SMGroup

Advanced MR Imaging Techniques in Alcoholics Showing No Clinical Evidence of Cognitive Impairment

Namita Singh Saini[1]* and Giriraj Singh Gujral[1]

[1]NMR Research Centre, Institute of Nuclear Medicine and Allied Sciences (INMAS), DRDO, India

***Corresponding author:** Namita Singh Saini, NMR Research Centre, Institute of Nuclear Medicine and Allied Sciences (INMAS), DRDO, India, Email: namita23m@gmail.com

Published Date: May 10, 2016

Alcohol is a common substance of abuse. Consumption of alcohol activates the reward circuitary in the brain compelling individuals to consume more and more alcohol. Prolonged consumption of alcohol is known to have a damaging effect on the brain. There are conflicting reports on the amount and duration of alcohol consumption that leads to cognitive impairment. But it is known that chronic alcohol consumption leads to white and gray matter atrophy leading to volume loss. Advanced Magnetic Resonance Imaging **(MRI)** techniques such as Magnetic Resonance Spectroscopy **(MRS)** and Diffusion Tensor Imaging **(DTI),** functional Magnetic Resonance Imaging **(fMRI)** as well as Positron Emission Tomography **(PET)** have characterised cerebral atrophy, metabolic abnormality, white matter atrophy and reduced glucose metabolism and have correlated their findings with cognitive impairment.

Numerous MRS studies have examined the metabolite ratios of the cortex and some of white matter of the brain in alcoholics. Glucose metabolism of the brain has been studied using PET imaging. The integrity of the white matter tracts has been examined using DTI. Activation of specific areas on performance of predesigned neuropsychological tests to investigate a specific brain function are often correlated with functional neuroimaging studies **(fMRI)** to gain deeper insight into the functioning of the alcoholic brain.

Motor coordination as well as neurocognition are grossly affected by alcohol consumption. Frontal and prefrontal regions of the brain, which are responsible for executive functions, face the brunt of the damaging effect of alcohol. CT and MRI have consistently demonstrated reduction in the volumes of the gray mater and white matter of the fronto-parietal lobes [1], medial temporal lobes, cerebellar cortex [2,3] brain stem [4].

The frontal lobe of the brain is connected to the parietal, temporal and occipital lobes through white matter tracts which send and receive nerve impulses to various subcortical structure, deep gray matter nuclei and the spinal cord. Fronto-parietal network commonly subserve cognitive functions related to perception, memory, language and information processing. Chronic alcoholism is associated with cognitive deficits and impaired visual perception. Frontal and prefrontal regions of the brain are affected in alcoholics resulting in impaired executive functions and blunting of working memory. Understanding the mechanisms that affect the mental capability in chronic alcoholism will be a step forward in understanding the etio-pathogenesis of damage caused by excess alcohol intake. Hence a number of studies have focussed on understanding the changes brought about at macro and microscopic level in the brain due to both acute and chronic consumption of alcohol. Chronic alcohol consumption results in brain atrophy that is most profound in the frontal lobes [5-7]. Studies performed on chronic alcoholics have reported altered cerebral metabolism [8,9] and impaired metabolite ratios in both the gray and white matter of the cerebral hemisphere, cerebellum and brain stem [4,10,11,]. Visual processing functionality is seen to be impaired in chronic alcoholism but their verbal abilities are relatively preserved [12,13]. Visual cortex is thought to participate in perception of form and motion. Physiological studies have demonstrated that a number of visual functions such as visual acuity, contrast sensitivity and motion perception can be impaired by acute alcohol exposure [14]. Fama et al, Modi et al have shown that the impairment in visual processing seen in chronic alcoholics is due to impaired functioning of the visual cortex.

