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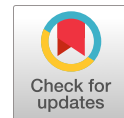
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Caffeine Boosts Preparatory Attention for Reward-related Stimulus Information

Berry van den Berg^{1*}, Marlon de Jong^{1*}, Marty G. Woldorff², and Monicque M. Lorist¹

Abstract

■ The intake of caffeine and the prospect of reward have both been associated with increased arousal, enhanced attention, and improved behavioral performance on cognitive tasks, but how they interact to exert these effects is not well understood. To investigate this question, we had participants engage in a two-session cued-reward cognitive task while we recorded their electrical brain activity using scalp electroencephalography. The cue indicated whether monetary reward could be received for fast and accurate responses to a color–word Stroop stimulus that followed. Before each session, participants ingested decaffeinated coffee with either caffeine (3-mg/kg bodyweight) or placebo (3-mg/kg bodyweight lactose). The behavioral results showed that both caffeine and reward-prospect improved response accuracy and speed. In the brain,

reward-prospect resulted in an enlarged frontocentral slow wave (contingent negative variation, or CNV) and reduced posterior alpha power (indicating increased cortical activity) before stimulus presentation, both neural markers for preparatory attention. Moreover, the CNV enhancement for reward-prospect trials was considerably more pronounced in the caffeine condition as compared to the placebo condition. These interactive neural enhancements due to caffeine and reward-prospect were mainly visible in preparatory attention activity triggered by the cue (CNV). In addition, some interactive neural enhancements in the processing of the Stroop target stimulus that followed were also observed. The results suggest that caffeine facilitates the neural processes underlying attentional preparation and stimulus processing, especially for task-relevant information. ■

INTRODUCTION

Humans have always searched for ways to enhance their cognitive capacities to efficiently cope with the vast amount of information they encounter in everyday life. One of the most useful set of mechanisms humans have available to distinguish between relevant and irrelevant information is our attention system (Petersen & Posner, 2012). In particular, this system selectively guides attention toward environmental stimuli and events that are the most important to us, including being associated with the possibility of gaining rewards (Van den Berg, Geib, San Martín, & Woldorff, 2019; Hickey & van Zoest, 2012; Aarts, van Holstein, & Cools, 2011; Hickey, Chelazzi, & Theeuwes, 2010; Roelfsema, van Ooyen, & Watanabe, 2010; Engelmann & Pessoa, 2007). It is also the case that, caffeine-containing substances (e.g., coffee, tea), arguably the most widely used psychoactive cognitive enhancers in the world, are being used on a daily basis to boost this attention system (Saville, de Morree, Dundon, Marcora, & Klein, 2018; Wilhelmus et al., 2017; Lorist & Tops, 2003).

The enhancing effects of reward-prospect and caffeine on attention have both been linked to their putative influence on the dopaminergic systems of the brain. More specifically, the prospect of reward has been found to increase dopamine release directly and acutely (Schultz, 2000,

2015). Caffeine, on the other hand, influences the central nervous system mainly through antagonizing adenosine receptors (Dunwiddie & Masino, 2001; Fredholm, Bättig, Holmén, Nehlig, & Zvartau, 1999). Adenosine A1 receptors are found throughout both cortical and subcortical brain areas. Adenosine A2A receptors, on the other hand, have been found to be specifically present in dopamine-rich areas of the brain, with highest levels at postsynaptic neurons in the striatum where they are colocalized with dopamine D2 receptors (Ferré, 2008; Fredholm, Irenius, Kull, & Schulte, 2001; Gevaerd, Takahashi, Silveira, & Da Cunha, 2001). The dosage of caffeine in one cup (200 ml) of coffee (typically regarded as 90 mg [European Food Safety Authority]) has been shown to work as an antagonist at both A1 and A2A receptors and to facilitate the signaling of dopamine in the brain (Ferré, 2016; Quarta et al., 2004; Davis et al., 2003; Okada, Mizuno, & Kaneko, 1996), particularly in the striatum, which is an essential part of the reward system (Schultz, 2000, 2015). This inverse relationship between adenosine and dopamine on the receptor level might underlie findings, showing nonspecific adenosine antagonists, such as caffeine, can increase dopamine levels (Ferré, Díaz-Ríos, Salamone, & Prediger, 2018; Ferré, 2008; Ferré et al., 2001).

Both the prospect of gaining reward and the consumption of caffeine-containing substances have been found to improve behavioral performance. For instance, cueing for the prospect of gaining monetary rewards has been found

¹University of Groningen, The Netherlands, ²Duke University
*Both authors contributed equally.

to guide attention *selectively* toward the potentially rewarding events or stimuli (Schevernels, Krebs, Santens, Woldorff, & Boehler, 2014; Van den Berg, Krebs, Lorist, & Woldorff, 2014). Neurally, the prospect of gaining rewards on an upcoming visual task triggers increased activity in cortical regions involved in attentional control and improved processing of relevant information in the visual cortices on that task, thereby improving behavioral performance (Van den Berg et al., 2019; Hickey et al., 2010; Roelfsema et al., 2010). Similarly, caffeine, compared to placebo, has also been found to increase neural activation in cortical areas involved in the selection of relevant information. Specifically, caffeine biases the processing of relevant stimuli over irrelevant ones, by modulating task-related brain activation related to the processing of relevant and/or irrelevant stimuli (Ruijter, Lorist, Snel, & De Ruiter, 2000; Kenemans & Lorist, 1995; Lorist, Snel, Mulder, & Kok, 1995; Lorist, Snel, Kok, & Mulder, 1994). In addition to these specific effects of caffeine on attention, several studies have also shown a broad sustained increase in neural arousal after the intake of caffeine (*vs.* placebo), consistent with the more general stimulating effects of caffeine on behavior (Kenemans & Lorist, 1995). Consistent with these neural modulations, caffeine doses, as low as the dose in half a cup of coffee, speed up RTs and improve accuracy (Lieberman, Wurtman, Emde, Roberts, & Coviella, 1987).

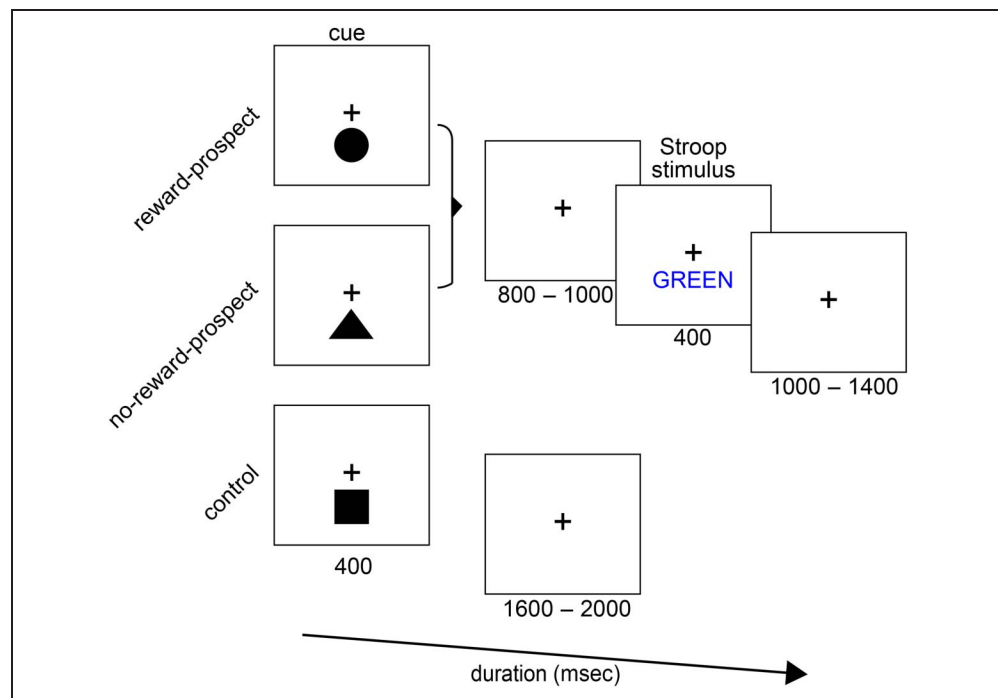
Although both reward-prospect and caffeine intake have substantial beneficial effects on behavioral performance, the nature of their interaction has remained elusive. Given that both reward-prospect and caffeine enhance the dopaminergic system, one might expect interactive properties in terms of cortical modulation between tonic modulation of caffeine and acute modulations by reward-prospect. There is substantial evidence, however, that both reward-prospect and caffeine influence behavior through an effect on attentional preparation. In studies employing high spatial resolution fMRI and ones using high temporal resolution EEG recordings, attentional preparation elicited brain activity in regions of a frontoparietal attentional control network (Corbetta & Shulman, 2002). This set of brain regions is thought to be the main contributor to the frontocentrally distributed contingent negative variation (CNV; Grent-'t-Jong & Woldorff, 2007), a negative-polarity slow-wave ERP that is elicited when expecting an imperative stimulus to be presented (Brunia, van Boxtel, & Böcker, 2012; Walter, Cooper, Aldridge, McCallum, & Winter, 1964). Importantly, research has suggested a link between dopamine levels and the processes underlying the CNV (Linssen et al., 2011). The amplitude of the CNV has further been found to predict behavioral performance (Van den Berg, Appelbaum, Clark, Lorist, & Woldorff, 2016; Van den Berg et al., 2014; Hillyard, 1969). Although all aspects of the cognitive functions reflected by the CNV are not fully understood, it is generally thought that a larger CNV indicates increased arousal or stronger anticipation of upcoming task-relevant events or stimuli (Van den Berg et al., 2014, 2016; Brunia et al., 2012; Hillyard, 1969).

