Profiles of Long COVID patients and effects of two psychoeducation interventions

Preliminary results of COVCOG study

Carmen Cabello Fernández
c.cabello@uliege.be
KCE Trials Number : LCOV21 - 1303

Summary

I. Long COVID

II. COVCOG study

III. Characterization of Long COVID patients – Baseline results

IV. Effects of psychoeducative interventions – Preliminary results at 2 months follow-up

V. Conclusions and perspectives

Long COVID

What do we call Long COVID ?

▶ Definition :

- Continuation or development of new symptoms **3 months after SARS-CoV-2 infection**

- Symptoms lasting for **at least 2 months**

- Symptoms **cannot be explained** by alternative diagnosis

▶ Following severe COVID-19 disease but also in mild and moderate infections

WHO, 2021 ; Salamanna et al., 2021

Manifestations of Long COVID

▶ Multisystemic syndrome affecting several organs:

▶ Fatigue and cognitive difficulties are among the most common reported symptoms

- Subjective complaints (i.e. concentration, memory, multitasking)

- Objective impairment (i.e. attentional, memory, executive)

Mehandru et Merad, 2022 ; Salamanna et al., 2021; Liu et al., 2023 ; Han et al., 2022; Tavares-Júnior et al., 2022

How symptoms evolve ?

▶ Persist even two years after infection

▶ Improvement observed but 30% still report symptoms affecting everyday life (related to cognition, sensorimotor function and mental fatigue)
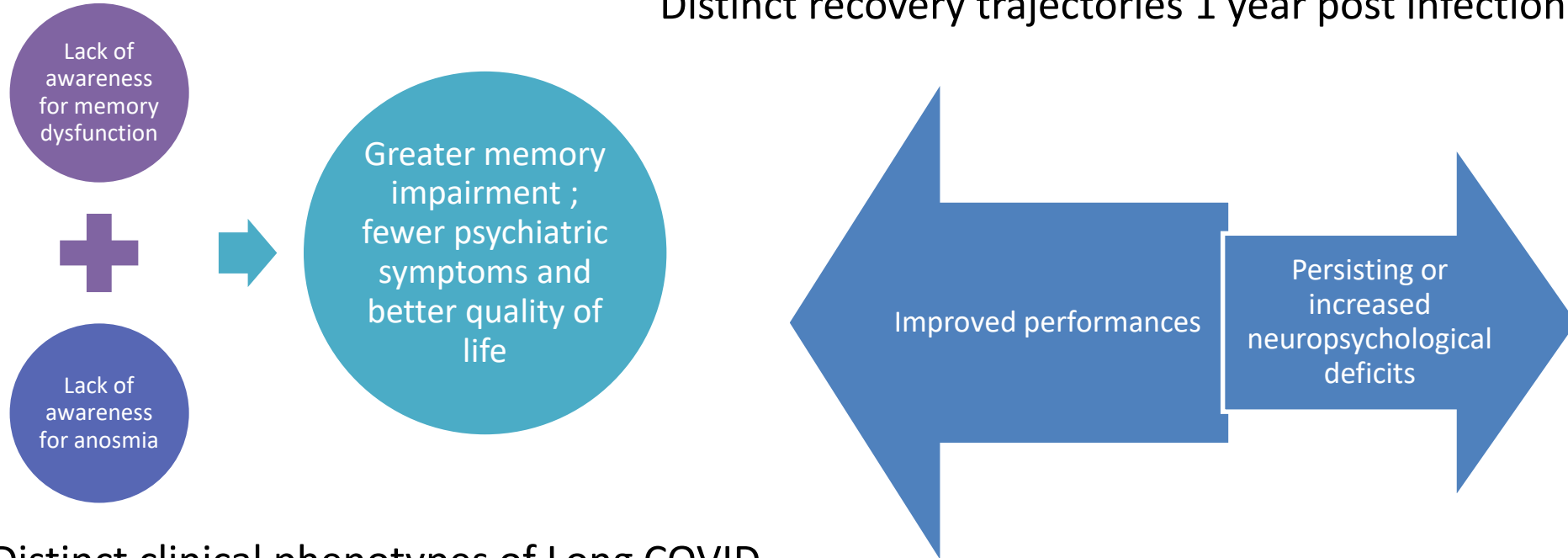
Wahlgrend et al., 2023 ; Han et al., 2022

Pathophysiology of Long COVID

▶ Complex interplay of factors from different aetiologies

▶ Among the most discussed hypothesis:

- Direct viral infection of CNS

- Hypoxia

- Maladaptative inflammatory response

- Neuropsychiatric comorbidities

- Dysfunction of the autonomic nervous system

Politi et al., 2020 ; Dondaine et al., 2022 ; Najjar et al., 2020; Wu et al., 2024; Molnar et al., 2024 ; Poletti et al., 2022 ; Dani et al., 2021

7

Different profiles of patients

Distinct recovery trajectories 1 year post infection

Lack of awareness for memory dysfunction

➕

Lack of awareness for anosmia

➡ Greater memory impairment ; fewer psychiatric symptoms and better quality of life

Improved performances

Persisting or increased neuropsychological deficits

Distinct clinical phenotypes of Long COVID

Voruz et al., 2022; 2024

What are the treatment options ?

▶ Adaptation of pre-existing therapies (i.e. cognitive rehabilitation programs in ABI or PCS)

▶ Multiplicity of symptoms, including psychological factors = Cognitive behavioural therapy (CBT)

▶ Specific rehabilitation pathways based on clinical profiles ?

Mathern et al., 2022; Tay et al., 2021

Objectives

1. Different profiles of patients ? (baseline evaluation)

2. What is the most effective treatment ? (cognitive vs. affective at 2 months follow-up)

COVCOG STUDY

Effects of two interventional programmes (cognitive vs. Affective psychoeducations) in Long COVID patients with cognitive difficulties

BMC Neurology

STUDY PROTOCOL   **Open Access**

COVCOG: Immediate and long-term cognitive improvement after cognitive versus emotion management psychoeducation programs - a randomized trial in covid patients with neuropsychological difficulties

Sylvie Willems[1,2*], Vincent Didone[1], Carmen Cabello Fernandez[1], Gael Delrue[3], Hichem Slama[4], Patrick Fery[4], Julien Goin[2], Clara Della Libera[2], COVCOG Group and Fabienne Collette[1,5]

Willems et al., 2023

- ▶ Pre-registration (clinicaltrials.gov: NCT05167266)
- ▶ Randomized control trial
- ▶ Data collection between march 2022 and june 2024
- ▶ N=130 randomized in either cognitive or affective intervention (ratio 1:1)
- ▶ Patients with cognitive complaints and at least 3 months after SARS-CoV-2 infection

Chronology of the study (10,5 months)

Phone screening : pre-inclusion

RANDOMIZATION

INTERVENTION Cognitive vs. Affective (4 sessions of 1h30)

