Caffeine and cognition: The short and the long term

(or Experimental Psychology to Epidemiology)

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Outline

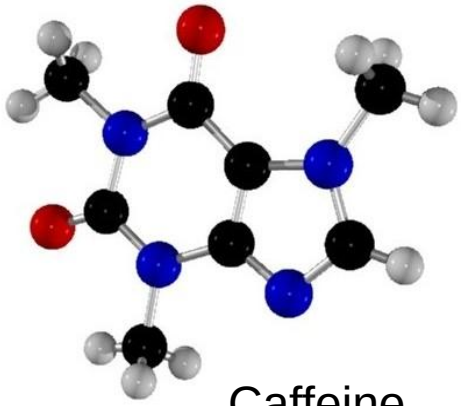
- Plan
- Caffeine consumption and physiological effects
- Acute alerting, anxiogenic and performance effects
  - Non-consumers vs consumers
- Tea, coffee and cognitive decline

Acknowledgements

- Colleagues
  - Sue Heatherley
  - Henk Smit
  - Emma Mullings
  - Jess Smith

- Funders

Humankind’s favourite drug



Caffeine
(1,3,7-trimethylxanthine)

Around 6 billion caffeine-containing drinks are consumed worldwide every day

Coffee ranks second only to oil in terms of monetary value traded worldwide


Tea
Maté
Cola
Cocoa
Coffee
Guarana

Physiological actions of caffeine

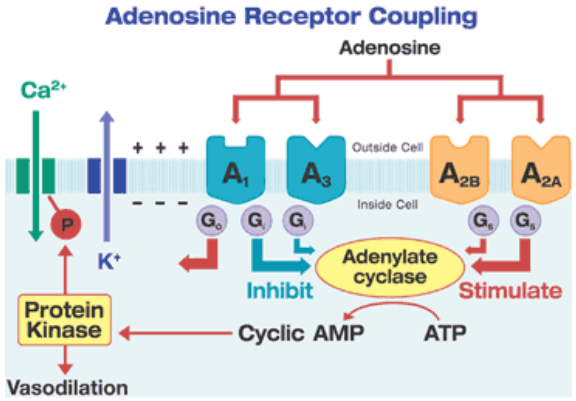
- Caffeine acts at cell surface receptors widely distributed throughout the body
  - It is a non-selective adenosine A_1 and A_{2A} receptor antagonist
- Adenosine modulates neural activity
  - Activation of adenosine postsynaptic receptors by endogenous adenosine slows neural activity
  - Caffeine prevents activation of adenosine receptors by adenosine, thus removing this brake on neural activity

Caffeine

Adenosine

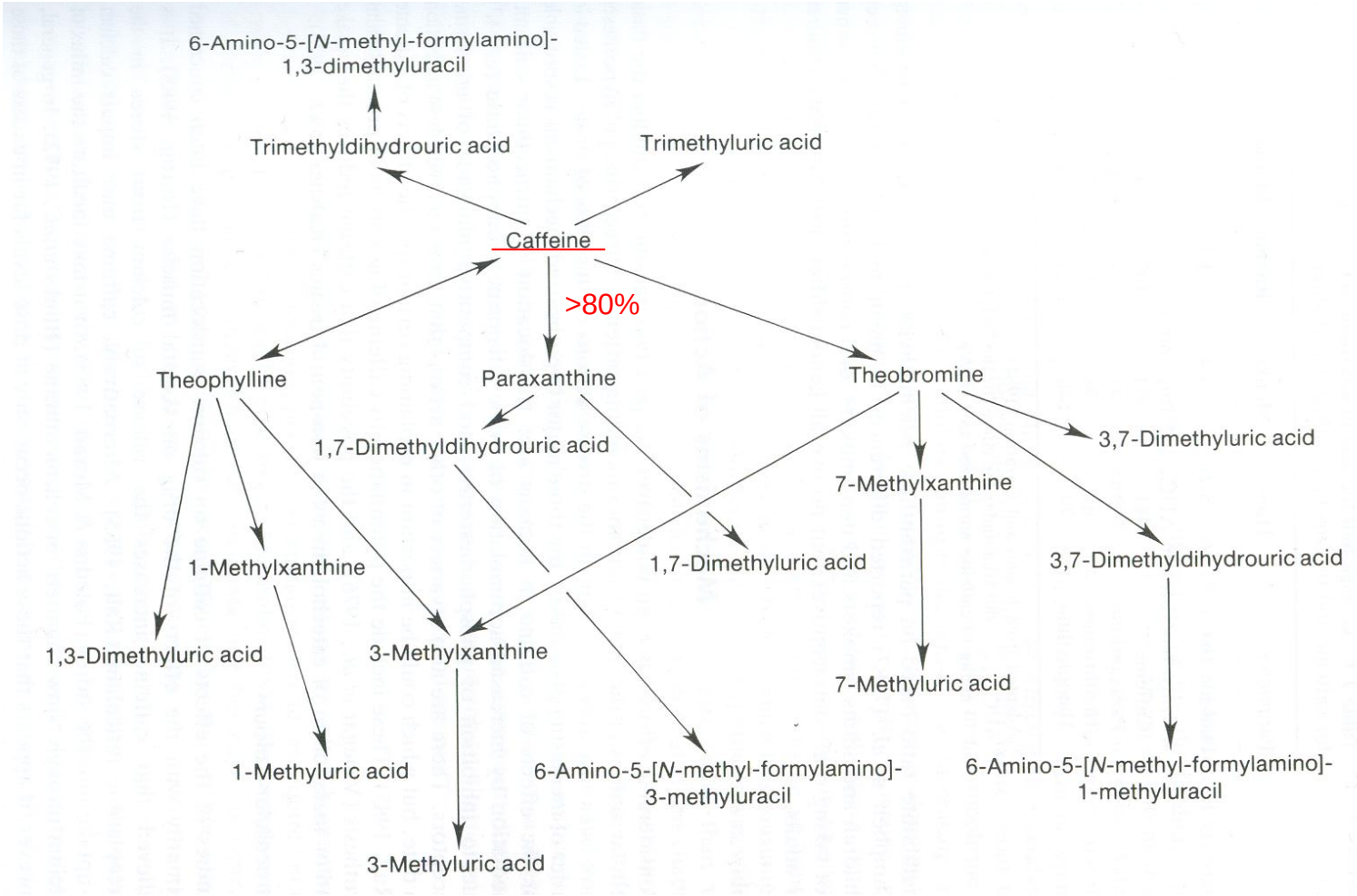
Physiological actions of caffeine

- Caffeine has significant CNS, cardiovascular, cerebrovascular, renal, gastrointestinal, and metabolic effects
- Exposure to caffeine leads to changes in adenosine signalling that oppose the effects of caffeine (**tolerance**)



Metabolism of caffeine

- Peak blood level 30-60 minutes after ingestion in a drink
- Elimination half life of 3-7 hours
  - Faster in smokers and slower during pregnancy



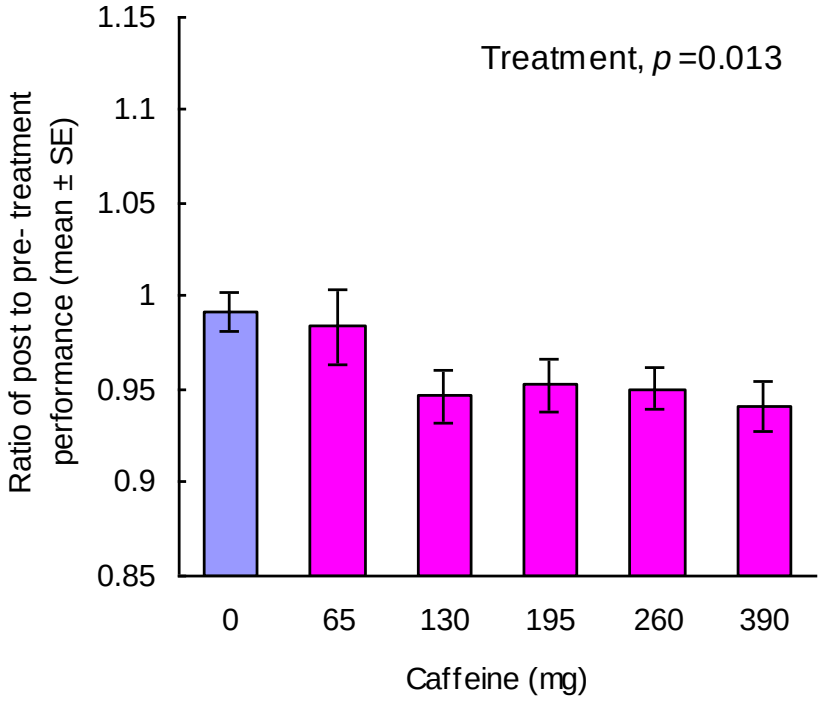
James (1991) *Caffeine and health*. London: Academic Press

Hollingworth, H. L. (1912) The influence of caffein on mental and motor efficiency. *Archives of Psychology,* 22, 1-166.

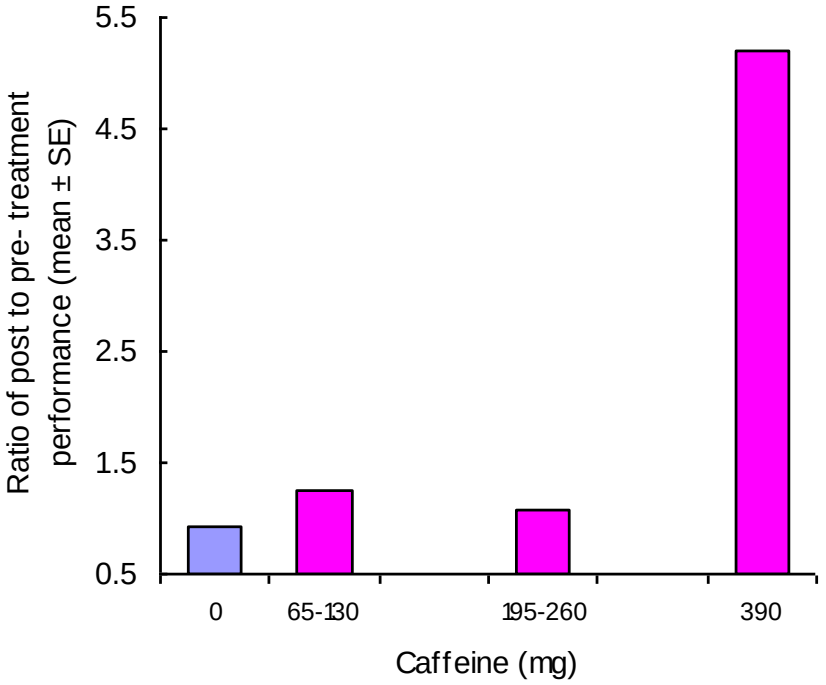
- n=16, 6 female, 19-39 years
- Varied levels of habitual caffeine consumption
  - Abstainer=2, Occasional=3, Moderate=2, Regular=8
- Attended laboratory (six-room apartment) for 40 days up to 12 hours each day
- Various studies (n=1 to 5 per group)
  - Caffeine swallowed in a capsule in doses between 1 and 6 grains (65-390 mg)
  - Placebo capsule contained ‘sugar of milk’ (lactose)
- Tests of motor and mental performance included
  - Hand steadiness, Tapping, Coordination
  - Choice reaction time, Number cancellation, Calculation, Naming opposites, Colour naming, Typewriting

Effects of caffeine on tapping performance and hand steadiness

Tapping (time taken to make 400 taps)



Hand steadiness (number of contacts)



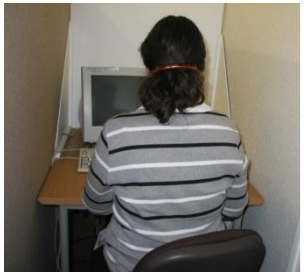
Hollingworth (1912) *Archives of Psychology* **22**, 1-166

“The widespread consumption of caffeinic beverages. . . . seems to be justified by the results of this experiment.”

Hollingworth, 1912 (p 165-166)

Test schedule for typical caffeine experiment

Pre-treatment tasks
(baseline)



↓

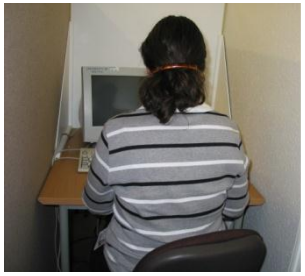
Caffeine or Placebo

↓

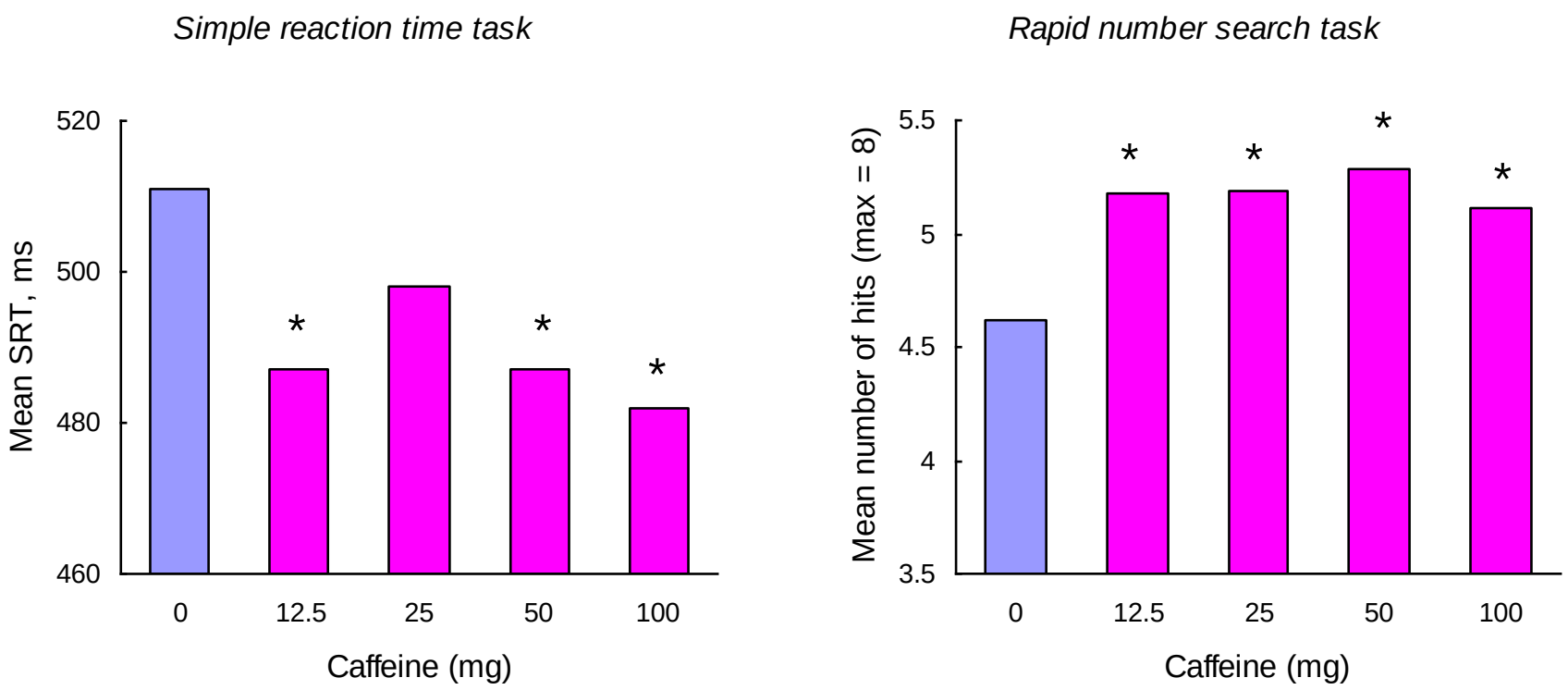
Wait (30 minutes)

↓

Post-treatment tasks



Effects of caffeine on performance of tasks requiring sustained attention



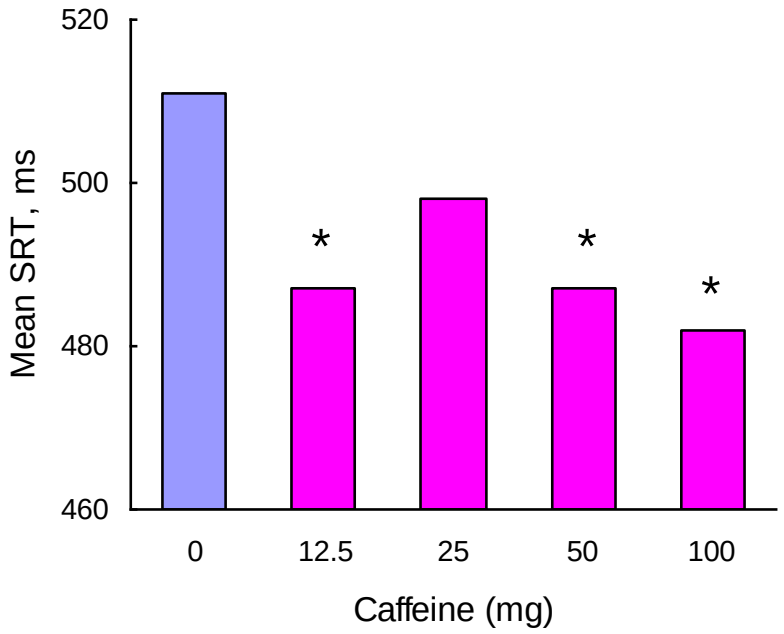
* $p<0.05$, versus placebo

Adapted from Smit & Rogers (2000) *Psychopharmacology, 152*, 167-173

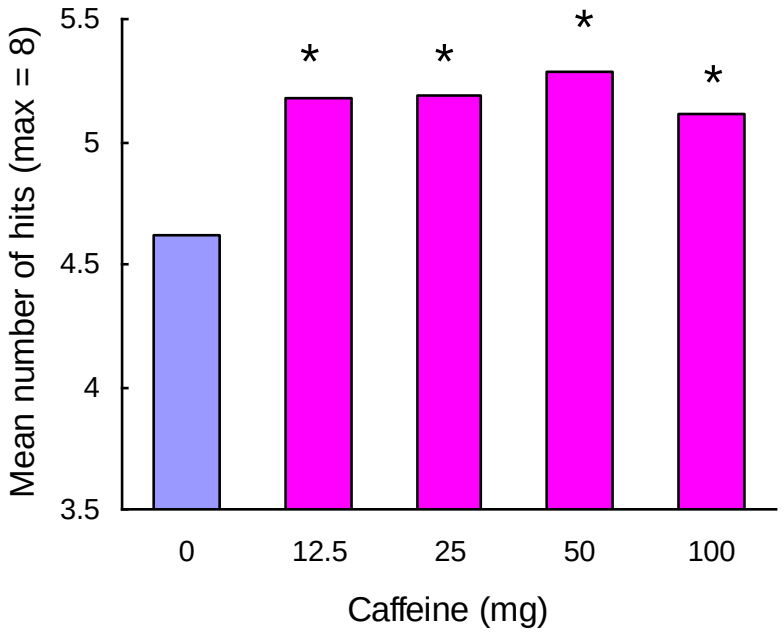
Effects of caffeine on performance of tasks requiring sustained attention

Moderate caffeine consumers, overnight caffeine deprived

Simple reaction time task



Rapid number search task



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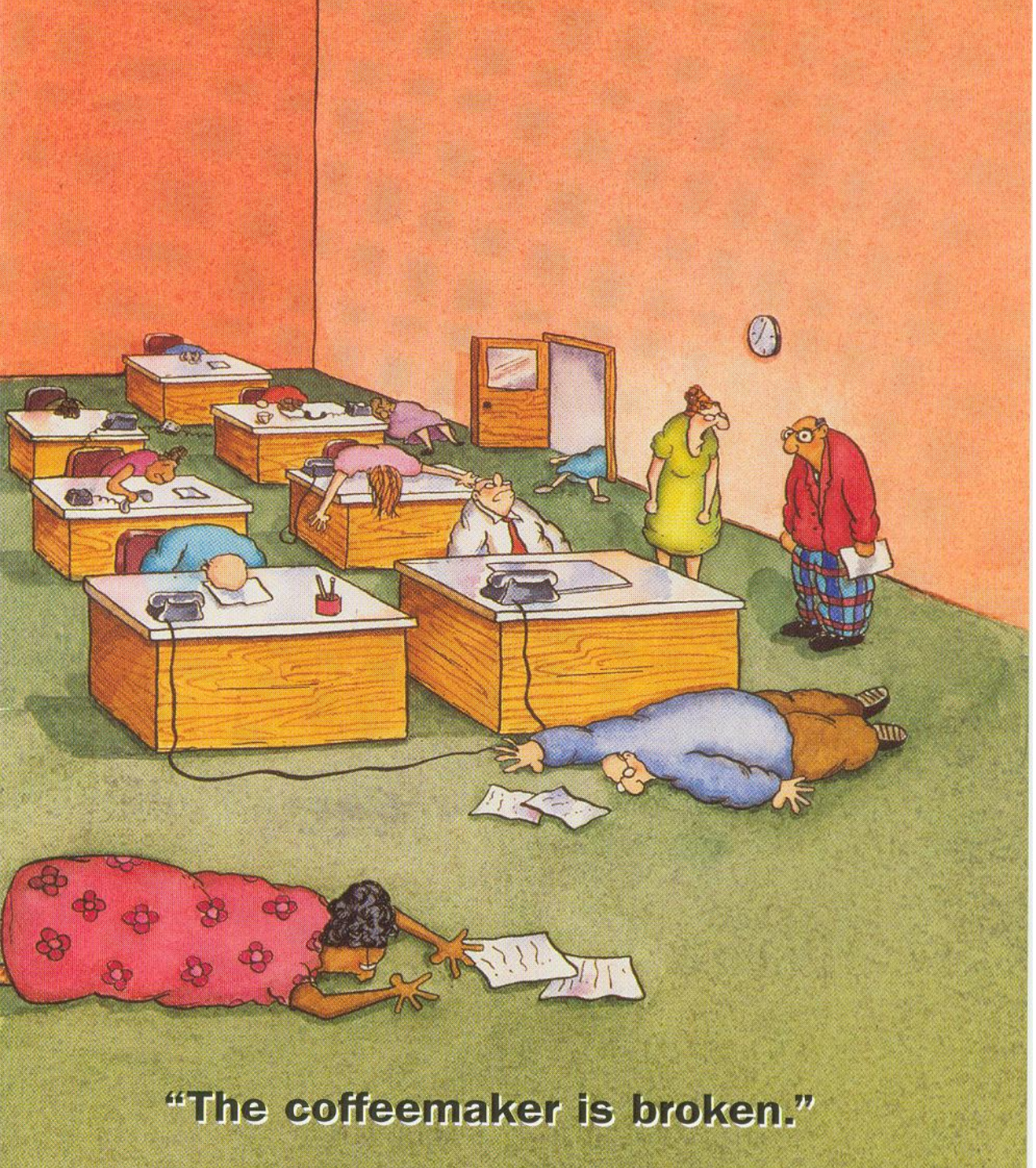


Caffeine withdrawal symptoms?

Psychostimulant effects of caffeine: net benefit or withdrawal reversal?

