Media Release: European College of Neuropsychopharmacology (ECNP)

"For the science and treatment of disorders of the brain"

Heavy alcohol use alters brain functioning differently in young men and women

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Scientists have found that brain functions in young men and women are changed by long-term alcohol use, but that these changes are significantly different in men and women. This indicates not only that young people might be at increased risk of long-term harm from alcohol use, but also that the risks are probably different in men and in women, with men possibly more at risk. This work is presented today at the ECNP meeting in Paris.

A Finnish research group worked with 11 young men and 16 young women who had a heavy 10-year alcohol use, and compared them with 12 young men and 13 young women who had little or no alcohol use. All were between 23 to 28 years old at the time the measurements were taken. The researchers examined the responses of the brain to being stimulated by magnetic pulses – known as Transcranial Magnetic Stimulation (TMS), which activates brain neurons. The brain activity was measured using EEG (electroencephalogram).

Previously, the researchers had found that heavy alcohol users showed a greater electrical response in the cortex of the brain than non-alcohol users, which indicates that there had been long-term changes to how the brain responds. This time, they found that young men and young women responded differently, with males showing a greater increase in electrical activity in the brain in response to a TMS pulse. As researcher Dr Outi Kaarre (University of Eastern Finland and Kuopio University Hospital, Finland) said:

"We found more changes in brain electrical activity in male subjects, than in females, which was a surprise, as we expected it would be the other way around. This means that male brain electrical functioning is changed more than female brains by long-term alcohol use"

The EEGs also allowed the researchers to show that male brains have greater electrical activity associated with the GABA (gamma-amino butyric acid) neurotransmission than do female brains.

Dr Kaarre continued, "Generally, our work showed that alcohol causes more pronounced changes in both electrical and chemical neurotransmission in men than women. There are two types of GABA receptors, A and B. Long-term alcohol use affects neurotransmission through both types in males, but only one type, GABA-A, is affected in females.

We're still trying to figure out what this means, but GABA is a pretty fundamental neurotransmitter in the inhibition of many brain and central nervous systems functions. It's involved in many neurological systems, and is important in anxiety and depression. Generally it seems to calm down brain activity.

We know from animal studies that GABA-A receptor activity seems to affect drinking patterns, whereas GABA-B receptors seem to be involved in overall desire for alcohol. It has been suggested

that women and men may respond differently to alcohol. Our work offers a possible mechanism to these differences."

We know that long-term alcohol use can be risky for young people. What this work means is that long-term alcohol use affects young men and women very differently, and we need to find out how these differences manifest themselves. It may be that we need to look at tightening regulations on youth drinking, since none of our study participants met the diagnostic criteria for alcohol use disorders and still these significant changes in brain functioning were found. It may also mean that gender differences should be taken into account when planning pharmacological treatment for alcoholism".

Commenting, Professor Wim van den Brink (Professor of Psychiatry and Addiction at the Academic Medical Centre, University of Amsterdam, and ex Chair of the ECNP Scientific Programme Committee)*:*

"These are very interesting findings, especially since young women are catching up with young men when it comes to drinking and heavy drinking in Europe. This may also mean that a different group of women is getting involved in early heavy alcohol use than used to be the case; in other words, when heavy drinking occurs more frequently and tends to become the norm, women do not need to have some aberrant personal characteristic to become an early heavy user of alcohol.

The finding of a different EEG-pattern in male and female early heavy drinkers may indeed have important consequences for the treatment of male and female patients with an alcohol use disorder. One of the most recent new medications for the treatment of alcohol dependence is the GABA-B agonist Baclofen, which has shown mixed results which may be explained by this work.

A limitation of the study is that it says nothing about possible pre-existing neurobiological differences between the groups, an explanation for the observed differences that is equally valid".

Note: this is an edited version of a longer comment, available from the press officer.