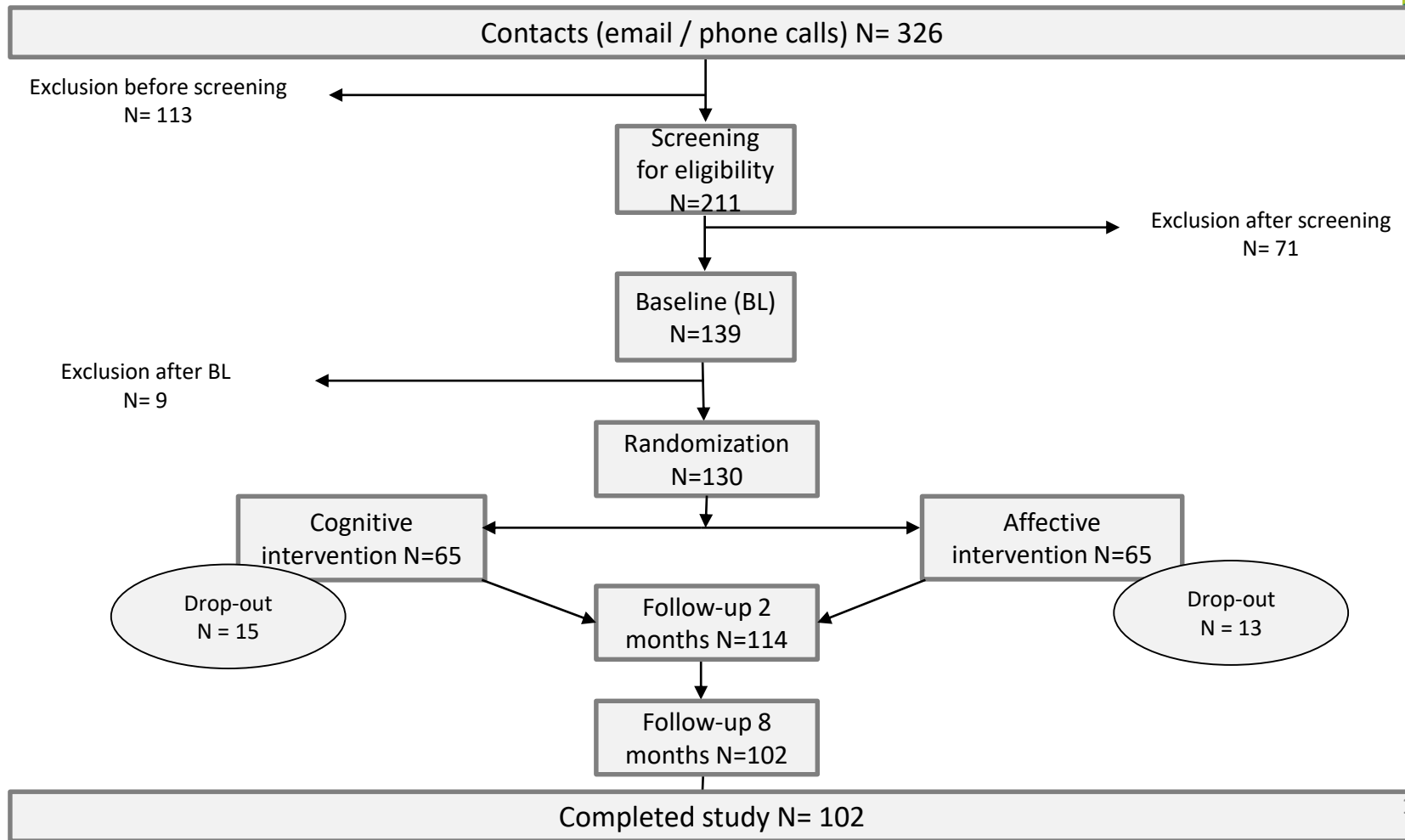Follow-up evaluation 8 months post-intervention

Baseline evaluation

Follow-up evaluation 2 months post-intervention

13

Neuropsychological evaluations (BL and FUs)

Domains	Functions	Test
Memory	Episodic verbal	Word-list of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
	Episodic visuospatial	Brief Visuospatial Memory Test (BVMT-Revised)
Attention	Selective attention	Test of Attentional Performance (TAP) ; D2-R
	Divided attention	Test of Attentional Performance (TAP)
	Processing speed	Test of Attentional Performance (TAP) ; STROOP test (reading and naming conditions); D2-R
	Attentional fluctuation	Tests of Attentional Performance (TAP)
Executive functions	Inhibition	STROOP test (interference condition)
	Flexibility	Flexibility task of the Test of Attentional Performance (TAP)
	Working memory	Updating task of the Test of Attentional Performance (TAP); BROWN-PETERSON test
Language		Phonetic and semantic fluency

+ Self-reported questionnaires: cognitive complaints, fatigue, sleep difficulties, quality of life, psychological distress and impact on daily activities

14

Contacts (email / phone calls) N= 326

Exclusion before screening
N= 113

Screening
for eligibility
N=211

Exclusion after screening
N= 71

Baseline (BL)
N=139

Exclusion after BL
N= 9

Randomization
N=130

Cognitive
intervention N=65

Affective
intervention N=65

Drop-out
N = 15

Drop-out
N = 13

Follow-up 2
months N=114

Follow-up 8
months N=102

Completed study N= 102

15

Characterization of Long COVID patients

BASELINE RESULTS

Demographics

		Total
Demographics	Age (mean ± SD) [range]	47 ± 10.1 [21-66]
	Sex (female)	85 (69.1%)
	Years of education (mean ± SD) [range]	14 ± 3 [6-17]
History of COVID-19	Asymptomatic *	1 (0.8%)
	Mild infection *	67 (54.5%)
	Moderate infection *	41 (33.3%)
	Severe infection *	14 (11.4%)
	Hospitalized	17 (13.8% ; 10 female)
	ICU treatment; mean stay	9 (7.3% ; 3 female) ; 14 days
	Number of infections (mean ± SD) [range]	1.7 ± 0.9 [1-5]
	Time since first infection (months)	20.9 ± 8.6 [4-39]

# Spontaneous somatic and functional complaints

- Sleep difficulties: 84.6
- Fatigue: 80.5
- Pain: 33.3
- Respiratory: 32.5
- Headaches/migraines: 30.1
- Fluctuations: 27.6
- Altered taste/smell: 27.6
- Work difficulties: 95.1
- Social difficulties: 70.7
- Familial difficulties: 45.5