- Withdrawal reversal hypothesis
  - Acute (e.g., overnight) caffeine withdrawal lowers alertness and degrades mental performance
  - Caffeine restores alertness and mental performance to, but not above, baseline (normal) levels
  - Withdrawal reversal (negatively) reinforces liking for the caffeine-containing vehicle

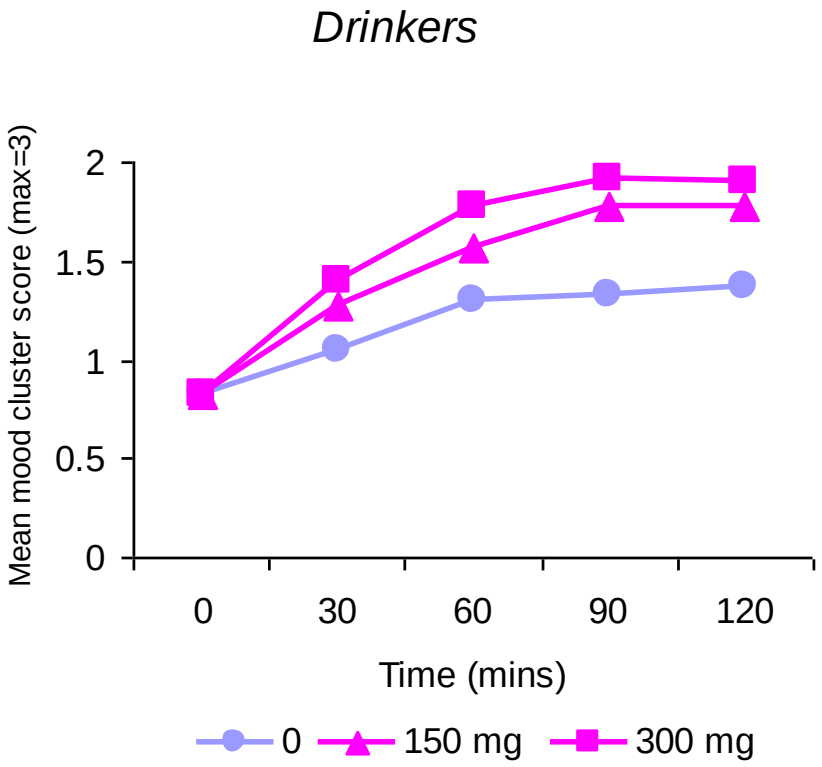
For example, James and Rogers (2005) *Psychopharmacology, 182,* 1-8

Psychostimulant effects of caffeine: net benefit or withdrawal reversal?

- Caffeine consumers versus ‘non-consumers’
  - Compare the effects of caffeine in people who consume caffeine frequently with those in people who usually do not consume caffeine

Effects of caffeine on alertness* in coffee drinkers

Coffee drinkers overnight caffeine deprived

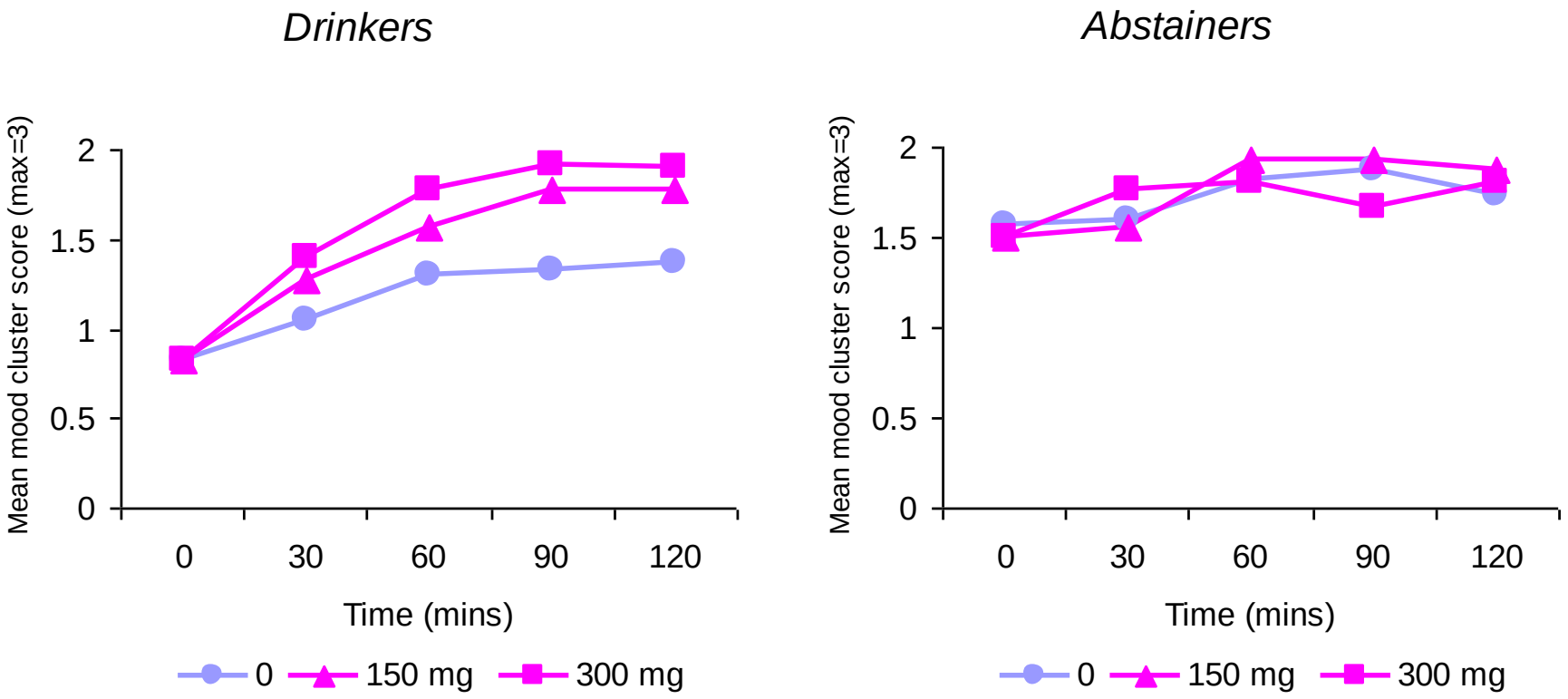


* Alert, Attentive, Observant, Able to concentrate

Goldstein, Kaizer & Whitby (1969) *Clinical Pharmacology and Therapeutics*, *10*, 489-497

Effects of caffeine on alertness* in coffee drinkers and abstainers

Coffee drinkers overnight caffeine deprived



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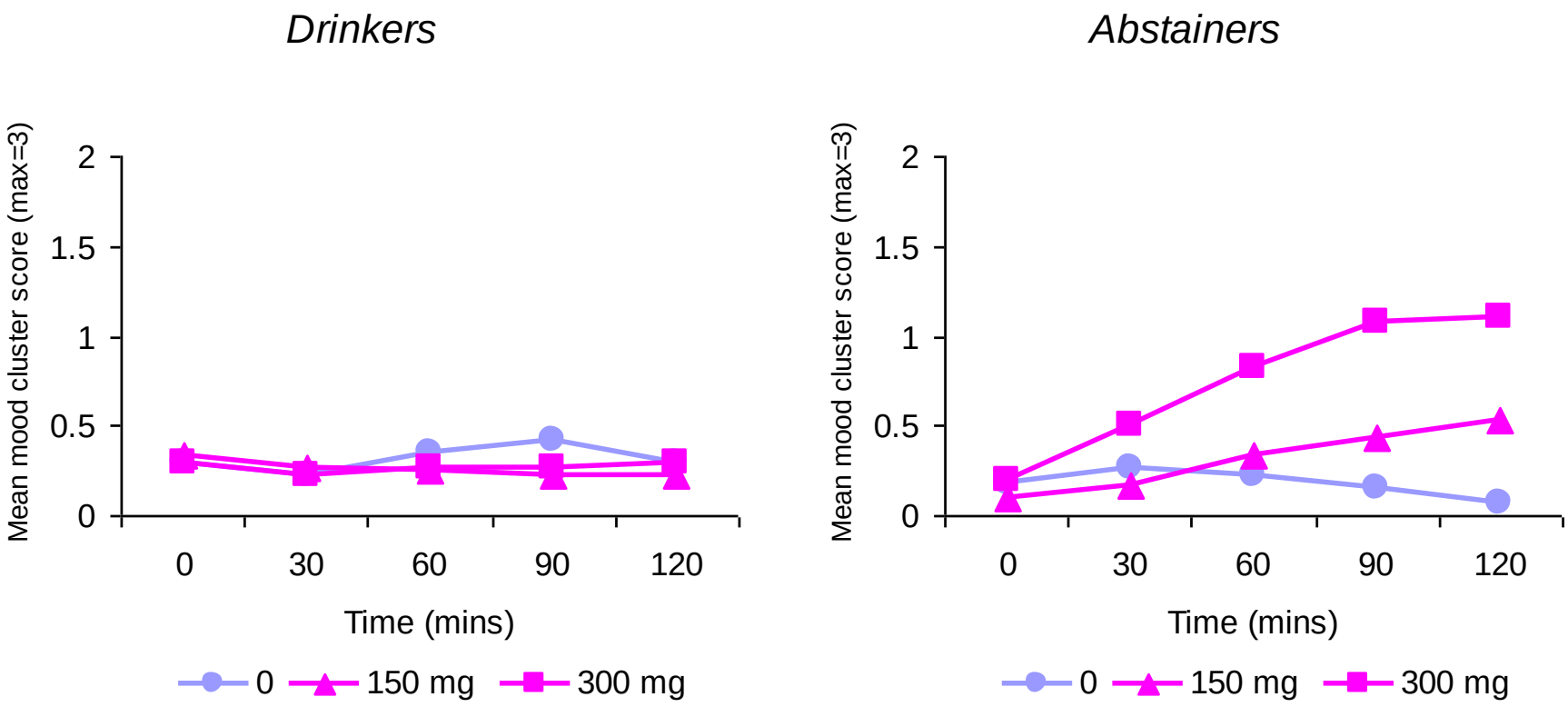
Goldstein, Kaizer & Whitby (1969) *Clinical Pharmacology and Therapeutics*, *10*, 489-497

Psychostimulant effects of caffeine: net benefit or withdrawal reversal?

- Effects of caffeine in people who do not usually consume caffeine (‘non-consumers’)
  - But this is a self-selected group

Effects of caffeine on jitteriness* in coffee drinkers and abstainers

Coffee drinkers overnight caffeine deprived

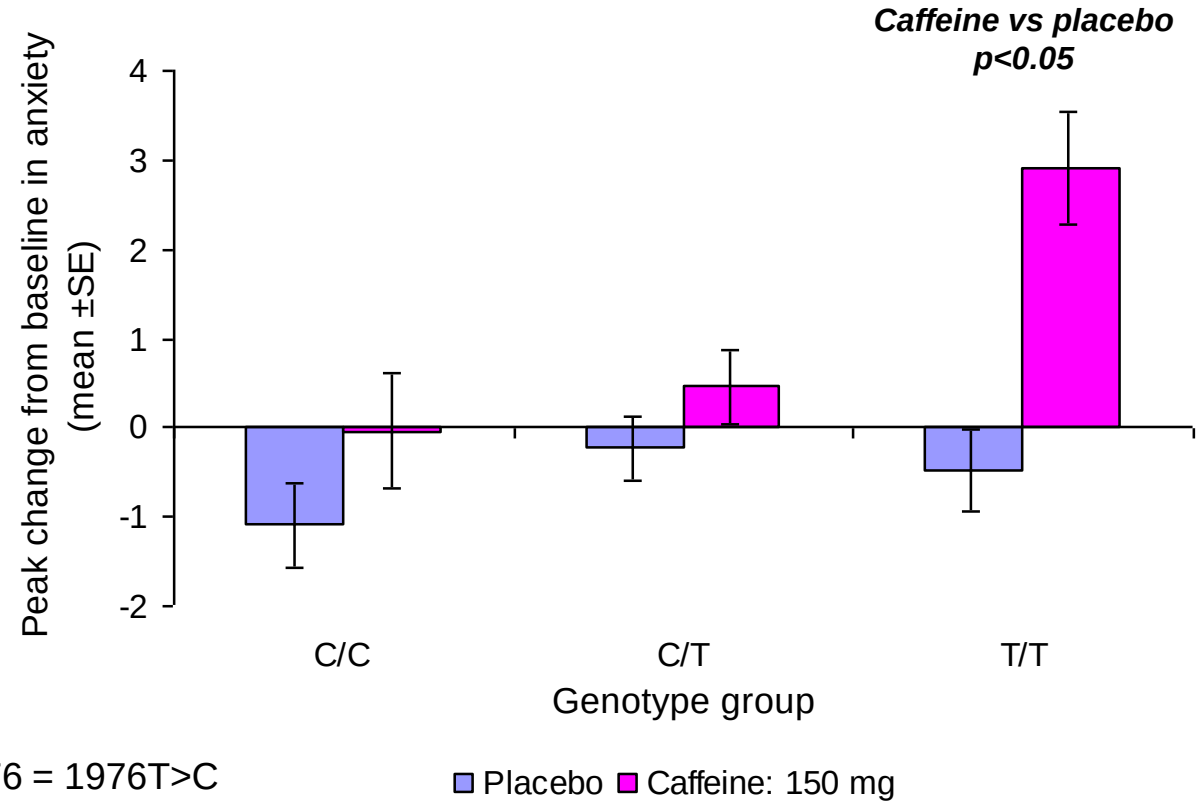


* Jittery, Nervous, Shaky

Goldstein, Kaizer & Whitby (1969) *Clinical Pharmacology and Therapeutics*, *10*, 489-497

