

La hipótesis de la disfunción del nervio vago en la condición post-COVID-19

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21 abril 2022, Barcelona

- ¿DE DÓNDE VENIMOS?
- CONDICIÓN POST COVID-19, MUY BREVE
- CÓMO EXPLICAR EL PORQUÉ
- LA TEORIA DEL NERVIO VAGO
- VAGUS-COVID STUDY
- ¿HACIA DÓNDE VAMOS?
- CONCLUSIONES

¿DE DÓNDE VENIMOS?



WUHAN
3-8 FEBRERO 2020

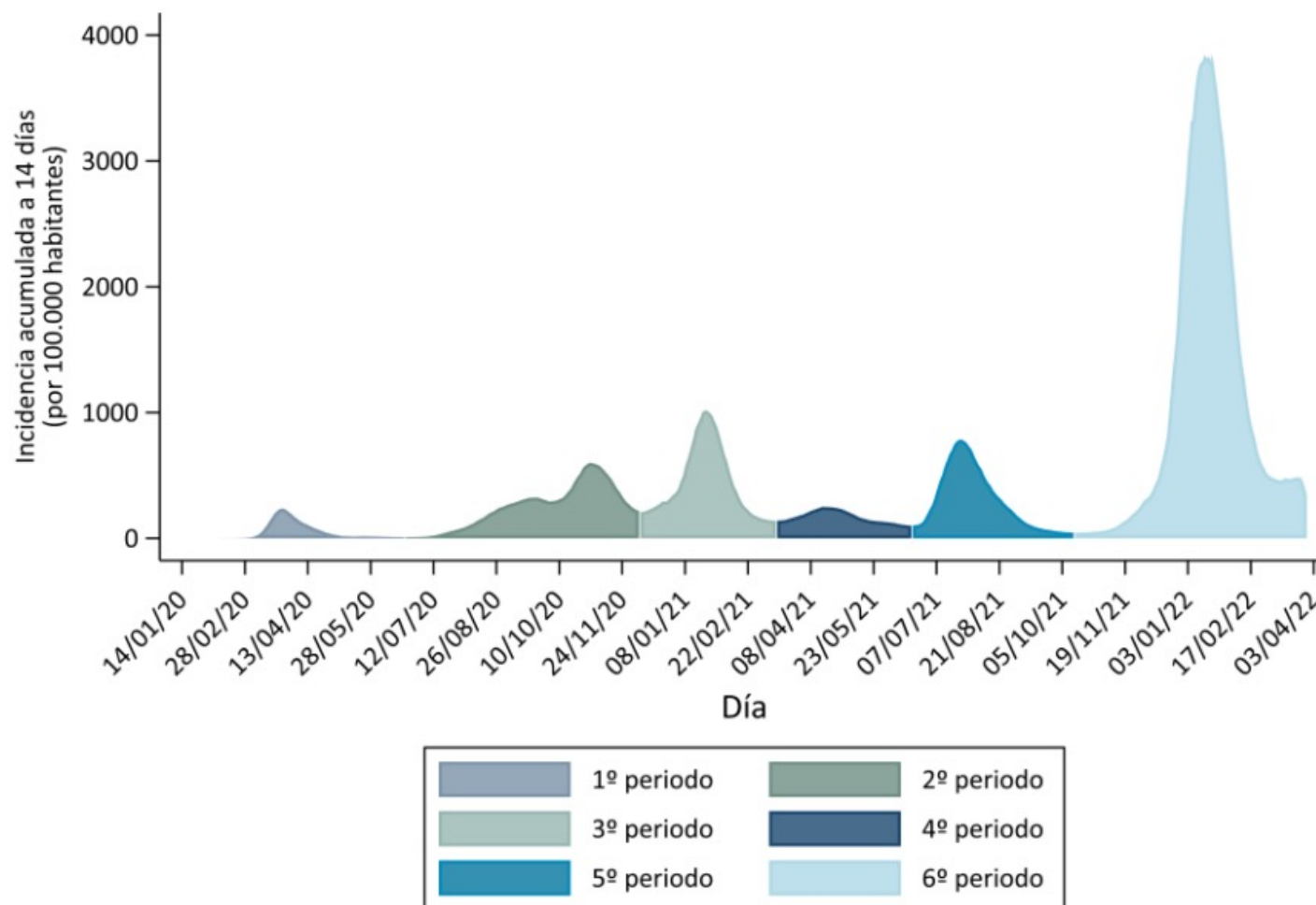
¿DE DÓNDE VENIMOS?



PRIMER CASO COVID-19 EN ESPAÑA
31 ENERO 2020

Condición
POST COVID-19
Un largo camino hacia la recuperación

¿DE DÓNDE VENIMOS?



Fuente: CNE, ISCIII. Red Nacional de Vigilancia Epidemiológica.

Condición
POST COVID-19
Un largo camino hacia la recuperación

¿DE DÓNDE VENIMOS?



MARCOS, 101 DÍAS EN UCI

TOT
ANIRÀ
BÉ!



¿DÓNDE ESTAMOS?



SILVIA, > 750 DÍAS CON SÍNTOMAS QUE PERSISTEN



CONDICIÓN POST COVID-19



A clinical case definition of post COVID-19 condition by a Delphi consensus

6 October 2021



Public health problem

- 10-20% of COVID-19 surviving subjects worldwide **
- All infected individuals are at risk
- Young and healthy
- Disability syndrome
- No treatments

CÓMO EXPLICAR EL PORQUÉ

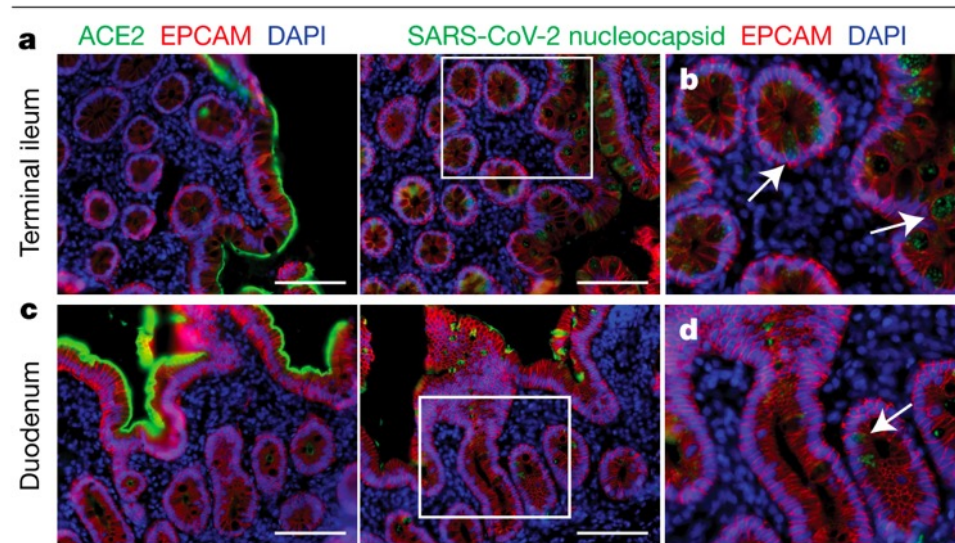
Persistent inflammation/long-term tissue damage

Autoimmune disease

Immune dysregulation

Post-viral syndrome-like

Viral reservoirs



Gaebler et al Nature, 2021

Condición
POST COVID-19
Un largo camino hacia la recuperación

LA TEORIA DEL NERVIO VAGO

¿QUÉ NOS PREGUNTAMOS?

LA HIPÓTESIS

VIRUS



NEUROINVASIÓN/NEUROTROPISMO



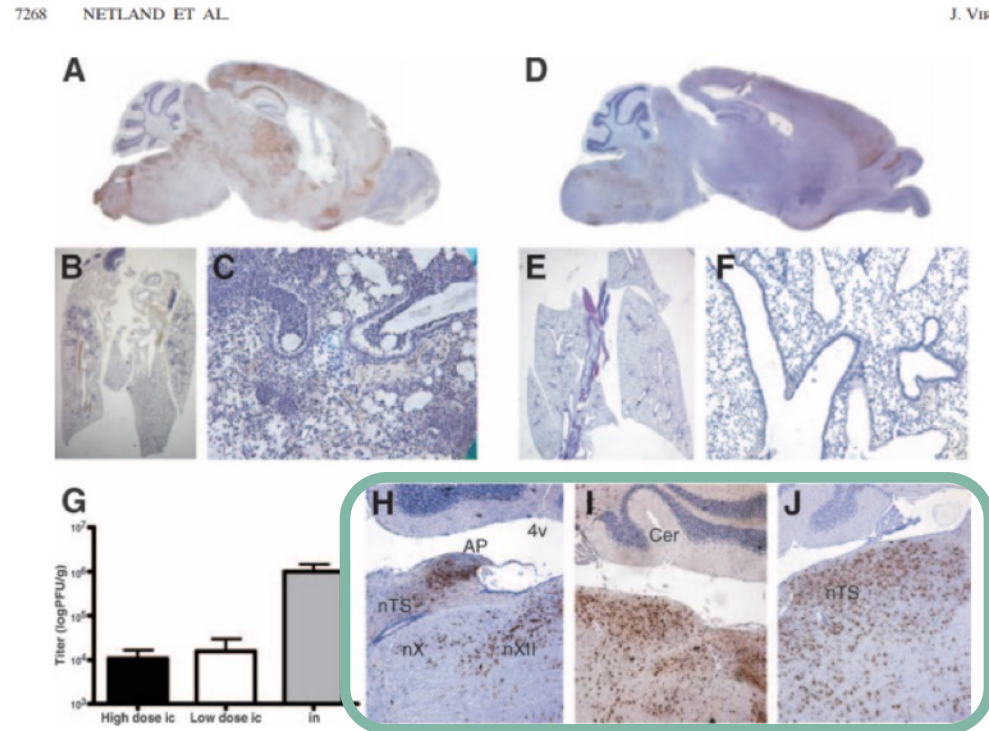
ALTERACIÓN ESTRUCTURAL Y/O FUNCIONAL NEURAL



