Regional cerebellar metabolism (^{18}FDG PET) predicts the clinical outcome of the short-term inpatient treatment of alcohol addiction

Lubos Janu [1], Sylva Rackova [2], Jiri Horacek [3]

1 MedAvante Inc., Czech Republic, Pilsen, Czech Republic
2 Department of Psychiatry, University Hospital and Medical Faculty of Charles University, Pilsen, Czech Republic
3 Prague Psychiatric Center and 3rd Medical Faculty of Charles University, Prague, Czech Republic

Correspondence to: Lubos Janu, MD., PhD.
MedAvante Inc.,
Smrkova 23, Pilsen, 301 00, Czech Republic.
TEL: +420 777242101; FAX: +420 374440012; E-MAIL: lubos.janu@seznam.cz

Submitted: 2012-06-18 Accepted: 2012-06-19 Published online: 2012-08-28

Key words: **alcohol dependence; relapse prediction; positron emission tomography; cerebellum; vermis; regional brain metabolism**

Neuroendocrinol Lett 2012; **33**(4):419–424 **PMID:** 22936263 NEL330412A06 © 2012 Neuroendocrinology Letters • **www.nel.edu**

Abstract

OBJECTIVES: The acute and maintenance treatment of alcohol addiction represents the clinical challenge. The aims of our study were to evaluate the influence of alcohol consumption on regional brain metabolism and the predictive value of PET by means of the duration and quality of remission which followed the sub-acute treatment.

METHODS: PET investigation with ^{18}fluoro-deoxyglucose (^{18}FDG) were performed in detoxified patients with alcohol dependence at the end of short-term treatment. Abstinence was evaluated in patients during the one year follow-up period.

RESULTS: We detected the positive correlation between ^{18}FDG uptake in the cerebellar vermis (FWE, $p<0.05$) and duration of abstinence within one year.

DISCUSSION: Our findings support the assumption that the cerebellum would be involved in the maintenance of abstinence in alcohol dependent subjects. Cerebellar connections with cortical areas critical for addiction such as frontal, parietal, temporal regions would mediate the influence of the cerebellum on emotional systems related to addiction.

CONCLUSIONS: Our study is the first to document that the cerebellum and particularly the vermis is involved in the clinical outcome in terms of abstinence during one year. Our findings support the role of the cerebellum in addiction and the possibility to predict therapeutic outcome.

INTRODUCTION

The acute and maintenance treatment of alcohol addiction represents the clinical challenge. Burden of alcohol abuse and its treatment ranks among the top ten most expensive illnesses in the world (Rehm and Schield 2012). Alcohol addiction is a chronic relapsing disorder. Short-term abstinence during one year is 23% in untreated subjects and 40% in patients who are under specialized therapeutic programs (Weisner *et al.* 2003). The pathogenesis of addiction involves complex interactions between biological and environmental factors. The development of addiction comes from genetic pre-

ORIGINAL ARTICLE

dispositions, repeated exposure to addictive substance and withdrawal, accompanying stress and reinforcement of motivational experience of pleasure (Heinz *et al.* 2009).

The past two decades have brought accumulating evidence supporting the role of several cortico-subcortical circuits in reward, conditioning and addiction development. The disruption of these circuits mediated by the reduction of D2 receptors leads to dysfunctional inhibitory control and compulsive behavior, essential mechanisms for addiction (Parvaz *et al.* 2011). It is hypothesized that initial frontal vulnerability for drug or alcohol abuse together with repeated exposure to these substances reduce striatal D2 receptors availability. The reduction of the striatal D2 receptors has been associated with the decreased metabolism in orbitofrontal cortex, anterior cingulate gyrus and dorsolateral prefrontal cortex. Vice versa the normal prefrontal function would protect against the drug and alcohol dependence development (Volkow *et al.* 2009). Alcohol addiction is also associated with subsequent morphological and metabolic cerebellar abnormalities, particularly in the vermis (Durazzo and Mayerhoff 2008, Sullivan and Pfefferbaum 2005). However, the role of alcohol mediated neurotoxic cerebellar abnormalities in the mechanism of alcohol addiction has yet to be clarified (Durazzo *et al.* 2010).

