01
Dizzy--Vision	0.23	0.22	0.07	0.09	0.36	0.05
Forget--Decide	0.32	0.31	0.05	0.22	0.41	0.00
Forget--Head	0.25	0.24	0.05	0.15	0.35	0.01
Forget--Organize	0.13	0.12	0.08	-0.02	0.29	0.29
Head--Frustrated	0.14	0.10	0.08	-0.02	0.29	0.36
Head--Sleep	0.17	0.14	0.08	0.00	0.33	0.23
Hearing--Numb	0.28	0.27	0.06	0.15	0.41	0.02
Light--Hearing	0.25	0.24	0.06	0.13	0.37	0.03
Nausea--Vision	0.19	0.16	0.10	0.00	0.39	0.24
Noise--Numb	0.23	0.21	0.09	0.05	0.42	0.14
Organize--Frustrated	0.20	0.20	0.06	0.09	0.31	0.03
Organize--Head	0.18	0.16	0.08	0.02	0.34	0.16
Organize--Sad	0.17	0.15	0.08	0.01	0.33	0.18
Sad--Annoyed	0.13	0.09	0.08	-0.03	0.29	0.41
Sleep--Sad	0.14	0.09	0.08	-0.03	0.31	0.42
Taste--Appetite	0.17	0.11	0.10	-0.04	0.38	0.44
Tense--Frustrated	0.23	0.22	0.06	0.12	0.34	0.02
Tense--Sad	0.32	0.32	0.06	0.21	0.43	0.00

Note: LCI = Lower-bound of the confidence interval, UCI = Upper-bound of the confidence interval, P0 = proportion of the 1,000 sample bootstrap that did not contain a given edge.

Table 3.6. Edge Weight Estimates and Bootstrap Results for All Edges Included in the COVID+ Network.

Edge	Weight	Mean	SD	LCI	UCI	P0
Annoyed--Frustrated	0.31	0.30	0.04	0.22	0.40	0.00
Appetite--Concentrate	0.21	0.19	0.08	0.06	0.36	0.11
Balance--Clumsy	0.33	0.32	0.04	0.25	0.41	0.00
Clumsy--Decide	0.15	0.14	0.04	0.07	0.23	0.03
Clumsy--Organize	0.09	0.06	0.06	-0.04	0.21	0.52
Clumsy--Taste	0.13	0.09	0.08	-0.02	0.28	0.39
Concentrate--Fatigue	0.13	0.09	0.08	-0.03	0.30	0.45
Decide--Fatigue	0.11	0.08	0.06	-0.02	0.23	0.36
Decide--Head	0.23	0.23	0.05	0.14	0.33	0.00
Dizzy--Balance	0.47	0.46	0.04	0.39	0.54	0.00
Dizzy--Nausea	0.15	0.14	0.06	0.04	0.26	0.10
Dizzy--Vision	0.18	0.17	0.06	0.06	0.29	0.07
Fatigue--Tense	0.22	0.22	0.05	0.13	0.31	0.00
Forget--Decide	0.34	0.33	0.05	0.25	0.43	0.00
Forget--Head	0.28	0.28	0.04	0.19	0.36	0.00
Forget--Sleep	0.14	0.14	0.05	0.05	0.24	0.05
Head--Sleep	0.14	0.13	0.05	0.04	0.23	0.06
Hearing--Numb	0.31	0.31	0.04	0.23	0.40	0.00
Light--Hearing	0.28	0.28	0.04	0.20	0.37	0.00
Nausea--Hearing	0.15	0.14	0.06	0.03	0.28	0.13
Nausea--Sleep	0.12	0.08	0.07	-0.02	0.26	0.40
Noise--Numb	0.31	0.30	0.04	0.23	0.40	0.00
Numb--Forget	0.12	0.10	0.06	0.01	0.23	0.18
Organize--Frustrated	0.14	0.12	0.05	0.03	0.24	0.11
Organize--Head	0.41	0.40	0.05	0.32	0.50	0.00
Sad--Annoyed	0.15	0.14	0.05	0.05	0.26	0.07
Sad--Frustrated	0.30	0.30	0.04	0.21	0.38	0.00
Sleep--Tense	0.10	0.07	0.06	-0.03	0.22	0.40
Taste--Fatigue	0.13	0.09	0.08	-0.03	0.30	0.42
Tense--Frustrated	0.23	0.23	0.04	0.15	0.31	0.00
Tense--Sad	0.33	0.33	0.04	0.25	0.42	0.00
Vision--Concentrate	0.17	0.14	0.08	0.00	0.33	0.21
Vision--Hearing	0.20	0.19	0.06	0.09	0.31	0.04

Note: LCI = Lower-bound of the confidence interval, UCI = Upper-bound of the confidence interval, P0 = proportion of the 1,000-sample bootstrap that did not contain a given edge.

3.2.1. NETWORK STRUCTURE

The COVID+ network emerged as a relatively sparse, yet well-connected, network (33/231 possible edges) such that each symptom assessed by the NSI was connected to the network. The COVID+ network also evinced many connections between the three symptom groups, and all edges in the COVID+ network were positive in direction (Figure 3.2). Conversely, the COVID– network yielded relatively fewer edges (27/231 possible edges), and the Fatigue node was not connected to any other node in the network. The COVID– network was largely disjointed, with most of the Somatosensory symptoms forming their own cluster with no edges to the other symptom groups. The Cognitive and Affective items in the COVID– network were also largely connected to symptoms from within their own groups except for four edges: the Appetite—Organize edge and the edges shared among the Head node and the Organize, Forget, and Decide nodes (Figure 3.3).

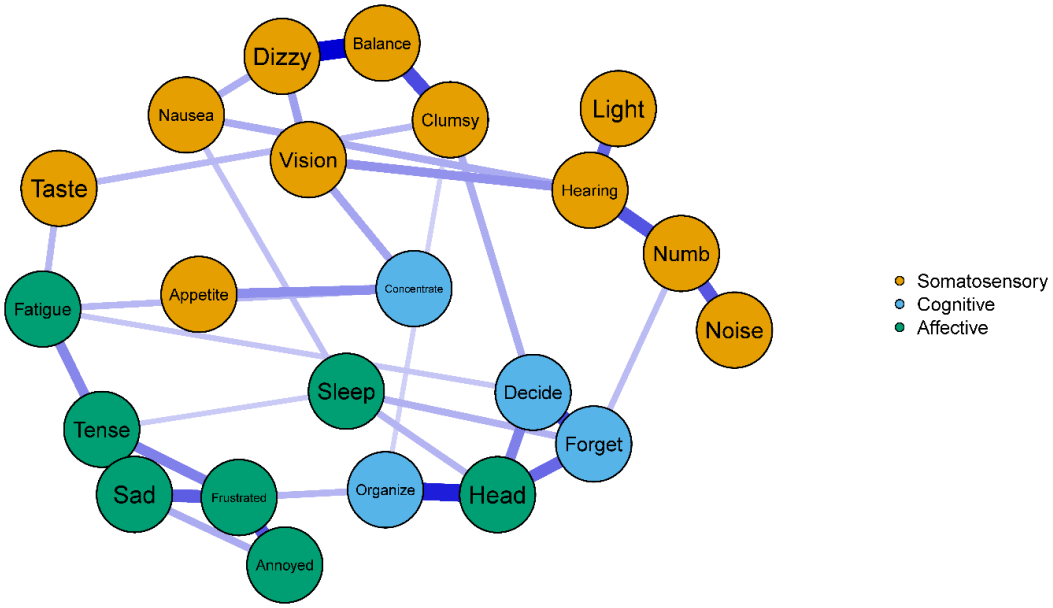

Figure 3.2. The COVID + network. Solid edges indicate positive associations with width and depth of color indicating the strength of associations.

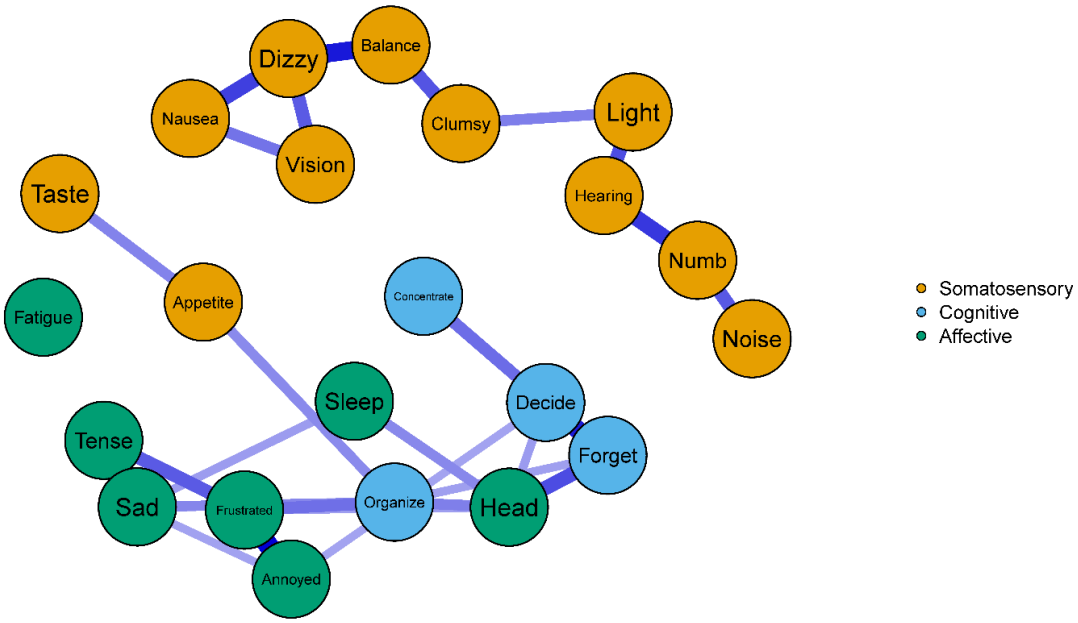

Figure 3.3. The COVID - network. Solid edges indicate positive associations with width and depth of color indicating the strength of associations.

3.2.2. GLOBAL NETWORK COMPARISONS

Our network comparison test revealed that the structure of the COVID+ network differed significantly from the COVID– network, M = .30, p = .010. We also compared the global strength of the networks, which failed to yield a significant difference, S = 1.34, p = .074.

3.2.3. EDGE COMPARISONS

Examination of the specific edge comparisons resultant from the network comparison test revealed several notable differences. The network comparison test identified nine significantly different edges between the networks. As such, we only discuss the two significant differences of edges that appeared in both networks here (see Table 3.7 for all edge comparisons). Of these, the largest difference between networks was the Organize—Head edge. In the COVID+ network, this edge had a weight of .41, but was .18 in the COVID– network, less than half the associative strength, p < .001. The Dizzy—Balance edge was also significantly different across networks. In the COVID+ network this edge yielded a weight of .47, compared to .32 in the COVID– network, p = .023.

Table 3.7. Edge Weight Comparisons from the Network Comparison Test.

Edge	*p*-value
Annoyed--Frustrated	0.487
Appetite--Concentrate	0.145
Appetite--Organize	0.005
Balance--Clumsy	0.197
Clumsy--Decide	0.142
Clumsy--Light	0.037
Clumsy--Organize	0.499
Clumsy--Taste	0.191
Concentrate--Fatigue	0.088
Concentrate--Forget	0.022
Decide--Annoyed	0.250
Decide--Fatigue	0.769
Decide--Head	0.200
Dizzy--Balance	0.023
Dizzy--Nausea	0.064
Dizzy--Vision	0.432
Fatigue--Tense	0.025
Forget--Decide	0.758
Forget--Head	0.704
Forget--Organize	0.294
Forget--Sleep	0.210
Head--Frustrated	0.178
Head--Sleep	0.682
Hearing--Numb	0.621
Light--Hearing	0.608
Nausea--Hearing	0.500
Nausea--Sleep	0.210
Nausea--Vision	0.170
Noise--Numb	0.241
Numb--Forget	0.052
Organize--Frustrated	0.337
Organize--Head	< .001
Organize--Sad	0.024
Sad--Annoyed	0.715
Sad--Frustrated	0.002
Sleep--Sad	0.063
Sleep--Tense	0.147
Taste--Appetite	< .001

Taste--Fatigue	0.331
Tense--Frustrated	0.966
Tense--Sad	0.840
Vision--Concentrate	0.284
Vision--Hearing	0.108

3.2.4. CENTRALITY COMPARISONS

To quantify the similarity of centrality implied by the global strength invariance test, we conducted a Spearman's rank-order correlation analysis using the strength estimates from each network. This analysis indicated that less than half of the total variance in centrality overlapped between networks, $\rho = 0.69$, $p < .001$. We thus explored the individual strength centrality comparisons across networks despite our marginal global test. See Table 3.8 for all strength centrality estimates and comparison *p*-values. The network comparison test revealed four significant differences. First, the Tense node yielded significantly greater strength centrality in the COVID+ network, $p = .029$. In the COVID– network, this node was connected only to the Frustrated node, where in the COVID+ network it was connected to the Sleep and Fatigue nodes in addition to the Frustrated node. As such, this suggests that feelings of tension among COVID+ patients played a crucial role in connecting the Affective symptoms measured by the NSI. Next, the Hearing node had significantly greater strength centrality in the COVID+ network, $p = .034$. As observed with the Tense node, this was due to denser connections with other symptoms within its own group (e.g., Somatosensory symptoms; Vision, Nausea, Numb, and Light). Third, the Numb node was significantly more central in the COVID+ network, $p = .038$. This difference appeared to be due largely to the Numb—Forget edge that emerged in the COVID+ network, but not COVID– network. Finally, the Fatigue node was significantly more central to the COVID+ network, $p < .001$, because it shared no connections with the COVID– network and thus had a centrality estimate of zero.

