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Effects of acute caffeine consumption following sleep loss on cognitive, physical, occupational and driving performance: A systematic review and meta-analysis

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Highlights:

- Meta-analysis indicates caffeine has large effects on performance after sleep loss
- Meta-regression suggests dose explains some of the variability of caffeine's effect
  - Doses <80 mg up to 600 mg provide a likely positive effect, however is task dependent
  - Caffeine is an effective countermeasure to impairments associated with sleep loss

Abstract

Caffeine is widely used to counteract the effects of sleep loss. This systematic review and meta-analysis examined the impact of acute caffeine consumption on cognitive, physical, occupational and driving performance in sleep deprived/restricted individuals. 45 publications providing 327 effect estimates (EEs) were included in the review. Caffeine improved response

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time (44 EEs; *g*=0.86; 95% CI: 0.53-0.83) and accuracy (27 EEs; *g*=0.68; 95% CI: 0.48-0.88) on attention tests, improved executive function (38 EEs; *g*=0.35; 95% CI: 0.15-0.55), improved reaction time (12 EEs; *g*=1.11; 95% CI: 0.75-1.47), improved response time (20 EEs; *g*=1.95; 95% CI: 1.39-2.52) and accuracy (34 EEs; *g*=0.43; 95% CI: 0.30-0.55) on information processing tasks, and enhanced lateral (29 EEs; *g*=1.67; 95% CI: 1.32-2.02) and longitudinal (12 EEs; *g*=1.60; 95% CI: 1.16-2.03) measures of vehicular control on driving tests. Studies also typically indicated benefit of caffeine on memory (25 EEs), crystallized intelligence (11 EEs), physical (39 EEs) and occupational (36 EEs) performance. Ingestion of caffeine is an effective counter-measure to the cognitive and physical impairments associated with sleep loss.

Keywords: Sleep debt; Restricted sleep; Sustained wakefulness; Caffeinated; Cognition; Attention; Reaction time; Vigilance; Information processing; Executive function; Memory; Intelligence; Driving

1.0 Introduction

Sleep is arguably one of the most important, yet underappreciated, components of health (Luyster et al., 2012). Sleep is a biological requirement, proposed to assist with recovery and maintenance of physiological systems (i.e. cellular, neural, endocrine), the conservation of energy, ecological adaptations, and brain plasticity (Cirelli & Tononi, 2008; Mignot, 2008; Roth, Rattenborg, & Pravosudov, 2010). Despite research consistently demonstrating that lack of sleep is associated with a myriad of negative health-related effects (Buxton & Marcelli, 2010; Buxton et al., 2010; Cappuccio, D'Elia, Strazzullo, & Miller, 2010; Faraut, Boudjeltia, Vanhamme, & Kerkhofs, 2012; Spiegel, Knutson, Leproult, Tasali, & Van Cauter, 2005), many individuals routinely fail to get adequate amounts of sleep (Adams et al., 2017; Krueger & Friedman, 2009).

National Sleep Foundation recommendations indicate that the optimal sleep duration (in every 24-hour cycle) is 7 to 9 hours for adults aged 18–64 years (Hirshkowitz et al., 2015). However, a range of behavioral, environmental, occupational, societal and biological factors can prevent an individual from obtaining adequate sleep (Adams et al., 2017; Bixler, 2009). For most, sleep loss is simply a reduction in the total amount of sleep time below an individual's normal amount or that needed to maintain optimal performance (i.e. sleep restriction) (Reynolds & Banks, 2010). However, others may undergo complete elimination of

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sleep for extended periods (i.e. ≥24 h), resulting in prolonged wakefulness (i.e. sleep deprivation) (Reynolds & Banks, 2010). The implications of both sleep restriction and deprivation have been well described (for meta-analytical reviews see (Koslowsky & Babkoff, 1992; Lim & Dinges, 2010; Pilcher & Huffcutt, 1996)). Inadequate sleep has been consistently shown to cause mood disturbances and acutely impair cognitive performance (Alhola & Polo-Kantola, 2007; Killgore, 2010; Reynolds & Banks, 2010). Evidence indicating a detrimental effect of sleep loss on physical performance is less consistent; however, impairments in sport-specific skill execution, submaximal strength, and muscular/anaerobic power have been observed (Fullagar et al., 2015). Collectively, these effects may have substantial personal, economic and societal costs (e.g. increased risk of motor vehicle crashes and workplace accidents, decreased workplace performance and productivity) (Hillman & Lack, 2013; Rosekind et al., 2010; Swanson et al., 2011; Tefft, 2018).

Caffeine (1,3,7-trimethylxanthine), the world's most popular psychoactive drug, has well documented psychostimulant properties (Cappelletti, Daria, Sani, & Aromatario, 2015). It acts as an adenosine receptor antagonist, enhancing behavioral functions such as vigilance, attention, mood, arousal and enhanced motor activation (McLellan, Caldwell, & Lieberman, 2016). Caffeine is readily available from various food, beverage and drug sources; and, in low to moderate doses (e.g. ~0.5–4 $mg \cdot kg^{-1}$ body mass (BM), approximately equivalent to 37.5–300 mg in a 75 kg individual), does not typically induce negative side effects (Temple et al., 2017). For these reasons, caffeine is widely used to counteract performance impairments associated with sleep loss (Roehrs & Roth, 2008). Its efficacy may, however, depend on a number of factors, including the dose consumed, timing of administration, the nature of the performance task, individual expectations, and the magnitude of sleep loss (McLellan et al., 2016). Nonetheless, understanding the efficacy of caffeine intake (including doses and timing) to counteract the harmful effects of acute sleep loss is important.

The aim of this systematic review and meta-analysis was to examine the effects of acute caffeine consumption on cognitive, physical, occupational and driving performance in sleep deprived/restricted individuals. Findings will provide a better understanding of caffeine's efficacy to improve performance under these conditions; thus, help inform recommendations for use of caffeine in the context of sleep loss.

2.0 Methods

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The methodology of this review was developed in accordance with specifications outlined in the *Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols PRISMA-P 2015 Statement* (Moher et al., 2015) and registered at the International Prospective Register of Systematic Reviews ahead of the formal study selection process (ID: CRD42018109393).

2.1 Literature Search

Potential research studies were identified by searching the online databases PubMed (MEDLINE), Web of Science (via Thomas Reuters) and Scopus from inception until September 2018 using the terms sleep*, wakefulness, tired*, drowsy and drowsiness in combination with caffeine, caffeinated, 1,3,7-trimethylxanthine, coffee, tea, cola, "soft drink*", "carbonated drink*", "carbonated beverage*", "sport* drink*", "sport* beverage*", "energy drink*" and "chewing gum". The star symbol (*) was used to capture the derivatives (by suffixation) of a search term and the enclosed quotation marks were used to search for an exact phrase. No other search restrictions were imposed. Two investigators (D.M. and S.K.) independently screened potential studies to identify relevant texts. Initially, all irrelevant titles were discarded. The remaining articles were then systematically screened for eligibility by abstract and full text, respectively. The decision to include or discard potential research studies was made between three investigators (D.M., S.K. and C.I.). Any discrepancies were resolved in consultation with a fourth investigator (B.D.). Full details of the screening process are displayed in Figure 1.

