Energy Products in a 24/7 World:
Illustrations from Research and Possible Research Gaps

David F. Dinges, PhD

Professor and Director, Unit for Experimental Psychiatry
Chief, Division of Sleep & Chronobiology
Department of Psychiatry, Perelman School of Medicine
University of Pennsylvania

National Institutes of Health
The Use and Biology of Energy Drinks:
Current Knowledge and Critical Gaps
August 15-16, 2013

Disclosures:

Member, Mars Scientific Advisor Council (MSAC of Mars, Inc.)

Editor in Chief of *SLEEP* (AASM and SRS)

Coffee drinker

Goal of this presentation is to identify research needs relative to three areas

- Determine the *cumulative* effects of caffeine on behavior and physiology.
- Identify populations that may be vulnerable to the cumulative effects of caffeine if these pose risks.
- Discuss methods for assessing the accuracy of the claims made relative to energy drink consumption.

“Energy” has changing meanings

Medical Definition:

1. The force driving and sustaining mental activity
2. The capacity for doing work

(MedlinePlus Medical Dictionary, http://www.merriam-webster.com/medlineplus/stimulant)

NUTRITION REVIEWS 70 YEARS 1942-2012

Special Article

Do energy drinks contain active components other than caffeine?

Tom M McLellan and Harris R Lieberman

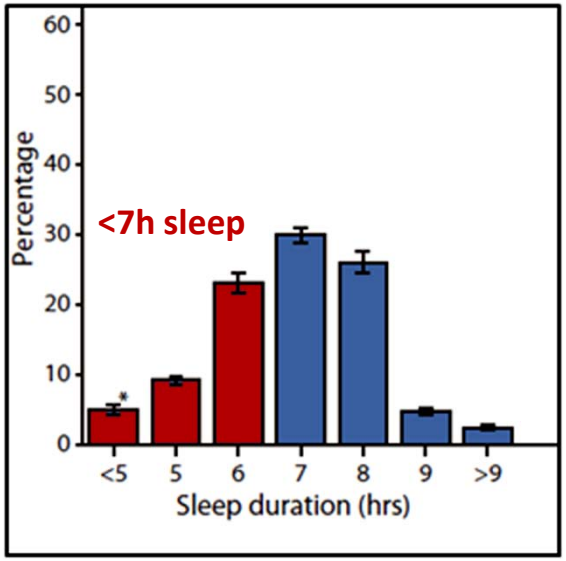
By its classic physiologic definition, energy represents work performed per unit of time and is a purely physical concept. More recently, however, the concept of mental energy has been introduced to define a uniquely cognitive domain of energy that refers to cognitive performance and mood.[26–30] Energy drinks are marketed to

Common causes of 'Low Energy'
(Increased fatigue* / Decreased alertness)

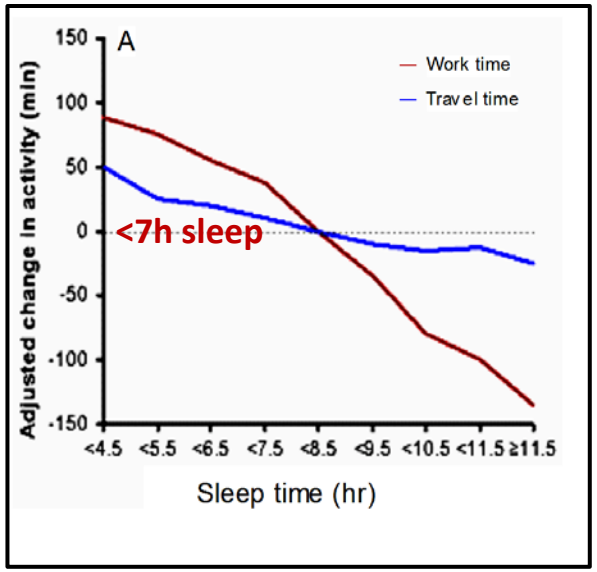
- **Sleep loss = Sleepiness from inadequate sleep**
  - Chronic Partial Sleep Restriction (e.g., *Habitually sleeping <7h/night*)
  - Acute Total Sleep Deprivation (e.g., *Pulling 'all-nighters' to meet deadlines)*
- **Circadian phase / Time of day = Tiredness/sleepiness/fatigue**
  - 'Dips' in alertness at 0200h-0800h, 1300h-1500h (e.g., *Night work; need for a nap*)
- **Sleep inertia = Grogginess and low energy after awakening**
  - Performance impairment and tendency to return to sleep immediately after awakening. (e.g., *Early work/school start times; long commute*)
- **Time on task = Decreasing energy as activity continues**
  - Accuracy and/or reaction times degrade over time when performing a cognitive task. (e.g., W*orking >8h shifts; inadequate rest breaks from work; high rate of work intensity*)