Table 3.8. Strength Centrality Estimates from Both Networks.

Node	Symptom Group	COVID +	COVID -
Annoyed	Affective	0.46	0.61
Appetite	Somatosensory	0.21	0.34
Balance	Somatosensory	0.80	0.56
Clumsy	Somatosensory	0.70	0.42
Concentrate	Cognitive	0.51	0.21
Decide	Cognitive	0.83	0.59
Dizzy	Somatosensory	0.79	0.82
Fatigue	Affective	0.60	0.00
Forget	Cognitive	0.88	0.91
Frustrated	Affective	0.97	0.92
Head	Affective	1.06	0.87
Hearing	Somatosensory	0.95	0.53
Light	Somatosensory	0.28	0.43
Nausea	Somatosensory	0.42	0.46
Noise	Somatosensory	0.31	0.23
Numb	Somatosensory	0.75	0.51
Organize	Cognitive	0.64	0.85
Sad	Affective	0.78	0.76
Sleep	Affective	0.49	0.30
Taste	Somatosensory	0.27	0.17
Tense	Affective	0.88	0.55
Vision	Somatosensory	0.54	0.42

3.3. Discussion

This study applied psychometric network analysis to investigate the patterns of cognitive, affective, and somatic neurobehavioral symptoms in an international sample of Spanish-speaking individuals with a history of COVID-19 and non-COVID controls. A large sample of 1,093 individuals (650 COVID+ and 443 COVID–) completed an online self-report survey assessing their neurobehavioral symptoms. Relative to the COVID– network, the COVID+ network was very well-connected such that each neurobehavioral symptom was positively connected to the network. The COVID– network was largely disjointed, with most of the somatosensory symptoms forming their own cluster with no connections to other symptom groups and fatigue not being connected to any symptom. The cognitive and affective symptoms in the COVID– network were also largely connected to symptoms from within their own groups.

As an application of dynamic systems theory, psychometric network analysis can be a compelling approach to understand the associations among constellations of *symptoms* that make up clinical *syndromes*. The most important difference the analysis uncovered between the two networks was the coherence and well-connectedness of the COVID+ network compared to the disjointed COVID– network. This difference is likely due to the fact that a COVID– subsample by definition would not have patterns of lingering COVID-19 neurobehavioral symptoms. As a result, the subsample's symptoms, when present, would be due to other potential health conditions or disabilities and only interrelate if the symptoms were extremely similar. In contrast, the COVID+ network showed tremendous cross-talk across symptom types and greater connectivity overall, indicating that any given symptom has greater associations with other symptoms *because*

of a history of COVID-19. This analysis—for the first time in the literature—identified an interrelated network of lingering COVID-19 symptoms above and beyond those expected in a COVID– sample simply because specific neurobehavioral symptoms are similar. When compared to the COVID– network, the coherence of the COVID+ network suggested the utility of conceptualizing long-term neurobehavioral symptoms as a post-COVID *syndrome*.

In terms of specific relations among symptoms, the organize-to-headache bridge in the COVID+ network was stronger than in the COVID– network. Individuals with a history of COVID-19 uniquely showed a very strong connection between headaches and organization; while the COVID– sample showed the same edge, it was much weaker, perhaps reflecting the difference between a headache that is annoying/distracting among controls versus one that is truly debilitating among individuals with a history of COVID-19. Because the data were cross-sectional, it is unknown whether headaches cause organizational problems after COVID-19, or perhaps whether some other unknown variable (e.g., brain lesions) causes both. Similarly, the dizzy-to-balance bridge was stronger in the COVID+ network, consistent with emerging literature demonstrating vestibular symptoms being a common component of COVID-19 (104).

3.3.1. IMPLICATIONS

Lingering, post-COVID concerns commonly include depressed mood, insomnia, anxiety, irritability, fatigue, and “brain fog” (42–53,105,106); indeed, a subjective sense of persistent cognitive impairment is a central feature (47–52). The current findings suggest the high degree to which these symptoms co-occur after COVID-19. Among such patients who participated in comprehensive neuropsychological assessment, Krishnan et

al. (2022) (107) found a general pattern of mild impairment on measures of processing speed, attention, and executive functioning. Of note, 70% of these authors' participants also had a history of mood disorder prior to infection, and approximately 35% of their sample endorsed moderate-to-severe mood symptoms at the time of assessment. The current study found hearing, numbness, and tense symptoms were more central to the COVID+ network with the latter connected to sleep, fatigue, and frustrated symptoms. These current findings in light of those from Krishnan et al. (2022) (107) implicate an affective (e.g., mood, tension, frustration) component associated with post-COVID syndrome and suggest a potential role for psychotherapeutic and rehabilitation strategies to disrupt this network of affective distress. Given the potential benefit of conceptualizing post-COVID neurobehavioral symptoms as a syndrome, the current findings also suggest that the nodes with greater strength centrality estimates could be key targets for intervention—e.g., headaches, poor frustration tolerance, hearing difficulty, forgetfulness, and feeling anxious or tense.

The strength of the association between the central symptoms and other items on the NSI provide a framework for conceptualizing what may be clusters of symptoms experienced by individuals with a history of COVID-19. As our understanding of persistent COVID-19 symptoms evolves, these constellations of symptoms can be further investigated to examine premorbid factors that contribute to greater vulnerability to ongoing complications so that affected individuals can be triaged for specialized treatment in a patient-centered model of care. There are a variety of biological, psychological, and environmental factors that likely contribute to persistent COVID-19 neurobehavioral symptoms (e.g., sensitivity of multiple organ systems to COVID-19 that could affect cognitive health; pre-infection psychological and social vulnerabilities;

pandemic-related stress and isolation) (108). Rehabilitation clinicians would likely benefit from adopting a comprehensive approach targeting as many of these potential influences on neurobehavioral symptoms as possible. Cognitive and behavioral rehabilitation strategies targeting in particular these central symptom network features may hold promise to help those experiencing unresolved post-COVID symptomatology.

3.3.2. LIMITATIONS

Despite the importance of these findings, the current study had several limitations, and as a result, directions for future research. First, while the NSI has been used primarily among individuals with concussion, the items contain a wide variety of symptoms across somatic, affective, and cognitive domains, and the rating structure includes the degree to which items interfere with functioning, all of which may be useful to clinicians treating a wide variety of neurological conditions. However, there may be additional symptoms specific to COVID-19 not tapped by the NSI that future similar network analysis research should incorporate, such as tingle. Second, the current Spanish-speaking sample was from an extremely wide array of over 20 countries, and as a result, the findings have a high degree of generalizability, far more than in traditional studies. But nonetheless, the internet-based data collection presumed that participants had access to the internet and were fluent in Spanish. As a result, the findings may have limited generalizability to participants without internet access or who speak languages other than Spanish. Finally, the data were cross-sectional and correlational, and as a result, causal influence of symptoms on each other cannot be ascertained. Future longitudinal research can better tease apart the relative causal influence of COVID-19 symptoms on each other.

3.4. Conclusions

Considering these limitations, this study was the first to identify a coherent network of post-COVID-19 neurobehavioral symptoms and to compare the network to that of a group of individuals without a history of COVID-19. These findings suggest that many of the long-term neurobehavioral symptoms of COVID-19 form a discernable network and that headaches, frustration, hearing problems, forgetfulness, and tension are the most central symptoms. Cognitive and behavioral rehabilitation strategies targeting these central symptom network features may hold promise to help fracture the lingering symptom network of COVID-19.

CAPÍTULO 4. COGNITIVE AND BRAIN CONNECTIVITY TRAJECTORIES IN CRITICALLY ILL COVID-19 PATIENTS[4]

[4] Ramos-Usuga, D., Jimenez-Marin, A., Cabrera-Zubizarreta, A., Benito-Sanchez, I., Rivera, D., Martínez-Gutiérrez, E., Panera, E., Boado, V., Labayen, F., Cortes, J. M., Arango-Lasprilla, J. C. Cognitive and brain connectivity trajectories in critically ill COVID-19 patients. (Under review). Neurorehabilitation.

Multiple organ failure (MOF) is one of the main reasons for admitting patients infected with SARS CoV-2 to the Intensive Care Unit (ICU) and can cause short- and long-term neurological and neuropsychological deficits. Although various studies have been conducted to describe the sequelae of these critical patients, very few combine neuroimaging techniques with cognitive tests in the longitudinal assessment of these patients. Furthermore, to date, there is no study comparing patients with MOF due to COVID-19 with patients with MOF due to other causes. Since merely being admitted to the ICU can entail sequelae, comparing these two types of patients may allow for the identification of characteristics specific to COVID-19. Therefore, in this research, a neuropsychological evaluation and assessment of the functional connectivity of a group of patients with MOF due to COVID-19 or other causes have been carried out, and their functioning has been compared. Additionally, a control group of healthy individuals was included.

4.1. Methods

4.1.1. PARTICIPANTS

The sample was composed by 12 patients who suffered MOF after COVID-19 infection (COVID-19 group) and 12 MOF patients without COVID-19 infection (MOF group) who had been treated at the ICU of the Cruces University Hospital, as well as 12 HC, mainly relatives of the patients, matched with them by age, sex, and years of education.

The inclusion and exclusion criteria for MOF patients were the following: a) age between 18 and 65 years old; b) report of MOF due to respiratory failure, cardiogenic shock, or septic shock; c) no structural brain injury detected in T1 (no T1-BD); d) no history

of developmental problems, learning disabilities, or neurological or psychiatric conditions prior to admission to the ICU; e) no cerebral hypoxia during ICU admission; f) no previous chronic organ injury that might alter functional connectivity (109); g) no history of daily consumption and/or use of an illicit substance or other medications that may impact cognitive functioning; h) SOFA score ≥ 4 for at least 48 hours during ICU admission, implying an associated mortality rate of at least 20% (110); i) MMSE score ≥ 23 (111); and j) no contraindications for magnetic resonance imaging (e.g., morbid obesity, pacemaker, metal prostheses, or pregnancy); k) no severe visual and/or hearing deficit at the time of the evaluation; and l) ability to read and write at the time of evaluation. For COVID-19 participants, the inclusion criteria were the same as the aforementioned criteria for MOF plus additional criteria of m) diagnosed COVID-19 infection demonstrable by positive PCR test; and n) not having received any COVID-19 vaccine.

The inclusion criteria and exclusion for the HC were the following: a) age between 18 and 65 years old; b) no history of developmental problems, learning disabilities, or neurological or psychiatric conditions prior to admission to the ICU; c) no history of daily consumption and/or use of an illicit substance or other medications that may impact cognitive functioning; d) MMSE score ≥ 23; e) scored ≤ 4 on the Patient Health Questionnaire–9 (PHQ-9) for assessing depression; f) no contraindications for magnetic resonance imaging; g) no severe visual and/or hearing deficit at the time of the evaluation; and h) ability to read and write at the time of evaluation.

4.1.2. MEASURES

4.1.2.1. Screening tests

- The Sequential Organ Failure Assessment (SOFA) was used to assess the severity of MOF, quantifying the extent of organ dysfunction in patients after the failure. Through a 5-point scale (0-4), the functioning of the respiratory, cardiovascular, hepatic, renal, neurological, and coagulation systems is assessed (112).

- The Mini-Mental State Examination (MMSE) was included to assess the overall cognitive status of participants. This is a screening test composed of 30 items that assess temporal and spatial orientation, short-term and long-term memory, visuoconstructive skills, attention, calculation, reading and writing, and comprehension of simple commands. A cut-off point of ≤ 23 is often used to indicate mild cognitive impairment.

4.1.2.2. Neuropsychological evaluation

The assessment protocol included the following neuropsychological tests:

- Rey-Osterrieth Complex Figure (ROCF) (113). The ROCF is a tool used to assess perceptual organization and visual memory, as well as visuoconstructive ability. In the first part, the examinee is presented with the figure to copy onto a blank sheet of paper. After completing it, the figure is removed, a three-minute wait is done, and then the examinee is asked to reproduce the figure from memory. The figure is composed of 36 elements that are evaluated independently based on the location and accuracy of the shape, as follows: 2 points are awarded when the element is correctly drawn and located; 1 point when the element is correctly drawn but misplaced, or when it is well-placed but distorted or incomplete, although recognizable; 0.5

points when the element is distorted or incomplete, but recognizable and misplaced; 0 points when the element is absent or unrecognizable. The test score is the sum of the points awarded to each element, so it ranges from 0 to 36 points.

