Caffeine Effects on ERP Components and Performance in an Equiprobable Auditory Go/NoGo Task

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Background: Research has reliably demonstrated that caffeine produces a general increase in physiological arousal in humans, but we previously failed to obtain the expected arousal-based changes in manually quantified event-related potential (ERP) components in response to the stimuli in a simple Go/NoGo task.

Methods: A single oral dose of caffeine (250 mg) was used in a randomized double-blind placebo-controlled repeated-measures cross-over study. Adult participants ($N=24$) abstained from caffeine for 4 hours before each of two sessions, approximately 1 week apart. An equiprobable auditory Go/NoGo task was used, with a random mix of 75 tones at 1,000 Hz and 75 at 1,500 Hz. All tones were 50 ms duration (rise/fall time 5 ms) at 60 dB SPL, with a fixed stimulus-onset asynchrony of 1100 ms. Principal component analysis (a form of factor analysis) was used to quantify orthogonal ERP components.

Results: ERP components reflected the different sequential processing of each stimulus type in this paradigm, replicating previous results. Caffeine was associated with a reduction in reaction time and fewer omission errors. The major ERP effects of caffeine were apparent as a slightly enhanced Processing Negativity and larger P3b amplitudes to Go stimuli. There were few effects on components to NoGo stimuli.

Conclusions: The results confirm our previous findings that caffeine improves aspects of the differential processing related to response production and task performance, but may be interpreted as supporting the simple amplification of ERP component amplitudes predicted by the general arousal induced by caffeine.

Introduction

OUR PREVIOUS STUDIES OF CAFFEINE showed that it reliably increases skin conductance level (SCL), globally reduces electroencephalographic (EEG) power in the alpha band, and globally increases alpha frequency in adults^{1–3} and children.^{4,5} These changes are peripheral (SCL) and central (EEG) markers of a simple increase in arousal.⁶ This caffeine/arousal perspective provides the conceptual context for investigations of how caffeine affects stimulus processing, which we track using task-dependent event-related potentials (ERPs). ERPs are formed by averaging epochs of EEG data time-locked to particular events. The different stages of such processing, specific to the task-related requirements, are marked by different components in the ERP. We follow Picton et al.'s restatement⁷ of the Donchin et al. criteria⁸ identifying an ERP component as “a temporal pattern of activity in a particular region of the brain that relates in a specific way to how the brain processes information” (p. 141).⁷

Caffeine's stimulant effects primarily are mediated by adenosinergic antagonism, modulating a variety of neurotransmitter

systems^{9,10}; presynaptic adenosine receptors are widely distributed over almost all types of neurones.¹¹ Our laboratory has repeatedly confirmed simple amplifying effects of arousal in relation to physiological responses in skin conductance.^{12–19} In relation to ERP components, a general arousal effect of caffeine would analogously be expected to act broadly as a stimulant, amplifying all aspects of brain function, and affect all ERP components similarly. In particular, arousal would globally amplify a component's amplitude, without changing its scalp distribution, or topography. Focal changes in topography have been taken to imply activation of different brain areas, contrary to the arousal expectation.

In this context, the existing literature regarding caffeine effects on ERPs is limited and has not concentrated on global/focal differences. Caffeine has been reported generally to increase the amplitude of a range of ERP components derived from a variety of paradigms, sometimes with reductions in reaction time (RT), but results are somewhat variable. For example, Lorist et al.²⁰ found that some ERP components derived in a choice reaction paradigm were enhanced by caffeine, but some effects were restricted to

fatigued participants. In a visual selective attention task, Lorist et al.²¹ reported that caffeine decreased RT, with no effect on errors, and produced focal increases in some components. Kenemans and Lorist⁹ found that caffeine decreased RT, with little effect on component amplitudes in a selective attention task. Ruijter et al.²² examined ERPs in focal areas in a sustained attention task, and found that caffeine increased an early frontal and a later posterior positive component, without RT effects. In a similar task, Ruijter et al.²³ found that the major effect of caffeine was on RT, an early frontal positive component, and a later negative component. There are also suggestions that caffeine increases some positive component amplitudes in the oddball task, with no effect on their latency or RT.²⁴

