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Spectral Signatures of the Effects of Caffeine and Occipitally Applied Transcranial Magnetic Stimulation in a Task-Free Experimental Setup

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Spectral activity of the brain strongly depends on the subject's arousal state. To study the dynamics of state-dependent activity in response to occipitally applied brain stimulation free from task-related confounds, we used a combination of transcranial magnetic stimulation (TMS), electroencephalography (EEG), and caffeine administration in a double-blind experimental setup with eight male subjects. Caffeine increased pre–TMS baseline gamma-band power compared with placebo control in both low-gamma (30–50 Hz) and high-gamma (50–80 Hz) bands. Surprisingly, TMS led to a decreased relative power of the poststimulation low-gamma-band activity under caffeine as compared with TMS in a placebo condition. In addition, caffeine administration was associated with a reduction of TMS-evoked alpha power of about 400 ms after TMS. When we analyzed the TMS-related raw power without baseline normalization, the gamma-band activity in both frequency bands was stronger for the caffeine conditions. These results show that caffeine increases the gamma power in human EEG recordings. Furthermore, TMS-related spectral perturbations are brain-state dependent and lead to different spectral signatures under different physiological conditions.

Introduction

Psychophysiological states considerably influence information processing in the conscious and unconscious brain.[1–8] For example, caffeine is known to affect perception, attention, and psychomotor performance.[5,9,10] However, state-dependent neural dynamics are difficult to study with typical psychophysiological methods, as the tasks and task-related stimuli interact with physiological states in a manner that is difficult to control. One can overcome this problem by combining the manipulation of states in a task-free manner with the artificial perturbations of neural dynamics. Experiments using transcranial magnetic stimulation (TMS) simultaneously with electroencephalography (EEG) recording and in combination with controlled general brain states serve as an example of this strategy.[6,11–14]

In the majority of cases, the EEG studies of state-dependent processes in response to perturbation by TMS have focused on the effects of sleep/wake states and anesthetic interventions.[6,11,12,15] This is in contrast to a normal arousal state (involving brain processes in their up-states) and a state of decreased arousal (involving brain processes in their down-states). The oppositely directed manipulation from normal wakefulness in its resting arousal state to the increased arousal state has been rarely studied in this context.

Recently, Murd *et al.*[13] combined occipitally applied, neuronavigated TMS, EEG, and caffeine treatment to compare the task-free effects of TMS-evoked perturbations in a higher arousal state (caffeine) with the effects in a control state (placebo). They found that the amplitude of the frontally and parietally recorded event-related potential (ERP/N1) and slow negative potential increased under caffeine, but the latencies of TMS-evoked ERP components did not decrease. However, the effects of TMS on oscillatory activity under caffeine influence remained unexplored. In the present article, we ask how spectral EEG responses to occipitally applied TMS depend on caffeine versus placebo treatment.

With regard to this question, it is well known that the brain in the higher aroused state tends to produce relatively more higher-frequency oscillations in the gamma range (e.g., 30–100 Hz) and less low-frequency oscillations in the alpha range (8–14 Hz).[2,16,17] Moreover, it has been previously shown that caffeine decreases the EEG power in the alpha band[1] and it increases the gamma power in the hippocampal slices.[18] Therefore, we expected that compared with the placebo condition, the pre–TMS baseline gamma-band power

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is stronger, and the alpha-band power is decreased under caffeine. However, the main motivation behind the current analysis was the following question: How do the TMS-evoked responses interact with the ongoing baseline activity? This allows us to study the dynamical interactions of the caffeine-aroused brain state with the perturbation caused by the TMS free from task- and stimulus-related confounds.

Materials and Methods

As we reanalyzed EEG data from a previous study,[13] all the methods pertaining to subjects, study design, TMS, and EEG recordings correspond to the Methods part of that study.[13] Here, we only repeat the most important facts, while a thorough description can be acquired from our previous publication.[13]

Subjects

Eight subjects (men, aged 23–30) participated in the TMS-EEG experiments. All subjects were nonsmoking men who were not using any medication. We avoided using heavy coffee drinkers. Three subjects reported that they were not coffee drinkers at all; five reported that they consumed 1–2 small cups per day maximum. We believed the reports of our subjects on their habits, on abstaining, and on the typical frequency of coffee consumption. None of the subjects reported any noticeable effects of pre-experimental abstinence.

