Caffeine and Cognition During Sleep Deprivation

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RUNNING HEAD: Caffeine and Sleep Loss

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Caffeine is used by 80% of adults in the United States,[1] at a per capita intake of greater than 200 mg per day.[1] An Institute of Medicine review of the use of caffeine to sustain mental task performance was published in 2001[2], and a review of the effects of caffeine when used during sleep deprivation was published by the American Academy of Sleep Medicine in 2005[3]. The use and potential benefits of caffeine in individuals who are not sleep deprived is a large and controversial area that will not be reviewed here. This chapter will focus on the many studies that have examined the interaction of sleep loss and caffeine as measured by numerous cognitive tests.

The efficacy of caffeine in sleepy individuals is dependent upon several variables including: length of sleep deprivation or amount of sleepiness, dose of caffeine, type of measure, and previous experience with, or tolerance to, caffeine. The doses of caffeine administered in studies evaluated here ranged from 32 to 600 mg in single doses and up to 1200 mg per day in divided doses. Multiple formulations, including liquid, chewing gum, and tablets or capsules (some in time release formulation) have been studied. Because caffeine is widely used, most studies have specified the amount of habitual caffeine intake in participants. It is common to only select participants who have relatively low habitual caffeine intake (usually less than 200-300 mg per day). As such, much of the literature may not generalize to individuals with greater habitual caffeine use. Despite the fact that many studies limit habitual caffeine use, in part to avoid caffeine withdrawal problems, withdrawal may still be a significant issue in some studies. A separate literature has begun to address the magnitude of potential withdrawal issues by studying caffeine-free populations or statistically controlling for
level of habitual use. In addition, tolerance to the effects of caffeine may develop over time even within studies with repeated administration.

Caffeine formulations and half-life

When evaluating the caffeine literature, it is important to understand that effects are dependent both upon the dose and the method used to deliver the caffeine (see Table 1). In one study that examined the availability of caffeine from Stay Alert™ chewing gum compared to a capsule formulation,[4] higher plasma concentration was seen for the first 10-40 minutes after administration of the gum, and an overall shorter time to maximum blood level (Tmax 0.73-1.34 hours versus 1.4-2.0 hours from the capsule) was identified. There was a lower maximum blood concentration (Cmax) from the gum formulation. In another study,[5] ingestion of an aqueous solution of 350 mg of caffeine resulted in a Tmax of 0.78 hours with a Cmax of 8.3 ug/ml. Half-life typically ranges from three to six hours.[6] The slow release formulation of caffeine (capsule) at 600 mg revealed a Tmax of 4.4 hours and a Cmax of 7.7 ug/ml. Elimination half-life (average of 4.4 hours in this study) was significantly shorter in habitual smokers compared to non-smokers but was not shorter in habitual caffeine users compared to occasional users.[6] The slow release caffeine data are consistent with the assertion that this formulation remains active for a longer period with a lower peak level than other forms of caffeine at comparable doses. The data from the liquid formulation suggest that the reported difference in onset attributed to the caffeine gum may be more related to digestion of a capsule in the stomach, because the Tmax for the liquid caffeine solution was comparable to that of the gum.
Many outcome measures have been used to assess the impact of caffeine during periods of sleep loss. The most common measures, subjective and objective sleepiness, are reviewed in detail elsewhere[3]. This chapter will focus on cognitive measures. However, “cognitive” will be broadly addressed as all psychomotor tasks because performance on true cognitive tasks must be based on underlying ability to maintain attention and respond within a measurable time. Simpler tasks will be described first.

