1 The enhancing effect of 200 mg caffeine on mnemonic discrimination is at best small

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Abstract

Mnemonic discrimination is the ability to discriminate among similar memories, which requires separable representations of similar information. The neurocomputational process that assumedly decorrelates representations during encoding and consolidation is referred to as pattern separation. Deficits in pattern separation contribute to age-related declines in mnemonic functioning, which has motivated the development of targeted interventions. We followed-up a recent report that one 200 mg-dose of caffeine administered post-study enhances mnemonic discrimination (Borota et al., 2014). To test whether the reported enhancements are an artifact of performance-impairing withdrawal symptoms in the control group, we did not restrict preexperimental caffeine consumption and statistically adjusted treatment effects for habitual caffeine consumption. We detected no effects of caffeine and nonsuperiority testing ruled out medium and large enhancements in both average (1200 mg per week) and low-consumers (50 mg per week). Our results raise doubts about a caffeine-mediated enhancement of mnemonic discrimination on two counts: If the effect exists, it (1) is substantially smaller than originally reported and (2) may reflect an offset of performance-impairing withdrawal symptoms rather than genuinely enhanced consolidation. We recommend that future studies employ an alternating exposure-abstinence protocol, use an active control group, and verify posttreatment caffeine abstinence via saliva or blood samples.

Keywords: pattern separation; hippocampus; caffeine; episodic memory; consolidation; false memory

Word count: 6258

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34 A central challenge for memory systems is separable encoding of similar information to
35 enable subsequent discrimination among similar memories. Mnemonic discrimination is
36 studied experimentally by presenting a list of items and subsequently probing participants'
37 memory with old (target), new but similar (lure), and dissimilar new items (foils; e.g., Brady,
38 Konkle, Alvarez, & Oliva, 2008; Brainerd, Reyna, & Mojardin, 1999; Roediger & McDermott,
39 1995; Stark, Stevenson, Wu, Rutledge, & Stark, 2015). Failure to adequately discriminate
40 targets from lures can result in a wide range of phenomena, from minor confusions to
41 high-confidence, vividly experienced false memories (Brainerd & Reyna, 2005; Gallo, 2006).

42 Failure to discriminate among similar memories is generally thought to result from
43 similarity-based activation of memories without access to distinctive details (Arndt &
44 Hirshman, 1998; Brainerd et al., 1999; McEvoy, Nelson, & Komatsu, 1999; Reyna &
45 Brainerd, 1995; Roediger et al., 2001a). Some theories specify process assumptions about
46 similarity-based activation of memories in terms of spreading activation in a semantic
47 associative network or feature overlap (Arndt & Hirshman, 1998; McEvoy et al., 1999;
48 Roediger et al., 2001b). Determinants of successful mnemonic discrimination comprise, on
49 the retrieval side, participants' metacognition and response strategies (e.g., Brainerd, Reyna,
50 Wright, & Mojardin, 2003; Dodson & Schacter, 2001, 2002; Roediger & McDermott, 1995).
51 For instance, Nosofsky and Zaki (2003) have proposed a retrieval-based process account of
52 the distinctiveness heuristic—a mnemonic discrimination process that capitalizes on unique
53 distinctive stimulus features (e.g., Dodson & Schacter, 2001, 2002). On the encoding side,
54 the neurocomputational operations assumed to subserve mnemonic discrimination are
55 referred to as pattern separation (Leal & Yassa, 2018; Yassa & Stark, 2011). Pattern
56 separation decorrelates the neural representations of similar information during encoding and
57 consolidation (e.g., O'Reilly & McClelland, 1994; Yassa & Stark, 2011) and is assumed to
58 occur in the dentate gyrus of the hippocampus (DG; Leal & Yassa, 2018; Yassa & Stark,

2011). Deficits in pattern separation have been found to contribute to age-related declines in mnemonic functioning and this has motivated several intervention studies (for a review see Leal & Yassa, 2018).

A recent widely-received study specifically targeted pattern separation to improve mnemonic discrimination (Borota et al., 2014, cited 171 times, Google Scholar, May 13, 2020). The authors tested whether one dose of 100 mg, 200 mg, or 300 mg caffeine enhances pattern separation. Caffeine (or a placebo) was administered after completion of the study phase to specifically investigate effects on the decorrelation of the information, rather than on input quality of the to-be-decorrelated information due to heightened attention or motivation. Participants returned for testing after a 24 h-wash out period of caffeine abstinence that served to rule out any effects of caffeine on metacognition or response strategies during retrieval. The authors found better mnemonic discrimination in the caffeine compared to the placebo group for one dose of 200 mg and 300 mg caffeine, the equivalent of one to two cups of coffee. No effect of caffeine on overall mnemonic sensitivity (i.e. old-responses to targets relative foils) was detected. In the following we focus on the dose of 200 mg caffeine, because Borota et al. (2014) report an inverse U-shaped dose-response relationship, suggesting that a dose of 300 mg may reduce the treatment effect compared to 200 mg.

Beyond its clear applied value, the enhancing effect of caffeine on mnemonic discrimination is theoretically interesting for at least two reasons. First, it highlights the potential importance of a continued encoding (or consolidation) process after completion of the nominal study phase. Considering that plasma concentration peaks around 60-120 minutes after ingestion of 200 mg caffeine capsules (Kamimori et al., 2002; Liguori, Hughes, & Grass, 1997) the reported findings seem to suggest that pattern separation continues for a substantial amount of time after study. Second, it informs the theory of pattern separation by implicating neurotransmitters, such as adenosine and norepinephrine, in the modulation mechanism and brain structures, such as DG and the CA2 subregion of the hippocampus, in

the neural computations subserving pattern separation. Probing the robustness of this effect and understanding its underlying cognitive mechanism is therefore important for the study of memory. Here we present an attempt to replicate and extend the original finding, while also addressing some methodological concerns about the original study.