- Hopkins Verbal Learning Test-Revised (HVLT-R) (114). This is a verbal learning and memory test composed of a list of 12 words from three categories: professions, food, and sports. For verbal learning, the list is read aloud, and the examinee must say all the words she/he remembers, over three trials. Once this first part is completed, a 20-minute wait is done before administering the delayed recall trial, in which the examinee must evoke the words from the list. Finally, the recognition section is completed, consisting of the 12 words from the initial list (correct), 12 semantically related words, and another 12 semantically unrelated words. The examinee's task is to indicate whether each of the words belongs to the initial list or not. Three scores are obtained: immediate recall (0-36 points), delayed recall (0-12 points), and recognition (0-12 points).

- Stroop Color and Word Test (115). This test measures the inhibitory control of executive functions through three tasks. In the first task (Stroop-word), the examinee is asked to read the names of three colors (red, blue, and green) printed in black ink. In the second task (Stroop-color), the examinee must say the color of a series of stimuli (XXXX) printed in red, blue, and green ink. Finally, in the third task (Stroop Word-color), the examinee must say the name of the color in which the word is written, which in turn, is the name of another color.

To complete each task 45 second are given, and the score for each one is the number of items correctly named. In addition, the interference score is calculated using the following formula: Interference = C x W / C + W.

- Trial Making Test (TMT) (116). The TMT is used to assess various cognitive functions, such as attention, visual-motor speed, cognitive flexibility, visual search, and executive functions. The test is divided into two parts: the TMT-A contains 25 numbered circles distributed on a sheet of paper, which must be joined in an ascending fashion as quickly as possible. In the TMT-B the circles include both numbers (1-13) and letters (A-L) and must be joined by interleaving the numbers in ascending order and the letters in alphabetical order (1-A-2-B-3-C). The score for each condition is the time taken to complete the tasks.

- Brief Test of Attention (BTA) (117). The BTA is a test of attention consisting of two tasks. In the first (form N), the participant is read 10 alphanumeric series (e.g., A-9-3-B-L) that increase in length to increase difficulty, and the examinee must count the number of numbers in each series. The other task (form L) contains the same stimuli, but in this case the examinee must count the number of letters. For each correct item one point is awarded, with 20 being the maximum score.

- Symbol Digit Modalities Test (SDMT) (118). The SDMT assesses processing speed, attention, visual scanning, and motor speed. In this test, the participant has 90 seconds to assign the corresponding number to a series of symbols

according to a reference key. For each correct item, one point is awarded, with 110 being the maximum score.

- Modified Wisconsin Card Sorting Test (M-WCST) (119). The M-WCST is a test developed to assess abstract reasoning and the ability to adapt cognitive strategies to the changing environment. In this test the participant must categorize 48 cards into 4 key cards based on shape (triangle, square, and circle), color (red, yellow, and green), and number (1-5). Four scores are obtained: number of correct categories, number of perseverative errors, total number of errors and percentage of perseverative errors.

- Verbal Fluency Test (VFT) (116). This is a measure of verbal fluency composed of two independent tests; in the semantic verbal fluency test the examinee must produce for one minute as many words as he/she can think of that belong to a certain category (animals and fruits), while in the phonological verbal fluency test the examinee must say words that begin with a certain letter (F, A, S, M, P, R).

- Boston Naming Test (BNT) (120). The BNT is a tool designed to measure vocabulary, consisting of 60 black and white line drawings that the examinee must name. If the examinee does not give a spontaneous response, a semantic or phonological cue may be given.

4.1.2.3. Neuroimaging

Imaging acquisition

The brain Magnetic Resonance Images (MRIs) were acquired in a Philips 3-Tesla Achieva dStream MRI scanner with a 32-channel head coil and included the following sequences:

- Anatomical data: High resolution T1 images were acquired with a 3D Turbo Field Echo (TFE): repetition time TR = 7.4 ms, echo time TE = 3.4 ms, inversion time IT = 850 ms, voxel size = 1.1 × 1.1 × 1.2 mm^3, slice thickness = 1.2 mm, field of view FOV = 250 × 250 mm^2, 300 contiguous sagittal slices covering the entire brain and brainstem.

- Resting state functional data: A session with a total duration of 7.40 minutes was acquired, using SENSE (with a factor of 2.2) the following parameters: 214 whole-brain gradient echo echo-planar images with TR/TE = 2100/27 ms, FOV = 240 × 240 mm^2, voxel size = 3 × 3 × 3 mm^3, 80 × 80 matrix, slice thickness of 3 mm, 45 axial slices, interleaved in ascending order.

Imaging preprocessing

The resting-state fMRI (rs-fMRI) images were preprocessed using the CONN toolbox v21a (121). The default pipeline was used only modifying the outlier-frame criteria, marking as outlier such frames with FD>0.5. The voxel dimensions were also modified to 3 x 3 x 3 mm^3, and the spatial smoothing were modified to 6mm full width at half maximum (FWHM). For nuisance regression and temporal filtering, the chosen option was to do both steps simultaneously. The confounds removed were scrubbing, 12 movement parameters, 5 CSF components, and 5 White matter (WM) components.

Imaging statistical considerations

- Multiple comparisons correction: For any of the image analyses, statistics was assessed independently for all the number of voxels. To correct for multiple comparisons, a two-sided parametric correction was applied using a voxel threshold *p*-uncorrected < .05 and cluster threshold *p*-FDR < .05.

- Hypothesis contrasts for voxel brain morphometry differences: For addressing the morphological differences, the contrasts used were [1 -1] (COVID-19 > HC) and [-1 1] (COVID-19 < HC).

- Hypothesis contrasts for functional connectivity differences: For addressing the connectivity differences, the contrasts used were [1 -1 0] (COVID-19 > HC controlling by the effect of MOF) and [-1 1 0] (COVID-19 < MOF controlling by the effect of MOF). This ensured that any possible differences observed between groups may be due to the COVID-19 condition and not because participants in the COVID-19 group had also experienced MOF.

Functional connectivity and neuropsychological performance association: For the association with neuropsychological composites, the contrast used were [0 1 0 0 0] (group, composite, age, years of education, and SOFA). The reason for including SOFA variable as covariate is because in Jimenez-Marin et al. (2020) (122) authors reported an association between SOFA and brain connectivity in critically ill patients and may impact to the association between neuropsychological performance and connectivity. In this case, composites were calculated with *z*-scores of the tests computed using the mean and standard deviation of each single group, as this association was performed in each group separately.

4.1.3. PROCEDURE

The study began in Hospital (Code CEIC E16/52) and was performed in accordance with the Helsinki Declaration. All participants gave their written informed consent.

4.1.4. DATA ANALYSES

4.1.4.1. Descriptive analyses and neuropsychological performance

Means and standard deviations of demographic and clinical variables were calculated.

Performance differences on each neuropsychological test were assessed by One-Way ANOVA. To determine which specific groups differed post hoc tests (Tukey-Kramer when there was a normal distribution or Games-Howell when there was not a normal distribution) were run. Effect sizes were also assessed using eta-squared (η^2). Furthermore, each test was grouped into a composite (e.g., executive functioning, language), which was calculated by the sum of the *z*-scores of the tests based on the means and standard deviations of the three groups together, then divided by the square root of the number of tests included in each composite. Group comparisons among composites were performed using One-Way ANOVA. All the analyses were run in Matlab 2021b (The MathWorks, Inc.) and SPSS Statistics 20.

3.1.4.2. Imaging analyses

<u>Structural abnormalities</u>

Voxel-based morphometry (VBM) was applied with FSL-VBM (123), FSL version 6.0.1, an optimized VBM protocol carried out with FSL tools. The modulated gray matter images resulting from the tool were then smoothed with an isotropic Gaussian kernel of

full width at half maximum of 9.42 mm (σ=4 mm). Final images were used for group comparison.

Functional connectivity analyses

Connectivity maps per each subject for eight resting state networks (RSN) included in CONN were generated using the seed-based-correlation (SBC) analyses (124). The seeds were obtained by averaging the fMRI time-series across all regions within each RSN. As a result, we obtained for each subject a corresponding brain map for each RSN. These maps were next used for group comparisons and for the association between brain functional connectivity and cognitive performance as represented by each composite. For all the details for assessing the statistical significance, see the supplementary material.

4.2. Results

4.2.1. DESCRIPTIVE ANALYSES

Demographic and clinical variables for the three groups are shown in Table 4.1. The mean age for the sample ranged from 54.83 to 55.50, and the mean of the years of education ranged from 12.17 to 13.42. Moreover, more than half of the sample in all three groups were males. There were no significant differences in terms of age, sex, or years of education between the HC and COVID-19 groups, nor between the MOF and COVID-19 groups. During ICU admission, the mean SOFA scores of the MOF and COVID-19 groups were 9.42 and 6.83, respectively. On the other hand, the mean MMSE scores of HC, MOF, and COVID-19 groups were 29.22, 28.83, and 28.81, respectively. There were no significant differences in SOFA and MMSE across the three groups.

Table 4.1. Demographic and clinical variables

Variables, units	HC	MOF	COVID	t_{HC}	p_{HC}	Effect Size HC	t_{MOF}	p_{MOF}	Effect Size MOF
Demographics									
Age, years	55.17 (6.60)	55.50 (5.68)	54.83 (6.46)	-0.13	0.90	-0.05	-0.27	0.79	-0.11
Males, n (%)	6 (50)	7 (58.33)	7 (58.33)	0.17	0.68	0.16	0	1	0
Education, years	12.67 (5.55)	12.17 (4.13)	13.42 (4.58)	0.36	0.72	0.15	0.70	0.49	0.29
MMSE	29.22 (0.83)	28.83 (1.46)	28.81 (1.17)	-0.87	0.40	-0.39	-0.03	0.98	-0.01
SOFA	NA	9.42 (3.99)	6.83 (2.08)	NA	NA	NA	-1.98	0.06	-0.81

4.2.2. NEUROPSYCHOLOGICAL PERFORMANCE

The neuropsychological assessment at 6 months from ICU discharge revealed that the COVID-19 group generally performed worse across all tests compared to HC and MOF group, although exhibiting fewer pronounced distinctions in comparison to this last group. The One-Way ANOVAs shown a marginally significant differences in HVLT-R Recall ($F= 3.1$; $p=0.05$), with the Tukey-Kramer post hoc showing significant differences between COVID-19 group and HC ($p> 0.05$). Additionally, the effect size was large ($\eta^2= 0.16$). At 12 months after ICU discharge, there were no significant differences between groups, although scores on most tests were also lower in the COVID-19 group compared to the other two groups.

4.2.3. BRAIN MORPHOLOGY

Structural brain comparisons using voxel-based morphometry provided no significant differences between the COVID-19 and HC groups.

4.2.4. FUNCTIONAL CONNECTIVITY

Group differences were assessed in the functional connectivity of eight well-known RSNs following an image preprocessing pipeline detailed in Figure 4.1. After multiple comparison correction, the only network with significant differences in the contrasts COVID-19 > HC controlling for MOF, and COVID-19 < HC controlling for MOF in both time-points (e.g., 6 and 12 months) was the salience network (see Figure 4.2, brain plot). These significant connectivity alterations consisted of a combination of decreased positive correlations from the salience region Anterior Cingulate Cortex (ACC) and decreased negative correlations between the salience node and DMN in the angular gyrus, precuneus, ACC, and superior frontal gyrus. For each of the clusters resulting from

the group comparisons (represented in different colors in Figure 4.2), we obtained its median value in the SBC map for each participant and compared the different groups. Notably, the boxplots illustrate a general trend, indicating that both positive connections (yellow cluster) and negative connections (green, purple, red, and blue clusters) increased from HC to MOF and further from MOF to COVID-19, demonstrating a progressive decrease in connectivity from healthy to MOF and from MOF to COVID-19.

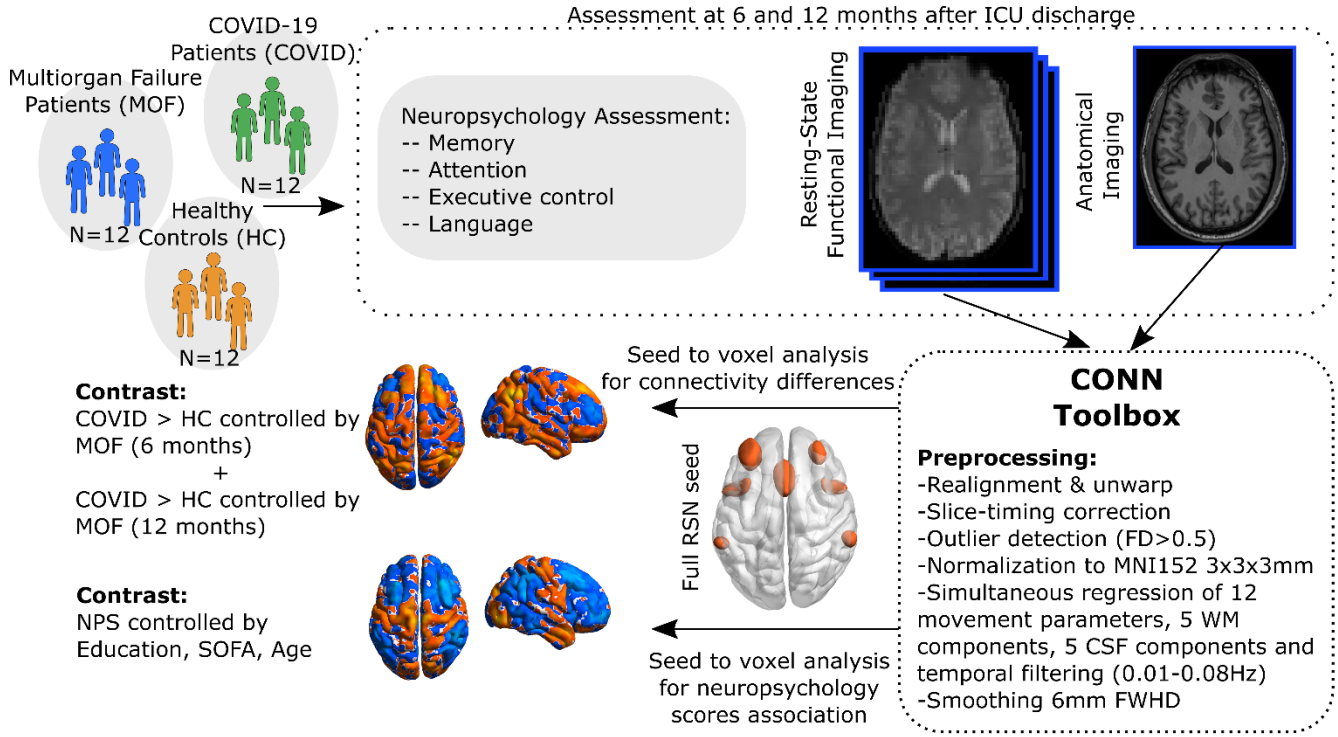

Figure 4.1. Resting-state fMRI preprocessing and analysis pipeline.

Note: Double acquisition is needed: High resolution anatomical images (T1) and functional images at rest. Following state-of-the-art CONN pipeline of neuroimaging preprocessing, time-series of the blood oxygenation level dependent (BOLD) signal were obtained for each voxel. Using as seeds the average functional dynamics across all the voxels belonging to each resting state network, and applying seed to voxel analysis (a.k.a. seed-based correlation), we built functional connectivity brain maps for each RSN, used for group comparison and for assessing the association with neuropsychological measures.

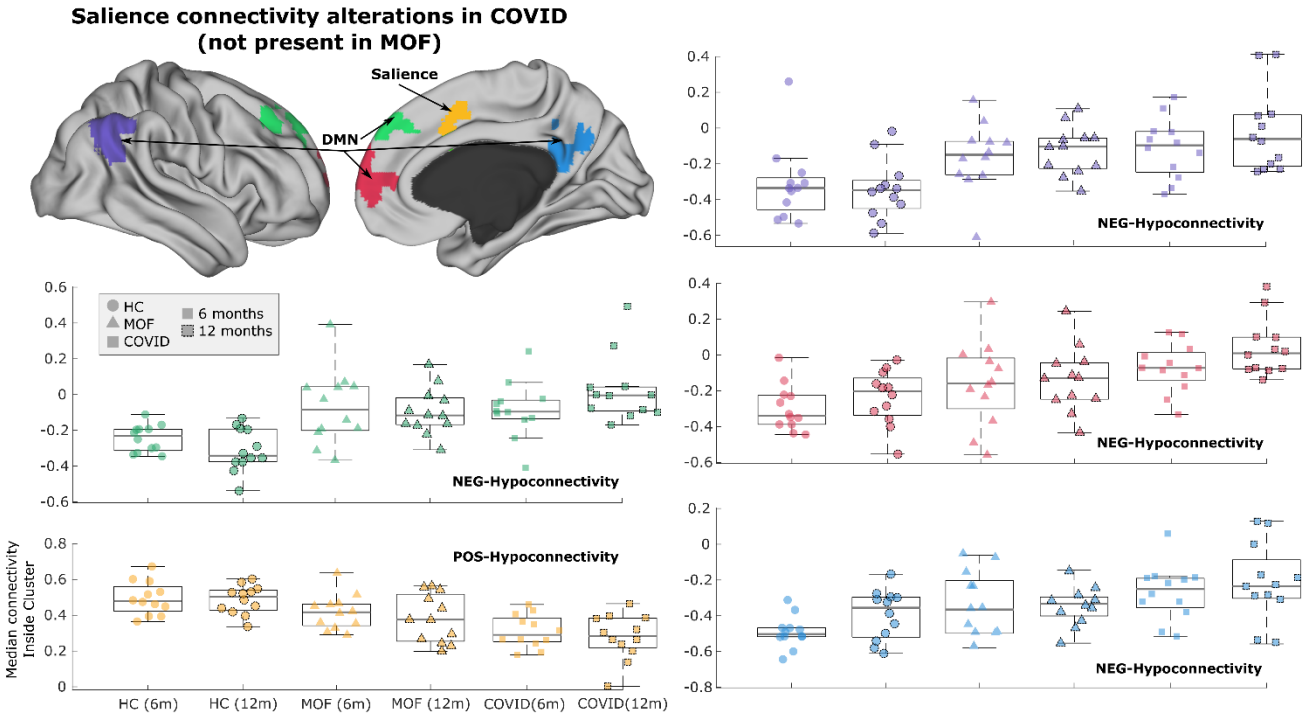

Figure 4.2. Salience connectivity alterations in critically ill COVID-19 patients.

Note: Statistically significant connectivity alterations not present in MOF were found in a cluster inside the salience network (yellow) and in several clusters belonging to the DMN (purple, green, red, and blue). For each participant, the median connectivity within each cluster was calculated and represented in the boxplots (different colors refer to different clusters). Each dot represents a different participant, being circles for the HC group, triangles for the MOF group, and squares for the COVID-19 group. No line around the shapes represents the 6 months' median connectivity, and the dotted line represents the one at 12 months. NEG-Hypoconnectivity refers to hypoconnectivity occurring in negative functional connections (green, purple, red, and blue), while POS-Hypoconnectivity indicates hypoconnectivity in positive functional connections (yellow).

4.2.5. ASSOCIATION BETWEEN FUNCTIONAL CONNECTIVITY AND NEUROPSYCHOLOGICAL PERFORMANCE

The SBC maps of the salience network were used for voxel-based associations with the four different composites. After multiple comparison correction, significant associations surviving at the two time points only existed for the attention domain (Figure 4.3), in a cluster of voxels located in the superior frontal gyrus. At +12m time point, a second cluster also emerged in the angular gyrus (colored in red in Figure 4.3). The two clusters are part of the DMN. The scatterplots in Figure 4.3 represent the association between median values of salience connectivity and the attention score for both time-points. Negative correlations (r=-0.83, p=.002 at 6 months; r=-.92, p<0.001 at 12 months) were found for the COVID-19 group, whereas no associations were found in those regions in the MOF and HC groups. The negative correlations indicated that the patients with the highest attention scores had a relatively more negative correlation between salience and DMN.

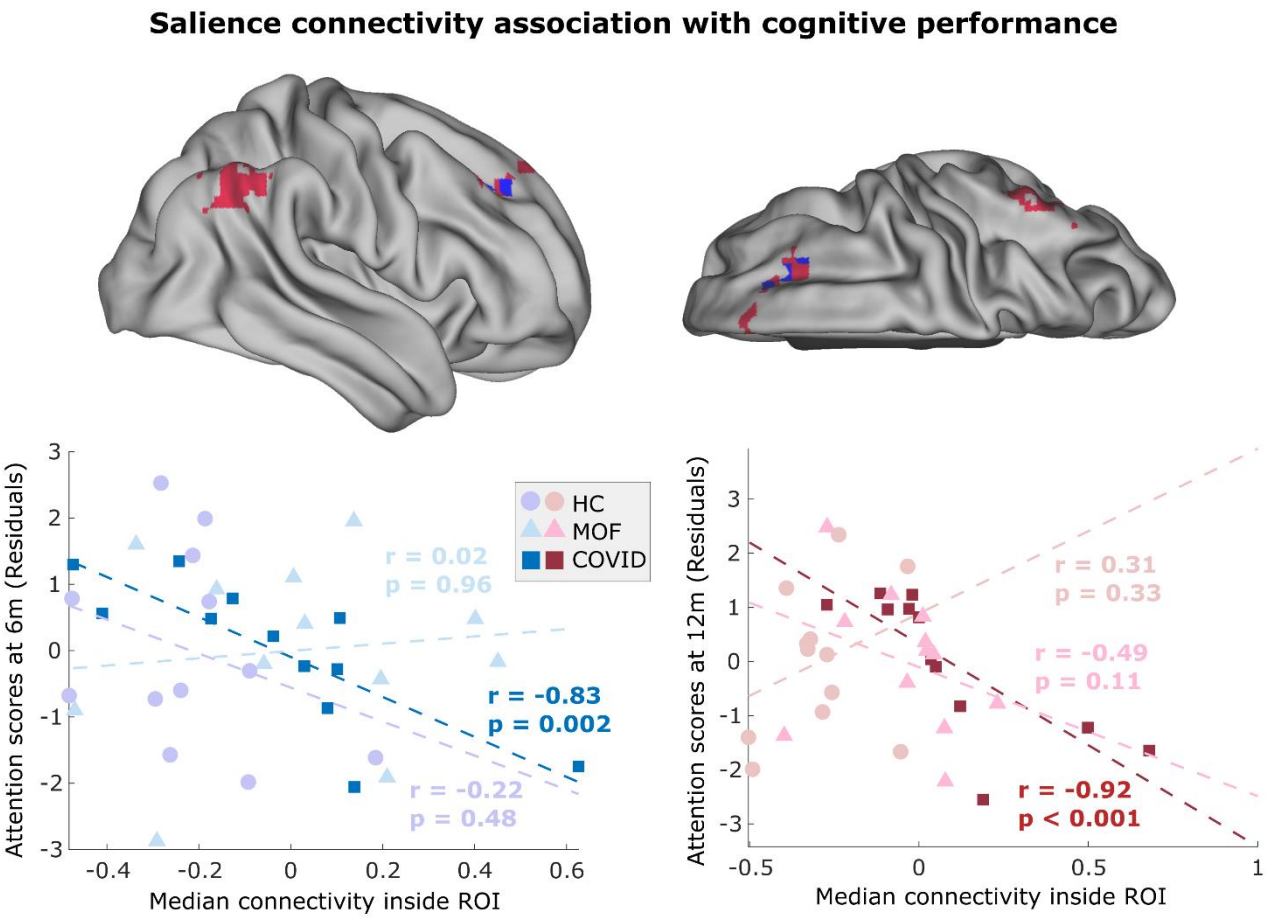

Figure 4.3. Association between functional connectivity of the salience network and cognitive performance in critically ill COVID-19 patients.

Note: The association between the salience connectivity was correlated with the attention domain at 6 (blue clusters) and 12 months (red clusters) after ICU discharge. The two scatterplots show that statistically significant associations were only found in the COVID-19 group.

4.3. Discussion

The goals of this study were: 1) to compare the cognitive functioning of the COVID-19, MOF, and HC groups through a neuropsychological battery; 2) to assess the functional connectivity differences between the COVID-19 and HC groups, correcting for the MOF group, and 3) to assess the association between cognitive functioning and functional connectivity across the three groups.

Firstly, the COVID-19 group performed worse at 6 months after ICU discharge across almost all neuropsychological tests compared to the other two groups, although significant differences were only found in the HVLT-R Recall compared to the HC group. At 12 months there were no significant differences in any of the tests, although the means of the COVID-19 group continued being, in general, lower than those of the other two groups. It should be noted that the effect size of the HVLT-R Recall was large (η^2= 0.16).

Previous literature has shown that even months after hospital discharge, patients infected with SARS CoV-2 present cognitive alterations related to memory (43,45,46,56), attention and processing speed (42–44,46), executive functions (45,46) and even language (46) and motor skills (44,46). In the present study, significant differences have only been found in one HVLT-R score that measures verbal learning and memory, which partially agrees with previous studies (43,45,46,56). Although it is true that it is only a score, the effect size has been large, so one could speculate that, if the sample size were increased, the differences would be more evident and significant, even in the rest of the scores. Furthermore, it should be noted that the evaluation protocols of the present study and that of Díez-Cirarda et al. (2022) (56) share five neuropsychological tests, and that the means of COVID-19 patients from both studies are similar. Although the two

samples may vary in many aspects, they are Spanish patients who have been hospitalized for COVID-19. One of the factors that most influences the variability of results in research is the type of tests selected to evaluate the participants, therefore, it would be recommended to establish a specific neuropsychological evaluation protocol for patients with COVID-19 who present cognitive complaints, in order to compare the results of the different studies. This is especially relevant since it is a syndrome that is still very unknown and still requires further research.

The results of the functional connectivity demonstrated an atypical connectivity pattern in the COVID-19 group compared to the HC group in both 6 and 12 months, characterized by hypoconnectivity of the SN to one of its nodes (ACC) and with the DMN to four of its nodes (angular gyrus, precuneous, ACC, and superior frontal gyrus). These findings are in agreement to those of (55) who found that the functional connectivity of patients with COVID-19 was significantly lower than that of HC patients both within the DMN and between the DMN and the NS. In addition, (56) also found hypoconnectivity between the left and right parahippocampal gyrus and between the left cerebellum III and the left and right frontal superior orbital cortex. The literature on functional connectivity in populations with neurological disorders is varied, as some studies report hyperconnectivity (125,126), whereas others find hypoconnectivity (62,63,65) in these clinical populations. However, a recent study by (127) evaluated people with preclinical profiles of Alzheimer's disease (AD) with fMRI and PET-tau, finding hyperconnectivity between the DMN and SN in participants with low TAU levels, yet hypoconnectivity among participants with higher TAU levels. According to the authors, the initial hyperconnectivity could be a compensatory mechanism in the early phases of a brain disorder, such as AD, which would later lead to a decrease in functional connectivity once

these compensatory mechanisms are saturated by neuronal loss. Future studies are needed that include larger sample sizes and that evaluate the trajectories of functional connectivity from the acute phase to more chronic states of the disease, which thus may be able to replicate the pattern of findings in the present study and those of (55).

Finally, when studying the relationship between cognitive functioning and functional connectivity, the connectivity between the SN and certain areas of the DMN (angular gyrus and superior frontal gyrus) was correlated with the attention domain and information processing speed in the COVID-19 group at both 6 months and 12 months. The patients who had a more negative connectivity between SN and DMN had better scores. This association was not present in the HC and MOF groups. The SN, also known as the ventral attention network (VAN), is comprised mainly by the anterior insula and the anterior cingulate cortex. The VAN is involved in the detection and integration of outgoing stimuli, attention, and memory, including exchanging information with other networks on a large scale, which ultimately makes it possible to initiate behavior in accordance with the highlighted stimuli (128). VAN and DMN have been shown to have a mutual negative correlation in healthy populations (129–132), in agreement with our findings showing that, the patients with better attention functioning have consistently higher VAN-DMN negative correlations

To date, only the cross-sectional study by (56) has examined both cognitive functioning and functional connectivity in the resting state among patients with COVID-19. Their results indicated that hypoconnectivity between the bilateral frontal superior orbital cortex and the cerebellum was associated with poorer performance on tests of learning and memory. Both neuropsychological assessment and neuroimaging are

increasingly used tools in the field of neuroscience research for the study of neurological diseases and in the clinic for evaluation and diagnostic purposes. For this reason, the combined use of these tools is essential in future longitudinal studies with people with COVID-19.

4.3.1. LIMITATIONS

The results of this study must be considered while taking into account several limitations. First, the study sample size is small. Future research should include larger sample sizes in a replication of study findings. Second, the neuropsychological evaluation included measures of processing speed and attention, learning and memory, executive functioning, and language; however, it is possible that participants also experienced problems in other areas of cognitive functioning that were not evaluated, such as perception, motor skills, or orientation. It is recommended that future studies conduct more comprehensive evaluations. Third, it was not possible to determine if all individuals who participated had the same type of variant of COVID-19. As has been reported in the literature, there are some COVID-19 variants that have been associated with the presence of milder symptoms (133), and for this reason, future studies should try to homogenize the groups according to the variants that caused the infection to assess whether the profiles of cognitive functioning and/or functional connectivity varies between groups. Likewise, this study did not assess if the patients with COVID-19 had been infected for the first time or if they previously been diagnosed with the disease. This is important, as some studies have found that COVID-19 reinfections may increase the severity of lung, heart, and CNS problems, and even the risk of death (134). Fourth, the patients with COVID-19 who participated in this study did not received any dose of the

COVID-19 vaccine, which is relevant given that various studies have found that the number of vaccine doses received significant reduced symptoms in those subsequently infected people (135), which could also be associated with a neuropsychological and functional connectivity profile different from that found in this study. Finally, we did not acquire neuroimaging sequences for determining the presence of microhemorrhages, previously reported in other studies on COVID-19, which may affect brain connectivity.

4.4. Conclusions

To the best of the authors' knowledge, this is the first study to merge neuropsychological assessment and functional connectivity examination longitudinally in critically ill COVID-19 patients, all of whom have experienced multi-organ failure (MOF). The main result is that patients with COVID-19 present a different functional connectivity pattern than healthy participants, characterized by hypoconnectivity between the DMN and SN, which is associated with worse scores on attention and information processing speed both at 6 and 12 months after discharge from the ICU.

There is an extensive literature on COVID-19, particularly on the neurological alterations that some patients present. However, most research has been based on case studies, research with a cross-sectional design, and neuroimaging limited to the study of brain structure. Given that functional connectivity may provide relevant information on the neurological alterations of this disease, the present study employed a longitudinal design to study the neuropsychological functioning and the brain connectivity while also including two control groups (HC and MOF not due to COVID-19) with which to compare the outcomes of COVID-19 patients. COVID-19 continues to be a global public health emergency, and its long-term consequences are largely unknown. Longitudinal,

multidisciplinary research is essential to understand the nature of the disease and its sequelae to improve prevention, diagnosis, and treatment and minimize disease burden in the global population.

CAPÍTULO 5. CONCLUSIONES

A pesar de que la COVID-19 ya no se considera una emergencia sanitaria internacional, y los casos de infección y muerte por este virus han disminuido considerablemente, existe una preocupación generalizada por las secuelas que está dejando esta enfermedad en un alto porcentaje de personas infectadas. La COVID persistente o síndrome post-COVID, como así se le ha llamado a este síndrome, puede cursar con una amplia variedad de síntomas que difieren de una persona a otra y que pueden seguir presentes más de dos meses después de la infección. No obstante, según los estudios realizados en este campo, los síntomas más prevalentes son la fatiga y los problemas cognitivos, principalmente dificultades atencionales, procesamiento lento de la información y olvidos frecuentes. Además, algunos estudios también han reportado problemas emocionales como ansiedad y depresión. Por otra parte, en las pocas investigaciones en las que se ha evaluado la conectividad funcional en estos pacientes, se ha encontrado una hipoconectividad entre diversas redes neuronales, como la red de saliencia o la red neuronal por defecto (RND), que se asocia con alteraciones cognitivas medidas con pruebas neuropsicológicas.

Si bien la literatura en este tema es extensa y no deja de incrementar, aún existen diversas cuestiones que todavía no han sido abordadas y ciertas limitaciones en la investigación actual que deben ser consideradas. Atendiendo a estos aspectos, se plantearon dos investigaciones con el objetivo principal de examinar la evolución del funcionamiento neuroconductual, cognitivo y de la conectividad cerebral funcional de un grupo de personas infectadas por el SARS CoV-2. De estas dos investigaciones se han desarrollado tres estudios que forman parte de la presente tesis doctoral.

En el primer estudio se comparó la presencia de los síntomas neuroconductuales antes de la infección, durante y después (al momento de realizar la encuesta), a través de una escala estandarizada, en una gran muestra internacional. Se encontró un incremento de todos los síntomas durante la infección en comparación con el estado premórbido de los participantes, siendo más notorios la fatiga y los dolores de cabeza (síntomas afectivos), los mareos y los cambios en el gusto/olfato y apetito (síntomas somáticos), así como los problemas de atención y procesamiento lento de la información (síntomas cognitivos). Al examinar la evolución de estos síntomas, incluso 5 meses después de superar la enfermedad, se encontró una ligera mejora de los síntomas somáticos y afectivos, mas no de los síntomas cognitivos. Además, los factores de riesgo relacionados con el aumento de estos síntomas fueron: ser mujer/trans, estar desempleado, ser joven, tener menor nivel educativo, tener otra condición de salud crónica, mayor gravedad de la COVID-19, mayor número de días desde el diagnóstico de la COVID-19, no haber recibido oxigenoterapia y haber sido hospitalizado. Por otra parte, las personas de América del Norte, Europa y Asia Central reportaron tener mayores síntomas neuroconductuales tras la infección que aquellas personas de América Latina y África subsahariana.

En el segundo estudio se quiso complementar los resultados previamente expuestos estudiando las interrelaciones entre dichos síntomas como un sistema dinámico. En este caso, tan solo se utilizó una muestra de participantes de habla hispana con el fin de poder compararla con una muestra de otro estudio en el que se utilizó la misma escala en participantes sin COVID-19. En la muestra con COVID-19 se obtuvo una red bien interrelacionada, en la que cada síntoma neuroconductual estaba conectado positivamente a la red, siendo los dolores de cabeza, la frustración, los problemas de

audición, los olvidos y la ansiedad los síntomas más centrales. En cambio, la red de la muestra sin COVID-19 resultó estar en gran medida desarticulada, con la mayoría de los síntomas somáticos formando su propio grupo, sin conexiones con otros grupos de síntomas y la fatiga estando desconectada de todos los síntomas.

Los resultados de estos dos estudios recalcan la presencia de secuelas a largo plazo tras la infección por el SARS CoV-2, que coinciden con las reportadas previamente en la literatura. Además, el hecho de que los síntomas estén interrelacionados es un hallazgo relevante, ya que es muy probable que la presencia de ciertos síntomas influya en la aparición o agravamiento de otros. De hecho, los resultados muestran, por ejemplo, una estrecha conexión entre los dolores de cabeza con la lentitud en el procesamiento de la información, los olvidos y las dificultades en la toma de decisiones. Esta relación entre el dolor y la cognición, particularmente, el efecto negativo que tiene el dolor en funciones cognitivas como la atención, memoria, procesamiento, funcionamiento ejecutivo y toma de decisiones ha sido ampliamente demostrado en estudios previos (136). Por lo tanto, conocer estas conexiones podría ser de utilidad a la hora de determinar qué tratamientos podrían ser más adecuados para cada paciente, teniendo en cuenta que un enfoque terapéutico dirigido a un síntoma, como puede ser el dolor, podría mejorar otros síntomas indirectamente.

Finalmente, en el tercer estudio, se comparó longitudinalmente el funcionamiento cognitivo y la conectividad funcional de un grupo de pacientes ingresados en la UCI por un FMO debido a la COVID-19 con el de otro grupo de pacientes con FMO debido a otra causa y un grupo de controles sanos. El principal hallazgo fue un patrón de hipoconectividad entre la RND y la red de saliencia en los pacientes con COVID-

19, que se asoció con peores puntuaciones en atención y velocidad de procesamiento de la información. En personas sanas, la RND y la red de saliencia presentan una conectividad negativa, es decir, que una mayor activación de una de las redes implica una menor activación en la otra. Esto es debido a que la RND se asocia con un estado de reposo o introspectivo, mientras que la red de saliencia está implicada en la integración de información sensorial, emocional y cognitiva para facilitar procesos cognitivos superiores como la comunicación, la autoconciencia y el comportamiento social (137). Por lo tanto, la disminución de la conectividad funcional entre estas redes, encontrada en los pacientes con COVID-19, supone un patrón atípico ya reportado en el estudio de Fischer et al. (2022) (55), y que, de hecho, ha sido observado en otras poblaciones clínicas (62,63,65).

En conclusión, la evidencia presentada apoya la idea de que, a pesar de ser principalmente un síndrome respiratorio, la COVID-19 cursa con un amplio abanico de síntomas de diferente índole, que se relacionan entre sí, y que pueden persistir tiempo después de que el virus ha sido eliminado. Que esto ocurra parece estar influido por una serie de factores demográficos (p. ej., edad, género, lugar de residencia) y clínicos (p. ej., comorbilidades, gravedad de la enfermedad). Dentro de estos síntomas predominan los problemas cognitivos, particularmente las dificultades atencionales y una lentitud en el procesamiento de la información, lo que concuerda con los criterios de disfunción cognitiva en el síndrome post-COVID (IC-CoDi-COVID) propuestos recientemente por Matias-Guiu et al. (2023) (138). Además, estas dificultades atencionales parecen estar relacionadas con un patrón de hipoconectividad funcional entre la RND y la red de saliencia.

Si bien estas investigaciones no están exentas de limitaciones, cabe destacar que en los dos primeros estudios se cuenta con una muestra grande de personas de diferentes regiones del planeta, lo que ha permitido hacer comparaciones globales y conocer parte de la realidad de algunos lugares poco estudiados, como Latinoamérica y África. Además, se han encontrado una serie de factores de riesgo para la presencia de síntomas persistentes que no han sido previamente reportados. Finalmente, a pesar de incluir una muestra pequeña, en el último estudio se ha combinado la neuroimagen y la neuropsicología en un estudio longitudinal, dos disciplinas muy relevantes en la actualidad en el estudio de las alteraciones cognitivas y neurológicas a nivel internacional.

REFERENCIAS

1. Hasöksüz M, Kiliç S, Saraç F. Coronaviruses and SARS-COV-2. Turk J Med Sci. 2020 Apr 21;50(SI-1):549–56.

2. Zhang XY, Huang HJ, Zhuang DL, Nasser MI, Yang MH, Zhu P, et al. Biological, clinical and epidemiological features of COVID-19, SARS and MERS and AutoDock simulation of ACE2. Infect Dis Poverty. 2020 Dec;9(1):99.

3. Kesheh MM, Hosseini P, Soltani S, Zandi M. An overview on the seven pathogenic human coronaviruses. Reviews in Medical Virology. 2022 Mar;32(2):e2282.

4. Hui DSC, Zumla A. Severe Acute Respiratory Syndrome. Infectious Disease Clinics of North America. 2019 Dec;33(4):869–89.