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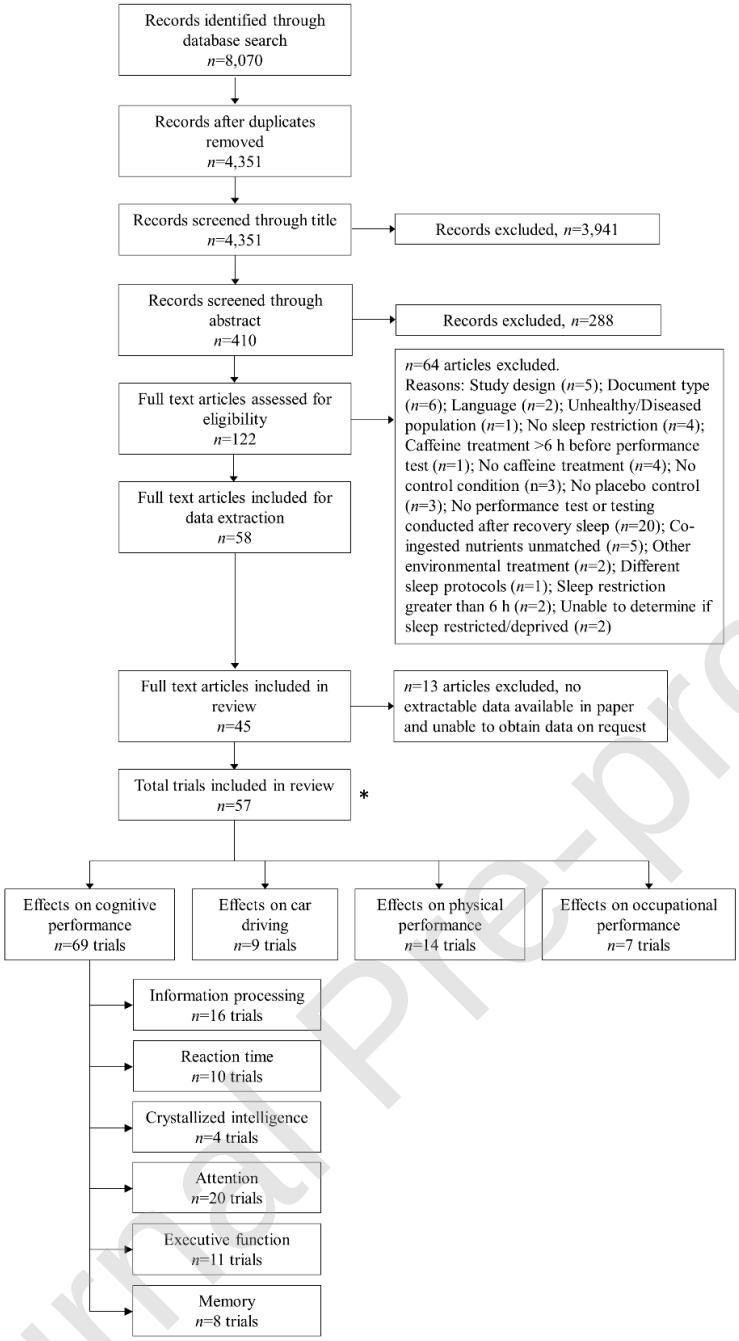

Figure 1. PRISMA Flow Chart (study selection methodology). Where a study contained more than one "intervention-arm", the separate "arms" were treated as discrete 'studies', termed as *trials*. *As single trials often measured performance multiple times and/or on multiple tests that generated several different outcomes, each one can be attached to more than one effect estimate and/or categorized into several different outcome domains

2.2 Inclusion and Exclusion Criteria

Studies were required to fulfil the following inclusion criteria:

1. Placebo-controlled (within- or between-subject) experimental trials;
2. Adult participants (≥18 y) with no known medical conditions (e.g., including head/CNS injuries and diagnosed sleep disorders);

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3. An objective measurement of physical, cognitive and/or occupational performance (see *2.4 Primary and Secondary Research Outcomes*) was obtained following a period of *sleep loss*, defined as ≤6 h sleep per 24-hour cycle, under control ('placebo') and intervention ('caffeine') conditions. Data were only included if performance was assessed <6 h post-caffeine administration, i.e. the approximate half-life of caffeine (Benowitz, 1990), or within 12 h, if slow release caffeine (SRC) (with a longer half-life) was used (Beaumont et al., 2001);
4. Full-text original research studies published in English. All other documents were discarded.

Studies were excluded from the review if: (1) treatments were co-administered with other pharmacological or psychoactive substances (e.g. dextroamphetamine, modafinil, melatonin, alcohol), or intentionally alerting stimulus (e.g. bright light, transcranial direct current stimulation); Studies that administered caffeine in combination with other dietary constituents (e.g. taurine in "energy drinks") were accepted if the effect of caffeine could be isolated; that is, the control treatment contained the same dietary constituents except caffeine (e.g. the control drink also contained taurine, but not caffeine; (2) studies were performed under unusually stressful conditions (e.g. "Hell Week" in Tharion, Shukitt-Hale, and Lieberman (2003) and Lieberman, Tharion, Shukitt-Hale, Speckman, and Tulley (2002)); and/or (3) performance data were not adequately reported, i.e. neither the Mean ± Standard Deviation (SD) nor an appropriate effect size were reported or calculatable. If data were not adequately reported, and the research was published in the previous 10 years (2009–2019), the corresponding author was contacted via email in an attempt to retrieve the missing data. Where data were presented in graphical format only, a web-based tool ('WebPlotDigitizer', https://automeris.io/Web/PlotDigitizer/) was used to extract numeric values.

If a study contained multiple "intervention-arms" (e.g. involving different doses of caffeine, dosing regimens or participant populations) – more than one of which was eligible for inclusion – the separate "arms" were treated as discrete 'studies', termed *trials* (i.e. identifiable by the additional letters (e.g. a–c) in the citation). As single trials often measured performance multiple times and/or on multiple tests that generated several different outcomes, each one can be attached to more than one effect estimate (EE).

2.3 Quality Assessment

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Included studies were examined for publication bias using the Rosendal Scale (van Rosendal, Osborne, Fassett, & Coombes, 2010), which assesses a number of factors associated with the minimization of bias in areas such as randomization, blinding, participant selection, and data reporting (see Table II in van Rosendal et al., 2010). Excellent methodological quality is indicated by a Rosendal Score ≥60% (Jadad et al., 1996). Scoring was determined by dividing the number of 'Yes' responses by the total number of applicable items. Studies were ineligible for meta-analysis if they received a Rosendal score <50% (note: no study received a score <50% in this review).

2.4 Performance Outcomes

All objective measurements of physical, cognitive and occupational performance are considered in this review. The different cognitive performance tests were categorized on the basis of the specific function (i.e. neuropsychological domain) they assessed, as recognized by the *Current Cognitive Psychology* and *Neuropsychology* texts (Lezak, Howieson, & Loring, 2004) and demonstrated previously by Chang, Labban, Gapin, and Etnier (2012); these domains were: (a) *Information Processing*; (b) *Reaction Time*; (c) *Crystallized Intelligence*; (d) *Attention*; (e) *Executive Function*; and (f) *Memory* (Table 1). The 'response speed' and 'response accuracy' data were handled separately within each domain. Occupational performance tests included those that involved or simulated an applied activity (e.g. the operation of a motor vehicle or performing military activities); tests of speed, strength, endurance, and/or motor-coordination were considered 'physical' performance.

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Table 1. Categorization of the cognitive performance tests.

Information Processing
Critical Tracking Task
CFF Task
Digit Symbol Substitution
Finger Tapping
Stroop Congruent & Incongruent
Symbol Cancellation Task
Visual Tracking Task
Reaction Time
Choice Reaction Time Task
Simple Reaction Time Task
Crystallized Intelligence
Addition and Subtraction (math)
Attention
Auditory Vigilance Task
Psychomotor Vigilance Task
Focus of Attention Task
Mackworth Clock Test
Executive Function
Digit Span (backwards)
Grammatical Reasoning
Response Inhibition Task
Logical Reasoning
Random Number Generation
Stroop Interference
Tower of Hanoi Task
Tower of London Task
Wisconsin Card Sorting Task
Semantic Fluency
Word Association
Biber Cognitive Estimation Test
Memory
Delayed Match to Sample Task
Digit Span (forward)
Free Recall
Learning
Memory Search Task

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2.5 Data Extraction

Data were extracted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions *Checklist of Items to Consider in Data Collection or Data Extraction* (Higgins & Green, 2011). Extracted data included: (1) the study design; (2) participant characteristics (e.g. population, age, body mass (BM), gender, usual sleep and caffeine consumption

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behavior); (3) the sleep protocol employed (e.g. standardization procedures, type of environment, protocol duration, length of wakefulness); (4) treatment characteristics (e.g. caffeine dose, dosing regime, mode of caffeine delivery); and (5) performance test characteristics (e.g. testing procedures, test duration, number of assessments, time of day), where available. All caffeine doses were converted to absolute values (i.e. mg) because a relative dose (i.e. $mg \cdot kg^{-1}$ BM) could not usually be derived (i.e. few studies reported participants' BM).