Current theorizing about pattern separation assumes a representational hierarchy in which early sensory representations are more confusable than integrated representations (Leal & Yassa, 2018). That is, pattern separation is thought to progress along the cortico-hippocampal processing pathway. Representations of simple visual features are decorrelated at sensory cortical levels whereas more complex features at higher (e.g. hippocampal) levels. Thus, if the suspected neurotransmitter-mediated modulation of hippocampal subareas DG and CA2 is indeed responsible for caffeine-enhanced pattern separation, the effect should be most pronounced in mnemonic discrimination of materials that share complex codes. Hitherto, caffeine enhanced mnemonic discrimination has been reported for photographs of similar objects. These photographs are similar both visually and conceptually (Stark, Yassa, Lacy, & Stark, 2013). Enhanced mnemonic discrimination could thus be caused by separable representations at early or higher levels along the processing pathway, or both. Showing that caffeine enhancements are moderated by the representational level at which stimuli overlap would, thus, enlighten the mechanisms by which caffeine affects pattern separation and would provide support for the representational-hierarchy perspective on pattern separation.

But before investigating potential mechanisms, it is pertinent to first replicate the caffeine-mediated enhancement of pattern separation. Replications with varying operationalizations are generally an important first step in any research program (Tunç & Tunç, 2020). But there are also methodological concerns that motivate further scrutiny of the effect. First, a recent reanalysis of the reported statistics for 200 mg caffeine indicates that the Bayesian evidence for a caffeine-mediated enhancement is inconclusive, favoring the

111 null hypothesis of no effect 1.16-to-1 (Faulkenberry, 2018).¹ By this standard, it remains
 112 unclear whether caffeine indeed enhances pattern separation.

113 Relatedly, the interval estimate of the effect size for 200 mg caffeine ranged from
 114 negligible to large effects, Cohen’s d 95% CI [0.00, 0.93], Δ LDI 95% CI [0.00, 0.13]. So even
 115 assuming that caffeine does enhance pattern separation, it is unclear by how much. A
 116 back-of-the-envelope calculation may be illustrative. An applied researcher could relate these
 117 estimates to, for example, age-related declines in mnemonic discrimination. Using the
 118 BPS-O material, age-related declines across the life span have been estimated at Δ LDI 95%
 119 CI [.09, .29] (Stark & Stark, 2017; Stark et al., 2015, 2013). An optimistic interpretation of
 120 the estimate from Borota et al. (2014) is consistent with an incredible enhancement: One
 121 dose of 200 mg caffeine may offset a decline in mnemonic discrimination expected in 1.5 life
 122 spans. The somewhat less optimistic point estimate still suggests an impressive offset of
 123 about one third of the expected life span decline. This comparison suggests that reported
 124 estimates are larger than what may realistically be expect from a large cup of coffee. Hence,
 125 more data is needed.

126 Second, the experimental design used by Borota et al. (2014) leaves room for
 127 alternative accounts for the difference between caffeine and placebo treatment groups. In
 128 fact, inferring enhancing effects of caffeine on cognition from standard randomized
 129 placebo-controlled designs is difficult in general (James, 2014): In contrast to most drug
 130 intervention studies, the underlying assumption that participants are caffeine-naïve is most
 131 likely violated. It must be assumed that many participants regularly consume caffeine, are
 132 likely to be caffeine dependent—at least mildly—and may acutely have caffeine in their
 133 systems. This violation of the caffeine-naïvety assumption threatens inference in two ways:

¹ Faulkenberry (2018) computed the Bayes factor using BIC approximation. Another approach is to compute default Bayes factors that assign a Cauchy prior to the standardized effect size estimated under the alternative hypothesis (Morey & Rouder, 2011; Rouder, Speckman, Sun, Morey, & Iverson, 2009). This default Bayes factor (with prior scale $r = \sqrt{2}/2$) for the effect of caffeine on pattern separation is also inconclusive although slightly more enthusiastic, favoring the alternative hypothesis of an effect 1.32-to-1.

(1) Short abstinence periods prior to measurement may induce performance-impairing withdrawal symptoms. Thus, any observed difference between placebo and treatment groups could reflect withdrawal reversal rather than enhancement. (2) Caffeine tolerance from habitual consumption may substantially reduce the effect of an intervention. Thus, researchers need to account for participants' habitual caffeine consumption.

Borota et al. (2014) addressed caffeine-non-naivety by studying low-consumers, i.e., participants who self-reported to consume less than 500 mg caffeine per week (equivalent to roughly 4-5 cups of coffee per week). Additionally, participants were instructed to abstain from consuming caffeine prior to their participation—compliance was verified by assessing caffeine concentration in saliva samples. These precautions ensure that participants exhibit comparable systemic levels of caffeine at baseline and limits the intensity of withdrawal symptoms. However, including only acutely caffeine abstinent low-consumers is no guarantee for valid inference. Even in low-consumers short-term abstinence has been found to induce withdrawal that sets in at about 12 h and peaks around 24-48 h (p. 118, James, 2014). In fact, this procedure may inadvertently select for withdrawn participants—those who forwent their routine weekday morning coffee. Hence, studying only acutely caffeine abstinent low-consumers by itself cannot conclusively rule out that enhancing effects of the intervention reflect withdrawal reversal. Additional research with complementary methods is needed.