Many researchers have used Diffusion Tensor Imaging to study the integrity of the white matter in the brain of alcoholics since white matter damage is known to precede atrophy in chronic alcoholics. Pfefferbaum and Sullivan in 2002 have found that alcoholism affects the coherence of the microstructure of the white matter which results in deficits in attention and working memory of chronic alcoholics. Bagga et al performed a study on 35 detoxified alcoholics and 35 healthy controls using 3T MRI. Each subject underwent Proton MRS, DTI & fMRI evaluation of their cerebral hemispheres. [15,16]. The investigators correlated the DTI and 1HMRS findings with

the visual processing tasks of the Post graduate Institute Battery of Brain Dysfunction **(PGIBBD)** namely the Bender-Gestalt test, Nahor-Benson test and Koh's block test. The study investigated the extent of white matter damage caused by chronic alcohol consumption on visual information processing tasks. On analysis of the results it was seen that there was an inverse correlation of Fractional Anisotropy **(FA)** values with the raw dysfunction scores of the visual information processing tasks in fibres connecting the Frontal and Occipital lobes namely the Inferior Fronto Occipital tract **(IFO),** Superior Longitudinal Faciulus **(SLF)** and the Superior Fronto Occipital **(SFO).** Mean Diffusivity **(MD)** values of these fibre tracts correlated directly with the raw dysfunction scores of the visual information processing tasks of the PGIBBD [15]. Thus it was clear that an alteration in the integrity of the white matter of the Fronto Occipital fascilculus on prolonged alcohol consumption could be responsible for impaired visual information processing in alcoholics who exhibit no neurological deficit.

The metabolite ratios of the alcoholic subjects were correlated with the dysfunction scores on all the three visual information processing tests [16]. Convention MRI did not show any morphological abnormality in the alcoholic subjects. The alcoholics performed poorly on the visual information processing tests as compared to the controls. Proton spectra obtained from the visual cortex showed an elevated Cho/Cr, mI/Cr and reduced NAA/Cr and Glu-Gln/Cr ratios. A significant inverse correlation between NAA/Cr and BG and NB tests as well as Glu-Gln/Cr and NB and BG tests were noted while a significant direct correlation between Cho/Cr and BG and NB tests were noted. No correlation was noted between mI/Cr and the dysfunction scores. A similar trend was noted with Koh's block design but it did not reach statistical significance. No correlation between the metabolite ratios and dysfunction scores were noted in case of the control subjects.

Prolonged alcohol consumption is associated with decreased brain energy metabolism [8,17]. Lower ATP levels are associated with high Choline levels [18]. Other authors who have also found raised Cho/Cr levels in chronic alcoholics [19,20] have suggested that a high Cho/Cr ratio in these subjects is most likely a reflection of increase in membrane turnover, as Cho peak is a potential biomarker of the status of membrane phospholipid metabolism. The positive correlation with Cho/Cr and the dysfunction scores on the visual information processing tasks indicates that the alcohol induced damage to the neuronal cell membranes of the Occipital cortex as well as reduced glucose metabolism was responsible for the poor performance by the subjects on the visual information processing tasks.

A reduced NAA/Cr is indicative of either neuronal loss or neuronal dysfunction and has also been noted by researchers in earlier studies [10,21,22]. A positive correlation of NAA/Cr with the dysfunction scores of the visual information processing tasks indicated that neuronal damage/ dysfunction in the occipital cortex, caused by chronic alcohol intake, was responsible for the poor performance of the alcoholic subjects. This study has brought out evidence of altered metabolite ratios in the occipital cortex and the corresponding dysfunction in the visual information processing tests in chronic alcoholics. This is suggestive of disordered metabolism of the occipital

lobe translating into impaired visual skills in chronic alcoholics. Such a theory is supported by fMRI study [23] wherein reduced activation of the occipital lobes was noted in alcoholic subjects when they were made to perform visuo-spatial and visual processing tasks.

