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REVIEW

Inhibitory Control Deficits in Individuals with Amnestic Mild Cognitive Impairment: a Meta-Analysis

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Abstract

Amnestic mild cognitive impairment (aMCI) is a prodromal stage of Alzheimer's disease that is characterized by impairments in episodic memory. Recent evidence has shown that inhibitory control is also impaired in aMCI. The aim of the present meta-analysis was to quantify inhibitory control ability in individuals with aMCI by examining performance across a range of well-defined inhibition paradigms that tapped into one of three inhibitory control subtypes (i) interference control (e.g., Stroop task), (ii) response inhibition (e.g., Go/Nogo task), or (iii) inhibition of cognitive sets (Wisconsin Card Sort Task). Reference databases (PsychINFO, PubMed, and Web of Science) were searched for studies comparing individuals with aMCI to healthy controls on behavioural measures of inhibition. Across 70 effect sizes involving 2184 adults with aMCI and 3049 controls, overall inhibition deficits of moderate magnitude ($g = -0.73$) were found among individuals with aMCI. Inhibition deficits were moderate in size regardless of inhibitory control subtype: interference control ($g = -0.74$), response inhibition ($g = -0.71$), inhibition of cognitive sets ($g = -0.76$). Subgroup analyses revealed that Stroop outcome measure (reaction time vs. accuracy) and recruitment source (clinical vs. community) moderated interference control deficits. Together these findings support a generalized inhibition deficit in aMCI, and suggest that inhibition tasks should be included routinely in neuropsychological test batteries to provide a more comprehensive overview of executive dysfunction in aMCI.

Keywords Mild cognitive impairment · Inhibitory control · Interference control · Response inhibition · Cognitive tests · Neuropsychology · Meta-analysis

Introduction

The goal of this meta-analysis was to examine the presence, pattern, and magnitude of inhibitory control deficits in the amnestic subtype of mild cognitive impairment (MCI). MCI is characterized by a decline in cognitive abilities greater than expected for an individual's age, intelligence, and education level that does not significantly interfere with activities of daily living (Petersen et al., 2001). Individuals with MCI can be grouped into four subtypes (see Table 1) based on the presence or absence of episodic memory impairment (amnestic and non-amnestic subtypes respectively) and number of cognitive domains affected (single-domain affected and multiple-domains affected: Petersen, 2004). Due to variability in the way research involving individuals with MCI has been reported, for the purposes of the present meta-analyses the term MCI will refer to a mix of individuals with amnestic MCI (aMCI) and non-amnestic MCI (naMCI) and the term aMCI will refer to a mix of individuals with single-domain aMCI (sd-aMCI) and multiple-domain aMCI (md-aMCI).

Prior research has shown that the aMCI subtypes are more likely to progress to Alzheimer's disease (AD) than the naMCI subtypes, with md-aMCI considered to reflect a more severe form of aMCI than sd-aMCI (Petersen & Negash,

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Table 1 Classifying Subtypes of MCI According to the Type and Number of Cognitive Impairments

		Type of Impairment:	
		Memory impairment	Non-memory impairment
Number of impairments:	1 impairment	**amnestic MCI single domain (sd-aMCI)**	non-amnestic MCI single domain (sd-naMCI)
	2 or more impairments	**amnestic MCI multiple domains (md-aMCI)**	non-amnestic MCI multiple domains (md-naMCI)

All four subtypes of mild cognitive impairment (MCI), namely, amnestic and non-amnestic presentations of MCI fall under the umbrella of MCI. Only the amnestic subtypes (bolded) were of interest in the current meta-analyses, namely, single domain (sd-aMCI) or multiple domain (md-aMCI)

2008; Tabert et al., 2006). Among individuals with md-aMCI, in addition to memory, executive functioning tends to be the most commonly impaired cognitive domain (Duchek et al., 2009; Hutchison, Balota, & Ducheck, 2010; Johns et al., 2012). Executive function encompasses top-down cognitive processes that help us regulate, control, and manage our thoughts and actions. These processes include working memory, inhibitory control, cognitive flexibility, planning, reasoning, and problem-solving (Diamond, 2013). Studies have shown that, even among individuals diagnosed with sd-aMCI, impairments in executive function may be present (Crowell, Luis, Vanderploeg, Schinka, & Mullan, 2002; Kramer et al., 2006; Royall, Chiodo, & Polk, 2004). In a study by Johns et al. (2012), inhibitory control was the most frequently impaired executive domain in aMCI, regardless of whether the study physician diagnosed them initially with sd-aMCI or md-aMCI. These findings may be explained by the fact that many inhibition tests are not standardized tests used for diagnostic purposes (e.g., Flanker task, Stop-Signal task, Go/Nogo task), so an individual with sd-MCI might have undetected inhibition impairments. Inhibitory dysfunction may contribute to or exacerbate memory deficits in people with aMCI. For example, being less able to inhibit information that is no longer relevant would lead to intrusions from prior memory lists. We discuss the link between inhibitory control and episodic memory in more detail in the Discussion, but in light of the evidence from Johns et al., the present meta-analyses focused on examining inhibitory control performance in aMCI. The results of this meta-analysis will shed light on the presence of inhibition deficits in the subgroup of individuals most at risk of progressing to AD.

Inhibitory Control in Amnestic Mild Cognitive Impairment

Of the studies discussed reporting executive function impairments in aMCI, inhibitory control is a domain that is frequently impaired (Traykov et al., 2007; Brandt et al., 2009; Johns et al., 2012). Inhibitory control is defined as the ability to suppress irrelevant information and restrain activation of inappropriate prepotent responses (Zacks & Hasher, 1994). While studied less frequently in aMCI, inhibition deficits have been identified as one of the most noticeable impairments in AD (Amieva et al., 1998; Amieva et al., 2004; Belleville et al., 2006a). Therefore, it is possible that inhibition deficits may develop early during the preclinical stages of the disease (i.e., aMCI). Further evidence for this hypothesis comes from a functional magnetic resonance imaging study by Van Dam et al. (2013), who showed decreased activation of the anterior cingulate cortex, a brain region that plays a key role in inhibitory control, in individuals with aMCI compared to age-matched healthy controls.

Inhibitory control is considered a multifaceted construct comprising several similar yet distinct processes (Nigg, 2000; Friedman & Miyake, 2004; Dillon & Pizzagalli, 2007). It is commonly divided into interference control and prepotent response inhibition. Some add a third component of inhibition termed inhibition of cognitive sets (Dillon & Pizzagalli, 2007). Interference control refers to the ability to filter out competing information which is present in the target or the environment but irrelevant to the task being performed. The Flanker task (Eriksen & Eriksen, 1974), Simon task (Simon & Wolf, 1963), and Stroop task (Stroop, 1935) are the most commonly used tasks to assess interference control. Typically in these tasks, individuals must inhibit irrelevant information (i.e., incongruent condition) while responding as quickly as possible. The main dependent measure is accuracy or speed in the incongruent condition relative to the congruent condition (i.e., control condition). Prepotent response inhibition refers to the ability to suppress an automatic or dominant response (Casey, Durston, & Fossella, 2001; Nigg, 2000). The Go/Nogo task (Mesulam, 1985), Stop-Signal task (Logan & Cowan, 1984), Continuous Performance test (Rosvold, Mirsky, Sarason, Bransome Jr, & Beck, 1956), Sustained Attention to Response task (Robertson et al., 1997), and Hayling task (Burgess & Shallice, 1997) are common measures of prepotent response inhibition. In these tasks, participants must respond as quickly as possible while suppressing the tendency to execute a prepotent behavioural response. The main dependent measures are the time take by the participant to inhibit the response and the percentage of incorrect responses (i.e., commission errors). Inhibition of cognitive sets refers to the ability to inhibit a previously relevant mental set. Such inhibitory abilities are commonly assessed in set-shifting

paradigms such as the Wisconsin Card Sorting Test (Berg, 1948). In this test, participants are asked to match test cards to reference cards according to the colour, shape, or number of stimuli on the cards. No instructions for how to match the cards are provided but feedback is given after each match, enabling the participant to acquire the correct classification rule. While the Wisconsin Card Sort Test is most widely used to evaluate cognitive flexibility (i.e., set-shifting), successful performance on this task also depends on the ability to inhibit previously relevant rules, and for this reason inhibition of cognitive sets can be assessed by measuring perseverative errors (i.e., incorrectly responding based on the category used before the rule change).

To date, individual studies have shown that adults with aMCI encounter problems in interference control (e.g., Wylie, Ridderinkhof, Eckerle, & Manning, 2007; Bélanger, Belleville, & Gauthier, 2010; Wang et al., 2013; Borsa et al., 2018), prepotent response inhibition (e.g., Johns et al., 2012; Cid-Fernández, Lindín, & Díaz, 2014; Lopez Zunini et al., 2016), and inhibition of cognitive sets (Nagahama et al., 2003; Traykov et al., 2007; Chen et al., 2009; Ryan et al., 2012). Only one study to our knowledge found no difference between individuals with aMCI and healthy controls in tasks assessing interference control and response inhibition (Zhang, Han, Verhaeghen, & Nilsson, 2007). Zheng et al. (2012) found that aMCI participants were impaired relative to age-matched controls on one measure of response inhibition (stop-signal task) but not on another (Stroop task). These findings raise the question of whether methodological differences, for example, the use of different tasks or assessing different outcome measures,B may partly explain the mixed results regarding inhibition deficits in aMCI.

Purpose of the Current Meta-Analyses

The purpose of the present meta-analyses was to investigate the extent to which the inhibitory control sub-domain of executive function, as a whole, as well as its components (interference control, response inhibition, and inhibition of cognitive sets), are affected in individuals with aMCI relative to healthy controls. We chose to focus on the inhibitory control sub-domain of executive function for two key reasons. First, the working memory sub-domain of executive function involves memory processes which are quite different from the attentional processes involved in inhibitory control. In fact, in order to ensure that the studies included in our meta-analyses were process-pure indictors of attentional inhibition, we controlled for speed of processing and excluded any studies that included paradigms that confounded inhibition and memory processes. For example, the Negative Priming paradigm was excluded from the present meta-analyses because the task involves both inhibition and episodic binding and retrieval processes (Neill, Valdes, Terry, & Gorfein, 1992). Likewise, tasks involving proactive semantic interference were excluded because vulnerability to proactive interference effects may reflect impairments at the interface between memory function and inhibitory control (Loewenstein, Acevedo, Agron, & Duara, 2007). Second, relative to other executive functions like working memory, comparatively little is known about inhibitory deficits in aMCI. Substantial evidence for working memory deficits in aMCI have been demonstrated in both systematic reviews (Huntley & Howard, 2010; Kirova, Bays, & Lagalwar, 2015) and empirical research (Emrani et al., 2018; Gagnon & Belleville, 2011; Huntley & Howard, 2010; Migo et al., 2015).

There has been no attempt to consolidate the results from this literature, despite evidence of a core inhibitory deficit in aMCI. Past meta-analytic studies have broadly examined executive functioning in individuals with MCI (Bäckman, Jones, Berger, Laukka, & Small, 2005) and executive functioning as a predictor of progression from MCI to AD (Belleville, Fouquet, Hudon, Zomahoun, & Croteau, 2017). However, such reviews focus on executive functioning in a broad sense, highlighting the need for a more focused review of inhibitory control abilities in aMCI.

The aim of this meta-analytic study was to identify the presence, pattern, and magnitude of inhibitory control deficits in aMCI. We conducted a series of meta-analyses, which included classic tasks known to measure the three core components of inhibitory control (i) *interference control* was assessed with the Stroop, Flanker, and Simon tasks, (ii) *prepotent response inhibition* was assessed with the Go/Nogo, Stop-Signal (SST), Continuous Performance Test, Sustained Attention to Response Task and Hayling tasks, and (iii) *inhibition of cognitive sets* was measured with the Wisconsin Card Sorting test.

Methods

The search process and meta-analyses performed complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Liberati et al., 2009). See Table S1 for a PRISMA checklist. The research protocol for this meta-analysis was not registered prior to conducting the review, but it was predetermined, and PICOS (Participants, Interventions/Action of Interest, Control Outcomes, and Study Design) statements were used to identify the studies to be included in the meta-analyses.

Eligibility Criteria

Criteria for including or excluding articles were determined a priori. To be eligible for inclusion, studies had to a) be written in English, b) published in a peer-reviewed journal, c) classified participants as having aMCI based on

established criteria (i.e., Petersen et al., 1999; Winblad et al., 2004; Albert et al., 2011), d) include a healthy older adult control group, e) report sufficient statistical information in order to allow for calculation of effect sizes, f) include at least one test of inhibitory function (Stroop, Flanker, Simon, Go/Nogo, Stop-signal, Continuous Performance Test, Sustained Attention to Response Task, Hayling, WCST), and g) clearly specify the outcome measure (e.g., reaction time, accuracy, error rate, etc.). Given that measurement of reaction time is a sensitive measure, we wanted to ensure that our data came from a peer-reviewed source that met widely accepted methodological standards. For this reason, we excluded grey literature from our search. An additional moderator analysis looking at study focus was included to examine the likelihood of publication bias. Studies were specifically excluded a) if there was no definition of the criteria used for the diagnosis of MCI, b) if the MCI group was solely composed of individuals with na-MCI, c) if the MCI group was composed of individuals with neurodegenerative disorders other than preclinical AD (e.g., Parkinson's disease, MCI due to subcortical vascular disease, cerebral small vessel disease, or cerebrovascular disease), or depressive symptomatology, and d) if there were insufficient methodological details to derive the necessary statistics and the study authors did not reply to a request for these data.

