Quantitative EEG Changes Under Continuous Wakefulness and with Fatigue Countermeasures: Implications for Sustaining Aviator Performance

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Abstract. Sleep management, naps, and pharmacological countermeasures may be combined to assist operators requiring around the clock tasks. We used QEEG methodologies to elucidate the CNS effects of stimulants (caffeine, modafinil, and dextroamphetamine) combined with sleep deprivation. Thirty-two UH-60 pilots were tested during 87 hours of continuous wakefulness using frequency analysis to quantify eight EEG channels for up to 20 frequency bands. Data were analyzed using brain mapping techniques and repeated measure analysis of variance. After 50 hours awake, all groups showed the sleep deprivation effects: increases in slow-waves and decreases in alpha activity. Caffeine and modafinil groups appeared to have the greatest degree of effect, producing delays on the electrophysiological deterioration for up to 46 hours into the sleep deprivation cycle. Additional analysis of these data could systematically correlate cognitive tasks and QEEG data for each pharmacologic intervention.

Keywords: QEEG, CNS, Brain Mapping, Artifact, Epoch.

1 Introduction

Military operations require Army aviation units to operate around the clock during time of conflict. The success of military operations, particularly in special operations units, depends on maintaining the speed and momentum of continuous day-night operations [1]. To achieve optimal cognition, sustain judgment and decision-making, and enhance performance, we need to understand how to best manage personnel and missions involving acute total sleep deprivation, partial chronic sleep deprivation, and demanding cognitive workloads. To this end, sleep management, naps, and pharmacological fatigue countermeasures may be combined to assist in achieving successful military outcomes.

Amphetamine-like stimulants and caffeine are known to increase wakefulness, and their effects on the brain are well reported. Modafinil, unlike amphetamines, ameliorates sleep deprivation effects without generally stimulating the central nervous system (CNS).

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The most direct indicator of CNS functionality is the electroencephalogram (EEG). The validity and reliability of quantitative electroencephalography (QEEG) methodologies in the classification of psychotropics were demonstrated based on retrospective and prospective studies [2, 3]. Itil [4] discovered psychotropic properties of new drugs that could not be predicted by animal pharmacology and biochemistry. Additionally, EEG signals are clearly influenced by sleep deprivation [5, 6].

In the context of such research, a large number of studies have employed different approaches in efforts to detect and classify patterns of EEG changes associated with pharmacological interventions or with total sleep deprivation. In the present study, QEEG methodologies were used in an effort to elucidate the CNS effects of the study drugs combined with the sleep deprivation factor. To determine the electrophysiological effects and help reveal the performance enhancing modes of action of the study drugs (caffeine 200 mg, dextroamphetamine 5 mg, and modafinil 100 mg) on sleep deprived pilots, the following neurophysiological hypotheses are stated: a) sleep deprivation of up to 68 hours will fragment awake EEG patterns, producing an increase on slow wave activities (1.3 – 7.5 cps) and a decrease on alpha and faster activities (7.5 – 14 cps) and b) caffeine, dextroamphetamine, and modafinil will generate predictable and significant improvements on the EEG patterns when compared to placebo.

2 Methods

2.1 EEG Recording and Processing

EEG was continuously recorded from scalp electrodes in a standard unipolar setting (F7-A1, F8-A2, C3-A1, C4-A2, FZ-A1, CZ-A2, O1-A1, and O2-A2). The EEG isolated amplifier low and high filter was set at 1.3Hz and 70Hz respectively. To accomplish the analog to digital conversion of the EEG signal, a 12 bit, 16 channels A-D board was used.

All EEG channels were processed and quantified using frequency analysis, where up to 20 frequency bands on each channel can be analyzed on-line using time-domain [7]. The resulting variables are average amplitude, amplitude variability, average frequency, and frequency deviation, along with twenty frequency bands (1.3-2.5, 2.5-3.5, 3.5-4.5, 4.5-5.5, 5.5-6.5, 6.5-7.5, 7.5-8.5, 8.5-9.5, 9.5-10.5, 10.5-11.5, 11.5-12.5, 12.5-13.5, 13.5-15.0, 15.0-17.0, 17.0-20.0, 20.0-26.0, 26.0-32.0, 32.0-38.0, 38.0-48.0, 48.0Hz and up.). The selected epoch size for all channels was 5 seconds. Automatic online artifact detection was used during EEG recording, followed by an off-line visual inspection of the EEG to further select artifact free epochs for the analysis.