MANIFESTACIONES CLÍNICAS

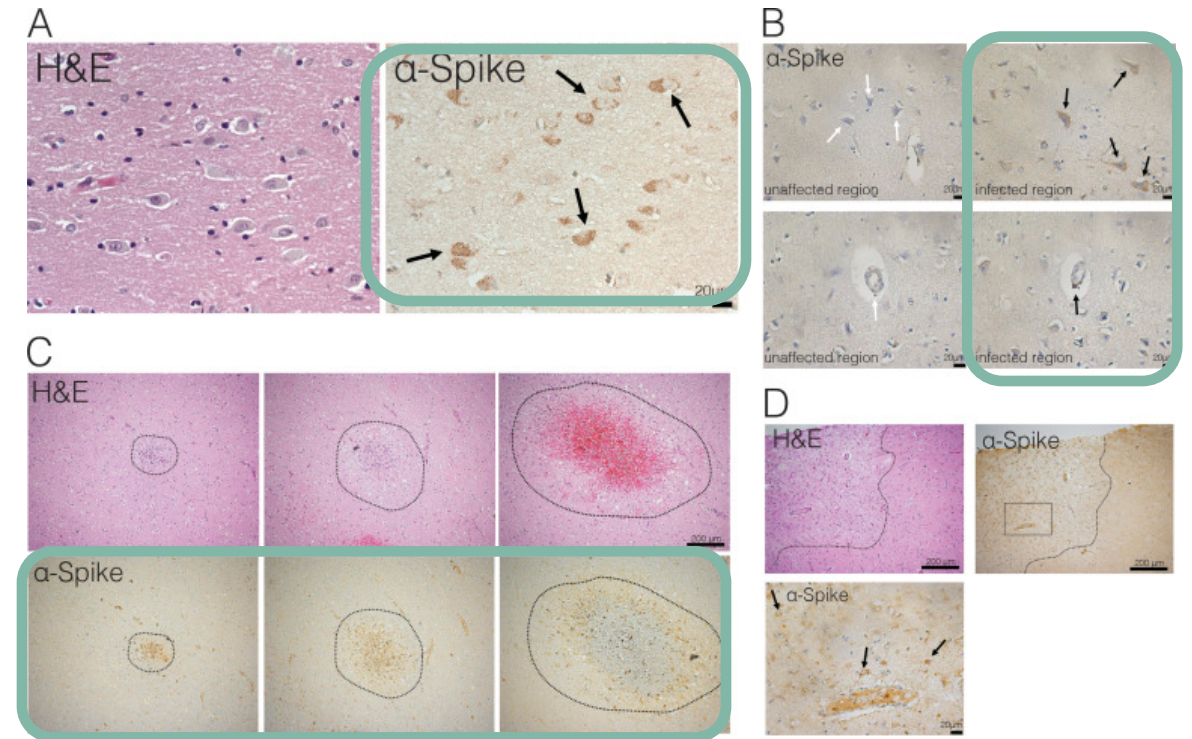
NEUROINVASIÓN/NEUROTROPISMO

SARS-CoV virus



Netland J, et al. doi.org/10. 1128/JVI.00737-08

SARS-CoV-2 virus



Song E, et al. doi: 10.1084/jem.20202135. PMID: 33433624; PMCID: PMC7808299.