The ^{18}fluoro-deoxyglucose (^{18}FDG) positron emission tomography (PET) evaluating the regional brain glucose metabolism (Thanos *et al.* 2008) represents an important tool for alcohol dependency research (Schiffer *et al.* 2005). ^{18}FDG PET in resting condition primarily reflects the regional glutamate turnover at the synaptic (particularly, presynaptic) level and provides a probe for relative synaptic strength and consequent metabolic activity (Rocher *et al.* 2003, Shulman 2001).

The aims of our study were to evaluate the influence of alcohol consumption on regional brain metabolism (^{18}FDG PET) and the predictive value of PET means of the duration and quality of remission which followed the sub-acute treatment. We hypothesized that the length and severity of alcohol abuse would result in the impairment of frontal lobe metabolism. We also expected that the clinical outcome of treatment in terms of the length of abstinence could be predicted by ^{18}FDG utilization specifically within the brain region involved in reward control. Persons with lower distributions should be likely to reach better outcome than persons with more disturbed control mechanism.

MATERIAL AND METHODS

Study population

Patients included in the study fulfilled the following criteria: 1) aged 18–65 years diagnosed of alcohol dependence according to the ICD-10 (International classification of Diseases, 10th revision) and DSM IV criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th revision), 2) no other concomitant drug abuse or dependence, 3) the absence of other psychiatric disorders than alcohol dependence. The co-morbidities were excluded by structured interview 4) patients hospitalized at the detoxification unit of the Psychiatric Department of the University Hospital in Pilsen, Czech Republic, who continued short-term treatment of addiction for 7 weeks between 2009 and 2010.

We included 29 patients (12 males, 17 females, mean age 42.21 years, SD=9.76, range=21–61years). The duration of alcohol abuse ranged from 2 to 30 years (mean 10.45 years, SD=7.88).

Study design

The PET examinations were performed at the end of the short-term intensive psychotherapeutic and detoxification treatment lasting for 7 weeks in all subjects. Patients abstained from alcohol and other illicit drugs during the entire treatment program. The abstinence was verified by alcohol breath tests and toxicological analyses (including ethylglucuronide) in urine on a regular weekly basis. The severity of alcohol dependence was evaluated by Severity Dependence Scale (SDS, Lawrinson *et al.* 2007).

All patients were without any withdrawal symptoms at the time of scanning. During the follow-up period of the study we re-evaluated the clinical conditions and the length of total abstinence following the discharge from the inpatient program. Patients were contacted (repeatedly if necessary) by phone. The relapse was defined as the consumption of 5 or more drinks (alcohol units) for men and 4 or more drinks for women per one occasion (drinking day) (O´Malley *et al.* 1992). The data on alcohol consumption and severity of alcohol dependence were obtained from patients, medical examination records and verified by their relatives.

The written informed consent was obtained from all patients, and the local Ethics committee of Faculty of Charles University in Pilsen, Czech Republic approved the study.

PET investigation

Patients were fasted for at least 6 hours before the investigation. In a dimly-lit and quiet room, ^{18}FDG was administered via a peripheral vein catheter. Applied activity (= dose of ^{18}FDG) (MBq) = recommended activity for 70kg (= 250 MBq) × coefficient of EANM (European Association of Nuclear Medicine). The coefficient of EANM is defined for concrete weight of examined patient (Jacobs *et al.* 2005). The patients rested for 30 min in a specified condition that is described as Random Episodic Silent Thinking (REST, Andreasen 1995). The subjects were instructed to avoid focusing on any specific mental process during scanning to eliminate stimuli and the undesirable (unwanted) activity of brain structures. PET images were acquired with a dedicated PET/CT scanner (Biograph LSO, Siemens Medical Solutions/CTI). The 2D "hot" transmission

Copyright © 2012 Neuroendocrinology Letters ISSN 0172–780X • www.nel.edu

scans were immediately followed by 3D emission scanning which lasted 15 minutes.