Another neural marker that has been associated with preparatory attentional processes is oscillatory activity in the alpha-band frequency range (8–14 Hz). Decreases of the power in this frequency band has been related to increased cortical activity and enhanced selective attention (Scheeringa, Petersson, Kleinschmidt, Jensen, & Bastiaansen, 2012; Worden, Foxe, Wang, & Simpson, 2000), indicative of heightened information sensitivity in visual regions (Jensen & Mazaheri, 2010). In addition, power in the alpha frequency band has been shown to predict behavioral performance (Van den Berg et al., 2016; van Dijk, Schoffelen, Oostenveld, & Jensen, 2008) and has previously been found to be modulated by reward-prospect as well as caffeine (Van den Berg et al., 2014; Tiegens, Snel, Kok, Plat, & Ridderinkhof, 2007; Kenemans & Lorist, 1995; Ashton, Millman, Telford, & Thompson, 1974).

The aim of this study was to examine whether and how the prospect of reward and the consumption of caffeine-containing substances, two factors that enhance attention in everyday life, interact on both the behavioral and/or neural levels. To investigate this interaction, participants participated in a two-session study in which they either received coffee with caffeine or with lactose (placebo) before the experimental session, in which they performed an adapted version of the cued-reward task of Van den Berg et al. (2014). In this task (Figure 1), participants were instructed to respond as fast and accurately as possible to target Stroop stimuli. At the beginning of each trial, participants were presented with a cue that indicated that there was prospect of receiving a reward on that trial or that there was no such prospect. On reward-prospect trials, participants could earn money if they responded accurately and sufficiently fast.

Based on previous findings, our first main hypothesis was that both reward-prospect and caffeine would improve behavioral performance. Neurally, we hypothesized they would both enhance preparatory cortical activity, as indexed by the CNV and alpha power. In addition, we had two main competing hypotheses in terms of potential interactions of these factors. On the one hand, previous research has indicated that caffeine specifically improves selective attention toward relevant information (Ruijter et al., 2000; Lorist et al., 1994, 1995). Based on these studies, one might expect that caffeine would lead to enhanced attentional preparation for more important stimuli (*i.e.*, on reward-prospect trials) as compared to less important ones (*i.e.*, on no-reward-prospect trials). On the other hand, there is evidence that the stimulating effects of caffeine are most pronounced in situations when attentional control of perceptual functions is reduced, such as in the presence of mental fatigue or a lack of motivation (Ruijter, Lorist, & Snel, 1999; Lorist et al., 1994; Koelega, 1993; Weiss & Laties, 1962). Based on these findings, an alternative hypothesis was that the effects of caffeine would be most pronounced in the no-reward-prospect condition compared to the reward-prospect one, where the attentional system is already getting boosted by the anticipation of reward. Finally, we inspected the effects

Figure 1. Task and stimuli. Each trial started with a cue, consisting of a symbol that indicated reward-prospect, no-reward-prospect, or a control cue indicating that no Stroop stimulus would appear on that trial. After a fixation interval, the Stroop stimulus would appear after the first two cue types. In case of the control cue, no Stroop stimulus follows, but instead the next trial would begin after a variable delay.



of the factors caffeine and reward on the processing of the Stroop stimulus, as reflected by the late positive complex (LPC), a component that indicates the level of processing of target stimulus information (Van den Berg et al., 2014; Kappenman & Luck, 2012). Because the LPC has generally been found to be related to response speed, we expected its amplitude modulations to parallel the effects of reward and caffeine on behavioral performance.

METHODS

Participants

Thirty-one healthy adults (10 men), ranging in age from 18 to 31 ($M = 22.0$ year, $SD = 3.6$), participated in the two-session experiment. Participants received either course credits or 7 euros per hour for participation. In addition, they received a monetary reward that depended on their performance ($M = €10.6$, $SD = €3.9$). All participants were native Dutch speakers, right-handed, and regular coffee drinkers who ingested a minimum of 2 cups per day ($M = 4.2$ cups/day, $SD = 1.7$). We did not further explore how variations in habitual caffeine intake interacted with potential neural and behavioral effects of caffeine and reward. They had a regular sleep schedule and had normal or corrected-to-normal visual acuity. Participants indicated that they were not lactose intolerant and that they did not smoke. Data from two participants were excluded because of technical issues during recording, whereas data from another three were excluded because of excessive noise in the EEG (i.e., > 30% of the EEG epochs rejected because of artifacts; see EEG preprocessing below). The experiment was approved by the ethics committee of the Psychology Department of the University of Groningen, and participants

gave their written informed consent before the start of the first experimental session.

Apparatus

The experiment was conducted in a sound- and light-attenuated room, with the stimuli being presented on a 100-Hz LCD monitor with a resolution of 1920×1080 (Iiyama ProLite G2773HS). Participants sat in a comfortable desk chair at a viewing distance of 70 cm from the monitor and gave behavioral responses using a gamepad with four bumper buttons, using the index and middle finger of their left and right hands (Logitech Rumblepad, www.logitech.com). The experimental task was programmed using the Presentation software package (Version 18.1 06.09.15, www.neurobs.com/). Stimuli were randomized using the R statistical programming software package (R Development Core Team, 2013).

Task and Stimuli

During the entire task, a central fixation cross was continually visible in the middle of the screen. At the start of each trial (Figure 1), a cue stimulus (circle, triangle, or square [visual angle: 1.23°]) was presented, 1 cm below the fixation cross, for 400 msec. This cue stimulus indicated whether the trial was a reward-prospect trial (40% of the trials), in which a monetary reward would be given if a response to the subsequent imperative stimulus (a Stroop stimulus) was both correct and met a predefined RT criterion (see below), or whether it was a no-reward-prospect trial (40%), or whether it was a control trial (20%), in which case no imperative Stroop stimulus followed the cue. The

meaning-shape mapping of the cue stimuli was counterbalanced across participants. After a fixation screen was presented for 800–1000 msec, in the reward-prospect and no-reward-prospect trials, a Stroop color–word stimulus (i.e., Dutch words for “RED,” “GREEN,” “BLUE,” and “YELLOW” [visual angle: $1.23^\circ \times 4.91^\circ$]) was presented below the fixation mark for 400 msec. Participants were instructed to indicate the font color of the Stroop stimulus fast and accurate. In half of the trials, the Stroop stimulus was congruent (i.e., word meaning matched the font color) and in the other half the stimuli were incongruent (i.e., word meaning did not match the font color). The interval between the offset of the Stroop stimulus and the next cue varied randomly between 1000 and 1400 msec. The interval between the control cue (i.e., the one indicating that no Stroop target stimulus would follow) and the cue for the next trial was varied randomly between 1600 and 2000 msec.