NEUROINVASIÓN/NEUROTROPISMO

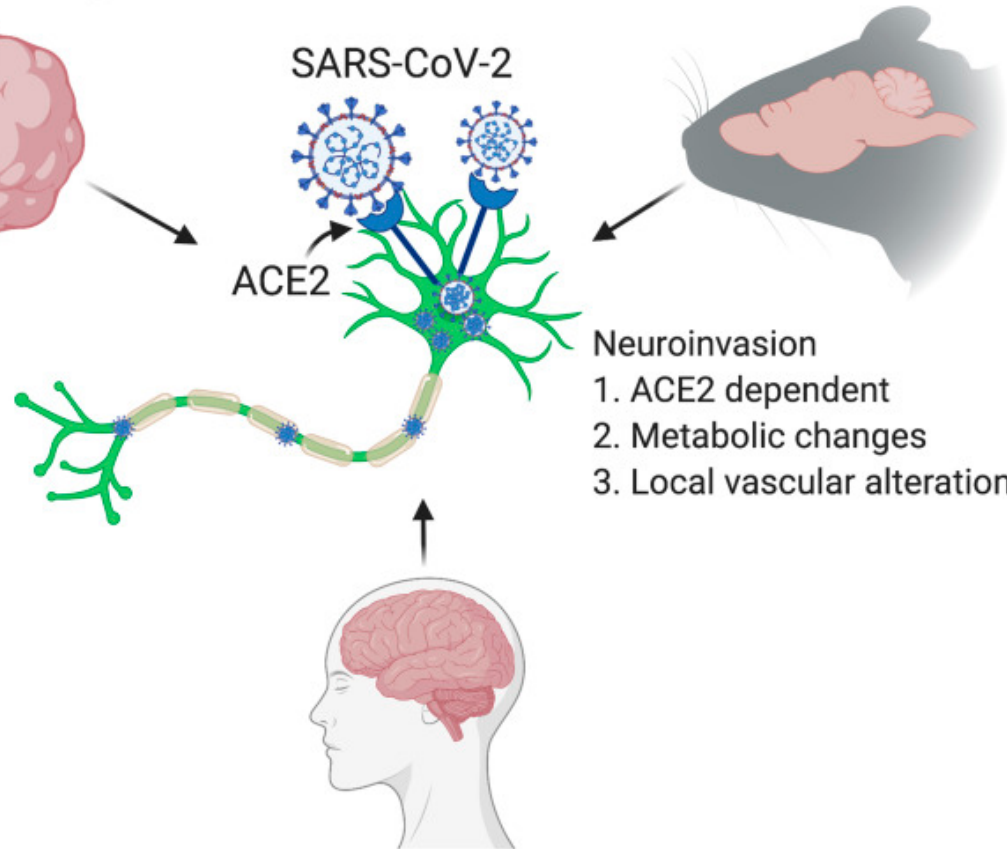
In vitro
Human brain organoids

In vivo
SARS-CoV-2 mouse model



SARS-CoV-2

ACE2

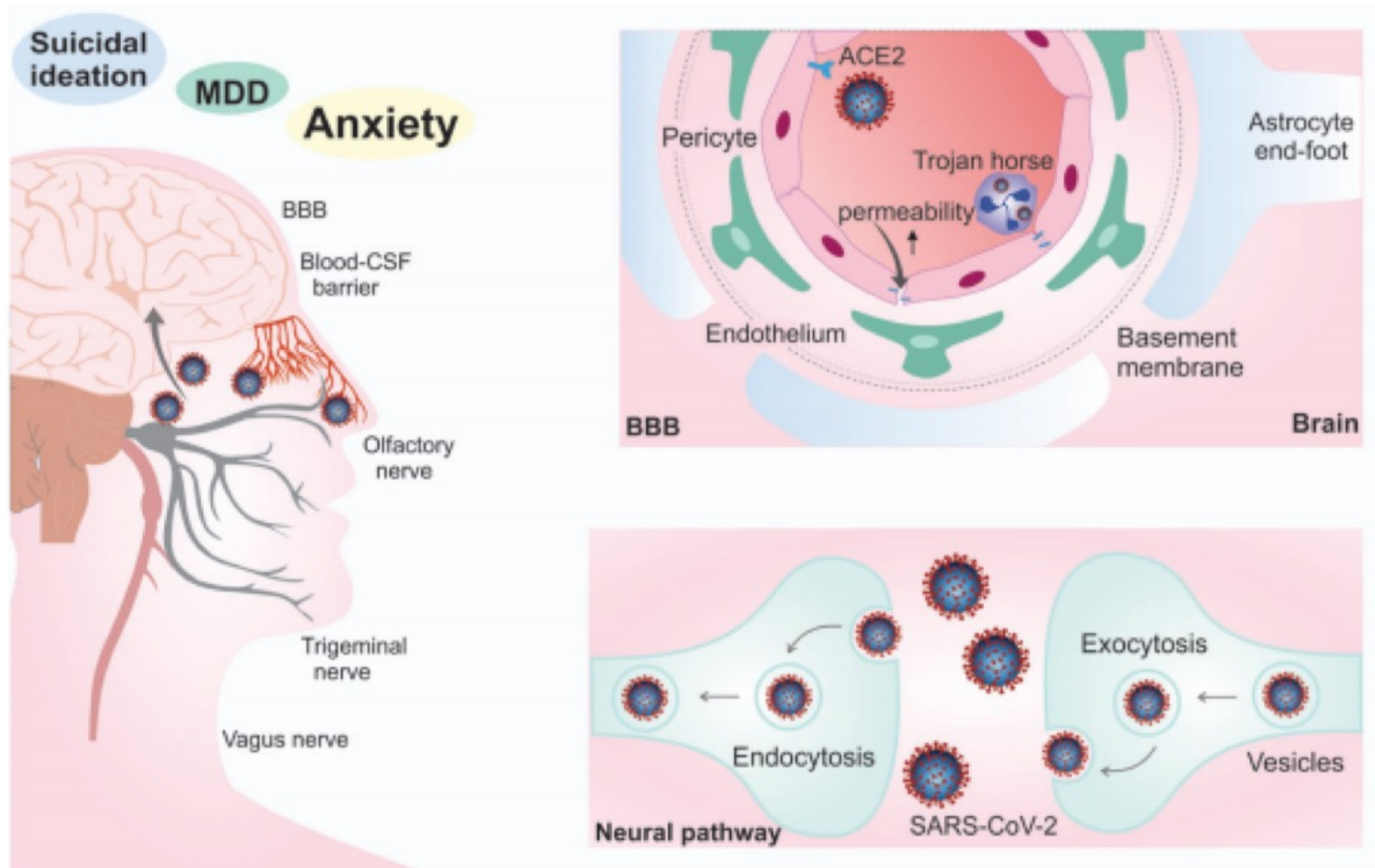


Neuroinvasion

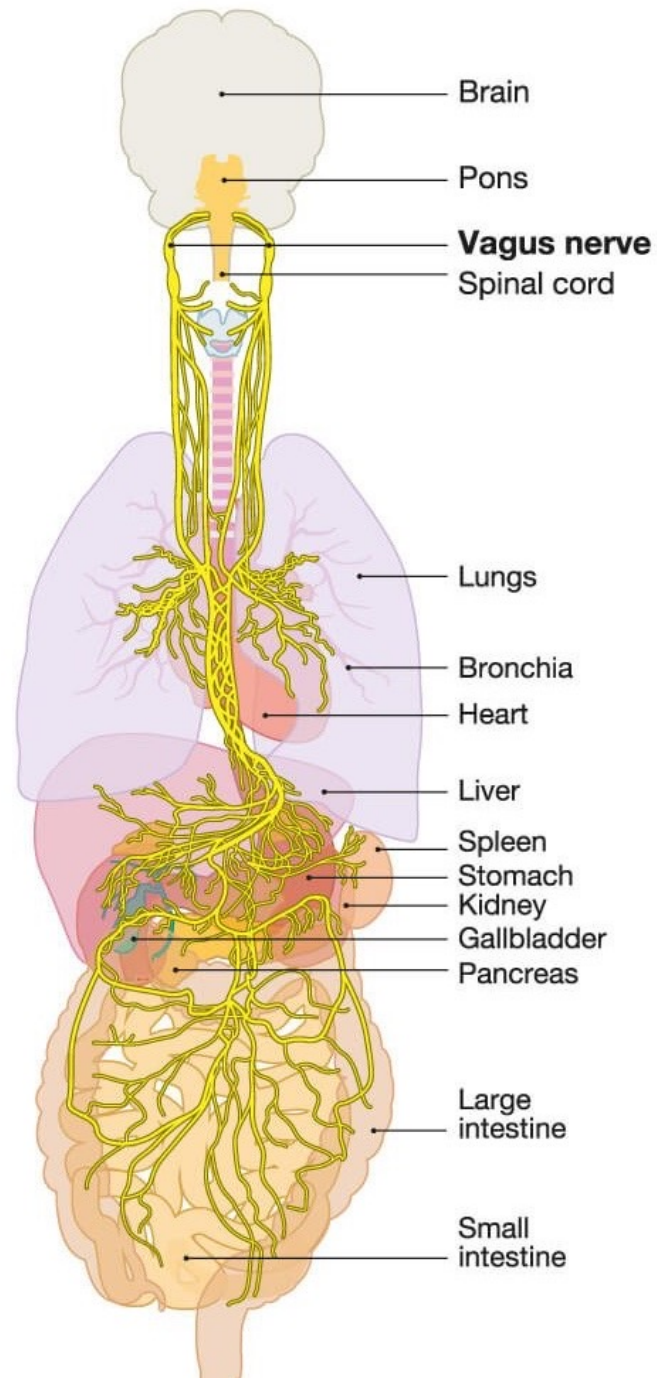
1. ACE2 dependent
2. Metabolic changes
3. Local vascular alteration