*excludes medical conditions that use the word "fatigue"

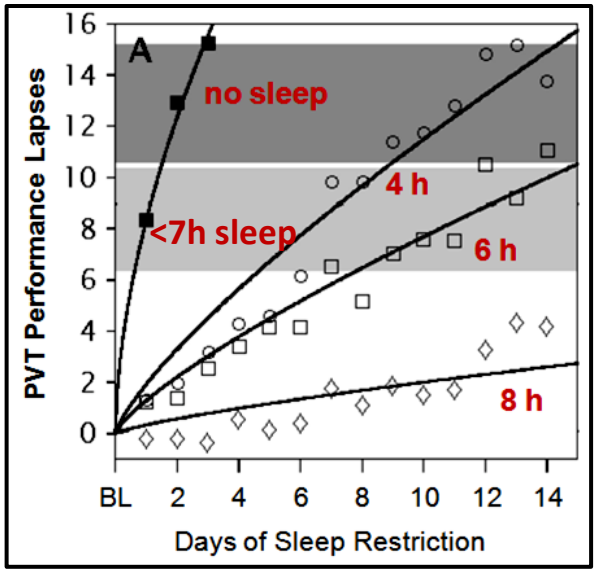
Inadequate sleep is a major cause of 'Low Energy'



Self-reported sleep duration among US adults ≥ 20y from 2005-08: 37% of Americans reported <7h sleep; CDC National Health and Nutrition Examination Survey (NHANES).



American Time Use Survey (ATUS) revealed that paid work and travel time were associated with less sleep (Basner et al. SLEEP, 2007).



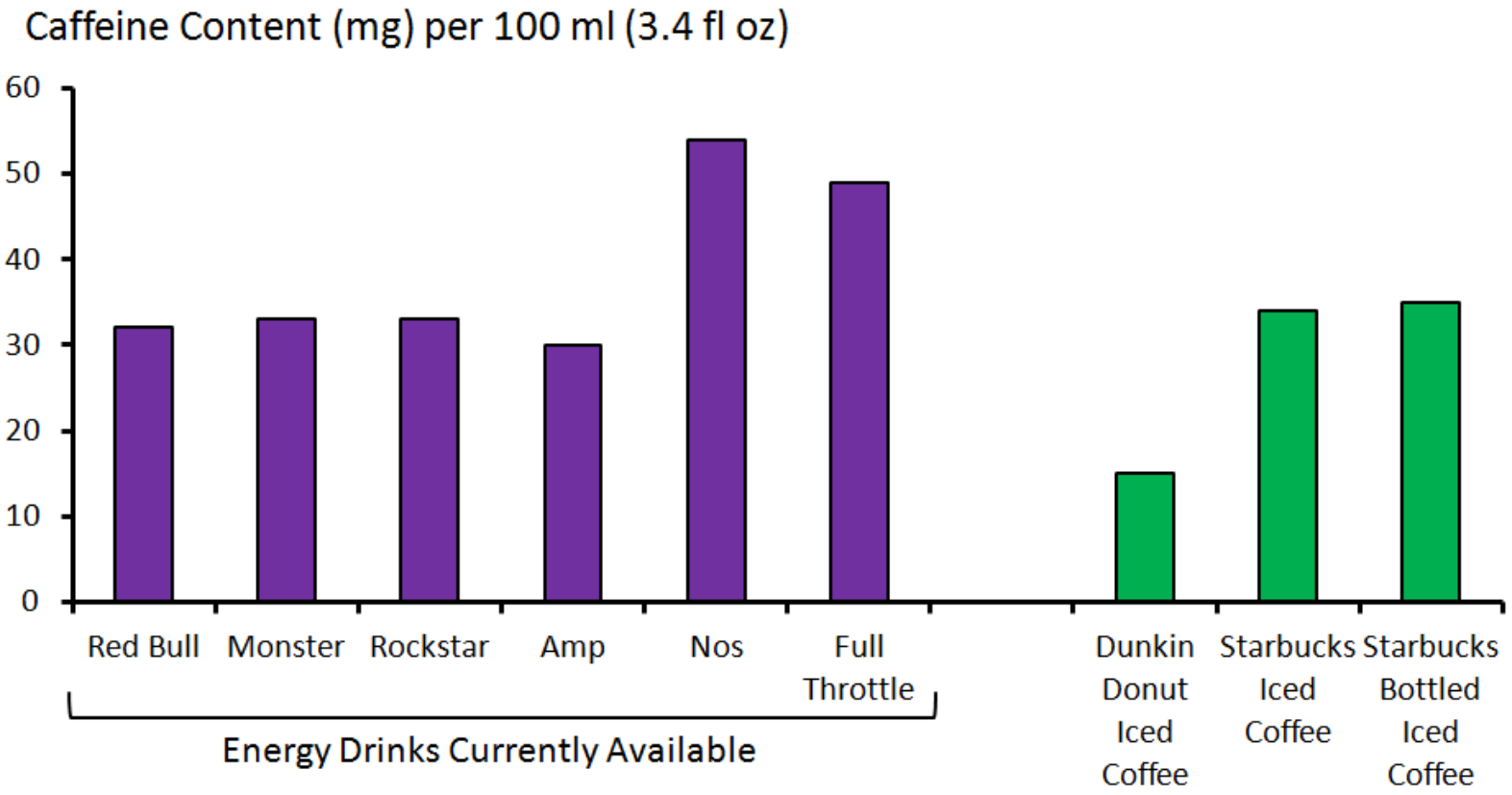
Nightly sleep durations <7h results in cumulative deficits in behavioral alertness (Van Dongen et al. SLEEP, 2003).