Information Sources and Search

No publication date restriction was imposed. Studies on MCI that included inhibitory control data were identified by searching PsychINFO, PubMed, and Web of Science electronic databases. The last search was carried out on May 30th, 2019. Additionally, the reference sections from identified articles were examined for potentially eligible studies missed by the electronic searches. The full electronic search strategy was similar across databases (see Table S2 (*Supplementary material)* for an example of a search strategy). The primary search parameters included terms representative of the MCI diagnostic category (i.e., 'mild cognitive impairment', 'MCI', 'preclinical Alzheimer's disease', 'very mild dementia of the Alzheimer's type', 'memory impairment', prodromal Alzheimer disease', 'cognitive impairment', 'cognitive decline'), combined with keywords focusing on inhibitory control (i.e., 'inhibitory control', 'inhibition', 'response inhibition', 'interference'), as well as keywords associated with common inhibitory paradigms (i.e., 'Stroop', 'color-word interference' 'flanker', 'Simon', 'go/nogo or nogo', 'stop-signal', 'continuous performance test' or 'CPT', 'sustained attention to response task', 'SART', 'Hayling', 'Wisconsin card sort' or 'WCST'). The first author (RR) performed the search and the search terms were confirmed after discussion with two other authors (BPV and NDA).

Study Screening & Selection

The process by which studies were identified, screened, and considered for eligibility is outlined in Fig. 1. Following the literature search, two authors (RR & BPV) screened potential studies following the search criteria described above. The screening process was done independently with periodic confirmation of the eligibility criteria. In cases where eligibility for inclusion was unclear, the final decision on inclusion was reached through consensus and through consultation with a third author (NDA).

Data Collection Process and Data Items

Data extraction was independently performed by the first and second author (RR & BPV). The authors regularly discussed the data retrieval process to ensure consistency. Additionally, a standardized form was used to record extracted information concerning authors, sample characteristics, demographic information, inclusion and exclusion criteria, outcome variables, and analytic strategy. Table S3 (*Supplementary material*) lists the type of information collected for all of the studies included in the meta-analyses.

Risk of Bias in Individual Studies

The risk of bias in individual studies and quality of each study was assessed by author RR using the Quality Assessment Tool for Quantitative Studies (National Collaborating Centre for Methods and Tools, 2008). The key areas of assessment included selection bias, study design, confounding variables, blinding, data collection method, and withdrawal and dropouts. Based on the criteria used, most studies had a relatively low risk of bias. Furthermore, the studies were relatively homogenous in their methodological approach and relied on well-recognized clinical criteria to identify their aMCI sample. Additionally, it should be noted that studies for which the inhibition measure was not the primary focus of the paper sometimes used this inhibition measure for diagnostic purposes. The risk of bias may have been elevated in these studies as there is no independence between clinical diagnosis and the inhibition measures examined. To address this potential risk of bias, we included study focus in our categorical moderator analyses.

Data Extraction

Data (mean, standard deviation) were sometimes combined from two groups, using the formula from the Cochrane handbook (Higgins & Green, 2011). Data were combined when a paper separately displayed inhibition data for individuals with sd-aMCI and md-aMCI. Although it would be interesting to examine inhibition performance in different subtypes of aMCI, only a

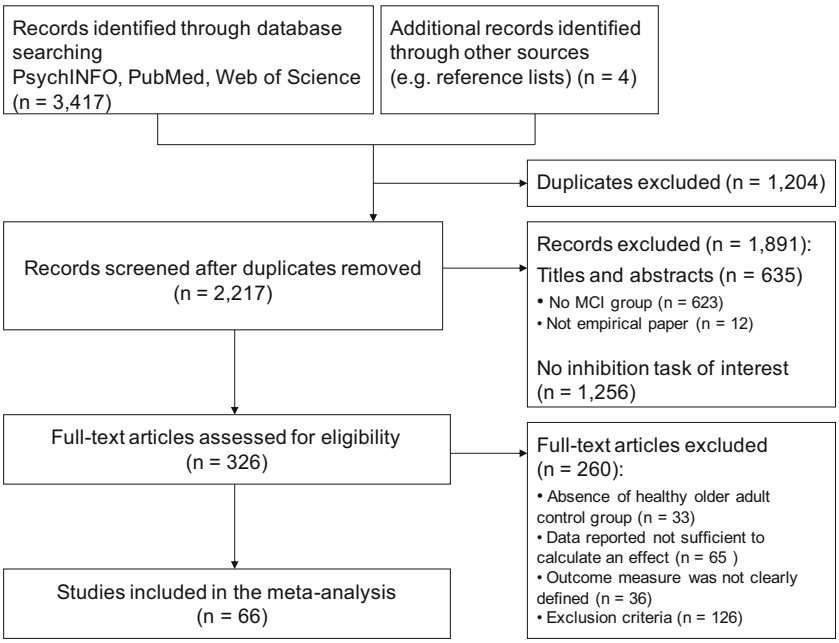

Fig. 1 The process of study selection and search results

limited number of studies displayed data by aMCI subtype, preventing us from exploring this relationship further. Studies that grouped inhibition data based on whether or not individuals later converted to AD (i.e., converter and non-converters) also were combined. Finally, studies that grouped inhibition data based on whether individuals with aMCI were ApoE-4 carriers or non-carriers were combined. Once again, although the main focus of these meta-analyses was on aMCI, six studies combined data from individuals with aMCI and naMCI (Apostolova et al., 2012; Clark et al., 2016; De Looze et al., 2018; Pa et al., 2010; Stricker et al., 2013; & Zihl et al. 2010). In five of these six studies, 60 % or more of the MCI sample were amnestic. In the Stricker et al. (2013) study, 44% of the MCI sample was amnestic. Additionally, two studies in the current meta-analysis did not clearly specify whether people with naMCI were included in the MCI group (i.e., Fernández et al. 2011; Mirandez, Aprahamian, Talib, Forlenza, & Radanovic, 2017). Fernández et al. (2011) cited Petersen et al. (2001) criteria and Mirandez, Aprahamian, Talib, Forlenza, and Radanovic (2017) cited Petersen (2011) criteria. Both of these papers by Petersen make reference to the different subtypes of MCI, making it challenging to determine whether individuals with naMCI were included in the studies. Additional analyses excluding these studies were conducted to ensure that effect sizes were not influenced by the naMCI data (see results section). In the case of intervention studies which reported inhibition performance pre- and post-intervention, we only included pre-intervention inhibition performance. With respect to the three subtypes of inhibition (i.e., interference control, response inhibition, and inhibition of cognitive sets), there were two approaches when a paper included multiple inhibition tasks. In one case, the authors examined Flanker performance in aMCI (main focus of the paper) and Stroop performance was part of the neuropsychological battery (Wylie, Ridderinkhof, Eckerle, & Manning, 2007). In this case, the meta-analysis was run twice, once including data only from the task which was the major focus of the study and a second time averaging data from both tasks. In other studies, tasks indexing different inhibition subtypes were reported. In these cases, the effect sizes of individual tasks were included. For a list of studies assigned to each of the data extraction scenarios described above, see supplementary materials Table S4. Data extraction decisions for a handful of more ambiguous studies are provided in supplementary materials Table S5. These were studies where decisions needed to be made regarding task conditions to include, as well as MCI groups to include in difference score calculations.

Outcome Measures

Interference control tasks included the Stroop task, Flanker task, and Simon task. For these three tasks, the inhibition measure is the difference score between a basic processing condition and an inhibition condition. The Stroop task requires individuals to inhibit the automatic tendency to read a word name, and instead name the incongruent ink colour in which the word is written. In the Stroop task, the relevant measure of inhibition is the difference score between colour naming and interference-word naming (i.e., colour words are printed in an incongruent ink colour). When Stroop colour naming data were not available in a study, word reading was used as an alternative control condition (Pa et al., 2010). Since colour naming is most often slower than word reading, analyses were conducted to confirm that Stroop control condition did not influence effect sizes. Performance in the Stroop task can be measured in three different forms, including a)

accuracy - number of items stated correctly, b) total time on task (in s), and c) mean reaction time per trial (in ms). When accuracy was the outcome measure, the Stroop difference score was calculated as *colour naming score – colour-word interference score*. When reaction time was the outcome measure (either total time or time per item), the Stroop difference score was calculated as *colour-word interference RT – color naming or word reading RT*. A larger Stroop difference score represents greater interference from conflicting response sets, or poorer inhibitory control. When the Stroop difference scores were not reported in a study, we calculated them from the means and SDs in separate task conditions that were reported. The standard deviation of the interference score was calculated with the following equation (e.g., Lansbergen, Kenemans, & Van Engeland, 2007; Dimoska-Di Marco, McDonald, Kelly, Tate, & Johnstone, 2011):

$$SD\text{int} = \sqrt{2 \times \left\{ \frac{\left[(SD_{\text{con}})^2 + (SD_{\text{inc}})^2 \right]}{2} \right\} \times (1-r)}$$

In this equation, SD_{con} is the pooled standard deviation across the aMCI group and the control group for the control-condition score, SD_{inc} is the pooled standard deviation across the aMCI group and the control group for the incongruent-condition score (i.e., color-word interference), and r is the Pearson coefficient of correlation between performance in the control condition and performance in the incongruent condition as derived from a data set of 34 healthy older adult individuals (Rabi & Minda, 2016). For the Stroop task this correlation was set to .86. This correlation is in line with prior work in younger adults ($r = .95$; Kenemans, Wieleman, Zeegers, & Verbaten, 1999). With the exception of three studies, all Stroop data included in the current meta-analysis either reported the Stroop difference score or provided sufficient data allowing us to calculate the difference score ourselves. Johns et al. (2012) computed a Stroop Interference time ratio score (i.e., colour-word interference divided by colour naming) and Lopez et al. (2006) and Sinai et al. (2010) both computed an interference time relative score (i.e., [colour-word interference - colour naming] divided by colour naming). Given that all of three of these studies accounted for individual differences in basic reading speed, we included their data in our meta-analysis. Of note for the Bélanger, Belleville, and Gauthier (2010) study, the authors included three conditions (i) *0% Congruency condition* (i.e., 100% incongruent trials), (ii) *75% Congruency condition* (i.e., 25% incongruent trials) and (iii) a control colour naming condition. We computed the Stroop difference score by the following formula: 0% Congruency condition RT – colour naming condition RT.

In the Flanker and Simon task, participants must inhibit interfering information (e.g., surrounding arrows; spatial location of stimuli). The interference difference score corresponds to the difference in RT between congruent and incongruent trials. For the Flanker task, congruent trials refer to flankers that are associated with the same response as the target and incongruent trials refer to flankers that are associated with a competing response. For the Simon task, congruent trials refer to trials in which the location of the stimulus corresponds with the location of the response and incongruent trials refer to trials in which the location of the stimulus and response do not correspond. For both the Flanker and Simon tasks, the standard deviation of the difference score was computed using the formula described above. For the Flanker task the correlation in the formula was set to .96 and for the Simon task the correlation was set to .92. These correlations were based on data collected by Rabi and Minda (2016) with healthy older adults.

Response inhibition tasks include the Go/Nogo, Continuous Performance Test, Sustained Attention to Response Task, Stop-signal, and Hayling tasks. In the Go/Nogo, Continuous Performance Test and Sustained Attention to Response Task tasks, stimuli are presented one at a time and participants must respond to certain stimuli while withholding responses to other stimuli. The outcome measure for the Go/Nogo, Continuous Performance Test, and Sustained Attention to Response Task were commission errors (i.e., making a 'go' response to 'nogo' stimuli). When Nogo accuracy was reported instead of commission errors, the formula *1 - Nogo accuracy* was used to convert accuracy to errors. For two Go/Nogo studies, only Go/Nogo accuracy was reported (Ahn et al., 2011; Dwolatzky et al., 2003). In this case, the formula *1 – Go/Nogo accuracy* was used to compute Go/Nogo errors. Because the number of commission errors was not specified in these two studies, the Go/Nogo error score calculated may have consisted of both commission and omission errors. In the Stop-signal task, participants must respond to a go signal as quickly as possible. However, shortly following the presentation of the go-signal participants occasionally receive a stop signal that requires them to stop the go response. The outcome measure used was the stop-signal reaction time, which is an estimate of the time required to stop the response upon presentation of the stop signal (i.e., the latency of the inhibition process). In the Hayling Sentence Completion Test, participants complete two conditions. In condition 1 (*initiation*), participants must produce a word that best completes each sentence. In condition 2 (*inhibition*), participants must complete the sentences using a contextually unconnected word. The second condition requires inhibition of the automatic semantically activated response. When RT data were available for both conditions (Bastin et al., 2013; Bélanger & Belleville, 2009), a difference score was computed by subtracting condition 1 RT from condition 2 RT. The

time difference between response latencies in the two conditions reflects the time needed to inhibit the automatic response and to retrieve a contextually unconnected word (Burgess & Shallice, 1996). Inhibition of cognitive sets was assessed by the Wisconsin Card Sorting Test, where the outcome measure was perseveration errors.