Design

Each subject participated in two sessions that were carried out with at least 3 days between them. The subjects were instructed not to drink or eat anything containing caffeine during the time starting 3 days before the first session until the end of the second session. Both sessions were carried out at the same time of day, and the TMS pulses were delivered by the same person. Both the sessions had 2 phases that consisted of 12 blocks each. The first phase of both the sessions contained six blocks of stimulation trials without the capsule. This allowed us to measure the baseline level of EEG to be later subtracted from the EEG data of main interest. Therefore, we controlled that there were no other differences between the caffeine and the placebo conditions due to different measuring days or durations and the succession of experimental blocks. After six blocks, there was a longer break. At the beginning of this break, the subject received a capsule [either placebo (200 mg) or caffeine (200 mg)]. The capsules were identical in their appearance. In addition, the double-blind study format was used, so that neither the subject nor the person delivering TMS pulses knew which capsule was administered to the subject. Since caffeine takes about 20 minutes to reach its noticeable stimulating effect, the time after the administration of the capsule was taken to ensure that the second phase with another 12 blocks of stimulation started 20 minutes after the delivery of the capsule. The subject's environment and activity were standardized for the placebo and caffeine conditions. After the capsule, they continued receiving stimulation in the no-capsule regimen; for the next 10 minutes, they sat in the subjects' chair and had a quiet time for rest. During the second session, the subject was administered the other capsule. The capsule's order was counterbalanced across the subjects.

Transcranial magnetic stimulation

To ensure the high precision of magnetic stimulation, we employed an magnetic resonance imaging (MRI)-assisted navigated brain stimulation system (Nexstim Ltd.). One target location in V1 was placed over the calcarine fissure in the right hemisphere, about 2 cm laterally from the inion; the other target location was placed in a mirror-symmetric location in the left hemisphere.

Stimulation parameters

The TMS-system (Nexstim Ltd.) with a figure-of-eight coil was used for stimulation. Single pulses with a duration less than 1 ms were applied. Stimulation intensity was 30% of the maximum output (0.7 T in cortex) of the stimulator and corresponded to a maximum estimated mean electric field of 31 V/m (SD 7 V/m). The chosen pulse intensity guaranteed that the subjects did not experience phosphenes. The TMS was delivered with an inter-stimulus interval varying randomly between about 2 and 3 seconds.

EEG recordings

A Nexstim eXimia EEG-system with 60 carbon electrodes cap (Nexstim Ltd.) was used. The impedance at all electrodes was kept below 10 KΩ. The EEG signals were referenced to an additional reference electrode placed on the forehead and at a sampling rate of 1450 Hz. All signals were amplified with a gain of 2000 and with a bandpass filter of 0.1–350 Hz. The vertical electro-oculogram was recorded.

EEG preprocessing

All EEG data were analyzed with EEGLAB[19] running under Matlab (Mathworks, Inc.). Data were filtered (2–90 Hz bandpass) and segmented around TMS-stimulation (−600 to +800 ms). For spectral analysis, it is important to obtain clean signals, so we disregarded the channels with strong muscle or other artifacts. As such, clean channels were different from subject to subject; so, we included in the analysis only the channels that were clean in all of the subjects and could be grouped into meaningful regions of interest (ROIs). From these channels, we obtained two ROIs: frontal (electrodes AF1, AFz, AF2, Fz, and Fpz) and parietal (electrodes CP3, CPz, CP4, P1, Pz, and P2). Since we expected no differences due to the stimulation site, we pooled the data from left and right stimulation. Due to this approach, we had around 230 trials (mean: 233, S.D: 6.5) from each subject in each condition, which allows us to have the required sensitivity in the spectral analysis.

EEG analysis

After the preprocessing, event-related spectral perturbations (ERSPs) were computed for each subject in each condition and for each electrode. This requires the calculation of the power spectrum over a sliding latency window and then averaging this power spectrum across the trials. The color of each data point in the image of spectral perturbation indicates the power relative to baseline (in dB). In order to achieve good time and frequency resolution all over the frequency range, we used a complex Morlet wavelet transform with the number of wavelet cycles increasing with the frequency

(3 cycles at 8 Hz to 12 cycles at 80 Hz). This method allows obtaining a better frequency resolution than by applying a constant cycle length.[19] The time-varying power was calculated in the frequency range from 8 to 80 Hz with 37 linear 2-Hz wide wavelet steps. The baseline was −600 to −100 ms relative to the TMS-impulse. In order to analyze the power changes across the time and frequencies, the mean baseline log-power spectrum was subtracted from each spectral estimate, which led to the baseline normalized ERSP. The time-frequency transformed data were averaged for the frontal and parietal ROIs.