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Notes for Editors

<u>The European College of Neuropsychopharmacology (ECNP)</u>

The ECNP is an independent scientific association dedicated to the science and treatment of disorders of the brain. It is the largest non-institutional supporter of applied and translational neuroscience research and education in Europe. Website: www.ecnp.eu

The 30th annual ECNP Congress takes place from 2nd to 5th September in Paris. It is Europe's premier scientific meeting for disease-oriented brain research, annually attracting between 4,000 and 6,000 neuroscientists, psychiatrists, neurologists and psychologists from around the world. Congress website: http://2017.ecnp.eu/

Conference abstract: P.6.b.008 Gender differences in the alcohol-related alterations in cortical activity – a combined TMS-EEG studyO. Kaarre[1]*, E. Kallioniemi[2], M. Könönen[3], T. Tolmunen[4], V. Kekkonen[4], P. Kivimäki[5], N. Heikkinen[5], F. Ferreri[6], E. Laukkanen[4], S. Määttä[2]

Background Long-term alcohol use is known to harm brain functioning in adolescence. In the central nervous system, the effects of alcohol are particularly mediated by alterations in GABAergic neurotransmission [1]. Combining simultaneous electroencephalogram (EEG) recording with transcranial magnetic stimulation (TMS) enables direct, in vivo exploration of cortical excitability and assessment of effective and functional connectivity. After motor cortex stimulation, the TMS-evoked EEG potentials (TEPs) N45 and N100 are known to reflect GABA-A- and GABA-B-ergic function, respectively [2].Sexual differentiation of the brain begins in the prenatal and early postnatal periods [3]. Changes in sex steroid secretion in adolescence continue remodeling the brain and facilitating the sexual differentiation, since the sex hormones act directly on the neurons and supporting neural processes [3]. The effects are region- and sex-specific, the female brain developing earlier than the male brain [3].

Aims Previously, we have demonstrated that alcohol use in adolescence is associated with altered cortical activity [4]. The aim of the current study was to explore whether long-term alcohol use in adolescence affects the cortical activity of the male and female brain differently. Our hypothesis was that females are more vulnerable to effects of alcohol and that this difference is seen in the GABAergic TEPs N45 and N100.

Methods In this study, a total of 27 (11 males) young adults with heavy 10-year alcohol use in adolescence and 25 (12 males) controls with little or no alcohol use participated in TMS-EEG measurements. The motor cortex (M1) was stimulated with an intensity of 90% of the resting motor threshold (rMT) of the abductor pollicis brevis muscle and 61-channel EEG was registered. Data analysis was conducted using MATLAB and the EEGLAB toolbox. Statistical analyses were performed for both genders separately using IB M SPSS Statistics, version 22

Results In the linear mixed model analysis, in both genders, a statistically significant group*AP interaction (group=case/control, AP=anteroposterior location of the EEG channels) was found in the GABA-A-ergic TEP amplitude N45 (females: p=0.003, males: p<0.001). In males, group*AP difference was also encountered in the GABA-B-ergic N100 (p<0.001). Post hoc analysis was performed to determine the statistically significant interaction factors, i.e. regions in which the differences existed. The average peak amplitudes and statistical significance in the between-groups comparison in the post hoc analysis are presented in Table 1. The significant difference in the N45 was located frontally. The N100 was topographically differently distributed in male subjects and controls. In males, the mean N45 and N100 latencies also differed between the groups (Table 1). All reported p-values are Bonferroni corrected for multiple comparisons.

Conclusions Our results support the hypothesis that alcohol use affects the developing brain differently in males and females. Interestingly, in males, alcohol use was associated with altered GABA-A- and GABA-B-ergic cortical functioning, whereas in females the alterations were found only in the GABA-A-ergic activity. The relationship between sex hormones and neurotransmission should be further studied. Note: references not included, but available from the press officer

Table 1

	Females, controls	Females, alcohol users	Females: Between-group comparison, statistical sig.	Males, controls	Males, alcohol users	Males: Between-group comparison, statistical sig.
N45 (μV), frontal	-0.864	-1.460	p=0.015*	-1.067	-1.732	p=0.002*
N45 (μV), central	-0.998	-0.913	ns	-1.098	-1.170	ns
N45 (μV), parieto-occipital	-0.377	-0.368	ns	-0.409	-0.585	ns
N45 mean latency (ms)	47	46	ns	44	51	p=0.002*
N100 (μV), frontal	-1.052	-1.098	ns	-0.484	-1.191	ns
N100 (μV), central	-1.258	-1.129	ns	-1.194	-1.621	ns
N100 (μV), parieto-occipital	-0.972	-1.032	ns	-1.130	-0.665	ns
N100 mean latency (ms)	97	96	ns	99	85	p=0.038*

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How this press release was reviewed?

There were 1003 abstracts accepted for this conference, this work was amongst the top-scoring 170 abstracts. After initial approval from the ECNP media group, the press release was developed by the press officer and the author, with the final version being approved by the ECNP media review group. We then sought an additional view and comment from someone with expertise in the field – this is the person who comments in the press release. None of the reviewers have been involved in the work.