Effects of caffeine on self-reported anxiety for the three genotypic groups at the rs5751876 adenosine A2a receptor gene polymorphism locus

Non/low caffeine consumers



Note: rs5751876 = 1976T>C

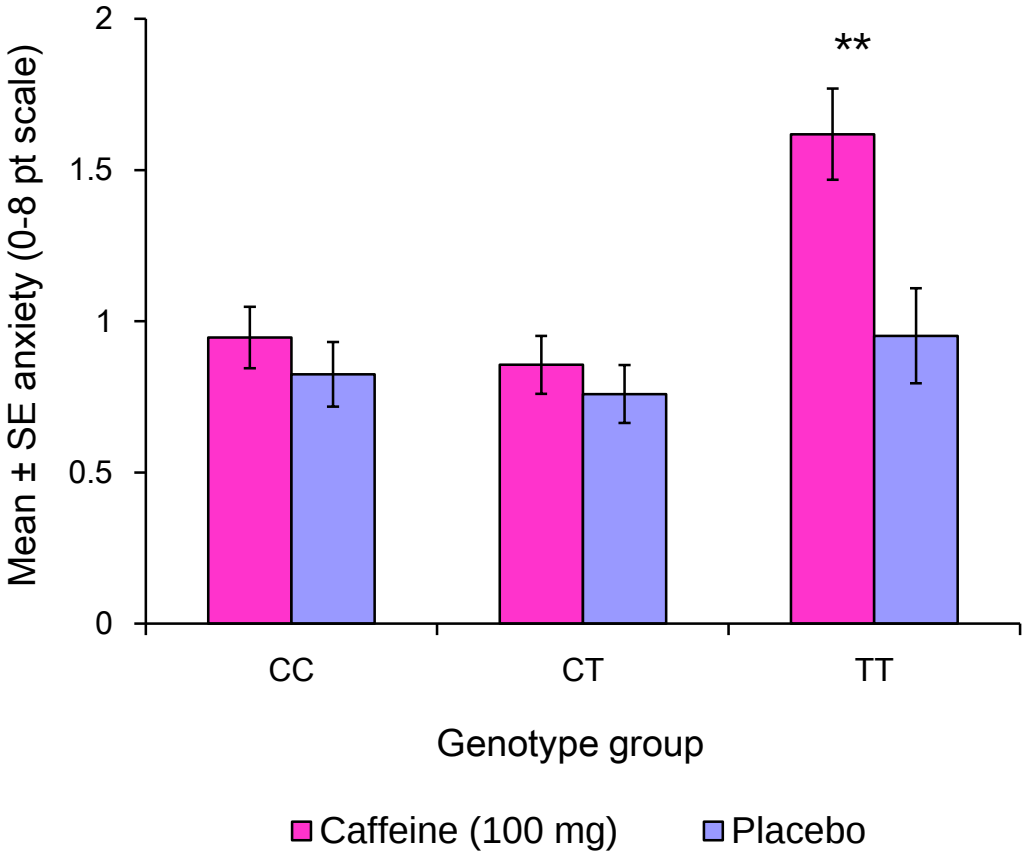
Alsene, Deckert, Sand & de Wit (2003) *Neuropsychopharmacology, 28,* 1694-1702

Association between A2a receptor gene polymorphisms and caffeine-induced anxiety

Alsene et al (2003) *Neurpsychopharmacology, 28,* 1694-1702
Childs et al (2008) *Neuropsychopharmacology, 33,* 2791-2800

- Variation in the gene that codes for the adenosine A2a receptor predicts caffeine-induced anxiety
  - studies tested only non/low-caffeine consumers
- Perhaps susceptibility to caffeine-induced anxiety causes avoidance of coffee, tea, etc Cornelis et al. (2007) *American Journal of Clinical Nutrition, 86,* 240-44

Caffeine-induced anxiety as a function of *ADORA2A* rs5751876 genotype group



Rogers et al. (2010) *Neuropsychopharmacology, 35*, 1973-1983

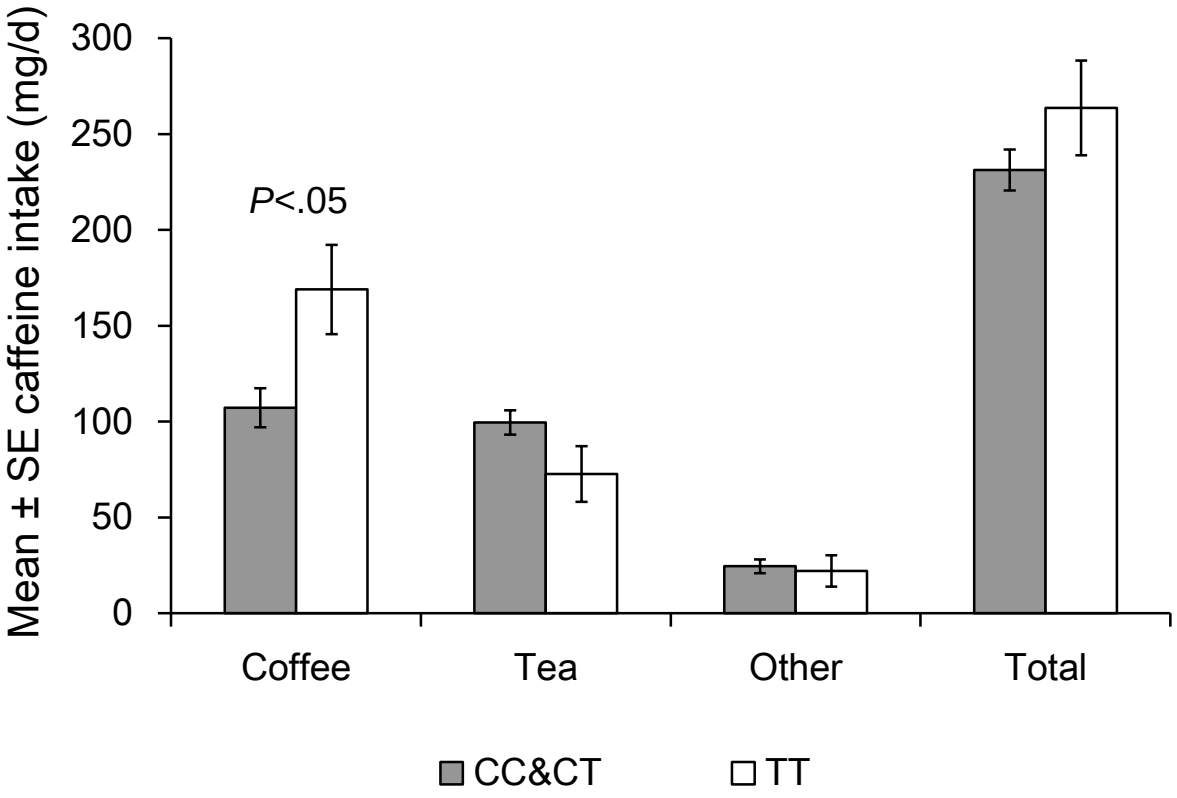
ADORA2A rs5751876 genotype group distribution in caffeine consumers and non-consumers

	CC & CT	TT
Consumers	182 (84%)	35 (16%)
Non-consumers	132 (81.5%)	30 (18.5%)

Chi-square = 0.37, *P* = .54

Rogers et al. (2010) *Neuropsychopharmacology, 35*, 1973-1983

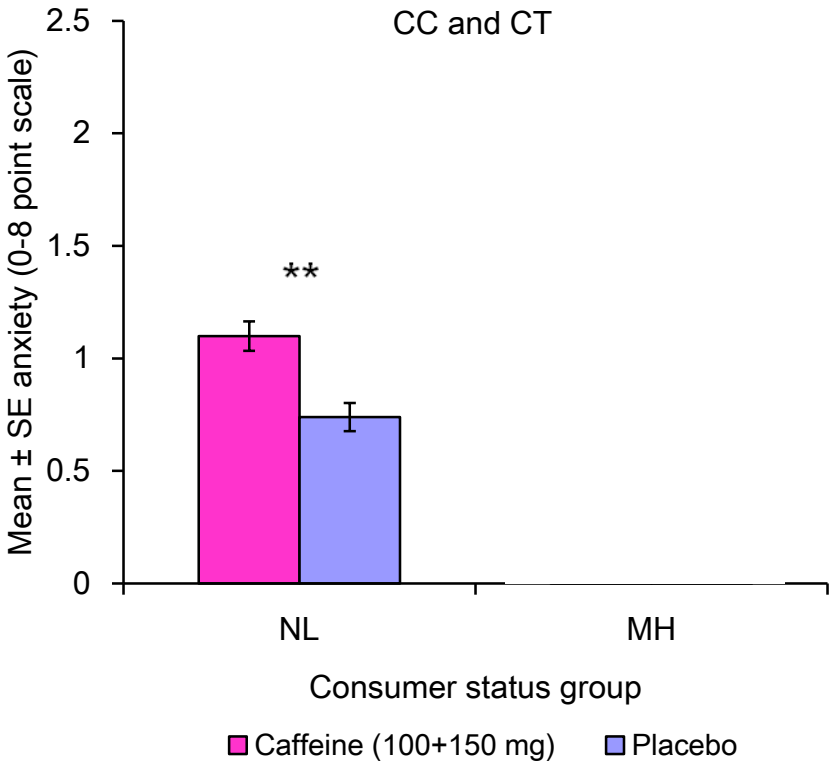
Sources of caffeine intake in caffeine consumers* as a function of *ADORA2A* rs5751876 genotype group

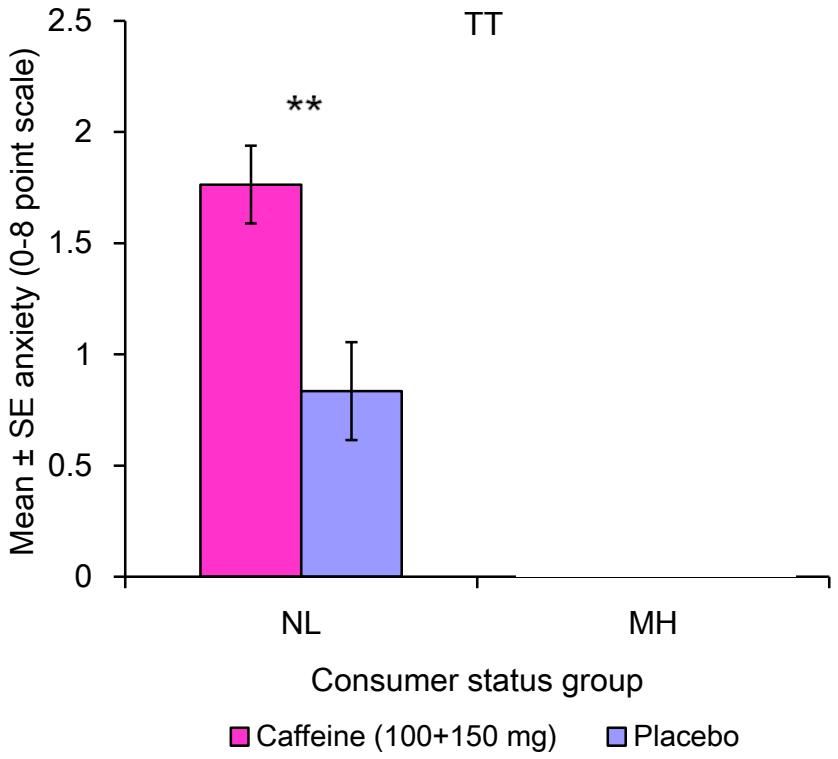


* ≥40 mg caffeine per day

Rogers et al. (2010) *Neuropsychopharmacology, 35*, 1973-1983

Caffeine-induced anxiety as a function of *ADORA2A* rs5751876 genotype group and consumer status





