Sex Differences in Korsakoff's Syndrome for Inhibition but Not for Episodic Memory or Flexibility

Mohamad El Haj, Roy P.C. Kessels, Jean-Louis Nandrino

Short title: Sex differences

Sex differences in Korsakoff's syndrome for inhibition but not for episodic memory or flexibility

Mohamad EL HAJ Ph.D [1, 2, 3]

Roy P. C. KESSELS Ph.D [4, 5, 6]

Jean-Louis NANDRINO Ph.D [7]

[1] Nantes Université, Univ Angers, Laboratoire de Psychologie des Pays de la Loire (LPPL - EA 4638), F-44000 Nantes, France

[2] Unité de Gériatrie, Centre Hospitalier de Tourcoing, Tourcoing, France

[3] Institut Universitaire de France, Paris, France

[4] Radboud University Medical Center, Radboudumc Alzheimer Center, Nijmegen, the Netherlands

[5] Radboud University Medical Center, Donders Institute for Brain Cognition and Behaviour, Department of Medical Psychology, Nijmegen, the Netherlands

[6] Center for Cognition, Donders Institute for Brain Cognition and Behaviour, Radboud University, Nijmegen, the Netherlands

[7] Univ. Lille, CNRS, CHU Lille, UMR 9193 SCALab - Sciences Cognitives et Sciences Affectives, F-59000 Lille, France

Abstract: 175 words. Narrative: 2935 words. One table + 35 references

Correspondence concerning this manuscript should be addressed to :

Mohamad EL HAJ

Faculté de Psychologie, LPPL – Laboratoire de Psychologie des Pays de la Loire, Université de Nantes, Chemin de la Censive du Tertre, BP 81227, 44312 Nantes Cedex 3, France. E-Mail: mohamad.elhaj@univ-nantes.fr

Background and objectives: While sex differences in cognitive abilities has been extensively studied in healthy populations, little is known about these differences in patients with Korsakoff syndrome (KS).

Methods: We investigated sex differences in verbal episodic memory, inhibition and flexibility in 25 patients with KS and 25 control participants.

Results: Analysis demonstrated no significant differences between women with KS and men with KS on episodic memory and flexibility, but higher inhibition was observed in women with KS compared to men with KS. Regarding control participants, no significant differences were observed between women and men on inhibition or flexibility, but higher verbal episodic memory was observed in women compared to men. Verbal episodic memory and flexibility seem to be equally affected in women and men with KS, whereas inhibition seems to be more affected in men than in women with KS.

Conclusions and Scientific Significance: Our findings highlight cognitive sex differences in KS in executive function. Critically, our findings are the first quantitative data about episodic performances (and cognitive performances in general) of women and men with KS.

Keywords*:* episodic memory; flexibility; sex differences; inhibition; Korsakoff's syndrome

Sex differences in cognitive abilities have been studied intensely in healthy populations as well as in patients with amnesia, such as in patients with Alzheimer's Disease. However, little is known about sex differences in cognitive abilities of patients with Korsakoff syndrome (KS). This syndrome refers to an acute neurologic syndrome caused by thiamine deficiency, malnutrition, often in the context of alcohol use disorder [1]. Because little is known about sex differences in cognitive abilities of patients with KS we investigated these differences in the syndrome.

KS is mainly associated with severe impairment of episodic memory. Previous studies have consistently demonstrated difficulties in patients with KS to remember the episodic context in which information was encoded (e.g., where, when, and how an item was previously encountered) [2-9]. Another characteristic of the decline of episodic memory in KS is confabulations [10,11], i.e., the tendency of patients with KS to construct fictitious memories without intent to deceive. Although episodic memory impairment has been considered as the main cognitive characteristic of KS, executive dysfunction has been put forward as another prominent cognitive impairment in the syndrome [12,13], including disinhibition, poor judgment and planning abilities [14]. Patients also tend to demonstrate impairment on neuropsychological measures of general executive function such as tests of inhibition and flexibility [15]. Taken together, KS is mainly characterized by decline of episodic memory and, to some extent, by executive dysfunction; we therefore investigated sex differences for all these cognitive domains in KS.

Sex differences in episodic memory have been widely investigated for healthy individuals, and generally speaking, studies suggest that women perform higher than men on verbal episodic memory tasks [16]. This advantage has been reported in cross-sectional studies in children, adolescents, and young adults reporting that the female advantage is present in verbal episodic memory tasks from the age of five onwards which lasts until old age [17,18].

