



Choline intake effects on psychophysiological indicators of students in the pre-exam period

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Abstract:

Introduction. Choline has a wide range of physiological functions. It has a neuroprotective effect on brain dysfunctions, while its deficiency has a negative effect on antenatal development of the nervous system. We aimed to study the impact of exogenous choline on the psychophysiological indicators in students.

Study objects and methods. 87 students were surveyed by questionnaire to determine their background intake of dietary choline. One month before the exams, we measured their simple and complex visual-motor reaction times, functional mobility and balance of nervous processes, as well as indicators of their short-term memory, attention, health, activity, and mood. Then, we divided the students into a control and an experimental group, regardless of their choline intake. The experimental group took 700 mg choline supplements on a daily basis for one month, followed by a second psychophysiological examination.

Results and discussion. Students with a low choline intake had lower functional mobility and balance of nervous processes, but better attention stability than students with a high choline intake. The second examination showed improved short-term memory, health, and activity indicators in the experimental group, compared to the control. The visual-motor reaction times also increased, but only in students with an initially low level of choline intake.

Conclusion. Choline supplementation can be recommended to students under pre-exam stress to enhance the functional state of their central nervous system.

Keywords: Choline, intake level, choline supplements, students, psychomotor reactions, cognitive functions

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INTRODUCTION

There has been a lot of research into choline over the past few decades. It is a vitamin-like nutrient that takes part in many physiological processes and has a wide range of physiological functions [1, 2].

Choline is ingested with food as part of phosphatidylcholine or formed endogenously. The human need for choline is met mainly through food. Its adequate daily intake is 425 mg for women and 550 mg for men, but not more than 3.5 g/day [3]. Metabolic pathways for the conversion of dietary choline and its endogenous synthesis are genetically heterogeneous. This determines individual sensitivity to a deficiency of choline [4, 5].

Choline has a significant effect on the development and functioning of the nervous system. As part of phosphatidylcholine, it participates in the construction, stabilization, and repair of cell membranes, including neurons. As a component of sphingolipids, it myelinates nerve fibers [6, 7]. As a precursor of betaine (a methyl group donor), choline is a factor in epigenetic regulation of gene expression during neurogenesis [8, 9]. DNA methylation is a dynamic process that can modulate the expression of genes that regulate synaptic plasticity. Since neurogenesis continues throughout life, dietary intake of choline as a source of methyl groups can affect cognitive functions at various stages of ontogenesis [10].

Our special interest is in choline as a precursor of acetylcholine, the most important neurotransmitter of the central and peripheral nervous system. Cholinergic systems of the brain have been in the center of neuroscientific and medical research due to their importance for cognitive functions and motor skills [11–14]. The influence of choline, either ingested or synthesized endogenously, on the effects of cholinergic neurotransmission is determined by a large number of genetic and epigenetic factors. These factors include enzyme systems that transport choline to the presynaptic terminals of neurons, the synthesis of acetylcholine from choline and acetylcoenzyme A and its inactivation after its use in synapses, as well as localization and activity of muscarinic and nicotinic cholinergic receptors. Therefore, it is difficult to interpret experimental data on the relationship between exogenous choline and the effects of acetylcholine.

The effects of choline on the nervous system have also been extensively studied. For example, its deficiency has a negative impact on the intrauterine development of the nervous system. Some studies on animals found that choline-enriched nutrition of pregnant females improved the cognitive functions of their offspring at various stages of ontogenesis and slowed down age-related involution. Its most pronounced effect was found in the study of learning and spatial memory in rodents using the Morris water maze, which indicated the involvement of hippocampal neurons [10]. However, the studies on humans, which examined the effect of a choline-fortified diet for pregnant women on the development of their children's cognitive abilities, produced conflicting data [15–17].