In summary, based on all of the inhibition tasks discussed involving difference scores (i.e., Stroop, Flanker, Simon, Hayling) a larger inhibition difference score refers to poorer inhibitory control. Likewise, a larger number of commission errors, a higher stop-signal reaction time, and more perseveration errors indicate weaker inhibitory abilities.

Data Analysis

All analyses were performed using a random effects model in Comprehensive Meta-Analysis (CMA) version 3 (Biostat, Englewood, New Jersey). The primary outcome was Hedges' g, the standardized mean difference in inhibition performance between individuals with aMCI and healthy control groups. Four separate random effect model meta-analyses were conducted: one overall inhibitory control meta-analysis collapsed across subtype and one meta-analysis for each of the inhibitory control subtypes (interference control, response inhibition, and inhibition of cognitive sets). Hedges' g was used to calculate effect sizes because it corrects for small sample sizes (Lipsey & Wilson, 2001). The effect size was a negative value if the aMCI group performed more poorly than the healthy control group and a positive value if the aMCI group performed better than the control group. The magnitude of Hedges' g coefficient is equivalent to Cohen's d effect sizes, where 0.2, 0.5, and 0.8 are considered small, medium and large effect sizes, respectively. A significance level of $p < .05$ was used for all analyses, including main effects, sub-group analyses, meta-regression, and publication bias.

Heterogeneity was assessed with the Q statistic and corresponding p value. Given that random effects models were used in the current meta-analyses, the Tau^2 statistic was calculated to determine the extent of true variation among the effects observed in different studies (Borenstein, Hedges, Higgins, & Rothstein, 2011; Higgins & Green, 2011). Additionally, we reported the I^2 statistic as a measure of relative heterogeneity. I^2 is an index of the proportion of the variance across studies that is due to true heterogeneity across populations (i.e., not an absolute measure of the heterogeneity of effect size; Borenstein, Higgins, Hedges, & Rothstein, 2017). Heterogeneity study effects were assessed via moderator analyses (i.e., subgroup analyses and meta-regressions). As suggested by Rosenthal (1995), moderator variables were analyzed irrespective of I^2 values. In the presence of substantial heterogeneity, a number of variables were examined in efforts to explain this heterogeneity.

For categorical moderators, subgroup analyses were conducted using a mixed-effects model, in which studies within subgroups are pooled using the random-effects model, with determination of significant differences between subgroups established using a fixed-effects model (Borenstein et al., 2009). Subgroups with fewer than three studies were not reported. Categorical moderators (displayed in Table 4) included inhibition subtype (interference control, response inhibition, or inhibition of cognitive sets), Stroop outcome measure (total time, reaction time per trial, or accuracy), aMCI subtype (sd-aMCI or aMCI), recruitment source (community, clinical), aMCI criteria (conventional or other) and study focus (whether the inhibition task was the main or ancillary focus of the paper). A study was classified as "main focus" if the inhibition measure was a primary dependent variable of interest in the journal article and a study was classified as "ancillary focus" if the inhibition measure was not a primary dependent variable of interest (e.g., it was part of a neuropsychological battery). For continuous moderator variables, we conducted meta-regression analyses using the following continuous variables: mean age, proportion of male participants, mean education level, and mean MMSE score of the aMCI group (as a general index of level of cognitive impairment).

Outlier Analysis and Publication Bias

Data were screened to identify outliers and determine the potential influence of publication bias. Standardized residuals (i.e., how much each study differed from the overall effect) were inspected to identify outliers, defined as studies where the standardized residual z-score of the effect size exceeded 3.0 (Lipsey & Wilson, 2001). Sensitivity analyses were conducted to examine the impact of removal of outliers on the overall effect estimate using the *one-study removed* method (Borenstein et al., 2009). In this iterative procedure, CMA repeatedly recalculates effect sizes and confidence intervals excluding one study at a time from the analysis. This technique reveals whether any particular study was influential enough to change the decision about whether or not to reject the null hypothesis.

Multiple procedures were used to assess publication bias in the current meta-analysis. First, the *Fail Safe N* statistic (Rosenthal, 1979) was used to estimate the number of unpublished papers with non-significant results that would be necessary to make the group difference non-significant. Second, funnel plots were visually inspected and formally tested using *Egger's regression test* (Egger, Smith, Schneider, & Minder, 1997) to assess for funnel plot asymmetry. If funnel plot asymmetry was detected, Duval and Tweedie's *trim-and-fill method* was applied (Duval and Tweedie, 2000). This method adds or removes studies to balance the distribution of studies in an asymmetrical funnel plot and provide an unbiased estimate of effect size.

Lastly, in an additional attempt to identify publication bias we conducted a unique analysis looking at the focus of each

paper. More specifically, we conducted a categorical moderator analysis to determine whether studies where the main focus was on inhibitory control performance in aMCI would be more likely to publish findings with significant effects (i.e., large effect sizes) relative to studies where the inhibition measure was not the primary outcome measure of interest and inhibition performance was used for diagnosis or reported primarily to describe the samples, along with other neuropsychological data.

Results

Study Selection

Of 3417 identified articles, 326 were selected for full-text screening (see Fig. 1). Based on full-text evaluation of the 326 articles, 66 met inclusion criteria. Reasons for exclusion are documented in Fig. 1.

Study Characteristics

The included studies and their characteristics are shown in Table 2. The studies on which the meta-analysis is based, involved a total of 2184 participants with MCI and 3049 healthy controls. As discussed earlier, six studies included a mix of individuals with aMCI and naMCI (Apostolova et al., 2012; Clark et al., 2016; De Looze et al., 2018; Pa et al., 2010; Stricker et al., 2013; Zihl et al. 2010) and two studies did not clearly specify the MCI subtype but cited using Petersen's criteria for diagnosis (Fernández et al., 2011; Mirandez, Aprahamian, Talib, Forlenza, & Radanovic, 2017). Excluding these eight studies with mixed or unclear MCI subtypes, there were 58 studies with a total of 1870 participants with purely aMCI. Eight of these studies included only single-domain aMCI and the remaining 50 studies did not specify the proportion of single-domain and multiple domain aMCI participants. Fifty-nine of the 66 studies used conventional MCI criteria like Petersen (1995, 1999, 2001, 2003; 2004; 2009), Winblad et al. (2004), or National Institute of Aging-Alzheimer's Association (NIA-AA) diagnostic guidelines (Albert et al., 2011) to identify individuals with aMCI, including a memory complaint usually corroborated by an informant, objective memory impairment for age, essentially preserved general cognitive function, preservation of general functional abilities, and the absence of diagnosed dementia. The remaining seven studies required the presence of a memory impairment for aMCI diagnosis but did not follow conventional criteria. A neuropsychologist on our team (NDA) determined that the aMCI criteria used in these seven studies was sufficient. Table 3 displays the descriptive statistics of the ages, sex distributions, education, and MMSE in the aMCI group relative to the healthy control group.

Results of the Meta-Analyses

The first analysis was conducted with all studies to assess overall inhibitory control abilities, regardless of inhibition subtype. There were a total of 66 studies included in the meta-analysis. Four studies were included twice (Clark et al., 2016; Johns et al., 2012; Zhang, Han, Verhaeghen, & Nilsson, 2007; Zheng et al., 2012) as they each included data from two tasks of different inhibitory control subtypes. The overall effect size for the difference between the aMCI and control comparison groups in all studies ($k = 70$) was moderate and statistically significant (Hedges' $g = -0.73$, 95% CI -0.88 to −0.58, $p < .001$), implying that individuals with aMCI show general deficits in inhibitory control relative to healthy age-matched controls. The Fail-safe N analysis revealed that 8598 studies with null results (i.e., approximately 130 times those included here) would be required to reduce this effect to non-significance. There was significant heterogeneity across studies ($Q = 419.07$, $df = 69$, $p < .001$, $I^2 = 83.54\%$, $\tau^2 = 0.31$), supporting the need for more refined analyses. The funnel plot showed significant asymmetry (Egger's intercept = −3.69, t = 4.2; two-tailed $p < .001$) suggesting that smaller studies reported larger effects. Given that the inhibition subtypes are considered related yet distinct processes (Dempster et al. 1993; Friedman & Miyake, 2004; Hasher, Zacks, & May, 1999; Nigg et al. 2000; van Boxtel et al. 2001), this main analysis was followed by separate analyses for each inhibitory control subtype.

Interference Control

A total of 37 studies, including 1201 individuals with MCI and 1950 controls, reported outcome measures associated with interference control. The effect size for this inhibition subtype was moderate and significant (Hedges' $g = -0.74$, 95% CI -1.00 to −0.49, $p < .001$). The Wylie, Ridderinkhof, Eckerle, and Manning (2007) study included data from both the Stroop and Flanker task. Since both of these are interference control tasks, we could not include the same sample of participants twice. We included only the Flanker data as this task was the major focus of the paper. We also re-ran the meta-analysis including the Stroop and Flanker data (by averaging the data from both tasks) and the interference control effect size remained moderate in size (Hedges' g = −0.68, 95% CI -0.94 to −0.42, p < .001). One study (Pa et al., 2010) used word reading instead of colour naming as their control condition in the Stroop task. To confirm that Stroop control condition did not impact the results, we re-ran the meta-analysis excluding the Pa et al. (2010) study. The interference control effect size remained moderate (Hedges' g = −0.70, 95% CI -0.95 to −0.46, p < .001), as did the Stroop task effect size (Hedges' g = −0.63), indicating that it is unlikely that Pa study altered our findings (see Fig. 2 for a breakdown of interference

Table 2 Characteristics of included studies

Study	Inhibition	Task	*n*		Age		% Male		Education		MMSE	
	Type		Control	MCI	Control	MCI	Control	MCI	Control	MCI	Control	MCI
Ahn et al. (2011)	Response	Go/Nogo	142	99	66.0	72.3	39	47	10.8	11.0	28.7	26.2
Apostolova et al. (2012)	Interference	Stroop	46	33	66.4	73.1	54	67	17.2	16.3	29.5	27.8
Ballesteros et al. (2013)	Cognitive Sets	WCST	20	20	69.2	74.5	60	50	13.8	12.0	29.4	24.7
Bastin et al. (2013)	Response	Hayling	24	40	73.2	73.9	25	66	12.5	13.0	N/A	N/A
Bélanger and Belleville (2009)	Response	Hayling	13	13	N/A	N/A	N/A	N/A	N/A	N/A	29.2	27.3
Bélanger, Belleville, and Gauthier (2010)	Interference	Stroop	20	20	71.1	72.7	N/A	N/A	13.5	13.6	28.8	27.4
Binnewijzend et al. (2012)	Interference	Stroop	43	23	69.0	71.0	53	65	N/A*	N/A	29.0	27.0
Borella et al. (2017)	Interference	Stroop	18	15	69.7	72.7	39	40	6.7	7.4	29.5	27.4
Borsa et al. (2016)	Interference	Flanker	7	7	68.7	73.3	71	71	14.6	14.6	28.4	27.1
Brenner et al. (2018)	Cognitive Sets	WCST	33	43	69.5	71.8	12	51	16.6	16.1	29.4	28.2
Cespon et al. (2013)	Interference	Simon	25	30	65.2	68.7	56	53	10.8	9.0	28.4	25.6
Cespon et al. (2015a)	Interference	Simon	18	25	68.3	70.1	39	52	11.1	9.7	28.5	25.4
Cespon et al. (2015b)	Interference	Simon	15	27	66.0	68.1	42	N/A	10.2	9.3	28.3	25.8
Chen et al. (2009)	Cognitive Sets	WCST	16	13	69.0	73.2	56	62	10.5	11.4	N/A	N/A
Chiu et al. (2014)	Cognitive Sets	WCST	30	20	64.4	71.2	43	45	13.1	12.0	28.8	26.3
Cid-Fernández, Lindín, and Díaz (2014)	Response	Go/Nogo	63	30	65.9	69.5	35	47	8.9	9.7	28.2	25.9
Cid-Fernández et al. (2017)	Response	Go/Nogo	20	34	67.0	69.9	30	45	9.8	9.1	28.0	25.7
Clark et al. (2016)	Cognitive Sets	WCST	51	107	68.9	69.8	55	43	17.6	16.0	28.9	27.3
Clark et al. (2016)	Interference	Stroop										
Davidson, Cooper, and Taler (2016)	Interference	Stroop	34	19	70.1	75.6	38	47	16.1	16.7	N/A	N/A
De Looze et al. (2018)	Response	SART	36	16	71.1	73.8	47	69	13.7	13.4	N/A	26.1
Duong, Whitehead, Hanratty, and Chertkow (2006)	Interference	Stroop	60	61	74.4	74.7	N/A	N/A	11.7	11.0	29.1	27.2
Dwolatzky et al. (2003)	Response	Go/Nogo	39	30	73.4	77.2	33	57	15.0	13.1	29.0	27.6
Fernández et al. (2011)	Interference	Flanker	19	15	70.3	66.7	53	53	5.6	4.8	29.3	25.9
Guerdoux, Dressaire, Martin, Adam, and Brouillet (2012)	Interference	Stroop	17	17	72.0	71.0	65	59	11.6	12.8	28.4	27.5
Guild et al. (2014)	Cognitive Sets	WCST	47	13	70.7	73.1	46	14	15.9	14.6	28.9	28.1
Hampstead, Towler, Stringer, and Sathian (2018)	Cognitive Sets	WCST	31	47	70.4	72.2	N/A	N/A	16.8	15.9	N/A	N/A
Johns et al. (2012)	Interference	Stroop	32	36	71.8	72.4	41	45	14.4	13.1	28.9	28.1
Johns et al. (2012)	Response	Hayling										
Li, Tang, and Chen (2016)	Interference	Stroop	19	16	70.2	69.5	63	63	14.4	13.4	29.0	26.4
Lopez et al. (2006)	Interference	Stroop	374	10	79.5	79.9	38	60	N/A	N/A	N/A	N/A
Lopez Zunini et al. (2016)	Response	Go/Nogo	17	15	72.4	75.6	35	47	15.6	14.7	N/A	N/A
Luks et al. (2010)	Interference	Flanker	22	9	64.0	66.0	55	67	N/A	N/A	N/A	N/A
Lv et al. (2010)	Interference	Flanker	45	42	64.8	68.5	42	45	N/A	N/A	N/A	N/A
Martín et al. (2016)	Interference	Stroop	142	81	71.0	71.5	44	48	9.5	8.2	28.1	26.5
Mirandez, Aprahamian, Talib, Forlenza, and Radanovic (2017)	Interference	Stroop	37	30	72.5	74.5	30	27	13.5	12.0	29.2	27.8
Mudar et al. (2016)	Response	Go/Nogo	25	25	65.4	68.5	36	36	16.6	16.0	28.6	28.4
Nagahama et al. (2003)	Cognitive Sets	WCST	22	17	70.8	72.8	N/A	N/A	11.1	10.9	29.1	26.4
Nguyen et al. (2017)	Response	Go/Nogo	22	22	65.3	68.7	27	36	16.6	16.2	28.8	28.3
Okonkwo et al. (2008)	Response	CPT	56	60	64.6	68.1	32	43	15.2	14.9	29.6	28.4
Pa et al. (2010)	Interference	Stroop	40	57	65.2	69.8	50	53	17.6	16.8	29.8	28.4

