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Enhancement of Functional Connectivity, Working Memory and Inhibitory Control on Multi-modal Brain MR Imaging with Rifaximin in Cirrhosis: Implications for the Gut-Liver-Brain Axis

Vishwadeep Ahluwalia, PhD^{1,2}, James B Wade, PhD³, Douglas M Heuman, MD², Thomas A Hammeke, PhD⁴, Arun J Sanyal, MD², Richard K Sterling, MD², R. Todd Stravitz, MD², Velimir Luketic, MD², Mohammad S Siddiqui, MD², Puneet Puri, MD², Michael Fuchs, MD², Micheal J Lennon, MD¹, Kenneth A Kraft, PhD¹, HoChong Gilles, NP², Melanie B White, RN², Nicole A Noble, RN², and Jasmohan S Bajaj, MD²

¹Radiology, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA

²Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA

³Psychiatry, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA

⁴Psychiatry, Medical College of Wisconsin, Milwaukee, WI

Abstract

Objective—Minimal hepatic encephalopathy (MHE) impairs daily functioning in cirrhosis, but its functional brain impact is not completely understood.

Aim—To evaluate the effect of rifaximin, a gut-specific antibiotic, on the gut-liver-brain axis in MHE.

Hypothesis—Rifaximin will reduce endotoxemia, enhance cognition, increase activation during working memory(N-back) and reduce activation needed for inhibitory control tasks.

Methods—Cirrhotics with MHE underwent baseline endotoxin and cognitive testing, then underwent fMRI, diffusion tensor imaging and MR spectroscopy(MRS). On fMRI, two tasks; N-back (outcome: correct responses) and inhibitory control tests(outcomes: lure inhibition) were performed. All procedures were repeated after 8 weeks of rifaximin. Results were compared before/after rifaximin.

Results—20 MHE patients (59.7 years) were included; sixteen completed pre/post-rifaximin scanning with 92% medication compliance. Pre-rifaximin patients had cognitive impairment. At trial-end, there was a significantly higher correct 2-back responses, ICT lure inhibitions and reduced endotoxemia(p=0.002). This was accompanied by significantly higher activation from baseline in subcortical structures (thalamus, caudate, insula and hippocampus) and left parietal operculum (LPO) during N-back, decrease in fronto-parietal activation required for inhibiting lures, including LPO during ICT compared to baseline values. Connectivity studies in N-back

showed significant shifts in linkages after therapy in fronto-parietal regions with a reduction in fractional anisotropy (FA) but not mean diffusivity (MD), and no change in MRS metabolites at the end of the trial.

Conclusion—A significant improvement in cognition including working memory and inhibitory control, and fractional anisotropy without effect on MD or MRS, through modulation of fronto-parietal and subcortical activation and connectivity was seen after open-label rifaximin therapy in MHE.

INTRODUCTION

Minimal hepatic encephalopathy (MHE) is a prevalent neuro-cognitive disorder in cirrhosis that affects daily functioning due to impairment in working memory, inhibitory control and psychomotor speed and is an important issue for clinical and patho-physiological research of the gut-brain-liver axis.(Ortiz et al. 2005; Bajaj et al. 2009), (Weissenborn et al. 2005; Amodio et al. 2004) Altered activation of fronto-parietal structures is associated with working memory and inhibitory control impairment but the effect of rifaximin, a non-absorbable and gut-specific antibiotic effective in MHE, on activation, connectivity and associated cognitive improvement is unclear and could serve as a model for studying the gut-liver-brain axis(Zafiris et al. 2004; Sidhu et al. 2011; Bajaj et al. 2011). Therefore a better understanding how the cognitive impairments in MHE change with therapy will improve insight into treatment targets.

Aims and Hypotheses

We aimed to evaluate the effect of MHE treatment with rifaximin on brain function using several methodologies (i) fMRI activation during a working memory (N-back) and an inhibitory control task (inhibitory control test (ICT))(Garavan et al. 1999), (ii) white matter tract integrity and brain edema using diffusion tensor imaging (DTI) and (iii) change in cerebral metabolites using MR spectroscopy (MRS).