Effect of genotype $P<.01$ Effect of Consumer status $P<.01$

Rogers et al. (2010) *Neuropsychopharmacology, 35*, 1973-1983

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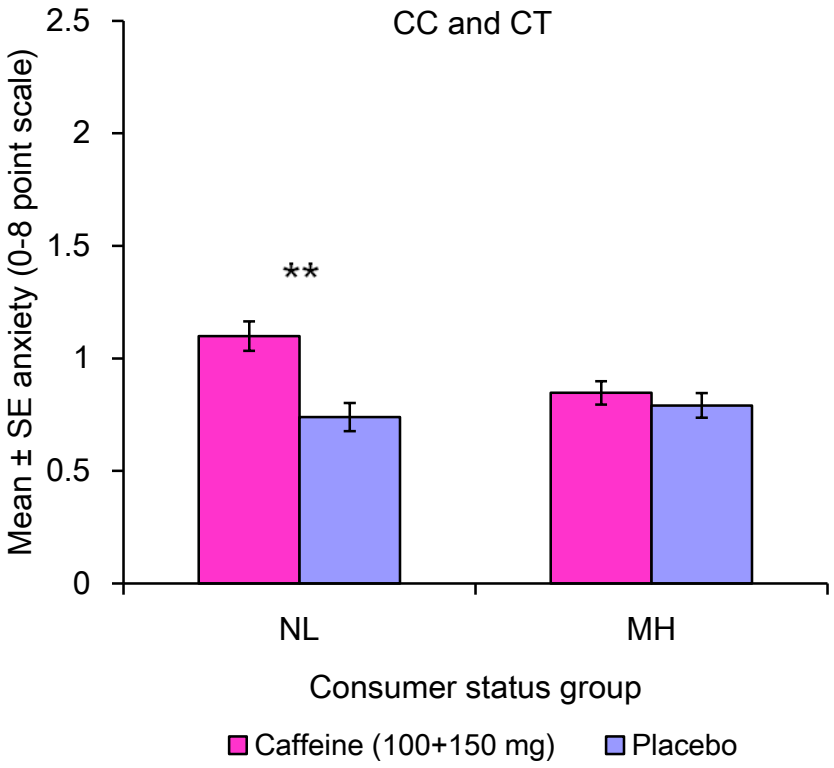
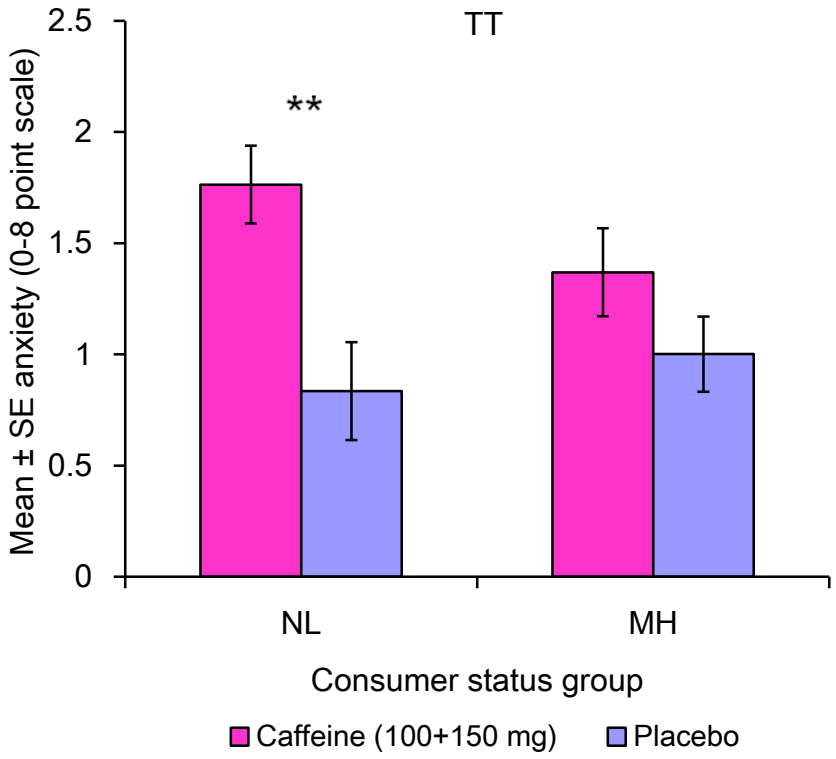




Effect of genotype *P*<.01 Effect of Consumer status *P*<.01

Rogers et al. (2010) *Neuropsychopharmacology, 35*, 1973-1983

Anxiety effect does not deter caffeine consumption

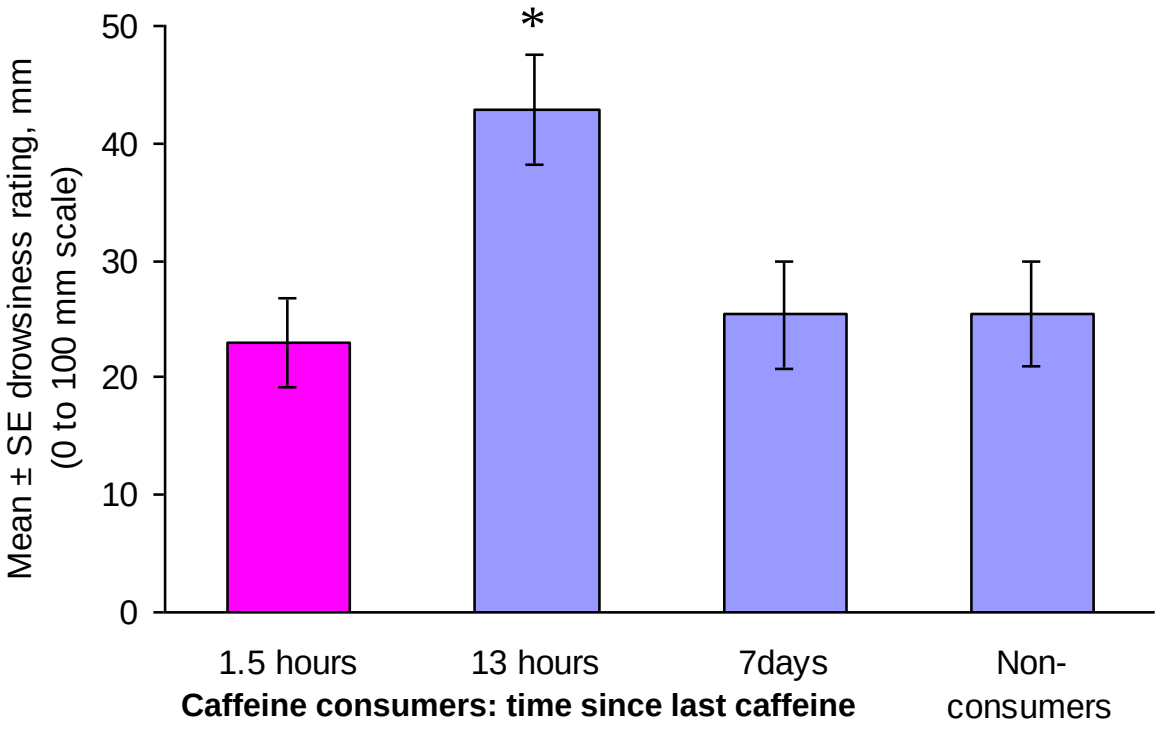
Rogers et al. (2010) *Neuropsychopharmacology, 35*, 1973-1983

- Anxiety-susceptible individuals (rs5751876 TT genotype) no less likely to be caffeine non-consumers
  - and they drank more coffee!
- Regular consumption leads to reduced anxiety effect (tolerance)
- Even in non-consumers ‘anxiety’ effect is rarely severe (and perhaps even pleasant)

Back to withdrawal reversal

- Effects of caffeine in acutely (overnight) withdrawn versus long-term withdrawn caffeine consumers

Morning drowsiness in caffeine consumers and non-consumers



* $p<0.05$, versus 1.5 hours, 7 days and non-consumers

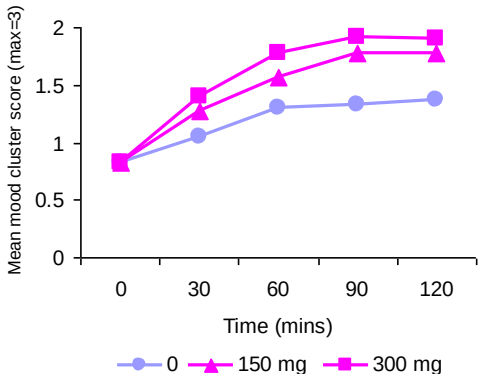
Richardson, Rogers, Elliman & O'Dell (1995) *Pharmacology Biochemistry and Behaviour* **52**, 313-320

Alerting effects of caffeine in consumers and non-consumers

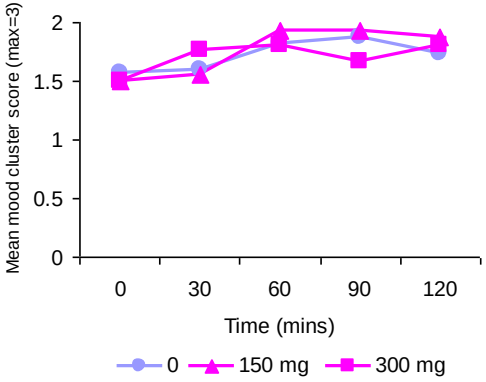
- *Withdrawal reversal hypothesis (consumers)*
  - Acute (e.g., overnight) caffeine withdrawal lowers alertness and degrades mental performance
  - Caffeine restores alertness and mental performance to, but not above, baseline (normal) levels

- *But why doesn't caffeine increase alertness in non-consumers?*
  - Might expect improvement initially, then tolerance with repeated consumption

Drinkers

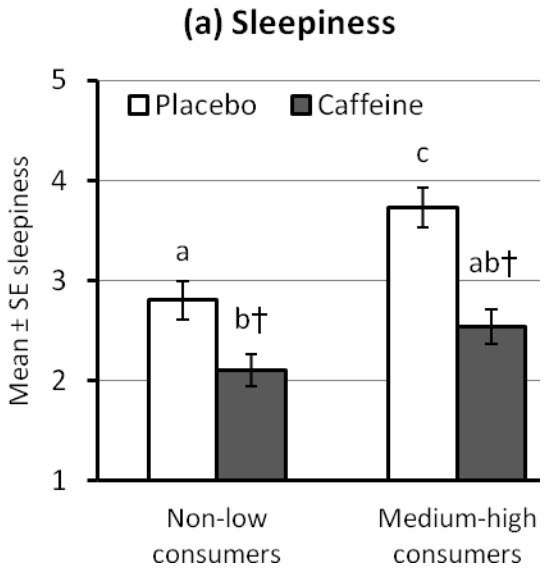


Abstainers

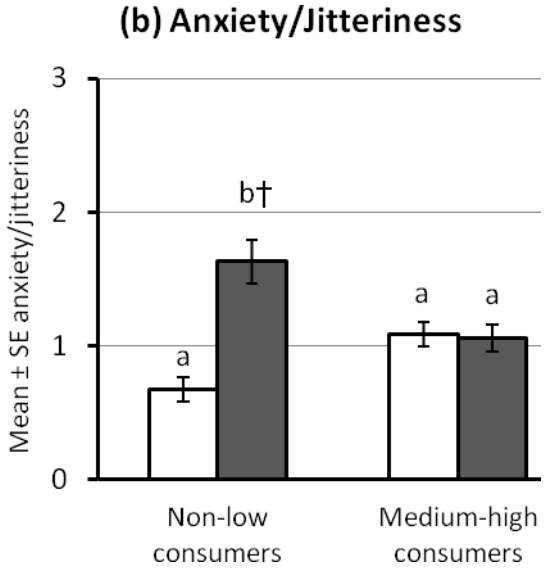


Alert, Attentive, Observant, Able to concentrate

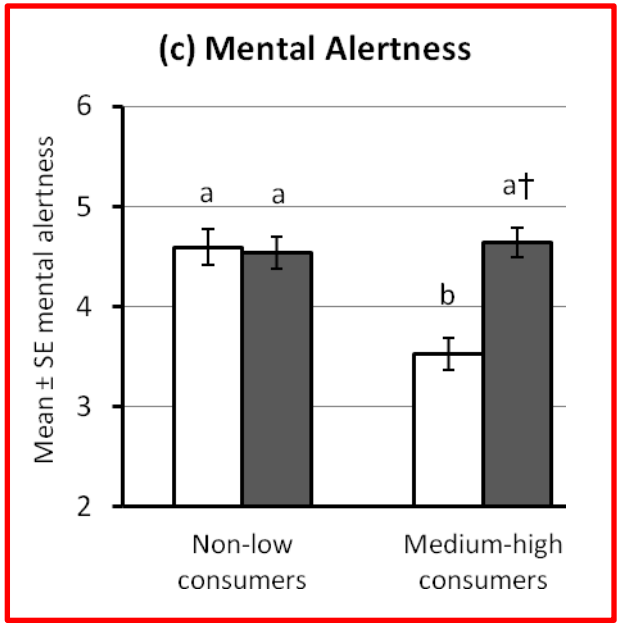
Effects of caffeine on sleepiness, anxiety and mental alertness in caffeine consumers and non-consumers



Sleepiness:
'I feel sleepy / drowsy / half awake'



Anxiety/Jitteriness:
I feel anxious / tense / nervous / on edge and I feel jittery / shaky.



