

Whole-Brain Magnetic Susceptibility Alterations in Minimal Hepatic Encephalopathy Associated With Hepatitis B Virus-Related Decompensated Cirrhosis

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Abstract

Minimal hepatic encephalopathy (MHE) is a clinically covert complication of cirrhosis, but its whole-brain magnetic susceptibility pattern remains incompletely characterized. We investigated regional relative susceptibility in 31 healthy controls (HCs), 26 patients with hepatitis B virus-related decompensated cirrhosis without MHE (NMHE), and 13 patients with MHE. Multi-echo 3.0-T gradient-echo data were reconstructed using quantitative susceptibility mapping, and 249 regional labels were analyzed with nonparametric pairwise tests and Benjamini-Hochberg false discovery rate (FDR) correction. Twenty-one labels differed between HCs and MHE and 21 between HCs and NMHE, whereas no label differed between MHE and NMHE after FDR correction. Seven cortical regions were shared by both patient-versus-control comparisons and showed a numerical $HC < NMHE < MHE$ order. In exploratory analyses, left A22r susceptibility was inversely associated with serum albumin ($\rho = -0.551$, FDR $q = 0.0281$). Age- and sex-adjusted analyses attenuated the cortical findings; only the left accumbens area remained significant for HC versus NMHE. These results demonstrate distributed susceptibility abnormalities in HBV-related decompensated cirrhosis and identify shared inferior frontal and superior temporal/auditory association regions as candidate markers for further study.

1. Introduction

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome arising from liver failure and/or portosystemic shunting, with manifestations ranging from subtle disturbances in attention and psychomotor function to disorientation, altered consciousness, and coma [1–4]. Minimal hepatic encephalopathy (MHE), within the spectrum of covert HE, generally lacks overt abnormalities on routine neurological examination but impairs attention, executive control, visual search, working memory, and psychomotor speed [5–12]. Objective imaging markers capable of capturing cerebral alterations before overt neurological deterioration are therefore clinically relevant. The liver is a major source of hepcidin and a central regulator of systemic iron balance; the reported association between reduced serum hepcidin and cerebral iron deposition in HBV-related cirrhosis raises the possibility that altered brain iron handling contributes to liver-brain axis dysfunction [26, 29–31].

Recent MRI studies have increasingly highlighted the value of neuroimaging for early identification and quantitative phenotyping of MHE [50]. Iron-sensitive MRI, particularly quantitative susceptibility mapping (QSM), has added a complementary perspective. In HBV-related MHE, elevated susceptibility has been reported in the caudate nucleus, thalamus, substantia nigra, and hippocampus, with associations with NCT-A and DST performance [23, 25, 26]. A more recent whole-brain QSM study identified widespread susceptibility abnormalities in prefrontal, parietal, insular, thalamic, sensorimotor, visual, and auditory regions and linked these abnormalities to psychometric hepatic encephalopathy scores [24]. Nevertheless, previous studies have often relied on relatively coarse regions of interest, voxelwise clusters, or conventional anatomical parcellations, and the direction and location of reported abnormalities have not been fully consistent across cohorts.

The Human Brainnetome Atlas provides fine-grained cortical parcellation based on connectional architecture and offers detailed anatomical and functional annotations [13]. Such a framework may be useful for diseases such as MHE, in which distributed network-level abnormalities are expected. Moreover, previous synthetic MRI (SyMRI)/QSM work in HBV-related decompensated cirrhosis detected T1, T2, and proton-density (PD) abnormalities in the caudate and putamen, whereas conventional limited-ROI QSM analysis showed no robust corrected differences [27]. This discrepancy suggests that more granular whole-brain spatial sampling may identify regional effects that are missed by traditional ROI approaches.

Accordingly, we compared whole-brain relative susceptibility distributions among HCs, NMHE patients, and MHE patients. Our primary aims were to: (1) identify regions showing FDR-corrected group differences; (2) determine abnormalities shared by NMHE and MHE and characterize their cross-group pattern; (3) explore the clinical relevance of these abnormalities in relation to NCT-A, DST, and routine laboratory markers; and (4) examine the concordance and complementarity of the current susceptibility findings with previous SyMRI T1, T2, and PD abnormalities. Because age and sex were not fully matched across the three groups, we additionally performed age- and sex-adjusted sensitivity analyses to assess the robustness of the main findings to demographic confounding.

2. Materials and Methods

2.1 Study participants

This was a single-center cross-sectional imaging study. Patients who fulfilled clinical diagnostic criteria for HBV-related decompensated cirrhosis were included. Exclusion criteria included overt HE, a history of major neurological or psychiatric disease, alcohol-related encephalopathy, clinically significant cerebrovascular events, medications or metabolic disorders likely to affect central nervous system function, and contraindications to MRI. The final cohort available for whole-brain regional susceptibility analysis included 31 HCs, 26 patients with HBV-related decompensated cirrhosis without MHE (NMHE), and 13 patients with MHE, for a total of 70 participants. The final imaging sample was defined by successful completion of regional parcellation and susceptibility extraction. Some clinical variables contained missing values; therefore, the effective sample size varies slightly across variables in Table 1.

Table 1
Demographic, clinical, and neuropsychological characteristics

Variable	HC	NMHE	MHE	P value
Sex (male/female)	10/18	22/4	10/3	0.0005
Age	45.00 (29.50, 50.50)	51.00 (44.25, 56.00)	55.00 (52.00, 60.00)	< 0.001
Alanine aminotransferase	17.65 (10.82, 27.80)	31.25 (26.27, 46.73)	41.35 (26.90, 70.38)	< 0.001
Aspartate aminotransferase	18.95 (15.60, 25.90)	45.85 (28.35, 77.35)	74.55 (41.07, 83.45)	< 0.001
Platelet count	231.00 (211.25, 271.50)	104.50 (73.75, 133.75)	87.00 (45.00, 151.50)	< 0.001
Albumin	45.44 ± 2.15	36.15 ± 8.19	34.57 ± 5.97	< 0.001
Globulin	28.26 ± 3.12	30.84 ± 7.03	30.92 ± 6.60	0.256
A/G	1.61 ± 0.22	1.26 ± 0.41	1.18 ± 0.35	< 0.001
Direct bilirubin	2.95 (2.23, 3.50)	9.40 (5.20, 19.90)	15.20 (7.47, 44.77)	< 0.001
Total bilirubin	10.15 (7.82, 13.50)	24.90 (15.20, 43.00)	52.90 (15.68, 103.72)	< 0.001
PT	—	12.90 (12.05, 13.45)	14.40 (13.10, 15.12)	0.079
AFP	—	17.01 (4.90, 50.60)	19.54 (8.99, 195.20)	0.576
MMSE	—	29.00 (27.00, 30.00)	28.00 (25.75, 28.75)	0.561
NCT-A (s)	—	46.47 ± 13.34	88.15 ± 19.01	< 0.001
DST	—	38.87 ± 9.87	21.62 ± 4.21	< 0.001
<i>Data are presented as mean ± SD or median (Q1, Q3), according to distribution. NCT-A, DST, PT, AFP, and MMSE were compared only between patient groups. Some demographic/laboratory variables were missing in HCs; available-case analysis was used.</i>				

The study was approved by the Clinical Medical Ethics Committee of Xiangya Hospital, Central South University and was conducted in accordance with the Declaration of Helsinki and relevant institutional guidelines. Written informed consent was obtained from all participants before examination.