The *a priori* hypothesis was that MHE therapy will result in overall cognitive improvement accompanied by an increased brain activation in specific fronto-parietal regions to increase correct N-back responses, a reduction in activation needed to achieve the inhibitory control on ICT, improved white matter integrity and brain edema on DTI, and a reduction in glutamate+glutamine and increase in myoinositol on MRS.

METHODS

Overall design

We included cirrhotic patients with MHE diagnosed using a recommended cognitive battery [2 abnormal compared to local healthy controls, number connection test A and B, Digit symbol and Block Design] within 3 months of the trial(pre-baseline)(Ferenci et al. 2002). Other tests administered at the pre-baseline were line tracing test (has two outcomes; errors and time), serial dotting and ICT (two outcomes; lures and targets). Cirrhosis was diagnosed through biopsy, radiological evidence or endoscopic evidence of varices. Patients on psychoactive medications other than anti-depressants, alcohol/illicit drug use within 6

months, those with TIPS placement or on medications for HE, were excluded. This paper describes the change in N-back, ICT testing with fMRI, MRS and fractional anisotropy (FA) and mean diffusivity (MD) changes with DTI; microbiome and metabolomic effects of rifaximin have been previously published (Bajaj et al. 2013). For the first visit, we re-administered all cognitive tests to account for any learning effect and ensure a similar degree of familiarity with tasks. If subjects still had MHE, two additional tests, and rifaximin 550mg PO BID was prescribed for 8 weeks. At week 8, all 6 tests were repeated using different versions (apart from Block design test which had one version) (Weissenborn et al. 2001). MELD score (validated measure of cirrhosis severity with bilirubin, INR and creatinine) (Kamath et al. 2001), endotoxin, serum sodium and venous ammonia were checked at baseline and week 8. Adherence was assessed at week 8 by the percentage of pills returned.

N-back and ICT tasks

While ICT was administered outside the scanner during pre-baseline, during the trial it was administered in the scanner. N-back was administered for the first time during the trial itself. Both tasks were administered in the scanner following a training run. During a single run of the N-back task, subjects were required to respond to 0-back, 1-back and 2-back conditions. Six runs of the ICT required the subjects to respond to targets and inhibit lure responses (supplementary information).

MR Imaging Methods and analyses (supplementary information)

We acquired whole-brain anatomical images, fMRI for ICT and N-back tasks, DTI and MRS on a 3T GE Signa (Milwaukee, WI) using a quadrature head coil. We used FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk) for all imaging analyses (Smith et al. 2004). fMRI analyses included standard preprocessing followed by time-series statistical analyses with local autocorrelation correction using the General Linear Model (GLM). For ICT, the model included correct/incorrect responses to lures and targets as regressors of interest and six motion parameters as confound regressors. Contrasts for each regressor vs. baseline were created and registered to MNI standard space template. The contrasts were combined over six runs using fixed effects analysis within subject.

Functional MRI analysis

N-back time-series statistical analyses was done using 0-back, 1-back, 2-back and six motion parameters as regressors. We created (1-back–0-back) and (2-back–0-back) contrasts and registered these to standard space. Using mixed effects analysis, a paired group comparison was done at the next level to investigate brain areas with significant changes in activation to correct inhibition for ICT and (2-back–0-back) for the N-back task following rifaximin. Pre>Post and Post>Pre z-statistic images were thresholded using a cluster-based thresholding method with $z > 1.8$ and $p < 0.05$. Psychophysiological Interaction (PPI) analysis was done for N-back task to investigate any changes in effective connectivity between a seed region in the white matter network and other areas as a result of rifaximin. Right and Left Inferior Frontal Gyri (IFG) and Precentral Gyrus were used as seed points and mean time-series were extracted and entered into separate PPI analyses. Pre>Post and Post>Pre-Rifaximin contrasts for each PPI analysis were computed at the group level and

the z-statistic images were thresholded using a cluster-based thresholding method with $z > 1.8$ and $p < 0.05$.

Diffusion Tensor Imaging analysis

Diffusion-weighted volumes were acquired using a single shot, spin-echo echo-planar imaging sequence. Fractional Anisotropy (FA) and Mean Diffusivity (MD) maps were computed using the diffusion Toolbox in FSL and registered to standard MNI template. Twelve *a priori* ROIs for major white matter tracts were created using the DTI-based probabilistic white matter atlases and mean FA and MD values were extracted from individual maps (Wakana et al. 2007; Hua et al. 2008).

MR spectroscopy analysis

Brain spectra were analyzed using LCModel software (Provencher 1993, 2001). Choline, myo-Inositol and Glutamate+Glutamine creatine ratios were computed in three areas; anterior cingulate cortex (ACC), RPWM (right parietal white matter) and posterior gray matter (PGM).

Statistical analysis and sample size

Cognitive (including N-Back and ICT responses in the scanner), MELD and other laboratory values were compared between patients before and after rifaximin using paired t-tests and Chi-square and Fisher's exact test as applicable. Pre-baseline cognitive testing was also compared to baseline using paired t-tests. In our prior study in which we found a change in brain spectroscopy in 7 advanced cirrhotics (Bajaj et al. 2012); we anticipated 15 patients would be adequate to detect MRI changes in this compensated population.

Ethics statement

The study was approved by the McGuire VA Medical Center Institutional Review Board. Written informed consent was obtained from all participants. The trial is registered at www.clinicaltrials.gov NCT01069133.

RESULTS

Rifaximin trial

We included 20 right-handed patients, 14 men and 6 women (age 59.7 ± 3.5 years, 14 ± 1.7 years education, 70% Caucasian and 30% African-American, Figure 1). The predominant etiology was hepatitis C (7, 35%), by alcohol+hepatitis C (4, 20%), non-alcoholic steatohepatitis (4, 20%), alcohol (3, 15%) and others (2, 10%). None of the patients were on HE therapy and had ever had HE. The overall medication adherence was 92% and 16 were able to complete the scanning (3 were claustrophobic and one stopped the scan early). There was a significant improvement in serum bilirubin and endotoxin after rifaximin. Compared to the pre-baseline, there was a statistically insignificant improvement in cognitive performance on baseline (supplementary table 1). All cognitive tests, apart from Block Design, 0/1-back, and ICT targets improved after rifaximin at the second assessment (Table 1).

fMRI analysis (N-back)

Working memory load effects—Since our behavioral data primarily showed a significant difference in the 2-back state, we concentrated our voxel-based analysis on this state. There were widespread voxel activations through several cortical and sub-cortical regions across the fronto-temporal lobes. There was bilateral representation of the middle frontal gyrus, thalamus and pallidum (Supplementary table 2 and figure 2A).

Effect of rifaximin on 2-Back—Several cortical (left parietal operculum (LPO), temporal occipital fusiform, right temporal pole and bilateral insular) and subcortical (caudate, thalamus and hippocampus) regions were found to have a significantly higher activation after rifaximin compared to pre-rifaximin scans (Figure 2/Table 2).

Psychophysiological Interaction—Spherical ROIs of 8mm radius were drawn voxels in the left IFG (MNI -46,18,22), right IFG (MNI 54, 20, 14), left Precentral Gyrus (MNI -46,6,32) and right Precentral Gyrus (MNI 50,10,32).

Left IFG seed—Left Superior Frontal Gyrus ($Z=2.69$) and Left Frontal Pole ($Z=2.79$) exhibited higher effective connectivity with the seed region in the pre-rifaximin compared to the post-rifaximin state (Figure 3). LPO ($Z=2.45$) and Left Postcentral Gyrus ($Z=2.34$) exhibited higher effective connectivity with the seed region in the post-rifaximin compared to the pre-rifaximin state.

Right IFG seed—No significant difference in effective connectivity with Right IFG was found.

Left Precentral Gyrus seed—Left Supramarginal Gyrus ($Z=2.46$) and Left Frontal Pole ($Z=2.43$) exhibited higher effective connectivity with the seed region in the pre-rifaximin compared to the post-rifaximin state. LPO ($Z=2.33$) and Left Frontal Operculum ($Z=2.59$) exhibited higher effective connectivity with the seed region in the post-rifaximin compared to the pre-rifaximin state.