It is apparent that, in the generality of this inconsistent literature, there has been little exploration of topographic effects, with analyses often limited to a few sites. The topographic distribution of caffeine effects on ERPs has not been resolved. In the arousal context, the question of whether caffeine produces a simple amplification of ERP component sources, or triggers the activity of different sources, had not been resolved adequately. Hence, the aim of our previous study²⁵ was to explore caffeine effects in the context of our reported arousal effects. We tested whether ERP components were globally amplified by caffeine in the equiprobable Go/NoGo task. In a typical Go/NoGo task, the Go stimuli require a physical button-press response, and the NoGo stimuli should not be responded to. We use an equiprobable auditory Go/NoGo task, in which the random presentation of equal numbers of two different tones provides equal numbers of EEG responses for averaging. This allows us to efficiently form ERPs that chart the two different processing chains involved in identifying each stimulus presented and responding to it appropriately by executing (Go) or withholding (NoGo) the button-press response, all within several hundred milliseconds. We found the major effects of caffeine were on Go stimuli, with an RT reduction and focal increases in three positive components (identified as P1, P2, and P3b), but no effects on the negative N1 or N2 components. There were no effects on any components in response to NoGo stimuli. These changes in component topography with caffeine implied differential effects in different areas of the brain, arguing against the simple arousal model.

The present study revisits this question, with the advantage of a new methodological tool that has given us further insight into the processing stages involved in this paradigm. Principal components analysis (PCA) is a variant of factor analysis that allows summary and partitioning of the ERP variance into components that have been shown to be closely related to the traditional ERP components described above. Essentially, rather than manually identifying positive and negative peaks in the ERP waveforms within certain latency ranges, and measuring these at all electrode sites to estimate the components present, PCA can be used to find orthogonal data-driven components mathematically. Measuring peak amplitudes from the ERPs, as was done in Barry et al.,²⁵ depends on the expertise of the experimenter; with PCA, the identification and labeling of the components obtained requires similar expertise, but the tedium and subjectivity of repetitive peak-picking is avoided. Using PCA on adult data from this paradigm, Barry and De Blasio²⁶ proposed a sequential schema relating the components in the Go and

NoGo ERPs to the processing stages involved. Briefly, a negative component around 100 ms (N1) marks the beginning of Go/NoGo stimulus differentiation. Completion of the identification stage was marked by differences in another negativity around 200 ms (N2), followed by different processing chains. For NoGo, this nonresponse was associated with a frontocentral positivity around 300 ms (P3a), followed by a large late positivity (LP) around 650 ms indicating cortical deactivation at the cessation of processing. For Go stimuli, the directed surge in activation leading to the RT response was associated with a posterior P3b and a frontal-negative/posterior-positive slow wave (SW). We subsequently confirmed this schema in adults and children.²⁷ Here, in an adult population, we examine effects on this schema of a single oral dose of caffeine in a randomized double-blind placebo-controlled repeated-measures cross-over design.

Materials and Methods

Participants

Twenty-four students (13 females) from the undergraduate psychology pool at the University of Wollongong volunteered in exchange for course credit. Their age ranged from 17 to 36 years ($M=21.4$ years, $SD=4.8$ years), and 20 participants were right handed. Participants were required to be nonsmokers and moderate caffeine users (two to four cups of coffee or equivalent daily). Those with a history of seizures, psychiatric illness, or severe head injury, and those currently taking psychoactive drugs were excluded. Participants were asked to abstain from caffeine for at least 4 hours before the first session, and to follow the same pattern before the second session. Participation was voluntary, and informed consent was obtained according to a protocol approved by the local ethics committee.

Physiological recording

EEG was recorded from 19 sites, using an electrode cap with tin electrodes, referenced to linked ears and grounded by a cap electrode between Fz and Fpz. Vertical and horizontal electro-oculograms (EOGs) were recorded from electrodes above and below the left eye, and beyond the outer canthi of the eyes. EEG gain was $\times 20,000$, EOG gain $\times 5,000$, and the data from 0.15 to 30 Hz were sampled by a 16 bit A/D system (AMLAB II) at 512 Hz and recorded for offline analysis. The continuous EEG was subjected to an EOG correction procedure²⁸ and then low-pass filtered below 25 Hz (zero-phase shift, 24 dB/Octave).