Women also tend to demonstrate a superiority in some episodic memory tasks involving non-verbal stimuli, such as retention of unfamiliar faces [19,20]. Although women tend to perform at a higher level than men when the material to be recalled or recognized is verbal, the reverse can be observed for memory of visuospatial information [21,22]. Overall, a higher performance on tasks of visuo-spatial memory has been observed in men compared to women [23].

Sex differences in memory, and cognition in general, have been attributed to social and biological factors. Social accounts generally assume that most sex differences are a result of differential socialization of women and men, which influence their roles and behavior in childhood, as well as their educational and occupational choices during adulthood, and in turn, cognitive differences [24]. In contrast, biological accounts highlight the involvement of biological factors, such as in levels of sex hormones and genetic factors and their influence on the brain, in sex differences [25]. Another account of sex differences in cognition is the Declarative/Procedural Model [16]. This model proposes that declarative memory system is tied to the hippocampus, whose function is known to be enhanced by estrogen which may explain the advantage of women on tasks of declarative memory in general and [26], more specifically, on tasks requiring declarative processing of verbal information.

We focused on episodic memory in KS because decline of episodic memory is considered as the cognitive hallmark of the syndrome [1]. We also compared sex differences for inhibition and flexibility because executive dysfunction, especially decline of inhibition and flexibility, has been considered as a prominent cognitive feature of KS [12].

Method

Participants

The study included twenty-five patients diagnosed with KS (13 women and 12 men; *M* age = 56.56 years, *SD* = 5.36; *M* years of formal education = 9.34, *SD* = 3.05), recruited from several alcohol-dependence medical units and day-care facilities at Lille and Nantes. As a control group, we recruited 25 participants without previous or current substance addiction and without psychiatric or neurological history (13 women and 12 men; *M* age = 55.56, years, *SD* = 5.63; *M* years of formal education = 9.68, *SD* = 4.22). The control group was matched with the KS group according to sex distribution [$\chi^2(1, N = 50) = .00$, $p = 1.00$], age [$t(48) = .64$, $p = .52$], and educational level [$t(48) = .59$, $p = .56$]. The diagnosis of KS was made by psychiatrists, using the DSM-IV-TR criteria for alcohol-induced persisting amnestic disorder. The diagnosis was also based on an extensive history of alcoholism and nutritional depletion, notably thiamine deficiency. All KS patients were in a chronic (more than one-year post-onset) and stable condition, but had no confusional Wernicke psychosis at the time of testing or signs of alcohol-related dementia. Participants freely consented to participate and were free to withdraw whenever they wished. The study was conducted in compliance with principles involving human subjects of Helsinki Declaration.

When recruiting participants, we were careful to match women and men with KS regarding general cognitive functioning as assessed with the Mini Mental State Exam [(*M* women= 25.42, *SD*= 2.19, *M* men= 24.20, *SD*= 2.30, $t(23)= 1.13$, $p = .27$] and the same precaution was taken for control participants [(*M* women= 28.77, *SD*= 1.36, *M* men= 29.00, *SD*= 1.13, $t(23)= .46$, $p = .65$]. We were also careful to match women and men with KS according to age [(*M* women= 57.70, *SD*= 6.08, *M* men= 55.60, *SD*= 4.72, $t(23) = 1.26$, $p = .22$] and educational level [(*M* women= 8.67, *SD*= 2.67, *M* men= 8.60, *SD*= 3.95, $t(23)= .75$, *p*

= .46], and the same precaution was taken for control participants [(*M* age of women = 56.23, *SD*= 3.78, *M* age of men= 54.83, *SD*= 4.83, *t*(23)= .61, *p* = .55; *M* educational level of women= 9.62, *SD*= 1.68, *M* educational level of men= 9.75, *SD*= 2.06, *t*(23)= .08, *p* = .94]. By doing this, we were careful to ensure that any potential sex differences in patients with KS or control participants would not be caused by differences in general cognitive ability, age, or educational level. Note that, by applying these precautions, we excluded six patients with KS and nine control participants from the original sample (original sample of KS patients= 31, original sample of control participants= 34).

