Physio-Cognitive Modeling: Explaining the Effects of Caffeine on Fatigue

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Abstract

Most computational theories of cognition lack a representation of physiology. Understanding the effects of compounds present in the environment on cognition is important for explaining and predicting changes in cognition and behavior given exposure to toxins, pharmaceuticals, or the deprivation of critical compounds like oxygen. This research integrates physiologically-based pharmacokinetic (PBPK) model predictions with ACT-R's fatigue module to predict the effects of caffeine on fatigue. Parameter mapping between PBPK model parameters and ACT-R are informed by neurophysiological literature and established mappings between ACT-R modules and brain regions. Predicted caffeine concentrations in the brain are used to modulate a parameter in the fatigue module to explain caffeine's effects on multiple performance metrics.

Keywords: caffeine; fatigue; ACT-R; physiologically based pharmacokinetic modeling; computational modeling

Introduction

Human cognition is intimately tied to the environment. Indeed, there have been decades of research and discovery on how subtle differences in interactive tasks impact cognitive performance (Anderson, 1990; Gray & Boehm-Davis, 2000). Cognitive performance can also be altered through the deliberate or accidental exposure to compounds in the environment, such as pharmaceuticals, nutriceuticals, and toxins. For example, most countries limit alcohol consumption to avoid accidents that stem from alcohol-induced impairments to cognitive processing (Japan's blood alcohol concentration is 0.03; Canada's is 0.08). In the current paper, an approach toward integrating models of physiology with models of cognition to explain and predict the impacts of chemical compounds on cognitive performance is described and evaluated.

Caffeine is one of the most widely used chemical compounds (Barone & Roberts, 1996), and its effects on performance (Aidman et al., 2021) and fatigue mitigation (Lorist & Tops, 2003) are well documented. Fatigue negatively affects many cognitive functions, including attention, memory, learning, and executive function (Jackson & Van Dongen, 2011). A moderate use of caffeine seemingly reverses some of fatigue's negative effects (Bonnet & Arand, 2012), but too much caffeine decreases those benefits and increases negative subjective experiences (Kaplan et al., 1997).

Integrating the effects of caffeine and fatigue into cognitive architectures through the integration of models of physiology will provide a broader and more detailed understanding of cognition. Even with the wide variety of studies related to caffeine, it is difficult to accurately account for the effects of caffeine on cognition (Lorist & Tops, 2003). The accrual and integration of theories into a single framework to better understand cognition is precisely the promise of cognitive architectures (Newell, 1973).

The objective of the presented research was to develop a task-independent mechanism within a cognitive architecture to account for the fatigue mitigating effects of caffeine. In the following sections we review the literature on caffeine, physiological and cognitive modeling, and an earlier approach to integrating the modeling approaches. We then present observed data of fatigue mitigation through caffeine and present a model that accounts for the data.

Related Literature

Research has been conducted across constituent facets of physio-cognitive modeling. In the following sections we first provide background on our target compound, caffeine. Next, models of physiology are described. Finally, prior attempts to integrate computational models of physiology and cognition are provided.

Caffeine

Caffeine is a widely used stimulant known to provide benefits to cognitive performance (Kamimori et al., 2015). Caffeine and its metabolites (e.g., paraxanthine) act as adenosine antagonists (inhibitors) on two types of receptors: A_1 and A_{2A} (Kaplan et al., 1997). A_1 receptors are distributed throughout the brain, but are most concentrated in the thalamus, cerebral cortex, and hippocampus. A_{2A} receptors are less widely distributed, existing in dopamine rich regions like the striatum, but are more central to caffeine's stimulatory effects on cognition (Lorist & Tops, 2003).

Physiologically-based Pharmacokinetic Models

A physiologically-based pharmacokinetic (PBPK) model is an *in silico* representation of the movement of chemicals in the arterial blood, flowing to each major organ or lumped tissue compartment(s), including the brain. They provide the time-course of compounds via ordinary differential equations to account for absorption, distribution, metabolism, and excretion processes (Pearce, Setzer, Strope, Sipes, & Wambaugh, 2017). Thus, PBPK models enable predictions

of the amount and time course of a compound in the brain and enable dose-response predictions.