Task and procedure

The task was a simple equiprobable auditory Go/NoGo task. Participants received two blocks (practice and experimental), each containing 150 tones of 50 ms duration, with 5 ms rise/fall times, presented via headphones at 60 dB SPL with a fixed stimulus-onset asynchrony of 1,100 ms. Half the tones were 1,000 Hz, and half were 1,500 Hz, presented in random order. Participants were asked to button-press with their dominant hand to one of the tones, with the target frequency, which differed within subject between sessions, balanced between subjects. When participants arrived at the laboratory, they read an information sheet, signed a consent form, and completed a screening questionnaire.

They were then asked to swallow (with water) one of two identical gelatine capsules, containing either 250 mg caffeine or placebo, in a predetermined randomized order. Participants were then fitted with the physiological measurement equipment, and seated in an air-conditioned sound-attenuated recording booth. Both participants and experimenters were blind to the contents of the capsules. Recording began approximately 30 minutes after capsule ingestion, when plasma levels are estimated to be maximal.²⁹ Participants returned for a second test approximately 1 week later ($M=8.3$ days, $SD=4.7$ days), when the same procedure was followed and the alternate capsule was administered. The Go/NoGo task began 35.0 minutes ($SD=5.9$ minutes) after capsule ingestion for caffeine, and 34.5 minutes ($SD=6.4$ minutes) after capsule ingestion for placebo; these did not differ between the conditions.

ERP quantification

Waveforms were epoched offline using Neuroscan software (Compumedics v4.5.1). Single trials containing muscular or other artifact exceeding $\pm 75 \mu V$ at any scalp site, or incorrect responses (commission errors to NoGo trials; omission errors or RTs > 600 ms to Go trials), were automatically detected and excluded from further analysis. ERPs were derived for a period from -100 to $+750$ ms relative to stimulus onset, and baselined relative to the 100 ms prestimulus period. These were averaged within each subject, for each drug condition (caffeine/placebo) and each stimulus (Go/NoGo), at each electrode site, forming four average ERPs at the 19 electrodes sites for each subject.

PCA was carried out in MATLAB[®] (The Mathworks, v8.0.0.783, R2012b) using the ERP PCA toolkit³⁰ (v2.23). The input data consisted of the average ERPs defined above, constituting 1,824 cases (2 stimuli $\times$ 2 drug conditions $\times$ 19 EEG electrode sites $\times$ 24 subjects), each case being an ERP containing 850 ms of data. For our data recorded at 512 Hz, 850 ms contains 436 data points, the variables for the PCA, leading to a case/variable ratio of ~ 4.2 . The data were subject to a temporal PCA using the covariance matrix with Kaiser normalization, followed by an unrestricted Varimax rotation (i.e., all 436 factors were Varimax rotated), following Kayser and Tenke.³¹ The waveform of each factor loading can be rescaled to microvolts by multiplying each point by the standard deviation of the corresponding raw data point. For each subject and condition, the product of the factor score at a particular site with the rescaled factor loading gives the component waveform at that site, and their peak amplitudes yield the topographic distribution of the component. Starting with those that accounted for the most variance in the data, components were identified as ERPs based on their latency, topography, consistency with the raw ERP

waveform, similarity to published data, and known stimulus-specific properties.

Statistical analysis

Behavioral data were analyzed using paired *t*-tests. The peak amplitudes derived from the waveforms of the ERP components identified for both Go and NoGo stimuli were analyzed from nine core sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4), except for the Processing Negativity (PN), which is known to have a temporal distribution.^{26,27,32} When analyzing the PN, we simply replaced the F3/4, C3/4, P3/4 electrode pairs with the corresponding F7/8, T7/8, P7/8 pairs of the outer electrode rows. An initial analysis of each component identified topography and stimulus effects for comparison with previous literature. This used a three-way repeated-measures MANOVA,^{33,34} with factors of Stimulus (Go vs. NoGo), and topographic factors of sagittal (frontal [F3, Fz, F4], central [C3, Cz, C4], parietal [P3, Pz, P4]) and lateral (left [F3, C3, P3], midline [Fz, Cz, Pz], right [F4, C4, P4]) dimensions. Planned contrasts for the sagittal factor compared frontal (F) versus parietal (P), and central (C) versus the mean of frontal and parietal regions (F/P). Contrasts for the lateral factor compared left (L) versus right (R) hemispheres, and midline (M) versus the mean of the hemispheres (L/R). These orthogonal contrasts, and their interactions, allow complete specification of the focal distribution across these sites. Subsequently, the effects of caffeine were examined for each component in response to Go and NoGo stimuli separately. These three-way repeated-measures MANOVAs were similar in structure, but replaced the stimulus factor with condition (caffeine vs. placebo). As the contrasts were all planned and did not exceed the degrees of freedom for effect, no Bonferroni-type adjustment of alpha levels was required.³⁵ All *t*-tests had $df=23$, and all component contrasts reported had $df=(1, 23)$. Effects approaching significance (i.e., $0.10 > p > 0.05$) are reported to promote future research, although only those reaching significance are discussed.

Results

Behavioral data

The mean and standard deviation data for the behavioral outcomes in the placebo and caffeine conditions are presented in Table 1. In Go trials, caffeine significantly reduced the number of omission errors ($t=2.24$, $p=0.017$, one-tailed), and somewhat reduced the number of delayed reaction time response errors ($t=1.61$, $p=0.060$, one-tailed); these contributed to a significant reduction in the overall number of Go errors ($t=2.84$, $p=0.005$, one-tailed). Although there was some indication of a reduction in the number of NoGo commission

TABLE 1. BEHAVIORAL OUTCOMES, M (SD)

Condition	Go error %			NoGo error %	
	Omissions	RT > 600 ms	Total	Commissions	Go response RT (ms)
Placebo	2.1 (3.0)	2.6 (3.3)	4.7 (4.9)	1.4 (2.4)	323.6 (59.8)
Caffeine	0.7 (0.9)	1.6 (2.4)	2.3 (2.5)	0.8 (1.1)	307.0 (42.9)

RT, reaction time.

errors with caffeine, this failed to approach significance ($t=1.16$, $p=0.129$, one-tailed). Mean Go RT was significantly reduced with caffeine ($t=2.01$, $p=0.028$, one-tailed).

ERPs

On average, there were 69.3 ($SD=4.7$) accepted trials in each mean ERP, with no ERP including fewer than 56 trials, and these did not differ with stimulus type or condition. The ERPs for Go and NoGo stimuli at midline frontal (Fz), central (Cz), and parietal (Pz) sites are shown in

Figure 1A. There was a small global P1 around 40 ms, followed by a clear frontocentral N1 around 100 ms. This was followed by marked P3s around 250–350 ms, with apparent topographic differences between the NoGo (frontocentral) and Go (parietal) responses. Between N1 and P3, P2 and N2 could be readily identified in individual responses. P3 was followed by a classic frontal-negative/parietal-positive SW and LP. Caffeine appeared to have substantial effects on the early part of the ERPs to Go stimuli (see Fig. 1B), but mainly later effects on NoGo responses (see Fig. 1C).

FIG. 1. The left column shows event-related potentials (ERPs) at the midline sites for Go versus NoGo (A), and caffeine effects on responses to Go (B) and NoGo stimuli (C). The right column shows the corresponding reconstituted ERPs from the sum of the first six principal components analysis (PCA)-derived components for Go versus NoGo (D), and caffeine effects on responses to Go (E) and NoGo stimuli (F).

PCA outcomes

After rotation, the first six factors in variance order accounted for 83.1% of the total variance in the data set. The sums of these components are displayed in Figure 1D–F, adjacent to the corresponding raw ERPs. It can be seen that the PCA has separated out components that display effects in their sums similar to those in the raw ERPs (compare right panels with left). Correlations between the raw (Fig. 1A) and reconstituted (Fig. 1D) mean waveforms at each of the midline sites ranged between 0.91 and 0.99, and were all highly significant ($p < 0.0001$), confirming a good approximation to the raw data.

Figure 2A displays topographic headmaps of peak component amplitudes for the six identified components, averaged across conditions and stimulus. These are plotted above the component factor number, percent variance accounted for, and peak latency. The component labels are based on their sequence, latency, similarity to the raw ERP components, and the previous PCA outcomes found in this paradigm. The factor loadings, which represent the distribution of each component over time, are also illustrated. These have been rescaled to microvolts by multiplying the unitless factor

loadings by the standard deviation in the mean ERP, at each time point. Note that the first two components are subcomponents of the N1³²; the frontocentral “Component 1” around 100 ms, and the subsequent PN. These were followed, in temporal order, by a small positive P2, a later large P3, the classic SW, and LP. For each component, Figure 2B displays the separate Go/NoGo peak amplitude topographies (corresponding to the ERPs in Fig. 1D), and Figure 2C and D display the separate caffeine and placebo peak amplitude topographies for the Go, and NoGo responses respectively (corresponding to the ERPs in Fig. 1E and F respectively).

Response topographies and Go versus NoGo effects

Across all conditions, Figure 2A shows that N1 was a frontocentral negativity ($F > P$: $F = 15.64$, $p = 0.001$, $\eta_p^2 = 0.40$, and $C > F/P$: $F = 52.78$, $p < 0.001$, $\eta_p^2 = 0.70$), and this component was dominant in the midline ($M > L/R$: $F = 20.31$, $p < 0.001$, $\eta_p^2 = 0.47$). The frontal enhancement was increased somewhat in the right hemisphere ($F > P \times L < R$: $F = 2.95$, $p = 0.099$, $\eta_p^2 = 0.11$), and was significantly larger in the hemispheres than midline ($F > P \times M < L/R$: $F = 22.71$, $p < 0.001$, $\eta_p^2 = 0.50$).

FIG. 2. (A) The topographic headmaps for each component across conditions and stimuli, in temporal order from the left. Below these is shown the rank order of the factor, the explained variance, and the component peak latency. This information is displayed above the scaled factor loadings. (B) The component topographies for Go versus NoGo, averaged across condition. These are shown separated by condition for Go responses in (C) and NoGo responses in (D). A color version of this figure can be obtained from the first author.

TABLE 2. TOPOGRAPHY AND STIMULUS EFFECTS FOR THE IDENTIFIED ERP COMPONENTS, IN LATENCY ORDER

<i>Effect</i>	<i>NI-I</i>			<i>PN*</i>			<i>P2</i>			<i>P3</i>			<i>SW</i>			<i>LP</i>		
	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
<u>F < P</u>	15.64	0.001	0.40	20.38	< 0.001	0.47				26.70	< 0.001	0.54	35.82	< 0.001	0.61	3.34	0.081	09.13
<u>C > F/P</u>	52.78	< 0.001	0.70	37.03	< 0.001	0.62	23.47	< 0.001	0.51	34.16	< 0.001	0.60	12.47	0.002	0.35	13.91	0.001	0.38
<u>L < R</u>				5.46	0.029	0.19												
<u>M < L/R</u>	20.31	< 0.001	0.47				6.59	0.017	0.22	36.13	< 0.001	0.61	12.57	0.002	0.35	10.84	0.003	0.32
<u>F > P × L < R</u>	2.95	0.099	0.11							5.40	0.029	0.19	19.70	< 0.001	0.46			
<u>F > P × M < L/R</u>	22.71	< 0.001	0.50							9.48	0.005	0.29	20.34	< 0.001	0.47	16.55	< 0.001	0.42
<u>C > F/P × L > R</u>	5.71	0.025	0.20				5.08	0.034	0.18									
<u>C < F/P × M < L/R</u>				11.73	0.002	0.34				15.05	0.001	0.40	7.23	0.013	0.24	9.97	0.004	0.30
<u>Go > NoGo</u>				3.06	0.093	0.12							25.14	< 0.001	0.52	15.34	0.001	0.40
<u>Go > NoGo × F < P</u>				22.02	< 0.001	0.49	20.63	< 0.001	0.47	41.17	< 0.001	0.64	34.97	< 0.001	0.60	14.27	0.001	0.38
<u>Go > NoGo × C < F/P</u>										18.23	< 0.001	0.44	7.27	0.013	0.24			
<u>Go > NoGo × L < R</u>							5.11	0.034	0.18	11.76	0.002	0.34	5.87	0.024	0.20			
<u>Go > NoGo × M < L/R</u>				16.82	< 0.001	0.42	22.49	< 0.001	0.49	21.01	< 0.001	0.48						
<u>Go > NoGo × F > P × L > R</u>							7.15	0.014	0.24				23.26	< 0.001	0.50			
<u>Go > NoGo × F < P × M > L/R</u>				28.95	< 0.001	0.56	30.44	< 0.001	0.57	24.23	< 0.001	0.51	57.16	< 0.001	0.71			
<u>Go > NoGo × C > F/P × L < R</u>	6.45	0.018	0.22	4.12	0.054	0.15	4.12	0.054	0.15	9.75	0.005	0.30				4.89	0.037	0.18
<u>Go > NoGo × C > F/P × M > L/R</u>				21.75	< 0.001	0.49	18.50	< 0.001	0.45	20.40	< 0.001	0.47				6.90	0.015	0.23

Note: Paired effect and component statistic underlining indicates a reversal of that effect. Reversals of any two directional indicators within an effect indicate a statistically equivalent interpretation. Probability is bolded for significant effects.

*Analysis included temporal sites (see Methods).

ERP, event-related potential; C, central; F, frontal; L, left, M, midline; P, parietal; R, right; PN, processing negativity; SW, slow wave; LP, late positivity.

The central enhancement was larger on the left ($C > F/P \times L > R$: $F = 5.71$, $p = 0.025$, $\eta_p^2 = 0.20$). Although it is not evident in Figure 2B, Go N1 was enhanced in the right central region ($Go > NoGo \times C > F/P \times L < R$: $F = 6.45$, $p = 0.018$, $\eta_p^2 = 0.22$). All MANOVA statistical effects (including these) are listed in Tables 2 and 3, and to save space, will be omitted from the text below. Note that some statistical entries in Table 2 (and Table 3) have pairs of greater than ($>$) and/or less than ($<$) signs reversed from the text descriptions. This capitalizes on the logical equivalence of such pair reversals, allowing us to tabulate component differences efficiently in each effect.

Over conditions, PN was frontocentrally negative, larger in the right than left hemisphere, and largest centrally in the hemispheres (i.e., in temporal regions); see Figure 2A. Figure 2B shows how the response to NoGo was more frontal, while the response to Go was more hemispheric. NoGo PN was somewhat larger across the assessed sites. However, the defining PN temporal topography,³² a central enhancement in the hemispheres, was larger for Go, and a frontal enhancement in the midline was larger for NoGo.

Figure 2A shows that P2 was a central positivity, generally larger in the hemispheres. The central positivity was larger in the left than the right hemisphere. Figure 2B shows that the Go P2 was more positive frontally and in the midline, and less positive in the left hemisphere than NoGo P2. The frontal Go increase was greater in the midline, and in the left hemisphere. NoGo P2 showed some indication of a central elevation in the left hemisphere, and a significant central elevation in the hemispheres.

P3 is apparent in Figure 2A as a strong centroparietal positivity, dominant in the midline. These effects interacted, with both the parietal and central effects larger in the midline. The parietal effect was also larger in the left compared with right hemisphere. Go P3 ($P3b^{36}$) was enhanced parietally; NoGo P3 ($P3a^{36}$) was enhanced centrally, in the midline, and on the left (see Figure 2B). The parietal Go increase was larger in the midline, and the central NoGo increase was greater in the midline and the left hemisphere.

SW failed to show the expected frontal negativity, but was centroparietally positive, with a much-reduced frontal positivity apparent in Figure 2A. The SW was larger in the hemispheres than midline. The parietal enhancement was larger in the midline and left hemisphere, and the central enhancement was smaller in the midline. The Go SW was marked by elevated centroparietal and left hemisphere positivity (see Fig. 2B). The parietal Go elevation was larger in the midline and left hemisphere, and contributed to the overall enhanced Go SW.

The LP was a central positivity with some indication of parietal positivity and frontal negativity (see Fig. 2A). It was larger in the hemispheres, and the parietal positivity/frontal negativity difference was larger in the midline. At all analyzed sites the NoGo LP was positive and Go LP was negative, resulting in a significant main effect of stimulus (see Fig. 2B). Also, there were relative NoGo elevations parietally, and centrally in the hemispheres, particularly in the left hemisphere.

Caffeine effects on Go ERP components

There were no caffeine effects in the Go N1. Figure 2C indicates that Go PN was slightly reduced in the midline/enhanced in the hemispheres by caffeine; this effect approached signif-

TABLE 3. EFFECTS OF CAFFEINE ON THE IDENTIFIED ERP COMPONENTS, IN LATENCY ORDER

Effects	N1-I		PN*		P2		P3		SW		LP	
	F	η_p^2	F	η_p^2	F	η_p^2	F	η_p^2	F	η_p^2	F	η_p^2
Go												
Caffeine > Placebo					3.27	0.084						
Caffeine > Placebo $\times$ M > L/R							6.50	0.018				
Caffeine > Placebo $\times$ F > P $\times$ L > R					5.46	0.028						
Caffeine > Placebo $\times$ F > P $\times$ M < L/R							2.97	0.098				
Caffeine > Placebo $\times$ C > F/P $\times$ M > L/R			3.90	0.060								
NoGo												
Caffeine > Placebo $\times$ F > P $\times$ L < R	3.65	0.069					3.55	<u>0.072</u>	5.01	0.035		
Caffeine > Placebo $\times$ C > F/P $\times$ M < L/R												0.18