Mental alertness:
'I feel mentally alert / attentive / able to concentrate / observant'

Rogers et al. (2012) *Psychopharmacology* **226,** 229-40

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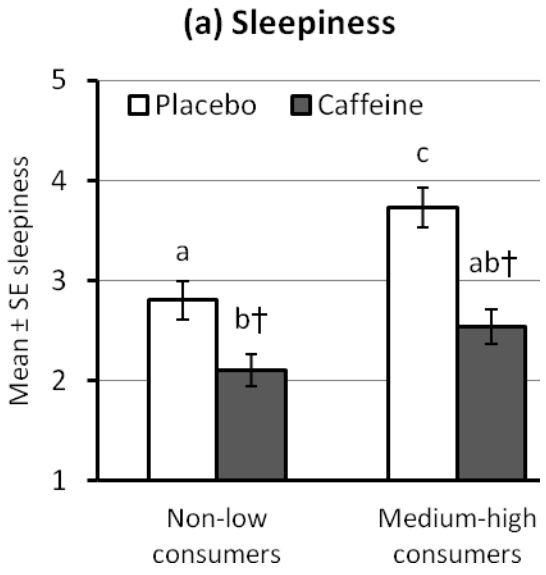

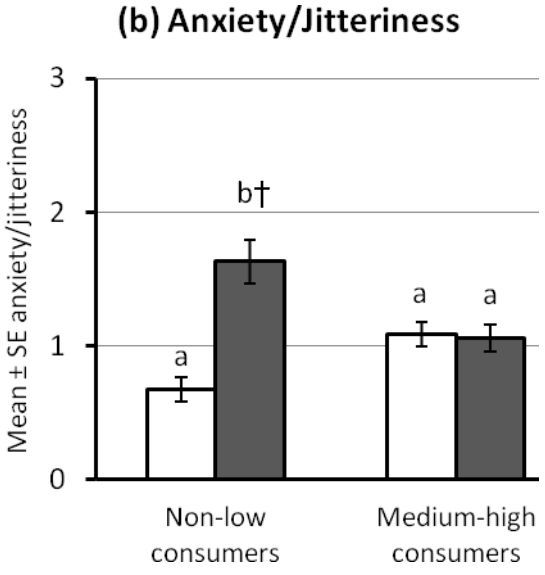

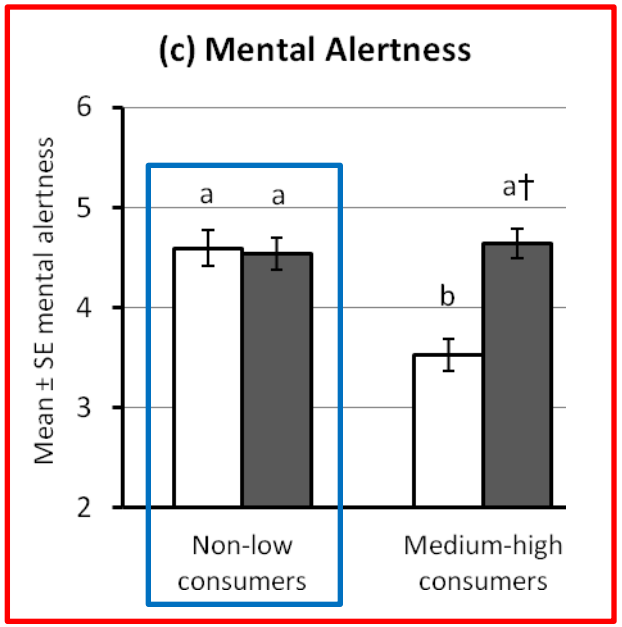

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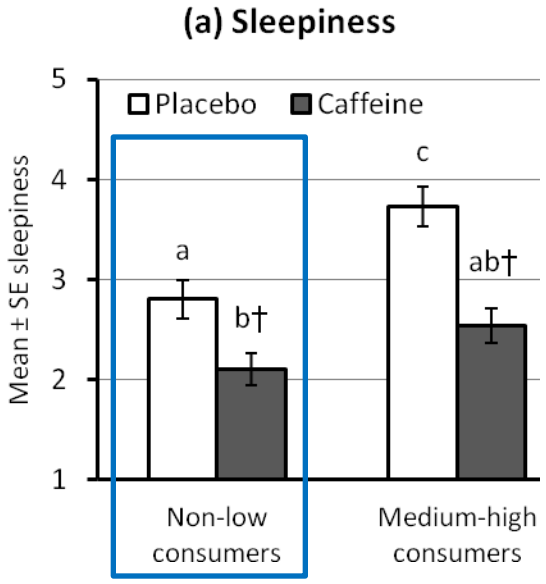

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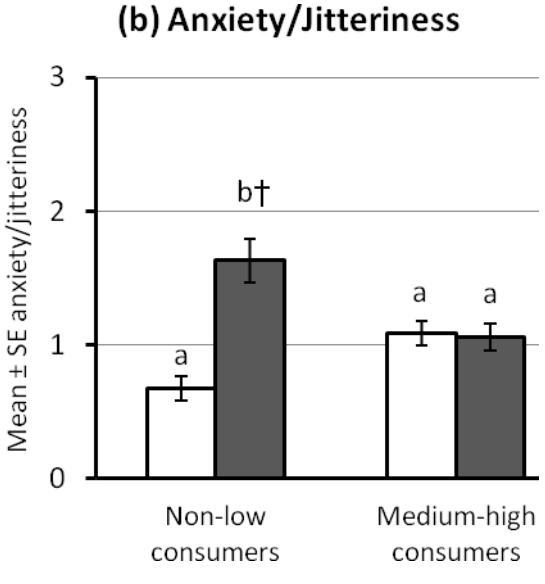

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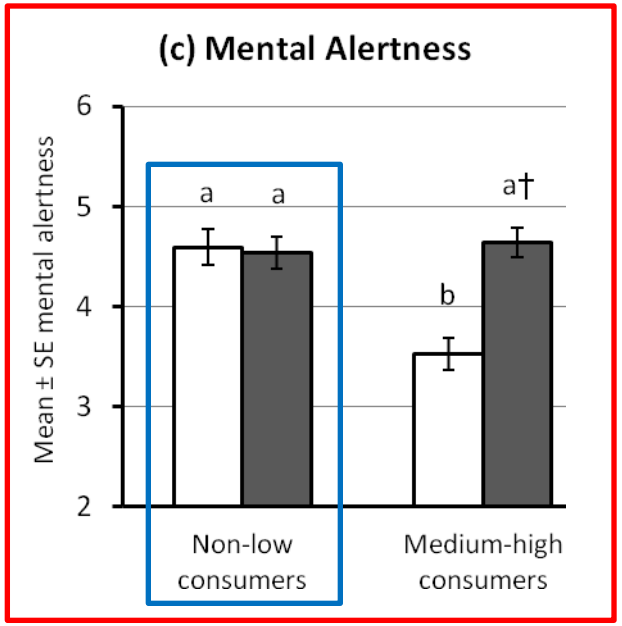

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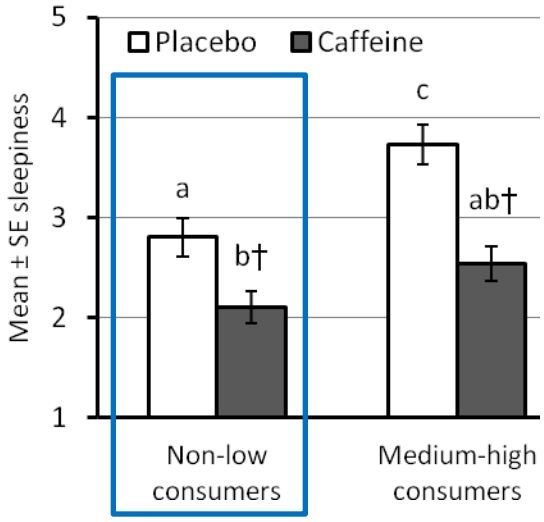

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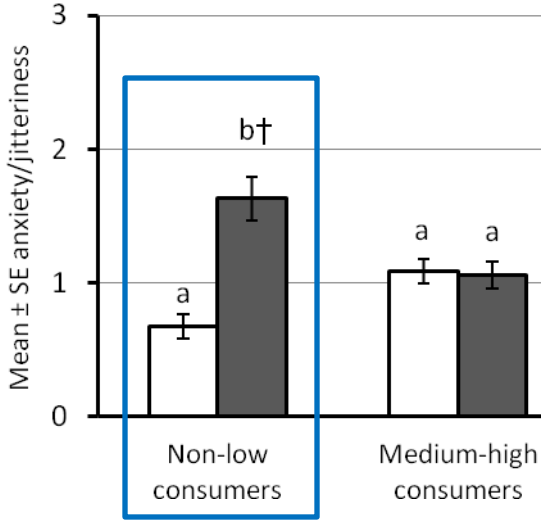

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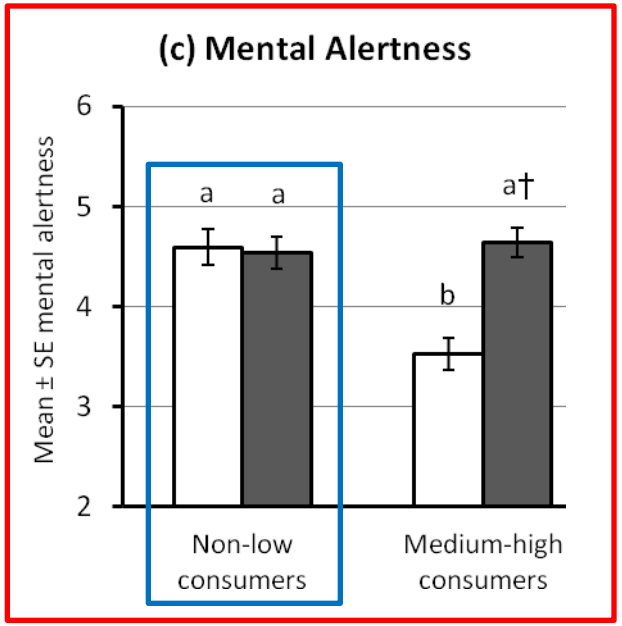


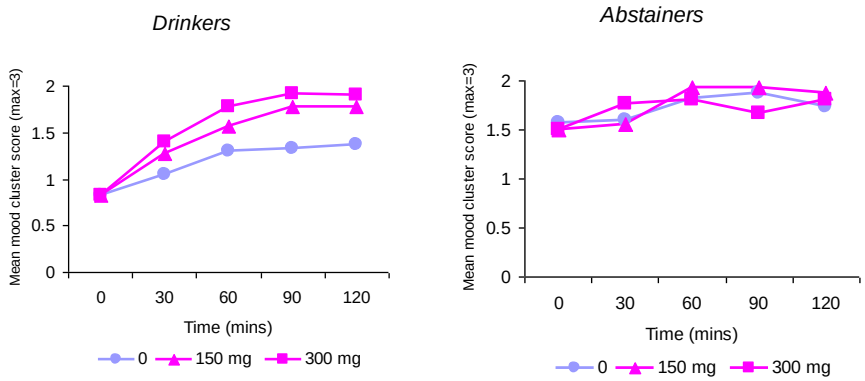
Mental alertness:
'I feel mentally alert / attentive / able to concentrate / observant'

