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Meta-analysis of cognitive performance in fibromyalgia

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Abstract

Introduction: Fibromyalgia is a condition with symptoms of pain, physical function difficulties, and emotional problems, but is also characterized by complaints of poor cognition (often called ‘FibroFog’). Over the last two decades, a number of studies have examined cognitive differences between individuals with and without fibromyalgia. The purpose of the current study was to conduct a quantitative synthesis of these differences across multiple cognitive domains.

Methods: Following Cochrane guidelines, we identified 37 eligible studies for analysis where persons with fibromyalgia (total $n = 964$) were compared to participants from age-matched control groups without fibromyalgia (total $n = 1,025$) on a range of neuropsychological measures. Group differences between persons with fibromyalgia and healthy controls were examined for cognitive domains including processing speed, long- and short-term memory, and executive functions

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Ethical approval:
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained by all participants in studies used for the meta-analysis.

(inhibitory control, set shifting, updating, and accessing). Random-effect meta-analyses were conducted to determine effect sizes for these differences in cognitive performance.

Results: Fibromyalgia was significantly and negatively associated with performance on all domains of cognitive function. The largest effect size was found for inhibitory control ($g = 0.61$), followed by memory ($g = 0.51$ for short-term, 0.50 for long-term memory). The smallest cognitive difference between those with fibromyalgia and controls was for set shifting ($g = 0.30$).

Conclusion: These findings support the hypothesis that the self-reported cognitive impact of fibromyalgia is also found in objective neuropsychological measures. Routine screening for cognitive dysfunction in those with fibromyalgia may be warranted in addition to assessment of the traditional fibromyalgia symptoms.

Keywords

Fibromyalgia; *Chronic Pain*; *Cognition*; *Executive Function*; *Memory*; *Meta-analysis*

Introduction

Fibromyalgia is a condition affecting 2% of the general population at any given time (Lawrence et al., 2008) with most being female (>90%; Schaefer et al., 2016). Common symptoms of fibromyalgia include pain, stiffness, fatigue, sleep dysfunction, and headaches (Bennett, 2009; Mease, 2005; Schmidt-Wilcke & Clauw, 2011). Previously, fibromyalgia diagnosis involved pain lasting at least three months across five body quadrants (axial, left, right, upper, and lower segment pain) and the presence of 11 out of 18 tender points, places of high sensitivity to pressure pain (Wolfe et al., 1990). Criteria was later revised to include presence of pain in 7 out of 19 regions, and ratings greater than 5 out of 12 on a newly created scale rating symptoms of fatigue, sleep, and cognition on difficulty from 0 (no problem) to 3 (severe) and general symptom severity from 0 (no symptoms) to 3 (a great deal) (Wolfe et al., 2010). With addition of this symptom scale, one of the most common fibromyalgia symptoms was included: self-reported cognitive difficulties known as “FibroFog”. To better understand this emerging symptom cluster, the current study examined objective difficulties with cognitive performance in those with fibromyalgia.

Approximately 75% of fibromyalgia patients report significant problems with concentration, memory and multitasking (Donaldson, Sella, & Mueller, 1998; Leavitt, Katz, Mills, & Heard, 2002). In addition, self-reported cognitive difficulty is associated with higher levels of pain, stiffness, poor sleep, and elevated depression and anxiety symptoms in fibromyalgia (Leavitt et al., 2002; Wolfe et al., 2010). Cognitive difficulties have been reported in focus groups (Arnold et al., 2008), surveys (Bennett, Jones, Turk, Russell, & Matallana, 2007), and in observer reports of cognitive impairment from medical professionals (Zachrisson, Regland, Jahreskog, Kron, & Gottfries, 2002). While cognitive difficulties are thought to be relevant to clinical care in fibromyalgia, it remains unclear whether these subjective reports correspond to *objective* cognitive difficulties in fibromyalgia, which can impact quality of life, treatment adherence, and negative health outcomes (Skoog et al., 2005; Tesio et al., 2015; Zinn et al., 2004). Better understanding of the impact of this pain condition on objective cognitive difficulties may help provide a more comprehensive view of FibroFog

and its impact on daily living and health. Moreover, prior research shows that the association between pain and cognitive performance is not universal across domains, but more specific to complex task completion (such as tasks involving executive functions) than simple processing tasks (Moore, Keogh, & Eccleston, 2012). Thus, by understanding the objective impact of fibromyalgia on specific cognitive domains, clinicians may be able to predict and improve treatment outcomes for this population more accurately.

To date, a large body of research has assessed task-based neuropsychological performance in fibromyalgia. Overall, research has documented cognitive difficulties in several domains including processing speed (Reyes Del Paso, Montoro, & Duschek, 2015), short-term memory (Park, Glass, Minear, & Crofford, 2001), long-term memory (Cánovas, León, Roldán, Astur, & Cimadevilla, 2009), inhibtory control (Walitt, Roebuck-Spencer, Bleiberg, Foster, & Weinstein, 2008), and working memory (Coppieters et al., 2015). However, some mixed results regarding specific cognitive domains have also been reported. In a review of literature by Glass (2009), people with fibromyalgia show consistent difficulties in episodic/semantic memory and working memory (Cánovas et al., 2009), but there are other studies showing no signficant differences in other cognitive domains (Cánovas et al., 2009; Di Tella et al., 2015; Walitt et al., 2008; Walteros et al., 2011), making generalizations from previous research more difficult. In order to clarify the objective nature of cognitive problems in those with fibromyalgia, a meta-analysis is needed to quantitatively synthesize results across multiple studies and guide futher investigation.

Theoretical Foundations for the Current Meta-Analysis

Studies examining the cognitive difficulties in fibromyalgia and other chronic pain conditions have hypothesized compromised attention systems due to shared networks with pain (Cánovas et al., 2009 Correa, Miro, Martinez, Sanchez, & Lupianez, 2011; Glass et al., 2011). Eccleston and Crombez (1999) proposed that pain is an obstacle for efficient cognitive processing. In this model, attention leads to selection of information salient to cognitive goals, which are triggered by internal and external stimuli. Attentional resources, however, are limited, and cognitive goals must be selected by their degree of saliency. Due to the evolutionary mechanism of pain (i.e., escape and survival), pain-processing is prioritized at the cost of attentional resources for other goal-related behavior. Consequently, Eccleson and Crombez. (1999) theorized that constant goal disruption by pain may cause cognitive difficulties throughout the different stages of the information processing model. Applying this theory, the current study tested for cognitive difficulties in fibromyalgia throughout information processing domains using a model incorporating long-standing theories of working memory (Atkinson & Shiffrin, 1968; Baddeley & Hitch, 1974) and executive functioning (Miyake et al., 2000).

The cognitive model guiding the current study describes the mechanics of information processing, which begins at sensory perception and ends with a behavioral response. In this model, attended information is initially processed through sensory registries, and low-priority or task-irrelevant information is filtered out. Relevant information is then stored into short-term memory, which is limited and held very briefly in systems specific to auditory-verbal and visuospatial information. Rehearsal and elaboration can then move information

into long-term memory to be stored and recalled for an unlimited amount of time. The storage of relevant information, however, is not sufficient to achieve goal-related behavior. Instead, a central executive cognitively controls information to produce an appropriate response; such control is possible through specific, though related sets of executive functions within the central executive.

Executive functions are higher-level cognitive processes implemented in goal creation, planning, and response execution (Lezak, Howieson, & Loring, 1983; Lezak, 2004). Miyake et al. (2000) provided evidence for separate but non-orthogonal components of the central executive, falling into the subcategories of inhibition, set shifting, and updating, which are moderately interrelated. Inhibiting involves purposive prevention of interference from prepotent responses (responses previously reinforced and associated with stimuli; Barkley, 2013); shifting involves changing mental sets to provide an appropriate response; and updating involves adding and deleting representations in working memory by goal relevance. Recently, Fisk and Sharpe (2004) have expanded on the work of Miyake et al. (2000) with the addition of a new executive function known as accessing (often measured as verbal fluency), which involves executive action to retrieve information from long-term memory. Assessing individual executive functions may add additional insight into the integrity of the central executive in fibromyalgia.