Studying non- or low-consumers creates an additional problem. Assuming caffeine indeed enhances pattern separation in this self-selected minority, it is unclear whether this finding generalizes to the wider population. Non- and low-consumers may exhibit an innately reduced caffeine tolerability (James, 2014). For example, low-consumers appear to more frequently experience adverse reactions to the ingestion of as little as 100 mg caffeine (Rogers, Martin, Smith, Heatherley, & Smit, 2003) that may be related to genetic differences (Alsene, Deckert, Sand, & de Wit, 2003). Thus, additional research is needed to strengthen the claim that caffeine generally enhances pattern separation.

One approach to address concerns about withdrawal reversal and generalizability is to waive experimental control of preexperimental and habitual caffeine consumption. So-called *ad libitum* (“as you desire”) consumption studies investigate the effect of caffeine in the context of habitual caffeine consumption (James & Rogers, 2005). By not restricting preexperimental caffeine consumption, participants who receive a placebo are less likely to be in withdrawal during performance measurement and consequently observed enhancements are less likely to reflect withdrawal reversal. A drawback of *ad libitum* consumption is that it does not guarantee the absence of withdrawal symptoms in *all* participants and, more importantly, it surrenders control over systemic levels of caffeine (James & Rogers, 2005). These drawbacks can be somewhat mitigated with appropriate statistical analyses. In addition to studying treatment effects, an unrestricted sample allows estimating the extent to which mnemonic discrimination covaries with habitual caffeine consumption in the caffeine and placebo group, respectively. Specifically, the effect of habitual caffeine consumption and, critically, its interaction with the treatment can be entered into the statistical model. In addition to a simple main-effect model assuming a stable enhancement effect (Figure 1, left panel), we also considered two interaction patterns: Assuming that higher habitual consumption on average leads to stronger dependence and withdrawal symptoms, withdrawal reversal would manifest in estimated treatment effects that increase with habitual caffeine consumption due to impairing mnemonic discrimination in the control group (Figure 1, middle panel). Similarly, the model can reveal tolerance to the effects of caffeine: Assuming that higher habitual consumption on average leads to reduced effects of caffeine, tolerance would manifest in estimated treatment effects that decrease with habitual caffeine consumption due to impairing mnemonic discrimination in the experimental group (Figure 1, right panel). This analysis moreover allows the analyst to compare treatment effect estimates for different groups of caffeine consumers, such as average or low-consumers. Focused examination of the effects for low-consumers furthermore addresses concerns that the treatment effects may be distorted by caffeine tolerance or high systemic levels of caffeine

due to preexperimental ad libitum consumption. Thus, ad libitum consumption studies of the wider population of caffeine consumers, paired with the appropriate statistical analysis, can reduce the likelihood (and allow to test for the presence) of withdrawal reversal effects.

Current study

We performed a randomized placebo-controlled experiment to replicate the enhancing effect of caffeine on mnemonic discrimination. To test the alternative explanations discussed above, we adapted the experimental design as follows: (1) We performed an ad libitum consumption study to mitigate effects of caffeine withdrawal. (2) Instead of studying only caffeine low-consumers (≤ 500 mg per week), we did not restrict the to-be-sampled population. As outlined above, these changes allows us to estimate the treatment effect for low-consumers and to test for potential effects of withdrawal reversal and tolerance. To also gain first mechanistic insights, we extended the original study by including additional materials. (3) In addition to the photographs of similar objects, we presented words in print for which similarity was primarily conceptual (Stahl & Klauer, 2008), and conceptually distinct but visually similar drawings of objects (Rouder, Ratcliff, & McKoon, 2000; Stahl, Henze, & Aust, 2016). If, as speculated, caffeine specifically modulates activity of hippocampal subareas, enhanced mnemonic discrimination should be more pronounced for conceptually similar printed words than for conceptually distinct drawings of objects. Sampling from a wider population of caffeine consumers and including additional materials allowed us to examine the generality of caffeine-enhanced mnemonic discrimination.

Methods

Our study followed the principles of the Declaration of Helsinki. Experimental software (Mathôt, Schreij, & Theeuwes, 2012), data, and analysis scripts are available at <https://osf.io/p7f4m/>.

Participants

We recruited 109 students of the University of Cologne, Germany, 100 (91.74%) of whom returned on the second day for the recognition phase. After exclusions, we analysed a sample of 75 participants (Table 1), which allowed us to detect medium to large effects of caffeine on mnemonic discrimination with a $\alpha = \beta = .05$ (Figure 2). According to the criteria of the original study, we excluded participants with a history of serious head injuries ($n = 4$) and psychiatric disorders ($n = 3$). Furthermore, we excluded 14 participants who reported that they had consumed more than 50 mg caffeine during the 24h retention interval. We, additionally, excluded 5 participants who, due to an initial programming error, missed more than 4 trials with unrelated distractor items (no other criteria were explored).

Material & Procedure

The study realized a two-day double-blind, randomized, placebo-controlled intervention. On the first day participants performed an incidental study task prior to ingesting either a 200 mg caffeine or a placebo pill. Following a 24 h retention interval, participants returned to the lab to perform a surprise old/similar/new recognition task.