2.2 Procedures

QEEGs were performed for 10 minutes, awake and with eyes closed. Each period was divided into two sub-periods, with a 1-2 minute break between. During the first five minutes, standard eyes closed, resting EEG was performed and no attempt was made

to control the subject's vigilance level (resting recording labeled RR). During the second sub-period, a random acoustic stimulus was presented at 7-45 second intervals and subjects were asked to respond to the stimulus by raising their thumb (simple reaction time task labeled RT). The RT task was not intended to measure performance but rather to keep the vigilance at a relative constant level (control of spontaneous drowsiness).

Thirty-two subjects were scheduled for a full week at the Laboratory in groups of two and under the same drug condition. Due to technical mishap, data from two pairs of subjects (on placebo and caffeine) could not be included in the analysis. Thus, data presented represents six subjects on caffeine, eight on dextroamphetamine, eight on modafinil, and six on placebo. Among several other tests performed on this study, participants completed three QEEG training sessions during the first three days to adapt to the procedure and also to compare their QEEGs to a normative database to ensure that there were no significant deviations from normative patterns. Subsequent testing took place on 13 additional QEEG sessions (Fig. 1).

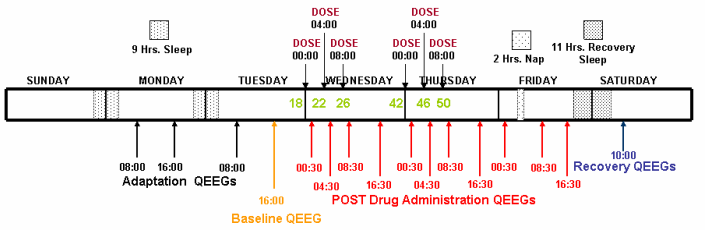

Fig. 1. Timeline for drug and QEEG administration. Green numbers indicate hours awake at the dose time. QEEGs were recorded 30-40 minutes after drug administration.

3 Results

3.1 Multi-lead Evaluation

To determine the effects on multiple areas of the brain, a dynamic brain map system was used. With dynamic brain mapping, it is possible to view delta, theta, alpha, and beta activities of a multichannel QEEG recording in the form of a brain map. This way, the average amounts of activities are displayed by color coding on an anatomically correct brain image. The QEEG data are displayed on the brain image in the exact location where the recording electrodes were placed and the areas between electrode locations are interpolated using blending algorithms that depict the regional spread of the brain's electrical activity. The means of delta (1.3-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-13.0 Hz), and beta (13.0 Hz and up) activity, over all subjects, for each session and for each drug group were averaged. Fig. 2 shows maps for the baseline QEEGs for each group.

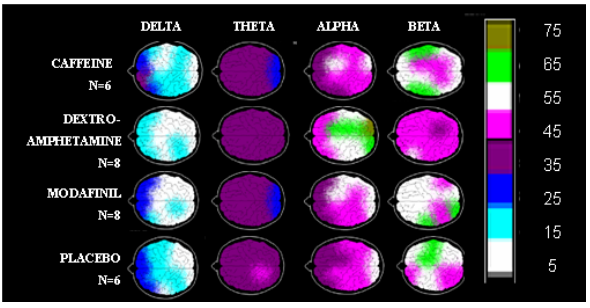

Fig. 2. Frequency bands and drug groups represented as brain maps. As expected for baseline QEEGs all groups showed similar average power (color code) on each frequency band. The dextroamphetamine group showed a slight different alpha and beta activities when compared to caffeine, modafinil, and placebo.