Energy drinks and "stimulants"*
(as I understand the current use of terminology)

- FDA does not formally define the phrase **"energy drink"**.
- **"Energy drinks"** typically contain **stimulants** (primarily caffeine) and are marketed as providing mental or physical stimulation or energy.
- **"Energy shots"** contain similar ingredients to energy drinks, but in a smaller amount of liquid (~50 ml).
- From 2011-12 to 2012-13 U.S. energy drink sales **increased 6.7% to $9.7 billion** (source: Symphony IRI data compiled by Bloomberg)

* A stimulant or "psychostimulant" is typically a chemical agent that produces a temporary increase in the functional activity or efficiency of an organism or its parts; or that accelerates physiological or organic activity. (sources: MedlinePlus Medical Dictionary, http://www.merriam-webster.com/medlineplus)

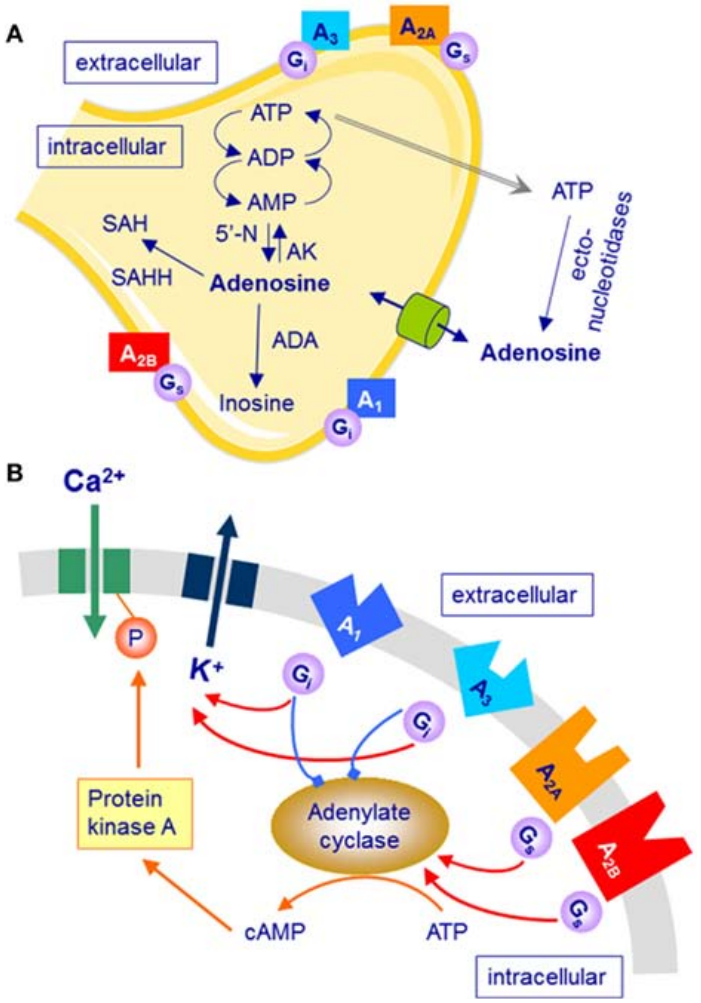
Web-based claims for caffeine levels in top-selling energy drinks, shots and other foods



Source: http://www.energyfiend.com/ -- website mission statement: “Accurate caffeine information must be freely available to all”

Caffeine as the most common stimulant

- Found naturally in seeds, leaves and fruit of some plants (natural pesticide)
- Most widely consumed psychoactive substance in the world
- Third most frequently detected organic wastewater compound (source: Lee et al. U.S. Geological Survey Updated 9/2012)
- Absorption from the GI tract is relatively rapid (~45 min post-ingestion)
- Primary mechanism of action
  - Antagonizes Adenosine receptors A_1 and A_{2A} (via competitive inhibition)
  - Chronic treatment with caffeine results in upregulation of A1 receptors in the CNS (Boulenger et al., 1983; Marangos et al., 1984)



(A) Neurons, astrocytes, and microglia cells can release adenosine and adenosine-tri-phosphate. All cell types express adenosine receptors, adenosine transporters (cylinder), and ecto-nucleotidases that convert ATP into adenosine.

