

Table S1. Psychometric test results of control subjects and cirrhotic patients at baseline and follow-up according to response to rifaximin treatment.

Psychometric test	Control	Cirrhotic patients		MHE patients treated with rifaximin			
		NMHE	MHE	R0	R6	NR0	NR6
PHES	1.1 ± 0.3	-0.3 ± 0.2***	-7.4 ± 0.5***/ $\alpha\alpha\alpha$	-7.2 ± 0.9***/ $\alpha\alpha\alpha$	-3.5 ± 0.6 $\delta\delta\delta$	-7.7 ± 0.7***/ $\alpha\alpha\alpha$	-7.7 ± 0.8 $\beta\beta\beta$
Stroop test							
Congruent task	51.1 ± 2.1	45.3 ± 1.7	32.8 ± 1.5***/ $\alpha\alpha\alpha$	33.6 ± 2.6***/ $\alpha\alpha$	38.9 ± 2.8 δ	33.3 ± 2.5***/ $\alpha\alpha$	31.8 ± 2.9 β
Neutral task	51.3 ± 1.8	43.7 ± 1.5**	33.9 ± 1.1***/ $\alpha\alpha\alpha$	34.3 ± 2***/ $\alpha\alpha$	39.2 ± 2.3 δ	32.8 ± 1.6***/ $\alpha\alpha\alpha$	31.4 ± 2.2 β
Incongruent task	50.7 ± 2	43.9 ± 1.9*	34.8 ± 1.3***/ $\alpha\alpha\alpha$	33.3 ± 2.3***/ $\alpha\alpha$	40.4 ± 2.1 δ	34 ± 2.1***/ $\alpha\alpha$	36.1 ± 3.1
d2 test							
TR	395.6 ± 15.7	330 ± 13.5**	257.4 ± 15.3***/ $\alpha\alpha$	283.1 ± 20.4***	317.1 ± 19.3 δ	214.1 ± 25.4***/ $\alpha\alpha\alpha/\beta$	240 ± 21.9 $\beta\beta$
TA	145.1 ± 8.8	122.5 ± 6.8	87.4 ± 6.4***/ $\alpha\alpha$	94.4 ± 7.7**	114.4 ± 9 δ	74.5 ± 12.9***/ $\alpha\alpha$	89.9 ± 10.8 β
O	15.2 ± 3.3	13.9 ± 2.1	22.1 ± 4	26.4 ± 7.2	18.5 ± 5.7	16.3 ± 4	11.6 ± 2.8
C	2.5 ± 0.9	4.2 ± 1.4	8.3 ± 2.4	9.2 ± 4.1	5.1 ± 2.8	11 ± 4.1	5.5 ± 2.4
TOT	372.2 ± 18.7	304.3 ± 15.2*	227.9 ± 14.9***/ $\alpha\alpha$	247.5 ± 18.7***	293.7 ± 19.4 δ	189.2 ± 27.9***/ $\alpha\alpha/\beta$	222.9 ± 24.8 β
CON	145.6 ± 7.1	119 ± 7.3	79.1 ± 7.5***/ $\alpha\alpha\alpha$	85.2 ± 10.5***/ α	109.3 ± 10.4 δ	63.5 ± 14.3***/ $\alpha\alpha\alpha$	84.4 ± 12.4
Oral SDMT Test							
Correct pairing	51 ± 1.5	38.8 ± 1.6***	23.5 ± 1.8***/ $\alpha\alpha\alpha$	26.9 ± 3.1***/ $\alpha\alpha\alpha$	33.6 ± 2.4 $\delta\delta$	18.9 ± 2.4***/ $\alpha\alpha\alpha/\beta$	19.8 ± 2.4 $\beta\beta\beta$
Scaled score	13.3 ± 0.4	10.2 ± 0.4***	7.3 ± 0.4***/ $\alpha\alpha\alpha$	7.3 ± 0.8***/ $\alpha\alpha\alpha$	9.0 ± 0.5 $\delta\delta$	7.0 ± 0.6***/ $\alpha\alpha\alpha$	7.0 ± 0.6 $\beta\beta$
Errors pairing	0.5 ± 0.2	1.3 ± 0.3*	1.5 ± 0.3**	1.3 ± 0.3*	1.8 ± 0.4	1.9 ± 0.6	1.3 ± 0.4
Total pairing	47.2 ± 4.3	40.1 ± 1.6	25 ± 1.7***/ $\alpha\alpha\alpha$	28.2 ± 3.1***/ $\alpha\alpha$	35.4 ± 2.3 $\delta\delta$	20.8 ± 2.5***/ $\alpha\alpha\alpha/\beta$	21.1 ± 2.4 $\beta\beta\beta$
Digit span test							
Digits forward	9.9 ± 0.6	7.9 ± 0.4**	6.6 ± 0.3***/ α	6.8 ± 0.3***	7.4 ± 0.6	6 ± 0.5***/ α	6.7 ± 0.5
Digits backward	6.8 ± 0.5	4.5 ± 0.3***	3.9 ± 0.3***	3.9 ± 0.5***	5.2 ± 0.7 δ	3.6 ± 0.3***	4 ± 0.4
Digits total	16.7 ± 0.9	12.4 ± 0.5***	10.5 ± 0.6***	10.8 ± 0.7***	12.6 ± 1.3 δ	9.6 ± 0.7***/ α	10.7 ± 0.8 δ
Number-letter test	9.1 ± 0.6	7.4 ± 0.5	5.4 ± 0.5***/ $\alpha\alpha$	6.1 ± 0.8**	6.2 ± 0.9	4.4 ± 0.7***/ $\alpha\alpha$	4.6 ± 0.7
Coordination test							
Bimanual	2.1 ± 0.1	2.3 ± 0.1*	3.5 ± 0.2***/ $\alpha\alpha\alpha$	3.1 ± 0.2**/ $\alpha\alpha$	2.9 ± 0.2	3.9 ± 0.5**/ α	3.6 ± 0.3 β
Visuo-motor	2.4 ± 0.1	2.8 ± 0.1***	4.0 ± 0.2***/ $\alpha\alpha\alpha$	3.5 ± 0.2***/ $\alpha\alpha$	3.4 ± 0.2	4.4 ± 0.4***/ $\alpha\alpha/\beta$	4.4 ± 0.4 β