There are three components to PBPK models: 1) species-specific physiological parameters, 2) chemical-specific parameters, and 3) experiment-specific details for the studies to be simulated. Species-specific physiological parameters are the organ weights and blood flow rates for the defined organs in the PBPK model and are derived from the closest like species when not available. Chemical-specific parameters that are unique for each chemical are the tissue solubility (partition coefficient), metabolism of the parent compound, and plasma and tissue binding characteristics.

Atomic Components of Thought–Rational (ACT-R)

ACT-R is a cognitive architecture that specifies how cognitive processes interact to produce cognition and overt behavior (Anderson, 2009). Models developed within ACT-R posit a common set of processes and mechanisms, which are instantiated as a computer simulation. Independent modules operate in parallel and include declarative memory, vision, attention, and motor modules. Procedural memory coordinates the behavior of the architecture through a set of production rules. Production rules follow an "if-then" structure that encodes the conditions under which specific actions are taken.

Prior research in ACT-R has related the striatum and the thalamus to the architecture's action-selection system (Anderson, 2009). Both of these regions are associated with adenosine receptors, which would suggest ACT-R's action-selection system is likely to be affected by caffeine.

Including Physiology within Cognitive Modeling

A few previous research efforts have integrated physiological mechanisms into computational cognitive modeling. Some cognitive architectures include physiological constraints from the brain (e.g., spiking neural networks in Spaun; Eliasmith et al., 2012), but the vast majority of architectures tend not to include physiological constraints. A few efforts have integrated simplified aspects of non-brain physiology into computational cognitive models, like Ritter, Kase, Klein, Bennett, and Schoelles (2009) that explored how ACT-R parameters could be varied to explain effects of stress and caffeine. Work by Dancy, Ritter, Berry, and Klein (2015) used a more complete model of human physiology to affect behavior within ACT-R (i.e., HumMod; Hester et al. 2011).

The research of Dancy and colleagues inspired the development of a similar, yet novel, approach to integrating models of physiology with models of cognition. This novel approach provided compound blood concentrations to ACT-R mechanisms through PBPK models. The result was a cognitive model capable of predicting cognitive performance effects of a common volatile organic compound, toluene (Fisher et al., 2017). The present research extends the research by Fisher et al. in three ways: (1) another compound, caffeine, is explored, (2) the mapping of PBPK predictions to ACT-R parameters is informed by neurophysiological literature, and (3) the research is focused on how caffeine mitigates fatigue, and so ACT-R's fatigue module is used (Walsh, Gunzelmann, & Van Dongen, 2017).

Observed Data

Sleep deprivation data were collected and analyzed by McIntire, McKinley, Goodyear, and Nelson (2014). All participants were kept awake for 30 hours, and some were given caffeine. A summary of the study and data are provided here (additional details can be found in the original paper).

Thirty active-duty military personnel (22 male) participated in the study and were compensated for their time. Participants were randomly assigned to one of three conditions: transcranial direct current stimulation (tDCS) active stimulation with placebo caffeine, caffeine with sham tDCS, and sham tDCS and placebo caffeine. Data from the active stimulation condition was omitted from the present study. Two participants' data were excluded from data presented here as those two were non-compliant.

The psychomotor vigilance task (PVT) was used to assess alertness. On each trial, digits were presented that show the number of milliseconds since the stimulus was presented. Each trial lasts for a minute, or until the participant responds by pressing a button. The interstimulus interval varied randomly from 2 to 12 s. The total task duration was 10 minutes.

Participants were instructed to sleep for at least 7 hours for the two nights prior to the study. Participants awoke at 6 a.m. and were awake for 30 continuous hours. One session of PVT was administered every two hours starting at 6 p.m. Participants in the caffeine condition received 200mg of caffeine chewing gum at 3:15 a.m. Participants in the control group received gum without caffeine.

All data were normalized to 2 a.m. values, just prior to caffeine administration. McIntire et al. (2014) found a significant difference in mean response times, and a marginal difference in lapses, between caffeinated and control participants (see Figure 1, solid lines). No mention is made of false starts, but Figure 1 shows little to no difference in false starts. Lapses are responses that occur 500 ms after stimulus presentation or later. False starts are responses that occur 150 ms after stimulus presentation or earlier. Both are common PVT metrics used in the sleep literature to understand the effects of fatigue (Lim & Dinges, 2008).