Procedures

We evaluated episodic memory with the verbal memory test of Grober and Buschke on which participants were invited to retain 16 words, each of which described an item (e.g., chair) that belonged to a different semantic category (e.g., furniture). Afterward, participants were invited, as a distraction condition, to count backwards from 374 in 20s. Counting was followed by two minutes of free recall; participants were prompted to recall the previously memorized 16 words. As for inhibition, we used the Stroop Color Word Test which consists of three subtests: word-reading, color-naming and color-word interference. In the word-reading subtest, participants had to read 100 color names printed in black ink. In the color-naming subtest, they had to name the color of 100 colored ink squares. In the color-word interference subtest, they had to name the color of 100 color-words printed in incongruously colored ink (for instance, the word “red” was written in blue). The interference score was used which is the completion time for the interference condition minus the average completion time for word-reading and color-naming; a higher score indicates more interference. As for flexibility, we used the Plus-Minus task, this following the model of Miyake, Friedman, Emerson, Witzki, Howerter, Wager [27] who considered this task as a reliable evaluation of cognitive shifting (as well as the Stroop task as a reliable evaluation of inhibition). The Plus-Minus task included three lists, each

containing 20 numbers. On List 1, participants had to add one to each number, on List 2 they had to subtract one from each number, and on List 3 they had to add and subtract one alternately. Participants were instructed to complete the lists quickly and accurately, and list completion times were measured by a stopwatch. The score referred to the difference between the time participants needed to complete List 3 and the average time that they needed to complete Lists 1 and 2 (the higher the score, the lower the shifting).

Results

Scores are summarized in Table1. We investigated sex differences between patients with KS and control participants regarding episodic memory, inhibition, and flexibility. Because data were not distributed normally as observed by Kolmogorov-Smirnov tests, Mann-Whitney U-test was used for inter-groups comparisons and Wilcoxon's signed-rank test was used for within-groups comparisons. We provided effect sizes using Cohen's *d:* 0.20= small, 0.50= medium, 0.80= large.

No sex differences on episodic memory in KS

Regardless of sex, lower episodic memory was observed in patients with KS (M= 5.32, SD= 1.34) than in control participants (M= 10.80, SD= 1.73) (Z= -6.11, $p < .001$, Cohen's d= 3.43). Also, lower episodic memory was observed in women with KS than in control women (Z= -4.26, $p < .001$, Cohen's d= 3.04), and lower episodic memory was observed in men with KS than in control men (Z= -3.99, $p < .001$, Cohen's d= 3.97). Critically, no significant differences were observed between women with KS and men with KS (Z = -.57, p = .56, Cohen's d= .23), but higher episodic memory was observed in control women than in control men (Z = -2.92, p = .003, Cohen's d= 1.44).

Higher inhibition in women than in men in KS

Regardless of sex, lower inhibition was observed in patients with KS (*M*= 58.24, *SD*= 11.45) than in control participants (*M*= 31.40, *SD*= 10.97) (*Z*= -5.32, *p* < .001, Cohen's *d*= 2.28). Also, lower inhibition was observed in women with KS than in control women (*Z*= -3.24, *p* < .001, Cohen's *d*= 1.64), and lower inhibition was observed in men with KS than in control men (*Z*= -3.98, *p* < .001, Cohen's *d*= 3.89). Critically, higher inhibition was observed in women with KS compared to men with KS (*Z*= -2.98, *p* = .003, Cohen's *d*= 1.42), but no significant differences were observed between control women and control men (*Z*= -.99, *p* = .32, Cohen's *d*= .40).

No sex differences on flexibility in KS

Regardless of sex, lower flexibility performance was observed in patients with KS (*M*= 12.24, *SD*= 6.53) than in control participants (*M*= 6.29, *SD*= 4.11) (*Z*= -3.57, *p* < .001, Cohen's *d*= 1.17). Also, lower flexibility was observed in women with KS than in control women (*Z*= -2.02, *p* = .043, Cohen's *d*= .86), and lower flexibility was observed in men with KS than in control men (*Z*= -2.82, *p* = .005, Cohen's *d*= 1.62). Critically, no significant differences were observed between women with KS and men with KS (*Z*= -.38, *p* = .70, Cohen's *d*= .33), or between control women and control men (*Z*= -.38, *p* = .70, Cohen's *d*= .15).