Blumenfeld RS and Ranganathan C (2007) [24] reviewed and integrated findings from neuropsychology and neuroimaging studies dealing with the relationship between prefrontal cortex and long term memory encoding. They concluded that the dorsolateral and venterolateral regions of the Prefrontal Cortex **(PFC)** are responsible for encoding various processes that enhance or attenuate memory for certain events/ situations. Muscovitch (2006) [25] stated that the hippocampus played a vital role in re-living episodic or spatial memories irrespective of when such memories were formed. Nikos Markis et al (2008) performed morphometric analysis using Magnetic resonance Imaging on 21 abstinent chronic alcoholics. They found volume of the part of the brain subserving the reward network in chronic alcoholics was significantly reduced when compared to control subjects. Using DTI, Trivedi et al (2013) [26], studied ten abstinent alcoholics and ten control subjects. They reconstructed the major fibers of the brain using continuous fiber tracking and studied the following fiber tracts of the brain: Superior Longitudinal Fasciculus **(SLF),** Inferior Llongitudinal Fasciulus **(ILF),** Corticospinal Tracts **(CST)**, Cingulum **(CNG)**, Superior **(SCP)**, Middle **(MCP)** and Inferior Cerebellar Peduncles **(ICP),** Fornix **(FX)**, Arcuate Fasciulus **(AF)**, Uncinate Fasciulus **(UNC)**, Thalamic radiations [Anterior **(ATR)**, Superior **(STR)** and Posterior **(PTR)** thalamic radiations] Inferior Fronto Occipital fasciulus **(IFO)**. These fiber tracts were quantified using an in house JAVA based soft ware [27]. Student's independent t test was used to compare the memory dysfunction score between alcoholics and control groups. The alcoholic subjects were found to have a significantly higher memory dysfunction score as compared to the control group.

FA was found to be significantly reduced in CC, FX, Right Anterior Fasciculus **(RAF)**, Right Anterior Thalamic Radiation **(RATR)** and Right Inferior Longitudinal Fasciculus **(RILF)** in the chronic alcoholics. CNG, UNC and ILF which form part of the reward circuitary, showed an inverse correlation in chronic alcoholics with memory dysfunction scores. No such correlation was noted in the controls. Fractional Anisotrpy is universally accepted as a measure of the organisation of fiber tracts within the white matter. Factors which cause a reduction of FA are degradation of myelin sheaths and axonal membranes [28] or reduced density of axonal fibers or abnormalities of the myelin sheath with sparing of the axonal fibers [29]. The reduced FA in these white matter tracts is indicative of degradation of myelin sheaths or reduced density of axonal fibers [28,29]. Thus white matter damage due to chronic alcohol intake was responsible for memory decline in these subjects.

Significant increase in MD was noted in the FX and CC. At a cellular level, free diffusion of water molecules is restricted by the cell membranes. Increase in MD is indicative of higher microscopic diffusion of water which was noted in FX and CC in this study. This is suggestive of alcohol related brain damage causing cell death, loss of axons, dendrites or synapses, which would increase the diffusivity of water molecules. This is supported by the post mortem findings of demyelination [30,31], microtubule disruption and axonal deletion [32,33] in the alcoholic brain.

Activation in the inferior frontal and middle temporal gyrus on fMRI has been implicated in the processing of abstract concepts while concrete concepts are associated with greater activation in posterior cingulate, precuneus, fusiform gyrus and parahippocampal gyrus [34]. The language processing areas [35,36] rest in the parietal and temporal lobes. Atrophy of these areas have been reported in various neuroimaging studies [1,37,38]. Inspite of the atrophy of the language processing areas in chronic alcoholism, the language skills of these subjects is relatively preserved. To explore the preserved language skills in chronic alcoholics a lexico-semantic component of the language domain was used in a fMRI study by Bagga et al [39]. The study investigated the neural representation of semantic processing in alcohol dependent subjects. The subjects were given a semantic judgement task in which they had to judge whether the word presented to them was abstract or concrete. Thirteen words were presented during the activation phase and non words were given in the baseline in which the subjects had to judge whether the words were in upper case or lower case. The study showed that there was no significant difference in the accuracy of the response to the tasks assigned when the chronic alcoholics were compared to controls. However a significant difference was noted in the time to accomplish the task between the two groups with the alcoholic subjects taking a longer time. The increased time taken by the alcoholic subjects to complete the task could be interpreted as increased task demand for achieving the same level of accuracy as the controls. When compared to controls, the alcoholic subjects were seen to recruit additional brain areas namely the precuneus bilaterally, left angular gyrus and left postcentral gyrus, to complete the task. Thus recruitment of additional areas to complete tasks involving interpretation of word meanings and word categorization is suggestive of compensatory mechanisms being brought into play, to maintain accuracy, in lexico semantic judgement tasks in alcoholics.

