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Letter to the Editor

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Authors' response to editorial on Vital-Lopez et al.

Francisco G. Vital-Lopez[1,2], Tracy J. Doty[3] and Jaques Reifman[1,*]

[1]Department of Defense Biotechnology High Performance Computing Software Applications Institute, Telemedicine and Advanced Technology Research Center, U.S. Army Medical Research and Development Command, Fort Detrick, MD, USA
[2]The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, USA
[3]Behavioral Biology Branch, Walter Reed Army Institute of Research, Silver Spring, MD, USA

[*]Corresponding author. Jaques Reifman, Department of Defense Biotechnology High Performance Computing Software Applications Institute, Telemedicine and Advanced Technology Research Center, U.S. Army Medical Research and Development Command, ATTN: FCMR-TT, 504 Scott Street, Fort Detrick, MD 21702-5012, USA. Email: jaques.reifman.civ@health.mil.

This issue of *Sleep* features our paper "When to sleep and consume caffeine to boost alertness," which presents the first computational algorithm to simultaneously optimize sleep schedule and caffeine consumption so as to maximize alertness of a "group of individuals" during work and non-work hours [1]. This research is the culmination of two decades of predictive analytics efforts in sleep modeling by our US Department of Defense team, where we sequentially introduced and systematically validated new modeling capabilities to predict the effects of sleep loss and caffeine countermeasures on alertness. Based on Borbély's seminal two-process model of sleep regulation [2], over the years, we developed models that bridged the continuum from chronic sleep restriction to total sleep deprivation in one unified framework [3], the capability to personalize the predictions [4, 5] and to account for the effects of caffeine on alertness [6–8], the ability to personalize and make predictions in real time using a smartphone [9, 10], and the capability to optimize caffeine consumption [11].

This issue of the journal also published an Editorial on our paper by Dawson and Sprajcer [12], which reiterates the same points raised (and addressed by us) during the review process. We believe that opposite views are an integral and essential element of research that helps improve scientific rigor by questioning the underlying assumptions of the research methodology and its conclusions. In what follows, we address the three specific points raised in their Editorial by restating our answers provided during the review process.

Point 1: Dawson and Sprajcer correctly state that caffeine metabolism varies significantly between individuals. To address this point in our paper, we performed Monte Carlo simulations with caffeine half-life ranging from 1.2 hours (fast metabolism) to 6.8 hours (slow metabolism), consistent with a systematic review of 141 caffeine studies involving over 4700 participants [13]. As expected, we found that these individual differences in caffeine metabolism led to differences in model-predicted alertness-impairment reductions.

However, Dawson and Sprajcer incorrectly state that individual variability caused by differences in caffeine metabolism will impact the uncertainty in model predictions "when projected forward into the future … especially for predictions greater than 24 hours." This statement wrongly assumes that individual differences in alertness predictions caused by differences in caffeine half-life will increase as a function of time, and necessarily disregards the dynamics of caffeine metabolism: after initially increasing and reaching a maximum between 3 and 8 hours after consumption, the concentration of caffeine in the plasma monotonically decreases with time. As the concentration of caffeine decreases and asymptotes to zero, so do the individual differences in alertness predictions due to caffeine metabolism. In fact, after 16 hours of caffeine consumption, the discrepancy in alertness predictions between an average individual and one with an extreme caffeine metabolism (half-life of 1.2 or 6.8 hours) is less than the within-subject variability of alertness impairment (reaction time of 30 milliseconds) [1]. After 48 hours of caffeine consumption, the difference in alertness predictions is nearly zero. Indeed, our results based on repeated caffeine doses demonstrate that the differences in alertness prediction do not increase over several days [1]. Therefore, contrary to the statement by Dawson and Sprajcer, individual variability caused by differences in caffeine metabolism has a vanishingly small effect on the model predictions as time increases.

Notably, the optimization algorithm applied to the group-average model discussed in the paper is equally applicable to our personalized model [9, 10, 14], which learns an individual's trait-like response to sleep loss and provides personalized caffeine recommendations that would have lessened the impact of differences in caffeine metabolism. Indeed, in last year's publication in *Sleep*, we demonstrated the capability to provide personalized caffeine recommendations in real time during a prospective 62-hour total sleep deprivation challenge. These recommendations allowed individuals to reach the desired alertness level 80% of the time, regardless of their phenotypical response to sleep loss or caffeine [14].

Point 2: Dawson and Sprajcer note "the paper's overly simplistic conceptualization of the relationship between alertness, error, task performance, and implied safety." This statement does not

accurately reflect what is actually written in the paper [1]. On the two occasions where we allude to safety or accidents in the manuscript (first sentence of the Abstract and first paragraph of the Introduction section), we do so in the context of insufficient sleep. It is well-documented that insufficient sleep impairs alertness, increases fatigue, and reduces safety [15–18]. Their statement continues by correctly pointing out that "pharmacologically reversed sleepiness can also lead to errors, performance decrements, and reduced safety." Indeed, in the Discussion section, we reiterate this very same point, saying that "performance on different tasks may not necessarily monotonically improve with an increase in arousal resulting from a larger consumption of caffeine because, after an initial improvement, performance can potentially deteriorate with higher levels of arousal [19]. Thus, caffeine-dosing strategies that induce high levels of arousal, by prescribing large amounts of caffeine in short periods of time, may be detrimental to cognitive performance. The optimization algorithm partially mitigates this limitation by identifying caffeine-dosing strategies that recommend the minimum amount possible of caffeine required to achieve the desired alertness target."

Point 3: Their last concern relates to the use of the model in real-world settings. Instead of using the proposed optimization algorithm to determine the best times to sleep and consume caffeine, they argue that two other strategies are better suited to reduce alertness impairment caused by insufficient sleep. The first strategy is to rely on an individual's "subjective experience" of when to consume caffeine. While this is certainly an option that is used by most people in everyday life, for deployed US military personnel during high-tempo operations exacerbated by chronic sleep restriction, self-administration of caffeine could be problematic. As previously reported, self-administration of caffeine could result in a vicious cycle in which fatigued individuals consume excessive amounts of caffeine, leading to sleep disruptions followed by a subsequent increase in fatigue and even larger caffeine consumption [20–22]. Moreover, subjective reports of sleepiness do not change when performance improves due to caffeine administration, making it an unreliable indicator of when caffeine should be consumed [23]. The second strategy is to rely on heuristics (i.e., rules of thumb). This suggestion is puzzling, as it is in direct contradiction to their first concern regarding individual differences in caffeine metabolism, where each individual should have their own caffeine recommendation based on their own caffeine clearance rate. Heuristic recommendations assume a "one-size-fits-all" approach that disregards individual differences. Are individual differences important in algorithm-provided recommendations but not in heuristic-provided recommendations? In the paper, we benchmark the algorithm-predicted optimal sleep and caffeine recommendations against the one-size-fits-all US Army caffeine guidelines to counteract insufficient sleep [24]. Overall, the model's recommendations reduced alertness impairment by 24 percentage points over the guidelines [1].

In conclusion, the optimization algorithm described in this issue of *Sleep* [1] provides additional capabilities beyond those already provided by our previous efforts. We expect to integrate these capabilities with the publicly accessible *2B-Alert* Web [25], which already supports nearly 35 000 registered users from research and operational communities in more than 100 countries.

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Disclaimer

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