Post mortem
COVID-19 patient brain samples

NEUROINVASIÓN/NEUROTROPISMO

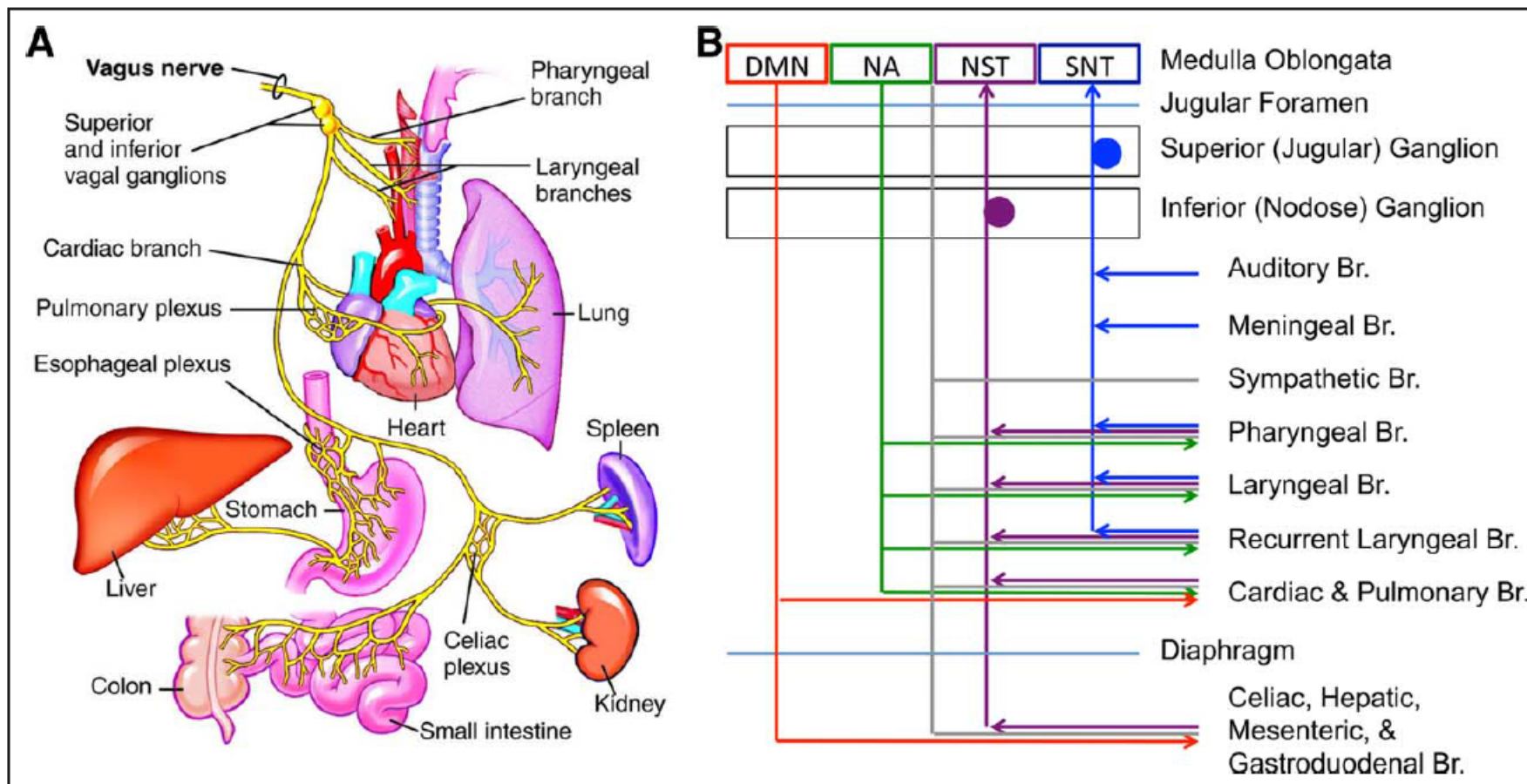


NERVIO VAGO



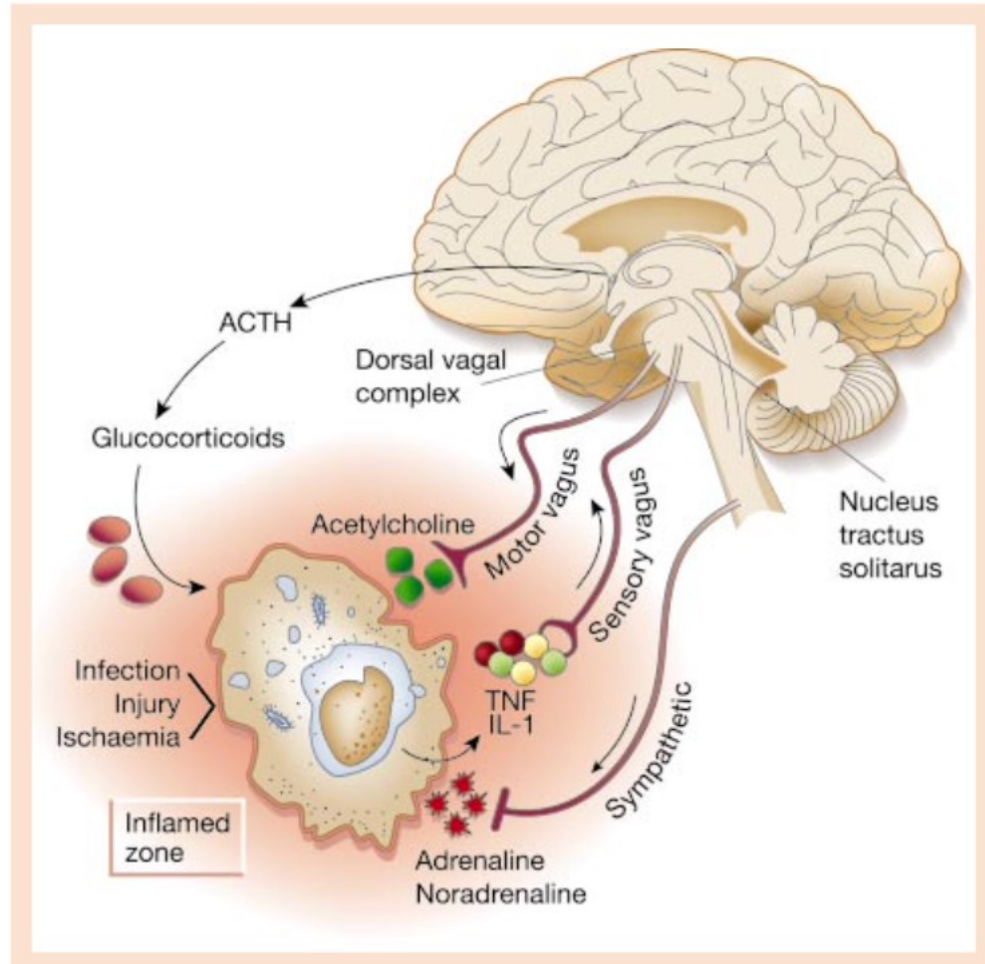
NERVIO VAGO

FUNCIONES



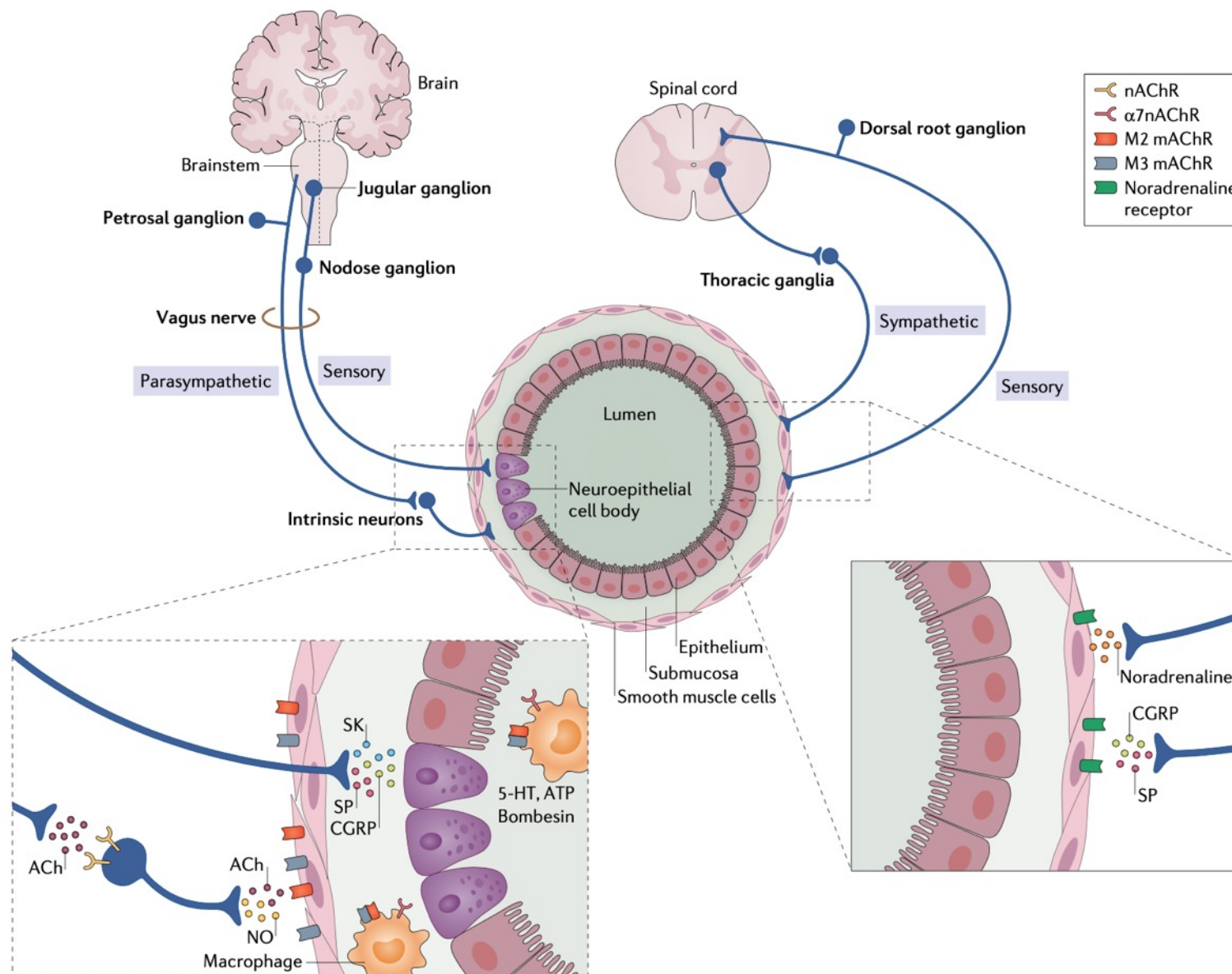
NERVIO VAGO

CHOLLINERGIC ANT-INFLAMMATORY PATHWAY



Tornero, C., et al

¿DÓNDE ESTÁ LA AFECTACIÓN?



VAGUS-COVID STUDY

¿QUÉ NOS PREGUNTAMOS?

LA HIPÓTESIS

SARS-COV-2



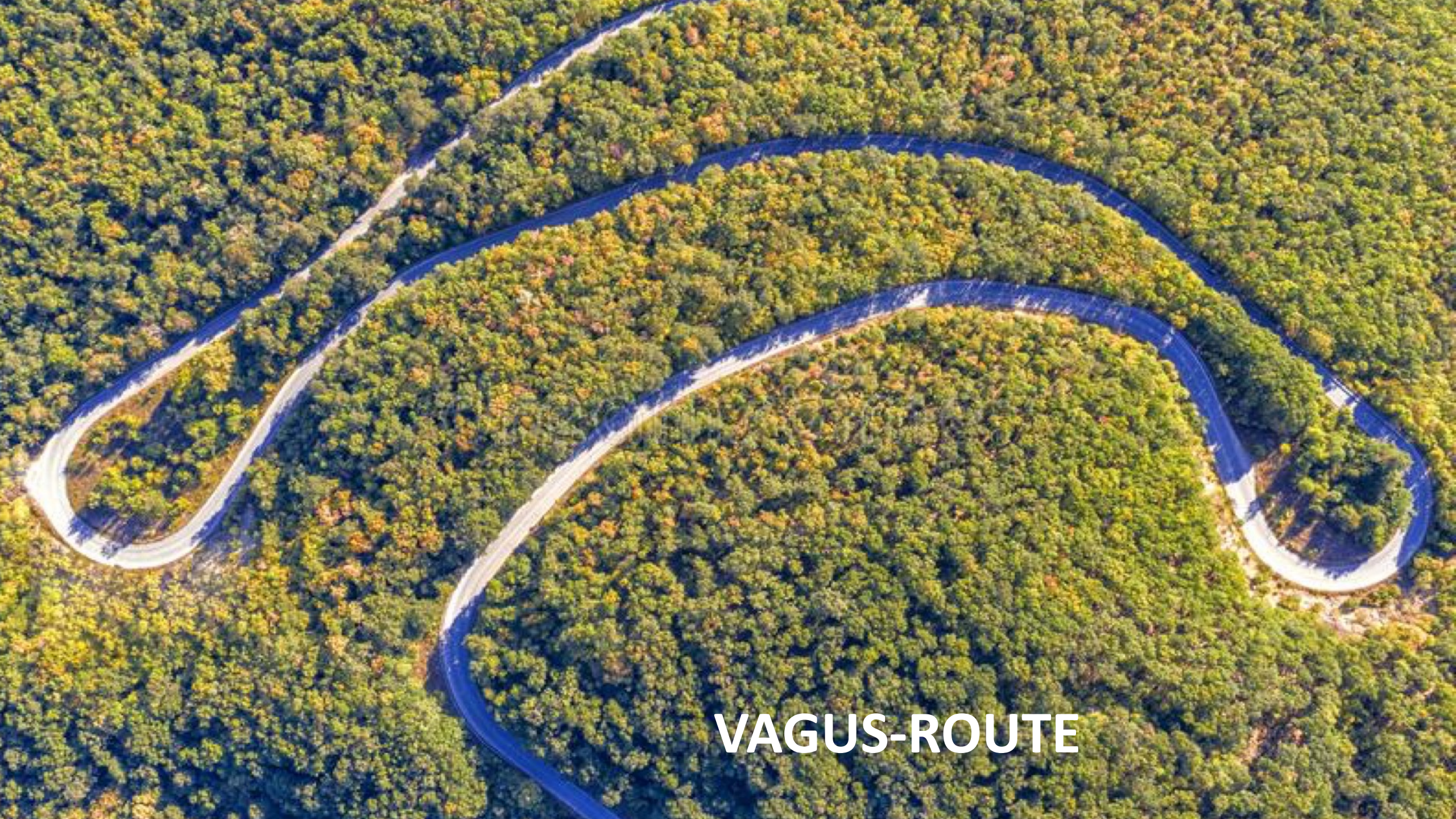
NEUROINVASIÓN/NEUROTROPISMO DEL NERVIO VAGO



