



A biomathematical model of the restoring effects of caffeine on cognitive performance during sleep deprivation

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HIGHLIGHTS

- We model the restoring effects of caffeine on sleep-deprived individuals.
- Caffeine effects were modeled as a multiplying factor on caffeine-free performance.
- Individualized caffeine models outperformed population-average models.
- The model captured the effects of both single and repeated caffeine doses.

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ABSTRACT

Rationale: While caffeine is widely used as a countermeasure to sleep loss, mathematical models are lacking.

Objective: Develop a biomathematical model for the performance-restoring effects of caffeine in sleep-deprived subjects.

Methods: We hypothesized that caffeine has a multiplicative effect on performance during sleep loss. Accordingly, we first used a phenomenological two-process model of sleep regulation to estimate performance in the absence of caffeine, and then multiplied a caffeine-effect factor, which relates the pharmacokinetic–pharmacodynamic effects through the Hill equation, to estimate the performance-restoring effects of caffeine.

Results: We validated the model on psychomotor vigilance test data from two studies involving 12 subjects each: (1) single caffeine dose of 600 mg after 64.5 h of wakefulness and (2) repeated doses of 200 mg after 20, 22, and 24 h of wakefulness. Individualized caffeine models produced overall errors that were 19% and 42% lower than their population-average counterparts for the two studies. Had we not accounted for the effects of caffeine, the individualized model errors would have been 117% and 201% larger, respectively.

Conclusions: The presented model captured the performance-enhancing effects of caffeine for most subjects in the single- and repeated-dose studies, suggesting that the proposed multiplicative factor is a feasible solution.

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1. Introduction

Cognitive performance decrement due to sleep loss is recognized as a threat to safety and productivity in both civilian and military settings, prompting the investigation of pharmacological countermeasures against the adverse effects of reduced sleep on cognitive performance (Balkin et al., 2004; Caldwell and Caldwell, 2005). Among the various pharmacological sleep and fatigue countermeasures available, caffeine is the most widely used stimulant drug in both occupational and non-occupational settings. Over the past decade, results of numerous laboratory and

Abbreviations: PD, Pharmacodynamic; PK, Pharmacokinetics; PVT, Psychomotor Vigilance Test; RMSE, Root Mean Squared Error

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14. ABSTRACT Rationale: While caffeine is widely used as a countermeasure to sleep loss, mathematical models are lacking. Objective: Develop a biomathematical model for the performance-restoring effects of caffeine in sleep-deprived subjects. Methods: We hypothesized that caffeine has a multiplicative effect on performance during sleep loss. Accordingly, we first used a phenomenological two-process model of sleep regulation to estimate performance in the absence of caffeine, and then multiplied a caffeine-effect factor, which relates the pharmacokinetic/pharmacodynamic effects through the Hille equation, to estimate the performance-restoring effects of caffeine. Results: We validated the model on psychomotor vigilance test data from two studies involving 12 subjects each: (1) single caffeine dose of 600 mg after 64.5 h of wakefulness and (2) repeated doses of 200 mg after 20, 22, and 24 h of wakefulness. Individualized caffeine models produced overall errors that were 19% and 42% lower than their population-average counterparts for the two studies. Had we not accounted for the effects of caffeine, the individualized model errors would have been 117% and 201% larger, respectively. Conclusions: The presented model captured the performance-enhancing effects of caffeine for most subjects in the single- and repeated-dose studies, suggesting that the proposed multiplicative factor is a feasible solution.		
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field studies in which caffeine was administered as either a single or repeated dose have demonstrated that, when used at appropriate doses, caffeine can restore or maintain performance in sleep-deprived individuals, with minimal side effects (Bonnet et al., 2005; Brice and Smith 2002; Institute of Medicine, 2001; Kamimori et al., 2000; Wesensten et al., 2005).

The pharmacokinetics (PK) of caffeine and its dose-dependent metabolism in humans have been well characterized (Bonati et al., 1982; Denaro et al., 1990) and the mechanism of action (antagonism of adenosine receptors) is also well-understood (Bertorelli et al., 1996). However, only very few attempts have been made to quantify or model the performance-enhancing effects of caffeine in humans. Recently, Seng et al. (2010) developed population-average PK–Pharmacodynamic (PD) models that capture the psychomotor effects of caffeine on a battery of tests, including oculomotor assessment (saccadic velocity) and neuropsychological performance assessment (in which mean reaction times were measured). An assumption of these PK–PD models, however, is that individuals are fully alert (i.e., they are not sleep deprived) at the time of caffeine administration, thus limiting the potential utility of these models to predictions of caffeine-enhanced performance under optimal or semi-optimal alertness conditions. Nevertheless, mathematical models that accurately predict the restoring effects of caffeine on the performance of sleep-deprived individuals could serve as a tool to determine the precise time and amounts of caffeine doses that result in performance peaks at the desired time and that can safely prolong peak performance.

Only two models that account for the effects of caffeine on fatigue and performance of sleep-deprived individuals have been published to date (Benitez et al., 2009; Puckeridge et al., 2011). Benitez et al. used a novel performance-inhibitor model that consists of a homeostatic component (assumed to be proportional to the concentration of the adenosine receptor–inhibitor complex in the brain, with incorporation of the antagonistic effect of caffeine on the adenosine receptors via a receptor binding equation) and a circadian component (modeled as a four-harmonic sinusoidal equation with a 24-h period). This 13-parameter model was used to characterize the average restorative effects of repeated doses of 200 mg of fast-acting caffeinated chewing gum on a population of nine subjects following 77 h of total sleep loss. However, because the homeostatic component of the model is novel and has not been adequately validated on caffeine-free performance data of sleep-deprived individuals, the model fidelity before caffeine administration and after the effects of caffeine have dissipated is not known. Moreover, caffeine absorption is not represented in the model (it is assumed to be instantaneous), limiting its application to fast-acting caffeine formulations.

Puckeridge et al. (2011) incorporated the effects of caffeine by expanding a physiologically based model of sleep–wake dynamics (Phillips and Robinson, 2008), which represents the homeostatic and circadian processes by describing several interactive neuronal mechanisms. Although their model represents the complex dynamics of the sleep/wake system and the effects of caffeine on sleep–wake timing and fatigue, it requires the estimation of a large number of model parameters (21; 16 to characterize the homeostatic and circadian processes and five to represent caffeine effects). The model was individualized to characterize the restoring effects of a single dose of 600 mg of caffeine on performance data from 12 subjects confined to 49 h of total sleep deprivation. However, the effects of caffeine were validated only on subjective sleepiness scores, which may not reflect objective cognitive performance measures (Van Dongen et al., 2003).

In this work, we attempt to overcome some of the above-mentioned limitations by proposing a more parsimonious

individualized biomathematical model that quantifies the performance-restoring effects of both single and repeated doses of caffeine when sleep/wake history and circadian phase are unknown. The proposed model consists of two components: (1) our previously developed individualized model of the effects of sleep loss on performance under caffeine-free (placebo) conditions (Rajaraman et al., 2008, 2009) and (2) a model of the PD effects of caffeine on performance restoration based on the PK–PD Hill relationship (Wagner, 1968). In particular, we propose that caffeine has a multiplicative effect on performance during sleep loss.

2. Methods

2.1. Study data

Psychomotor vigilance test (PVT) data from two studies were used to evaluate the proposed model. The PVT is a visual vigilance task in which subjects press a button in response to a visual stimulus that is presented on a random interval (2–10 s) schedule over a 10-min period, resulting in ~100 stimulus–response pairs (Dinges and Powell, 1985; Dorian et al., 2005). In a PVT session, a time (initially set to “000”) is displayed in the center of a computer screen and subjects are instructed to press a response key as soon as the time display begins to scroll. The subject’s response stops the timer, displays the reaction time for ~0.5 s, and then initiates the next trial. The subject’s response times are automatically recorded, as are the number of responses larger than a specified “lapse” threshold (generally 500 ms). The latter is used to quantify performance impairment, with larger number of lapses indicating greater impairment.