2.6 Data Synthesis

Independent-groups Hedges' *g* intervention EEs (Durlak, 2009) were calculated for each performance outcome by standardizing the mean difference between the control and intervention performance scores against the pooled SD and correcting for bias due to small sample size. The magnitude of effect was defined in accordance with Cohen (1988): Hedges' $g \leq 0.2$ = small; 0.2–0.5 = medium; and ≥ 0.8 = large, where a positive value indicates a beneficial effect of caffeine, irrespective of the performance outcome measured. If a trial repeated the same performance test two (or more) times within a 6 h period, and no additional caffeine was provided between tests, the resulting Hedges' *g* values were combined (averaged) into a single EE (with an increased sample size). Meta-analyses were performed to determine the effect of caffeine on: (1) information processing (response speed and accuracy); (2) reaction time (response speed); (3) attention (response speed and accuracy); (4) executive function (response speed and accuracy); and (5) simulated driving performance (lateral and longitudinal vehicular control). The remaining performance outcomes (i.e. crystallized intelligence, memory, occupational performance and physical performance) were unsuitable for meta-analysis, either because the data were derived from a small number of studies or the performance tests and outcomes were too heterogeneous to consolidate into a meaningful meta-analysis (*see sections 3.2.3 Crystallized Intelligence, 3.2.6 Memory, 3.4 Occupational Performance, 3.5 Physical Performance for specific details*).

2.6.1 Statistical Analysis

All statistical procedures were performed using IBM SPSS Statistical Software Version 25.0 and Comprehensive Meta-Analysis Version 3.0. All data are presented as Mean ± SD.

2.6.1a Meta-Analysis

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Weighted mean treatment effects were calculated using random-effect models, where trials were weighted by the inverse variance for the performance change. Statistical significance was attained if the 95% Confidence Interval (CI) did not include zero. Heterogeneity was assessed using Cochran's Q and the I^2 index. Low, moderate and high heterogeneity was indicated by an I^2 value of 25, 50 and 75%, respectively (Higgins, Thompson, Deeks, & Altman, 2003). A *p*-value <0.10 for Cochran's Q was used to indicate significant heterogeneity (Higgins & Green, 2011). Sensitivity analyses were performed by sequentially removing trials from the meta-analysis and assessing the impact of excluding trials on the overall effect estimate and heterogeneity.

2.6.1b Meta-Regression Analysis

Restricted maximum likelihood, random-effects multiple meta-regression analyses were performed to determine whether the Hedges' *g* effect of acute caffeine consumption on information processing, reaction time, attention, executive function and car driving was influenced by: (a) the dose of caffeine provided; or (b) the period of wakefulness. The dose of caffeine provided was estimated as the total amount of caffeine consumed <6 h prior to the relevant performance test (or <12 h, if SRC was used); caffeine consumed ≥6 h (or ≥12 h, if it was SRC), was not included in this total. The period of wakefulness for studies employing sleep deprivation protocols was calculated as the time from first waking (i.e. at the beginning of the experiment) to the relevant performance test. For studies employing sleep restriction protocols (i.e. where a period of sleep was included in the protocol, but where the total sleep duration was ≤6 h sleep per 24-hour cycle) the period of wakefulness was estimated as the time from first waking (i.e. at the beginning of the experiment) to the relevant performance test, minus any time spent sleeping throughout the study protocol. Where data were collapsed (e.g. because a trial repeated the same performance test ≥2 times within a 6 h period, as described in *2.5 Data Extraction*) such that one EE reflected ≥2 measurements taken at separate times, the average period of wakefulness was used. At least 10 data points were required for a variable to quality for meta-regression analysis. Regression analyses were examined for influential cases and outliers (i.e. studentized residuals, Cook's distance and centered leverage values) and multicollinearity (variance inflation factor). Statistical significance was accepted as $p<0.05$.

3.0 Results

3.1 Overview of Included Studies and Study Quality

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The literature search initially identified 58 investigations that were eligible for review. However, no extractable data was available in *n*=13 of the published papers (and was unable to be obtained via request from the corresponding author). As such, 57 trials (*n*=988 participants) derived from 45 publications were included in this review. Methodological quality assessment yielded an average Rosendal score of 65±6%; all trials scored >50% (Range: 53–75%). Full results of the quality assessment can be found in Supplementary Table S1. Across the 327 EEs calculated, the average dose of caffeine provided was 340±170 mg and the period of wakefulness was 31±13 h. The dose of caffeine provided was ≤200 mg, between 201–400 mg and between 401–600 mg in 40%, 37% and 23% of cases, respectively; while the period of wakefulness was ≤24 h, between 25–48 h and between 49–72 h in 41%, 48% and 11% of cases, respectively.

3.2 Cognitive Performance

3.2.1 Information Processing

Sixteen trials measured information processing performance (Supplementary Table S2). These trials provided a total of 54 EEs (outcomes), of which 20 were measures of 'response speed' (e.g. speed, response time, cancelled symbols, limit of detection) and 34, 'response accuracy' (e.g. tracking accuracy, response accuracy, control losses). Caffeine significantly improved both speed (Hedges' g=1.95, 95% CI: 1.39-2.52, p<0.001, I^2=91.9%) and accuracy (Hedges' g=0.43, 95% CI: 0.30-0.55, p<0.001, I^2=35.8%) of information processing (Figures 2 & 3, respectively). The magnitude and significance of each effect was stable during sensitivity analyses where trials were sequentially removed (speed: Hedges' g range=1.72–2.05; accuracy: Hedges' g range=0.41–0.45). Neither the dose of caffeine provided (p=0.785) nor the period of wakefulness (p=0.373) influenced the magnitude of the Hedges' g effect on overall information processing performance (R^2=0.0). Four trials (5 EEs) reported negative effects of caffeine on the accuracy component of information processing, however, the magnitude of these effects was generally small to medium (Hedges' g = -0.02 to -0.29).

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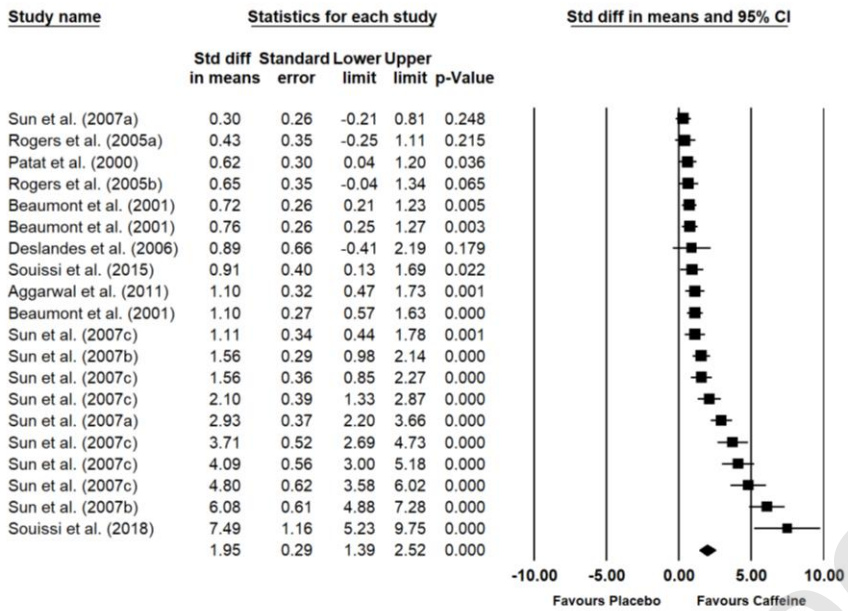

Figure 2. Forest plot displaying the effect of acute caffeine consumption on response speed during information processing tasks. The size of the squares is proportional to the weight of the study. A positive effect estimate indicates a beneficial effect of caffeine.