Another area of choline research is its neuroprotective effect and impact on cognitive functions in adults. Pharmaceutical choline-containing drugs are often prescribed for pathologies of the nervous system. The neuroprotective effects of choline alfoscerate and cytidine-5'-diphosphocholine (citicoline) have been proven in treating cognitive impairment associated with trauma, vascular disorders, or neurodegenerative diseases [18–21]. The studies of choline effect on cognitive functions of healthy individuals in postnatal ontogeny have yielded mixed results. For example, memory tests on 1391 adult men and women without cognitive impairment revealed a positive effect of choline consumption, with similar results found for cognitive tests on 2195 people aged 70–74 [22, 23].

Knott *et al.* examined the effect of a single dose of citicoline in low and medium concentrations. They found that the effect was determined by the initial level of choline, i.e., the subjects with initially low levels of choline had improved cognitive functions after citicoline treatment [24].

According to another study, choline bitartrate improved the accuracy (rather than the time) of visual-motor task performance in students [25]. A positive relationship was found between the plasma choline content in 15-year-olds and their school

performance [26]. Other researchers, however, did not observe a positive effect of short-term choline bitartrate treatment on the memory function of students [27].

Studies on school and college students are especially relevant. Childhood and adolescence are the periods of life when the morphofunctional maturation of the nervous system is combined with intensive cognitive activity during schooling. Of paramount importance therefore is nutrition that satisfies the plastic and functional needs of the nervous system. Choline is one of such nutrients. However, more research is needed to clarify the relationship between choline and cognitive functions in different age groups, including students.

We should also mention a potential negative effect of high choline intake on human health. This problem has been widely discussed in recent years due to the existence of choline metabolic pathways with the participation of intestinal microflora. A certain composition of intestinal microbiota produces a large amount of trimethylamine (TMA), which is absorbed by the epithelium, entering the liver through the portal vein, where it is converted into trimethylamine N-oxide (TMAO). The cumulative effects of TMAO are currently associated with the risk of atherosclerosis, insulin resistance, stomach and intestinal cancer, as well as kidney pathology [28–30]. Therefore, increasing choline intake should be recommended to adults with caution.

We aimed to expand our awareness of exogenous choline effect on psychophysiological functions under increased nervous stress. For this, we set the following objectives:

- assessing levels of choline intake in university students;
- analyzing the relationship between choline intake levels and psychophysiological characteristics;
- studying the effect of choline supplementation on the functional indicators of the central nervous system in students in the pre-exam period.

STUDY OBJECTS AND METHODS

Study design. First, we formed a cohort of 87 study subjects (13 males and 74 females) aged 19 from the 1st- and 2nd-year students of the Department of Social Work and Psychology at Kemerovo State University (Kemerovo, Russia) and obtained their informed written consent to participate in the study. All the study subjects were surveyed by questionnaire to assess their dietary choline intake. In addition, they underwent a psychophysiological examination to assess their neurodynamic and cognitive functions.

Next, the 2nd-year students were divided into a control and an experimental group, 20 people each (4 males and 16 females) by pairwise selection based on mechanical memory. The experimental group took a mono-component dietary supplement “Choline 350 mg Vegetable Capsules” (Solgar, USA). The supplement was registered under No. RU.77.99.11.003.E.004764.10.18 of 29.10.2018 in the Customs Union's Register of State Registration Certificates. Choline was taken for one

month, one capsule twice a day with a meal. At the end of the intake period, both groups underwent another psychophysiological examination.

Finally, the data were statistically processed and analyzed.

Choline determination methods. Food frequency questionnaire (FFQ) was used to determine the frequency of consumption of choline-containing foods and to estimate the absolute daily intake by portion size [26]. The survey followed the Russian guidelines¹.

The questionnaire included foods with a choline content of at least 10% of the daily intake per 100 g. It also listed dairy products (milk, kefir) which had a choline content of 5–8% of the daily intake per 100 g, but could be consumed in fairly large amounts. The subjects were surveyed in a group, with the interviewer giving explanations about the questionnaire. The respondents were asked to estimate the frequency of consumption of the listed products during the last month, as well as indicate the approximate size of the portions. Then, we analyzed the responses to determine the approximate amount of choline intake using available sources [31, 32] and ranked the results by the quartile method.

