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Evaluation of the Transient Hypofrontality Theory in the Context of Exercise:

A Systematic Review with Meta-Analysis

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Short Title: Exercise and Transient Hypofrontality

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Abstract

Accumulating research suggests that, as a result of reduced neural activity in the prefrontal cortex (PFC), higher-order cognitive function may be compromised while engaging in high-intensity acute exercise, with this phenomenon referred to as the transient hypofrontality effect. However, findings in this field remain unclear and lack a thorough synthesis of the evidence. Therefore, the purpose of this meta-analysis was to evaluate the effects of in-task acute exercise on cognitive function, and further, to examine whether this effect is moderated by the specific type of cognition (i.e., PFC-dependent vs. non-PFC-dependent). Studies were identified by electronic databases in accordance with the PRISMA guidelines. In total, twenty-two studies met our inclusion criteria and intercept only meta-regression models with robust variance estimation were used to calculate the weighted average effect sizes across studies. Acute exercise at all intensities did not influence cognitive function ($\beta = -0.16$, 95% CI = [-0.58, 0.27], $p = .45$) when exercise occurred during the cognitive task, and no significant moderation effects emerged. However, there was evidence that cognitive task type (PFC-dependent vs. non-PFC-dependent) moderated the effect of high-intensity acute exercise on a concomitant cognitive performance ($\beta = -0.81$, 95% CI = [-1.60, -0.02], $p = .04$). Specifically, our findings suggest that PFC-dependent cognition is impaired while engaging in an acute bout of high-intensity exercise, providing support for the transient hypofrontality theory. We discuss these findings in the context of a cognitive-energetic perspective.

Keywords: Cognitive decline, intense physical activity, mental resources, prefrontal activation, transient hypofrontality theory.

Introduction

Cognitive functions in the brain are mental processes enabling individuals to receive, select, store, transform, develop, and remember information that originated from external stimuli (Zhang, 2019). There are various types of cognitions, including attention, memory, and executive function, which play a significant role in optimal daily functioning across the lifespan, for instance, in making decisions and completing tasks demanding complex reasoning and information processing (Aretouli & Brandt, 2010; Warren et al., 1989). Neuroimaging studies on healthy participants have shown that a critical brain region involved in such higher-order cognitive functions is the prefrontal cortex (PFC), and these results provided evidence of increased activation in a wide range of prefrontal regions during task performance (Blumenfeld & Ranganath, 2006; D'Esposito et al., 1999; Petrides, 2000). The role of PFC is to provide the infrastructure to compute executive processing, which is strongly associated with the ability to engage in goal-consistent behaviors and inhibit goal-inconsistent behaviors (Funahashi, 2017; Goethals et al., 2004). Taken together, several cognitive tasks, such as the Stroop task or the Digit Symbol Substitution test, which depend largely on frontal-prefrontal network and require substantial prefrontal engagement, are generally regarded as PFC-dependent tasks. In contrast to the PFC-dependent tasks, non-PFC-dependent cognition encompasses relatively automatized, simple decisional tasks (e.g., Choice Reaction Time [RT] and Visual Recognition task) that rely less on cognitive effort (Dienes & Perner, 1999). Using brain imaging techniques, it is suggested that such tasks are primarily dependent on early sensory and late motor processes rather than prefrontal cognitive processes (Grèzes et al., 2003).

Over the past few decades, exercise psychologists have been interested in the immediate effect of acute exercise on multiple subdomains of cognition and, in particular, attempted to evaluate whether the type of cognitive task (e.g., PFC-dependent vs. non-PFC-dependent) influences the acute exercise-cognition relationship in protocols in which the cognitive task is carried out during exercise (i.e., concomitance protocols). With this protocol, some studies have indicated that acute exercise has the selective potential to enhance cognitive function (Audiffren et al., 2008; Davranche et al., 2005; Lambourne et al., 2010), whereas others have suggested a particular pattern of cognitive impairment occurred during a single bout of exercise (Del Giorno et al., 2010; Dietrich & Sparling, 2004; Komiyama et al., 2020; Loprinzi et al., 2019). This facilitation or impairment effect is likely to be influenced based on the exercise intensity and type of cognitive task. Various theoretical accounts have been developed to explain these contradicting effects, such as arousal, attention, and cognitive-energetic models (see Tomporowski & Qazi, 2020). Central to the present review is the potential impairment effects of cognitive function during an acute bout of exercise. We evaluate this phenomenon within a cognitive-energetic model, namely the transient hypofrontality theory (Dietrich, 2003, 2006).

The transient hypofrontality theory posits that in dual-task conditions where acute exercise at higher intensity and cognitive tasks are performed simultaneously, the neural activation in non-motor areas of the PFC may be reduced as more metabolic and cognitive resources may be allocated toward sensory and motor cortices to maintain physical movement. Given that the brain operates on a limited amount of such resources (Miller & Cohen, 2001), the widespread activation of motor and sensory cortices while exercising at higher intensity may come at the expense of activity in other neural structures that are not essential for controlling motor movement. As such, this may result in a temporary deactivation of prefrontal structures involved in higher-order cognitive processing, and ultimately, compromise task performance (Audiffren, 2016; Dietrich, 2003). This basic assumption has been supported in experimental studies in animals showing that exercise at a high intensity ($\geq$ 85% VO_{2max}) increases neural activity in areas (e.g., motor cortex) of the frontal lobe involved in motor control (39% Δ (increase) from baseline, *p* = .001), with no such changes in the PFC (11% Δ from baseline, *p* > .05) or frontal cortex (6% Δ from baseline, *p* > .05) (Vissing et al., 1996). Moreover, in a human sample, exercise above 80% of VO_{2max} significantly decreased cerebral oxygenation in the right frontal cortex (Ando et al., 2011), which plays an important role in planning-based cognition (Henson et al., 1999). Although speculative, the reduction in cerebral oxygenation of the PFC induced by this exercise protocol may impair PFC-dependent cognition. For example, not only does high-intensity acute exercise decrease PFC oxygenation, but research also shows that PFC-dependent cognition is compromised while engaging in acute high-intensity exercise (Mekari et al., 2015). Further, prior work shows that premotor time of the Eriksen Flanker task did not improve while engaging in exercise above 80% VO_{2max}, but improved at 60% VO_{2max} of exercise, compared to a resting condition (Ando et al., 2011). Thus, high-intensity exercise may decrease regional levels of cerebral oxygenation (e.g., frontal cortex), which may fail to meet cerebral metabolic demands and cause a concomitant transient inhibition of the PFC function, leading to PFC-dependent cognitive decline (Dietrich & Audiffren, 2011; Subudhi et al., 2007). Collectively, the results from these animal and human studies suggest that high-intensity acute exercise increases neural activity in the motor cortex, but either plateaus or downregulates neural activity and oxygenation in other areas of the PFC not specifically involved in motor control.

As stated previously, per the tenets of the transient hypofrontality theory, such detrimental effects may be moderated by cognitive task types according to their dependence on prefrontal functioning (i.e., PFC-dependent task vs. non-PFC-dependent task). For example, Bue-Estes et al. (2008) showed that working memory (PFC-dependent task) was impaired during short-term maximal incremental treadmill exercise. Schmit et al. (2015) reported that the error rate of the modified version of the Eriksen Flanker task (PFC-dependent task) was higher during cycling at 85% of maximal aerobic power compared to a non-exercise condition. On the other hand, an experimental study by Rattray and Smee (2016) found that response time in the Speed Match task (non-PFC-dependent task) was faster during exercise at 90% VO_{2peak} than at rest. Summarily, during high-intensity acute exercise, performance on tasks demanding PFC-dependent cognition may be potentially compromised, whereas cognitive tasks requiring less prefrontal activity may be enhanced or unaffected. A few near-infrared spectroscopy studies, however, showed deleterious effects of acute low- and moderate-intensity exercise on a concomitant PFC-dependent cognitive performance measured by the Eriksen Flanker task and the Simon task (Davranche & McMorris, 2009; Pontifex & Hillman, 2007). In addition to these findings, other studies showing positive impacts of acute in-task exercise on PFC-dependent cognition provided suggestive evidence that other potential moderators (e.g., too short duration of exercise, too light-intensity exercise, and too high level of participants' physical fitness) would influence the relationship between acute exercise and PFC-dependent cognitive task performance under dual-task conditions (Lucas et al., 2012; Martins et al., 2013; Pesce & Audiffren, 2011). Accordingly, additional research is needed to fully understand the transient hypofrontality effect and whether this is moderated by multiple characteristics, in particular, by different types of cognition.