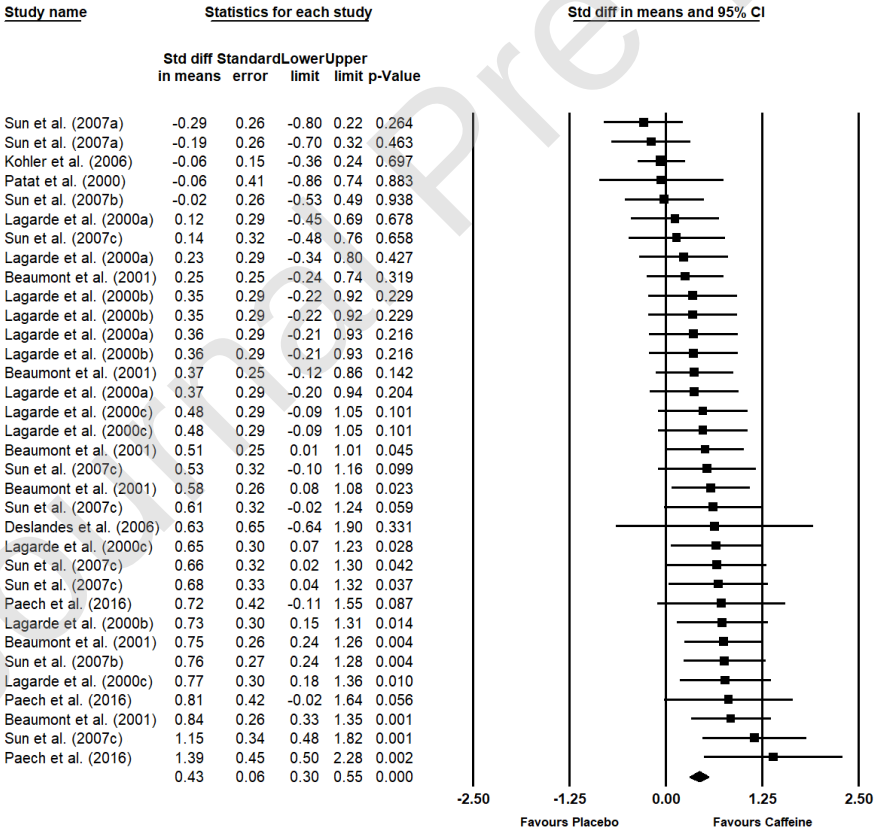

Figure 3. Forest plot displaying the effect of acute caffeine consumption on response accuracy during information processing tasks. The size of the squares is proportional to the weight of the study. A positive effect estimate indicates a beneficial effect of caffeine.

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3.2.2 Reaction Time

Ten trials measured reaction time performance (Supplementary Table S3). These trials provided a total of 12 EEs (outcomes), all of which were measures of 'response speed' (e.g. response time, throughput). Caffeine significantly improved response speed (Hedges' g=1.11, 95% CI: 0.75-1.47, p<0.001, I^2=73.4%) on the reaction time tasks (Figure 4). The magnitude and significance of this effect was stable during sensitivity analyses where trials were sequentially removed (Hedges' g range=0.98–1.21). The magnitude of the Hedges' g effect on reaction time performance increased as the dose of caffeine increased (p=0.020) but was not significantly related to the period of wakefulness (p=0.896) (R^2=0.36). One trial (1 EE) reported a negative effect of caffeine on reaction time, but the magnitude of this effect was small (Hedges' g = -0.06).

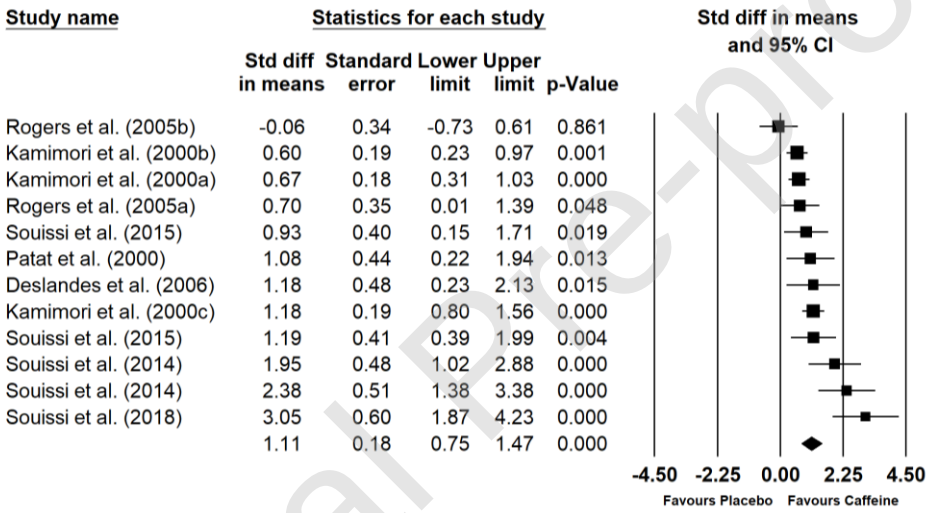

Figure 4. Forest plot displaying the effect of acute caffeine consumption on response speed during reaction time tasks. The size of the squares is proportional to the weight of the study. A positive effect estimate indicates a beneficial effect of caffeine.

3.2.3 Crystallized Intelligence

Four trials (11 EEs) measured crystallized intelligence (Supplementary Table S4). These data were derived from two publications, only; thus, were not meta-analyzed. Overall, results are inconsistent with Aggarwal, Mishra, Crochet, Sirimanna, and Darzi (2011) finding no effect of caffeine (150 mg) on mental arithmetic performance and Sun, Zhang, He, Liu, and Miao (2007a-c) indicating a positive effect of caffeine (200–400 mg) on response speed, but not accuracy, during a continuous addition test. One trial (1 EE) reported a negative effect of

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caffeine on crystallized intelligence, but the magnitude of this effect was small (Hedges' g = -0.05).

3.2.4 Attention

Twenty trials measured attention (Supplementary Table S5). These trials provided a total of 71 EEs (outcomes), of which 44 were measures of 'response speed' (e.g. response time, the Erikson effect) and 27, 'response accuracy' (e.g. detected targets, lapses, response accuracy). Caffeine significantly improved speed (Hedges' g=0.86, 95% CI: 0.53-0.83, p<0.001, I^2=58.9%) and accuracy (Hedges' g=0.68, 95% CI: 0.48-0.88, p<0.001, I^2=64.9%) on the attention tests (Figures 5 & 6, respectively). The magnitude and significance of each effect was stable during sensitivity analyses where trials were sequentially removed (speed: Hedges' g range=0.64–0.71; accuracy: Hedges' g range=0.64–0.71). The magnitude of the Hedges' g effect on attention increased as the dose of caffeine increased (p=0.004) but was unrelated to the period of wakefulness (p=0.371) (R^2=0.29). One trial (1 EE) reported negative effects of caffeine on the response speed component, while two trials (3 EEs) observed negative effects of caffeine on the accuracy component of attention. The magnitude of these negative effects was small (Hedges' g = -0.03 to -0.21).

