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

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

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

Caffeine (1,3,7-trimethylxanthine)
Tea | Maté | Cola
---|---|---
Coffee | Cocoa | 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
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


- 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)**

- Ratio of post to pre-treatment performance (mean ± SE)
- Treatment, $p = 0.013$

**Hand steadiness (number of contacts)**

- Ratio of post to pre-treatment performance (mean ± SE)

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

*Simple reaction time task*

*Rapid number search task*

* * 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

* $p<0.05$, versus placebo

Adapted from Smit & Rogers (2000) *Psychopharmacology*, 152, 167-173
Caffeine withdrawal symptoms?

“The coffeemaker is broken.”
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

*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

* Alert, Attentive, Observant, Able to concentrate

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

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


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

**ADOR2A rs5751876 genotype group distribution in caffeine consumers and non-consumers**

<table>
<thead>
<tr>
<th></th>
<th>CC &amp; CT</th>
<th>TT</th>
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</thead>
<tbody>
<tr>
<td>Consumers</td>
<td>182 (84%)</td>
<td>35 (16%)</td>
</tr>
<tr>
<td>Non-consumers</td>
<td>132 (81.5%)</td>
<td>30 (18.5%)</td>
</tr>
</tbody>
</table>

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

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

* ≥40 mg caffeine per day

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

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

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

Anxiety effect does not deter caffeine consumption


- 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

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

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

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

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

Rogers et al. (2012) *Psychopharmacology* 226, 229-40
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Effects of caffeine on sleepiness, anxiety and mental alertness in caffeine consumers and non-consumers

**Sleepiness:**
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**Mental Alertness:**
'I feel mentally alert / attentive / able to concentrate / observant'

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

<table>
<thead>
<tr>
<th></th>
<th>Sleepiness</th>
<th>Anxiety/Jitteriness</th>
<th>Mental alertness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-low consumer, after caffeine</td>
<td>↓</td>
<td>+ ▼ ▲</td>
<td>= →</td>
</tr>
<tr>
<td>Medium-high consumer, caffeine withdrawn</td>
<td>↑</td>
<td>+ ▲ →</td>
<td>= ↓</td>
</tr>
<tr>
<td>Medium-high consumer, after caffeine</td>
<td>▲ →</td>
<td>+ ▲ →</td>
<td>= →</td>
</tr>
</tbody>
</table>

→ normal level  
↑ increased  
↓ decreased

**Drinkers**

**Abstainers**

Alert, Attentive, Observant, Able to concentrate
Not smarter: No benefit for mental alertness and (therefore) no benefit for cognitive performance

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

But faster: caffeine enhances motor performance

(c) Mental Alertness

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

(d) Simple Reaction Time

(h) Tapping Speed

Rogers et al. (2012) Psychopharmacology 226, 229-40
Relationship between habitual coffee and tea consumption and cognitive performance

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 tranquiliser use.

Jarvis (1993) Psychopharmacology, 110, 45-52
Relationship between habitual caffeine consumption and cognitive performance as a function of age

<table>
<thead>
<tr>
<th>Caffeine and performance association for each age group</th>
<th>Caffeine X age interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-34 years n=2243</td>
<td>35-54 years n=2637</td>
</tr>
<tr>
<td>Simple reaction time</td>
<td>ns</td>
</tr>
<tr>
<td>Choice reaction time</td>
<td>ns -7 ms</td>
</tr>
<tr>
<td>Incidental verbal memory</td>
<td>ns +0.04 items</td>
</tr>
<tr>
<td>Visuo-spatial reasoning</td>
<td>ns</td>
</tr>
</tbody>
</table>

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

Caffeine effect, $p < 0.001$

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

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

- **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
  - **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
  - **Coffee** consumption associated with reduced risk of hypertension
  - **Sugared and ‘diet’ cola** consumption associated with increased risk of hypertension

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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?