2.2 Neuropsychological assessment and group classification

Patients underwent NCT-A and DST on the day of MRI. NCT-A primarily assesses visual search, sustained attention, sequential processing, and psychomotor speed; longer completion time indicates poorer performance. DST requires rapid digit-symbol matching and depends on processing speed, attention, working memory, and visuomotor integration; lower scores indicate poorer performance [9–12]. Using established age-adjusted thresholds, patients with abnormal performance on both NCT-A and DST were classified as MHE, whereas decompensated cirrhotic patients without overt HE who did not meet these criteria were classified as NMHE.

2.3 MRI acquisition

MRI was performed on a GE SIGNA Premier 3.0-T scanner (GE HealthCare, Chicago, IL, USA) using a 48-channel head coil. Participants were scanned in the supine position with eyes closed, were instructed to remain awake, and were asked to minimize active thinking and head motion. Multi-echo three-dimensional gradient-echo enhanced susceptibility-weighted angiography (ESWAN) was acquired with the following parameters: repetition time (TR) = 53.52 ms, first echo time (TE) = 5.076 ms, delta TE = 6.24 ms, 8 unipolar echoes, field of view (FOV) = 240×240 mm², slice thickness = 2 mm; and total acquisition time = 8 min. High-resolution three-dimensional T1-weighted structural imaging was additionally acquired for registration and anatomical parcellation: TR = 5.7 ms, TE = 2.2 ms, FOV = $256 \times 205 \times 170$ mm³, recon voxel size = $1 \times 1 \times 1$ mm³ isotropic, and total scan time = 4 min 34 s.

2.4 QSM reconstruction and spatial normalization

Quantitative susceptibility maps were reconstructed from ESWAN magnitude and phase data using the deep-learning QSM pipeline described by Gao et al. [19]. Briefly, raw wrapped phase was first processed with a Laplacian-of-Trigonometric-functions (LoT) operator, enabling concurrent phase unwrapping, background field removal, and local field estimation within a single framework. This LoT module was subsequently integrated into a 3D residual U-Net (LoT-Unet) to implement two end-to-end networks: iQFM for near-instant quantitative field mapping and iQSM for near-instant quantitative susceptibility mapping.

Individual T1-weighted images were registered to fsaverage space during recon-all. The first-echo magnitude image was rigidly registered to the corresponding T1-weighted image, and the resulting composite inverse transformations were applied to the Brainnetome Atlas in fsaverage space so that regional extraction was performed in individual space.

Regional values were expressed as whole-brain-referenced relative susceptibility derived from the analysis pipeline. We therefore use the term “relative susceptibility” throughout the manuscript and do not interpret these values as absolute tissue iron concentrations.

2.5 Brain parcellation and regional extraction

The cerebral cortex was finely parcellated using FreeSurfer 7.3 (freely available at <http://surfer.nmr.mgh.harvard.edu/>) with the standard recon-all pipeline. The Human Brainnetome Atlas, which defines 210 cortical/subcortical subdivisions based on structural and functional connectivity and

provides detailed anatomical and functional annotation [13], was then mapped from fsaverage space into individual space. The exported matrix additionally retained standard subcortical, posterior fossa, and several non-parenchymal segmentation labels from the preprocessing pipeline, resulting in 249 labels in the final numerical matrix. All labels were retained in the statistical analysis to preserve the prespecified extraction framework; however, ventricular, WM-hypointensity, optic-chiasm, and other non-target segmentation labels were explicitly separated from brain parenchymal/gray-matter regions in biological interpretation.

For each participant, the median QSM value within each region was used as the representative regional measure. Region names and numerical label identifiers were cross-checked against the original parcellation table for statistical reporting and subsequent mask construction.

2.6 Statistical analysis

Demographic and clinical variables were summarized as mean $\pm$ standard deviation or median (interquartile range), as appropriate. Categorical variables were compared using the chi-square test. Continuous variables across the three groups were analyzed using one-way analysis of variance or the Kruskal-Wallis test according to distributional assumptions. Variables measured only in the patient groups, including NCT-A, DST, prothrombin time, alpha-fetoprotein, and Mini-Mental State Examination scores, were compared using Welch's t test or the Mann-Whitney U test as appropriate.

The primary regional susceptibility analysis used nonparametric pairwise rank-based comparisons. Multiple testing was controlled with the Benjamini-Hochberg FDR procedure, and only regions with FDR-adjusted $q < 0.05$ were considered primary positive findings. Family-wise error-corrected findings were not used for interpretation in the present manuscript. When no region survived FDR correction for MHE versus NMHE, uncorrected P values were not used to generate additional "positive" regions.

Because the HC, NMHE, and MHE groups differed in age and sex distribution, whole-brain sensitivity analyses were performed across all 249 labels. Separate linear models were fitted for HC versus MHE and HC versus NMHE, with group as the primary predictor and age and sex as covariates. Benjamini-Hochberg correction was then applied to the 249 group-effect P values in each comparison. These analyses were intended to assess the sensitivity of the main nonparametric findings to demographic confounding rather than to replace the prespecified primary analysis.

Clinical correlation analyses were conducted in two stages. First, within NMHE and MHE separately, FDR-positive regions were correlated with clinical variables using Spearman rank correlations followed by FDR correction. Second, to reduce the exploratory testing burden, a post hoc restricted analysis focused on the seven cortical regions that were significant in both patient-versus-control comparisons. In the combined cirrhosis cohort, these seven regions were correlated with eight variables—platelet count, albumin, albumin/globulin ratio (A/G), aspartate aminotransferase (AST), direct bilirubin, total bilirubin, NCT-A, and DST—yielding 56 tests, which were again corrected using Benjamini-Hochberg FDR. Associations surviving FDR correction were further examined in linear models including age, sex, and

MHE/NMHE group as covariates. Two-sided $P < 0.05$ denoted nominal significance, whereas FDR $q < 0.05$ defined significance after multiple-comparison correction.