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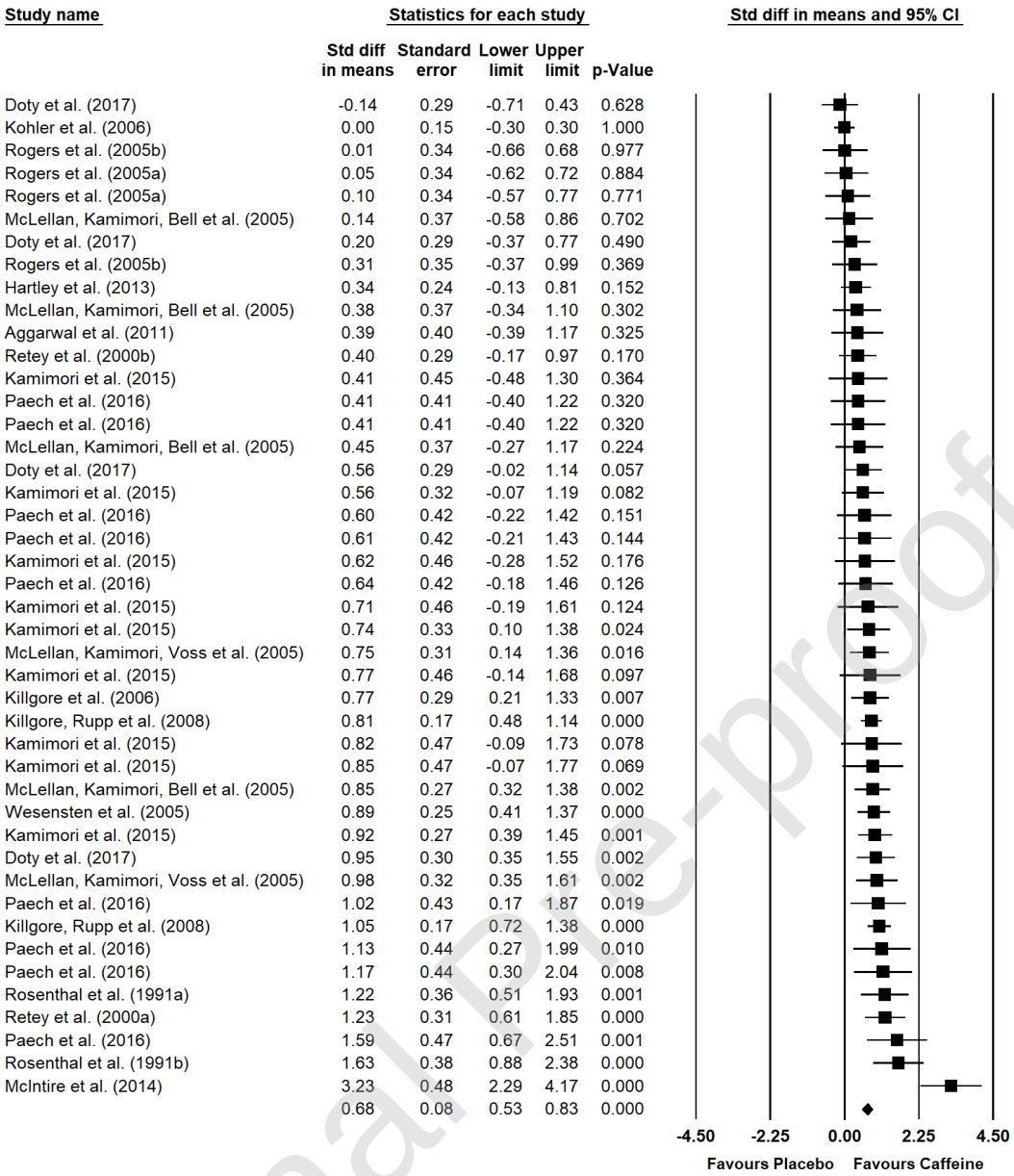

Figure 5. Forest plot displaying the effect of acute caffeine consumption on response speed during attention tasks. The size of the squares is proportional to the weight of the study. A positive effect estimate indicates a beneficial effect of caffeine.

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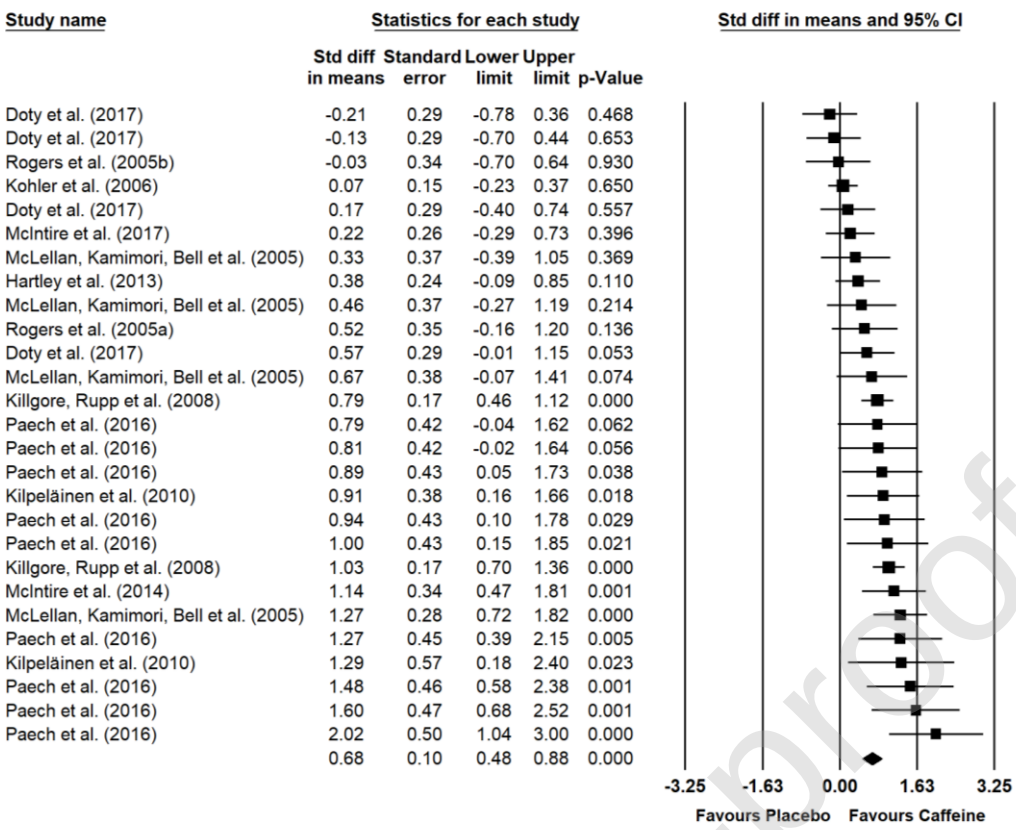

Figure 6. Forest plot displaying the effect of acute caffeine consumption on response accuracy during attention tasks. The size of the squares is proportional to the weight of the study. A positive effect estimate indicates a beneficial effect of caffeine.

3.2.5 Executive Function

Eleven trials measured executive function (Supplementary Table S6). These trials provided a total of 38 EEs (outcomes), all of which were compiled into one meta-analysis (as they could not be categorized as measures of 'response speed' or 'response accuracy'). Caffeine significantly improved executive function (Hedges' g=0.35, 95% CI: 0.15-0.55, p=0.001, I^2=61.2%) (Figure 7). The magnitude and significance of this effect was stable during sensitivity analyses where trials were sequentially removed (Hedges' g range=0.29–0.39). The magnitude of the Hedges' g effect on executive function increased as the dose of caffeine increased (p=0.007) and the period of wakefulness decreased (p=0.021) (R^2=0.24). Six trials (9 EEs) observed negative effects of caffeine on executive function. The magnitude of these effects was generally small to medium (Hedges' g = -0.13 to -0.49), however three trials reported a medium to large negative effect (Hedges' g = -0.57 to -1.45).