Somatic

Functional

18
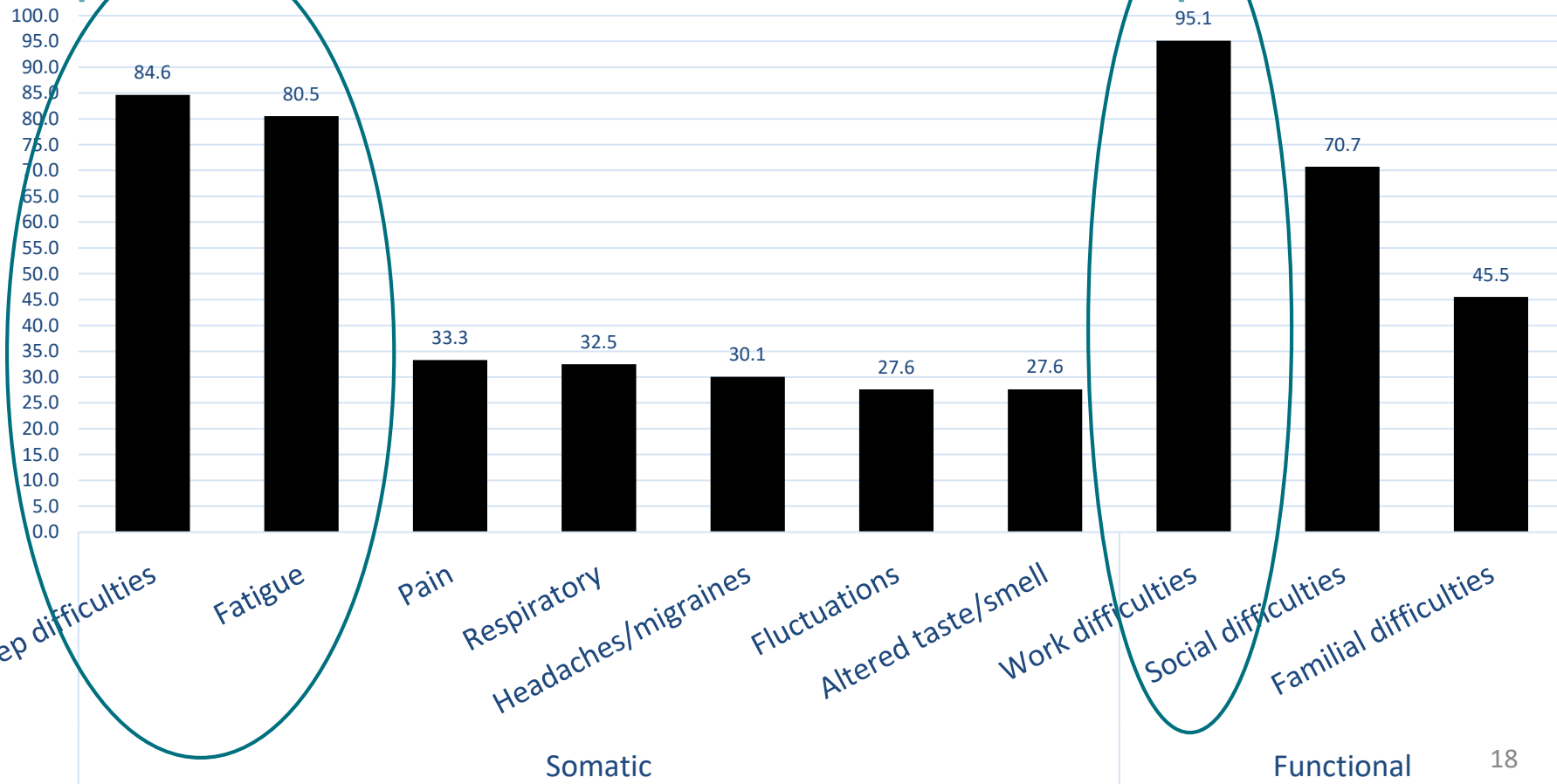
Spontaneous cognitive complaints
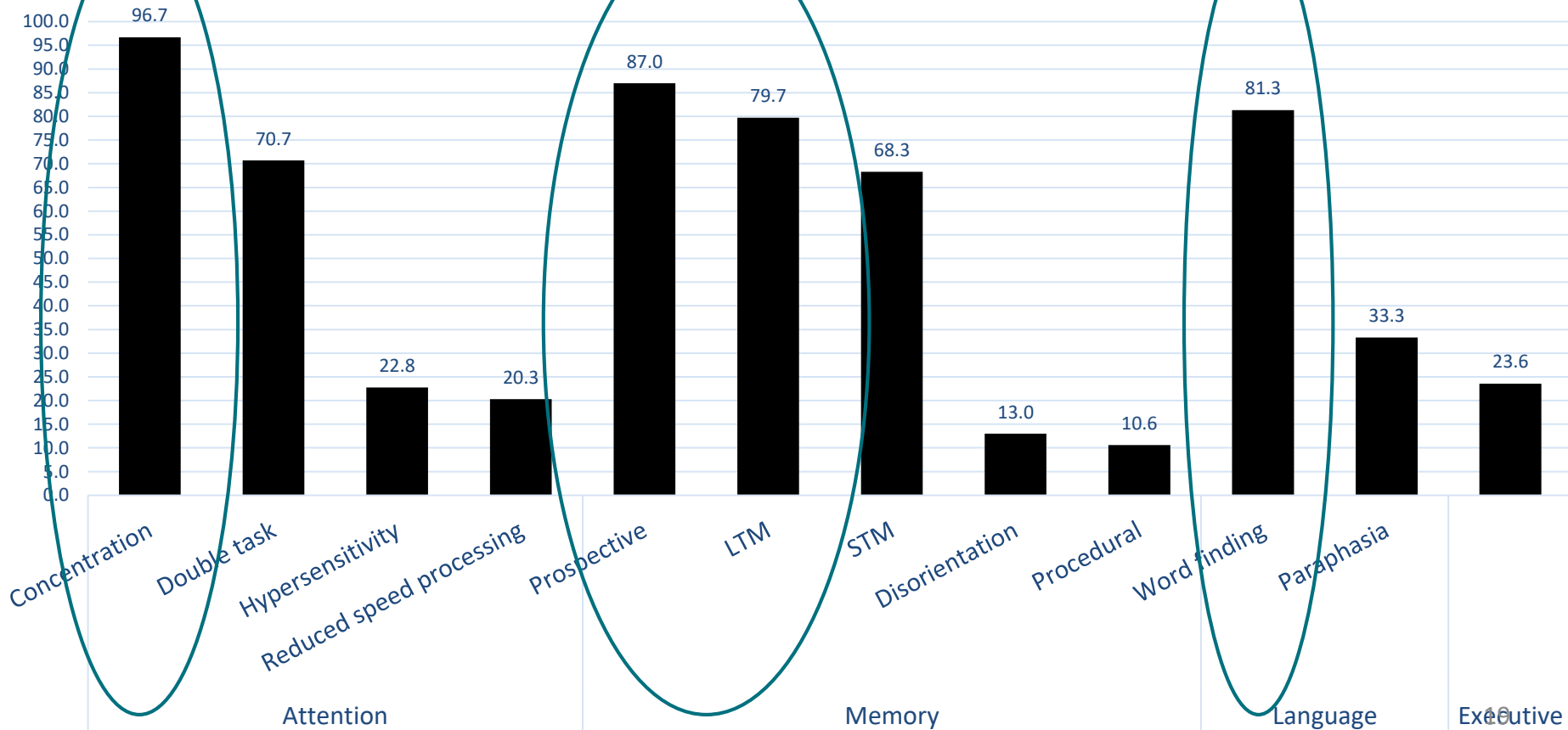
Objective impairment
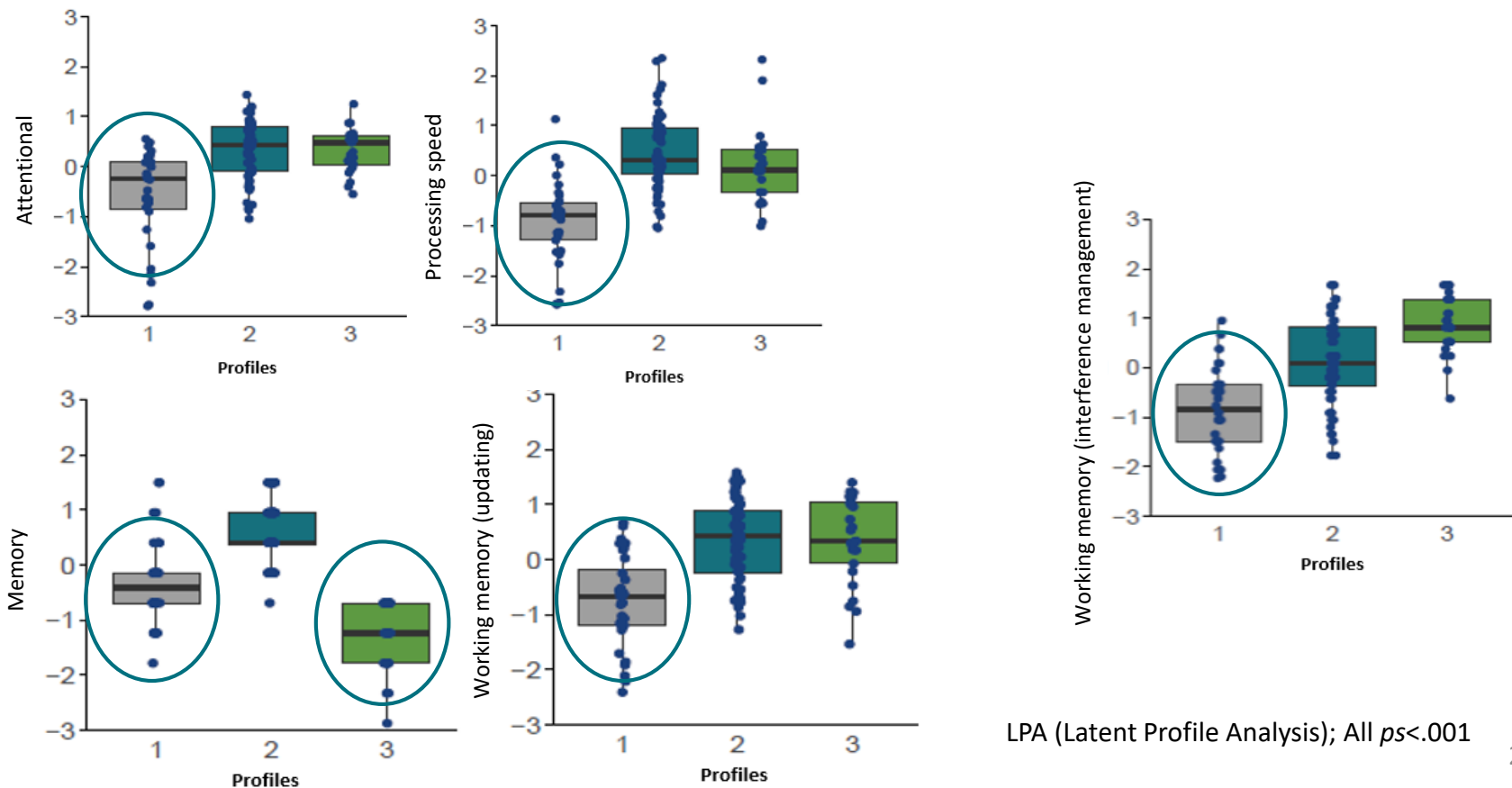