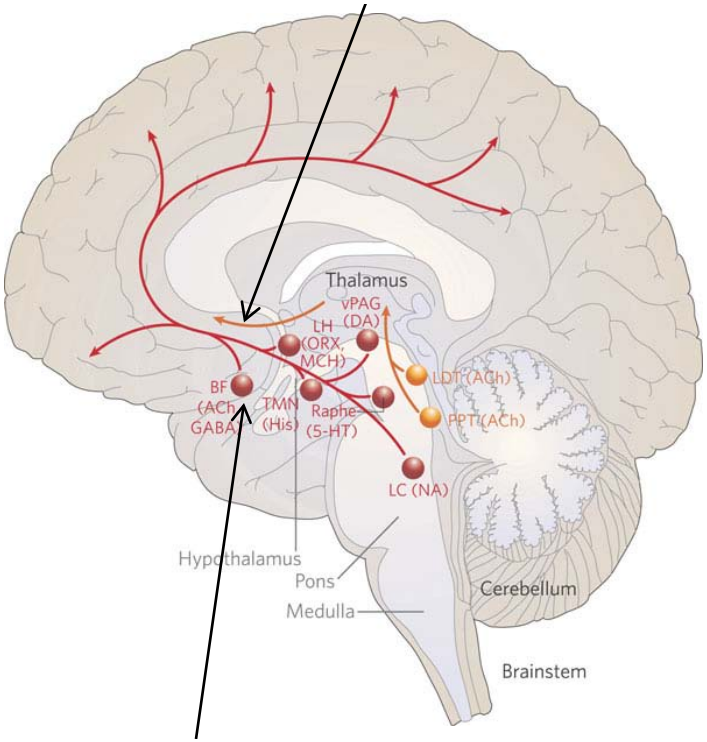
(B) Activation of adenosine receptors either inhibits ($A_{1/3}$ receptors) or stimulates ($A_{2A/2B}$ receptors) adenylate cyclase and the cyclic AMP pathway.

Source: Landolt et al. (2012) *Frontiers in Sleep and Chronobiology*

<u>Research need</u>: Caffeine (and likely all energy drinks) are not chemical substitutes for sleep. There is a need to identify how biological mechanisms of energy drinks relate to the growing body of knowledge on the neurobiological regulation of sleep-wake states and circadian rhythms.

Ascending Arousal System

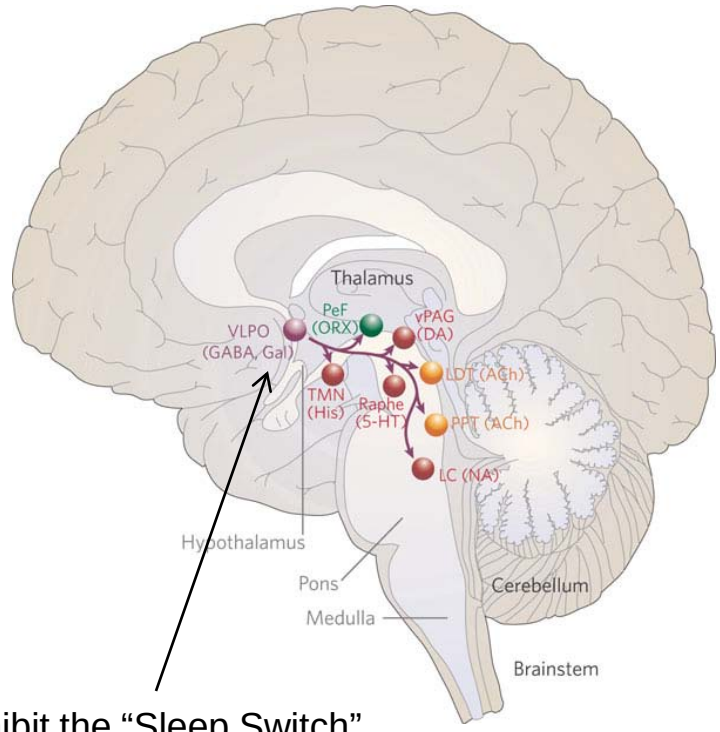
Inhibit Orexin/Hypocretin Neurons



Block the build-up of adenosine in the Basal Forebrain (thus inhibiting excitatory cholinergic neurons)

Ventrolateral Preoptic Nucleus (VLPO)