The current study examines differences between persons with fibromyalgia and healthy adults on cognitive function including processing speed, short-term memory, long-term memory, and executive functions. The potential moderating role of age is also examined as older adults with fibromyalgia may show greater cognitive difficulties due to age-related declines.

Methods

Data sources

The current study employed a systematic search of the literature using the Cochrane Collaborations (Higgins & Green, 2011) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). Pubmed, PsychInfo, and OVID databases were searched (from January 1950 to July 2015) using Boolean terms including “fibromyalgia” and words describing cognition: (“fibromyalgia” AND “attention,”); (“fibromyalgia” AND “cognition”); (“fibromyalgia” AND “cognitive”); (“fibromyalgia” AND “executive”); (“fibromyalgia” AND “memory”); (“fibromyalgia” AND neuropsychological”). Identified articles were then indexed by database and key terms.

Study selection and inclusion

Two steps were involved in study article selection (see Figure 1). The first step involved two independent reviewers (TB, MB) screening all possible citations to filter out articles which did not relate to fibromyalgia and cognition based on information from titles and abstracts. The key terms searched in the databases provided 2,355 citations, and after removing duplicates (n = 882), there were 1,472 articles to be screened. After review, 1,367 articles

were excluded based on irrelevance to the meta-analysis focus (fibromyalgia and task-measured cognitive performance). For example, 28.9% (n = 396) involved diagnosis and treatment/interventions for fibromyalgia, 28.9% (n = 396) did not pertain to objective task-measured cognition, 19.2% (n = 263) were not peer-reviewed empirical articles (e.g., reviews, commentaries), 12.5% (n = 171) did not specifically pertain to fibromyalgia, and 8.2% (n = 112) related to neurophysiological aspects of fibromyalgia with no cognitive performance measures. Other reasons for exclusion included the use of animals, no control group, or the article was only available as an abstract (less than 1% for each). A total of 105 studies were deemed eligible for inclusion in the next step of screening, with high inter-rater reliability above chance agreement (Kappa = .78, $p < .001$).

The second step involved applying the following inclusion criteria to each study: (1) The study was not characterized by comorbid conditions that included any neurological condition with cognitive effects (including all forms of dementia, neural degeneration or demyelinating disorders, epilepsy, sleep disorders, ADHD) in the control group or in the patient group (other than a primary diagnosis of fibromyalgia); (2) the study looked at objective task-measured cognitive performance; (3) the study did not assess cognition with solely a mental status exam or other screening measure; (4) the study was peer-reviewed; (5) the study included a healthy age-matched control group; (6) the data were not related to the effects of a drug or treatment intervention (baseline comparisons only); (7) the paper was not a review or conference abstract; (8) the study included human participants and did not investigate animals; (9) the study did not make use of emotion-inducing stimuli (i.e., did not use negative or pain-related stimuli) during cognitive tasks, which includes the use of non-neutral (positive or negative) stimuli; (10) the article was available in English; and (11) the study pertained to fibromyalgia specifically (not aggregated with other pain conditions).

Of the 105 articles included in this step of eligibility, 39 studies were initially found to meet the criteria while 66 articles were excluded (98% reviewer agreement). Disagreements were settled by discussion between MB and TB as well as consulting co-authors. Further inspection led to the exclusion of two additional articles, one which was not fully available in English, and one which did not have an age-matched control group (total excluded = 68). The primary reasons for article exclusion were as follows: of the 68 studies excluded, 25 (36.76%) did not include a healthy (age-matched) control group, 16 (23.53%) did not look specifically at cognitive performance, 10 (14.71%) were not full-text research studies (e.g., review, commentary, conference abstract), 6 (8.82%) did not pertain to fibromyalgia specifically, 3 (4.41%) were not peer-reviewed, 4 (5.88%) were not available in English, 1 (1.47%) included emotional stimuli (induced pain), and 3 (4.41%) only assessed cognition using a mental status exam or other screening measure. This process left 37 eligible studies for data extraction and subsequent analyses. It is important to note that these numbers reflect primary reasons for exclusion, as many of the excluded articles failed to meet multiple inclusion criteria. For this step of selecting the 37 of 105 potential articles, there was a high inter-rater reliability (Kappa = .96, $p < .001$). All included studies with descriptive information can be seen in Table 1.

Data extraction

Data were extracted by two independent reviewers (TB, MB) using a standardized form (Berryman et al., 2013) tailored to current needs. Data extraction included keywords and the location of the study (Europe, North America, etc.). Next, data regarding sample size, participant gender, participant age, and other demographic information were examined. Data was collected for each cognitive task, including the name of the test, the cognitive domain assessed, and the means and standard deviations of scores in the fibromyalgia and the healthy control group. Moreover, score means, standard deviations, sample sizes, sample mean age, *t*-statistics, and *p*-values were recorded to compute effect sizes. For each measure, the domain that the measure most directly assessed was determined by study description and initial review (e.g., Stroop – inhibition), scoring type (response time, accuracy, or errors), as well as primary stimuli type (verbal auditory versus visuospatial).

Data synthesis

Outcome measures from each study were synthesized into cognitive domains of interest guided by established theoretical cognitive models (Atkinson & Shiffrin, 1968; Baddeley & Hitch, 1974; Miyake et al., 2000). These included processing speed, short-term and long-term memory, and executive functions of selective attention/response inhibition, set shifting, working memory/updating, and accessing. Because cognitive tasks can be measured by accuracy (higher scores indicating better performance), errors (more errors indicating worse performance) or response time (higher scores indicating worse performance), effect sizes were transformed so that higher effect sizes indicated worse performance (expected direction).

Data pooling

For each group comparison, effect sizes were converted into standardized mean differences using Hedges' *g*, calculated from group means and pooled standard deviations for each cognitive task or directly from Cohen's *d*. Hedges' *g* statistic was calculated using OpenMeta software (Wallace et al., 2012). In cases where standard errors were reported, standard deviations were calculated by multiplying the standard error by the square root of the sample size for each group. Hedges' *g* is similar to Cohen's *d* and can be interpreted as how many standard deviations the fibromyalgia group is performing above or below the healthy control group. Unlike Cohen's *d*, Hedges' *g* removes the bias of small and unequal sample sizes, which may overestimate group differences. Effect sizes for Hedges' *g* are equivalent to that of Cohen's *d*, where small, medium, and large effects correspond to values of .20, .50, and .80 (Cohen, 1988). An estimate of Hedges' *g* is considered significant if 0 is not included in the 95% confidence interval (Nakagawa & Cuthill, 2007).

Data were collected from independent samples to meet the assumption of independence in our statistical analyses, allowing only one effect size for a cognitive domain to be collected from each study. Thus, reviewers decided on which measures of a certain domain were most valid for inclusion (had high construct validity) based on current neuropsychological assessment texts and research (Lezak, 2004; Strauss, Sherman, & Spreen, 2006) and discussion with co-authors. In many cases, studies used multiple measures of the same domains, for which composite Hedges' *g*s were calculated to provide an optimal estimate.

For example, a study using 2 measures of processing speed would provide 2 corresponding effect sizes for that domain, which were then averaged to make a composite effect size for processing to meet the assumption of independence. In the current study, random-effects meta-analysis (Borenstein, Hedges, Higgins, & Rothstein, 2010) was then used to provide pooled Hedges' *g*s for each cognitive domain, along with 95% confidence intervals and a measure of between-study heterogeneity (I^2).

Risk of bias assessment

Risk of bias was assessed using guidelines provided by the Cochrane Collaboration (Higgins & Green, 2011). Each article was strictly assessed on the criteria provided, including domains of selection bias (biased from non-random generation of groups, non-comparable recruitment), attrition bias (bias due to amount, nature, or handling of missing data), reporting bias (bias due to selective outcome reporting), and other bias (bias due to other sources identified by author reviewers). Other important concerns derived from reviews were noted, such as study limitations and accurate use and interpretation of neuropsychological measures. To handle bias, any studies that were at high risk were not included in analyses.

