# Combined Effects of Caffeine and Sidnocarb on Operative Comparation of Digital Symbols in Man

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Neurotropic effects of caffeine and sidnocarb were studied on a model of fast operating activity of man involved in operative memorizing: reproduction and comparation of digital symbol flows. Subtherapeutic doses of caffeine (1 mg/kg) and sidnocarb (1 mg) alone were virtually ineffective, while their combination accelerated mental operations in the context of operative mnestic processes.

**Key Words:** *perception; operative memory; caffeine; sidnocarb*

Even moderate daily doses of caffeine (150-300 mg or about 2-4 mg/kg body weight) cause cardiovascular or gastrointestinal disorders [7,10]. A decrease in the dose of alimentary caffeine to 1 mg/kg attenuates the psychostimulating effect. Some people (10-20%) [8,9] are obviously tolerant to moderate doses of caffeine or react to the agent inversely: as to a neuroleptic. The psychostimulating drug sidnocarb (SC), which is related to amphetamines, also leads to the development of pathological craving if regularly used in therapeutic doses of 5-15 mg per intake [1,6].

Combination of subtherapeutic doses of caffeine and SC is expected to produce an additive effect and cause minimal side effects. The additive effect is possible because the neurotropic action of caffeine and SC is realized through different neurochemical mechanisms: blockade of adenosine $A_1$ receptors and inhibition of phosphodiesterase [7] (caffeine) and activation of dopaminergic transmission [4] (SC).

The combined effect of caffeine and SC was originally studied in rats [3]; both drugs were used in doses much higher than therapeutic (10 mg/kg) [6].

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Our purpose was to evaluate the effect of a combination of low doses of caffeine (1 mg/kg) and SC (1 mg per intake) and compare it to individual effects of these drugs on test operator activity in humans.

## MATERIALS AND METHODS

Twelve volunteers were the University students aged 18-22, healthy right-handed males with normal or corrected vision. Before testing they were informed about the protocol of investigation. Besides operating activity, they were to take coffee drinks with caffeine concentrations no higher than single therapeutic doses of pure drug and as a rule 2-3 times lower than the doses used by strong coffee drinkers. SC was taken in single doses of 1 mg, which is 5 times lower than a single therapeutic dose [6].

The operator activity test assessed the rate of mental operations in man involved in comparison of digital symbol flows under conditions of time deficiency. A characteristic feature of our study was the orientation of the method to differentiated evaluation of the efficacy of the left and right hemispheres in the symbol comparation test, because the drug effects might be asymmetrical. If this circumstance is neglected, the mean statistical effect of the drug for both brain hemispheres might be leveled.

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A single cycle of stimuli presentation consisted of a short-term (250 msec per number) demonstration at a PC monitor the first of three arbitrary two-digit numbers (image numbers) for memorizing and then, at 2-sec intervals, of one two-digit test number ($\tau$=200 msec). The volunteer was shown a block of 320 single cycles of stimuli (35 min) before and 35-40 min after a coffee drink or SC. The volunteer was instructed to press the button as soon as possible every time when a test number in the next cycle was the same as one of the three image numbers presented before. The image numbers were presented accidentally in three different sectors of the screen: on the left, in the center, and on the right; only in 50% cases there was a number the same as the test number. The eccentricity of lateral positions of image numbers was 4.0-4.5°, which left these stimuli in the simultaneous perception field without saccadic movements of the eyes [2] and permitted their projection predominantly to the contralateral hemisphere [5]. By measuring the time of reaction (TR) during presentation of memorized and test numbers in different positions of the visual field (9 combinations) we studied the effects of individual or joint work of cerebral hemispheres involved in symbol comparation before and during drug effect. For further analysis we selected the results of subjects who missed no more than 15% presentations and made no more than 20% erroneous reactions. The mean TR (in msec) was calculated for each test block for every combination of mutual positions of the correct image and test numbers.

Coffee drinks were prepared from commercial instant coffee in which the caffeine concentration was measured by reverse-phase high performance liquid chromatography (Prodekspertiza). The concentration of pure caffeine in instant coffee was 3.9-4.1%, in decaffeinated coffee no more than 0.32%. All tests were carried out with a single blind control test, i. e., the examine was not informed about the composition of coffee drink (with or without caffeine or in combination with SC) which he was given on one of the three test days, because the drinks did not differ by taste and aroma.