PET data preprocessing and statistical analyses

PET data analyses were performed using Statistical Parametric Mapping, SPM5 (http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab (Mathworks, USA). The PET scans were normalized into standard stereotactic space and smoothed with an isotropic Gaussian filter (full width at half maximum of 12 mm). The global intensity differences were corrected by proportional scaling (global mean to 50, analysis threshold 0.8) and global calculation was performed by the mean voxel value. The t-test was used to determine the differences between responders and non-responders by the means of the full abstinence during the one year follow-up period after discharge from hospital. The associations between previous duration of alcohol consumption, age and the length of abstinence during the follow-up period were tested by regression models. Age was used as a nuisance covariate if appropriate. For rigorous control of type I error we accepted only findings corrected for the multiple comparisons by conservative family-wise error (FWE) correction with p-level <0.05 and the extent threshold consisting of 30 voxels per cluster as being significant. The coordinates for local maxima in MNI (Montreal Neurological Institute) template were converted to stereotactic Talairach x, y, z coordinates (Lancaster *et al*. 2007).

Statistical analyses

All statistical analyses were performed using the Statistica 9 program. The analyses were performed by t-tests in comparisons between responders and non-responders in terms of age, duration and severity (SDS) of alcohol abuse. We used Pearson and M-V chi-square test for categorical measures as education. The p-values <0.05 were considered as significant.

RESULTS

Treatment response

The demographic data of 29 inpatients included in this prospective study are displayed in Table 1. PET investigation was performed in 28 patients, because 1 participant finished the treatment prematurely. 26 patients completed over the 12 months period of monitoring; 14 abstained for 12 months and 12 patients relapsed. These two groups did not significantly differ in age, the duration of alcohol abuse, the severity of alcohol dependence (measured by SDS) and gender before the treatment and in clinical status evaluated by scales. They differed in age and education, abstainers were more educated (see Table 1).

The influence of previous alcohol consumption on PET

The correlation between age and ^{18}FGD uptake was not significant at the voxel FWE corrected level. However, by the use of less conservative corrections for multiple comparisons FDR (p=0.05) and cluster correction (p=0.05) we detected a negative correlation with age for a cluster consisting of right cerebellum (1602 voxels in cluster, local maximum xyz= 8, –74, –28). The positive correlation with age was found in one region on the right (1382 voxels covering lentiform nc., insula and caudate (local maximum xyz= 34, –6, 6) and one on the left side (972 voxels located in precuneus and superior temporal gyrus (local maximum xyz=–22, –32, 44). Due to the fact that these regions correspond with the expected effect of alcohol consumption we covariated out age in all other analysis even if the effect of age did not reach FWE level.

The length (years) and severity of alcohol abuse measured by SDS (Severity Dependence Scale) did not result in any significant regional brain metabolic changes detected by ^{18}FDG PET.

Tab. 1. Sample description for demographic and clinical data. Data are displayed in means (standard deviation).

	Whole sample (n=29)	Abstainers (n=14)	Non-abstainers (n=12)	*p*-value (t-test)	*p*-value (Mann-Whitney U test)
Age (years)	42.21 (9.76)	44.86 (11.53)	38.62 (6.24)	0.096	0.07
Duration of alcohol abuse (years)	10.45 (7.88)	8.93 (8.16)	12.38 (7.95)	0.26	0.15
SDS	8.62 (3.66)	9.46 (2.93)	7.71 (3.81)	0.20	0.35
				***p*-value (Pearson χ^2 test)**	***p*-value (M-V χ^2 test)**
M/F	12/15	5/9	5/7	0.58	0.58
Education U/S/P	4/21/4	4/10/0	**0/10/2**	**0.03**	**0.01**

Abbreviations: SDS, Severity Dependence Scale; U/S/P, University/Secondary/Primary school education.
Significant results (p<0.05) are in bold font.