2.7 Use of generative AI in manuscript preparation

During manuscript preparation, the authors used ChatGPT (OpenAI) as an assistive tool for English-language editing, manuscript organization, and preparation of draft tables and figures. All AI-assisted outputs were reviewed and revised by the authors, who take full responsibility for the final scientific content.

3. Results

3.1 Demographic, clinical, and neuropsychological characteristics

The final imaging cohort comprised 31 HCs, 26 NMHE patients, and 13 MHE patients. Sex distribution differed significantly among the three groups ($P = 0.0005$), and age also differed across groups ($P < 0.001$), with the MHE group being oldest. Compared with HCs, the cirrhosis groups generally had higher aminotransferase and bilirubin values and lower platelet count, albumin, and A/G. Between the NMHE and MHE groups, alanine aminotransferase, AST, platelet count, albumin, globulin, A/G, direct bilirubin, total bilirubin, prothrombin time, alpha-fetoprotein, and Mini-Mental State Examination score did not differ significantly (all $P > 0.05$), whereas MHE patients were older than NMHE patients ($P = 0.011$). Neuropsychological impairment was marked: NCT-A completion time was significantly longer in MHE than in NMHE (88.15 ± 19.01 s vs 46.47 ± 13.34 s, $P < 0.001$), and DST score was significantly lower (21.62 ± 4.21 vs 38.87 ± 9.87 , $P < 0.001$). Demographic, clinical, and neuropsychological characteristics are summarized in Table 1.

3.2 Regional susceptibility differences after FDR correction

In the prespecified pairwise FDR-corrected analysis, 21 labels reached $q < 0.05$ for HC versus MHE and 21 for HC versus NMHE. No label survived FDR correction for MHE versus NMHE.

Among the 21 positive labels in HC versus MHE, 19 represented brain parenchymal regions after excluding the left lateral ventricle and WM-hypointensities. The predominant MHE pattern was higher relative susceptibility and involved the left amygdala, left A10l and inferior frontal sulcus, bilateral A45c/A45r, bilateral primary motor hand regions, bilateral TE1.0/TE1.2, left A22r, right A22c, right anterior superior temporal sulcus (aSTS), left superior parietal A7pc, supramarginal A40rd/A40c, angular A39rv, and left primary somatosensory trunk area A1/2/3tru.

HC versus NMHE likewise yielded 21 positive labels. After excluding the bilateral lateral ventricles, WM-hypointensities, and optic chiasm, 17 parenchymal regions remained, including the left cerebellar cortex, left putamen, brainstem, left accumbens area, right pallidum, left A45c/A45r, bilateral TE1.0/TE1.2, left A22r, left A28/34, right A9l, right A10m, right A45c, right aSTS, right vla, and right A23c. Most cortical

regions and the left putamen showed higher relative susceptibility, whereas the left accumbens area, right pallidum, and right A23c showed lower values. Detailed parenchymal/cortical results are provided in Tables 2 and 3, and effect directions are shown in Fig. 2.

Table 2
FDR-significant brain parenchymal/cortical regions in HC vs MHE

Comparison	Region	HC mean ± SD	Patient mean ± SD	Direction	FDR q
HC vs MHE	Left amygdala	-0.0111 ± 0.0030	-0.0079 ± 0.0028	Higher	0.0171
HC vs MHE	A10l_L (lateral frontopolar region)	-0.0142 ± 0.0031	-0.0107 ± 0.0034	Higher	0.0243
HC vs MHE	IFS_L (inferior frontal sulcus)	-0.0068 ± 0.0037	-0.0024 ± 0.0026	Higher	0.0064
HC vs MHE	A45c_L (inferior frontal gyrus, triangular division)	-0.0036 ± 0.0035	0.0004 ± 0.0037	Higher	0.0099
HC vs MHE	A45r_L (inferior frontal gyrus, opercular division)	-0.0079 ± 0.0029	-0.0049 ± 0.0041	Higher	0.0171
HC vs MHE	A4hf_L (primary motor cortex, hand region)	0.0036 ± 0.0032	0.0073 ± 0.0036	Higher	0.0185
HC vs MHE	TE1.0/TE1.2_L (temporal auditory association cortex)	-0.0068 ± 0.0030	-0.0028 ± 0.0023	Higher	0.0034
HC vs MHE	A22r_L (superior temporal gyrus)	-0.0094 ± 0.0038	-0.0066 ± 0.0026	Higher	0.0171
HC vs MHE	A7pc_L (posterior superior parietal lobule)	0.0002 ± 0.0037	0.0051 ± 0.0043	Higher	0.0076
HC vs MHE	A40rd_L (posterior supramarginal region)	-0.0028 ± 0.0022	-0.0002 ± 0.0020	Higher	0.0141
HC vs MHE	A40c_L (central supramarginal region)	-0.0037 ± 0.0031	-0.0013 ± 0.0021	Higher	0.0106
HC vs MHE	A39rv_L (ventral angular region)	0.0002 ± 0.0029	0.0025 ± 0.0025	Higher	0.0344
HC vs MHE	A1/2/3tru_L (primary somatosensory cortex, trunk region)	0.0031 ± 0.0046	0.0088 ± 0.0039	Higher	0.0064
HC vs MHE	A45c_R (inferior frontal gyrus, triangular division)	-0.0063 ± 0.0037	-0.0025 ± 0.0037	Higher	0.0064
HC vs MHE	A45r_R (inferior frontal gyrus, opercular division)	-0.0066 ± 0.0028	-0.0031 ± 0.0033	Higher	0.0064
HC vs MHE	A4hf_R (primary motor cortex, hand region)	0.0006 ± 0.0028	0.0040 ± 0.0037	Higher	0.0243
<i>Direction indicates the MHE group relative to HC. Non-parenchymal segmentation labels are excluded from the table.</i>					

Comparison	Region	HC mean ± SD	Patient mean ± SD	Direction	FDR q
HC vs MHE	TE1.0/TE1.2_R (temporal auditory association cortex)	-0.0075 ± 0.0036	-0.0047 ± 0.0033	Higher	0.0243
HC vs MHE	A22c_R (superior temporal gyrus)	-0.0005 ± 0.0035	0.0026 ± 0.0038	Higher	0.0171
HC vs MHE	aSTS_R (anterior superior temporal sulcus)	-0.0105 ± 0.0027	-0.0083 ± 0.0021	Higher	0.0215
<i>Direction indicates the MHE group relative to HC. Non-parenchymal segmentation labels are excluded from the table.</i>					