Abstract reasoning is known to get affected after years of heavy alcohol consumption [40]. The fronto-parietal region is actively involved in tasks like reasoning, attention and decision-making. In another fMRI study Bagga et al [41] looked at the neural recruitment pattern evoked by alcoholics to complete tasks requiring abstract reasoning. The subjects were trained to respond to an abstract reasoning task and after they were able to comprehend the nature of the reasoning task, they were subjected to the fMRI study. The alcoholics were able to accurately perform the abstract reasoning task but took longer than the controls for the same amount of accuracy. In both the alcoholics and the controls the frontoparietal region was activated in the abstract reasoning task. The alcoholics in addition, showed greater activation, when compared to controls, in the following regions: the Inferior Frontal Gyrus **(IFG)**, Occipito Temporal Gyrus **(OTG)**, Post Central Gyrus **(PG)** and Superior Parietal Lobule **(SPL)** in the right hemisphere. Earlier studies investigating abstract reasoning in alcoholics have also found activation of SPL and PG [42,43,44]. These areas are considered to be a part of a network that maintains reasoning [45]. The greater activation of the right SPL and right PG in chronic alcoholics as compared to controls could indicate the increased effort required by the compromised alcoholic brain in accurately

completing the abstract reasoning task. The IFG is the key area that supports reasoning and problem solving [42,43,46]. The greater activation of IFG in the alcoholic subjects is indicative of the difficulty faced by these subjects in processing information to solve the abstract reasoning problems. Recruitment of additional area of the IFG was required by these subjects to reach the same level of accuracy in solving the abstract reasoning problem. OTG is associated with spatial stimuli and visual perception [43]. Greater activation of OTG in the alcoholic subjects, is indicative of greater neuronal recruitment by the alcoholic brain to process a visual task. These findings indicate that the alcoholics are able to perform the same tasks as the control subjects, albeit with reduced ability. Pfefferbaum, et al (2001) [47] have tried to determine whether the alcoholics recruit the same brain regions or different brain regions as compared to controls for equal performance in working memory tasks. The results of the fMRI studies conducted by them led them to the conclusion that alcoholics recruited addition brain regions as compared to controls for equal performance of the working memory task. Hence the alcoholic brain undergoes functional reorganisation to accomplish the task accurately.

Spadoni et al (2005) [48] recruited 22 youths (aged 10 -18 yr) with a history of heavy prenatal alcohol exposure (ALC gp) and subjected them to a Spatial Working Memory **(SWM)** task. They studied the (Blood Oxygen level dependent) BOLD response of these youths in an fMRI study. They found that the youths with history of prenatal alcohol exposure did not differ in the accuracy of the response to the SWM task but their brain showed a greater BOLD response. They concluded that the neural connections of the ALC group subserving the SWM task were either working inefficiently or were recruiting additional areas as a compensatory mechanism for deficiency at the neural level.

Despite the metabolic and functional brain damage caused by chronic alcohol consumption some of it can be reversed on abstinence. Benzdus et al (2001) [11] performed a sequential MR study on recently detoxified alcoholics. They studied seventeen alcohol dependent subjects on days 1 through3 and days 36 through 39 of abstinence. They found reduced NAA/Cr in frontal lobes and cerebellum and reduced Cho/Cr in the cerebellum immediately on abstinence (days 1 through 3). These ratios showed a significant increase on the examination performed on days 36 through 39. The increased NAA/Cr correlated with improved performance on neuropsychological test. They also recorded a decrease in the enlarged CSF spaces on cessation of alcohol consumption. Bartsch et al (2007) [49] have shown that NAA loss caused by chronic alcohol intake gets reversed in the first few weeks of abstinence and this is accompanied by improved cognitive performance. In addition they have also documented a two per cent global brain volume gain on attaining soberity.