Although recent experiments (Chang et al., 2017; Loprinzi et al., 2019; Siddiqui & Loprinzi, 2018), narrative reviews (Loprinzi et al., 2017; Netz, 2019), and meta-analytic reviews (Chang et al., 2012; Jung et al., 2020; Lambourne & Tomporowski, 2010; Loprinzi et al., 2019; Roig et al., 2013) have demonstrated that acute exercise can influence cognitive function, we have less knowledge as to whether cognitive function is impaired during an acute bout of exercise and whether the specific type of cognition (i.e., PFC-dependent vs. non-PFC-dependent) moderates this effect. In fact, while a number of past meta-analytic publications have confirmed the moderating effects of cognitive task type on the acute exercise-cognition association by grouping this into six categories (i.e., information processing, reaction time, attention, crystalized intelligence, executive function, and memory) using a general approach (Chang et al., 2012, Jung et al., 2020), we divided the task type into PFC-dependent and non-PFC-dependent tasks, which is a novel approach in this field. Therefore, the purpose of this meta-analytic review was to investigate the potential differential effects of acute exercise on PFC-dependent and non-PFC-dependent cognition. In this meta-analysis, we specifically focused on articles that directly compared a non-exercise control group to acute exercise that occurred during the cognitive task and evaluated studies separately based upon exercise intensity (i.e., all studies from comparisons with low-, moderate-, and high-intensity acute exercise [Aim 1] and only studies from comparisons with high-intensity acute exercise [Aim 2]). Parallel to the predictions of the transient hypofrontality effect, we hypothesized that only PFC-dependent cognition will be impaired while engaging in high-intensity acute exercise.

Methods

Data Sources and Search Strategy

Studies were identified by electronic databases in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines: PubMed (1951–present), Scopus (2004–present), PsycINFO (1981–present), Google Scholar (2004–present), and SPORTDiscus (1985–present). All documents were retrieved from inception to March 14th, 2020. The search terms, including their combinations, were: acute exercise, physical activity, cognitive function, prefrontal cortex, and transient hypofrontality. To minimize the possibility of errors during searching articles, we used database-appropriate syntax for each database, in combination with the selected terms, based on a recently developed systematic search strategy (Bramer, et al., 2018). Table 1 represents the database-appropriate syntax for each database.

[Insert Table 1 Here]

Study Selection

Two separate authors (Jung and Ryu) independently employed the computerized searches to determine the number of eligible studies. Each of the searches in each respective database was imported into EndNote, and then, duplicate references were removed in EndNote from March 16th to 18th, 2020. Agreement on eligible studies was reached from these two independent reviews. In addition to the aforementioned databases, to identify additional relevant articles for inclusion, two authors reviewed key review papers on acute exercise and cognition (Chang et al., 2012; Loprinzi et al., 2019; Roig et al., 2013; Tomporowski, 2003) as well as transient hypofrontality papers (Dietrich, 2003, 2006; Dietrich & Audiffren, 2011; Dietrich & Sparling, 2004). Notably, the Scopus database was used to identify all citations of these four transient hypofrontality papers. Any studies that cited any of these four transient hypofrontality papers were reviewed for possible inclusion in our meta-analysis. All studies appearing to meet the inclusion criteria were reviewed and cross-checked at the full text level from March 20th to 22nd, 2020. If any disagreement occurred, a third review author was invited to reach consensus through discussion.

Inclusion Criteria

Studies were included if they: (1) employed an experimental design with a comparison to a control group/visit (i.e., no exercise), (2) included human participants, (3) assessed exercise as an independent variable, (4) performed acute exercise (defined as a single bout of exercise), (5) evaluated cognitive function as a primary outcome, (6) conducted cognitive tasks during an acute bout of exercise, (7) provided sufficient data (e.g., sample size, mean, and standard deviation [SD]) for computing an effect size (ES) estimate, and (8) were published in English.

Methodological Quality of Evaluated Studies

Two authors independently reviewed the included studies for methodological quality using the modified Downs and Black checklist (Downs & Black, 1998). This checklist was developed for the assessment of the methodological quality of randomized and nonrandomized studies and was based on 27 criteria across 4 domains (e.g., reporting, external validity, internal validity, and power), providing a total maximum score of 28 (1 point per question except question five [2 points]). All disagreements in quality ratings between reviewers were solved by consensus. To avoid confusion of power calculation for users, the last question was revised from a 5-point to a 1-point rating, where 1 was scored if a power or sample size computation was reported, and 0 was scored when there was no power computation or indication of whether the number of subjects was appropriate for the study design. Of the 27 items, 3 items, “Have the characteristics of patients lost to follow-up been described?”, “In trials and cohort studies, do the analyses for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?” and “Were losses of patients to follow-up taken into account?” were removed from the checklist as they did not fit the inclusionary criteria of our meta-analysis. Thus, we utilized the modified version of the Downs and Black checklist including 24 items; scoring ranging from 0 to 25, with a higher score indicating a higher level of methodological quality.

Data Extraction of Included Studies

Detailed data from each of the included studies were extracted and coded, including the following information: (1) author, date, and country of study, (2) sample size and characteristics, (3) study design, (4) exercise protocol (e.g., exercise type, exercise intensity, and exercise duration), (5) type of cognitive task (e.g., PFC-dependent task and non-PFC-dependent task), and (6) mean and SD of cognitive function between performing tasks under control (no exercise) and exercise conditions.

Categorization of Moderators

The evaluated moderators included age, sex, exercise protocol, and specific cognitive task type. These evaluated moderators were selected since they have been shown to potentially affect cognitive performance or influence the effects of acute exercise on cognitive function (Chang et al., 2012). Sex was categorized as males, mixed samples, and predominantly female. Predominantly female was defined as a study including > 71% females (Barha et al., 2017). Age was categorized as young adult (18–30 years), middle-aged adult (31–60 years), and older adult (> 60 years) (Chang et al., 2012). Exercise protocol included exercise intensity, exercise duration, and exercise modality. Exercise intensity was based on thresholds suggested by the American College of Sports Medicine (Garber et al., 2011). For instance, according to maximum heart rate estimates, low-, moderate-, and high-intensity exercise were defined as < 64%, 64%–76%, and > 76%, respectively. Exercise duration was defined as short (< 20 min), medium (20–40 min), and long duration (> 40 min) (Roig et al., 2013). Exercise modality was defined as treadmill-based walking/running and cycling. Lastly, in alignment with other reviews (Chang et al., 2012), cognitive task type was categorized as PFC-dependent task and non-PFC-dependent task. For example, the Wisconsin Card Sorting Task is commonly associated with increased neural activity in the PFC, whereas Basic Choice RT and/or Visual Recognition Task are considered tasks that require little prefrontal activation (see Supplementary Tables 1 and 2, respectively, for PFC-dependent and non-PFC-dependent cognitive tasks).

Data Analyses

The ESs were calculated as Hedges' g indices and expressed as a standardized mean difference (g) between the exercise and control groups. Hedges' g was used as the ES for analysis, given that it is a relatively unbiased estimate of the population standardized mean difference ES, while Cohen's d is a biased estimate. In the below formula, $\overline{X_1}$ and $\overline{X_2}$ are the means for the exercise group (EG) and the control group (CG), respectively. $SD *_{pooled}$ is the weighted and pooled standard deviation of EG and CG. SD_1 and SD_2 are the standard deviations for EG and CG, respectively, and n_1 and n_2 are the sample sizes for EG and CG, respectively.

$$\text{Hedges}'\text{g} = \frac{\overline{X_1} - \overline{X_2}}{SD *_{pooled}}$$

$$SD *_{pooled} = \sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{(n_1 + n_2 - 2)}}$$

To calculate ES measures, mean differences in cognitive function between performing tasks during acute exercise ($\overline{X_1}$) and non-exercise ($\overline{X_2}$) were divided by the weighted and pooled SD ($SD *_{pooled}$). Standardized mean differences adjusted for sampling error were subsequently computed as a measure of individual ES by assigning more weight to studies with larger sample sizes. The ESs were estimated so that a negative effect indicated the existence of a deleterious acute exercise effect on cognitive performance. When we calculated the ESs for RT, $\overline{X_1} - \overline{X_2}$ was replaced with $\overline{X_2} - \overline{X_1}$, so that a negative effect also indicated cognitive impairment. Effect sizes values were classified as small effect (0.2), moderate effect (0.5), and large effect (0.8) (Hedges & Olkin, 2014).

Inverse variance weighted random-effects models were used to meta-analyze the ESs since they make inferences about the effects of acute exercise on cognitive function across various procedures and settings. Most research addresses multiple outcomes due to the multifaceted nature of cognitive function. Multiple outcomes pose a problem for traditional meta-analytic approaches, as averaging ESs through studies without considering their correlations can lead to unreliable ES estimates. We meta-analyzed all qualifying ESs in each sample, enabling studies to contribute several ESs to preserve as much data as possible (i.e., multiple ESs based on the same sample in a study). Thus, we used the robust variance estimation in the meta-analytic technique, a random-effects meta-regression that can account for the dependence between ES estimates (Hedges et al., 2010). By correcting the within-study standard errors for correlations between ESs, this estimation approach enables clustered data (i.e., ESs nested within samples) to be meta-analyzed. This approach includes estimating the mean correlation between all pairs of within-study ESs (ρ), which is then used to modify the within-study sampling variance (τ^2) to account for these statistical dependencies. We conducted a sensitivity analysis by setting ρ = 0.8 based on Tanner-Smith and Tipton (2014), and the findings were consistent across various rational values of ρ (ranging from 0 to 1). We also reported I^2, which quantifies the proportion of ES variance due to between-sample heterogeneity. Notably, I^2 values of 25%, 50%, and 75% indicate low, moderate, and high levels of heterogeneity, respectively (Higgins et al., 2003).