[INSERT TABLE 1 APPROXIMATELY HERE]

Discussion

We investigated sex differences in KS regarding verbal episodic memory and executive function (i.e., inhibition and flexibility). No significant differences were observed between women with KS and men with KS on episodic memory and flexibility, but higher inhibition

performance was observed in women with KS compared to men with KS. Regarding control participants, no significant differences were observed between women and men on inhibition and flexibility, but higher verbal episodic memory was observed in women than in men.

Countering our hypothesis, we did not find any significant differences between women with KS and men with KS regarding verbal episodic memory. These findings are important because decline of episodic memory has been considered as the cognitive hallmark of KS [1], our findings extend this consideration by demonstrating that the decline of episodic memory can be observed for both men with KS and women with KS; noteworthy that this assumption is supported by our findings showing lower episodic memory in women with KS compared with control women and lower episodic memory in men with KS compared with control men. At the clinical level, these findings are important because, to the very best of our knowledge, there is no episodic memory test including normative data about performances of women and men with KS. Our findings address this gap by providing first quantitative data about episodic memory performances (and cognitive performances in general) of women and men with KS. Also, our paper demonstrates how the advantage of women on verbal episodic memory, as observed in normal aging [18], disappears in KS. In our view, these findings may have implications for research on sex-differences as our findings illustrate the trajectory of sex-related performances on episodic memory from normal aging to amnesia. The available evidence suggests that the advantage of women on verbal episodic memory in normal aging turns into a disadvantage in Alzheimer's Disease [28]; in other words, and compared with men, women with Alzheimer's Disease tend to demonstrate lower verbal episodic memory than men. As for KS, verbal episodic memory seems to be equally affected in women and men, at least as observed in our participants.

In addition, we found that flexibility is equally affected in women and men with KS whereas inhibition seems to be more affected in men than in women with KS. Because

executive dysfunction has been put forward as a prominent cognitive impairment in KS [12,13], our findings are important as they suggest how executive performances can vary between women and men with KS according to the considered executive function. Regarding inhibition, the higher inhibitory performances in women with KS worth consideration as inhibitory decline has been associated with cognitive decline in general, and more specifically, with perseveration and impulsivity [29]. Our findings therefore suggest less inhibitory-related dysfunctions in women than in men with KS, at least as observed in our participants.

Regarding control participants, and consistent with our hypothesis, we observed higher verbal episodic memory performance in women than in men. These findings mirror a body of research in normal aging suggesting a women advantage for verbal episodic. For instance, Jorm, Anstey, Christensen, Rodgers [30] assessed verbal episodic memory in a cohort aged 20 to 64, reporting that women outperformed men and that the magnitude of this difference did not vary with age. Women's advantage for verbal episodic memory was also reported by Maller, Anstey, Reglade-Meslin, Christensen, Wen, Sachdev [31] who reported that women (aged from 60 to 64 years) outperformed men on a test of verbal learning. Interestingly, research in normal aging have demonstrated no significant differences between women and men regarding executive function. For instance, Munro, Winicki, Schretlen, Gower, Turano, Munoz, Keay, Bandeen-Roche, West [32] examined sex differences in a cohort aged from 67 to 89 years. While women outperformed men on tests of verbal learning and memory, men outperformed women on tests of visuo-construction and visual perception, interestingly, women and men were indistinguishable on tests of executive function. Together, our findings mirror evidence obtained from normal aging demonstrating a women advantage for verbal episodic memory but no sex differences for executive function.

Possibly, the sex differences on cognitive tests in KS can be explained as being the result of differential effects of alcohol dependence on brain structure between women and men.

For instance, Hommer, Momenan, Kaiser, Rawlings [33] observed that women with alcohol dependence had significantly smaller volumes of grey and white matter than women without alcohol dependence. These differences, particularly in grey matter, were significantly larger than those found between men with and without alcohol dependence. In a similar vein, a study reported lower levels of N –acetylaspartate, a marker of neuronal integrity, in women with alcohol dependence compared with women without alcohol dependence; however, there were no differences in the levels of this marker between men with alcohol dependence and men without alcohol dependence [34]. Another study reported cortical atrophy after several months of abstinence in men with alcohol dependence, but not in women with alcohol dependence [35]. The authors attributed these findings to factors such as smoking in men, or possibly to a more rapid recovery of cortical brain volume in women. Building on this available evidence, future research may consider potential relationships between sex-related cognitive performances in KS and the different consequences of alcohol dependence on brain structure between women and men.