The experimental conditions were caffeine and placebo administration. Since caffeine and placebo conditions had to be recorded on different days, we always subtracted for each condition the time-frequency transformed activity measured in the phase without the pill (phase 1) from that with the pill (phase 2) (see Fig. 2 for illustration). This subtraction ensured that we ruled out any potential unspecific effects related to the different measurement days.

The statistical analysis was performed on the baseline (pre-TMS) time and on the post-TMS epoch. For the comparison of the baseline spectral activity, the mean power of the baseline (−600 to −100) was extracted for the frequency bands 8–14 Hz (alpha), 15–30 Hz (beta), 30–50 Hz (low gamma), and 50–80 Hz (high gamma). Repeated-measures analysis of variance (ANOVA) was run with the factors condition (caffeine and placebo), ROI (frontal, parietal), and frequency (alpha, beta, low gamma, and high gamma). Where necessary, *p*-values were Greenhouse–Geisser corrected for violations of sphericity.

For the post–TMS epoch, we analyzed the ERSP, which reflects the activity change relative to the corresponding baseline value. We analyzed the same frequencies as in the baseline (alpha, beta, low gamma, and high gamma). The time windows for the post–TMS ERSP-analysis were defined in the following way. We first averaged the ERSPs from the ROIs and from the second phases of both the conditions (caffeine and placebo). We then visualized this average activity and extracted the time windows from this plot by choosing vertical lines that separate the different activities most reasonably. Significantly, since this activity represents the mean activity of the conditions and ROIs, the selection of the time windows is orthogonal to our factors condition and ROI. From this method, we derived the time windows 50–150 ms, 150–400 ms, and 400–600 ms. For the statistical analysis, we averaged the ERSP values over these frequency and time windows. Finally, we conducted a 4-way repeated-measures ANOVA with the factors condition (caffeine and placebo), ROI (frontal, parietal), frequency (alpha, beta, low gamma, and high gamma), and time (50–150 ms, 150–400 ms, and 400–600 ms). Where necessary, *p*-values were Greenhouse–Geisser corrected for violations of sphericity.

Results

The pre–TMS baseline power values for the investigated frequencies are shown in Figure 1. One can see that in the caffeine condition, the higher frequencies are augmented, and the lower frequencies are less pronounced in both frontal and parietal electrodes. Correspondingly, three-way ANOVA with the factors condition, ROI, and frequency revealed a main effect of frequency [$F(3,21)=6.897$, $p=0.028$], but more importantly, there was a significant interaction between condition and frequency [$F(3,21)=10.427$, $p=0.008$]. Subsequent two-way ANOVAs with factors condition and ROI per frequency band confirmed that there was stronger pre–TMS baseline power in the caffeine condition for the low gamma [$F(1,7)=12.540$, $p=0.009$] and the high gamma [$F(1,7)=6.714$, $p=0.036$] bands. There was no effect of caffeine in the alpha frequency band ($p>0.1$). The three-way ANOVA also revealed an interaction between frequency and ROI [$F(3,21)=11.785$, $p=0.005$]. As can be seen in Figure 1, there was relatively more alpha frequency activity in the parietal electrodes. In addition, the two-way ANOVAs per frequency revealed the main effects of ROI: High frequency activity was stronger in the frontal ROI in both low [$F(1,7)=9.689$, $p=0.017$] and high [$F(1,7)=6.492$, $p=0.038$] gamma bands. Taken together, the analysis of the pre–TMS baseline power confirmed the hypothesis that there is more high-frequency (30–80 Hz) activity in the caffeine condition.

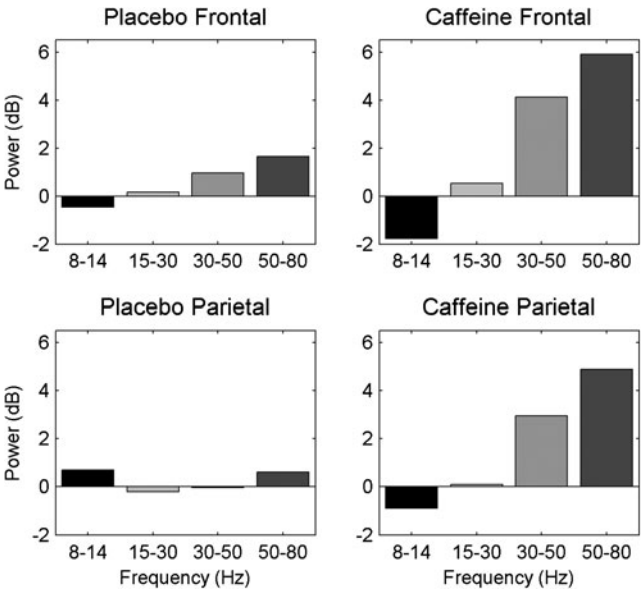

FIG. 1. Caffeine increases gamma power in the pre–TMS baseline interval. Pre–TMS baseline spectral power in the caffeine (right) and placebo (left) conditions obtained by frontal (upper row) and parietal (bottom row) electrodes. Note that the values always represent the result of the subtraction of the activity of the first phase from the activity of the second phase (where caffeine or placebo was administered). Caffeine increases gamma power in both the low (30–50 Hz) and high (50–80 Hz) gamma bands. TMS, transcranial magnetic stimulation.

The effects of caffeine on the TMS-related spectral perturbation are presented in Figure 2. The TMS-impulse creates an artifactual broadband activity, but more interestingly, it leads to several spectral components. Significantly, all the ERSP values in Figure 2 are in relation to the baseline; so, the values represent not the absolute power, but the power changes relative to the baseline.

The four-way ANOVA revealed a significant interaction between the condition, frequency, and ROI [$F(3,21)=3.323$, $p=0.039$]. In order to understand the possible statistical dependencies, we conducted 2-way ANOVAs with the factors condition and the ROI per time and frequency window. This

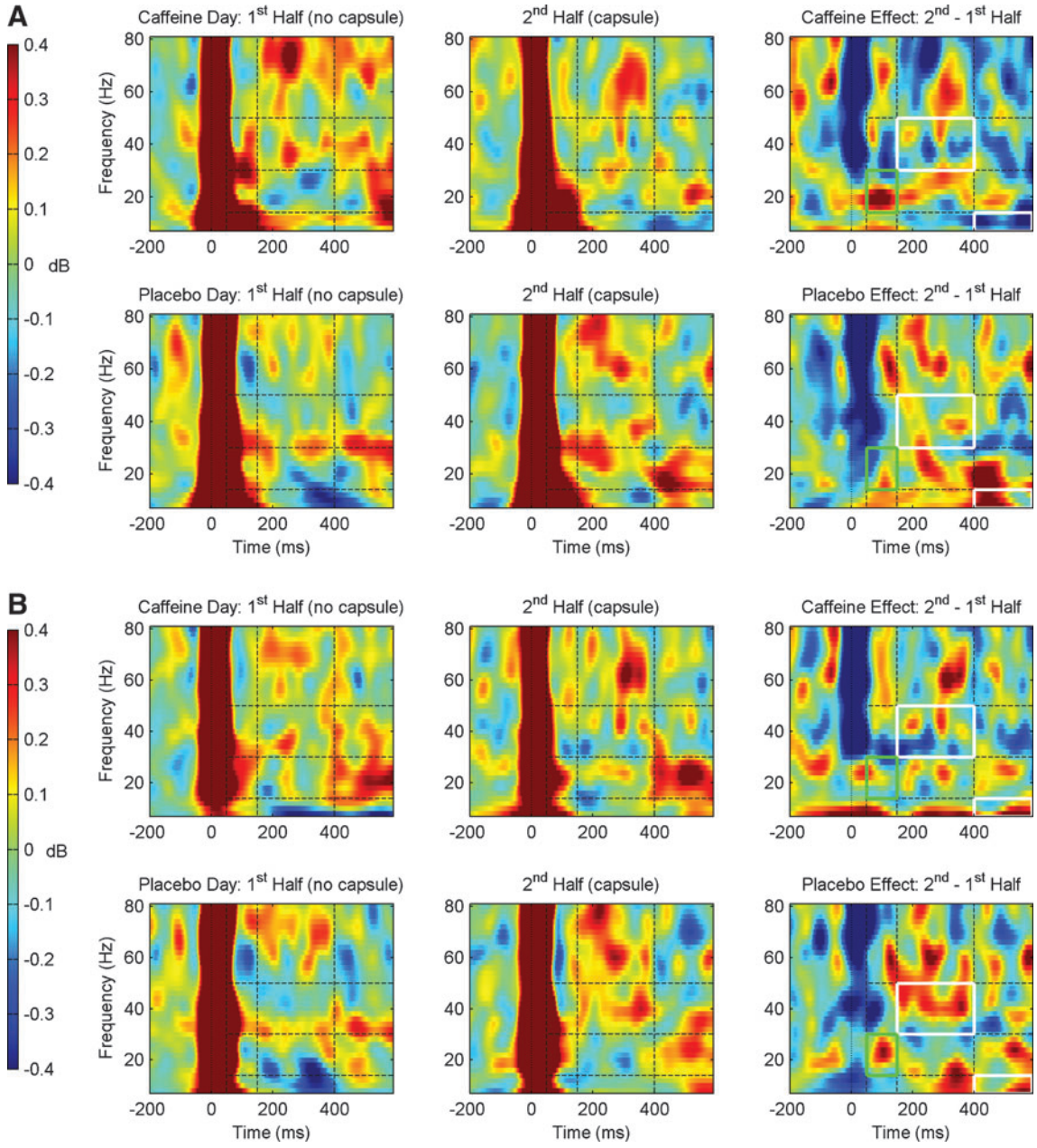

FIG. 2. TMS evokes a stronger relative power in the placebo condition in the alpha and low-gamma bands. TMS-related spectral perturbations from frontal electrodes **(A)** and parietal electrodes **(B)** obtained in the caffeine and placebo conditions before capsule (left column) and after capsule (central column). The effect of the condition (2nd minus 1st half of experiment) is depicted by the right column. The vertical stripe at zero marks the onset of the TMS. The remaining vertical and horizontal stripes mark the time-frequency windows of analysis. A significant interaction between the ROI and condition is marked by the green dotted line, and the significant main effects of the condition are marked by the white dotted lines. Significantly, all the spectral perturbation values are in relation to the baseline, so the values represent not the absolute power, but the power relative to the baseline. It is evident that the TMS evokes a stronger relative power in the placebo condition in the alpha (8–14 Hz) and the low-gamma (30–50 Hz) bands in the time windows 400–600 ms and 150–400 ms, respectively. ROI, region of interest.

provided several interesting results. First, in the beta band and at the earliest time window (50–150 ms), we observed a significant interaction between condition and ROI [$F(1,7) = 9.428$, $p = 0.018$]. Although caffeine did not produce a beta-range ERSP that would be different from placebo in either of the ROIs, the beta ERSP was in the caffeine condition stronger frontally but weaker parietally than in the placebo condition. Second, TMS evoked a stronger alpha-band ERSP in the placebo condition than in the caffeine condition at the last time window, 400–600 ms [$F(1,7) = 8.473$, $p = 0.023$]. Third, and maybe most interestingly, TMS led to a significantly weaker high-frequency ERSP in the lower-gamma band in the caffeine condition at the middle time window, 150–400 ms post-TMS [$F(1,7) = 7.419$, $p = 0.030$]. This means that there is

relatively more power evoked by the TMS in the alpha and low-gamma frequency ranges during the placebo as compared with the caffeine condition. The fact that these effects are temporally specific (e.g., 150–400 ms post-TMS for low gamma) shows that they are not (artifactual) the effects of different baseline values for caffeine and placebo conditions (For the low-gamma frequency range, the comparison between the caffeine and placebo conditions in the other time windows yields $p > 0.4$ for the 50–150 ms interval and $p > 0.7$ for the 400–600 ms epoch). To summarize, the TMS-related spectral perturbation analysis showed that there is a stronger additional TMS-evoked power in the alpha and low-gamma bands in the placebo condition.

Since the spectral perturbation measure captures the power changes relative to the baseline, these results leave open how the absolute power—power without any baseline normalization—behaves. Namely, we showed that there is a stronger pre–TMS power in the low-gamma band for the caffeine condition but that there is a stronger relative power in the post–TMS epoch at the same frequency range for the placebo condition. However, the relative power change gives us no direct information regarding the question in which condition there is more absolute power in the post–TMS epoch. To investigate this question, we re-ran the analysis on the post–TMS time-frequency data without normalizing over the baseline (Fig. 3). From this analysis, it was clear that the absolute power in the post–TMS epoch behaved similarly to the pre–TMS results: In the low- and high-gamma range, there was a stronger absolute power in the caffeine condition over all time windows (the weakest

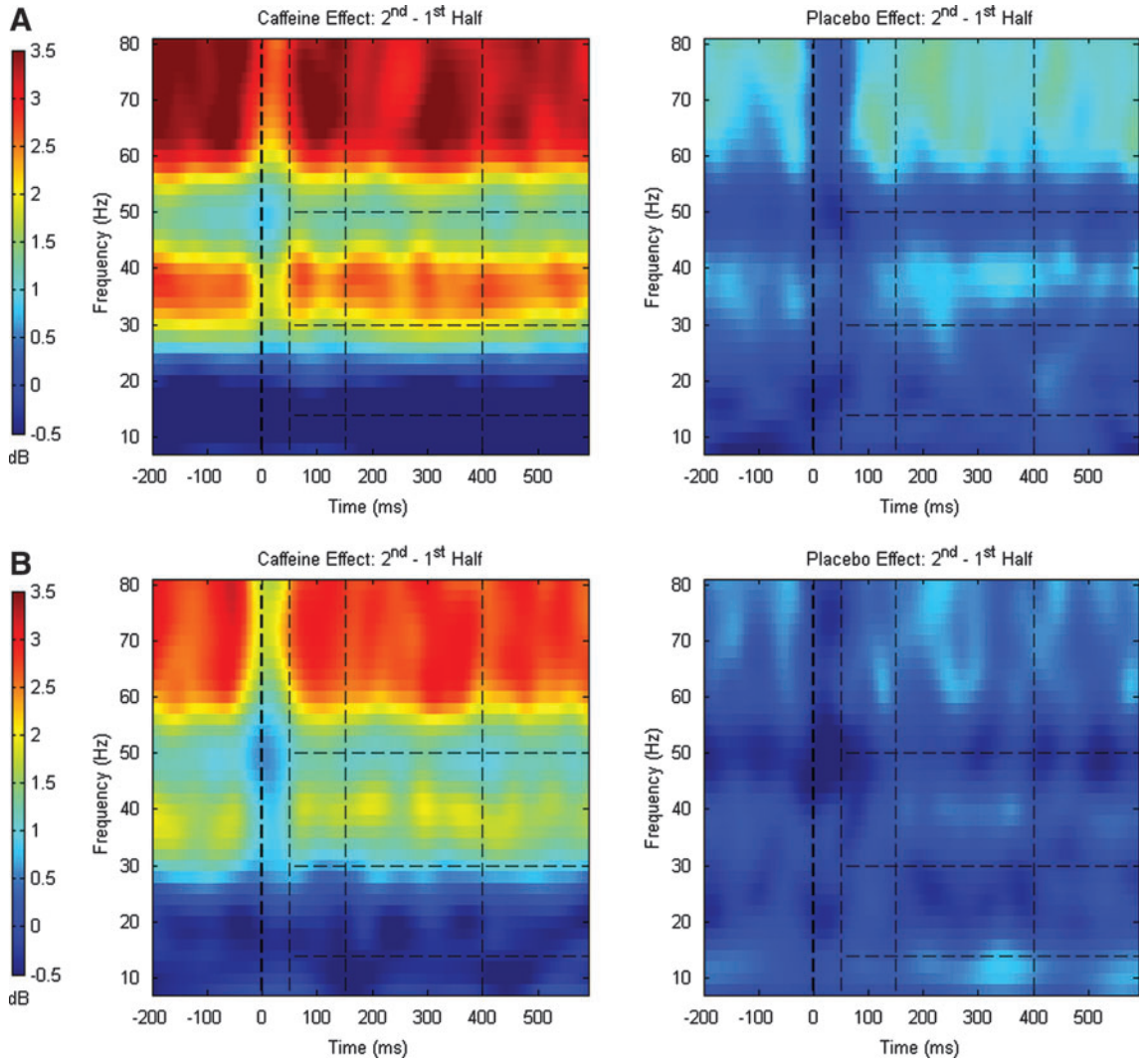

FIG. 3. Absolute power remains stronger in the caffeine condition in the low- and high-gamma bands. Absolute power around the TMS at frontal electrodes **(A)** and parietal electrodes **(B)** obtained in the caffeine (left column) and placebo (right column) conditions. The plots illustrate the effect of the condition (2nd minus 1st half of the experiment). The vertical stripe at zero marks the onset of the TMS. The remaining vertical and horizontal stripes mark the time-frequency windows of analysis. It is evident that caffeine increases absolute power in both low- and high-gamma frequency bands (Please note that the band around 50 Hz with a seemingly smaller enhancement than elsewhere between 30 and 80 Hz appears to be due to the small increase in electrode impedance over the course of the experiment, which leads to a small increase in the 50 Hz noise.).