Participants were instructed to respond to the font color of the Stroop stimulus as fast and as accurately as possible, by pressing one of the four buttons corresponding to the font color on the gamepad. After receiving instructions, the participants first performed a practice block of 30 trials, in which they received positive feedback (“correct”) if their response was correct and faster than 900 msec, or negative feedback (“incorrect”) if the response was incorrect or slower than 900 msec. If participants did not achieve a hit rate of over 80%, they performed a second practice block of 30 trials; otherwise, the experimental task started.

After the practice trials, participants performed a block of 30 trials, which was used to calculate the RT criterion ($RT_{crit} = \text{mean RT} + 200 \text{ msec}$) in the reward-prospect condition. The number of points participants could earn was based on the RT on each individual trial (RT_i in msec) according to the formula: $RT_{crit} - RT_i$. These points were converted to euros (i.e., 3000 points represented 1 euro). Participants did not receive a penalty if they responded too slowly or incorrectly, and hence they could only gain money and not lose any.

Thereafter, participants performed six experimental blocks of 200 trials each. After each block, participants could take a self-timed break. Within each block, there were 5-sec breaks every 15 trials and a 30-sec break every 100 trials. After every 30 trials, a screen was presented for 2000 msec that provided feedback, namely, indicating the total amount of money made thus far.

Procedure

The experiment consisted of two sessions that were scheduled exactly 1 week apart. Both sessions started at 9:00 a.m., and each took approximately 3.5 hr. Participants were instructed to abstain from alcohol and caffeine-containing substances for at least 12 hr before each session. Participants were told that they would receive a cup of coffee at the start of an experimental session. Approximately 45 min before the start of the task, participants received a cup of decaffeinated coffee, to which either caffeine or lactose (both 3-mg/kg

bodyweight [bodyweight was reported by the participant]) had been added. The experimenter was blind to whether caffeine or lactose had been added. In addition, participants were not informed that the coffee could contain either caffeine or lactose to avoid potential anticipation effects (Mills, Dar-Nimrod, & Colagiuri, 2017). The order of both conditions was counterbalanced over sessions across participants.

EEG Recording and Data Analysis

EEG was recorded using a 64-channel ANT waveguard electrode cap (10–10 system), using an on-line average reference. The sampling rate was 512 Hz, and the data were filtered during recording using a finite impulse response filter with a corner frequency at 102 Hz ($0.2 \times \text{sampling rate}$). Additional electrodes were placed on both the left and right mastoids, and vertical and horizontal EOG activity was recorded from two electrodes placed above and below the right eye and from two electrodes placed lateral to the outer canthi of the two eyes, respectively. Electrode impedances were kept below 5 k Ω . The analyses were performed using custom MATLAB scripts (MATLAB - Release 2015b, The MathWorks) in combination with the EEG analysis toolboxes Fieldtrip (Oostenveld, Fries, Maris, & Schoffelen, 2011) and EEGLab (Delorme & Makeig, 2004).

Data were off-line rereferenced to the algebraic average of the mastoid electrodes. Channels that contained excessive noise were replaced by interpolated values of the surrounding electrodes (spherical spline interpolation). Eye blinks and eye movements were corrected using independent component analysis (ICA) to reconstruct the data excluding those components that reflected eye blinks. The data were filtered using a 0.01-Hz high-pass filter. Epochs were extracted from -1500 to 2500 msec surrounding the onset of the cue stimulus and from -1500 to 2500 msec surrounding the onset of the Stroop stimulus. Epochs containing any remaining artifacts (amplitude $> 150 \mu\text{V}$, -500 to 1500 msec surrounding cue and stimulus onset) were excluded from the analysis (average epochs rejected per participant per session, cue epochs rejected: $M = 7.2\%$, $SD = 7.6\%$; target epochs rejected: $M = 5.9\%$, $SD = 6.3\%$).

After artifact rejection, the mean number of epochs per condition for the cue was as follows: On average, each session consisted of 455 ($SD = 41$) reward-prospect trials, 453 ($SD = 39$) no-reward-prospect trials, and 219 ($SD = 21$) control trials. The mean number of epochs per condition for the target was as follows: On average, each session consisted of 461 ($SD = 39$) reward-prospect trials and 458 ($SD = 37$) no-reward-prospect trials.

ERPs

To statistically examine cue-evoked brain activation, the mean amplitude of the CNV was derived from a frontocentral ROI (ROI_{fc} : FCz, FC1, FC2, Cz, C1, and C2), consistent with previous literature (Brunia et al., 2012), measured in the 700- to 1100-msec interval after cue presentation for

every trial. Stimulus-evoked brain activation was examined in two ROIs to investigate the “early” reward-related frontal positivity (Van den Berg et al., 2014), and the influence of reward and caffeine on the LPC, while at the same time considering the effect of Stroop stimulus conflict on electrical brain activity. The first ROI consisted of frontocentral channels (ROI_{fc}: FCz, FC1, FC2, Cz, C1, and C2), in which brain activity was examined between 400 and 500 msec poststimulus. Note that this ROI and latency interval is consistent with the location and latency range in which the incongruency-related negativity (N_{inc}) is usually found, a central negative deflection (incongruent vs. congruent) that has been related to the processing of stimulus conflict (Van den Berg et al., 2014; Liotti, Woldorff, Perez, & Mayberg, 2000; West & Alain, 2000; West & Bell, 1997). The second ROI, defined to investigate the LPC, consisted of parietal channels (ROI_p: Pz, P3, P4, POz, PO3, and PO4), from which the ERP signal was extracted between 700 and 800 msec poststimulus. Note that the second interval overlapped with the later stage of conflict processing, a larger positive deflection for incongruent compared to congruent stimuli. As such, these ROIs enabled investigation of the influence of reward and caffeine on the processing of the Stroop stimulus, while taking into account the different neural processes that are evoked by stimulus conflict.

Power Analysis

We used two different approaches to estimate oscillatory power in the EEG data surrounding the cue. Although we were primarily interested in alpha band (8–14 Hz) activity, we estimated power for a wider range of frequencies to ensure that potential effects were specific for the alpha band. First, to obtain sustained/tonic changes in power, which are expected as a result of caffeine-induced changes in cortical arousal, the frequency contents of cue-locked epochs were analyzed. The data were first multiplied by a Hanning window, and subsequent power estimates were obtained using a Fourier transformation. As these epochs ranged from –1500 msec until 2500 msec post-cue, the resulting activity contained pre-cue activity, cue-evoked activity, and stimulus-evoked activity. We measured alpha power (8–14 Hz; log₁₀-transformed power) on each epoch in an occipital ROI_o (PO7, PO8, PO3, PO4, O1, O2).

Second, to examine changes in power, and specifically related to cue-evoked activity, time–frequency decomposition was done by multiplying the cue-epoch data with a moving Hanning window (steps of 50 msec). The temporal width of the Hanning window decreased with increasing frequency (seven cycles per frequency from 5 to 40 Hz; for 5 Hz [200 msec per cycle], the width of the window is 1400 msec). Finally, obtained power was log₁₀-transformed. No baseline correction was performed for the power analyses. To assess the effects of reward and caffeine on alpha activation, we measured alpha power (8–14 Hz; log₁₀-transformed power) between 700 and 1100 msec after cue presentation on each trial in an occipital ROI (PO7,

PO8, PO3, PO4, O1, O2), consistent with previous studies (Van den Berg et al., 2014; Worden et al., 2000).