For the first study, we used PVT data obtained from a controlled laboratory experiment (single-dose study, labeled *study A*) involving 24 healthy young adults who were kept awake for 85 consecutive hours (Wesensten et al., 2005). Our analysis was based on a subset of 12 subjects who were administered 600 mg of caffeine (Vivarin® pills) after 64.5 h of wakefulness (i.e., at 0000 h on *day 4*). The remaining 12 subjects were administered a placebo pill after the same period of wakefulness. All subjects completed a 10-min PVT every 2 h starting at 0800 hours on *day 1*, which continued through 1800 h on *day 4*, for a total of 42 PVT sessions.

The data from the second study (repeated-dose study, labeled *study B*) were collected during a laboratory experiment in which 48 healthy young adults were kept awake for 29 consecutive hours (Kamimori et al., 2005). Our analysis was based on a subset of 12 subjects who were administered 200 mg of Stay Alert® (Amuro Confectioners, Yorkville, IL) caffeinated chewing gum at the beginning of each of three 2-h test blocks occurring after 20, 22, and 24 h of sleep loss (corresponding to 0300, 0500, and 0700 h, respectively, on *day 2*). The remaining subjects were administered either placebo ($N=12$), 50 mg of caffeinated gum ($N=12$), or 100 mg of caffeinated gum ($N=12$) in a similar manner. All subjects completed 10-min PVTs starting at 0800 h on *day 1* and ending at 1200 h on *day 2*, for a total of 29 PVT sessions, including nine sessions prior to caffeine administration, six sessions during each of the three subsequent 2-h test blocks, and two additional tests after the third 2-h test block.

All subjects in both studies reported a total sleep time of approximately 6–9 h for the night immediately before the beginning of the studies. Further, they were habitually low to moderate caffeine users, with average, self-reported daily caffeine consumption of < 400 mg. Both studies were approved by the Walter Reed Army Institute of Research Human Use Committee (Silver Spring, MD) and the United States (U.S.) Army Medical Research

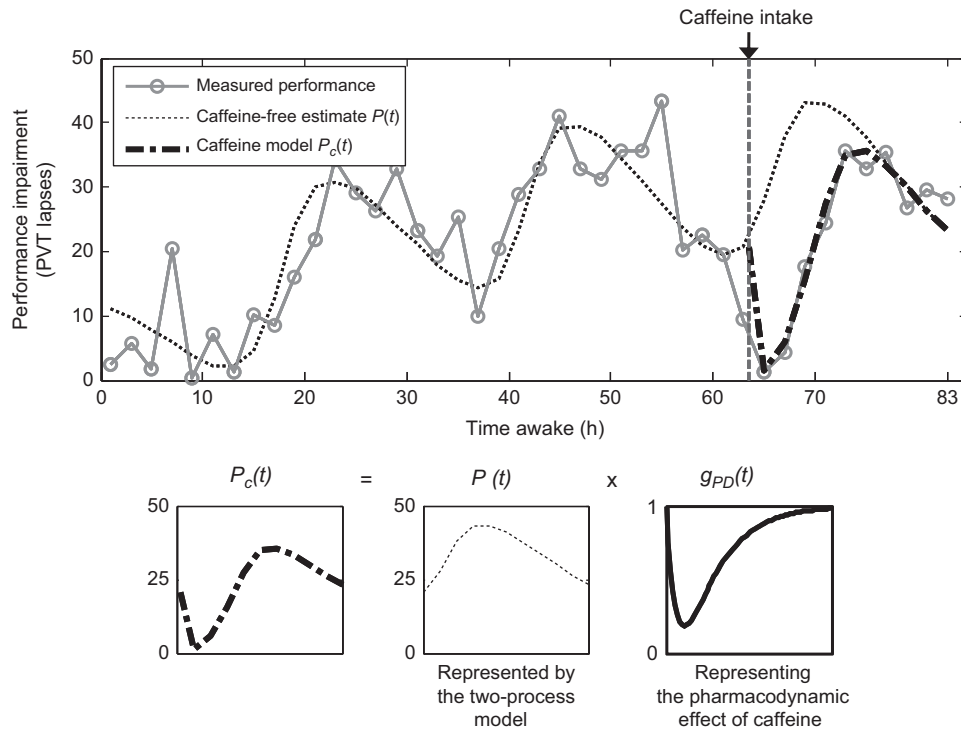


Fig. 1. Proposed approach to model the performance-enhancing effects of caffeine. We hypothesized that performance impairment $P_c(t)$ at discrete-time index t after-caffeine intake can be modeled as the product of caffeine-free performance $P(t)$, which is represented by the two-process model of sleep regulation, and the pharmacodynamic effect of caffeine $g_{PD}(t)$, with $0 \leq g_{PD}(t) \leq 1$, which was assumed to have a temporal structure governed by the pharmacokinetics of caffeine in the plasma.

and Materiel Command Human Subjects Review Board (Ft. Detrick, MD). Written informed consent was obtained from all subjects prior to their participation.

2.2. Model of the effects of caffeine on performance restoration

We hypothesized that caffeine has a multiplicative effect on performance during sleep loss. In other words, the cognitive performance impairment estimate $[P_c(t)]$ of a sleep-deprived individual after caffeine intake at a discrete-time index t can be formulated as

$$P_c(t) = P(t) \times g_{PD}(t), \quad (1)$$

where $P(t)$ represents the individual's caffeine-free performance impairment at time awake t and $g_{PD}(t)$ represents the PD effect of caffeine, with $0 \leq g_{PD}(t) \leq 1$, where 1 corresponds to PD effects in the absence of caffeine, i.e., the most impaired performance, and 0 corresponds to the maximal PD effect on cognitive performance, i.e., complete restoration with no impairment. Hence, with this multiplicative model, performance impairment levels decrease after caffeine intake and, eventually, as caffeine is cleared, return to the levels that would be observed if caffeine had not been administered. Fig. 1 shows a schematic of the proposed model, which requires estimates of both $P(t)$ and $g_{PD}(t)$.

2.3. Model for caffeine-free performance

To obtain the caffeine-free performance estimate $P(t)$ during the period following caffeine administration, we used the two-process model of sleep regulation (Borbely, 1982), which forms the basis of the majority of the “legacy” population-average performance prediction models (Mallis et al., 2004) as well as the recently proposed individualized fatigue and performance models (Rajaraman et al., 2008, 2009; Van Dongen et al., 2007).

The model assumes that the temporal pattern of alertness can be represented as the additive interaction of two separate processes (Achermann and Borbely, 1994): Process S (sleep homeostasis), which is dependent on sleep/wake history, increases exponentially with time awake and decreases exponentially with sleep/recovery time to a basal value (Daan et al., 1984; Porkka-Heiskanen et al., 1997), whose rates of increase/decrease are individual-specific, assumed to be constant, and have unknown values; and Process C (circadian), which is independent of sleep/wake history and represents a self-sustaining oscillator with a 24-h period (Achermann and Borbely, 1992; Fuller et al., 2006). Thus, mathematically, in discrete-time notation, $P(t)$ at time awake t can be expressed as (Rajaraman et al., 2008)

$$P(t) = \alpha - \alpha S_0 \exp[-(t-1)\rho T_s] + \beta \sum_{i=1}^5 a_i \sin\left\{\frac{2\pi}{\tau} i[(t-1)T_s + \phi]\right\}, \quad (2)$$

where α and β are the parameters that control the relative effect of the two processes S and C on performance, respectively, ρ represents the buildup rate of homeostatic pressure, T_s denotes the sampling period, S_0 represents the initial homeostatic state, which depends on the prior sleep/wake history, τ denotes the fundamental time period of the circadian clock (~ 24 h), a_i , $i=1, \dots, 5$, represent the amplitudes of the five harmonics of Process C, and ϕ denotes the initial circadian phase. Here, we chose to keep the amplitudes of the five harmonics ($a_1=0.97$, $a_2=0.22$, $a_3=0.07$, $a_4=0.03$, and $a_5=0.001$) and the fundamental period ($\tau=24$ h) constant over time, thereby enforcing the shape of Process C to be identical among all individuals (Achermann and Borbely, 1992).