Table 2 (continued)

Study	Inhibition Type	Task	*n*		Age		% Male		Education		MMSE	
			Control	MCI	Control	MCI	Control	MCI	Control	MCI	Control	MCI
Pereiro, Juncos-Rabadán, and Facal (2014)	Interference	Simon	39	62	67.3	68.7	N/A	N/A	10.9	9.4	28.6	25.7
Puente, Faraco, Terry, Brown, and Miller (2014)	Interference	Stroop	26	17	74.0	75.0	38	41	17.0	14.4	28.0	25.9
Rabin et al. (2006)	Cognitive Sets	WCST	30	29	72.0	74.1	30	55	17.0	16.7	28.9	26.8
Ramos-Goicoa, Galdo-Alvarez, Diaz, and Zurrón (2016)	Interference	Stroop	45	39	65.4	70.7	38	46	10.1	9.9	28.5	25.5
Riby et al. (2009)	Response	SART	24	24	71	73	N/A	N/A	12.6	12.5	29.1	27.7
Ryan et al. (2012)	Cognitive Sets	WCST	40	40	69.7	73.2	35	55	15.7	16.0	28.7	26.7
Sánchez-Benavides (2014)	Interference	Stroop	356	79	64.9	72.8	40	43	10.4	8.0	28.7	25.7
Serra et al. (2013)	Cognitive Sets	WCST	28	15	63.4	70.9	66	73	13.1	11.3	28.4	25.4
Sherod et al. (2009)	Response	CPT	85	113	67.2	70.3	35	43	15	14.6	29.4	28.1
Sinai et al. (2010)	Interference	Stroop	19	27	75.7	76.3	37	41	14.5	11.6	28.6	27.3
Spieler, Balota, and Faust (1996)	Interference	Stroop	25	22	70.5	73.2	N/A	N/A	N/A	N/A	N/A	N/A
Stricker et al. (2013)	Cognitive Sets	WCST	81	32	67.7	68.5	37	41	15.0	14.8	28.1	27.5
Sun et al. (2016)	Cognitive Sets	WCST	38	50	68.7	68.8	37	34	12.4	12.1	28.5	26.6
Taler, Voronchikhina, Gorfine, and Lukasik (2016)	Interference	Stroop	39	19	70.6	75.0	46	52	16.2	16	N/A	N/A
Tran, Speck, Pisupati, Gallagher, and Bakker (2017)	Interference	Stroop	35	39	69.0	72.4	51	45	16.1	15.5	28.5	26.1
Traykov et al. (2007)	Cognitive Sets	WCST	20	20	73.3	73.2	70	80	12.8	12.1	29.5	28.9
Van Dam et al. (2013)	Interference	Flanker	8	8	74.6	77.6	25	50	16.9	14.6	28.8	27.1
Villeneuve, Belleville, Massoud, Bocti, and Gauthier (2009)	Interference	Stroop	77	68	70.4	70.7	25	43	14.0	14.5	29.0	27.5
Wang et al. (2013)	Interference	Flanker	16	15	69.3	72.9	56	60	14.0	12.8	29.3	27.0
Weniger, Ruhleder, Lange, Wolf, and Irle (2011)	Cognitive Sets	WCST	29	29	59.0	59.0	66	76	9.6	9.9	N/A	28.0
Wylie, Ridderinkhof, Eckerle, and Manning (2007)	Interference	Flanker	20	20	71.5	73	45	40	16.0	15.6	29.3	26.0
Zhang, Han, Verhaeghen, and Nilsson (2007)	Interference	Stroop	30	30	73.5	73.7	N/A	N/A	12.1	10.7	28.7	27.4
Zhang, Han, Verhaeghen, and Nilsson (2007)	Response	Go/Nogo										
Zhang et al. (2015)	Interference	Flanker	15	12	67.8	69.3	53	58	9.2	8.5	28.7	23.8
Zheng et al. (2012)	Response	Stop-signal	36	34	67.4	67.9	50	41	11.1	10.0	29.5	28.3
Zheng et al. (2012)	Interference	Stroop										
Zheng et al. (2014)	Response	Stop-signal	48	50	69.2	69.8	40	32	10.4	9.8	29.5	27.9
Zhou and Jia (2009)	Interference	Stroop	80	30	66.9	72.1	56	40	10.1	10.5	28.8	26.2
Zihl et al. (2010)	Response	Go/Nogo	20	24	63.4	65.8	45	46	11.3	12.8	29.8	27.8

*Education level was reported using an atypical scale from 1 to 7 (Verhage's classification; Verhage, 1964)

MCI = mild cognitive impairment. MMSE = Mini-Mental Status Test

CPT Continuous Performance Test, *SART* Sustained Attention to Response Task, *WCST* Wisconsin Card Sorting Task

control effect sizes as a function of task type). Neither outlier analysis conducted through evaluation of standardized residuals nor the one-study removed method detected any study that significantly affected the overall effect size estimated. At first glance, Wang et al. (2013) and Zhou and Jia (2009) appear to be outliers on the funnel plot. However, both of these studies had standardized residuals under 3.0 (i.e., −2.36 for Wang et al. and − 2.72 for Zhou et al.). The Fail-safe N analysis indicated that 1971 null studies would need to be included to render the effect size non-significant.

Table 3 Descriptive Statistics of Control and aMCI group

	Control	aMCI
N	3049	2184
Mean age	69.1	71.6
Age range	59–79.5	59–79.9
Sex distribution (% male)	44	50
Sex distribution range (% male)	12–71	14–80
Mean Education level	13.2	12.6
Education level range	5.6–17.6	4.8–16.8
Mean MMSE	28.9	26.9
MMSE range	27.7–29.8	22.6–29.2

aMCI amnestic mild cognitive impairment

Heterogeneity across studies was significant ($Q = 338.41$, $df = 36$, $p < .001$, $I^2 = 89.36\%$, $\tau^2 = 0.54$). The funnel plot showed significant asymmetry (Egger's intercept = −5.26, $t = 4.23$; two-tailed $p = < .001$), but the trim and fill analysis was not suggestive of publication bias, as no studies were imputed (see Fig. 3). Based on the data included in the analysis, it appears that aMCI-related impairments were greatest on the Flanker task ($g = -1.39$) relative to the Stroop task ($g = -0.68$) and Simon task ($g = -0.006$).

We re-ran the interference control meta-analysis excluding the five studies which included a mixed sample of individuals with aMCI and naMCI to confirm the presence of interference control deficits in individuals with aMCI. Results revealed that the total effect size remained moderate, $g = -0.61$, 95% CI -0.86 to −0.36 (original effect size was −0.74), with significant heterogeneity ($Q = 238.73$, $df = 31$, $p < .001$, $I^2 = 87.02\%$, $\tau^2 = 0.43$).

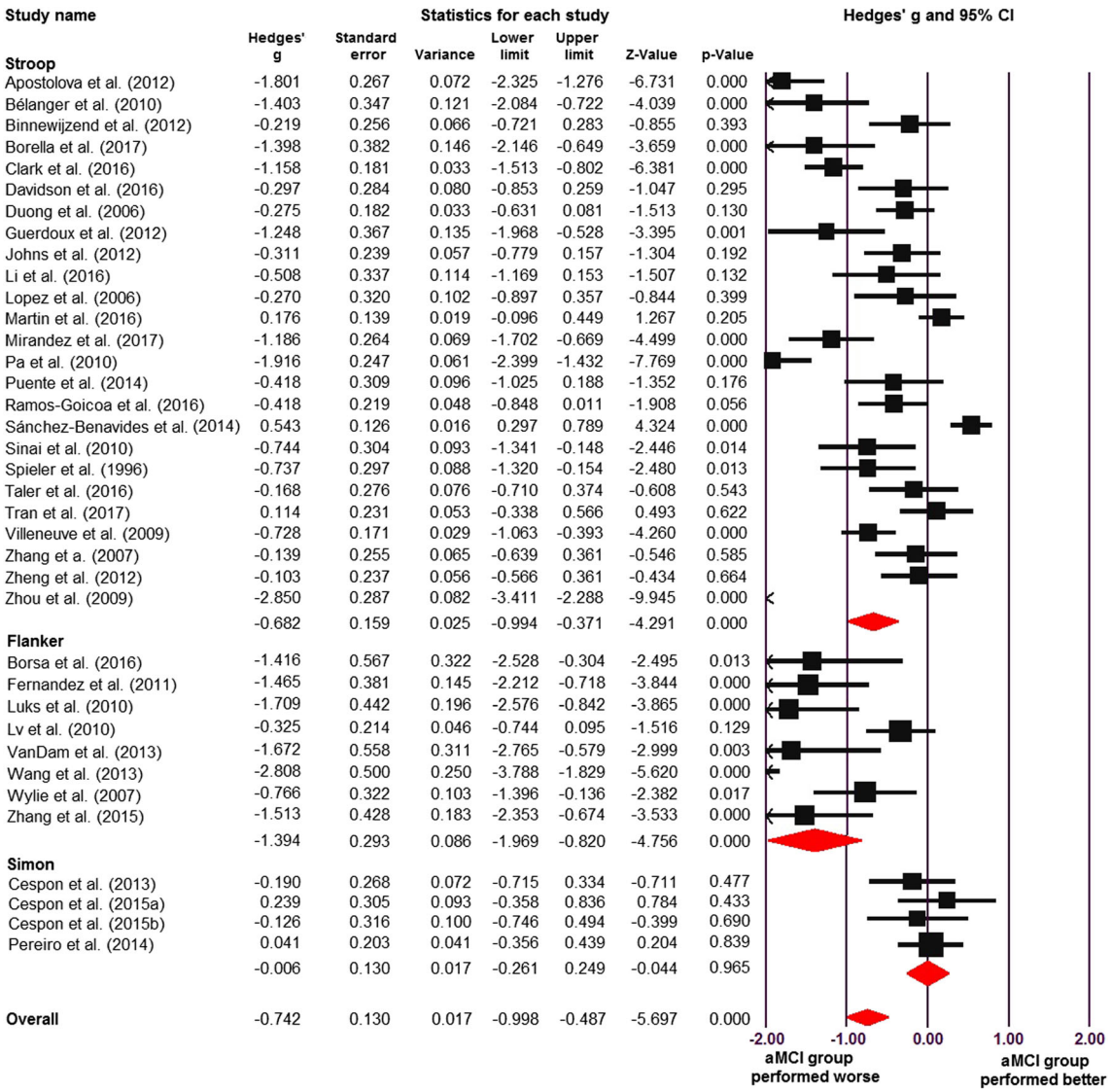

Fig. 2 Forest plot of interference control performance by individuals with amnestic MCI aMCI) and controls