Methods for studying psychophysiological functions. The neurodynamic and cognitive indicators were determined with the psychophysiological complex “Status PF”¹¹. The testing was carried out in a group in the university computer classroom on Tuesday and Wednesday mornings before classes with minimum extraneous irritants. Prior to the testing, we explained its meaning and significance in order to form a positive attitude among the study subjects. The tests that we selected did not require significant mental strain or much time to perform. In particular, we used the following well-known diagnostic tools.

The latent period of a simple visual-motor reaction is the most common psychomotor indicator that reflects the rate of excitation along the reflex arc and, therefore, the excitability of the central nervous system. This is a rather labile indicator that adequately characterizes its functional state. The general simple visual-motor reaction time is determined by the subject’s anatomical features of the sensory system, nervous processes, psychophysiological state, and the motor-coordination potential. The subjects were asked to press a key on the computer keyboard as quickly as possible in response to a light stimulus. The average time of a motor reaction (ms) was determined after 30 light stimuli with various random intervals.

The latent period of a complex visual-motor reaction reflects the time spent on analyzing information in the integrative-triggering cortical zones and making a decision about how to respond. The subjects were asked to react to a red signal with their right hand, to a green signal with their left hand, and not to react to a yellow signal. The average time of a motor reaction (ms) was determined after 30 light stimuli.

Functional mobility of nervous processes was determined by the method of Khilchenko (1958) modified by Makarenko *et al.* (1987). The level of functional mobility is an indicator of neurodynamic constitution that does not depend as much on the actual functional state of the central nervous system as the simple and complex sensorimotor reactions. This method is based on a complex visual-motor differentiation reaction in the feedback mode. In contrast to the previous method, the intervals between signals depended on the correctness of motor reactions, decreasing by 20 ms after a correct reaction and increasing after an incorrect one. The test included 120 standard stimuli. The test time (s) was a quantitative level of functional mobility of the subject’s nervous processes – the less time it took to do the test, the more accurate the responses were. The accuracy of responses was determined by the rate of changes between excitation and inhibition, that is, the functional mobility of nervous processes.

Balance of the nervous system in response a moving object reflects the relationship between excitatory and inhibitory processes in the cerebral cortex. This method determines the accuracy of visual-motor reaction to an object moving at the same speed in a circle. When the object overlapped the marker on the circle, the subjects had to press a key and “stop” it, with the time of deviation between the object and the marker recorded up to 1 ms. The subject’s reaction was considered accurate if the deviation was within ± 5 ms. We recorded the number of accurate reactions, anticipatory and lagging reactions (total and average), as well as the average deviation time.

Short-term visual memory is a phase of imprinting characterized by a short storage of a limited number of objects in memory. The stimuli on the monitor screen included two-digit numbers (Ebbinghaus method), syllables (Luria method), and unrelated words (Leser method). They were presented one at a time for 1 s with an interval of 2 s. The capacity of short-term memory was determined by the number of correctly reproduced stimuli immediately after presentation.

Attentional capacity was determined by the maximum number of simultaneously perceived objects. The subjects were shown a lined field (5 by 5), with objects (crosses) randomly located in the cells. With every exposure, the number of objects increased by one. After a 500 ms exposure, the objects disappeared and the subjects had to locate them on the field. Attentional capacity was determined by the maximum number of correctly located objects, expressed in points.

¹ Martinchik AN, Baturin AK, Baeva VS. Razrabotka metoda issledovaniya fakticheskogo pitaniya po analizu chastoty potrebleniya pishchevykh produktov: sozdanie voprosnika i obshchaya otsenka dostovernosti metoda [Developing a method to determine nutrition by the frequency of food consumption: creating a questionnaire and assessing the method’s reliability]. *Problems of Nutrition*. 1998;67(3):8–13. (In Russ.).