All procedures involving the participation of volunteers strictly adhered to the Helsinki Declaration of Human Rights.

## RESULTS

Pharmacological testing of humans for operator activity showed essential individual variability of the initial parameters and of the caffeine and SC effects. In order to detect the basic tendency in the effects of the test drugs, the data were averaged for examines given SC (Fig. 1, *c*), instant and decaffeinated coffee (Fig. 1, *a*, *b*), and SC: the differences (msec) between TR before and after drug test for each of 9 combinations of digital symbol positioning (CDSP). The directions of effects, depending on CDSP, were different in all drug tests (Fig. 1), but as a rule, were statistically insignificant. A slight statistically significant acceleration of reactions in combinations of unilateral positioning of image numbers with central positioning of the test number was noted only for alimentary caffeine (Fig. 1, *a*).

In the next series of tests the examines were offered a coffee drink with 1 mg/kg alimentary caffeine and 1 mg SC. This test led to an appreciable (by 55-80 msec, depending on CDSP) decrease in TR (Fig. 1, *d*). These data may be indicative of the additive psychostimulating effect of SC+caffeine mixture. However, after caffeine extraction the coffee drink lacked many other alkaloids (theophylline, theobromine, etc.) possessing neurotropic activity.

For modeling the "pure" caffeine effect, the volunteers were offered a mixture of 1 mg SC and caffeine benzoate in a dose of 1 mg/kg pure caffeine, dissolved in water (Fig. 1, *e*). A mixture of pure caffeine with SC markedly decreased TR. Thus, caffeine is the active ingredient of a coffee drink, additive to SC in manifestation of the joint psychostimulating effect.

The effect of pure caffeine combined with SC was lower than that of alimentary caffeine with SC (Fig. 1, *d*). In some variants of CDSP the differences between the effects of alimentary and pure

**TABLE 1.** Relationship between Changes in the Rate of Operative Memorizing and Comparation of Digital Symbols in Man after Drug Intake and the Initial Values of These Parameters

| Test | Coefficient of correlation | Significance | Freedom degree |
|---|---|---|---|
| Common coffee (caffeine 1 mg/kg) | -0.30 | $p<0.001$ | 106 |
| Decaffeinated coffee | -0.27 | $p<0.001$ | 106 |
| SC (1 mg per intake) | -0.16 | $p<0.05$ | 106 |
| SC+caffeine benzoate | -0.60 | $p<0.001$ | 106 |
| SC+alimentary caffeine (1 mg/kg) | -0.76 | $p<0.001$ | 106 |