Thus chronic alcohol consumption for prolonged periods is bound to affect the functionality of the human brain. The prefrontal cortex that subserves higher cognitive functions gets impaired and these subjects show lack of inhibition, indulge in impulsive and risky behaviour, make decisions based on poor judgement are unable to plan or regulate their behaviour. Memory is impaired in

these subjects. The reward circuitary is affected as has been seen by DTI studies investigating the reward circuitary leading to compulsive drinking and finally addiction. Visual information processing is also affected in these individuals. The damage inflicted by alcohol results in atrophy of white mater tracts and sophisticated neuroimaging techniques can objectively identify the damage caused. The alcoholic brain recruits additional areas to complete tasks involving higher cognition such as abstract reasoning, memory, language skills etc. indicating functional reorganisation of the brain.

Over the years, neuroimaging studies have brought out the various facets of brain damage caused by chronic alcohol consumption. These non invasive methods can be used to monitor the treatment and to gauge the success of newer methodologies to wean these individuals from alcohol intake. Utilising these techniques one can study reversal of metabolites, document extent of areas showing increased brain activation and make a note of markers of white matter damage (FA and MD) when chronic alcoholics are subjected to abstinence.

References

1. Chanraud S, Martelli C, Delain F, Kostogianni N, Douaud G, et al. Brain morphometry and cognitive performance in detoxified alcohol-dependants with preserved psychosocial functioning. Neuropsychopharmacology. 2007; 32: 429-438.
2. Sullivan EV. Compromised pontocerebellar and cerebellothalmocortical systems: speculations on their contributions to cognitive and motor impairment in nonamnesic alcoholism. Alcohol Clin Exp Res. 2003; 27: 1409-1419.
3. Cardenas VA, Studholme C, Gazdzinski S, Durazzo TC, Meyerhoff DJ. Deformation-based morphometry of brain changes in alcohol dependence and abstinence. Neuroimage. 2007; 34: 879-887.
4. Bloomer CW, Langleben DD, Meyerhoff DJ. Magnetic resonance detects brainstem changes in chronic, active heavy drinkers. Psychiatry Res. 2004; 132: 209-218.
5. Pfefferbaum A, SullivaN EV, Mathalon DH, Lim KO. Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. Alcohol Clin Exp Res. 1997; 21: 521-529.
6. Ratti MT, Soragna D, Sibilla L, Giardini A, Albergati A, et al. Cognitive impairment and cerebral atrophy in “heavy drinkers”. Prog Neuropsychopharmacol Biol Psychiatry. 1999; 23: 243-258.
7. Ratti MT, Bo P, Giardini A, Soragna D. Chronic alcoholism and the frontal lobe: which executive functions are imparied? Acta Neurol Scand. 2002; 105: 276-281.
8. Samson Y, Baron JC, Feline A, Bories J, Crouzel C. Local cerebral glucose utilisation in chronic alcoholics: a positron tomographic study. J Neurol Neurosurg Psychiatry. 1986; 49: 1165-1170.
9. Adams KM, Gilman S, Johnson-Greene D, Koeppe RA, Junck L, et al. The Significance of family history status in relation to neuropsychological test performance and cerebral glucose metabolism studied with positron emission tomography in older alcoholic patients. Alcohol Clin Exp Res. 1998; 22: 105-110.
10. Jagannathan NR, Desai NG, Raghunathan P. Brain metabolite changes in alcoholism: an in vivo proton magnetic resonance spectroscopy (MRS) study. Magn Reson Imaging. 1996; 14: 553-557.
11. Bendszus M, Weijers HG, Wiesbeck G, Warmuth-Metz M, Bartsch AJ, et al. Sequential MR imaging and proton MR Spectroscopy in patients who underwent recent detoxification for chronic alcoholism: correlation with clinical and neuropsychological data. AJNR Am J Neuroradiol. 2001; 22: 1926-1932.
12. Stavro K, Pelletier J, Potvin S. Widespread and sustained cognitive deficits in alcoholism: a meta-analysis. Addict Biol. 2013; 18: 203-213.
13. Wegner AJ, Gunthner A, Fahle M. Visual performance and recovery in recently detoxified alcoholics. Alcohol Alcohol. 2001; 36: 171-179.
14. Chen B, Xia J, LiG, Zhou Y. The effects of acute alcohol exposure on the response properties of neurons in visual cortex area 17 of cats. Toxicol Appl Pharmacol. 2010; 243: 348-358.