Right Precentral Gyrus seed—Right Superior Frontal ($Z=2.44$) and Left Supplementary motor areas ($Z=2.61$) exhibited higher effective connectivity with the seed region in the pre-rifaximin compared to the post-rifaximin state but again, post-rifaximin the LPO ($Z=2.76$) exhibited higher effective connectivity with the seed region in the post-rifaximin compared to the pre-rifaximin state.

fMRI analysis (Inhibitory control)

Effect of inhibitory control—Main effect of inhibition across rifaximin states ($n=32$), revealed widespread activation in areas within the supplementary motor area, dorsolateral prefrontal, paracingulate, posterior cingulate, precuneous and posterior parietal cortical regions (Supplementary Table 2/Figure 2B).

Effect of rifaximin on ICT—Significant differences in activation between pre and post-rifaximin states were seen (Figure 2/Table 2). There was a significantly higher activation in

the inferior frontal gyrus, middle frontal gyrus, frontal pole, pre and postcentral gyrus and insular cortex pre-rifaximin than in the post-rifaximin state during correct inhibition. No brain region showed higher activation post-rifaximin compared to the pre-rifaximin state.

Diffusion Tensor Imaging

Paired t-tests revealed significant effect of rifaximin on mean FA in five ROIs; left Frontal White Matter [$FA_{pre}=0.364\pm0.03$, $FA_{post}=0.371\pm0.03$; $p=0.041$], left External Capsule [$FA_{pre}=0.363\pm0.011$, $FA_{post}=0.367\pm0.015$; $p=0.046$], left Inferior Longitudinal Fasciculus [$FA_{pre}=0.449\pm0.032$, $FA_{post}=0.467\pm0.034$; $p=0.05$], right Inferior Longitudinal Fasciculus [$FA_{pre}=0.442\pm0.025$, $FA_{post}=0.456\pm0.03$; $p=0.019$] and left Cingulum [$FA_{pre}=0.433\pm0.032$, $FA_{post}=0.442\pm0.026$; $p=0.044$] (figure 4). There were no significant corresponding changes in mean MD values (Supplementary Table 3).

MR Spectroscopy

Only those spectra with linewidth $< 10\text{Hz}$ during prescan autoshim were considered for analysis. Furthermore, metabolite ratios from LCModel were rejected in the case where %SD (Cramer-Rao inequality) was greater than 20%. One patient could not complete the spectroscopy scans for any volume of interest (VOI). Another patient's spectra for the ACC VOI could not be acquired due to scanner issues. LCModel analysis revealed %SD of Cho/Cr and Glx/Cr ratios for all spectra were $<20\%$ i.e. these ratios were reliably detected. However %SD for mI/Cr ratios were $>20\%$ in 9 out of 34 total spectra for RPWM, 4 out of 34 total spectra for PGM and 5 out of 32 total spectra for the ACC VOI, and hence these ratios and their respective post-rifaximin pairs were excluded from the statistical analysis. We found no significant changes or trends in any metabolite ratios in any VOI between pre- and post-rifaximin states (Supplementary table 4).

DISCUSSION

We found that therapy of MHE with rifaximin is associated with improved cognition, working memory performance on an N-back task and inhibitory control in MHE patients. On N-back fMRI analysis, there was a significantly higher LPO and subcortical activation without significant differences in the traditional "N-back" regions. However, the PPI analysis seeded from the traditional N-back regions (left inferior frontal, right and left precentral gyri), showed a significant change in connectivity, from predominantly frontal regions at baseline, towards the parietal regions, with the LPO being significantly more coupled with all three seed regions after therapy. The improvement in ICT suggests lesser neuronal recruitment is required at the end of the trial to achieve the same control of the lure response. While there was a reduction in FA, no change on MD or MRS was observed.