Rogers et al. (2012) *Psychopharmacology,* DOI 10.1007/s00213-012-2889-4

How the effects of caffeine on sleepiness and anxiety might combine to influence mental alertness (and mental performance)

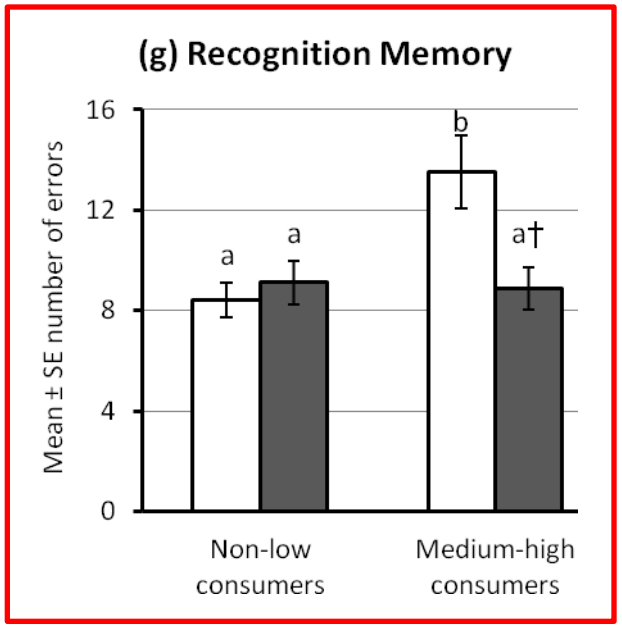
	Sleepiness	Anxiety/ Jitteriness	Mental alertness
Non-low consumer, after caffeine	↓	+ ↑	= →
Medium-high consumer, caffeine withdrawn	↑	+ →	= ↓
Medium-high consumer, after caffeine	→	+ →	= →

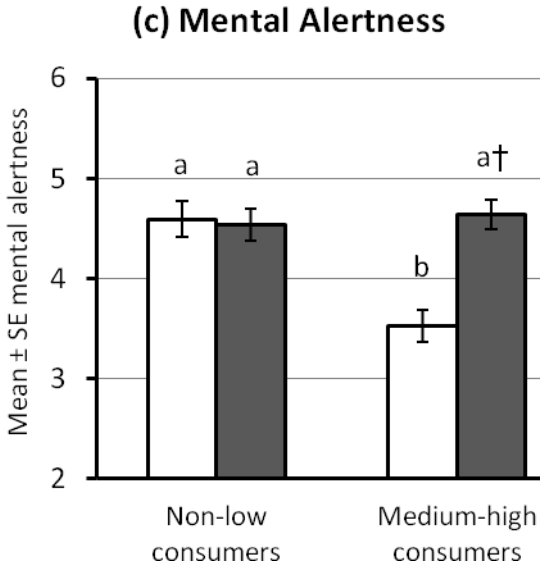
→ normal level
↑ increased
↓ decreased



Alert, Attentive, Observant, Able to concentrate

Not smarter: No benefit for mental alertness and (therefore) no benefit for cognitive performance





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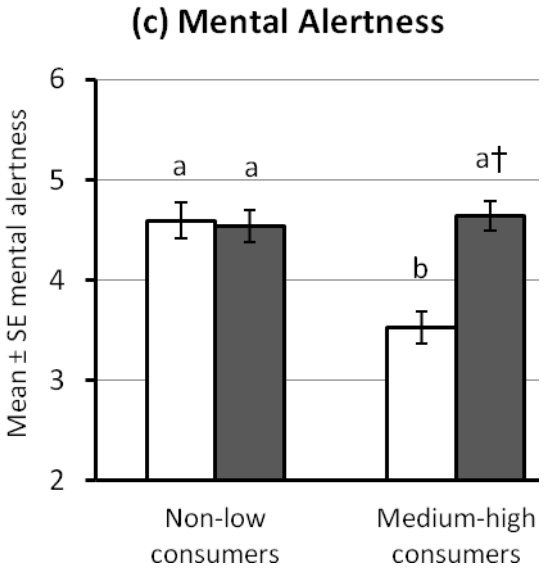
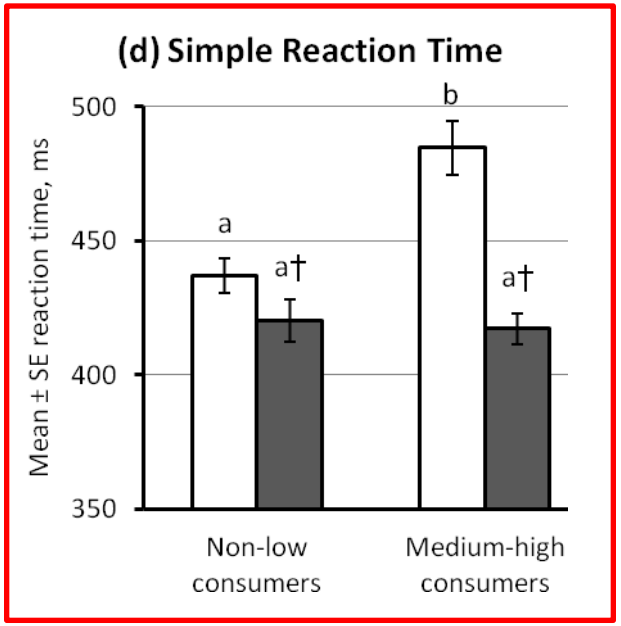
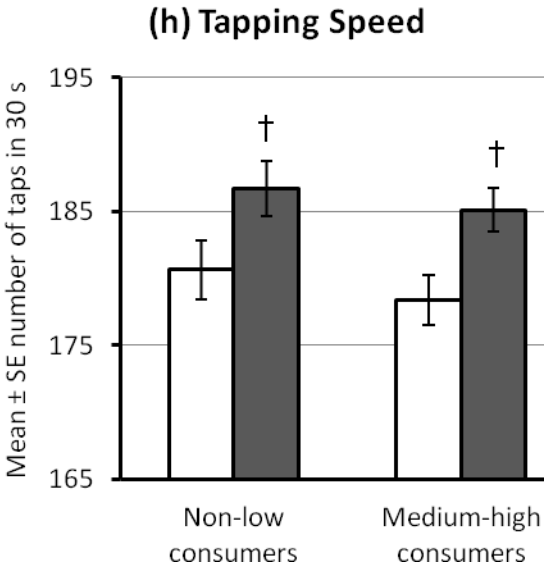
But faster: caffeine enhances motor performance



Mental alertness:
'I feel mentally alert / attentive / able to concentrate / observant'

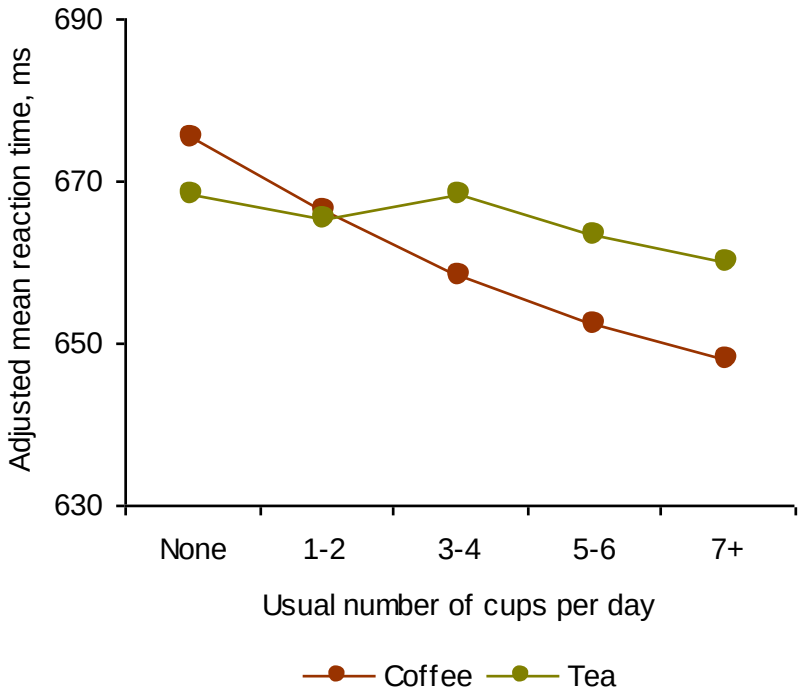




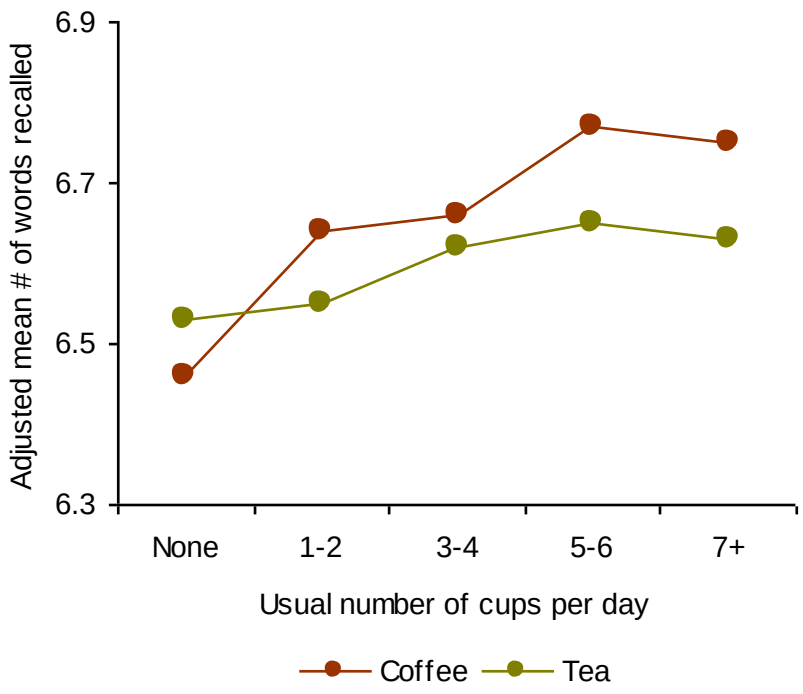
Rogers et al. (2012) *Psychopharmacology* **226,** 229-40

Relationship between habitual coffee and tea consumption and cognitive performance

Choice reaction time



Incidental verbal memory



Data are from the Health and Lifestyle Survey of British adults, n=7087
Relationship between 'caffeine' consumption and task performance, $p<0.0001$*

*Controlling for: demographic variables (age, sex, SES, etc), general health, and tobacco, alcohol and tranquilliser use.