Day 1. To safeguard the incidental nature of the study task, we pretended to study effects of caffeine on sleep quality and cognitive resource regeneration through response time measurement. After providing informed consent, participants filled in a demographics questionnaire. We assessed participants habitual weekly caffeine consumption using the Caffeine Consumption Questionnaire (CCQ; Shohet & Landrum, 2001) after adapting it to and supplementing it with additional foods, drinks, and drugs available in Germany. During the incidental study task we presented three stimulus materials in separate blocks. The order of material blocks as well as the sequence of stimuli within each block was randomized for each participant anew. Each participant studied 128 photographs of everyday objects—a random selection of one exemplar from 128 out of the 192 pairs of similar objects. These object photographs were the same as those used in the original study (BPS-O, Set C; Stark

et al., 2015, 2013). Additionally, we presented 20 out of 30 pairs of perceptually similar but conceptually dissimilar drawings (e.g., banana and crescent; Rouder et al., 2000) as well as 48 out of 72 pairs of conceptually similar words (e.g., *bronze* and *gold*; Stahl & Klauer, 2008). In photograph- and drawing-blocks participants were instructed to judge whether the depicted objects belonged to the categories *indoor* or *outdoor* using the *a*- and *l*-keys within 2 s. Because the indoor-outdoor-distinction was not applicable to the word material, participants judged the words as either positive or negative. After completion of the study task (duration: $M = 19.09$ min, $SD = 3.26$), participants randomly (based on atmospheric noise, <https://www.random.org/>) ingested either a 200 mg caffeine or a placebo pill; the administration was double blind. Finally, we instructed participants to abstain from consuming any caffeinated drinks, foods, or drugs before their return to the lab the next day.

Day 2. Participants returned after an approximate 24h retention interval ($M = 23.65$ h, $SD = 2.10$) to perform a surprise old/similar/new-recognition task. During the recognition task (duration: $M = 20.41$, $SD = 2.84$), we presented stimuli from the study list (target), new but similar counterparts from previously studied pairs (lure), and new dissimilar stimuli from previously unstudied pairs (foils). The recognition task involved equal numbers of targets, lures, and foils such that all stimulus pairs from each material were used once. We tested the three materials in separate blocks—the order of material blocks was the same order as in the study task. The sequence of memory probes within each block was randomized for each participant anew. Participants responded using the *v*-, *b*-, and *n*-keys to indicate that stimuli were *old*, *similar*, or *new*. Following the recognition task, participants filled in the CCQ again to indicate whether they had consumed any caffeinated drinks, foods, or drugs during the 24 h-retention interval. Comparable retrospective self-report of caffeine intake over the short-term has been found to be strongly correlated with caffeine concentration in saliva ($r = 0.86$, Addicott, Yang, Peiffer, & Laurienti, 2009). Finally, participants reported whether they had experienced any treatment-related side effects, and guessed whether they had been assigned to the caffeine or placebo group before being debriefed.

Data analysis

As in the original study, we compared treatment groups with respect to mnemonic discrimination as indexed by the lure discrimination index, $LDI = f(\text{"similar"}|\text{lures}) - f(\text{"similar"}|\text{foil})$ and mnemonic sensitivity for targets, $d' = \Phi^{-1}(f(\text{"old"}|\text{target})) - \Phi^{-1}(f(\text{"old"}|\text{foil}))$ ². We first performed a 2 (*Treatment*: Caffeine vs. Placebo) $\times$ 3 (*Material*: BPS-O vs. drawings vs. words) ANOVA with planned one-sided contrast to compare treatment groups. To replicate the analyses from the original study, we additionally performed planned one-sided contrasts comparing treatment groups only for the BPS-O material. Any other post-hoc follow-up tests were corrected for multiple comparisons using the multivariate t distribution. For planned contrasts and post hoc comparisons, we compared estimated marginal means (Lenth, 2019).

To test hypotheses about the absence of effects, we performed two one-sided equivalence tests (TOST; Lakens, 2017a; Rogers, Howard, & Vessey, 1993; Wellek, 2002) or nonsuperiority tests for directional comparisons between treatment groups. For TOST the analyst defines a (usually symmetric) region of equivalence around the null value. Using one-sided tests or a 90% confidence interval, the analyst compares the mean difference to the upper and lower bound of the equivalence margin. If the mean difference is significantly smaller than the upper bound and significantly larger than the lower bound, the means are deemed equivalent. Thus, in case of two significant one-sided tests the analyst rejects the hypothesis that an effect is outside the equivalence margin. For reasons of brevity only the test that yields the larger p value is reported. Nonsuperiority tests can be thought of as one-sided TOST: The analyst compares the mean difference only to one bound of the equivalence margin. If the mean difference is significantly smaller than the upper bound of the equivalence margin, the treatment is deemed nonsuperior to the placebo.

² Relative frequencies of 0 and 1 were corrected by adding or subtracting a half response (Murdock & Ogilvie, 1968).

High power to detect small effects ($d = 0.2$, Cohen, 1988, that is $|\Delta_{\text{LDI}}| = 0.03$ for $\hat{\sigma}_{\text{LDI}} = 0.15$)³ requires a large sample ($N = 650$). Given limited resources and the large uncertainty of the magnitude of the effect of caffeine on mnemonic discrimination (95% CI [0.00, 0.93]) we aimed at testing for medium and large effects. Hence, we defined $|\Delta_{\text{LDI}}| \leq 0.07$ ($d \leq 0.50$, $\hat{\sigma}_{\text{LDI}} = 0.15$) and $|\Delta_{d'}| \leq 0.37$ ($d \leq 0.50$, $\hat{\sigma}_{d'} = 0.75$) equivalent or nonsuperior. In case of a significant result, these equivalence bounds allow us to rule out roughly half of the interval estimate reported by Borota et al. (2014).