Statistical Analysis

For statistical significance testing, we employed a mixed-modeling approach using the *lme4* statistical package (Bates, Kliegl, Vasishth, & Baayen, 2015). The data provided to the model included the RT and a mean amplitude of the various neural measurements on each trial (excluding trials marked as artifacts, for the cue interval, the data consisted of ~62,400 observations [2 sessions × 1200 trials × 26 participants]; for the target interval [excluding trials in which the participant responded incorrectly to the Stroop stimulus], this was ~41,000 observations). A mixed-modeling approach has the advantage of taking into consideration the individual data points (as opposed to binning trials into various conditions per participant as, for example, in standard general linear model [GLM]-ANOVA) and therefore allows accounting for variance that is related to between-session effects, introduced in this study by counterbalancing the session order of administration of caffeine across participants. In other words, because we counterbalanced the session order of administration of caffeine across participants, a mixed modeling allows for the accounting of session-related variance. To establish the random-effects structure, we used a procedure in which we started with a full model (containing random slopes per participant for all corresponding fixed effects, including the interaction terms) and we subsequently reduced model complexity by stepwise removing random factors (starting with the interaction terms) until the model was not singular (Bates et al., 2015). This stepwise procedure has been shown to result in a “hybrid” model that avoids overfitting the data while containing relevant random effects to control for the Type 1 error rate (Matuschek, Kliegl, Vasishth, Baayen, & Bates, 2017).

The formulas in Table 1 reflect the resulting models used to statistically test the effects of congruency, caffeine, and reward (and their interactions) on the behavioral and neural dependent variables. For all models (behavioral, cue-, and target interval models), we used a random intercept for each participant and a random slope per participant for session and reward-prospect. For the behavioral and target interval models, a random slope by participant for congruency was added. To obtain information about statistical significance, the degrees of freedom were approximated using the Satterthwaite approximation of effective degrees of freedom as calculated by the R package *lmerTest*, which has been shown to control relatively well for Type 1 error rate (Kuznetsova, Brockhoff, & Christensen, 2017; Luke, 2017). In addition to the mixed-model single-trial statistical analysis, we provide GLM-ANOVA tables, based on the means per condition per participant (collapsed over session), as Supplementary Material S1 (available from http://berryvdb.org/SuppS1_vandenberg_et_al_JOCN2020.pdf). We also incorporated the alternative GLM-ANOVA approach proposed by Kenemans, Wieleman,

Table 1. Models Used to Statistically Test the Effects of Congruency, Caffeine, and Reward-Prospect on the Behavioral and Neural Dependent Variables

| | |
|--------------------------|---|
| Behavioral analysis | $p(\text{hit})_n = \text{logit}^{-1}(\beta_{0,j} + \beta_1 \text{congruency}_{j[n]} + \beta_2 \text{reward}_{j[n]} + \beta_3 \text{caffeine}_n + \beta_4 \text{session}_{j[n]} + \beta_5 \text{congruency}_n \times \text{reward}_n + \beta_6 \text{congruency}_n \times \text{caffeine}_n + \beta_7 \text{reward} \times \text{congruency}_n + \beta_8 \text{congruency} \times \text{reward} \times \text{caffeine}_n + \epsilon_n)$ $\text{RTs}_n = \beta_{0,j} + \beta_1 \text{congruency}_{j[n]} + \beta_2 \text{reward}_{j[n]} + \beta_3 \text{caffeine}_n + \beta_4 \text{session}_{j[n]} + \beta_5 \text{congruency}_n \times \text{reward}_n + \beta_6 \text{congruency}_n \times \text{caffeine}_n + \beta_7 \text{reward}_n \times \text{congruency}_n + \beta_8 \text{congruency}_n \times \text{reward}_n \times \text{caffeine}_n + \epsilon_n$ |
| Cue interval analysis | $\text{Marker}_n = \beta_{0,j[n]} + \beta_1 \text{reward}_{j[n]} + \beta_2 \text{caffeine}_n + \beta_3 \text{session}_{j[n]} + \beta_4 \text{reward} \times \text{caffeine}_n + \epsilon_n$ |
| Target interval analysis | $\mu V_n = \beta_{0,j} + \beta_1 \text{congruency}_{j[n]} + \beta_2 \text{reward}_{j[n]} + \beta_3 \text{caffeine}_n + \beta_4 \text{session}_{j[n]} + \beta_5 \text{congruency}_n \times \text{reward}_n + \beta_6 \text{congruency}_n \times \text{caffeine}_n + \beta_7 \text{reward}_n \times \text{congruency}_n + \beta_8 \text{congruency}_n \times \text{reward}_n \times \text{caffeine}_n + \epsilon_n$ |
| Sustained alpha power | $\text{alpha power}_n = \beta_{0,j} + \beta_1 \text{caffeine}_n + \beta_2 \text{session}_{j[n]} + \epsilon_n$ |

Within the formulas the subscript n indicates single trials, the subscript j indicates the individual participant. For instance, the notation $\beta_{0,j}$ indicates the intercept, which varies by participant (the random effect).

Zeegers, and Verbaten (1999) to examine session effects in Supplementary Material S1, in which Order (i.e., caffeine session followed by placebo session, or vice versa) was added as a between-subject factor. Finally, we tested if the additional effect of Order improved the *mixed* model fit. The results presented in Supplementary Table 2 show that the addition of this factor did not substantially improve the fit of any of the models tested, providing support for exclusion of this factor.

RESULTS

Behavioral Performance

Participants responded, on average, 58 msec ($SE = 5$ msec) more slowly and 2.9% ($SE = 0.5\%$) less accurately to incongruent than to congruent Stroop stimuli, replicating a multitude of studies of the behavioral effects of Stroop incongruency (MacLeod, 1991; main effect of congruency; RT: $F(1, 25) = 192.6, p < .001$; accuracy: $\chi^2(1) = 72.7, p < .001$). In addition, they responded more quickly (~ 25 msec) and more accurately to the font color of the Stroop stimulus if the cue for that trial indicated reward-prospect as compared to the no-reward-prospect (main effect of Reward; RT: $F(1, 25) = 42.3, p < .001$; accuracy: $\chi^2(1) = 12.9, p < .001$; Figure 2). Moreover, we found that RTs decreased (~ 23 msec) and the proportion of hits increased in the Caffeine condition compared to the placebo condition (main effect Caffeine; RT: $F(1, 24) = 7.1, p = .014$; accuracy: $\chi^2(1) = 13.3, p < .001$; Figure 2). On the behavioral level, no significant interactions were observed between the independent variables of Congruency, Reward, and Caffeine.

EEG Results

Cue-evoked Brain Activation: Influence of Reward and Caffeine on the CNV

Visual inspection of Figure 3 shows that the ERPs evoked by both the reward-prospect and no-reward-prospect cues started to diverge from the control trials around 700 msec

after cue onset. In the conditions for which the participants were cued that an upcoming Stroop stimulus would appear, a more pronounced frontocentral slow-wave negative deflection (CNV) was observed compared to the control condition (in which the participant knew no Stroop stimulus would be coming). The amplitude of the CNV was more negative after a reward-prospect cue versus a no-reward-prospect cue, replicating the results of Van den Berg et al. (2014; main effect of reward: $F(1, 25) = 9.8, p = .004$). Whereas we did not observe a significant interaction between Reward and Caffeine on the behavioral measures, the effects of Reward on CNV amplitude were found to be dependent on the Caffeine condition. More precisely, the CNV after reward-prospect cue (vs. no-reward-prospect) was larger when participants had received caffeine before the experiment as compared to placebo, whereas this CNV difference between reward-prospect and no-reward-prospect was not significant in the placebo condition (Figure 3A and B; Reward \times Caffeine interaction: $F(1, 45850) = 8.4, p = .004$; caffeine_{reward-prospect} minus no-reward-prospect: $t(36) = 4.04, p < .001$; placebo_{reward-prospect} minus no-reward-prospect: $t(36) = 1.7, p = .11$).

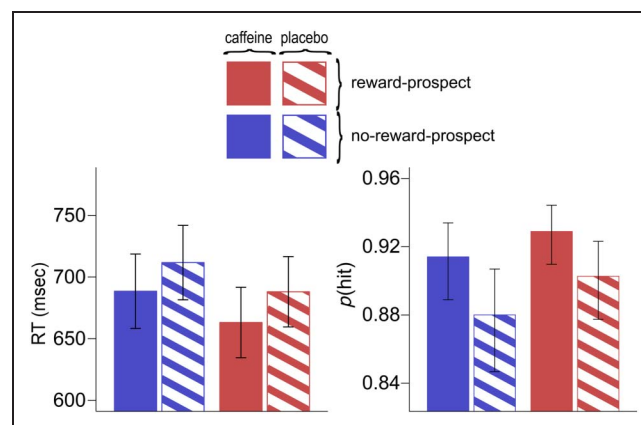


Figure 2. Behavioral results. Participants responded faster and more accurately when cued with reward-prospect vs. no-reward-prospect and when receiving caffeine vs. placebo. Error bars reflect 95% CIs.