Tab. 2. Regional brain metabolism (PET) results.

Brain region	R or L	cluster *p*(cor)	Cluster size	voxel *p*(FWE)	Talairach coordinates x	y	z	BA
Abstinence dutarion (posit.)								
Cerebellum (Vermis, Lob. 6)	**R**	**0.000**	**1517**	**0.005**	**6**	**–69**	**–24**	**–**
Cerebellum (Vermis, Lob. 7)	**L**			**0.006**	**–3**	**–69**	**–20**	**–**
Lingual Gyrus	R			0.933	6	–88	–15	18
Supramarginal Gyrus	L	0.486	113	0.799	–55	–48	22	40
Cerebellum (Hemisphere, Lob. 1)	L	0.780	56	0.943	–42	–70	–26	–
Fusiform Gyrus	L			0.983	–38	–75	–16	19
Abstinence dutarion (negat.)								
Claustrum	R	0.006	624	0.077	28	–11	18	–
Caudate	R			0.567	23	–35	16	–
Lentiform Nucleus	R			0.980	27	–13	–2	–
Cerebellum (Hemisphere, Lob.6)		0.874	38	0.906	31	–58	–21	–
Lingual Gyrus	R	0.888	35	0.973	21	–64	4	19
Responders < non-responders								
Cerebellum (Hemisphere, Lob. 6)	R	0.540	102	0.309	38	–54	–25	–
Caudate	L	0.853	42	0.722	–16	–7	18	–
Caudate	R	0.481	115	0.728	15	–7	18	–
Responders > non-responders								
Cerebellum (Hemisphere, Lob.6)	R	0.151	240	0.360	7	–67	–25	–
Supramarginal Gyrus	L	0.239	190	0.647	–57	–49	24	40
Middle Frontal Gyrus	L	0.535	103	0.844	–44	7	47	6
Postcentral Gyrus	L	0.887	35	0.870	–60	–6	15	43
Parahippocampal Gyrus	L	0.265	179	0.887	–38	–30	–10	36

The results for clusters consisting of ≥ 30 voxels and exceeding *p*-level <0.001 for height threshold T=3.48 (comparison between responders and non-responders) and T=3.50 (positive and negative correlation with duration of abstinence in the follow-up period) are displayed. The significant findings corrected for the multiple comparisons by family-wise error (FWE, $p<0.05$) are in bold.
Abbreviations: L or R, left or right hemisphere; Lob., Lobulus; x, y, z, Talairach coordinates of voxel of maximum significance; BA, Brodmann' s area; – , no BA for the cluster.