This paper has several strengths. Because very little is known about sex-differences in cognitive function in KS, our paper sheds the light on these issues by demonstrating similarities and dissimilarities in cognitive function between women and men with KS. Another merit of this paper is the effort that was made to match women and men with KS, as well as control women and men, according to general cognitive ability, age, and educational level; by doing this, we were careful to ensure that any potential sex differences in patients with KS or control participants would not be caused by these factors. Another merit of this paper is that we did not only investigate the main cognitive hallmark of KS (i.e., decline of episodic memory) but also executive dysfunction. However, there is one limitation to this study that should be considered when interpreting our results. We used one test to investigate episodic memory, inhibition, or flexibility. Future research should address this issue through the assessment of

several episodic memory facets, such as memory for visuospatial information or source memory. The same thing can be said for inhibition and flexibility as these cognitive processes should be investigated with several tests.

To summarize, sex differences in cognition have long been a topic of intense interest. Regardless of the social and biological debates concerning the basis of any sex differences, these differences do exist. As demonstrated by our findings, these differences exist for inhibition but not for episodic memory or flexibility. This is however a preliminary assumption and further work remains to be done to test cognitive sex-differences in KS more fully.

Conflicts of Interest:

The authors declare no conflict of interest

References

1. Arts NJM, Walvoort SJW, Kessels RPC. Korsakoff's syndrome: a critical review. *Neuropsychiatr. Dis. Treat.* 11/27 2017;13:2875-2890.
2. Holdstock JS, Mayes AR, Cezayirli E, Aggleton JP, Roberts N. A comparison of egocentric and allocentric spatial memory in medial temporal lobe and Korsakoff amnesics. *Cortex.* Sep 1999;35(4):479-501.
3. Kessels RP, Kortrijk HE, Wester AJ, Nys GM. Confabulation behavior and false memories in Korsakoff's syndrome: role of source memory and executive functioning. *Psychiatry Clin. Neurosci.* Apr 2008;62(2):220-225.
4. El Haj M, Nandrino JL, Coello Y, Miller R, Antoine P. Source monitoring in Korsakoff's syndrome: "Did I touch the toothbrush or did I imagine doing so?". *Cortex.* Jun 2017;91:262-270.
5. Postma A, Van Asselen M, Keuper O, Wester AJ, Kessels RP. Spatial and temporal order memory in Korsakoff patients. *J. Int. Neuropsychol. Soc.* May 2006;12(3):327-336.
6. El Haj M, Kessels RP, Matton C, et al. Destination Memory in Korsakoff's Syndrome. *Alcohol. Clin. Exp. Res.* Jun 2016;40(6):1321-1327.
7. Brion M, de Timary P, Pitel AL, Maurage P. Source Memory in Korsakoff Syndrome: Disentangling the Mechanisms of Temporal Confusion. *Alcohol. Clin. Exp. Res.* Mar 2017;41(3):596-607.
8. Fama R, Pitel AL, Sullivan EV. Anterograde episodic memory in Korsakoff syndrome. *Neuropsychol. Rev.* Jun 2012;22(2):93-104.
9. Postma A, Morel SG, Slot ME, Oudman E, Kessels RPC. Forgetting the new locations of one's keys: spatial-memory interference in Korsakoff's amnesia. *Exp. Brain Res.* Jul 2018;236(7):1861-1868.

10. Borsutzky S, Fujiwara E, Brand M, Markowitsch HJ. Confabulations in alcoholic Korsakoff patients. *Neuropsychologia.* Nov 2008;46(13):3133-3143.

11. Aarts H, Bijleveld E, Custers R, et al. Positive priming and intentional binding: Eye-blink rate predicts reward information effects on the sense of agency. *Soc. Neurosci.* 2012/01/01 2012;7(1):105-112.

12. Brion M, Pitel AL, Beaunieux H, Maurage P. Revisiting the continuum hypothesis: toward an in-depth exploration of executive functions in korsakoff syndrome. *Front. Hum. Neurosci.* 2014;8:498.

13. Van Oort R, Kessels RP. Executive dysfunction in Korsakoff's syndrome: Time to revise the DSM criteria for alcohol-induced persisting amnestic disorder? *Int. J. Psychiatry Clin. Pract.* 2009;13(1):78-81.

14. Oscar-Berman M. Function and dysfunction of prefrontal brain circuitry in alcoholic Korsakoff's syndrome. *Neuropsychol. Rev.* Jun 2012;22(2):154-169.

