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Supplementary Information

Detailed MRI methods

MR Single-voxel Spectra from two sites were used in the study: Site 1: 1.5T GE Signa (Milwaukee, WI, USA) and Site 2: 1.5T Siemens Avanto (Erlangen, Germany). High-resolution T1-weighted images were acquired using magnetization-prepared rapid gradient echo (MPRAGE) sequence: TR=1800ms, TE=3ms, TI=1100ms, NEX=1, $1 \times 1 \times 1 mm^3$ in-plane resolution; for voxel-based morphometry and localization of spectroscopic volumes of interest (VOI). Spectroscopic volumes were prescribed for right posterior white matter (RPWM), posterior gray matter (PGM) and anterior cingulate cortex (ACC). All spectroscopy protocols were performed using a point resolved spectroscopy (PRESS) pulse sequence (TE/TR/NS/Volume = $35/1500/128/8 cm^3$) with automated shimming and water suppression. Outer-volume suppression bands contiguous with the PRESS-selected volume were manually placed in all three dimensions. Creatine (Cr), myo-inositol (mI) and glutamate+glutamine (Glx) complex peak areas were computed among other metabolites, using a quantitative assessment of the metabolite concentration by means of LCModel software [1, 2]. Concentration ratios were computed with respect to creatine. Ratios to an internal reference such as Cr greatly reduces the effect of arbitrary inter-scan signal variations. LCModel utilizes a basis set of reference *in vitro* MR spectra for all major metabolites to deduce absolute concentrations of corresponding compounds from *in vivo* MR brain spectra. The model corrects for residual eddy current and RF coil loading effects and allows for an estimate and subtraction of the spectral baseline nonlinearity which is normally present at the short echo time (TE) used in this study. This quantification method enables the combination of metabolite concentration ratios acquired from different sites in an analysis, as long as the acquisition protocol is the same. Details of the method and reproducibility of the technique are described by Provencher et al. (10-11)

Diffusion tensor images were acquired using a single shot, spin-echo echo-planar imaging sequence (FOV=240mm, slice thickness=2.5mm, 96 x 96 matrix, TR =6800ms, TE=100ms, b-value=$1000s/mm^2$, # b0 images = 3, # Diffusion Directions = 30, 3 averages). Only DTI images for patients scanned at Site 2 were used for analysis due to the relatively large sample size of patients scanned at that site and because inter-site reproducibility measures were not observed for DTI imaging.

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<u>Voxel-based morphometry</u>: First, structural images were brain-extracted and gray matter-segmented before being registered to the MNI 152 standard space using non-linear registration. The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific gray matter template. Second, all native gray matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated gray matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm. Finally, voxelwise GLM was applied using permutation-based non-parametric testing, correcting for multiple comparisons across space.

Supplementary references:

1. Provencher SW. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magn Reson Med 1993;30:672-9.
2. Provencher SW. Automatic quantitation of localized in vivo 1H spectra with LCModel. NMR Biomed 2001;14:260-4.
3. Jenkinson M, Bannister P, Brady M, et al. Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 2002;17:825-841.
4. Smith SM. Fast robust automated brain extraction. Human brain mapping 2002;17:143-155.
5. Woolrich MW, Ripley BD, Brady M, et al. Temporal autocorrelation in univariate linear modeling of FMRI data. NeuroImage 2001;14:1370-1386.
6. Westin CF, Maier SE, Mamata H, et al. Processing and visualization for diffusion tensor MRI. Med Image Anal 2002;6:93-108.
7. Wakana S, Caprihan A, Panzenboeck MM, et al. Reproducibility of quantitative tractography methods applied to cerebral white matter. Neuroimage 2007;36:630-44.
8. Hua K, Zhang J, Wakana S, et al. Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. Neuroimage 2008;39:336-47.

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Supplementary Table 1: <u>VBM results;</u> Localisation and z-scores of gray matter regions with lower density in alcoholic cirrhosis group as compared to non-alcoholic cirrhotics as revealed by Voxel-based morphometry. (Permutation-based inference, Cluster-forming threshold z=2.7 p<0.05)

Location	Hemisphere	Voxels	MAX z-score	MAX X (mm)	MAX Y (mm)	MAX Z (mm)
Superior Frontal Gyrus	L	349	4.34	-18	36	32
Anterior Cingulate Gyrus		293	4.1	-8	34	14
Middle Frontal Gyrus	R	251	3.75	32	28	38
Middle Frontal Gyrus	L	230	4.35	-36	8	44
Anterior Cingulate Gyrus		117	3.84	-2	10	30
Precentral Gyrus	L	109	4.28	-50	6	12
Sup Frontal Gyrus	R	54	3.82	16	24	44
Inferior Frontal gyrus	R	13	3.37	38	12	20
Central Opercular cortex	R	10	3.38	48	-2	14
Postcentral Gyrus	L	7	3.34	-16	-34	62

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Supplementary Table 2: <u>TIPS MRS results</u>; Overall there was an increase in Glx and decrease in mI after TIPS. These differences appear significantly less in the Alc group possibly because of their limited brain reserve to tolerate TIPS related insult.

	Alc+Nalc		Alc		Nalc	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
RPWM Glx	2.776	3.257*	2.983	3.260	2.402	3.253*
RPWM mI	0.431*	0.173	0.352*	0.157	0.609*	0.193
PGM Glx	2.932	2.807	3.131	3.062	2.634	2.552
PGM mI	0.402*	0.312	0.343	0.388	0.491*	0.236

*p<0.05 Pre vs. Post TIPS within each group.

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Supplementary Table 3: <u>Follow-up study results;</u> Brain metabolite ratios (/Cr) did not change significantly after 1 year follow-up, although metabolite ratios were worse in Alc compared to Nalc in both visits.

	Right Parietal White Matter			Posterior Gray Matter			Anterior Cingulate Cortex		
	Cho	Glx	ml	Cho	Glx	ml	Cho	Glx	ml
Visit 1	0.267	2.589	0.516	0.188	2.707	0.527	0.247	3.169	0.575
Visit 2	0.273	2.380	0.606	0.199	2.722	0.737	0.263	2.964	0.613
Alc Visit 1	0.240	2.873	0.393	0.175	3.064*	0.340	0.238	3.525	0.432
Nalc Visit 1	0.289	2.361	0.615	0.198	2.427	0.674**	0.251	3.005	0.641
Alc Visit 2	0.273	2.821*	0.426	0.128	3.268*	0.487	0.246	3.453*	0.439
Nalc Visit 2	0.274	2.012	0.756*	0.239*	2.410	0.881*	0.274	2.614	0.737*

*$p<0.05$ **$p<0.005$ Alc vs. Nalc (for each visit)