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Post-study caffeine administration enhances memory consolidation in humans

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Abstract

It is currently not known whether caffeine has an enhancing effect on long-term memory in humans. We used post-study caffeine administration to test its effect on memory consolidation using a behavioral discrimination task. Caffeine enhanced performance 24 h after administration according to an inverted U-shaped dose-response curve; this effect was specific to consolidation and not retrieval. We conclude that caffeine enhanced consolidation of long-term memories in humans.

Many studies have documented the effects of caffeine as a cognitive enhancer[1]. However, its effects on long-term memory have not been investigated in detail. The general consensus among past studies is that caffeine has little or no effect on long-term retention[1]. However, caffeine has been always administered before learning; thus, effects on memory are impossible to dissociate from other effects of caffeine such as increased arousal, vigilance, attention and processing speed. We used a post-study design (drug administered after subjects have had an opportunity to study the material) based on animal studies[2], where effects of certain agents on memory consolidation are optimally detected after the learning experience.

We conducted a randomized, double-blind, placebo-controlled trial in caffeine-naive participants. On day 1, participants incidentally studied images of objects, then received either 200 mg of caffeine or placebo. We collected salivary samples at baseline and 1 h, 3 h and 24 h after administration of caffeine or placebo to quantify caffeine metabolites (Fig. 1a

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Any Supplementary Information and Source Data files are available in the online version of the paper.

AUTHOR CONTRIBUTIONS

D.B., J.P.T. and M.A.Y. designed the study. D.B., E.M., G.K., A.C., J.M.W. and M.L. conducted the experiments. D.B. and M.A.Y. wrote the manuscript with input from all authors.

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The authors declare no competing financial interests.

and Supplementary Fig. 1). Twenty-four hours after the study session, we evaluated participants' recognition performance using some items they saw the previous day (targets), some new items (foils) and some items that were similar but not identical to ones they saw before (lures; Fig. 1a). Correctly identifying these lures as 'similar' has been previously shown to be associated with hippocampal activity[3].

We found that participants in the group that received caffeine had a significant increase in caffeine metabolites (Supplementary Fig. 2) at the 1 h and 3 h time points, which then returned to baseline amounts over a 24-h washout period. Participants who received caffeine were more likely to call lure items 'similar' rather than 'old' compared to participants who received the placebo (Fig. 1b), whereas we found no group differences in rates of target hits (Fig. 1c) or foil rejection (Fig. 1d). D' (z(target hits) – z(false alarms)) was not significantly different among groups ($t_{42} = 0.60$, two-tailed $P = 0.55$), hence basic recognition memory was unaltered. We calculated a lure discrimination index (LDI) as P('similar'|lure) minus P('similar'|foil) to correct for response bias and found a significant difference between groups ($t_{42} = 2.0$, two-tailed $P = 0.05$; Fig. 2a). This suggests that caffeine enhanced consolidation of the initial study session such that discrimination during retrieval was improved. Both groups had similar variance as assessed by Levene's test for (D') ($P = 0.44$) and LDI ($P = 0.96$).

To rule out any effects of caffeine on retrieval, we conducted a delayed manipulation, in which we administered caffeine 1 h before a test (24 h after the initial study session). We observed no significant enhancement compared to placebo, suggesting that caffeine does not affect any other aspect of retention performance ($t_{55} = 0.63$, $P = 0.53$; Fig. 2a).

Next, we determined whether the effects of caffeine were consistent across lure similarity. In prior work, we had quantified the similarity of the stimuli based on the tendency of participants to erroneously produce false alarms[4] and used that metric here to classify stimuli according to similarity. A two-way analysis of variance (ANOVA) revealed a significant main effect of similarity ($F_{2,88} = 12.87$, $P = 0.05$) and a significant main effect of caffeine ($F_{1,42} = 4.07$, $P = 0.001$) with a nonsignificant interaction ($F_{2,84} = 1.0$, $P = 0.37$; Fig. 2b).