¹¹ Ivanov VI, Litvinova NA. Programma dlya EHVM “Otsenka psikhofiziologicheskogo sostoyaniya organizma cheloveka (Status PF)” [Computer program “Assessment of the psychophysiological state of the human body (Status PF)”]; № 2001610233. 2001.

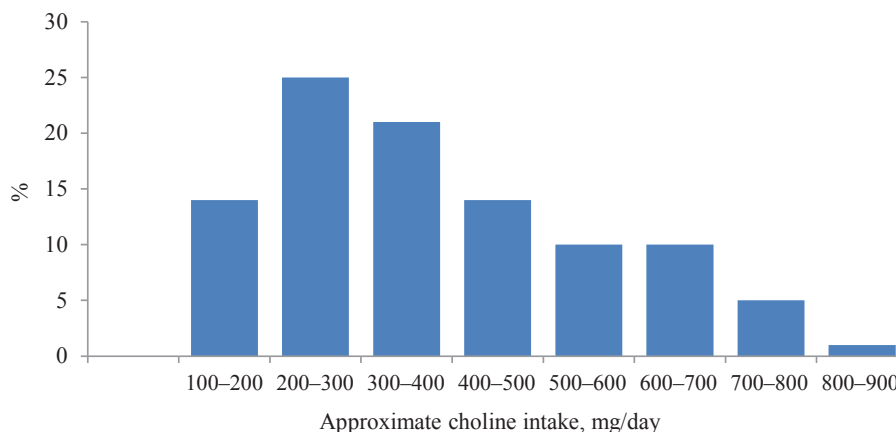


Figure 1 Students distribution by choline intake (according to the food frequency questionnaire)

Attention concentration was assessed with the Schulte table presented on the monitor screen. The subjects were to indicate the numbers from 1 to 25 in ascending order. The time taken to complete the test was an indicator of concentration. The less time one spent, the higher their attention concentration.

Attentional set-shifting was assessed with a red and black Schulte-Gorbov table. The subjects were invited to indicate black numbers in ascending order and red numbers in descending order: 1 – black, 24 – red, 2 – black, 23 – red, 3 – black, etc. The time taken to complete the test was a measure of attentional set-shifting (the less time, the better the indicator).

Attention stability was determined with a computer version of the dot cancellation test. The subjects were asked to look through lines of letters in the table and mark the given four letters for 4 min. The test assessed the speed of performance (number of letters viewed) and its accuracy (number of errors), with their ratio calculated as the total productivity index.

The *HAM (health, activity, mood) test*^{III} was used for the students' additional self-assessment of their functional state. The questionnaire had 30 pairs of subjective characteristics with opposite meanings (for example, “funny-sad”, “slow-fast”, etc.). The subjects were asked to indicate their current state on a scale between these poles. The neutral state was marked as “0” and the extreme (most pronounced) state as “3” (both poles). The points were added up for each scale (health, activity, and mood).

Statistical processing was carried out in Excel and Statistica 6.0. Mean values and standard errors were determined for all the indicators under study. In addition, we performed the analysis of histograms and the percentile analysis. Normality of the distribution was measured by the Kolmogorov-Smirnov test. Due to the small size of our sample, most indicators did not

have a normal distribution. Therefore, we applied the Mann-Whitney test to compare two groups and the median test for multiple comparisons. The Wilcoxon rank test was used to assess changes in indicators. The χ^2 test measured the statistical significance of differences in percentage ratios ($P < 0.05$). Spearman's correlation analysis was also applied.

RESULTS AND DISCUSSION

The food frequency questionnaire (FFQ) results showed that the approximate level of choline intake with the products included in the questionnaire ranged from 100 to 900 mg per day (Fig. 1). We found that 60% of the respondents had a choline intake below the recommended value (400 mg). The average choline consumption was 448.7 ± 50.6 mg for males and 373.4 ± 21.6 mg for females, also below the recommended value. Our data were generally consistent with the results of various international studies, as reported by Canadian authors [2]. Their review also emphasized that the reported low intake of total choline did not take into account its form (water-soluble or fat-soluble) and did not always indicate its deficiency in the body. When interpreting our results, we also assumed that the actual intake of choline was higher than the level shown by the FFQ, since the questionnaire did not include all the foods consumed by students. Yet, we had enough grounds for recommending that students who consume less than 400 mg of choline per day adjust their diet by including foods high in choline.