Thus, the performance of an individual under total sleep deprivation, in the absence of countermeasures, is modeled as a nonlinear function of five unknown parameters (α , ρ , β , S_0 , and ϕ)

whose values are uniquely estimated from a set of prior (caffeine-free) performance measurements for that individual, i.e., measurements from PVT sessions conducted prior to the first caffeine dose administration. However, in order to obtain reliable individualized two-process model parameter estimates, the method requires a certain minimum number of prior performance measurements (Rajaraman et al., 2008). In the absence of sufficient measurements prior to caffeine intake to individualize the model parameters, we used a Bayesian approach that combines performance data from the available sessions with *a priori* performance data estimated from a population-average prediction model, with both data sets assumed to be normally distributed (Rajaraman et al., 2009). Here, the population-average model consisted of the two-process model in Eq. (2) with fixed (population-average) model parameters ($\alpha = 29.70$ lapses, $\rho = 0.035 \text{ h}^{-1}$, $\beta = 4.30$ lapses, $S_0 = 0.94$, and $\phi = 6.90 \text{ h}$) obtained from Van Dongen et al. (2007). After using the Bayesian approach to obtain individualized parameters for the two-process model in Eq. (2), we used it to predict individual-level caffeine-free performance estimates $P(t)$ for the period following caffeine administration.

2.4. Model for the PD effect of caffeine

The PD effect of caffeine $g_{PD}(t)$ was modeled using the PK model of caffeine through the Hill equation (Csajka and Verotta, 2006). In particular, to model the PD effect of caffeine on performance (quantified by PVT lapses, where more lapses reflect a greater degree of performance impairment), we assumed that the antagonistic effect of caffeine on the A_1 and A_{2A} adenosine receptors (Fisone et al., 2004; Fredholm et al., 1999) can be modeled using the E_{max} model, popularly known as the Hill equation [PK–PD relationship] (Csajka and Verotta, 2006), reflecting the classical receptor occupancy theory (Ariens, 1954; Wagner, 1968). Here, we used the following inhibitory E_{max} model to formulate the PD effect:

$$g_{PD}(t) = 1 - \frac{g_{PK}(t)}{g_{PK_{50}} + g_{PK}(t)}, \quad (3)$$

where $g_{PK}(t)$ denotes the concentration of caffeine at the effect site in the brain and $g_{PK_{50}}$ represents the caffeine concentration at which g_{PD} attains half of its maximum effect, i.e., $1/2$. Note that the maximal effect is observed when g_{PK} is infinitely large, i.e., when g_{PD} approaches zero. Also, the baseline effect, i.e., the effect in the absence of caffeine, was set to 1 so that $P_c(t)$ would be equal to $P(t)$ in the absence of caffeine, both before caffeine administration and after the effect of caffeine has dissipated. Because PK data may not always be available, we first modeled the PK profile of caffeine, and then estimated the parameters of the model from the available PD data (Jacqmin et al., 2007).

The PK disposition of caffeine in plasma is often assumed to follow a one-compartment model with the first-order absorption kinetics (Bonati et al., 1982; Kamimori et al., 2002). Thus, the temporal profile of the plasma concentration $g_{PK}(t)$ at discrete-time index t , with $t = 1, 2, \dots$, for an orally administered caffeine dose given at time index t_0 can be expressed by the following bi-exponential function (Bonate, 2005; Gibaldi and Perrier, 1982):

$$g_{PK}(t) = \frac{DF}{V_d} \frac{k_a}{k_a - k_e} \{ \exp[-k_e T_s(t - t_0)] - \exp[-k_a T_s(t - t_0)] \} \quad \text{for } t \geq t_0, \quad (4)$$

where T_s denotes the sampling period, k_a and k_e denote the absorption rate and the elimination rate, respectively, D denotes the dosage amount, F denotes the bioavailability of caffeine, and V_d denotes the volume of distribution in the body. Note that Eq. (4) represents the profile of caffeine concentration in the plasma only, and not the caffeine concentration in the brain, although it is

the latter, vis-à-vis Eq. (3), that governs the PD effect of caffeine on cognitive performance. However, experimental studies on mice have shown that plasma and brain caffeine concentrations are linearly related (Kaplan et al., 1989). Therefore, we assumed that Eq. (4) is also valid for expressing the caffeine concentration in the brain.

When we substituted the PK model of caffeine in Eq. (4) into Eq. (3), we obtained the following expression:

$$g_{PD}(t) = \left[1 + \bar{A}_c \frac{k_a}{k_a - k_e} \{ \exp[-k_e T_s(t - t_0)] - \exp[-k_a T_s(t - t_0)] \} \right]^{-1} \quad \text{for } t \geq t_0, \quad (5)$$

where we combined DF/V_d and $g_{PK_{50}}$ into one unknown constant parameter, $\bar{A}_c = DF/V_d g_{PK_{50}}$, terming it the amplitude factor. In what follows, we refer to the expression of $g_{PD}(t)$ in Eq. (5) as the three-parameter ($\bar{A}_c$, k_e , and k_a) PD model.

2.5. Individual-specific PD model

Using the expression for $g_{PD}(t)$ in Eq. (5), we computed individual-specific model fits $P_c(t)$ to the performance data $P_{cm}(t)$ measured after caffeine intake as follows: using an individual's measured data $P_{cm}(t)$ and an estimate of $P(t)$, we first calculated $g_{PD}(t)$ at discrete time points t by solving Eq. (1) for $g_{PD}(t)$. Using these calculated data points, we then obtained least-squares fits of the model in Eq. (5) to estimate the caffeine model parameters $\bar{A}_c$, k_e , and k_a for each individual, and thus individualized $g_{PD}(t)$ models. Finally, we used Eq. (1) to obtain individualized caffeine model performance fits $P_c(t)$, i.e., the individualized performance estimates after caffeine intake. We assessed the accuracy of these individualized performance fits by calculating the root mean squared error (RMSE) between the fits $P_c(t)$ and the measured performance data $P_{cm}(t)$, i.e., $\text{RMSE} = \sqrt{(1/M) \sum_{t=t_0}^{t_0+M-1} [P_c(t) - P_{cm}(t)]^2}$, where M represents the number of PVT performance measurements taken after caffeine intake.

2.6. Population-average PD model

We also obtained population-average caffeine model parameters and the corresponding PD model by minimizing the sum of the squared errors of the $g_{PD}(t)$ model fits of all subjects taken together, i.e., we minimized the following objective function:

$$J(\bar{A}_c, k_e, k_a) = \sum_{i=1}^N \sum_{t=t_0}^{t_0+M-1} \left[\frac{P_{cm}^i(t)}{P^i(t)} - g_{PD}(t) \right]^2, \quad (6)$$

where $P_{cm}^i(t)$ denotes the measured data of the i -th subject, $P^i(t)$ represents the caffeine-free estimate of the i -th subject, and N represents the total number of subjects. To compare the accuracy of the population-average model with the individual-specific model fits, we computed the RMSE between the population-average model fit and the measured performance data for each subject in a similar way as described above for the individual-specific PD model.

We programmed our own codes in MATLAB[®] v7.14.0 to obtain the individualized two-process model fits and caffeine-free performance estimates. However, to obtain the caffeine model parameters, we used the *fminsearch* multidimensional unconstrained optimization routine from the MATLAB[®] v7.14.0 Optimization Toolbox to perform the least-squares minimization.

2.7. PD model for repeated doses

Thus far, we have described our procedure to obtain individualized and population-average PD caffeine models representing

