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Beyond Structural Injury: Clinical and Experimental Correlates of Delayed Neuropsychological Sequelae After Acute Carbon Monoxide Poisoning

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Abstract

Background/Objectives: Delayed neuropsychological sequelae (DNS) after acute carbon monoxide (CO) poisoning include cognitive and behavioral abnormalities that may not correspond to regional findings on structural magnetic resonance imaging (MRI). We examined relationships among acute serum S100B, regional MRI abnormalities, MRI lesion burden, and neuropsychological impairment, and considered whether previously reported experimental neurochemical changes suggest a mechanism for cognitive impairment. **Methods:** This retrospective secondary analysis included 16 patients with DNS who underwent brain MRI and completed the Seoul Neuropsychological Screening Battery. Exploratory nonparametric analyses evaluated regional MRI lesions, MRI lesion burden, impairment across five cognitive domains, acute serum S100B, and clinical variables. Previously published experimental findings informed interpretation only. **Results:** Acute serum S100B was not significantly correlated with MRI lesion burden (Spearman's $\rho = 0.390$, $p = 0.151$) or cognitive burden ($\rho = 0.367$, $p = 0.178$). More involved MRI regions were associated with more impaired cognitive domains ($\rho = 0.535$, unadjusted $p = 0.033$). Frontal/executive impairment was most frequent (12/16, 75.0%), with no statistically significant association with any individual MRI region. Longer CO exposure was associated with greater cognitive burden ($\rho = 0.555$, unadjusted $p = 0.032$), and longer unconsciousness with greater MRI lesion burden ($\rho = 0.606$, unadjusted $p = 0.022$). **Conclusions:** Among patients with DNS who completed comprehensive testing, structural MRI and domain-level neuropsychological assessment provided complementary information. Acute serum S100B showed no statistically significant correlation with either burden measure. The predominance of frontal/executive impairment warrants direct investigation of dopaminergic function in patients with DNS.

Keywords: carbon monoxide poisoning; delayed neuropsychological sequelae; magnetic resonance imaging; S100B; neuropsychological assessment; dopamine; translational research

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1. Introduction

Acute carbon monoxide (CO) poisoning remains an important cause of toxic exposure and neurological morbidity [1–3]. Although many patients recover from acute intoxica-

tion, a substantial proportion subsequently develop delayed neuropsychological sequelae (DNS) after a lucid interval of days to weeks [4–6]. DNS encompasses heterogeneous neurological and neuropsychiatric manifestations, including cognitive impairment, executive dysfunction, gait disturbance, parkinsonism, psychiatric symptoms, and behavioral abnormalities [4,7,8]. DNS may manifest as psychomotor slowing, impaired set-shifting, inhibitory control, planning and cognitive flexibility, together with memory disturbances, apathy, social withdrawal, gait abnormalities and parkinsonian features. These symptoms may interfere with everyday functioning even when global cognitive screening scores are relatively preserved. The mechanisms underlying DNS remain incompletely understood and have been associated with delayed demyelination, neuroinflammation, oxidative stress, mitochondrial dysfunction, and neuronal injury [9–14].

Magnetic resonance imaging (MRI) commonly demonstrates abnormalities involving the globus pallidus, cerebral white matter, centrum semiovale, and cerebral cortex, with white matter injury particularly associated with delayed neurological deterioration and unfavorable outcomes [15–18]. However, conventional MRI may not fully account for the variability of delayed cognitive and behavioral manifestations [15,18–20]. Comprehensive neuropsychological assessment can characterize impairment across multiple cognitive domains [21], whereas circulating biomarkers may provide information regarding neurological injury during the acute phase. Serum S100B has been investigated as a predictor of DNS [19,22], but its relationship with the subsequent extent of structural brain abnormalities and cognitive impairment remains unclear.

Experimental studies have demonstrated delayed behavioral abnormalities, neuroinflammation, neuropathological changes, and region-specific neurochemical alterations after acute CO exposure [9,23]. In our previously published rat model, delayed deficits were observed in working-memory performance, exploratory and locomotor behavior, and sensorimotor integration, accompanied by reduced dopamine concentrations in the cerebral cortex and basal ganglia. In a separate mouse study, repeated marinobufagenin administration altered striatal dopamine turnover and increased locomotor activity, providing indirect experimental evidence that changes in monoamine metabolism can accompany behavioral changes [24]. These findings suggest a candidate link between frontostriatal neurochemical alterations and delayed behavioral dysfunction, but do not establish the mechanism of executive impairment in the present clinical cohort.

This study is a secondary analysis of the same 16-patient cohort previously reported by Lee et al. [25]. The earlier report described regional MRI–cognitive associations and correlations of cognitive burden with MRI lesion burden and estimated CO exposure duration. The present analysis focuses on the relationships of acute serum S100B with early MRI lesion burden and later cognitive burden. It also reports effect estimates and multiplicity-adjusted q values for regional lesion–domain associations and compares available clinical and MRI characteristics by SNSB completion status. Previously published experimental findings informed the interpretation of the clinical observations.

2. Materials and Methods

2.1. Study Design and Population

This retrospective secondary analysis was based on an institutional cohort of 192 patients admitted to the intensive care unit for acute CO poisoning at Ajou University Medical Center between January 2011 and December 2020. Among these patients, 28 subsequently developed clinically diagnosed DNS. Of 28 patients with clinically diagnosed DNS, 16 completed the SNSB and 12 could not complete the battery because of severe cognitive impairment. Accordingly, the analytic sample was conditioned on the ability to complete detailed testing and is not representative of the entire DNS severity spectrum (Figure 1). Available base-

line characteristics of included and excluded patients were compared descriptively and statistically in Supplementary Table S3.

