LONG COVID AND CARDIOVASCULAR DYSAUTONOMIA: A PRELIMINARY STUDY OF NEUROPSYCHOLOGICAL SEQUELAE

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ABSTRACT

Background: The COVID-19 pandemic has resulted in a major global health crisis, with millions experiencing persistent symptoms collectively referred to as Long COVID Syndrome. A growing body of evidence suggests that cognitive impairment is a common manifestation of this condition, affecting attention, memory, and executive functioning. Although the underlying mechanisms remain unclear, emerging research implicates both neurological and cardiovascular dysfunctions. In particular, cardiovascular dysautonomia—characterised by impaired autonomic nervous system regulation—has been associated with cognitive deficits in various neurological disorders. **Objective:** This study aimed to examine the neuropsychological sequelae of Long COVID Syndrome accompanied by cardiovascular dysautonomia (LC-DYS) and to explore the potential role of autonomic cardiovascular dysfunction in the observed cognitive impairments. **Methods:** A retrospective case–control study was conducted, comparing cognitive function in 30 adult patients (76.6% female) with LC-DYS to 30 healthy controls (73.3% female). A standardised neuropsychological battery was used to assess multiple cognitive domains, including visuospatial abilities, attention, verbal learning and memory, executive functions, and processing speed. Self-reported symptoms of anxiety and depression were also measured and analysed for their potential association with cognitive performance. **Results:** The LC-DYS group demonstrated significantly lower performance than controls in verbal learning, retroactive interference on verbal recall, delayed verbal recall, inhibition control and processing speed. Although the LC-DYS group exhibited higher levels of anxiety and depressive symptoms, subjective mood assessments were not predictive of cognitive performance. **Conclusion:** These findings suggest a potential link between neuropsychological impairments and cardiovascular dysautonomia in individuals with LC-DYS. Central autonomic network dysfunction may contribute to the observed neuropsychological deficits. Further research is warranted to elucidate the underlying mechanisms and to inform targeted cognitive and autonomic rehabilitation strategies for individuals with Long COVID Syndrome.

Keywords: Long COVID, cardiovascular dysautonomia, central autonomic network, cognitive impairments