effect was in the high-gamma range in the latest time window, where $p = 0.053$, $p < 0.05$ in all other cases, Fig. 3). Specifically, for the low-gamma range in the time window 150–400 ms, there was a stronger absolute power for the caffeine condition than in the placebo condition [$F(1,7) = 11.081$, $p = 0.013$]. In addition, similar to the pre–TMS results, in this time window, there was more power in the low-gamma-band range for the frontal ROI [$F(1,7) = 7.950$, $p = 0.026$]. Taken together, this means that during the whole epoch, there is a stronger high-frequency band activity in the caffeine condition, but that relative to the pre–TMS baseline, TMS leads to less additional power in the caffeine condition in the low-gamma band around 150–400 ms after TMS.

We also re-ran the same analysis on the absolute power values for the alpha-band activity, where we had also observed a stronger relative power in the placebo condition, 400–600 ms after TMS. The analysis of absolute power did not yield significant differences between the caffeine and placebo conditions.

This analysis (and Fig. 3) also shows that TMS-related spectral perturbations have a rather small effect on top of the strong gamma-band increase due to caffeine modulation.

Discussion

Combining TMS, EEG, and modulated brain states provided us with interesting findings. When we studied the effects of caffeine on the pre–TMS baseline, we observed that in the pre–TMS baseline, there is a stronger low-gamma (30–50 Hz) and a high-gamma (50–80 Hz) band power in the caffeine condition as compared with the placebo condition. Moreover, when we analyzed the absolute power values in the post–TMS epoch without baseline normalization, it appeared that the power in these high-frequency bands is stronger in the caffeine condition throughout the stimulation period. Thus, caffeine generally increases the power in the gamma band, which is in accordance with the general notion that the activity of the gamma band is a signature of cortical activation.[16] Previously, caffeine was found to enhance gamma oscillations in the hippocampal slices of mice,[18] but our work is the first that shows such an effect in human EEG.

Previous research has also found that caffeine decreases the power in the alpha band.[1] Although we did not obtain such an effect for the pre–TMS time window, we do not think that this null result reflects a contradiction to the previous research. Namely, we only had data from 8 subjects, whereas the previous alpha-band effect was observed in a population of 18 subjects.[1] Our small sample size might also have prevented us from finding other potential spectral effects in the baseline and in the TMS-evoked power. In addition, it might be said that allowing only 20 minutes for caffeine to reach its effect is too short to bring about all the caffeine-related spectral effects. Finally, it could be said that the effect of caffeine on the alpha-band power is weaker and, therefore, harder to find experimentally than the effect of caffeine on high-frequency power.

Caffeine-related power increase in the gamma range observed in this study and a decrease in the alpha-band activity reported by others[1] are markers of aroused physiological states,[2,16,17] and, therefore, potentially constitute the neurophysiological basis of the generally known arousing effects of caffeine. However, care should be taken with this interpretation, as many of the effects previously considered to be arousing effects of caffeine might actually be attributed to caffeine withdrawal reversal.[20,21]

We also investigated the TMS-related spectral perturbations. The spectral perturbation measure reflects the change of the post–TMS power relative to the pre–TMS power in a given frequency range. Thus, this measure provides information regarding the power increases or decreases caused by TMS. As we compared the caffeine and placebo conditions, this measure reveals which TMS-related relative power changes are different between the caffeine and placebo conditions. We observed that in the placebo condition, the TMS-related spectral perturbation was stronger than in the caffeine condition for the low-gamma frequency in the time window 150–400 ms and for the alpha frequency in the time window 400–600 ms. When arousal was manipulated by caffeine[13] and NREM sleep[14] slow cortical potential negativity was found after about 400 ms post-TMS. The relative alpha suppression with caffeine compared with the relative alpha augmentation with placebo found here for these long delays allows us to speculate that evoked slow cortical potential negativity might be accompanied by relatively suppressed long-latency alpha activity. This conjecture should be tested directly in future experiments.