Percentage of impairment in cognitive domains
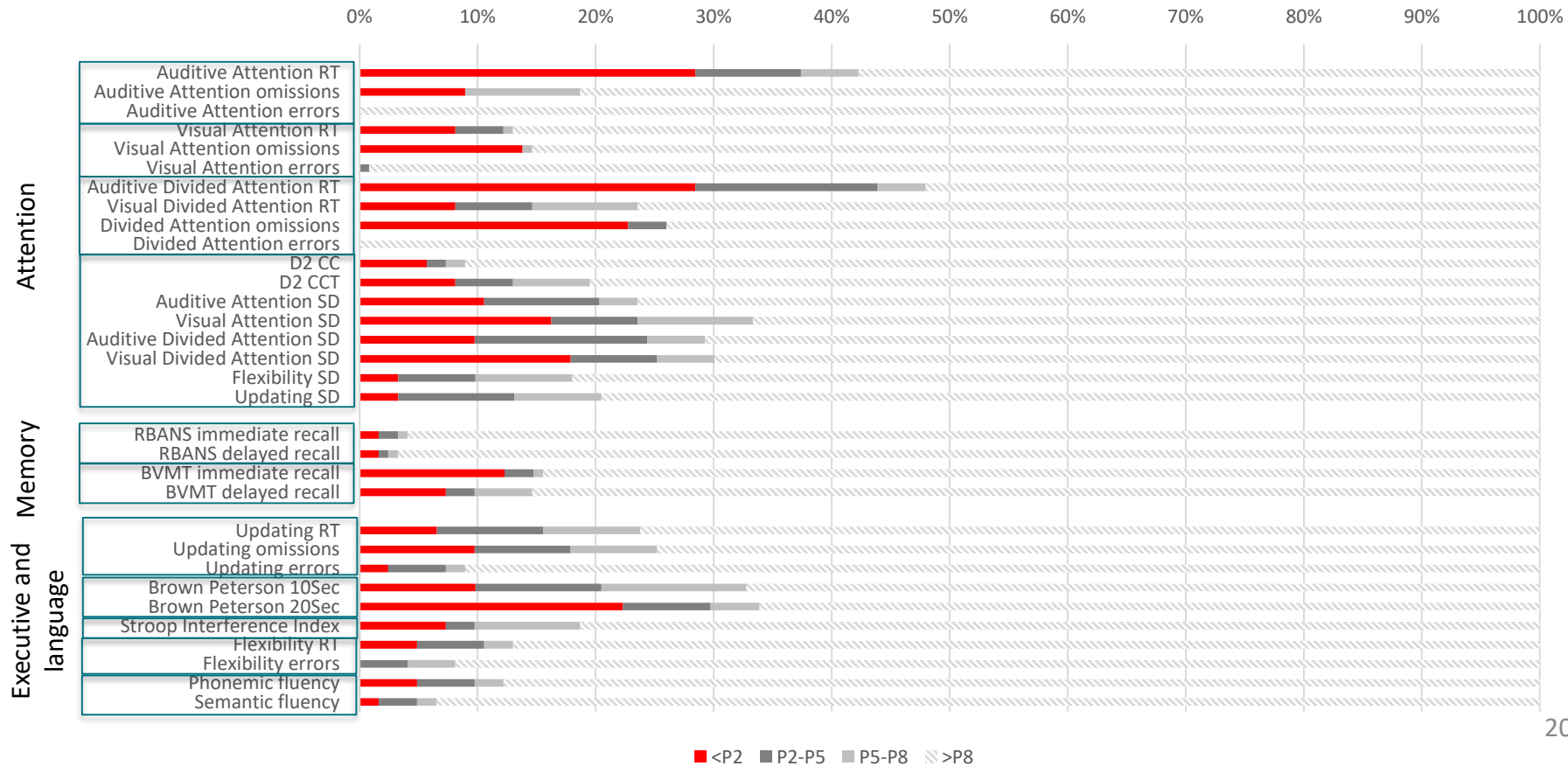
Legend: <P2, P2-P5, P5-P8, >P8