LONG COVID ΚΑΙ ΚΑΡΔΙΑΓΓΕΙΑΚΗ ΔΥΣΑΥΤΟΝΟΜΙΑ: ΜΙΑ ΠΡΟΚΑΤΑΡΚΤΙΚΗ ΜΕΛΕΤΗ ΝΕΥΡΟΨΥΧΟΛΟΓΙΚΩΝ ΕΠΙΠΤΩΣΕΩΝ

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ΠΕΡΙΛΗΨΗ

Εισαγωγή: Η πανδημία COVID-19 έχει οδηγήσει σε μια μείζονα παγκόσμια υγειονομική κρίση, με εκατομμύρια ανθρώπους να βιώνουν επίμονα συμπτώματα που περιγράφονται συλλογικά ως Σύνδρομο Long COVID. Ο αυξανόμενος όγκος ερευνητικών δεδομένων δείχνει ότι η γνωστική έκπτωση αποτελεί συχνή εκδήλωση του συνδρόμου, επηρεάζοντας την προσοχή, τη μνήμη και τις εκτελεστικές λειτουργίες. Αν και οι υποκείμενοι μηχανισμοί παραμένουν ασαφείς, πρόσφατες μελέτες εμπλέκουν τόσο νευρολογικές όσο και καρδιαγγειακές δυσλειτουργίες. Ειδικότερα, η καρδιαγγειακή δυσαυτονομία, η οποία χαρακτηρίζεται από διαταραχή στη ρύθμιση του αυτόνομου νευρικού συστήματος, έχει συσχετιστεί με γνωστικά ελλείμματα σε διάφορες νευρολογικές διαταραχές. **Σκοπός:** Σκοπός της παρούσας μελέτης ήταν η διερεύνηση των νευροψυχολογικών επιπτώσεων ασθενών με Σύνδρομο Long COVID και συνυπάρχουσα καρδιαγγειακή δυσαυτονομία (LC-DYS). **Μέθοδος:** Διενεργήθηκε αναδρομική μελέτη ασθενών–μαρτύρων, στην οποία συγκρίθηκαν οι γνωστικές λειτουργίες 30 ενηλίκων ασθενών με LC-DYS (76,6% γυναίκες) με εκείνες 30 υγιών μαρτύρων (73,3% γυναίκες). Για την αξιολόγηση πολλαπλών γνωστικών τομέων, όπως οπτικοχωρικές ικανότητες, προσοχή, λεκτική μάθηση και μνήμη, εκτελεστικές λειτουργίες και ταχύτητα επεξεργασίας, χρησιμοποιήθηκαν σταθμισμένες νευροψυχολογικές δοκιμασίες. Επιπλέον, καταγράφηκαν αυτοαναφερόμενα συμπτώματα άγχους και κατάθλιψης, τα οποία εξετάστηκαν για πιθανή συσχέτιση με τις γνωστικές επιδόσεις. **Αποτελέσματα:** Η ομάδα LC-DYS παρουσίασε χαμηλότερες επιδόσεις σε σχέση με τους μάρτυρες στη λεκτική μάθηση, στην οπισθενεργό παρεμβολή και στην καθυστερημένη λεκτική ανάκληση, στον έλεγχο αναστολής και στην ταχύτητα επεξεργασίας. Παρότι η ομάδα LC-DYS εμφάνισε υψηλότερα επίπεδα άγχους και καταθλιπτικών συμπτωμάτων, οι υποκειμενικές αξιολογήσεις διάθεσης δεν προέβλεψαν τις γνωστικές επιδόσεις. **Συμπέρασμα:** Τα ευρήματα της παρούσας μελέτης υποδηλώνουν πιθανή σύνδεση μεταξύ των νευροψυχολογικών ελλειμμάτων και της καρδιαγγειακής δυσαυτονομίας στο σύνδρομο Long COVID. Η δυσλειτουργία του κεντρικού αυτόνομου δικτύου ενδέχεται να συμβάλλει στα παρατηρούμενα νευροψυχολογικά ελλείμματα.

Λέξεις-κλειδιά: Long COVID, καρδιαγγειακή δυσαυτονομία, κεντρικό αυτόνομο δίκτυο, γνωστικά ελλείμματα

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a viral illness caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Although SARS-CoV-2 infection initially manifests as a respiratory illness, it is now recognised as a multisystem disease that frequently involves the nervous system.[1] According to the World Health Organisation[2] the persistence, recurrence, or development of new symptoms in individuals three months after the initial SARS-CoV-2 infection, lasting for at least two months and not explained by an alternative diagnosis, is defined as post COVID-19 condition, commonly referred to as Long COVID (LC). LC is characterised by multi-organ involvement, including cardiovascular, neurological, psychiatric, and pulmonary dysfunction.[3] Common symptoms include fatigue, dyspnoea, and cognitive impairment, among others, and are generally associated with significant disruption in daily functioning.[4] Cognitive dysfunction in LC or post-COVID cognitive dysfunction is conceptualised as a new-onset impairment across various cognitive domains, occurring at least three months following the acute phase of COVID-19 and not attributable to other medical or psychiatric conditions.[1,2,4]

Recent systematic reviews and meta-analyses have confirmed that cognitive dysfunction is a frequent and persistent consequence of LC. Meta-analytic findings indicate that symptoms such as fatigue (37%), subjective cognitive complaints (commonly referred to as "brain fog") (32%), memory problems (28%), attention difficulties (22%), and sleep disturbances (31%) persist in a substantial proportion of individuals beyond three months post-infection.[5,6] In a multicentre prospective study, Hartung et al. reported that 26% of participants experienced mild cognitive impairment and 1% moderate impairment 6–11 months after infection, with risk factors including age, sex, education, and neuropsychiatric history.[7] More recently, a multicentre cross-sectional study by Zhao et al. reported significant impairments in processing speed and sustained attention in LC patients, compared to recovered COVID-19 controls.[8] Furthermore, a systematic review by Panagea et al., synthesising data from 36 studies, confirmed consistent impairments in executive functions, memory, attention, and processing speed in individuals with