The TMS-related spectral perturbations have not been studied extensively earlier. In one elegant study, Rosanova *et al.*[22] showed that TMS induced so-called natural-frequency oscillations when applied to different cortical areas having a dominant frequency characteristic for each particular cortical area independently from where TMS was applied. Related to our work, they showed that TMS evoked global and reliable alpha oscillations 20–200 ms after TMS when TMS was applied to area 19, which is close to our stimulation target. We failed to find any alpha-band effects in that time frame in our data. However, the most likely explanation is that our TMS intensities were too low (mean over the subjects 31 V/m), as the authors[22] reported not to have observed any significant power modulations below TMS intensities of <40 V/m. On the other hand, since we, nevertheless, obtained significant results from the analysis of TMS-related spectral perturbations, we can conclude that interesting patterns of TMS-related power modulations could also exist at lower TMS intensities.

Perhaps the most puzzling result of our study is an unexpected relative decrease of the gamma-band power of the TMS-evoked perturbation with caffeine compared with the placebo condition. Caffeine is a well-known adenosine antagonist, and it has agonistic effects on acetylcholine-based potentiation processes. Muscarinic receptors play an important role in mediating the effects of adenosine agonists and antagonists. In a couple of studies where the functionality of muscarinic receptors has been experimentally manipulated, a strong association between the facilitation of visual functions and increased activity of this system has been demonstrated.[23–26]The effects include boosting gamma-band responses and supporting more effective feature binding.[24,26] Since in the present experiment, TMS was applied occipitally and, therefore, the spread of activity must have been originating from the visually specialized areas, one would have expected an augmenting of gamma responses under caffeine. We can provide three explanations for this apparent discrepancy. First, we measured the effects not from visual areas *per se*,

but from the more remote parietal and frontal locations, where processes may have behaved in a different way. Second, in our experiment, the task-free experimental design of the content-wise unspecific TMS-stimulation was used without natural visual stimuli (i.e., without features to be bound); in the aforementioned studies, natural visual stimuli were presented, and explicit tasks measuring effective encoding of the visual contents were used. If this difference were the reason behind the absence of a caffeine-supported gamma boost in our study, then we should conclude by saying that gamma-band responses are more characteristic to neural operations associated with the transmission and encoding of specific stimuli contents rather than to the content-free artificial perturbations. The fact that caffeine facilitates baseline gamma, but does not facilitate gamma in response to unspecific TMS perturbation, is consistent with this assumption. In future studies, to be carried out under otherwise identical conditions, the influence of caffeine on TMS effects versus natural visual stimulation effects should be compared. Third, it is possible that it is biophysically easier to increase the neural activity in the nonaroused state as compared with the state where caffeine has already increased the baseline activity (as evidenced by our other results).

While caffeine acts against an increase in the adenosine level, prolonged wakefulness fosters natural adenosine buildup. Therefore, sleep deprivation should lead to especially high adenosine levels. Consequently, sleep deprivation effects should be conspicuously opposite to the effects of caffeine and vice versa. This means that EEG recordings from sleep-deprived brains should show a picture opposite to the one recorded after caffeine administration, and caffeine should presumably decrease the typical signatures of sleepiness—depress slow oscillations and increase the power of higher-frequency oscillations. Precisely, these results were recently found, including an increase in the EEG spectral power in the low beta range.[27] Our results about pre–TMS baseline effects did not conform to this regularity, as we obtained no effect in the beta range. Two possible explanations can be put forward. First, the beta range used in the present study was broader (15–30 Hz). Second, our subjects were not sleep deprived. It would be interesting in future to explore whether the caffeine effects obtained in the present study would also be replicated with sleep-deprived subjects.

Conclusion

To conclude our work presented here, we point out the findings that could be used as departure points in subsequent research. (1) The artificial means that augment arousal levels of the brain (e.g., caffeine) can have different effects on the baseline levels of oscillatory brain processes and the TMS-induced perturbations of these processes. (2) TMS-induced, task-free perturbations of the oscillatory brain processes when combined with pharmacological manipulations of the arousal level may lead to unexpected power effects such as a relative decrease in the power of high-frequency bands. (3) TMS-related spectral perturbations are brain-state dependent and lead to different spectral signatures in different physiological states. (4) The spread of activation originating from the primary visual cortex may lead to different expressions of oscillatory activity depending on whether these processes are brought about by natural visual stimuli or by artificial, specific content-free perturbations.

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Author Disclosure Statement

The authors declare that no competing financial interests exist.

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