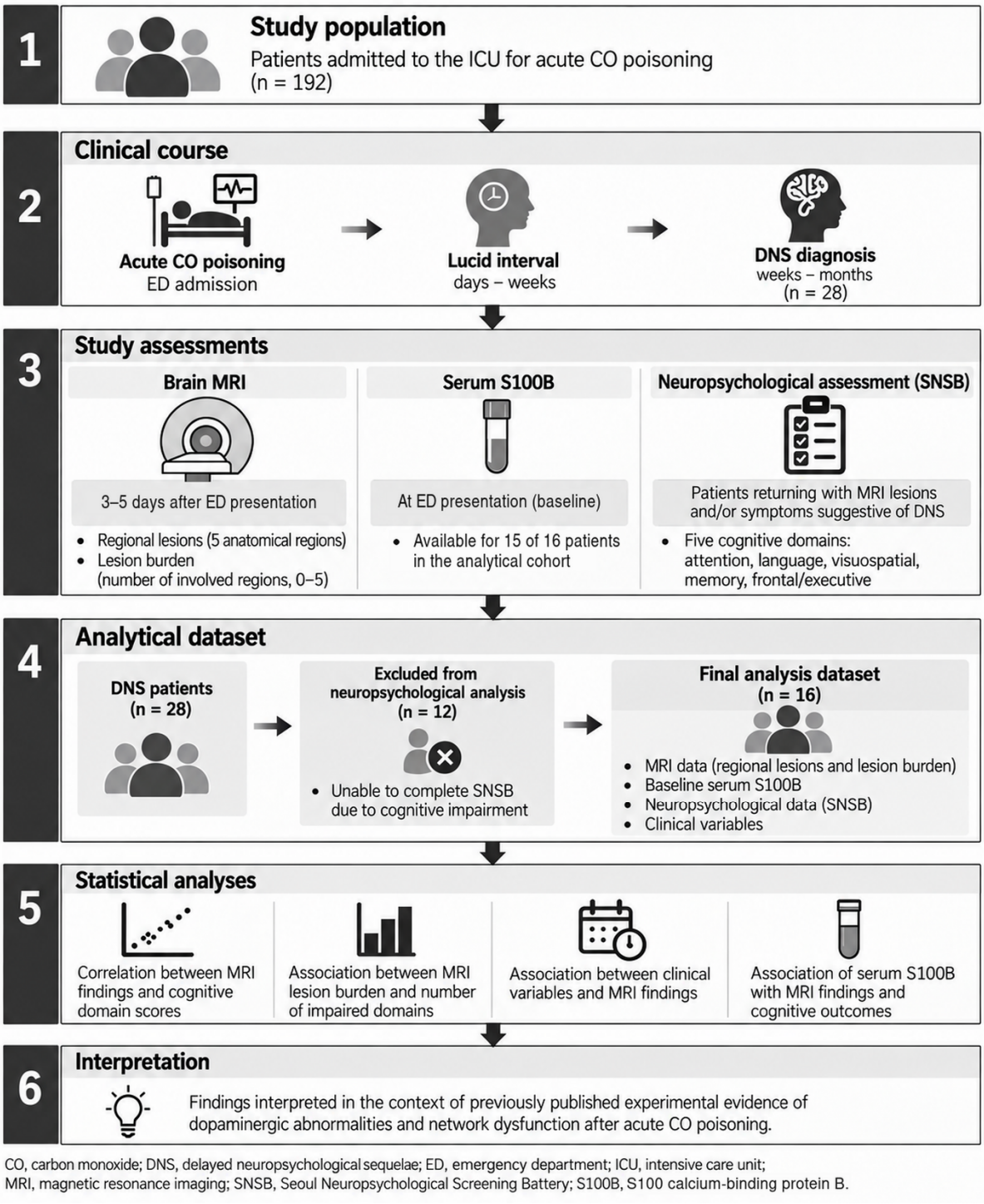


Figure 1. Study Design and Analytical Workflow. Patients with acute carbon monoxide (CO) poisoning underwent acute clinical evaluation, including serum S100B measurement and brain magnetic resonance imaging (MRI). Among 28 patients who subsequently developed delayed neuropsychological sequelae (DNS), 16 completed comprehensive neuropsychological assessment using the Seoul Neuropsychological Screening Battery (SNSB) and constituted the final analytical cohort; 12 were unable to complete the full SNSB because of severe cognitive impairment. Clinical characteristics, regional MRI abnormalities, MRI lesion burden, serum S100B concentrations, and neuropsychological findings were analyzed to assess associations between structural brain abnormalities

and domain-specific cognitive impairment. Previously published experimental findings were not included in the statistical analyses but were considered in the translational interpretation of clinical findings not fully explained by conventional structural MRI.

DNS was defined as the development of new or worsening neurological or psychiatric symptoms following an initial recovery period (lucid interval), including cognitive impairment, executive dysfunction, behavioral or personality changes, gait disturbance, parkinsonism, urinary dysfunction, or psychiatric manifestations.