LC.[9] A study by Dacosta-Aguayo et al.[10] observed that memory impairment in Long COVID patients was associated with microstructural white matter alterations and abnormal functional brain network activity, possibly reflecting compensatory or maladaptive neural mechanisms. Similarly, Besteher et al.[11] demonstrated associations in LC patients group between cognitive impairment of LC patients according to Montreal Cognitive Assessment, systemic inflammation biomarkers, and bilateral cortical thickness alterations in several areas like the prefrontal cortex, temporal gyri, insula, posterior cingulate cortex and parahippocampal gyrus. These findings highlighted the need for domain-specific neuropsychological evaluations to more precisely define the cognitive phenotype of LC.

Interestingly, studies have revealed that a significant percentage of patients with LC develop new-onset cardiovascular dysfunction, even in individuals without pre-existing comorbidities. These dysfunctions are linked to the autonomic nervous system and include arrhythmia and hypertension,[12] heart rate variability (HRV) abnormalities,[13-15] inappropriate sinus tachycardia,[13] orthostatic hypotension and fatigue[16] and postural orthostatic tachycardia syndrome.[17] The impact of these autonomic disturbances on various neurocognitive systems remains incompletely understood. In this context, autonomic imbalance—dysautonomia—and its potential relationship to cognitive dysfunction should be considered by future studies as a contributing factor to LC symptoms. Cognitive and autonomic processes are linked via the central autonomic network (CAN), which is involved both in cognitive functions and autonomic regulation of cardiovascular functions.[18] The CAN is a complex network of brainstem and forebrain—cortical and subcortical—regions that are implicated in baseline-autonomic nervous system function.[19] Moreover, executive functions appear to deteriorate under conditions of cardiovascular autonomic dysfunction[20,21] and rely on the top-down inhibitory control of prefrontal-subcortical networks.[22-24] These cognitive control processes, have also been associated with parasympathetic activity and vagally mediated HRV.[25,26,27] Thayer et al. proposed that physiological regulation of cardiac control shares common neural mechanisms with executive functions**,** both cognitive and affective regulation, particularly inhibitory processes,[18] supporting the Neurovisceral Integration Model (NIM) introduced by Thayer and Lane.[28] Elevated parasympathetic activity, as indexed by increased resting vagally-mediated HRV, is considered a biomarker of the functional integrity of prefrontal-subcortical circuits. These circuits are critically involved in self-regulatory processes, facilitating flexible and adaptive responses to environmental demands and executive function tasks.[18,28]

In their systematic review**,** Forte et al. analysed 20 studies involving 19,431 healthy adults between 18.4 and 76.0 years old and found that higher HRV was significantly associated with better cognitive performance on neuropsychological executive functions tasks.[29] These associations remained robust even after controlling for confounding variables commonly associated to HRV, including age, sex, years of education, body mass index, blood pressure, and cardiovascular disease.

Overall, the reviewed studies provide empirical support for the NIM, which posits cortical integration between executive functions and cardiac autonomic regulation.[18] The findings by Forte et al.[29] underscore the influence of the autonomic nervous system on cognitive performance and suggest that lower resting HRV, as observed in cardiovascular dysautonomia (CV-Dys), may reflect diminished prefrontal regulatory control over subcortical structures, indicating potential disruption in neurovisceral integration and self-regulatory capacity.

More recent neuroimaging and tractography studies suggest that medial temporal structures, including the hippocampus and parahippocampal gyrus, should also be considered integral nodes of CAN.[30-33] These regions exhibit both resting-state functional connectivity and task-based activation patterns that are closely associated with cardiovascular autonomic regulation, thereby underscoring their contribution to neurovisceral integration.[30,33,34]

The objective of the present study is to evaluate the cognitive functions profile of patients suffering from LC and CV-Dys (LC-DYS). Our study is the first study in Greece that records data for cognitive functions in LC-DYS patients.

METHOD

Study Design

This study employed a retrospective case–control design to investigate the cognitive profiles of individuals with LC-DYS. Their performance then was compared to a control group of individuals who had recovered from COVID-19 but exhibited no persistent symptoms and no evidence of autonomic or cognitive dysfunction. This design is particularly appropriate given the hypothesised link between cardiovascular autonomic dysregulation and domain-specific cognitive impairments in LC patients, as stated in the introduction.

The present case–control design was selected over a cross-sectional approach to allow for better control of confounding variables through careful selection and matching of controls. This methodological choice enhances the internal validity of the study by minimising bias related to potential confounders.

A subset of participants did not complete the

emotional self-report questionnaires, potentially due to time constraints or response fatigue toward the end of the assessment session. In contrast, missing data on cognitive measures were minimal, with less than 5% missing per variable. To preserve statistical power and reduce potential bias associated with listwise deletion, multiple imputation was applied to all variables with missing data. The imputation was conducted using fully conditional specifications, under the assumption that the data were missing at random. Five imputed datasets were generated and pooled for all subsequent analyses. In addition, outlier detection was performed to ensure data integrity.

Lastly, to ensure comprehensive and transparent reporting, the study adhered to the STROBE guidelines for case-control studies.[35]

Study Subjects

A total of 60 individuals participated in the present study. Thirty patients (mean [SD] age, 41.3 [10.8] years) were recruited through referrals to the Laboratory of Clinical Neuropsychology at the LC Centre of Evangelismos General Hospital between June 2022 and February 2024, as part of their multidisciplinary medical evaluations for LC symptoms. These patients also exhibited CV-Dys, thus forming the LC-DYS group. All patients in this group underwent comprehensive clinical assessments, including pulmonological, high-resolution MRI, neurological, cardiological, and psychiatric evaluations.

The control group (CG) also consisted of 30 healthy participants (mean [SD] age, 43.1 [11.4] years), who had recovered from COVID-19 within the clinically accepted timeframe of up to three months. They were recruited and matched to the experimental group based on age, sex, and educational level. **Table 1** presents additional demographic details concerning the study sample.

Inclusion criteria for this study were: (a) adults over 18 years old, (b) native speakers of the Greek language, and (c) diagnosis of LC and CV-Dys by a multidisciplinary medical team for the experimental group and documented evidence of prior SARS-CoV-2 infection for the control group, and (d) no patients in the LC-DYS group was undergoing any specific therapy at the time of the study and taking antidepressant or other psychiatric medication.

Exclusion criteria included: (a) pre-existing or co-existing neurological conditions that could affect cognitive functioning, based on clinical history and/or MRI findings (e.g., structural brain lesions, cerebrovascular disease, demyelinating disorders, or epilepsy); (b) other significant cardiovascular conditions that could independently affect heart rate or autonomic regulation, such as structural heart disease or non-dysautonomic arrhythmias; and (c) the presence of a major psychiatric comorbidity.

Ethical considerations

All participants were informed about the study procedures and provided written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Scientific Board of Evangelismos General Hospital (Ref. No. 200/9-6-2022).

Procedure

All patients in the LC-DYS group underwent the full assessment procedure at Evangelismos General Hospital, which included a multidisciplinary medical evaluation comprising pulmonary, neurological, cardiac, psychiatric, and neuropsychological assessments. The cardiological examination, conducted by the hospital's Cardiology Clinic, included standardised assessments of cardiovascular autonomic function. The neurological examination

Table 1. Demographic characteristics of the samples.

Variables	Group	n	Mean (SD)	Range
Age (years)	CG	30	43.07 (11.34)	23–62
	LC-DYS	30	41.33 (10.82)	23–64
Education (years)	CG	30	16.63 (2.21)	14–23
	LC-DYS	30	16.30 (2.09)	12–18
Sex (female/male)	CG	22 / 8		
	LC-DYS	23 / 7		
Right/Left-handed	CG	29 / 1		
	LC-DYS	27 / 3		

took place at the hospital's LC Centre and involved a clinical assessment of motor, sensory, and reflex functions to rule out other underlying neurological conditions. In addition, paraclinical investigations were conducted as indicated, including brain MRI, electroencephalography and electromyography. Psychiatric assessments were conducted at the Psychiatric clinic of the hospital by trained psychiatrists to identify major psychiatric comorbidities and to ensure the mental health status of participants. Pulmonary assessments, conducted at the hospital's Pulmonary Clinic, included spirometry, oxygen saturation measurements, and additional tests as clinically indicated.