Impaired working memory and inhibitory control negatively impacts daily functioning in MHE patients and is associated with poor driving skills, falls and a lower socio-economic status (Liao et al. 2012). The N-back task requires volunteers to constantly monitor inputs and update information in their working memory to respond appropriately; a variation of this, the Scan test, has been validated to diagnose MHE (Amodio et al. 2004). We found that there was a decrease in accuracy of responses on N-back as the cognitive load increased.

Accuracy in the difficult 2-back state significantly improved at the end of the trial and was accompanied by enhanced performance in most paper-pencil tests which span several cognitive domains. Paralleling this was a significant increase in correct lure inhibition using behavioral analysis. This pattern parallels prior placebo-controlled trials of rifaximin therapy (Sidhu et al. 2011; Bajaj et al. 2011). We found that only the 2-back state improved; likely due to the less challenging nature of the 0 and 1-back states, thereby producing a ceiling effect. This was accompanied by a differential activation of structures in the 2-back state compared to baseline. While there was an activation of both fronto-parietal regions involved in working memory before and after treatment, there was no significant activation of the important sub-cortical structures that form the prefrontal – subcortical circuit during the baseline scan (Pardo et al. 1991; Grahn and Manly 2012). In prior N-back studies, the prefrontal cortex (represented by the inferior and middle frontal gyri), anterior cingulate and basal ganglia (subcortical) structures have consistently shown activation indicating this is a common network responding to working memory demands (Zhang et al. 2007). Subcortical structures like the basal ganglia are involved in executive dysfunction, have been implicated in cirrhosis-related cognitive dysfunction and extra-pyramidal abnormalities (Tryc et al. 2012) and have important “gating” functions in visual working memory (Frank et al. 2001). Our results reflect this complementary relationship with the activation of basal ganglia at the end of the trial with activation of bilateral prefrontal cortical regions. These findings extend prior studies in cirrhosis that have evaluated alteration in the resting-state network connectivity, during Stroop tasks and critical flicker frequency between basal ganglia, thalamus and prefrontal cortex pre and post-treatment and underscore the need for appropriate subcortical activation to achieve optimum 2-back performance. (Zafiris et al. 2004; Zhang et al. 2007; Zhang et al. 2012a)

Interestingly, though there were significant improvements on the 2-back task, voxel-wise activations in the traditional fronto-parietal N-back regions did not change. However on PPI analysis, the “traditional” N-back areas showed significant connectivity changes from a pre-rifaximin frontal, to a post-rifaximin parietal predominance. We found that LPO had the highest activation at trial end on voxel-based analysis and had the highest connectivity with three traditional N-back seed areas; left inferior frontal and left and right pre-central gyri, on PPI analysis. The left operculum, especially fronto-parietal, is involved in verbal processing and forms the principal memory storage area for verbal working memory or the phonological buffer). Left and right opercula have been associated with the performance of both verbal and spatial working memory tasks (Cohen et al. 1997; Petrides et al. 1993; Owen et al. 1996). Therefore, it is not surprising that the LPO plays a crucial role in N-back and is likely part of a robust fronto-parietal network mediating working memory. (Pandya and Selzer 1982; Cavada and Goldman-Rakic 1993), (Klingberg et al. 1997)

The increased activation in three other areas at the end of the study; the left and posterior aspect of the hippocampus, the left temporal occipital fusiform cortex and the right temporal pole, is intriguing. The fusiform cortex helps identify patterns or lack of patterns when letter strings are presented; as in our letter-based N-back task. Activation in this region has been shown to be affected in MHE using Stroop tasks (Zhang et al. 2007). Therefore, the identification of potential patterns in the letters could be a strategy employed to assess correct responses and improve performance on the N-back task. The temporal pole is

involved in semantic processing(Griffith et al. 2006; Helmstaedter et al. 2008) while the role of the hippocampus in short-term and working memory is recognized(Leszczynski 2011). Therefore the activation of these areas would facilitate successful 2-back responses.