Association of cognitive impairment and complaints

▶ Objective measure : patient's worst score

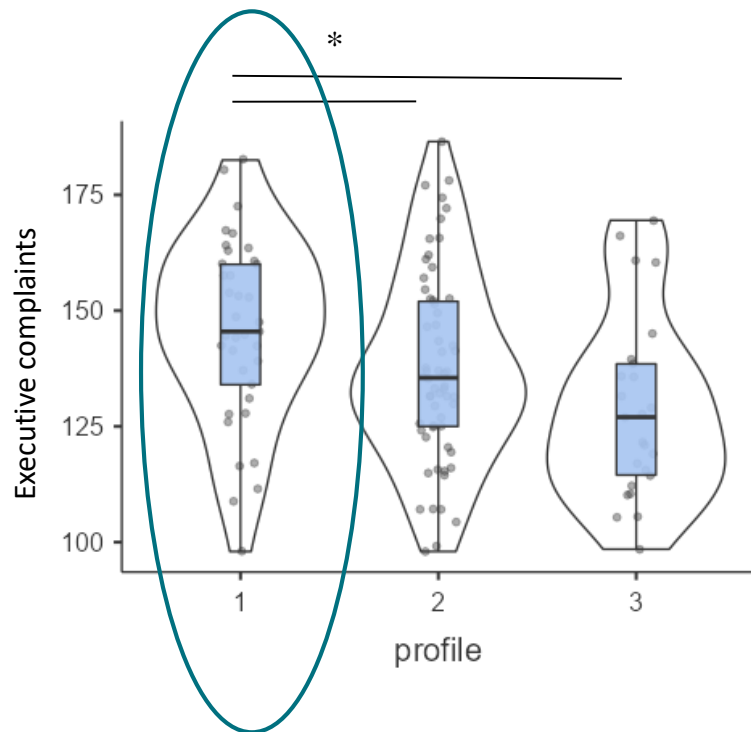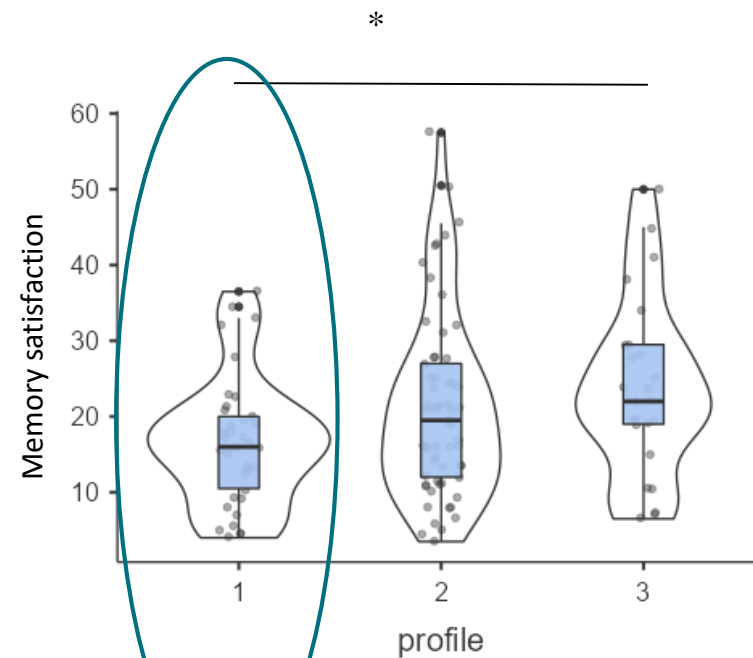▶ Subjective measure : importance of cognitive complaint (questionnaires BRIEF and MMQ)

Attention_worst

Executive_worst

BRIEF

MMQ

R = .280**

R = .252**

R = .320***

R = .338***

21

3 profiles of Long COVID patients

LPA (Latent Profile Analysis); All *ps*<.001

Profiles of Long COVID patients

*

p=.002

*

p=.013

Profiles of Long COVID patients

Profile 1 (30%)

Greater impairments (attention and executive functions)

More cognitive and fatigue complaints

+
Moderate/severe infections

Profile 2 (50%)

Also widespread pattern of cognitive difficulties

Less pronounced than profile 1

Profile 3 (20%)

Specific impairment in verbal episodic memory

No deficit in executive functions

Lower cognitive and fatigue complaints, including memory functioning

+ males

24

In summary

- ▶ Objective deficits for all patients in addition to (and correlated to) subjective complaints

- ▶ Those deficits are significant even using a conservative threshold
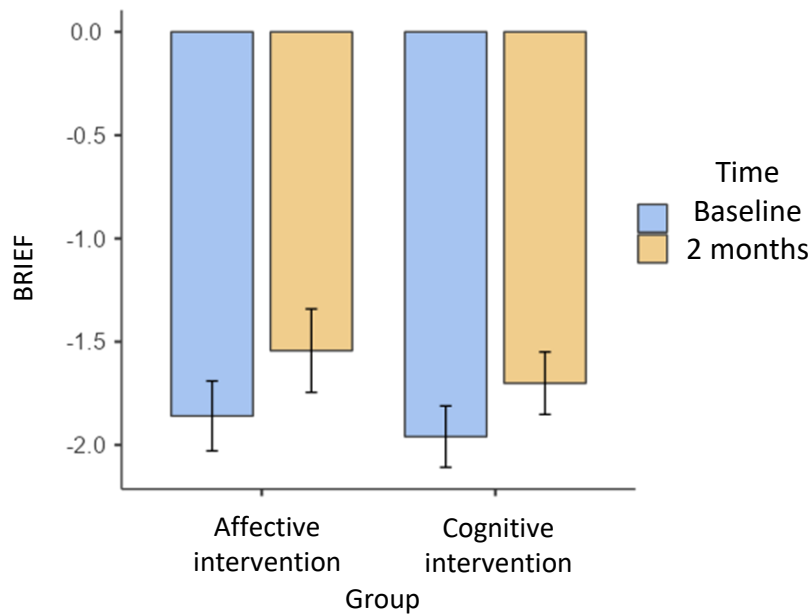
- ▶ Distinct profiles of Long COVID patients

How to treat them ?