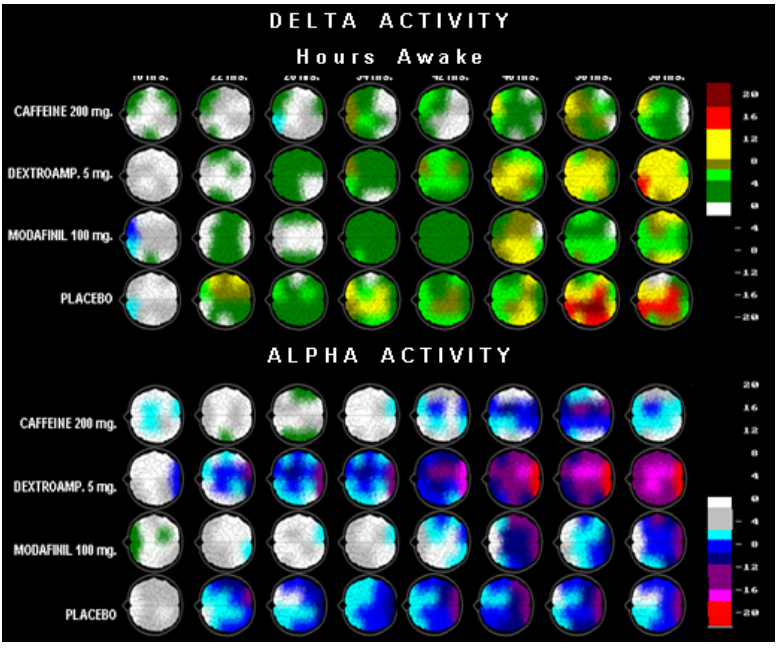

Fig. 3. Dynamic brain map changes from baseline for each of the drug groups tended to show a systematic increase of delta activity and a decrease of alpha activity in all time periods

The percentage of delta, theta, alpha, and beta bandwidths in the recorded time periods were calculated before- and after- drug administrations, and the changes in each of the time periods (18, 22, 26, 34, 42, 46, 50, and 58 hours awake) were compared with baselines. To measure the absolute difference before and after drug, the pre-drug (baseline) was subtracted from each post-drug brain map to obtain a change from baseline state. Accordingly, any changes in brain map can be attributed

to the effect of drug, sleep deprivation, or both combined. In this way, the effects of caffeine, dextroamphetamine, modafinil and placebo could be visualized as independent factors, as depicted in Fig. 3.

Caffeine, modafinil and dextroamphetamine, in that order, showed less increases of delta activity over all areas of the brain up until 42 hours of sleep deprivation (after three doses). Although alpha activity had the tendency to decrease as the number of hours awake increased, modafinil and caffeine groups showed virtually no changes from baseline until 46 hours of sleep deprivation, suggesting a delay in the deterioration or decrease of alpha activity. Dextroamphetamine and placebo, however, produced a systematic decrease of alpha activity after the second dose (22 hours awake) with the highest increases shown on dextroamphetamine rather than placebo.

A systematic but slight increase of theta after the fourth session is seen in all drug groups with the least increase in the caffeine group. However, no marked changes for any of the drug groups were seen in the theta activity levels. Beta activity showed a systematic but slight increase in all sessions and in all drug groups, with modafinil having the least changes from baseline. The placebo group had a decline in beta activity after 46 hours, which produced a marked decrease of the activity after 50 and 58 hours of SD.

3.2 Detection of Drug Effects

Measures of the 20 frequency bands were collapsed into 4 frequency bands to generate delta, theta, alpha, and beta activities for an occipital (O2), central (CZ), and frontal (FZ) electrode. To remove variability among subjects in the same group and to determine performance trends over the sleep deprivation cycle, a repeated measures analysis of variance (ANOVA) was carried out for each frequency band. We used the four drug groups (caffeine 200 mg, dextroamphetamine 5 mg, modafinil 100 mg, and placebo) as between-subjects factors, and the eight QEEG sessions (18, 22, 26, 34, 42, 46, 50, and 52 hours) as a repeated measure. Each of these QEEGs was subtracted from the baseline QEEG to create score changes on delta, theta, alpha, and beta bandwidths at O2, CZ, and FZ. The analysis was performed on the overall recording time using both RR and RT segments. In checking assumptions, Box's M and Mauchly's test of sphericity were used. To circumvent the compound symmetry violation in all variables, we used lower-bound epsilon adjustment which represents the most conservative approach.