ALTERACIÓN ESTRUCTURAL Y/O FUNCIONAL VAGAL

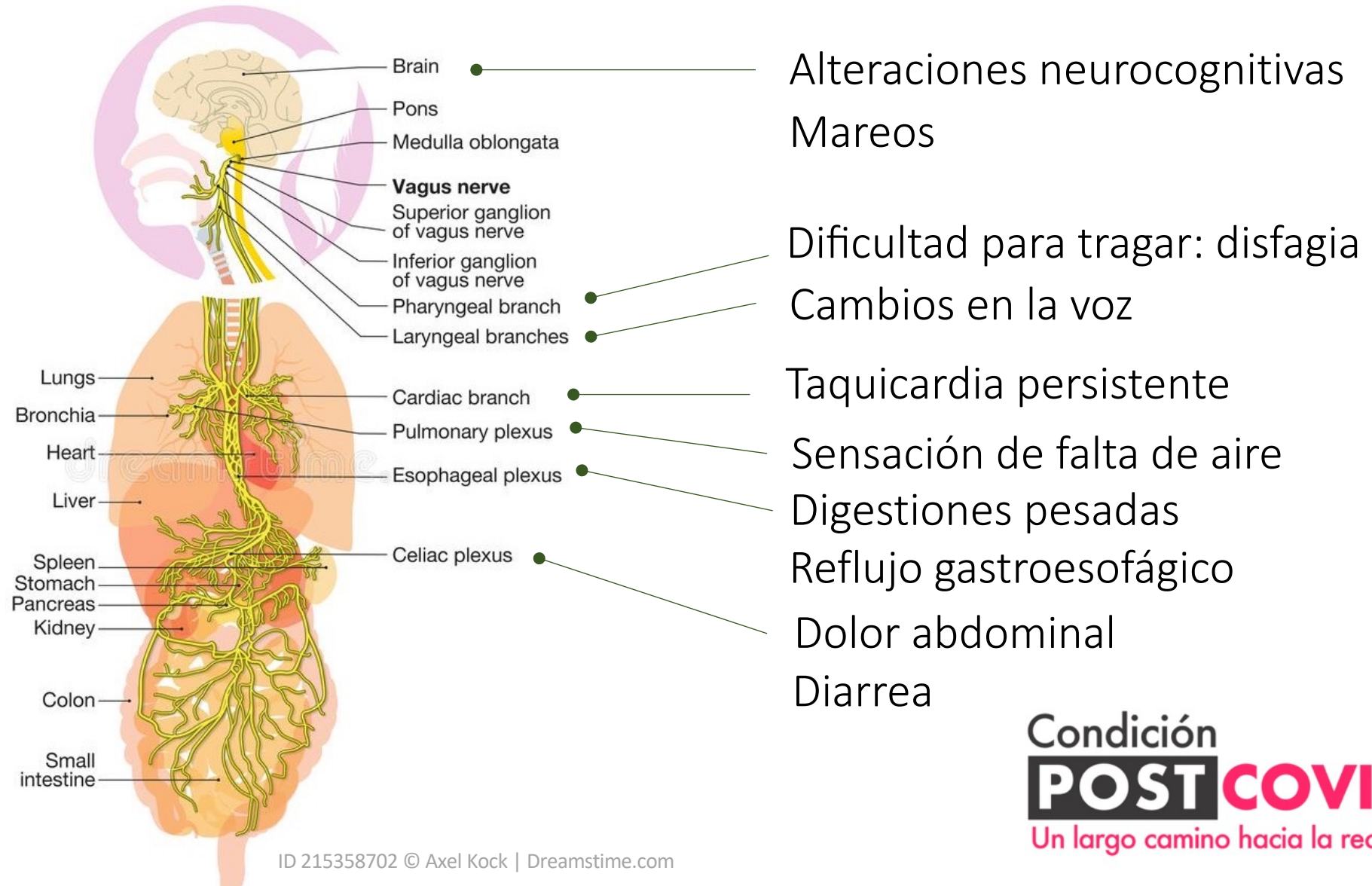


**MANIFESTACIONES CLÍNICAS SUGESTIVAS DE DISFUNCIÓN
DEL NERVIO VAGO**



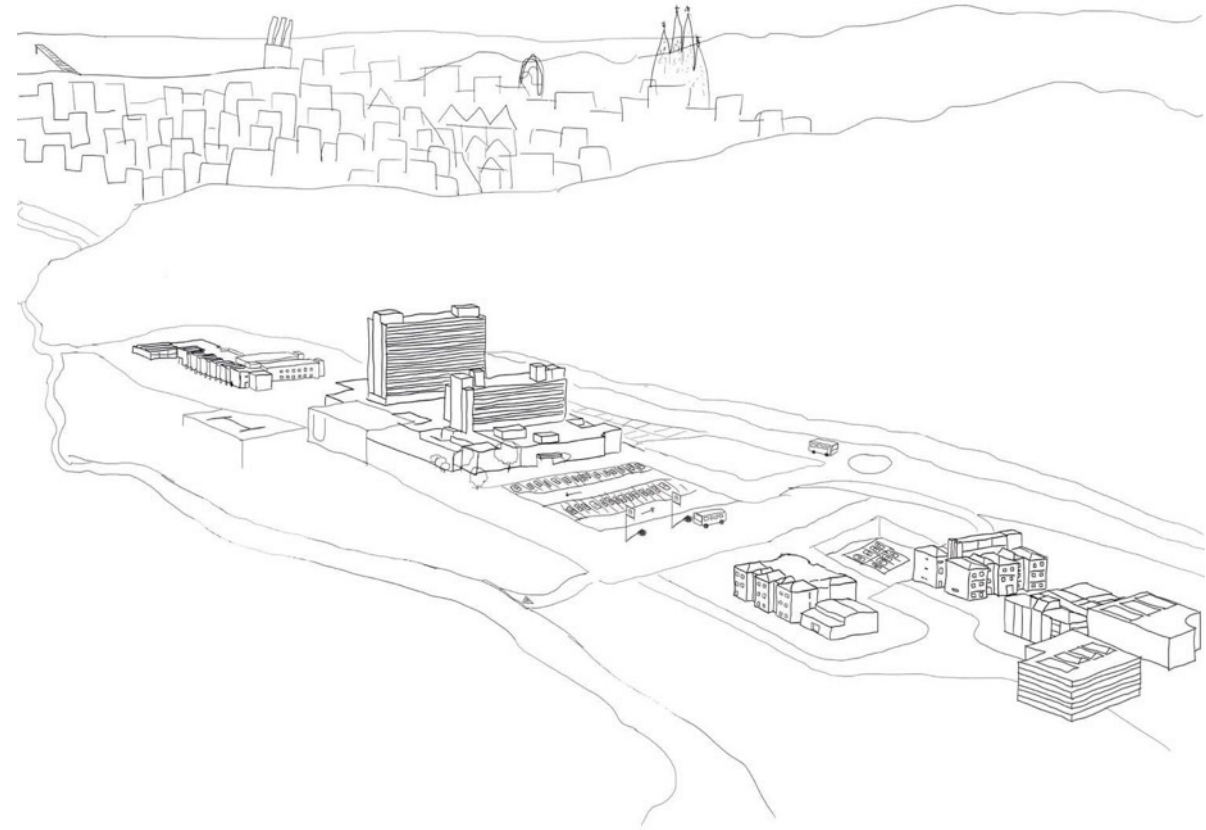
VAGUS-ROUTE

MANIFESTACIÓN CLÍNICAS SUGESTIVAS DE AFECTACIÓN DEL N.VAGO



OBJECTIVE and STUDY DESIGN

- **PRIMARY OBJECTIVE:** To evaluate **the structure** and **function** of the vagus nerve in post COVID-19 condition
- **PILOT CROSS SECTIONAL STUDY**
- **MARCH 2021-MARCH 2022**



VAGUS-COVID STUDY

Study population

PCC: Post COVID Condition
VND: Vagus Nerve Dysfunction

N= 691
from King cohort*

* Prospective observational cohort of SARS-COV-2 exposed participants

N=108 Uninfected
N= 205 Without persistent symptoms
N= 36 Unknown/lost of follow up

N= 342 Patients with PCC

N = 228 Patients with at least 1 symptom of VND

Exclusion criteria (<18 years, diabetes mellitus, pregnancy, dementia)

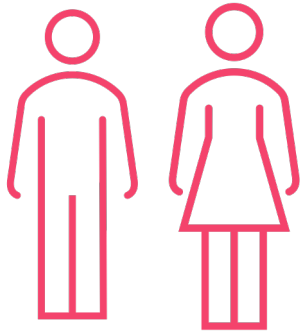
The first 30^a patients were selected

N= 30 PCC

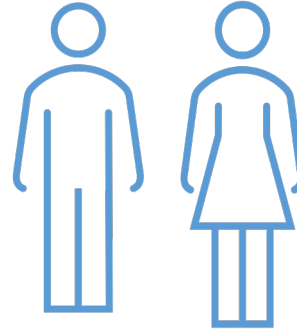
Inclusion criteria:

- 18 years
- Confirmed SARS-CoV-2 infection
- Symptoms compatible with VND (≥ 1):
 - Dysphonia
 - Dysphagia
 - Cough
 - Dyspnea
 - Tachycardia
 - Orthostatic hypotension
 - Dizziness
 - Gastrointestinal dysfunction