The ‘robumeta’ package in R was used to conduct inverse variance weighted random-effects meta-analyses with Hedges et al. (2010) robust variance estimation (Fisher & Tipton, 2015). We ran the test twice, once with all of the studies included and then with only the studies from the high-intensity exercise comparisons. An intercept-only meta-regression model was fitted to assess the overall effect of acute exercise on a concomitant cognitive performance. The constant coefficient in this model has the interpretation of the weighted average effect of acute in-task exercise on cognitive function. Exercise-induced cognitive enhancement is represented by a positive constant coefficient, while the exercise-induced cognitive impairment is represented by a negative constant coefficient. Next, to test for the possibility that sex, exercise intensity, exercise duration, exercise modality, and cognitive task type explain between-study differences in the weighted average effect of acute in-task exercise on cognitive function (Aim 1), we added several covariates to our intercept-only meta-regression model. Sex was a categorical variable with three levels (males, mixed samples, and predominantly female) and thus, we included two dummy covariates for sex. The first, males, reflected the males versus others contrast (coded males = 1, predominantly female and mixed samples = 0) while the second, predominantly female, reflected the predominantly female versus others contrast (coded predominantly females = 1, males and mixed samples = 0). Mixed samples was the reference group when these dummy variables were inserted into the meta-regression model. We added two dummy covariates for exercise intensity as it was a categorical variable with three levels (low-, moderate-, and high-intensity). The first, low-intensity, reflected the low-intensity versus others contrast (coded low = 1, moderate- and high-intensity = 0) while the second, moderate-intensity, reflected the moderate-intensity versus others contrast (coded moderate = 1, low- and high-intensity = 0). The reference group was high-intensity when these dummy variables were entered to the meta-regression model. We included two dummy covariates for exercise duration because it was a categorical variable with three levels (short duration, medium duration, and long duration). The first, medium duration, reflected the medium duration versus others contrast (coded medium = 1, short duration and long duration = 0) while the second, long duration, reflected the long duration versus others contrast (coded long = 1, short duration and medium duration = 0). The short duration was the reference group when these dummy variables were entered into the meta-regression model. Exercise modality (0 = treadmill-based walking/running, 1 = cycling) and cognitive task type (0 = non-PFC-dependent task, 1 = PFC-dependent task) were categorical variables with two levels. We had also intended to use age as a moderator for Aim 1, but we were unable to include this moderator in the analysis due to a lack of studies (described below).

The 'robumeta' function utilizes the method of moments estimator to estimate τ^2 (Thompson & Sharp, 1999). This estimator and its degrees of freedom were modified for small sample sizes, as suggested by Tipton (2015). Nevertheless, robust variance estimation with small sample adjustment remains biased (i.e., increased type I error rate) when the adjusted degrees of freedom are less than 4 (Tanner-Smith & Tipton, 2014). Consequently, despite our plans to look at sex, age, exercise duration, and exercise modality as moderators of the ESs for Aim 2, we were unable to perform moderator analyses due to a lack of studies in each category (i.e., fewer than five studies). Thus, in Aim 2, only the cognitive task type was included in the moderator analyses. Finally, using the 'metafor' package in R (Viechtbauer, 2010), Egger's regression test for funnel plot asymmetry (Egger et al., 1997) and Duval and Tweedie's trim and fill method (Duval & Tweedie, 2000) were conducted to evaluate potential risk of publication bias across studies. First, Egger's regression test was performed to examine the relationship between the observed ESs and their corresponding standard errors. If a significant result for the Egger's regression test indicates funnel plot asymmetry, publication bias may be present. Next, in the presence of publication bias, Duval and Tweedie's trim and fill analysis is generally carried out to obtain the estimated number of missing studies from a meta-analysis in the funnel plot. This method augments the observed data, which in turn makes the funnel plot more symmetric and adjusts the observed average ES (Rodgers & Pustejovsky, 2020). A two-sided $p < .05$ was considered statistically significant.

Results

Retrieved Articles

Figure 1 displays the flow chart of the literature search process. The computerized searches yielded 585 articles. Furthermore, 13 additional articles were identified in reference lists of key review articles on acute exercise and cognition (Chang et al., 2012; Loprinzi et al., 2019; Roig et al., 2013; Tomporowski, 2003) as well as transient hypofrontality papers (Dietrich, 2003, 2006; Dietrich & Audiffren, 2011; Dietrich & Sparling, 2004). Among the 598 articles, 176 were eliminated due to duplication and 422 articles were screened. After initial screening of 422 titles and abstracts, 69 full text articles were reviewed. Among these 69 articles, 47 were ineligible as they did not meet the inclusion criteria (e.g., acute exercise not occurring during the cognitive task, not directly comparing a non-exercise control group to an exercise group, and/or not providing sufficient information for an ES calculation). As a result, 22 studies met our eligibility for the systematic review via the computerized searches, and thus, a total of 22 studies were chosen for the meta-analysis.

[Insert Figure 1 Here]

Article Synthesis

Detailed information on the study characteristics is displayed in Table 2. Sample sizes ranged from 8 to 79 participants, with the majority of studies (95%) testing young adults (18–30 years). Among the 22 studies, 18 (82%) employed a within-subject design.

[Insert Table 2 Here]

Study Quality

Based on the modified Downs and Black checklist, the methodological quality of the included studies was fair to good (18.74 ± 1.82, mean ± SD), ranging from 16 to 23 (Hooper et al., 2008). All studies were scored within an acceptable range of methodological quality and thus, were included in the quantitative meta-analysis.

Quantitative Analysis

Figure 2 displays the weighted average ESs with robust variance estimation for the studies comparing cognitive task performance during acute exercise of all intensities with performance during a control condition. Among these 22 studies, 75 ESs were calculated. As illustrated by Figure 2 and Table 3, there was no statistically significant effect of acute in-task exercise of all intensities on cognitive function ($\beta = -0.16$, 95% CI: -0.58, 0.27, $p = .45$). Between-study heterogeneity was 0.66 (τ^2) with approximately 87% ($I^2 = 87.18$) of variance attributable to systematic error. Table 3 shows the results of the moderation analyses for the studies comparing acute exercise of all intensities during a cognitive task vs. control group. No significant moderation effects were observed, indicating that sex, exercise intensity, exercise duration, exercise modality, and cognitive task type did not play a moderating role in the acute exercise-cognition associations under the dual-task protocols. The Egger's regression test for funnel plot asymmetry was not statistically significant ($z = 0.45$, $p = .65$), indicating that there was no evidence of publication bias across studies.

[Insert Figure 2 Here]

[Insert Table 3 Here]

Figure 3 displays the weighted average ESs with robust variance estimation for the studies comparing cognitive task performance during high-intensity acute exercise with performance during a control condition. Among these 12 studies, 27 ESs were calculated. As illustrated by Figure 3 and Table 4, there was no statistically significant effect of high-intensity acute in-task exercise on cognitive function ($\beta = 0.03$, 95% CI: -0.41, 0.46, $p = .89$). Between-study heterogeneity was 0.46 (τ^2) with approximately 80% ($I^2 = 79.82$) of variance attributable to systematic error. Table 4 shows the results of the moderation analyses for the studies comparing high-intensity acute exercise during a cognitive task vs. control group. Significant moderation effect was observed for cognitive task type ($\beta = -0.81$, 95% CI = -1.60, -0.02, $p = .04$), indicating that PFC-dependent cognition was impaired during high-intensity acute exercise compared to non-PFC-dependent cognition. The Egger's regression test for funnel plot asymmetry was statistically significant ($z = 3.51$, $p < .001$), suggesting that there was evidence of publication bias across studies. After applying the Duval and Tweedie's trim and fill methods (see Figure 4), all four estimated missing studies were located to the left of the average ES and the observed outcomes were distributed symmetrically in the funnel plot ($z = 0.95$, $p = .34$). Further, a negative adjustment to the ES was shown and decreased to -0.2 (SE = 0.13).

[Insert Figure 3 Here]

[Insert Table 4 Here]

[Insert Figure 4 Here]

Discussion

The present meta-analysis evaluates the transient hypofrontality theory by investigating the impact of acute exercise on PFC-dependent cognition. In alignment with our hypothesis as well as the transient hypofrontality theory, our meta-analysis demonstrates high-intensity acute exercise had a selective effect on cognition, in that PFC-dependent cognition was compromised while exercising at a high intensity compared to non-PFC-dependent cognition.