We additionally explored effects of caffeine withdrawal and tolerance on mnemonic discrimination by entering the effect of habitual caffeine consumption and its interaction with the treatment into the statistical model. To do so, we used a hierarchical generalized additive models (HGAM; Pedersen, Miller, Simpson, & Ross, 2019; Wood, 2011, 2017). Compared to hierarchical generalized linear models, HGAM allow the analyst to add covariates without parametric specification of the shape of the functional relationship between the covariate and outcome variable (e.g., linear or quadratic). In the absence of prior data to inform our choice of the functional relationship between weekly caffeine consumption and LDI, we used a thin regression plate smoothing function, which allows for linear and a wide range of nonlinear functional forms, and estimated the shape of the relationship from the data using restricted maximum likelihood optimization. To test whether there were any effects of habitual caffeine consumption on mnemonic discrimination we compared a model assuming no effect of habitual caffeine consumption ($\mathcal{M}_0$) to three competing models. One model assumed a common smoothing function for weekly caffeine consumption in both caffeine and placebo groups (i.e. a main effect, $\mathcal{M}_C$). The remaining two models specified group-specific smoothing functions (i.e., interactions between weekly caffeine consumption and treatment). Both models accommodate for withdrawal and tolerance effects but differ in flexibility of the estimated functional relationship. The model

³ We estimated the LDI standard deviations by pooling the averaged residual variances from our ANOVA and the estimate obtained from Borota et al. (2014).

$\mathcal{M}_{CT_1}$ used a common smoothing parameter λ , which controls the complexity (“wiggiliness”) of the smooths. The second, more flexible model $\mathcal{M}_{CT_2}$ allowed smoothing parameters to vary between groups. To account for the uncertainty about the appropriate model specification, we tested our hypotheses by comparing sets of AIC weights $w_i(\text{AIC})$ (Wagenmakers & Farrell, 2004; Wood, Pya, & Säfken, 2016). Given the data and a set of models, AIC weights estimate the probability that a model is the best model (i.e., it best minimizes the Kullback–Leibler discrepancy). To quantify the evidence against any effect of habitual caffeine consumption ($\mathcal{H}_0$), we compared $\mathcal{M}_0$ to the average of all other models,

$$\frac{w_{\mathcal{H}_0}(\text{AIC})}{w_{\mathcal{H}_C}(\text{AIC})} = \frac{w_{\mathcal{M}_0}(\text{AIC})}{\frac{1}{3}[w_{\mathcal{M}_C}(\text{AIC}) + w_{\mathcal{M}_{CT_1}}(\text{AIC}) + w_{\mathcal{M}_{CT_2}}(\text{AIC})]}.$$

Values of $\frac{w_{\mathcal{H}_0}(\text{AIC})}{w_{\mathcal{H}_C}(\text{AIC})} > 1$ indicate that the data favor no association between habitual caffeine consumption and mnemonic discrimination; $\frac{w_{\mathcal{H}_0}(\text{AIC})}{w_{\mathcal{H}_C}(\text{AIC})} < 1$ indicate the opposite. Similarly, to quantify evidence against withdrawal or tolerance effects ($\mathcal{H}_{-CT}$), we compared models with group-specific smooths to the competing models,

$$\frac{w_{\mathcal{H}_{-CT}}(\text{AIC})}{w_{\mathcal{H}_{CT}}(\text{AIC})} = \frac{w_{\mathcal{M}_0}(\text{AIC}) + w_{\mathcal{M}_C}(\text{AIC})}{w_{\mathcal{M}_{CT_1}}(\text{AIC}) + w_{\mathcal{M}_{CT_2}}(\text{AIC})}.$$

Values of $\frac{w_{\mathcal{H}_{-CT}}(\text{AIC})}{w_{\mathcal{H}_{CT}}(\text{AIC})} > 1$ indicate that the data favor the absence of withdrawal or tolerance effects; $\frac{w_{\mathcal{H}_{-CT}}(\text{AIC})}{w_{\mathcal{H}_{CT}}(\text{AIC})} < 1$ indicate the opposite. We used R (Version 3.6.3; R Core Team, 2019) and the R-packages *afex* (Version 0.27.2; Singmann, Bolker, Westfall, & Aust, 2019), *emmeans* (Version 1.4.5; Lenth, 2019), *mgcv* (Version 1.8.31; Wood, 2011, 2003, 2004; Wood et al., 2016), *papaja* (Version 0.1.0.9942; Aust & Barth, 2018), *pwr* (Version 1.3.0; Champely, 2018), *shadowtext* (Version 0.0.7; Yu, 2019), and *TOSTER* (Version 0.3.4; Lakens, 2017b) for all our analyses.

Results

First, we compared the treatment groups with respect to their demographic characteristics and subjective reaction to the treatment. Despite random assignment, participants in the caffeine group, on average, reported a higher habitual caffeine consumption, $\Delta M = 732.99$, 95% CI [164.07, 1,301.91], $t(69.27) = 2.57$, $p = .012$ (Table 1). Taking these differences into account we report treatment effects separately for caffeine low-consumers and average consumers in addition to the aggregate analysis. To foreshadow, the results confirm that the difference in habitual caffeine consumption between treatment groups does not affect our conclusions. We detected no difference between the groups' self-reported caffeine consumption during the 24 h-retention interval, $\Delta M = 1.02$, 95% CI [-4.72, 6.75], $t(72.88) = 0.35$, $p = .725$. Overall, caffeine consumption during the retention interval was low (Table 1). Equivalence testing indicated that the difference was no larger than 10 mg, the equivalent of one cup of cocoa, $\Delta M = 1.02$, 90% CI [-3.78, 5.81], $t(72.88) = 3.12$, $p = .001$. In line with the original study, we detected no difference in the prevalence of side effects between the treatment groups, $\Delta p = -0.15$, 95% CI [-0.34, 0.05], $\chi^2(1, n = 75) = 1.73$, $p = .188$. However, contrary to the results of the original study, we did find that participants who ingested 200 mg caffeine more often guessed that they were in the caffeine group compared to participants in the placebo group, $\phi = 0.25$ 95% CI [0.04, 0.48], $\chi^2(1, n = 74) = 4.66$, $p = .031$. It, thus, appears participants were sensitive to the effects of caffeine, which may have resulted in inadvertent unblinding.