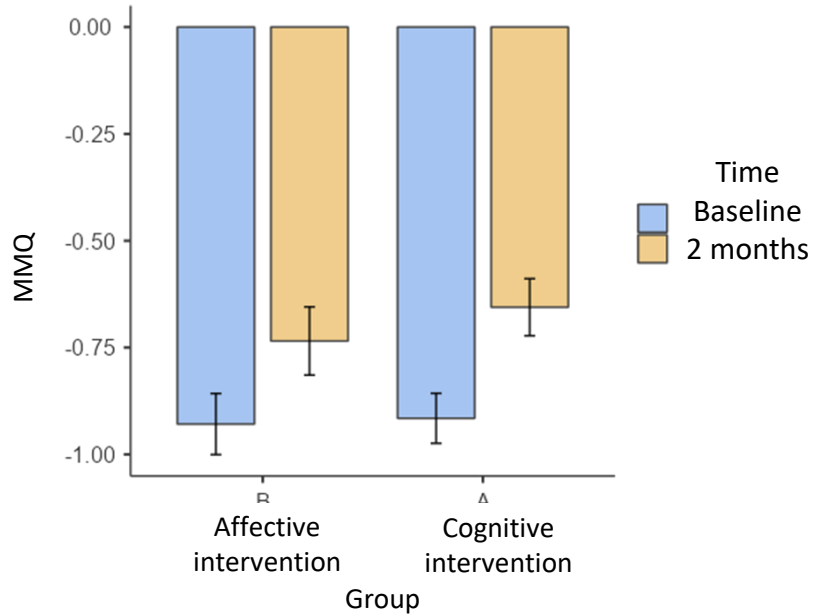# Effects of psychoeducative interventions
RESULTS AT 2 MONTHS FOLLOW-UP
(in prep.)

BRIEF-A : executive functioning

Time
Baseline
2 months

▶ Executive complaints decreased at 2 months FU for both intervention groups

p<.0001

27

MMQ : memory functioning

Time
Baseline
2 months

p<.0001

▶ Memory complaints decreased at 2 months FU for both intervention groups

Conclusions and perspectives

Conclusions and discussion

▶ Decrease in cognitive complaints in both intervention groups

▶ Influence of spontaneous recovery ?

▶ Linear regressions :

- No time effect between first infection and baseline evaluation (BRIEF-A, p=0.77; MMQ, p=0.64)

- No time effect between first infection and follow-up evaluation (BRIEF-A, p=0.69; MMQ, p=0.15)

- => Spontaneous recovery is highly unlikely

Perspectives

▶ Further research to:

- Comprehensively characterise the full spectrum of patient profiles

- Develop specific rehabilitation programs

▶ Trajectory analysis in progress (3 profiles vs. Intervention type)

THANK YOU

REFERENCES

Dani, M., Dirksen, A., Taraborrelli, P., Torocastro, M., Panagopoulos, D., Sutton, R., & Lim, P. B. (2021). Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. *Clinical Medicine*, *21*(1), e63.

Dondaine, T., Ruthmann, F., Vuotto, F., Carton, L., Gelé, P., Faure, K., ... & Bordet, R. (2022). Long-term cognitive impairments following COVID-19: a possible impact of hypoxia. *Journal of neurology*, *269*(8), 3982-3989.

Han, Q., Zheng, B., Daines, L., & Sheikh, A. (2022). Long-term sequelae of COVID-19: a systematic review and meta-analysis of one-year follow-up studies on post-COVID symptoms. *Pathogens*, *11*(2), 269.

Liu, T. C., Yoo, S. M., Sim, M. S., Motwani, Y., Viswanathan, N., & Wenger, N. S. (2023). Perceived Cognitive Deficits in Patients With Symptomatic SARS-CoV-2 and Their Association With Post–COVID-19 Condition. *JAMA network open*, *6*(5), e2311974-e2311974

Mathern, R., Senthil, P., Vu, N., & Thiyagarajan, T. (2022). Neurocognitive rehabilitation in COVID-19 patients: a clinical review. *Southern Medical Journal*, *115*(3), 227.

Mehandru, S., Merad, M. Pathological sequelae of long-haul COVID. *Nat Immunol* **23**, 194–202 (2022). https://doi.org/10.1038/s41590-021-01104-y

Molnar, T., Lehoczki, A., Fekete, M., Varnai, R., Zavori, L., Erdo-Bonyar, S., ... & Ezer, E. (2024). Mitochondrial dysfunction in long COVID: mechanisms, consequences, and potential therapeutic approaches. *GeroScience*, 1-20.

Najjar, S., Najjar, A., Chong, D. J., Pramanik, B. K., Kirsch, C., Kuzniecky, R. I., ... & Azhar, S. (2020). Central nervous system complications associated with SARS-CoV-2 infection: integrative concepts of pathophysiology and case reports. *Journal of neuroinflammation*, *17*, 1-14.

Poletti, S., Palladini, M., Mazza, M. G., De Lorenzo, R., Furlan, R., Ciceri, F., ... & Benedetti, F. (2022). Long-term consequences of COVID-19 on cognitive functioning up to 6 months after discharge: role of depression and impact on quality of life. *European archives of psychiatry and clinical neuroscience*, 1-10.

Politi, L. S., Salsano, E., & Grimaldi, M. (2020). Magnetic resonance imaging alteration of the brain in a patient with coronavirus disease 2019 (COVID-19) and anosmia. *JAMA neurology*, *77*(8), 1028-1029.

Salamanna, F., Veronesi, F., Martini, L., Landini, M. P., & Fini, M. (2021). Post-COVID-19 syndrome: the persistent symptoms at the post-viral stage of the disease. A systematic review of the current data. *Frontiers in medicine*, *8*, 653516

Tavares-Júnior, J. W., de Souza, A. C., Borges, J. W., Oliveira, D. N., Siqueira-Neto, J. I., Sobreira-Neto, M. A., & Braga-Neto, P. (2022). COVID-19 associated cognitive impairment: A systematic review. *Cortex*, *152*, 77-97.

Tay, M. R. J., Low, Y. H., Lim, C. C. T., Umapathi, T., Thio, J. M. L., Lui, W. L., ... & Chua, K. S. G. (2021). Covert subclinical neurocognitive sequelae during the rehabilitation course of severe Coronavirus Disease 2019. *American journal of physical medicine & rehabilitation*, *100*(1), 39-43.