Table 3
FDR-significant brain parenchymal/cortical regions in HC vs NMHE

Comparison	Region	HC mean ± SD	Patient mean ± SD	Direction	FDR q
HC vs NMHE	Left cerebellar cortex	-0.0103 ± 0.0015	-0.0093 ± 0.0014	Higher	0.0220
HC vs NMHE	Left putamen	0.0065 ± 0.0058	0.0104 ± 0.0058	Higher	0.0233
HC vs NMHE	Brainstem	-0.0143 ± 0.0019	-0.0127 ± 0.0025	Higher	0.0233
HC vs NMHE	Left accumbens area	0.0062 ± 0.0079	-0.0015 ± 0.0073	Lower	0.0130
HC vs NMHE	Right pallidum	0.0549 ± 0.0110	0.0462 ± 0.0124	Lower	0.0233
HC vs NMHE	A45c_L (inferior frontal gyrus, triangular division)	-0.0036 ± 0.0035	-0.0009 ± 0.0034	Higher	0.0220
HC vs NMHE	A45r_L (inferior frontal gyrus, opercular division)	-0.0079 ± 0.0029	-0.0055 ± 0.0027	Higher	0.0181
HC vs NMHE	TE1.0/TE1.2_L (temporal auditory association cortex)	-0.0068 ± 0.0030	-0.0044 ± 0.0031	Higher	0.0159
HC vs NMHE	A22r_L (superior temporal gyrus)	-0.0094 ± 0.0038	-0.0074 ± 0.0029	Higher	0.0422
HC vs NMHE	A28/34_L (entorhinal/perirhinal region)	-0.0097 ± 0.0188	0.0018 ± 0.0095	Higher	0.0160
HC vs NMHE	A9l_R (lateral dorsolateral prefrontal cortex)	-0.0021 ± 0.0029	0.0001 ± 0.0036	Higher	0.0381
HC vs NMHE	A10m_R (medial frontopolar region)	-0.0037 ± 0.0034	-0.0012 ± 0.0030	Higher	0.0284
HC vs NMHE	A45c_R (inferior frontal gyrus, triangular division)	-0.0063 ± 0.0037	-0.0039 ± 0.0034	Higher	0.0220
HC vs NMHE	TE1.0/TE1.2_R (temporal auditory association cortex)	-0.0075 ± 0.0036	-0.0049 ± 0.0037	Higher	0.0207
HC vs NMHE	aSTS_R (anterior superior temporal sulcus)	-0.0105 ± 0.0027	-0.0089 ± 0.0029	Higher	0.0233
HC vs NMHE	vla_R (ventral visual cortex)	-0.0153 ± 0.0055	-0.0122 ± 0.0047	Higher	0.0381

Direction indicates the NMHE group relative to HC. Non-parenchymal segmentation labels are excluded from the table.

Comparison	Region	HC mean ± SD	Patient mean ± SD	Direction	FDR q
HC vs NMHE	A23c_R (posterior cingulate cortex)	0.0017 ± 0.0041	-0.0009 ± 0.0039	Lower	0.0332
<i>Direction indicates the NMHE group relative to HC. Non-parenchymal segmentation labels are excluded from the table.</i>					

3.3 Shared cortical regions

HC versus MHE and HC versus NMHE shared nine FDR-positive labels. Figure 1B shows nine overlapping labels, including the left lateral ventricle and WM-hypointensities. After excluding these two non-target segmentation labels, seven shared cortical regions remained: A45c_L, A45r_L, TE1.0/TE1.2_L, A22r_L, A45c_R, TE1.0/TE1.2_R, and aSTS_R. The overall overlap and regional values are summarized in Fig. 1, and participant-level distributions are shown in Fig. 3.

3.4 Age- and sex-adjusted sensitivity analyses

Given the marked differences in age and sex distribution across groups, age- and sex-adjusted linear models were applied to each of the 249 labels. No region remained significant after FDR correction in HC versus MHE. In HC versus NMHE, only the left accumbens area remained significant (group beta=-0.0103, unadjusted P = 0.00014, FDR q = 0.0354).

3.5 Associations with clinical variables and neuropsychological tests

Within-group region-clinical correlation analyses in NMHE and MHE yielded no association that survived full multiple-comparison correction at FDR q < 0.05.

In the post hoc restricted analysis of seven shared cortical regions by eight clinical variables, only the association between left A22r and serum albumin survived FDR correction: higher relative susceptibility was associated with lower albumin (Spearman rho=-0.551, P = 0.0005, q = 0.0281; n = 36). In a subsequent linear model including age, sex, and MHE/NMHE group, albumin remained independently associated with A22r relative susceptibility (beta=-2.19 x 10⁻⁴, P = 0.001). The left A22r-albumin association is illustrated in Supplementary Fig. S1.

In a dedicated exploratory analysis of platelet count, no association between platelet count and any FDR-positive brain region survived multiple-comparison correction. The lowest uncorrected P value was observed for the brainstem (rho=-0.475, P = 0.0045, q = 0.148). Figure 4 summarizes correlations between the seven shared cortical regions and the eight clinical/neuropsychological variables.

4. Discussion

This study systematically characterized whole-brain relative magnetic susceptibility in HBV-related decompensated cirrhosis using fine-grained regional analysis. Three principal observations emerged. First, in the prespecified unadjusted FDR-corrected analysis, both MHE and NMHE were associated with multiregional susceptibility abnormalities. In MHE, parenchymal abnormalities were concentrated in the inferior frontal/prefrontal cortex, superior temporal and auditory association cortex, left parietal association cortex, sensorimotor cortex, and amygdala; NMHE showed a more heterogeneous pattern spanning cortex, basal ganglia, limbic structures, cerebellum, and brainstem. Second, the two patient groups shared seven frontotemporal cortical regions whose mean values followed a consistent $HC < NMHE < MHE$ numerical pattern, although the direct MHE-versus-NMHE comparison did not survive FDR correction. Third, in the restricted clinical correlation analysis, left A22r relative susceptibility was inversely associated with serum albumin, whereas platelet count and most cognitive or liver-function associations did not remain significant after multiple-comparison correction. Taken together, these findings suggest that susceptibility abnormalities in MHE are better conceptualized as distributed network-level and local microenvironmental alterations than as a simple model of monotonically increasing iron deposition in one or a few deep gray nuclei.