Statistical analysis

Analysis was conducted using OpenMeta software (Wallace et al., 2012) using the random-effects model with the DerSimonian method (DerSimonian & Laird, 1986). Random-effects analysis was used following the logic that each study might have its own true effect size due to study-specific characteristics with the goal of the current study to provide an estimate for the average of these true standard mean differences and not one true value for these differences. Furthermore, random effect models were used to obtain measures of heterogeneity known as I^2, which specifies the percent of variability in the effect size across studies. In addition to the pooled standard mean differences (Hedges' *g*), 95% confidence intervals, I^2 estimates, and forest plots for each cognitive domain were produced.

Results

Characteristics of included studies

Of the 37 studies analyzed, 26 were based in Europe (71.1%), 9 in North America (23.7%), and 2 (5.3%) in Asia. Regarding participant characteristics, the mean age for participants with fibromyalgia across these studies was 47.85 (SD = 8.23), and the mean age for the healthy control samples was 45.99 (SD = 8.83). The average percent of females in the fibromyalgia samples was 96.4%, and 94.5% in the healthy control groups. Either years of education or highest education level was recorded from each study. Using studies with available data on years of education (15 studies), the average education for participants with fibromyalgia was 12.93 years (SD = 3.61), and 13.34 years (SD = 2.68) for participants in the healthy control groups. A total of 964 participants with fibromyalgia and 1,025 age-matched participants without fibromyalgia were included from these studies. Characteristics of all studies can be seen in Table 1.

Regarding bias, five studies showed unclear selection bias due to a lack information on recruitment, two had unclear selection bias due to attrition bias (unclear handling of missing

data), and three had unclear reporting biases due to incomplete output reporting. Because none of the studies showed a high risk of bias, all studies were used for subsequent analyses. Meta-analytical results described by cognitive domain below are also summarized in Table 2.

Processing Speed

Information processing speed, typically defined as the average time elapsed from stimuli presentation to a task-appropriate response, was measured in 10 studies using diverse measures. The main measures involved the speed at which one completed a simple task or the number of accurately completed problems within an allotted time. These measures included the Digit Symbol Substitution task (Wechsler, 1997), Pattern/Letter/Number Comparison (Salthouse & Babcock, 1991), and Trail Making Task Part A (Reitan, 1958), as well as congruent conditions during the Attention Network Task-Interactions (ANT-I; Callejas, Lupiánez, & Tudela, 2004) and Stroop task (Stroop, 1935). Measures also included reaction times on a lab-developed mental arithmetic task (Montoro, Duschek, Muñoz Ladrón de Guevara, Fernández-Serrano, & Reyes del Paso, 2015), a cued reaction time task (Montoro et al., 2015), and reaction time on the Psychomotor Vigilance Task (Dinges & Powell, 1985). Looking at measures of response speed (14 outcome measures), there was a larger effect size (average $g = .59$ than for measures of accuracy (4 outcome measures; average $g = .49$). However, as seen in Figure 2, the random-effects model for processing speed showed a significant and medium-sized difference between those with fibromyalgia and healthy control groups using both measures of response time and accuracy ($g = .46$, 95% CI: .25 to .67), with no significant between-study heterogeneity ($I^2 = 39.08\%$, $p = .097$).

Memory

Short-term memory—We identified 12 studies that assessed short-term memory, defined as the ability to retain information over a very brief period of time. These tasks were mainly comprised of immediate recall and recognition of verbal and visuospatial stimuli. Measures included outcomes from ANAM Code Substitution-Immediate Recall (Kane & Reeves, 1997), Attentional Blink (McLaughlin, Shore, & Klein, 2001), Benton Forms and Lines (Benton, 1994), CERAD-Immediate Recall (Morris et al., 1989), Corsi Block Test Forward (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000), Digit Span Forward (English and Korean; Orsini et al., 1987; Yeom, Park, Oh, Kim, & Lee, 1992), Kimura Recurring Figures Recognition Test (Kimura, 1963), 10/36 Spatial Recall Task (Achiron et al., 2005), Rey Auditory Verbal Learning Task immediate recall (English and Korean versions; Rey, 1964), Rey Complex Figures Task-Immediate recall (Rey, 1941), Spatial Span Forward (Ha et al., 2002), and Wechsler's Verbal Memory test (Wechsler, 2004). Additional short-term memory measures included lab-developed tasks, such as a virtual reality version of the Hole Board Test (Oades & Isaacson, 1978), known as the Boxes Room task (Cánovas et al., 2009), as well as classic free recall and recognition tasks. Looking at tasks using auditory/verbal stimuli, there was a moderate-sized difference between those with fibromyalgia and healthy controls (17 outcome measures; average $g = .36$). The effect size for this difference was larger for visuospatial tasks (14 outcome measures; average $g = 1.07$).

Composite effect sizes were made for each study. For example, the average effect size on measures of short-term memory was calculated for Canovas et al. (2009), which included mean differences on Digit Span Forward, Corsi Block Forward, and the 10/36 Spatial Recall Test. Using composite effect sizes for 12 studies, random effects analysis confirmed a moderate difference in short-term memory ability in fibromyalgia compared to healthy adults (g = .51, 95% CI: .29 to .74), seen in Figure 3. There was also a significant amount of between-study heterogeneity (I^2 = 46.99, p = .036), suggesting substantial differences in short-term memory measurement and study characteristics.

Long-term memory—Many of the studies examining short-term memory also included delayed recall conditions that measured a person's ability to retrieve information after a pre-specified delay of time. These measures included delayed recall and recognition subtests of the 10/36 Spatial Recall Task (Achiron et al., 2005), 15-item Rey Memory Test (Rey, 1964), ANAM Code Substitution delayed (Kane & Reeves, 1997), CERAD-Delayed Recall and Recognition (Morris et al., 1989), Code Memory Test Part 1 (Levander & Elithorn, 1987), Complex Figure Test-Delayed Recall (Osterrieth, 1944); Rey Auditory Verbal Learning Task (English and Korean versions; Rey, 1964), Randt Memory Task (Randt, Brown, & Osborne, 1983), Rey Figure (15-min and 5-min delay recall; Rey et al., 1941), Wechsler Memory Test-Delayed Recall (Wechsler, 2004), as well as paradigm free recall task. Of the eligible studies, 11 studies assessed long-term memory. The average effect size for tasks using auditory/verbal stimuli was .49 (11 outcome measures), and was .53 for visual-spatial stimuli (5 outcome measures).

As seen in Figure 4, random-effects modeling showed a significant small to moderate difference in long-term memory ability in fibromyalgia compared to healthy adults (g = .50, 95% CI: .28 to .72). There was not a significant amount of between-study heterogeneity for long-term memory (I^2 = 39.76, p = .084).

Executive Functions

Inhibitory control—Eighteen studies assessed inhibitory control, involving the prevention of inappropriate responses (response inhibition) and ability to ignore goal-irrelevant stimuli (selective attention). The primary measure of inhibitory control was the interference score from the classic Stroop task (Stroop, 1935) but also included interference calculated from the Go/No-Go paradigm (Fillmore & Rush, 2002), Coding Memory Test Part 2 (a measure of inhibition to task-irrelevant verbal stimuli, i.e., proactive interference; Levander & Elithorn, 1987), and the Test of Everyday Attention (TEA)-Selective Attention subscale (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994).

Across these instruments, moderate difficulties were found for the Stroop task (12 outcome measures; g = .61), and the TEA-Selective Attention (1 outcome measure; g = .54), whereas differences on the Go/No-Go paradigm were small (2 outcome measures; g = .34). As seen in Figure 5, results from the random effects meta-analysis showed a moderate-to-large difficulty in inhibitory control across these measures that was statistically significant comparing those with fibromyalgia to healthy controls (g = .61, 95% CI: .38 to .83). There was a large amount of heterogeneity in effect sizes (I^2 = 65.66, p <.001), greater than the

amount expected by chance. Sensitivity analyses revealed that removing the measure of selective attention did not reduce heterogeneity (I^2 = 67.53%, p < .001) or significantly change the average of the standard mean differences (g = .61, 95% CI: .37 to .85). This indicates that pooling estimates of selective attention and response inhibition did not confound the standard mean difference. To test if the small differences found on the Go/No-Go paradigm were driving heterogeneity in the true effect size, the model was re-analyzed without this measure. After removing the Go/No-Go paradigm from the model, there was still a significant amount of between-study heterogeneity (I^2 = 68.17%, p = .001), though the standard mean effect size increased (g = .63, 95% CI: .39 to .88). Thus, the differences in inhibitory control appear to vary significantly between studies, and this was not accounted for by inclusion of both selective attention and response inhibition tasks or inclusion of Go/No-Go paradigm.