Model

In this section, the constituent parts of the model are discussed. The ACT-R model is described first, followed by the PBPK model. Finally, variants of the model are discussed along with the strengths and weaknesses of each.

ACT-R Model

This modeling builds on previous research that integrates ACT-R with biomathematical models (BMM) of fatigue (Walsh et al., 2017), and PBPK models (Fisher et al., 2017). The initial ACT-R model was identical to that in previous research investigating sleep loss and vigilance with the PVT (Veksler & Gunzelmann, 2018). Initial parameters of the

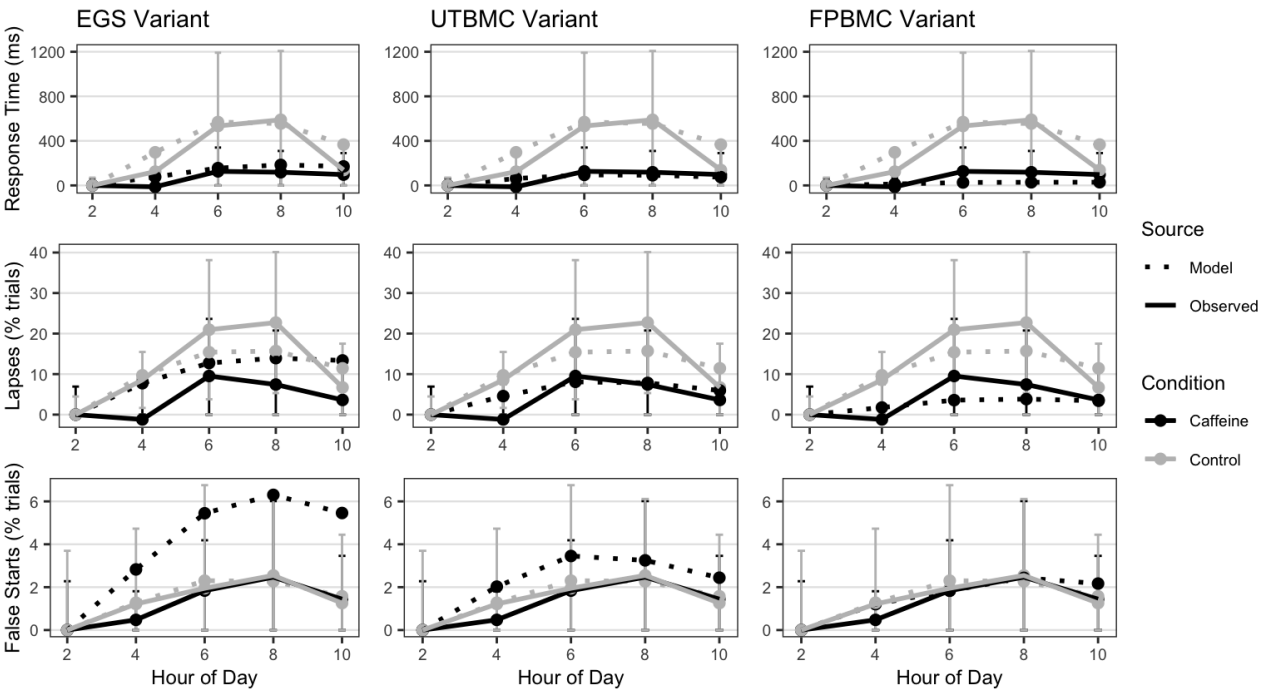

Figure 1: Predictions of the best fitting models for the EGS, UTMBC, and FPBMC variants. Error bars indicate ± 1 standard deviation of participant means.

model were set to the mean of individual participants' parameter estimates from Walsh et al. (2017; Table 5).

The PVT model contains only three productions: *wait*, *attend*, and *respond*. False starts, which are responses before or within 150ms of stimulus onset, can occur due to partial matching between the wait and attend goals. Additional details on the model can be found in Veksler and Gunzelmann (2018).

The fatigue module accounts for the effects of sleep homeostasis and circadian rhythms. The module consists of a theory of *microlapses* and a BMM of fatigue. The BMM predicts alertness levels based on sleep schedule and the time of day. Lower levels of alertness increase the likelihood of microlapses, a brief interruption of cognitive processing. Microlapses affect ACT-R's production utility mechanism by reducing the utility of all productions. The production utility decrement caused by microlapses is determined by the fatigue module's *FPBMC* parameter. Microlapses also impact a fatigue compensatory mechanism that decreases ACT-R's utility threshold. The degree of compensation by this mechanism is determined by the fatigue module's *UTBMC* parameter. Additional details on the fatigue module can be found in Walsh et al. (2017).