The neuropsychological assessment was conducted at the Laboratory of Clinical Neuropsychology by trained clinical neuropsychologists and lasted approximately 90 minutes. It included a standardised battery of tests designed to assess attention, memory, executive functioning, and processing speed. Participants in the CG also underwent the same neuropsychological assessment under identical conditions. These individuals scheduled appointments with the Laboratory based on availability and underwent testing in a single session.

Measurement tools

Participants underwent a comprehensive neuropsychological assessment of cognitive functions. The Greek version of the Rey Auditory Verbal Learning Test (RAVLT) was administered according to the standardised Greek adaptation[36] to assess verbal learning and memory performance, including immediate recall across five learning trials (RAVLT-T1:T5), total learning (RAVLT-Total), proactive interference (RAVLT-T6), retroactive interference (RAVLT-T7), delayed recall (RAVLT-DR), and recognition memory (RAVLT-Recog). The Babcock Story Recall Test (BSRT) was used to evaluate verbal episodic memory, including immediate (BSRT-IR) and delayed recall (BSRT-DR), based on the standardised Greek version.[37] The Rey–Osterrieth Complex Figure Test (ROCFT) was administered to assess visuoperceptual and constructional abilities (ROCFT-Copy), as well as visuospatial memory via the immediate (ROCFT-IR) and delayed recall (ROCFT-DR) conditions.[38] The Trail Making Test (TMT-A and TMT-B) was administered to evaluate attention, visual scanning, and graphomotor speed (TMT-A), and to assess selective attention shifting, divided attention, working memory, and cognitive flexibility (TMT-B).[39] The Digit Span test (DS) was administered to assess auditory attention using the digit span forward condition (DS-Fw), and verbal working memory—as a specific subcomponent of short-term memory—using the digit span backward condition (DS-Bw) of the Wechsler Adult Intelligence Scale–Fourth Edition, Greek adaptation.[40] The Digit Symbol Coding test (DSC) [40] was used to evaluate mental processing speed, visual scanning, mental flexibility, and divided attention. The Verbal Phonological Fluency test (VF-Phon) was administered to assess lexical access speed and linguistic executive functioning, while the Verbal Semantic Fluency test (VF-Sem) was used to evaluate verbal productivity, semantic memory, and cognitive flexibility.[41] Finally, the Stroop Neuropsychological Screening Test (SNST) was administered to assess response inhibition and interference control.[42] In this study, statistical analyses were conducted using raw scores, and impairment percentages were derived based on standardised z-scores from Greek normative data to highlight patients' levels of cognitive difficulties.

In addition, the Beck Anxiety Inventory (BAI)[43,44] and the Centre for Epidemiologic Studies Depression Scale (CES-D)[45] were administered in order to measure anxiety and depression symptoms' levels.

The evaluation of the CV-Dys was based on 4 clinical techniques: (1) HR response to Valsava Maneuver, (2) HRV with respiration (Respiratory Sinus Arrhythmia), (3) the 30:15 Ratio (Active Standing) and (4) isometric handgrip test.[46,47] The patients with two or more positive tests were considered to have CV-Dys.

Statistical Analysis

Prior to hypothesis testing, the distribution of each variable was assessed for normality using the Shapiro-Wilk test. For consistency across outcomes and to facilitate pooled inference, independent samples t-tests were used even for non-normal variables, given that t-tests are known to be reasonably robust to violations of normality, particularly when each group has at least 30 participants and there are no extreme outliers.[48,49] This approach allowed use of Rubin's Rules to pool test statistics and confidence intervals across multiple imputed datasets (5 datasets).

To ensure the robustness of the results, non-parametric analyses were also performed for variables that violated the normality assumption. Results from the Mann-Whitney U test were computed separately for each imputation and average U statistic, median p-value, and range of p-values across imputations are reported.

The calculated effect size used for the parametric analysis is Cohen's d and for the non-parametric is Rank-biserial correlation. Also, Holm-Bonferroni correction was employed in order to control for Type I error inflation arising from multiple testing.