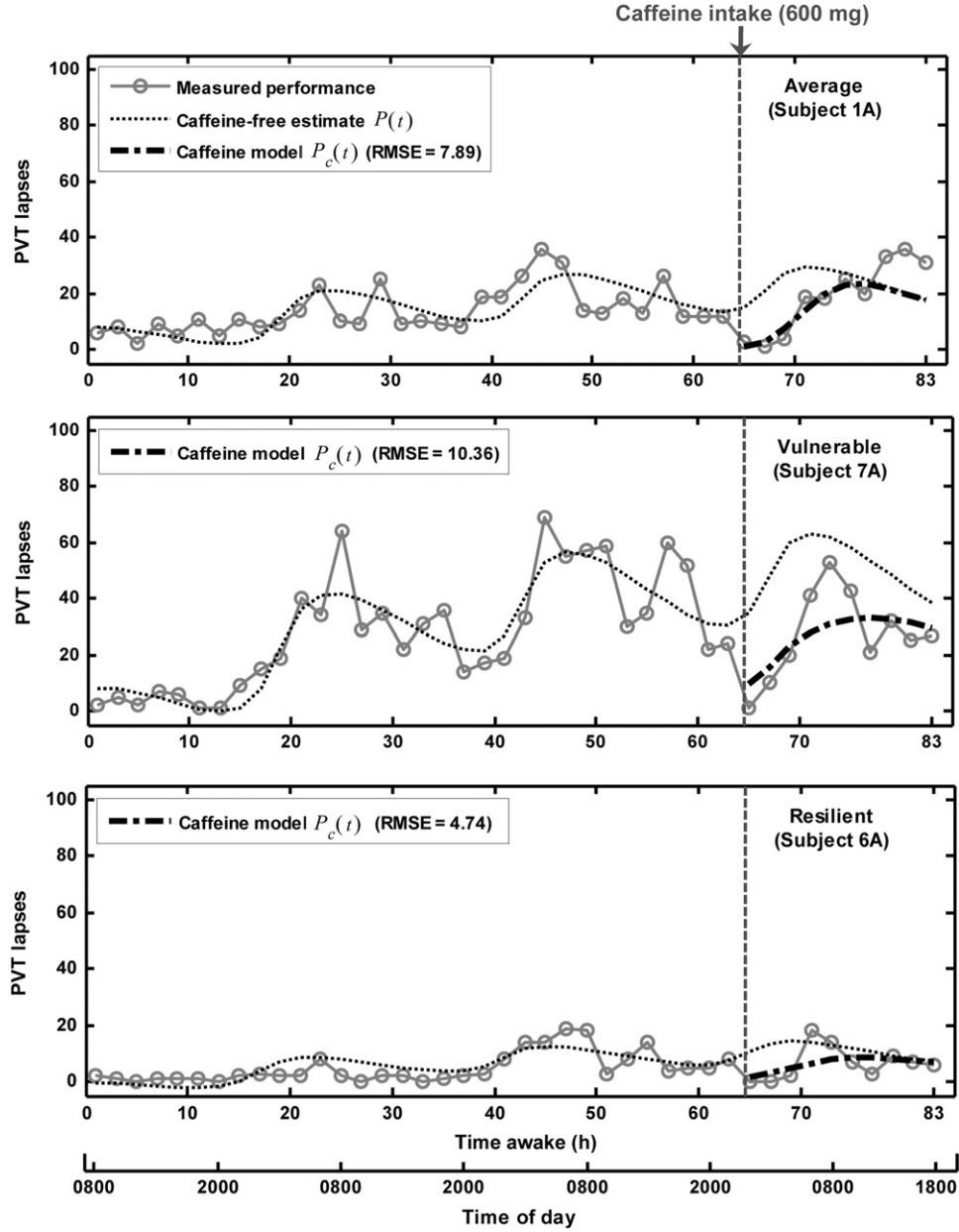


Fig. 2. Individualized caffeine model fits for three subjects with distinct sleep-loss phenotypes [average sensitivity to sleep loss (top), vulnerable to sleep loss (middle), and resilient to sleep loss (bottom)] from the single-dose study A. The gray circles represent psychomotor vigilance test (PVT) lapses, measured once every 2 h. The dashed vertical line at 64.5 h denotes the time of caffeine (600 mg) administration. The dotted lines represent the caffeine-free individualized two-process model performance estimates based on PVT measurements obtained prior to caffeine administration. The dashed-dotted lines represent the individualized caffeine model fits to the performance data measured after-caffeine intake. RMSE, root mean squared error.

the performance-enhancing effects of a single dose of caffeine. Using the same procedure, we extended our models to capture the effects of repeated caffeine doses. This extension required the assumptions that (1) caffeine concentrations in the human brain may be characterized by linear pharmacokinetics, i.e., caffeine concentrations resulting from each caffeine dose may be additively combined based on the principle of superposition (Cutler, 1978; Gibaldi and Perrier, 1982); (2) each of the repeated caffeine doses have the same formulation and dosage strength; and (3) $g_{PK_{50}}$ of the E_{max} model in Eq. (3) remains constant with repeated dosing, which may not be a valid assumption under extreme conditions, such as for frequent caffeine doses, in which case individuals might develop tolerance to the effects of caffeine. Under these assumptions, we reformulated the PK model in Eq. (4) to reflect the net plasma concentration of caffeine under a

repeated-dosing regimen, and expressed it as

$$g_{PK}(t) = \sum_{l=1}^L H(t-t_l) \frac{DF}{V_d} \frac{k_a}{k_a - k_e} \{ \exp[-k_e T_s(t-t_l)] - \exp[-k_a T_s(t-t_l)] \}, \quad (7)$$

where $H(\bullet)$ represents the Heaviside step function, whose value is 0 for $t < t_l$ and 1 for $t \geq t_l$ (Bracewell, 2000), L denotes the number of doses, and t_l denotes the discrete-time index of when the l -th caffeine dose was administered. Accordingly, the three-parameter $g_{PD}(t)$ model for repeated doses can be expressed as

$$g_{PD}(t) = \left[1 + \sum_{l=1}^L H(t-t_l) \bar{A}_c \frac{k_a}{k_a - k_e} \{ \exp[-k_e T_s(t-t_l)] - \exp[-k_a T_s(t-t_l)] \} \right]^{-1}, \quad (8)$$

where the amplitude factor $\bar{A}_c$ bears the same meaning as in Eq. (5).

2.8. Two-parameter PD model

The PD models in Eqs. (5) and (8) are based on PK models that account for the absorption rate k_a of caffeine. However, in some cases the $g_{PD}(t)$ data may not be sampled with sufficient frequency to capture the absorption phase of the caffeine PK or the study may involve fast-acting caffeine associated with significantly large values of k_a ($\gg k_e$). For instance, the PVT data in single-dose *study A* were obtained only once every 2 h; however, the caffeine pills administered to the subjects typically cause the plasma concentrations to peak within 30–90 min after the caffeine intake (Newton et al., 1981). In contrast, the PVT data in repeated-dose *study B* were measured once every 15 min following caffeine intake; however, the Stay Alert[®] gum administered to the subjects is fast acting, releasing ~85% of the caffeine dose within the first 5 min of gum chewing (Kamimori et al., 2002). In either of these scenarios, the PK profile can be reduced to the following mono-exponential function:

$$g_{PK}(t) = \frac{DF}{V_d} \exp[-k_e T_s(t-t_0)] \quad \text{for } t \geq t_0. \tag{9}$$

The single- and repeated-dose PD models in Eqs. (5) and (8) can then be simplified to the following two-parameter PD models:

$$g_{PD}(t) = 1 + \bar{A}_c \exp[-k_e T_s(t-t_0)]^{-1} \quad \text{for } t \geq t_0 \text{ and} \tag{10}$$

$$g_{PD}(t) = \left\{ 1 + \sum_{l=1}^L H(t-t_l) \bar{A}_c \exp[-k_e T_s(t-t_l)] \right\}^{-1}, \tag{11}$$

respectively. The above simplification, however, cannot be indiscriminately generalized to the other studies without due consideration to the type of caffeine formulation used and the sampling time following caffeine administration. For instance, in studies where slow-release caffeine is used (Beaumont et al., 2001), the original three-parameter PD model may be more appropriate.

3. Results

We used data from the single-dose study (*study A*) and the repeated-dose study (*study B*) to first obtain individualized caffeine-free performance estimates, and subsequently obtain individual-specific and population-average caffeine model performance fits using the proposed approach. Finally, we compared the individualized caffeine model performance fits against those obtained using the population-average models.

3.1. Single-dose study A

Performance data from one of the 12 subjects in *study A* did not show the expected enhancing effects of caffeine, i.e., the estimated caffeine-free performance $P(t)$ had fewer lapses than the measured performance following caffeine intake $P_{cm}(t)$. Therefore, we excluded this subject's data from the analysis, and used data from the remaining 11 subjects to evaluate the single-dose caffeine model. The individualized two-process model parameters obtained for each of these 11 subjects are listed in Table A1 in Appendix A. Note that in this study the sampling period T_s was 2 h, before and after caffeine intake.

Using the two-parameter PD model, we computed individual-specific caffeine model fits to PVT data of each of the 11 subjects. Fig. 2 shows the caffeine model performance fits for three subjects, 1A (*top panel*), 7A (*middle panel*), and 6A (*bottom panel*),

who had distinct sleep-loss phenotypes (i.e., average sensitivity, vulnerable, and resilient to sleep loss, respectively) determined based on visual inspection of the performance impairment profile before caffeine administration. When we compared the caffeine-free performance estimates with the measured performance after caffeine intake for the average and vulnerable subjects (1A and 7A, respectively), we observed a significant improvement in performance immediately after caffeine administration and a subsequent return to caffeine-free levels, with their corresponding caffeine model fits exhibiting a similar pattern. For the resilient subject 6A, we observed a similar qualitative behavior although with a much reduced performance improvement after caffeine administration when compared to the caffeine-free estimate.

Table 1 shows the individualized parameter estimates of the two-parameter caffeine model along with the corresponding RMSEs of the model fits for the 11 subjects in *study A*. It also shows the population-average parameter values and the related RMSEs of the model fits. We observed that the differences in RMSEs between the individualized models and the population-average model for the majority of the subjects were no more than three lapses. The average RMSE of the population-average model fits across the 11 subjects was 9.61 lapses, and for the individualized fits it was 19.25% lower at 7.76 lapses. These results suggest that between-subject performance variability was not significantly different following caffeine intake. To further investigate the hypothesis that caffeine intake reduced inter-subject performance variability, we performed a two-sample *F* test for equal variances (Zar, 1999) between PVT data from the placebo and caffeine-administered subjects across all PVT sessions, both before and after caffeine/placebo intake. The analysis revealed that the inter-subject variances of the subjects administered caffeine were significantly ($P < 0.05$) smaller than those of the placebo subjects for the initial 6 h (three PVT sessions) after caffeine intake, but were not statistically different in the subsequent sessions and before caffeine intake.

To quantify the benefit of extending the caffeine-free model to account for caffeine effects through the g_{PD} multiplier in Eq. (1), we computed the RMSEs between the individualized caffeine-free model estimates $P(t)$ and the measured performance $P_{cm}(t)$ after

Table 1
Individualized and population-average parameter estimates of the two-parameter caffeine model and the corresponding root mean squared errors (RMSEs) of the model fits for the 11 subjects from the single-dose *study A*. $\bar{A}_c$, modified amplitude factor; k_e , elimination rate.

Subject	Sensitivity to sleep loss	Individualized parameter estimates		RMSE (lapses)	
		$\bar{A}_c$	k_e (h ⁻¹)	Individualized	Population-average
1A	Average	17.37	0.45	7.89	11.73
2A	Vulnerable	26.80	0.38	14.94	19.89
3A	Average	30.04	0.39	9.77	11.85
4A	Average	6.07	0.23	11.24	12.26
5A	Vulnerable	6.03	0.13	4.00	6.06
6A	Resilient	5.23	0.25	4.74	5.27
7A	Vulnerable	2.67	0.12	10.36	11.65
8A	Resilient	2.40	0.01	1.77	1.90
9A	Average	4.67	0.26	7.56	10.45
10A	Resilient	3.88	0.01	7.76	9.48
11A	Resilient	3.38	0.04	5.36	5.14
Population-average parameters		4.32	0.15		
Mean				7.76	9.61

caffeine intake for each subject. We obtained an average RMSE of 16.82 lapses, which was $\sim 117\%$ larger than the average individualized caffeine model error (7.76 lapses).

3.2. Repeated-dose study B

In study B, one of the 12 subjects did not exhibit the expected performance-enhancing effects of caffeine, resulting in an estimated $P(t)$ that was lower than the measured performance $P_{cm}(t)$ following each of the three caffeine administrations. Consequently, we excluded this subject's data from our analysis, and used data from the remaining 11 subjects to evaluate the repeated-dose caffeine model. The individualized two-process model parameters obtained for each of these 11 subjects are listed in Table A2 in Appendix A. Note that in this study the sampling period T_s was set to 2 h before caffeine intake and to 15 min after caffeine intake.

Fig. 3 shows the two-parameter repeated-dose individualized and population-average caffeine model fits obtained for each of the 11 subjects in study B. We observed that the individualized caffeine model fits for the average subjects (1B, 7B, and 11B) and

resilient subjects (4B, 5B, 6B, 8B, 9B, and 10B) matched reasonably well with the measured performance in the first two 2-h test blocks, but to a lesser extent in the third test block. In contrast, for the vulnerable subjects (2B and 3B), the individualized caffeine model fits deviated significantly from the data at multiple points. This was primarily because the caffeine-free performance estimates $P(t)$ obtained using the two-process model were considerably lower than the measured PVT lapses $P_{cm}(t)$ at those points (results not shown). The lack of fidelity of the caffeine-free performance estimates was primarily due to the limited number of performance measurements prior to caffeine intake (nine), which prevented the Bayesian algorithm from adequately “learning” these subjects' vulnerable sleep-loss phenotype. Compared to the individualized caffeine model fits, the population-average caffeine models performed well for the resilient subjects, but less well for the average and vulnerable subjects. This was attributed to a bias in the population-average model towards the six subjects (out of 11) with a resilient sleep-loss phenotype in detriment to the two vulnerable subjects (2B and 3B). Although the individualized models for these two subjects underpredicted the number of PVT lapses, in comparison to the population-average

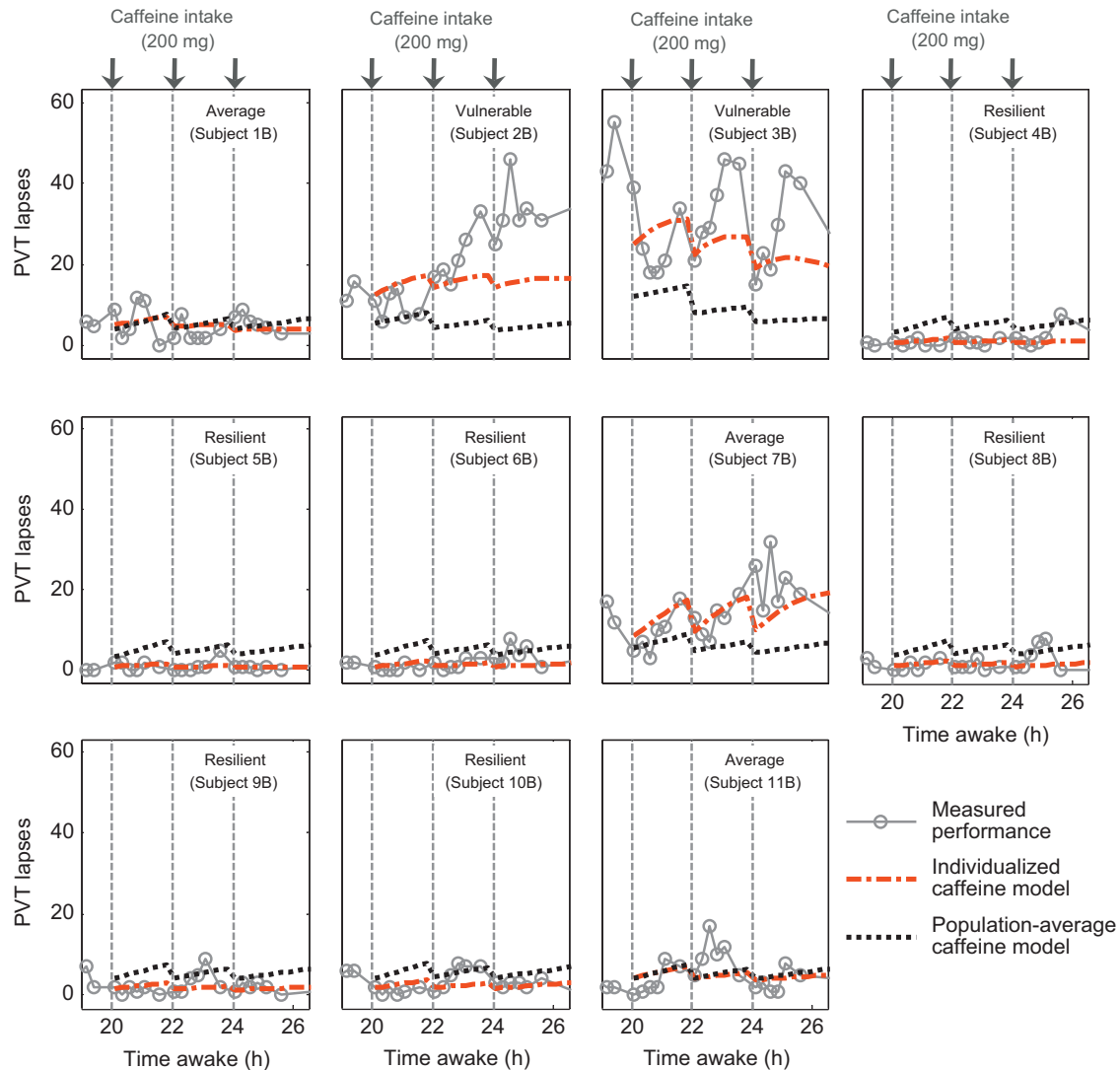


Fig. 3. Individualized and population-average caffeine model fits for 11 subjects of the repeated-dose study B. The dashed vertical lines at 20, 22, and 24 h denote the times of caffeine dose (200 mg) administration. The gray circles in each of the plots represent the measured psychomotor vigilance test (PVT) lapses. The dashed-dotted and dotted lines represent the individualized and population-average caffeine model fits, respectively, to the performance data measured after the first caffeine dose administration.

Table 2
Individualized and population-average parameter estimates of the two-parameter caffeine model and the corresponding root mean squared errors (RMSEs) of the model fits for the 11 subjects administered with three doses of 200 mg caffeine in the repeated-dose study B. $\bar{A}_c$, modified amplitude factor; k_e , elimination rate.

Subject	Sensitivity to sleep loss	Individualized parameter estimates		RMSE (lapses)	
		$\bar{A}_c$	k_e (h ^{−1})	Individualized	Population-average
1B	Average	1.36	0.01	3.39	3.90
2B	Vulnerable	0.24	0.97	12.25	20.06
3B	Vulnerable	0.43	1.25	10.75	21.88
4B	Resilient	11.54	0.23	1.80	4.23
5B	Resilient	9.29	0.06	1.18	4.32
6B	Resilient	9.64	0.28	2.34	4.01
7B	Average	1.02	1.13	6.81	11.13
8B	Resilient	9.16	0.28	2.28	4.11
9B	Resilient	6.51	0.20	2.12	3.96
10B	Resilient	5.68	0.26	2.40	3.71
11B	Average	1.77	0.14	4.35	4.43
Population-average parameters		1.90	0.25		
Mean				4.51	7.80

model, they provided considerably improved model fits with ~45% smaller RMSEs (12.25 vs. 20.06 for subject 2B and 10.75 vs. 21.88 for subject 3B; Table 2).

Table 2 lists the individualized parameter estimates of the two-parameter caffeine model along with the corresponding RMSEs in the model fits for the 11 subjects in study B. For comparison purposes, we also show the RMSEs of the fits obtained with the population-average caffeine model. Here, we observed that the differences in RMSEs of the fits were no more than three lapses for the resilient subjects, but were at least seven lapses for the vulnerable subjects. The average RMSE of the population-average model fits across the 11 subjects was 7.80 lapses, and for the individualized fits it was almost 42% lower at 4.51 lapses, suggesting that between-subject performance was significantly different following caffeine intake. In fact, when we performed a two-sample *F* test for equal variances (Zar, 1999) between PVT data from the placebo and caffeine-administered subjects across all PVT sessions, both before and after caffeine/placebo intake, we observed no statistical differences in inter-subject variances between the two groups. This was in contrast to the single-dose study A results, where caffeine reduced inter-subject variability immediately after its administration. We believe that the larger inter-subject variability in study B was caused by the large between-subject variability in the PK of the Stay Alert[®] caffeine gum (Syed et al., 2005) and the increased frequency of the PVTs conducted in the three 2-h test blocks immediately following caffeine administration; six 10-min PVTs were conducted at 5, 20, 35, 50, 65, and 95 min in each 2-h test block.

Although the population-average caffeine model did not perform as well as the individualized model, when compared to the individualized caffeine-free model estimates it provided an average improvement of ~43% (RMSE of 7.80 lapses vs. 13.58 lapses). This average RMSE of the individualized caffeine-free model estimates was ~201% larger than the average individualized caffeine model error, highlighting the benefit of accounting for caffeine effects in the performance model.

4. Discussion

Caffeine is an efficacious and widely used fatigue countermeasure. Although the dose-related PK profile of caffeine is well

established, its PD effects on the cognitive performance of sleep-deprived individuals have not been adequately characterized, limiting the development of quantitative mathematical models describing the performance-enhancing effects of caffeine under operationally relevant conditions. If available, such models could serve as a tool to better manage the administration of caffeine countermeasures by determining the precise time and amounts of caffeine doses that result in performance peaks at the desired time and that can safely prolong peak performance.

Here, we propose a new modeling approach that builds on the phenomenological two-process model of sleep regulation with the assumption that caffeine has a multiplicative effect on the cognitive performance of sleep-deprived individuals. Accordingly, we modeled caffeine effects on performance by first using the two-process model to estimate performance impairment due to sleep loss in the absence of caffeine, and then multiplying this estimate by a caffeine-effect factor g_{PD} , ranging between 0 (maximal performance restoration) and 1 (no restoration), that relates the PK of caffeine to its PD effect on performance through the Hill equation.

We assessed the performance of our proposed modeling approach by computing the post-caffeine administration performance fits on data from two separate studies: (1) single-dose study A and (2) repeated-dose study B. In these studies, we assessed the performance of individualized as well as population-average caffeine models using a two-parameter ($\bar{A}_c$ and k_e) g_{PD} model. However, depending on the post-administration sampling rate of performance data and the caffeine formulation, it may be necessary to use the three-parameter model to account for absorption rate k_a in the PK of caffeine. Although the results shown here are limited to PVT data, the model output can be readily scaled to represent other cognitive performance metrics.

The individualized caffeine model fits (from both studies) suggest that the proposed model adequately characterized the performance-enhancing effects of caffeine of most subjects. For the single-dose study, the individualized caffeine models produced fits that were 19% better than those obtained with the population-average model. For the repeated-dose study, this difference doubled to 42%. A smaller difference between population-average and individualized models supports the hypothesis that caffeine reduces inter-subject variability during the duration of its PD effects. Statistical analyses, where we compared inter-subject variances between placebo and caffeine groups prior and post-caffeine administration, support this hypothesis for the single-dose study but not for the repeated-dose study. We support the hypothesis that caffeine does reduce inter-subject variability and speculate that such reduction was not observed in study B primarily because it was counterbalanced by time-on-task effects. Indeed, unlike study A where 10-min PVTs were performed once every 2 h post-caffeine administration, in study B PVTs were performed six times during each of the three 2-h test blocks post-caffeine administration.

We also assessed the benefit of accounting for the caffeine effects in the model, i.e., the effects of the g_{PD} multiplier in Eq. (1). In the absence of the multiplier, i.e., considering individualized caffeine-free estimates $P(t)$, the average model error was 117% larger for study A and 201% larger for study B. We also found that the proposed model represented the performance enhancing effects of caffeine to the same extent as those observed in the measured data. When we used the measured PVT data to compute the average percentage improvement in performance after caffeine administration between the caffeine and placebo groups, we observed a 64% improvement for study A and a 78% improvement for study B. These results were in close agreement with the 67% and 70% improvements, respectively, for studies A and B, when we compared the model fits of the population-

average caffeine model with those of the population-average caffeine-free model. Although the two groups involved different subjects and these constitute indirect comparisons, they do provide additional evidence to the validity of our caffeine modeling framework.

The proposed approach for modeling the restoring effects of caffeine on the PVT performance of sleep-deprived individuals is fundamentally different from the models proposed by Benítez et al. (2009) and Puckeridge et al. (2011) in a number of ways. One of the major differences is the model structure. The proposed approach is a direct extension of Borbely's widely used two-process model of sleep regulation (Mallis et al., 2004; Rajaraman et al., 2008, 2009; Van Dongen et al., 2007), consisting of five parameters that describe the additive effect of the homeostatic and circadian processes and three (or two) additional parameters to model caffeine effects. In contrast, the performance-inhibitor model proposed by Benítez et al. uses 11 parameters to model the multiplicative effect of the homeostatic and circadian processes plus two additional parameters to model the effects of caffeine (i.e., caffeine absorption is not represented), whereas the expanded sleep–wake dynamics model proposed by Puckeridge et al. uses 16 parameters to model the additive effect of the homeostatic and circadian processes and five additional parameters to model the effects of caffeine. The larger degrees of freedom afforded by these two models (13 and 21 parameters, respectively, vs. eight for the present approach) facilitate model fitting; however, they also increase the complexity and amount of data required for model parameter specification, especially for individualized models.