Projections to the Ascending Arousal System



Inhibit the "Sleep Switch" (VLPO) from turning on

Saper, 2005, *Nature*

Ferre, 2010, *J Alzheimers Dis*

Goal of this presentation is to identify research needs relative to three areas

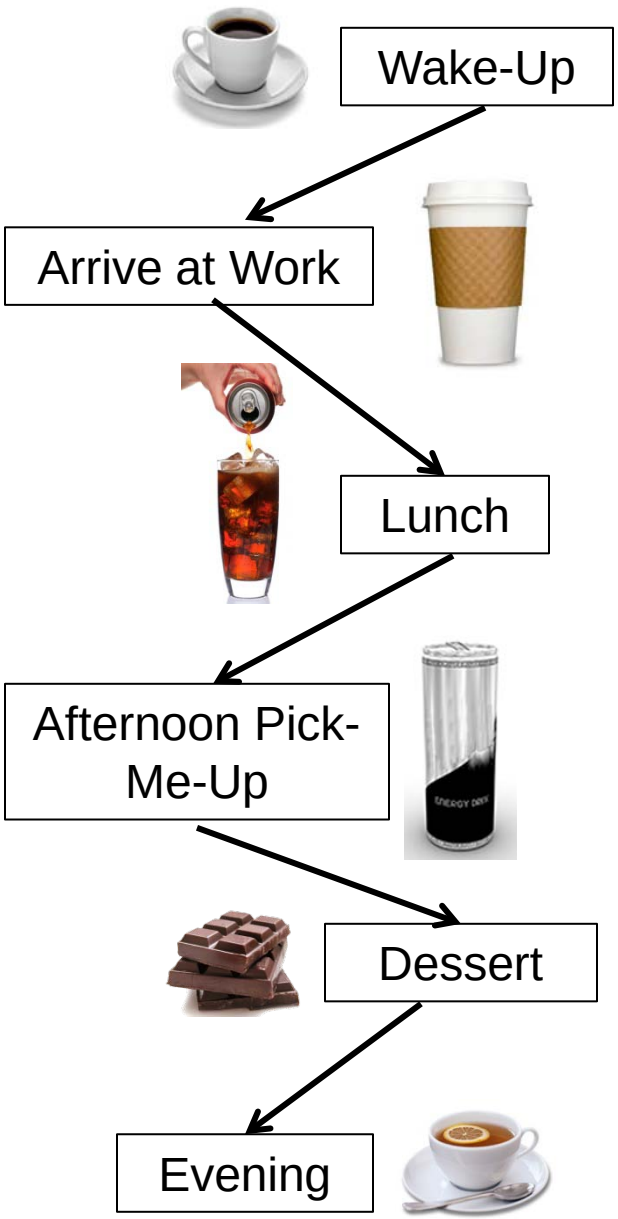
- Determine the *cumulative* effects of caffeine on behavior and physiology.
- Identify populations that may be vulnerable to the cumulative effects of caffeine if these pose risks.
- Discuss methods for assessing the accuracy of the claims made relative to energy drink consumption.

Caffeine ingestion from multiple sources

- 80-90% of adults in the U.S. consume caffeine <u>every day</u> (Frary et al., 2005).
- Caffeine is a drug and a food additive.

  People are not always aware that caffeine is added to many products to increase flavor and to medications to increase speed of relief.
- Multiple caffeine sources make estimating habitual caffeine intake difficult.

  Actual caffeine consumption was up to 250% higher than self-reported values in one study (Wendte et al. 2003).



Caffeine use may not be associated with some medical risks, or may even be beneficial (examples)

Title: Coffee and tea consumption are associated with a lower incidence of chronic liver disease in the United States
Author(s): Ruhl, CE; Everhart, JE
Source: GASTROENTEROLOGY Volume: 129 Issue: 6 Pages: 1928-1936 DOI: 10.1053/j.gast.2005.08.056 Published: DEC 2005
Conclusion: Coffee and tea drinking decreases the risk of clinically significant chronic liver disease.

Title: Coffee consumption and coronary heart disease in men and women - A prospective cohort study
Author(s): Lopez-Garcia, E; van Dam, RM; Willett, WC; et al.
Source: CIRCULATION Volume: 113 Issue: 17 Pages: 2045-2053 DOI: 10.1161/CIRCULATIONAHA.105.598664 Published: MAY 2 2006
Conclusion: These data do not provide any evidence that coffee consumption increases the risk of coronary heart disease.

Title: Long-term alcohol and caffeine intake and risk of sudden cardiac death in women
Author(s): Bertoia, Monica L.; Triche, Elizabeth W.; Michaud, Dominique S.; et al.
Source: AMERICAN JOURNAL OF CLINICAL NUTRITION Volume: 97 Issue: 6 Pages: 1356-1363 DOI: 10.3945/ajcn.112.044248 Published: JUN 2013
Conclusion: Total caffeine, regular coffee, decaffeinated coffee, and regular tea intake were not associated with the risk of sudden cardiac death in women.

Effects of sustained low-dose (0.3mg/kg) caffeine on sleep inertia (PVT performance)

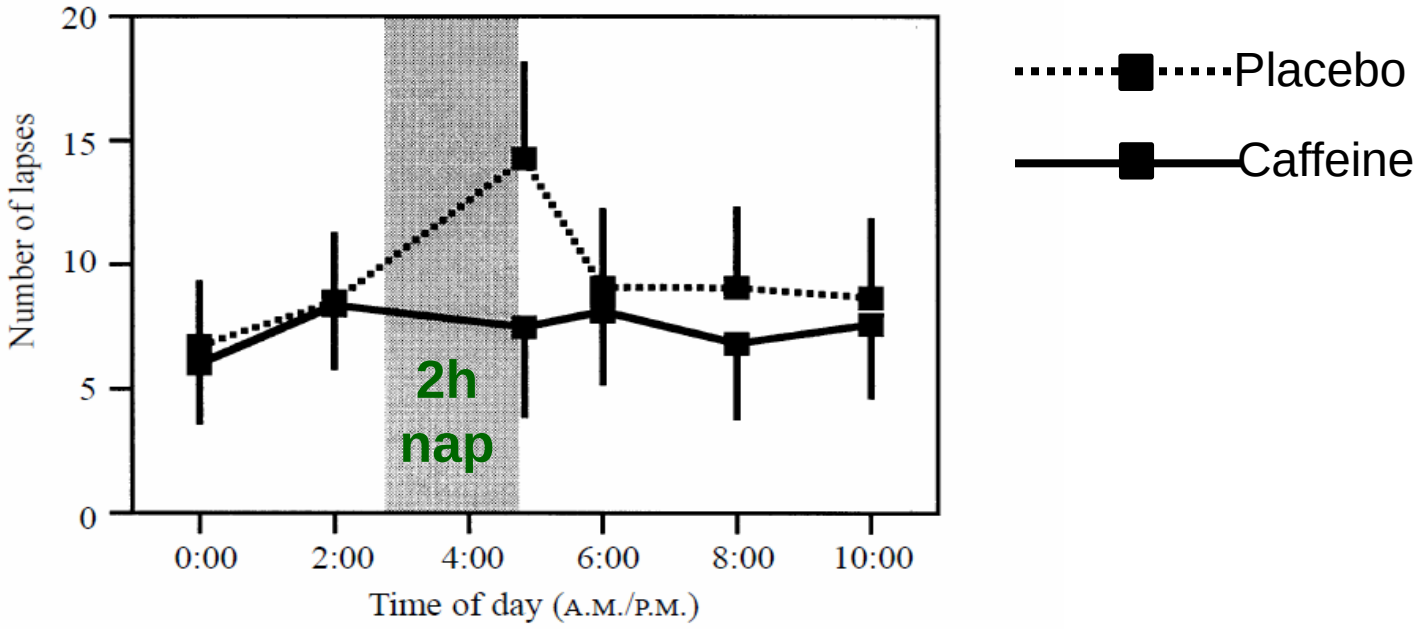


Figure 3—Psychomotor vigilance performance and sleep inertia. Mean number of performance lapses (total per test bout) and standard errors of the mean (vertical bars) on the psychomotor vigilance task are shown. Dotted lines indicate the placebo condition; solid lines indicate the caffeine condition. The data are presented as collapsed over the consecutive 12-hour segments around the last five naps of the experiment. Thus, the abscissa is collapsed over P.M. and A.M. times of day; naps (gray bar) took place from 14:45 until 16:45 and from 02:45 until 04:45. Sleep inertia was consistently observed immediately after each nap in the placebo condition, but not in the caffeine condition.

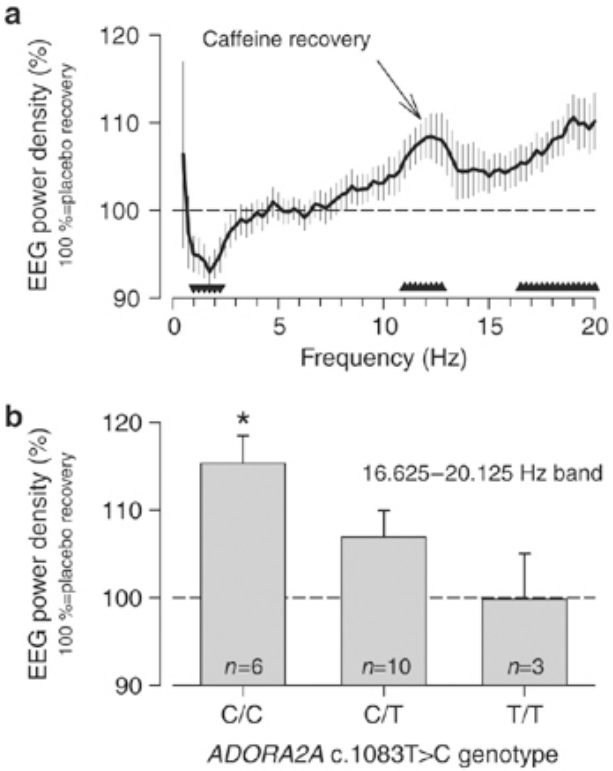
Van Dongen. et al. (2001). Caffeine eliminates psychomotor vigilance deficits from sleep inertia. *Sleep, 24*, 813-819.