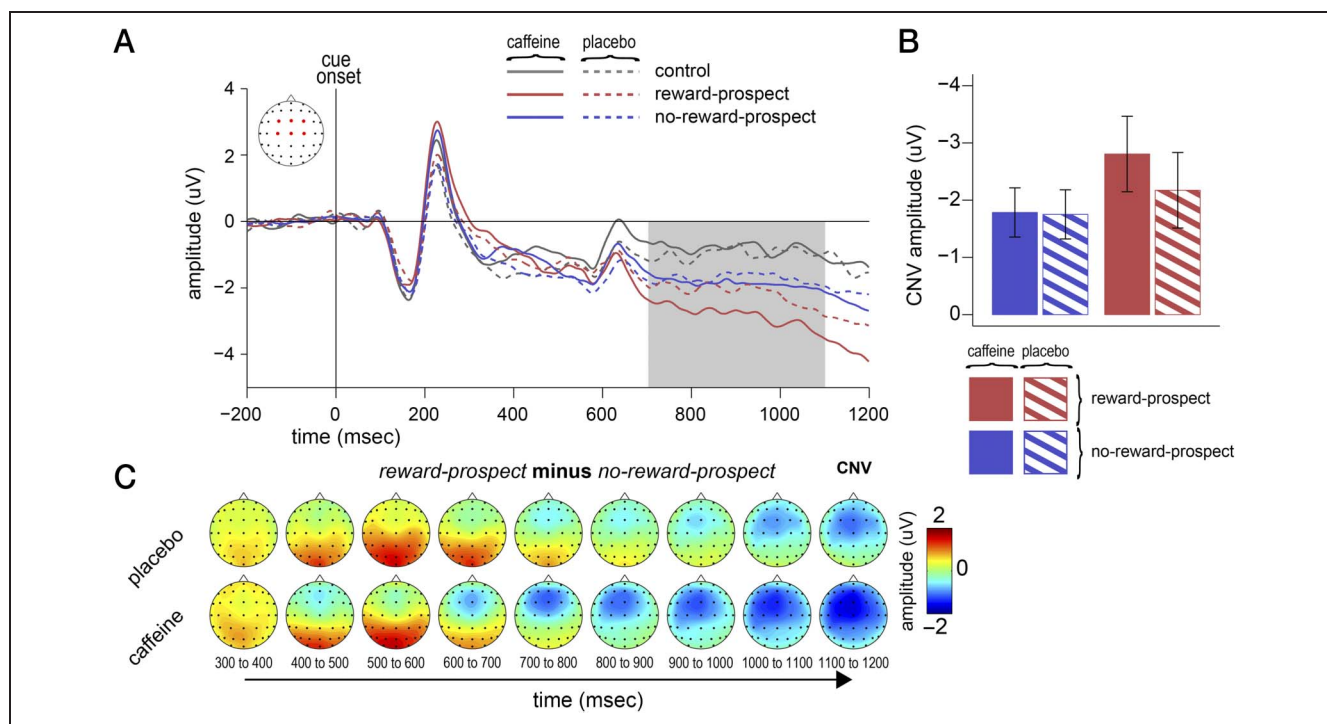


Figure 3. Cue-evoked ERPs. (A) Grand average cue-evoked responses from ROI_{IC} for the different conditions. (B) CNV amplitude for the different conditions. (C) Topographical distributions of the effects across time of the reward-prospect versus no-reward-prospect conditions.

Cue-evoked Brain Activation: Influence of Reward and Caffeine on Alpha Power

The frequency analyses revealed lower levels of sustained alpha power (8–14 Hz; i.e., sustained across the whole session) over occipital brain regions if participants received coffee with caffeine before the experiment as opposed to coffee with placebo (Figure 4A; main effect of Caffeine: $F(1, 24) = 7.96, p = .009$), replicating previous work (Kenemans & Lorist, 1995). In addition to these sustained session effects of caffeine, we observed cue-evoked changes in alpha power over occipital scalp. More specifically, after presentation of the cue, occipital alpha power was lower in the caffeine condition as compared to the placebo condition (main effect of Caffeine: $F(1, 24) = 14.3, p < .001$; Figure 4B and C). In addition, alpha power decreased in response to reward-prospect cues compared to no-reward-prospect ones (main effect of Reward: $F(1, 25) = 13.3, p = .001$; Figure 4B and C), replicating previous results for this preparatory-attention effect (Van den Berg et al., 2014). In contrast to the CNV effects, no interactions between the effect of caffeine and reward were observed in terms of cue-triggered alpha power, $F(1, 45847) = 0.01, ns$.

Differential Effects of Reward and Caffeine on CNV and Alpha Power

In the above analysis, we observed distinctive effects of caffeine and reward on CNV amplitude and cue-evoked alpha power. To statistically test if these relationships were indeed distinctive, we first z -transformed both CNV

amplitude and alpha power, ensuring a comparison on the same scale. Next, we added a neural marker (CNV or alpha) as a predictor variable to the model that is described in Table 1 under cue-interval analysis:

$$z_n = \beta_{0,j} + \beta_1 \text{reward}_{j[n]} + \beta_2 \text{caffeine}_n + \beta_3 \text{session}_{j[n]} + \beta_4 \text{reward} \times \text{caffeine}_n + \beta_5 \text{reward} \times \text{marker}_n + \beta_6 \text{caffeine} \times \text{marker}_n + \beta_7 \text{reward} \times \text{caffeine} \times \text{marker}_n + \epsilon_n$$

This analysis revealed a significant three-way interaction (Caffeine \times Reward \times Marker: $F(1, 91719) = 4.9, p = .027$), providing supporting statistical evidence for differential effects of caffeine and reward on CNV amplitude and evoked alpha power. Specifically, this analysis shows that the interaction between reward and caffeine was observed for the amplitude CNV, but not for alpha power.

Influence of Reward and Caffeine on the Processing of the Stroop Stimulus

As expected, conflict processing was found to evoke the classical early incongruity-related negativity, $F(1, 24) = 28.4, p < .001$, and a larger LPC, $F(1, 24) = 14.7, p < .001$. Consistent with the behavioral effects of congruency, these congruency effects were not significantly modulated by caffeine or reward (Figure 5C).

In the target–stimulus interval, we also observed a more positive, widespread, and long duration ERP amplitude in the reward-prospect condition compared to the no-reward-prospect trials, starting around 300 msec poststimulus