Next, we tested our main hypotheses of interest. Our planned contrast analyses did not detect a treatment effect on mnemonic discrimination (i.e., LDI), neither when averaged across all materials, $\Delta M = 0.01$, 95% CI [-0.03, ∞], $t(73) = 0.28$, $p = .390$, nor specifically for the BPS-O material used in the original study, $\Delta M = 0.01$, 95% CI [-0.03, ∞], $t(73) = 0.46$, $p = .322$ (Figure 3). In both cases, nonsuperiority tests indicated the absence of medium and large effects, $\Delta M = 0.01$, 95% CI [- ∞ , 0.04], $t(73) = -3.56$, $p < .001$ and

$\Delta M = 0.01$, 95% CI $[-\infty, 0.06]$, $t(73) = -2.09$, $p = .020$, respectively. The average LDI differed between the three stimulus materials, $F(1.62, 117.94) = 4.09$, $MSE = 0.03$, $p = .027$, $\hat{\eta}_G^2 = .038$. Post hoc follow-up tests indicated that discrimination was more difficult for words than for BPS-O stimuli, $\Delta M = 0.07$, 95% CI $[0.02, 0.12]$, $t(73) = 3.61$, $p = .002$. We did not detect differences in treatment effects between the three stimulus materials, $F(1.62, 117.94) = 0.30$, $MSE = 0.03$, $p = .697$, $\hat{\eta}_G^2 = .003$.

Similarly, our planned contrast analyses did not detect a treatment effect on mnemonic sensitivity (i.e., d'), neither when averaged across all materials, $\Delta M = 0.04$, 95% CI $[-0.23, 0.31]$, $t(73) = 0.30$, $p = .768$, nor specifically for the BPS-O material, $\Delta M = -0.16$, 95% CI $[-0.45, 0.12]$, $t(73) = -1.14$, $p = .257$. Equivalence tests indicated the absence of medium and large effects when averaged across all materials, $\Delta M = 0.04$, 95% CI $[-0.23, 0.31]$, $t(73) = -2.45$, $p = .008$, but not specifically for the BPS-O material, $\Delta M = -0.16$, 95% CI $[-0.45, 0.12]$, $t(73) = -1.48$, $p = .072$. The omnibus ANOVA detected no effects of our experimental manipulations.

Because the effects of caffeine unblinded some participants, we compared treatment effects between participants who correctly guessed their treatment group and those who guessed incorrectly. This exploratory analysis detected no effect of participants' guessing accuracy and, in particular, the effect of caffeine was not moderated by participants' guessing accuracy, neither for mnemonic discrimination ($F[1, 70] = 3.40$, $MSE = 0.02$, $p = .069$, $\hat{\eta}_G^2 = .014$) nor memory sensitivity, $F(1, 70) = 1.38$, $MSE = 1.03$, $p = .244$, $\hat{\eta}_G^2 = .012$.

Effect of habitual caffeine consumption

Given that we did not observe an enhancing effect of caffeine on mnemonic discrimination, withdrawal reversal cannot explain our results. However, caffeine tolerance may have attenuated the treatment effects. We therefore continued to explore whether habitual caffeine consumption affected mnemonic discrimination. Unfortunately, our

exploration was at best mildly informative (Figure 4). The model comparisons mildly favored the absence of any effects of habitual caffeine consumption by a factor of $\frac{w_{\mathcal{H}_0}(\text{AIC})}{w_{\mathcal{H}_C}(\text{AIC})} = 1.61$, $w_{\mathcal{H}_0}(\text{AIC}) = .617$. Accordingly, whether our measurements were affected by withdrawal or tolerance remained inconclusive, $\frac{w_{\mathcal{H}_{\neg CT}}(\text{AIC})}{w_{\mathcal{H}_{CT}}(\text{AIC})} = 1.08$, $w_{\mathcal{H}_{\neg CT}}(\text{AIC}) = .520$. Our data, therefore, neither conclusively supported nor contradict effects of habitual caffeine consumption on mnemonic discrimination.

Nonetheless, we may have failed to observe caffeine enhanced mnemonic discrimination because, in contrast to the original study, we did not restrict sampling to the population of caffeine low-consumers (≤ 500 mg per week). Enhancing effects of caffeine may, thus, have been masked by participants' tolerance to caffeine or high systemic levels of caffeine due to preexperimental ad libitum consumption. Modelling the effects of habitual caffeine consumption allowed us to estimate the effects of caffeine on mnemonic discrimination for low-consumers, that is, with minimal effects of tolerance, withdrawal symptoms, and preexperimental caffeine consumption. We chose to define low-consumers as consuming 50 mg per week because weekly consumption for most of Borota and colleagues' participants was less than 70 mg (c.f., James, 2014). In the following we report the results for model $\mathcal{M}_{CT_1}$ with group-specific smooths but common smoothing parameters. The results from the other models yield the same conclusions, except where noted.

The treatment effects on mnemonic discrimination estimated for caffeine low-consumers closely mirrored our previous results. We did not detect a treatment effect on mnemonic discrimination, neither averaged across all materials, $\Delta M = 0.00$, 95% CI $[-0.03, \infty]$, $t(218.62) = 0.09$, $p = .464$, nor specifically for the BPS-O material used in the original study, $\Delta M = 0.01$, 95% CI $[-0.05, \infty]$, $t(218.62) = 0.27$, $p = .392$. In both cases nonsuperiority tests indicated the absence of medium and large effects, $\Delta M = 0.00$, 95% CI $[-\infty, 0.04]$, $t(218.62) = -3.26$, $p = .001$ and $\Delta M = 0.01$, 95% CI $[-\infty, 0.07]$,

$t(218.62) = -1.75, p = .041$, respectively.⁴ Because self-reports of high habitual caffeine consumption using the CCQ have been found to overestimate consumption compared to diary estimates (Addicott et al., 2009) we also analysed the data after excluding four participants who reported consuming more than 3000 mg per week. These analyses confirmed that our conclusions were not affected by these participants. In sum, our estimated treatment effects for low-consumers are consistent with our overall estimates and suggest that our failure to observe enhancing effects of caffeine on mnemonic discrimination was not caused by tolerance or preexperimental caffeine consumption.