Values are the mean ± SEM. Values significantly different from the control are indicated by an asterisk (*), from NMHE patients by α , from responder patients by β and from patients before treatment by δ (*/ $\alpha/\beta/\delta$ p<0.05; **/ $\alpha\alpha/\beta\beta/\delta\delta$ p<0.01; ***/ $\alpha\alpha\alpha/\beta\beta\beta/\delta\delta\delta$ p<0.001). NMHE, patients without minimal hepatic encephalopathy; MHE, patients with minimal hepatic encephalopathy; R0/R6, responder patients before and after treatment; NR0/NR6, non-responder patients before and after treatment; PHES, psychometric hepatic encephalopathy score; TR, total responses; TA, total right answer; O, omission errors; C, commission errors; TOT, effectiveness index; CON, concentration index; SDMT, symbol digit modalities test (oral version).

Table S2. Plasma inflammatory parameters of control subjects and cirrhotic patients at baseline and follow-up according to their response to rifaximin treatment.

Inflammatory parameters	Control	Cirrhotic patients		MHE patients treated with rifaximin			
		NMHE	MHE	R0	R6	NR0	NR6
IL-6 ^a	1.3 ± 0.2	2.4 ± 0.3	2.9 ± 0.6	2.9 ± 0.5**	2.0 ± 0.4	3.2 ± 1.4	2.2 ± 1.4
IL-18 ^a	197.7 ± 33.2	387.4 ± 36**	445 ± 72.5**	441.1 ± 83.3**	493.3 ± 91.9	503.1 ± 147.7	641.5 ± 289.6
IL-13 ^a	1.4 ± 0.9	3.8 ± 1.6	3.3 ± 0.8	3.8 ± 1.6	3.1 ± 1.6	1.9 ± 0.4	1.4 ± 0.3
CCL20 ^a	6.7 ± 1.4	20.1 ± 2.9**	39.3 ± 8.9**	32 ± 7.3*	38.4 ± 8.2	34.7 ± 13.8	23.5 ± 8.6
IL-22 ^a	27.5 ± 2.9	34.8 ± 4.4	82.8 ± 15.1**/α	77.5 ± 17.1*	91.5 ± 16.1	101.2 ± 33.1	87.2 ± 17.5
TGF-β ^b	115.2 ± 24.9	96.5 ± 17.8	111.5 ± 17.1	114.0 ± 30.8	100.3 ± 44.8	117.2 ± 21.2	44.4 ± 15
CX3CL1 ^a	305.2 ± 64.4	335.2 ± 30	716.8 ± 57.4**/ααα	750.7 ± 70.6**/ααα	726.6 ± 72	715 ± 107.5*/α	733.1 ± 121.6
CCL2 ^a	11.6 ± 2.4	11.5 ± 2.1	54.4 ± 15.4*/α	65.1 ± 27.3	8.7 ± 1.7 ^δ	51.7 ± 22.7	13.1 ± 2.9

Values are the mean ± SEM. ^a pg/mL; ^b ng/mL. Values significantly different from control are indicated by an asterisk (*), from NMHE patients by ^α and from patients before treatment by ^δ (*/*α/δ p<0.05; ** p<0.01; ***/ααα p<0.001). NMHE, patients without minimal hepatic encephalopathy; MHE, patients with minimal hepatic encephalopathy; R0/R6, responders before and after treatment; NR0/NR6, non-responders before and after treatment; IL, interleukin; CCL20, C-C Motif Chemokine Ligand 20; TGF-β, transforming growth factor-β; CX3CL1, C-X3-C motif chemokine ligand 1; CCL2, C-C motif chemokine ligand 2.

Table S3. Plasma NfL levels in control subjects and cirrhotic patients according to cirrhosis etiology.

	Control	Cirrhotic patients		
		HBV/HCV	Alcohol	NASH
Total group	11.6 ± 0.5	10.5 ± 0.9	15.2 ± 1.4*/ε	19.5 ± 4.1
NMHE	-	9.2 ± 0.8	12.9 ± 1.0 ^ε	11.7 ± 4.4
MHE	-	11.4 ± 1.4	17.5 ± 2.5*/ε	21.4 ± 4.9

Values are expressed in pg/ml and are the mean ± SEM. Values significantly different from the control are indicated by an asterisk (*) and from HBV/HCV etiology patients by ^ε (*/*ε p<0.05). PHES, psychometric hepatic encephalopathy score; NMHE, patients without minimal hepatic encephalopathy; MHE, patients with minimal hepatic encephalopathy; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis.