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Dose-dependent model of caffeine effects on human vigilance during total sleep deprivation

Sridhar Ramakrishnan [a], Srinivas Laxminarayan [a], Nancy J. Wesensten [b], Gary H. Kamimori [b], Thomas J. Balkin [b], Jaques Reifman [a,*]

[a] DoD Biotechnology High Performance Computing Software Applications Institute, Telemedicine and Advanced Technology Research Center, U.S. Army Medical Research and Materiel Command, 504 Scott Street, Fort Detrick, MD 21702, USA
[b] Department of Behavioral Biology, Walter Reed Army Institute of Research, 503 Robert Grant Avenue, Silver Spring, MD 20910, USA

HIGHLIGHTS

- We modeled the dose-dependent effects of caffeine on human vigilance.
- The model predicted the effects of both single and repeated caffeine doses.
- We developed and validated the model using two laboratory studies.
- Individual-specific caffeine models outperformed population-average models.

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ABSTRACT

Caffeine is the most widely consumed stimulant to counter sleep-loss effects. While the pharmacokinetics of caffeine in the body is well-understood, its alertness-restoring effects are still not well characterized. In fact, mathematical models capable of predicting the effects of varying doses of caffeine on objective measures of vigilance are not available. In this paper, we describe a phenomenological model of the dose-dependent effects of caffeine on psychomotor vigilance task (PVT) performance of sleep-deprived subjects. We used the two-process model of sleep regulation to quantify performance during sleep loss in the absence of caffeine and a dose-dependent multiplier factor derived from the Hill equation to model the effects of single and repeated caffeine doses. We developed and validated the model fits and predictions on PVT lapse (number of reaction times exceeding 500 ms) data from two separate laboratory studies. At the population-average level, the model captured the effects of a range of caffeine doses (50–300 mg), yielding up to a 90% improvement over the two-process model. Individual-specific caffeine models, on average, predicted the effects up to 23% better than population-average caffeine models. The proposed model serves as a useful tool for predicting the dose-dependent effects of caffeine on the PVT performance of sleep-deprived subjects and, therefore, can be used for determining caffeine doses that optimize the timing and duration of peak performance.

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1. Introduction

Caffeine is the most widely used stimulant drug in both occupational and non-occupational settings. Results from numerous laboratory and field studies have shown that caffeine maintains (Kamimori et al., 2005) or restores (Penetar et al., 1993) neurobehavioral performance in sleep-deprived individuals, with minimal side effects (Bonnet et al., 2005; Brice and Smith, 2002). In the majority of these studies, caffeine has been administered as a single bolus dose of 600 mg (Wesensten et al., 2002; Wesensten et al., 2005) or as smaller, repeated doses of 50, 100, 200, or 300 mg (Kamimori et al., 2005; LaJambe et al., 2005). In these dose ranges, increasing caffeine intake progressively enhances its stimulant effects.

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 its mechanism of action (antagonism of adenosine receptors) is also well-understood (Bertorelli et al., 1996). However, the pharmacodynamic (PD) effects of caffeine on neurobehavioral performance under sleep loss conditions are not well characterized. A limited number of studies (Wesensten et al., 2002, 2005; Killgore et al., 2008; Kamimori et al., 2005;

* Corresponding author. Tel.: +301 619 7915; fax: +301 619 1983.
E-mail address: jaques.reifman.civ@mail.mil (J. Reifman).

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LaJambe et al., 2005; Penetar et al., 1993) have assessed the effects of caffeine on objective measures of performance during total sleep deprivation (TSD), but none under the more realistic chronic sleep-restriction condition. Further, the TSD studies differed widely in terms of (1) caffeine dose used, (2) frequency of dosing, (3) timing of dose across the sleep-loss period, and (4) neurobehavioral outcome metric utilized, making it difficult to characterize the caffeine effects. Although the TSD studies provide a basic understanding of the PD effects of caffeine, their utility could be enhanced by the use of mathematical models that could describe and predict such effects. In fact, mathematical models could be used to quantify the dosage and timing of caffeine intake so as to *safely* achieve performance peaks at the desired time of day.

Only two studies have been published that focus on modeling the neurobehavioral performance-enhancing effects of caffeine in humans, especially under acute sleep-loss conditions. In a seminal work, Puckeridge et al. (2011) proposed a 21-parameter model of caffeine's effects on sleep-wake dynamics, with five of the 21 parameters representing caffeine effects. While such a large number of parameters often provide the necessary degrees of freedom for the model to fully capture and fit the variability in the data, it also presents an inherent practical limitation, particularly if the goal is to develop individual-specific models, where the model parameters need to be customized (from limited data) to a particular individual. In addition, their caffeine model assumes a dose-independent PK elimination rate, which contradicts the well-established dose-dependent metabolism of caffeine that results in lower PK elimination rates at higher doses and is particularly prevalent under TSD scenarios (Denaro et al., 1990; Kamimori et al., 1995; Kaplan et al., 1997). Finally, in their work, the effects of caffeine were validated only on subjective sleepiness scores, which may not reflect objective cognitive performance measures (Van Dongen et al., 2003).