- Matched by age and gender



PCC
N=30



COVID-19 RECOVERED
Past SARS-CoV-2 infection without
persistent symptoms
N=16



UNINFECTED
N=14

STRUCTURE AND FUNCTION STUDY

VAGUS NERVE

Neck soft tissue ultrasound

DYSPHONIA

Voice Handicap Index 30 (VHI)

DYSPHAGIA

- Eating Assessment Tool-10 (EAT 10)
- Volume-viscosity clinical examination (MECV)
- Esophagogastric-duodenal transit

RESPIRATORY MUSCLES

- Diaphragm ultrasound
- Maximum inspiratory pressure (MIP)

AUTONOMIC NERVOUS SYSTEM

- Parasympathetic system: R-R
- Sympathetic-reflex response

VAGUS-COVID STUDY

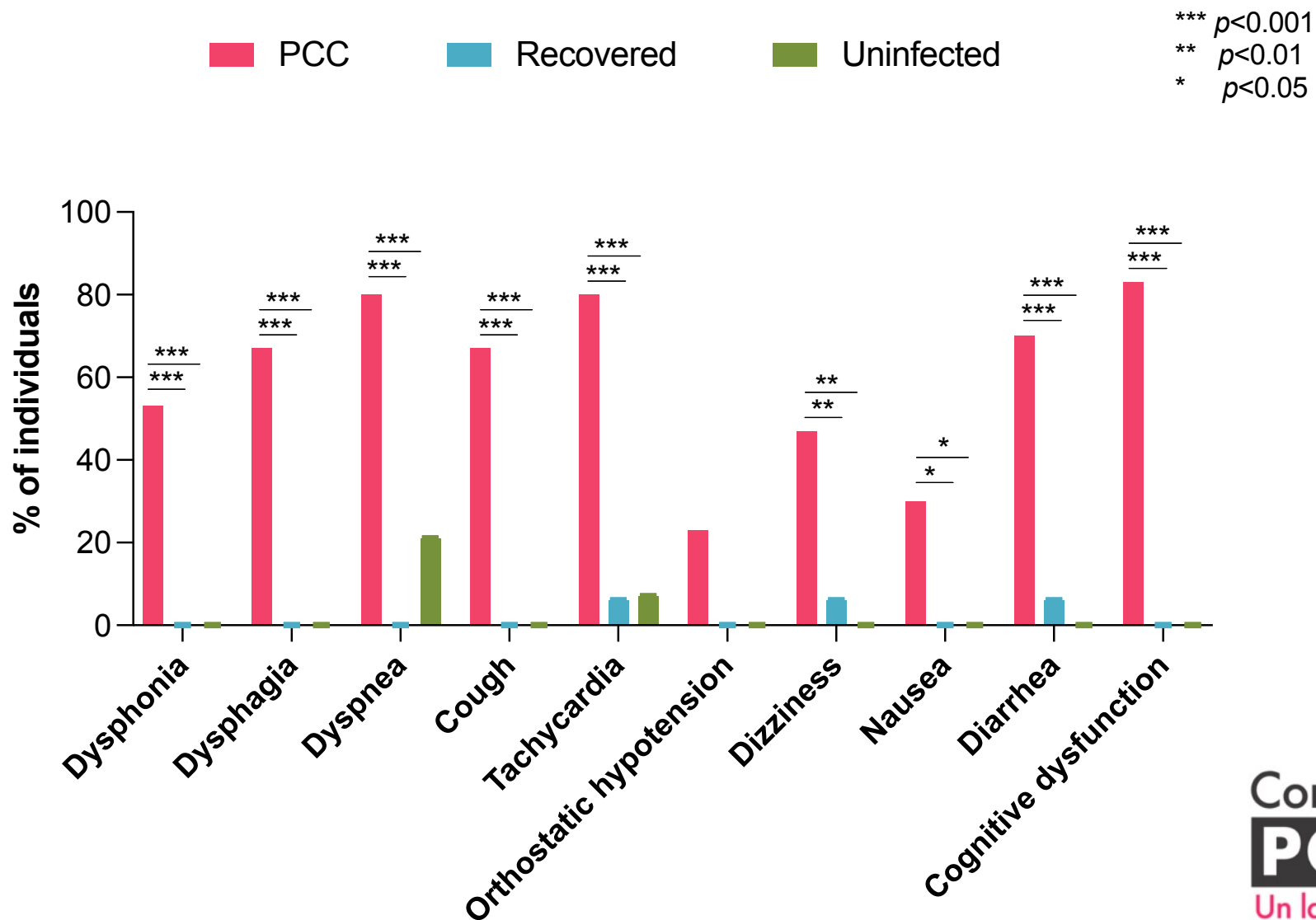
Characteristics of the Participants



PCC: Post COVID Condition

	PCC N=30	Recovered N=16	Uninfected N=14
Age, median [IQR]	44 [35-51]	41 [33-44]	49 [40-53]
Sex, n (%)			
Female	24 (80)	12 (75)	12 (86)
Comorbidities, n (%)			
Allergies	14 (47)	6 (38)	2 (14)
Pneumopathy	4 (13)	1 (6)	0 (0)
Obesity	4 (13)	0 (0)	2 (14)
Autoimmune disease	7 (23)	1 (6)	0 (0)
Oncologic disease	3 (10)	0 (0)	0 (0)
Immunosuppressive treatment	0 (0)	0 (0)	0 (0)
SARS-CoV-2 diagnosis, n (%)			
PCR	9 (30)	13 (81)	-
Serology	7 (23)	3 (19)	-
Clinical manifestations	14 (47)	0 (0)	-
Hospitalization, n (%)			
Ambient air or low-flow oxygen	6 (20)	0 (0)	-
Months since infection, median [IQR]	19 [18-20]	23 [15-24]	-

Condición
POST COVID-19
Un largo camino hacia la recuperación



VAGUS-COVID STUDY

Symptoms of PCC

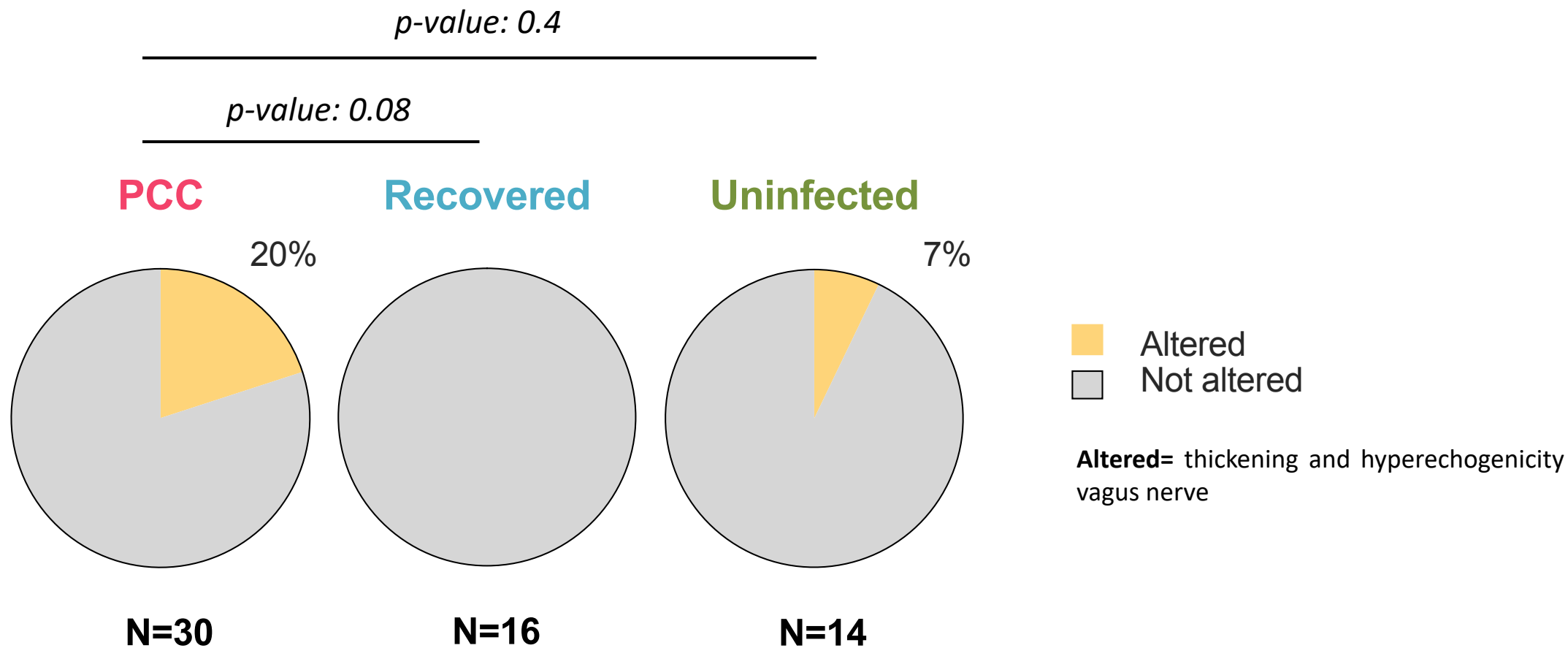
VAGUS-COVID STUDY

Symptoms of PCC

[illegible]

VAGUS-COVID STUDY

Study of vagus nerve ultrasound



Study of Dysphonia

Variable–no. (%)	PCC
Dysphonia questionnaire (VHI) altered	21/28 (78)