Delta Activity. The different pharmacological conditions resulted in distinct changes in delta activity. Drug main effects and Session effects were present at the three electrodes. The drug effects at O2, $F(3, 52) = 3.01$, $p = 0.038$; CZ, $F(3, 52) = 7.51$, $p = 0.0002$; and FZ, $F(3, 52) = 3.56$, $p = 0.020$ were tested using Tukey HSD post-hoc comparisons. This test revealed significant differences between modafinil and placebo at O2 and CZ and between caffeine and placebo at CZ and FZ. Caffeine was also discriminated with dextroamphetamine at CZ. The session effects at O2, $F(1, 52) = 6.39$, $p = 0.015$; CZ, $F(1, 52) = 26.81$, $p < 0.0001$; and FZ, $F(1, 52) = 52.49$, $p < 0.0001$ were primarily due to a significant linear increase in delta activity from the first to the last sessions of the sleep deprivation cycle. In addition, there was a session by drug interaction at CZ, ($F = 3.36$, $p = 0.026$). The mean score changes for the three leads are shown in Fig. 4.

Alpha Activity. There was no drug main effect in the frontal electrode, FZ. However, alpha activity showed significant drug effects at O2, $F(3, 52) = 3.12$, $p = 0.034$ and CZ, $F(3, 52) = 3.61$, $p = 0.019$. Post-hoc analysis disclosed that dextroamphetamine is significantly different from modafinil at O2 and significantly different from caffeine at CZ. There were significant session effects at O2, $F(1, 52) = 27.14$, $p < 0.0001$; CZ, $F(1, 52) = 34.90$, $p < 0.0001$; and FZ, $F(1, 52) = 44.94$, $p < 0.0001$, produced by significant linear and quadratic decreases in all leads. The session by drug interactions at CZ, $F = 3.51$, $p = 0.022$ and at FZ, $F = 2.39$, $p = 0.042$ were essentially the result of high variability over time among the four groups. Fig. 5 depicts the score changes for alpha over the sessions.

Theta Activity. Theta activity did not show drug effects or interactions at any of the three leads. The only significant change was a session effect at O2, $F(1, 52) = 4.84$, $p = 0.032$, due to a constant linear increase across all sessions. Fig. 6 shows mean changes.

Beta Activity. Similar to theta activity, beta did not produced drug effects or interactions at any electrode. There were, however, session effects at CZ, $F(1, 52) = 4.35$, $p = 0.042$ and FZ, $F(1, 52) = 9.89$, $p = 0.003$, due to a significant linear decrease in both leads. Beta activity is shown in Fig. 6b.