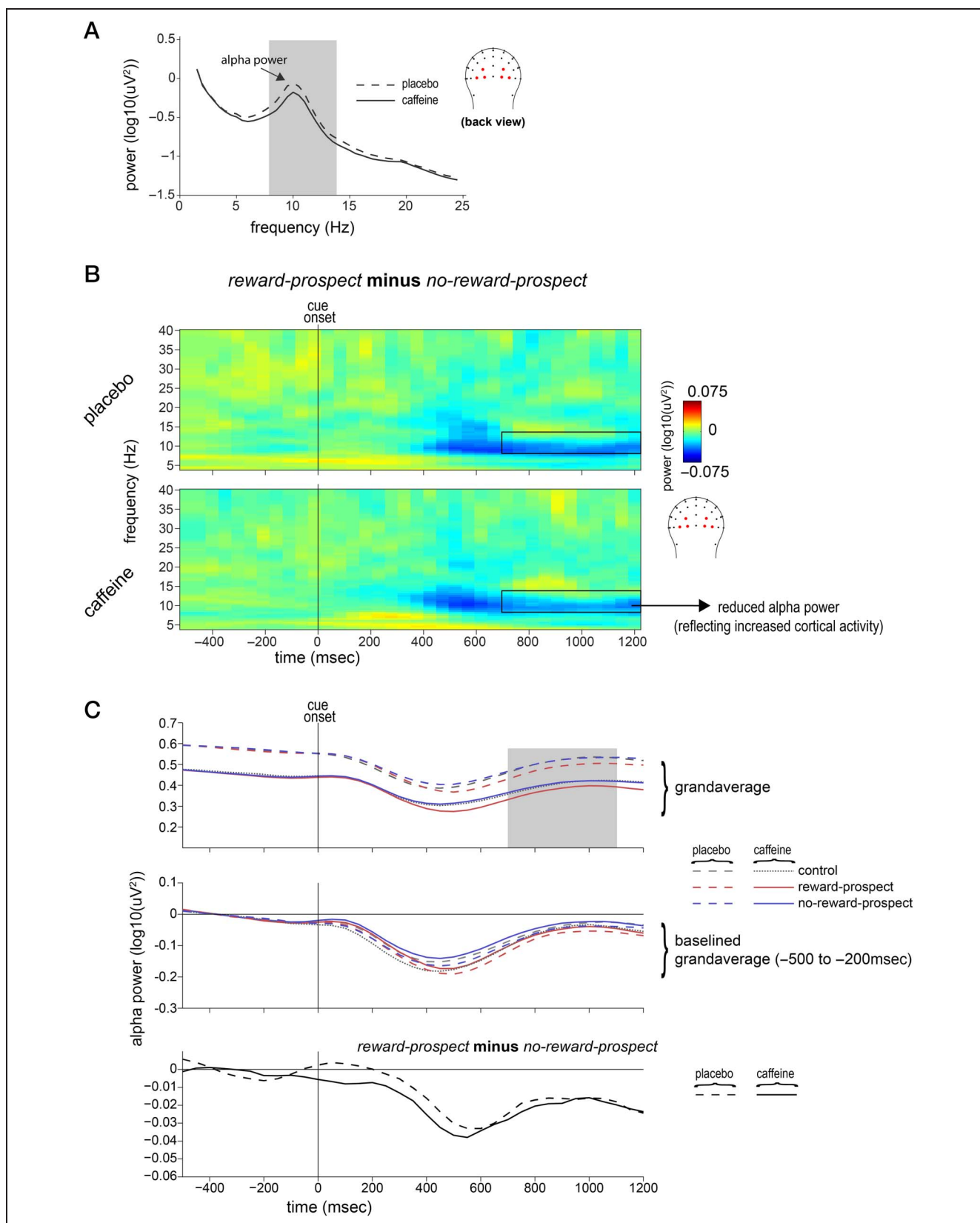


Figure 4. Sustained and cue-locked changes in oscillatory power measured over the occipital channels. (A) Sustained EEG power across the entire session revealed lower alpha power when participants received caffeine vs. placebo. (B) Cue-locked spectral power revealed a decrease in alpha power before the presentation of the imperative Stroop stimulus, irrespective of caffeine condition. (C) Changes in alpha power over time relative to the onset of the cue-stimulus.

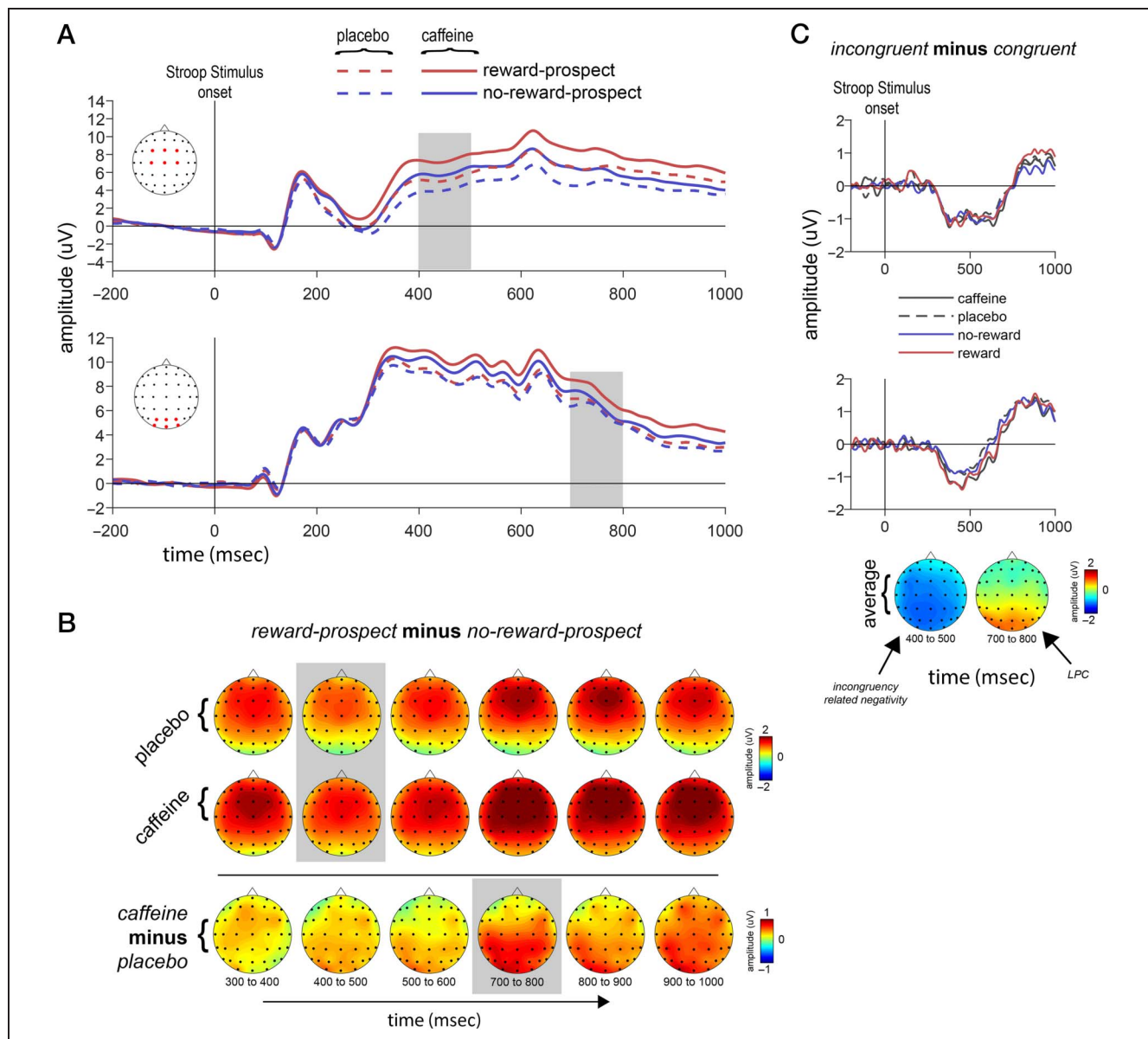


Figure 5. Stimulus-evoked ERPs (collapsed over congruency). (A) ERP traces from the frontocentral (top panel) and parietal (lower panel) ROIs, showing the large LPC [also early interval is indicated by a grey bar] wave. (B) Topographical distribution of the difference in ERP amplitude between the reward-prospect and no-reward-prospect trials for the caffeine and the placebo conditions separately, and, (bottom row) the difference of the reward effect in the caffeine vs. placebo conditions, showing the effects of these manipulations on the LPC. (C) ERP difference waves (incongruent minus congruent) for the caffeine and placebo sessions (collapsed across the levels of reward), and for reward-prospect and no-reward-prospect (collapsed across caffeine condition). Topographical scalp plots show the difference in ERP amplitude between incongruent and congruent trials.

in both the frontocentral and parietal ROIs (ROI_{fc} : 400–500 msec; main effect of Reward: $F(1, 25) = 18.6, p < .001$; ROI_p : 700–800 msec; main effect of Reward: $F(1, 25) = 6.7, p = .016$). In addition, in the caffeine condition, more positive amplitudes were observed in the ROI_{fc} compared to the placebo condition (ROI_{fc} : 400–500 msec; main effect of Caffeine: $F(1, 24) = 4.3, p = .047^1$). This effect, however, did not reach the level of significance in the parietal ROI (ROI_p : 700–800 msec; main effect of Caffeine: $F(1, 24) = 1.0, p = ns$). Visual inspection of Figure 5A shows that the largest positive-polarity activity was observed in the condition in which the participant both

received caffeine and was cued with reward-prospect, whereas the lowest positivity was elicited in the no-reward-prospect condition during which the participant received placebo. This observation was supported by an interaction Under Armour Infil Ops Ankle Boot.between caffeine and reward-prospect, which was significant at trend level (at $p < .1$) in the ROI_{fc} , while it reached significance in the parietal ROI (Caffeine \times Reward interaction; ROI_{fc} : $F(1, 40793) = 3.2, p = .07$; ROI_p : $F(1, 40789) = 10.6, p = .001$). In the parietal ROI, we observed an effect of reward-prospect in the caffeine condition (caffeine_{reward-prospect} minus no-reward-prospect: $t(33) = 3.6, p = .001$), whereas there was no observable

effect of reward-prospect in the placebo condition (placebo_{reward-prospect} minus no-reward-prospect: $t(34) = 1.2$, $p = ns$).