Reaction time is a frequently reported performance outcome in caffeine trials. Reaction time may not be considered a true cognitive task. However, almost all cognitive tasks require a response, and changes in response speed could help to account for reported benefits or mask potential deficits reported on more complex tasks. The most used measure has been simple reaction time. At least 17 studies ([7], [8], [9], [10], [11], [12] [13], [14], [15], [16], [17], [18] [19], [20], [21], [22], [23]) have measured simple reaction time during sleep loss after caffeine administration ranging from 200-600 mg for individual doses and 75 mg for repeated doses, and all except one [24], with an approximate dose of 84 mg, have reported significant improvement compared with placebo groups. In an unblinded, non-placebo-controlled study of more than 7000 adults who were not sleep deprived, both simple reaction time and choice reaction time (see below) decreased in a linear fashion as a function of amount of habitual caffeine consumption for amounts ranging from none to seven or more cups of coffee per day with the greatest effect seen in older (55+) individuals.[25]
Choice reaction time (usually four-choice) has also been examined in several studies. Various aspects of performance on this task including reaction time, [26], [13], [27], [21], [28] accuracy,[19], throughput[29] and response failures[30] were improved significantly after caffeine administration in single doses of 150 – 600 mg compared with placebo in sleep-deprived subjects. Two studies did not find significant effects for choice reaction time [24], [22]. The Rogers study[24], also mentioned earlier, is somewhat different from the others in that it involved a low dose of caffeine (about 84 mg) administered to “moderate to high” caffeine users after one night with sleep reduced to 5 hours.

A number of caffeine studies have included measures of auditory or visual vigilance. As with reaction time, ability to maintain attention, as measured by vigilance, may not be considered a significant cognitive task. However, attention is an essential component for cognitive performance. Thirteen studies that included well-defined vigilance tasks all showed decreases in vigilance performance during sleep deprivation that were significantly smaller after administration of caffeine in single doses of 300 – 600 mg or repeated doses of 75 mg or more as compared with placebo.[31], [32], [33], [34], [13], [26], [14], [15], [16], [35], [17], [36]

Short-term memory has been examined with several types of task including the Digit Symbol Substitution Task (DSST), coding, short term memory recall, or digit span. During sleep loss, significant beneficial effects of caffeine relative to placebo have been found in several studies with the DSST [7] [32], [33], [35] [23] (but not [18]) at single doses of 300 – 400 mg or repeated doses at about 21 mg per hour. Three studies of
short term memory tasks during sleep loss showed improved performance after caffeine administration [34], [13], [26] of 200 – 300 mg but three did not [35], [24], [23] after single administration of 84-300 mg or repeated administration at about 21 mg per hour. Two studies including digit span have not found significant improvement after caffeine administration of 300 – 400 mg [33], [9]. In one study specifically designed to test the interaction of sleep loss with caffeine on memory performance,[37] it was found that caffeine 350 mg had no significant effect on temporal memory (recency) after normal sleep (recency was non-significantly better after placebo) but improved this aspect of memory compared with placebo after 36 hours of sleep loss.

Grammatical reasoning ability significantly improved after administration of caffeine at doses ranging from 150 – 600 mg in eight of nine studies involving a component of sleep loss[30], [31], [32], [33], [38], [26], [35], [27] (but not [24] with a dose of about 84 mg).

Several studies have specifically examined the effect of caffeine at doses ranging from 80 – 300 mg during simulated driving after sleep restriction.[39], [40], [41], [42], [43], [44], [45], [46] All of these studies measured lane drifting (i.e., the number of times the simulated car drifted across a lane marker), and all found a significant reduction when caffeine, as compared with placebo, when administered after a night of restricted sleep. However, in one study after a full night of sleep deprivation, the beneficial effects of 200 mg of caffeine (relative to placebo) were not maintained after 30 minutes.[43] The shorter effective time could be related to greater sleep loss in this study.
Two studies followed Navy SEAL trainees through 72 hours of sleep deprivation prior to administration of caffeine and measurement of marksmanship. In one study,[13] no significant effect of caffeine 100 – 300 mg was found on marksmanship. In two other studies that specifically concentrated on marksmanship parameters,[47], [48] accuracy, which was decreased during the period of sleep deprivation, did not recover after caffeine administration (100 – 400 mg+), but there was a significant reduction in sighting time. Another study of marksmanship measured during a three-hour tour of sentry duty in non-sleep deprived soldiers showed an interaction of caffeine 200 mg or placebo use with time on duty.[49] There was little difference in time to respond to a new target at the beginning of the tour, but response time stayed constant for the three hours after administration of caffeine while increasing by 400 msec at the end of three hours in the placebo condition. A similar relationship was seen when “failure to fire” (i.e., percent of times that the soldier simply did not detect a target) was measured. About 10% of targets were not seen in each 30-minute period after caffeine. After placebo, failures increased from 12% at the beginning of the tour to 20% at the end (a statistically significant increase), but accuracy did not change. All of these findings suggest that caffeine primarily aided subjects by improving reaction times to more normal levels or improving attention as suggested by previous studies of those specific attributes.