Several theories have been proposed to test these effects, namely arousal, attention, and cognitive-energetic theories (Tomporowski & Qazi, 2020). Although there is some theoretical overlap among these theories, each theory highlights a specific concept. First, arousal theory hypothesizes that in a dose-dependent inverted U-shaped fashion (Yerkes & Dodson, 1908), exercise-induced arousal influences cognition and cognitive task performance is improved with moderate, but not high, levels of arousal (McMorris & Hale, 2015). On the basis of hypotheses drawn from the arousal theory, a meta-analysis by Lambourne and Tomporowski (2010) reported that the negative ESs on information-processing tasks were observed while engaging in exercise protocols designed to assess the impacts of the inverted-U hypothesis. Second, attention theory dictates that attention is a focusing process that plays an important role in cognitive function (Jonides et al., 2008). The basic assumption of attention theory is that attention acts as a gate, which determines what information enters into consciousness (Tomporowski & Qazi, 2020). In the dual-task paradigm, motor-related cognitive interference (i.e., while motor performance remains stable, cognitive performance deteriorates; Plummer et al., 2013) may occur due to greater attentional allocation toward physical movement. Next, cognitive-energetic theory suggests that when multicomponent tasks compete for available energetical resources, more metabolic resources may be allocated to one task that optimizes behavioral actions (e.g., exercise) and the other(s) is likely to be impaired or unaffected (e.g., cognitive performance) depending on the dual-task workloads.

Potential mechanisms of the exercise-induced cognitive impairment effect have been discussed elsewhere (Audiffren, 2016; Dietrich & Audiffren, 2011), which align with the cognitive-energetic theory discussed above. Briefly, acute changes in cerebral blood flow (CBF) induced by exercise may be closely associated with cognitive fluctuations as a result of alterations in regional neuronal activation and metabolism in the brain. For example, during acute moderate-intensity exercise, CBF increases in response to neuronal activity and metabolism, whereas during acute high-intensity exercise, regional levels of CBF (e.g., frontal cortex) progressively decrease despite global levels of blood flow, metabolism, and oxygen uptake to the brain remaining stable (Ide & Secher, 2000; Ogoh & Ainslie, 2009). This high-intensity exercise-induced decrease in CBF lowers partial pressure of arterial carbon dioxide and the total cardiac output rate to the brain, and thus, metabolic demands of the brain may not be fulfilled (Ogoh & Ainslie, 2009; Smith & Ainslie, 2017). Moreover, based on the neurovascular coupling, local neural activation of brain structures involved in physical exercise facilitates an elevation of CBF in the motor cortex, whereas neural deactivation in other local brain areas, not involved in exercise, leads to a reduction of CBF in the PFC. As such, reduced CBF may attenuate cerebral metabolism in the prefrontal areas while exercising at a high intensity and ultimately may compromise PFC-dependent cognition (Mekari et al., 2015). This, however, is in contrast to a recent publication (Komiyama et al., 2020), which demonstrated that a decline in CBF is not a major factor in impairment of executive function during acute vigorous-intensity exercise. Specifically, CBF restoration through CO_2 inhalation did not prevent executive degradation due to acute intense exercise. Although it was different from their expected results, we cannot rule out the plausibility that CBF is not related to exercise-induced cognitive impairment given the methodological limitations of this study (e.g., they did not directly measure changes in CBF in the prefrontal regions); thus, this is an area where future research is needed.

Alternatively, from a neurochemical perspective, it is possible that the mechanisms of such a debilitating effect may be due to modulation of select neurotransmitters, such as dopamine (DA) and noradrenaline (NA). Plasma concentrations of catecholamine neurotransmitters in the brain released under high arousal conditions play a significant role in brain networks that are particularly involved in cognitive function (McMorris et al., 2016). Studies in human (Dalsgaard et al., 2004) and animals (Hattori et al., 1994; Kitaoka et al., 2010) provide suggestive evidence that arousal induced by moderate-intensity exercise induces an acute increase in firing of the high affinity α_{2A}-adrenoreceptors by NA, which helps to strengthen neuronal signals in the target stimuli by inhibiting cyclic adenosine monophosphate (cAMP) activity (Deutch & Roth, 1990; Roth et al., 1988). Likewise, the high affinity D_1-receptors by DA reduces neuronal noise by inhibiting the firing of non-target stimuli (Finlay et al., 1995). This improvement of signal-to-noise ratio may help individuals to facilitate effective encoding of the stimuli, discrimination, and decision-making processes (Berridge & Waterhouse, 2003). In consequence, modest elevations in DA and NA via moderate-intensity exercise may activate prefrontal neuronal networks and further enhance PFC-dependent cognition (McMorris, 2016).

On the other hand, excessively elevated levels of DA and NA may deteriorate cognitive ability during a single bout of heavy exercise. Extreme stimulation of α_1-adrenoreceptors may lead to reduced neuronal firing in the PFC and too high levels of D_1-receptors and β-adrenoreceptors may responsible for greater cAMP activation (Arnsten, 2011). These may cause hyperpolarization, which inhibits action potentials by closing voltage-gated Na^+ channels and opening of nearby K^+ channels (Arnsten, et al., 2012). While hyperpolarized, the neuron is in a period of physiological refractory, which may prevent the neuron from generating subsequent action potentials (Becker et al., 2009; Pack, 2011). Hence, these effects may lead to synaptic inhibition that lessens the likelihood that a postsynaptic neuron will fire and may contribute to a temporal reduction in neural activity in the prefrontal areas, and thereby PFC-dependent cognition may be impaired (Arnsten, 2009, 2011; Cooper, 1973; McMorris et al., 2016). Another notable plausibility linking altered catecholamines and cognitive impairment during exposure to acute stress (e.g., a single bout of strenuous exercise) can be explained from Arnsten's Dynamic Network Connectivity (DNC) mechanisms (Arnsten et al., 2010). Arnsten and her colleagues posited that DNC is a form of neuroplasticity that can rapidly vary the strength of PFC network connections depending on momentary alterations in arousal state. Under maximal arousal conditions, excessive release of DA and NA through D_1-receptors and β-adrenoreceptors, respectively, may induce activation of cAMP signaling (Ramos et al., 2005; Vijayraghavan et al., 2007). These actions may increase opening HCN channels[1], thereby weakening PFC network connectivity and PFC-dependent cognition (Wang et al., 2007). In a similar manner, high levels of NA release by α_1-adrenoreceptors may activate Ca^{2+}/PKC[2] signaling, which could facilitate the loss of dendritic spines in the PFC, and thus, suppress PFC neural activity (Birnbaum et al., 2004). As a result, precise control of DNC in prefrontal regions is likely to play a key part in prevention of cognitive deficits. As most of these findings came from animal studies, future research in human subjects calls on us to identify novel neurophysiological mechanism(s) to explain as to why PFC-dependent cognitive dysfunction is usually observed during higher intensity acute exercise.

Furthermore, these impairment effects may be explained from neurophysiological-based arousal and cognitive-energetic theories as discussed above, which also may impact psychological attention-related mechanisms. Exercise-induced arousal has long been regarded as a means of improving attention. The amount of available attentional resources depends on the arousal level, which in turn, is determined by the intensity of exercise and task demand

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[1] Hyperpolarization-activated cyclic nucleotide-gated channels are integral membrane proteins, which act as nonselective voltage-gated cation channels in the plasma membranes of brain cells.

[2] Protein kinase C is a family of enzymes that their activity is controlled by Ca^{2+} or diacylglycerol. It works for controlling signal transduction pathway of other proteins, playing a critical part in intracellular signaling.

(Kahneman, 1973). In the inverted U-shape fashion, if arousal reaches its peak through high-intensity acute exercise, this may elicit peripheral and central mental fatigue (McMorris & Hale, 2015). Further, this may result in a narrowing of attention, and thus, even task-related cues may be missed, ultimately impairing cognitive performance (Easterbrook, 1959). Further, in spite of PFC-dependent tasks requiring higher levels of attention capability, additional resources (i.e., mental effort) may not be allocated toward top-down processing in the PFC, but toward the supplementary motor cortex for maintaining dynamic physical movement. Thus, and although speculative, reduced attention may mediate impaired PFC-dependent cognition during high-intensity acute exercise. In contrast to the PFC-dependent cognition, maximal arousal level induced by high-intensity acute exercise is unlikely to impair non-PFC-dependent cognition because stimulus-driven and automatized tasks may be less sensitive to attentional resources (i.e., low attentional cost and low mental workload) and less dependent on the prefrontal functioning (Audiffren et al., 2008; Dietrich & Audiffren, 2011).