The model was initially fit to the control data. Solid lines in Figures 1 and 3, and Table 1, show the fit of this baseline model. The same parameters were varied as in Walsh et al. (2017), and the best fitting values were very near the mean parameters found in that study:

- Initial utility (IU) = 5.1
- Utility threshold (UT) = 4.62
- Production utility noise (EGS) = 0.43
- Default action time (DAT) = 0.04
- Fatigue production utility BMM constant (FPBMC) = 0.025
- Utility threshold BMM constant (UTBMC) = 0.0155
- Fatigue procedural decrement (FPDEC) = 0.99

PBPK Model

The blood pharmacokinetics of caffeine after oral consumption of a 200 mg caffeine gum by a 70 kg individual (i.e. 2.86 mg/kg), was simulated using the R package "high throughput toxicokinetics" (httk; Pearce et al., 2017). In addition to the default tissue compartments in the PBPK model structure selection of the httk platform (lung, G.I. tract, liver, kidney, rest of body), we added a brain and an adipose tissue compartment (fat), in order to address the main pharmacodynamic target tissue for caffeine, that of the central nervous system (CNS) and other peripheral tissue concentrations (fat). This allows mapping of the pharmacokinetics of caffeine in the CNS in addition to the plasma compartment.

The blood plasma concentration time-course from the controlled human pharmacokinetic study of Syed, Kamimori, Kelly, and Eddington (2005) after an acute oral chewing gum dosage is plotted in Figure 2, with the PBPK model results overlayed on the data. An excellent match to the data confirms the ability to predict accurately the concentration of caffeine in plasma after this unique dosing route.

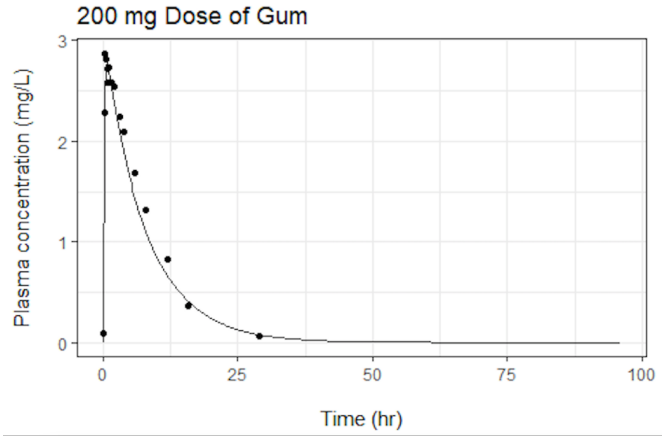

Figure 2: PBPK model results (solid line) of human caffeine plasma (dots) concentration time-course after an acute caffeine dose (200 mg) in chewing gum (n=1 human subject).

Table 1: Model fits for the baseline model and four variants.

Variant	Mean RT		Lapses		False Starts	
	RMSE	R^2	RMSE	R^2	RMSE	R^2
Baseline	146	.95	5.1	.89	0.3	.80
EGS	68	.88	7.6	.65	3.5	.91
UTBMC	44	.82	3.2	.98	1.3	.76
FPBMC	77	.91	3.8	.79	0.5	.80
with PBPK	55	.93	2.7	.73	0.5	.99

Model Variants

Table 1 shows a list of the model variants and their fit to the observed data. Each model variant explored the use of a single parameter affecting production selection. Production selection was the focus of this research for two reasons. First, the effects of alertness in previous modeling of the PVT have been explained with procedural effects (Walsh et al., 2017). Second, pharmacological research has noted that a primary mechanism for stimulation by caffeine is as an antagonist of A_{2A} receptors in regions of the *basal ganglia*, most notably in the *striatopallidal* and *striatonigral* pathways (Fredholm, Bättig, Holmén, Nehlig, & Zvartau, 1999). The striatopallidal pathway in the basal ganglia has been mapped to ACT-R procedural processor, with the striatum more directly linked to production matching and the pallidum more directly linked to production selection (Anderson, 2009).