The physical basis of susceptibility imaging is central to interpretation. Susceptibility-weighted imaging (SWI) and quantitative susceptibility mapping (QSM) exploit local magnetic susceptibility differences to characterize paramagnetic and diamagnetic tissue components [15–18]. Increased susceptibility in gray matter is often associated with ferritin- and hemosiderin-bound iron [17, 18]. However, QSM is not iron-specific: myelin and calcium also contribute to susceptibility contrast [14, 16, 17], while venous deoxyhemoglobin, tissue water content, and the choice of susceptibility reference can further influence measured values [14, 17, 18, 20]. Accordingly, a susceptibility abnormality should not automatically be translated into “iron deposition.” The 2024 ISMRM consensus specifically recommends transparent reporting of susceptibility referencing and recognizes age and sex as important biological determinants [14]. Brain iron increases with age in healthy adults, and sex-related differences have been reported in several deep gray nuclei [21, 22]. In the present cohort, MHE patients were older than both HCs and NMHE patients. This demographic imbalance provides a plausible explanation for the widespread higher susceptibility observed in the unadjusted analysis and for the marked attenuation of cortical findings after age and sex adjustment. Accordingly, the unadjusted analysis is most useful for describing the spatial pattern observed in this sample, whereas the adjusted sensitivity analysis is more relevant when considering disease-specific attribution.

The most prominent unadjusted MHE pattern involved the inferior frontal and superior temporal/auditory association cortices. A45c/A45r are fine-grained subdivisions of the inferior frontal gyrus implicated in higher-order language, semantic selection, cognitive control, and attentional selection. TE1.0/TE1.2 and A22 subdivisions participate in auditory processing, language/semantic integration, and multimodal transformation, while the anterior superior temporal sulcus contributes to complex social-perceptual and audiovisual integration [13]. These regions are not the deep gray nuclei most commonly sampled in conventional HE ROI studies, yet their functions align closely with the deficits in attention, processing speed, working memory, and complex information integration that characterize MHE. Resting-state fMRI

studies have repeatedly demonstrated abnormal interactions among default-mode, salience, central-executive, dorsal-attention, auditory, and visual networks in MHE [32–38]. The present frontotemporal susceptibility pattern may therefore be viewed as spatially convergent with known functional-network abnormalities rather than as evidence of isolated focal iron accumulation.

The shared seven-region frontotemporal pattern is particularly noteworthy. All seven regions showed a concordant numerical increase from HC to NMHE to MHE. A consistent direction across multiple anatomically and functionally related regions is potentially more informative at the network level than an isolated ROI difference. It raises the possibility that frontotemporal information-processing pathways become abnormal before patients cross the neuropsychological threshold for MHE and that the same regions deviate further as cognitive impairment becomes clinically measurable. However, because the direct FDR-corrected MHE-versus-NMHE comparison was negative, the present data do not establish a statistically significant longitudinal or linear progression. MHE may instead reflect a network-level critical transition: multiple mild abnormalities may already be present in NMHE, whereas overt psychometric impairment emerges only when compensatory interactions among frontoparietal control, auditory/semantic, sensorimotor, and thalamostriatal systems can no longer maintain performance. Structural covariance, dynamic activity, NODDI, and longitudinal diffusion-kurtosis studies likewise indicate that cirrhosis-related brain injury is distributed and dynamic rather than a simple monotonic change in one location [36–44].

Involvement of left parietal association and sensorimotor regions in MHE further supports a network-based interpretation. A7pc, A40rd/A40c, and A39rv occupy superior parietal, supramarginal, and angular subdivisions that contribute to visuospatial attention, working memory, multimodal integration, and goal-directed behavior. Bilateral A4hf and left A1/2/3tru represent primary motor and somatosensory systems. NCT-A requires visual search, sequential number processing, sustained attention, and motor execution, whereas DST depends on rapid visual-symbol matching, processing speed, working memory, and fine motor output. Although correlations between these regions and NCT-A/DST did not survive FDR correction, their functional anatomy is highly compatible with the processes required by these tests. Previous MHE studies have also reported abnormalities involving precentral/postcentral cortices, parietal regions, thalamus, and connecting white matter [23, 24, 32, 40, 43]. Thus, psychometric impairment may arise from reduced efficiency of integrated cognitive-sensorimotor networks rather than from susceptibility in any single region [45].

The NMHE pattern was not merely a milder version of the MHE pattern. In addition to the shared frontotemporal regions, NMHE abnormalities involved the left putamen, left accumbens area, right pallidum, left cerebellar cortex, brainstem, A28/34, right A9l/A10m, right v1a, and A23c, and the directions of change were not uniform. Basal ganglia-prefrontal circuits contribute to psychomotor and executive control; entorhinal/perirhinal regions support memory encoding and contextual integration; and v1a and posterior cingulate regions are related to visual and default-mode systems, respectively. Functional MRI studies have already identified abnormalities in default-mode, visual, attentional, and frontoparietal networks in cirrhotic patients without MHE [32, 35, 36]. Our findings therefore support the

concept that cerebral abnormalities precede the conventional neuropsychological threshold used to define MHE.

The opposite directions of susceptibility change in subcortical NMHE regions warrant particular caution. Lower susceptibility in the right pallidum and left accumbens area, alongside higher susceptibility in the left putamen, cannot simply be interpreted as “less iron” or “more iron.” Pallidal T1 hyperintensity in chronic liver disease is classically associated with manganese deposition, and manganese and iron have different effects on tissue susceptibility and relaxation [28]. In addition, reference-normalized QSM can be influenced by changes in the reference tissue itself. Importantly, after age and sex adjustment, the left accumbens area was the only region that remained significant in HC versus NMHE at the whole-brain FDR level, with lower values in patients. The nucleus accumbens, within the ventral striatum, is a key node for reward, motivation, effort allocation, and cognitive control and communicates with prefrontal and thalamic systems [46–48]. This comparatively robust finding makes the ventral striatum a high-priority target for independent replication, although its histopathological substrate cannot be established from QSM alone.

Our findings both converge with and diverge from previous MHE QSM studies. Wang et al. reported increased susceptibility in the bilateral caudate nuclei, left thalamus, right substantia nigra, and left hippocampus in HBV-related MHE, with correlations with NCT-A/DST [23]. Cai et al. subsequently described widespread elevations in prefrontal, parietal, insular, thalamic, sensorimotor, visual, and auditory regions and associations with PHES [24]. The unadjusted MHE pattern in the present study similarly involved prefrontal, parietal, motor, somatosensory, auditory, and temporal regions, supporting a broad network-level phenotype. However, we found no FDR-significant difference between MHE and NMHE, and all MHE-versus-HC findings attenuated after age and sex adjustment. Differences in sample size, age distribution, susceptibility referencing, parcellation granularity, and multiple-testing burden may account for this discrepancy. Rather than viewing these results as contradictory, they highlight the sensitivity of QSM findings to cohort composition, reference strategy, and spatial analysis methodology.

Clinical correlations were largely negative after multiple-comparison correction. The only FDR-significant association in the restricted analysis was the inverse relationship between left A22r susceptibility and serum albumin; platelet count and the other tested clinical or neuropsychological variables did not retain significance. This exploratory association is consistent with the established clinical relevance of serum albumin in cirrhosis-related hepatic encephalopathy, but its biological meaning for regional susceptibility requires independent validation [49].