The current study has several strengths. This is the first meta-analytic review that evaluates the cognitive impairment effect observed during acute exercise based on the transient hypofrontality theory. This meta-analysis is significant in that it will help future work to reconcile existing inconsistencies as to how and why acute exercise impacts cognitive decline in dual-task protocols. Second, we also tested multiple moderating variables to identify the cause of heterogeneity regarding the detrimental effects of acute in-task exercise on cognition. Third, our meta-analytic approach addressed the issue of non-independent ESs that can be found in outdated meta-analytic techniques by employing robust variance estimation in meta-regression model. Multiple ESs that emanate from the same study can be problematic because the correct sampling variance for that aggregate is unknown for each study, and thus, it makes the standard error calculations underestimated and loses statistical power particularly for moderators (Hedges et al., 2010). Although there are appropriate techniques for handling this problem, several previous meta-analysis publications that investigated the relationship between acute exercise and cognitive function have relied on traditional meta-analytic methods without consideration of such measurement errors (Chen et al., 2020; Jung et al., 2020). Given the characteristics of cognitive function research (i.e., multiple ESs are generated from a single study), future meta-analysis on this topic should handle this issue carefully.

Despite these strengths, there are some limitations worth considering. First, several moderation effects should be carefully interpreted due to the limited number of studies within each category. In future research, the identification of additional moderators (e.g., mood, exercise preferences, hypoxia, hypoxia with exercise, and contextual factors related to cognition encoding) will provide insight as to under what circumstances such detrimental effects of in-task exercise on cognitive function occurs. Relatedly, it would be also noteworthy for subsequent studies to consider the degree of PFC activation in each PFC-dependent cognitive task as one of the moderators. Some tasks classified as “prefrontal-dependent” require higher demands on prefrontal activity while others do only mildly so. In spite of being aware of this, it was difficult to evaluate how much PFC activation occurs across the different PFC-dependent tasks due to limited research directly comparing the degree of PFC activation across different tasks within the same individuals. As such, more work is needed in this area. Second, considering that the threshold for high-intensity exercise varies substantially across research protocols (McMorris, 2015), further work should assess participant’s maximum heart rate, oxygen consumption or power output using metabolic measurements to better individualize exercise intensity. Third, we found evidence of publication bias for high-intensity acute exercise studies; however, we adjusted for this using the trim and fill method. It typically occurs when the publication of research results depend not only on the hypothesis tested but also the significance and direction of effects detected (Dickersin, 1990). Accordingly, findings showing evidence of publication bias in meta-analyses should be cautiously interpreted and require special attention in future work. Fourth, other cognitive performance indexes not used in this study may play an important role in validating the transient hypofrontality theory. As an example, the interference cost (incongruent RT – congruent RT) in select PFC-dependent tasks (e.g., Flanker task, Simon task, or Stroop task) may be more sensitive to inhibitory control than raw RT (reaction time) data. Given that employing raw RT contains a larger variance, which is more related to speed of information processing rather than executive functioning, additional studies on this topic should be careful in choosing the appropriate performance indexes. Another limitation of this field (not our meta-analysis) is a lack of neural mechanistic measures for the observed PFC-dependent cognitive impairment effects during acute high-intensity exercise. Future research should evaluate which prefrontal areas are activated when high-intensity acute exercise occurs during PFC-dependent and non-PFC-dependent cognitive tasks. Functional near-infrared spectroscopy or electroencephalogram (EEG) can measure the temporal changes in neuronal activation within broad regions of the PFC. For instance, with EEG, P3 and/or N2 amplitude can be altered across frontal and lateral electrode sites during stimulus engagement (e.g., stationary cycling) (Grego et al., 2004). If these event related potentials observed through EEG data can provide useful information on how exercise-induced prefrontal activation/deactivation influences the cognitive task type (PFC-dependent vs. non-PFC-dependent), this may shed additional insight into the neurophysiological mechanisms of the exercise-related cognitive impairment effect.

In conclusion, our meta-analysis demonstrates that PFC-dependent cognition is likely to be impaired when high-intensity acute exercise occurs during a cognitive task, which provides support for the transient hypofrontality theory. Further work is needed to determine which mechanism(s) underlies PFC-dependent cognitive impairment observed during high-intensity acute exercise (e.g., Dietrich's prefrontal deactivation, Arnsten's DNC, or a combination of both mechanisms).

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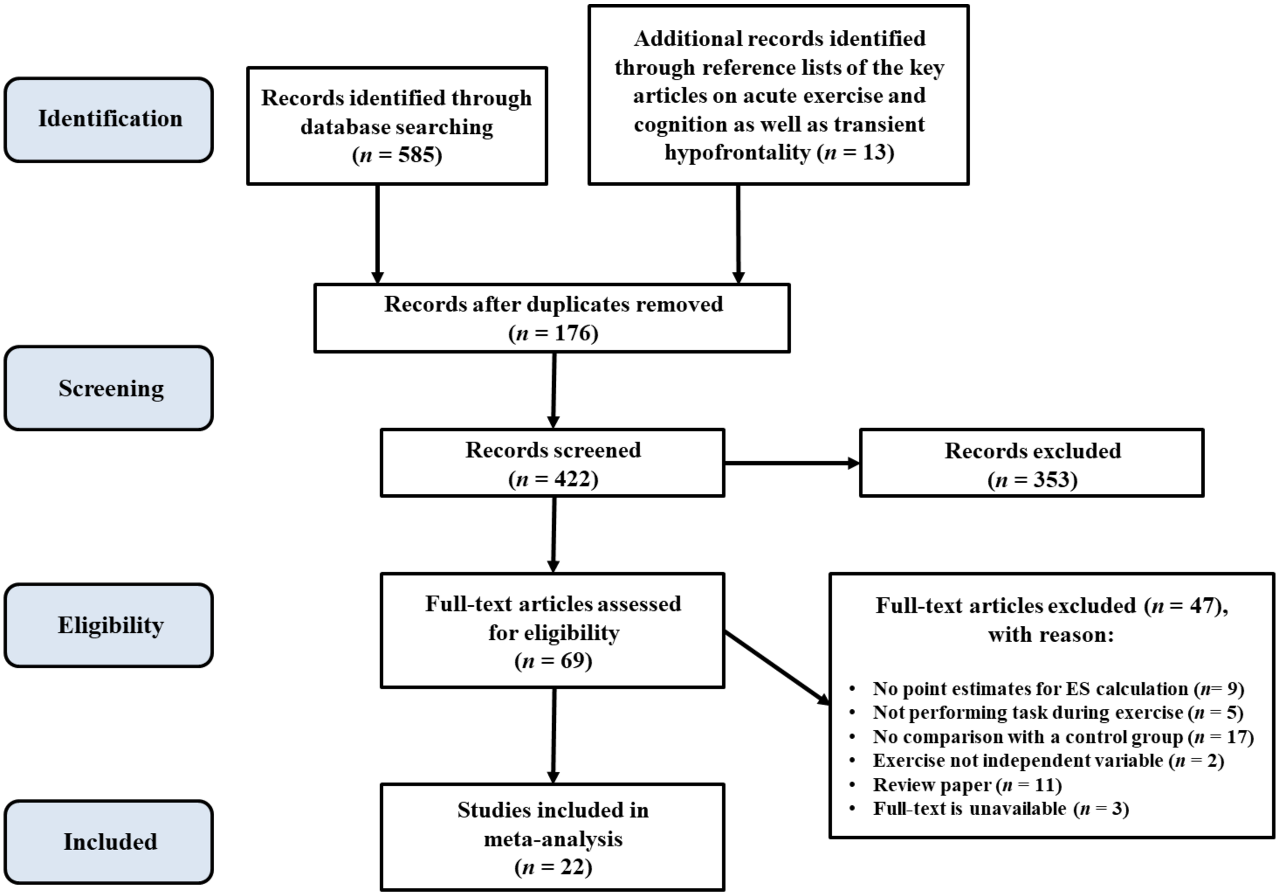

Figure 1. PRISMA flowchart of the evaluated studies and final number of included studies in a meta-analysis.