DISCUSSION

Two factors that are separately known to influence preparatory attention are caffeine and the prospect of reward. The goal of this study was to investigate if and how these factors interact to enhance attentional preparatory activity and subsequently improve the processing of and response to task-relevant information that can potentially lead to monetary rewards. To do this, we conducted a two-session experiment in which participants performed a cued-reward Stroop task while behavioral and neural-activity measures were acquired. Each trial of the task consisted of a cue that indicated whether a color–word Stroop stimulus would or would not follow, and whether there was a prospect of gaining monetary rewards for good performance on discriminating that color–word Stroop stimulus. Before the start of each experimental session, participants received either a cup of decaffeinated coffee with caffeine or with lactose (placebo; both 3-mg/kg bodyweight). The key results showed that caffeine intake indeed resulted in greater enhancements of cue-triggered attention-related neural processes and better behavioral performance, especially when the cue indicated that there was a potential for reward for good performance on the subsequent Stroop task. The findings described in this article advance our understanding of how two previously separately studied factors, both of which impact behavioral performance, interact on a neural level to improve behavioral performance.

The level of general neural arousal substantially increased after the intake of caffeine (vs. placebo). Replicating previous studies, we observed reductions of power in the alpha frequency band (8–14 Hz), reflecting an increase in cortical brain activity and alertness (Scheeringa et al., 2012; Kenemans & Lorist, 1995). This increased state of alertness when participants had received caffeine before the start of the experimental session was paired with improved behavioral performance (both RTs and accuracy), suggesting that caffeine intake improves the general state of the brain to such an extent that individuals can react more effectively to external stimuli and events.

In line with previous research, the behavioral responses to the color–word Stroop stimuli were faster and more accurate when preceded by a reward-prospect (Schevernels et al., 2014; Van den Berg et al., 2014; Padmala & Pessoa, 2011). The effects of reward-prospect and caffeine, however, appeared to be additive in terms of RTs and accuracy, and thus, behavioral performance was most optimal when there was both a prospect of reward and caffeine had been ingested. In contrast to these results, some previous studies have reported that caffeine is especially effective when, because of the participant's state, behavioral

performance was *not* optimal. For instance, it has been found that caffeine can have a profound impact on RTs and accuracy particularly when participants are fatigued (Nehlig, 2010; Lorist & Tops, 2003). Mental fatigue is a state that has been associated with decreased behavioral performance, usually after continuously performing a taxing task for an extended period (Lorist & Faber, 2011). Thus, our finding that caffeine actually boosted behavioral performance similarly in both the more optimal reward-prospect condition and the suboptimal no-reward-prospect condition would seem to differ from previous reports that have suggested that the stimulant effects of caffeine on behavior are most pronounced in situations when attentional control of perceptual functions is reduced.

Increased behavioral performance was preceded by changes in brain activity related to event-related attentional preparation. These effects were modulated by caffeine and reward, resulting in enhancements of both the frontocentral CNV and posterior alpha power starting at ~ 700 msec after the cue, reflecting the marshalling of neural circuits that have been associated with preparatory attention (Corbetta & Shulman, 2002; Hillyard, 1969) and the enhancement of sensitivity to visual information (i.e., alpha power; Van den Berg et al., 2019; Worden et al., 2000), after caffeine consumption and during reward-prospect trials.

In this study, we used the CNV amplitude and occipital alpha power as markers for cue-triggered preparatory attention. First, we replicated that both caffeine and reward-prospect have an enhancing effect on the slow-wave CNV (Schevernels et al., 2014; Van den Berg et al., 2014; Ashton et al., 1974) and on posterior alpha power (Van den Berg et al., 2014; Kenemans & Lorist, 1995). Second, and probably even more intriguingly, we observed that the modulation of the CNV by reward-prospect could be increased even further after the intake of caffeine. It is important to note that in previous studies, both the amplitude of the CNV and power in the alpha frequency band have been statistically linked through correlation to improved target processing and more optimal behavioral performance (Van den Berg et al., 2014, 2016; Grent-'t-Jong, Boehler, Kenemans, & Woldorff, 2011). Hence, one might expect that the CNV and alpha power could be reflective of the same underlying neural mechanism that is involved in attentional preparation. However, this hypothesis did not seem to hold in these studies, because no direct relationship between the CNV amplitude and alpha power could be established.

Here, we observed that the effects of reward and caffeine interacted on the CNV but were additive for alpha power. This dissociation suggests that these markers reflect windows into two different facets of preparatory attention. Although their specific neural and cognitive functions are not fully understood, the CNV has been suggested to reflect a general arousal effect related to anticipation for a task or event. For the CNV, this effect is thought to originate from the frontoparietal attentional control circuits (Grent-'t-Jong & Woldorff, 2007). Decreases in occipital

alpha power have been correlated with increased BOLD signal in the visual cortices (Scheeringa et al., 2012), suggesting that the amplitude of this prestimulus oscillatory activity is inversely reflective of receptibility to information in the visual sensory cortices, serving as a mechanism that can filter specific incoming sensory information.

In this study, we found that, on the one hand, caffeine influenced the neural circuitry underlying the CNV when cued with reward-prospect but not when cued with no-reward-prospect. On the other hand, alpha power was influenced by caffeine regardless of cue information. These results suggest that caffeine might work on our neural information processing system in at least two ways. First, by enhancing the general state of the participant, caffeine increases sensory processing capabilities (as reflected by lowered alpha power). Second, the effect of caffeine depends on the context of an event, that is, on its behavioral relevance for the upcoming task. Neurally, this can be illustrated by a larger CNV to reward-predicting cues under the influence of caffeine (vs. placebo), whereas there is little effect of caffeine on the CNV triggered by cues that predict no reward. Our finding that the prospect of gaining reward and the consumption of caffeine speeded up reactions to subsequent Stroop stimuli in an additive manner confirms, at least partly, the differential effect these factors have on our attention system at the underlying neural level.

With regard to these effects of caffeine, previous studies have found a pronounced behavioral effect when mental fatigue occurs (and thus when slower RTs would have been observed), indicating that caffeine enhances the state of the participants in such a way that it helps them overcome (or at least compensate for) low levels of neural arousal that tend to impair behavioral task performance. In line with these observations, we found that caffeine did indeed seem to improve the general arousal state of the participant (as indexed by session-level reductions in alpha power, thus reflecting higher levels of cortical activation). Here, we manipulated the behavioral importance of events through reward-prospect cues. Under these circumstances, we found that caffeine resulted in greater enhancement of preparatory attention (CNV) for the more important rewarding events. Thus, in addition to the more general arousal effect, caffeine can specifically boost attentional preparation for more salient or behaviorally important external events (as signaled by the reward-prospect cue) compared to other events that are less important. These findings suggest that improved behavioral performance because of the enhanced arousal state induced by caffeine depends on the context, and that this context is behavioral relevance.