Previous SyMRI work in HBV-related decompensated cirrhosis identified T1, T2, and PD abnormalities mainly in the caudate nucleus and putamen, whereas limited-ROI QSM showed no robust differences after multiple-comparison correction [27]. The present whole-brain susceptibility findings, including recurrent involvement of the left putamen in NMHE, provide partial anatomical convergence while suggesting that SyMRI and QSM capture complementary tissue properties.

This study has several strengths. First, the cohort was etiologically restricted to HBV-related decompensated cirrhosis, reducing heterogeneity related to liver-disease etiology. Second, fine-grained whole-brain parcellation was used rather than limiting analysis to a few deep nuclei, enabling detection of frontotemporal and parietal subregional patterns. Third, primary positive findings were strictly defined by FDR correction; uncorrected P values were not used to manufacture additional positive regions. Fourth, participant-level values were used to visualize the shared cortical pattern. Fifth, age- and sex-adjusted sensitivity analyses were performed and the marked attenuation of findings was reported transparently, improving interpretability and reproducibility.

Several limitations should also be acknowledged. First, the sample was modest, particularly the MHE group ($n = 13$), limiting power in a fine-grained 249-label analysis. Second, age and sex were not well matched; sensitivity analyses were performed, but demographic imbalance may remain correlated with disease severity, nutritional status, and other residual confounders. Third, NCT-A and DST are clinically practical but do not constitute the complete Psychometric Hepatic Encephalopathy Score, and their thresholds may be influenced by age, education, and cultural background [2, 9–12]. Finally, cortical parcellation and the standard subcortical/posterior fossa segmentation labels were derived from different segmentation components. This mixed framework preserves whole-brain information but does not provide uniform spatial granularity; the principal findings should therefore be validated using a harmonized parcellation strategy in independent cohorts.

Future studies will address several unresolved issues. First, absolute or alternative-reference QSM and complementary $R2^*$ mapping will be incorporated to evaluate the influence of susceptibility referencing. Second, systemic biomarkers including hepcidin, ferritin, transferrin saturation, ammonia, inflammatory mediators, and blood manganese will be collected to better distinguish contributions from iron, manganese, myelin, and tissue water. Third, longitudinal cohorts will be established to determine whether the shared $HC < NMHE < MHE$ pattern reflects within-subject progression toward MHE. These efforts should be pursued in larger, well-matched cohorts using harmonized parcellation strategies.

In summary, the present data support early and distributed cerebral susceptibility abnormalities in HBV-related decompensated cirrhosis but argue against a simplistic model of progressively increasing whole-brain iron deposition with worsening MHE. In the unadjusted analysis, inferior frontal-superior temporal/auditory association cortices formed a shared candidate vulnerability network across NMHE and MHE, and the left-A22r/albumin association provided a link between hepatic functional reserve and the cerebral microenvironment. At the same time, the disappearance of most cortical findings after demographic adjustment emphasizes the need for larger, strictly age- and sex-matched, longitudinal cohorts with standardized QSM referencing and multimodal biological markers before these regional patterns can be interpreted as MHE-specific iron-metabolism pathology or used for individualized prediction.

5. Conclusions

Whole-brain relative susceptibility analysis demonstrated distributed cerebral susceptibility abnormalities in both NMHE and MHE stages of HBV-related decompensated cirrhosis. The unadjusted primary analysis identified a shared inferior frontal-superior temporal/auditory association phenotype across stages and a descriptive $HC < NMHE < MHE$ numerical pattern in several regions, although the direct MHE-versus-NMHE comparison was not significant after FDR correction. The exploratory inverse association between left A22r susceptibility and serum albumin suggests that local cerebral microenvironmental alterations may be linked to systemic hepatic functional reserve. Because most cortical findings did not remain significant after age and sex adjustment, these results should be regarded as candidate imaging phenotypes requiring confirmation in larger, well-matched, longitudinal cohorts.

Declarations

Competing Interests

The authors declare no competing interests.

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Author Contribution

(I) Conception and design: X. N. and D. W.; (II) Administrative support: W. X.; (III) Provision of study materials or patients: D. W., X. N., and H. J.; (IV) Collection and assembly of data: X. N., D. W., X. C., and D. H.; (V) Data analysis and interpretation: X. N., Y. J., and X. C.; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Data Availability

Data AvailabilityThe original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author/s.