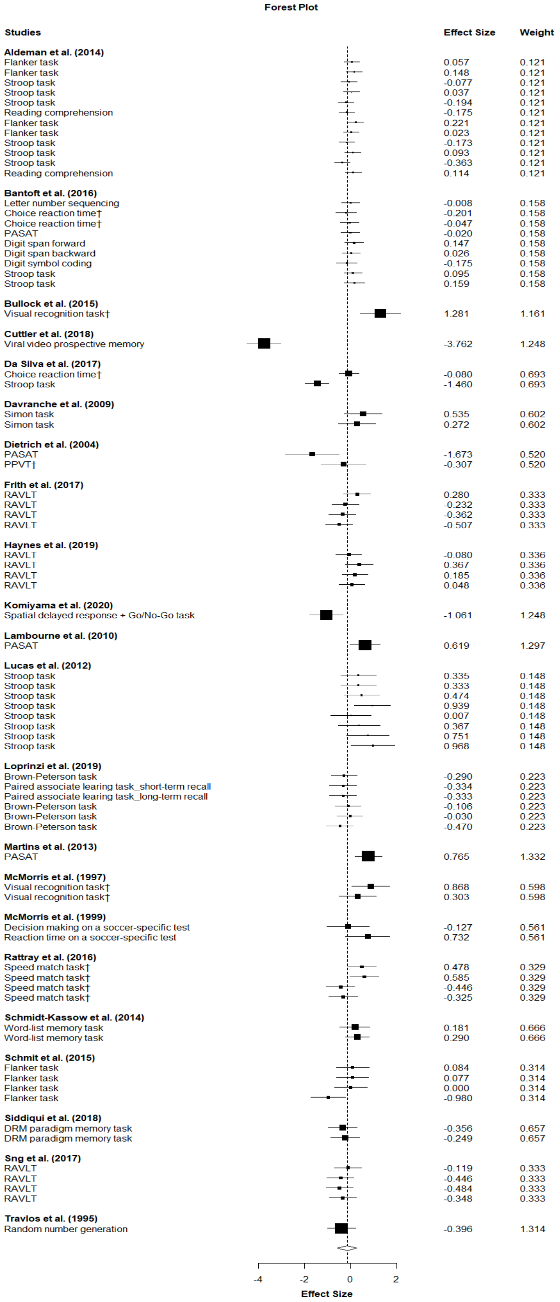

Figure 2. Forest plot depicting the effect size estimates for acute exercise studies including all intensities. The black boxes symbolize the point estimates from each study. The white diamond symbolize s the pooled estimates result. The horizontal lines symbolize the length of the 95% confidence intervals of the study result. † Non-PFC-dependent cognitive task.

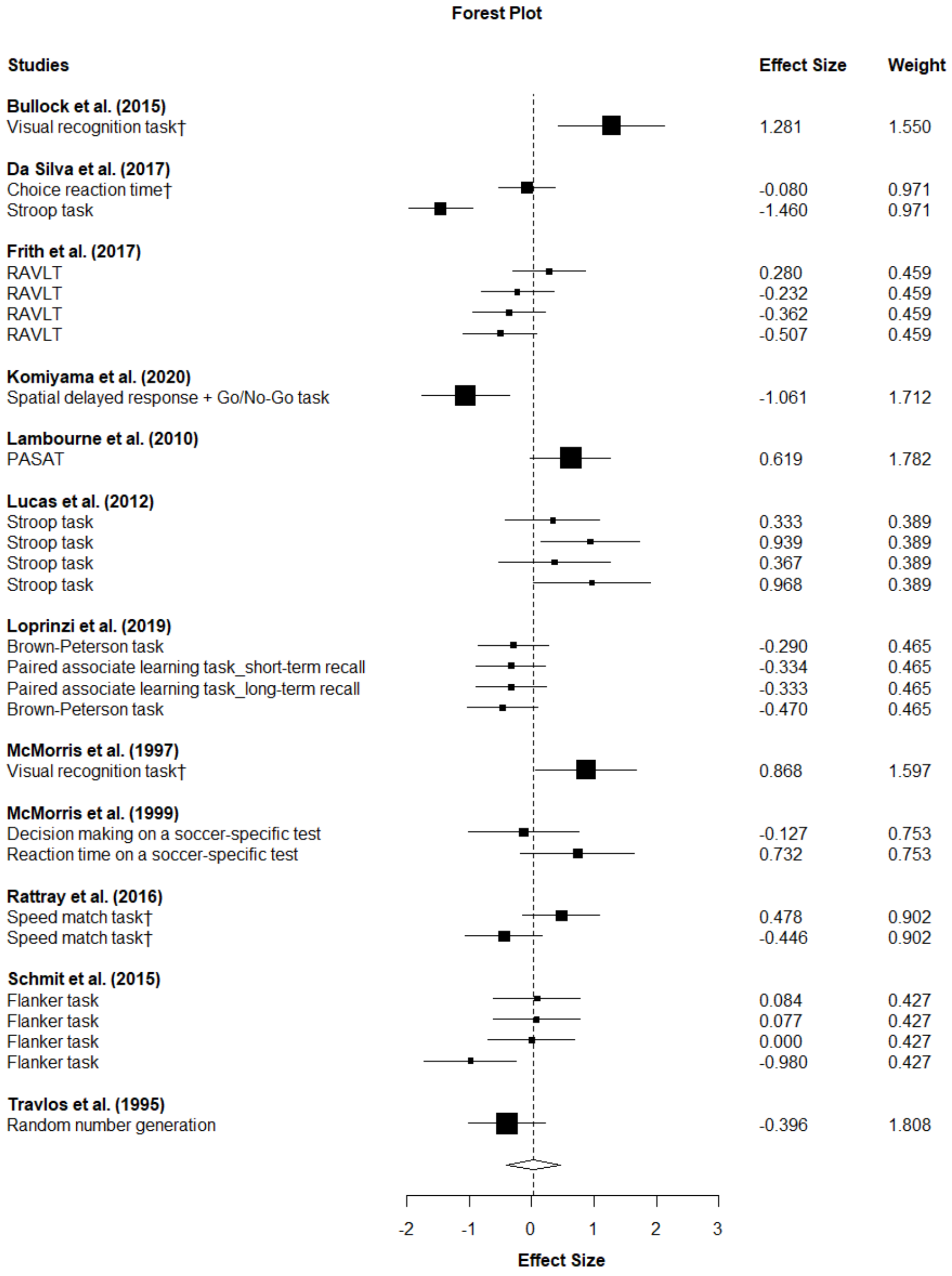

Figure 3. Forest plot depicting the effect size estimates for high-intensity acute exercise studies. The black boxes symbolize the point estimates from each study. The white diamond symbolize s the pooled estimates result. The horizontal lines symbolize the length of the 95% confidence intervals of the study result. † Non-PFC-dependent cognitive task.

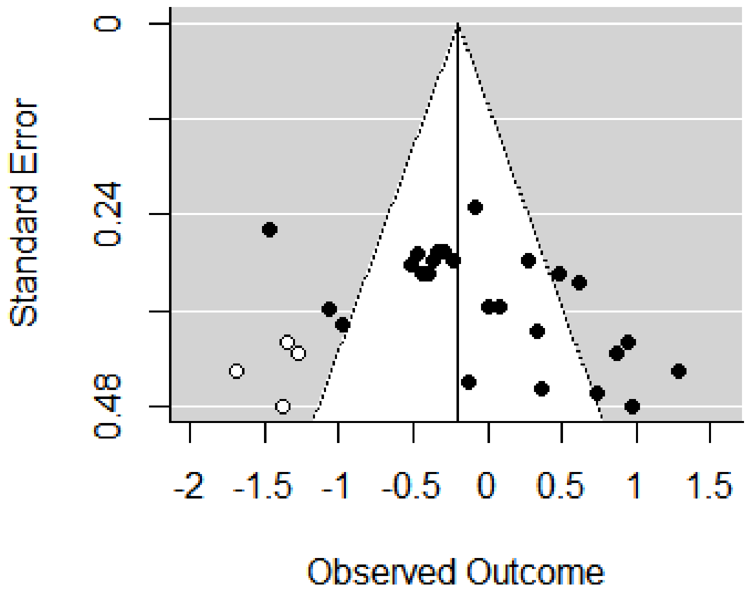

Figure 4. Funnel plot obtained with the Duval and Tweedie's trim and fill methods of the effect size estimates for high-intensity acute exercise studies. Closed circles represent the observed studies included in the meta-analysis. Open circles represent the estimated, imputed studies by suggested by trim and fill analysis. The reference line indicated the adjusted mean effect size.

Table 1. Employed syntax for each database

Database	Search Query
PubMed	((“exercise”[mh] OR (exercise*[tiab])) AND ((“Cognitive function”[mh] OR cognitive*[tiab])) AND ((“hypofrontality”[mh] OR (hypofrontality*[tiab]))
Scopus	TITLE-ABS-KEY(((Exercise OR exercise*))) AND (((Cognitive function OR cognitive*))) AND (((Hypofrontality OR hypofrontality*)))
PsycINFO	(Exercise / OR exercise*).ab,kf,ti.) AND (Cognitive function / OR cognitive*))).ab,kf, ti.) AND (hypofrontaility / OR hypofrontality*))).ab,kf,ti.)
Google Scholar	Exercise | Acute exercise | Cognitive function | Hypofrontality
SPORTDiscus	(MH Exercise OR TI (exercise*)) OR AB (exercise*))) AND (MH Cognitive function+ OR TI (cognitive*)) OR AB (cognitive*))) AND (MH Hypofrontality OR TI (hypofrontality*)) OR AB (hypofrontality*)))