Patients were eligible if they were ≥18 years of age, had confirmed acute CO poisoning, subsequently developed clinically diagnosed DNS, and underwent both brain MRI and comprehensive neuropsychological assessment using the Seoul Neuropsychological Screening Battery (SNSB). Patients with previous stroke, dementia, traumatic brain injury, other causes of hypoxic brain injury, incomplete medical records, or incomplete neuropsychological assessment were excluded.

The study protocol was approved by the Institutional Review Board of Ajou University Medical Center (IRB No. AJOUIRB-DB-2026-483), which waived the requirement for informed consent because of the retrospective study design. This study used a previously established institutional cohort that was partially described in a Korean-language publication; the present study represents a secondary analysis addressing distinct objectives and incorporating additional clinical and biomarker variables.

2.2. Clinical Data and Serum S100B

Demographic and clinical variables included age, sex, psychiatric history, estimated duration of CO exposure, duration of unconsciousness, initial Glasgow Coma Scale score, carboxyhemoglobin concentration, serum lactate concentration, serum S100B concentration, and interval from acute poisoning to DNS onset. Functional status was assessed using the Korean Mini-Mental State Examination (K-MMSE), Clinical Dementia Rating (CDR), and Barthel Activities of Daily Living (Barthel-ADL) index.

Serum S100B was measured in samples collected at emergency department presentation and was available for 15 of the 16 patients in the analytical cohort. Rather than assessing its ability to predict the occurrence of DNS, the present analysis examined whether acute S100B concentrations were associated with subsequent MRI lesion burden or cognitive burden among patients who developed DNS.

2.3. Brain MRI Assessment

All patients underwent brain MRI 3–5 days after emergency department presentation using a 1.5-T scanner (Signa EXCITE, GE Healthcare, Milwaukee, WI, USA). The imaging protocol included diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) maps, axial T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR) imaging, sagittal T1-weighted imaging, and axial gradient-recalled imaging. Sagittal T1-weighted images were acquired using a spin-echo sequence with a repetition time (TR) of 550 ms, an echo time (TE) of 11 ms, and a slice thickness of 5 mm. DWI was acquired using a single-shot spin-echo echo-planar sequence (TR, 8000 ms; TE, 87 ms) with diffusion gradients applied in three orthogonal directions ($b = 1000$ s/mm^2), a slice thickness of 5 mm, and a 1-mm interslice gap. ADC maps were reconstructed from the diffusion-weighted images. Sagittal T1-weighted images were used for anatomical assessment. Regional lesions were evaluated primarily on diffusion-weighted images, ADC maps, T2-weighted images, and FLAIR images.

Lesion locations were abstracted from routine clinical neuroradiology reports. No study-specific image rereading was performed. Each of five anatomical regions was coded

as involved or uninvolved (globus pallidus, periventricular white matter, deep white matter, centrum semiovale, and cerebral cortex). Each involved region contributed one point, regardless of lesion laterality or the number of lesions within the region. An unweighted count of involved regions (range, 0–5) was used to summarize the anatomical distribution of lesions because region-specific weights were unavailable for this cohort.

2.4. Neuropsychological Assessment and Cognitive Phenotyping

Patients presenting with clinical features of DNS underwent comprehensive neuropsychological assessment using the SNSB, a standardized neuropsychological battery for the Korean population [21]. The SNSB evaluates five major cognitive domains: attention, language and related functions, visuospatial function, memory, and frontal/executive function. The neuropsychological domain framework was based on that used in our previous report of this cohort [25]. The principal measures used for domain-level classification are summarized in Supplementary Table S2.

Quantitative subtest scores were interpreted using age- and education-adjusted normative data from the SNSB. Scores below the 16th percentile were classified as impaired, whereas borderline performance was not considered impairment. Qualitative measures without percentile scores were classified as normal or abnormal according to standardized SNSB criteria. Each of the five cognitive domains was subsequently classified as impaired or unimpaired based on the corresponding measures shown in Supplementary Table S2.

Overall cognitive burden was defined as the number of impaired cognitive domains, yielding a score ranging from 0 to 5, with higher scores indicating broader neuropsychological impairment. Domain-specific impairment patterns were used to characterize the delayed neuropsychological phenotype and were examined in relation to regional MRI abnormalities and overall MRI lesion burden. Final domain-level classifications were reviewed and confirmed by a board-certified neurologist before statistical analysis.

2.5. Statistical Analysis

Given the exploratory nature of the study and the small sample size, non-parametric methods were used. Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables as frequencies and percentages.

Associations between regional MRI lesions and domain-level impairment were assessed using two-sided Fisher's exact tests and summarized using phi coefficients. The Benjamini–Hochberg procedure was applied across the 25 regional comparisons, and both unadjusted p values and adjusted q values are reported. Conditional odds ratios and exact 95% confidence intervals are provided in Supplementary Table S1. Spearman rank correlations were used to assess monotonic associations using available paired observations. Scatterplots were examined for the form of the associations and potentially influential observations. All Spearman p values were two-sided and unadjusted and were interpreted as exploratory.

All tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 33 (IBM Corp., Armonk, NY, USA) and R version 4.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

2.6. Translational Interpretation

Previously published experimental findings were not included in the present statistical analyses. Experimental observations were considered only when they addressed neurobehavioral or neurochemical abnormalities relevant to the clinical findings identified in the present cohort. In particular, previously reported alterations in dopaminergic function after

CO exposure were considered in relation to the predominance of executive dysfunction without a consistent focal structural MRI correlate.