Study of Dysphagia

Variable–no. (%)	PCC
Dysphagia questionnaire (EAT-10) altered	21/28 (75)
Functional evaluation of dysphagia (MECV) altered	7/27 (26)
Inefficacy	6/27 (22)
Unsafe	3/27 (11)

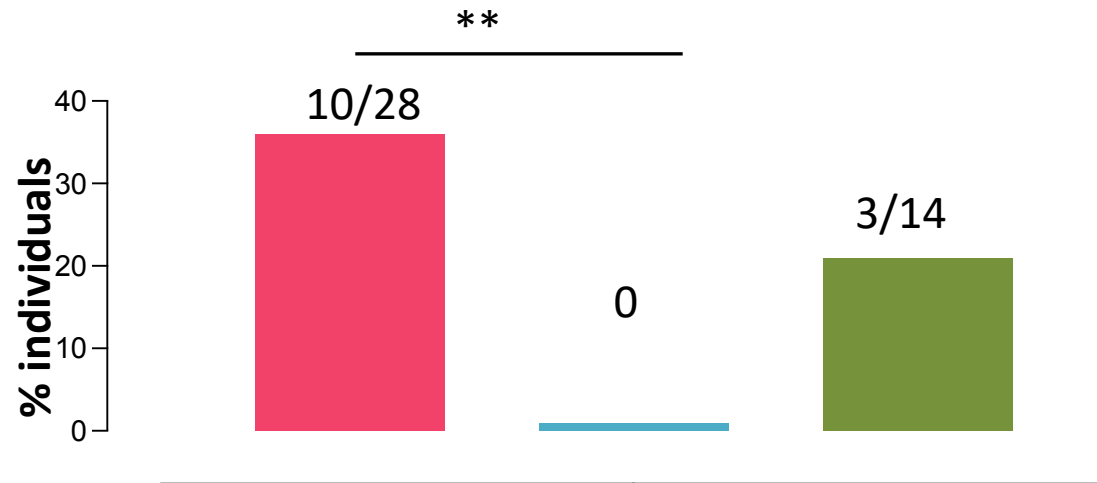
All this assessments were not altered in CONTROLS

■ PCC

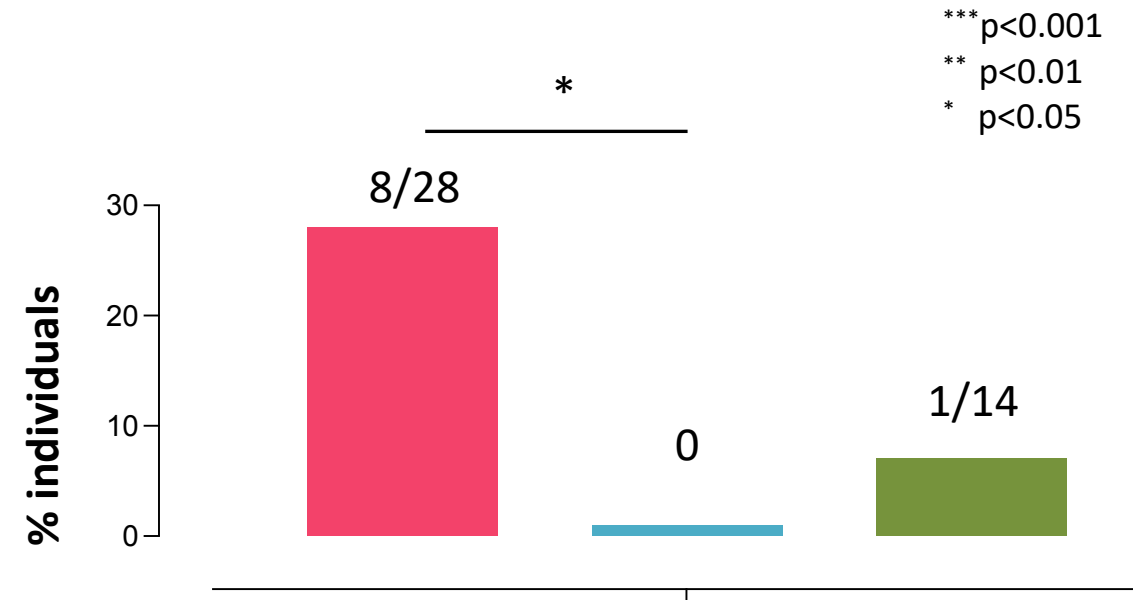
■ Recovered

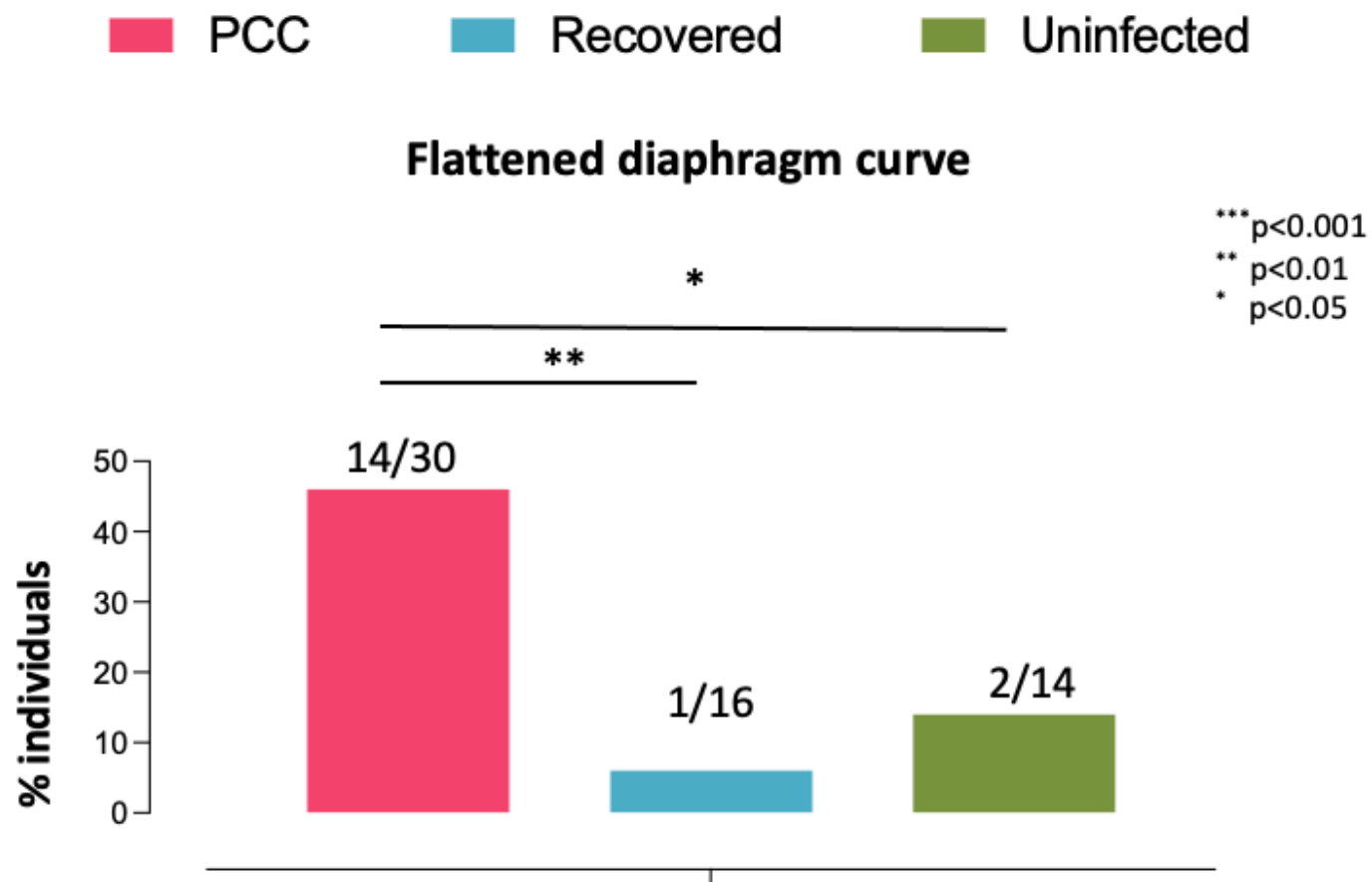
■ Uninfected

Reduced esophageal persistalsis



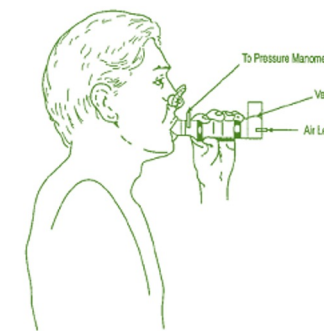
Hiatal hernia





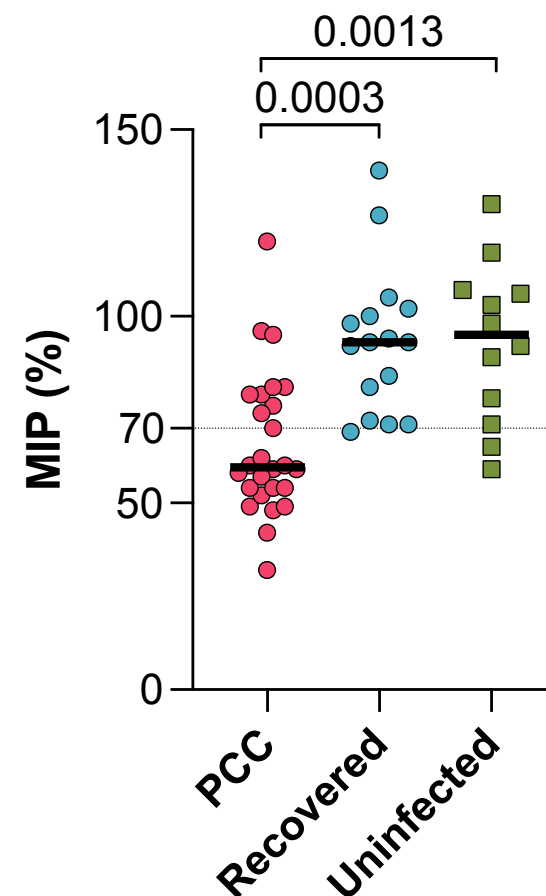
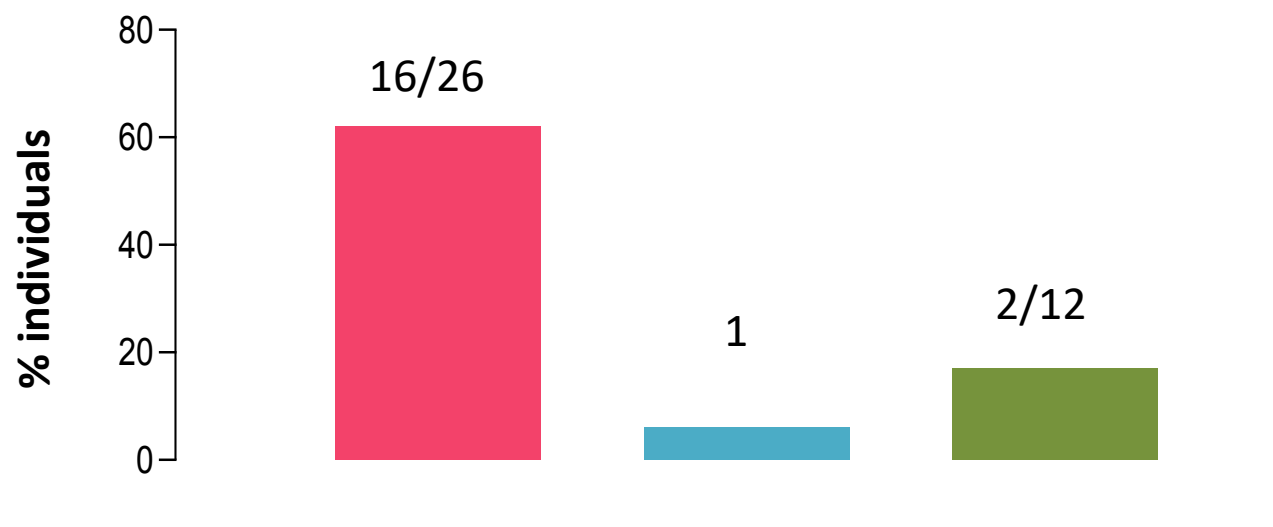
VAGUS-COVID STUDY

Study of respiratory muscles



■ PCC ■ Recovered ■ Uninfected

Maximum inspiratory pressure <70%



Kruskal Wallis
 $p < 0.0001$

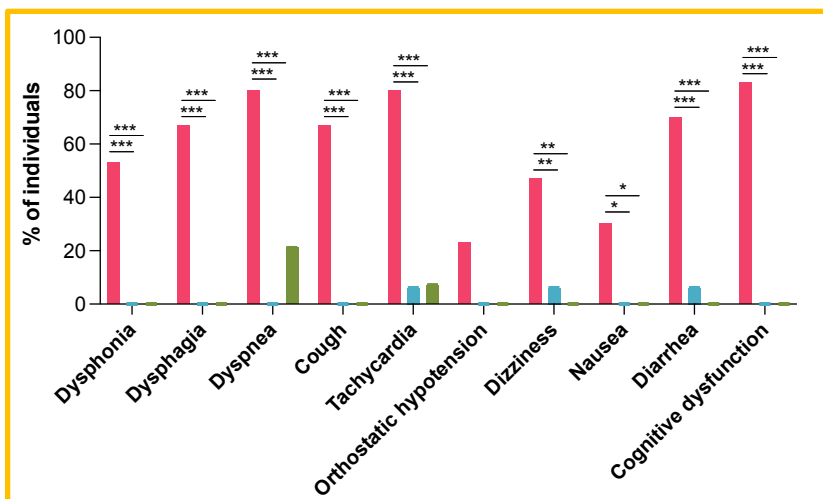
VAGUS-COVID STUDY

Study of Autonomic Nervous System

	CASES N=30	Recovered N=16	Uninfected N=14
Variable–no. (%)			
Parasympathetic system	1/27	0	1/30
Sympathetic-reflex response	1/27	0	0

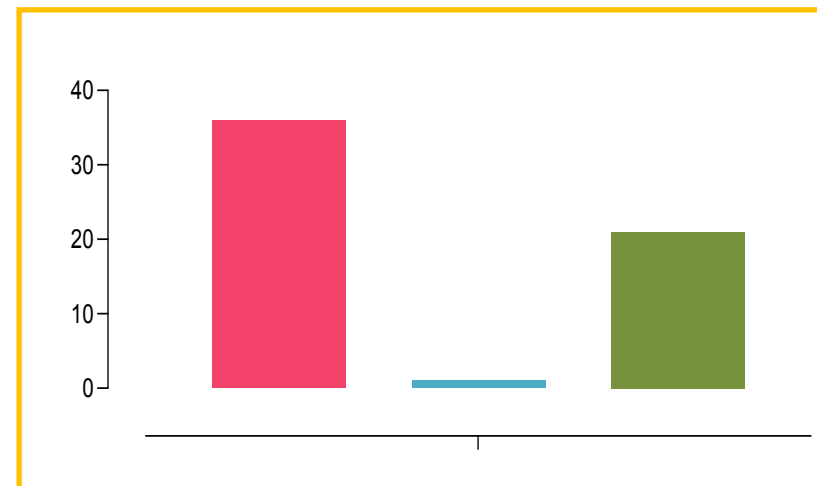
1

Symptoms of VND



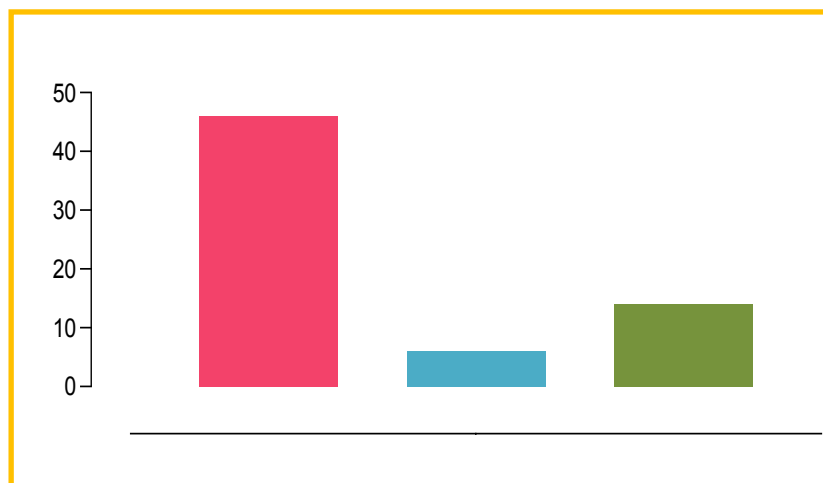
2

Reduced esophageal persistalsis



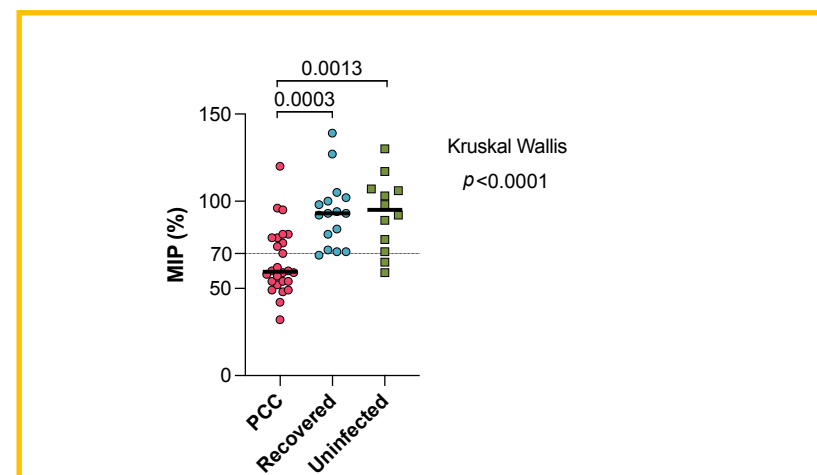
3

Flattened diaphragm curve



4

Maximum inspiratory pressure <70%



- Pilot study
- Small sample size
- Some explorations are observer-dependent

¿HACIA DÓNDE VAMOS?



- ¿Y ahora qué? Poner etiquetas
- Rehabilitación respiratoria
- Más tratamientos posibles:
 - estimulación del vago
 - tratamiento farmacológicos

- En los pacientes con Condición Post Covid-19 y sintomatología sugestiva de disfunción del nervio vago, presentan alteraciones significativas y clínicamente relevantes en las exploraciones realizadas en comparación con los controles.
- Estos hallazgos sitúan la disfunción del nervio vago como mecanismo fisiopatológico a estudio en la Condición Post Covid-19.
- Son necesarios estudios prospectivos y ensayos clínicos

Condición **POST COVID-19**

Un largo camino hacia la recuperación



Gràcies!