Table 2. Extraction table of evaluated studies

Study	Subject Characteristics	Study Design	Exercise Protocol	Cognitive Function Assessment	Mean (SD)	Results
Travlos & Marisi (1995)	*n* = 20, Age = 23.0 (3.0)	Within-subject	Cycle ergometer exercise for 50-min at high-intensity of 80% of heart rate reserve (HRR)	Random number generation	^{ns} EX: 68.77 (5.81) Ctrl: 70.86 (4.46)	There were no differences in cognitive performance across the control and exercise conditions.
McMorris & Graydon (1997)	*n* = 12, Age = 20.8 (1.34)	Within-subject	Cycle ergometer exercise with progressive load (0%, 70%, 100% MPO)	Visual recognition task† (1. 100% MPO_RT) (2. 70% MPO_RT)	1.* EX: 776 (167) Ctrl: 923 (160) 2.* EX: 872 (165) Ctrl: 923 (160)	Performance during maximal exercise was significantly better than in the other two conditions.
McMorris et al. (1999)	*n* = 9, Age = 22.0 (2.4)	Within-subject	Cycle ergometer exercise with progressive load (0%, anaerobic threshold, 100% MPO)	Decision making on a soccer-specific test (1. ACC) Reaction time on a soccer-specific test† (2. RT)	1.^{ns} EX: 8.22 (1.48) Ctrl: 8.44 (1.81) 2.* EX: 1.32 (0.20) Ctrl: 1.47 (0.19)	There was no significant effect of exercise on accuracy, but speed of decision to be significantly affected by exercise.
Dietrich & Sparling (2004)	*n* = 8, Age = 25.1 (6.3)	Within-subject	Running for 65-min at 70-80% of maximum heart rate	PASAT (1. ER) PPVT† (2. ER)	1.* EX: 52 Ctrl: 32 2.^{ns} EX: 13 Ctrl: 12	For the PASAT, exercise condition committed more errors than control group. For the PPVT, exercise did not affect cognitive performance.
Davranche & McMorris (2009)	*n* = 12, Age = 32 (9)	Within-subject	Cycle ergometer exercise for 21 minutes at moderate-intensity	Simon task (1. RT congruent) (2. RT incongruent)	1.* EX: 305 (33) Ctrl: 323 (32) 2.* EX: 344 (42) Ctrl: 355 (36)	Response time was better when the cognitive task is performed simultaneously with exercise.
Lambourne et al. (2010)	*n* = 19, Age = 21.1 (1.7)	Within-subject	Cycle ergometer exercise for 40-min at high-intensity of 90% VO_{2peak}	PASAT	^{ns} EX: 0.94 (0.02) Ctrl: 0.93 (0.01)	PASAT scores did not change when comparing performance during exercise and non-exercise conditions.
Lucas et al. (2012)	*n* = 22 (13 young adults) (9 older adults), Age = 24 (5), Age = 62 (3)	Within-subject	Two 8-min bouts of cycle ergometer exercise at 30% followed by 70% HRR	Stroop task (1. Younger: Simple task RT at 30% HRR) (2. Younger: Simple task RT at 70% HRR) (3. Younger: Difficult task RT at 30% HRR) (4. Younger: Difficult task RT at 70% HRR) (5. Older: Simple task RT at 30% HRR) (6. Older: Simple task RT at 70% HRR) (7. Older: Difficult task RT at 30% HRR) (8. Older: Difficult task RT at 70% HRR)	1.^{ns} EX: 633 (119) Ctrl: 677 (135) 2. ^{ns} EX: 635 (108) Ctrl: 677 (135) 3.* EX: 1060 (215) Ctrl: 1157 (180) 4.* EX: 978 (189) Ctrl: 1157 (180) 5.^{ns} EX: 830 (172) Ctrl: 829 (84) 6.^{ns} EX: 787 (129) Ctrl: 829 (84) 7.* EX: 1434 (176) Ctrl: 1603 (247) 8.* EX: 1371 (208) Ctrl: 1603 (247)	Difficult-task response times on the Stroop task improved during exercise, with the enhancement greater at high intensity than at rest and low intensity.
Martins et al. (2013)	*n* = 24, Age = 20.5 (0.89)	Between-subject	Cycle ergometer exercise at moderate-intensity	PASAT	* EX: 89 (9) Ctrl: 82 (9)	For the PASAT, the exercise group outperformed the control group.

Alderman et al. (2014)	*n* = 66, Age = 21.06 (1.6)	Within-subject	Self-paced treadmill walking for 15 minutes.	Flanker task (1. ACC congruent) (2. ACC incongruent) (3. RT congruent) (4. RT incongruent) Stroop task (5. ACC neutral) (6. RT neutral) (7. ACC interference word) (8. RT interference word) (9. ACC interference color) (10. RT interference color) Reading comprehension (11. ACC) (12. RT)	1.* EX: 98.73 (2.82) Ctrl: 97.58 (6.76) 2.* EX: 93.29 (5.63) Ctrl: 93.13 (8.14) 3.* EX: 318.39 (59.31) Ctrl: 322.10 (69.31) 4.* EX: 380.40 (60.16) Ctrl: 390.63 (76.13) 5.* EX: 95.14 (5.43) Ctrl: 95.97 (4.03) 6.* EX: 672.19 (115.84) Ctrl: 663.34 (111.39) 7.* EX: 94.08 (10.84) Ctrl: 92.91 (13.91) 8.* EX: 808.26 (195.11) Ctrl: 815.88 (213.17) 9.* EX: 83.60 (23.57) Ctrl: 90.96 (16) 10.*EX: 932.56 (215.98) Ctrl: 892.84 (189.98) 11.*EX: 76.72 (14.18) Ctrl: 75.22 (11.92) 12.*EX: 3310.85 (757.89) Ctrl: 3452.12 (849.13)	There were no significant differences in response speed or accuracy between walking and sitting conditions for any of the cognitive tests.
Schmidt-Kassow et al. (2014)	*n* = 49, Age = 21.7 (2.7)	Within-subject	Self-selected walking pace for 30-min	Recall memory task using 40-item (unfamiliar) word list (1. Experiment 1) (2. Experiment 2)	1.* EX: 5.5 (3.3) Ctrl: 4.8 (4.2) 2.* EX: 5.3 (4.6) Ctrl: 4.1 (3.5)	Experiment 1 & 2: Words recalled during walking was higher than non-exercise.
Bullock et al. (2015)	*n* = 12, Age = 20 (1.08)	Within-subject	Cycling for 50-min at low and high intensities	Visual recognition task† (RT)	* EX: 505 Ctrl: 525	Behavior target detection was faster during high-intensity exercise compared to rest.
Schmit et al. (2015)	*n* = 15, Age = 22.1 (0.6)	Within-subject	Cycling for 20-min at high-intensity of 85% MAP	Flanker task (1. RT congruent) (2. ER congruent) (3. RT incongruent) (4. ER incongruent)	1. ^{ns} EX: 410 (49) Ctrl: 414 (43) 2. ^{ns} EX: 0.7 (2.1) Ctrl: 0.7 (1.7) 3.* EX: 456 (76) Ctrl: 461 (46) 4.* EX: 20.6 (14.2) Ctrl: 9.9 (4.9)	The frequency of errors was lower during rest than when exercising for incongruent trials, but not for congruent trials.
Bantoft et al. (2016)	*n* = 45, Age = 22.6 (6.2)	Within-subject	Low intensity treadmill walking	Letter number sequencing (1. ACC) Choice reaction time† (2. ACC) (3. RT) PASAT (4. ACC) Digit span forward (5. ACC) Digit span backward	1. ^{ns} EX: 11.47 (2.55) Ctrl: 11.49 (2.35) 2.^{ns} EX: 91.56 (4.75) Ctrl: 91.79 (4.87) 3.^{ns} EX: 466.16 (60.44) Ctrl: 455.13 (47.36) 4.^{ns} EX: 37.45 (14.83) Ctrl: 37.76 (15.23) 5.^{ns} EX: 11.73 (2.20) Ctrl: 11.40 (2.24)	There were no significant differences in cognitive tasks across three conditions (sitting vs. standing vs. walking).