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Figures

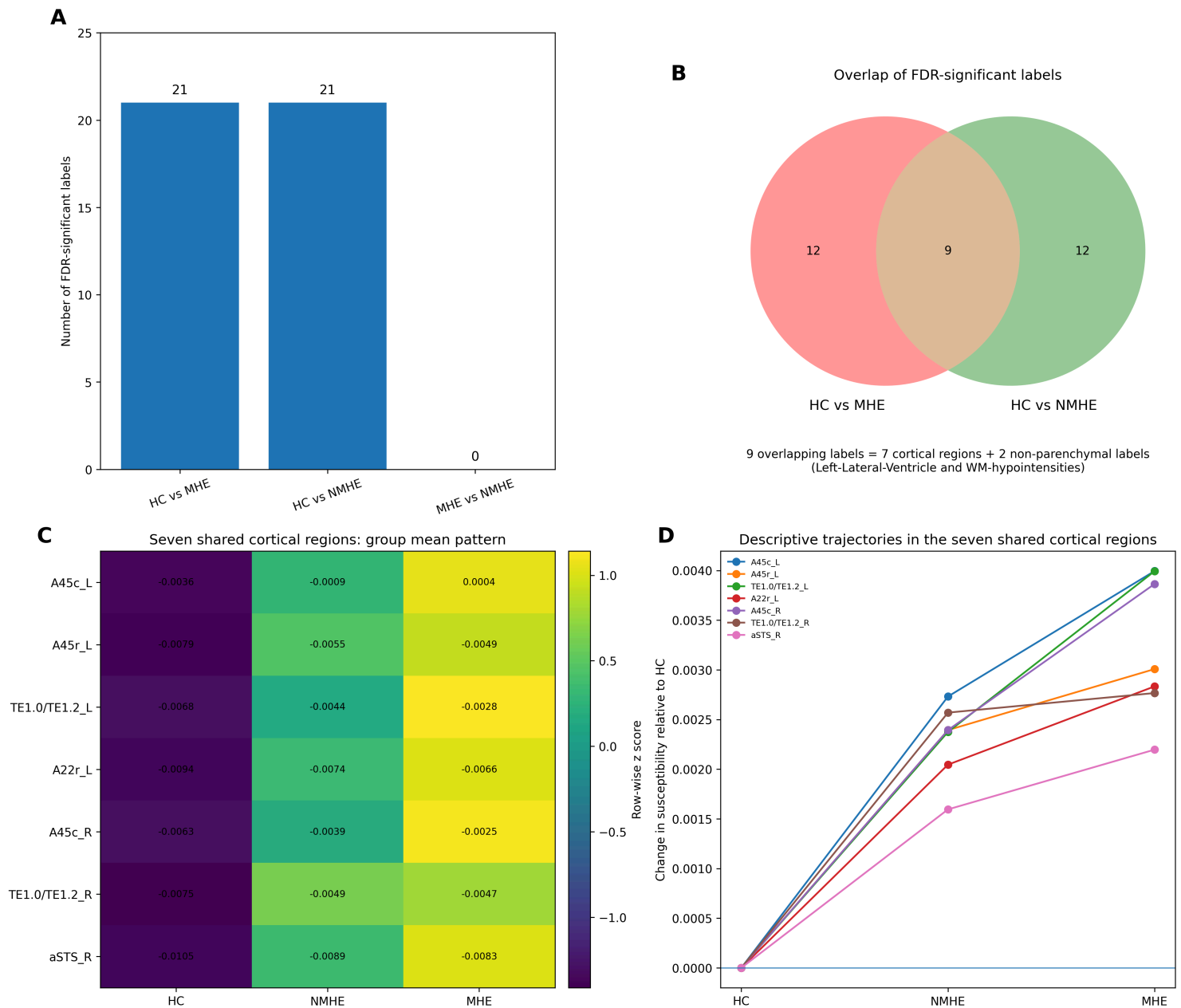


Figure 1

Overall pattern, overlap, and regional values of FDR-corrected abnormalities. (A) Number of FDR-positive labels in each pairwise comparison. (B) Overlap between HC-vs-MHE and HC-vs-NMHE positive labels. Nine labels overlapped, comprising seven shared cortical regions plus two non-target segmentation labels (left lateral ventricle and WM-hypointensities). (C) Mean relative susceptibility across the seven shared cortical regions in HC, NMHE, and MHE. (D) Relative susceptibility values in the seven shared cortical regions, normalized to the HC mean.

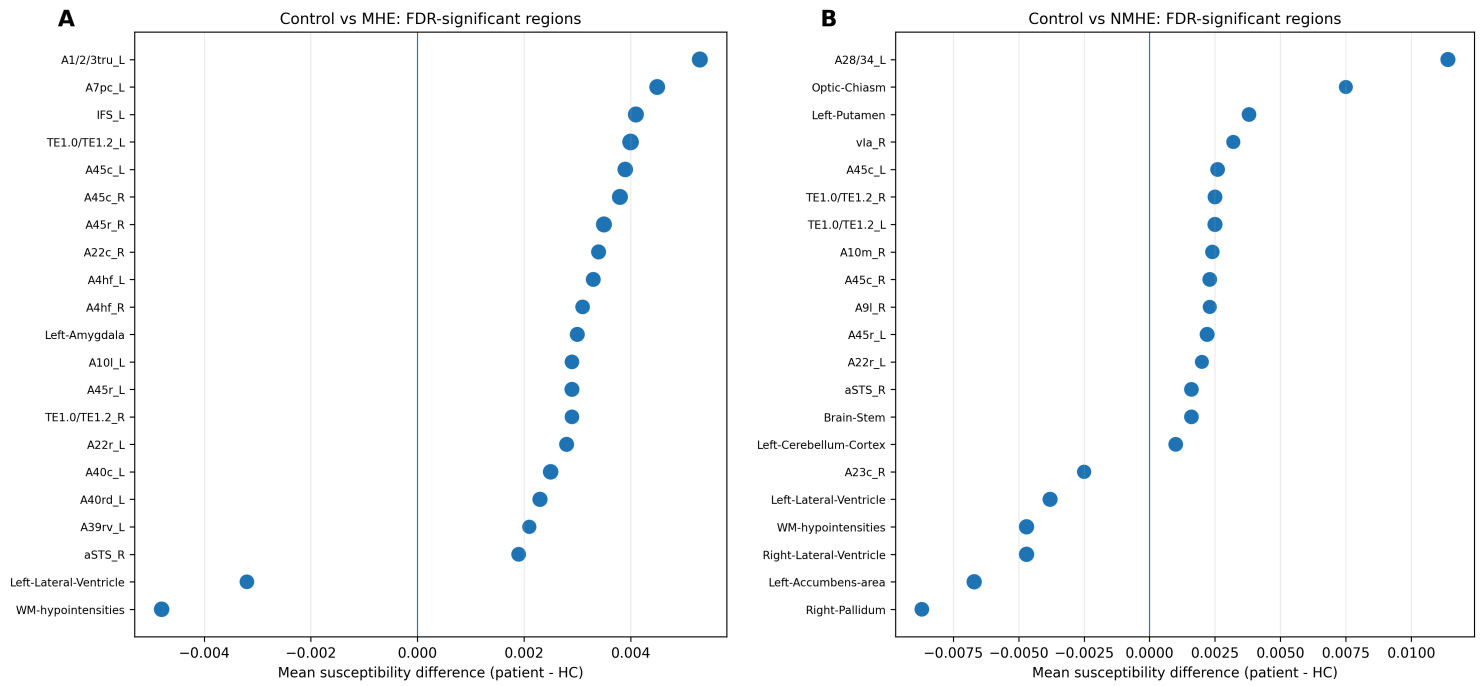


Figure 2

Mean relative susceptibility differences for FDR-positive labels in HC vs MHE (A) and HC vs NMHE (B). The x-axis represents the patient-group mean minus the HC mean; zero indicates identical group means, positive values indicate higher relative susceptibility in patients, and negative values indicate lower relative susceptibility.