15. Bagga D, Sharma A, Kumari A, Kaur P, Bhattacharya D, et al. Decreased white matter integrity in fronto-occipital fasciculus bundles: relation to visual information processing in alcohol-dependent subjects. Alcohol. 2014; 48: 43-53.

16. Bagga D, Khushu S, Modi S, Kaur P, Bhattacharya D, et al. Impaired Visual Information Processing in alcohol-dependent subjects: a proton magnetic resonance spectroscopy Study of the Primary Visual Cortex. J Stud Alcohol Drugs. 2014; 75: 817-826.

17. Braunova Z, Kasparova S, Mlynarik V, Mierisova S, Liptaj T, et al. Metabolic changes in rat brain after prolonged ethanol consumption measured by 1H and 31P MRS experiments. Cell Mol Neurobiol. 2000; 20: 703-715.

18. Zeisel SH. Formation of unesterified choline by rat brain. Biochim Biophys Acta. 1985; 835: 331-343.

19. Meyerhoff DJ, Blumenfeld R, Truran D, Lindgren J, Flenniken D, et al. Effects of heavy drinking, binge drinking, and family history of alcoholism on regional brain metabolites. Alcohol Clin Exp Res. 2004; 28: 650-661.

20. Modi S, Bhttacharya M, Kumar P, Deshpande SN, Tripathi RP, et al. Brain metabolite changes in alcoholism: localised proton magnetic resonance spectroscopy study of the occipital lobe. Eur J Radiol. 2011; 79: 96-100.

21. Fein G, Di Sclafani V, Cardenas VA, Goldmann H, Tolou-Shams M, et al. Cortical gray matter loss in treatment-naïve alcohol dependent individuals. Alcohol Clin Exp Res. 2002; 26: 558-564.

22. Schweinsburg BC, Alhassoon OM, Taylor MJ, Gonzalez R, Videen JS, et al. Effects of alcoholism and gender on brain metabolism. Am J Psychiatry. 2003; 160: 1180-1183.

23. Hermann D, Smolka MN, Klein S, Heinz A, Mann K, et al. Reduced fMRI activation of an occipital area in recently detoxified alcohol-dependent patients in a visual and acoustic stimulation paradigm. Addict Biol. 2007; 12: 117-121.

24. Blumenfeld RS, Ranganath C. Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. Neuroscientist. 2007; 13: 280-291.

25. Moscovitch M, Nadel L, Winocur G, Gilboa A, Rosenbaum RS. The cognitive neuroscience of remote episodic, semantic and spatial memory. Curr Opin Neurobiol. 2006; 16: 179-190.

26. Trivedi R, Bagga D, Banerjee D, Kaur P, Khushu S, et al. White Matter Damage Contributes to Memory Decline in Chronic Alcoholics: A Quantitaive Diffusion Tensor Tractography Study. Behav Brain Res. 2013; 250: 192-198.

27. Rathore RK, Gupta RK, Agarwal S, Trivedi R, Tripathi RP, et al. Principal eigenvector field segmentation for reproducible diffusion tensor tractography of white matter structures. Magn Reson Imaging. 2011; 29: 1088-100.

28. Pierpaoli C, Barnett A, Pajevic S, Chen R, Penix LR, et al. Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. Neuroimage. 2001; 13: 1174-1185.

29. Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, et al. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage. 2002; 17: 1429-1436.

30. Tarnowska-Dziduszko E, Bertrand E, Szpak GM. Morphological changes in the corpus callosum in chronic alcoholism. Folia Neuropathol. 1995; 33: 25-29.

31. Lewohl JM, Wang L, Miles MF, Zhang L, Dodd PR, et al. Gene expression in human alcoholism: microarray analysis of frontal cortex. Alcohol Clin Exp Res. 2000; 24: 1873-1882.