To determine whether there is an optimal dose range, we repeated the experiment with a placebo and different doses of caffeine (100 mg, 200 mg and 300 mg). We combined data across the two experiments for the placebo and 200 mg caffeine conditions to increase power. We found that performance for the 200 mg caffeine condition was higher than that for placebo ($t_{71} = 2.0$, two-tailed $P = 0.049$; $n = 35$ subjects for 200 mg caffeine condition, $n = 38$ subjects for placebo condition; Fig. 2c). Also, performance for the 200 mg caffeine condition was higher than that for 100 mg ($t_{48} = 2.19$, two-tailed $P = 0.033$), which was not significantly different from that for placebo ($t_{51} = 1.0$, two-tailed $P = 0.32$). Finally, performance for the 300 mg caffeine condition was marginally higher than that for placebo ($t_{46} = 1.81$, $P = 0.07$) but not different from the 200 mg caffeine condition ($t_{43} = 0.32$, $P = 0.75$). We combined the higher doses together and compared them against the combination of placebo and 100 mg dose. The comparison was significant ($t_{96} = 2.77$, $P = 0.007$). Thus,

we conclude that a dose of at least 200 mg is required to observe the enhancing effect of caffeine on consolidation of memory.

Finally, we examined the relationship between the enhancement in performance and change in amounts of caffeine metabolites found in saliva to account for individual differences in metabolic function. We found a pattern similar to the dose-response results reported above (Fig. 2d). There was additional evidence of an inverted U-shaped dose-response curve. We compared the linear fit versus a second-degree polynomial (quadratic). The quadratic-curve fit R^2 was 0.81, whereas the linear fit R^2 was 0.45. A change F test demonstrated that the quadratic fit was significantly better than the linear fit ($F = 29.5$, $P = 0.001$).

Numerous studies in animals have shown that caffeine has neuroprotective effects[5–8]. Prior work also found a positive effect of post-training administration of caffeine on consolidation of memory[9]. Notably, a recent study suggests that caffeine in floral nectar may boost memory for reward in honeybees[10], suggesting that the mnemonic effects of caffeine may not be limited to mammals. No study to our knowledge has demonstrated a positive effect of caffeine on human long-term memory while excluding nonmnemonic effects. Our results demonstrate that caffeine enhanced consolidation once these effects are appropriately controlled.

Limitations of this study include subjects' awareness of being involved in a caffeine study. To address this, we asked subjects whether they thought they were administered caffeine or placebo, and responses were distributed equally between perceived placebo and caffeine regardless of condition. Our final sample size for the 300 mg dose was small ($n = 10$ subjects) after eliminating subjects who did not conform to the protocol, thus the enhanced effect at the 300 mg dose could have been weakened by the smaller sample.

Although the mechanisms by which caffeine enhances memory consolidation remain largely unclear, there are several possibilities. First, by blocking adenosine, caffeine can prevent it from inhibiting norepinephrine, which has positive effects on consolidation of memory[2]. We have previously demonstrated a relationship between norepinephrine and pattern separation[11]. Another possibility is that caffeine's action in the CA2 region of the hippocampus, which is highly enriched in adenosine A1 receptors[12], enhances long-term potentiation in this subfield[13], which may have a role in certain types of memories[14]. In addition to the hippocampus, several other regions may have a role in consolidating memories, including the anterior cingulate cortex[15] and the medial prefrontal cortex[16]. Other brain regions may have a role in modulating consolidation such as the basolateral amygdala[17,18] and mesolimbic dopaminergic areas[19]. Examining the contributions of these regions and the effects of caffeine on their processing is further crucial to understanding of psychostimulant-induced memory potentiation.

Future experiments should be conducted to understand the mechanisms by which caffeine can potentiate memory. Given the widespread use of caffeine and the growing interest in its effects both as a cognitive enhancer and as a neuroprotectant, these questions are of critical importance.

ONLINE METHODS

Subjects

160 healthy, caffeine-naive subjects between the ages of 18 and 30 (mean age, 20; s.d., 2; 80 female subjects) participated in the study, which was approved by the local Institutional Review Board. All subjects were screened using the Caffeine Consumption Questionnaire (CCQ)[20] and a detailed medical history questionnaire screening against major physical and psychiatric disorders. We excluded subjects who reported average caffeine intakes exceeding 500 mg per week. All subjects included in the study provided written informed consent. No serious adverse events or side effects of caffeine were reported. Minor side effects such as headaches and jitteriness were reported in less than 25% of all participants (16% in the placebo group, 20% in 100 mg caffeine group, 23% in 200 mg caffeine group and 45% in 300 mg caffeine group). Participants were excluded because of compromised saliva samples (5 participants), caffeine content in baseline salivary sample (18 participants) or in 1 h sample (1 participant) or in 24 h sample (9 participants), at chance discrimination performance (8 participants) and mini mental state examination scores below 26 (2 participants). Subject characteristics for the main experiment are listed in Supplementary Table 1. The sample sizes we initially chose are similar to those used in previous publications.