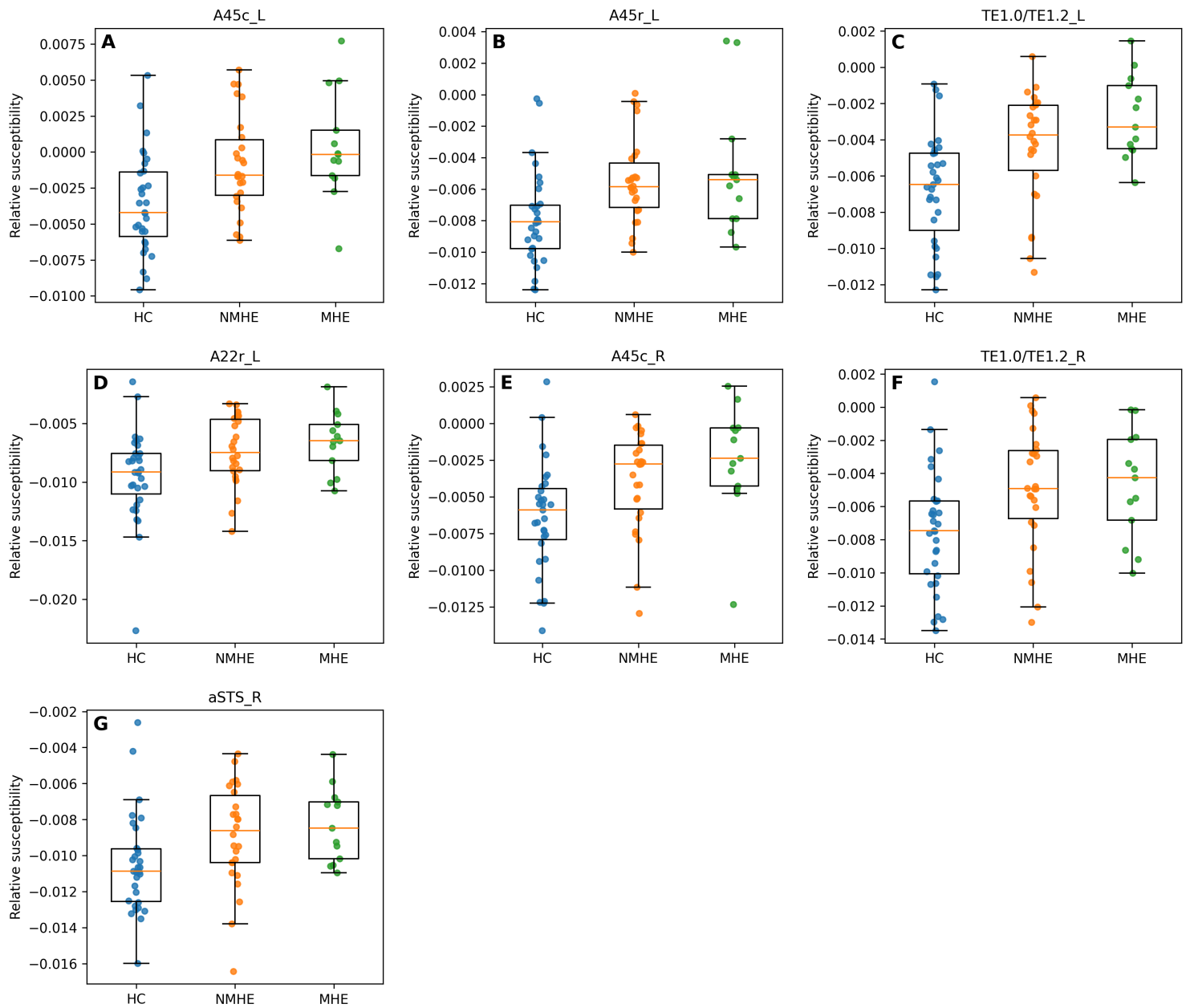


Figure 3

Participant-level distributions of relative susceptibility in the seven cortical regions that were FDR-significant in both patient-versus-control comparisons. Each point represents one participant; boxplots show the median and interquartile range. All seven regions showed a numerical HC < NMHE < MHE order, while the direct MHE-versus-NMHE comparison was not significant after FDR correction.

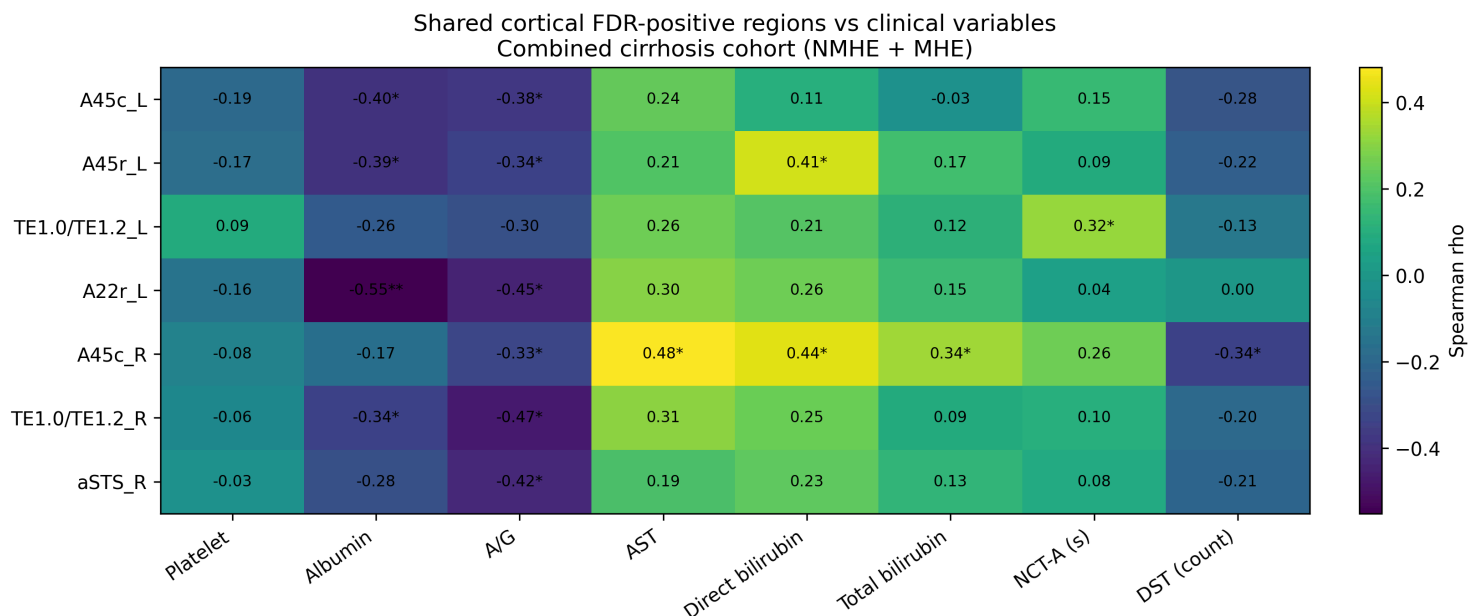


Figure 4

Spearman correlation heatmap between the seven shared FDR-positive cortical regions and major clinical/neuropsychological variables in the combined cirrhosis cohort. Rows represent cortical regions and columns represent platelet count, albumin, A/G, AST, direct bilirubin, total bilirubin, NCT-A, and DST. Values within cells are Spearman rho. *Uncorrected $P < 0.05$; **FDR $q < 0.05$ across the 56 restricted tests. Only the negative association between left A22r and albumin survived FDR correction.

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