To study the relationship between neurodynamic characteristics and choline intake, the students were divided into three groups based on the quartile analysis: a) low choline intake (under 240 mg/d, quartile 1; b) medium choline intake (240–499 mg/d, quartiles 2 and 3; c) high choline intake (over 500 mg/d, quartile 4). The comparison of the neurodynamic parameters in these groups revealed some statistically significant differences (Tables 1 and 2).

We found that the students with a high choline intake had the best indicators for functional mobility of nervous

^{III} Doskin VA, Lavrent'eva NA, Miroshnikov MP, Sharay VB. Test differentsirovannoy samootsenki funktsional'nogo sostoyaniya [A test for differentiated self-assessment of the functional state]. *Voprosy Psichologii*. 1973;19(6):141–145. (In Russ.).

Table 1 Neurodynamic parameters in students with different levels of choline intake

Neurodynamic parameters	Choline intake			Mann-Whitney U-test*		
	Low (1)	Medium (2)	High (3)	1–2	1–3	2–3
Latent period of a simple visual-motor reaction, ms	292.3 ± 8.7	303.1 ± 23.3	279.6 ± 7.3			
Latent period of a complex visual-motor reaction, ms	446.5 ± 17.2	444.1 ± 10.6	435.6 ± 9.6			
Functional mobility of nervous processes – time, s	66.6 ± 1.8	65.2 ± 1.2	63.1 ± 1.3		0.04	
Reaction to a moving object: average deviation from accurate reactions, ms	29.8 ± 2.4	27.9 ± 3.3	30.4 ± 5.8			
Reaction to a moving object: total anticipatory reactions, ms	297.1 ± 52.0	246.5 ± 75.4	298.2 ± 62.5			
Reaction to a moving object: total lagging reactions, ms	513.6 ± 66.9	519.5 ± 51.4	340.4 ± 62.6		0.04	0.04

* $P < 0.05$ **Table 2** Memory and attention parameters in students with different levels of choline intake

Cognitive functions	Choline intake			Mann-Whitney U-test		
	Low (1)	Medium (2)	High (3)	1–2	1–3	2–3
Short-term memory (numbers), points	6.3 ± 0.4	6.0 ± 0.3	5.8 ± 0.3			
Short-term memory (words), points	7.13 ± 0.2	7.0 ± 0.3	7.1 ± 0.3			
Short-term memory (syllables), points	4.4 ± 0.4	4.6 ± 0.3	4.7 ± 0.4			
Attentional capacity, points	6.7 ± 0.4	6.5 ± 0.4	6.8 ± 0.4			
Attention concentration test completion time, s	45.4 ± 2.7	47.4 ± 2.4	45.0 ± 2.3			
Attentional set-shifting test completion time, s	173.4 ± 7.9	169.7 ± 5.6	167.2 ± 7.0			
Attention stability: total productivity index	62.6 ± 5.5	45.9 ± 5.9	48.9 ± 6.4	0.03		

* $P < 0.05$

processes and the least time of lagging reactions to a moving object.

The assessment of cognitive functions produced quite unexpected results. The integral indicator of attention stability based on the dot cancellation test was the highest among students with a low choline intake (Table 2). There were no other statistically significant differences.

We found no statistically significant correlations between dietary choline intake and psychophysiological indicators in the sample as a whole. However, there were significant differences in the groups with high, medium, and low choline intake.

The group with a low choline intake showed statistically significant correlations between the choline value and the number of anticipatory reactions to a moving object ($r = 0.46$, $P < 0.05$), the number of accurate reactions ($r = -0.68$, $P < 0.01$), the average time of lagging reactions to a moving object ($r = 0.54$, $P < 0.05$), and the short-term memory for numbers ($r = -0.31$, $P < 0.05$). Thus, the best indicators of psychomotor accuracy and short-term memory were found in students with the lowest choline intake.