Finally, we tested treatment effects for average caffeine consumers (i.e., 1200 mg per week; Mahoney et al., 2019). The results, by and large, did not diverge from those for low-consumers. Only the nonsuperiority test for the BPS-O material did not indicate the absence of medium and large effects when assuming different effects of weekly caffeine consumption on mnemonic discrimination with different smoothing parameters for both treatment groups, $\mathcal{M}_{CT_2}$, $\Delta M = 0.03$, 95% CI $[-\infty, 0.09]$, $t(216.75) = -1.17, p = .121$. However, given the estimated effects of weekly caffeine consumption, any treatment effects in this model would indicate a withdrawal reversal effect rather than enhancement (Figure 4). Hence, we found no caffeine enhanced mnemonic discrimination for neither low- nor average consumers.

Discussion

We attempted to replicate a widely-received study showing that one post-study dose of 200 mg caffeine enhances mnemonic discrimination (Borota et al., 2014). To address the concern that the observed effect may reflect reversal of withdrawal symptoms rather than a performance enhancement (James, 2014) we conducted an ad libitum consumption

⁴ When assuming the same effect of habitual caffeine consumption on mnemonic discrimination for both treatment groups ($\mathcal{M}_C$), nonsuperiority testing did not indicate the absence of effects for the BPS-O material, $\Delta M = 0.02$, 95% CI $[-\infty, 0.08]$, $t(218.00) = -1.54, p = .062$. But note that this model was least supported by the data, $wAIC = .171$ (Figure 4).

experiment. That is, we did not instruct participants to abstain from caffeine prior to the experiment. Moreover, to explore the generality of the previously reported results, we assessed mnemonic discrimination with two additional types of stimulus material and did not restrict our population to caffeine low-consumers. We found no enhancing effect of caffeine on mnemonic discrimination, neither for low-consumers (≈ 50 mg per week) nor for average consumers (≈ 1200 mg per week), regardless of the stimulus material. Nonsuperiority testing ruled out medium and large effects of $\Delta\text{LDI} \geq 0.07$ ($d \geq 0.50$, $\hat{\sigma}_{\text{LDI}} = 0.15$) and our overall interval estimate for low-consumers renders even small effects unlikely, ΔLDI 95% CI $[-0.04, 0.05]$.

Using a HGAM, we additionally explored effects of habitual caffeine consumption on mnemonic discrimination to test for withdrawal reversal or tolerance effects. Descriptive estimates of the treatment effects resembled withdrawal reversal effects. However, our data neither conclusively supported nor contradict any effects of habitual caffeine consumption on mnemonic discrimination. Hence, despite participants' unrestricted preexperimental caffeine intake, we cannot rule out that at least some participants were experiencing withdrawal symptoms during the experiment. Any such withdrawal effects are no concern for our conclusions, because they cannot explain the absence of caffeine effects in our study. Withdrawal symptoms should be more pronounced in the placebo control group who underwent prolonged abstinence during the experiment. Thus, if anything, impaired mnemonic discrimination in the control group may have artificially inflated the observed treatment effects. Taken together, our findings indicate that enhancing effects of caffeine on mnemonic discrimination, if they exist, are small.

Of course, the scale that is applied to judge the size of an effect is context dependent. Coming back to our back-of-the-envelope calculation, an optimistic interpretation of the present data is consistent with a considerable enhancement: Our estimate may be taken to suggest that one dose of 200 mg caffeine may offset one sixth or even half of the life span

decline in mnemonic discrimination (Δ LDI 95% CI [.09, .29]; Stark et al., 2013, 2015; Stark & Stark, 2017)—an impressive effect. However, all things considered this interpretation, to us, seems overly optimistic. Theorists may apply a different scale, and as is often the case, it is unclear what minimum effect size should be deemed theoretically relevant; even very small effects may be relevant to the theory of pattern separation. Our valuation of the effect size is relative to interindividual differences—a perspective largely stripped of substantive context but useful for planning future studies.

Limitations

Although we tried to address some methodological critiques of the original study, the experimental design can, of course, be improved further. First, Borota et al. (2014) measured caffeine levels in saliva to assess participants' compliance with the caffeine abstinence during the 24 h washout period. In contrast, we relied on participants' self-report. Comparable self-reports over the short-term have been found to be strongly correlated with caffeine concentration in saliva ($r = 0.86$, Addicott et al., 2009), objective measures are preferable. Note, however, that Addicott et al. (2009) report that for the low amounts relevant to this study, self-report was even found to overestimate caffeine concentration in saliva. Like Borota et al. (2014) we assessed habitual caffeine consumption using retrospective self-report on the CCQ. Although, in general, the validity of the CCQ assessment is decent, physiological assessment or diary methods (Addicott et al., 2009) provide more accurate estimates and could improve the sensitivity of the tests of withdrawal reversal and tolerance and experimental controls.