15. Pitel AL, Beaunieux H, Witkowski T, et al. Genuine episodic memory deficits and executive dysfunctions in alcoholic subjects early in abstinence. *Alcohol. Clin. Exp. Res.* Jul 2007;31(7):1169-1178.

16. Ullman MT, Miranda RA, Travers ML. Sex differences in the neurocognition of language. In: Becker JB, Berklry KJ, Geary N, Hampson E, Herman JP, Young EA, eds. *Sex differences in the brain from genes to behavior*. Oxford: Oxford University Press; 2008:291−309.

17. de Frias CM, Nilsson LG, Herlitz A. Sex differences in cognition are stable over a 10-year period in adulthood and old age. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* Sep-Dec 2006;13(3-4):574-587.

18. Gerstorf D, Herlitz A, Smith J. Stability of sex differences in cognition in advanced old age: the role of education and attrition. *J. Gerontol. B Psychol. Sci. Soc. Sci.* Jul 2006;61(4):P245-249.

19. Shapiro PN, Penrod S. Meta-analysis of facial identification studies. *Psychol. Bull.* 1986;100(2):139-156.

20. Megreya AM, Bindemann M, Havard C. Sex differences in unfamiliar face identification: evidence from matching tasks. *Acta Psychol. (Amst.).* May 2011;137(1):83-89.

21. Herlitz A, Rehnman J. Sex Differences in Episodic Memory. *Curr. Dir. Psychol. Sci.* February 1, 2008 2008;17(1):52-56.

22. Lewin C, Wolgers G, Herlitz A. Sex differences favoring women in verbal but not in visuospatial episodic memory. *Neuropsychology.* 2001;15(2):165-173.

23. Voyer D, Postma A, Brake B, Imperato-McGinley J. Gender differences in object location memory: a meta-analysis. *Psychon Bull Rev.* Feb 2007;14(1):23-38.

24. Bem SL. Gender Schema Theory and Its Implications for Child Development: Raising Gender-Aschematic Children in a Gender-Schematic Society. *Signs: Journal of Women in Culture and Society.* 1983;8(4):598-616.

25. Berenbaum SA, Beltz AM. Sexual differentiation of human behavior: effects of prenatal and pubertal organizational hormones. *Front. Neuroendocrinol.* Apr 2011;32(2):183-200.

26. Sherwin BB. Estrogen and cognitive functioning in women. *Endocr. Rev.* Apr 2003;24(2):133-151.

27. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cogn. Psychol.* 2000;41(1):49-100.

28. Ryan JJ, Glass Umfleet L, Kreiner DS, Fuller AM, Paolo AM. Neuropsychological differences between men and women with Alzheimer's disease. *Int. J. Neurosci.* 2018/04/03 2018;128(4):342-348.

29. Stuss DT, Floden D, Alexander MP, Levine B, Katz D. Stroop performance in focal lesion patients: dissociation of processes and frontal lobe lesion location. *Neuropsychologia.* 2001;39(8):771-786.

30. Jorm AF, Anstey KJ, Christensen H, Rodgers B. Gender differences in cognitive abilities: The mediating role of health state and health habits. *Intelligence.* 2004/01/01/ 2004;32(1):7-23.

31. Maller JJ, Anstey KJ, Reglade-Meslin C, Christensen H, Wen W, Sachdev P. Hippocampus and amygdala volumes in a random community-based sample of 60-64 year olds and their relationship to cognition. *Psychiatry Res.* Dec 15 2007;156(3):185-197.

32. Munro CA, Winicki JM, Schretlen DJ, et al. Sex differences in cognition in healthy elderly individuals. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* Nov 2012;19(6):759-768.

33. Hommer D, Momenan R, Kaiser E, Rawlings R. Evidence for a gender-related effect of alcoholism on brain volumes. *Am. J. Psychiatry.* Feb 2001;158(2):198-204.

34. Yonker JE, Nilsson LG, Herlitz A, Anthenelli RM. Sex differences in spatial visualization and episodic memory as a function of alcohol consumption. *Alcohol Alcohol.* 2005;40(3):201-207.

35. Pfefferbaum A, Rosenbloom M, Deshmukh A, Sullivan E. Sex differences in the effects of alcohol on brain structure. *Am. J. Psychiatry.* Feb 2001;158(2):188-197.