Production Noise Parameter (EGS). In the fatigue module, as alertness decreases, noise plays a larger role in production selection. Our initial hypothesis was that caffeine may offset some of the effects of noise as alertness decreases.

The left plot in Figure 1 shows the best fitting predictions of the model with EGS varied as a function of caffeine presence. Noise was increased to 0.5 (from the baseline model's 0.43) in the caffeinated condition. As shown in the first row of Table 1, the fit is not good. An increase in noise increases false starts, just as a decrease in noise (not shown) decreases false starts. In the observed data, the presence of caffeine has no effect on false starts.

Utility threshold compensatory mechanism (UTBMC). The next parameter explored was UTBMC. This parameter determines how utility threshold is affected by the fatigue module. Alertness predictions are scaled by UTMBC and summed with the utility threshold. Changes to UTBMC affects the complex interaction between activation of the model's response production, "misfiring" of the model's response production (due to partial matching), and microlapses.

Previous research has associated ACT-R action selection, of which production utility threshold is a part, with the *pallidum* in the brain (Anderson, 2009). Other research has identified regions rich in dopamine receptors, especially striatopallidal regions, as playing pivotal roles in caffeine's effect on behavior (Lorist & Tops, 2003). Therefore, caffeine could modulate production utility thresholds, with greater caffeine concentrations making it more likely that a production will fire and therefore less likely that a micro-lapse will occur.

The center plot in Figure 1 shows the best fitting predictions for the model with a UTBMC value of 0.018 when caffeine is present. These predictions are a substantial improvement over the previous mechanisms. Mean response time predictions remain good, and a differentiation of lapses as a function of caffeine presence is predicted. However, there is a slight, but substantial, increase in the number of false starts, which is not present in the observed data.

Fatigue production utility decrement (FPBMC). The final parameter explored was FPBMC. This parameter determines how production utilities are affected by the fatigue module. Alertness predictions are scaled by FPBMC, and then production utilities are scaled by one minus the scaled alertness predictions. A decrease in FPBMC results in higher utilities, and an increase results in lower utilities.

Just as with UTMBC, the literature suggests a link between FPBMC and caffeine effects. Production utilities are as much a part of action selection in ACT-R as utility threshold, and so are also associated with the *pallidum* (Anderson, 2009) and could also be modulated by caffeine (Lorist & Tops, 2003).

The right plot in Figure 1 shows the best fitting predictions for the model with a FPBMC value of 0.02 with caffeine and 0.025 without caffeine (control). As with the UTBMC model, this variant predicts a differentiation of lapses as a function of caffeine. As shown in Table 1, the fits to the false starts is better than with the UTBMC, and the fits to the response times and lapses are comparable to those with the UTMBC model.

Scaled by caffeine predictions. Once we had a good candidate parameter that could account for changes in performance due to caffeine, the fatigue module (Walsh et al., 2017) was modified to allow caffeine concentration predictions to modify the FPBMC parameter similar to the method used by Fisher et al. (2017). The modified FPBMC parameter, $FPBMC_p$, is:

$$FPBMC_p(t) = FPBMC - \beta PBPK(t)$$

where *PBPK* is the predicted concentration of caffeine in the brain tissue at time *t*, FPBMC is the fatigue module's production utility decrement parameter, and β determines the degree to which the PBPK predictions modulate FPBMC. The PBPK values used were the mean caffeine concentrations during each task presentation in the McIntire et al. (2014) protocol. The concentrations varied little during the ten minutes of task presentation. The scaling parameter was varied a few times until the ACT-R predictions approximated the observed performance.

Figure 3 and Table 1 show the results for the best fitting β parameter, which was 0.0045. The model continues to do a good job of predicting most of the trends that the static FPBMC model did, with most metrics improving slightly and the R^2 for false starts improving substantially.