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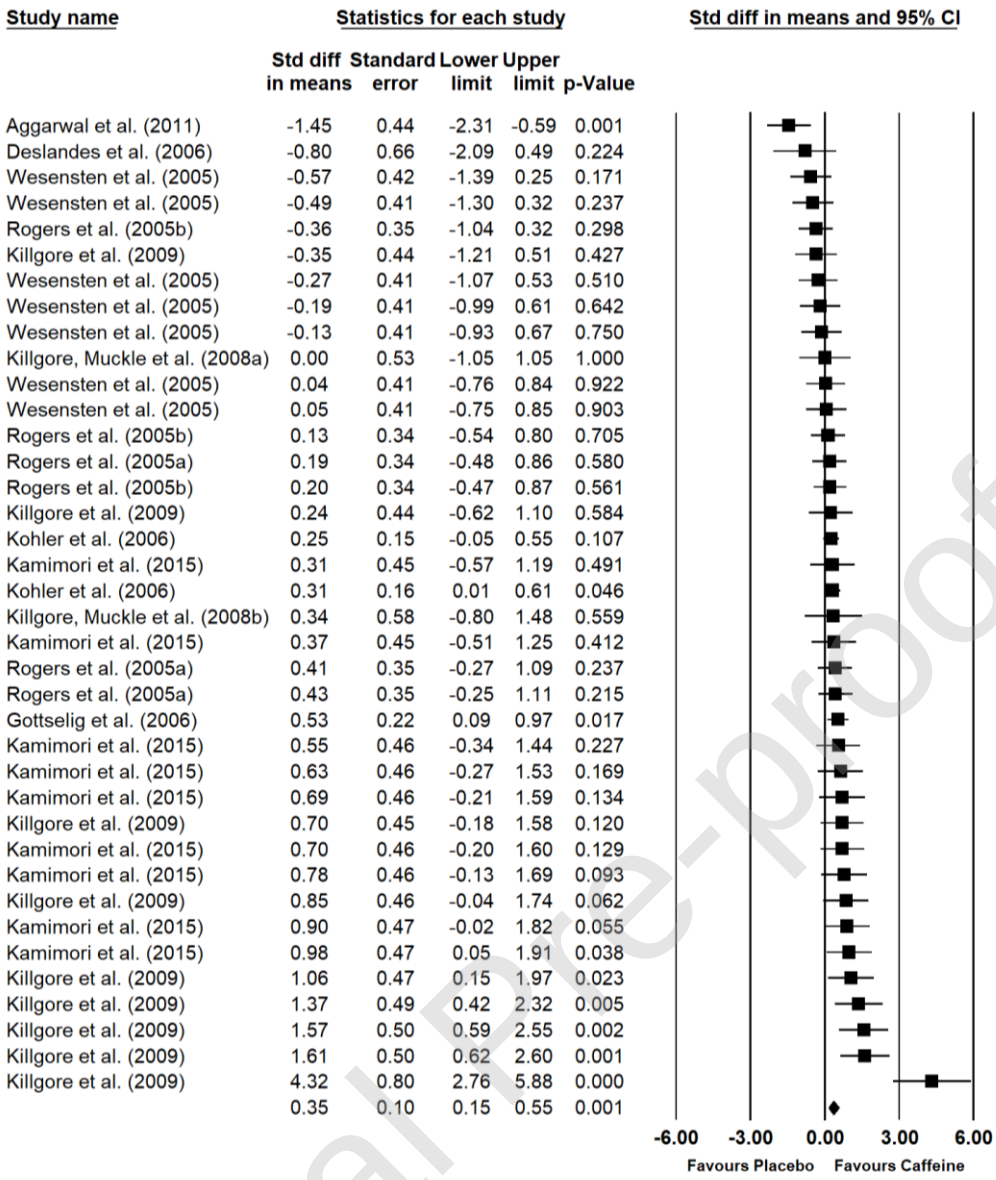

Figure 7. Forest plot displaying the effect of acute caffeine consumption on executive function. The size of the squares is proportional to the weight of the study. A positive effect estimate indicates a beneficial effect of caffeine.

3.2.6 Memory

Eight trials (25 EEs) measured memory performance (Supplementary Table S7). These data were not meta-analyzed as >70% of the EEs were derived from one publication. Overall, the majority of trials observed a small to medium positive effect of caffeine on memory; Rogers et al. (2005a), however, did report a medium to large (Hedges' g = - 0.57 to -1.16) detrimental effect of caffeine (80 mg) on delayed (but not immediate) recall in individuals who had been subjected to either overnight or prolonged (i.e. 3-weeks) caffeine withdrawal ahead of the experiment.

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3.3 Car Driving

Nine trials measured driving performance (Supplementary Table S8). However, Philip et al. (2006) was omitted from meta-analysis because the total period of wakefulness could not be calculated – the trial was included in the review because the test was conducted at 2AM, at which point, one would expect participants to be "sleep deprived" as per our definition. The remaining trials provided a total of 41 EEs (outcomes), of which 29 were measures of 'lateral control' (e.g. lane crossing, standard deviation of lateral position [SDLP], crashes) and 12, 'longitudinal control' (e.g. standard deviation of speed [SDSP]). Caffeine significantly improved lateral (Hedges' g=1.67, 95% CI: 1.32-2.02, p<0.001, I^2=75.9%) and longitudinal (Hedges' g=1.60, 95% CI: 1.16-2.03, p<0.001, I^2=60.9%) vehicular control (Figures 8 & 9, respectively). The magnitude and significance of each effect was stable during sensitivity analyses where trials were sequentially removed (lateral: Hedges' g range=1.61–1.73; longitudinal: Hedges' g range=1.54–1.69). The magnitude of the Hedges' g effect on car driving performance increased as caffeine dose increased (p<0.001) (R^2=0.35); the 'period of wakefulness' was not included in this model as all of the 'longer periods of wakefulness' (e.g. >24 h) were derived from two investigations. No trials indicated a negative effect of caffeine.

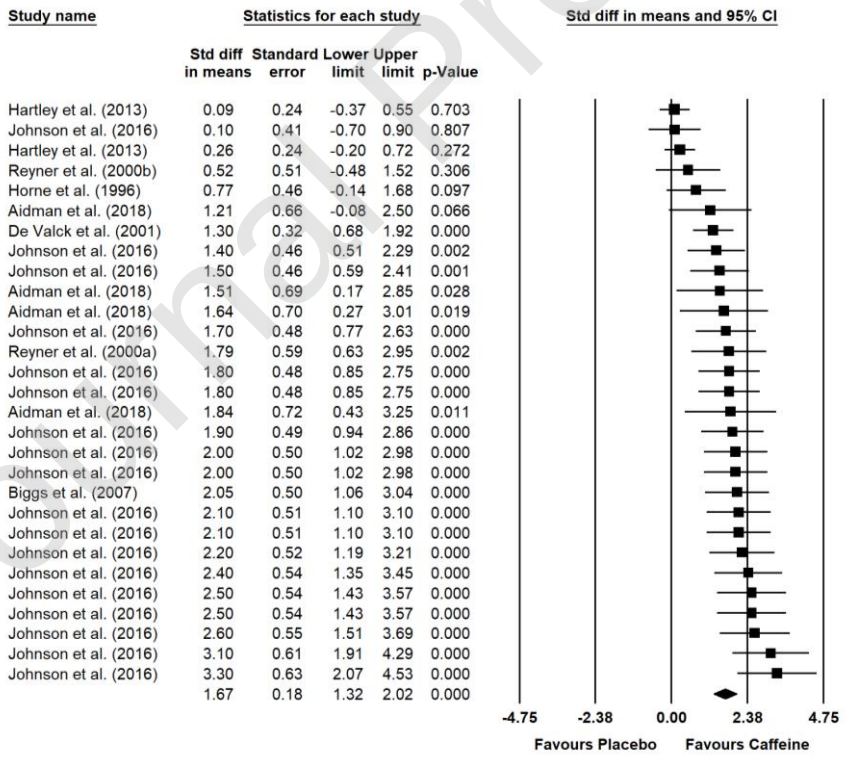

Figure 8. Forest plot displaying the effect of acute caffeine consumption on lateral vehicular control. The size of the squares is proportional to the weight of the study. A positive effect estimate indicates a beneficial effect of caffeine.