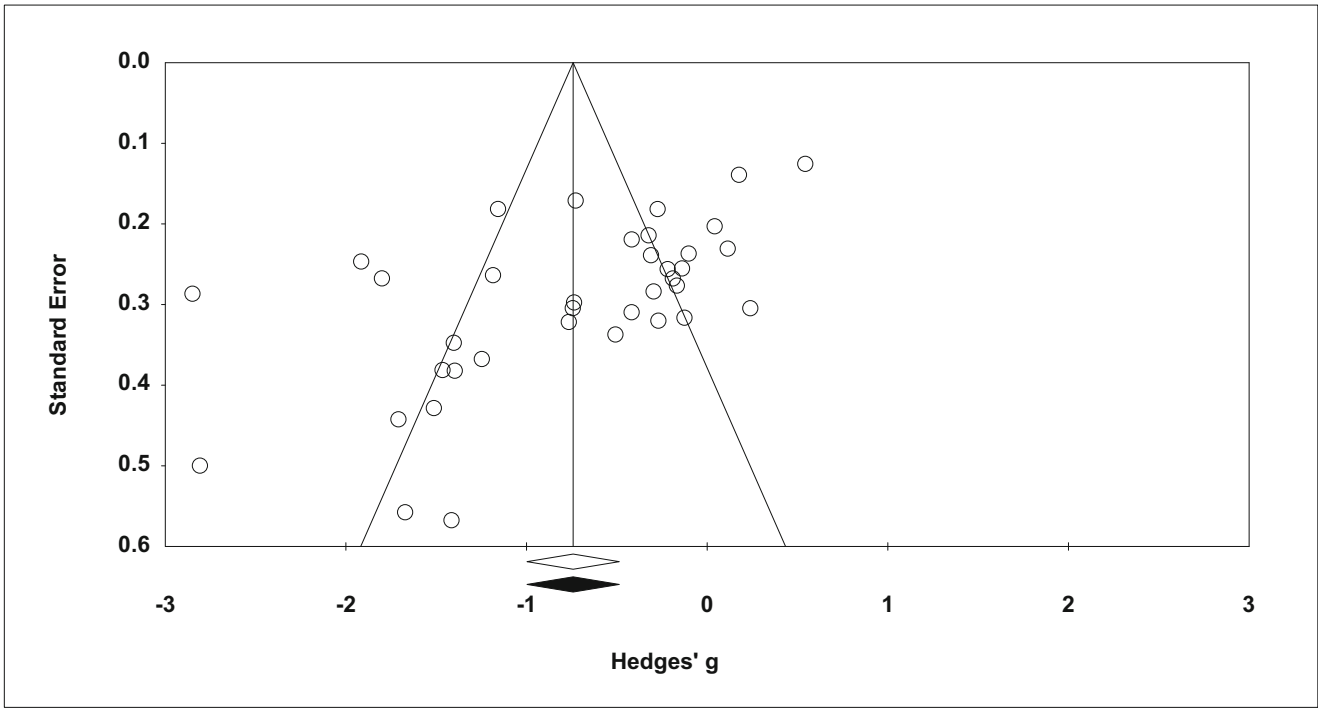

Fig. 3 Funnel plot of interference control. No imputed studies

Response Inhibition

A total of 18 studies, including 695 individuals with MCI and 732 controls, reported outcome measures associated with response inhibition. The effect size for this inhibition subtype was moderate and significant ($g = -0.71$, 95% CI -0.882 to −0.53, $p < .001$: see Fig. 4 for a breakdown of response inhibition effect sizes as a function of task type). The Fail-safe N analysis revealed that 671 null studies would need to be included to render the effect size non-significant. The Johns et al. (2012) study was identified as an outlier based on the standardized residual criteria ($z = -3.82$). However, the Johns et al. (2012) study was retained in the analysis because the one-study removed procedure did not identify any outliers. Heterogeneity between studies was significant ($Q = 40.77$, $df = 17$, $p = .001$, $I^2 = 58.30\%$, $\tau^2 = 0.079$). Inspection of funnel plot asymmetry (Egger's intercept = −1.37, $t = 1.13$; two-tailed $p = .28$) and the trim and fill analysis (no imputed studies) did not suggest probable publication bias (see Fig. 5). While all of the response inhibition tasks had moderate effect sizes, there were not enough studies in each task type to examine differences across task (i.e., 9 in Go/Nogo, 3 in Hayling, 2 in Continuous Performance Test, and 2 in Stop-Signal).

We analyzed the response inhibition data once more excluding the two studies which included a sample of both aMCI and naMCI individuals. There was no change in the overall effect size after excluding the two studies, $g = -0.71$, 95% CI -0.89 to −0.51 (original effect size was −0.71), with significant heterogeneity ($Q = 40.60$, $df = 15$, $p < .001$, $I^2 = 63.05\%$, $\tau^2 = 0.091$).

Inhibition of Cognitive Sets

A total of 15 studies, including 495 individuals with MCI and 516 controls, reported outcome measures associated with inhibition of cognitive sets. The effect size for this inhibition subtype was moderate and significant ($g = -0.76$, 95% CI -0.93 to −0.59, $p < .001$: see Fig. 6), suggesting that individuals with aMCI had worse inhibition of cognitive sets on the WCST than healthy controls. The Fail-safe N analysis demonstrated that 472 null studies would need to be included to render the effect size non-significant. Outlier analyses revealed no outliers. Test for heterogeneity was not significant ($Q = 22.44$, $df = 14$, $p = .07$, $I^2 = 37.62\%$, $\tau^2 = 0.04$). Inspection of the funnel plot (Egger's intercept = 0.53, $t = 0.33$; two-tailed $p = .75$) did not show evidence of publication bias. The trim and fill analysis imputed two studies (see Fig. 7), which did not change the overall effect size substantially, $g = -0.69$, 95% CI -0.87 to −0.51 (original effect size was −0.76).

We analyzed the inhibition of cognitive sets data once more excluding the two studies that had a sample of combined aMCI and naMCI individuals. There was minimal influence on the overall effect size, changing from a Hedges' g of −0.76 to −0.72 (95% CI -0.92 to −0.52, $p < .001$), with non-significant heterogeneity ($Q = 20.27$, $df = 12$, $p = .062$, $I^2 = 40.81\%$, $\tau^2 = 0.05$).

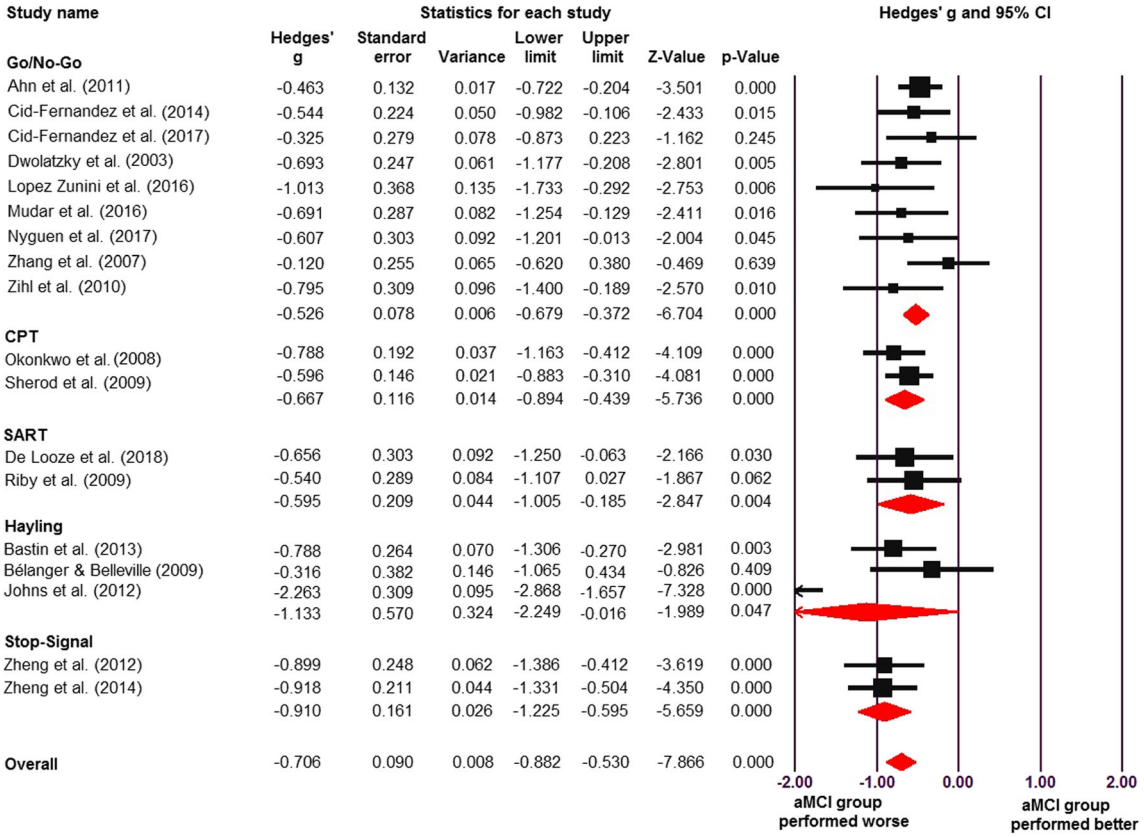

Fig. 4 Forest plot of response inhibition performance by individuals with amnestic MCI (aMCI) and controls. CPT = Continuous Performance Test and SART = Sustained Attention to Response Task

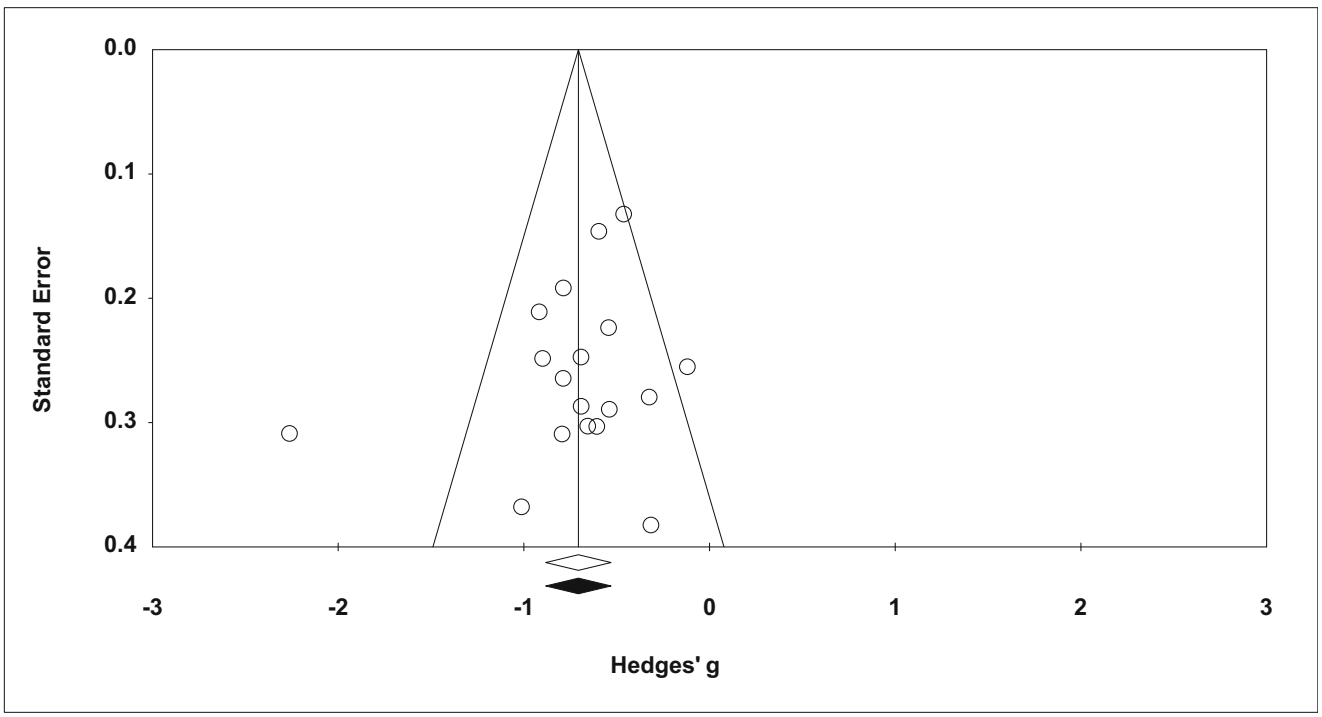

Fig. 5 Funnel plot of response inhibition. No imputed studies

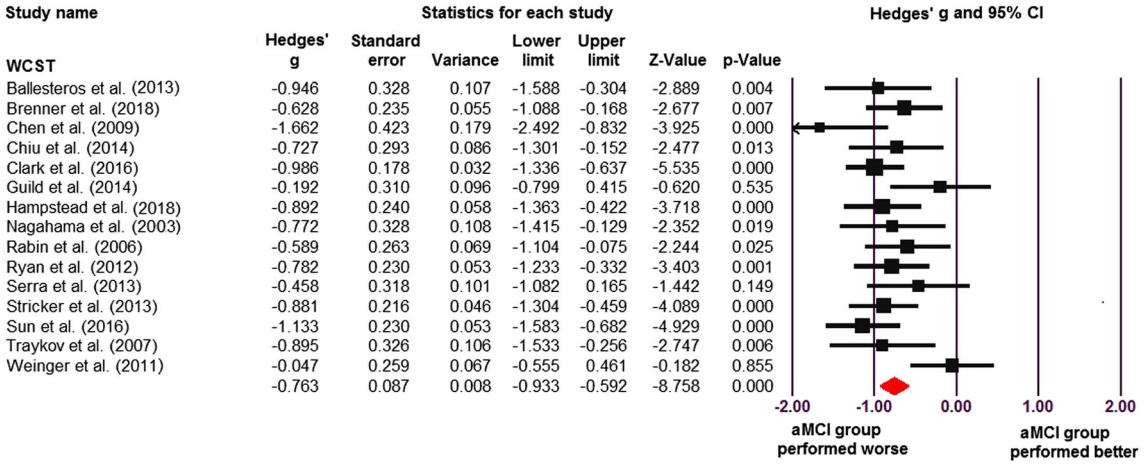

Fig. 6 Forest plot of inhibition of cognitive sets performance by individuals with amnestic MCI (aMCI) and controls. WCST = Wisconsin Card Sorting Task

Moderator Analyses

Categorical Moderators For categorical moderators, we conducted subgroup analyses using a mixed effects model, which uses a random-effects model within subgroups and a fixed-effects model across subgroups**.** The following moderator variables were examined: inhibition subtype, Stroop outcome variable (total time on the task, accuracy, or reaction time per trial), aMCI subtype (sd-aMCI or md-aMCI), recruitment source (whether participants were recruited from clinical sources like hospitals, dementia research centres, and memory clinics, or directly from the community), study focus (whether the inhibitory task was a main focus of the paper, or included only for descriptive purposes), and aMCI criteria (conventional or other). Studies that did not clearly indicate the recruitment source or included a mix of participants recruited from clinical and community sources were not included in this categorical moderator analysis. The details concerning the studies included and findings for each moderator examined are provided in Tables 4 and 5.