This predominant effect on fronto-parietal structures was also demonstrated when the ICT analysis of successful lure inhibitions was performed. Using behavioral analysis, only lure inhibitions improved given the already high correct targets in this highly compensated population. We expected patients to require less activation to achieve the same correct lure response after the trial, which indeed was observed in fronto-parietal regions (especially prefrontal cortex and insula) mediating the inhibitory control network without involvement of subcortical structures. This change in activation had two clusters within either hemisphere; right frontal and mostly parietal on the left side, including the LPO. Since the ICT is also processed verbally given the alphabets, it is not surprising that the left cluster is involved. The right sided change replicates Garavan *et al*'s ICT study reflecting the right-sided dominance of inhibitory control that is enhanced after this trial (Garavan et al. 1999).

We found a significant increase in FA but no change in MD after therapy. This is interesting because different studies have shown varying results regarding FA and MD in differentiating minimal or overt HE patients from controls(Zhang et al. 2012b; Sugimoto et al. 2008). While FA demonstrates white matter microstructural integrity, MD is a measure of interstitial brain edema; an increased FA without MD change would imply intracellular or cytotoxic edema correction. Therefore our results indicate that an improvement in white matter integrity throughout a wide range of brain structures without any change in MRS metabolites in the VOIs chosen for this study after rifaximin. This replicates the findings of McPhail *et al* using open-label L-ornithine-L-aspartate (LOLA) in MHE(McPhail et al. 2013). Lactulose therapy for MHE, using another open-label design, however, has shown to increase choline and decrease glutamine+glutamate and also affect MD but not FA in prior studies(Jain et al. 2013; Kale et al. 2006). This potentially points to a difference in mechanism of action of LOLA and rifaximin compared to lactulose that may only be apparent on brain imaging but could also reflect the insensitivity of this field strength to detect subtle MRS changes.

We hypothesize that the metabolic changes associated with MHE disrupt neural connectivity and rifaximin, perhaps by modulating gut bacteria and reducing systemic endotoxemia, affects the gut-brain axis which facilitates activation of particular brain regions, enhances cortico-cortical and subcortical-cortical connectivity, and improves white matter integrity, (Bajaj et al. 2013). Our study is limited by the lack of a placebo group and the open-label design which remains a limitation of several prior MHE MRI studies (McPhail et al. 2013, Jain et al. 2013). It is however possible that being in a trial could improve outcomes and that learning effect could improve test performance after not being present between the pre-baseline/baseline testing. We tried to ameliorate this by administering different test versions, comparing patients to a pre-baseline performance and indeed found improvement on all tests except block design test. We did not use an alternate version of the block design test, which would have improved if it were a learning-associated improvement. There was also a biochemical improvement in serum bilirubin and reduction in endotoxemia which point towards the potential of a learning-independent mechanism of these findings. Regardless of

the mechanism of improvement our data showed an associated of enhanced cognition with improved multi-modal MRI findings after this trial. The current trial also provides a proof-of-concept for gut-liver-brain axis modulation in future, placebo-controlled trials in MHE utilizing brain MR imaging.

We conclude that there was a significant improvement in working memory performance via facilitation of the functioning of subcortical structures, greater inhibitory control by modulation of fronto-parietal activation, and improved white matter integrity in MHE after they received open-label rifaximin. This was associated with an enhanced neural network connectivity between frontal and parietal structures, and in particular facilitation of the left parietal operculum. Further studies using rifaximin in a placebo-controlled manner are required to confirm and extend these results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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CONSORT DIAGRAM FOR THE OPEN-LABEL STUDY OF THE EFFECT OF
RIFAXIMIN ON MULTI-MODAL BRAIN IMAGING IN MINIMAL HEPATIC
ENCEPHALOPATHY

Figure 1.
CONSORT diagram for the trial

Figure 2.

Change in working memory and inhibitory control

(A) Post-Rifaximin>Pre-Rifaximin for 2-back condition; (B) Post-Rifaximin>Pre-Rifaximin for Correct Inhibition to Lures (CIL) condition; all cluster corrected $Z=1.8$, $p<0.05$, color scale representing Z-scores (Red-Yellow), R: right hemisphere.

Figure 3.