Randomization

The study was conducted as a randomized, double-blind, placebo-controlled intervention study. Randomization used block-stratified assignments with 1:1 caffeine to placebo, with block size of 4 and a linear congruential algorithm (Park and Miller with Bays-Durham shuffling).

Memory task

We used a hippocampal memory–dependent task particularly taxing pattern separation[3], whereby overlapping experiences are made orthogonal to one another in order to overcome interference[21–23]. The task involved two phases. During the incidental encoding phase, participants viewed pictures of objects and decided whether the picture depicted an indoor or an outdoor item. During the test, participants were shown exact repetitions, new items and items that were similar but not identical to previously shown pictures (lures). For each image, they were instructed to decide whether the image was ‘old’, ‘new’ or ‘similar’.

Saliva collection and caffeine analysis

Subjects provided 1 ml samples of saliva following a standardized saliva collection protocol (Salimetrics kit) in 2-ml cryovial test tubes, which were refrigerated at −80 °C within 24 h of collection and subsequently analyzed using a previously published procedure[24].

Statistical analysis

LDI was calculated as P(‘similar’|lure) minus P(‘similar’|foil), which corrects for response bias. As the data were normally distributed; group comparisons were conducted using

unpaired *t*-tests, one-way and two-way ANOVAs. All final significance levels were set at alpha = 0.05.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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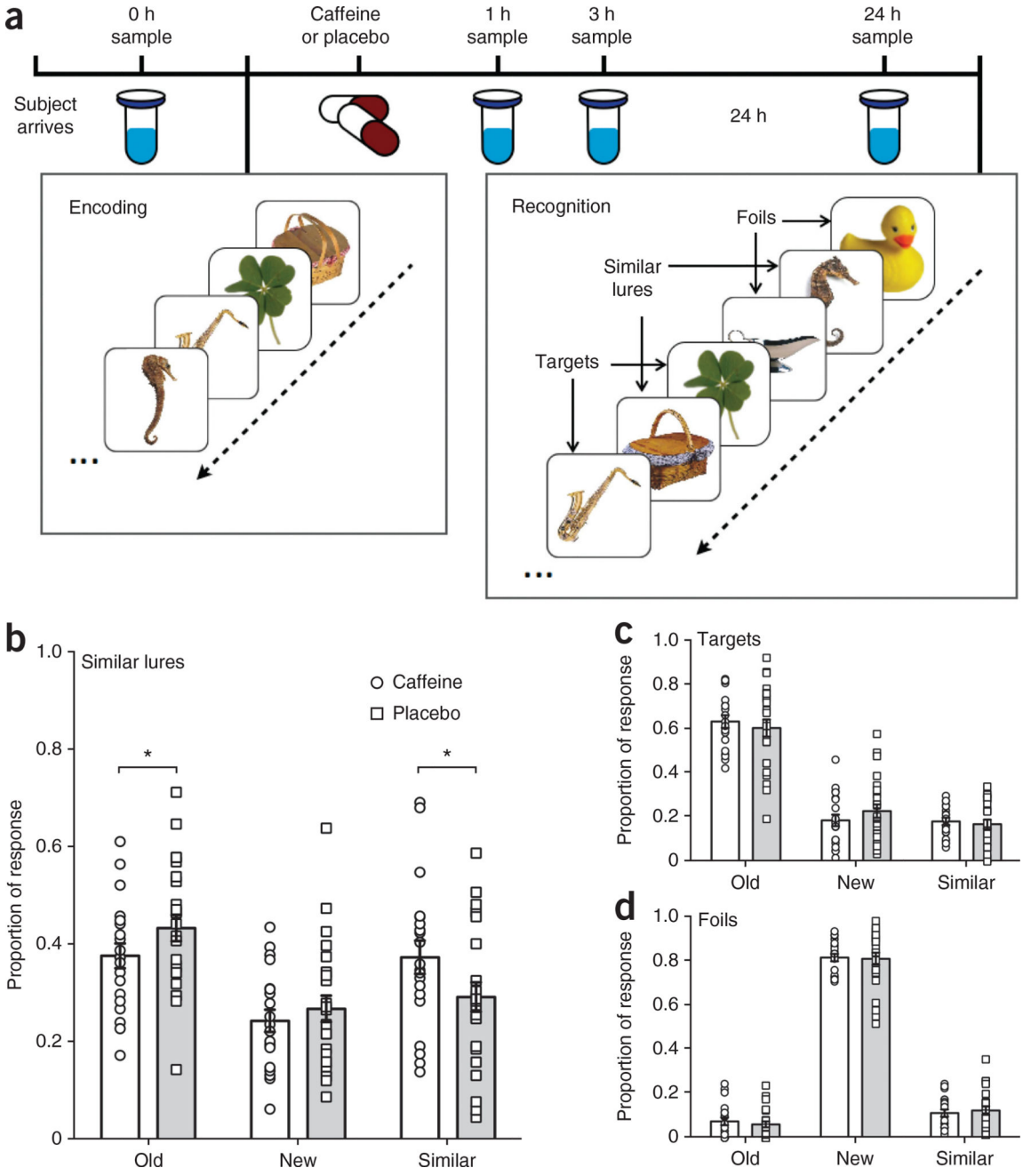