3. Results

3.1. Patient Characteristics

A total of 16 patients with DNS after acute CO poisoning were included in the analysis. The median age was 37.5 years (interquartile range [IQR], 31.8–45.8 years), and 13 patients (81.2%) were male. All patients had charcoal-burning CO exposure, and 13 of 16 patients (81.2%) had intentional CO exposure, while four (25.0%) had a documented psychiatric history. Intentional exposure was not assumed to establish a specific psychiatric diagnosis. The median estimated CO exposure duration was 12.0 h (IQR, 5.2–19.8 h). Loss of consciousness occurred in 14 patients (87.5%), with a median duration of 7.8 h (IQR, 3.8–15.9 h).

The median interval from acute CO poisoning to the clinical diagnosis of DNS was 17.5 days (IQR, 10.2–22.0 days). During the acute hospitalization, nine patients (56.3%) underwent mechanical ventilation. Baseline demographic and clinical characteristics are summarized in Table 1.

Table 1. Clinical characteristics and structural MRI findings of patients with delayed neuropsychological sequelae ($n = 16$).

Characteristic	Value
Age, yr	37.5 (31.8–45.8)
Male sex	13 (81.2)
Psychiatric history	4 (25.0)
Suicidal exposure	13 (81.2)
Charcoal source	16 (100.0)
CO exposure duration, hr	12.0 (5.2–19.8)
Loss of consciousness	14 (87.5)
Duration of unconsciousness, hr	7.8 (3.8–15.9)
Initial Glasgow Coma Scale	9.0 (6.5–14.5)
Initial COHb, %	12.4 (4.3–28.9)
Initial lactate, mmol/L	4.5 (3.1–8.3)
Serum S100B, μg/L	0.167 (0.105–0.391)
K-MMSE	28.5 (25.5–29.0)
Hyperbaric oxygen therapy	12 (75.0)
Mechanical ventilation	9 (56.3)
DNS latency, day	17.5 (10.2–22.0)
MRI lesion: Globus pallidus	10 (62.5)
MRI lesion: Periventricular white matter	5 (31.2)
MRI lesion: Deep white matter	3 (18.8)
MRI lesion: Cerebral cortex	2 (12.5)
MRI lesion: Centrum semiovale	4 (25.0)

Values are presented as mean ± standard deviation, median (interquartile range), or number (%), as appropriate. Missing values were excluded from the calculation of the corresponding summary statistic. CO, carbon monoxide; COHb, carboxyhemoglobin; K-MMSE, Korean mini-mental examination; DNS, delayed neuropsychological sequelae; MRI, magnetic resonance imaging.

Of the 28 patients diagnosed with DNS, 16 were able to complete the comprehensive SNSB and constituted the analytical cohort, whereas 12 were unable to complete the full assessment because of severe cognitive impairment. Thus, comprehensive domain-level neuropsychological data were available in 57.1% of patients with clinically diagnosed DNS. Available clinical and MRI characteristics by SNSB completion status are summarized in Supplementary Table S3.

3.2. Neuropsychological Phenotypes

Comprehensive neuropsychological assessment demonstrated heterogeneous patterns of cognitive impairment. Frontal/executive dysfunction was the most frequent abnormality, occurring in 12 patients (75.0%). Memory and visuospatial dysfunction were each identified in four patients (25.0%), language and related function impairment in three (18.8%), and attention impairment in one (6.2%).

The median K-MMSE score was 28.5 (IQR, 25.5–29.0), whereas comprehensive SNSB assessment identified impairment in at least one cognitive domain in most patients. Domain-specific neuropsychological findings are summarized in Table 2.

Table 2. Domain-level neuropsychological impairment and behavioral manifestations in patients with delayed neuropsychological sequelae (n = 16). (**a**) Domain-Level Neuropsychological Impairment. (**b**) Behavioral Manifestations.

(**a**) **Domain-Level Neuropsychological Impairment**		
Cognitive Domain	**Impaired, n (%)**	**Not Impaired, n (%)**
Attention	1 (6.3)	15 (93.8)
Language	3 (18.8)	13 (81.2)
Visuospatial function	4 (25.0)	12 (75.0)
Memory	4 (25.0)	12 (75.0)
Frontal/executive function	12 (75.0)	4 (25.0)
(**b**) **Behavioral Manifestations**		
Manifestation	**Present, n (%)**	**Not Present, n (%)**
Psychomotor slowing	9 (56.3)	7 (43.7)
Disorientation	3 (18.8)	13 (81.2)
Abstract thinking difficulty	7 (43.8)	9 (56.2)
Aggressive behavior	0	16 (100)
Apathy	2 (12.5)	14 (87.5)
Social withdrawal	4 (25.0)	12 (75.0)
Gait disturbance	6 (37.5)	10 (62.5)
Severe rigidity/posturing	2 (12.5)	14 (87.5)

Domain impairment was defined according to the prespecified SNSB criterion.

3.3. Structural MRI Findings and Lesion-Specific Neuropsychological Patterns

The globus pallidus was the most frequently involved region (10/16, 62.5%), followed by the periventricular white matter (PVWM; 5/16, 31.2%), centrum semiovale (CS; 4/16, 25.0%), deep white matter (3/16, 18.8%), and cerebral cortex (2/16, 12.5%). Bilateral involvement was common.

In the exploratory analyses of regional MRI lesions and cognitive domains (Table 3), CS lesions were associated with language impairment ($\varphi = 0.832$, $q = 0.036$), visuospatial impairment ($\varphi = 1.000$, $q = 0.007$), and memory impairment ($\varphi = 1.000$, $q = 0.007$) after

Benjamini–Hochberg correction across 25 comparisons. All four patients with CS lesions had both visuospatial and memory impairment, and neither impairment was observed in the remaining 12 patients. PVWM lesions were associated with visuospatial and memory impairment after correction (both $\varphi = 0.856$, $q = 0.017$). The association between PVWM lesions and language impairment fell short of the adjusted significance threshold ($q = 0.074$). Frontal/executive impairment was the most frequent cognitive deficit, and no individual MRI region showed a statistically significant association with this domain.

Table 3. Associations between regional MRI lesions and impaired cognitive domains.

Cognitive Domain	Globus Pallidus	PVWM	DWM	Cerebral Cortex	Centrum Semiovale
Attention	0.20 ($p = 1.000$; $q = 1.000$)	0.38 ($p = 0.312$; $q = 0.651$)	−0.12 ($p = 1.000$; $q = 1.000$)	−0.10 ($p = 1.000$; $q = 1.000$)	0.45 ($p = 0.250$; $q = 0.568$)
Language	0.37 ($p = 0.250$; $q = 0.568$)	0.71 ($p = 0.018$; $q = 0.074$)	0.18 ($p = 0.489$; $q = 0.922$)	−0.18 ($p = 1.000$; $q = 1.000$)	0.83 ($p = 0.007$; $q = 0.036$)
Visuospatial function	0.45 ($p = 0.234$; $q = 0.568$)	0.86 ($p = 0.003$; $q = 0.017$)	0.09 ($p = 1.000$; $q = 1.000$)	−0.22 ($p = 1.000$; $q = 1.000$)	1.00 ($p = 0.001$; $q = 0.007$)
Memory	0.45 ($p = 0.234$; $q = 0.568$)	0.86 ($p = 0.003$; $q = 0.017$)	0.09 ($p = 1.000$; $q = 1.000$)	−0.22 ($p = 1.000$; $q = 1.000$)	1.00 ($p = 0.001$; $q = 0.007$)
Frontal/executive function	0.15 ($p = 0.604$; $q = 1.000$)	0.08 ($p = 1.000$; $q = 1.000$)	−0.46 ($p = 0.136$; $q = 0.485$)	0.22 ($p = 1.000$; $q = 1.000$)	0.33 ($p = 0.516$; $q = 0.922$)

Values are phi coefficients (φ), with two-sided Fisher exact p values and Benjamini–Hochberg-adjusted q values. The false discovery rate was controlled across 25 comparisons. $q < 0.05$ was considered statistically significant. PVWM, periventricular white matter; DWM, deep white matter; MRI, magnetic resonance imaging.

3.4. MRI Lesion Burden and Cognitive Burden

MRI lesion burden ranged from 0 to 4 involved anatomical regions and was positively correlated with the number of impaired cognitive domains (Spearman's $\rho = 0.535$, unadjusted $p = 0.033$; n = 16; Figure 2A).

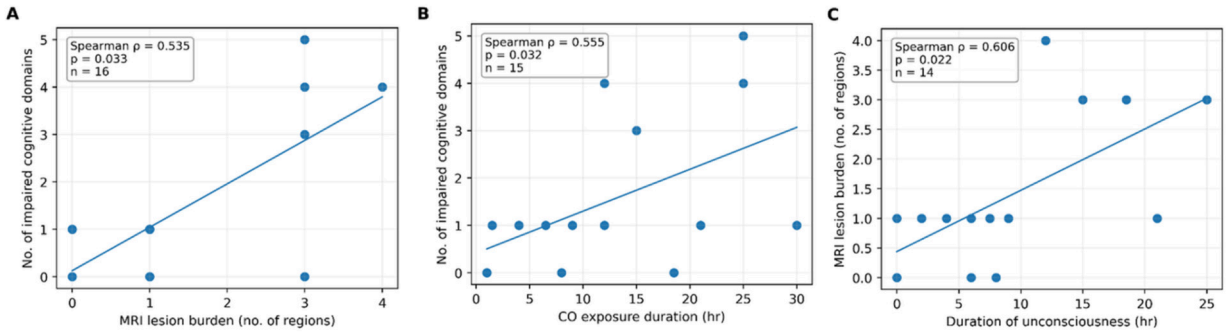


Figure 2. Associations among MRI lesion burden, cognitive burden, and clinical variables after acute carbon monoxide poisoning. (**A**) Correlation between MRI lesion burden and the number of impaired cognitive domains. Greater structural lesion burden was significantly associated with impairment across a larger number of cognitive domains (Spearman's $\rho = 0.535$, $p = 0.033$). (**B**) Correlation between carbon monoxide exposure duration and the number of impaired cognitive domains. Longer

exposure duration was associated with greater cognitive impairment (Spearman's ρ = 0.555, $p = 0.032$; n = 15). (**C**) Correlation between duration of unconsciousness and MRI lesion burden. Patients with prolonged unconsciousness demonstrated more extensive structural brain involvement (Spearman's ρ = 0.606, $p = 0.022$; n = 14). Lines represent the fitted linear regression for visualization only; correlation coefficients were calculated using Spearman's rank correlation analysis.

Among the clinical severity measures, longer estimated CO exposure was correlated with greater cognitive burden (ρ = 0.555, unadjusted $p = 0.032$; n = 15; Figure 2B), and longer duration of unconsciousness was correlated with greater MRI lesion burden (ρ = 0.606, unadjusted $p = 0.022$; n = 14; Figure 2C). All other clinical severity correlations in Table 4 had unadjusted p values above 0.05.

Table 4. Correlations of clinical variables with MRI lesion burden and cognitive burden.

Clinical Variable	n	MRI Lesion Burden, ρ	*p* Value	n	Cognitive Burden, ρ	*p* Value
Age	16	0.471	0.065	16	0.057	0.833
Estimated CO exposure duration	15	0.477	0.072	15	**0.555**	**0.032**
Duration of unconsciousness	14	**0.606**	**0.022**	14	0.447	0.109
Initial Glasgow Coma Scale	15	−0.443	0.098	15	−0.348	0.203
Initial COHb	15	−0.102	0.718	15	−0.225	0.421
Initial lactate	15	0.316	0.252	15	−0.112	0.690
DNS latency	16	−0.082	0.762	16	0.444	0.085
Serum S100B	15	0.390	0.151	15	0.367	0.178

Values are Spearman's rank correlation coefficients. Analyses were performed using available observations for each variable. MRI lesion burden was defined as the number of involved anatomical regions, and cognitive burden was defined as the number of impaired cognitive domains. Bold values indicate $p < 0.05$. p values for Spearman correlations are two-sided and unadjusted. CO, carbon monoxide; COHb, carboxyhemoglobin; DNS, delayed neuropsychological sequelae; GCS, Glasgow Coma Scale; MRI, magnetic resonance imaging.

3.5. Exploratory Associations of Serum S100B

Among the 15 patients with DNS who had an acute serum S100B measurement, S100B was not significantly correlated with the number of regions involved on early MRI (Spearman's ρ = 0.390, $p = 0.151$) or the number of impaired cognitive domains assessed after DNS onset (ρ = 0.367, $p = 0.178$).

4. Discussion

In this cohort of patients with DNS who completed the SNSB, a greater number of MRI regions involved was correlated with a greater number of impaired cognitive domains. Frontal/executive impairment was the most frequent finding (12/16, 75%), and no individual MRI region showed a statistically significant association with this domain. Acute serum S100B showed no statistically significant correlation with early MRI lesion burden or later cognitive burden. Figure 3 summarizes the clinical MRI and cognitive findings alongside previously reported reductions in cortical and basal ganglia dopamine in a rat model [23], highlighting a possible dopaminergic contribution to executive dysfunction in patients with DNS.