Change in functional connectivity during N-back. Psycho-physiological interaction (PPI) analysis for N-back PPI analysis showing differences in effective connectivity for Pre>Post-Rifaximin (Red-Yellow) and Post>Pre-Rifaximin (Blue-Light Blue) for seed areas (Green) left IFG (A), left precentral gyrus (B & C) and right precentral gyrus (D). (cluster corrected $Z=1.8$, $p<0.05$)

Figure 4.

White matter tracts with significant differences in Fractional Anisotropy (FA) between pre and post-rifaximin states. FWM = Frontal White Matter, EC = External Capsule ILF = Inferior Longitudinal Fasciculus, Cing = Cingulum, L/R = Left/Right

Table 1

Changes in cognition and cirrhosis severity during the trial

	Baseline	End-of-Trial
MELD score	9.8±3.3	9.4±3.1
INR	1.2±0.2	1.2±0.2
Serum creatinine (mg/dl)	0.9±0.1	0.9±0.2
Serum bilirubin (mg/dl)	1.3±0.8	1.1±0.7*
Serum sodium (meq/L)	138.1±2.8	138.9±2.7
Venous ammonia	46.2±23.4	42.9±23.1
Serum endotoxin (Eu/ml)	0.55±0.21	0.48±0.24*
Cognitive tests		
Number connection-A (seconds)	42.3±13.4	37.3±8.9*
Number connection-B (seconds)	97.2±31.9	85.7±25.8*
Digit symbol (raw score)	50.0±12.3	55.1±13.9*
Block design (raw score)	25.9±11.9	28.5±9.6
Line tracing time (seconds)	121.7±32.1	96.4±33.1*
Line tracing errors (number)	41.2±28.3	24.8±17.1*
Serial dotting (seconds)	69.6±25.7	61.0±17.3*
Tests during fMRI scanning		
N-back median correct responses		
0-back	16	16
1-back	14	15
2-back	8	10*
ICT median responses		
Lures responded to (n/% CIL)	18 / 56%	13 / 68%*
Targets (% correct)	96.50%	98.10%

* p<0.05 on paired t-test; a higher score on block design and digit symbol while a low score on the rest of the cognitive tests indicates poor performance; a significant improvement in most cognitive tests apart from block design test was seen. There was also a significant reduction in systemic endotoxemia and in serum bilirubin but overall MELD score remained similar. There was a significant increase in the correct responses on 2-back and a significantly higher correct inhibitions to lures compared to baseline. A lower lure response and higher correct inhibition of lures (CIL) on ICT indicates better cognition.

Table 2

Brain areas showing changed activation patterns before and at the end of the trial on N-back and Inhibitory Control tests

N Back: Higher activation during 2-back state post > baseline during N-Back		
Z-score	Localization	MNI (x,y,z) mm
3.74	L Parietal Operculum Cortex	-48, -30, 18
2.87	L Hippocampus	-24, -40, -6
3.40	L Insular Cortex	-32, -24, 10
3.06	L Temporal Occipital Fusiform Cortex	-36, -44, -14
3.90	R Temporal Pole	44, 12, -34
3.43	R Insular Cortex	36, 14, 2
3.10	L Thalamus	-2, -6, 2
2.78	R Caudate	16, 14, 10
ICT: Lower activation during "correct inhibition to lures" state post > baseline		
Z-score	Localization	MNI (x, y, z) mm
<i>Cluster 1 = 3962 voxels</i>		
3.42	R Middle Frontal Gyrus	34, 4, 48
3.35	R Inferior Frontal Gyrus	46, 28, 18
3.1	R Inferior Frontal Gyrus	48, 16, 24
2.83	R Middle Frontal Gyrus	36, 32, 28
2.83	R Frontal Pole	48, 48, -4
2.73	R Frontal Pole	40, 40, 10
<i>Cluster 2 = 2134 voxels</i>		
2.72	L Precentral Gyrus	-44, -12, 52
2.7	L Postcentral Gyrus	-42, -22, 44
2.67	L Insular Cortex	-32, 20, -4
2.66	L Inferior Frontal Gyrus	-42, 18, 22
2.64	L Central Opercular Cortex	-46, 2, 12
2.51	L Frontal Orbital Cortex	-14, 20, -14