These models also differ with respect to the approaches used to represent caffeine effects. As discussed previously, the proposed approach isolates the effects of caffeine from the two-process model components and represents them through a bounded (0–1) multiplying factor that scales both the homeostatic and circadian processes equally. In contrast, the model proposed by Puckeridge et al. (2011) ignores the effects of caffeine on the circadian process and solely affects the homeostatic process through a multiplying factor. While the effects of caffeine on circadian amplitude and phase are not well understood, independent studies have shown that caffeine suppresses melatonin secretion (Shilo et al., 2002; Wright et al., 1997), which in turn affects the circadian process. In addition, unlike the proposed approach, their multiplying factor $[1 - \zeta_H f_{PK}(t)]$, where ζ_H is a positive constant representing the strength of the PD effects of caffeine and $f_{PK}(t)$ denotes the PK profile as a function of time t , is not bound from below. Thus, for large caffeine doses (e.g., 600 mg) and/or highly caffeine-sensitive individuals, the multiplying factor can become negative, causing the model to produce negative performance impairment values after caffeine administration (Puckeridge et al., 2011).

The proposed model also has some limitations. One key limitation is the requirement for accurate individualized caffeine-free performance estimates following caffeine administration. This necessitates the availability of sufficient performance data prior to caffeine intake so that the parameters of the two-process model can be adapted and “learn” an individual's sleep-loss phenotype, which typically requires about 20 PVT data points (Rajaraman et al., 2008, 2009). This limitation was apparent in *study B*, in which only nine performance measurements were available prior to caffeine intake (200 mg), biasing the Bayesian adaptive approach towards the population-average prior and yielding inadequate results for the two subjects with the vulnerable sleep-loss phenotype. Because the model outputs are primarily driven by the caffeine-free-estimate portion of the model, this limitation becomes more pronounced when individuals are administered smaller caffeine doses (e.g., 50 and 100 mg), which often result in restoring effects that are indistinguishable from

those of placebo. One approach to address this limitation (i.e., when sufficient performance data prior to caffeine intake are not available for an individual) is to use the limited available data to classify the individual into one of three sleep-loss phenotypes (vulnerable, average, or resilient) and substitute the adaptive, individualized caffeine-free model with one of these three phenotype-specific “population-average” models. Another limitation is the assumptions that, in repeated doses, caffeine concentrations resulting from each caffeine dose can be additively combined and that individuals do not develop caffeine tolerance. However, the validity of these assumptions may vary as a function of the extent to which the repeated dosing regimen involves frequent administrations, relatively large doses, or dosing over extended periods of time.

To enhance the utility and effectiveness of the proposed model, we seek to incorporate additional capabilities. In particular, we are developing strategies to incorporate caffeine dosage as an input to the model so that the same model—with a range of dosage-dependent parameter values—can be used to reflect the effects of different doses of caffeine. We are also exploring the use of the predictive modeling framework previously developed by our group (Rajaraman et al., 2008, 2009) to extend the proposed model from one where we characterize (i.e., fit) the effects of caffeine on cognitive performance to one where we *predict* performance levels after caffeine intake for a desired prediction horizon.

In summary, the described work constitutes a new approach to modeling the effects of caffeine on fatigue and performance of sleep-deprived individuals. By integrating a biomathematical PD model of caffeine with the well-established two-process model of sleep regulation, this approach allows us to estimate the restoring effects of single and repeated caffeine doses on the temporal dynamics of cognitive performance variations during total sleep deprivation. While many challenges remain, the proposed model provides a first step towards development of *predictive* caffeine models under sleep-loss conditions, a capability that has been elusive.

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Disclosure statement

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Appendix A. Individualized two-process model parameter estimates

Using the method described in Section 2.3, we obtained the individualized two-process model parameters for each of the 11 subjects in *studies A* and *B*, and tabulated them in *Tables A1* and *A2*, respectively.

Table A1

Individualized two-process model parameter estimates for the 11 subjects from the single-dose study A. α , upper asymptote of the homeostat; ρ , homeostatic buildup rate; β , circadian amplitude; S_0 , initial homeostatic level; ϕ , circadian phase.

Subject	α (lapses)	ρ (h ⁻¹)	β (lapses)	S_0 (unitless)	ϕ (h)
1A	23.92	0.04	7.66	1.00	4.82
2A	47.27	0.04	11.74	0.92	4.73
3A	24.84	0.03	7.88	1.31	4.86
4A	24.13	0.03	7.77	1.08	4.81
5A	41.31	0.04	18.80	0.92	6.06
6A	11.77	0.03	3.91	1.28	7.29
7A	52.46	0.04	15.65	1.16	5.15
8A	3.37	0.03	1.29	1.13	6.31
9A	34.70	0.04	11.45	0.98	6.27
10A	23.42	0.04	9.11	1.29	5.61
11A	8.36	0.03	4.09	1.57	4.03

Table A2

Individualized two-process model parameter estimates for the 11 subjects from the single-dose study B. α , upper asymptote of the homeostat; ρ , homeostatic buildup rate; β , circadian amplitude; S_0 , initial homeostatic level; ϕ , circadian phase.

Subject	α (lapses)	ρ (h ⁻¹)	β (lapses)	S_0 (unitless)	ϕ (h)
1B	31.22	0.04	5.32	1.32	4.07
2B	18.79	0.04	6.29	0.81	5.58
3B	18.03	0.03	17.06	0.01	8.72
4B	27.56	0.03	6.88	1.30	3.89
5B	26.09	0.03	7.33	1.30	4.14
6B	25.56	0.03	7.28	1.29	4.44
7B	25.68	0.04	5.29	0.91	4.86
8B	25.81	0.03	7.04	1.25	4.21
9B	30.42	0.03	6.26	1.33	4.42
10B	34.05	0.03	5.98	1.33	4.18
11B	27.92	0.03	5.83	1.22	4.24

References

Achermann, P., Borbely, A.A., 1992. Combining different models of sleep regulation. *J. Sleep Res.* 1, 144–147.

Achermann, P., Borbely, A.A., 1994. Simulation of daytime vigilance by the additive interaction of a homeostatic and a circadian process. *Biol. Cybern.* 71, 115–121.

Ariens, E.J., 1954. Affinity and intrinsic activity in the theory of competitive inhibition. I. Problems and theory. *Arch. Int. Pharmacodyn.* Ther. 99, 32–49.

Balkin, T.J., Kamimori, G.H., Redmond, D.P., Vigneulle, R.M., Thorne, D.R., Belenky, G., Wesensten, N.J., 2004. On the importance of countermeasures in sleep and performance models. *Aviat. Space Environ. Med.* 75, A155–A157.

Beaumont, M., Batejat, D., Pierard, C., Coste, O., Doireau, P., Van Beers, P., Chauffard, F., Chassard, D., Enslin, M., Denis, J.B., Lagarde, D., 2001. Slow release caffeine and prolonged (64-h) continuous wakefulness: effects on vigilance and cognitive performance. *J. Sleep Res.* 10, 265–276.

Benitez, P.L., Kamimori, G.K., Balkin, T.J., Greene, A., Johnson, M.L., 2009. Modeling fatigue over sleep deprivation, circadian rhythm, and caffeine with a minimal performance inhibitor model. *Methods Enzymol.: Comput. Methods* 454, 405–421.

Bertorelli, R., Marina, N., Adami, M., Ongini, E., 1996. Effects of selective agonists and antagonists for A1 or A2A adenosine receptors on sleep-waking patterns in rats. *Drug Dev. Res.* 37, 65–72.

Bonate, P.L., 2005. *Pharmacokinetic-Pharmacodynamic Modeling and Simulation*. Springer, New York.