Overall inhibitory control performance was not moderated by inhibition subtype ($p = .902$). For the interference control meta-analysis, Stroop outcome measure was found to significantly moderate inhibitory control performance (Total Between $Q = 23.09$; $df = 2$; $p < .001$). There was a significant effect for total time on task ($g = -1.04$; $p < .001$) and RT per trial ($g = -0.49$; $p = .005$), and a non-significant effect for accuracy ($g = 0.14$; $p = .37$). The lack of group differences on

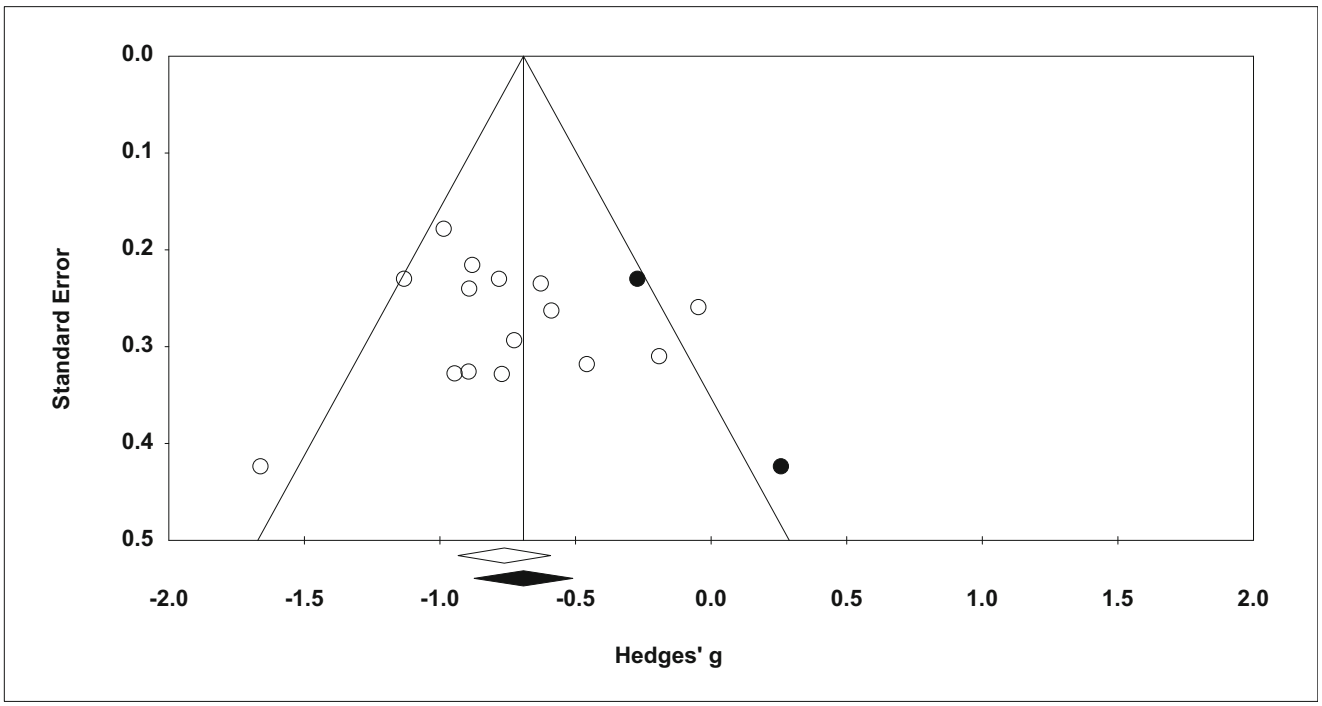

Fig. 7 Funnel plot of inhibition of cognitive sets. Two imputed studies

Table 4 Categorical moderators of included studies

Study	Stroop Outcome	MCI Group	Recruitment Location	Focus	MCI Criteria
Ahn et al. (2011)	N/A	aMCI	Clinical	Main	Conventional-P
Apostolova et al. (2012)	Total time	MCI	Clinical	Ancillary	Conventional-P
Ballesteros et al. (2013)	N/A	aMCI	Community	Main	Other
Bastin et al. (2013)	N/A	sd-aMCI	Clinical	Ancillary	Conventional-P
Bélanger and Belleville (2009)	N/A	aMCI	Clinical	Main	Conventional-P
Bélanger, Belleville, and Gauthier (2010)	RT per trial	aMCI	Clinical	Main	Conventional-P
Binnewijzend et al. (2012)	Total time	aMCI	Clinical	Ancillary	Conventional-P
Borella et al. (2017)	Total time	aMCI	Clinical	Main	Conventional-P
Borsa et al. (2016)	N/A	sd-aMCI	Clinical	Main	Conventional-P
Brenner et al. (2018)	N/A	aMCI	Clinical	Ancillary	Conventional-P
Cespon et al. (2013)	N/A	aMCI	Community	Main	Conventional-P
Cespon et al. (2015a)	N/A	aMCI	Community	Main	Conventional-P
Cespon et al. (2015b)	N/A	aMCI	Community	Main	Conventional-P
Chen et al. (2009)	N/A	aMCI	Clinical	Main	Conventional-P
Chiu et al. (2014)	N/A	aMCI	Clinical	Ancillary	Conventional-N
Cid-Fernández, Lindín, and Díaz (2014)	N/A	aMCI	Clinical	Main	Conventional-P
Cid-Fernández et al. (2017)	N/A	aMCI	Clinical	Main	Conventional-P
Clark et al. (2016)	Total time	MCI	Clinical	Ancillary	Conventional-P
Davidson, Cooper, and Taler (2016)	Accuracy	aMCI	Clinical	Ancillary	Conventional-P
De Looze et al. (2018)	N/A	MCI	Clinical	Ancillary	Conventional-N
Duong, Whitehead, Hanratty, and Chertkow (2006)	Total time	aMCI	Clinical	Main	Conventional-P
Dwolatzky et al. (2003)	N/A	aMCI	Clinical	Main	Conventional-P
Fernández et al. (2011)	N/A	MCI	Clinical	Main	Conventional-P
Guerdoux, Dressaire, Martin, Adam, and Brouillet (2012)	Total time	sd-aMCI	Unclear	Main	Conventional-P
Guild et al. (2014)	N/A	sd-aMCI	Community	Ancillary	Conventional-P
Hampstead, Towler, Stringer, and Sathian (2018)	N/A	aMCI	Clinical	Ancillary	Conventional-P
Johns et al. (2012)	Total time	aMCI	Clinical	Main	Conventional-P
Li, Tang, and Chen (2016)	Total time	aMCI	Clinical	Ancillary	Conventional-P
Lopez et al. (2006)	Total time	sd-aMCI	Community	Main	Other
Lopez Zunini et al. (2016)	N/A	aMCI	Clinical	Main	Other
Luks et al. (2010)	N/A	aMCI	Clinical	Main	Conventional-P
Lv et al. (2010)	N/A	aMCI	Clinical	Main	Conventional-P
Martín et al. (2016)	Accuracy	aMCI	Clinical	Main	Conventional-P
Mirandez, Aprahamian, Talib, Forlenza, and Radanovic (2017)	Total time	MCI	Mixed	Ancillary	Conventional-P
Mudar et al. (2016)	N/A	aMCI	Clinical	Main	Conventional-P
Nagahama et al. (2003)	N/A	aMCI	Clinical	Main	Conventional-P
Nguyen et al. (2017)	N/A	aMCI	Clinical	Main	Conventional-N
Okonkwo et al. (2008)	N/A	aMCI	Mixed	Ancillary	Conventional-P
Pa et al. (2010)	Total time	MCI	Clinical	Main	Conventional-W
Pereiro, Juncos-Rabadán, and Facal (2014)	N/A	aMCI	Clinical	Main	Conventional-P
Puente, Faraco, Terry, Brown, and Miller (2014)	RT per trial	aMCI	Community	Main	Other
Rabin et al. (2006)	N/A	aMCI	Mixed	Ancillary	Conventional-P
Ramos-Goicoa, Galdo-Alvarez, Diaz, and Zurrón (2016)	RT per trial	aMCI	Clinical	Main	Conventional-P
Riby et al. (2009)	N/A	sd-aMCI	Clinical	Main	Conventional-P
Ryan et al. (2012)	N/A	aMCI	Clinical	Main	Conventional-P
Sánchez-Benavides (2014)	Accuracy	sd-aMCI	Clinical	Main	Other
Serra et al. (2013)	N/A	sd-aMCI	Clinical	Ancillary	Conventional-P
Sherod et al. (2009)	N/A	aMCI	Community	Ancillary	Conventional-P
Sinai et al. (2010)	Total time	aMCI	Clinical	Ancillary	Conventional-P

Table 4 (continued)

Study	Stroop Outcome	MCI Group	Recruitment Location	Focus	MCI Criteria
Spieler, Balota, and Faust (1996)	RT per trial	aMCI	Clinical	Main	Other
Stricker et al. (2013)	N/A	MCI	Mixed	Ancillary	Other
Sun et al. (2016)	N/A	aMCI	Clinical	Ancillary	Conventional-P
Taler, Voronchikhina, Gorfine, and Lukasik (2016)	Accuracy	aMCI	Clinical	Ancillary	Conventional-P
Tran, Speck, Pisupati, Gallagher, and Bakker (2017)	Accuracy	aMCI	Mixed	Ancillary	Conventional-P
Traykov et al. (2007)	N/A	aMCI	Clinical	Main	Conventional-P
VanDam et al. (2013)	N/A	aMCI	Clinical	Main	Conventional-P
Villeneuve, Belleville, Massoud, Bocti, and Gauthier (2009)	Total time	aMCI	Clinical	Main	Conventional-P
Wang et al. (2013)	N/A	aMCI	Clinical	Main	Conventional-P
Weinger et al. (2011)	N/A	aMCI	Clinical	Ancillary	Conventional-P
Wylie, Ridderinkhof, Eckerle, and Manning (2007)	N/A	aMCI	Clinical	Main	Conventional-P
Zhang, Han, Verhaeghen, and Nilsson (2007)	RT per trial	aMCI	Community	Main	Conventional-P
Zhang et al. (2015)	N/A	aMCI	Unclear	Main	Conventional-P
Zheng et al. (2012)	RT per trial	aMCI	Community	Main	Conventional-P
Zheng et al. (2014)	N/A	aMCI	Clinical	Main	Conventional-P
Zhou et al. (2009)	Total time	aMCI	Clinical	Main	Conventional-P
Zihl et al. (2010)	N/A	MCI	Clinical	Main	Conventional-W

Studies listed as mild cognitive impairment (MCI) included both individuals with amnestic (aMCI) and and nonamnestic MCI (naMCI) in their sample. Among these studies, Apostolova et al. (2012) included 91% aMCI, Clark et al. (2016) included 65% aMCI, De Looze et al. (2018) included 88% aMCI, Pa et al. (2010) included 61% aMCI, Stricker included 44% aMCI, and Zihl (2010) included 92% aMCI. Studies with an asterisk next to the MCI group did not clearly specify whether individuals with naMCI were included in the MCI group. Conventional-P represents Petersen criteria, Coventional-W represents Winblad criteria, and Petersen-N represents NIA-AA criteria. "Other" represents unconventional aMCI criteria that was determined as acceptable by a neuropsychologist

Stroop accuracy measures may reflect a type of speed-accuracy trade-off, where aMCI participants may have maintained accuracy but at a slower pace. Recruitment source was also found to significantly moderate interference control (Total Between $Q = 14.02$; $df = 1$; $p < .001$). There was a significant effect for studies that recruited from clinical samples ($g = -0.89$; $p < .001$), and a non-significant effect for studies that recruited from the community ($g = -0.14$; $p = .19$). aMCI subtype, study focus, and aMCI criteria were not significant moderators of interference control effect size.