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS),

Table 2. Comparation of LC-DYS and CG on cognitive performance and psychiatric self-report scales scores (pooled data).

	n = 30		n = 30				
Cognitive Measure-ments	**LC-DYS**		**CG**		**t**	**P***	**Cohen d**
	M	**SD**	**M**	**SD**			
RAVLT-T1	6.53	1.852	7.50	1.756	2.074	0.462	0.535
RAVLT-Total	50.23	8.877	58.13	6.290	3.977	0.000	1.027
RAVLT-T6	6.80	2.325	8.10	1.918	2.362	0.273	0.609
RAVLT-T7	9.70	3.715	12.53	2.145	3.617	0.000	0.934
RAVLT-DR	9.73	2.981	12.46	2.239	4.014	0.000	1.036
RAVLT-Recog	12.83	2.118	13.93	1.112	2.518	0.252	0.650
BSRT-IR	14.13	3.285	14.88	2.967	0.928	0.783	0.239
BSRT-DR	12.85	3.393	13.86	3.980	1.054	0.767	0.272
ROCFT-Copy	34.68	1.886	35.46	1.272	1.885	0.640	0.486
ROCFT-IR	18.79	7.079	20.88	8.102	1.063	0.767	0.247
ROCFT-DR	18.55	6.792	20.88	8.140	1.205	0.754	0.311
TMT-A	31.10	8.281	30.53	7.582	-0.276	0.783	0.071
TMT-B	70.86	24.913	67.03	20.213	-0.654	0.783	0.168
VF-Phon	41.03	8.751	47.53	12.710	2.307	0.312	0.595
VF-Sem	56.12	10.818	61.93	16.866	1.587	0.701	0.410
DSC	65.63	13.142	77.70	14.591	3.365	0.013	0.869
DS-Fw	9.43	2.207	9.60	1.886	0.314	0.783	0.081
DS-Bw	7.60	2.313	8.06	1.89	0.855	0.783	0.220
SNST	102.59	14.498	116.87	20.678	3.096	0.047	0.799
BAI	15.82	8.830	8.01	5.150	-4.185	0.000	1.080
CES-D	19.85	10.423	9.84	7.188	-4.332	0.000	1.118

RAVLT: Rey Auditory Verbal Learning Test; T1:T5: immediate recall trials 1–5; Total: total learning score; T6:proactive interference; T7: retroactive interference; DR: delayed recall; Recog: recognition; BSRT: Babcock Story Recall Test; IR: immediate recall; ROCFT: Rey–Osterrieth Complex Figure Test; TMT-A/B: Trail Making Test A and B; VF-Phon: Verbal Phonological Fluency; VF-Sem: Verbal Semantic Fluency; DSC: Digit Symbol Coding; DS-Fw: Digit Span Forward; DS-Bw: Digit Span Backward; SNST: Stroop Neuropsychological Screening Test; BAI: Beck Anxiety Inventory; CES-D: Center for Epidemiological Studies Depression Scale; LC-DYS: Long COVID with dysautonomia; CG: control group; M: mean; SD: standard deviation; P*: Holm–Bonferroni adjusted p-values (α: .05); Cohen's d: effect size.

version 26. The significance threshold was set at α = 0.05 (two-tailed), with 95% confidence intervals.

RESULTS

Concerning the independent samples analysis, as shown in **Table 2**, the pooled results indicated significant group differences in RAVLT-Total scores (*t*(58) = 3.98, P < .001, Cohen d = 1.03), RAVLT-T7 scores (*t*(58) = 3.62, P < .001, Cohen d = 0.93), RAVLT-DR scores (*t*(58) = 4.01, P < .001, Cohen d = 1.04), DSC scores (*t*(58) = 3.37, P = .013, Cohen d = 0.87), SNST scores (*t*(58) = 3.10, P = .047, Cohen d = 0.80), BAI scores (*t*(58) = –4.19, P < .001, Cohen d = 1.08), and CES-D scores (*t*(58) = –4.33, P < .001, Cohen d = 1.12). These results reflect statistical significance as

well as large effect size, indicating clinically meaningful group differences.

No significant group differences were found in the remaining neuropsychological tests.