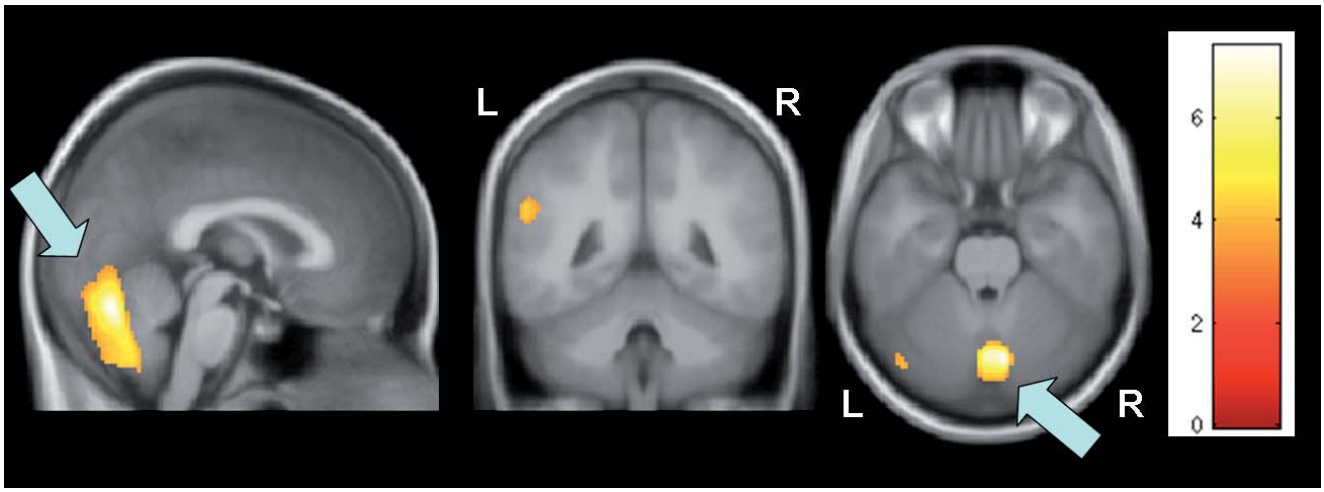

Fig. 1. The positive correlation between ^{18}FDG uptake and abstinence duration after discharge from the inpatient treatment program. The bar on the left represents T-value. Significant results ($p \leq 0.001$, uncorrected) are displayed. The arrow indicates the FWE corrected association in cerebellar vermis. For list of anatomical specifications and technical details, see Table 2. L or R, left or right hemisphere.

Copyright © 2012 Neuroendocrinology Letters ISSN 0172–780X • www.nel.edu

Regional brain metabolism (PET) and the duration of abstinence in the follow-up period

The ^{18}FDG uptake in cerebellar vermis (FWE $p<0.05$) exerted the positive correlation with abstinence in terms of its duration after discharge from the inpatient treatment program. Other regions did not reach the conservative corrected *p*-level (Table 2, Figure 1).

The predictive role of the cerebellum was also supported to be the comparison between responders and non-respoders to the therapeutic program. Patients who relapsed during 12 month after discharge compared to successful abstainers exerted lower regional metabolism in the cerebellum (Table 2). However, these findings did not survive FWE correction.

DISCUSSION

The main finding of this study is represented by the positive association between the duration of abstinence after discharge from hospitalization and ^{18}FDG uptake in cerebellar vermis. In other words, the higher the metabolism in vermis is, the better the prognosis is in terms of the duration of abstinence. The fact that the differences between responders and non-responder in cerebellar metabolism did not reach the conservative FWE level supports the assumption that the continual measure of remission (duration) is more sensitive for the detection of neurobiological (metabolic) parameters.

The cerebellum has been attributed mainly to its sensitivity for neurotoxic changes in heavy drinkers (Cardenas *et al.* 2007) and its role in the pathophysiology of alcohol dependence was neglected. The cerebellum plays an important role in many control mechanisms of emotional reactivity and cognitive functions (Kaufman *et al.* 2009). Our findings support the assumption that the cerebellum would be involved in the maintenance of abstinence in alcohol dependent subjects. Cerebellar connections with cortical areas critical for addiction such as frontal, parietal, temporal regions would mediate the influence of cerebellum on emotional systems related to addiction. The cerebellum could play an essential role in addiction, as well as in executive skills, learning, memory and reward processing in general (Harper *et al.* 2009, Kaufman *et al.* 2009). It is still unclear whether morphological and metabolic cerebellar abnormalities, particularly in the vermis are made by the direct neurotoxic effect of alcohol only or other mechanisms are involved (Durazzo and Mayerhoff 2008, Sullivan and Pfefferbaum 2005). It has not been clarified yet whether the cerebello-thalamo-cortical and cortico-ponto-cerebellar circuits are involved in the initiation or maintenance of alcohol addiction (Durazzo *et al.* 2010).