5. Centro para el Control y la Prevención de Enfermedades (CDC). Severe Acute Respiratory Syndrome (SARS) [Internet]. 2020. Available from: https://www.cdc.gov/sars/index-sp.html

6. Organización Mundial de la Salud (OMS). Coronavirus causante del síndrome respiratorio de Oriente Medio (MERS-CoV) [Internet]. 2022. Available from: https://www.who.int/es/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov)

7. World Health Organization. WHO Coronavirus (COVID-19) Dashboard [Internet]. 2023. Available from:

https://covid19.who.int/#:~:text=Globally%2C%20as%20of%2012%3A00pm%20CET%2C,vaccine%20doses%20have%20been%20administered

8. Food and Drug Administration (FDA). Vacunas contra el COVID-19 [Internet]. 2023. Available from: https://www.fda.gov/about-fda/fda-en-espanol/vacunas-contra-el-covid-19

9. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Información de vacunas autorizadas [Internet]. Available from: https://www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid%E2%80%9119/vacunas-contra-la-covid%E2%80%9119/informacion-de-vacunas-autorizadas/

10. Pastrian-Soto G. Presencia y Expresión del Receptor ACE2 (Target de SARS-CoV-2) en Tejidos Humanos y Cavidad Oral. Posibles Rutas de Infección en Órganos Orales. Int J Odontostomat. 2020 Dec;14(4):501–7.

11. Cevik M, Kuppalli K, Kindrachuk J, Peiris M. Virology, transmission, and pathogenesis of SARS-CoV-2. BMJ. 2020 Oct 23;m3862.

12. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol. 2021 Mar;19(3):141–54.

13. Sanz JM, Gómez Lahoz AM, Martín RO. Papel del sistema inmune en la infección por el SARS-CoV-2: inmunopatología de la COVID-19. Medicine - Programa de Formación Médica Continuada Acreditado. 2021 May;13(33):1917–31.

14. Paola TP. Visión panorámica del sistema inmune. Revista Médica Clínica Las Condes. 2012 Jul;23(4):446–57.

15. Mokhtari T, Hassani F, Ghaffari N, Ebrahimi B, Yarahmadi A, Hassanzadeh G. COVID-19 and multiorgan failure: A narrative review on potential mechanisms. J Mol Hist. 2020 Dec;51(6):613–28.

16. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020 May;368(6490):473–4.

17. Marshall JC. The multiple organ dysfunction syndrome. In: Holzheimer RG, Mannick JA, editors. Surgical Treatment: Evidence-Based and Problem-Oriented. Munich: Zuckschwerdt; 2001. Available from: https://www.ncbi.nlm.nih.gov/books/NBK6868/. Holzheimer RG, Mannick JA, editors.

18. Centro para el Control y la Prevención de Enfermedades (CDC). Factores que aumentan el riesgo de enfermarse gravemente a causa del COVID-19 [Internet]. 2023. Available from: https://espanol.cdc.gov/coronavirus/2019-ncov/your-health/risks-getting-very-sick.html

19. Elrobaa IH, New KJ. COVID-19: Pulmonary and Extra Pulmonary Manifestations. Front Public Health. 2021 Sep 28;9:711616.

20. Oran DP, Topol EJ. The Proportion of SARS-CoV-2 Infections That Are Asymptomatic: A Systematic Review. Ann Intern Med. 2021 May;174(5):655–62.

21. Organización Mundial de la Salud (OMS). Coronavirus [Internet]. s.f. Available from: https://www.who.int/es/health-topics/coronavirus#tab=tab_1

22. Umakanthan S, Sahu P, Ranade AV, Bukelo MM, Rao JS, Abrahao-Machado LF, et al. Origin, transmission, diagnosis and management of coronavirus disease 2019 (COVID-19). Postgraduate medical journal. 2020;96(1142):753–8.

23. Gil R, Bitar P, Deza C, Dreyse J, Florenzano M, Ibarra C, et al. CUADRO CLÍNICO DEL COVID-19. Revista Médica Clínica Las Condes. 2021 Jan;32(1):20–9.

24. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004 Jun;203(2):631–7.

25. Vázquez JB, Menchén DA, Lloréns MMM, Moreno JS. Manifestaciones sistémicas y extrapulmonares en la COVID-19. Medicine - Programa de Formación Médica Continuada Acreditado. 2022 May;13(55):3235–45.

26. Nolen LT, Mukerji SS, Mejia NI. Post-acute neurological consequences of COVID-19: an unequal burden. Nat Med. 2022 Jan;28(1):20–3.

27. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review. Clin Neurol Neurosurg. 2020 Jul;194:105921.

28. Pezzini A, Padovani A. Lifting the mask on neurological manifestations of COVID-19. Nat Rev Neurol. 2020 Nov;16(11):636–44.

29. Ahmed MU, Hanif M, Ali MJ, Haider MA, Kherani D, Memon GM, et al. Neurological Manifestations of COVID-19 (SARS-CoV-2): A Review. Front Neurol. 2020;11:518.

30. Mishra R, Banerjea AC. Neurological Damage by Coronaviruses: A Catastrophe in the Queue! Front Immunol. 2020;11:565521.

31. Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol. 2020 Nov;7(11):2221–30.

32. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, et al. Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System? Viruses. 2019 Dec 20;12(1):14.

33. Wang F, Kream RM, Stefano GB. Long-Term Respiratory and Neurological Sequelae of COVID-19. Med Sci Monit [Internet]. 2020 Nov 1 [cited 2022 Sep 30];26. Available from: https://www.medscimonit.com/abstract/index/idArt/928996

34. Matschke J, Lütgehetmann M, Hagel C, Sperhake JP, Schröder AS, Edler C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. The Lancet Neurology. 2020 Nov;19(11):919–29.

35. Li Y, Zhang Y, Tan B. What can cerebrospinal fluid testing and brain autopsies tell us about viral neuroinvasion of SARS-CoV-2. Journal of Medical Virology. 2021 Jul;93(7):4247–57.

36. Isacson O. The Consequences of Coronavirus-Induced Cytokine Storm Are Associated With Neurological Diseases, Which May Be Preventable. Front Neurol. 2020;11:745.

37. Hirunpattarasilp C, James G, Freitas F, Sethi H, Kittler JT, Huo J, et al. SARS-CoV-2 binding to ACE2 triggers pericyte-mediated angiotensin-evoked cerebral capillary constriction. bioRxiv; 2021 Apr.

38. Hugon J, Msika EF, Queneau M, Farid K, Paquet C. Long COVID: cognitive complaints (brain fog) and dysfunction of the cingulate cortex. J Neurol. 2021 Jun 18;269(1):44–6.

39. Mahase E. Covid-19: What do we know about “long covid”? BMJ. 2020 Jul 14;370:m2815.

40. Méndez R, Balanzá-Martínez V, Luperdi SC, Estrada I, Latorre A, González-Jiménez P, et al. Short-term neuropsychiatric outcomes and quality of life in COVID-19 survivors. J Intern Med. 2021 Sep;290(3):621–31.

41. Meo SA, Abukhalaf AA, Alomar AA, Al-Hussain F. Magnetic Resonance Imaging (MRI) and neurological manifestations in SARS-CoV-2 patients. European Review for Medical and Pharmacological Sciences. 2021 Jan;25(2):1101–8.

42. Zhou H, Lu S, Chen J, Wei N, Wang D, Lyu H, et al. The landscape of cognitive function in recovered COVID-19 patients. J Psychiatr Res. 2020 Oct;129:98–102.

43. Ferrucci R, Dini M, Rosci C, Capozza A, Groppo E, Reitano MR, et al. One-year cognitive follow-up of COVID-19 hospitalized patients. Euro J of Neurology. 2022 Jul;29(7):2006–14.

44. Poletti S, Palladini M, Mazza MG, De Lorenzo R, The COVID-19 BioB Outpatient Clinic Study group, Irene B, et al. Long-term consequences of COVID-19 on cognitive

functioning up to 6 months after discharge: role of depression and impact on quality of life. Eur Arch Psychiatry Clin Neurosci. 2022 Aug;272(5):773–82.

45. Miskowiak KW, Johnsen S, Sattler SM, Nielsen S, Kunalan K, Rungby J, et al. Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables. Eur Neuropsychopharmacol. 2021 May;46:39–48.

46. Schild AK, Goereci Y, Scharfenberg D, Klein K, Lülling J, Meiberth D, et al. Multidomain cognitive impairment in non-hospitalized patients with the post-COVID-19 syndrome: results from a prospective monocentric cohort. J Neurol. 2023 Mar;270(3):1215–23.

47. Orrù G, Bertelloni D, Diolaiuti F, Mucci F, Di Giuseppe M, Biella M, et al. Long-COVID Syndrome? A Study on the Persistence of Neurological, Psychological and Physiological Symptoms. Healthcare (Basel). 2021 May 13;9(5):575.

48. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. E Clinical Medicine. 2021 Aug;38:101019.

49. Frontera JA, Lewis A, Melmed K, Lin J, Kondziella D, Helbok R, et al. Prevalence and Predictors of Prolonged Cognitive and Psychological Symptoms Following COVID-19 in the United States. Front Aging Neurosci. 2021;13:690383.

50. Ziauddeen N, Gurdasani D, O'Hara ME, Hastie C, Roderick P, Yao G, et al. Characteristics and impact of Long Covid: Findings from an online survey. Sutcliffe CG, editor. PLoS ONE. 2022 Mar 8;17(3):e0264331.

51. Moy FM, Hairi NN, Lim ERJ, Bulgiba A. Long COVID and its associated factors among COVID survivors in the community from a middle-income country—An online cross-sectional study. Hafeez Kamran S, editor. PLoS ONE. 2022 Aug 30;17(8):e0273364.

52. Kim Y, Bitna-Ha, Kim SW, Chang HH, Kwon KT, Bae S, et al. Post-acute COVID-19 syndrome in patients after 12 months from COVID-19 infection in Korea. BMC Infect Dis. 2022 Dec;22(1):93.

53. Mclaughlin M, Cerexhe L, Macdonald E, Ingram J, Sanal-Hayes NEM, Meach R, et al. A Cross-Sectional Study of Symptom Prevalence, Frequency, Severity, and Impact of Long-COVID in Scotland: Part I. The American Journal of Medicine. 2023 Jul;S0002934323004606.

54. Huang Y, Ling Q, Manyande A, Wu D, Xiang B. Brain Imaging Changes in Patients Recovered From COVID-19: A Narrative Review. Front Neurosci. 2022 Apr 22;16:855868.

55. Fischer D, Snider SB, Barra ME, Sanders WR, Rapalino O, Schaefer P, et al. Disorders of Consciousness Associated With COVID-19: A Prospective Multimodal Study of Recovery and Brain Connectivity. Neurology. 2022 Jan 18;98(3):e315–25.

56. Díez-Cirarda M, Yus M, Gómez-Ruiz N, Polidura C, Gil-Martínez L, Delgado-Alonso C, et al. Multimodal neuroimaging in post-COVID syndrome and correlation with cognition. Brain. 2022 Oct 26;awac384.

57. Cecchetti G, Agosta F, Canu E, Basaia S, Barbieri A, Cardamone R, et al. Cognitive, EEG, and MRI features of COVID-19 survivors: a 10-month study. J Neurol. 2022 Jul;269(7):3400–12.

58. Klinkhammer S, Horn J, Visser-Meily JMA, Verwijk E, Duits A, Slooter AJC, et al. Dutch multicentre, prospective follow-up, cohort study comparing the neurological and neuropsychological sequelae of hospitalised non-ICU- and ICU-treated COVID-19 survivors: a study protocol. BMJ Open. 2021 Oct;11(10):e054901.

59. Hafiz R, Gandhi TK, Mishra S, Prasad A, Mahajan V, Di X, et al. Higher limbic and basal ganglia volumes in surviving COVID-negative patients and the relations to fatigue. Neuroimage: Reports. 2022 Jun;2(2):100095.

60. Kremer S, Lersy F, de Sèze J, Ferré JC, Maamar A, Carsin-Nicol B, et al. Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. Radiology. 2020 Nov;297(2):E242–51.

61. Proal E, Alvarez-Segura M, de la Iglesia-Vayá M, Martí-Bonmatí L, Castellanos FX, Spanish Resting State Network. [Functional cerebral activity in a state of rest: connectivity networks]. Rev Neurol. 2011 Mar 1;52 Suppl 1:S3-10.

62. Calhoun VD. Functional brain networks in schizophrenia: a review. Front Hum Neurosci [Internet]. 2009 [cited 2022 Sep 30];3. Available from: http://journal.frontiersin.org/article/10.3389/neuro.09.017.2009/abstract

63. Dennis EL, Thompson PM. Functional Brain Connectivity Using fMRI in Aging and Alzheimer's Disease. Neuropsychol Rev. 2014 Mar;24(1):49–62.

64. Luo C, Qiu C, Guo Z, Fang J, Li Q, Lei X, et al. Disrupted Functional Brain Connectivity in Partial Epilepsy: A Resting-State fMRI Study. Sporns O, editor. PLoS ONE. 2012 Jan 5;7(1):e28196.

65. Palacios EM, Yuh EL, Chang YS, Yue JK, Schnyer DM, Okonkwo DO, et al. Resting-State Functional Connectivity Alterations Associated with Six-Month Outcomes in Mild Traumatic Brain Injury. Journal of Neurotrauma. 2017 Apr 15;34(8):1546–57.