According to the series of Mann-Whitney U tests that were conducted and the pooled analysis, as presented in **Table 3**, there were statistically significant differences in RAVLT-T7, RAVLT-DR and CES-D scores between the groups, suggesting that CG performed significantly better than LC-DYS at these neuropsychological tasks.

To examine the influence of anxiety and depressive symptoms on cognitive performance, multiple linear regression analyses were conducted using pooled results from five imputed datasets concerning LC-DYS group. The results indicated that neither BAI nor CES-D significantly predicted scores on any of the 19 cognitive variables. These findings suggest that, although anxiety and depressive symptoms occurred, they were not significantly associated with cognitive functioning in this group.

According to our finding we found that the cognitive performance that is impacted the most when compared to the two group was associated with the RAVLT-Total scores, RAVLT-T7 scores, RAVLT-DR scores, DSC scores, SNST scores, BAI scores and CES-D scores.

DISCUSSION

The present study examined cognitive performance as well as self-reported symptoms of anxiety and depression in patients with LC-DYS compared to a CG, using a comprehensive neuropsychological battery. Participants with LC-DYS exhibited significant cognitive impairments, particularly in verbal-learning, retroactive interference on verbal recall, delayed verbal recall and processing speed. These difficulties likely reflect impaired encoding and consolidation under increased cognitive load, slowed information processing, and heightened vulnerability of memory traces to retroactive interference, thereby affecting verbal recall. COVID-related myelin damage compromise the way neurons receive and send information.[50] Indeed, multi-lineage neural cell and myelin deregulation has been put forward by a study on the rapport between even mild COVID infections and lasting cognitive impairment, suggesting the presence of memory, concentration, and processing information abnormalities attributed to long-COVID.[51]

These cognitive deficits may, in the context of central autonomic network (CAN) dysfunction associated with cardiovascular dysautonomia (CV-Dys), reflect abnormal dynamic switching between large-scale brain networks. According to the Triple Network Model,[52] dysfunction of the salience network (SN)—which includes core CAN structures such as the anterior insula (AI) and dorsal anterior cingulate cortex (dACC)[53]—may lead to inappropriate disengagement of the default mode network (DMN) and inefficient modulation of inter-network dynamics during externally directed cognitive tasks, resulting in inadequate activation of frontoparietal network (FPN) regions,[54–57] which are essential for verbal learning, resistance to retroactive interference on verbal recall and delayed verbal recall. A dysfunctional SN, which normally facilitates transitions between the internally oriented DMN and the externally focused FPN,[54,57] may therefore play a central role in the observed impairments. This interpretation aligns with intracranial EEG findings of study by Das and Menon,[58] which demonstrated that the AI exerts dynamic, context-dependent influence on both the DMN and FPN, directly contributing to verbal memory encoding and recall. Furthermore, in LC-DYS patients,

Table 3. Mann-Whitney U test concerning non-normally distributed cognitive measurements.

Cognitive Measurements	Mean U*	Median	Range
RAVLT-T1	595.0	0.090	0.000
RAVLT-T6	610.5	0.064	0.000
RAVLT-T7	660.5	0.005	0.000
RAVLT-DR	691.5	0.000	0.000
RAVLT-Recog	584.5	0.090	0.000
ROCFT-Copy	576.0	0.090	0.000
CES-D	166.0	0.000	0.000

RAVLT: Rey Auditory Verbal Learning Test; T1: immediate recall trial 1; T6: proactive interference; T7: retroactive interference; DR: delayed recall; Recog: recognition; ROCFT: Rey–Osterrieth Complex Figure Test; CES-D: Center for Epidemiological Studies Depression Scale; U: Mann–Whitney U statistic; P*: Holm–Bonferroni adjusted pvalues (α: .05).

memory breakdowns may arise from core deficits in verbal learning and recall, together with increased vulnerability to retroactive interference and inhibitory control impairments. The domains of inhibitory control and susceptibility to retroactive interference share a common neurocognitive substrate. Specifically, they rely on the FPN and the dACC,[59] which mediate conflict monitoring and inhibitory control. Additionally, slowed information processing speed, consistent with findings from Forn et al.,[60] may be negatively correlated with functional connectivity within the FPN, suggesting inefficient modulation of FPN inter-network dynamics. Taken together, these findings support the hypothesis that the cognitive impairments observed in LC-DYS patients may stem from overlapping neural mechanisms, wherein CAN dysregulation contributes to dysfunctional SN-mediated switching between the DMN and FPN, thereby disrupting the network coordination required for efficient verbal learning, resistance to retroactive interference on verbal recall, and processing speed.