The cerebellar changes are a clinical problem specific for alcohol addiction (Harper *et al.* 2009). Our data indicate that improvement of disrupted cerebellum and its connections could lead to a better outcome and the course of the addiction (and emotional consequences) not only as a simple marker of long-term sobriety. The possible explanation of this finding is the destruction of the cerebellum as a direct consequence of high alcohol drinking and outcome of the life before treatment. Brain atrophy of the fronto-ponto-cerebellar network is less pronounced in patients who maintained long-term sobriety (Cardenas *et al.* 2007).

The vermis not only plays an important role in reward processing, memory and cue reactivity, but in maintaining attention as well (Yalachkov *et al.* 2010, Allen *et al.* 2009). Reciprocal connection between the cerebellum and frontal circuits are involved in motivational behavior and its tuning (Zahr *et al.* 2010). Regarding high sensitivity these structures are involved not only in addiction behavior but in extinction as well.

The change in the vermis may be connected with the ability to manage emotions/stress and/or reflect ability in cognitive functions. This is an important part in treatment of alcohol addiction. To receive such information as soon as possible could be used for the individualization of treatment. Early individualization and change in treatment intensity and strategy may lead to improving in outcome of the overall care.

We did not find any association between the length and severity of preceding alcohol abuse and regional brain metabolism at the baseline of our study. The possible explanation is that our patients were selected to be suitable for this short term therapeutic intervention. Hence, the more severe cases with longer term history of abuse and severe cognitive deficit were not included in this treatment program. Frequently relapsed, heavy drinkers and older patients would have significantly different outcomes, the long term destruction of the functional and structural connection of the cerebellum and the rest of the brain could lead to another connectivity between those regions.

CONCLUSION

Our study is the first to document that the cerebellum and particularly the vermis is involved in the clinical outcome in terms of abstinence during one year. The treatment stability during long-term out-patient treatment is the key factor for improving the outcome of addiction treatment. Our findings support the role of the cerebellum in addiction and the possibility to predict therapeutic outcome.

ACKNOWLEDGEMENTS

This work was supported by grant No. IGA NS 10253-3 from the Internal Grant Agency of the Ministry of Health, Czech Republic.

The authors acknowledge Tomas Novak MD (Psychiatric Center Prague) (who performed) for the statistical analyses and Jan Zahlava MD (Department of Imaging Methods Charles University Hospital in

Pilsen) who performed the PET/CT scans. The authors of this study did not receive any other financial support.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LJ designed the study protocol, obtained the approval of the local ethical committee, wrote the manuscript, performed inform consent from all participants, the clinical evaluation of psychiatric patients, the evaluation of psychiatric patients with psychiatric scales and anamnestic questionnaires.

SR designed the study protocol, wrote the manuscript, performed inform consent from all participants, performed the clinical evaluation of psychiatric patients, performed the evaluation of psychiatric patients with psychiatric scales and anamnestic questionnaires

JH designed the study protocol, wrote manuscript, performed statistical analysis of PET data