Note: Paired effect and component statistic underlining indicates a reversal of that effect. Reversals of any two directional indicators within an effect indicate a statistically equivalent interpretation. Probabilities for effects reaching significance are bolded.
* Analysis included temporal sites (see Methods).

inance in the frontal region, slightly enhancing its defining topography. This and other component effects of caffeine are shown in Table 3. Caffeine significantly reduced Go P2 in the frontal right region, and led to an overall smaller positivity, an effect that approached significance. In the Go P3, caffeine produced a significant midline enhancement, and a vertex enhancement approached significance (see Fig. 2C). There were no effects of caffeine on the Go SW or Go LP.

Caffeine effects on NoGo ERP components

Caffeine produced some increase in NoGo N1 in the right frontal region, but there was no caffeine effect on the NoGo PN or NoGo P2. Figure 2D shows that caffeine produced some relative reduction in the left parietal region in NoGo P3. The NoGo SW showed a significant central enhancement in the hemispheres with caffeine (see Fig. 2D), but the NoGo LP was not affected.

Discussion

In our recent work, we began to chart the sequential processing involved in accurately identifying the Go versus NoGo stimuli in this paradigm, and responding with a speeded button-press response to the former while refraining from responding to the latter.^{26,27} We reliably obtained a series of robust PCA-derived ERP components over the first 650 ms, in temporal order: N1, PN, P2, N2, P3, SW, and LP. N1, reflecting sensory processing, showed the beginning of discrimination, with the Go N1 slightly enhanced. The Go PN appeared more representative of the expected PN topography (strongly hemispheric) than the NoGo PN, which appeared similar to the N1—in essence, a distinctive PN was more strongly elicited by the Go stimulus, marking the beginning of attentional focus on the Go stimulus. P2 was larger to NoGo than Go, compatible with withdrawal of attention from the NoGo stimulus, indicating (with the subsequent N2) that stimulus discrimination was complete. Subsequently, the processing streams were quite distinct. For the NoGo stimulus, basic stimulus processing winds down to completion, and is shown in a frontocentral P3a, a minimal SW, and a LP marking widespread reduced activation of the cortex. For the Go stimulus, the energetic button-press response is associated with a large centroparietal P3b, a substantial SW, and a small LP (cortical deactivation delayed by the response requirement).

The same series of components was obtained here, except for the N2, a marginal component that carried only some 2% of the variance in our previous studies.^{26,27} As shown in Figure 2A, these components resemble those described above and reported in our previous studies^{26,27} in terms of temporal order, latency, and topography. The Go/NoGo effects found here also generally replicate those found previously. Although it is not evident in the statistics of Table 2 or the headmaps of Figure 2B, across the nine analyzed sites, N1 showed a slight enhancement to Go, suggesting an early sign of sensory discrimination. PN showed its defining central hemispheric topography to Go, signaling the attentional shift to that stimulus, whereas the NoGo response appeared as a remnant N1, suggesting little PN elicited by NoGo. P2 showed a central enhancement marking disengagement of attention from the NoGo stimulus, and the beginning of the chain of NoGo ERP markers – the central P3a, minimal SW, and dominant LP. In contrast, the attention switch

marked by the Go PN is followed by a large centroparietal P3b associated with the button-press, and a large SW in the Go processing stream. We examined caffeine effects in these markers of Go and NoGo processing separately.