Figure 1.

Caffeine enhances discrimination performance 24 h after study. (**a**) Outline of study design. After arrival of screened subjects, a baseline salivary sample was collected. Then the encoding task was administered. This was an incidental indoor-outdoor judgment task (stimuli every 2,500 ms, with an interstimulus interval (ISI) of 500 ms). After encoding, subjects were administered either 200 mg caffeine or placebo pills. After 1 h and 3 h, additional saliva samples were collected. Subjects returned 24 h later for testing. Before a recognition test, a final saliva sample was collected. Recognition was tested using an old-similar-new judgment task (stimuli every 2,500 ms with a 500-ms ISI) using targets, foils

and similar lures that are particularly sensitive to hippocampal pattern separation. (**b**) Lure discrimination by subjects (i.e., whether subjects had a higher propensity to call lure items 'similar' rather than 'old') (t_{42} = 1.79, one-tailed P = 0.04). *P < 0.05, one-tailed. (**c,d**) Target hit rates (**c**) and foil rejection rates (**d**) (t_{42} = 0.59, one-tailed P = 0.27 and t_{42} = 0.15, one-tailed P = 0.44 between groups that received caffeine and placebo, for data in **c** and **d**, respectively). Error bars, ±s.e.m.; n = 20 subjects (caffeine) and n = 24 subjects (placebo).