Goal of this presentation is to identify research needs relative to three areas

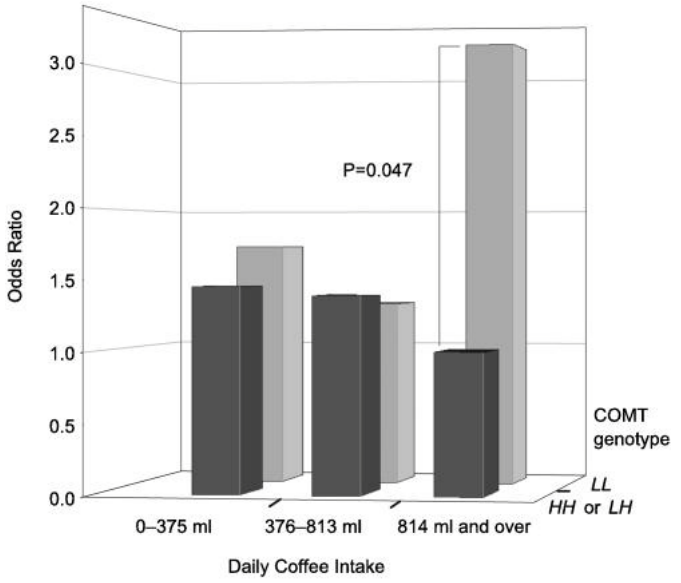
- Determine the *cumulative* effects of caffeine on behavior and physiology.
- Identify populations that may be vulnerable to the cumulative effects of caffeine if these pose risks.
- Discuss methods for assessing the accuracy of the claims made relative to energy drink consumption.

There appear to be genotypic vulnerabilities to caffeine effects

- Adenosine A_{2A} receptor gene (*ADORA2A*), *c.1083T>C polymorphism*
  - *ADORA2A:* Single nucleotide C →T polymorphism(rs5751876)
  - *C/C* genotype may be more prevalent in subjectively "caffeine sensitive" people
  - Caffeine produced higher beta band power in recovery sleep following sleep deprivation in men with the *C/C* genotype (Retey et al., 2007)



- *Catechol-O-methyltransferase (COMT), Val158Met polymorphism*
  - Enzyme responsible for metabolism of catecholamines
  - Caffeic acid directly inhibits COMT activity
  - Caffeine inhibits adenosine deaminase causing further inhibition of COMT activity
  - Risk of acute myocardial infarction in middle-aged male heavy coffee drinkers was higher in subjects possessing lower COMT activity allele (*Met/Met* or *LL* genotype) (Happonen et al., 2006)



Health issues and caffeine

- Hypertensive individuals
  - Caffeine increases noradrenaline and blood pressure and may affect heart rate (Fredholm, 1984)
- Ulcer patients
  - Caffeine indirectly leads to the secretion of gastrin which leads to increased gastric acid (Cohen & Booth, 1975)
- Those with anxiety-related disorders
  - Caffeine can be anxiogenic (Rogers et al., 2010)
- Diabetic patients
  - Caffeine affects insulin sensitivity (Zaharieva & Riddell, 2013)
- Those is environments/situations that may lead to dehydration and/or increased body temperature
  - Caffeine is a diuretic and increases core temperature
- Individuals with sleep complaints or disorders

Identifying potentially vulnerable populations

- Age
  - The maximum recommended daily caffeine intake for children and adolescents should not exceed 100 mg/day or 2.5 mg/kg/day (Seifert et al., 2011, *Pediatrics*)
- Race
  - Asian and African populations metabolize caffeine at a slower rate than Caucasians due to the CYP1A2 polymorphism (Gunes and Dahl, 2008)

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

RESULTS: According to self-report surveys, energy drinks are consumed by 30% to 50% of adolescents and young adults. Frequently containing high and unregulated amounts of caffeine, these drinks have been reported in association with serious adverse effects, especially in children, adolescents, and young adults with seizures, diabetes, cardiac abnormalities, or mood and behavioral disorders or those who take certain medications. Of the 5448 US caffeine overdoses reported in 2007, 46% occurred in those younger than 19 years. Several countries and states have debated or restricted their sales and advertising.