66. Palacios EM, Sala-Llonch R, Junque C, Roig T, Tormos JM, Bargallo N, et al. Resting-State Functional Magnetic Resonance Imaging Activity and Connectivity and Cognitive Outcome in Traumatic Brain Injury. JAMA Neurol. 2013 Jul 1;70(7):845.

67. Cicerone KD, Kalmar K. Persistent postconcussion syndrome: The structure of subjective complaints after mild traumatic brain injury. J Head Trauma Rehabil. 1995 Jun;10(3):1–17.

68. Lequerica AH, Arango-Lasprilla JC, Krch D. Factor analysis of the Neurobehavioral Symptom Inventory among a sample of Spanish-speakers. Neuropsychol Rehabil. 2020 Aug 31;1–14.

69. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. medRxiv. 2021 Jan 30;2021.01.27.21250617.

70. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021 Jan 16;397(10270):220–32.

71. Evans RA, McAuley H, Harrison EM, Shikotra A, Singapuri A, Sereno M, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med. 2021 Nov;9(11):1275–87.

72. Sigfrid L, Drake TM, Pauley E, Jesudason EC, Olliaro P, Lim WS, et al. Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. Lancet Reg Health Eur. 2021 Sep;8:100186.

73. Maciaszek J, Lenart M, Misiak B, Grzebieluch J, Gawłowski P, Ciułkowicz M, et al. Unknown Enemy and Psychopathological Responses: A Cross-Sectional Nationwide Study Assessing the Knowledge About COVID-19. Front Psychiatry. 2021;12:704558.

74. Augustin M, Schommers P, Stecher M, Dewald F, Gieselmann L, Gruell H, et al. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. Lancet Reg Health Eur. 2021 Jul;6:100122.

75. Kolakowsky-Hayner SA, Goldin Y, Kingsley K, Alzueta E, Arango-Lasprilla JC, Perrin PB, et al. Psychosocial Impacts of the COVID-19 Quarantine: A Study of Gender Differences in 59 Countries. Medicina (Kaunas). 2021 Jul 31;57(8):789.

76. Glowacz F, Schmits E. Psychological distress during the COVID-19 lockdown: The young adults most at risk. Psychiatry Res. 2020 Nov;293:113486.

77. Klaiber P, Wen JH, DeLongis A, Sin NL. The Ups and Downs of Daily Life During COVID-19: Age Differences in Affect, Stress, and Positive Events. J Gerontol B Psychol Sci Soc Sci. 2021 Jan 18;76(2):e30–7.

78. Kolakowsky-Hayner SA, Shen J, Goldin Y, Kingsley K, Alzueta E, Arango-Lasprilla JC, et al. The COVID-19 Pandemic: Age Differences in Sleep Quality and Mental Health Across 59 Countries. Epidem Pub Hel Res. 18(29):22–6.

79. Bruine de Bruin W. Age Differences in COVID-19 Risk Perceptions and Mental Health: Evidence From a National U.S. Survey Conducted in March 2020. J Gerontol B Psychol Sci Soc Sci. 2021 Jan 18;76(2):e24–9.

80. Pearman A, Hughes ML, Smith EL, Neupert SD. Age Differences in Risk and Resilience Factors in COVID-19-Related Stress. J Gerontol B Psychol Sci Soc Sci. 2021 Jan 18;76(2):e38–44.

81. Carstensen LL, Shavit YZ, Barnes JT. Age Advantages in Emotional Experience Persist Even Under Threat From the COVID-19 Pandemic. Psychol Sci. 2020 Nov;31(11):1374–85.

82. Zhong BL, Luo W, Li HM, Zhang QQ, Liu XG, Li WT, et al. Knowledge, attitudes, and practices towards COVID-19 among Chinese residents during the rapid rise period of the COVID-19 outbreak: a quick online cross-sectional survey. Int J Biol Sci. 2020;16(10):1745–52.

83. Pierre M, Keller M, Altschul D, Fawns-Ritchie C, Hartley L, Nangle C, et al. Socioeconomic position and mental health during the COVID-19 pandemic: a cross-sectional analysis of the CovidLife study. Wellcome Open Res. 2021 Jun 3;6:139.

84. Wachtler B, Michalski N, Nowossadeck E, Diercke M, Wahrendorf M, Santos-Hövener C, et al. Socioeconomic inequalities and COVID-19 – A review of the current international literature. J Health Monit. 2020 Oct 9;5(Suppl 7):3–17.

85. Rao S, Lau A, So HC. Exploring Diseases/Traits and Blood Proteins Causally Related to Expression of ACE2, the Putative Receptor of SARS-CoV-2: A Mendelian Randomization Analysis Highlights Tentative Relevance of Diabetes-Related Traits. Diabetes Care. 2020 Jul;43(7):1416–26.

86. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, et al. The impact of COPD and smoking history on the severity of COVID-19: A systemic review and meta-analysis. J Med Virol. 2020 Oct;92(10):1915–21.

87. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020 Apr;8(4):e21.

88. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020 May;17(5):259–60.

89. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507–13.

90. Zhu F, Cao Y, Xu S, Zhou M. Reply to Comments on “Co-infection of SARS-CoV-2 and HIV in a patient in Wuhan city, China.” J Med Virol. 2020 Sep;92(9):1417–8.

91. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. J Infect Public Health. 2020 Dec;13(12):1833–9.

92. Daste C, Ficarra S, Dumitrache A, Cariou A, Lefèbvre A, Pène F, et al. Post-intensive care syndrome in patients surviving COVID-19. Ann Phys Rehabil Med. 2021 Nov;64(6):101549.

93. Senniappan K, Jeyabalan S, Rangappa P, Kanchi M. Hyperbaric oxygen therapy: Can it be a novel supportive therapy in COVID-19? Indian J Anaesth. 2020 Oct;64(10):835–41.

94. Oliaei S, SeyedAlinaghi S, Mehrtak M, Karimi A, Noori T, Mirzapour P, et al. The effects of hyperbaric oxygen therapy (HBOT) on coronavirus disease-2019 (COVID-19): a systematic review. Eur J Med Res. 2021 Aug 19;26(1):96.

95. Institute of Health Metrics and Evaluation. Global Health Data Exchange (GHDx) [Internet]. 2021. Available from: http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/d780dffbe8a381b25e1416884959e88b

96. Benzakour L, Assal F, Péron JA. Neuropsychological long-COVID: neurologic or psychiatric origin? Rev Med Suisse. 2021 Apr 28;17(736):822–6.

97. Marí-Dell'Olmo M, Gotsens M, Pasarín MI, Rodríguez-Sanz M, Artazcoz L, Garcia de Olalla P, et al. Socioeconomic Inequalities in COVID-19 in a European Urban Area: Two Waves, Two Patterns. Int J Environ Res Public Health. 2021 Jan 30;18(3):1256.

98. Epskamp S, Borsboom D, Fried EI. Estimating psychological networks and their accuracy: A tutorial paper. Behav Res. 2018 Feb;50(1):195–212.

99. Epskamp S, Fried EI. A tutorial on regularized partial correlation networks. Psychological Methods. 2018 Dec;23(4):617–34.

100. Epskamp S, Cramer AOJ, Waldorp LJ, Schmittmann VD, Borsboom D. qgraph : Network Visualizations of Relationships in Psychometric Data. J Stat Soft [Internet]. 2012 [cited 2023 Nov 4];48(4). Available from: http://www.jstatsoft.org/v48/i04/

101. Golino HF, Epskamp S. Exploratory graph analysis: A new approach for estimating the number of dimensions in psychological research. Voracek M, editor. PLoS ONE. 2017 Jun 8;12(6):e0174035.

102. Van Borkulo CD, Van Bork R, Boschloo L, Kossakowski JJ, Tio P, Schoevers RA, et al. Comparing network structures on three aspects: A permutation test. Psychological Methods [Internet]. 2022 Apr 11 [cited 2023 Nov 4]; Available from: http://doi.apa.org/getdoi.cfm?doi=10.1037/met0000476

103. Zhao T, Liu H, Roeder K, Lafferty J, Wasserman L. The huge Package for High-dimensional Undirected Graph Estimation in R. J Mach Learn Res. 2012 Apr;13:1059–62.

104. Gallus R, Melis A, Rizzo D, Piras A, De Luca LM, Tramaloni P, et al. Audiovestibular symptoms and sequelae in COVID-19 patients. VES. 2021 Oct 4;31(5):381–7.

105. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiat. 2020 Jul;7(7):611–27.

106. Badenoch JB, Rengasamy ER, Watson C, Jansen K, Chakraborty S, Sundaram RD, et al. Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. Brain Communications. 2022 Jan 4;4(1):fcab297.

107. Krishnan K, Lin Y, Prewitt KRM, Potter DA. Multidisciplinary Approach to Brain Fog and Related Persisting Symptoms Post COVID-19. J Health Serv Psychol. 2022 Feb;48(1):31–8.

108. Mukaetova-Ladinska EB, Kronenberg G. Psychological and neuropsychiatric implications of COVID-19. Eur Arch Psychiatry Clin Neurosci. 2021 Mar;271(2):235–48.

109. Li S, Ma X, Huang R, Li M, Tian J, Wen H, et al. Abnormal degree centrality in neurologically asymptomatic patients with end-stage renal disease: A resting-state fMRI study. Clinical Neurophysiology. 2016 Jan;127(1):602–9.

110. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001 Oct 10;286(14):1754–8.

111. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189–98.

112. Jones AE, Trzeciak S, Kline JA. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. Crit Care Med. 2009 May;37(5):1649–54.

113. Rey A. FTest de Copia y Reproducción de una Figura Compleja. Tea Ediciones, S.A.; 2009.

114. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. The Clinical Neuropsychologist. 1998 Feb;12(1):43–55.

115. Golden C. Manual de test de colores y palabras. Publicaciones de psicología aplicada: TEA Ediciones.; 2010.

116. Reitan RM, Wolfson D. The Halstead–Reitan Neuropsycholgical Test Battery: Therapy and Clinical Interpretation. Neuropsychological Press; 1985.

117. Schretlen D, Bobholz J, Brandt J. Development and psychometric properties of the brief test of attention. Clin Neuropsychol. 1996;10:80–9.

118. Smith A. Test de simbolos y digitos. TEA Ediciones S.A.; 2013.

119. Schretlen D. Brief test of attention professional manual. Psychological Assessment Resources; 1997.

120. Kaplan E, Goodglass H, Weintraub S. Test de Vocabulario de Boston. Editorial Medica Paramericana, S.A.; 2005.

121. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2012;2(3):125–41.

122. Jimenez-Marin A, Rivera D, Boado V, Diez I, Labayen F, Garrido I, et al. Brain connectivity and cognitive functioning in individuals six months after multiorgan failure. NeuroImage: Clinical. 2020;25:102137.

123. Douaud G, Smith S, Jenkinson M, Behrens T, Johansen-Berg H, Vickers J, et al. Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. Brain. 2007 Sep;130(Pt 9):2375–86.

124. Nieto-Castanon A. Handbook of functional connectivity magnetic resonance imaging methods in CONN. Boston, MA: Hilbert Press; 2020. 108 p.

125. Baker JT, Holmes AJ, Masters GA, Yeo BTT, Krienen F, Buckner RL, et al. Disruption of Cortical Association Networks in Schizophrenia and Psychotic Bipolar Disorder. JAMA Psychiatry. 2014 Feb 1;71(2):109.

126. Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW, et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc Natl Acad Sci USA. 2009 Jan 27;106(4):1279–84.

127. Schultz AP, Chhatwal JP, Hedden T, Mormino EC, Hanseeuw BJ, Sepulcre J, et al. Phases of Hyperconnectivity and Hypoconnectivity in the Default Mode and Salience

Networks Track with Amyloid and Tau in Clinically Normal Individuals. J Neurosci. 2017 Apr 19;37(16):4323–31.

128. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct. 2010 Jun;214(5–6):655–67.

129. Gopinath K, Krishnamurthy V, Cabanban R, Crosson BA. Hubs of Anticorrelation in High-Resolution Resting-State Functional Connectivity Network Architecture. Brain Connect. 2015 Jun;5(5):267–75.

130. Martinez-Gutierrez E, Jimenez-Marin A, Stramaglia S, Cortes JM. The structure of anticorrelated networks in the human brain. Front Netw Physiol. 2022;2:946380.

131. Uddin LQ. Salience processing and insular cortical function and dysfunction. Nat Rev Neurosci. 2015 Jan;16(1):55–61.

132. Uddin LQ, Kelly AM, Biswal BB, Castellanos FX, Milham MP. Functional connectivity of default mode network components: correlation, anticorrelation, and causality. Hum Brain Mapp. 2009 Feb;30(2):625–37.

133. Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, Nogal A, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. The Lancet. 2022 Apr;399(10335):1618–24.

134. Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. Nat Med. 2022 Nov;28(11):2398–405.

135. Barda N, Dagan N, Cohen C, Hernán MA, Lipsitch M, Kohane IS, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. The Lancet. 2021 Dec;398(10316):2093–100.

136. Khera T, Rangasamy V. Cognition and Pain: A Review. Front Psychol. 2021 May 21;12:673962.

137. Menon V. Salience Network. In: Toga AW, editor. Brain Mapping: An Encyclopedic Reference. Academic Press: Elsevier; 2015. p. 597–611.