Jarvis (1993) *Psychopharmacology, 110*, 45-52

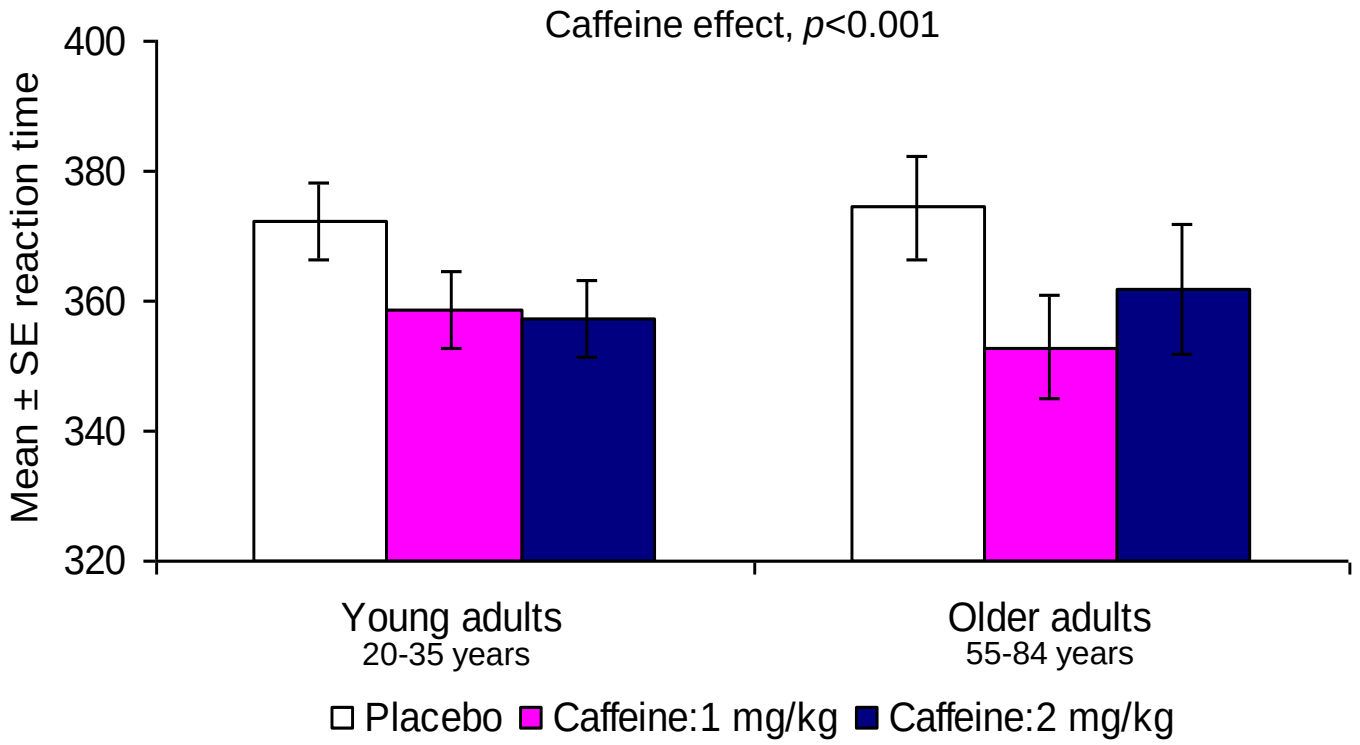
Relationship between habitual caffeine consumption and cognitive performance as a function of age

	Caffeine and performance association for each age group			Caffeine X age interaction
	16-34 years n=2243	35-54 years n=2637	54+ years n=2207	
Simple reaction time	ns	ns	ns	$p<0.001$
Choice reaction time	ns **-7 ms**	$p<0.05$	$p<0.05$ **-32 ms**	$p<0.001$
Incidental verbal memory	ns **+0.04 items**	ns	$p<0.01$ **+0.52 items**	$p<0.001$
Visuo-spatial reasoning	ns	$p<0.05$	$p<0.05$	ns

Jarvis (1993) *Psychopharmacology, 110*, 45-52

Effects of caffeine on performance of a simple reaction time task in young and older adults

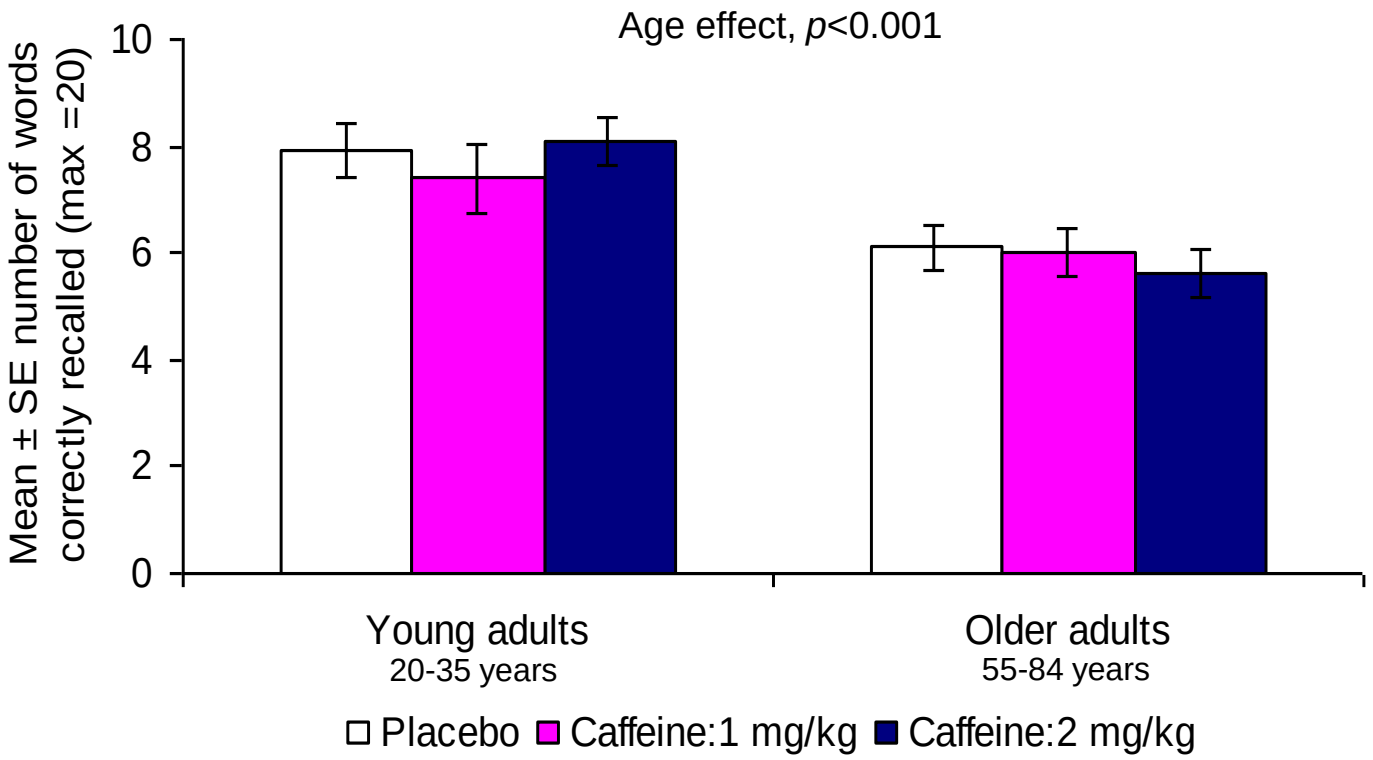
Moderate to high caffeine consumers, overnight caffeine deprived



Adapted from Rogers and Dernoncourt (1998) *Pharmacology Biochemistry and Behavior* **59**, 1039-1045

Lack effect of caffeine on memory performance in young and older adults

Moderate to high caffeine consumers, overnight caffeine deprived

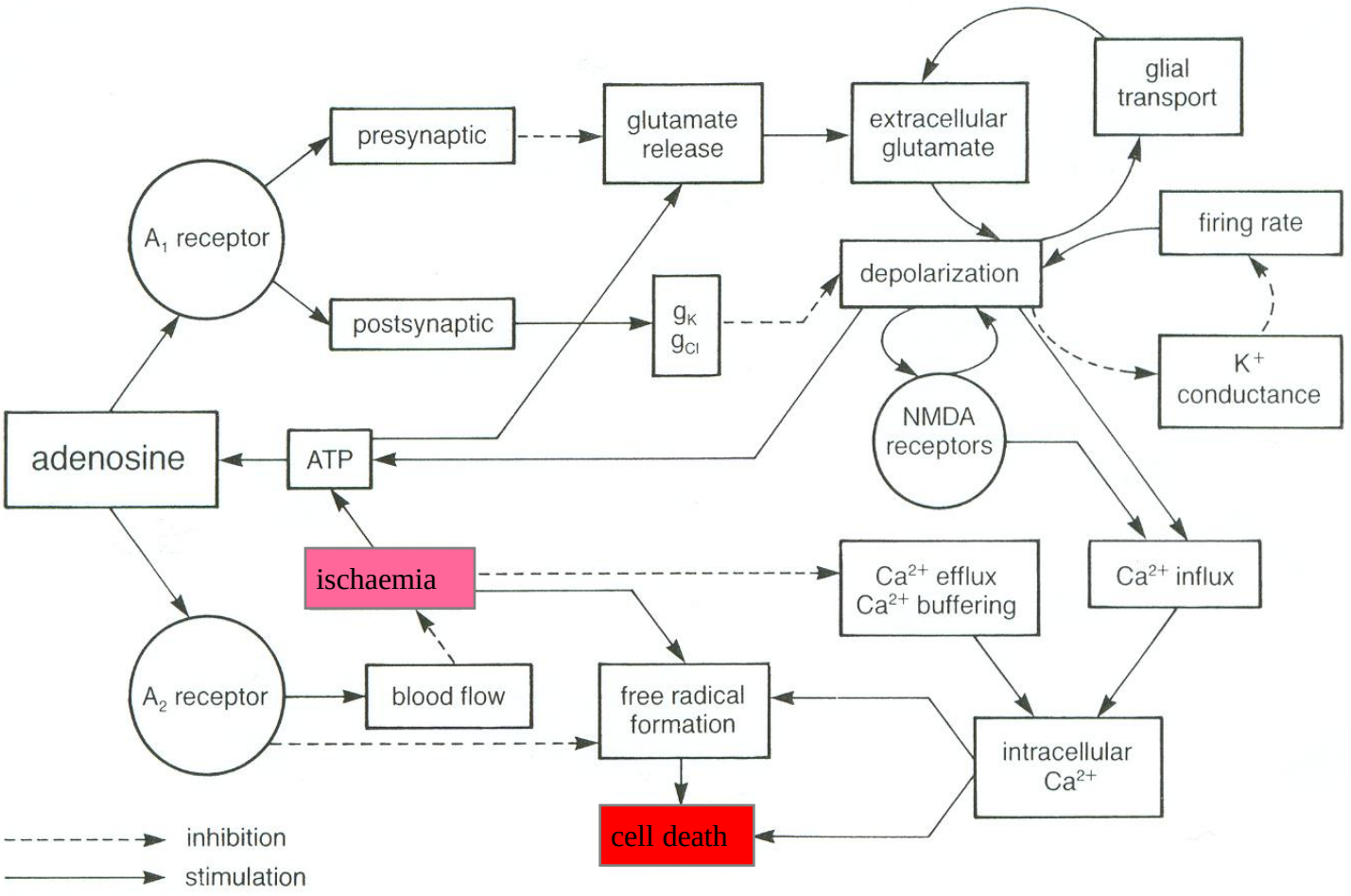


Adapted from Rogers and Dernoncourt (1998) *Pharmacology Biochemistry and Behavior* **59**, 1039-1045

How tea and coffee may help to protect against cognitive decline

- Neuroprotective role of adenosine during brain ischaemia
- Polyphenols and other compounds in tea and coffee may protect against vascular disease
  - effects on blood cholesterol, blood coagulation and inflammatory processes, vasorelaxant effects

Neuroprotective actions of adenosine in brain ischaemia



Rudolphi et al. (1992) *Trends in Pharmacological Sciences, 13,* 439-445

Actually a balance of bad good effects?

- Caffeine increases blood pressure
  - this ought to increase risk of cardiovascular disease and stroke, and contribute to greater risk cognitive decline later in life
    James (2004) *Psychosomatic Medicine 6,* 63-71
- Cafestol in coffee (conc varies with brewing method) increases LDL cholesterol
- Presumably these bad effects are outweighed by
  - beneficial vascular and other effects of polyphenols, etc (tea and coffee)
  - possible sensitisation of the neuroprotective action of adenosine by caffeine consumption
- Note
  - Theanine (tea) reduces blood pressure
    Rogers et al (2008) *Psychopharmacology 195,* 560-577
  - Coffee consumption (caf and decaf) associated with **reduced** risk of type-2 diabetes
  - Sugared cola consumption (caf and decaf) associated with **increased** risk of type-2 diabetes
    Bhupathiraju et al (2013) *American Journal of Clinical Nutrition 97,* 155-66
  - Coffee consumption associated with **reduced** risk of hypertension
  - Sugared and 'diet' cola consumption associated with **increased** risk of hypertension
    Winkelmayer et al (2005) *JAMA 294,* 2330-5

Rogers & Smith (2011) In Benton (ed) Lifetime nutritional influences on cognition, behaviour and psychiatric illness.

Caffeine summary

- Widely consumed; various physiological and behavioural effects
- Is caffeine a cognitive enhancer? Day to day, the frequent caffeine consumer probably does not benefit from caffeine consumption
  - due to tolerance to the alerting effect of caffeine
  - though significant adverse effects of withdrawal are normally avoided by the typical daily pattern of caffeine intake
  - tolerance also develops to the small anxiogenic effect of caffeine
- Physical performance
  - enhanced motor speed and endurance
  - decreased hand steadiness
- Frequent caffeine consumers are caffeine dependent, addiction potential of caffeine is low
- Tea and coffee protect against cognitive decline
  - role of caffeine and other compounds?