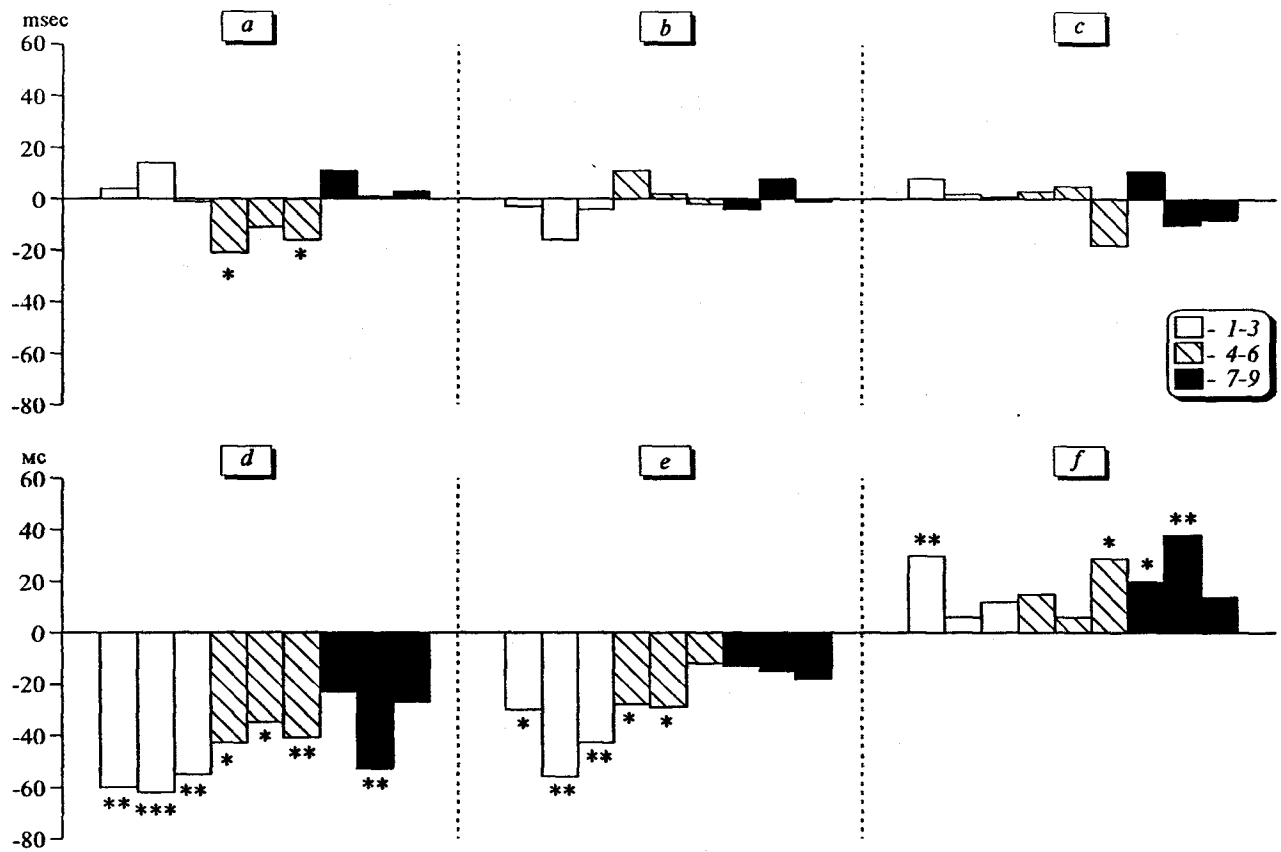


**Fig. 1.** Changes in the latent period of solving a problem for memorizing and comparation of digital symbols after caffeine, sidnocarb, or both. Averaged data for 12 volunteers are presented. Abscissa: variants of mutual position of the correct image number and test number in the visual field: *1-3*) test number on the left; *4-6*) test number in the center; *7-9*) test number on the right, with the image number in each block on the left, in the center, and on the right, respectively. Ordinate: the difference between the time of reaction before and after drug test, msec. *a*) alimentary caffeine, 1 mg/kg; *b*) decaffeinated coffee; *c*) sidnocarb, 1 mg; *d*) alimentary caffeine+sidnocarb; *e*) sidnocarb+caffeine benzoate; *f*) difference between *d* and *e*, msec. *$p<0.05$, **$p<0.01$, ***$p<0.001$ *vs.* values before drug intake.

caffeine in combination with SC were statistically significant: 35-40 msec in favor of the latter combination (Fig. 1, *f*). The data do not permit an unambiguous interpretation of these differences, because the water mixture lacked the alkaloids complementary to alimentary caffeine and the aroma typical of a coffee drink and probably inducing conditioned reflex effects.

Does the effect of caffeine-CS mixture depend on mutual position of digital symbols in visual field? No statistically significant relationships were detected, but the equation averaged for all examines demonstrated a tendency to an increase in this effect during left-side presentation of test numbers, *i. e.*, when it was projected into the right hemisphere (Fig. 1).

Probable adaptation to modulating effects of caffeine and CS on the activity of an operator is especially interesting. Do the parameters of operator activity after exposure depend on their initial level? Table 1 shows the coefficients of linear correlation between the TR values averaged for each volunteer (for each CDSP individually: $n=12$, a total of 108 dates) before and after coffee, SC, or their combination. The coefficients of correlation between the effects of caffeine or SC alone on TR and the initial TR values were not high (Fig. 1, *a-c*), while after combination of SC with alimentary caffeine or caffeine benzoate, a strong negative correlation was observed. This implies that a mixture of subtherapeutic doses of caffeine with SC produces an adaptive effect: the slower are the processes of memorizing and comparation of symbols the faster are they after the drug intake. In cases with a certain optimal rate of "mental processes", the effect of caffeine with CS may be null. This may account for a great variety of individual effects of the caffeine and CS combinations.

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