Behaviorally, caffeine produced a significant reduction in RT and a significant reduction in the number of omission errors. The effect on RT indicates increased efficiency in the processing of Go stimuli, as does the reduction in omission errors. These behavioral results framework the caffeine effects in the Go ERP components indicated in Figure 2C and Table 3. Go PN, a subcomponent of the N1 defined in terms of its hemispheric negativity,³² was somewhat enhanced by caffeine in the frontal region, perhaps marking an enhanced attentional shift to the Go stimulus and possibly contributing to the enhanced behavioral outcomes. Unexpectedly, caffeine was associated with a reduced Go P2, suggesting that attention is being withdrawn from the stimulus. Given the pattern of caffeine effects across the PN (increased frontal hemispheric negativity) and P2 (reduced frontal right positivity), it is possible that stimulus discrimination is being completed more efficiently, and the reduction in Go P2 could therefore mark an earlier shift toward the P3b. The Go P3b was larger with caffeine, indicating that the final active button-press response stage of processing was also enhanced by caffeine. These data provide a coherent picture of the sequential activation of this processing stream by caffeine, culminating in faster RTs and fewer errors related to the Go stimuli.

In contrast, caffeine had no significant effect on the number of commission errors—that is, although there was some beneficial impact on the erroneous responding to NoGo stimuli, this failed to approach significance. Caffeine was associated with a slight enhancement in NoGo N1, which may suggest some increased early sensory processing, and with a slight reduction in P3a. The only effect on the NoGo ERP components to reach statistical significance was a central enhancement in the hemispheres that occurred in the SW (Fig. 2C). The effects in the P3a and SW may reflect a faster progression of processing stages, contributing to an earlier onset of the LP marking the end of stimulus processing, but this interpretation is purely speculative. Overall, caffeine had little apparent effect on any aspect of NoGo performance in this study.

These results largely replicate our previous ERP/caffeine study, which reported that caffeine reduced RT but had no effect on omission or commission errors.²⁵ In that study, we found enhancements in P1 (not assessed here), P2, and P3b components to Go stimuli (SW and LP were not assessed), but no effects in any NoGo components. Some of the differences in findings between this and our previous study probably reflect peak picking versus PCA extraction of component estimates. For example, perhaps the Go P2 peak in our previous caffeine study was not measured compatibly with the nonmidline Go P2 PCA component derived here, contributing to the different Go/NoGo and caffeine effects. Unfortunately, such detailed comparisons of peak versus PCA-derived components are beyond the scope of the present paper. We identified the previous caffeine enhancements as focal in nature, as there were no main effects but many topographic component changes.²⁵ This led us to conclude that our results did not support the simple arousal interpretation of caffeine effects—we sought global component changes and found instead focal changes, which we interpreted then in terms of specific processing-related localized brain activations.

In the context of our sequential processing model of responding in this paradigm, the present results, although broadly similar to results in our previous caffeine study, allow a very different interpretation. Consider Figure 2B as an outline of the different components being evoked by the sequential processing of the two stimulus types, and consider them on an all-or-none basis. N1 is very similar to both, as differentiation is just beginning at this sensory processing stage. PN, with its distinctive central negativity in the hemispheres, is apparent to Go but not NoGo. P2, here with a central hemispheric positivity, is apparent to NoGo and marks the withdrawal of attention; the positivity in this component is more frontal to Go, and interpretable as our central hemispheric enhancement not being present to Go. Two different P3 components follow: a centroparietal P3b to Go and a central P3a to NoGo. The Go P3b is followed by a SW; P3a is not, but is instead followed by a LP marking the end of processing.

An arousal perspective would require that these different components be amplified by caffeine. For Go components, this appears to be so for PN and P3b as evident in Figure 2C. For NoGo components (Fig. 2D), it appears to be so for P2 and the speculative early start for LP suggested by the NoGo SW. This interpretation is also compatible with the behavioral effects obtained here. Given that we have repeatedly found effects in the electrodermal skin conductance response and EEG alpha band that support the arousal interpretation of caffeine effects,^{2–5} this view of the ERP component findings deserves further consideration and exploration in future research.

Conclusions

In a simple equiprobable Go/NoGo task, sequential processing and behavioral measures in the Go condition showed sensitivity to, and enhancement with, caffeine. Caffeine-enhanced Go processing was reflected by increased PN and P3b responses, a reduction in omission errors, and improved reaction times. Although the topographic nature of these enhancements appears to oppose a simple (i.e., global) arousal amplification model of caffeine, the regional modulations reflected the prominent topography of these components, suggesting amplification of the component reflected in the known topography. Caffeine had less of an effect on NoGo sequential processing, but there is some evidence to suggest more efficient processing also in this stream, possibly resulting in an earlier completion/resolution of this processing stream. This arousal interpretation of the ERP component changes should be tested in other paradigms.

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Author Disclosure Statement

No competing financial interests exist.

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