Voruz, P., Cionca, A., Jacot de Alcântara, I., Nuber-Champier, A., Allali, G., Benzakour, L., ... & Péron, J. A. (2022). Functional connectivity underlying cognitive and psychiatric symptoms in post-COVID-19 syndrome: is anosognosia a key determinant?. *Brain communications*, *4*(2), fcac057.

Voruz, P., de Alcântara, I. J., Nuber-Champier, A., Cionca, A., Guérin, D., Allali, G., ... & Péron, J. A. (2024). Persistence and emergence of new neuropsychological deficits following SARS-CoV-2 infection: A follow-up assessment of the Geneva COVID-COG cohort. *Journal of Global Health*, *14*.

Wahlgren C, Forsberg G, Divanoglou A, Balkhed ÅÖ, Niward K, Berg S, Levi R (2023) Two-year follow-up of patients with post-COVID-19 condition in Sweden: A prospective cohort study. The Lancet Regional Health–Europe 28 https://doi.org/10.1016/j.lanepe.2023.100595

Willems, S., Didone, V., Cabello Fernandez, C., Delrue, G., Slama, H., Fery, P., ... & Collette, F. (2023). COVCOG: Immediate and long-term cognitive improvement after cognitive versus emotion management psychoeducation programs-a randomized trial in covid patients with neuropsychological difficulties. *BMC neurology*, *23*(1), 307.

Wu, X., Xiang, M., Jing, H., Wang, C., Novakovic, V. A., & Shi, J. (2024). Damage to endothelial barriers and its contribution to long COVID. *Angiogenesis*, *27*(1), 5-22.
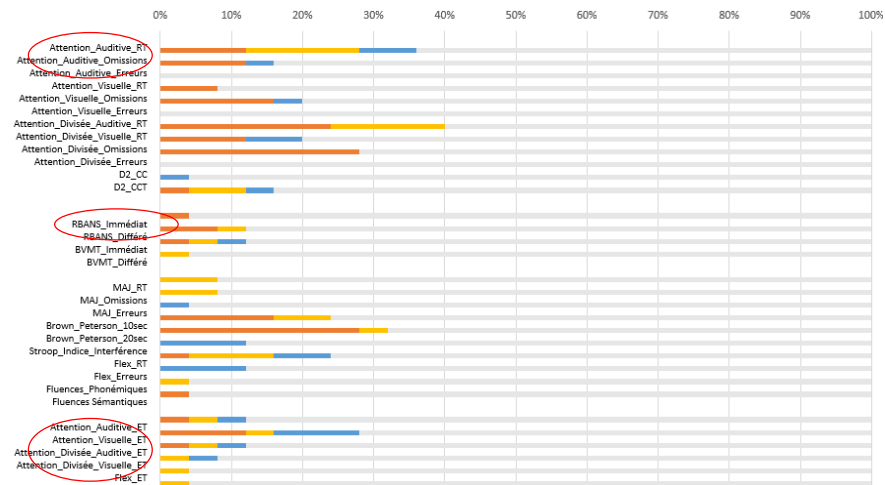
Profile 1
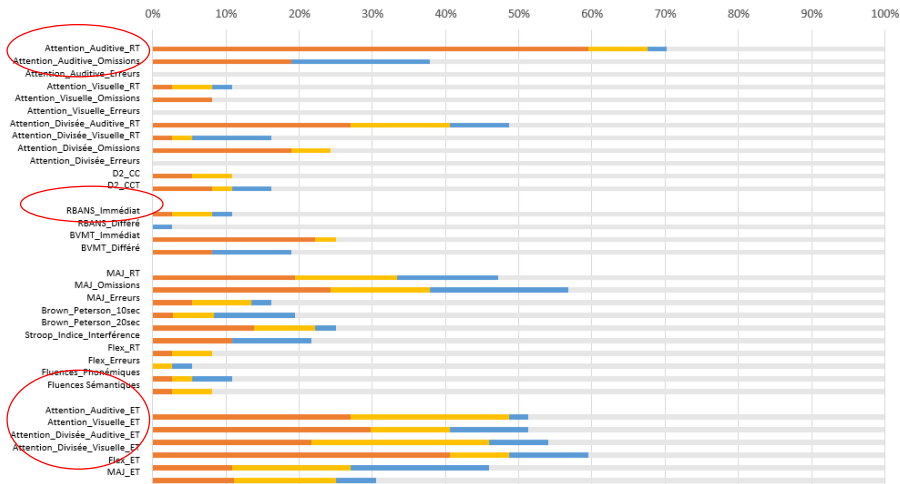
Profile 2
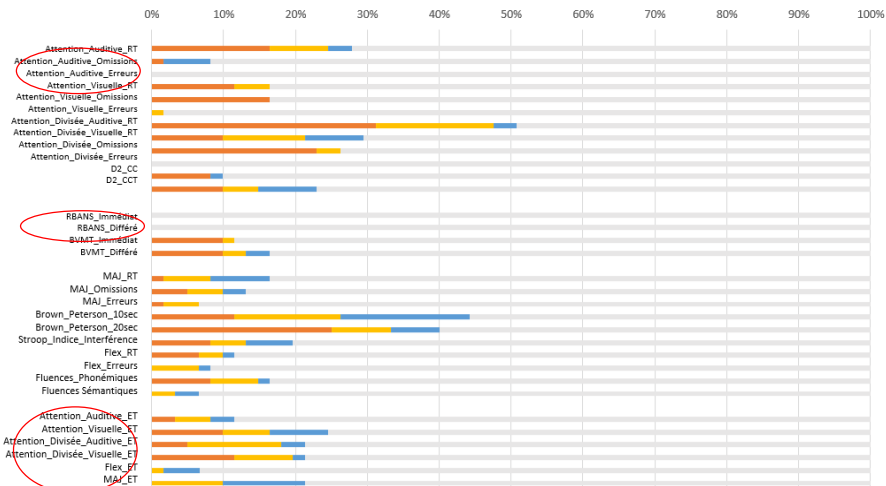
Profile 3

🟧	<P2
🟨	P2-P5
🟦	P5-P8
⬜	>P8

34

Cognitive intervention

- 4 sessions of 1h30 + reactivation session 30min (after 1 month)

- Intensified by videotherapy and home exercices

- Psychoeducation targetting metacognition to teach appropriate behaviours and strategies

Fatigue and sleep (i.e. recognise and management of energy)

Module 1

Working memory and attention (i.e. adapt the environnement)