In the group with a medium choline intake, its daily value had a negative effect on the number of accurate reactions to a moving object ($r = -0.35$, $P < 0.05$) and a positive effect on the average deviation time in the same test ($r = 0.32$, $P < 0.05$), just as in the low choline intake group. We found no statistically significant correlations between choline values and indicators of memory and attention in this group.

The group with a high choline intake revealed an inverse relationship between choline values and the latent period of a simple visual-motor reaction ($r = -0.5$, $P < 0.05$) and the time of completing the attention concentration test ($r = -0.4$, $P < 0.05$), as well as a direct relationship with attention stability ($r = 0.45$, $P < 0.05$). This meant that those students who consumed more choline in this group performed best in the visual-motor reaction and attention tests.

Thus, we found that the level of dietary choline intake had a greater effect on neurodynamic parameters than on cognitive functions. Higher choline values improved the mobility of nervous processes and accuracy in complex visual-motor reactions. However, their effects on cognitive functions were quite contradictory. We assumed that our results should be interpreted with other factors taken into account, which affected the students' choline intake and psychophysiological state. Yet, these additional factors were beyond the scope of this study.

The control and the experimental groups of 20 students in each were formed regardless of the choline

Table 3 Choline intake in the control and experimental groups, mg/day

Group	Median value	25–75 percentiles
Control (no choline treatment)	401	264–652
Experimental (with choline treatment)	416	315–492
P (Mann-Whitney U-Test)	0.91	

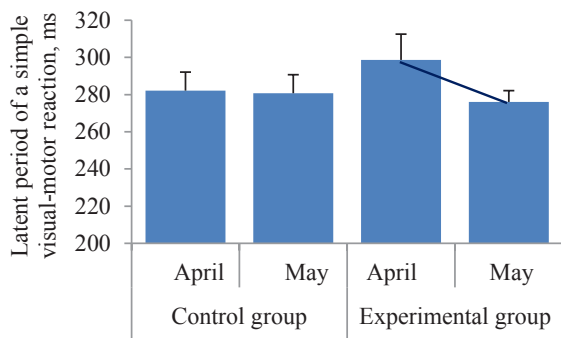


Figure 2 Changes in the simple visual-motor reaction times ($P < 0.05$)

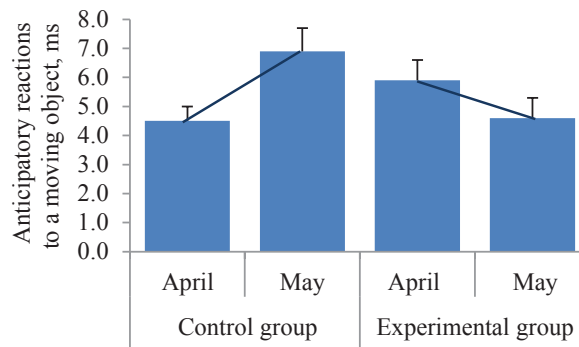


Figure 3 Changes in reactions to a moving object ($P < 0.05$)

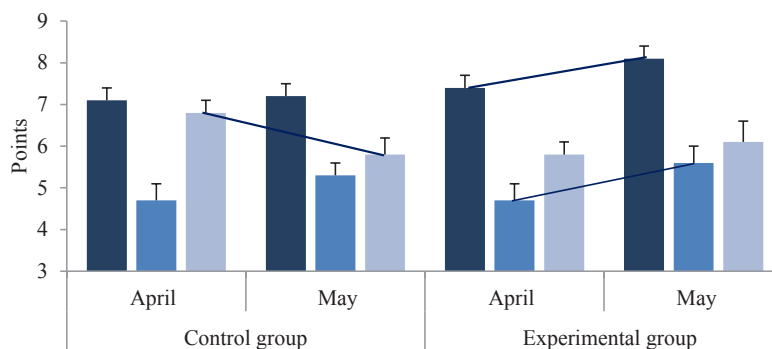


Figure 4 Changes in short-term memory and attention indicators ($P < 0.05$)