CONCLUSIONS: Energy drinks have no therapeutic benefit, and many ingredients are understudied and not regulated. The known and unknown pharmacology of agents included in such drinks, combined with reports of toxicity, raises concern for potentially serious adverse effects in association with energy-drink use. In the short-term, pediatricians need to be aware of the possible effects of energy drinks in vulnerable populations and screen for consumption to educate families. Long-term research should aim to understand the effects in at-risk populations. Toxicity surveillance should be improved, and regulations of energy-drink sales and consumption should be based on appropriate research. *Pediatrics* 2011;127:511–528

Goal of this presentation is to identify research needs relative to three areas

- Determine the *cumulative* effects of caffeine on behavior and physiology.
- Identify populations that may be vulnerable to the cumulative effects of caffeine if these pose risks.
- Discuss methods for assessing the accuracy of the claims made relative to energy drink consumption.

The language of energy drink claims

- Improves performance especially during times of increased stress or strain
- Increases concentration
- Improves reaction speed
- Increases alertness
- Contributes to normal mental performance
- Reduces tiredness and fatigue
- Increases endurance
- Stimulates the metabolism

http://energydrink-us.redbull.com/red-bull-energy-drink

There is a need to relate the energy drink claims to measureable neurobehavioral and physiological effects

- **Concentration**
  - The capacity to choose what to pay attention to and what to ignore
  - Maintain attention over time
- **Alertness**
  - Paying close and continuous attention
  - Being quick to perceive and respond to stimuli
  - Stability in responses
- **Reaction Speed**
  - How quickly an individual can perceive and respond to a stimulus
- **Mental Performance**
  - May include attention, memory, perception, problem solving, decision making, and learning
- **Fatigue**
  - Feeling of tiredness or exhaustion
  - A need to rest due to lack of energy or strength

Neurobehavioral tasks relevant to claims

- **Concentration**
  - 10 / 20 Minute PVT
  - Driving Simulator
- **Alertness**
  - 10 Minute PVT
  - Digit Symbol Substitution Test
- **Reaction Speed**
  - PVT (psychomotor response speed)
  - Motor Praxis
- **Tiredness/Fatigue**
  - Subjective Sleepiness Measures Karolinska Sleepiness Scale
  - Stanford Sleepiness Scale
    - POMS (Fatigue-Inertia Subscale)
    - Visual Analogue Scales for Fatigue
    - Physiological Sleepiness Tests
      - Multiple Sleep Latency Test
      - Maintenance of Wakefulness Test

- **Mental Performance**
  - Attention/Working Memory
    - Serial Addition Subtraction Test
    - N-Back Test
  - Memory
    - Delayed Digit Symbol Substitution Test
    - Visual Scene Episodic Memory
    - Digit Span
  - Perception (Visual)
    - Line Orientation Test
    - Emotion Recognition Task
  - Problem Solving
    - Matrix Reasoning
    - Abstract Matching
  - Decision Making
    - Abstract Matching
    - Matrix Reasoning
    - Balloon Analogue Risk Test

Research issues: Factors influencing assessment of the efficacy of energy drinks

- **Sleep**
  - Habitual sleep duration
  - Recent sleep history
  - Time awake prior to caffeine and/or assessment
- **Circadian**
  - Time of Testing
  - Chronotype
- **Caffeine**
  - Habitual caffeine use
  - Recent caffeine ingestion
  - Caffeine sensitivity
- **Assessment**
  - Type of assessment
  - Sensitivity of test (learning curve/practice effects)
  - Timing of test relative to caffeine
- **Nutrition Status**
  - Fasted vs Fed
- **Individual Differences**
  - Genotype
  - Response to caffeine
  - Response to situations leading to ‘low energy’

Summary of research needed

- Studies of the neurobiological and physiological effects of energy drinks and their constituents (e.g., relative to sleep-wake and circadian neurobiology).
- Studies examining the efficacy and risks of energy drinks (beyond caffeine only) as a countermeasure to situations involving low energy.
- Studies examining the differential cognitive and physiological effects of cumulative energy drink/caffeine use (e.g., sedation and judgment when combined with alcohol).
- Studies examining the biological effects of caffeine/energy drinks in different populations. Includes at-risk populations as well as individuals who may benefit (i.e. neurodegenerative disease patients).
- Studies of how well individuals can perceive the amount of caffeine being consumed.
- Studies with large sample sizes examining the cumulative effects of caffeine and energy drinks on subjective experiences (i.e. headaches, feeling too hot, confused) and clinical outcomes.

Acknowledgments

For help in preparing the presentation.

Andrea Spaeth

Namni Goel, PhD

The research results presented on the effects of sustained low-dose caffeine were supported by the Air Force Office of Scientific Research (grant number F49620-95-1-0388); by the National Institutes of Health (grant number RR00040 to the General Clinical Research Center of the Hospital of the University of Pennsylvania); and in part by the Institute for Experimental Psychiatry Research Foundation. Dr. Dinges currently receives support from NIH NR004281.