Second, to prevent withdrawal effects we did not restrict participants' preexperimental caffeine intake. This came at the expense of control over preexperimental systemic levels of caffeine. From an applied perspective our estimates may provide more realistic estimates of caffeine effects in everyday life. From a theoretical perspective a tighter control may be preferred. Although habitual caffeine consumption correlates moderately with systemic levels

of caffeine during the experiment (Addicott et al., 2009), statistically controlling for a habitual consumption measure does not fully level out interindividual differences in systemic caffeine levels. Such interindividual differences may have reduced the sensitivity of our experimental design. As discussed, neither preexperimental caffeine abstinence nor preexperimental caffeine treatments are appropriate to address this concern without risking withdrawal effects (James, 2014). Hence, researchers should consider using a more elaborate alternating exposure-abstinence protocol in future studies (James, 1998). In this design, participants repeatedly undergo periods of controlled caffeine abstinence or consumption long enough to complete withdrawal or build a caffeine dependence and tolerance, e.g. six days. Subsequently, participants receive one dose of caffeine or a placebo before performing the behavioral task of interest. Crossing preassessment abstinence or consumption with caffeine or placebo administration yields independent estimates of acutely caffeinated, caffeine-naïve, -tolerant, and -withdrawn performance. We opted for the less costly ad libitum design here because it is closer to the original study while mitigating concerns about withdrawal reversal. Seeing that caffeine enhancements of mnemonic discrimination are at best small, researchers should consider using the alternating exposure-abstinence protocol as both a sensitive and rigorously controlled alternative.

Finally, in contrast to Borota et al. (2014) we found that participants were sensitive to the effects of caffeine, which resulted in some inadvertent unblinding. This divergence, however, cannot explain our failure to replicate the enhancing effect of caffeine on mnemonic discrimination in our study. Borota et al. (2014) exclusively studied caffeine-naïve participants and in some cases administering a 50% larger dose of 300 mg caffeine; that is, if anything, in that study unblinding should have been more prevalent. Moreover, we did not detect a difference between treatment effects for participants who correctly or incorrectly guessed their treatment allocation. Nonetheless, the unblinding in our study suggests that researchers should consider including an active control in addition to a placebo to control for any effects caused by unblinding in future studies.

Conclusion

Our study provides no indication that 200 mg caffeine enhances memory consolidation and subsequent mnemonic discrimination. We can only speculate why our findings diverge from those reported by Borota et al. (2014). After statistical adjustment of treatment effects for habitual caffeine consumption, the biggest difference between the experiments pertains to the control of the preexperimental caffeine intake. Given the empirical evidence that preexperimental caffeine abstinence may induce performance-impairing withdrawal effects even in caffeine low-consumers, it seems plausible that the previously reported enhancement in fact reflects withdrawal reversal. Resolving this issue conclusively requires additional experimental efforts. Based on our findings and previous considerations we recommend that future studies employ an alternating exposure-abstinence protocol, use an active control group, and verify posttreatment caffeine abstinence via saliva or blood samples.

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Table 1

Participant demographics for the caffeine and placebo groups

	Mean	SD	Min	Max
Caffeine [200 mg] (n = 39, 11M:28F [19HC], 10S)				
Age	21.44	2.17	18.00	28.00
Body Mass Index	21.81	3.03	18.59	31.31
Weekly hours of exercise	3.99	4.00	0.00	20.00
Daily hours of sleep	7.36	0.85	5.00	9.00
Weekly caffeine consumption (mg)	1,458.29	1,420.88	45.00	6,808.00
Post-study caffeine consumption (mg)	6.46	13.21	0.00	50.00
Placebo (n = 36, 9M:27F [23HC], 2S)				
Age	22.31	3.01	18.00	30.00
Body Mass Index	21.96	2.63	18.21	28.06
Weekly hours of exercise	4.03	2.93	1.00	15.00
Daily hours of sleep	7.46	0.70	6.00	9.00
Weekly caffeine consumption (mg)	725.31	1,031.82	0.00	5,820.00
Post-study caffeine consumption (mg)	5.44	11.70	0.00	41.00

Note. M:F = Male-to-female ratio, some participants chose not to disclose their sex; HC = women on hormonal contraceptives; S = smokers.

Figure 1. Hypothetical result patterns for caffeine treatment effects on mnemonic discrimination as a function of habitual caffeine consumption, assuming that higher habitual consumption on average leads to stronger dependence and withdrawal symptoms.

Figure 2. Sensitivity curves for planned one-sided treatment contrast in the ANOVA analysis. Grey dotted lines represent the treatment effects size reported by Borota et al. (2014) with upper and lower bound of the 95% confidence interval (Cohen's d 95% CI [0.00, 0.93]). Points indicate the sensitivity of contrasts for the BPS-O material only. Effect sizes above the dashed pink line can be ruled out if we fail to detect a treatment effect and reject effects larger than $|\Delta LDI| \leq 0.07$ ($d \leq 0.50$) in nonsuperiority tests. Conversion to ΔLDI is based on our estimate $\hat{\sigma}_{LDI} = 0.15$. ϵ = Nonsphericity correction.

Figure 3. Effects of one 200 mg post-study caffeine-does on memory performance following a 24 h-wash out and -retention interval for each stimulus material. Filled points represent condition means, error bars represent 95% bootstrapped confidence intervals, small points represent individual participant data, and violins represent estimated densities of the sample distributions.

Figure 4. Group-level predictions (with 95% confidence intervals) from hierarchical generalize additive models of the effect of habitual caffeine consumption on mnemonic discrimination. The panels show fits for model $\mathcal{M}_C$ with one common smooth for caffeine and placebo groups (top), model $\mathcal{M}_{CT_1}$ with a common smoothing parameter λ , which determines the complexity (“wiggiliness”) of the smooths (middle), and model $\mathcal{M}_{CT_2}$ with separate smoothing parameters (bottom). Reported AIC differences (Wood et al., 2016) are relative to the model $\mathcal{M}_0$, which includes no effects of habitual caffeine consumption. Points represent individual observations.