From a theoretical perspective, the effects of both caffeine and reward-prospect on preparatory attention are expected to influence subsequent Stroop stimulus processing. For example, reward-prospect cues have been argued to enhance the saliency of specific impending events (Schevernels et al., 2014; Van den Berg et al., 2014), resulting in the recruitment of the attentional-control circuits to improve the processing of those events. The effect of

cueing of the potential for obtaining a monetary reward (vs. no-reward) was followed in time by a larger frontocentral distributed positivity to the Stroop stimulus, which was similar to the effect observed by Van den Berg et al. (2014), but was not further modulated by caffeine (additive effects of caffeine and reward). However, the neural interaction effects on the later parietal LPC elicited by the Stroop stimulus paralleled the effects on the preceding cue-triggered CNV, with a larger enhancement of the LPC with reward prospect when caffeine was administered as opposed to a placebo. The observation that modulations of cue-related brain activity (CNV) by caffeine and reward was followed, in time, by a larger Stroop stimulus-related (LPC) neural activity, suggests that recruitment of the attentional-control circuits indeed ramifies in enhanced processing of task-relevant information. However, such an effect did not seem to result into a corresponding behavioral interaction between caffeine and reward in the current paradigm.

Further Consideration and Future Directions

Next, we consider various open standing questions with regard to the findings as described above.

Caffeine did not significantly influence preparatory alpha power differentially as a function of reward. Hence, although caffeine can modulate the anticipatory processes reflected by the CNV, caffeine does not seem to influence the sensory-specific processes as reflected by posterior alpha power. Perhaps, because of the complex nature of the Stroop task (with 50/50 incongruent vs congruent stimuli), it is difficult to prepare the sensory cortex to the reception for specific task-relevant information. For instance, in the classic Worden et al. (2000) study (and numerous replications and extensions since), the cue contained information as to where in space a potential target would occur, and this information resulted in alpha modulation (increase on the irrelevant side and decrease over the relevant one) over sensory cortices. Similar effects can be observed when learning to associate specific stimuli (e.g., faces and houses) with rewards (Van den Berg et al., 2019). In this probabilistic learning study, we found that when faces were rewarded (i.e., a gain), this was followed by a reduction in alpha power over the face-specific sensory brain regions.

Given the findings, the conclusion that it might be difficult for the participants to prepare given the demands of the word-color Stroop task seems also illustrated by our behavioral findings that showed that the classic congruency RT effect (MacLeod, 1991) was not significantly modulated by reward-prospect, replicating findings from Van den Berg et al. (2014). An important point here is that, in this study, our main question was not focused on the interaction between reward-prospect and stimulus-conflict processing. Furthermore, we did not find an interaction between caffeine and trial congruency, similar to previous research (Tieges et al., 2007; Kenemans et al., 1999). On the other hand, when the stimulus congruency

conditions were blocked, Kenemans et al. (1999) did find an influence of caffeine on conflict processing. Accordingly, a point for future research is to understand if and how factors such as reward and caffeine can and do modulate the processing of incoming information to reduce conflict.

Another important point to consider when interpreting these effects of caffeine is the potential role of withdrawal. Withdrawal symptoms typically emerge 12–24 hr after stopping the consumption of caffeine (Juliano & Griffiths, 2004; Nehlig, Daval, & Debry, 1992), which are manifested in the form of headaches, difficulty in concentrating, and effects on mood. Here, we asked our participants to abstain from drinking coffee for 12 hr before the experimental session that started at 9:00 a.m. The choice of this timeline was specifically to have participants be tested after an overnight abstinence period during which they would normally have not drunk coffee and before withdrawal effects tend to kick in, thereby minimizing the potential for withdrawal effects. Besides, different studies have found that when there are caffeine withdrawal effects, they are more pronounced for subjective symptoms compared to performance effects (Mills, Boakes, & Colagiuri, 2016). In addition, to reduce the effect of expectancy on the experience of withdrawal symptoms (Mills et al., 2017), participants were not informed that, in one of the sessions, the coffee contained placebo instead of caffeine.

To check for withdrawal effects, behavioral performance in the neural and cognitive placebo condition of this study was compared to behavioral performance in a previous study by Van den Berg et al. (2014), which used a similar experimental design with the main difference the absence of the caffeine manipulation and a higher overall monetary reward. Comparison of the behavioral RT effect of reward of the two studies (30 msec in Van den Berg et al., 2014, vs. 25 msec here) suggests that the effect of caffeine observed in this study is unlikely to be explained by withdrawal effects in the placebo condition. Similarly, Kenemans and Lorist (1995) found that, average response speed in their placebo condition was comparable to the results of a similar experiment without the caffeine manipulation; participants responded faster in caffeine condition than in the other condition/experiment, suggesting that withdrawal effects are unlikely to explain the observed caffeine effects (see also: Kenemans et al., 1999; Kenemans & Verbaten, 1998).

Finally, it should be emphasized that we did not find an interaction between caffeine and reward on the behavioral responses, as well as some aspects of the neural responses, to the Stroop stimulus. However, it is important to note that the effects of caffeine by means of antagonism of adenosine receptors also include the modulation of other neurotransmitter systems (e.g., acetylcholine, noradrenaline, serotonin) that are known to influence other cognitive processes besides preparatory attention (McLellan, Caldwell, & Lieberman, 2016; Fredholm et al., 1999). Accordingly, it is difficult to disentangle to what extent the effects on the Stroop stimulus processing were related to changes

in preparatory attention before the Stroop target stimulus or to session-level effects of caffeine on the processing of the Stroop stimulus. Thus, the interpretation of the observed behavioral and neural effects in response to the Stroop target stimulus should be made with caution. We speculate, for example, that even if there are interactive effects reward and caffeine on preparatory attention, potentially additional caffeine effects (accomplished through other neurotransmitter systems) may swamp out or otherwise affect the observability of these effects in the final behavioral output. As such, this would seem to be an important point for future studies to address.

Summary and Conclusions

In summary, we found various neural and cognitive processes were modulated by caffeine, reward, and the interaction between the two. The task consisted of a cue stimulus followed by a Stroop stimulus. After the cue, preparatory anticipatory attention (as reflected by the fronto-central CNV) was modulated by reward-prospect and caffeine in an interactive way, whereas preparatory activity in the sensory regions (alpha power) was modulated independently by those factors, with no interaction. We also found that the processing of the subsequently presented Stroop stimulus was modulated by these factors, but again in different patterns. The earlier phase of Stroop stimulus processing (conflict processing; Ninc) showed independent effects of caffeine and reward-prospect. In contrast, the effects on the later phase (LPC) of the Stroop stimulus processing did show interactions, being modulated differentially by reward-prospect as a function of caffeine. Finally, we observed that the behavioral responses, the final end product of this cascade of various processes, showed additive effects in terms of caffeine and reward-prospect, but with no interaction. Important to consider here is that the processing of the Stroop stimulus would be expected to be modulated by both preparatory attention, as well as by direct influences of caffeine, although perhaps through other neurotransmitter systems. Accordingly, we cannot rule out that, under different conditions, we might see interactions between caffeine and reward at a behavioral level. However, although no interactive effects were observed in the behavioral responses here, by measuring brain activity during various stages of information processing leading up to that final behavior, we showed how caffeine and reward can interact in their modulations of cognitive brain activity.

To conclude, we found that reward-prospect and caffeine intake can enhance neural attentional-preparatory activity, showing most optimal preparation and behavioral performance after caffeine intake and after a reward-prospect cue, as reflected by larger CNV and lowest alpha power being triggered by the cue. In addition, we found that caffeine appears to especially improve preparatory attention (CNV) for a task that could potentially result in a reward. In a broader sense, these findings indicate that

caffeine can specifically target attentional preparatory neural processes when expecting important events relative to events that are less consequential.

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Reprint requests should be sent to Berry van den Berg, Faculty of Behavioural and Social Sciences, Department of Experimental Psychology, University of Groningen, Grote Kruisstraat 2/1, Groningen, The Netherlands, 9700 AB, or via e-mail: berry.van.den.berg@rug.nl.

Note

1. In the GLM-ANOVA (Supplemental Material S1; http://berryvdenberg.org/SuppS1_vandenbergetal_JOCN2020.pdf), the effect of Caffeine was significant at trend level, $F(1, 25) = 3.6$, $p = .069$.

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