For the response inhibition meta-analysis, recruitment source and study focus did not significantly moderate effect size. There were not enough studies to carry out the moderator analysis for aMCI subtype and aMCI criteria. Lastly, for the inhibition of cognitive sets meta-analysis, study focus did not significantly moderate effect size. There were not enough studies in one of the subgroups to carry out the moderator analysis for recruitment source, aMCI subtype, or aMCI criteria.

Continuous Moderators Meta-regression analyses were also performed to explore the possible influence of continuous moderator variables. Continuous moderators examined included mean age, years of education, proportion of males, and MMSE. Studies that did not measure or report the relevant variables were excluded from meta-regressions associated with that variable. The relevant results are presented in Table 6 and demonstrate that there was no statistically significant association between inhibition performance (on all three inhibition subtypes) and age, education, proportion of males, or MMSE score.

Discussion

Findings from these meta-analyses provide new information regarding the presence of inhibitory control deficits in aMCI. To our knowledge, no study to date has reviewed and quantified the literature on inhibitory control in aMCI. We found a moderate effect size (Hedges' $g = -0.73$) for an overall deficit in inhibitory control across 66 studies in 2184 participants with aMCI compared to 3049 healthy controls. Importantly, to determine whether the size of inhibition deficits in aMCI depended on inhibition type, we explored each inhibition subtype in separate meta-analyses. Interference control ($g = -0.74$), response inhibition ($g = -0.71$), and inhibition of cognitive sets ($g = -0.76$) across tasks were all associated with moderate effect sizes. Effect sizes remained moderate after excluding studies with samples that consisted of a combination of individuals with aMCI and naMCI, supporting the idea that including a small subset of individuals with naMCI in the analysis did not distort the overall effect sizes.

Table 5 Moderator analysis for categorical variables as a function of inhibitory control subtype

Variable	*k*	*g*	*SE*	95% CI	*z*	*p*	$Q_{between}$	*p*(*Q*)
Inhibition Subtype								
Interference Control	37	-0.74	0.13	[-1.00, -0.49]	-5.70	< .001	0.21	.902
Response Inhibition	18	-0.71	0.09	[-0.88, -0.53]	-7.87	< .001		
Inhibition of Cognitive Sets	15	-0.76	0.09	[-0.93, -0.59]	-8.76	< .001		
Stroop Outcome Variable								
Interference Control								
RT per trial	6	-0.49	0.17	[-0.83, -0.15]	-2.84	.005	23.09	< .001
Total time	14	-1.04	0.20	[-1.43, -0.65]	-5.24	< .001		
Accuracy	5	0.14	0.15	[-0.16, 0.43]	0.91	.366		
Recruitment Source								
Interference Control								
Clinical	26	-0.89	0.17	[-1.22, -0.56]	-5.26	< .001	14.02	< .001
Community	7	-0.14	0.11	[-0.35, 0.07]	-1.31	.189		
Response Inhibition								
Clinical	13	-0.76	0.12	[-0.99, -0.52]	-6.16	< .001	0.81	.370
Community	3	-0.55	0.19	[-0.93, -0.17]	-2.85	.004		
Inhibition of Cognitive Sets*								
Clinical	11	-0.80						
Community	**2**	-0.56						
aMCI Subtype								
Interference Control								
sd-aMCI	4	-0.53	0.51	[-1.52, 0.47]	-1.04	.299	0.211	.646
aMCI	33	-0.77	0.13	[-1.02, -0.51]	-5.91	< .001		
Response Inhibition*								
sd-aMCI	**2**	-0.68						
aMCI	16	-0.71						
Inhibition of Cognitive Sets*								
sd-aMCI	**2**	-0.32						
aMCI	13	-0.82						
Study Focus								
Interference Control								
Main	27	-0.76	0.16	[-1.07, -0.44]	-4.71	< .001	0.02	.881
Ancillary	10	-0.72	0.20	[-1.11, -0.32]	-3.57	< .001		
Response Inhibition								
Main	14	-0.71	0.12	[-0.95, -0.48]	-5.89	< .001	0.04	.846
Ancillary	4	-0.68	0.10	[-0.88, -0.49]	-6.81	< .001		
Inhibition of Cognitive Sets								
Main	5	-0.92	0.14	[-1.19, -0.65]	-6.69	< .001	1.76	.185
Ancillary	10	-0.69	0.11	[-0.90, -0.48]	-6.36	< .001		
aMCI Criteria								
Interference Control								
Conventional	33	-0.81	0.13	[-1.07, -0.55]	-6.08	< .001	2.72	.099
Other	4	-0.19	0.35	[-0.88, 0.50]	-0.54	.590		
Response Inhibition*								
Conventional	17	-0.70						
Other	**1**	-1.01						
Inhibition of Cognitive Sets*								
Conventional	13	-0.74						
Other	**2**	-0.90						

Note. Asterisks represent cases where subgroup analysis of categorical moderators was not possible because fewer than three studies were available per subgroup

Inhibition subtype did not moderate overall inhibitory control performance, suggesting that individuals with aMCI are comparably impaired in all three inhibitory subtypes. Heterogeneity in effect sizes between studies was observed in the interference control and response inhibition meta-analyses but not in the inhibition of cognitive sets meta-analysis. For interference control, the presence of such heterogeneity reflected task type and methodological differences. With regard to task type, aMCI-related impairments were greatest on the Flanker task relative to the Stroop and Simon task. The Simon task had a very low effect size, which may suggest that individuals with aMCI are not impaired on this

Table 6 Moderator analysis for continuous variables as a function of inhibitory control subtype

Variable	Coefficient	*SE*	95% CI	*z*	*p*
Age					
Interference Control	−0.024	0.08	[−0.18, 0.13]	−0.30	.764
Response Inhibition	−0.040	0.04	[−0.12, 0.04]	−0.97	.333
Inhibition of Cognitive Sets	−0.040	0.02	[−0.09, 0.01]	−1.65	.098
Education					
Interference Control	−0.040	0.05	[−0.15, 0.06]	−0.83	.408
Response Inhibition	−0.027	0.05	[−0.12, 0.06]	−0.59	.554
Inhibition of Cognitive Sets	−0.039	0.04	[−0.12, 0.04]	−0.93	.353
Proportion of Males					
Interference Control	−2.605	1.89	[−6.31, 1.10]	−1.38	.169
Response Inhibition	−0.606	1.89	[−4.30, 3.09]	−0.32	.748
Inhibition of Cogntive Sets	0.552	0.68	[−0.77, 1.88]	0.82	.414
MMSE of aMCI group					
Interference Control	−0.186	0.16	[−0.50, 0.13]	−1.16	.244
Response Inhibition	−0.175	0.10	[−0.37, 0.02]	−1.77	.076
Inhibition of Cognitive Sets	0.081	0.09	[−0.09, 0.26]	0.90	.370

task, or alternatively, the Simon task may not be a sensitive measure of response inhibition. However, a closer look at the four studies that included Simon task data revealed that three out of the four studies recruited aMCI participants from the community. The lack of Simon task effects may therefore be driven by the community sample rather than the actual task design. However, Simon studies would need to be included in future analyses to confirm the extent of inhibition deficits on this task and the sources of variability in the effects of aMCI.

In terms of methodological influences on the magnitude of interference control deficits in aMCI, performance differences between individuals with aMCI and controls on interference control tasks were moderated by the Stroop outcome measure and recruitment source. Larger effect sizes were obtained for studies that employed "total time" and "reaction time per trial", relative to Stroop accuracy. Lansbergen, Kenemans, and Van Engeland (2007) obtained the same finding in a meta-analysis examining Stroop interference in children with ADHD, suggesting that outcome measure may be an important variable to consider when measuring inhibitory control via the Stroop task.

Aside from Stroop outcome measure, recruitment source was also found to moderate interference control performance. Relative to healthy controls, individuals with aMCI recruited from clinical samples performed significantly worse than those recruited from the community. This finding is supported by prior research demonstrating that clinical samples show higher rates of conversion to AD than community-based samples and suggests that individuals with aMCI actively seeking evaluation and treatment at clinical locations may be more severely impaired than those identified from the community (Tomaszewski Farias, Mungas, Reed, Harvey, & DeCarli, 2009). Alternatively, it is possible that the rate of misdiagnosis was higher in the community samples, specifically that more individuals who were in fact cognitively normal were misdiagnosed as having aMCI. Support for this latter proposition comes from a meta-analysis by Malek-Ahmadi (2016) showing substantial differences in aMCI reversion-to-normal rates, with clinic-based studies having a lower reversion rate (14%) relative to community-based studies (31%).

Amnestic MCI subtype did not moderate inhibition performance in any of the three inhibitory domains, supporting previous work showing that deficits in inhibitory control may be missed, resulting in a diagnosis of sd-aMCI, if an extensive cognitive evaluation is not conducted (Johns et al., 2012). Study focus did not moderate any effects in all three inhibitory domains, implying that this element did not contribute to publication bias since there was no tendency for primary focus studies to publish findings preferentially when individuals with aMCI were significantly more impaired on inhibition tasks relative to controls. Lastly, while the moderating role of aMCI criteria in response inhibition and inhibition of cognitive sets performance could not be examined due to a small number of studies, the fact that interference control performance was not moderated by aMCI criteria suggests that the type of diagnostic criteria used did not significantly influence effect size.

In terms of demographic variables, age, gender, education and MMSE score did not moderate inhibitory control performance in any of the three domains. While the MMSE score did not moderate inhibition performance, it is possible that a more sensitive screening measure like the MoCA may have led to significant results (Freitas, Simões, Alves, & Santana, 2013; Roalf et al., 2013; Trzepacz, Hochstetler, Wang, Walker, & Saykin, 2015). Given that the MoCA has been shown to be superior to the MMSE as a global assessment tool when discerning early stages of cognitive decline (Roalf et al., 2013), MoCA scores may have better captured aMCI severity as a moderator variable.

Overall, our meta-analyses suggest that individuals with aMCI do in fact show deficits in all three inhibitory control domains in comparison to healthy controls. Such findings are in line with the majority of small-scale prior research showing inhibition deficits among individuals with aMCI in interference control, response inhibition, and inhibition of cognitive sets (e.g., Wylie, Ridderinkhof, Eckerle, & Manning, 2007; Johns et al., 2012; Lopez Zunini et al., 2016; Nagahama et al. 2003; but see Zhang, Han, Verhaeghen, & Nilsson, 2007 for null findings). The comparison of the effect sizes suggests that the magnitude of the impairment is comparable across the different types on inhibition. Our findings demonstrate how factors such as outcome measures and recruitment source may influence the different facets of inhibition.

Theoretical Implications of Inhibition Deficits in aMCI

Results from the current meta-analyses have important theoretical implications for the cognitive mechanisms underlying aMCI. First of all, one topic frequently debated in the inhibitory control literature concerns whether inhibitory mechanisms can be classified as general or specific. Our meta-analyses revealed an overall difference in performance between individuals with aMCI and healthy controls in all three forms of inhibition (interference control, response inhibition, and inhibition of cognitive sets). These findings suggest that inhibitory deficits exhibited by individuals with aMCI are not tied to a specific function of inhibition, but rather to general inhibitory difficulties. It should be noted that the fractionation of inhibition is a hypothesis and the subtypes are likely to overlap to a certain degree. In fact, some research has demonstrated that prepotent response inhibition and interference control are related to each other and constitute a single construct (Friedman & Miyake, 2004; Kane et al., 2016). Consistent with this, neuroimaging studies have shown a subset of brain regions commonly activated across inhibition subtypes (i.e., anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex [DLPFC]), brain regions which have also been implicated in aMCI (Blasi et al., 2006; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Fassbender et al., 2004; Lie, Specht, Marshall, & Fink, 2006; Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Nieuwenhuis, Yeung, Van Den Wildenberg, & Ridderinkhof, 2003; Tanji & Hoshi, 2008; Swick & Jovanovic, 2002; Wager et al., 2005).

However, support also exists for the hypothesis that interference control and response inhibition are separable component processes of inhibitory control. For example, Brydges et al. (2012) demonstrated that interference control and response inhibition dissociate in an ERP Go/Nogo Flanker task, finding that the incongruent flanker condition elicited a more centrally distributed topography with a later N2 peak (neural index of inhibitory processing) than the Nogo condition. Additionally, studies have demonstrated differential developmental patterns for interference control relative to response inhibition (Rabi & Minda, 2014; Zhao, Chen, & Maes, 2018). Dissociable patterns of impairment (i.e., impairment in one inhibitory domain but not another) furthermore have been found in some populations, such as those with ADHD (Johnstone, Barry, Markovska, Dimoska, & Clarke, 2009) and schizophrenia (Westerhausen, Kompus, & Hugdahl, 2013), but not in those with bipolar disorder (Hıdıroğlu et al., 2015) and obsessive-compulsive disorder (van Velzen, Vriend, de Wit, & van den Heuvel, 2014). In sum, we are not concluding that there are no differences between inhibition subtypes, but rather that individuals with aMCI are impaired in all three of the inhibitory domains.