A large number of additional tests have been examined during sleep deprivation. Other tests that have been used in at least 3 published studies include addition problems completed, divided attention, tracking tests, and the Stroop test, which will be covered in the next paragraph. All four studies that examined the effect of caffeine after
single doses of 300 – 600 mg on additions during periods of sleep loss found significant beneficial effects [32], [26], [19], [23]. All three studies of divided attention at doses of 300 – 600 (but not 150) mg have shown significant positive effects of caffeine [7], [30], [38]. Five of the six studies of tracking found significant positive effects after caffeine administration at doses from 300 – 600 mg [30], [33], [34], [26], [38] (but not [16] after a 600 mg dose). The study that did not show a significant effect on tracking did show that performance was maintained at the same level after sleep loss after caffeine administration and decreased non-significantly in the placebo condition.

In recent years several experiments have used tests designed to evaluate “executive function” during sleep loss and after administration of caffeine. One early test that is considered to measure higher function is the Stroop test. Four of the six studies that assessed performance on the Stroop test found significant benefits from caffeine after single doses ranging from 300 – 600 mg [30], [26], [16], [7] (but not [9], [21] at doses of 400 and 600 mg). In one of the studies that did not find a positive effect for caffeine, there was also no decrement in performance associated with sleep loss [9]. About 15 other tasks have been used to assess executive function, but these complex tasks typically do not have parallel versions and cannot be repeated. This means that the tests cannot be given to the same subjects prior to sleep loss and during sleep deprivation to document sleep deprivation effects. Therefore, there is no clear evidence that sleep loss produces decrements on many of the tests. When comparisons have been made between caffeine and placebo groups, those comparisons have almost always been between groups comparisons during a period of sleep deprivation. With no
clear baseline to equate groups on performance ability, which may be related to education, intelligence, creativity or previous experience with similar tasks, differences or lack of differences in small groups of participants during sleep loss with or without caffeine are difficult to assess. In addition, it is rare for the tasks to be used in more than one experiment, and this means that replication of results is largely not available to help with evaluation. The most commonly reported task in addition to the Stroop is the Wisconsin Card Sorting Task, which is reported in three studies with none showing a statistical benefit in the caffeine 280 – 600 mg groups compared with placebo groups (no baseline data) [18], [21], [12]. One study [12] did show a significant improvement relative to placebo on this test after administration of modafinil 400 mg on two subscales, but the difference between modafinil and caffeine was not significant. Other executive function tasks including the Tower of London, Tower of Hanoi, the Optimal Telegram, the Torrance Test of Creative Thinking (Verbal and Figural), Thurstone’s Word Fluency Test, the Anagram Task, the Category Test, Controlled Oral Word Association, Animal Fluency, Biber Cognitive Estimation Test, and the Iowa Gambling Task have been used in individual studies with caffeine groups typically not differing statistically from placebo groups. Exceptions include significantly better performance after caffeine 600 mg administration on the Biber Cognitive Estimation Test [21] and on the Tower of Hanoi[12] where the caffeine group completed the task in significantly fewer moves than placebo, modafinil 400 mg and amphetamine 20 mg groups during sleep deprivation. However, in the latter study, the modafinil group had significantly better performance than both the placebo and caffeine groups on the Tower of London
test. The authors present a neurophysiological argument to support these differences, but lack of baseline testing and chance limit the generality of these findings until replication in larger studies has been done. In one study [18], the Torrance Tests of Creative Thinking were administered both at baseline and between 4-5:30 during night shifts following caffeine about 280 mg administered at about 22:30. The study design allowed analysis of change from baseline on the tests. Results for the verbal task showed significantly less performance decrement during the night in a condition that combined a nap with caffeine administration. Of interest, a group only given the nap (that ended six hours prior to this test) performed significantly worse than the nap plus caffeine group and nonsignificantly worse than the placebo group while the group only given caffeine performed nonsignificantly better than the placebo group. The major conclusion that can be drawn from these studies is that it is important to develop truly parallel forms for tests of executive function so that both sleep deprivation and medication effects can be assessed in the same study.

Caffeine Psychomotor Effects by Dose

The effects of caffeine during sleep loss have been examined over a large dose range. A few studies have looked at three caffeine doses within a single administration design.[29], [38], [13], [47], [10] In general, these studies included a low dose (100 mg – 150 mg), a medium dose (200 mg – 300 mg), and a high dose (300 mg – 600 mg). In three studies, [29], [38], [10] caffeine was administered after either 20 (3 doses of 50,
100 or 200 mg starting at 0300), 32 (midnight) or 49 (0800) hours of wakefulness and improved reaction time and other performance for as long as 13 hours. In the first study[29], caffeine 150, 300, or 600 mg was administered after 49 hours of wakefulness (second night awake at 0300). Performance on choice reaction time was improved with caffeine compared with placebo at all observation points (statistics not given) but the level was only more than one standard deviation better compared with placebo at 60-min post administration in all caffeine groups and at 3 and 4 hours post administration in the highest dose. In the second study [38], doses of 150, 300, or 600 mg of a slow-release caffeine preparation were given at midnight after 32 hours of sleep loss. Significant beneficial effects were reported for a number of tasks, including reasoning, spatial processing, visual tracking, and the dual task for the 300 and 600 mg doses and in the memory search task for all doses. In these studies, the low dose of 100 – 150 mg is almost always seen as ineffective, the medium dose of 200-300 mg is typically seen as optimal (i.e., significant improvement on many tasks) and the high dose typically did not result in significantly better performance than the medium dose and was therefore not recommended.

Two other studies examined performance when caffeine 100 mg, 200 mg, or 300 mg was administered at 2130 after about 72 hours with 1.5 hours of sleep.[13], [47] In this design, significant improvement was not found in any marksmanship or psychomotor performance tasks at the 100 mg dose. Performance was significantly improved for sighting time (marksmanship) and time to complete a memory/motor-learning task at one and eight hours post administration test points for the 200 mg and
300 mg doses (200 mg only for the learning task). On a vigilance task, hits were increased and false alarms reduced in a dose-dependent fashion with significantly improved performance at the 300 mg dose one hour after administration as compared to placebo. However, the authors of these studies recommended the 200 mg dose as the most efficacious. In another study[10] caffeine was administered in gum at levels of 50, 100, or 200 mg at three times during one night of sleep loss. Analysis of reaction time lapses showed fewer lapses compared with placebo in all of the caffeine conditions, and the caffeine conditions also all differed from each other in a dose-dependent manner with best performance at the highest dose. Only the 200 mg group did not have significantly more lapses than baseline at any point during the experiment. These studies tend to show an interaction between effective dose level and amount of sleep deprivation with lower doses showing more effectiveness during the first night of sleep loss and higher doses being recommended when sleep loss was greater.

Caffeine effects by degree of sleep loss

While there are a few studies of varied doses of caffeine used a different points during sleep deprivation, there are very few individual studies of the effects of a specific dose of caffeine used at different levels of sleep deprivation[20], [21], [32]. Wesensten et al reported the effect of 600 mg of caffeine on simple reaction time starting after 41.5 hours awake in one study and after 64 hours awake in another. No statistical comparison of the studies has been done. However, response speed (inverse of
reaction time * 1000) in the placebo groups was in the 1.75 – 2.0 range (equivalent to
mean reaction times of about 500 – 570 ms) in the 64 hour sleep-loss group compared
with 1.0 -2.0 (mean reaction times of about 500 – 1000 ms) in the 41.5 hour groups. Response speed was about 2.5 (400 ms) in the caffeine group 6-12 hours after
administration in the 64 hour study and about 2.75 (365 ms) in this time frame in the
41.5 hour study. These data imply that reaction time may have been more improved by
the same caffeine dose during the first night of sleep deprivation (level was about half of
placebo levels) compared with the second night (level declined to about 75% of placebo
levels). Bonnet et al [32] found decreased effectiveness for maintaining vigilance
performance for caffeine at 150 and 300 mg doses (repeated) during the second night
of sleep deprivation compared with the first night although the effect of a single
administration of 400 mg was similar on both nights (although both placebo and caffeine
performance levels decreased a similar amount on the second night). One general
conclusion is that higher doses of caffeine will be required to provide similar
performance benefits as time awake increases.

Caffeine effects by habitual use of caffeine

Habitual caffeine use is reported in most studies, and use above a certain amount,
frequently about 300 mg per day, has commonly been used as a study exclusion.
Studies involving sleep loss have not used habitual use to form groups for comparative
purposes. Some studies have controlled for habitual use by withdrawing subjects or
using statistical techniques to control for habitual use. These latter studies have not reported significant effects of habitual use level on outcome measures [48]. Studies that have withdrawn Ss from caffeine prior to participation have either used novel tests that do not allow comparison with other literature[50] or have been focused on showing negative effects of immediate withdrawal from medium to high doses (i.e., 160 – 445 mg) of caffeine.[51]

Caffeine effects by repeated versus single dosing

Because caffeine has a relatively short half-life, a number of studies have used repeated doses during extended periods of sleep loss as opposed to a single large dose. Repeated dosing also approximates the manner in which normal individuals typically use caffeine. In a study to maximally explore repeated dosing, Wyatt et al[23] administered approximately 21 mg of caffeine each hour to a group of Ss in a forced desynchrony protocol that included 28.6-hour wake periods (total administration of about 567 mg of caffeine per wake period). When examined from the perspective of time awake, significant benefit from the caffeine was found on reaction time, additions and the DSST but not on a short-term memory test. Test-related differences were similar when the data were compared based on circadian phase, but beneficial effects for caffeine were maximal at the nadir of the circadian rhythm and least at the peak of the rhythm. Unfortunately, the report did not examine the possible development of tolerance to caffeine over 14 repeated 28.6 hour days. A rough effect size (data
approximated from figure) at the end of the 28.6 hour wake period for the beneficial effect of caffeine was about .92. These data can be roughly compared with a study by Smith et al[27] where caffeine about 200 mg was given three times during one night without sleep. At the end of the night, reaction time was improved by caffeine and the ES was about .80. Therefore, these data do not suggest that hourly very low doses of caffeine resulted in decreased performance levels compared with larger doses given less frequently. However, as much other research suggests that tolerance to caffeine can develop relatively quickly, additional studies with both repeated small doses and less frequently repeated larger doses perhaps across multiple periods of sleep loss would help to better define development of tolerance to caffeine when used in this manner.

Caffeine effects associated with tolerance to caffeine and withdrawal from caffeine

Caffeine has been widely used in our society for many years. For this reason, it is very difficult to study individuals who do not already have significant experience with caffeine use that may have produced physiological or psychological changes. Published research has displayed varying sensitivity to historical use patterns in participants. Administration of caffeine typically produces both physiological effects such as increased blood pressure, respiratory rate and urine production and mood changes such as increased energy and alertness. With regular use, tolerance (i.e., requirement for increased dose to obtain the same effect) commonly develops. If caffeine use is
terminated at this time, withdrawal, which include symptoms including headache, fatigue, decreased energy/alertness, and sleepiness may occur [52].

In recent years, a case has been made that many of the historically reported results showing that caffeine has produced beneficial performance effects could be secondary to inadequate control of habitual caffeine use followed by deficits that could actually be attributed to caffeine withdrawal rather than to a particular schedule of sleep restriction [53], [52]. In this view the “alerting” effect of caffeine is primarily a reinstatement of baseline function that overcomes the deleterious effects of caffeine withdrawal. One review of caffeine withdrawal [52] concluded that some withdrawal symptoms could be seen after withdrawal from doses as low as 100 mg and that symptoms became apparent 12-24 hours after the beginning of abstinence with peak intensity at 20-51 hours and a duration of symptoms for 2-9 days [52]. A few studies have been designed specifically to examine tolerance and withdrawal effects in relation to sleep restriction (usually by restricting sleep to 3-5 hours for one night prior to testing) [24], [51]. In one study[51], participants received about 110 mg of caffeine or placebo at 0900, 1100, and 1500 for a week prior to sleep restriction (or normal sleep). The following morning, a final 110 mg dose was given about 50 min prior to testing. A significant interaction was found for a beta EEG measure (unchanged with caffeine administration in rested Ss but decreased in sleep restricted Ss given placebo and increased in sleep restricted Ss given caffeine). However, no significant effects for either sleep restriction or caffeine administration were found for a sustained attention task not used in other sleep deprivation research. In the other study[24], a group that used about
400 mg of caffeine per day were given either placebo or caffeinated beverages for 3 weeks prior to sleep restriction (no study control to determine if tasks were sensitive to sleep loss). In the morning, Ss who had undergone only overnight withdrawal had significantly poorer performance on a reasoning and an attention task. Ss were then given placebo or about 84 mg of caffeine. The caffeine improved performance on a tapping test for both groups and restored performance to baseline levels in the overnight withdrawal group in an attention task but not in hand steadiness. These studies concluded that caffeine had weak or inconsistent effects and that there was little benefit. Unfortunately, both studies looked at low doses after minimal sleep restriction and either did not report the effect of sleep restriction itself[24] or found no significant impact of sleep restriction on the task used[51].

In addition, several traditional studies have controlled for caffeine use in a number of ways. One study has examined the impact of caffeine on performance after sleep deprivation in the marmoset monkey (to eliminate issues of previous caffeine exposure). In this model[36], dosing cannot be equated to human levels, but it was found that performance on a hand/eye coordination task that also involved a vigilance component measured during 24 hours of sleep loss was significantly worse than baseline following placebo administration but not caffeine. The caffeine benefit tended to be retained over a 2-week administration period. In a human study, Gottselig et al [50] withdrew their subjects from all caffeine for 2 weeks prior to two 40-hour sleep deprivation sessions in a crossover design. In this experiment, Ss completed a random number generation task (executive function task) every 3 hours. In the caffeine condition, Ss were given 200 mg
of caffeine twice. As sleep deprivation progressed, Ss generated significantly fewer random numbers in the placebo condition compared with the caffeine condition. Increasing rule violations and response stereotypy were also found during sleep loss, and these components were not improved with caffeine. At least two studies have used statistical controls for historical caffeine intake to assess possible tolerance or withdrawal effects. Tikuisis et al [48] performed a regression analysis to determine if performance or engagement time after 22 hours of sleep loss were related to habitual caffeine use and did not find significant relationships. However two subjects with very high historical caffeine use (> 800 mg) did have larger deficits compared with the rest of the placebo group. Childs and de Wit [8] used average caffeine consumption as a covariate in their analyses of covariance. This experiment found a significant decrease in simple reaction time during a single night of sleep deprivation that was significantly greater than that found after administration of caffeine 200 mg. The covariate habitual caffeine consumption had no significant impact on the results. These latter four studies with controls for habitual caffeine consumption all reported significant beneficial effects of caffeine on performance when used during a period of sleep loss. The study results are generally consistent with findings in other caffeine and sleep loss experiments where previous caffeine exposure was not as well controlled and suggest that the benefits of caffeine consumption during the sleep loss are more than an artifact of habitual caffeine use. At the same time, maximal benefit of caffeine during sleep loss is likely to occur in individuals who are not already tolerant to the amount of caffeine administered. Whether this might simply be a dose effect remains to be tested.
Effects of caffeine compared with other stimulants during sleep deprivation

There are relatively few studies of caffeine compared with other stimulant medications during sleep loss. Two major series of studies have compared caffeine 600 mg with modafinil 400 mg and dextroamphetamine 20 mg after varying periods of sleep loss [21], [54], [12], [11], [55]. The Wesensten et al study [21] found that all of the stimulants improved performance during sleep loss. As expected by half-life, the most prominent effects related to caffeine were found during the first 4 hours after administration where reaction time, for example, was very similar in the caffeine and modafinil conditions. However, performance after caffeine administration then deteriorated to placebo levels 12 hours after administration while performance was maintained in the modafinil group. Reaction time performance after dextroamphetamine improved more slowly and did not differ from the other drug groups except shortly after administration. Several executive function tests were included in the experiment but there were no significant drug differences and only two significant differences from placebo (performance was improved relative to placebo on the Biber cognitive estimation task for both caffeine and modafinil). Two other studies by Wesensten et al showed that effects of caffeine on reaction time, choice reaction time and an addition task were similar to those seen after administration of modafinil at the 200 and 400 (but not the 100 mg) level. In general the 600 mg caffeine dose seemed to fall between the 200 and 400 mg modafinil doses [19], [20]. The several publications by Kilgore et al
seem to primarily report results from individual tasks administered during the second night of total sleep deprivation. Subjects were assigned to receive one of the three stimulants or placebo and then performance on reaction time and a number of executive function tasks was measured during the next several hours. On the reaction time task, performance was improved with all three medications compared with placebo by 3.5 hours after administration. Effects from modafinil and dextroamphetamine remained different from placebo until about 11.5 hours after administration while the last point of significant improvement after caffeine administration was 7.5 hours after administration. However, differences were not found when the drug groups were compared with each other [55]. Other test results showed that humor appreciation during the second night of sleep deprivation was improved only by modafinil as compared with the other stimulants and placebo [11]. On the Tower of London task, performance was improved in the modafinil group compared with both caffeine and placebo groups and was improved in the dextroamphetamine group as compared with the placebo group [12]. However, on the Tower of Hanoi task, performance was improved in the caffeine group compared to all other groups and performance was improved in the modafinil group compared with the placebo group [12]. On the Wisconsin Card Sorting Test, performance was significantly better in the modafinil group compared to all others, which did not differ [12]. On the Emotion Hexagon test, performance was improved with all of the stimulant medications compared with placebo, but there was no significant difference between medications [56]. In general, these studies suggest that, at the doses studied, all of the stimulant medications improve reaction time in comparison with placebo and that this
effect is related to the half-life of the medication. The reported effects on executive function tasks appear much more complex. For example, it appears that caffeine provided a large positive benefit for the Tower of Hanoi test but little benefit on the Tower of London and Wisconsin tests. The authors provide a possible explanation of these differing results based upon hypothesized function of different areas of the prefrontal cortex and suggested differing stimulant activation of specific prefrontal areas with respect to sleep loss and functions measured by the test\[12\]. Conversely, because time of test administration was not controlled (the Wisconsin was always given 1 hour after drug administration, the Tower of Hanoi was always 3.5 hours after administration, and the Tower of London was always 4.5 hours after administration), it is possible that the large positive benefit of caffeine in the Tower of Hanoi test occurred simply because the test was administered at the peak of caffeine effectiveness and that caffeine provided less benefit on the other tests because caffeine was not fully available during the first test (or the blood level was too high) and already partially metabolized during the final test. However, it is also possible that these results could be based upon random group differences as these tests do not have parallel forms and were only administered once during the study. In comparison, the Emotion Hexagon test was administered repeatedly and consistent improvement was found for all of the medication groups compared with the placebo group.

One other study has examined caffeine 300 mg and dextroamphetamine 20mg \[26\] on a number of standard sleep deprivation tests following 30 hours of sleep loss. Both stimulants showed significant improvements in all sleep-deprivation sensitive
measures (running memory, logical reasoning, math, Stroop, four-choice, time estimation, tracking, visual vigilance, trails, long term memory) at both 1.5 and 5.5 hours after administration with one exception (logical reasoning at 1.5 hours) for dextroampheta
mine and two exceptions (tracking at 5.5 hours and visual vigilance at 1.5 hours) for caffeine. In one final study, caffeine 200 mg and modafinil 200 mg were compared with placebo all administered at 23:00 preceding 12 hours of flight simulator observations. Both medications improved aspects of flight simulator performance at 0300 and 0500 compared with the placebo group [57].

Overall, these studies suggest that performance on simple tasks involving reaction time can be improved with any of these stimulants and that effects are related to the half-life of the medication. Additional work needs to be done to determine the extent to which different stimulants might be preferentially beneficial for specific types of executive function tasks and at what time during a period of sleep deprivation.

Summary

Many studies have examined caffeine use during periods of sleep loss. The data overwhelmingly support positive effects of caffeine in improving reaction time and vigilance at sufficient doses and within the expected half-life. At least five significant positive results support beneficial effects from caffeine in more complex tasks such as short-term memory (as measured by DSST), grammatical reasoning, driving, completion of addition problems, and tracking. Positive benefits from caffeine on executive function tasks are less clear because less work has been done, the tasks generally do not allow
repeated administration, and the relatively small group studies published have looked at many tasks with little replication of effects. There appears to be an interaction of effective caffeine dose with degree of sleep loss. Doses of 200-300 mg were often recommended for the first night of sleep loss, and doses of 300-600 mg were recommended for a second night of sleep loss. Studies that have suggested that the positive effects of caffeine are related to withdrawal and resumption of caffeine use are limited due to evaluation of very short periods of sleep restriction and very low doses (less than 100 mg) of caffeine. Other studies that have allowed sufficient time for caffeine withdrawal or have used statistical techniques to control for habitual level of caffeine use suggest that caffeine does provide positive benefit during sleep deprivation.

In general, the benefits of caffeine during sleep loss are similar to those of dextroamphetamine and modafinil except that they are shorter acting related to the shorter half-life of caffeine. Recent work showing that modafinil may provide more benefit than caffeine on some tests of executive function require replication in better controlled studies with larger populations.

Significant research remains to be done to further define both active effects and side effects of caffeine. Additional studies of caffeine and modafinil impact on executive function during sleep loss are important. There has also been little work to clearly define the effects of habitual caffeine use, tolerance, and response during sleep loss. One would expect greater effects on individuals with less prior caffeine exposure, but this could imply either greater efficacy at lower doses or increased likelihood of side effects. There are significant individual differences in caffeine sensitivity, but it is not clear
whether these are entirely based on habitual use level or inherent sensitivity (genetics could play a role). Regardless, no studies have really examined the interaction of caffeine sensitivity, sensitivity to sleep loss and potential beneficial effects related to caffeine to allow better generalization of the accepted effects of caffeine.
References


Caffeine and Sleep Loss


Table 1: Caffeine Time to Peak and Maximal Level Based on Route of Administration

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Tmax</th>
<th>Cmax</th>
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<tbody>
<tr>
<td>Gum [4]</td>
<td>50-200 mg</td>
<td>.73-1.34 Hr</td>
<td>0.70-3.70 ug/ml</td>
</tr>
<tr>
<td>Capsule [4]</td>
<td>50-200 mg</td>
<td>1.4-2.0 Hr</td>
<td>1.17-4.13 ug/ml</td>
</tr>
<tr>
<td>Aqueous [5]</td>
<td>350 mg</td>
<td>.78 Hr</td>
<td>8.3 ug/ml</td>
</tr>
<tr>
<td>Slow Release Capsule [6]</td>
<td>600 mg</td>
<td>4.4 Hr</td>
<td>7.7 ug/ml</td>
</tr>
</tbody>
</table>