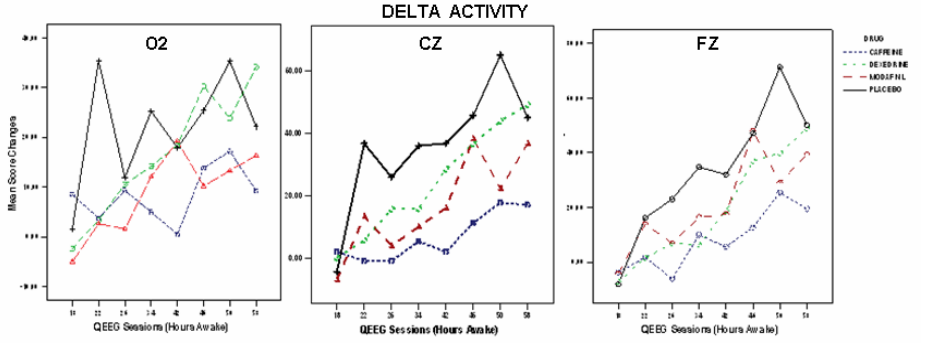

Fig. 4. Mean score changes for delta activity at O2, CZ, and FZ

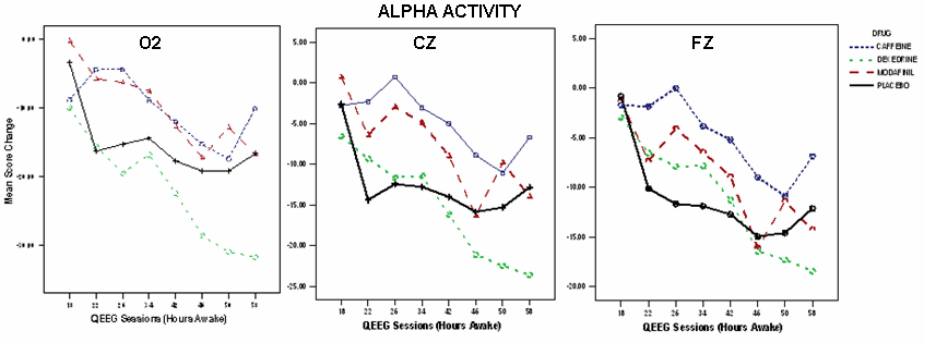

Fig. 5. Mean score changes for alpha activity at O2, CZ, and FZ

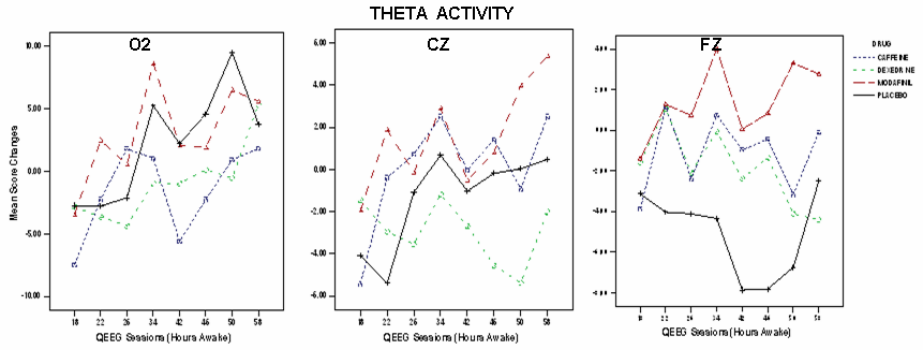

Fig. 6. Mean score changes for theta activity at O2, CZ, and FZ

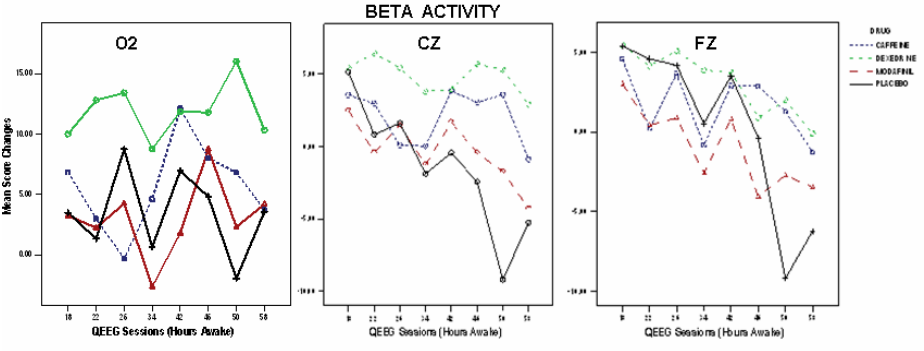

Fig. 6b. Mean score changes for beta activity at O2, CZ, and FZ

4 Discussion

The results from the repeated measure ANOVA during the drug sessions tend to confirm the trends observed on the multi-lead evaluation using brain mapping. Theta and beta activities were not sensitive to pilot fatigue due to sleep deprivation or drug effects. The most predominant changes were established in delta and alpha activities showing session effects at all electrodes with linear increase on delta and linear and quadratic decrease on alpha. Delta activity showed significant between-subject responses at the three leads and alpha at the occipital and central leads. Also, all three significant interactions were produced at these activities mainly in the central and frontal regions.