				(6. ACC) Digit symbol coding (7. ACC) Stroop task (8. ER) (9. RT)	6.^{ns} EX: 7.28 (2.56) Ctrl: 7.22 (1.98) 7.^{ns} EX: 88.91 (15.46) Ctrl: 91.60 (14.99) 8.^{ns} EX: 0.38 (0.68) Ctrl: 0.49 (0.69) 9.^{ns} EX: 17.39 (5.94) Ctrl: 17.92 (5.09)	
Rattray & Smee (2016)	*n* = 20, Age = 26.6 (5.2)	Within-subject	Cycle ergometer exercise for 50-min at low- and high-intensity of 50% VO_{2max} and 90% VO_{2max}.	Speed match task† (1. Low-intensity EX ACC) (2. Low-intensity EX RT) (3. High-intensity EX ACC) (4. High-intensity EX RT)	1.* EX: 93.6 (5.9) Ctrl: 95.3 (4.2) 2.* EX: 643 (52) Ctrl: 672 (45) 3.* EX: 93.1 (5.4) Ctrl: 95.3 (4.2) 4.* EX: 648 (53) Ctrl: 672 (45)	The exercise conditions facilitated response time, but reduced accuracy scores compared to control condition.
Da Silva et al. (2017)	*n* = 37 Age = 25.1 (4.6)	Within-subject	Cycle ergometer exercise for 20 minutes at high-intensity	Choice reaction time† (1. RT) Stroop task (2. ER)	1.* EX: 322.2 (261.7) Ctrl: 305.2 (138.2) 2.* EX: 1.7 (1.2) Ctrl: 0.3 (0.6)	Exercise at higher intensities was negatively associated with reaction time and inhibitory control.
Frith et al. (2017)	*n* = 88, Age = 21.9 (2.4)	Between-subject	15 minutes treadmill walking/running of progressive high-intensity aerobic exercise	RAVLT (1. Trial 1 recall) (2. 20 min delayed recall) (3. 24h recognition recall) (4. 24h attribution recall)	1.* EX: 6.55 (1.14) Ctrl: 6.18 (1.44) 2.* EX: 8.86 (2.51) Ctrl: 9.41 (2.13) 3.* EX: 35.23 (4.0) Ctrl: 36.59 (3.36) 4.* EX: 31.68 (5.09) Ctrl: 33.95 (3.57)	High-intensity exercise before memory encoding was effective in improving long-term memory, 20-min delayed recall, and 24-h delayed recall.
Sng et al. (2017)	*n* = 88, Age = 23.3 (3.7)	Between-subject	15 minutes self-paced treadmill walking at moderate-intensity	RAVLT (1. Trial 1_recall) (2. 20 min delay recall) (3. 24h recognition recall) (4. 24h attribution recall)	1.* EX: 6.45 (1.63) Ctrl: 6.64 (1.50) 2.^{ns} EX: 10.23 (2.20) Ctrl: 11.23 (2.20) 3.* EX: 34.09 (3.44) Ctrl: 35.95 (4.08) 4.* EX: 31.73 (4.36) Ctrl: 33.36 (4.84)	Exercising prior to memory encoding was superior for improving learning, 24-h memory recognition, and 24-h memory attribution.
Cuttler et al. (2018)	*n* = 120, Age = 19.77 (0.15)	Between-subject	30-min self-paced treadmill walking/running at moderate-intensity	Viral video prospective memory	* EX: 14 (0.94) Ctrl: 17.59 (0.95)	The control group had better prospective memory than the exercise group.
Siddiqui & Loprinzi (2018)	*n* = 20, Age = 21.1 (1.0)	Within-subject	20-min treadmill bout of self-paced brisk walking (moderate-intensity exercise)	Deese-Roediger-McDermott (DRM) paradigm (1. Immediate memory recall) (2. Delayed memory recall)	1.* EX: 8.20 (1.6) Ctrl: 8.80 (1.7) 2.* EX: 5.90 (1.7) Ctrl: 6.40 (2.2)	For both short-term and long-term memory, the exercise group during memory encoding resulted in the worst memory performance.
Haynes et al. (2019)	*n* = 24, Age = 20.9 (1.9)	Within-subject	Self-selected brisk walking pace for 15 minutes at moderate-intensity	RAVLT (1. Trial 1 recall) (2. 20 min delayed recall) (3. 24h recognition recall) (4. 24h attribution recall)	1.* EX: 6.0 (1.7) Ctrl: 6.13 (1.5) 2.^{ns} EX: 11.2 (2.9) Ctrl: 10.04 (3.3) 3.^{ns} EX: 22.48 (4.2) Ctrl: 22.26 (4.8)	Short-term memory was superior in the visit that involved exercise before the memory task. Similar outcomes occurred for long-term memory, but there were no

					4.^{ns} EX: 19.08 (5.0) Ctrl: 17.96 (6.8)	exercise effects on prospective memory.
Loprinzi et al. (2019)	*n* = 48, Age = 21.9 (1.9)	Within-subject	Treadmill exercise at low (30% HRR), moderate (50% HRR), and high-intensity (80% HRR)	Experiment 1 Brown-Peterson task (1. Memory recall) Paired associate learning task (2. Short-term recall) (3. Long-term recall) Experiment 2 Brown-Peterson task (4. Memory recall at low-intensity EX) (5. Memory recall at moderate-intensity EX) (6. Memory recall at high-intensity EX)	1.* EX: 10.75 (3.41) Ctrl: 11.67 (2.79) 2.* EX: 3.67 (2.88) Ctrl: 4.71 (3.23) 3.* EX: 3.50 (2.84) Ctrl: 4.50 (3.06) 4.^{ns} EX: 9.41 (3.9) Ctrl: 9.83 (3.9) 5.^{ns} EX: 9.70 (4.5) Ctrl: 9.83 (3.9) 6.* EX: 7.66 (5.1) Ctrl: 9.83 (3.9)	Experiment 1: Both working memory and episodic memory were compromised during high-intensity exercise when compared to rest. Experiment 2: Similar results occurred for working memory, but memory function was not impaired during low- and moderate-intensity exercise.
Komiyama et al. (2020)	*n* = 17, Age = 22.1 (1.7)	Within-subject	Cycle ergometer exercise for 15 minutes at high-intensity of 80% VO_{2peak}	Spatial delayed response + Go/No-Go task	* EX: 84.1 (13.3) Ctrl: 95.1 (5.3)	Accuracy of the cognitive tasks was impaired during high-intensity exercise in the exercise group relative to the control group.

Note. ACC = accuracy, ER = error rate, EX = exercise condition, Ctrl = control, HRR = heart rate reserve, MAP = maximal aerobic power, MPO = maximum power output, ms = millisecond, PASAT = paced auditory serial addition task, PPVT = peabody picture vocabulary test, RAVLT = rey auditory verbal learning task, RT = reaction time, SD = standard deviation, VO_{2max} = maximum oxygen uptake, † non-PFC-dependent cognitive task. All reaction time units are milliseconds. * significantly different, ^{ns} not significantly different

Table 3. Weighted average effects with robust variance estimation and moderation analyses for acute exercise at all intensities during cognitive task vs. control

Variable	***k***	***o***	***b***	***SE***	**95% CI**		***p***	***t* (*df*)**	**Heterogeneity**	
					LL	***UL***			τ^2	I^2
Cognitive function	22	75								
Intercept only									0.66	87.18
Constant			-0.16	0.20	-0.58	0.27	.45	-0.77 (20.9)		
Moderators									0.77	87.46
Constant			0.21	0.61	-1.17	1.59	.74	0.34 (9.17)		
Males			-0.40	0.69	-2.05	1.25	.58	-0.57 (6.70)		
Predominantly female			-0.38	0.52	-1.89	1.14	.51	-0.72 (4.63)		
Low-intensity exercise			0.58	0.51	-0.60	1.75	.29	1.14 (7.58)		
Moderate-intensity exercise			-0.01	0.51	-1.16	1.14	.98	-0.02 (8.71)		
Medium duration exercise			-0.87	0.88	-3.00	1.26	.36	-0.99 (6.27)		
Long duration exercise			-0.44	0.72	-2.19	1.31	.56	-0.61 (6.37)		
Cycling			0.95	0.61	-0.44	2.34	.16	1.56 (8.41)		
PFC-dependent cognitive task			-0.66	0.33	-1.48	0.16	.10	-1.99 (5.77)		

Note. *k* = number of studies, *o* = total number of comparisons, *b* = coefficient in the meta-regression model, *SE* = standard error of the coefficient, 95% CI = 95% confidence interval for the coefficient, *LL* = lower limit of the 95% confidence interval for the coefficient, *UL* = upper limit of the 95% confidence interval for the coefficient, *t* = *t*-statistic calculated based on the predicted mean, *df* = small sample corrected degrees of freedom of the distribution of the *t*-statistic, τ^2 = between-study sampling variance, I^2 = proportion of effect size variance due to between-sample heterogeneity, PFC = prefrontal cortex.

Table 4. Weighted average effects with robust variance estimation and moderation analyses for high-intensity acute exercise during cognitive task vs. control

Variable	***k***	***o***	***b***	***SE***	**95% CI**		***p***	***t* (*df*)**	**Heterogeneity**	
					LL	***UL***			τ^2	I^2
Cognitive function	12	27								
Intercept only									0.46	79.82
Constant			0.03	0.20	-0.41	0.46	.89	0.14 (10.9)		
Moderators									0.37	76.01
Constant			0.57	0.29	-0.27	1.41	.13	1.97 (3.60)		
PFC-dependent cognitive task			-0.81*	0.33	-1.60	-0.02	.04	-2.46 (6.71)		

Note. *k* = number of studies, *o* = total number of comparisons, *b* = coefficient in the meta-regression model, *SE* = standard error of the coefficient, 95% CI = 95% confidence interval for the coefficient, *LL* = lower limit of the 95% confidence interval for the coefficient, *UL* = upper limit of the 95% confidence interval for the coefficient, *t* = *t*-statistic calculated based on the predicted mean, *df* = small sample corrected degrees of freedom of the distribution of the *t*-statistic, τ^2 = between-study sampling variance, I^2 = proportion of effect size variance due to between-sample heterogeneity, PFC = prefrontal cortex. $^*p < .05$.