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Original Research

A Comparison of the Effects of Transcranial Direct Current Stimulation and Caffeine on Vigilance and Cognitive Performance During Extended Wakefulness

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ABSTRACT

Background: Sleep deprivation from extended duty hours is a common complaint for many occupations. Caffeine is one of the most common countermeasures used to combat fatigue. However, the benefits of caffeine decline over time and with chronic use.
Objective: Our objective was to evaluate the efficacy of anodal transcranial direct current stimulation (tDCS) applied to the pre-frontal cortex at 2 mA for 30 min to remediate the effects of sleep deprivation and to compare the behavioral effects of tDCS with those of caffeine.
Methods: Three groups of 10 participants each received either active tDCS with placebo gum, caffeine gum with sham tDCS, or sham tDCS with placebo gum during 30 h of extended wakefulness.
Results: Our results show that tDCS prevented a decrement in vigilance and led to better subjective ratings for fatigue, drowsiness, energy, and composite mood compared to caffeine and control in sleep-deprived individuals. Both the tDCS and caffeine produced similar improvements in latencies on a short-term memory task and faster reaction times in a psychomotor task when compared to the placebo group. Interestingly, changes in accuracy for the tDCS group were not correlated to changes in mood; whereas, there was a relationship for the caffeine and sham groups.
Conclusion: Our data suggest that tDCS could be a useful fatigue countermeasure and may be more beneficial than caffeine since boosts in performance and mood last several hours.

Introduction

Sleep deprivation from extended duty hours is a common complaint in many occupations. These extended periods of wakefulness can lead to serious decrements in mood and performance. For example, a study of sleep deprived medical residents reported higher scores in hostility, anger, and fatigue compared to their non-sleep deprived counterparts [1]. Furthermore, a review by Krueger [2] found that sleep deprivation repeatedly resulted in increased reaction times, decreased accuracy, decreased attention, and alterations in mood. Many studies also relate performance during extended wakefulness to being legally intoxicated. For instance, Williamson and Feyer [3] found that after 17 h of continued wakefulness participants had performance equivalent to an individual with a BAC of 0.05%, which is considered illegal to drive a car in most countries. Unfortunately, many occupations require shifts lasting even longer than this.

Clearly, fatigue is a detrimental problem for many occupations; however, it is unlikely that conditions in these environments will change to allow for more time off for rest. Therefore, it is necessary to investigate fatigue countermeasures that can enhance alertness. One common method used in the military and in other fields is caffeine. Due to its ease of access, it has become a commonplace and popular intervention to counter the effects of fatigue. Not only are caffeinated beverages readily available, but military rations also include caffeinated gum [4]. Caffeine has been found to improve performance during inadequate sleep and circadian variation [5,6]. For example, SEAL trainees who were given caffeine after 72 h of sleep deprivation significantly improved visual vigilance, choice reaction time, and self-reported fatigue [7]. However, the benefits from caffeine decline over time with chronic use [4] and the effects are relatively short-lived [6]. Also, while caffeine may increase the ability to stay awake, it does not necessarily aid in making good decisions [8], a skill that is critically important to military and most other occupations. It is also unclear whether or not caffeine has a

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positive or negative effect on mood. For example, one study found that small doses of caffeine (100, 200, or 300 mg) lead to an increase in depression and confusion [9], while others have found that doses of 100–300 mg are associated with improved mood and that only at higher doses (above 400 mg) does mood deteriorate [10–12]. Clearly, the research is conflicting and may be that the effects of caffeine are dependent on the individual. Therefore, it is necessary to investigate another form of fatigue countermeasure to enhance alertness and performance.

Although originally used to address neurological disorders such as Parkinson's disease, major depressive disorder, schizophrenia, stroke, dementia, chronic pain, etc., there has been a rapid expansion of research over the past decade showing a form of non-invasive brain stimulation, known as transcranial direct current stimulation (tDCS), is effective in enhancing human performance (see Refs. [13] and [14] for reviews). This technology uses a mild direct electrical current passed between electrodes on the scalp to modify neuronal membrane resting potential in a polarity dependent manner, elevating or lowering neuron excitability in a region [15,16]. For a detailed description of these technologies, design, physics, and principles of activation, see Wagner et al. [17]. Past studies have shown that tDCS applied to scalp locations over areas of the frontal cortex significantly improve cognitive abilities such as working memory [18] and visuomotor coordination [19]. Such abilities are often negatively affected by fatigue. Further, our own research has indicated that tDCS can improve individuals' cognitive skills, such as learning and attention. For example, tDCS successfully accelerated the learning of target detection in a simulated image analysis task. Participants who received brain stimulation improved performance accuracy 2.5 times over the sham and control group [20]. In another study, we found that tDCS could prolong human sustained attention by at least two-fold when compared to sham [21]. Luber et al. [22] has provided some initial evidence that these performance improvements produced from a similar technique – transcranial magnetic stimulation (TMS) – may extend to humans experiencing cognitive declines resulting from sustained wakefulness. Luber found that 5 Hz repeated or "rTMS" applied to the upper-middle occipital brain region significantly reduced the sleep-deprivation induced deficits in reaction times in subjects experiencing 48 h of sustained wakefulness. The authors also discovered that stimulation of this region aides in the engagement of the cortical networks engaged in normal wakefulness cycles. Because working memory and attention performance are sensitive to the effects of fatigue [23], this study sought to extend our results on cognitive enhancement by examining the effect of tDCS on cognitive performance following a period of extended wakefulness. We also compared these effects to those of caffeine to determine whether there are any benefits of tDCS in mitigation of fatigue that are above simple intake of caffeine. Based on the literature, we hypothesized that both tDCS and caffeine would induce a measureable and statistically significant improvement in task performance (i.e. a reduction of the performance decline) when compared to the sham/placebo group. Because tDCS has much greater specificity in terms of targeted brain region, we expected that it would produce greater performance improvements and fewer negative side effects than caffeine.

Methods and materials

Equipment

tDCS stimulator

The MagStim DC stimulator (Magstim Company Limited; Whitland, UK) was used to provide the tDCS stimulation. This battery-powered device was controlled with a microprocessor to ensure constant current at up to 5000 μA. For safety, multistage monitoring of the output current and electrode/tissue impedance was included. The device automatically shuts off if the impedance becomes greater than 50 kΩ to prevent electric shocks or burns. This device was investigational only (not FDA approved).

tDCS electrodes

In place of the standard wet sponge electrodes delivered with the Magstim unit, we used a custom set of silver/silver chloride electroencephalographic (EEG) electrodes as described in McKinley et al. [20]. These new electrodes were shown to be more stable over time, produce lower sensation levels, and produce fewer skin reactions when compared to standard sponge electrodes [24]. Both the anode and cathode consist of a separate array of 5 EEG electrodes as pictured in Fig. 1. Each electrode had an inner diameter of 1.6 cm yielding a contact area of 2.01 cm^2 for each electrode. Within the array, electrodes were spaced 0.75 cm from the center and 0.1 cm apart as measured from the outer edge of the electrode to the outer edge of the neighboring electrodes to either side. At 2 mA of supplied current, the average current density was 0.199 mA/cm^2 as calculated by current (2 mA) divided by area (10.05 cm^2).

tDCS paradigm

For the active anodal stimulation condition, tDCS was applied at 2 mA for 30 min. Sham tDCS was applied at the same intensity but for only 30 s. The anode was applied to scalp location F3 according to the 10-20 EEG electrode placement system while the cathode was placed over the contralateral (i.e. right) bicep. Electrodes were secured using medical bandages, and connectivity was ensured using highly conductive gel (SignaGel, Parker Laboratories, Fairfield, NJ).

Wrist activity monitor (WAM)

Two days prior to data collection, each participant wore a wrist activity monitor (WAM; Ambulatory Monitoring, Inc.). The WAM was a non-invasive small electronic device that can be worn on the wrist like a wristwatch. It recorded limb and body movements to determine when a participant was active and when they are asleep. It was used to ensure the participants received at least 7 h of sleep in each of the two days prior to data collection.

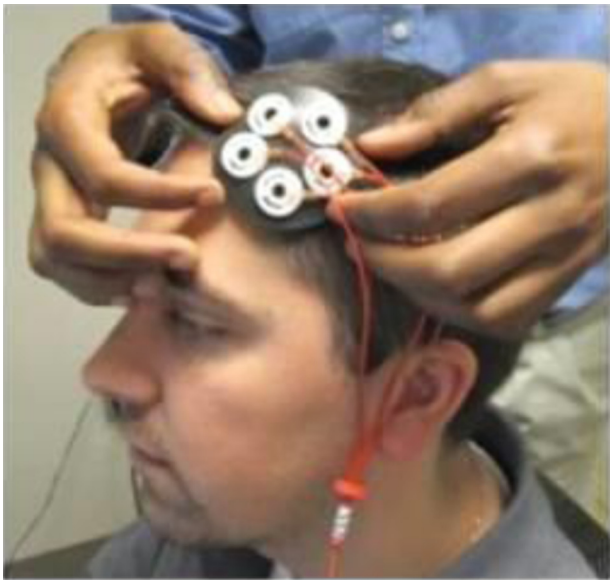

Figure 1. tDCS electrode array (anode only pictured). All five elements are standard silver–silver chloride EEG electrodes placed in a plastic cup which is then filled with a conductive gel.

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Caffeine

StayAlert® gum (MarketRight, Inc., Plano, IL) was the delivery mechanism used to administer 200 mg of caffeine to participants in the caffeine group. Every participant received 2 pieces of gum (placebo or active) and asked to actively chew the gum for 5 min.

Subjects

Thirty active-duty military participants from Wright–Patterson Air Force Base completed this study. There were 22 male and 8 female participants with an average age of 29.3 ± 3.4. Participants were compensated for their time but were disqualified if they met any of the exclusion criteria described in McKinley et al. [20]. Of the 36 individuals that enrolled, 6 were dismissed because they met one or more of the study exclusion criteria. The remaining 30 were randomly assigned into three groups of 10 individuals each: tDCS active stimulation/placebo caffeine, caffeine/sham tDCS, and sham tDCS/placebo caffeine.

Performance tasks

Participants were required to perform three performance tasks at regular intervals throughout the night. They were also required to complete subjective questionnaires throughout the night. The tasks are described below.

Psychomotor vigilance task (PVT)

Participants were required to perform the PVT during testing. The PVT -192 (Ambulatory Monitoring, Inc.; Ardsley, NY) was a 8″ x 4/5″ x 2/4″ handheld, battery-operated computerized test presentation and data capture system that records visual reaction times. The visual stimulus was presented on a small liquid crystal display (LCD) that presents a number counted up by milliseconds. The stimulus was presented for up to 1 min (60,000 ms), allowing the participant to respond by using a button press with the thumb. Once the participant presses the microswitch the device records the reaction time of the stimulus. The interstimulus interval varies randomly from 2 to 12 s. The task was 10 min in duration. The PVT requires sustained attention and discrete motor responses.