138. Matias-Guiu JA, Herrera E, González-Nosti M, Krishnan K, Delgado-Alonso C, Díez-Cirarda M, et al. Development of criteria for cognitive dysfunction in post-COVID syndrome: the IC-CoDi-COVID approach. Psychiatry Research. 2023 Jan;319:115006.

LISTA DE PUBLICACIONES

Publicaciones dentro de la temática de la tesis

- Perrin, P. B., **Ramos-Usuga, D.,** West, S. J., Merced, K., Klyce, D. W., Lequerica, A. H., Olabarrieta-Landa, L., Alzueta, E., Baker, F. C., Iacovides, S., Cortes, M., & Arango-Lasprilla, J. C. (2022). Network Analysis of Neurobehavioral Symptom Patterns in an International Sample of Spanish-Speakers with a History of COVID-19 and Controls. *International journal of environmental research and public health*, *20*(1), 183. https://doi.org/10.3390/ijerph20010183
- **Ramos-Usuga, D.**, Perrin, P. B., Bogdanova, Y., Olabarrieta-Landa, L., Alzueta, E., Baker, F. C., Iacovides, S., Cortes, M., & Arango-Lasprilla, J. C. (2022). Moderate, Little, or No Improvements in Neurobehavioral Symptoms among Individuals with Long COVID: A 34-Country Retrospective Study. *International journal of environmental research and public health*, *19*(19), 12593. https://doi.org/10.3390/ijerph191912593
- Liozidou, A., Varela, V., Vlastos, D. D., Giogkaraki, E., Alzueta, E., Perrin, P. B., **Ramos-Usuga, D.**, & Arango-Lasprilla, J. C. (2023). Forced social isolation and lockdown during the COVID-19 pandemic: depression, anxiety, trauma-distress and coping mechanisms of a Greek sample. *Zeitschrift fur Gesundheitswissenschaften = Journal of public health*, 1–10. Advance online publication. https://doi.org/10.1007/s10389-023-01907-3
- Alzueta, E., Perrin, P. B., Yuksel, D., **Ramos-Usuga, D.**, Kiss, O., Iacovides, S., de Zambotti, M., Cortes, M., Olabarrieta-Landa, L., Arango-Lasprilla, J. C., & Baker, F.

C. (2022). An international study of post-COVID sleep health. *Sleep health*, *8*(6), 684–690. https://doi.org/10.1016/j.sleh.2022.06.011

- Ertl, M. M., Trapp, S. K., Alzueta, E., Baker, F. C., Perrin, P. B., Caffarra, S., Yüksel, D., **Ramos-Usuga, D.**, & Arango-Lasprilla, J. C. (2022). Trauma-Related Distress During the COVID-19 Pandemic In 59 Countries. *The Counseling psychologist*, *50*(3), 306–334. https://doi.org/10.1177/00110000211068112
- Yuksel, D., McKee, G. B., Perrin, P. B., Alzueta, E., Caffarra, S., **Ramos-Usuga, D.**, Arango-Lasprilla, J. C., & Baker, F. C. (2021). Sleeping when the world locks down: Correlates of sleep health during the COVID-19 pandemic across 59 countries. *Sleep health*, *7*(2), 134–142. https://doi.org/10.1016/j.sleh.2020.12.008
- Alzueta, E., Perrin, P., Baker, F. C., Caffarra, S., **Ramos-Usuga, D.**, Yuksel, D., & Arango-Lasprilla, J. C. (2021). How the COVID-19 pandemic has changed our lives: A study of psychological correlates across 59 countries. *Journal of clinical psychology*, *77*(3), 556–570. https://doi.org/10.1002/jclp.23082
- Kolakowsky-Hayner, S. A., Goldin, Y., Kingsley, K., Alzueta, E., Arango-Lasprilla, J. C., Perrin, P. B., Baker, F. C., **Ramos-Usuga, D.**, & Constantinidou, F. (2021). Psychosocial Impacts of the COVID-19 Quarantine: A Study of Gender Differences in 59 Countries. *Medicina (Kaunas, Lithuania)*, *57*(8), 789. https://doi.org/10.3390/medicina57080789
- Di Giusto, M. L., Grover, P., Castillo, C., Jimenez, I. H., García, J. C., Tijerina, R., **Ramos-Usuga, D.** & Arango-Lasprilla, J. C. (2021). The state of pulmonary rehabilitation in Latin America during the COVID-19 pandemic. *Journal of the International Society of Physical and Rehabilitation Medicine*, *4*(1), 40-50.

- Jimenez-Marin, A., Rivera, D., Boado, V., Diez, I., Labayen, F., Garrido, I., **Ramos-Usuga, D.**, Benito-Sánchez, I., Rasero, J., Cabrera-Zubizarreta, A., Gabilondo, I., Stramaglia, S., Arango-Lasprilla, J. C., & Cortes, J. M. (2020). Brain connectivity and cognitive functioning in individuals six months after multiorgan failure. *NeuroImage. Clinical*, *25*, 102137. https://doi.org/10.1016/j.nicl.2019.102137

Otras publicaciones realizadas durante el doctorado

- Di Giusto, M. L., Ertl, M. M., **Ramos-Usuga, D.**, Carballea, D., Degano, M., Perrin, P. B., & Arango-Lasprilla, J. C. (2023). Sexual Health and Sexual Quality of Life Among Individuals With Spinal Cord Injury in Latin America. *Topics in spinal cord injury rehabilitation*, *29*(1), 54–69. https://doi.org/10.46292/sci21-00080
- Olabarrieta-Landa, L., **Ramos-Usuga, D.**, Benito-Sánchez, I., Gonzalez, I., López Hernandez, K., Logatt Grabner, C. Y., Perrin, P., & Arango-Lasprilla, J. C. (2023). School professionals' knowledge about pediatric traumatic brain injury: an international study. *Brain injury*, *37*(4), 329–336. https://doi.org/10.1080/02699052.2022.2145364
- Monette, S., Bertrand, J. A., Perreau-Linck, E., **Ramos-Usuga, D.**, Rivera, D., & Arango-Lasprilla, J. C. (2023). The profession of neuropsychologist in Canada: Findings of a national survey. *The Clinical neuropsychologist*, *37*(1), 1–33. https://doi.org/10.1080/13854046.2021.2002934
- Lasprilla, J. C. A., Rodríguez-Irizarry, W., Oliveras-Rentas, R. E., **Ramos-Usuga, D.**, Gonzalez, I., Perez, P. K., & Romero-García, I. (2022). Hispanic neuropsychologists in the United States: What do we know about them and how can the field address their needs?. *NeuroRehabilitation*, *51*(1), 101–121. https://doi.org/10.3233/NRE-210333
- Arango-Lasprilla, J. C., Watson, J. D., Rodriguez, M. J., **Ramos-Usuga, D.**, Mascialino, G., & Perrin, P. B. (2022). Employment probability trajectories in hispanics over the 10 years after traumatic brain injury: A model systems study. *NeuroRehabilitation*, *51*(3), 397–405. https://doi.org/10.3233/NRE-220066

- Olabarrieta-Landa, L., **Ramos Usuga, D.**, Rivera, D., Leal, G., Bailey, K. C., Calderón Chagualá, A., Rabago, B., Esenarro, L., Mascialino, G., & Arango-Lasprilla, J. C. (2022). Prevalence of low scores on language tests as a potential factor in misdiagnosis of cognitive impairment in a Spanish-speaking adult population. *Applied neuropsychology. Adult*, *29*(1), 41–52. https://doi.org/10.1080/23279095.2019.1704409
- Rivera, D., **Ramos Usuga, D.**, Fuentes Mendoza, E. M., Aguayo Arelis, A., Rabago Barajas, B. V., Macías Islas, M. Á., Krch, D., Lequerica, A. H., & Arango-Lasprilla, J. C. (2022). Validation of the Norma Latina neuropsychological assessment battery in individuals with multiple sclerosis in Mexico. *Multiple sclerosis and related disorders*, *59*, 103685. https://doi.org/10.1016/j.msard.2022.103685
- Longoni Di Giusto, M., Ertl, M. M., **Ramos-Usuga, D.**, Carballea, D., Degano, M., Perrin, P. B., & Arango-Lasprilla, J. C. (2022). A Survey of Latin American Rehabilitation Professionals on Addressing Sexuality-Related Concerns After Spinal Cord Injury. *Sexuality and disability*, *40*(3), 439–459. https://doi.org/10.1007/s11195-022-09735-1
- Bailey, K. C., Goatte, W., **Ramos-Usuga, D.**, Rivera, D., & Arango-Lasprilla, J. C. (2021). Cross-validation of the utility of Test of Memory Malingering (TOMM) cut-offs in a large Colombian sample. *Psychological Injury and Law*, *14*(2), 114-126.
- Vicente, S. G., **Ramos-Usuga, D.**, Barbosa, F., Gaspar, N., Dores, A. R., Rivera, D., & Arango-Lasprilla, J. C. (2021). Regression-Based Norms for the Hopkins Verbal Learning Test-Revised and the Rey-Osterrieth Complex Figure in a Portuguese Adult Population. *Archives of clinical neuropsychology : the official journal of the National*

Academy of Neuropsychologists, *36*(4), 587–596. https://doi.org/10.1093/arclin/acaa087

- Rodríguez-Lorenzana, A., **Ramos-Usuga, D.**, Díaz, L. A., Mascialino, G., Yacelga Ponce, T., Rivera, D., & Arango-Lasprilla, J. C. (2021). Normative data of neuropsychological tests of attention and executive functions in Ecuadorian adult population. *Neuropsychology, development, and cognition. Section B, Aging, neuropsychology and cognition*, *28*(4), 508–527. https://doi.org/10.1080/13825585.2020.1790493
- McKee, G. B., Olabarrieta-Landa, L., Pérez-Delgadillo, P. K., Valdivia-Tangarife, R., Villaseñor-Cabrera, T., **Ramos-Usuga, D.**, Perrin, P. B., & Arango-Lasprilla, J. C. (2020). Longitudinal Growth Curve Trajectories of Family Dynamics after Pediatric Traumatic Brain Injury in Mexico. *International journal of environmental research and public health*, *17*(22), 8508. https://doi.org/10.3390/ijerph17228508
- De Las Heras, J., Diez, I., Jimenez-Marin, A., Cabrera, A., **Ramos-Usuga, D.**, Diaz-Fernandez, M. V., Torices, L., Nunes-Xavier, C. E., Pulido, R., Arango-Lasprilla, J. C., & Cortes, J. M. (2020). Brain Circuit Alterations and Cognitive Disability in Late-Onset Cobalamin D Disorder. *Journal of clinical medicine*, *9*(4), 990. https://doi.org/10.3390/jcm9040990
- Oliveras-Rentas, R. E., Romero-García, I., Benito-Sánchez, I., **Ramos-Usuga, D.**, & Arango-Lasprilla, J. C. (2020). The Practice of Child Neuropsychology in Spanish-speaking Countries: What We've Learned and Where to Go from Here. *Developmental neuropsychology*, *45*(4), 169–188. https://doi.org/10.1080/87565641.2020.1721502

ANEXO I

Neurobehavioral Symptom Inventory (NSI)

Please rate the following symptoms with regard to how much they have disturbed you IN THE LAST 2 Weeks.
The purpose of this inventory is to track symptoms over time. Please do not attempt to score.

0 = None – Rarely if ever present; not a problem at all

1 = Mild – Occasionally present, but it does not disrupt my activities; I can usually continue what I'm doing; doesn't really concern me.

2 = Moderate – Often present, occasionally disrupts my activities; I can usually continue what I'm doing with some effort; I feel somewhat concerned.

3 = Severe – Frequently present and disrupts activities; I can only do things that are fairly simple or take little effort; I feel I need help.

4 = Very Severe – Almost always present and I have been unable to perform at work, school or home due to this problem; I probably cannot function without help.

Symptoms	**0**	**1**	**2**	**3**	**4**
Feeling Dizzy	O	O	O	O	O
Loss of balance	O	O	O	O	O
Poor coordination, clumsy	O	O	O	O	O
Headaches	O	O	O	O	O
Nausea	O	O	O	O	O
Vision problems, blurring, trouble seeing	O	O	O	O	O
Sensitivity to light	O	O	O	O	O
Hearing difficulty	O	O	O	O	O
Sensitivity to noise	O	O	O	O	O
Numbness or tingling on parts of my body	O	O	O	O	O
Change in taste and/or smell	O	O	O	O	O
Loss of appetite or increased appetite	O	O	O	O	O
Poor concentration, can't pay attention, easily distracted	O	O	O	O	O
Forgetfulness, can't remember things	O	O	O	O	O
Difficulty making decisions	O	O	O	O	O
Slowed thinking, difficulty getting organized, can't finish things	O	O	O	O	O
Fatigue, loss of energy, getting tired easily	O	O	O	O	O
Difficulty falling or staying asleep	O	O	O	O	O
Feeling anxious or tense	O	O	O	O	O
Feeling depressed or sad	O	O	O	O	O
Irritability, easily annoyed	O	O	O	O	O
Poor frustration tolerance, feeling easily overwhelmed by things	O	O	O	O	O

Date:

Name:

Medical Record #: