October 24, 2019

Cover Page:

Official Title of the Study:

A Study to Determine if Caffeine Accelerates Emergence From Propofol Anesthesia

NCT Number:

NCT03360903

Statistical Calculation:

The sample size described above is an estimate, since we could not find good data on human "waking" times from propofol anesthesia in the literature. Thus, we used our own animal studies to estimate sample size. There are at least three reasons why our sample size might be in error. First, rats are not people. They may get rid of propofol differently than do humans due to differences in their P450 enzymes. In addition, rats are genetically more similar to each other than are humans. That would tend to increase human variance relative to that of the rat, leading to errors in sample size estimates. In the animal studies rats were used 4 times (twice with a saline injection twice with an injection of saline containing caffeine), a strategy that also reduced variance.

Additional caveats: The 15 mg caffeine citrate that we propose is equivalent to 7.5 mg/ kg of pure caffeine. We have never tested 7.5 mg/ kg caffeine in rats. Note that all the rat studies were done with pure caffeine, not caffeine citrate.

You will notice that we have kept using the stats for isoflurane below, even though we proposed a propofol study. That is because caffeine was almost identically successful in accelerating emergence from propofol anesthesia as it was for isoflurane anesthesia. The numbers would not change. We had more data with isoflurane.

Finally, we have already completed a small human trial. We observed that caffeine accelerated emergence from isoflurane anesthesia. The reduction in waking time is almost exactly what we expected based on the rat studies. It appears that rat studies are predictive of what caffeine will do in humans.

We use the following stringent criteria to determine sample size: Power will be set to 95% and $p \leq 0.01$.

Rats waking from isoflurane anesthesia with 5 mg/ kg caffeine (isoflurane ~ 1.5 MAC):
(Control - saline injection) - Mean = 540 sec, SD = 159.04
(Test - 5 mg/ kg caffeine in saline injection) - Mean = 269.67 sec, SD = 103.69
At this concentration of caffeine we would need n=12 measurements for control and n=12 measurements for caffeine to meet our stated stringent criteria. If each person were used for one control and one caffeine measurements we would need 12 people for the study.

We are using human volunteers twice, not four times like the rat population, we expect higher variance. Nonetheless, we expect 8 total volunteers will satisfy our study. This is because we are using a higher concentration of caffeine (7.5 mg/ kg), which should produce a larger response than the 5 mg/ kg shown above, and we will employ a lower concentration of propofol (equivalent to ~1 MAC), which should be easier to antagonize.

Crossover study - Each volunteer receives anesthesia 2 times: once without drug (control) and once with caffeine (test). Our animal studies suggest that variance is dramatically minimized when test subjects can be used as their own controls, in this manner. If humans

recapitulate the rodent studies, then 8 volunteers should provide an adequately sized sample to answer the research question.

Statistical Test:

Data analysis for this crossover trial will use a paired t-test, comparing subjects receiving caffeine to those receiving saline.

Protocol:

Each test subject followed the schedule outlined below.
Schema:

Procedure	Screening Session 1	Study Session 1	Study Session 2
Time	1 week prior to study	Start of Study: week 0	Week 2-4
Explain Trial to subject Obtain Consent	X		
Medical History	X		
Physical exam	X		
Vital signs	X	X	X
EKG	X	X	X
Urine Toxicology screen	X	X	X
Enroll Subject in Trial	X		
Psychomotor Training session	X		
Propofol Induction – Isoflurane maintenance		X	X
**Saline Control injection		X	
**caffeine (15 mg/ kg) injection			X
Psychomotor session 1 + 2		X	X
Adverse Event report		X	X

**Please note that the drugs were given in a double-blind manner and were prepared by a hospital pharmacist.

SUBJECT SELECTION AND WITHDRAWAL

Number of Subjects

For this study 8 subjects were tested.

Gender, Age, Racial and Ethnic Origin of Subjects

Healthy male, ages 25 – 40, all race and ethnic origin inclusive.
Our animal studies were carried out in adult male rats equivalent to the age range listed above. The effects of anesthesia and the study drug on fetuses are not entirely known. The tests for early pregnancy are not 100% reliable. In males, pregnancy is not a possibility. Children can have adverse reactions to anesthetics, and they will not be recruited. Therefore, male volunteers exclusively were selected in this study. In order to further reduce the variables and minimize the risks for the subjects, exclusion criteria are used to select the subjects who are most suitable for this primary study.

[Note that future studies will employ female volunteers and that caffeine accelerated emergence from anesthesia in female rats to a similar extent as it did male rats].

Inclusion Criteria

1. Age 25-40
2. Male
3. Normal healthy subject without systematic diseases or conditions
4. Metabolic Equivalents of Functional Capacity ≥ 5
5. Low risk for Obstructive Sleep Apnea (OSA) based on the screening test (STOP-bang score established by American Society of Sleep Apnea): Yes to > 3 items- high risk of OSA
6. No History of Arrhythmia (Baseline EKG will be obtained during the history and physical session), seizure, liver and kidney diseases
7. BMI < 30 kg/m2
8. No prior difficulty with anesthesia
9. No personal or family history of malignant hyperthermia
10. No history of any mental illness
11. No history of drugs or alcohol abuse (urine drug screens required).
12. Subjects capable of giving consent.
13. Living less than 30 miles away from UC.
14. No history of seizure disorders.
15. No history of head trauma.

Exclusion Criteria

1. Age <25 or >40
2. Female
3. ASA physical status > 1 (normal healthy subject without systematic diseases or conditions)
4. Metabolic Equivalents of Functional Capacity (METs) < 5
5. High risks for Obstructive Sleep Apnea (OSA) based on the screening test (STOP-bang score established by American Society of Sleep Apnea): Yes to > 3 items- high risk of OSA
6. History Arrhythmia (Baseline EKG will be obtained during the history and physical session), seizure, liver and kidney diseases
7. BMI > 30 kg/m2
8. Prior difficulty with anesthesia
9. Personal or family history of malignant hyperthermia

10. History of any mental illness
11. History of drugs or alcohol abuse (urine drug screens required)
12. Subjects incapable of giving consent
13. Living more than 30 miles away.
14. History of seizure disorders.
15. History of head trauma.

Vulnerable Subjects

No vulnerable subjects were used.

Subject Identification & Recruitment

Brochures, flyers and posters were distributed throughout Chicago.

Location

The University of Chicago Center for Care and Discovery recovery room. This facility is outfitted with all the necessary emergency and equipment required to maximize safety. The isolation recovery room that we use is perfect for our purposes since it is soundproof.

Informed Consent Process

We emailed the informed consent document prior to meeting the test subject. We asked them to read the document prior to meeting with us. When they arrived at the University of Chicago for their first visit, one of the anesthesiologists provided a verbal explanation of the study to the subject and answered all questions regarding this study. Then, a written description of the study was provided to the subject, even though they had seen this already. Afterwards the subject was required to describe the study in their own words showing that they understood the purpose of the study, the risks involved and their own role in the study. If any risks were not well understood, the members of our team explained the trial again, in detail. The subject and the person who administered the informed consent signed and dated the document. A copy of the informed consent form was given to the subject and the original was kept in the subject's record.

Formulation of the Study Drug

Caffeine citrate (caffeine), is available commercially. It was ordered by the University of Chicago hospital pharmacy. Placebo control was a sterile saline solution.

Treatment Regimen

The study drug (caffeine citrate) or the placebo (a saline solution) was given intravenously 10 min before the end of 1.5 hour propofol anesthesia. Caffeine citrate was administered at a dose of 15 mg/ kg. There was a single injection of either caffeine or a saline placebo control solution in the anesthetized test subjects. The drug was injected slowly across a 10-minute interval, in order to prevent concentration spikes in the subject. A pump infuser was used to introduce the drug. The subjects were told not to eat or drink for 8 hours prior to anesthesia.

An example of the method of administration may be illustrative. The drug, caffeine citrate and comes in a single dosage of 20 mg caffeine per ml of solution. Let's say a volunteer

weighs 65 kg. The dose we used for this trial was 15 mg/ kg. Therefore the volunteer got a 48.75 ml injection of caffeine citrate. The 48.75 ml of caffeine citrate was introduced slowly, across a 10-minute time window, to prevent spikes in the circulating caffeine concentration. The caffeine was introduced via a pump infuser. In this case the subject will get 975 mg of caffeine citrate that is equivalent to 487.5 mg of pure caffeine.

Preparation and Administration of Study Drug

All drugs will be stored and/ or prepared by the IDS group and provided to the research team on the day of each session.

The IDS office has equipment necessary to store, prepare, and dispense all categories and dosage forms of drugs and biologics. IDS pharmacists and technicians along with other supporting pharmacy personnel provide services to faculty, investigators, pharmacy staff, nursing staff, and subjects enrolled in research protocols. The IDS office is open up to 10 hours per day on weekdays or a staff member is on call 7 days per week. Key staff members in the central pharmacy provide dispensing support twenty-four hours a day when IDS staff is not present

Required documents for every research study are placed in designated binders. They contain sections for: Randomization schedule, Drug Accountability Records, Drug Receipt Records, Subject scripts and consent signature pages, Drug Order Forms (if applicable) or information on how to get a re-supply of drug, and any other miscellaneous forms needed. For all studies, a protocol specific procedure sheet is prepared. Each subject's order is verified with the protocol assigned and with the subject's dispensing history prior to dispensing any study medications. Discrepancies are discussed with the study nurse or physician, as appropriate. The presence of the subject’s signed inform consent is verified by the pharmacist. The protocol is reviewed for all pharmaceutical information prior to attempting to prepare a study medication. A pharmacy protocol specific procedure sheet is reviewed before drug preparation is set up by the pharmacist processing the order. The Central Pharmacy area maintains all investigational drug supplies handled by the inpatient pharmacy. The IDS provides training to essential staff to provide service to protocols that require continuous service 24 hours per day, 7 days per week, and 365 days per year.

IDS maintains drug accountability records in compliance with state and federal regulations and the specific requirements of each protocol. At study termination when study drug has been either returned to the sponsor or destroyed, all drug accountability records and study-related documents are transferred to the investigator.

Medications and Therapies

Our goal is to identify a relatively young cohort of healthy volunteers. Thus patients taking drugs for chronic conditions were not chosen.

Propofol is the preferred agent for the induction phase because it does not cause airway irritation. Propofol will be used as the main anesthetic agent as it is an extremely safe anesthetic that has been used for decades. During this study, we do not plan to use other anesthetic agents, such as midazolam, fentanyl, and muscle relaxants to minimize the interactions of these drugs to our study drug. However, drugs are available at the bedside in case they are needed. If an unexpected airway emergency occurs, the ASA difficult

airway algorithm will be applied for airway management. The subject will be allowed to breathe spontaneously unless the tidal volume is less than 3 ml/kg. We will optimize the tidal volume at around 5 ml/kg. Pressure support mode may be applied to optimize the tidal volume if necessary. The study drug (caffeine citrate) or the placebo control will be given intravenously 10 min before the end of 1.5-hour propofol anesthesia. The anesthesiologists will be blinded to the medication injected to the subject since the drug or normal saline is prepared by the pharmacists in the OR pharmacy. When propofol is turned off, the subject eliminated propofol enzymatically.

There will be at least two anesthesiologists present during the entire period that anesthesia is administered. Each subject will be given a dose of antiemetic medication, zofran (4 mg) 20 minutes before the end of the anesthesia to minimize the incidence of post anesthesia nausea and vomiting. During the period of anesthesia, we will keep the subject's BP within 30% of its pre-anesthesia value. If the BP falls more than 30% of the baseline, we will first give IV fluid to replete the fluid deficit due to the restriction of fluid intake prior to the study. If that is not sufficient to raise the BP, we will reduce the concentrations of propofol by 0.1% at a time until we can maintain the BP close to the normal range. Vasoactive medications will be given only if absolutely necessary but they will be available. Volunteer safety is our first priority.

[Intraoperative hypotension is not well defined (Bijker *et al.*, 2007). In clinical practice, changes of 20 - 30% of the baseline mean MP or SBP are well accepted. Transient change of BP in this range is usually clinically insignificant. Healthy volunteers tolerate these changes better than sick surgical patients. In general, lowering of blood pressure by an anesthetic is also dose dependent. Hemodynamic changes are very fluid during anesthesia. It is important not to overcorrect the minor transient change of BP and heart rate. **Nonetheless, in this trial with healthy volunteer, we will use a change of 30% from the baseline (MBP or SBP) for more than 5 min as our trigger for intervention**].

In the previous clinical trial, IRB15-0897 that was just completed, no significant alterations in heart rate, blood pressure or blood oxygenation were observed.

Procedures:

Each subject will attend 4 sessions to complete the study.

5.1 Screening Session 1

In the first screening session, an anesthesiologist explained the purpose of the trial and carefully went over the consent form. If the subject was willing to enroll the consent form was signed. Next, the anesthesiologist took a detailed medical history and performed a physical examination of the subject. A baseline EKG and urine toxicology screen text will be obtained. If the subject met the criteria for the study, the subject was be enrolled in the trial. At this point a pre-study training session was provided to familiarize the subject with the psychomotor tests.

5.2 Study sessions 2 – 3

In the following two sessions, each subject received general anesthesia in one session (with a saline injection as a placebo control) and receive general anesthesia and caffeine citrate (15 mg/ kg equal to 7.5 mg/ kg of pure caffeine) in the other session in a randomized manner. For each subject, each session involving anesthesia was at least 2 weeks apart.

For each session, subjects were asked not to eat and drink 8 hours prior to the study in order to minimize the potential risk for aspiration during anesthesia. They were asked to refrain from alcohol or drug use for 24 hours prior to the sessions. A toxicology screen was used for each session. Once the subject was checked in, a peripheral intravenous catheter (IV) was be inserted on one of the arms by the anesthesiologist (Xie or Fong). The IV was used to administer medications during the course of the study. After the IV insertion, American Society of Anesthesiologists (ASA) standard monitoring, including EKG, blood pressure (BP), respiratory rate, end tidal CO_2, pulse oximetry, BIS monitor and temperature, was used to assess the subject (see below for further details). The BIS monitor measured depth of anesthesia. The subject was asked to breathe 100% O_2 via a nasal cannula for 10 minutes prior to starting anesthesia. A bolus of propofol (1 mg/kg) was be injected via the I-V line (induction). The subjects became unconscious within 1-2 minutes. This was followed by infusion of propofol at a rate of 150 μg/kg/min via an infusion pump for 90 min (maintenance phase). The goal was to keep the subject breathing spontaneously throughout the propofol anesthesia. However, obstruction of airway can occur even though we exclude subjects with history of obstructive sleep apnea (OSA) in this study. We monitored the breathing with end-tidal CO_2 ($ETCO_2$) measurements. This corresponds to the amount of CO_2 being expired. The $ETCO_2$ sample line, connected to the nasal cannula, allowed $ETCO_2$ and the respiration rate to be monitored throughout the duration of anesthesia. If $ETCO_2$ is lower than 20 or higher than 50 mmHg, or if the respiration rate falls below 8 breathes per minute or becomes irregular, then it was possible that some degree of airway obstruction had occurred. To relieve any possible airway obstruction, we took the following steps. 1. Reposition the head of the subject. For all test subjects in this trial who exhibited breathing irregularity, repositioning the head restored normal breathing. Nothing more was required. Nonetheless we were prepared to proceed as follows: 2. Change the nasal cannula to a face mask as this helps people who breathe via their mouths. If steps 1 and 2 do not remediate the problem, then 3. an oral airway will be inserted. 4. Insertion of a nasal airway if steps 1-3 do not work. In majority of the situations, airway obstruction can be avoided with these maneuvers even in the patients with obstructive sleep apnea.

The goals are to keep the pulse oximetry above 95% and ETCO2 between 20 to 50 mmHg sampled via nasal cannula. In rare occasions, airway obstruction can persist with these maneuvers. If the problem still persists, then a LMA will be inserted. Note that an LMA was inserted in every test subject in the isoflurane trial recently completed. In the current trial, we believe that a simpler solution, a nasal cannula, will suffice.

We kept BP and HR within the 30% of the baseline. In general, like most general anesthetics, propofol at a moderate dose (150 mcg/kg/min) lowers BP somewhat due to its anxiolytic and vasodilating effects. The effect is dose-dependent. If a drop in blood pressure was observed, we would increase the introduction of IV fluid to replete the fluid deficit due to the subject's NPO status upon arrival. In general, fluid repletion will help to rectify the hypotension due to the vasodilation effect of propofol. If fluid repletion does not work, phenylephrine (alpha 1 agonist) or ephedrine (alpha and beta agonist) was to be used, but none was required. These are short acting agents that are used commonly in anesthesia to overcome the temporary effect of anesthetics. (If these interventions did not work, the trial was to be stopped. This did not happen).

If a hypotensive event was not resolved by fluids, we would give vasoactive medications (phenylephrine, 100 μg per dose or ephedrine 5 mg per dose). These drugs work rapidly when given as a bolus. And they are short acting. They are commonly used in the OR to temporarily raise BP. These are relatively weak vasoactive drugs which do not cause long term effects on patients when given in small doses. If the heart rate (HR) is over 70 beats per second, phenylephrine will be used. Phenylephrine typically increases BP and lowers HR, as it acts on alpha adrenergic receptors. If the heart rate is under 70 beats per second, ephedrine will be used. Ephedrine usually increases both BP and HR as it acts on both alpha and beta adrenergic receptors. If a first dose did not resolve the event within 2 minutes, then a second dose was to be applied. We would limit the doses to a total 3 of either drug. That would allow us time to replenish the fluid due to the NPO status of the test subjects. If these measures did not resolve the hypotensive event, then the propofol was be terminated. Subject safety always remained our overriding priority. Although they were available, no vasoactive medications were required in this trial.

Originally, we had proposed measuring propofol levels in the blood in real time by a pelorus 1500 (Sphere Medical) machine at 30 min, 60 min, before the infusion of caffeine, at the first sign of emergence, 30 min post propofol infusion,1 hr post propofol infusion and at 90 min post propofol infusion. In total we envisioned 7 measurements of the propofol levels in the test subject's blood. Unfortunately, the Sphere Medical company went bankrupt just before our trial started. So we took very small blood samples (3 mls) at all the time points shown above. Each sample was put on ice during the anesthesia session. Afterwards, the blood samples had the propofol extracted and the quantified with a HPLC apparatus. In this manner, we obtained a time course of propofol in the blood throughout the anesthesia session.

Clinically, a maintenance dose of propofol is in the range of 100 to 400 μg/kg/min. For this study we chose a low to moderate dose of propofol at 150 μg/kg/min in order to lower any possible adverse hemodynamic effects and respiratory depression. A 90 minute infusion ensured that a stable concentration of propofol in the blood haf been achieved.

Ten minutes before terminating the propofol, volunteers were infused with a solution containing saline (control) or with caffeine (test). **After the termination of propofol, the subject was allowed to wake up. This phase is called the emergence phase of anesthesia. We will test whether the caffeine shortens the emergence phase of anesthesia.**

[EKG, respiratory rate, end tidal CO_2, pulse oximetry and temperature were monitored continuously, once the volunteer was connected to the monitoring machines. A bispectral index (BIS) monitor, continuously measured depth of anesthesia. Prior to starting the procedure, blood pressure was be measured every 5 minutes; this measurement of blood pressure provided the baseline for subsequent BP measurements. Blood pressure was measured every 2 minutes during the first 10 min of the anesthesia, which included the induction period. BP was measured every 5 min throughout the course of anesthesia and the first 30 min in the PACU. After that, BP was measured every 10 min until the subject was discharged. This data is stored automatically for each patient in our hospital's Epic database. For some of the test subjects a full EEG was obtained as well, in addition to the BIS measurements].

Propofol is the preferred agent for the induction phase because it does not cause airway irritation. Additionally, propofol is normally used for anesthesia induction in human patients. Propofol is also a safe and effective anesthetic for the maintenance phase of anesthesia. During this study, we do not plan to use other anesthetic agents, such as midazolam, fentanyl, and muscle relaxants to minimize the interactions of these drugs to our study drug. However, other drugs and muscle relaxants are available at the bedside in case they are needed.

Potential risks:
Severe:
Anaphylactic and anaphylactoid reactions. People who have severe allergic to eggs, egg products, soybeans or soy products will be excluded from this study.

Propofol infusion syndrome: A rare syndrome usually is related to long-term treatment with high doses of propofol (>4 mg/kg/h for more than 24 hours). Mostly it occurs during its use in ICU. It can lead to cardiac failure, rhabdomyolysis, metabolic acidosis and kidney failure. It rarely occurs in long-term use and is exceptionally rare in short term use.

Mild and moderate:
Common: transient local Pain on administration. The pain may be reduced by prior injection of IV lidocaine (3 ml 1% lidocaine). This practice is used every day in clinical practice.

Mild to moderate Hypotension and respiratory depression (addressed as above).
Rare: Myalgia, pruritus, nausea (generally works as antiemetic) and dizziness, somnolence.

Back-up plan:
Muscle relaxants are available at the bedside in case they are needed for the management of unexpected airway situations, such as laryngeal spasm. If an unexpected airway

emergency occurs, the ASA difficult airway algorithm was to be applied for airway management. The study drug (caffeine citrate) or the placebo control was given intravenously 10 min before the end of 90 min propofol anesthesia. The anesthesiologists were blinded to the medication injected to the subject since the drug or normal saline is prepared by the pharmacists in the IDS group pharmacy.