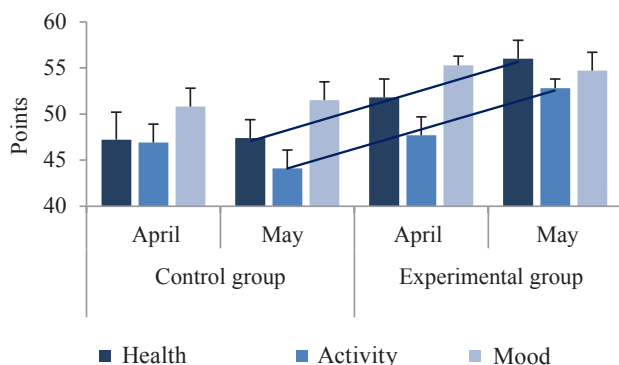


Figure 5 Changes in the HAM (health, activity, mood) test ($P < 0.05$)

values. The analysis of their dietary choline intake did not show any statistically significant differences between the groups (Table 3).

Thus, the control and the experimental groups, which had a homogeneous age and sex composition and similar cognitive indicators at the beginning of the study, were also quite similar in choline intake.

However, we identified some statistically significant changes in their neurodynamic parameters during the observation period (Figs. 2–5).

The experimental group showed significant improvements in the simple visual-motor reaction times (Fig. 2) within a month. The number of anticipatory reactions to a moving object decreased in the experimental group, but increased in the control group (Fig. 3). The students who received choline supplementation had better short-term memory for words and syllables. However, their attentional capacity remained the same, decreasing in the control group (Fig. 4).

The HAM (health, activity, mood) method revealed that during the second examination, the students taking choline supplements had significantly higher indicators of health and activity, compared to the control group (Fig. 5). Thus, the students in the experimental group were in a better state of health.

These changes showed that the pre-exam stress did not affect the functional state of the central nervous system of students in the experimental group – in fact, it improved.

Next, we divided the experimental group into two subgroups, depending on the level of choline intake: students with choline intake below the median value (416 mg) and students with choline intake above the median value. Thus, we could assess the effect of choline supplementation, taking into account the students' dietary choline intake.

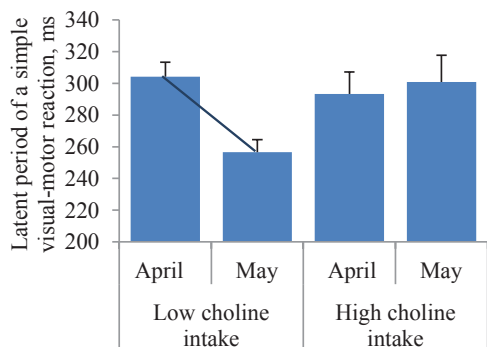


Figure 6 Changes in the simple visual-motor reaction times in students with choline supplementation vs. initial choline intake ($P < 0.05$)

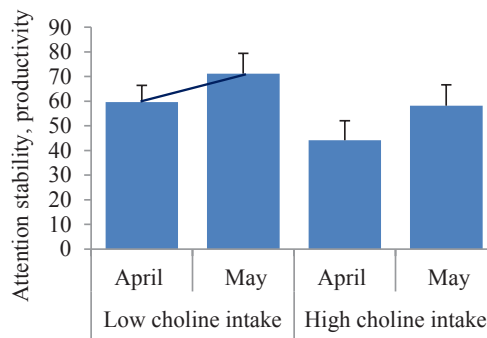


Figure 7 Changes in attention stability in students with choline supplementation vs. initial choline intake ($P < 0.05$)

We found statistically significant changes in neurodynamic parameters among students from the experimental group with a low choline intake. In particular, they showed a shorter simple visual-motor reaction time (Fig. 6) and improved attention stability (Fig. 7).