Recently, we proposed a parsimonious eight-parameter biomathematical model of the alertness-restoring effects of caffeine under TSD conditions (Ramakrishnan et al., 2013). Although the model was able to capture the effects of both single and repeated caffeine doses and was validated on objective measures of performance from two different studies, it was not a dose-dependent model as it did not provide a means to predict the effects of different caffeine doses.

In this work, we attempt to overcome this limitation by proposing a biomathematical model that quantifies caffeine's neurobehavioral effects as a function of dose under both single and repeated dosing scenarios, while accounting for the dose-dependent metabolism of caffeine in the body. This provides the needed capability to predict the effects of different caffeine doses using a single model. We developed and validated the proposed model, at both population-average and individualized levels, on objective measures of performance collected from two different TSD laboratory studies. Specifically, we developed a population-average model using data from subjects in one study and predicted the effects of a range of caffeine doses on psychomotor vigilance task (PVT) performance of subjects from a second study, and vice versa. In addition, we showed that the individual-specific model predictions were, on average, 23% better than those of the population-average model.

Because baseline measures of performance (i.e., first $\sim$20 h) generally vary from study to study, they need to be normalized to allow for proper inter-study comparisons. In addition, order-of-visit effects have been observed in crossover design studies involving repeated measures (Fayers and King, 2008; Senn, 1988), and require appropriate data processing to eliminate these effects before analysis of the data. Here, in addition to the proposed model, we also developed methods to normalize performance data and eliminate both within- and between-study baseline imbalances to facilitate model development and cross validation using data from different studies.

2. Methods

2.1. Study data

We used PVT data from two studies. The PVT is a simple (one-choice) reaction-time 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 $\sim$100 stimulus-response pairs (Dinges and Powell, 1985; Dorrian et al., 2005). For modeling purposes, we calculated the number of response times exceeding 500 ms (the conventional threshold for a lapse) to quantify performance impairment. More lapses indicate greater neurobehavioral performance impairment.

In the first study (*study A*), we used PVT data obtained from a controlled laboratory experiment involving 48 healthy young adults who were kept awake for 29 consecutive hours (Kamimori et al., 2005; Syed et al., 2005). The 48 subjects were randomly assigned to one of the four dose groups (placebo, 50, 100, or 200 mg, $n=12$ subjects/group) and were administered the corresponding dose of Stay Alert® (Amurol Confectioners, Yorkville, IL) caffeinated chewing gum at the beginning of each of three 2-h test blocks after 20, 22, and 24 h of sleep loss (corresponding to 0300, 0500, and 0700 h, respectively, on *day 2*). 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 before 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.

The data from the second study (*study B*) were collected as part of a randomized Latin Square crossover experiment across four laboratory sessions, each separated by at least 1 mo (washout period), in which 16 healthy young adults were kept awake for 27 consecutive hours (LaJambe et al., 2005). During each of the four laboratory sessions, subjects were administered placebo, 100, 200, or 300 mg of Stay Alert® caffeinated chewing gum three times (the same dose of caffeine was administered in each of the three times) after 20, 22, and 24 h of sleep loss (corresponding to 0300, 0500, and 0700 h, respectively, on *day 2*). Subjects completed 10-min PVTs starting at 0800 h on *day 1* and ending at 1000 h on *day 2*, for a total of 27 PVT sessions, including nine sessions before caffeine administration and six sessions after each of the three caffeine gum administrations.

All subjects in *study A* were habitually low to moderate caffeine users, with an average, self-reported daily caffeine consumption of <400 mg. However, subjects in *study B* were either habitually low (<100 mg/day, $n=8$) or habitually high (>400 mg/day, $n=8$) caffeine users; nevertheless, the differences in PVT performance between the habitually low and habitually high caffeine users were not statistically significant [Wilcoxon rank-sum test; $p>0.05$ (Zar, 1999)] for each of the four doses (placebo, 100, 200, and 300 mg). Consequently, we did not differentiate subjects based on their habitual caffeine usage in the ensuing analyses. All subjects in both studies reported a total sleep time of $\sim$6–9 h for the night preceding study participation. 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 and Materiel Command Human Subjects Review Board (Ft. Detrick, MD), and written informed consent was obtained from all subjects prior to their participation.

2.2. Data screening and normalization

For *study A*, two subjects (one from placebo and one from 100 mg group) were excluded from analyses due to missing data, resulting in a sample size of 11 subjects for placebo and 100 mg groups. Three subjects from *study B* (crossover design) were