REFERENCES

1 Allen AJ, Meda AS, Skudlarski P, Calhoun V, Astur R, Ruopp KC, Pearlson GD (2009). Effects of Alcohol on Performance on a Distraction Task During Simulated Driving. Alcohol Clin Exp Res. **33**(4): 617–625.
2 Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Watkins GL, Ponto LL, Hichwa RD (1995). Remembering the past: two facets of episodic memory explored with positron emission tomography. Am J Psychiatry.**152**: 1576–1585.
3 Cardenas VA, Studholme C, Gazdzinski S, Durazzo TC, Meyerhoff DJ (2007). Deformation-based morphometry of brain changes in alcohol dependence and abstinence. Neuroimage **34**: 879–887.
4 Durazzo TC, Meyerhoff DJ (2007). Neurobiological and neurocognitive effects of chronic cigarette smoking and alcoholism. Front Biosci. **12**: 4079–4100.
5 Durazzo TC, Pathak V, Gazdzinski S, Mon A, Meyerhoff DJ (2010). Metabolite Levels in the Brain Reward Pathway Discriminate Those Who Remain Abstinent From Those Who Resume Hazardous Alcohol Consumption After Treatment for Alcohol Dependence. J Stud Alcohol Drugs. **71**(2): 278–289.
6 Harper C (2009). The Neuropathology of Alcohol-Related Brain Damage. Alcohol & Alcoholism. **44**(2): 136–140.
7 Heinz A, Beck A, Grüsser SM, Grace AA, Wrase J (2009). Identifying the neural circuitry of alcohol craving and relapse vulnerability. Addict Biol. **14**(1): 108–118.
8 Jacobs F, Thierens H, Piepsz A, Bacher K, Van de Wiele C, Ham H *et al.* (2005). Optimised tracer-dependent dosage cards to obtain weightindependent effective doses. European Journal of Nuclear Medicine and Molecular Imaging. **32**: 581–588.
9 Kaufman KA, Harper C, Wilce P, Matsumoto I (2007). Cerebellar Vermis Proteome of Chronic Alcoholic Individuals. Alcohol Clin Exp Res. **31**(8): 1286–1296.
10 Lancaster JL, Tordesillas-Gutierrez D, Martinez M, Salinas F, Evans A *et al.* (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. Hum. Brain Mapp. **28**: 1194–1205.
11 Lawrinson P, Copeland J, Gerber S, Gilmour S (2007). Determining a cut-off on the Severity of Dependence Scale (SDS) for alcohol dependence. Addict Behav. **32**(7): 1474–1479.
12 O´Malley SS, Adam J, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B (1992). Naltrexone and coping skills therapy for alcohol dependence. A controlled study. Arch Gen Psychiatry. **49**: 881–887.
13 Parvaz MA, Alia-Klein N, Woicik PA, Volkow ND, Goldstein RZ (2011). Neuroimaging for drug addiction and related behaviours. Rev Neurosci. **22**(6): 609–624.
14 Rehm J, Shield KD (2012). Interventions for alcohol dependence in Europe: a missed opportunity to improve public health. May 2012. http://www.camh.net/Research/Research publication
15 Rocher AB, Chapon F, Blaizot X, Baron JC, Chavoix C (2003). Resting-state brain glucose utilization as measured by PET is directly related to regional synaptophysin levels: a study in baboons. Neuroimage. **20**: 1894–1898.
16 Schiffer WK, Lee DE, Brodie D, Dewey DS (2005). Imaging addiction with PET: Is insight in sight? Drug Discovery Today. **10**(8): 547–562.
17 Shulman RG (2001). Functional imaging studies: linking mind and basic neuroscience. Am J Psychiatry. **158**(1): 11–20.
18 Sullivan EV, Pfefferbaum A (2005). Neurocircuitry in alcoholism: A substrate of disruption and repair. Psychopharmacology (Berl). **180**: 583–594.
19 Thanos PK, Wang GJ, Volkow ND (2008). Position emission tomography as a tool for studying alcohol abuse. Alcohol Research & Health. **31**(3):233–237.
20 Volkow ND, Fowler JS, Wang GJ (2003). The addicted human brain: insights from imaging studies. J. Clin. Invest. **111**(10): 1444–1451.
21 Volkow ND, Fowler JS, Wang GJ, Baler J, Telang F (2009). Imaging dopamine's role in drug abuse and addiction. Neuropharmacology. **56**(Suppl1): 3–8.
22 Weisner C, Matzger H, Kaskutas LA (2003). How important is treatment? One-year outcomes of treated and untreated alcohol-dependent individuals. Addiction. **98**: 901–911.
23 Yalachkov Y, Kaiser J, Naumer MJ (2010). Sensory and motor aspects of addiction. Behav Brain Res. **207**(2): 215–222.
24 Zahr NM, Pitel AL, Chanraud S,Sullivan EV (2010). Contributions of Studies on Alcohol Use Disorders to Understanding Cerebellar Function. Neuropsychol Rev. **20**(3): 280–289.

Copyright © 2012 Neuroendocrinology Letters ISSN 0172–780X • **www.nel.edu**