32. Paula-Barbosa MM, Tavares MA. Long term alcohol consumption induces microtubular changes in the adult rat cerebellar cortex. Brain Res. 1985; 339: 195-199.

33. Putzke J, De Beun R, Schreiber R, De Vry J, Tolle TR, et al. Long term alcohol self-administration and alcohol withdrawal differentially modulate microtubule-associated protein 2 (MAP2) gene expression in the rat brain. Brain Res Mol Brain Res. 1998; 62: 196-205.

34. Wang J, Conder JA, Blitzer DN, Shinkareva SV. Neural representation of abstract and concrete concepts: a meta-analysis of neuroimaging studies. Hum Brain Mapp. 2010; 31: 1459-1468.

35. Mummery CJ, Patterson K, Wise RJ, Vandenberghe R, Price CJ, et al. Disrupted temporal lobe connections in semantic dementia. Brain. 1999; 122: 61-73.

36. Gilman JM, Davis MB, Hommer DW. Greater activation in left hemisphere language-related regions during simple judgment tasks among substance-dependent patients in treatment for alcoholism. Alcohol Clin Exp Res. 2010; 34: 331-341.

37. Sullivan EV, Harding AJ, Pentney R, Dlugos C, Martin PR, et al. Disruption of frontocerebellar circuitry and function in alcoholism. Alcohol Clin Exp Res. 2003; 27: 301-309.

38. Demirakca T, Ende G, Kammerer N, Welzel-Marquez H, Hermann D, et al. Effects of alcoholism and continued abstinence on brain volumes in both genders. Alcohol Clin Exp Res. 2011; 35: 1678-1685.

39. Bagga D, Singh N, Modi S, Kumar P, Bhattacharya D, et al. Assessment of lexical semantic judgment abilities in alcohol-dependent subjects: an fMRI study. J Biosci. 2013; 38: 905-915.

40. Ratti MT, Bo P, Giardini A, Soragna D. Chronic alcoholism and the frontal lobe: which executive functions are imparied? Acta Neurol Scand. 2002; 105: 276-281.

41. Bagga D, Singh N, Singh S, Modi S, Kumar P, Bhattacharya D, et al. Assessment of abstract reasoning abilities in alcohol-dependent subjects: an fMRI study. Neuroradiology. 2014; 56: 69-77.

42. Kroger JK, Sabb FW, Fales CL, Bookheimer SY, Cohen MS, et al. Recruitment of anterior dorsolateral prefrontal cortex in human reasoning: a parametric study of relational complexity. Cereb Cortex. 2002; 12: 477-485.

43. Lee KH, Choi YY, Gray JR, Cho SH, Chae JH, et al. Neural correlates of superior intelligence: stronger recruitment of posterior parietal cortex. Neuroimage. 2006; 29: 578-586.

44. Watson CE, Chatterjee A. A bilateral frontoparietal network underlies visuospatial analogical reasoning. Neuroimage. 2012; 59: 2831-2838.

45. Melrose RJ, Poulin RM, Stern CE. An fMRI investigation of the role of the basal ganglia in reasoning. Brain Res. 2007; 1142: 146-158.

46. Perfetti B, Saggino A, Ferretti A, Caulo M, Romani GL, et al. Differential patterns of cortical activation as a function of fluid reasoning complexity. Hum Brain Mapp. 2009; 30: 497-510.

47. Pfefferbaum A, Desmond JE, Galloway C, Menon V, Glover GH, et al. Reorganization of frontal systems used by alcoholics for spatial working memory: an fMRI study. Neuroimage. 2001; 14: 7-20.

48. Spadoni AD, Bazinet AD, Fryer SL, Tapert SF, Mattson SN, et al. BOLD response during spatial working memory in youth with heavy prenatal alcohol exposure. Alcohol Clin Exp Res. 2009; 33: 2067-2076.

49. Bartsch AJ, Homola G, Biller A, Smith SM, Weijers HG, et al. Manifestations of early brain recovery associated with abstinence from alcoholism. Brain. 2007; 130: 36-47.