Bonati, M., Latini, R., Galletti, F., Young, J.F., Tognoni, G., Garattini, S., 1982. Caffeine disposition after oral doses. *Clin. Pharmacol. Ther.* 32, 98–106.

Bonnet, M.H., Balkin, T.J., Dinges, D.F., Roehrs, T., Rogers, N.L., Wesensten, N.J., 2005. The use of stimulants to modify performance during sleep loss: a review by the sleep deprivation and Stimulant Task Force of the American Academy of Sleep Medicine. *Sleep* 28, 1163–1187.

Borbely, A.A., 1982. A two process model of sleep regulation. *Hum. Neurobiol.* 1, 195–204.

Bracewell, R.N., 2000. *The Fourier Transform and its Applications*. McGraw-Hill, Singapore.

Brice, C.F., Smith, A.P., 2002. Effects of caffeine on mood and performance: a study of realistic consumption. *Psychopharmacology (Berlin)* 164, 188–192.

Caldwell, J.A., Caldwell, J.L., 2005. Fatigue in military aviation: an overview of US military-approved pharmacological countermeasures. *Aviat. Space Environ. Med.* 76, C39–C51.

Csajka, C., Verotta, D., 2006. Pharmacokinetic–pharmacodynamic modelling: history and perspectives. *J. Pharmacokinet. Pharmacodyn.* 33, 227–279.

Cutler, D.J., 1978. Linear systems analysis in pharmacokinetics. *J. Pharmacokinet. Biopharm.* 6, 265–282.

Daan, S., Beersma, D.G., Borbely, A.A., 1984. Timing of human sleep: recovery process gated by a circadian pacemaker. *Am. J. Physiol.* 246, R161–R183.

Denaro, C.P., Brown, C.R., Wilson, M., Jacob 3rd, P., Benowitz, N.L., 1990. Dose-dependency of caffeine metabolism with repeated dosing. *Clin. Pharmacol. Ther.* 48, 277–285.

Dinges, D.F., Powell, J.W., 1985. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav. Res. Methods Instrum. Comput.* 17, 652–655.

Dorrian, J., Rogers, N.L., Dinges, D.F., 2005. Psychomotor vigilance performance: neurocognitive assay sensitive to sleep loss. In: Kushida, C.A. (Ed.), *Sleep Deprivation. Clinical Issues, Pharmacology, and Sleep Loss Effects*. Marcel Dekker, New York, pp. 39–70.

Fisone, G., Borgkvist, A., Usiello, A., 2004. Caffeine as a psychomotor stimulant: mechanism of action. *Cell. Mol. Life Sci.* 61, 857–872.

Fredholm, B.B., Battig, K., Holmen, J., Nehlig, A., Zvartau, E.E., 1999. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol. Rev.* 51, 83–133.

Fuller, P.M., Gooley, J.J., Saper, C.B., 2006. Neurobiology of the sleep–wake cycle: sleep architecture, circadian regulation, and regulatory feedback. *J. Biol. Rhythms* 21, 482–493.

Gibaldi, M., Perrier, D., 1982. *Pharmacokinetics*. Marcel Dekker, New York.

Institute of Medicine, 2001. *Caffeine for the Sustainment of Mental Task Performance: Formulations for Military Operations*. National Academy Press, Washington, DC.

Jacqmin, P., Snoeck, E., van Schaick, E.A., Gieschke, R., Pillai, P., Steimer, J.L., Girard, P., 2007. Modelling response time profiles in the absence of drug concentrations: definition and performance evaluation of the K-PD model. *J. Pharmacokinet. Pharmacodyn.* 34, 57–85.

Kamimori, G.H., Johnson, D., Thorne, D., Belenky, G., 2005. Multiple caffeine doses maintain vigilance during early morning operations. *Aviat. Space Environ. Med.* 76, 1046–1050.

Kamimori, G.H., Penetar, D.M., Headley, D.B., Thorne, D.R., Otterstetter, R., Belenky, G., 2000. Effect of three caffeine doses on plasma catecholamines and alertness during prolonged wakefulness. *Eur. J. Clin. Pharmacol.* 56, 537–544.

Kamimori, G.H., Karyekar, C.S., Otterstetter, R., Cox, D.S., Balkin, T.J., Belenky, G.L., Eddington, N.D., 2002. The rate of absorption and relative bioavailability of caffeine administered in chewing gum versus capsules to normal healthy volunteers. *Int. J. Pharm.* 234, 159–167.

Kaplan, G.B., Greenblatt, D.J., Leduc, B.W., Thompson, M.L., Shader, R.I., 1989. Relationship of plasma and brain concentrations of caffeine and metabolites to benzodiazepine receptor binding and locomotor activity. *J. Pharmacol. Exp. Ther.* 248, 1078–1083.

Mallis, M.M., Mejdal, S., Nguyen, T.T., Dinges, D.F., 2004. Summary of the key features of seven biomathematical models of human fatigue and performance. *Aviat. Space Environ. Med.* 75, A4–A14.

Newton, R., Broughton, L.J., Lind, M.J., Morrison, P.J., Rogers, H.J., Bradbrook, I.D., 1981. Plasma and salivary pharmacokinetics of caffeine in man. *Eur. J. Clin. Pharmacol.* 21, 45–52.

Phillips, A.J., Robinson, P.A., 2008. Sleep deprivation in a quantitative physiologically based model of the ascending arousal system. *J. Theor. Biol.* 255, 413–423.

Porkka-Heiskanen, T., Strecker, R.E., Thakkar, M., Bjorkum, A.A., Greene, R.W., McCarley, R.W., 1997. Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. *Science* 276, 1265–1268.

Puckeridge, M., Fulcher, B.D., Phillips, A.J., Robinson, P.A., 2011. Incorporation of caffeine into a quantitative model of fatigue and sleep. *J. Theor. Biol.* 273, 44–54.

Rajaraman, S., Gribok, A.V., Wesensten, N.J., Balkin, T.J., Reifman, J., 2008. Individualized performance prediction of sleep-deprived individuals with the two-process model. *J. Appl. Physiol.* 104, 459–468.

Rajaraman, S., Gribok, A.V., Wesensten, N.J., Balkin, T.J., Reifman, J., 2009. An improved methodology for individualized performance prediction of sleep-deprived individuals with the two-process model. *Sleep* 32, 1377–1392.

Seng, K.Y., Teo, W.L., Fun, C.Y., Law, Y.L., Lim, C.L., 2010. Interrelations between plasma caffeine concentrations and neurobehavioural effects in healthy volunteers: model analysis using NONMEM. *Biopharm. Drug Dispos.* 31, 316–330.

Shilo, L., Sabbah, H., Hadari, R., Kovatz, S., Weinberg, U., Dolev, S., Dagan, Y., Shenkman, L., 2002. The effects of coffee consumption on sleep and melatonin secretion. *Sleep Med.* 3, 271–273.

Syed, S.A., Kamimori, G.H., Kelly, W., Eddington, N.D., 2005. Multiple dose pharmacokinetics of caffeine administered in chewing gum to normal healthy volunteers. *Biopharm. Drug Dispos.* 26, 403–409.

Van Dongen, H.P., Maislin, G., Mullington, J.M., Dinges, D.F., 2003. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 26, 117–126.

- Van Dongen, H.P., Mott, C.G., Huang, J.K., Mollicone, D.J., McKenzie, F.D., Dinges, D.F., 2007. Optimization of biomathematical model predictions for cognitive performance impairment in individuals: accounting for unknown traits and uncertain states in homeostatic and circadian processes. *Sleep* 30, 1129–1143.
- Wagner, J.G., 1968. Kinetics of pharmacologic response. I. Proposed relationships between response and drug concentration in the intact animal and man. *J. Theor. Biol.* 20, 173–201.
- Wesensten, N.J., Killgore, W.D.S., Balkin, T.J., 2005. Performance and alertness effects of caffeine, dextro amphetamine, and modafinil during sleep deprivation. *J. Sleep Res.* 14, 255–266.
- Wright Jr., K.P., Badia, P., Myers, B.L., Plenzler, S.C., Hakel, M., 1997. Caffeine and light effects on nighttime melatonin and temperature levels in sleep-deprived humans. *Brain Res.* 747, 78–84.
- Zar, J.H., 1999. *Biostatistical Analysis*. Prentice Hall, Upper Saddle River, NJ.