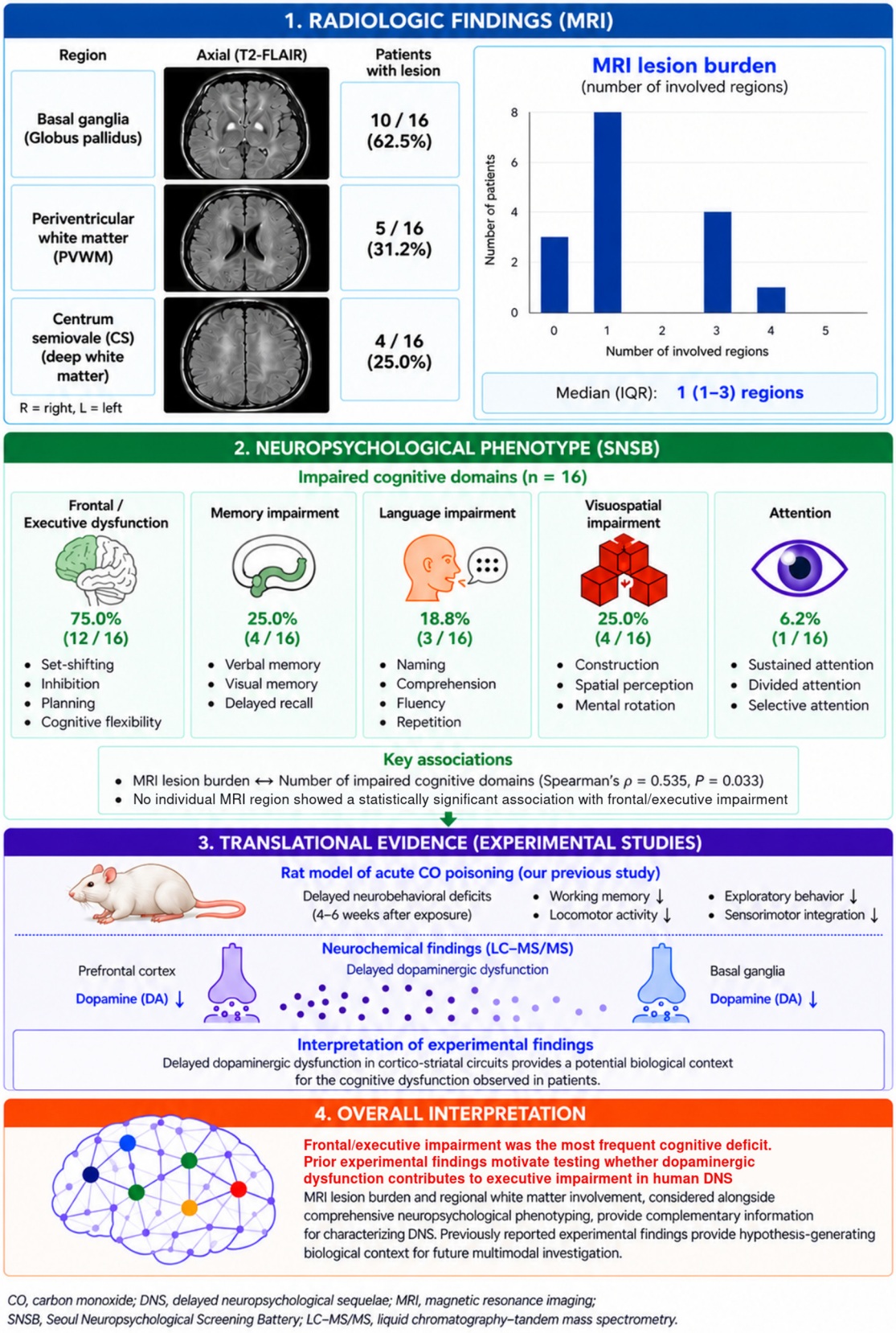


Figure 3. Clinical and experimental findings supporting a translational hypothesis for delayed neuropsychological sequelae after acute carbon monoxide poisoning. Representative MRI abnormalities are shown in the globus pallidus, periventricular white matter (PVWM), and centrum semiovale (CS). Frontal/executive impairment was the most frequent cognitive deficit, and no individual MRI region showed a statistically significant association with it. After correction for multiple comparisons,

PVWM involvement was associated with visuospatial and memory impairment, and CS involvement was associated with language, visuospatial, and memory impairment. A greater number of involved MRI regions was associated with impairment across more cognitive domains in an exploratory analysis. Previously published animal findings of reduced dopamine concentrations in the cerebral cortex and basal ganglia provide a rationale for testing the contribution of dopaminergic dysfunction to executive impairment in patients with DNS.

Notably, the associations between white matter lesions and cognitive impairment remained significant for selected domains after adjustment for multiple comparisons using the Benjamini–Hochberg procedure. Specifically, periventricular white matter lesions were associated with visuospatial and memory impairment, whereas centrum semiovale lesions were associated with language, visuospatial, and memory impairment. These findings suggest that white matter abnormalities may be relevant to cognitive dysfunction following acute carbon monoxide poisoning, potentially reflecting disruption of neural networks involved in higher cognitive processing. However, the observed associations should be interpreted cautiously. The small sample size, sparse contingency tables, and potential coexistence of lesions across different brain regions limit the precision of effect estimates and preclude conclusions regarding independent regional contributions or causality. Furthermore, the strong associations observed in certain domains, including perfect associations, may reflect the limited sample size rather than a consistent biological relationship. Therefore, these findings should be regarded as exploratory and require validation in larger cohorts with more comprehensive neuroimaging and neuropsychological assessments.

Serum S100B has previously been investigated as a predictor of DNS after acute CO poisoning [19,22]. Among the 15 patients who subsequently developed DNS and had a serum S100B measurement at emergency department presentation, S100B was not significantly correlated with the number of involved regions on MRI obtained 3–5 days after emergency department presentation or with the number of impaired cognitive domains assessed after DNS onset. The small sample limited the precision of these estimates, and the single acute-phase measurement precluded assessment of changes in S100B over time. Because the cohort was restricted to patients who developed DNS, the predictive value of S100B for DNS occurrence remains outside the scope of this analysis. Prospective studies with serial S100B measurements from the acute phase through follow-up and standardized assessments of DNS onset and severity could clarify whether S100B is associated with the risk of developing DNS or with its subsequent clinical course.

Experimental work has shown that lactate can increase Arc/Arg3.1 expression in astrocytes through HCAR1–β-arrestin2 signaling [26]. Whether this pathway is involved in DNS after CO poisoning, and whether it is related to circulating S100B, remain open questions.

Structural MRI has an established role in evaluating brain injury after CO poisoning, and acute MRI abnormalities have been associated with subsequent neurological sequelae [15–18]. More recent multimodal neuroimaging studies have further emphasized that conventional structural imaging captures only part of the neurological abnormalities following CO poisoning [20]. An important consideration in interpreting these neuropsychological findings is that detailed neuropsychological characterization was feasible in only 16 of the 28 patients with clinically diagnosed DNS. The remaining 12 patients could not complete the full SNSB because of severe cognitive impairment. Although the specific cognitive domains affected in these patients could not be determined, this observation underscores both the prominence of cognitive dysfunction in clinically significant DNS and the methodological difficulty of characterizing patients with severe impairment using conventional neuropsychological testing. Among patients who were able to complete comprehensive testing, frontal/executive dysfunction was the most frequent domain-specific

abnormality, affecting 75% of the analytical cohort. Thus, this predominance should be interpreted as a finding among patients capable of completing detailed testing rather than as an estimate of its prevalence across the entire spectrum of DNS. The difficulty of obtaining comprehensive neuropsychological data in more severely impaired patients also highlights the need for imaging and biomarker approaches capable of characterizing this population.

Clinical severity measures also showed different associations with subsequent structural and cognitive abnormalities. Longer estimated CO exposure was associated with a greater number of impaired cognitive domains, whereas longer duration of unconsciousness was associated with greater MRI lesion burden. In contrast, initial COHb concentration, lactate concentration, GCS score, and latency to DNS were not significantly associated with either outcome. These findings should be interpreted cautiously because exposure duration and duration of unconsciousness were retrospectively estimated. Lower acute GCS has been associated with an increased risk of developing DNS in a recent systematic review [27]. The apparent difference from our findings may again reflect the different outcomes being examined: previous studies evaluated the risk of developing DNS, whereas the present study evaluated structural and cognitive burden among patients who had already developed DNS. Thus, variables associated with the occurrence of DNS may not necessarily predict the subsequent severity of structural or cognitive impairment.