Module 2

Executive functions (i.e. planification)
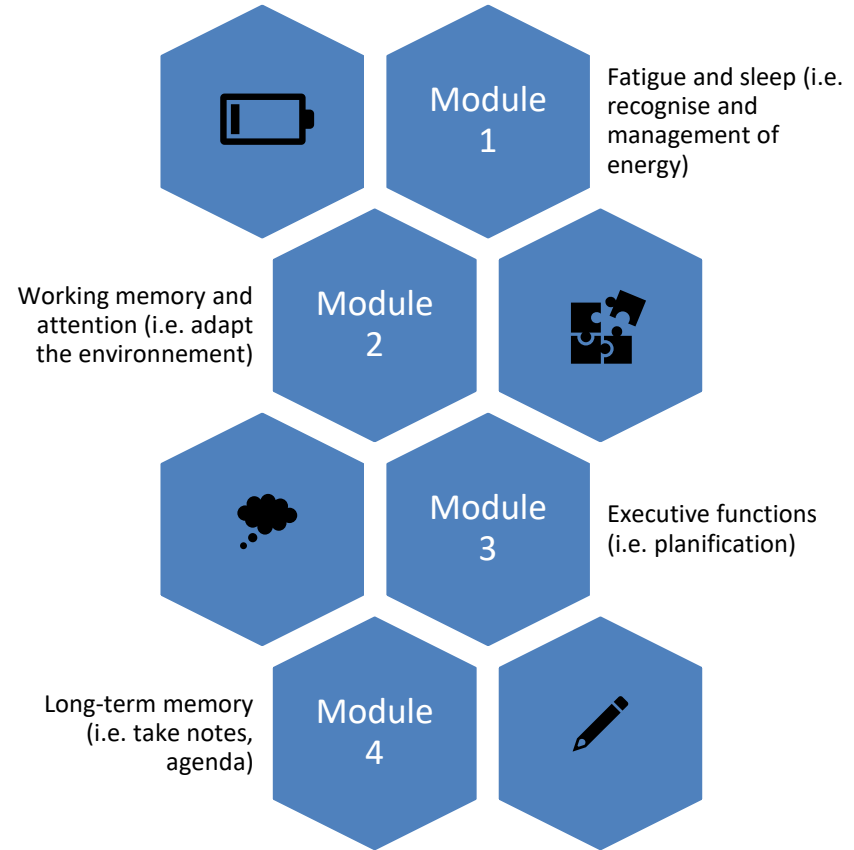
Module 3

Long-term memory (i.e. take notes, agenda)

Module 4

Affective intervention
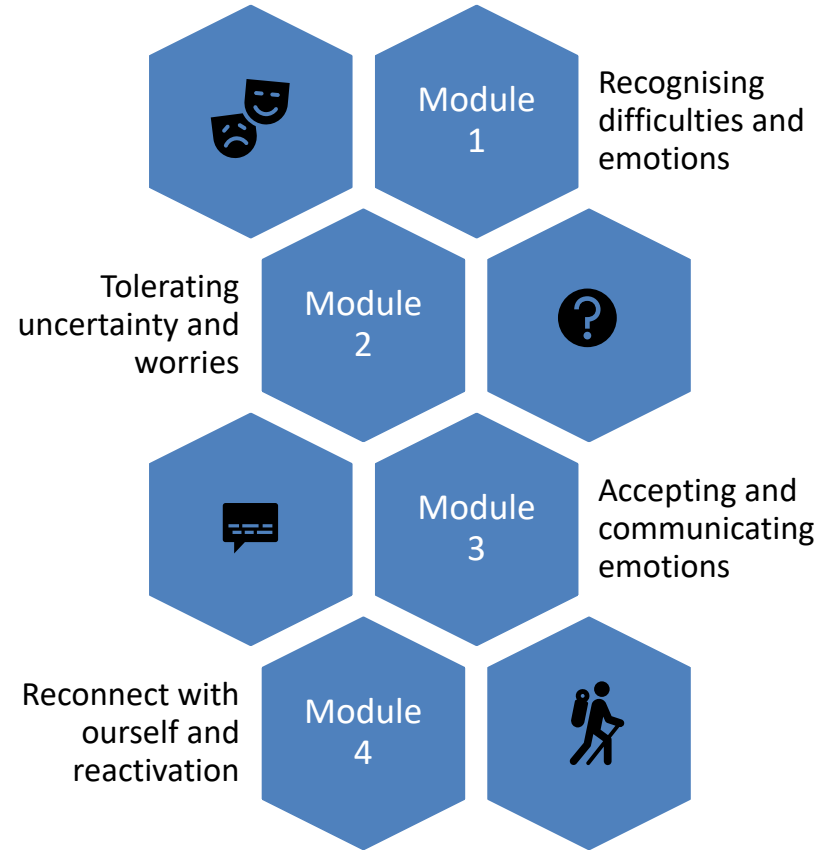
- ▶ 4 sessions of 1h30 + reactivation session 30min (after 1 month)

- ▶ Intensified by notes and home exercices

- ▶ CBT targetting regulation of emotion and behaviour impacting the perception of difficulties on daily living activities

Recognising difficulties and emotions

Module 1

Tolerating uncertainty and worries

Module 2

Accepting and communicating emotions

Module 3

Reconnect with ourself and reactivation

Module 4

Demographic

		Total
Demographics	Age (mean ± SD) [range]	47 ± 10.1 [21-66]
	Sex (female)	85 (69.1%)
	Years of education (mean ± SD) [range]	14 ± 3 [6-17]
	Actively employed/student before infection	120 (97.6%)
	Actively employed/student at study inclusion	73 (59.3%)
	At sick leave before infection	1 (0.8%)
	At sick leave at study inclusion	42 (34.15%)
History of COVID-19	Asymtomatic *	1 (0.8%)
	Mild infection *	67 (54.5%)
	Moderate infection *	41 (33.3%)
	Severe infection *	14 (11.4%)
	Hospitalized	17 (13.8% ; 10 female)
	ICU treatment; mean stay	9 (7.3% ; 3 female) ; 14 days
	Number of infections (mean ± SD) [range]	1.7 ± 0.9 [1-5]
	Time since first infection (months)	20.9 ± 8.6 [4-39]

Association of cognitive impairment and complaints

▶ Objective measure : patient's worst score

▶ Subjective measure : importance of cognitive complaint (questionnaires)

		LTM_pire	exe_pire	att_pire	brief_bri	brief_mi	brief_tot	mmq_abi
brief_bri	r de Pearson	0.036	0.183*	0.057	—			
	ddl	120	121	121	—			
	valeur p	0.692	0.042	0.534	—			
	Borne sup de l'IC95%	0.213	0.349	0.231	—			
	Borne inf de l'IC95%	-0.143	0.007	-0.122	—			
brief_mi	r de Pearson	-0.026	0.320***	0.280**	0.580***	—		
	ddl	120	121	121	121	—		
	valeur p	0.776	< .001	0.002	< .001	—		
	Borne sup de l'IC95%	0.152	0.470	0.436	0.686	—		
	Borne inf de l'IC95%	-0.203	0.151	0.109	0.449	—		
mmq_abi	r de Pearson	0.020	0.338***	0.252**	0.425***	0.637***	0.586***	—
	ddl	120	121	121	121	121	121	—
	valeur p	0.823	< .001	0.005	< .001	< .001	< .001	—
	Borne sup de l'IC95%	0.197	0.486	0.411	0.560	0.731	0.691	—
	Borne inf de l'IC95%	-0.158	0.171	0.079	0.269	0.518	0.456	

Note. * p < .05, ** p < .01, *** p < .001