Set shifting—For the total eligible studies, seven assessed set shifting in fibromyalgia, which is the ability to swtich between tasks, operations, and mental sets (i.e., cognitive flexibility). Measures included the Trail Making Task Part B (TMT-B; Reitan, 1958) and the number of perseveration errors on the Wisconsin Card Sorting Task (WCST; Rao, Hammeke, & Speech, 1987).

The average difference between those with fibromyalgia and controls for TMT-B was moderate (5 outcome measures; g = .44) and larger than shown for performance on the WCST (2 outcome measures; g = .06). As shown in Figure 6, a random-effects model showed that the average of standard mean differences was statistically significant, with worse set shifting abilities in fibromyalgia compared to healthy adults, but this effect was small (g = .30; 95% CI: .11 to .49). There was not significant heterogeneity between studies (I^2 = 0.00, p = .490).

Updating—Seventeen studies measured updating, defined as adding goal-relevant information and omitting goal-irrelevant information from active memory. Commonly used measures which involve numerical-verbal information included Digit Span Backward (Orsini et al., 1987), *n*-back task (Kirchner, 1958), accuracy on lab-developed mental arithmetic tasks (Montoro et al., 2015), math and letter-number sequencing subtests of the Automated Neuropsychological Assessment Metrics (ANAM; Bleiberg, Kane, Reeves, Garmoe, & Halpern, 2000) and Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997), and complex span tasks including Operational Span Task (OSPAN; Turner & Engle, 1989) and Reading Span tasks (Daneman & Carpenter, 1980). Along with tasks based on numerical-verbal information are tasks based on other forms of primary stimuli. The Auditory Consonant Trigrams paradigm (Stuss, Stethem, & Pelchat, 1988), the Paced Auditory Serial Addition Task (PASAT; Gronwall, 1977), and the TEA-Working Memory subscale (Robertson et al., 1994) were used to measure updating of auditory information, the Corsi Block Test Backward (Kessels et al., 2000), and failure to maintain set during the WCST (indicative of difficulties with updating; Rao et al., 1987) were used to measure updating ability for visuospatial information.

On average, the largest differences were found on complex span tasks (3 outcome measures including OSPAN and Reading Span, g = .93), followed by the PASAT (4 outcome

measures; g = .88) and the Digit Span Backward (8 outcome measures; g = .45). The smallest differences were found on arithmetic tasks (5 outcome measures; g = .36), *n*-back (3 outcome measures; g = .33), and failures to maintain set on WCST (2 outcome measures; g = .25). Moreover, tests which primarily used auditory/verbal information showed larger differences (29 outcome measures; g = .55) than those using visuospatial stimuli (4 outcome measures; g = .34). As seen in Figure 7, random effects modeling confirmed a significant small to moderate difficulty in updating ability in fibromyalgia (g = .51; 95% CI: .33 to .69); and there was significant between-study heterogeneity in the standard mean difference (I^2 = 44.14%, p = .026).

Accessing—Six studies evaluated accessing, the purposeful retrieval of information from remote memory. Accessing was measured with tasks of verbal fluency, where participants name as many words as possible in a semantic category within a limited amount of time. These included the Animal Fluency Task (Morris et al., 1989) and Controlled Oral Word Association Test (COWAT)-FAS task (Benton & Hamsher, 1976).

On the FAS task, there was an average moderate difficulty (5 outcome measures; g = .53). On the Animal Fluency Task, participants with fibromyalgia had better performance compared to healthy controls (1 outcome measure; g = −.22), though this was non-significant (95% CI: −.65 to .20). As shown in Figure 8, the random-effects model showed a modest difference in accessing in fibromyalgia (g = .38, 95% CI: 0.03 to 0.73), though there was significant heterogeneity (I^2 = 62.88%, p = .019). After removing the Animal Fluency Task, the standard mean difference increased (g = .52, 95% CI: .25 to .78) and heterogeneity was no longer present (I^2 = 18.55%, p = .297). The sample using the Animal Fluency Task involved older adults with fibromyalgia, which may have led to increased heterogeneity in effect size.

Effects of Sample Age

To test the possibility that higher sample age may lead to greater group differences, standard mean differences were meta-regressed on sample age for all cognitive domains with at least ten or more studies. Sample age was significantly associated with differences in long-term memory (b = −.03, 95% CI: −.05 to −.002). No significant associations were seen for short-term memory (b = −.02, −.040 to .002, p = .071), inhibitory control (p = .767), updating (p = .662), or processing speed (p = .521). Approximately 70% of differences in long-term memory, and 57% of differences in short-term memory were accounted for by the fibromyalgia sample age. Overall, studies with higher sample ages showed smaller differences between the fibromyalgia and healthy control participants on measures of long-term memory (i.e., delayed recall/recognition).

Discussion

The current study found significantly worse performance on neuropsychological testing for those with fibromyalgia compared to healthy controls for all investigated domains, ranging from small to moderate magnitude. This supports the idea that FibroFog involves both self-reported and objective problems in cognition. Comparing effect sizes, the largest difference between fibromyalgia participants and healthy controls was for the domain of inhibitory

control (g = .61), which includes measures of selective attention and response inhibition. Effect sizes for processing speed, short-term and long-term memory, and updating were medium, ranging from .46 to .51. Small differences were found for set-shifting and accessing, ranging from .30 to .38. Greater problems with inhibitory control parallels research showing substantial overlap in neural networks of inhibition and pain perception, and are in line with the hypothesis that consumption of attentional resources for constant pain perception can impair activation of inhibitory systems in fibromyalgia (Glass et al., 2011). Findings also provide objective evidence for the self-reported difficulties of mental slowing, memory loss, information overload, and difficulties multitasking in those with fibromyalgia (Leavitt & Katz, 2011; Leavitt et al., 2002).

Our results showed some selective difficulties in subdomains of executive function and memory, as defined by Miyake et al. (2000) and Baddeley and Hitch. (1974). For example, there appeared to be more difficulties in inhibitory control and updating than in set shifting or accessing. In addition, memory differences were larger for short-term compared to long-term memory; and visuospatial memory differences were larger than verbal memory differences. While some cognitive domains appeared to show larger differences than others, the finding of statistically significant differences across all measured domains may argue for impairment in the central executive which would lead to memory problems and slower processing speed. Thus, incorporating measures tapping into overall executive control and attention may be worthwhile in clinical and research settings for this population (Unsworth, Schrock, & Engle, 2004).

We also found that greater sample age was associated with smaller differences between individuals with fibromyalgia and age-matched control participants on measures of long-term memory (and just beyond statistical significance on measures of short-term memory), contrary to the idea that differences would increase with sample age. One explanation is that normal cognitive aging may reduce the discrepancy between persons with fibromyalgia and healthy peers on measures of memory encoding and retrieval. However, there was generally a lack of older adults included in the samples from previous research, and all studies were cross-sectional, preventing true measurement of cognitive trajectories. This highlights the need for research looking at cognitive aging in fibromyalgia.

It is important to note that although pain has been hypothesized to cause cognitive disruption, it is also possible that cognitive difficulties may contribute to maintenance or exacerbation of pain difficulties in fibromyalgia. For example, the attentional disengagement theory purports that difficulties shifting between mental sets and inhibiting other mental sets leads to greater rumination on negative self-referent material (Koster, De Lissnyder, Derakshan, & De Raedt, 2011). Among persons with fibromyalgia, difficulties in set shifting and inhibitory control, highlighted in the current meta-analysis, may lead to intrusions of catastrophizing mental sets and greater rumination about pain. Among healthy adults, poor inhibition has been associated with lower tolerance of pain and greater attention to pain (Oosterman, Dijkerman, Kessels, & Scherder, 2010; Verhoeven et al., 2011), and poor set shifting is associated with more persistent pain (Attal et al., 2014). Therefore, difficulties may explain the lack of top-down pain modulation in fibromyalgia.