Delayed Matching-To-Sample working memory task

The Delayed Matching-To-Sample (DMS) task was a working memory task from the Cambridge Neuropsychological Assessment Battery (CANTAB). The CANTAB software package housed a complete battery of tasks that probe various basic cognitive functions. The DMS task was designed to probe perceptual matching, immediate and delayed visual memory. The participant was presented with a complex arbitrary pattern with four colored quadrants. Four patterns were then presented either simultaneously with the original pattern or following a delay of 0, 4, or 12 s, where the original pattern was obscured from view. The participant was required to then choose the one pattern that matched the original. Each participant completed two sets of 20 randomized trials per session that included five simultaneous, five 0-sec delay, five 4-s delay, and five 12-s delay presentations. Should the participant select the incorrect pattern, an "x" is displayed over the pattern. The participant would then continue making selections until the proper pattern was chosen. The task took approximately 20 min to complete.

Mackworth Clock Test

The Sustained Attention task was developed according to the description of the task used by Kilpaläinen et al. [25]. The task was an adopted version of the Mackworth clock test with parameters adopted from Teikari [27] and run on a standard desktop computer. The participant was presented a visual display with 16 hole-like black circles against a black background. The circles were arranged to form a clock-like round figure with a radius of 20 cm (7.9 in.). Each circle changed from black to red for 0.525 s in turn, with each cycle lasting 8.4 s.

The red light moved in a clockwise pattern by one step, which was considered the normal stimulus appearance. The light moving twice the usual distance (i.e., skipping a circle) was considered a critical signal and the participant was required to respond to this signal by pressing the spacebar as fast as possible on the keyboard with his or her preferred index finger.

The response was defined as a correct hit when it occurred less than 8 s after the target signal and a false alarm if the reaction occurred outside this time range (+0.1–8.0 s). Undetected targets were defined as misses. The task set contained 3442 stimuli, including 12 targets, and takes 30 min to complete. The event rate used is Mackworth's classic stimulus series, with the critical signal event rate varying from 45 s to 10 min.

Subjective questionnaires

Profile of Mood States (POMS)

The Profile of Mood States (POMS) was a 65-item questionnaire that measures mood using 6 categories: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. Participants rated their feelings about each item (example items: Tense, Vigor, Fatigue) on a scale of 1–5, with 1 being "not at all" and 5 being "extremely." The overall scores for each of the six categories were totaled, resulting in six factor scores. Each of the factor scores, except for the vigor-activity score, was added together; next the vigor-activity score was subtracted from this total to produce a general composite mood disturbance score. We also analyzed each factor score independently.

Visual Analog Scale (VAS)

Subjective affect was measured via the Visual Analog Scale (VAS) [27]. The VAS required that participants indicate the points on different lines that correspond to how he/she feels along the specified affect continuum at the time at which the test is taken. The adjectives included in the VAS are as follows: Alert/Able to Concentrate, Anxious, Energetic, Feel Confident, Irritable, Jittery/Nervous, Sleepy, and Talkative.

Side-effects questionnaire

A side-effects questionnaire was administered at the end of each session. Participants responded "none," "slight," "moderate," or "severe" to 33 items. Examples of the items included: "Light Headed," "Headache," Drowsiness," and "Drugged Feeling."

Procedures

Using a similar methodology described in Caldwell et al. [28], participants underwent 30 h of continuous wakefulness. Participants were randomly assigned to one of three experimental groups ($n = 10$ for each group). Group 1 received anodal tDCS at 2 mA for 30 min with placebo gum, group 2 received sham tDCS with placebo gum, which is 2 mA for 30 s, and group 3 received 200 mg of caffeine in chewing gum form with sham tDCS. After consenting to participate in the study, participants filled out the medical screening questionnaire. Two days prior to their scheduled experimental trial, participants were given an activity wrist monitor and instructed that their daily schedules should include a minimum of 7 h of sleep per night between the hours of 1100 and 0600. Also during this time participants received training on all three performance tasks to be utilized in the study. Training on the Sustained Attention task consisted of 2–5 min practice sessions followed by

the full 30 min task. The training for the Delayed Matching-to-Sample task included 2–5 min practice session followed by the full task, which takes about 20 min to complete. Training on the PVT consisted of participants completing the 10 min task after instructions on the task were given. Participants were trained to asymptote on all three performance tasks to guard against learning effects during experimental testing. Participants were also familiarized with the subjective questionnaires at this time.

On the day of their experimental trial, participants were required to awaken at 0600 and perform their daily activities as normal. They were instructed to not consume any caffeine or central nervous system (CNS)-altering medications/substances on the experimental test day. Each participant arrived at the test facility at 1730 h. Their WAM data were analyzed to ensure that proper sleep amounts were maintained. Starting at 1800 h, participants completed one session of the sustained attention task (30 min), one session of the Delayed Matching-To-Sample task (20 min), one session of the PVT task (10 min), and filled out the POMS-B, VAS, and a side-effects questionnaire. Participants were provided a short break of approximately 45 min afterward, where they could talk, watch TV, walk, read, or play video games. The second session began at 2000 h and was exactly the same as the first session. These procedures were repeated every 2 h. The final testing session took place at 1000 h on the second day (30 h continuous wakefulness). Prior to testing session #8 (occurring at 0400), participants received their assigned experimental treatment (i.e. tDCS-placebo gum, sham-placebo gum, or caffeine gum-sham tDCS). Participants receiving either real or sham stimulation were instrumented with tDCS electrodes beginning approximately 30 min prior to the stimulation session. Caffeine and placebo gum were given at 0300 because it takes approximately an hour to reach peak levels in the blood [29]. The remaining test sessions allowed evaluation of the effects of the treatments on performance and alertness. Following the last session, participants were debriefed and driven home by a rested friend/family member (approximately 1115 on day 2). The aforementioned timeline is displayed below in Table 1.

Analysis

Because treatment conditions started at the 0400 session, the session occurring at 0200 was the last time point at which all 30 participants were treated the same. One-way ANOVAs with group as the factor (levels sham, caffeine, and tDCS) were conducted for the data at 0200. *F*-tests did not reveal any significant differences among the groups for all test and variables, thus the 0200 session could be used as the baseline for future comparisons with validity the 3 groups at 0200 were similar. A mixed design ANOVA was used to compare groups for the change from 0200 with group a between factor and session a within factor (levels 0400, 0600, and 0800). Due to repeated evidence of performance improvements at 1000 caused by session due to circadian effects (e.g. Refs. [30–32]), the 1000 time point was excluded from the analysis. If a significant interaction was found between group and session, a one-way ANOVA was performed at each session separately with group as the factor. Post-hoc paired comparisons of group used two-tailed *t*-tests with pooled error from the ANOVA. All comparisons used a per-comparison level of 0.05.

Table 1
Testing Schedule; all three performance tasks (Mackworth Clock Test, Delayed Match-to-Sample, and PVT) were run in the same order for each testing session. Subjective questionnaires were completed after the tests. Participants were then given a break period.

Testing schedule	
1730	Participant Arrives
1800	1st Testing Session (Baseline Data)
1915	Break
2000	2nd Testing Session
2115	Break
2200	3rd Testing Session
2315	Break
2400	4th Testing Session
0115	Break
0200	5th Testing Session
0315	Break: Caffeine Administered
0400	6th Testing Session: tDCS Administered
0515	Break
0600	7th Testing Session
0715	Break
0800	8th Testing Session
0915	Break
1000	9th Testing Session
1115	Debriefing

Results

Mackworth Clock Test

A significant main effect of "group" for the Mackworth task metric of accuracy ($F(2,27) = 8.50$, $P < 0.001$) was found. The post-hoc *t*-tests showed that the tDCS group performed significantly better (averaging sessions 0400, 0600, and 0800) than both the sham ($t = -4.64$, $P < 0.001$) and caffeine groups ($t = -2.84$, $P = 0.006$). The sham and caffeine groups were not statistically significant.

Mackworth task metric of accuracy showed a significant group and session interaction ($F(2,54) = 3.70$, $P = 0.010$). The *t*-tests showed that the tDCS group performed significantly better than both the sham ($t = -4.50$, $P < 0.001$) and caffeine ($t = -2.35$, $P = 0.034$) groups at 0400 while the caffeine and sham groups were not statistically significant from one another ($t = -1.79$, $P = 0.057$); however, the Cohen's *d* was 0.84. A value above 0.8 indicates a possible large effect that might be detected with a larger *n*-size. At 0600 the comparisons between the groups did not achieve statistical significance. However, at 0800 the performance of the tDCS group was significantly better than the sham ($t = -4.79$, $P < 0.001$) and caffeine group ($t = -3.95$, $P < 0.001$). The effects are shown in Fig. 2, top left quadrant.

Delayed Matching-To-Sample

A significant main effect of "group" was also found for Latency in the Delayed Matching-To-Sample task ($F(2,27) = 3.71$, $P = 0.038$). The *t*-tests showed that the caffeine group performed significantly better than the sham group ($t = 2.28$, $P = 0.015$). While the test between the sham and tDCS groups did not reach statistical significance ($t = 1.85$, $P = 0.056$); Cohen's *d* was 0.87. The caffeine and tDCS groups were not significantly different, $P = 0.552$. Based on these test results and Fig. 2, it was concluded that the caffeine and tDCS groups were similar, although we cannot conclude that tDCS showed improvement over the sham group. The High Cohen's *d* in the comparison between the tDCS and sham groups suggests that we cannot rule out the effect. The effects are shown in Fig. 2, top right quadrant.

Psychomotor vigilance task

For the PVT, we found a significant main effect of "group" on mean reaction time ($F(2,27) = 7.03$, $P = 0.004$). The *t*-tests showed that the caffeine and tDCS group performed significantly better than the sham group ($t = 2.88$, $P = 0.002$ and $t = 2.77$, $P = 0.005$, respectively). There was not a significant difference between the

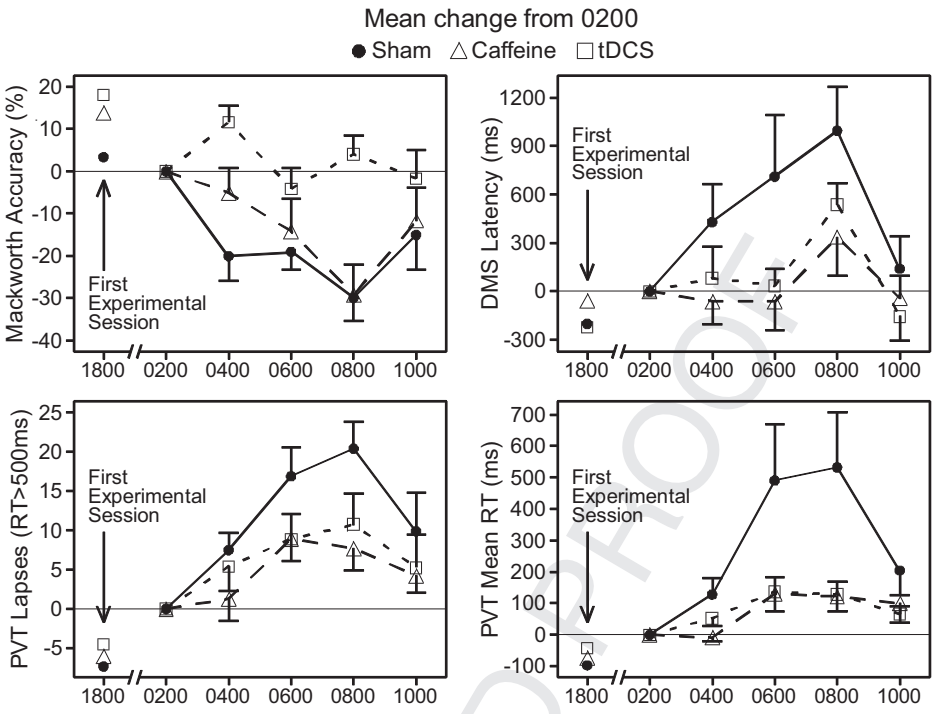

Figure 2. Performance tasks mean change from 0200 (baseline). The first data point is the initial session (1800) included for reference. Caffeine was given at 0315 (requires 1 h to be fully effective); tDCS was applied at 0400. Changes in performance were measured for each subject and averaged across groups ($n = 10$).

caffeine and tDCS group ($t = -0.34$, $P = 0.865$). Effect shown in Fig. 2, bottom right quadrant. While there was not main effect found for PVT Lapses ($F(2, 27) = 3.03$, $P = 0.065$); the Cohen's d between the sham and caffeine group was 1.22 and between the sham and tDCS group was 0.78. Therefore, we believe with a larger n-size there might have been an effect.

Subjective questionnaires

We found a significant main effect of "group" on drowsiness from the side-effects questionnaire ($F(2,27) = 4.90$, $P = 0.015$). The tDCS group was significantly less subjectively drowsy than the sham group ($t = 2.73$, $P = 0.004$). The comparison between the tDCS and caffeine group as well as the comparison between caffeine and sham group were not significant.

From the VAS questionnaire, "group" had a significant main effect on the ratings of Energetic ($F(2,27) = 3.39$, $P = 0.049$). The t-tests showed a significant difference between the sham and tDCS groups ($t = -2.35$, $P = 0.017$). There is not a significant difference between tDCS and caffeine or sham and caffeine.

We also created a composite score for the VAS by adding together Alert/Able to Concentrate, Energetic, Feel Confident, and Talkative together. We then subtracted Anxious, Irritable, Jittery/Nervous, and Sleepy from the previous total. A significant main effect of group ($F(2,27) = 3.04$, $P = 0.064$) was not quite found. Cohen's d for the difference between the sham and tDCS groups was 1.30 and ($t = -2.76$, $P = 0.020$). Therefore, we believe with a larger number of participants that this comparison may be significant although we cannot state this conclusively with the results reported herein.

Several significant interactions for the side effects questionnaire were found (Fig. 3). First, "Drowsiness" had a significant interaction with group and session ($F(2,54) = 3.46$, $P = 0.014$). The t-tests showed that at 0400 both the caffeine ($t = 3.22$, $P = 0.003$) and tDCS group ($t = 2.04$, $P = 0.025$) reported feeling significantly less drowsy than the sham group. The drowsiness ratings for the tDCS and caffeine group were not statistically different at 0400. At 0600, none of the groups' drowsiness ratings were significantly different from one another. At 0800, the tDCS group reported feeling less drowsy than the caffeine ($t = 2.59$, $P = 0.031$) and sham ($t = 2.94$, $P = 0.005$) groups. There was not a significant difference between the caffeine and sham group at this session. The second interaction from the side effects questionnaire was for "Fatigue" ($F(2,54) = 2.70$, $P = 0.040$). The t-tests showed no significant difference between the groups at 0400 but at 0600 the tDCS group had a perceived feeling of being less fatigued than both the caffeine ($t = 2.60$, $P = 0.013$) and sham ($t = 2.60$, $P = 0.013$) groups. There was not a significant difference between the sham and caffeine groups during this session. Again at 0800, the tDCS group's subjective ratings for fatigue were significantly lower than the ratings for the sham ($t = 2.46$, $P = 0.032$) and caffeine ($t = 2.40$, $P = 0.015$ groups). There was again no significant difference between the sham and caffeine group during this session. The final significant interaction in the side effects questionnaire was the Composite Score ($F(2,54) = 3.68$, $P = 0.010$). All thirty questions were added to get a composite number. The t-tests showed there was a significant difference at 0400 between the sham and caffeine group ($t = -1.95$, $P = 0.047$). At 0600 there was a significant difference between the tDCS and caffeine group ($t = -1.96$, $P = 0.042$). Finally, at 0800 there was also a significant difference in composite score between the tDCS and caffeine group ($t = -2.51$, $P = 0.013$). The comparison between the tDCS and sham group at 0800 was not significant ($t = -2.29$, $P = 0.061$); however, the effect size as measured by Cohen's d was 1.26.

Correlations

Partial correlations controlling for subject were determined between Accuracy on the Mackworth Clock Test and all other variables separately for each group using values at 0200, 0400, 0600, and 0800. Table 2 displays any partial correlation with $P \leq 0.01$.

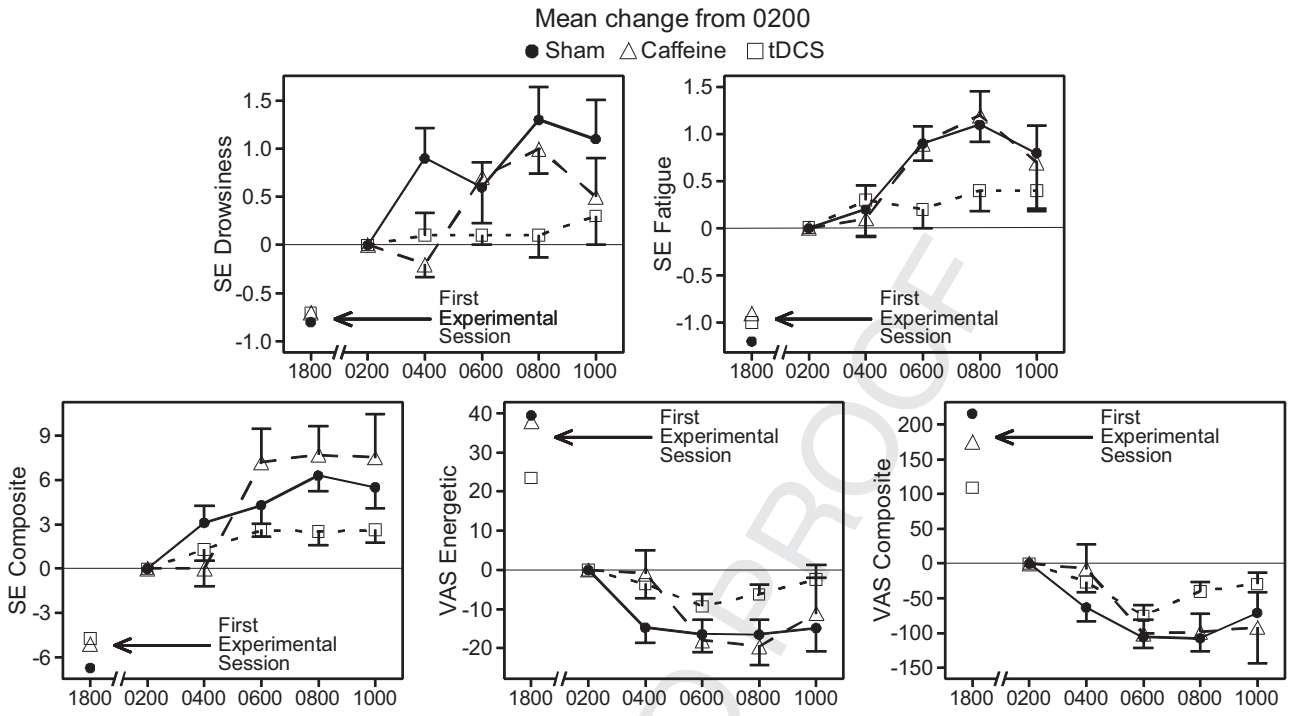

Figure 3. Subjective measures of fatigue mean change from 2 AM (baseline). The first data point is the initial session (1800) included for reference. Caffeine was given at 0315 (requires 1 h to be fully effective); tDCS was applied at 0400. Changes in performance were measured for each subject and averaged across groups ($n = 10$).

The tDCS group did not have a significant partial correlation with any subjective questionnaire variable. Significant correlations were found for both the sham and caffeine groups. Changes in Accuracy were related to subjective mood in all variables listed in the aforementioned table for the caffeine group. Most variables were significantly correlated in the sham group except for Difficulty Staying Awake and Drugged Feeling on the side effects questionnaire.

Discussion

This study examined the effects of anodal tDCS applied to the dorsolateral prefrontal cortex on attention, working memory, and psychomotor performance when in an induced state of fatigue caused by sleep deprivation. Because caffeine is the most common and readily available intervention used to counter the effects of fatigue, the effects of tDCS were also compared to the effects of caffeine to provide a more thorough basis for comparison. Our results suggest that tDCS not only has a larger transient effect on sustained attention (vigilance) than caffeine, but it also has lasting effects that remain at least 6 h when compared to less than 2 h of effect with caffeine. We have previously reported that 10 min of anodal tDCS applied to the dorsolateral prefrontal cortex remediates the "vigilance decrement" for at least 30 min [14] and therefore, we expected at least some transient effect in this experiment. However, we were uncertain of the duration of aftereffect. Previous studies found that the stimulation lasting as little as 9 or 13 min produced significant after effects in neural excitability for 30 and 90 min, respectively [33]. Our data suggest that 30 min of stimulation produces behavioral after effects lasting at least 6 h.

The improvement in vigilance performance with tDCS was accompanied by lower subjective ratings for fatigue and drowsiness. Thus, not only did the participants perform better, but they also felt less tired and sleepy than their counterparts given placebo or caffeine interventions. According to the responses from the VAS questionnaire, the tDCS group also reported feeling more energetic than those receiving sham/placebo. Furthermore, the composite score for the side effects questionnaires reflected better mood states in the tDCS group when compared to the responses from the caffeine group. This was further supported by the fact that the VAS composite score was approaching significance with a trend toward a difference between sham and tDCS. Additionally, our correlations imply that changes in accuracy on the Mackworth Clock Test for the tDCS group were not related to changes in subjective mood state, whereas, it was highly related for the sham and caffeine groups. This means that subjective mood plays a role in attention. In fact, several researchers have found that positive moods improved performance on attention-demanding tasks [34,35]. It was originally thought that tDCS caused alterations in mood because it is

Table 2
Using values at 0200, 0400, 0600, and 0800, Pearson partial correlations controlling for subject were determined between Mackworth Accuracy (%) and all other variables, separately for each group. Only statistically significant partial correlations were included in the table.

Variable	Sham		Caffeine		tDCS	
	r	*P*	*r*	*P*	*r*	*P*
SE-Difficulty Staying Awake	−0.36	0.0439	−0.66	0.0001	0.37	0.0410
SE-Drugged Feeling	0.04	0.8124	−0.64	0.0001	0.23	0.2171
SE-Fatigue	−0.41	0.0228	−0.54	0.0017	0.08	0.6682
SE-Drowsiness	−0.47	0.0071	−0.58	0.0006	−0.08	0.6801
SE-Trouble Staying Awake	−0.61	0.0003	−0.55	0.0012	0.06	0.7588
SE-Composite	−0.61	0.0003	−0.60	0.0004	0.02	0.9325
VAS-Alert/Able to Concentrate	0.72	0.0001	0.52	0.0029	0.14	0.4445
VAS-Sleepy	−0.60	0.0004	−0.39	0.0296	−0.03	0.8633
VAS-Energetic	0.55	0.0014	0.46	0.0098	−0.01	0.9413
VAS-Composite	0.57	0.0008	0.38	0.0333	0.07	0.7261
POMS-Fatigue/Inertia	−0.60	0.0004	−0.50	0.0046	0.11	0.5522
POMS-Confusion/Bewilderment	−0.46	0.0099	−0.53	0.0021	0.04	0.8633
POMS-Composite	−0.57	0.0008	−0.47	0.0078	0.08	0.6506

used to treat psychiatric diseases like major depressive disorder. However, recent research is showing that there is no difference in mood between sham and active stimulation for healthy volunteers [36,37]. We have found that tDCS does not alter mood but may also offset the negative effects on mood when introducing a stressor, such as fatigue.

When examining working memory performance reflected in the Delayed Matching-to-sample (DMS) task scores, the data suggest that both tDCS and caffeine interventions are effective at improving response times (i.e. reducing the increase in response time resulting from sleep loss), but not score/accuracy. While the differences in the means were not significant between groups at 0400 when the interventions were applied, large differences in response times were found 2 h later (the mean change from baseline for each group: Sham = 712 ms, caffeine = −64 ms, and tDCS = 35 ms). In fact, the overall mean change from baseline (averaging across the 0400, 0600, and 0800 sessions) in response time was at least 326% less for the tDCS and caffeine groups when compared to sham. Luber et al. [22], also found significant improvements in DMS response times but not accuracy when applying non-invasive brain stimulation to sleep deprived participants. In his study, Luber used a different method of stimulation known as transcranial magnetic stimulation (TMS) and the loci of stimulation were over regions of the parietal and occipital cortex rather than frontal. Only stimulation of the upper occipital site showed a significant improvement, although this difference was more modest than those reported here. While there are several notable differences in the stimulation paradigms, such as online tDCS vs. offline TMS, different performance tasks, etc., our paradigm appeared to produce a larger effect on working memory performance.

Declines in psychomotor performance that are commonly observed in sleep deprived individuals were also remediated by caffeine and tDCS. Despite its name, the PVT is not truly a test of vigilance. According to Parasuraman [38,39], to test vigilance, the task must have an infrequent target stimulus with a frequent non-target stimulus. Because the PVT has a frequently occurring target and is devoid of a non-target stimulus, it is simply a response time test of overall arousal. Because arousal is highly influenced by level of fatigue, the PVT is a sensitive test in sleep deprivation studies. Nevertheless, the results for the PVT are not directly comparable to the Mackworth Clock test. Caffeine and tDCS reduced reaction times when compared to sham, but there was no difference between the two interventions. There were no effects of either tDCS or caffeine on the other psychomotor performance metrics including the number of lapses and false starts. Thus it appears that both treatments merely improve the speed of the response without improving accuracy.

While there are fairly consistent findings that caffeine has beneficial effects on vigilance, attention, working memory, and subjective sleepiness ratings [5–7,9], the results reported herein suggest that tDCS produces similar results, although the effects on vigilance performance are far more profound. Although it is difficult to equate the dosages of tDCS and caffeine, we did observe a 2X larger transient effect and at least a 3X longer effect duration of a single dose of tDCS when compared to a single dose of caffeine (200 mg; twice the normal dosage in a cup of coffee). Extremely high (~600 mg) dosages of caffeine have been reported to produce longer durations of effect [40], but such dosages can trigger caffeine intoxication which is often accompanied by declines in mood, insomnia, nervousness, hallucinations, and intestinal complaints [10–12]. Additionally, in more traditional doses (100–300 mg) the effects are relatively short-lived as caffeine is quickly and completely removed from the brain (1–3 h depending on dosage) and caffeine becomes less effective at higher levels of fatigue [6]. Further, chronic use results in a reduction of its effectiveness [4]. Our data suggest that tDCS may be a promising alternative to counter the deleterious effects of fatigue given that it is more effective at improving vigilance, the effect lasts longer, and is associated with improvements in mood with minimal side effects. Importantly, it is currently not known whether chronic use of tDCS also leads to declines in effectiveness or if higher dosages would produce longer durations of effect. Of note, the effects seem to extend beyond the duration final data recording session in this experiment. Future experiments should continue recording measurements in performance more than 6 h after the tDCS is applied to examine the total duration of effectiveness.