Changes in cognitive functions indicated better short-term memory for syllables in all experimental students, regardless of their choline intake, and improved performance in the dot cancellation test only in those with a low choline intake (Fig. 8).

The self-assessment with the HAM (health, activity, mood) method did not reveal any significant trends associated with levels of choline intake.

In order to obtain more general information about how choline supplementation affected the functional state of the central nervous system, we analyzed correlations between different psychophysiological parameters throughout the study. The closer connectedness between various neurodynamic, cognitive, and subjective indicators was regarded as a sign of increased psychophysiological adaptation in the pre-exam period.

Figure 9 shows changes in the number of statistically significant correlations between various indicators in

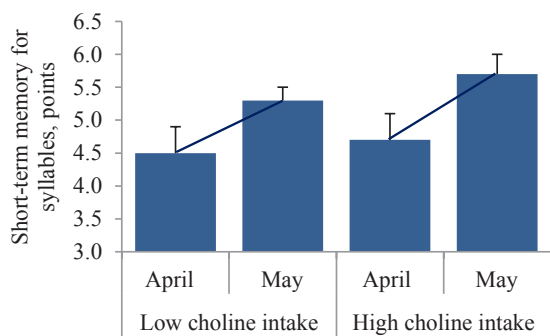


Figure 8 Changes in short-term memory in students with choline supplementation vs. initial choline intake ($P < 0.05$)

the control and experimental groups. We can see a clear difference in the number of correlations between the control and experimental groups, indicating a lesser degree of cognitive stress in the students who took choline supplements.

Thus, we found a positive effect of choline supplementation on the psychophysiological indicators of students in the stressful pre-exam period. Yet, some of the results were quite ambiguous and even conflicting: for example, negative correlations between background choline intake and attention indicators in both the control and the experimental groups, or general uselessness of choline supplementation for cognitive functions. As we know, a human need for choline and sensitivity to its deficiency are highly variable and genetically determined by heterogeneous metabolic pathways of endogenous synthesis and dietary choline conversion.

Our study showed that choline supplementation can be recommended to students, especially those with a low consumption of choline-rich foods.

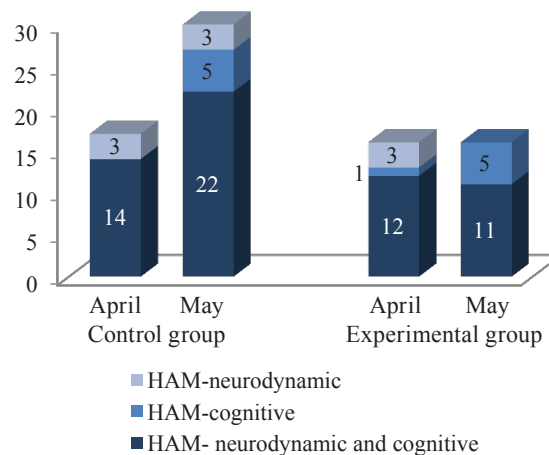


Figure 9 Statistically significant correlations between psychophysiological indicators in different groups

CONCLUSION

Half of the students had a dietary choline intake below the recommended value. The levels of choline intake had a greater effect on the neurodynamic parameters than on the cognitive functions. Increased choline intake correlated with higher functional mobility of nervous processes and faster reactions to a moving object. The students who took choline supplements for one month had positive changes in the functional state of the central nervous system, compared to the control group. Besides, these changes were more pronounced in those students who had a low intake of dietary choline. An additional daily intake of 700 mg choline supplements can be recommended to students under pre-exam stress, especially those with a dietary choline

deficiency, to improve the functional state of their central nervous system. However, we did not assess the effectiveness of smaller amounts of choline. We believe there is no need for continuous choline supplementation, since current research indicates possible negative health effects.

CONTRIBUTION

The authors were equally involved in preparing the manuscript.

CONFLICT OF INTEREST

The authors declare that there is not conflict of interest.

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