Findings from the current meta-analysis should be interpreted considering limitations. Primarily, the meta-analysis was unable to control for many possible confounds, including psychological disorders and medication use. A theoretical understanding of the impact of chronic pain on cognitive performance is limited without better understanding of depression and anxiety that is often found in these patient populations (Bair, Robinson, Katon, & Kroenke, 2003). In general, depression severity has been negatively related to cognitive performance, especially on measures of processing speed, executive function, and episodic memory (McDermott & Ebmeier, 2009), and this association has also been found for measures of memory performance in fibromyalgia (Suhr, 2003). Therefore, future research should control for depressive symptoms in statistical analyses or provide comparisons between subsamples with and without depression diagnosis, though several of the studies included in the current meta-analysis did this (Landro, Stiles, & Sletvold, 1997; Tesio et al., 2015; Walteros et al., 2011). Finally, medication use may lead to worse cognitive performance in fibromyalgia compared to participants in the healthy control groups. Current recommended treatments for fibromyalgia include antidepressant drugs and pregabalin as well as pain relief from various opioid therapies. Cognitive side effects are possible for these drugs (Zaccara, Gangemi, Perucca, & Specchio, 2011). To date, it is not clear how recommended drugs impact cognitive performance of these patients. In addition to unmeasured variables that may affect cognitive performance in those with fibromyalgia, methodological differences may have contributed to the heterogeneous effect sizes found for several cognitive domains. Foremost, many studies did not match controls on measures of estimated premorbid intelligence and three did not match on education. Matching control samples on these individual differences is important, as lower premorbid intelligence and lower years of education (i.e., lower cognitive reserve) may lead to overestimation of cognitive difficulties in fibromyalgia. Additionally, many studies recruited persons with fibromyalgia in a different manner than healthy control participants. Almost all the studies used physician referral or recruitment of fibromyalgia patients from healthcare clinics, while healthy control participants were recruited by community/campus advertisement, or through word-of-mouth. Though not tested in this study, differences in recruitment methods may lead to sample biases as persons recruited from clinical settings may differ from those recruited in communities (i.e., more health problems). Differences in cognition may also be affected by other control group characteristics. For example, most of the control groups volunteered without financial compensation, which may have led to a self-selection bias of participants who are internally motivated and show higher cognitive function due to greater cognitive effort. In addition, a few studies did not screen for issues of pain (not related to fibromyalgia), medication use, or history of psychiatric disorders in the control group. All included studies were cross-sectional and do not allow researchers to determine whether fibromyalgia leads to cognitive decline. Another limitation to be considered is that most study participants were middle-aged (range = 36.20 to 59.40), limiting the generalizability of findings to other age groups.

We also note statistical considerations. First, there were differences in the amount of included studies within each cognitive domain. For instance, seven studies measured set-shifting and seventeen studies measured inhibitory control. Unequal number of included studies should be considered when making comparisons across domains on between-study

heterogeneity as fewer included studies leads to less valid tests and non-significance should not be interpreted as homogeneity (Higgins, Thompson, Deeks, & Altman, 2003). Lastly, the large sample sizes accumulated from included studies could result in Type 1 error. For this reason, effect sizes rather than significance alone are important to consider.

Conclusion

The current meta-analysis strongly supports cognitive difficulty as a significant symptom cluster in fibromyalgia. A remaining question is whether we can improve cognitive difficulties in fibromyalgia. Improving pain and sleep, for example, may help reduce FibroFog (Suhr, 2003). There is also some evidence for more direct interventions to improve cognitive performance. For example, transcranial direct current stimulation has been found in some studies to improve processing speed, inhibition, memory, and accessing in fibromyalgia (Baudic et al., 2013; Curatolo et al., 2017). Cognitive-behavioral therapy may also lead to improved executive functions and alertness (Miró et al., 2011), possibly by rerouting attentional resources away from pain toward more adaptive behaviors (i.e., behavioral activation). Lastly, physical activity has been shown to improve short-term memory, updating, and accessing in those with fibromyalgia (Munguía-Izquierdo & Legaz-Arrese, 2007). Though more studies are needed to determine the clinical utility of neurocognitive interventions, symptoms of FibroFog could be modifiable. Helping physicians and patients see through FibroFog will continue to be a worthwhile endeavor with the potential for providing a better life for those living with this challenging condition.

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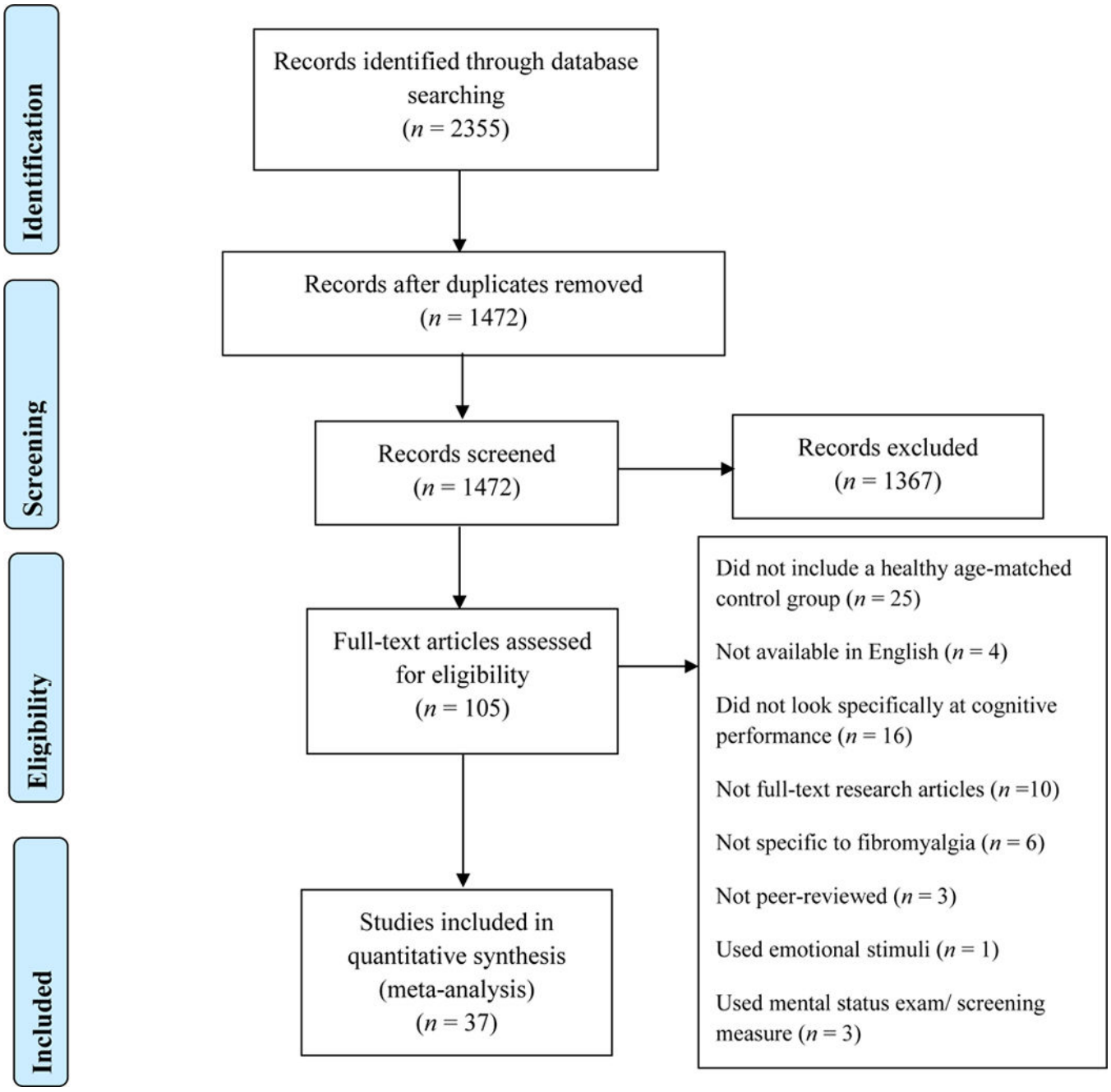

Figure 1.
PRISMA guided meta-analysis process.