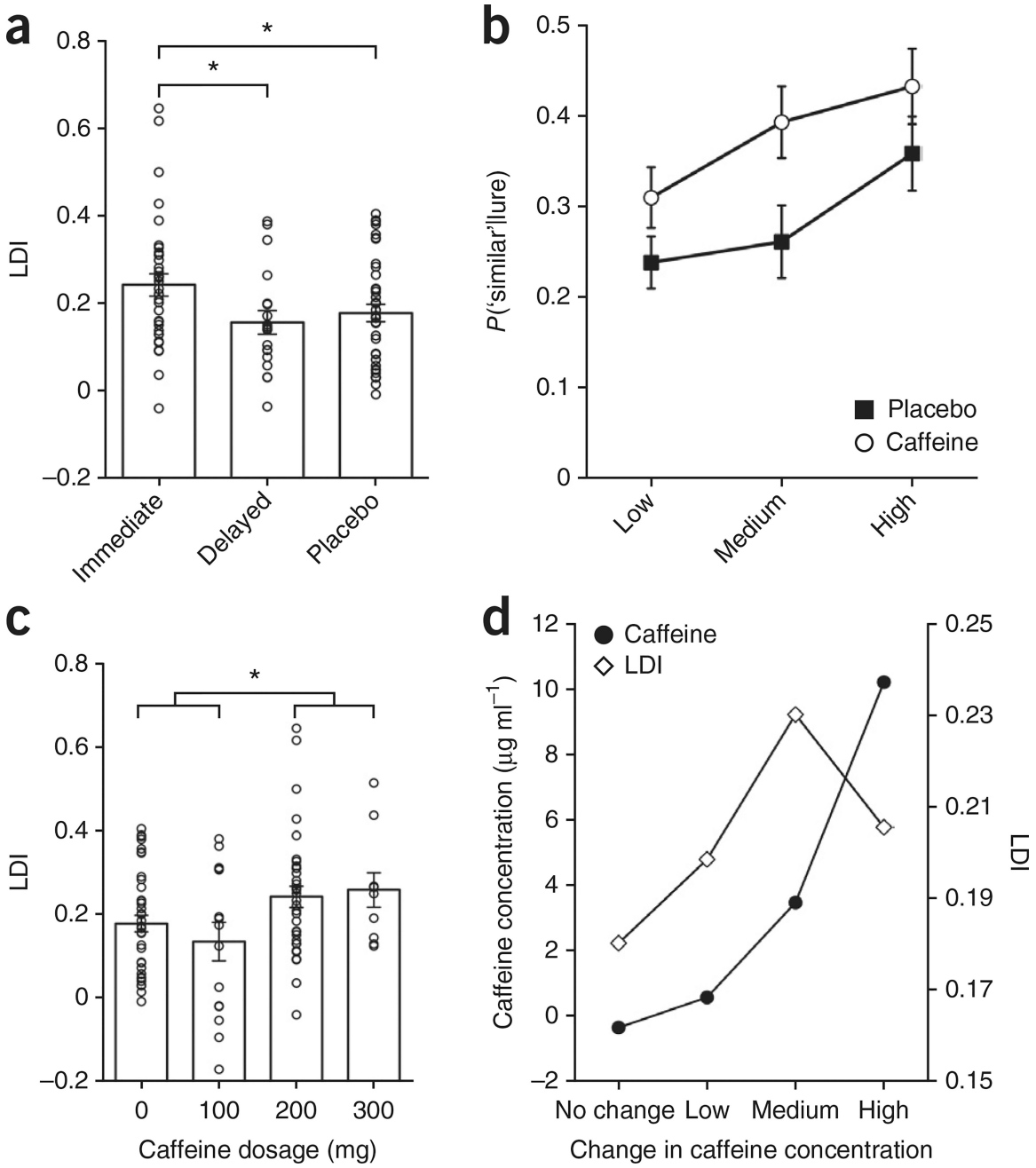

Figure 2.

Impact of caffeine on consolidation and variable dose effects. (**a**) LDI in subjects administered placebo or caffeine immediately after the study session (immediate), or caffeine 24 h after the study session (delayed). LDI in immediate caffeine group was enhanced compared to placebo (t_{71} = 2.0, two-tailed P = 0.049). LDI in the delayed group was no different from placebo (t_{55} = 0.63, P = 0.53). (**b**) Analysis by item similarity showed a significant main effect of similarity ($F_{2,88}$ = 12.87, P = 0.001) as well as a main effect of caffeine ($F_{1,42}$ = 4.07, P = 0.05). (**c**) Discrimination as a function of indicated caffeine dose (200 mg caffeine compared to placebo, t_{71} = 2.0, two-tailed P = 0.049 and compared to 100

mg caffeine, $t_{48} = 2.19$, two-tailed $P = 0.033$). Discrimination at 200 mg and 300 mg caffeine doses compared to placebo and 100 mg caffeine combined, $t_{96} = 2.77$, two-tailed $P = 0.007$. (**d**) Rebinned subject performance based on change in the amount of caffeine from baseline divided into quartiles (no change, low change, medium change and high change) showing evidence for an inverted U-shaped dose-response curve. The quadratic curve fit ($R^2 = 0.81$) was significantly better than the linear fit ($R^2 = 0.45$) for discrimination as a function of caffeine change ($F = 29.5$, $P = 0.001$). Error bars, ±s.e.m.*$P < 0.05$.