While the mechanisms of action cannot be deduced from the data collected in this experiment, there are theories to explain the effects of tDCS and caffeine on performance in a fatigued (sleep deprived) state. Increasing levels of fatigue are associated with greater concentrations of adenosine in the brain, which is a byproduct of neuronal metabolism [41]. As adenosine builds up and binds to its receptors (A1, A2), neuronal activity declines through the blockage of excitatory neurotransmitters such as dopamine and glutamate [41,42]. This is accompanied by greater levels of subjective sleepiness. According to Davis et al. [42], caffeine delays or reduces the effects of fatigue at least in part by blocking adenosine A2 receptors. This in turn prevents adenosine from blocking dopamine which limits the reduction in brain activity normally observed with a buildup of adenosine. Caffeine also causes the release of epinephrine which results in high blood pressure, increases in heart rate, and blood flow. Similarly, tDCS has been found to also block adenosine A1 receptors in rabbits, suggesting the acute mechanisms may be similar [43]. However, the distinguishing feature of tDCS here is the difference in duration of effect.

The aftereffects of tDCS are believed to have different mechanisms than the acute effects [44]. After-effects of tDCS are believed to be caused by effects that mirror long term potentiation (LTP) and long term depression (LTD). Much of the existing evidence for this hypothesis points to changes in neural plasticity associated with synaptic modulation via NMDA receptors which are responsible for natural plastic changes [45]. Ruohonen and Karhu [46] postulate that the enduring aftereffects may also be due in part to excitation of glial cells. Although there is little objective evidence to support this theory, it would help explain how the behavioral effects endure long past the stimulation treatment. Electrical stimulation of glial cells could mediate slow changes in neurotransmitter release that could indirectly cause long-lasting (minutes or hours) increased neural activity often observed after tDCS [47]. Ohn et al. [48] found that the duration of aftereffects has a relationship with the duration of the stimulation itself. In fact, their data imply that longer durations of tDCS produce larger and much longer lasting behavioral effects. Given our tDCS treatment lasted 30 min, long lasting aftereffects should be expected and were observed.

The performance results from this experiment provide some insight into theoretical rationale of these observations, particularly with regard to vigilance. The decline in vigilance performance over time is often referred to as the “vigilance decrement” and is characterized by a linear reduction of the detection rate of critical targets over time [49]. While this well-known phenomenon is robust and repeatable (e.g. Refs. [50,51]), the precise causes are not fully understood. Currently, there are two primary competing theories that attempt to explain the source of the vigilance decrement: arousal theory and resource theory [52]. Arousal theory contends that the observed vigilance performance decrements are caused by a general decline in arousal. Colloquially, the operator loses interest, becomes bored, or otherwise loses focus on the task at hand due to its monotonous nature. Resource theory posits that the declines in

performance are caused by a depletion of cognitive resources (i.e. the supply of these "resources" cannot keep up with the demand). As the "resources" continue to decline, there a corresponding decrease in cognitive processing that ultimately leads to performance decrements [53]. In this context, "resources" are not objectively defined and could include metabolic resources such as glucose and oxygen or cognitive constructs. As noted by Nelson [52], this lack of specificity makes empirical testing of these "resources" difficult.

Nevertheless, the results of our previous work examining the effect of tDCS on vigilance seemed to support resource theory over arousal theory [21]. Specifically, we found an increase in target (i.e. signal) detection that was not accompanied by an increase in false alarms. Generally, interventions that increase arousal generate significant changes in response bias characterized by both an increase in target detection *and* an increase in false alarm rate, which were not observed in our previous experiment [52,21]. In the current experiment, we did observe performance improvements in the PVT when comparing the sham and tDCS groups. Given the PVT is a test of general arousal, this provides evidence that tDCS does have some effect on arousal. Importantly, these tDCS-induced improvements in the PVT were equivalent to those produced with caffeine, which is an arousal-amplifying substance [54]. Examining the vigilance performance results however, it seems the change in arousal had little effect on vigilance. While false alarm rates in the Mackworth Clock Test (i.e. vigilance task) increased as a function of time for all three groups, there were no differences *between* the groups. Hence, tDCS again did not produce a larger response bias relative to sham but did yield an improvement in target/signal detection, just as it did in our previous experiment. This evidence again supports resource theory as the lack of change in response bias indicates a causal factor beyond general arousal. Further, the effects of tDCS on vigilance performance were far more profound than those of caffeine. If the vigilance performance improvements were a result of increased arousal, the vigilance performance results should have been similar between the tDCS and caffeine groups. These pieces of evidence suggest arousal theory is not sufficient to explain the effects of tDCS on vigilance performance. Taken together, we conclude that tDCS may have an effect on both arousal and modulation of cognitive resources, but that the effects on arousal are far less crucial for preventing the vigilance decrement. Based on the evidence collected to date, we argue that the vigilance decrement is primarily driven by a decline in resources rather than a decline in arousal and that tDCS is capable of attenuating this resource decrement.

Our findings suggest that both tDCS and caffeine have beneficial effects on vigilance, working memory, and psychomotor performance during periods of sleep-deprivation induced fatigue, although there is a differential effect on vigilance. The results show that tDCS enhances vigilance to a greater extent and for a much longer period of time when compared to caffeine. Additionally, the tDCS-induced performance benefits were coupled with improvements in mood including reductions in drowsiness and fatigue. Transient improvements in feelings of drowsiness were found for the caffeine group during the session immediately after caffeine was administered, but the effects were short-lived, lasting only 2 h or less. Caffeine was also not accompanied by improvements in subjective fatigue or overall mood. Both interventions had a similar effect on working memory and psychomotor performance that appeared to last at least until the 0800 session. Nevertheless, this is the first data to suggest that tDCS may have distinct advantages over caffeine in remediation of fatigue symptoms. Given these initial promising findings, we conclude that tDCS should be further examined as an intervention for fatigue.

Uncited reference

[26]. Q1

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