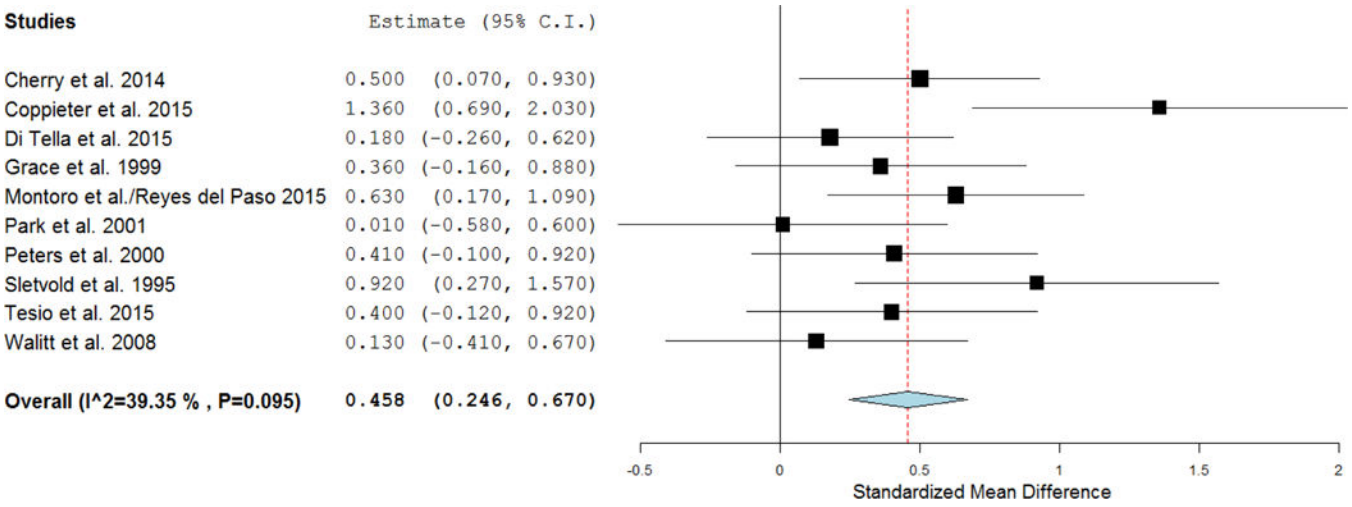

Figure 2.

Forest plot of the standard mean difference on measures of processing speed between people with fibromyalgia and healthy controls.

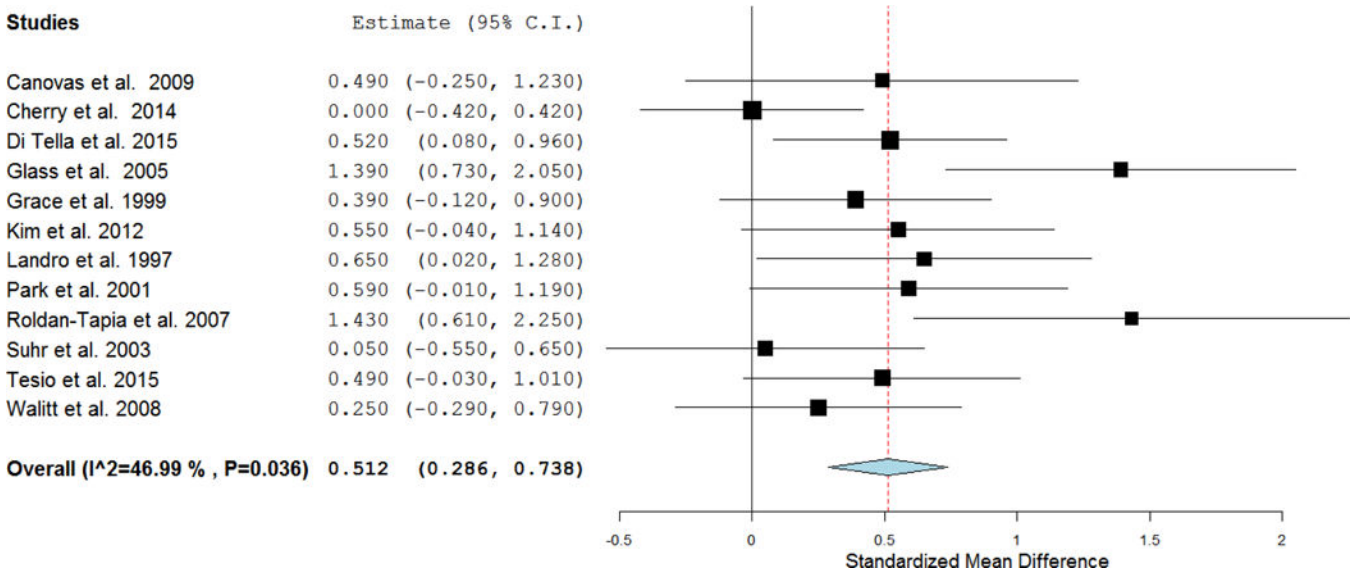

Figure 3.

Forest plot of the standard mean difference on measures of short-term memory between people with fibromyalgia and healthy controls.

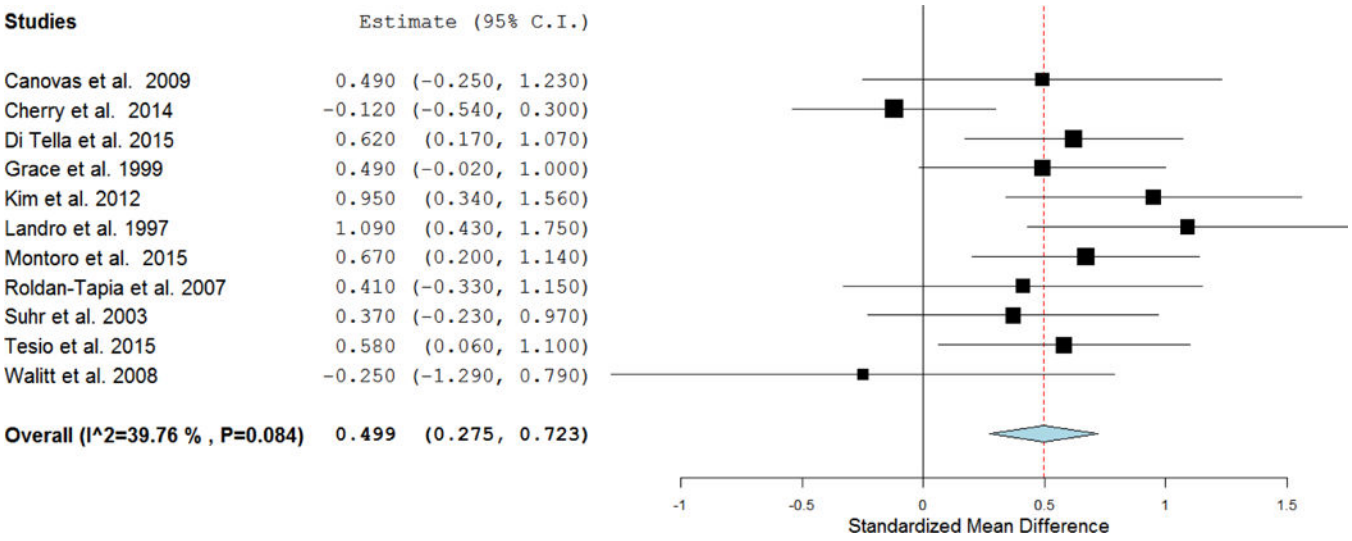

Figure 4.

Forest plot of the standard mean difference on measures of long-term memory between people with fibromyalgia and healthy controls.