Executive function depends on distributed neural networks that include the prefrontal cortex, basal ganglia, thalamus, and their white matter connections [28,29]. Frontal/executive impairment was common in this cohort, and the regional MRI analyses did not identify a statistically significant association with any individual region. Prior human studies have examined striatal dopamine transporter binding after CO poisoning [13], and our rat study found lower dopamine concentrations in the cerebral cortex and basal ganglia alongside delayed behavioral deficits [23]. These observations motivate investigation of the potential contribution of dopaminergic dysfunction to executive impairment in human DNS. Dopaminergic function was not measured in this cohort. Prospective studies could pair dopamine transporter imaging, structural MRI, and standardized executive testing at matched follow-up visits in patients who do and do not develop DNS, and assess whether transporter availability is associated with executive performance after accounting for structural lesion burden.

From this perspective, three questions emerge for prospective investigation. First, acute biomarkers such as S100B should be examined separately for their ability to predict the occurrence and the subsequent severity of DNS [19,22]. Second, advanced imaging studies should determine whether structural lesion burden is more closely related to the overall extent of cognitive impairment, whereas regional abnormalities contribute to specific patterns of impairment [15–18,20,25]. Third, the relationship between dopaminergic abnormalities and executive dysfunction should be examined directly in patients, given the existing human dopaminergic imaging evidence [13] and experimental evidence of persistent monoaminergic alterations after CO exposure [23,30]. These questions provide specific and testable directions for translating the present observations into prospective studies.

Early structural MRI characterizes the anatomical distribution of lesions, while domain-level neuropsychological testing characterizes the pattern of cognitive impairment after DNS onset. In this cohort, frontal/executive impairment was the most frequent deficit, and the regional MRI analysis detected no statistically significant association with any individual region. When feasible, domain-level testing may therefore complement MRI by identifying which cognitive domains are affected.

This study has several limitations. First, the retrospective, single-center design and small analytical cohort limited statistical power, precision, and generalizability. Of the

28 patients with clinically diagnosed DNS, 16 completed the SNSB, while 12 were unable to complete it because of severe cognitive impairment. Frontal/executive impairment was observed in 75% of patients who completed the SNSB, and its frequency across the full spectrum of DNS remains uncertain. The exclusion of patients with severe cognitive impairment may also have biased the estimated association between MRI lesion burden and cognitive burden in either direction. The descriptive comparisons in Supplementary Table S3 provide context for interpreting this potential bias. Future studies should include assessment methods suitable for patients who are unable to complete comprehensive neuropsychological testing.

Second, the Benjamini–Hochberg procedure was applied to the 25 comparisons between regional MRI lesions and cognitive domains in Table 3. All Spearman correlation analyses were reported with unadjusted p values. Sparse cell counts limited the precision of the regional effect estimates, and the small sample and number of associations examined warrant an exploratory interpretation of the correlation results.

Third, the unweighted MRI lesion count captured the number of anatomical regions involved. Lesion classification relied on routine neuroradiology reports, so inter-rater agreement for the study classifications could not be assessed. Lesion volume, severity, and functional significance were outside the scope of this measure. Conventional MRI also provided limited information on white matter connectivity, cerebral metabolism, and brain function [20].

Fourth, the durations of CO exposure and unconsciousness were estimated retrospectively and may have been imprecise. A single acute-phase serum S100B measurement limited assessment of changes over time, and restriction to patients who developed DNS precluded evaluation of S100B as a predictor of DNS occurrence. The proposed dopaminergic mechanism was informed by a previously published animal study [23] and requires direct evaluation in patients.

Finally, this secondary analysis used the same 16-patient cohort as our previous pilot study [25], which reported regional MRI–cognitive associations and correlations of cognitive burden with MRI lesion burden and estimated CO exposure duration. The present analysis extends that work by evaluating acute serum S100B, reporting multiplicity-adjusted results for regional comparisons, and descriptively comparing patients by SNSB completion status. The MRI and cognitive findings require validation in independent prospective cohorts that include patients across a broader range of DNS severity.

5. Conclusions

Among patients with DNS who completed comprehensive neuropsychological testing, a greater number of involved regions on early MRI was associated with impairment across more cognitive domains in an exploratory analysis. Frontal/executive impairment was the most frequent deficit, and no individual MRI region showed a statistically significant association with it. Acute serum S100B showed no statistically significant correlation with either early MRI lesion burden or later cognitive burden. Together, these observations illustrate how acute biomarker measurement, early structural MRI, and later neuropsychological assessment address different aspects of DNS and support interpreting MRI alongside domain-level cognitive findings. Prospective studies across the full spectrum of DNS severity should combine serial biomarker measurements, advanced neuroimaging, and longitudinal cognitive assessment. The potential contribution of dopaminergic dysfunction to executive impairment warrants direct investigation in patients.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biomedicines14122757/s1, Table S1: Contingency counts and conditional odds ratios with exact 95% confidence intervals; Table S2: Neuropsychological domains and measures used for cognitive domain classification; Table S3: Comparison of clinical characteristics and MRI findings between patients with complete and incomplete SNSB assessments.

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