There were at least two anesthesiologists present during the entire period that anesthesia was administered. A dose of antiemetic medication, zofran (4 mg) was given during the recovery period. During the period of anesthesia, the subject's BP was kept within 30% of its pre-anesthesia value. If the BP were to fall more than 30% of the baseline, we would first give IV fluid to replete the fluid deficit due to the restriction of fluid intake prior to the study. If that was not sufficient to raise the BP, vasoactive medications were to be given. None were needed. Volunteer safety was our first priority.

[Intraoperative hypotension is not well defined (Bijker *et al.*, 2007)). In clinical practice, changes of 20 - 30% of the baseline mean MP or SBP are well accepted. Transient change of BP in this range is usually clinically insignificant. Healthy volunteers tolerate these changes better than sick surgical patients. In general, lowering of blood pressure by an anesthetic is also dose dependent. Hemodynamic changes are very fluid during anesthesia. It is important not to overcorrect the minor transient change of BP and heart rate. **Nonetheless, in this trial with healthy volunteer, we will use a change of 30% from the baseline (MBP or SBP) for more than 5 min as our trigger for intervention**].

The study drug (caffeine citrate) or the placebo (saline) was given intravenously 10 min before the end of 1.5 hour propofol anesthesia. When propofol was turned off, the subject metabolized the drug. We measured the time between when the propofol was stopped to the awakening of the subject. We recorded the time until the subject's eyes opened, until the subject's mouth opened, and the time until the subject responded to the command to grip the hand of the attending physician. After the subject was awake and relatively alert, he performed psychomotor tests to measure his cognitive function. The subject were required to complete a simple set of cognitive tests to determine if they were still impaired by anesthetic. Both "control" and test subjects were required to complete the same tests. In total there are 3 different tests. The tests were repeated every 15 minutes in order to obtain a recovery time course.

There were two anesthesiologists present during the entire period of anesthesia. Each subject was given a dose of antiemetic medication, zofran (4 mg) 20 minutes before the end of the anesthesia to minimize the incidence of post anesthesia nausea and vomiting. During the period of anesthesia, the subject's BP was kept within 30% of its pre-anesthesia value. If the BP were to fall more than 30% of the baseline, for more than 5 minutes, we would first give IV fluid to replete the fluid deficit due to the restriction of fluid intake prior to the study. Vasoactive medications were to be given if necessary. None were required.

After the propofol was stopped and the subject awake, oriented and showing stable vital signs, one of the anesthesiologists was allowed to leave the room to prepare for the afternoon anesthesia session. There was always one anesthesiologist with the test subject at all times. Most of the time there were two anesthesiologists.

At the conclusion of the study, we discharged the subject based on the criteria used in our post anesthesia care unit in the hospitals. In general, the subject should be awake and alert with the stable vital signs. He should be able to drink clear liquid, void and ambulate before discharge home. We call an Uber car for him without cost to the subject. The subject lived within 30 miles of The University of Chicago to make sessions easily accessible. Upon discharge, the subject was required to be accompanied by a responsible adult. Each session for any given subject was at least 2 weeks apart. The total time of each session, including the pre-anesthesia preparation, testing and recovery from anesthesia, was be ~4 hours. We called the subject on the same day and the next day after each session to make sure the subject fully recovered without any adverse event. The subject received another call a week after the procedure.

Subjects were tested in this manner a total of two times. In one of the tests they were anesthetized with propofol and injected with a saline solution and in one test they were anesthetized with propofol and then injected with caffeine citrate (15 mg/ kg).

After terminating anesthesia, the subject performed psychomotor tests to measure his cognitive function. The subject was required to complete a simple set of cognitive tests to determine if he was still impaired by anesthetic. Both "control" (saline injection) and test subjects (those that obtain caffeine) were required to complete the same tests. Memory was tested with sequences of numbers, after which the subject was asked to recall the numbers. Similarly, subjects were shown a series of words and were asked to remember that sequence. Next, the test subject was shown a computer screen showing an airplane flying over a road. The road moves and winds continuously. Using a joystick the test subject is asked to keep the airplane flying over the road. While the flight is occurring, at random intervals, a target appears on the screen. The test subject was required to shoot the target down. Reaction times are measured.

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