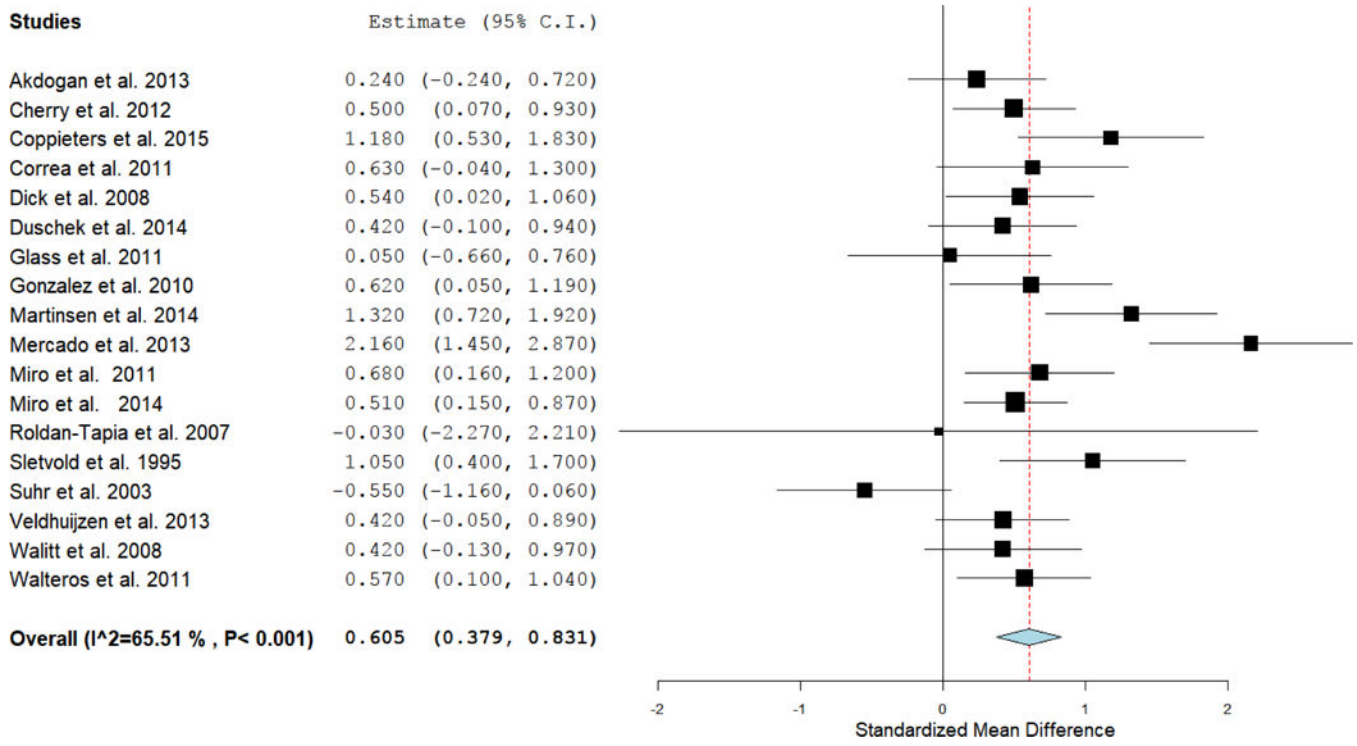

Figure 5.

Forest plot of the standard mean difference on measures of inhibitory control between people with fibromyalgia and healthy controls.

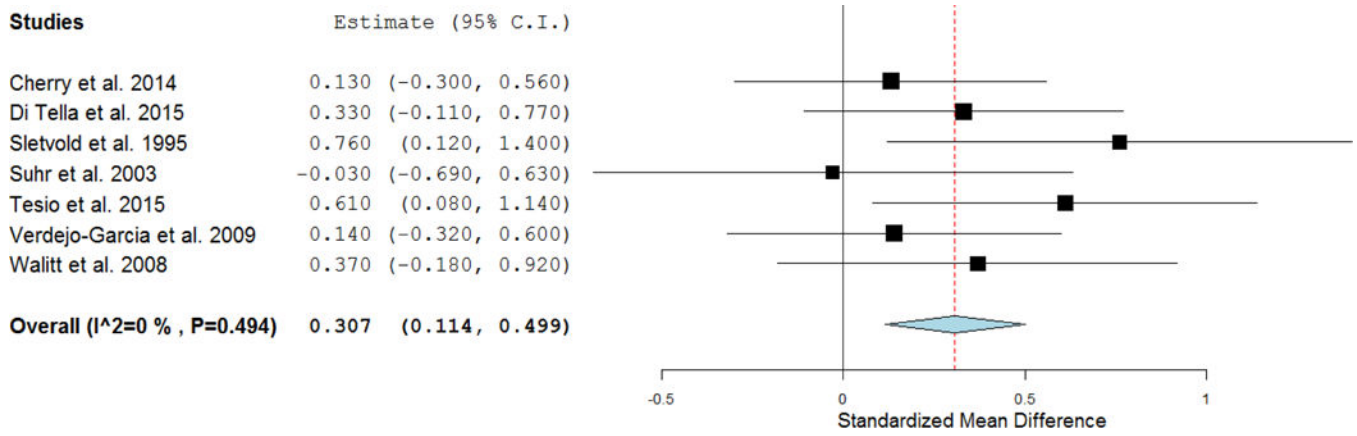

Figure 6.

Forest plot of the standard mean difference on measures of set shifting between people with fibromyalgia and healthy controls.

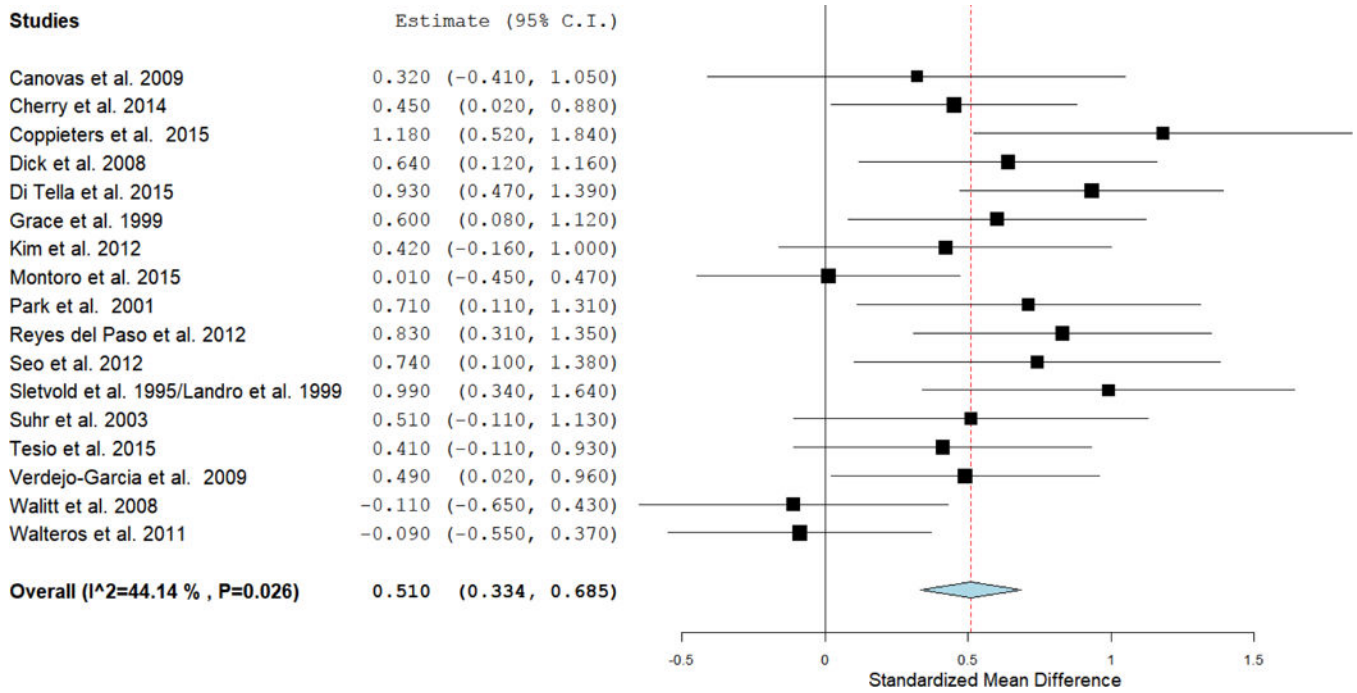

Figure 7.