Furthermore, significantly elevated anxiety and depressive self-reported measures were observed in the LC-DYS group, without significant associations with the cognitive functioning in this group. This pattern deviates from previous studies, which reports significant associations between affective symptoms and cognitive dysfunction in patients with cardiovascular dysautonomia.[61-63] One possible interpretation is that, in the context of CAN functional connectivity, affective symptoms and cognitive performance may be at least partially independent, reflecting a partial functional dissociation between affective and cognitive neural networks. Affective symptoms are known to modulate CAN activity through altered functional connectivity between the ACC, insula, amygdala, and brainstem autonomic centres.[28] Disruption of CAN may result in compromised neurovisceral integration, contributing to both cognitive inefficiencies and affective dysregulation[18,28,34,53] as observed in our study among patients with LC-related cardiovascular dysautonomia.

Collectively, these findings support the interpretation that CAN dysfunction may explain the co-occurrence of cardiovascular autonomic dysregulation, cognitive impairments (in verbal learning, delayed verbal recall, retroactive interference on verbal recall, inhibitory control and processing speed) and subjective measures of anxiety and depression symptoms in patients with LC-DYS.

LIMITATIONS AND FUTURE DIRECTIONS

While the present findings offer important insights into cognitive and emotional dysfunction in long COVID-related cardiovascular dysautonomia, several limitations should be acknowledged. First, an important limitation of the present study is the absence of a control group consisting of individuals with LC but without CV-Dys, which would have allowed for better control of confounding variables and a clearer understanding of the specific contribution of autonomic dysfunction to the observed neurocognitive outcomes. Second, the retrospective case–control design precludes causal interpretations and limits the ability to track changes over time.

Furthermore, the sex distribution was disproportionate, with an underrepresentation of male participants, which may affect the generalisability of the results and overlook potential sex-related differences in autonomic regulation and neurocognitive functioning.

Future studies should aim to address the aforementioned limitations by including well-defined control groups and employing longitudinal designs to better disentangle the specific effects of CV-Dys within the broader context of LC. In addition, future studies are encouraged to incorporate physiological markers such as HRV, along with structural neuroimaging data, to elucidate the neurobiological mechanisms underlying the observed deficits. Lastly, further exploration of affective and psychophysiological domains, including chronic stress, insomnia, and chronic fatigue syndrome, is necessary to clarify their interplay with cognitive outcomes.

CONCLUSIONS

Given the high global prevalence of LC, including cases with comorbid cognitive dysfunction and CV-Dys, research into the relationship between neurocognitive impairments and cardiovascular dysautonomia is important for informing appropriate rehabilitation strategies.

The present study adds to the growing body of evidence on the cognitive and emotional consequences of LC-related CV-Dys. The findings indicate that deficits in verbal learning, heightened susceptibility to interference, slowed processing speed are central features of the observed cognitive impairments. These cognitive impairments may reflect disruptions within the CAN, a neuronal network integrating autonomic regulation, cognitive control, and affective processing.

Overall, the results underscore the importance of comprehensive, multidisciplinary assessment and intervention strategies that address both neuropsychological and autonomic dysfunction in patients with LC-related cardiovascular dysautonomia. Integrating neurocognitive rehabilitation with autonomic monitoring and management may be essential for improving functional outcomes of LC patients with cardiovascular dysautonomia.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

None of the authors has any conflct of interest to disclose.

AVAILABILITY OF DATA

Under request from the correspondent author.

FUNDING STATEMENT

The authors did not receive support from any organisation for the submitted work.

CITATION DISCLOSURE

This manuscript does not cite prior work by the authors that are directly relevant to the development of the study and interpretation of the findings.

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