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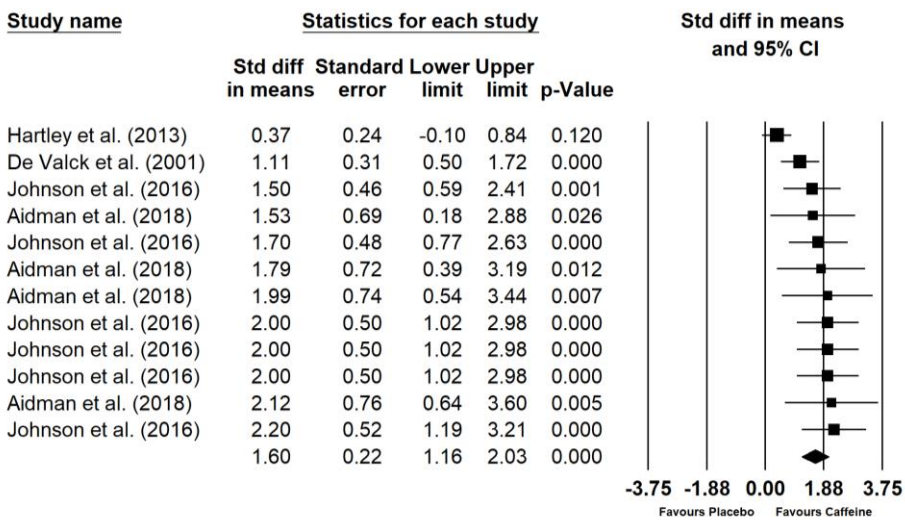

Figure 9. Forest plot displaying the effect of acute caffeine consumption on longitudinal vehicular control. The size of the squares is proportional to the weight of the study. A positive effect estimate indicates a beneficial effect of caffeine.

3.4 Occupational Performance

Seven trials (36 EEs) measured occupational performance (Supplementary Table S9). These data were not meta-analyzed as the performance tests and outcomes measured were too heterogeneous. Overall, all trials observed a positive effect of caffeine on occupational performance; however, the magnitude of improvement varied widely. No studies indicated a detrimental effect of caffeine.

3.5 Physical Performance

Fourteen trials (39 EEs) measured physical performance (Supplementary Table S10). These data were not meta-analyzed as the performance tests and outcomes measured were too heterogeneous. Overall, most trials observed a positive effect of caffeine on physical performance; however, the magnitude of improvement varied widely. Two studies (5 EEs) observed a small to medium (Hedges' g = -0.04 to -0.63) detrimental effect of caffeine on performance; specifically, Donald, Moore, McIntyre, Carmody, and Donne (2017) found that participants covered less distance on two endurance running tests when caffeine (480 mg) was provided and Moore, McDonald, McIntyre, Carmody, and Donne (2018) observed a small reduction in performance on the Illinois Speed–Agility test and the 5 m Multiple-shuttle test with caffeine (370 mg).

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3.6 Summary of Performance Effects

A summary of the likely effect of caffeine and predicted ergogenic dose required to elicit a medium and large effect (Hedges' g = 0.5, 0.8, respectively) for each performance outcome included in this review is provided in Table 2. The 'Caffeine Effect' describes the likely effect of caffeine (e.g. positive, negative or unclear) on a given performance outcome as determined by the evidence collated in this systematic review; and where sufficient data was available, meta-analysis. The 'Predicted Ergogenic Dose' (i.e. the caffeine dose likely to elicit a positive effect (rounded to nearest 5 mg)) was estimated on the basis of meta-regression equations for the various effect magnitudes (Hedges' g = 0.5, 0.8) and a period of 24 h wakefulness (*see Supplementary Table S11*); however, this method could only be used when the Hedges' g effect of caffeine and the dose provided were significantly related; otherwise the range of caffeine doses provided in trials that indicated an ergogenic effect is reported. Where the minimum predicted ergogenic dose estimated from the meta-regression equations to achieve the Hedges' g was smaller than the lowest dose administered in any of the studies included in this review, rather than using the calculated value, Table 2 instead describes the lowest dose administered from the relevant studies in this review.

Table 2. Summary of the effect of caffeine on cognitive, occupational, physical and car driving performance following sleep loss

Performance Outcome	**Caffeine Effect**	**Predicted Ergogenic Dose**	
		Hedges' *g* 0.5	**Hedges' *g* 0.8**
Reaction Time	**Positive**[§]	**<80 mg**[†*]	**125 mg**[†]
Car Driving Performance	**Positive**[§]	**<100 mg**[†*]	**<100 mg**[†*]
Attention	**Positive**[§]	**125 mg**[†]	**425 mg**[†]
Executive Function	**Positive**[§]	**305 mg**[†]	**455 mg**[†]
Information Processing	**Positive**[§]	80–600 mg	
Physical Performance	Positive	80–600 mg	
Memory	Positive	80–600 mg	
Occupational Performance	Positive	100–600 mg	
Crystallized Intelligence	Unclear	-	

§ Caffeine Effect is supported by meta-analytic evidence; '†' minimum dose was estimated on the basis of meta-regression equations (Supplementary Table S11); * the minimum dose estimated from the meta-regression equations was smaller than the lowest ergogenic dose administered to achieve this Hedges' g – the value listed therefore describes the lowest dose administered from studies included in this review. **Bolded** results have the greatest empirical support.

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4.0 Discussion

Caffeine is widely used to counteract mood and performance impairments associated with sleep loss. The present systematic review and meta-analysis examined the effects of acute caffeine consumption following a period of sleep loss on cognitive, physical, occupational and driving performance. Overall, results demonstrate that caffeine improves performance on a wide range of tasks (relative to placebo) in individuals who have experienced prior sleep restriction/deprivation. Thus, the ingestion of caffeine appears to be an effective counter-measure to the cognitive and physical impairments associated with sleep loss.

The overall weighted mean effect summaries specific to cognitive performance outcomes indicate that, following a period of sleep loss, caffeine significantly improves speed and/or accuracy across a variety of cognitive domains (i.e. information processing; reaction time; attention) and overall performance on higher-order cognitive processes (i.e. executive function). Although data was unable to be meta-analyzed, evidence for a distinct beneficial effect on crystallized intelligence and memory is less apparent (i.e. studies have demonstrated mixed effects) and requires further elucidation. Furthermore, it appears that some cognitive processes benefit more from caffeine ingestion under these circumstances than others; for instance, relatively small effects were observed for executive function (Hedges' g=0.35) and the accuracy component of information processing tasks (Hedges' g=0.43), whereas the effects on attention (speed and accuracy), reaction time (speed) and the speed component of information processing tasks were moderate to large (Hedges' g=0.68-1.95). In some cases, however, results were highly heterogenous (i.e. information processing speed, I^2=91.9%), making it difficult to reliably estimate the magnitude of improvement. Nonetheless, the collective evidence suggests that caffeine is efficacious at counteracting the effects of sleep loss on discrete cognitive tasks. The skills indicating the largest benefit appear to be simple and highly vigilance-dependent. This is in keeping with conclusions highlighted in previous review articles (although not employing meta-analytical techniques), indicating a general beneficial effect of caffeine on attention, vigilance and reaction time; but less consistent (or unclear) effects on memory and executive functions in sleep-deprived individuals (McLellan et al., 2016; Nehlig, 2010; Ruxton, 2008).