Caffeine produced less significant changes from baseline and was clearly differentiated from placebo and dextroamphetamine. Caffeine attenuated the slow waves and slightly increased beta activity, consistent with a recent study on the effects of caffeine on the brain [8]. Similar to caffeine, modafinil produced fewer changes from baseline on the slow activities during the first 34 hours and on alpha activity during the first 42 hours of wakefulness. Modafinil showed virtually no changes on beta activity throughout the entire cycle and showed improvement on

delta when compared to placebo at O2 and CZ but not on theta. These results partially agree with a similar previous modafinil study [9], which showed delta and theta improvements at CZ. However, they used twice the dose (200 mg) and a shorter sleep deprivation period (40 hours). The increase of delta activity under dextroamphetamine was similar to changes seen with placebo and the decrease on alpha even greater than placebo. These outcomes contradict the electroencephalographic results established in several studies with dextroamphetamine which reported significant attenuation of slow-wave increase and a more normal alpha activity [10]. These four studies each used 10 mg of dextroamphetamine (vs. 5 mg in the present study); three studied shorter periods of sleep deprivation (40 hours) and one studied 64 hours.

The present study showed increases in delta activity due to the sleep deprivation factor; an increase in delta activity is primarily associated with sleep in normal adults [11]. It is also known that sleepiness and fatigue elevates slow-wave activities [6]. However, this study revealed virtually no increases in theta activity across the sleep deprivation cycle, for all groups, including placebo. An increase in theta activity alone has been associated with generalized performance decrements on cognitive tasks [12] and reduced speed of response to incoming stimuli [13]. The lack of significant changes in theta activity may represent effort levels consistently across all groups. For example, motivation can counteract the effect of sleep deprivation, since the adverse effects of sleep loss on performance and behavior are very labile and can easily be cancelled by suitably arousing conditions [14]. Furthermore, it was also shown that monetary rewards for good performance maintained baselines levels for 36 hours without sleep [15].

5 Summary

We identified the extent and distribution of electrophysiological changes induced by sleep deprivation and three different wake promoting agents. We found that after 50 hours, the groups showed EEG signs of sleep deprivation: increases in slow-waves (mainly delta) and decreases in alpha waves. The electrophysiological effects of sleep deprivation are reversed during the initial 42 hours with smaller increases in delta activity by caffeine, modafinil, or dextroamphetamine, and less deterioration of alpha activities for caffeine and modafinil when compared to baseline levels. Caffeine and modafinil appeared to have the greatest degree of effect with respect to producing delays on alpha activity deterioration. Alpha activity remained close to baseline levels for the first 46 hours. A marked deterioration of alpha after the second dose (22 hours awake) was observed in the dextroamphetamine and placebo groups.

The multi-lead evaluation shows that the dynamic brain mapping of subjects from all drug groups had similar (normal) QEEG patterns when well rested and without drugs (baseline QEEGs)., We can confirm that sleep-deprived subjects have different QEEG spectrums (profiles) than those not sleep-deprived. Interestingly, those QEEG profiles for the sleep-deprived subjects are opposite to the QEEG changes induced by psychostimulants in well rested healthy volunteers. Based on this, we hypothesize that QEEG differences between non sleep-deprived and sleep-deprived subjects are due to quantifiable changes in the brain produced by sleepiness and fatigue. Correct doses of

psychostimulants would reverse that imbalance, so that the drug-induced changes of the QEEG would be toward the normalization of function of the sleep deprived brain.

In order to determine the best adaptability to sustained operations, future studies are needed to establish the CNS effective doses for the drugs, based on the magnitude of the deprivation. Individual differences that exist for personality features, physiological reasons, and circadian typology may be accounted for by titrating drug dose to both performance and electrophysiological measures. Additional analysis of this study data could systematically correlate cognitive tasks and QEEG data for each pharmacologic intervention. Through QEEG, measures are available that may be used to directly relate the brain effects of the drug to the performance effects.

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