The second major theoretical contribution of the current meta-analysis is that studies in the present meta-analyses were carefully selected in order to ensure that the cognitive profile of the aMCI participants represented individuals who were more likely to have AD as the underlying etiology (i.e., degenerative etiology) of their impairments. Although MCI is composed of heterogeneous subtypes and etiologies, aMCI is generally regarded as a pathological precursor to AD (Petersen et al., 2001). We tried to control for other etiologies by excluding studies if the aMCI group was composed of individuals with neurodegenerative disorders other than preclinical AD (e.g., Parkinson's disease, MCI due to subcortical vascular disease, cerebrovascular disease), or depressive symptomatology. Thus, while results from the current meta-analyses clearly point to the presence of inhibition deficits in MCI with probable AD etiology (i.e., aMCI), difficulties with inhibition may also be associated with MCI due to other etiologies. For example, deficits in inhibitory control have been identified in individuals with MCI due to vascular disease (Nordlund et al., 2007; Sudo, Amado, Alves, Laks, & Engelhardt, 2017), MCI with depressive symptomatology (Hudon, Belleville, & Gauthier, 2008; Zihl et al., 2010) and MCI in Parkinson's disease (Christopher & Strafella, 2013). In fact, Loewenstein, Acevedo, Agron, & Duara, (2006) compared the cognitive profiles of MCI participants with different etiologies, and found no differences in executive function between individuals with aMCI and those with vascular MCI. Future research should be directed at examining the interplay between MCI etiology and inhibitory functioning to delineate whether the nature and degree of inhibition deficits vary as a function of etiology.

One possible explanation for the presence of inhibition deficits in aMCI and AD is anatomical and functional evidence pointing toward aMCI and AD as a type of disconnection syndrome. Compared to healthy older adults, individuals with aMCI show significantly reduced parietal connectivity with the DLPFC, demonstrating a functional disconnection within a distributed frontal-parietal network and a disconnection between anterior and posterior brain regions (Liang, Wang, Yang, Jia, & Li, 2011; Liang, Li, Deshpande, Wang, Hu, & Li, 2014). The functional disconnection seen among individuals with aMCI may explain deficits in areas of cognition that depend on

distributed networks connecting different regions, like executive functions (Johns et al., 2012; Morris, 2004).

Additionally, altered prefrontal activation patterns, atrophy of the prefrontal cortex, and increased beta amyloid deposition in the prefrontal cortex have all been linked to aMCI (Chang, Jacobson, Fennema-Notestine, Hagler, Jennings, Dale, & McEvoy, 2010; Devanand et al., 2010; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005; Rosano et al., 2005). Fouquet and colleagues (2009) also showed reduction in prefrontal and anterior cingulate glucose metabolism among individuals with aMCI who later converted to AD. Neuroimaging studies have also demonstrated that poor inhibition in aMCI is associated with lower grey matter volume in the ACC and atrophy in the DLPFC-ACC network (Borsa et al. 2018; Luks et al., 2010). Thus, pathological changes in the neural network responsible for inhibitory control may be the basis for the global inhibition deficits seen in aMCI.

The third theoretical contribution of the current meta-analysis is the disentangling of processing speed from inhibition performance. Processing speed is an important topic that is sometimes neglected when examining inhibitory control performance. By computing a difference score for a number of inhibition tasks (Stroop, Flanker, Simon, and Hayling) in the current meta-analyses, we were able to control for response processing speed and demonstrate that inhibitory processing is preferentially compromised in aMCI. Our results argue against a *general slowing account* (Salthouse, 1996) and rather lend support to the *Inhibitory Deficit Theory* (Hasher & Zacks, 1988), given that inhibition deficits are present in aMCI after accounting for processing speed. The current findings suggest that inhibition deficits are present in aMCI not due to processing speed, but rather due to a pathological deficit (as evidenced by neuroimaging work showing that the PFC and ACC may be compromised in aMCI) that is distinct from cognitive aging.

An important theoretical implication of the current meta-analysis is consideration of the interplay between inhibitory control and memory performance in aMCI. Identification of components of executive function, like inhibitory control, that are compromised in aMCI may contribute to our understanding of memory deficits in aMCI. Episodic memory and working memory are impaired in aMCI. However, successful memory consolidation and working memory performance require inhibition of irrelevant information (Getzmann et al., 2018; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998; Lustig, May, & Hasher, 2001; Rowe, Turcotte, & Hasher, 2009; Rowe, Hasher, & Turcotte, 2010). For example, studies have shown that individuals with aMCI display significant disruptions of memory consolidation following post-learning interference (Cowan et al., 2005; Dewar, Garcia, Cowan, & Sala, 2009; Ebert & Anderson, 2009), from interference in the form of errors made during learning (Anderson, Guild, Cyr, Roberts, & Clare, 2012; Callahan & Anderson, 2019; Jean, Simard, van Reekum, & Bergeron, 2007; Lubinsky, Rich, & Anderson, 2009; Roberts et al., 2018), and from interference during a delayed match-to-sample working memory task (Aurtenetxe et al., 2016). Additionally, researchers have taken it one step further and not only identified that individuals with aMCI have increased susceptibility to proactive semantic interference effects in memory tasks (Brooks & Loewenstein, 2010; Ebert & Anderson, 2009). Together, these results suggest that inhibitory deficits in aMCI may contribute to the well-established episodic memory and working memory deficits reported in this group. Future research would benefit from quantifying the contribution of attentional inhibitory control deficits to performance on memory-related tasks involving inhibition among individuals with aMCI.

Clinical Implications of Inhibition Deficits in aMCI

Results from the current meta-analyses support the idea that inhibitory control deficits are prevalent in aMCI and inhibition tasks should be included in neuropsychological test batteries to fully capture cognitive dysfunction. However, more research is needed investigating the ecological validity of neuropsychological measures of inhibitory control to determine how deficits in inhibition performance extend to everyday functioning in aMCI. This is especially true, given that executive dysfunction has been shown to be an important contributor to everyday functioning among individuals with aMCI, even after controlling for the degree of memory impairment (Marshall, Rentz, Frey, Locascio, Johnson,, & Sperling, 2011). Some argue that tests of inhibition like the Stroop task lack ecological validity (Burgess et al., 2006; Chan, Shum, Toulopoulou, & Chen, 2008) and may therefore not reflect everyday inhibitory problems that individuals with aMCI encounter. Burgess et al. (2006) suggested that the Hayling Sentence Completion Test is a more ecologically valid test of inhibition, as it appears to mimic real-life inhibitory demands (i.e., the ability to suppress inappropriate words during social interactions). In addition to a call for more research looking at the ecological validity of a wider range of inhibition tasks, future research needs to further examine questionnaires that can measure inhibitory control failure in aMCI to better elucidate how inhibition deficits play out in everyday life. For example, Aretouli and Brandt (2010) used the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) to assess what types of functional abilities are compromised in MCI. Results revealed that executive functions involving attention, inhibition, and working memory (as assessed by tasks such as the Stroop test, Brief Test of Attention, and Trail Making Test) contributed significantly to functional status in MCI.

The Flanker task is a computerized task, and in our meta-analysis, Stroop outcome measures revealed larger effect sizes for studies that employed time rather than accuracy measures. While computerized tasks have not been traditionally included in neuropsychological assessment, over the past few decades more attention has been devoted to examining the

effectiveness of computer-based neuropsychological assessment tools (Morrison, Simone, Ng, & Hardy, 2015; Rabin et al., 2014). For example, the U.S. National Institute of Health developed computerized assessment tools like the NIH EXAMINER (Kramer et al., 2014) and the NIH Toolbox (Gershon et al., 2013), which can be used by researchers and clinicians to assess a series of domains including cognition (sub-domains of cognition include: attention & executive functioning, episodic memory, working memory, language and processing speed). Our findings highlight the utility of computerized inhibition tasks (e.g., Flanker and Stroop tasks), as they provide more accurate measurement of RT, and thus may be more sensitive to subtle cognitive differences.

Our finding that recruitment source moderated the interference control effect size also has important clinical implications. Rates of progression from MCI to dementia are lower in community settings relative to clinical settings (Tomaszewski Farias, Mungas, Reed, Harvey, & DeCarli, 2009), suggesting that clinic-recruited samples display more severe impairments and thus seek medical attention more so than community-recruited samples. Alternatively, the fact that individuals with aMCI recruited from community settings did not display evidence of deficits in interference control may suggest that aMCI was sometimes misdiagnosed among community-dwelling older adults. Research examining differential base rates of MCI in clinic samples versus community samples have reported a higher MCI misdiagnosis in community-based samples (Brooks, Iverson, & White, 2007, 2008; Crawford, Garthwaite, & Gault, 2007; Mistridis et al., 2015). To our knowledge, results from the current meta-analysis showing that interference control is moderated by recruitment location is the first finding to show differences in inhibitory control abilities between community and clinical samples of MCI participants.

Our current findings confirming the presence of inhibition deficits in aMCI may also inform intervention design, allowing more targeted interventions to be developed. To date, interventions have been developed addressing memory deficits in aMCI (Belleville et al. 2006b; Belleville et al., 2018; Rapp, Brenes, & Marsh, 2002; Troyer, Murphy, Anderson, Moscovitch, & Craik, 2008), but the current results suggest that the programs should address inhibitory functions as well. Training interventions for improving inhibitory control in the context of memory paradigms have been implemented in healthy older adults (Anderson, Ebert, Grady, & Jennings, 2018; Biss, Rowe, Weeks, Hasher, & Murphy, 2018) and variable priority training in dual-tasking has been carried out with individuals with MCI (Gagnon & Belleville, 2012), highlighting the potential effectiveness of inhibition interventions in MCI. Furthermore, effective inhibitory control is required in everyday life (e.g., driving, engaging in conversation, avoiding daily distractions), so understanding inhibition deficits in aMCI and developing interventions to address such deficits could be helpful for providing appropriate support to these individuals to preserve their level of independence.

Strengths and Limitations

A strength of the present meta-analyses is the number of well-studied tasks assessing three inhibitory mechanisms that were considered, allowing for a better understanding of subtype specific inhibition deficits in aMCI. In addition, individual differences in processing speed were accounted for by computing an inhibition difference score, which may be interpreted as a more process-pure measure of inhibitory control abilities (Verhaeghen, 2011). Prior studies have shown that relative to individual inhibition scores, difference scores better discriminate individuals with AD from healthy controls (e.g., Jacobson, Delis, Bondi, & Salmon, 2002; Arbuthnott & Frank, 2000). Also, by computing an inhibition difference score for each study, we could ensure that we were using the same metric to detect inhibition deficits. While some studies report the inhibition difference score, many studies report only the performance on the inhibition condition of the task (e.g., interference condition of the Stroop task; incongruent condition of the Flanker or Simon task), which incorporates both processing speed and inhibitory control. Although information processing speed tends to slow with age, disproportionate slowing appears related to aMCI (Phillips, Rogers, Haworth, Bayer, & Tales, 2013). Furthermore, the fact that some studies may be examining a "process-impure" measure of inhibitory control by focusing on individual inhibition scores rather than difference scores may explain the mixed results regarding inhibitory deficits in aMCI in the literature.

A limitation of the current meta-analyses is that aMCI subtype could not be clearly defined in the moderator analysis. Specifically, while some studies clearly classified their sample as including only individuals with sd-aMCI, a large subset of studies did not specify the proportion of single-domain and multiple-domain aMCI individuals. Furthermore, only a crude category coding could be applied (sd-aMCI vs. aMCI) because the available study data did not allow for more fine-grained differentiation. Additionally, there was a low number of available studies for some inhibition tasks (e.g., Simon, Continuous Performance Test, Sustained Attention to Response Task, Hayling, Stop-Signal), prohibiting us from carrying out a moderator analysis looking at task-specific effects. Given that subgroup analyses were significant for the inhibitory control subtype containing the most studies (i.e., interference control), it is possible that with more data, subgroup analyses may have been significant in the remaining two subtypes.

Conclusions & Future Directions

The main aim of this meta-analysis was to determine whether individuals with aMCI would show deficits in inhibitory control and its three forms (interference control, response inhibition, and inhibition of cognitive sets) as displayed by particularly poor performance on tasks commonly used to measure inhibition. The results of the meta-analyses indicated that relative to healthy controls, aMCI is associated with moderate inhibition deficits on all three inhibitory control subtypes. Future research should be directed at conducting longitudinal studies examining the predictive utility of inhibition tests for conversion of aMCI to dementia, as well as assessing the natural progression of inhibitory performance in the aMCI to dementia continuum. Future studies need to be conducted that include a range of inhibition tasks (controlling for processing speed), so that a more comprehensive understanding of inhibition deficits in aMCI can be achieved. Task difficulty and synchrony in circadian clocks (match between circadian arousal periods and time of testing) would also be interesting variables to consider when examining inhibition deficits in aMCI. Such deficits may be larger under more challenging conditions and during suboptimal test times, for example, testing a 'morning' person during an evening test time (Anderson, Campbell, Amer, Grady, & Hasher, 2014; Ngo, Biss, & Hasher, 2018). It would also be of interest for future studies to divide their aMCI sample into individuals with single or multiple domains (i.e., sd-aMCI vs. md-aMCI) in order to identify whether aMCI individuals with additional cognitive impairments (i.e., md-aMCI) have the most severe inhibition deficits. Finally, we encourage future research to explore more directly the contributions of inhibitory deficits to episodic and working memory deficits in aMCI, and to develop and validate interventions to improve inhibitory functioning in people with aMCI.

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