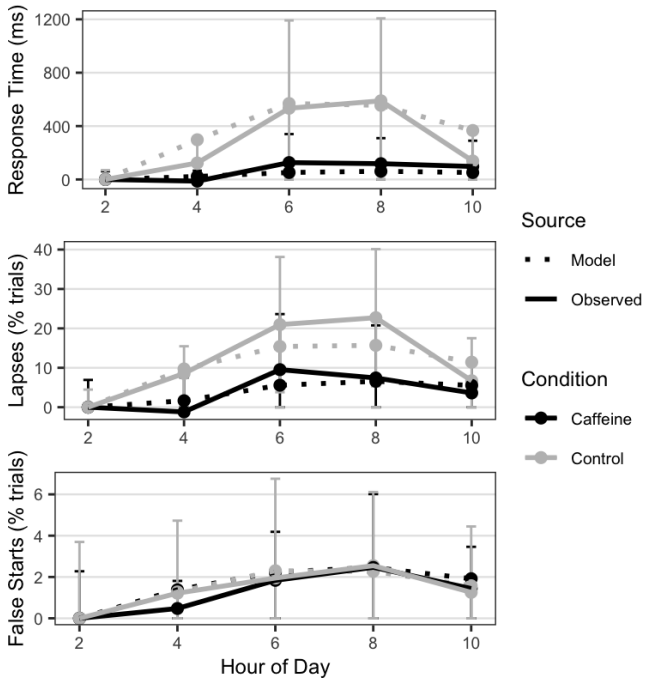

Figure 3: Predictions of the best fitting model varying FPBMC modulated by PBPK predictions. Error bars indicate ± 1 standard deviation of participant means.

Discussion

This work investigated the effects of caffeine on fatigued people. While the effects of caffeine have been studied extensively in psychology and physiology, few formal models have been used to study these effects; exceptions include Ritter et al. (2009) and Ramakrishnan et al. (2016). Ritter et al. investigated the effects of 200 or 400 mg of caffeine on the serial subtraction task without sleep restriction on three ACT-R parameters related to vocalization and memory retrieval (SYL, BLC, and ANS). Ramakrishnan et al. present a mathematical model that predicts human performance on the PVT from a large number of protocols, with different sleep restrictions and caffeine administration. While both models explain the data well, neither model seems to be informed by the underlying physiological processes.

The mapping of physiological to cognitive processes is not trivial. In both formal physiological and cognitive models, there are many variables that could potentially interact to produce behavior (Dancy et al., 2015). In this work, we limited our parameter space to those parameters associated with ACT-R's action selection mechanism, as the PVT is largely procedural. In addition, the caffeine literature suggests a critical connection between caffeine and action selection, with caffeine affecting A_{2A} receptors concentrated in dopamine rich areas like the basal ganglia (Lorist & Tops, 2003). Still, future research will need to employ other tasks that recruit other cognitive processes, as caffeine has also been shown to affect memory (Loke, 1988) and motor processes (Loke, 1988).

Walsh et al. (2017) integrated a mathematical model of alertness with a theory of microlapses to create the ACT-R fatigue module. The work presented here builds on that to explain how caffeine mitigates the effects of fatigue. The modeling revealed that caffeine may effectively "reverse" some of the decrement in production utility that result from fatigue. This reversal is supported by the physiology literature. Caffeine is an adenosine inhibitor and adenosine plays a role in sleep homeostasis (Landolt, 2008). This inhibition was implemented by scaling the fatigue production utility decrement (FPBMC) parameter as a function of predicted caffeine concentration in the brain. This one parameter captured the three substantial trends in the observed data without the need to vary other parameters explored in this research, namely the fatigue module's compensatory mechanism (UTBMC) and production utility noise (EGS).

This research requires validation of the link function between the PBPK caffeine level predictions and the fatigue module's FPBMC parameter. While the use of the PBPK model gives us some confidence that our mechanism will account for variations in caffeine, data from additional studies that include multiple administrations and dosages of caffeine will be required. Correspondingly, the mechanism does not currently account for potential negative effects of too much caffeine or individual differences (Kaplan et al., 1997). Future research will include extending the PBPK-to-FPBMC link function to account for known, physiological processes like paraxanthine (a metabolite of caffeine) and adenosine pharmacodynamics.

Conclusion

This research explains the effects of caffeine as a moderation of fatigue's effects on procedural utility. This is done by extending previous research that integrated biomathematical models of alertness (Walsh et al., 2017) and PBPK models (Fisher et al., 2017). Utilizing physiologically-valid predictions of compound levels in the brain, such as caffeine, to vary parameters of cognitive modules mapped to relevant neural mechanisms has the potential to increase the fidelity and accuracy of cognitive models of human performance.

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