Forest plot of the standard mean difference on measures of updating between people with fibromyalgia and healthy controls.

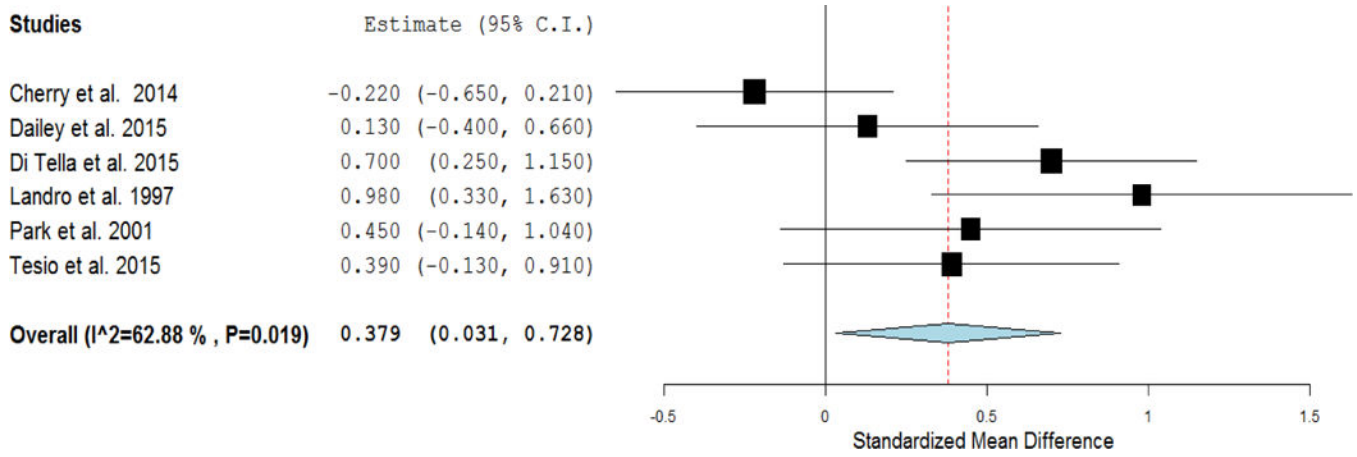

Figure 8.

Forest plot of the standard mean difference on measures of accessing between people with fibromyalgia and healthy controls.

Table 1:

Description of Studies Included (k = 37) and Cognitive Domains Assessed

Authors (Year)	Fibromyalgia Group				Healthy Control Group				Cognitive Domains Assessed						
	n	M_{age}	SD_{age}	F/M	*n*	M_{age}	SD_{age}	F/M	PS	LTM	STM	IC	SS	UP	A
Akdoğan et al. (2013)	40	36.2	7.3	40/0	30	33.7	8	30/0				X			
Cánovas et al. (2009)	15	53.33	6.29	15/0	15	53.67	6.71	15/0		X	X			X	
Cherry et al. (2014)	43	63	7.2	43/0	44	64.8	7.3	44/0	X	X	X	X	X	X	X
Coppieters et al. (2015)	21	44.52	9.47	16/5	22	38	13.9	14/8	X			X		X	
Correa et al. (2011)	18	48	6.5	18/0	19	42	8.9	19/0				X			
Dailey et al. (2015)	24	52.41	2.28	23/1	33	45.09	2.5	32/1							X
Di Tella et al. (2015)	40	51.75	7.76	40/0	41	51.83	7.78	41/0	X	X	X		X	X	X
Dick et al. (2008)	30	49.6	12.54	30/0	30	46.56	10	30/0				X		X	
Duschek, et al. (2013)	18	59.4	11.7	18/0	24	57.3	8.9	24/0							
Duschek, et al. (2014)	27	52.7	9.2	27/0	34	53.9	8.4	34/0				X			
Glass et al. (2005)	23	47.83	NR	23/0	23	47.83	NR	23/0			X				
Glass et al. (2011)	18	43.6	9.79	18/0	14	41.13	11.91	14/0				X			
González et al. (2010)	25	50.56	8.66	25/0	25	48.04	7.55	25/0				X			
Grace et al. (1999)	30	45.87	9.79	29/1	30	44.73	9.35	29/1	X	X	X			X	
Grisart, et al. (2002)	16	44.8	5.5	12/4	20	39.4	7.8	10/10							
Harker et al. (2011)	16	47.56	12.77	16/0	16	47.44	13.49	16/0							
Kim et al. (2012)	23	37.4	7.1	23/0	24	37.4	8.3	24/0		X	X			X	
Landrø et al. (1997)†	25	46.4	10.4	25/0	18	40.1	9.6	14/4		X	X	X		X	X
Martinsen et al. (2014)	23	49.8	25–64	23/0	32	46.3	20–63	32/0				X			
Mercado et al. (2013)	25	47.8	8.24	25/0	25	48	7.48	25/0				X			
Miró et al. (2011)	33	46.56	7.72	33/0	28	42.9	7.38	28/0				X			
Miró et al. (2014)	77	45.88	7.06	58/19	48	44.73	8.96	21/27				X			
Montoro et al. (2015)†	45	49.48	8.23	45/0	32	47.03	9.26	32/0	X	X				X	
Park et al. (2001)	22	47.83	NR	23/0	23	47.83	NR	23/0	X		X			X	X
Peters et al. (2000)	30	47.1	24–60	30/0	30	46.9	23–58	30/0	X						
Reyes del Paso, et al. (2015)†	46	49.48	8.23	46/0	32	47.03	9.26	32/0	X						

Authors (Year)	Fibromyalgia Group				Healthy Control Group				Cognitive Domains Assessed						
	n	M_{age}	SD_{age}	F/M	*n*	M_{age}	SD_{age}	F/M	PS	LTM	STM	IC	SS	UP	A
Reyes Del Paso, et al. (2012)	35	50.5	6.7	32/3	29	49.4	9.4	27/2						X	
Roldán-Tapia (2007)	15	48.5	7.49	15/0	15	44.33	5.99	15/0		X	X	X			
Seo et al. (2012)	19	38.73	7.65	19/0	22	38.27	8.48	22/0						X	
Shmygalev et al. (2014)	43	55	9	43/0	138	55	10	139/0							
Sletvold et al. (1995)†	25	46.4	10.4	25/0	18	40.1	9.6	18/0	X			X	X	X	
Suhr (2003)	23	48.1	10.9	21/2	21	45.9	12.7	17/4		X	X	X	X	X	
Tesio et al. (2015)	30	52.8	9.6	30/0	30	53.8	12.4	30/0	X	X	X		X	X	X
Veldhuijzen et al. (2012)	35	30.4	8.6	35/0	35	29.3	9.2	35/0				X			
Verdejo-García et al. (2009)	36	45.86	6.78	36/0	36	44.97	6.7	36/0					X	X	
Walitt et al. (2008)	27	45.2	NR	27/0	27	45.2	NR	27/0	X	X	X	X	X	X	
Walteros et al. (2011)	15	50.4	4.6	15/0	15	49	6.7	15/0				X		X	

Note. A = accessing; F = females; IC = inhibitory control; LTM = long-term memory; M = males; NR = not reported; PS = processing speed; SS = set shifting; STM = short-term memory; UP = updating. Range is included in places where *SD* was not reported.

†Part of the same study.

Table 2 :

Standard Mean Differences for Cognitive Domains between Persons with Fibromyalgia and without Fibromyalgia

Domain	Estimate (*g*)	95% LL	95% UL	I^2(%)	p^*
Processing Speed	.46	.25	.67	39.08	.097
Memory Storage					
Short-term Memory	.51	.29	.74	46.99	.036
Long-term Memory	.50	.28	.72	39.76	.084
Executive Functions					
Inhibitory control	.61	.38	.83	65.66	<.001
Set Shifting	.30	.11	.49	0.0	.490
Updating	.51	.33	.69	44.14	.026
Accessing	.38	.03	.73	62.88	.019

Note. LL = lower limit for 95% confidence interval; UL = upper limit for 95% confidence interval.

$^*p$-value for I^2.