The present meta-analyses also detected a large, significant effect (Hedges' g=1.60-1.67) of caffeine on vehicle control (both lateral and longitudinal parameters of car driving tasks) in sleep restricted/deprived individuals. These results are particularly important from a road safety standpoint, given that tiredness has been identified as a primary cause of road crashes (Horne

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& Reyner, 1995; Stutts, Wilkins, Scott Osberg, & Vaughn, 2003), and that drivers in sleep-related crashes are more likely to have experienced sleep loss (and work multiple jobs, night shifts, or unusual work schedules) (Stutts et al., 2003). It is, however, important to recognize that all of the studies included in these meta-analyses employed a simulated driving model (rather than on-road driving). While a number of studies have demonstrated direct translation of simulated driving to on-road driving (Lee, Cameron, & Lee, 2003; Mayhew et al., 2011; Risto & Martens, 2014), results of simulator studies may not be generalizable to on-road driving if the simulator used lacks behavioral validity (Mullen, Charlton, Devlin, & Bédard, 2011). Indeed, driving simulators appear to provide relative rather than absolute validity; approximating the effects observed in on-road driving, but with directional similarities (Mullen et al., 2011). Therefore, the driving performance improvements obtained in the present meta-analyses cannot be directly translated into on-road values to gauge reduction in crash risk when caffeine is administered to individuals under conditions of sleep loss.

It is well documented that caffeine has ergogenic potential to positively impact physical performance tasks; likely due to its mechanism of action as an adenosine receptor antagonist and resultant reductions in perceptions of effort during exercise (Doherty & Smith, 2005; Ganio, Klau, Casa, Armstrong, & Maresh, 2009). A recent narrative review indicated that caffeine is effective at enhancing physical performance (including endurance, strength/power and high-intensity/sprint activities) (McLellan et al., 2016). Doses of 3.0-10.0 $mg \cdot kg^{-1}$ BM in rested individuals and 8.0-10.7 $mg \cdot kg^{-1}$ BM (in a divided and repeated dosing protocol) in sleep deprived individuals were predicted to be beneficial. The authors also highlight the potential for caffeine to provide beneficial effects in occupational settings (particularly military operations, when there is little opportunity for sleep), where optimal physical and cognitive function are needed to ensure workplace safety and productivity (McLellan et al., 2016). Although data could not be meta-analyzed in the present study due to the heterogeneity of the outcome measures, the effect of caffeine (following sleep loss) on physical and occupational tasks was generally positive, despite being varied in magnitude. For the occupational tasks specifically, all studies included in the review indicated a positive effect of caffeine (following sleep loss) on performance. This may reflect that most of the occupational specific tasks were highly vigilance dependent and that caffeine exerts its most reliable beneficial effects on vigilance tasks (McLellan et al., 2016). However, in many occupations, individuals need to engage a variety of cognitive processes (other than vigilance). For example, medical professionals (i.e. nurses and doctors) and factory workers on night shift (who may experience sleep loss) also need to make important decisions. Thus, further research is required to examine

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the effects of caffeine (in a sleep loss paradigm) on a wider variety of occupational tasks, including those that require higher-order cognitive processes such as executive function. For physical performance, studies included in the present review generally indicated a benefit of caffeine following sleep loss. There were, however, two studies that demonstrated negative effects (Donald et al., 2017; Moore et al., 2018). This may partly reflect the fact that sleep loss does not always impair physical abilities (Fullagar et al., 2015). Indeed, the trials indicating negative effects employed high-intensity tasks (i.e. speed, agility, sprint, shuttle tasks) and evidence suggests that some maximal physical efforts and gross motor performances can be maintained under situations involving sleep loss (Fullagar et al., 2015). Furthermore, substantial individual differences in the ergogenic response to caffeine exist, and high doses (i.e. >450 mg) may produce symptoms (e.g. anxiety, gastro-intestinal distress) that can negatively impact physical performance (McLellan et al., 2016). Nonetheless, the summary of results from included studies in the present review suggest that caffeine is likely to have a positive impact on physical and occupational task performance in individuals who have experienced prior sleep loss.

The meta-analyses conducted as part of the present review indicated some degree of heterogeneity (I^2=35.8-91.9%) in the effect of caffeine on performance outcomes. Using meta-regression, the dose of caffeine provided was able to explain some proportion of that heterogeneity (except in the case of information processing). Specifically, results indicated that larger doses of caffeine (up to 600 mg) were more beneficial than lower doses. Importantly, however, this review identified that a limited number of research studies have examined the effects of low doses of caffeine (i.e. 0-100 mg) under a sleep loss paradigm. Indeed, the average amount of caffeine administered across all studies in this review was 340±170 mg. Furthermore, only three studies have specifically explored potential dose-response effects of caffeine in this context (Cook, Crewther, Kilduff, Drawer, & Gaviglio, 2011; Lagarde et al., 2000; Rosenthal, Roehrs, Zwyghuizen-Doorenbos, Plath, & Roth, 1991). Hence, further research is required to investigate the effects of ingesting lower doses of caffeine, in sources that are more ecologically valid (i.e. 50-100 mg, the equivalent of 1 cup of coffee) (Poole, Ewings, Parkes, Fallowfield, & Roderick, 2019), and explore potential dose-response effects directly. The period of wakefulness also explained some of the heterogeneity in executive function (but no other outcome variable), with caffeine becoming less efficacious as the period of wakefulness increased. However, most studies in this review employed severe sleep restriction protocols, and one should consider the ecological validity of these. Again, further research is needed to examine the effects of caffeine in sleep loss situations likely to reflect the

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circumstances of most individuals (i.e. 4-5 h TIB) (Adams et al., 2017). It is important to note that a relatively large proportion of the heterogeneity could not be explained in the models determined in this study. This may be partly due to the research methodology we employed. For example, we approximated the 'caffeine dose' as that consumed in the previous 6 h (unless slow release caffeine sources were used and 12 h was allocated). As such, it is likely that plasma caffeine levels varied considerably between and within studies. In addition, the caffeine dose was quantified as an absolute, rather than relative, amount in each study. However, this was unavoidable because too few studies reported participants' body mass to permit conversion of doses to relative amounts. Furthermore, a variety of cognitive tasks (using different outcome measures) were employed across different studies. We collapsed different outcome measures into categories based on best fit and as a means of simplifying analysis and interpretation. It is also important to note that most studies in this review were conducted on habitual caffeine consumers (although their habitual intake was not generally well reported). Thus, effects could be exacerbated by caffeine withdrawal (Rogers et al., 2005). As such, investigations exploring the effect(s) of acute caffeine administration following sleep loss in non-habituated individuals are required.

There are a number of limitations that should be considered when interpreting the findings of the present study. Most notably, comparisons are made between caffeine and placebo conditions in the context of sleep loss. A 'no sleep loss' control comparison has not been examined. As such, we are unable to determine if performance was impaired by sleep loss to begin with, or if performance was restored to baseline or simply improved by caffeine. In addition, there is a degree of data dependency in the present analyses. That is, some studies provided numerous EEs that were incorporated into meta-analysis. While we attempted to reduce this by combining data where possible, results may be biased in some analyses by one or two investigations. Furthermore, we were unable to extract meaningful information from studies on the sleep history of their included participants. Given that sleep debt is a known confounding factor influencing performance, understanding the sleep history of participants is an important consideration. While some studies provided information on general sleeping habits (e.g. 8 h per night, 6.5-10 h per night), the majority of studies did not report any information about participants sleep history. Nonetheless, our inclusion/exclusion criteria was such that only studies employing adult participants with no known medical conditions (including diagnosed sleep disorders) were included in this review.

Overall, this systematic review and meta-analysis supports the use of caffeine as a countermeasure to the detrimental effects of sleep loss on cognitive, physical, occupational and

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driving performance. Thus, results of this study can be used to inform individuals contemplating use of caffeine as a countermeasure to the effects of sleep loss.

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